Tetrahedron 66 (2010) 4888–4893

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 5-(3-indolyl)oxazole natural products. Structure revision of Almazole D

Fumiko Miyake, Michinao Hashimoto, Sorasaree Tonsiengsom, Kenichi Yakushijin, David A. Horne *

Department of Molecular Medicine, Beckman Research Institute at City of Hope, 1500 E. Duarte Road, Duarte, CA 91010, USA

ARTICLE INFO

Article history:
Received 15 February 2010
Received in revised form 28 March 2010
Accepted 29 March 2010
Available online 2 April 2010

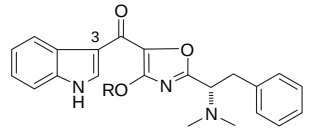
Keywords:
Oxazole
Synthesis
Natural products
Antibiotics

ABSTRACT

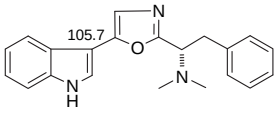
The synthesis and utility of β-oxotryptamine and β-oxytryptophan ester synthons provide a convenient entry to 5-(3-indolyl)oxazole natural products leading to a structure revision of almazole D.

1. Introduction

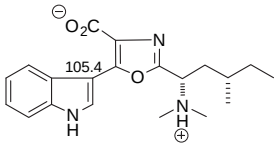
Almazole D (**1**) is a secondary metabolite isolated from red alga that possesses potent antibacterial activity against Gram-negative bacteria such as *Serratia marcescens* and *Salmonella typhi* LXD.[1] These and related pathogenic bacteria are of high concern due to the increasing number of infectious cases, virulence, and resistance to antibiotics. The structure elucidation of **1** has been reported by Pietra and co-workers in which chemical modification studies involving the treatment of **1** with diazomethane yielded methylated analog **2**. Comparison of NMR data obtained for **1** and **2** with those for almazole C (**3**)[2] led to the proposed structure **1** for almazole D. In this report, we describe the results of our synthetic efforts in this area for which a structure revision of almazole D is proposed.



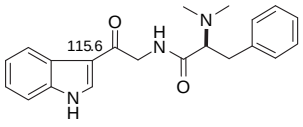
almazole D (**1**) R=H (C3 δ=105.1)
2 R=CH3 (C3 d=103.9)



almazole C (**3**)



martefragin A (**4**)



prealmazole C (**5**)

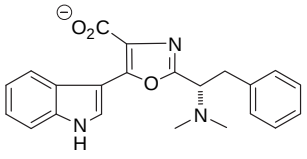
2. Results and discussion

One piece of data that remained at odds with proposed structure **1** is the ^{13}C chemical shift value of the indole C3. The reported value for C3 of **1** and **2** are 105.05 (s) and 103.90 (s) ppm, respectively. Upon examining related indole derivatives reported in the literature as well as those synthesized by our laboratory,[3] these values are more consistent with 5-(3-indolyl)oxazole structures that lack a carbonyl substituent at C3 and better correspond to almazole C (**3**) and martefragin A (**4**).[4] Indoles based on an oxotryptamine motif such as prealmazole C (**5**)[2] typically have C3 chemical shift values in the range of 113–116 ppm. This holds true for a number of oxotryptamine derivatives that we have investigated, particularly those found in the bisindole alkaloid series.[3] Additionally, the formation of almazole D (**1**) from a biosynthetic viewpoint involving tryptophan and *N*,*N*-dimethyl-L-phenylalanine would require an unprecedented oxidative deamination event to explain the extra carbonyl group and hydroxyl moiety contained in the oxazole ring. Based on these observations, we concluded that the original structure **1** proposed for almazole D is likely misassigned and that

* Corresponding author. Tel.: +1 626 471 7310; fax: +1 626 930 5410; e-mail address: dhorne@coh.org (D.A. Horne).

0040-4020/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tet.2010.03.109

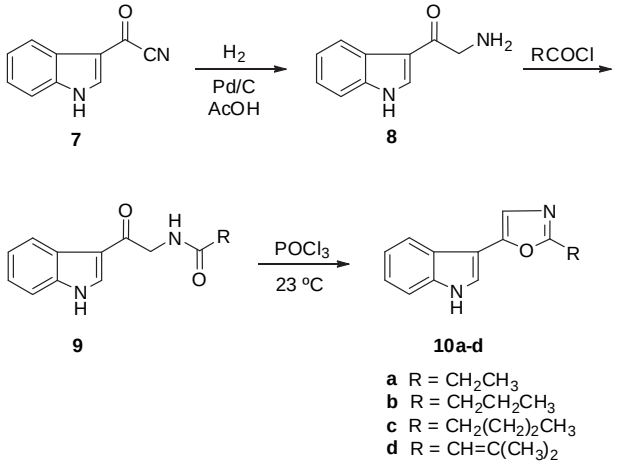
the correct structure of the antibiotic is 5-(3-indolyl)oxazole **6**. This new structure is also more reasonable from a biosynthetic viewpoint as delineated for martefragin A (**4**).[4]



revised structure of almazole D (**6**)

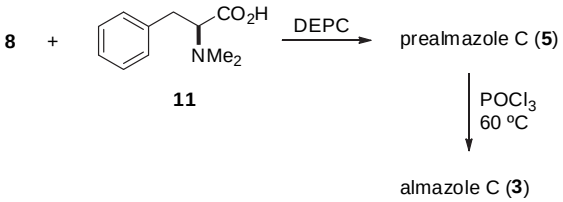
Our synthetic studies began with almazole C (**3**), a related secondary metabolite isolated from red alga. Structure **3** was previously confirmed through synthesis in which a Robinson–Gabriel[2] cyclization served as the key oxazole forming step. The optical rotation, however, reported for the natural material $[\alpha]_D^{23}$ +168 (*c* 1.08, MeOH) is significantly higher than the synthesized material $[\alpha]_D^{23}$ +138 (*c* 0.1, MeOH).[2] One possibility to account for this discrepancy is epimerization of the dimethylamino center during cyclization. While the Robinson–Gabriel method is one of the most widely used procedures for the preparation of oxazoles,[5] cyclodehydrations of chiral α-acylamino ketones having epimerizable centers often pose a problem under these conditions.[6] Thus, one of the key objectives of this study not only involves the structure confirmation of almazole D but the preparation of two key synthons, oxo-tryptamine (**8**) and -tryptophan ester (**13**) and their use in a Robinson–Gabriel approach to chiral, non-racemic oxazole synthesis.

In a previous communication,[3] the reduction of indole-3-carbonyl nitrile (**7**)[7] produced oxotryptamine (**8**), which is an important synthon found in many structural motifs of biologically active natural products. This procedure enables the convenient preparation of **8** in large quantities. With **8** in hand, initial studies were directed at examining reaction conditions necessary to effect the Robinson–Gabriel cyclization which is typically performed at elevated temperatures. Acylation of **8** with the corresponding acid chloride produced ketoamides **9a**–**d**. Treatment of **9a**–**d** with $POCl_3$ at room temperature produced excellent yields of streptomyces and/or streptoverticillium metabolites pimprinethine (**10a**),[8] WS-30581A (**10b**),[9] WS-30581B (**10c**),[9] and unnatural analog (**10d**) (Scheme 1).



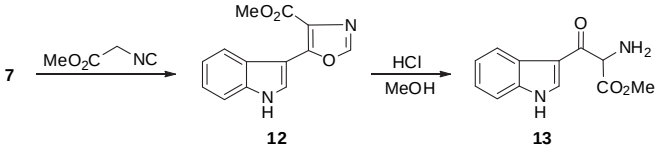
Scheme 1.

Next, using optically pure *N*,*N*-dimethyl-L-phenylalanine (**11**), diethylphosphoryl cyanide (DEPC)[10] facilitated acylation with **8** producing prealmazole C (**5**), $[\alpha]_D^{23}$ +99 (*c* 0.27, MeOH) (lit.[2] $[\alpha]_D^{23}$ +38, *c* 0.25, MeOH) (Scheme 2). It should be noted that a large discrepancy in specific rotation exists between our work and that reported by Pietra and co-workers. Treatment of **5** with $POCl_3$ at 23 °C for one day did not produce appreciable amounts of almazole C (**3**); however, heating the reaction to 60 °C for two days produced good yields of **3**, $[\alpha]_D^{23}$ +156 (*c* 0.27, MeOH). At 90 °C, almazole C (**3**) can be obtained in shorter reaction time but the higher temperature afforded **3** in lower optical purity ($[\alpha]_D^{23}$ +91, *c* 0.27, MeOH). The optical purity of **3** resulting from both sets of reaction conditions was also evaluated by NMR analysis in the presence of (*R*)-Mosher's acid.[11] Under 60 °C cyclization conditions, >97% enantiomeric product purity was obtained as indicated by the presence of a single methyl signal seen at δ 2.86 ppm in $CDCl_3$. At 90 °C, however, epimerization was evident in the product by the presence of two methyl signals at δ 2.86 and 2.84 ppm.



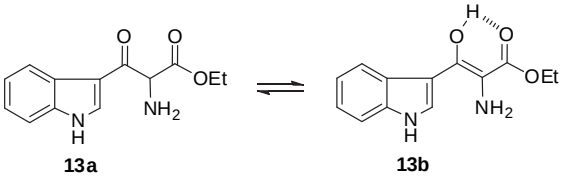
Scheme 2.

Our attention next turned to the synthesis of oxazole **6**, the revised structure proposed for almazole D. The synthesis required the preparation of oxotryptophan methyl ester **13** (Scheme 3). This was achieved through hydrolysis of oxazole **12**, which is easily obtained from the cycloaddition of methyl isocyanoacetate and acyl nitrile **7**.[12] Acid hydrolysis of **12** produced oxotryptophan **13** (75%) and minor amounts oxotryptamine **8** (5%), which occurred through decarboxylation.



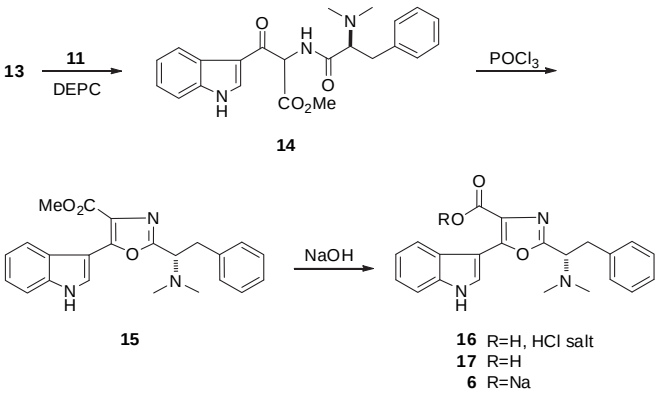
Scheme 3.

While Vinograd and co-workers[13] reported the keto–enol tautomeric behavior of oxotryptophan ethyl ester (**13a**/**13b**) (Eq. 1) (prepared in two steps from ethyl β-keto-β-(3-indolyl)propionate) in pyridine-d_5 and/or MeOH-d_4, we were unable to observe different tautomeric species in the ^{1}H NMR spectrum of **13** in a variety of solvents (pyridine-d_5, $CDCl_3$, DMSO-d_6, and MeOH-d_4) as well as in the ^{13}C NMR spectrum measured in DMSO-d_6. The methine hydrogen, however, did undergo rapid deuterium exchange in the presence of D_2O. While it is reported that some α-C-acylamino acid ester hydrochlorides exist predominantly as the enol tautomer observed by ^{1}H NMR measurements in DMSO-d_6,[12] we found the indole analog **13**·HCl resides predominantly in the keto form in both MeOH-d_4 and DMSO-d_6 as evidenced by their ^{1}H and ^{13}C NMR spectra.



(1)

DEPC coupling of **13** with *N*,*N*-dimethyl-L-phenylalanine (**11**) produced a 1:1 diastereomeric mixture of amides **14**. Although each diastereomer is initially separable by column chromatography, significant epimerization was observed upon standing in DMSO-d_6. Treatment of **14** with $POCl_3$ (60 °C, seven days) afforded oxazole **15** $[\alpha]_D^{23}$ +115 (*c* 0.13, MeOH) and recovered starting material in ~1:1 ratio. Cyclization of **14** was significantly slower than prealmozole C (**5**) presumably due to greater steric hindrance. Complete disappearance of starting material was observed at higher temperatures (90 °C, two days), however, significant epimerization occurred as evidenced by the presence of two -NMe_2 product signals at δ 2.97 and 2.95 ppm ($CDCl_3$) in the presence of (*R*)-Mosher's acid. Direct comparison of ^1H and ^{13}C NMR spectra of **15** and methylated almazole D **2** revealed a perfect match, suggesting a structure revision for **2** to **15**. Further evidence for this revision can be found in the hydrolysis of ester **15**, which produced carboxylic acid **16** upon acidification with HCl. The neutral (or zwitterionic) form **17** can be obtained through flash chromatography (Scheme 4).



Scheme 4.

Both the ^1H and ^{13}C NMR spectra of **17** (MeOH-d_4) as well as the UV spectrum in the presence of NaOH (1.5 equiv) were identical (Fig. 1) to corresponding spectra obtained for almazole D (**1**) isolated from natural sources.

In summary, we have demonstrated the utility of the Robinson–Gabriel oxazole synthesis with chiral, non-racemic ketoamides. In addition, a convenient preparation of β-oxotryptophan methyl ester has been developed. These investigations have led to a structure revision of the antibiotic, almazole D.

3. Experimental section

3.1. General methods

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification except for solvents, which were dried and distilled. $POCl_3$ and acid chlorides were freshly distilled before use. All reactions were carried out under inert atmosphere (N_2) unless otherwise specified. Silica gel (particle size 32–63 μ) was used for flash chromatography.

*3.1.1. β-Oxotryptamine (**8**).* A mixture of indolyl-3-carbonyl nitrile (**7**) (5.0 g, 29 mmol) and 10% Pd/C (1.5 g) in 150 mL of acetic acid was stirred under a balloon of hydrogen. After 16 h, the reaction mixture was filtered over Celite and the filtrate concentrated under reduced pressure. The resulting residue was dissolved in ethanol containing concd HCl (5% by volume). Concentration under vacuo yielded **7**·HCl as a reddish-brown solid (4.6 g, 90%). ^1H NMR (300 MHz, DMSO-d_6) δ 12.45 (1H, br s), 8.50 (1H, d, *J*=2.9 Hz), 8.36 (2H, br s), 8.15 (1H, dd), 7.52 (1H, dd), 7.23 (2H, td×2), 4.34 (2H, d, *J*=5.1 Hz), 3.42 (2H, s) ppm. Compound **7** (free base): ^1H NMR (300 MHz, DMSO-d_6) δ 12.45 (1H, br s), 8.31 (1H, s), 8.17 (1H, br s), 7.46 (1H, dd), 7.22–7.15 (2H, m), 3.89 (2H, br s) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 195.3 (s), 136.5 (s), 133.0 (d), 125.4 (s), 122.7 (d), 121.6 (d), 121.2 (d), 114.3 (s), 112.1 (d), 48.2 (t) ppm; MS *m*/*z* (relative intensity)=175 (M^++1, 100), 144 (30); HRMS calcd for $C_{10}H_{11}N_2O$ (M^++1): 175.0871; found:175.0869.

*3.1.2. N-[2-(1H-Indole-3-yl)-2-oxo-ethyl]-alkylamide **9**. General procedure A.* To a stirred solution of β-oxotryptamine **3** (0.30 g, 1.7 mmol) in 20 mL of THF and triethylamine (0.18 mL, 2.5 mmol) was added acid chloride (1.9 mmol) dropwise at 23 °C. The reaction mixture was stirred for 30 min and concentrated. The

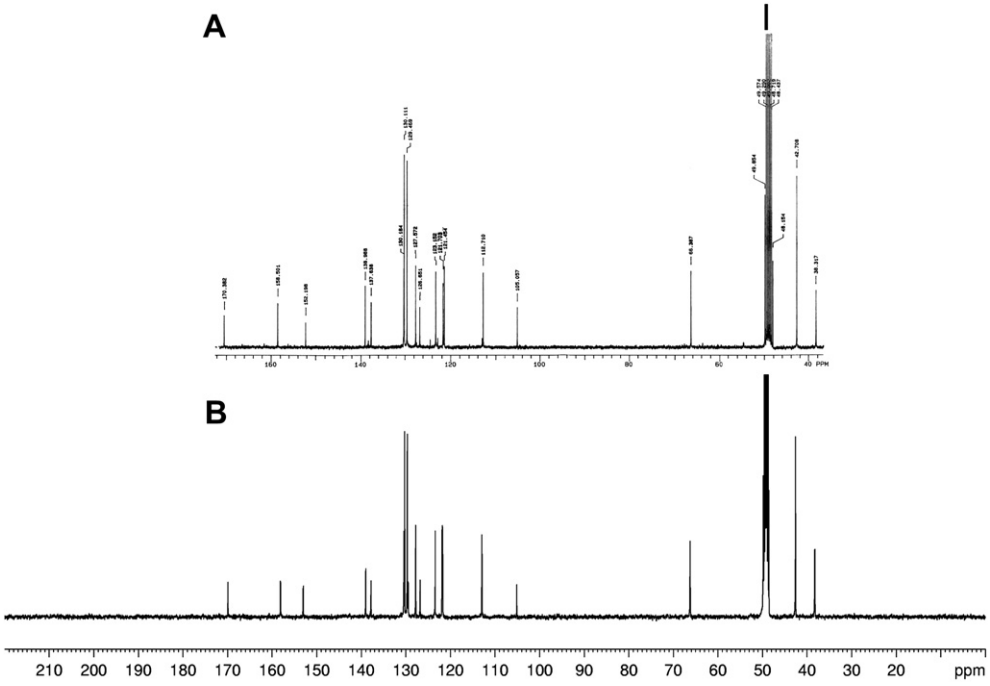


Figure 1. ^{13}C NMR spectra of almazole in MeOH-d_4. A. Natural material B. Synthetic material.

residual product was dissolved in 100 mL of ethyl acetate, washed with brine (2×50 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate under reduced pressure afforded indole-oxo-alkylamide **9**. The product was filtered and washed with methylene chloride.

*3.1.3. N-[2-(1H-Indole-3-yl)-2-oxo-ethyl]-propionamide (**9a**). General procedure A* was used to prepare indole-oxo-alkylamide **9a** from propionyl chloride (0.17 g, 1.9 mmol). Upon concentration under vacuum, compound **9a** crystallized as a light yellow solid (0.34 g, 85%); mp 221–223 °C; IR (KBr) 3299, 3188, 1662, 1616, 1439 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.98 (1H, br s), 8.40 (1H, d, J=3.1 Hz), 8.16–8.13 (1H, m), 8.06 (1H, bt, J=5.4 Hz) 7.48–7.45 (1H, m), 7.24–7.15 (2H, m), 4.44 (2H, d, J=5.6 Hz), 2.18 (2H, q, J=7.6 Hz), 1.03 (3H, t, J=7.6 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.4 (s), 173.2 (s), 136.4 (s), 133.5 (d), 125.4 (s), 122.8 (d), 121.8 (d), 121.1 (d), 114.1 (s), 112.1 (d), 45.6 (t), 28.4 (t), 10.0 (q) ppm; MS m/z (relative intensity)=231 (M^++1, 100), 175 (10), 154 (10), 144 (25), 114 (20); HRMS calcd for $C_{13}H_{15}N_2O_2$ (M^++1): 231.1134; found: 231.1133.

*3.1.4. N-[2-(1H-Indole-3-yl)-2-oxo-ethyl]-butyramide (**9b**). General procedure A* was used to prepare indole-oxo-alkylamide **9b** from butyryl chloride (0.20 g, 1.9 mmol) affording compound **3b** (0.36 g, 87%): ^1H NMR (300 MHz, DMSO-d_6) δ 11.97 (1H, br s), 8.40 (1H, d, J=3.1 Hz), 8.16–8.13 (1H, m), 8.08 (1H, br t, J=5.7 Hz) 7.48–7.44 (1H, m), 7.24–7.15 (2H, m), 4.44 (2H, d, J=5.7 Hz), 2.16 (2H, t, J=7.3 Hz), 1.55 (2H, q, J=7.3 Hz), 0.89 (3H, t, J=7.3 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.4 (s), 172.3 (s), 136.4 (s), 133.5 (d), 125.4 (s), 122.8 (d), 121.8 (d), 121.1 (d), 114.1 (s), 112.1 (d), 45.6 (t), 37.2 (t), 18.7 (t), 13.6 (q) ppm; MS m/z (relative intensity)=245 (M^++1, 100), 175 (15), 144 (25), 77 (10); HRMS calcd for $C_{14}H_{17}N_2O_2$ (M^++1): 245.1290; found: 245.1286.

*3.1.5. Pentanoic acid [2-(1H-indole-3-yl)-2-oxo-ethyl]-amide (**9c**). General procedure A* was used to prepare indole-oxo-alkylamide **9c** from valeryl chloride (0.23 g, 1.9 mmol) affording compound **9c** (0.37 g, 84%); mp 207–210 °C; IR (KBr) 3320, 3190, 1653, 1626, 1436 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.97 (1H, br s), 8.40 (1H, d, J=2.9 Hz), 8.16–8.13 (1H, m), 8.08 (1H, br t, J=5.3 Hz) 7.47–7.45 (1H, m), 7.23–7.15 (2H, m), 4.43 (2H, d, J=5.7 Hz), 2.18 (2H, t, J=7.3 Hz), 1.51 (2H, m), 1.29 (2H, m), 0.87 (3H, t) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.4 (s), 172.4 (s), 136.4 (s), 133.5 (d), 125.4 (s), 122.8 (d), 121.8 (d), 121.1 (d), 114.1 (s), 112.1 (d), 45.6 (t), 35.0 (t), 27.5 (t), 21.8 (t), 13.8 (q) ppm; MS m/z (relative intensity)=259 (M^++1, 100), 175 (20), 159 (5), 144 (30), 136 (10); HRMS calcd for $C_{15}H_{19}N_2O_2$ (M^++1): 259.1446; found: 259.1144.

*3.1.6. 3-Methyl-but-2-enoic acid [2-(1H-indole-3-yl)-2-oxo-ethyl]-amide (**9d**). General procedure A* was used to prepare indole-oxo-alkylamide **9d** from 3,3-dimethylacryloyl chloride (0.22 g, 1.9 mmol) affording compound **9c** (0.36 g, 81%); mp 230–233 °C; IR (KBr) 3333, 3220, 1626, 1515, 1435 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.98(1H, br s), 8.41(1H, d, J=3.0 Hz), 8.16–8.14 (1H, m), 8.03 (1H, br t, J=5.7 Hz) 7.49–7.46 (1H, m), 7.24–7.16 (2H, m), 5.8 (1H, s), 4.47 (2H, d, J=5.8 Hz), 2.08 (3H, s), 1.80 (3H, s) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.6 (s), 166.2 (s), 148.8 (s), 136.4 (s), 133.5 (d), 125.4 (s), 122.8 (d), 121.8 (d), 121.1 (d), 118.9 (d), 114.1 (s), 112.1 (d), 45.4 (t), 26.8 (q), 19.3 (q) ppm; MS m/z (relative intensity)=257 (M^++1, 100), 75 (10), 159 (5), 144 (25), 82 (40); HRMS calcd for $C_{15}H_{17}N_2O_2$ (M^++1): 257.1290; found: 257.1283.

*3.1.7. 1-Benzyl-3-[2-(1H-indole-3-yl)-2-oxo-ethyl]-1-isopropyl-urea (**5**).* To a stirred solution of β-oxotryptamine **3**·HCl (0.50 g, 1.3 mmol) in 100 mL of THF under nitrogen was added triethylamine (0.27 mL, 1.95 mmol) at 0 °C. After 30 min, *N*,*N*-dimethyl-L-phenylalanine (0.27 g, 1.4 mmol) and diethyl pyrocarbonate (0.17 mL, 1.4 mmol) was added and the resulting solution was allowed to warm to 23 °C. After 12 h, the reaction mixture was concentrated under vacuum. The residual product was dissolved in 100 mL ethyl acetate, washed with brine (2×50 mL), dried ($MgSO_4$), and filtered. Concentration under vacuum afforded a residue that was purified by flash chromatography (CH_2Cl_2/MeOH 39:1) to give prealmazole C (**5**) (0.38 g, 85% yield) as a solid; mp 141–143 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.65 (1H, br s), 8.32–8.29 (1H, m), 7.88 (1H, d, J=3.1 Hz), 7.83 (1H, br t, J=4.5 Hz), 7.42–7.37 (1H, m), 7.32–7.15 (7H, m), 4.63 (1H, dd, J=18.2, 5.0 Hz), 4.51 (1H, dd, J=18.2, 4.6 Hz), 3.41 (1H, dd, J=7.7, 5.8 Hz), 3.22 (1H, dd, J=13.8, 7.7 Hz), 3.01 (1H, dd, J=13.8, 5.8 Hz), 2.42 (6H, s) ppm. ^1H NMR (300 MHz, DMSO-d_6) δ 11.99 (1H, br s), 8.42 (1H, d, J=2.4 Hz), 8.16–8.10 (2H, m), 7.49–7.46 (1H, m), 7.24–7.13 (7H, m), 4.53 (1H, dd, J=17.4, 5.8 Hz), 4.36 (1H, dd, J=17.4, 5.3 Hz), 3.38 (2H, dd, J=8.1, 5.9 Hz), 2.99 (1H, dd, J=13.6, 8.1 Hz), 2.80 (1H, dd, J=13.6, 5.9 Hz), 2.31 (6H, s) ppm. ^1H NMR (300 MHz, acetone-d_6) δ 11.15 (1H, br s), 8.35 (1H, d, J=3.2 Hz), 8.32–8.26 (1H, m), 7.72 (1H, br s), 7.56–7.50 (1H, m), 7.33–7.11 (7H, m), 4.65 (1H, dd, J=18.0, 5.5 Hz), 4.50 (1H, dd, J=18.0, 4.9 Hz), 3.45 (1H, dd, J=7.6, 5.8 Hz), 3.16 (1H, dd, J=13.7, 7.6 Hz), 2.92 (1H, dd, J=13.7, 5.8 Hz), 2.39 (6H, s) ppm; ^{13}C NMR (100.1 MHz, acetone-d_6) δ 190.0 (s), 171.7 (s), 140.9 (s), 137.2 (s), 133.1 (d), 129.7 (d×2), 128.5 (d×2), 126.2 (s), 126.1 (d), 123.5 (d), 122.4 (d), 122.1 (d), 115.2 (s), 112.4 (d), 70.7 (d), 46.1 (t), 41.9 (q×2), 33.3 (t) ppm; MS m/z (relative intensity)=350 (M^++1, 40), 307 (5), 258 (10), 148 (100); HRMS calcd for $C_{21}H_{24}N_3O_2$ (M^++1): 350.1868; found: 350.1871.

*3.1.8. 3-(2-Alkyl-oxazole-5-yl)-1H-indole (**10**). General procedure B.* A mixture of **9** (~0.5 mmol) in 5 mL of $POCl_3$ was stirred at 23 °C. The reaction was allowed to proceed overnight and concentrated under reduced pressure. The residual product was dissolved in 50 mL of ethyl acetate, washed with saturated aqueous $NaHCO_3$ (50 mL), brine (2×50 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate under reduced pressure gave alkyl oxazole indole **10**. The product was filtered and washed with ether.

*3.1.9. 3-(2-Ethyl-oxazole-5-yl)-1H-indole (**10a**). General procedure B* was used to prepare alkyl oxazole indole **10a** from **9a** (0.10 g, 0.43 mmol) affording compound **10a** (0.082 g, 90%); mp 161–163 °C; IR (KBr) 3456, 3175, 2368, 2344, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.77 (1H, br s), 7.86–7.83 (1H, bd, J=8.3 Hz), 7.52 (1H, d, J=2.4 Hz), 7.45–7.42 (1H, bd, J=8.6 Hz), 7.31–7.22 (2H, bq), 7.17 (1H, s), 2.89 (2H, q), 1.42 (3H, t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (s), 147.3 (s), 136.3 (s), 124.1 (s), 122.9 (d), 121.6 (d), 120.8 (d), 119.9 (d), 119.6 (d), 111.6 (d), 105.9 (s), 21.7 (t), 11.3 (q); MS m/z (relative intensity)=213 (M^++1, 100), 154 (5), 136 (5); HRMS calcd for $C_{13}H_{13}N_2O$ (M^++1): 213.1028; 213.1028.

*3.1.10. 3-(2-Propyl-oxazol-5-yl)-1H-indole (**10b**). General procedure B* was used to prepare alkyl oxazole indole **10b** from **9b** (0.10 g, 0.40 mmol) affording compound **10b** (0.08 g, 88% yield); mp 161–163 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 11.52 (1H, br s), 7.82 (1H, br d J=7.7 Hz), 7.72 (1H, d, J=2.6 Hz), 7.46 (1H, br d, J=7.8 Hz), 7.28 (1H, s), 7.19 (1H, br t, J=7.7 Hz), 7.13 (1H, br t, J=7.7 Hz), 2.76 (2H, t), 1.76 (2H, m), 0.97 (3H, t); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.5 (s), 147.2 (s), 136.3 (s), 123.5 (s), 122.9 (d), 122.1 (d), 120.0 (d), 119.4 (d), 119.0 (d), 112.0 (d), 103.9 (s), 29.3 (t), 20.1 (t), 13.5 (q); MS m/z (relative intensity)=227 (M^++1, 100), 154 (5), 136 (5); HRMS calcd for $C_{14}H_{15}N_2O$ (M^++1): 227.1184; found: 227.1186.

*3.1.11. 3-(2-Butyl-oxazol-5-yl)-1H-indole (**10c**). General procedure B* was used to prepare alkyl oxazole indole **10c** from **9c** (0.10 g, 0.38 mmol) affording compound **10c** (0.079 g, 86% yield); mp 122–124 °C; IR (KBr) 3456, 3128, 2368, 2344, 1632 cm^{-1}; ^1H NMR

(300 MHz, DMSO-d_6) δ 11.50 (1H, br s), 7.80 (1H, br d, J=7.6 Hz), 7.70 (1H, d, J=2.6 Hz), 7.44 (1H, br d, J=7.8 Hz), 7.26 (1H, s), 7.18 (1H, br t, J=7.6 Hz), 7.11 (1H, br t, J=7.6 Hz), 2.78 (2H, t), 1.72 (2H, m), 1.38 (2H, m), 0.91 (3H, t); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.6 (s), 147.2 (s), 136.3 (s), 123.5 (s), 122.9 (d), 122.0 (d), 120.0 (d), 119.4 (d), 119.0 (d), 112.0 (d), 103.9 (s), 28.7 (t), 27.0 (t), 21.6 (t), 13.6 (q); MS m/z (relative intensity)=241 (M^++1, 100), 211 (5), 144 (5), 136 (5), 107 (5); HRMS calcd for $C_{15}H_{17}N_2O$ (M^++1): 241.1341; found: 241.1340.

*3.1.12. 3-[(2-Methyl-propenyl)-oxazol-5-yl]-1H-indole (**10d**).* *General procedure B* was used to prepare alkyl oxazole indole **10d** from **9d** (0.10 g, 0.39 mmol) affording compound **10d** (0.081 g, 87% yield); mp 128–131 °C; IR (KBr) 3166, 2368, 2344, 1631 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.56 (1H, br s), 7.84 (1H, br d, J=7.8 Hz), 7.74 (1H, d, J=2.8 Hz), 7.45 (1H, br d, J=8.2 Hz), 7.43 (1H, s), 7.18 (1H, br t, J=7.8 Hz), 7.12 (1H, br t, J=7.8 Hz), 6.19 (1H, s), 2.23 (3H, s), 1.96 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3 (s), 146.2 (s), 144.1 (s), 136.4 (s), 123.5 (s), 123.2 (d), 122.1 (d), 120.2 (d), 120.1 (d), 119.4 (d), 112.1 (d), 111.3 (d), 103.8 (s), 26.7 (q), 20.3 (q); MS m/z (relative intensity)=238(M^++1, 100), 209 (3), 182 (3), 168 (3), 144 (5), 136 (3); HRMS calcd for $C_{15}H_{15}N_2O$ (M^++1): 239.1184; found: 239.1182.

*3.1.13. {1-[5-(1H-Indol-3-yl)-oxazol-2-phenyl-ethyl}-dimethyl-amine (**10e**).* A mixture of **9e** (0.10 g, 0.29 mmol) in 5 mL of $POCl_3$ was stirred at 80 °C for 2 h. Concentration under vacuo afforded a residue that was dissolved in 50 mL of ethyl acetate, washed with saturated aqueous $NaHCO_3$ (50 mL), brine (3×50 mL), dried ($MgSO_4$), and filtered. Upon concentration of the filtrate under reduced pressure, **10e** crystallized from the solution. The product was collected by filtration and washed with hexane and ether to give **9e** (0.048 g, 50% yield); mp 115–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (1H, br s), 7.84–7.81 (1H, br d, J=7.3 Hz), 7.52 (1H, d, J=2.6 Hz), 7.45–7.43 (1H, br d, J=5.7 Hz), 7.21 (1H, s), 7.32–7.14 (7H, m), 4.09 (1H, dd, J=9.6, 5.5 Hz), 3.42 (1H, dd, J=13.5, 9.6 Hz), 3.24 (1H, dd, J=13.5, 5.5 Hz), 2.43 (6H, s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (1H, br s), 7.85 (1H, br d, J=7.5 Hz), 7.54 (1H, d, J=2.4 Hz), 7.46 (1H, br d, J=7.7 Hz), 7.24 (1H, s), 7.34–7.17 (7H, m), 4.13 (1H, dd, J=9.7, 5.3 Hz), 3.45 (1H, dd, J=13.5, 9.7 Hz), 3.28 (1H, dd, J=13.5, 5.3 Hz), 2.47 (6H, s). ^{1}H NMR (300 MHz, acetone-d_6) δ 10.67 (1H, br s), 7.90–7.88 (1H, br d, J=7.2 Hz), 7.74 (1H, d, J=2.6 Hz), 7.52–7.49 (1H, br d, J=5.8 Hz), 7.26 (1H, s), 7.29–7.10 (7H, m), 4.08 (1H, dd, J=9.2, 6.1 Hz), 3.38 (1H, dd, J=13.6, 9.1 Hz), 3.20 (1H, dd, J=13.6, 6.1 Hz), 2.36 (6H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 160.4 (s), 148.4 (s), 139.6 (s), 137.2 (s), 129.6 (d×2), 128.5 (d×2), 126.4 (d), 124.6 (s), 123.2 (d), 122.8 (d), 120.7 (d), 112.3 (d), 105.4 (s), 64.6 (d), 41.5 (q×2), 37.0 (t); MS m/z (relative intensity)=332 (M^++1, 55), 287 (100), 240 (30), 136 (45), 107 (15); HRMS calcd for $C_{21}H_{22}N_3O$ (M^++1): 332.1763; found: 332.1766.

*3.1.14. Almazole C (**3**).* A mixture of **5** (0.1 g, 0.29 mmol) in 5 mL of $POCl_3$ was stirred at 60 °C for two days. Concentration under reduced pressure afforded a residue that was dissolved in 50 mL of ethyl acetate, washed with saturated aqueous $NaHCO_3$ (50 mL), brine (3×50 mL), dried ($MgSO_4$), and filtered. Upon concentration of the filtrate under reduced pressure, **3** crystallized from the solution. The product was filtrated and washed with hexane and ether to give **3** in 0.045 g, 50% yield: mp 115–117 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.67 (1H, br s), 7.90–7.88 (1H, br d, J=7.2 Hz), 7.74 (1H, d, J=2.6 Hz), 7.52–7.49 (1H, br d, J=5.8 Hz), 7.26 (1H, s), 7.29–7.10 (7H, m), 4.08 (1H, dd, J=9.2, 6.1 Hz), 3.38 (1H, dd, J=13.6, 9.1 Hz), 3.20 (1H, dd, J=13.6, 6.1 Hz), 2.36 (6H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 160.4 (s), 148.4 (s), 139.6 (s), 137.2 (s), 129.6 (d×2), 128.5 (d×2), 126.4 (d), 124.6 (s), 123.2 (d), 122.8 (d), 120.7 (d), 112.3 (d), 105.4 (s), 64.6 (d), 41.5 (q×2), 37.0 (t); MS m/z (relative intensity)=332 (M^++1, 55), 287 (100), 240 (30), 136 (45), 107 (15); HRMS calcd for $C_{21}H_{22}N_3O$ (M^++1): 332.1763; found: 332.1761.

*3.1.15. Methyl 5-(3-indolyl) oxazole-4-carboxylate (**12**).* To a stirred solution of **7** (1.0 g, 5.9 mmol) in 50 mL of THF at 0 °C was dropwise added α-isocyanoacetate (0.65 mL, 7.1 mmol) and DBU (1.1 mL, 7.1 mmol). The mixture was stirred at room temperature for 10 h, and concentrated. The resulting residue was dissolved in 50 mL ethyl acetate, washed with water (3×30 mL), brine (50 mL), and dried ($MgSO)_4$. Filtration and evaporation afforded a residue, which was chromatographed over silica gel, eluted with hexane/ethyl acetate 3:2 to give **12** in 1.0 g, 70% yield. Mp 140–142 °C; IR (KBr) 3300, 1699, 1571, 1416 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.96 (1H, br s), 8.66 (1H, d, J=3.0 Hz), 8.45 (1H, s), 8.05 (1H, br d, J=7.4 Hz), 7.53 (1H, br d, J=7.2 Hz), 7.24 (1H, td, J=7.3, 1.8 Hz), 7.19 (1H, td, J=7.3, 1.8 Hz), 3.84 (3H, s); ^{13}C NMR (100.1 MHz, DMSO-d_6) δ 163.5 (s), 154.9 (s), 149.6 (d), 136.9 (s), 130.9 (d), 125.6 (s), 122.6 (s), 123.5 (d), 121.3 (d), 121.9 (d), 113.3 (d), 103.0 (s), 52.4 (q); MS m/z (relative intensity)=242 (M^++1, 100), 211 (60), 154 (45), 136 (33); HRMS calcd for $C_{13}H_{12}N_2O_3$ (M^++1): 244.0848; found: 244.0845.

*3.1.16. β-Oxotryptophan methyl ester (**13**).* Methyl 5-(3-indolyl) oxazole-4-carboxylate **12** (0.8 g, 3.3 mmol) was dissolved in the mixture of methanol (30 mL) and hydrochloric acid (3 mL). The mixture was stirred at 60 °C for three days and concentrated. Methanol was removed by evaporation and the reaction mixture was purified by flash chromatography using a 19:1–9:1 gradient of CH_2Cl_2/MeOH (NH_3) as the eluent to β-oxotryptophan methyl ester (0.58 g, 2.51 mmol, 76%) as a brown solid. Compound **13 free base**; IR (KBr) 3342, 3277, 1736, 1651, 1618, 1521 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.14 (1H, br s), 8.47 (1H, s), 8.17–8.11 (1H, m), 7.51–7.48 (1H, m), 7.26–7.18 (2H, m), 5.03 (1H, s), 3.59 (3H, s), 3.36 (1H, q), 2.38 (2H, br s), 1.08 (1H, t); ^{13}C NMR (100.1 MHz, DMSO-d_6) δ 190.7 (s), 172.7 (s), 137.5 (s), 136.7 (d), 126.5 (s), 124.1 (d), 123.0 (d), 122.1 (d), 115.1 (s), 113.2 (d), 61.3 (d), 53.4 (q). Compound **13·HCl salt**; mp 165–170 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.75 (1H, d, J=2.6 Hz), 9.03 (2H, s), 8.74 (1H, d, J=3.3 Hz), 8.15–8.12 (1H, m), 7.57–7.54 (1H, m), 7.31–7.23 (2H, m), 3.71 (3H, s), 3.36 (1H, q), 1.08 (1H, t); ^{13}C NMR (100.1 MHz, DMSO-d_6) δ 182.5 (s), 166.5 (s), 139.1 (d), 137.7 (s), 126.3 (s), 124.6 (d), 123.7 (d), 121.9 (d), 114.5 (s), 113.7 (d), 57.9 (d), 54.5 (q); HRMS calcd for $C_{13}H_{13}N_2O_3$ (M^++1): 233.0926; found: 233.0922.

*3.1.17. N-(N,N-Dimethyl-L-phenylalanyl)-β-oxotryptophan methyl ester (**14**).* To a stirred solution of β-oxotryptamine **8**·HCl (1.0 g, 4.27 mmol) in 100 mL of THF was added triethylamine (1.79 mL, 12.28 mmol) at 0 °C, and the solution was stirred for 30 min. To the mixture was then added diethyl pyrocarbonate (0.69 mL, 4.69 mmol), the mixture was stirred for 30 min. To the mixture was added *N*,*N*-dimethyl-L-phenylalanine (0.90 g, 4.70 mmol) and stirred at 23 °C under nitrogen. After 12 h, the reaction was concentrated under vacuum. The residual product was dissolved in 100 mL ethyl acetate, and washed with brine (2×50 mL), and dried ($MgSO_4$). Filtration and evaporation afforded a residue, which was chromatographed over silica gel, eluted with DCM/MeOH 49:1 to give **14** in 1.05 g, 60% yield: compound **14 Down**; IR (KBr) 3366, 3250, 1751, 1654, 1647, 1498 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.15 (1H, br s), 8.69–8.66 (1H, br d, J=7.7 Hz), 8.26 (1H, d, J=1.8 Hz), 8.11–8.08 (1H, br d, J=7.7 Hz), 7.52–7.49 (1H, br d, J=7.7 Hz), 7.27–7.01 (6H, m), 5.90 (1H, d, J=7.7 Hz), 3.64 (3H, s), 3.51 (1H, dd, J=8.6, 5.6 Hz), 2.95 (1H, dd, J=13.4, 8.6 Hz), 2.74 (1H, dd, J=13.2, 5.6 Hz), 2.30 (3H, s); ^{13}C NMR (100.1 MHz, DMSO-d_6) δ 186.4 (s), 171.2 (s), 169.4 (s), 140.1 (s), 137.6 (s), 137.1 (d), 129.9 (d), 128.8 (d), 126.6 (d), 126.4 (d), 124.3 (d), 123.2 (d), 122.0 (d), 114.6 (s), 113.3 (d), 68.5 (d), 59.2 (d), 53.2 (q), 42.2 (q), 34.7 (t). Compound **14 Up**;

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.22 (1H, br s), 8.68–8.65 (1H, br d, J=7.7 Hz), 8.48 (1H, d, J=2.7 Hz), 8.14–8.11 (1H, br d, J=7.7 Hz), 7.52–7.49 (1H, br d, J=7.7 Hz), 7.27–7.01 (6H, m), 5.97 (1H, d, J=7.7 Hz), 3.59 (3H, s), 3.51 (1H, dd, J=8.6, 5.6 Hz), 2.96 (1H, dd, J=13.4, 8.6 Hz), 2.78 (1H, dd, J=13.2, 5.6 Hz), 2.20 (3H, s); ^{13}C NMR (100.1 MHz, DMSO-d_6) δ 186.6 (s), 171.4 (s), 169.2 (s), 140.1 (s), 137.6 (s), 137.2 (d), 129.9 (d), 128.9 (d), 126.7 (d), 126.4 (d), 124.3 (d), 123.2 (d), 122.0 (d), 114.6 (s), 113.3 (d), 68.5 (d), 59.2 (d), 53.3 (q), 42.3(q), 34.7 (t); MS m/z (relative intensity)=408 (M^++1, 58), 316 (20), 154 (75), 148 (100); HRMS calcd for $C_{23}H_{26}N_3O_4$ (M^++1): 408.1923; found: 408.1921.

*3.1.18. Almazole D methyl ester; methyl 2-[1-(dimethylamino)-2-phenylethyl]-5-(3-indolyl)oxazole-4-carboxylate (**15**).* A mixture of **14** (0.4 g, 0.98 mmol) in 5 mL of $POCl_3$ was stirred at 60 °C. The mixture was stirred for seven days, and concentrated. The residual product was dissolved in 50 mL of ethyl acetate, washed with saturated aqueous $NaHCO_3$ (3×50 mL) and washed with brine (2×50 mL), and dried ($MgSO_4$). Filtration and evaporation afforded a residue, which was chromatographed over silica gel, eluted with DCM/MeOH 49:1 to give **15** as colorless solid in 0.19 g, 50% yield and recovered starting material: compound **15** mp 135–139 °C, $[\alpha]_D^{23}$ +115 (c 0.105, MeOH). UV λ_{max} (MeOH) 203, 218, 254, 272, 331 nm. IR (KBr) 3333, 2380, 2345, 1690, 1588, 1568, 1458 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD-d_6) δ 8.71 (1H, s), 8.15–8.11 (1H, m), 7.51–7.48 (1H, m), 7.29–7.20 (2H, m), 7.20–7.10 (5H, m), 4.87 (3H, s), 4.13 (1H, dd, J=10.7, 5.1 Hz), 3.90 (2H, s), 3.46 (1H, dd, J=13.3, 10.7), 3.30 (3H, dd, J=13.3, 5.1 Hz), 2.46 (3H, s); ^{13}C NMR (75 MHz, CD_3OD-d_6) δ 163.2 (s), 158.5 (s), 155.7 (s), 137.8 (s), 136.8 (s), 130.4 (d), 129.0 (d×2), 128.5 (d×2), 126.7 (d), 125.4 (s), 122.9 (d), 121.8 (s), 121.4 (d), 120.7 (d), 112.1 (d), 102.9 (s), 65.0 (d), 51.2 (q), 41.4 (q×2), 37.0 (t); MS m/z (relative intensity)=390 (M^++1, 23), 345 (77), 298 (100), 154 (50), 148 (49); HRMS calcd for $C_{23}H_{25}N_3O_3$ (M^++1): 391.1897; found: 391.1898.

*3.1.19. Almazole D; 2-[1-(N,N-dimethyl)-2-phenylethyl]-5-(3-indolyl)oxazole-4-carboxylic acid (**16**).* To the mixture of methanol (15 mL) and 3 N aqueous KOH solution (2 mL) was added **15** (0.1 g, 0.26 mmol) at room temperature for 10 h. The pH of resulting mixture was adjusted to 4 by addition of concd HCl and white precipitates **16** were formed. The precipitation was filtered and washed with water. Almazole D **16**·**HCl** was converted to free base **17** by flash chromatography (DCM/MeOH–NH_3 4:6) in 0.09 g, 90% yield. The addition of 1 N of NaOH solution to free base **17** provided almazole D **6** in 85 mg, 85% yield.

*3.1.20. Almazole D; 2-[1-(N,N-dimethyl)-2-phenylethyl]-5-(3-indolyl)oxazole-4-carboxylic acid (**16**)-HCl salt.* ^{1}H NMR (300 MHz, CD_3OD-d_6) δ 8.71 (1H, s), 7.86 (1H, br d, J=7.4 Hz), 7.46 (1H, br d, J=7.4 Hz), 7.30–7.15 (7H, m), 5.18 (1H, t, J=8.1 Hz), 4.88 (3H, s), 3.64 (1H, d, J=8.2 Hz), 3.13 (3H, s) ppm; ^{13}C NMR (75 MHz, CD_3OD-d_6) δ 163.8 (s), 156.9 (s), 151.9 (s), 136.8 (s), 134.1 (s), 131.3 (d), 129.3 (d×2), 129.1 (d×2), 127.9 (d), 125.2 (s), 123.6 (s), 123.1 (d), 121.5 (d), 120.7 (d), 112.1 (d), 102.4 (s), 64.0 (d), 40.8 (q×2), 35.0 (t); compound **17 free base**: UV λ_{max} (MeOH) 212, 271, 330 nm. IR (KBr) 3421, 2362, 2342, 1618, 1597 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD-d_6) δ 8.71 (1H, s), 8.07–8.05 (1H, m), 7.47–7.44 (1H, m), 7.24–7.09 (7H, m), 4.26 (1H, dd, J=10.8, 4.8 Hz), 3.48 (1H, dd, J=13.0, 10.8 Hz), 2.54 (3H, s) ppm; ^{13}C NMR (75 MHz, CD_3OD-d_6) δ 167.2 (s), 156.8 (s), 153.3 (s), 137.6 (s), 136.7 (s), 129.8 (d), 129.2 (d×2), 128.6 (d×2), 126.8 (d), 125.6 (s), 122.5 (s), 120.9 (d), 120.7 (d), 111.9 (s), 103.6 (s), 65.0 (d), 41.3 (q×2), 36.9 (t); MS m/z (relative intensity)=391 (M^++1, 12), 376 (90), 331 (100), 307 (70), 284 (35), 219 (18), 148 (40); HRMS calcd for $C_{22}H_{22}N_3O_3$ (M^++1): 376.1662; found: 376.1661.

*3.1.21. Almazole D, 2-[1-(dimethylamino)-2-phenylethyl]-5-(3-indolyl)oxazole-4-carboxylic acid sodium salt (**6**).* $[\alpha]_D^{23}$ +31, UV λ_{max} (MeOH) 208, 278, 310 nm. ^{1}H NMR (400 MHz, CD_3OD-d_6, NaOH in D_2O) δ 8.71 (1H, s), 8.06 (1H, br s, J=7.4 Hz), 7.47 (1H, br d, J=7.4 Hz), 7.24–7.09 (7H, m), 4.08 (1H, dd, J=10.8, 4.7 Hz), 3.48 (1H, dd, J=13.1, 11.0 Hz), 3.31 (1H, dd, J=13.1, 4.7 Hz); ^{13}C NMR (100.1 MHz, CD_3OD-d_6, NaOH in D_2O) δ 169.5 (s), 157.4 (s), 151.2 (s), 138.0 (s), 136.7 (s), 129.19 (s), 129.15 (d×2), 129.09 (d), 128.5 (d×2), 126.7 (d), 125.7 (s), 122.2 (d), 120.9 (d), 120.7 (d), 120.5 (d), 111.8 (d), 104.1 (s), 65.3 (d), 41.6 (q×2), 37.3 (t).

Acknowledgements

Financial support from Chugai Pharmaceutical Co. is gratefully acknowledged. The authors thank Professor Graziano Guella providing authentic spectra of natural almazole D for spectral comparison.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.109.

References and notes

1. N'Diaye, I.; Guella, G.; Mancini, I.; Pietra, F. *Tetrahedron Lett.* **1996**, *37*, 3049–3050.
2. Guella, G.; Mancini, I.; N'Diaye, I.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 1999–2006.
3. (a) Takahashi, S.; Matsunaga, T.; Hasegawa, C.; Saito, H.; Fujita, D.; Kiuchi, F.; Tsuda, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1527–1529; (b) Nishida, A.; Fuwa, M.; Fujikawa, Y.; Nakahata, E.; Furuno, A.; Nakagawa, M. *Tetrahedron Lett.* **1998**, *39*, 5983–5986; (c) Nishida, A.; Fuwa, M.; Naruto, S.; Sugano, Y.; Saito, H.; Nakagawa, M. *Tetrahedron Lett.* **2000**, *41*, 4791–4794.
4. Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 2121–2123.
5. Boyd, G. V. *Sci. Synth.* **2002**, *11*, 383–479.
6. A mild cyclodehydration procedure of α-acylamino ketones with epimerizable centers has been reported using Ph_3P and I_2. Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604–3606.
7. Hogan, I. T.; Sainsbury, M. *Tetrahedron* **1984**, *40*, 681–682.
8. (a) Noltemeyer, M.; Sheldrick, G. M.; Hoppe, H.-U.; Zeeck, A. *J. Antibiot.* **1982**, *35*, 549–555; (b) Koyama, Y.; Yokose, K.; Dolby, L. J. *Agric. Biol. Chem.* **1981**, *45*, 1285–1287; (c) Yoshioka, T.; Mohri, K.; Oikawa, Y.; Yonemitsu, O. *J. Chem. Res., Miniprint* **1981**, 2252–2281; (d) Doyle, K.; Moody, C. J. *Synthesis* **1994**, 1021–1022.
9. (a) Umehara, K.; Yoshida, K.; Okamoto, M.; Iwami, M.; Tanaka, H.; Kohsaka, M.; Imanaka, H. *J. Antibiot.* **1984**, *37*, 1153–1160; (b) Structure revision of APHEs: Kelly, T. R.; Fu, Y.; Xie, R. L. *Tetrahedron Lett.* **1999**, *40*, 1857–1860.
10. Yamada, S.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, 1595–1598.
11. (a) Baxter, C. A. R.; Richards, H. C. *Tetrahedron Lett.* **1972**, 3357–3358; (b) Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B. *Tetrahedron: Asymmetry* **1993**, *4*, 273–280; (c) Pellegrini, C.; Strassler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979–1992.
12. Suzuki, M.; Iwasaki, T.; Miyoshi, M.; Okumura, K.; Matsumoto, K. *J. Org. Chem.* **1973**, *38*, 3571–3575.
13. Vinograd, L. K.; Sorokina, P.; Turchin, K. F.; Dubinskii, R. A.; Suvorov, N. N. *Zh. Org. Khim.* **1980**, *16*, 2222–2226.