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A novel approach to the indoloquinoline alkaloids cryptotackieine and cryptosanguinolentine by application of cyclization of *o*-vinylsubstituted arylheterocumulenes

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Abstract—1-Methyl-3-(*o*-azidophenyl)quinoline-2-one prepared by cyclization of the corresponding *o*-vinylsubstituted isocyanate under microwave irradiation is directly converted into cryptotackieine **1** by an intramolecular aza-Wittig reaction with trimethylphosphine; alternatively heating followed by reduction of the resulting indoloquinoline derivative provided cryptosanguinolentine **2**.

1. Introduction

In recent years combined research efforts have led to the isolation of a diverse assortment of indoloquinoline alkaloids from *Cryptolepis sanguinolenta*[1] a shrub indigenous to tropical West Africa, which has long been used in folk medicine in the treatment of infectious diseases, amoebiasis, fever and as an antimalarial agent.[2] In 1996 two independent groups[3] reported the isolation of two new structurally and biosynthetically related alkaloids: cryptotackieine **1** (also named neocryptolepine) and cryptosanguinolentine **2** (also named isocryptolepine). Cryptotackieine **1**, which displays a strong antiplasmodial activity against *P. falciparum* chloroquine-resistant strains,[4] was found to be a *N*-methyl derivative of the linear indolo[2,3-*b*]quinoline ring system, whereas the cryptosanguinolentine **2** which differs in the fusion of the indole and quinoline ring, possesses an angular indolo[3,2-*c*]quinoline ring system. It has been reported that these compounds and some methyl derivatives display various biological properties such as antimuscarinic, antibacterial, antiviral, antimicotic, antihyperglycemic and cytotoxic activities as well as significant antitumor properties in vitro.[5]

In 1997 Timari et al.[6] reported the synthesis of cryptotackieine **1** and cryptosanguinolentine **2** by a palladium cross-coupling reaction of 3-bromoquinoline derivative with *N*-pivaloylaminophenyl boronic acid and further indolization. In the course of our studies directed towards the synthesis of azaheterocycles based on heterocyclization reactions of azahexatriene systems,[7] we have reported that arylheterocumulenes containing an appropriate either ethylenic or acetylenic side chain at the *ortho*-position undergo thermal cyclization to afford either quinoline derivatives or indolo[2,3-*b*]quinolines.[8] This protocol was used by us[9] for our first synthesis of the cryptotackieine at the same time of Timari's work. In our synthesis the reaction of iminophosphorane derived from *o*-aminophenylacetylene with phenyl isocyanate led to the indolo[2,3-*b*]quinoline albeit in low yield (14%), the 2-phenylaminoquinoline (electrocyclic ring closure product) being the major product (40%). Recently, this methodology has successfully been applied by the Wang[10] and Schmittel[11] groups for the synthesis of several kinds of fused-indole compounds.

2. Results

We have devised and improved a reliable divergent approach for the preparation of the target alkaloids **1** and **2**, which is based on the formation of the key common 1-methyl-(*o*-azidophenyl)quinoline-2-one intermediate **10** and its suitable use for the preparation of cryptotackieine **1** and cryptosanguinolentine **2** by a selective indolization process (Scheme 1).

Condensation of (2-nitrobenzyl)triphenylphosphonium bromide with *o*-azidobenzaldehyde[12] in the presence of anhydrous potassium carbonate and catalytic amounts of dibenzo-18-crown-6 yielded the stilbene derivative **3** in 85% yield as a 4:1 mixture of *Z*/*E* isomers. Staudinger reaction between triphenylphosphine and the azide **3** in dry dichloromethane provided the iminophosphorane **4a** in 92% yield as a 4:1 mixture of *Z*/*E* isomers. Thiophenol/AIBN-catalyzed isomerization afforded the *E*-iminophosphorane isomer **4a**

Keywords: alkaloids; aza-Wittig reaction; microwave heating; insertion reaction; nitrogen heterocycles.

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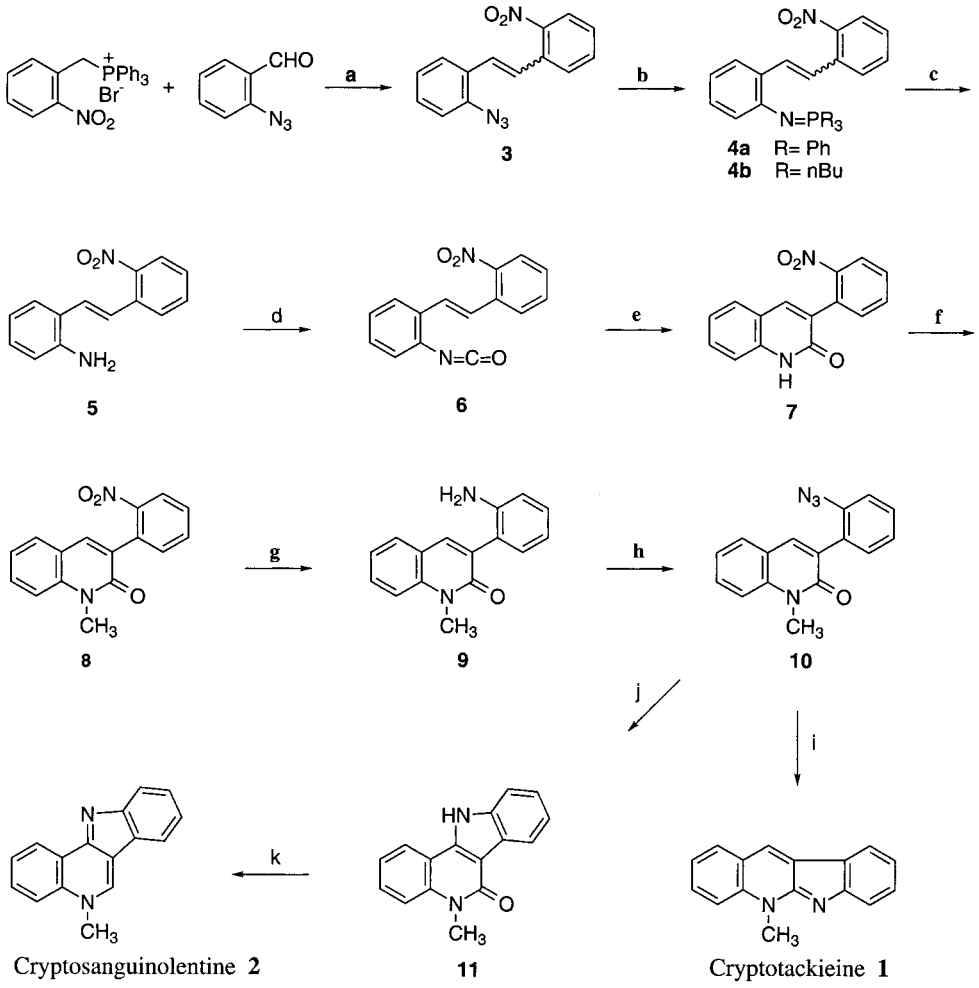

Scheme 1. *Reagents and conditions*: (a) K_2CO_3/dibenzo-18-crown-6/CH_2Cl_2, rt, 85%; (b) i: Ph_3P, CH_2Cl_2, rt, ii: PhSH/AIBN/benzene, reflux, E-**4a** 70%; (c) i: from **4b**, THF/H_2O, rt, 84%; ii: PhSH/AIBN/benzene, reflux, 92%; (d) triphosgene, CH_2Cl_2, 0°C→rt; (e) MW, nitrobenzene, 80%; (f) CH_3I, DMF, 60°C, 82%; (g) H_2, Pd/C, EtOH, rt, 91%; (h) $NaNO_2/H_2SO_4$, H_2O-NaN_3, 85%; (i) MW, Me_3P, nitrobenzene, 180°C, 40%; (j) *o*-xylene, 150°C, 82%; (k) Red-Al, toluene, reflux, 90%.

in 70% yield. Aza-Wittig reaction of the *E*-isomer **4a** with carbon dioxide in toluene at reflux temperature led to a mixture of the isocyanate **6** (minor product) and the corresponding diaryl carbodiimide (major product), presumably formed by intermolecular aza-Wittig reaction of the iminophosphorane **4a** with the isocyanate **6**. When the reaction was carried out at −78°C the isocyanate **6** was found to be the major product, being now the carbodiimide the minor product. However, all attempts for the isolation of **6** in pure state failed.

After these frustrating results, we turned our attention to the 'phosgene route' for the preparation of **6**. Surprisingly, iminophosphorane **4a** was recovered unaltered after treatment with hydrochloric acid in THF solution at room temperature for seven days. However, reaction of **3** with tri-*n*-butylphosphine followed by hydrolysis of the resulting iminophosphorane **4b** gave the stilbene derivative **5** in 84% yield as a 7:1 mixture of *Z*/*E* isomers, which were separated by column chromatography; *Z*→*E* isomerization led the (*E*)-2-amino-2′-nitrostilbene **5** in 92% yield. One-flask conversion of compound ***E*-5** into the quinoline-2-one derivative **7** was achieved in 80% yield by sequential treatment with bis(trichloromethyl)carbonate (triphosgene) and further microwave-promoted cyclization of the resulting isocyanate **6**. Conversely, isocyanate derived from the ***Z*-5** isomer did not undergo cyclization to the quinoline-2-one neither by classical heating nor under microwave irradiation.

Conversion of the quinoline-2-one **7** into **10** was achieved by the three-step sequence: (a) methylation to give **8** (82%); (b) catalytic hydrogenation in the presence of palladium on charcoal to afford **9** (91%) and (c) diazotization followed by the reaction with sodium azide provided **10** (85%).

Initial attempts to promote cyclization of the intermediate **10** into cryptotackieine **1** by treatment with triphenylphosphine and then thermal cyclization of the resulting iminophosphorane were unsuccessful even after an extended reaction time and high temperature (200°C). When **10** was treated with the more reactive tri-*n*-butylphosphine at room temperature, and further heating in *o*-xylene at reflux temperature for 24 h of the resulting iminophosphorane, the alkaloid **1** was obtained albeit in a very disappointing yield of 5%. However, treatment of **10** with trimethylphosphine at room temperature until nitrogen evolution was ceased followed by heating in nitrobenzene at reflux temperature for 24 h of the resulting reactive

iminophosphorane afforded **1** in low yield 24%. Switching from classical heating to microwave irradiation produced the best yield and shorter reaction time. Thus, when a solution of the iminophosphorane derived from **10** and trimethylphosphine in nitrobenzene was heated under microwave irradiation between 150 and 180°C for 30 min, cryptotackieine **1** was obtained in 40% yield. Although intramolecular aza-Wittig imination reactions involving amide carbonyl groups have been reported,[7] the conversion **10→1** represents the first example of an intramolecular aza-Wittig reaction involving a 2-pyridone carbonyl group, to the best of our knowledge.

Alternatively, when compound **10** was exposed to heat in *o*-xylene at reflux temperature indolization took place by a nitrene insertion process across the 4-position of the pyridone ring to give **11** in 82% yield, thus completing the assembly of the framework of the cryptosanguinolentine. The final step was to effect the reduction of the carbonyl group of the 2-pyridone ring. After several trials (DIBAL-H, 0°C; $LiAlH_4/AlCl_3$ and Na(Hg)/EtOH), the best results were obtained by using Red-Al as reducing agent. Thus, reaction of **11** with Red-Al in toluene at reflux temperature and then treatment of the crude product with anhydrous $MgSO_4$ provided cryptosanguinolentine **2** in 90% yield.

3. Conclusions

In conclusion, we have developed a new and divergent approach to the alkaloid cryptotackieine **1** (eight steps) and cryptosanguinolentine **2** (nine steps). Preparation of the key intermediate 3-arylquinoline-2-one **9** is based on the electrocyclic ring closure of the appropriate *o*-vinylsubstituted isocyanate, selective indolization is achieved either by intramolecular aza-Wittig reaction to give directly **1** or by nitrene insertion process followed by reduction to give **2**.

4. Experimental

4.1. General

All melting points were determined on a Kofler hot-plate melting point aparatus and are uncorrected. IR spectra were obtained as Nujol emulsion or films on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded on a Bruker AC200 (200 MHz) or a Varian Unity 300 (300 MHz). Mass spectra were recorded on a Hewlett–Packard 5993C spectrometer or a Fisons AUTOSPEC5000 VG. Microanalyses were performed on a Perkin Elmer 240C instrument. Reactions under microwave irradiation were preformed in a Synthewave 402 Prolabo microwave reactor (2.45 GH, adjustable power within the range 0–300 W with a simple mode focused system) fitted with a rotational system and an IR detector of temperature. The microwave oven is monitored by a computer that allows the temperature of the reaction mixture to be adjusted.

4.1.1. (*E*)-2-Nitro-2′-(triphenylphosphoranylidene)aminostilbene 4a. To a mixture of (2-nitrobenzyl)triphenylphosphonium bromide[13] (10.6 g, 22.16 mmol), dry CH_2Cl_2 (50 mL), anhydrous K_2CO_3 (4.17 g, 30.15 mmol), and dibenzo-18-crown-6 (5.0 mg) a solution of *o*-azidobenzaldehyde (3.0 g, 20.1 mmol) in the same solvent was added under N_2. The resultant mixture was stirred at room temperature for 16 h. After filtration the mixture was concentrated to dryness and the crude product was chromatographed on a silica gel column using CH_2Cl_2/hexane (1:1) as eluent to give **3** in 85% yield as a mixture of *Z*/*E* (4:1) isomers as revealed by the ^{1}H NMR spectrum.

To a cooled at 0°C solution of **3** (0.5 g, 1.88 mmol) in dry CH_2Cl_2 (10 mL) a solution of triphenylphosphine (0.49 g, 1.88 mmol) in the same solvent (10 mL) was added dropwise under N_2. After the addition was completed, the resultant solution was allowed to warm at room temperature and stirred for 5 h. The solvent was removed under reduced pressure and the residual material was slurried with diethyl ether (20 mL). The solid triphenylphosphine oxide was separated by filtration and the filtrated was concentrated to dryness to give the iminophosphorane **4a** in 92% yield as a mixture of *Z*/*E* (4:1) isomers as revealed by ^{1}H NMR.

To a solution **4a** *E*/*Z* mixture (2.0 g, 4.0 mmol) in dry toluene (50 mL), thiophenol (0.23 g, 2.07 mmol) was added. The mixture was refluxed for 15 min, then AIBN (0.85 g, 5.2 mmol) was added slowly over 5 h. The resultant solution was treated at reflux temperature overnight. After cooling, the solvent was removed under reduced pressure. The residue was extracted with dry benzene (3×15 mL) and the combined extracts were concentrated to dryness. The remaining solid was taken up in diethyl ether and the resultant red solid was separated by filtration to give (*E*)-**4a** in 70% yield, mp 172–174°C (red prisms from dichloromethane/diethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.49 (d, 1H, J=8.1 Hz, H-3′), 6.68 (t, 1H, J=7.2 Hz, H-5′), 6.84 (t, 1H, J=7.2 Hz, H-4′), 7.28 (t, 1H, J=7.5 Hz, H-4), 7.40–7.61 (m, 12H), 7.72–7.79 (m, 6H, H-*o*), 7.87 (d, 2H, J=8.1 Hz, H-3+H-6), 8.24 (d, 1H, J=16.2 Hz, H-7 or H-8). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 117 (C-5′), 119.7 (C-3), 122.2 (d, $^3J_{C-P}$=9.8 Hz, C-3′), 124.6 (C-7 or C-8), 126.4 (C-6′), 126.5 (C-6), 127.8 (C-4) 128.6 (d, $^3J_{C-P}$=12.15 Hz, C-*m*), 128.8 (C-4′), 130.7 (d, $^3J_{C-P}$=20.2 Hz, C-1′), 131.1 (d, $^1J_{C-P}$=95.7 Hz, C-*i*), 131.7 (d, $^4J_{C-P}$=2.9 Hz, C-*p*), 132.5 (d, $^2J_{C-P}$=9.8 Hz, C-*o*), 133.8 (C-5), 134.7 (C-1), 147.8 (C-2) 150.1 (C-2′). ^{31}P NMR (125 MHz, $CDCl_3$) δ: 2.57. IR (nujol) ν: 1602 (s), 1510 (s), 1347 (s), 1116 (s), 1000 (m), 750 (s), 721 (s), 702 (s) cm^{-1}. MS: *m*/*z* (%) (EI positive) 501 (M+1, 5), 500 (M, 14), 483 (100), 468 (47), 381 (51), 379 (36), 352 (87), 262 (69), 183 (81), 108 (39), 77 (17). Anal. Calcd for $C_{32}H_{25}NO_2P$: C, 76.79; H, 5.03; N, 5.60. Found: C, 76.72; H, 4.97; N, 5.64.

4.1.2. (*E*)-2-Amino-2′-nitrostilbene 5. To a cooled at 0°C solution of the azide **3** (1:4 *E*/*Z* isomers mixture) (2.5 g, 9.4 mmol) in dry THF (100 mL), tri-*n*-butylphosphine (2.0 g, 9.87 mmol) was added under N_2. The solution was stirred at room temperature for 1 h. Then, H_2O (80 mL) and hydrochloric acid (1 mL) were added and the mixture was stirred at room temperature for 24 h. After addition of 5% NaOH until basic pH, the combined organic layers were dried on Na_2CO_3. The solvent was removed under reduced pressure to give the crude product **5** as a mixture of *Z*/*E* isomers. Chromatographic separation on a silica gel column

using diethylether/hexane (4:1) as eluent afforded the *Z* isomer in 86% yield and the *E* isomer in 14% yield. (*Z*)-**5** mp 90–91°C (dichloromethane/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.77 (s, 2H, NH_2), 6.54 (td, 1H, *J*=7.6, 1.3 Hz, H-5), 6.59 (d, 1H, *J*=8.1 Hz, H-3), 6.7 (d, 1H, *J*=8.1 Hz, H-7 or H-8), 6.84 (dd, 1H, *J*=7.6, 0.8 Hz, H-6), 6.90 (d, 1H, *J*=11.8 Hz, H-7 or H-8), 6.99 (td, 1H, *J*=8.1, 1.6 Hz, H-4), 7.17–7.22 (m, 1H, H-5′), 7.26–7.31 (m, 2H, H-4′ and H-6′), 7.95–7.98 (m,1H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 115.5 (C-3), 118.1 (C-5), 121.4 (C-1), 124.3 (C-3′), 127.9 (C-4′ or C-6), 128.0 (C-7), 128.6 (C-8), 128.7 (C-4), 129.9 (C-6), 131.7 (C-5′), 132.7 (C-4′ or C-6″) 133.1 (C-1′), 144.1 (C-2); 148.04 (C-2′). IR (nujol) ν: 3449 (m), 3365 (m), 1639 (s), 1518 (s) cm^{-1}. MS: *m/z* (%) (EI positive): 240 (M, 47), 223 (M−17, 36), 206 (18), 194 (24), 165 (40), 93 (100). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.91; H, 4.96; N, 11.70.

To a solution of (*Z*)-**5** (91.7 g, 7.08 mmol) in dry benzene (30 mL), thiophenol (0.47 g, 4.25 mmol) was added under nitrogen. The mixture was heated at reflux tempertaure and AIBN (1.47 g, 10.62 mmol) was added slowly over 2 h. After cooling, the solvent was removed under reduced pressure and the residue was taken up in diethyl ether 925 mL) and recrystallized from CH_2Cl_2/hexane. To give the (*E*)-**5** in pure form in 92% yield. Mp 109–111°C (dichloromethane/diethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.89 (s, 2H, NH_2), 6.70 (dd, 1H, *J*=8.1, 1.0 Hz, H-3), 6.79 (t, 1H, *J*=7.5 Hz, H-5), 7.11 (d, 1H, *J*=16.0 Hz, H-7 or H-8), 7.11 (td, 1H, *J*=7.6, 1.0 Hz, H-4), 7.33–7.39 (m, 2H, H-4′ and H-6), 7.43 (d, 1H, *J*=16 Hz, H-7 or H-8), 7.56 (td, 1H, *J*=7.9, 0.8 Hz, H-5′), 7.71 (dd, 1H, *J*=7.9, 1.0 Hz, H-6′), 7.93 (dd, 1H, *J*=8.1, 1.3 Hz, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 116.5 (C-3), 119.0 (C-5), 122.7 (C-1), 124.6 (C-3′ and C-7 or C-8), 127.73 and 127.75 (C-4′ or C-6), 128.2 (C-6′), 129.6 and 129.9 (C-4 and C-7 or C-8), 133.1 (C-5′), 133.3 (C-1′), 144.4 (C-2); 147.7 (C-2′). IR (nujol) ν: 3441 (m), 3363 (m), 1637 (s), 1602 (s), 1516 (s), 1352 (s) cm^{-1}. MS: *m/z* (%) (EI positive): 240 (M, 100), 223 (M−17, 96), 206 (47), 194 (67), 165 (87), 93 (96). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.93; H, 4.95; N, 11.72.

4.1.3. 3-(*o*-Nitrophenyl)-1H-quinoline-2-one 7. To a solution of bis(trichloromethyl) carbonate (triphosgene) (0.45 g, 1.53 mmol) in dry dichloromethane (20 mL) was added dropwise over a period of 15 min a mixture of 2-amino-2′-nitrostilbene **5** (1 g, 4.17 mmol), triethylamine (0.47 g, 4.59 mmol) and dry dichloromethane (25 mL) at 0°C under N_2. Then, the resulting mixture was allowed to warm to room temperature and stirred for 1 h. The solvent was removed under reduced pressure to give **6**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.17 (dd, 1H, *J*=7.8, 1.8 Hz), 7.21–7.32 (m, 2H), 7.33 (d, 1H, *J*=15.9 Hz), 7.46 (td, 1H, *J*=8.4, 1.5 Hz), 7.60 (d, 1H, *J*=15.9 Hz), 7.66–7.69 (m, 2H), 7.80 (dd, 1H, *J*=7.8, 1.2 Hz), 8.00 (dd, 1H, *J*=8.1, 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 118.7, 124.3, 125.7, 125.8, 126.2, 127.9, 128.1 (2C), 129.1, 130.7, 131.3, 132.3, 133.1, 147.5. IR (nujol) ν 2281 (s), 1532 (s), 1330 (s) cm^{-1}.

The crude isocyanate **6** was dissolved in nitrobenzene (15 mL), in a glass tube which was placed in a Synthewave 402 reactor and irradiated for 12 min at 150°C. After cooling, the precipitated solid was separated by filtration, washed with water (2×15 mL), diethyl ether (2×15 mL) and air-dried, to give **7** (0.89 g, 80%); mp 318°C (yellow prisms from tetrahydrofuran/diethyl ether). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.25 (t, 1H, *J*=7.8 Hz, H-6), 7.36 (d,1H, *J*=8.1 Hz, H-8), 7.56 (t, 1H, *J*=8.1 Hz, H-7), 7.65 (d, 1H, *J*=7.8 Hz, H-5), 7.67 (t, 1H, *J*=7.8 Hz, H-4′), 7.78 (d, 1H, *J*=7.8 Hz, H-6′), 7.83 (t, 1H, *J*=7.8 Hz, H-5′), 8.06 (d, 1H, *J*=7.8 Hz, H-3′), 8.17 (s, 1H, H-4), 12.00 (s, 1H, NH). ^{13}C NMR (50 MHz, DMSO-d_6) δ 115.0 (C-8), 119.3 (C-4a), 122.1 (C-6), 123.9 (C-3′), 128.2 (C-6′), 129.4 (C-4′), 130.6 (C-7), 130.9 and 131.0 (C-1′ or C-3), 132.2 (C-5), 133.6 (C-5′), 137.5 (C-4), 138.5 (C-8a), 148.9 (C-2′), 160.0 (C-2). IR (nujol) ν 1662 (s), 1531 (s), 1365 (m) cm^{-1}. MS: *m/z* (%) (EI positive) 267 (M+1, 3), 266 (M, 18), 234 (14), 220 (100), 190 (13), 165 (20). Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52. Found: C, 67.61; H, 3.73; N, 10.60.

4.1.4. 1-Methyl-3-(*o*-nitrophenyl)-1H-quinoline-2-one 8. To a mixture of **7** (1.0 g, 3.76 mmol) in dry DMF (40 mL), and anhydrous K_2CO_3 (3.12 g, 22.56 mmol), methyliodide (1.6 g, 11.28 mmol) was added dropwise under N_2. The resultant mixture was stirred at 60°C for 2 h. After addition of H_2O (40 mL) the precipitated yellow solid was collected by filtration, washed with diethyl ether (2×10 mL), air-dried and recrystallized from CH_2Cl_2/diethyl ether (1:1) to give **8** in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.72 (s, 3H, CH_3), 7.27 (d, 1H, *J*=7.5 Hz, H-6), 7.38 (d, 1H, *J*=8.4 Hz, H-8), 7.45 (dd, 1H, *J*=7.6, 1.6 Hz, H-5), 7.52 (td, 1H, *J*=7.7, 1.3 Hz, H-4′), 7.56–7.67 (m, 3H, H-7, H-5′ and H-6′), 7.81 (s, 1H, H-4), 8.04 (dd, 1H, *J*=8.1, 1.0 Hz, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.9 (CH_3), 114.2 (C-8), 120.4 (C-4a), 122.4 (C-6), 124.3 (C-3′), 129.0 (C-6′), 129.1 (C-4′), 130.9 (C-7), 130.9 and 131.3 (C-3′ or C-1′), 131.9 (C-5), 133.1 (C-5′), 136.3 (C-4), 139.9 (C-8[a]), 149.4 (C-2′), 160.5 (CO). IR (nujol) ν 1642 (CO), 1529 (s), 1357 (s) cm^{-1}. MS: *m/z* (%) (EI positive) 280 (M, 96, 248 (17), 234 (82), 219 (100), 204 (44), 190 (63), 178 (22), 165 (44). Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32; N, 9.99. Found: C, 68.52; H, 4.27; N, 10.07.

4.1.5. 1-Methyl-3-(*o*-aminophenyl)-1H-quinoline-2-one 9. To a suspension of 10% Pd/C (0.1 g) in EtOH (45 mL) was added **8** (0.8 g, 2.86 mmol). The mixture was stirred at room temperature for 5 h, while a stream of the H_2 was bubbled over the solution. The solid was separated by filtration and washed with EtOH (3×10 mL). The combined filtrates were concentrated to dryness and residue product was dissolved in EtOAc (20 mL) and filtered over a celite pad. Concentration to dryness afforded a solid that was recrystallized from EtOAc/diethyl ether to give **9** in 91% yield. ^{1}H NMR. (300 MHz, $CDCl_3$) δ: 3.83 (s, 3H, CH_3), 4.10 (br, 2H, NH_2), 6.81 (ddd, 1H, *J*=7.6, 1.0, 0.8 Hz, H-3′), 6.87 (td, 1H, *J*=7.6, 1.3 Hz, H-5′), 7.20 (d, 1H, *J*=7.3 Hz, H-6′), 7.22 (td, 1H, *J*=7.3, 1.6 Hz, H-4′), 7.28 (td, 1H, *J*=7.6, 1.0 Hz, H-6), 7.42 (dd, 1H, *J*=8.1, 0.8 Hz, H-8), 7.60 (td, 1H, *J*=7.4, 1.6 Hz, H-7), 7.61 (d, 1H, *J*=7.6 Hz, H-5), 7.82 (s, 1H, H-4). ^{13}C NMR. (75 MHz, $CDCl_3$) δ: 29.9 (CH_3), 114.0 (C-8), 117.1 (C-3′), 118.9 (C-5″), 120.6 (C-4a), 122.3 (C-6), 124.4 (C-3), 128.8 (C-5), 129.2 (C-4′), 130.4 (C-7), 131.1 (C-6′), 132.4 (C-1′), 139.4 (C-4 and C-8a), 145.4 (C-2′), 161.1 (CO). IR (nujol) ν 3427 (m), 3330 (m),

1640 (CO) cm^{-1}.MS: *m/z* (%) (EI positive) 250 (M, 100), 233 (85), 219 (20). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.72; H, 5.58; N, 11.13.

4.1.6. 1-Methyl-3-(*o*-azidophenyl)-1H-quinoline-2-one 10. To a cooled at 0°C mixture of **9** (1.0 g, 4 mmol) H_2O (40 mL) and H_2SO_4 (0.9 mL) was added a cooled solution of $NaNO_2$ (0.4 g, 5.8 mmol) in H_2O (3 mL). The suspension was stirred at that temperature for 30 min. Then a solution of NaN_3 (0.54 g, 8.23 mmol) in H_2O (6 mL) was added dropwise. The resultant suspension was allowed to warm at room temperature and stirred for 5 h. The solid was filtered, washed with 10% aqueous Na_2CO_3 solution (2×20 mL) and H_2O (2×10 mL) and air-dried. Recrystallization from CH_2Cl_2/hexane (1:1) yielded **10** in 85% yield; mp 167°C (d) (brown prisms from dichloromethane/hexane). ^{1}H NMR. (300 MHz, DMSO-d_6) δ 3.68 (s, 3H, CH_3N), 7.25 (td, 1H, J=7.7, 1.3 Hz) and 7.30 (td, 1H, J=7.6, 0.9 Hz) (H-5′ or H-6), 7.34–7.38 (m, 2H, H-3′+H-6′), 7.49 (ddd, 1H, J=9.0, 7.3, 1.7 Hz) and 7.65 (ddd, 1H, J=8.6, 7.3, 1.7 Hz) (H-4′ or H-7), 7.56 (d, 1H, J=9.0 Hz, H-8), 7.75 (dd, 1H, J=7.7, 1.3 Hz, H-5), 7.91 (s, 1H, H-4). ^{13}C NMR. (75 MHz, DMSO-d_6) δ 29.7 (CH_3N), 114.6 (C-8), 119.0 (C-3′), 119.7 (C-4a), 122.2 and 124.9 (C-5′ or C-6), 129.9 (C-5), 129.2 and 129.5 (C-1′ or C-3), 129.7 and 131.0 (C-4′ or C-7), 131.6 (C-6′), 138.0 (C-2′), 138.6 (C-4), 139.6 (C-8a), 160.1 (C-2). IR (nujol) ν 2123 (s), 2086 (s), 1652 (m) cm^{-1}. MS: *m/z* (%) (EI positive) 277 (M+1, 5), 276 (M, 8), 248 (M−N_2, 100), 234 (28), 219 (67). Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.48; H, 4.32; N, 20.33.

4.1.7. Cryptotackieine 1. To a solution of azide **10** (80 mg, 0.29 mmol) in freshly distilled nitrobenzene (3.5 mL) placed in a glass tube, trimethylphosphine (0.29 mL of a 1 M toluene solution) was added dropwise under N_2. The reaction mixture was stirred at room temperature for 45 min (until N_2 evolution had ceased). The tube was placed in a Synthewave 402 reactor and irradiated in following sequence: 5 min at 150°C, 5 min at 165°C and 20 min at 180°C. Between each heating a period of 2 min was allowed for cooling to prevent excess of heating. After cooling the precipitated solid was collected and chromatographed on a silica gel column using acetone as eluent to give **1** in 40% yield.

4.1.8. 7-Methyl-1H-indolo[3,2-*c*]quinoline-6-one 11. A solution of the azide **10** (0.3 g, 1.09 mmol) in dry *o*-xylene (10 mL) was heated at 150°C for 20 h, After cooling the precipitated solid was collected by filtration, washed with diethyl ether and recrystallized from THF/hexane to give **11** in 82% yield. ^{1}H NMR (300 MHz, MeOH-d_4) δ: 3.84 (s, 3H, NCH_3), 7.28 (td, 1H, J=7.8,1.2 Hz), 7.34–7.41 (m, 2H), 7.56 (d, 1H, J=7.5 Hz), 7.60–7.68 (m, 2H), 8.16 (d, 1H, J=7.5 Hz), 8.29 (d, 1H, J=7.5 Hz). ^{13}C NMR. (75 MHz, DMSO-d_6) δ: 28.5, 106.0, 111.8, 113.0, 115.7, 121.0, 121.2, 121.7, 122.7, 124.2, 124.7, 129.7, 137.9, 138.8, 139.8, 159.2. IR (nujol) ν 3196 (NH), 1624 (CO). MS: *m/z* (%) (EI positive) 248 (M, 100), 219 (61), 204 (9), 190 (11), 165 (8). Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.35; H, 4.82; N, 11.35.

4.1.9. Cryptosanguinolentine 2. To a suspension of indoloquinolone **11** (50 mg, 0.2 mmol) in dry toluene (15 mL), sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) (0.42 mL of a 65% toluene solution) was added dropwise under N_2. The mixture was refluxed for 32 h. After cooling, the solution was poured into 20% aqueous NaOH solution (50 mL) and then stirred for 30 min. The mixture was extracted with diethyl ether (3×50 mL) and dissolved in dichloromethane (30 mL), anhydrous $MgSO_4$ was added and the mixture was stirred for 2 h. The solvent was removed under reduced pressure and the solid was washed with dichloromethane (3×20 mL). The remaining solid was dissolved in H_2O (75 mL) and the resultant solution was extracted with dichloromethane (2×20 mL). The combined organic layers were concentrated to dryness and the solid residue was chromatographed on a silica gel column using toluene/acetone/NH_4OH 25:25:1 as eluent to give cryptosanguinolentine **2** 90% yield.

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