Efficient protocol to quinazolino[3,2-*d*][1,4]benzodiazepine-6,9-dione *via* Staudinger-aza-Wittig cyclization: application to synthesis of Asperlicin D

Deeb Taher,[a] Zakariyya N. Ishtaiwi,[b] and Naim H. Al-Said[c*]

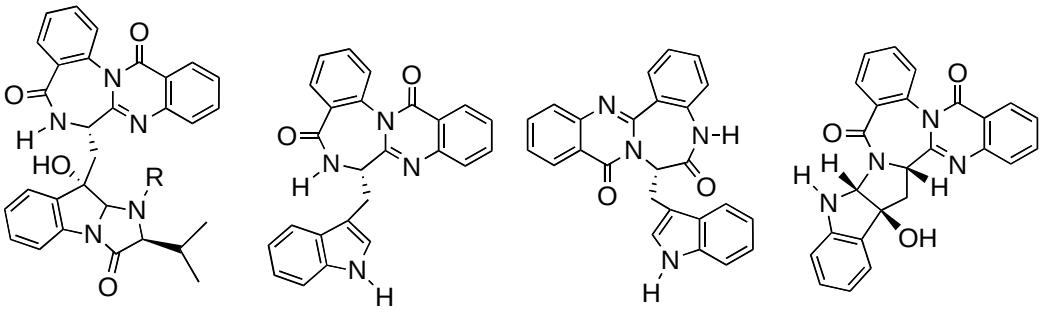
[a] *Department of Chemistry, Tafila Technical University, Tafila, Jordan*
[b] *Department of Applied Chemical Sciences, Jordan University of Science and Technology, Irbid 22110, Jordan*
[c] *Department of Chemistry, King Khalid University, Abha, Saudi Arabia*
E-mail: naim@just.edu.jo

Abstract
Tandem Staudinger and intramolecular aza-Wittig reactions followed by cyclodehydration of the linear *N*-[*N*-(2-azidobenzoyl)-2-aminobenzoyl]glycine ethyl ester furnished the tetracyclic quinazolino[3,2-*d*][1,4]benzodiazepine-6,9-dione ring system found in some biologically active natural alkaloids. This method was successfully implemented to synthesize asperlicin D from a linear peptide containing ester and azido terminal groups.

Keywords: Quinazolinobenzodiazepine, aza-Wittig, cyclodehydration, asperlicin D

Introduction

Naturally occurring alkaloids such as benzomalvins,[1] circumdatin F,[2] asperlicins,[3,4] and sclerotigenin[5] incorporating two anthranilic acid units and one or two amino acids combined together in a quinazolino[3,2][1,4]benzodiazepine system, have been isolated from different sources. These alkaloids display various biological activities. For instance, benzomalvin A shows inhibitory activity against substance P at the guinea pig, rat and human neurokinin NK1 receptors.[1] Sclerotigenin has insecticidal properties.[5] The asperlicin family displays strong affinity for pancreatic and gall bladder cholecystokinin (CCK) receptors.[3,4] Asperlicins A (**1**), B (**2**), C (**3**) and E (**5**) incorporate a quinazolino[3,2-*a*][1,4]benzodiazepine-5,13-dione, whereas asperlicin D (**4**) has a quinazolino[3,2-*d*][1,4]benzodiazepine-6,9-dione system.



1 (R = H)
2 (R = OH)

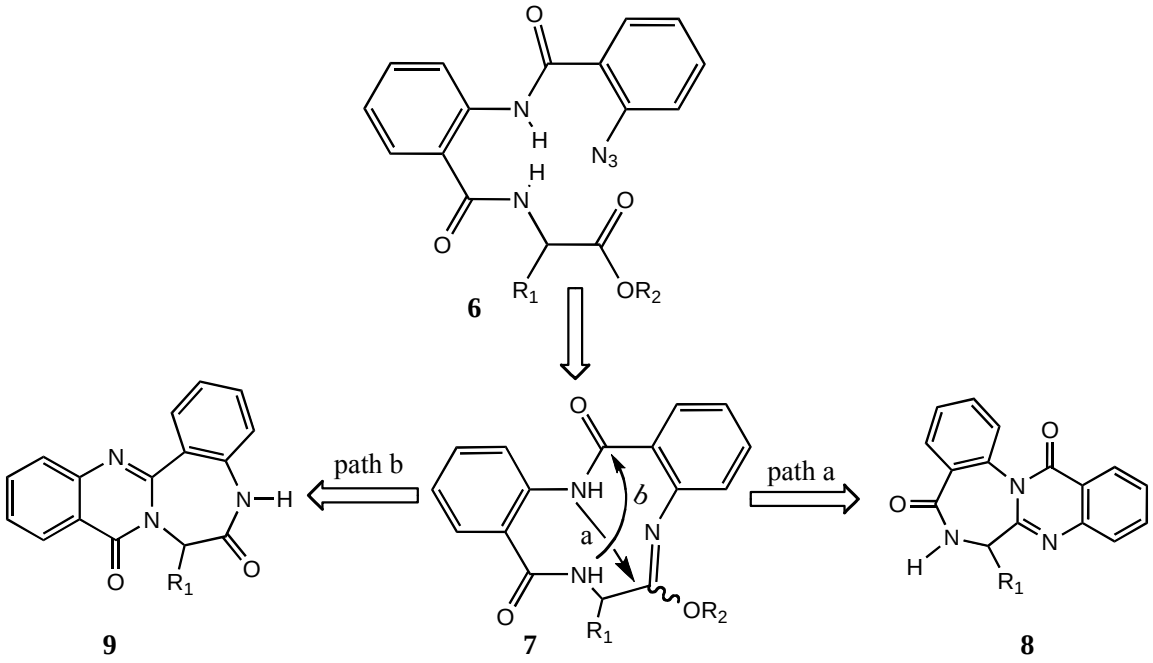
3 **4** **5**

Several tactical variants of the Eguchi aza-Wittig reaction have been of major value in the synthesis of this family of natural products. Globally, these tactics employed the overall sequence of selective acylation of a [1,4]benzodiazepine system with 2-azidobenzoyl chloride followed by aza-Wittig cyclization to attain the quinazolino[1,4]benzodiazepine structure after a multi-step sequence.[6-11]

Following on from our previous studies on the construction of the quinazolino[1,4]benzodiazepine ring system,[12] here we report a new and effective strategy for the synthesis of the quinazolino[3,2-*d*][1,4]benzodiazepine-6,9-dione system utilizing one-pot tandem Staudinger, intramolecular aza-Wittig and cyclodehydration reactions. This paper describes in detail the data of the preliminary communication that described the first total synthesis of asperlicin D.[13,14]

Results and Discussion

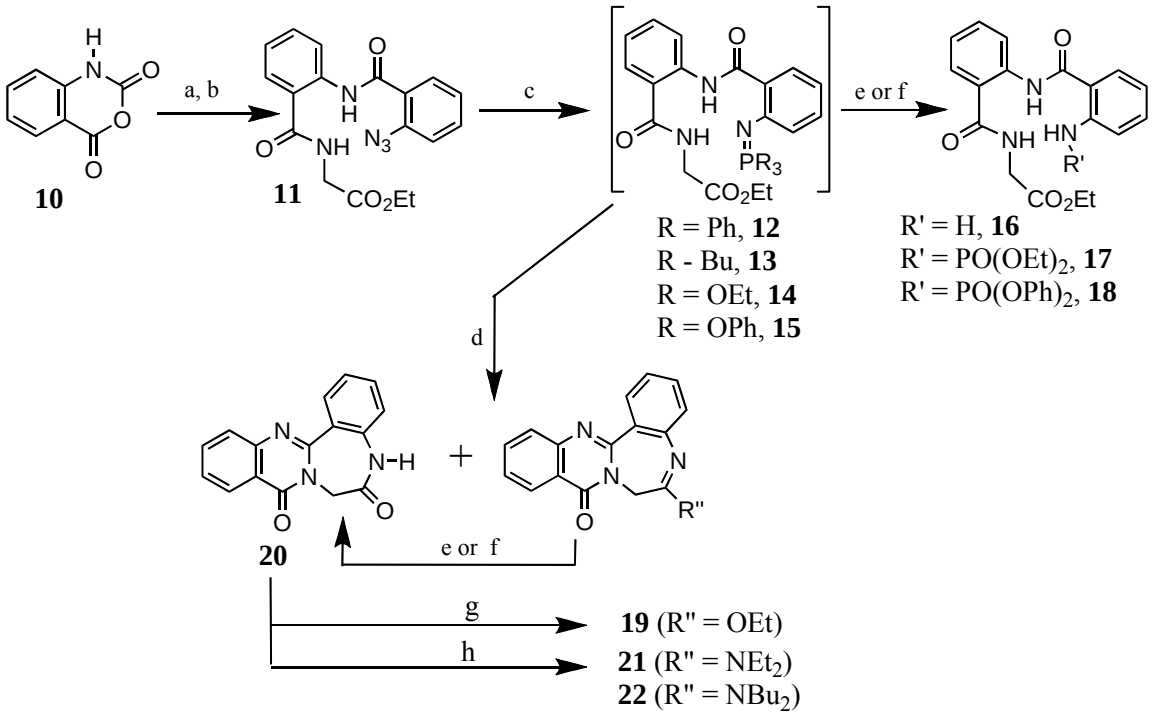
Retrosynthetically, we envisioned that these alkaloids could be derived from two consecutive intramolecular reactions from linear peptide **6** containing two termini capable of reacting with each other (Scheme 1). Therefore, azido and ester groups were selected to study the feasibility of intramolecular aza-Wittig cyclization[15-18] on a substrate incorporating amidic protons to form the proposed cylic intermediate **7**. This intermediate could furnish, after cyclization, either quinazolino[3,2-*a*][1,4]benzodiazepine **8** found in asperlicins A (**1**), B (**2**), C (**3**), and E (**5**) *via* path a or quinazolino[3,2-*d*][1,4]benzodiazepine **9** found in asperlicins D (**4**) through path b.



Scheme 1. Cyclization modes of aza-Wittig intermediate 7 generated from dipeptide **6**.

As shown in Scheme 2, our study commenced with the coupling of isatoic anhydride (**10**) with ethyl glycinate in dry acetonitrile followed by acylation with freshly prepared 2-azidobenzoyl chloride. This reaction furnished *N*-[*N*-(2-azidobenzoyl)-2-aminobenzoy]glycine ethyl ester **11**, as a model substrate, in good yield (80%).

Staudinger iminophosphorane intermediates **12**, **13**, **14** and **15** were generated *in situ* by stirring **11** in a dry solvent (benzene, toluene, mesitylene) with phosphorus reagents Ph_3P, Bu_3P, $(EtO)_3P$, and $(PhO)_3P$, respectively, at ambient temperature for an appropriate time to complete the reaction.[15-19] The formation of these intermediates was confirmed by their acidic hydrolysis ($PhSO_3H$, H_2O, THF) at ambient temperature. Iminophosphoranes **12** and **13** gave the known amine **16**,[13,14] whereas **14** and **15** gave the corresponding amidophosphates **17** and **18**, respectively. Similar results were obtained when iminophosphorane intermediates **12**, **13**, **14** and **15** were passed through a short column of silica gel. The amidophosphates (**17** and **18)** were isolated in pure form by column chromatography and their structures were confirmed by spectral data and elemental analysis.



Scheme 2. (a) $HCl.H_2NCH_2CO_2Et$, Et_3N, CH_3CN, reflux, 3 h; (b) 2-$N_3PhCOCl$, Et_3N, rt, 24 h; (c) R_3P, mesitylene, rt, 2 h; (d) reflux, mesitylene, 50 h; (e) THF-H_2O-$PhSO_3H$, rt, 2 h; (f) EtOAc, SiO_2, (g) I_2, PPh_3, CH_2Cl_2, Et_3N, rt, 24 h; (h) I_2, PPh_3, CH_2Cl_2, Bu_3N, rt, 24 h.

Next, we turned to explore the viability of tandem cyclization reactions of Staudinger intermediates **12-15** shown in Scheme 2. Suitable conditions for the intramolecular aza-Wittig reaction were optimized employing **12**. Initial attempts to promote cyclization of this intermediate at reflux temperature in toluene or xylene were unsuccessful even after an extended reaction time (48 h). However, when cyclization was conducted in boiling mesitylene for 40 h it furnished a significant amount of the expected imino ether, 7-ethoxy-quinazolino[3,2-*d*][1,4]benzodiazepine (**19**) along with its hydrolyzed product quinazolino[3,2-*d*][1,4]benzodiazepine (**20**)[20] in 20% and 15% yield, respectively, after separation by column chromatography. The two products were isolated in variable proportions depending on the reaction time and temperature. The methylene protons of the seven-membered ring in **19** were observed at δ 5.87 (d, 13.2 Hz) and 3.83 (d, 13.2 Hz), indicating that they are non-equivalent on the NMR time scale due to the significant barrier to flipping of the ring. Furthermore the methylene protons of the ethoxy group were displayed at δ 4.47 and 4.24 as two broad peaks. Since the reaction conditions were anhydrous, it seemed likely that the hydrolysis of **19** to **20** occurred on the silica gel during purification. Moreover, the imino ether **19** was cleanly hydrolyzed to **20** in wet THF containing a catalytic amount of $PhSO_3H$. To simplify the separation of the desired product **20** from the reaction mixture after conducting the reaction in boiling mesitylene, the crude product was hydrolyzed after concentration to give **20** in 30-40%

yield. The structure of the final product **20** was assigned based on the reported NMR spectral data and also by elemental analysis. The spectral data of **20** were identical to those reported previously.[20]

The yield of the final product **20** was significantly improved by switching to the more reactive iminophosphorane **13**. Stirring **11** and $(Bu)_3P$ in mesitylene at room temperature for 2 h then at reflux for 40 h, followed by hydrolysis, gave **20** in 55% yield. Lower yields of **20** (<30%) were obtained by performing the reaction in boiling xylene. The results of these experiments are summarized in Table 1. The cyclization of **14** failed in boiling xylene, affording only the hydrolysis product, amidophosphate **17**. However, **20** was obtained in 20% yield along with the amidophosphate **17** by conducting the reaction in mesitylene at reflux temperature. Similarly, **15** furnished **20** along with the corresponding amidophosphate **17.**

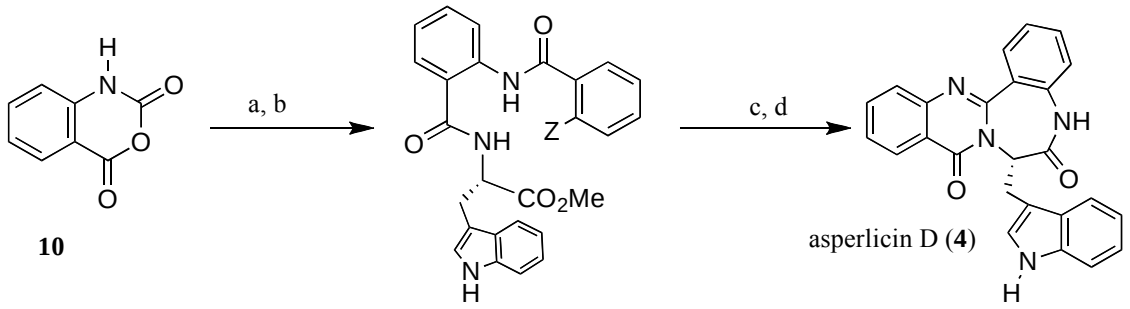
Table 1. Synthesis of Quinazolino[3,2-*d*][1,4]benzodiazepine-6,9-dione Ring System **20**

Phosphourus(III) reagent	% Yield of Method A[a]	% Yield Method B[b]
$(Ph)_3P$	37	52
$(Bu)_3P$	55	65
$(EtO)_3P$	20	30
$(PhO)_3P$	15	20

[a] In method A: the reactions were conducted in mesitylene at reflux temperature for 40 h.
[b] In method B: the reactions were conducted in sealed tube at 200 °C for 5 h.

An alternative procedure for the cyclization of the intermediates **12-15** was also explored. Thus, the cyclization process was performed in sealed tube. Table 1 details the efficiency of the cyclization of intermediates **12-15** at 200 °C in sealed tube followed by hydrolysis. In general, the yield of the desired product was enhanced.

Furthermore, implementation of Wipf methodology ($Ph_3P/I_2/Et_3N$)[21] with **16** afforded an inseparable mixture of products. Fortunately, we observed that the starting material **16** was completely consumed and a new product **21** was isolated (10% yield) in impure form when the reaction was conducted with excess reagent ($Ph_3P/I_2/Et_3N$). We believe that the product **21** is formed from **20** after it has been formed in the reaction mixture. Thus, to confirm this proposal, compound **20** was allowed to react with excess Wipf reagent ($Ph_3P/I_2/Et_3N$). This reaction furnished **21** in moderate yield (50%). Moreover, derivative **22** was isolated when **20** stirred with a mixture of $Ph_3P/I_2/Bu_3N$. Utilizing the experimental conditions established for the unsubstituted quinazolino[3,2-*d*][1,4]benzodiazepine (**20**), we next explored the application of these conditions to prepare asperlicin D (**4**) starting from tryptophan azido derivative **23**. This starting material was prepared in a one-pot reaction in good yield (>70%) by condensation of isatoic anhydride (**10**) with L-tryptophan methyl ester followed by acylation with freshly prepared 2-azidobenzoyl chloride (Scheme 3).



Scheme 3. (a) L-tryptophan methyl ester, Et_3N, CH_3CN; (b) 2-N_3-C_6H_4COCl, Et_3N; (c) $(Ph)_3P$, or $(Bu)_3P$, mesitylene, 150 °C; (d) THF-H_2O-$PhSO_3H$, rt, 2 h.

Staudinger iminophosphorane intermediate **24** was generated *in situ* by stirring **23** with $(Ph)_3P$ at room temperature until the evolution of nitrogen gas ceased (2 h). Initial attempts to promote cyclization of **24** at reflux in benzene or xylene were unsuccessful even after an extended reaction time. However, the TLC indicated the consumption of **24** when the reaction was conducted in boiling mesitylene for 40 h. This reaction afforded two products (by TLC). Fortunately, after hydrolysis (H_2O, THF, $PhSO_3H$) the crude reaction mixture furnished the natural product **4** in 30-40% yield together with amine **25**.[14] The two products were formed in variable proportions depending on the reaction time and temperature. The yield of asperlicin D was improved using $(Bu)_3P$ in mesitylene at reflux temperature. The isolated asperlicin D showed spectral properties identical to those previously described for the natural product.[4,13,14]

Table 2. Synthesis of asperlicin (**4**) using Ph_3P in mesitylene

Temperature (°C)	% Yield of **4**	% Yield **25**
100	22	40
125	28	33
150	35	22

Conclusions

The present work demonstrates the viability of aminophosphorane intermediates having a secondary amide proton to provide a one-step entry to quinazolino[1,4-*d*]benzodiazepine ring system *via* tandem intramolecular aza-Wittig reaction followed by cyclodehydration performed on a linear peptide. We have devised a general procedure with simple reagents for accomplishing successive cylization reactions *via* Staudinger intermediates. The power of this approach has resulted in the synthesis of asperlicin D.

Experimental Section

General Procedures. Melting points (mp) were determined on an electrothermal digital melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Nicolet-Impact 410 FT-IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker, Avance DPX-300 (300 MHz), Bruker 250 spectrometers. Tetramethylsilane (TMS) was used as an internal reference. The spectral data are reported in delta (δ) units relative to TMS reference line. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were taken using a Bruker Avance DPX-300 (75.5 MHz) spectrometer and signals are reported in delta (δ) units relative to TMS reference using the solvent peaks ($CDCl_3$) as internal standard. Mass spectra were recorded with a Mariner Biospectrometry Workstation 4.0 by Applied Biosystems.

Ethyl *N*-{2-[(2-azidobenzoyl)amino]benzoyl} glycinate (11)

Isatoic anhydride (0.327 g, 2 mmol) was added to ethyl glycinate hydrochloride (0.279 g, 2 mmol) dissolved by heating in acetonitrile (7 mL) containing triethylamine (0.212 g, 2.1 mmol). The mixture was heated and allowed to reflux for 3 h. The reaction mixture was cooled to 0 °C and then triethylamine (0.404 g, 4 mmol) was added. Then a solution of freshly prepared 2-azidobenzoyl chloride (0.417 g, 2.3 mmol) in acetonitrile (2 mL) was added to the mixture. The reaction mixture was stirred at 0 °C for 0.5 h and at room temperature for 24 h. The mixture was concentrated and extracted with ethyl acetate (2 x 40 mL) and water (20 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexane) to afford **11** (0.559 g, 77%). mp 106-107 °C; IR (KBr disk, cm^{-1}) 3312 and 3219 (NH), 2988, 2139 (N_3), 1743, 1671 and 1643 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.58 (br, 1H, NH), 8.73 (d, *J* 8.3 Hz, 1H, Ar-H), 7.91 (dd, *J* 1.7, 8.3 Hz, 1H, Ar-H), 7.58 (dd, *J* 1.3, 7.8 Hz, 1H, Ar-H), 7.52 (dq, *J* 1.5, 7.8 Hz, 2H, Ar-H), 7.24 (dq, *J* 1, 5.0 Hz,, 2H, Ar-H), 7.09 (dq, *J* 1.3, 7.7 Hz, 1H, Ar-H), 6.89 (t, *J* 5.3 Hz, 1H, N-H), 4.22 (q, *J* 7.1 Hz, 2H, -CH_2-), 4.17 (d, *J* 5.2 Hz, 2H, -CH_2-), 1.3 (t, *J* 7.1 Hz, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.8, 169.0, 164.4, 139.1, 137.7, 132.8, 132.5, 131.3, 127.4, 127.2, 125.2, 123.5, 122.4, 121.7, 119.3, 61.9, 41.9, 14.3. EIMS (*m/z*, relative intensity) cal for $C_{18}H_{17}N_5O_4$: 367.1; found 367.2 (14%). Anal. Calcd for $C_{18}H_{17}N_5O_4$: C, 58.85; H, 4.66; N, 19.06% Found: C, 58.72; H, 4.54; N, 18.78%

Ethyl *N*-{2-[(2-aminobenzoyl)amino]benzoyl} glycinate (16). A mixture of azide **11** (0.367 g, 1 mmol) and Ph_3P or Bu_3P (1 mmol) in mesitylene (10 mL) was stirred at room temperature for 2 h. After concentration, the residue was stirred in wet-THF, containing a catalytic amount of $PhSO_3H$, for 3 h. The reaction mixture was concentrated. The residue was purified by chromatography on silica gel (25% ethyl acetate in hexane) to afford **16** (0.324 g, 95%). mp 131-133 °C [lit. mp 131-132 °C[13,14]].

Ethyl *N*-{2-[(2-(diethylphosphate)amidobenzoyl)amino]benzoyl} glycinate (17). A solution of azide **11** (0.367 g, 1 mmol) and triethyl phosphite (0.183 g, 1.1 mmol) in mesitylene (5 mL) was stirred at room temperature for 2 h. After concentration, the residue was passed through a

short column of silica gel (25% ethyl acetate in hexane) to afford **17** (0.439 g, 92%). The same product was obtained by stirring the residue in wet-THF containing catalytic amount of $PhSO_3H$ for 3 h. mp 127-128 °C; IR (KBr disk, cm^{-1}) 3271 (N-H), 3080, 2993, 1751, 1650, 1643, 1605, 1510; ^1H NMR (400 MHz, $CDCl_3$) δ *J* 12.13 (br s, 1H,N-H), 9.68 (d, *J* 11.6 Hz, N-H) 8.72 (d, *J* 8.5 Hz, 1H, N-H), 7.81 (d. *J* 8.3 Hz, 1H, Ar-H), 7.68 (d, *J* 7.8 Hz, 1H, Ar-H) 7.54 (t, *J* 7.8 Hz, 1H, Ar-H), 7.47(d, *J* 7.8, 1H, Ar-H), 7.42 (d, *J* 1Hz , Ar-H), 7.29 (m, 1H, Ar-H), 7.14 (t, *J* 7.7 Hz, 1 H, Ar-H), 7.04 (t, *J* 7.8 Hz, 1H, Ar-H), 4.25 (q, *J* 7.3 Hz, 2H, OCH_2), 4.21 (dd, *J* 2.7, 8.7 Hz, 2H, NCH_2), 4.14 (m, 4H, 2 x $POCH_2$), 1.32 (t, *J* 7.0 Hz, 9H, 3 x CH_3) 1.27 (t, *J* 7.3 Hz, 3H, CH_3). EIMS (*m/z*, relative intensity) cal for $C_{22}H_{28}O_7N_3P$: 477.2; found 477.4 (6%). Anal. Calcd. for $C_{22}H_{28}O_7N_3P$: C, 55.34; H, 5.91; N, 8.80% Found: C, 55.74; H, 5.87; N, 8.90%

Ethyl *N*-{2-[(2-(diphenylphosphate)amidobenzoyl)amino]benzoyl} glycinate (18). A solution of azide **11** (0.367 g, 1 mmol) and triphenyl phosphite (0.62 g, 1.1 mmol) in mesitylene (5 mL) was stirred at 60 °C for 5 h After concentration, the residue was stirred in wet-THF containing catalytic amount of $PhSO_3H$ for 3 h. The reaction mixture was concentrated. The residue was purified by chromatography on silica gel (50% ethyl acetate in hexane) to afford **18** (0.35 g, 61%). mp 144-145 °C; IR (KBr disk, cm^{-1}) 3357 (N-H), 3061, 2995, 1742, 1656, 1644, 1597, 1529; ^1H NMR (300 MHz, $CDCl_3$) δ 12.10 (br s, 1H,N-H), 10.28 (d, *J* 12 Hz, N-H), 8.65 (d, *J* 7.8 Hz, 1H, N-H), 7.82 (d, *J* 8.1 Hz, 1H, Ar-H), 7.75 (d, *J* 7.8 Hz, 1H, Ar-H), 7.63 (d, *J* 7.7 Hz, 1H, Ar-H), 7.53 (t, *J* 7.7 Hz, 1H, Ar-H), 7.49 (t, *J* 7.71 Hz, 1H, Ar-H), 7.33-7.10 (m, 13H), 4.26-4.21 (m, 4H, CH_2), 1.31 (t, *J* 7.2 Hz, 3H, CH_3). Anal. Calcd. for $C_{30}H_{28}O_7N_3P$: C, 62.82; H, 4.92; N, 7.33% Found: C, 62.34; H, 5.18; N, 7.42%

7-Ethoxyquinazolino[3,2-*d*]-1,4-benzodiazepin-9(7*H*)-one (19) and quinazolino[3,2-*d*]-1,4-benzodiazepine-7,9(5*H*,7*H*)-dione (20). A mixture of azide **11** (0.367 g, 1 mmol) and phosphorus(III) reagent (1.1 mmol) in mesitylene (10 mL) was stirred at room temperature for 2 h then heated to reflux for 40-60 h. After concentration, the residue was purified on silica gel (20% ethyl acetate in hexane) to give **19** (15-25%). mp 165-167 °C, IR (KBr, cm^{-1}) 1670 (C=O), 1655 (C=N) 1602 (C=N), 1581, 1556, 1474, 1264; ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, 10.0 Hz, 1H, Ar-H), 8.16 (dd, *J* 1.3, 7.9 Hz, 1H, Ar-H) 7.83-7.77 (m, 2H, Ar-H), 7.59-7.48 (m, 2H, Ar-H), 7.32 (dt, *J* 1, 7.6 Hz, 1H, Ar-H), 7.25 (d, *J* 8.7, 1H, Ar-H), 5.87 (d, *J* 13.2, 1H, NC*H*H), 4.47 (br s, 1H, OC*H*H), 4.24 (br s, 1H, OCH*H*), 3.83 (d, *J* 13.2 Hz, 1H, NC*H*H), 1.38 (t, 7.10 Hz, 3H, -CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.4, 171.0, 153.6, 148.4, 147.1, 135.0, 132.3, 131.8, 128.2, 127.5, 127.2, 127.0, 125.1, 120.2, 110.0, 73.9, 41.1, 14.4. Further eluting with (35% ethyl acetate in hexane) furnished **20** (20-25%). The spectroscopic data for this compound were identical to those reported.[14,20]

General procedure for synthesis of 20

A mixture of azide **11** (0.367 g, 1 mmol) and phosphorus(III) reagent (1.1 mmol) in mesitylene (5 mL) was stirred at room temperature for 2 h then heated to reflux for 40-60 h. After concentration, the residue was stirred in wet-THF containing catalytic amount of $PhSO_3H$ for

3 h. The reaction mixture was concentrated and then the residue was purified on silica gel (35% ethyl acetate in hexane) to give **20** (15-40%).

General procedure for synthesis of 20 using sealed tube reactions

A tube containing a pulverized mixture of azide **11** (0.367 g, 1 mmol) and phosphorus(III) reagent (1.1 mmol) and mesitylene (5 mL) was sealed under reduced pressure and kept in oven at 190-200 °C for 5 h. The tube was cooled, wrapped with towel and crushed. The crude reaction mixture was stirred in wet-THF containing catalytic amount of $PhSO_3H$ for 3 h. Purification by chromatography on silica gel (20 % ethyl acetate in hexane) afforded **7**. Further eluting with (35% ethyl acetate in hexane) furnished **20** (20-52%).

6-(Diethylamino)-quinazolino[3,2-*d*]-1,4-benzodiazepin-9(7*H*)-one (21). Triethyl- amine (0.808 g, 8 mmol), triphenylphosphine (0.786 g, 3 mmol) and iodine (0.761 g, 3 mmol) were added to benzodiazepine **3** (0.295 g, 1.06 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred for 24 h at room temperature. The mixture was washed with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified on silica gel column (% ethyl acetate in hexane: 20%) to give **21** (0.173 g, 49%). mp 144-145 ^oC; IR (KBr disk, cm^{-1}) 1674 (C=O), 1608 (C=N), 1578 (C=N), 1557, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* 7.8 Hz, 1H, Ar-H) 8.12 (dd, *J* 1.41, 7.82 Hz, 1H, Ar-H), 7.82-7.74 (m, 2H, Ar-H), 7.50-7.45 (m, 2H, Ar-H), 7.17-7.11 (m, 2H, Ar-H), 5.97 (d, *J* 13.9, 1H, -CHH-), 4.32 (br.s, 1H, -CHH-), 3.81 (br.s, 1H, -CHH-), 3.81 (d, *J* 13.9 Hz, -CHH-), 3.27 (br.s, 2H, $-CH_2-$), 1.26 (br s, 6H, $2xCH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.83, 155.91, 154.58, 149.37, 148.28, 134.51, 131.86, 131.03, 127.83, 127.11, 126.78, 126.34, 125.81, 122.12, 119.59, 43.47, 42.81, 37.76, 15.68, 12.81, MS(EI) *m/z* (relative intensity %): 332.4 (M^+ ($C_{20}H_{20}ON_4$)), 75), 303.3 (100), 289.2 (7) 260.3 (54), 234.3 (44).

6-(Dibutylamino)-quinazolino[3,2-*d*]-1,4-benzodiazepin-9(7*H*)-one(22). Tributylamine (1.48 g, 8 mmol), triphenylphosphine (0.786 g, 3 mmol) and iodine (0.761 g, 3 mmol) were added to a solution of **20** (0.295 g, 1 mmol) in dry CH_2Cl_2 (20 mL). The resulting mixture was stirred for 24 h. The reaction mixture was washed with water (20mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified on silica gel column (% ethyl acetate in hexane: 10%) to give **22** (0.106 g, 26%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* 7.8 Hz, 1H, Ar-H) 8.12 (d, *J* 7.7 Hz, 1H, Ar-H), 7.83-7.75 (m, 2H, Ar-H), 7.47 (dt, *J* 1.6, 7.1 Hz, 2H, Ar-H), 7.17-7.11 (m, 2H, Ar-H), 5.98 (d, *J* 13.9 Hz, 1H, -CHH-), 4.33 (br., 1H, -CHH-), 3.82 (br., 1H, -CHH-), 3.80 (d, *J* 13.9 Hz, -CHH-), 3.40 (br.s, 2H, $-CH_2-$), 1.76-0.88 (br., 6H, $2xCH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.86, 156.24, 154.63, 149.43, 148.27, 134.51, 131.83, 130.98, 127.82, 127.11, 126.78, 126.32, 125.72, 122.00, 119.55, 49.54, 48.20, 37.85, 32.86, 29.97, 29.55, 29.51, 20.19, 13.95.

Methyl *N*-{2-[(2-azidobenzoyl)amino]benzoyl}tryptophanate (23). Tryptophan methyl ester was dissolved in acetonitrile, then triethylamine (5.5 g, 37.5 mmol) was added dropwise with stirring to the reaction mixture at 0 °C, followed by addition of isatoic anhydride **7** (4.0 g, 25.0 mmol) with stirring. The reaction mixture was refluxed for 3 h. The reaction mixture was

cooled to 0 °C then triethylamine (3.5 mL, 25.0 mmol) was added dropwise. Freshly prepared 2-azidobenzoyl chloride (25 mmol) dissolved in acetonitrile was added dropwise to the above solution at 0 °C with stirring over 10 min. The mixture was stirred at room temperature for 36 h. The solvent was evaporated under reduced pressure. The crude product **23** was dissolved in ethyl acetate (200 mL) and water (50 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated. Purification of the residue by column chromatography on silica gel (30% ethyl acetate in hexane) afforded pure **23** (7.72 g, 80%,). IR (KBr disk,) 3290 (N-H), 3051, 2949, 2160 (N_3), 1738 (C=O), 1668 (C=O) and 1652 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.56 (s, 1H, NH), 8.67 (d, *J* 8 Hz, 1H, NH), 8.17 (s, 1H, NH), 7.90 (dd, *J* 8, 2 Hz, 1H, Ar-H), 7,47 (m, 3H, Ar-H) 7.22 (m, 4H, Ar-H), 7.13 (t, *J* 8 Hz, 1H Ar-H), 7.00 (t, *J* 8 Hz, 1H, Ar-H), 6.96 (t, *J* 8 Hz, 1H, Ar-H), 6.90 (d, *J* 2 Hz, 1H, Ar-H), 6.67 (d, *J* 8 Hz, 1H, Ar-H), 5.04 (dd, *J* 8, 5 Hz, 1H, NCH), 3.69 (s, 3H, OCH_3), 3.42 (dd, *J* 15, 5 Hz, 1H, CHH), 3.36 (dd, *J* 15, 5 Hz, 1H, CHH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.0, 168.2, 164.2, 138.9, 137.6, 136.1, 132.6, 132.3, 131.2, 127.5, 127.2, 126.9, 125.0, 123.3, 122.8, 122.4, 122.3, 121.7, 119.9, 119.2, 118.5, 111.3, 109.8, 53.4, 52.6, 27.6.

Asperlicin D (4)

A mixture of **23** (0.468 g, 1 mmol) and Ph_3P or Bu_3P (1 mmol) in mesitylene (10 mL) was heated at 150 °C for 18 h, then the solvent was evaporated. The residue was stirred in H_2O-THF-$PhSO_3H_{(cat)}$ for 3 h. The reaction mixture was concentrated and residue was purified by column chromatography on silica gel (60% ethyl acetate in hexane) furnishing **4**[13,14] (30-52%).

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