Scientific Paper

A Biomimetic Approach to Quinazolino [3,2-*d*] [1,4]benzodiazepine Ring System: The First Total Synthesis of Asperlicin D

Naim H. Al-Said*, Lina S. Al-Qaisi

Department of Applied Chemical Sciences, Jordan University of Science and Technology
P.O. Box 3030, Irbid 22110, Jordan, Fax: 962-2-7095014. E-mail: naim@just.edu.jo

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Abstract

Lewis acid ($MgCl_2$, $ZnCl_2$) mediated cyclodehydration of a linear tripeptide comprised of three amino acid units in the order of anthranilic-anthranilic-glycine (C-terminal anthranoyl-anthranilate methyl ester) furnished the tricyclic quinazolino[3,2-*d*][1,4]benzodiazepine ring system found in various biologically active natural alkaloids. This methodology, implemented with a tripeptide encompassing the sequence of anthranilic-anthranilic-tryptophan methyl ester, furnish the first total synthesis of asperlicin D.

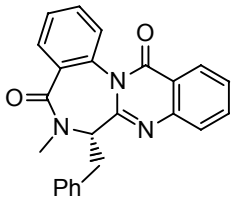
Key words: lewis acids, quinazolino[3,2-*d*][1,4]benzodiazepine, linear tripeptide, total synthesis, asperlicin D.

Introduction

Recently, several families of natural alkaloids such as the benzomalvins,[1] circumdatins,[2,3,4] asperlicins,[5,6] and sclerotigenin[7] incorporating quinazolino[1,4]-benzodiazepine system have been isolated from different sources. These natural alkaloids display important biological properties. For instance, benzomalvins A (**1**) display inhibitory activity against substance P at the guinea pig, rat and human neurokinin NK1 receptors.[1] Asperlicin A has antagonist activity against cholecystokinin. On the other hand, asperlicin C (**2**) and asperlicin D (**3**) display lower biological activity.[5,6] Furthermore, sclerotigenin (**4**) exhibits antiinsectant activity.[7,8]

Iminophosphorane-based methodologies are extensively employed for the synthesis of nitrogen containing heterocyclic natural products.[9-11] Different applications of Eguchi aza-Wittig protocols were executed to provide entry to this family of natural products. All these protocols attained the final products after many steps, since they required initially the preparation of protected bicyclic systems, selective acylation with 2-azidobenzoyl chloride, aza-Wittig cyclization and finally deprotection.[12-15]

As an extension to our studies toward the total synthesis of some biological interesting alkaloids,[16] we are interested in a concise synthetic route to the tetracyclic core of these natural alkaloids from a linear tripeptide. This paper describes the first total synthesis of asperlicin D (**3**) in a single step from a linear tripeptide.



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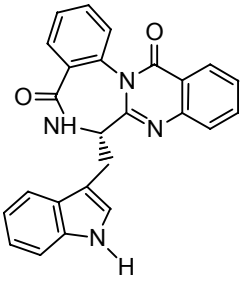

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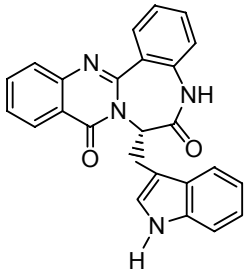

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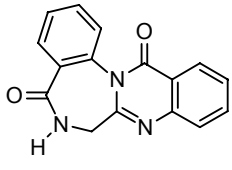

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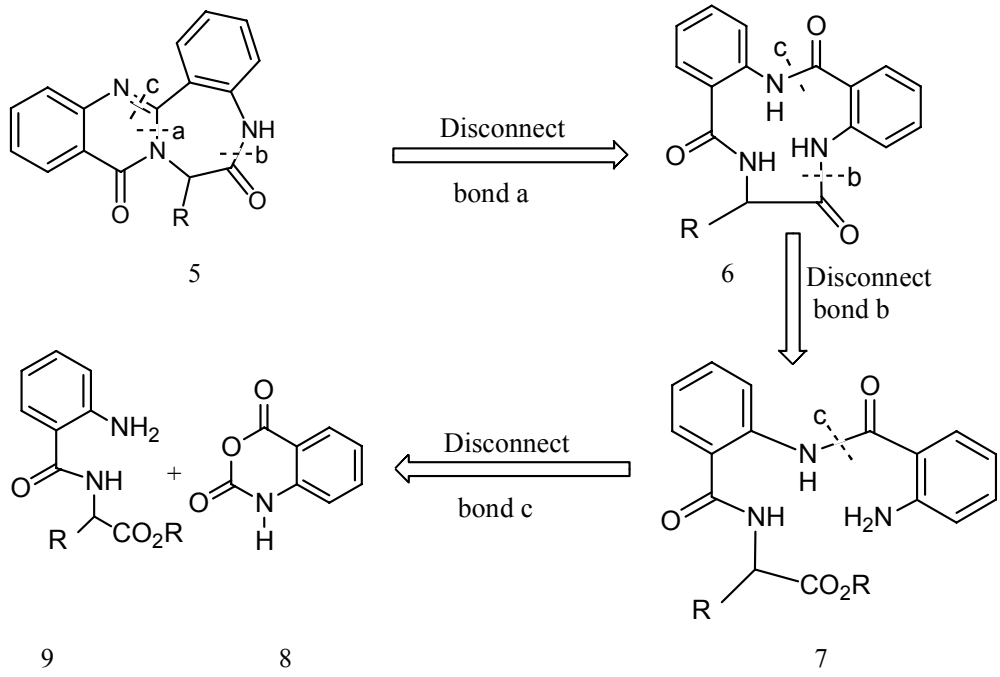
Results and discussion

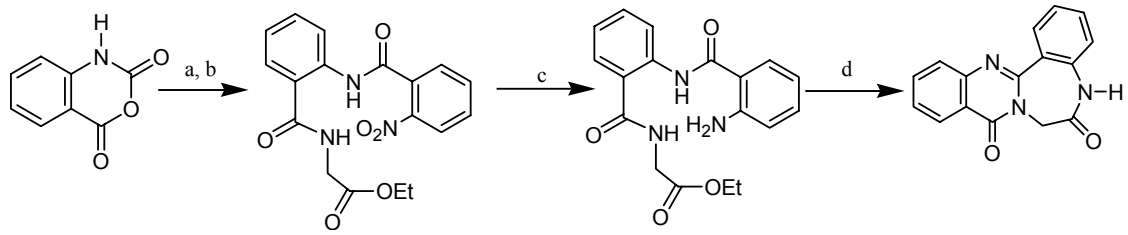
The biologically active alkaloids **1**-**4** vary in structural complexity, but they all seem to be retrosynthetically derivable from N- or C-terminal anthranilic acid dimer. Our aim is the preparation of asperlicin D because it is the only member of the asperlicin family that has not been synthesized.[12-15] Retrosynthetically, the bond disconnection strategy for the quinazolino[3,2-*d*][1,4]benzodiazepine ring system **5** found in asperlicin D is summarized in Scheme 1. The Scheme shows that this natural product may be derived from two consecutive intramolecular reactions. After disconnection of the amidinic group (bond a), the cyclic tripeptide **6** becomes a viable intermediate for the second intramolecular cylclodehydration step. Further disconnection of the C-N amide bond (bond b) reveals that the linear tripeptide **7** is a feasible starting material for the first intramolecular cyclization. This material can be synthesized by condensation of isatoic anhydride (**8**) with dipeptide **9**. The cyclization of **7** to the cyclic tripeptide **6** followed by cyclodehydration to quinazolino[3,2-*d*][1,4]benzodiazepine **5** represents a concise and biomimetic route to these natural products.

The initial investigation of the cyclodehydration of a model substrate was examined. Thus, the commercially available and inexpensive isatoic anhydride (**8**) was converted in a one-pot reaction to the nitro derivative **10**, as shown in Scheme 2. Condensation of **8** with ethyl glycinate in dry acetonitrile followed by acylation with freshly prepared 2-nitrobenzoyl chloride afforded **10** in good yield (>70%). Reduction of the nitro group in compound **10** was accomplished using $SnCl_2$ in methanol under reflux to furnish the required model substrate **11** in 92% yield. The structure of the linear tripeptide **11** was established on the basis of ^{1}H NMR, and mass spectral data. The spectroscopic (^{1}H NMR) data were found to be similar to those reported for the analogous ethyl ester derivative.[17]

With the tripeptide **11** in hand, we turned to the major chemical transformation step of cyclodehydration. Implementation of Wipf methodology ($Ph_3P/I_2/R_3N$)[18] failed to promote **11** to cyclize. It afforded an inseparable mixture of products. Fortunately, we observed that the starting material **11** was consumed and a new product was isolated when a neat solid **11** was heated (200-220°C) in a test tube. The isolated product was contaminated with an unidentifiable and inseparable impurity. This product was separated in pure form and in good yield (>60%) when the reaction was conducted at 130-135°C in DMF in the presence of anhydrous $MgCl_2$ or $ZnCl_2$. The presence of the salt ($MgCl_2$ or $ZnCl_2$) was essential for the reaction to proceed as expected, otherwise the starting material remained intact. The isolated product showed spectral properties identical to those previously described for quinazolino[3,2-*d*][1,4]benzodiazepine (**12**).[19] However, the proposed cyclic tripeptide **6** (R = H) was not observed. We believe that **11** underwent a thermal nucleophilic acyl substitution reaction to form a cyclic intermediate similar to **6**, which in-turn dehydrated to the expected tetracyclic skeleton



Scheme 1. General retrosynthetic analysis of the quinazolino[3,2-*d*][1,4]benzodiazepine



8 10 11 12

Scheme 2. a) $HCl.H_2NCH_2CO_2Et$, Et_3N, CH_3CN, reflux, 3 h; b) 2-O_2N-PhCOCl, Et_3N; c) $SnCl_2x2H_2O$, MeOH, reflux; d) $MgCl_2$, DMF, 135°C.

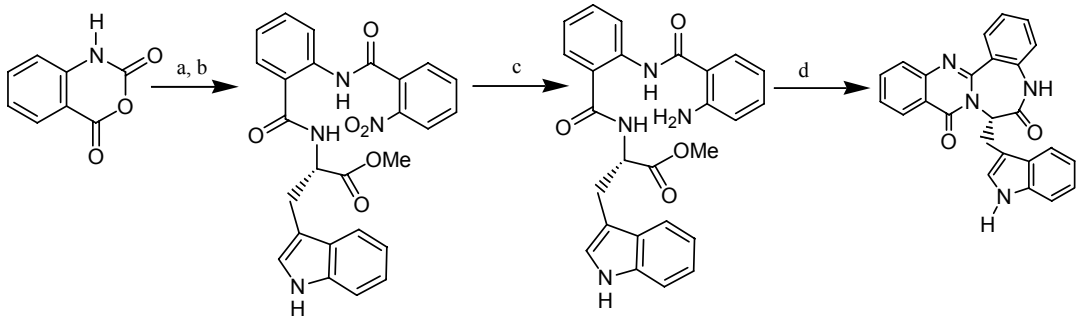
12 under the reaction conditions. The formation of **12** as the major reaction product could be explained based on the nucleophilicity of the nitrogen atoms. The nitrogen atom of the glycine unit in **11** is the most nucleophilic atom and is expected to initiate the cyclodehydration process by attacking the more electrophilic carbonyl group forming ring system **12**.

This result prompted us to apply our methodology on a linear tripeptide having the sequence of anthranilic-anthranilic-tryptophan. This tripeptide encompasses the three amino acid units found in the natural product asperlicin D (**3**). Our approach to asperlicin D commenced from the nitro compound **13** (Scheme 3). This compound was prepared in a one-pot reaction in good yield (75%) by condensation of isatoic anhydride (**7**) with L-tryptophan methyl ester in dry acetonitrile followed by acylation with freshly prepared 2-nitrobenzoyl chloride. The nitro group in **13** was conveniently reduced to the corresponding amine **14** employing $SnCl_2$ as shown in Scheme 3. The spectral properties (^1H and ^{13}C NMR) of **14** bear very close similarities with those of the ethyl ester derivative.[17]

With convenient access to amine **14**, we then focused on the completion of the target natural product. Toward this end, the cylcodehydration of **14** to asperlicin D was scrutinized. Fortunately, when the cyclodehydration reaction of **14** was conducted at similar conditions to those used for the model substrate **11** (130-135°C in DMF, $MgCl_2$ or $ZnCl_2$) asperlicin D (**3**) was isolated in moderate yield (30-40%). The scope of using $ZnCl_2$ and $MgCl_2$ in DMF as cyclodehydrating agents was examined at different temperatures and different reaction times. These experiments unveiled that the best conditions for this multiple cyclization reactions occurred when amine **14** and $MgCl_2$ (dried by fusing) were kept in DMF for 40 h at 130°C. When the reaction time exceeded 40 h excessive decomposition was observed. Similar results were obtained with $ZnCl_2$, but the product was isolated in lower yields (20-25%).

The moderate yield obtained with $MgCl_2$ or $ZnCl_2$ encouraged us to investigate an alternative methodology to achieve the cyclodehydration process. The fusing technique was implemented as an alternative approach to induce the cyclization process. The fusing process was conducted by keeping amine **14** in an oven pre-set at 200°C for four hours. The black solid was dissolved in ethyl acetate to extract all the soluble constituents. After separating the components soluble in ethyl acetate by silica gel column chromatography, the desired natural product asperlicin D (**3**) was isolated in low yield (20-25%) and was found to be contaminated with some impurities.

The isolated asperlicin D showed spectral properties identical to those previously described for



7 13 14 3 (Asperlicin D)

Scheme 3. a) L-tryptophane methyl ester. Et_3N, CH_3CN; b) 2-O_2N-PhCOCl, Et_3N; c) $SnCl_2x2H_2O$, MeOH, reflux; d) $MgCl_2$, DMF,

the natural occurring product.[6] The chemical ionization mass spectrum (CIMS) for this natural product showed a $[M+K]^+$ peak at m/z 445, consistent with the formula $C_{25}H_{18}N_4O_2$ (calc. 406). The ^{13}C NMR spectrum of **3** displayed twenty-five signals confirming the proposed structure. The spectrum showed the two sp^3 carbons at δ 56.1 (methine) and δ 24.2 (methylene). Furthermore, the ^{13}C-DEPT-135 spectrum exhibited all the carbons having hydrogen(s) at the expected resonance values and with the proper phase. It displayed one negative (antiphase) signal for the single methylene carbon at δ 24.2, one positive (phase) signal for the single methine carbon at δ 56.1 and thirteen positive signals for the thirteen aromatic sp^2 carbons.

The ^1H NMR spectrum of **3** was also consistent with the reported data.[6] The CH_2CHX protons were observed as an AMX system. The methylene protons of the tryptophan residue were displayed as two sets of signals, one at δ 3.15 (dd, J = 9.8, J´ = 14.8 Hz), and the other at δ 3.00 (dd, J = 8.3, J´ = 14.8 Hz). The methine proton of the tryptophan residue was observed as a broad triplet (J = 9 Hz) at δ 6.9 and is not coupled to the N-H proton. This supports the proposed structure and excludes the alternative structure for asperlicin C (**2**). The downfield chemical shift of the methine proton could be explained by the anisotropic effect of the adjacent two carbonyl groups. It is in eclipsed position with the carbonyl next to it and pointing towards the other carbonyl group.

Conclusions

In summary, we have developed a short method for the synthesis of asperlicin D in 20% overall yield from commercially available starting materials. This synthesis has been achieved in a single step involving two intramolecular cyclization reactions of a linear tripeptide mediated by $MgCl_2$.

Experimental

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 (^1H NMR) spectra were recorded on Bruker, Avance DPX-300 (300 MHz), Bruker 250 and Bruker 200 MHz 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-nitrobenzoyl)amino]benzoyl} glycinate (10)

Isatoic anhydride (**8**) (0.326 g, 2.0 mmol) was added to a solution of ethyl glycinate hydrochloride (0.279 g, 2 mmol) in acetonitrile (6 mL) containing triethylamine (0.212 g, 2.1 mmol). The mixture was heated under reflux for 3 h. The reaction mixture was cooled to 0°C and then triethylamine (0.404 g, 4.0 mmol) was added. A solution of freshly prepared 2-nitrobenzoyl chloride (0.427 g, 2.3 mmol) in acetonitrile (2 mL) was added drop-wise to the reaction 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 (2x40 mL) and water (20 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by column chromatography on a silica gel column (35% ethyl acetate in hexane) afforded **10** (0.534 g). Yield: 72%, mp 99-100°C. IR (KBr) 4443 and 3334 (N-H), 1750, 1677, and 1648 cm^{-1} (C=O). ^1H NMR (200 MHz, $CDCl_3$) δ 11.55 (br, 1H), 8.66 (d, 8.04 Hz, 1H), 8.04 (dd, 1.8, 7.1 Hz, 1H), 7.67-7.12 (m, 6H), 4.21 (q, 7.1 Hz, 2H), 4.12 (d, 5.2 Hz, 2H), 1.27 (t, 7.1 Hz, 3H). Anal. Calcd. for $C_{18}H_{17}O_6N_3$: C, 58.22; H, 4.61; N, 11.32. Found: C, 57.86; H, 4.74; N, 10.96.

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

A mixture of nitro derivative **10** (0.742 g, 2.0 mmol) and $SnCl_2{\cdot}H_2O$ (1.80 g, 8.0 mmol) in MeOH (10 mL) was heated under reflux for 1 h. After concentration, the organic residue was diluted with ethyl acetate (150 mL) and aqueous $NaHCO_3$ (60 mL). Few spatula of Celite were added to the mixture. The mixture was stirred vigorously for 2 h. The solid was removed by suction filtration and the organic layer was separated, dried and concentrated to give solid residue of **11** (0.626 g). Yield: 92%, mp 131-132°C. IR (KBr) 3456 and 3349 (NH_2), 3299 (N-H), 1750, 1651 and 1637 cm^{-1} (C=O). ^1H NMR (200 MHz, $CDCl_3$) δ 11.72 (br, 1H), 8.70 (d, 8.5 Hz, 1H), 7.74-6.64 (m, 8H), 5.75 (br, 2H), 4.27 (q, 7.1 Hz, 2H), 4.21 (d, 4.8 Hz, 2H), 1.25 (t, 7.1 Hz, 3H), MS (EI) m/z (relative intensity, %): 341.6 ($M^+(C_{18}H_{19}O_4N_3)$, 96), 322.5 (8), 296.4 (12).

Quinazolino[3,2-*d*][1,4]benzodiazepin-6,9(5*H*,7*H*)-dione (12)

A solution of amine **11** (0.682 g, 2.0 mmol) and anhydrous $MgCl_2$ (0.286 g, 3.0 mmol) in DMF (7.5 mL) was heated (135°C) for 26 h. The reaction mixture was poured into water (150 mL). The precipitated product

was filtered, dried and purified by passing through a short column of silica gel (chloroform) to give **12** (0.380 g). Yield: 65%, mp 316-318°C. IR (KBr disk) 3450 and 3197 (N-H), 1693 (C=O), 1606, 1588, 1557, and 767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, 7.82 Hz, 1H), 8.22 (dd, 1.26 Hz, 7.91 Hz, 1H), 7.85-7.77 (m, 2H), 7.63-7.51 (m, 2H), 7.42 (dt, 0.8 Hz, 7.6 Hz, 1H), 7.13 (d, 7.8 Hz, 1H), 5.89 (br, 1H), 4.04 (br, 1H), 1.71 (br, 3H). Anal. Calcd. for $C_{16}H_{13}O_3N_3$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.48; H, 4.02; N, 15.12.

Methy *N*-{2-[(2-nitrobenzoyl)amino]benzoyl} tryptophanate (13)

The tryptophan methyl ester was dissolved in acetonitrile, then triethyl amine (11.0 g, 75.0 mmol) was added dropwise with stirring to the reaction mixture at 0°C, followed by addition of isatoic anhydride **7** (8.0 g, 50.0 mmol) with stirring, and refluxed for 3 h. The reaction mixture was cooled to 0°C and triethyl amine (7 mL, 50.0 mmol) was added dropwise. Freshly prepared 2-nitrobenzoyl chloride (50 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 24 h. The solvent was evaporated under reduced pressure, and the crude product **13** dissolved in ethyl acetate (100 mL) and water (40 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated. Purification of the residue by column chromatography on silica gel (50% ethyl acetate in hexane) afforded **13** (18.20 g). Yield: 75%, mp 99-101°C. IR (KBr disk,) 3397 (N-H), 3051, 2949, 1732 (C=O), 1674 (C=O) and 1642 cm^{-1} (C=O). ^1H NMR (200 MHz, $CDCl_3$) δ 11.55 (bs, 1H), 8.65 (d, 8.3 Hz, 1H), 8.28 (bs, 1H), 8.03 (d, 7.8 Hz, 1H) 7.68-6.97 (m, 11H), 6.83 (d, J = 7.5 Hz, 1H), 5.01 (dt, 7.5, 5.4 Hz, 1H), 3.72 (s, 3H), 3.37 (dd, 5.4, 14.8 Hz, 1H), 3.45 (dd, 5.2, 14.8 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.9, 168.3, 164.3, 146.9, 139.5, 136.1, 133.7, 133.0, 132.9, 130.8, 128.4, 127.4, 126.9, 124.6, 123.7, 123.0, 122.3, 121.8, 120.0, 119.7, 118.3, 111.4, 109.5, 53.3, 52.6, 27.4. ^{13}C NMR (DEPT-135) δ 133.7 (+), 133.0 (+), 130.8 (+), 128.4 (+), 126.9 (+), 124.6 (+), 123.7 (+), 123.0 (+), 122.3 (+), 121.8 (+), 119.7 (+), 118.3 (+), 111.4 (+), 53.3 (+), 52.6 (+), 27.4 (-). CIMS $[M+K]^+$ 525 (calc. $C_{26}H_{22}N_4O_6$ 486).

Methy *N*-{2-[(2-aminobenzoyl)amino]benzoyl} tryptophanate (14)

The nitro derivative **13** (0.5 g, 1.0 mmol) was dissolved in methanol (10 mL) containing $SnCl_2x2H_2O$ (0.9 g, 4.0 mmol). The reaction mixture was refluxed for 3 h. Then solvent was evaporated under reduced pressure. The residue was dissolved with heating and stirring in ethyl acetate (10 mL) and methanol (1 mL). Saturated aqueous solution of $NaHCO_3$ (5 mL) was added with stirring to the reaction mixture, followed by addition of celite. The mixture was stirred at room temperature for 24 h, and passed through a short column of silica gel. The silica pad was washed with ethyl acetate (20 mL). The organic layer in the filtrate was separated and the aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic layer was washed with brine (20). The organic layer was dried over $MgSO_4$, filtered through celite and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (50% ethyl acetate in hexane) to afford **14** (0.35g). Yield: 77%, mp 168-169°C. IR (KBr disk) 3423, 3340 and 3244 (N-H), 3051, 2949, 1732 (C=O), 1649 (C=O), 1623 (C=O) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 11.68 (bs, 1H), 8.64 (dd, 8.4, 0.9 Hz, 1H), 8.21 (bs, 1H), 7.67 (dd, 8.0, 1.3 Hz, 1H), 7.3-6.69 (m, 7H), 5.76 (bs, 2H,), 5.12 (dt, 7.7, 5.3 Hz, 1H), 3.74 (s, 3H), 3.47 (dd, 9.6, 14.9 Hz, 1H), 3.39 (dd, 5.3, 14.9 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.0, 168.6, 160.0, 149.6, 139.8, 136.1, 132.8, 132.6, 127.8, 127.5, 126.8, 122.8, 122.7, 122.3, 121.6, 120.4, 119.8, 118.4, 117.4, 117.0, 115.8, 111.4, 109.7, 53.3, 52.5, 27.6; ^{13}C NMR (DEPT-135) δ 132.8 (+), 132.6 (+), 127.8 (+), 126.8 (+), 122.8 (+), 122.7 (+), 122.3 (+), 121.6 (+), 119.8 (+), 118.4 (+), 117.4 (+), 117.0 (+), 111.4 (+), 53.3 (+), 52.5 (+), 27.6 (-). CIMS $[M+K]^+$ 495 (calc. $C_{26}H_{24}N_4O_4$ 456).

Asperlicin D (3)

A solution of $MgCl_2$ (0.43 g, 4.5 mmol) and **14** (0.90 g, 2.0 mmol) in DMF (20 mL) was kept at 135°C for 40 h. Then the solvent was evaporated under reduced pressure. The crude product was dissolved in ethyl acetate (60 mL) and the organic layer was washed with water (60 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification of the residue by column chromatography on silica gel (60% ethyl acetate in hexane) furnished asperlicin D (**3**) (0.24 g). Yield: 30%, mp 119-121°C. IR (KBr disk) 3340 and 3237 (N-H), 3045, 2975, 2904, 1681 cm^{-1} (C=O). ^1H NMR (250 MHz, $CDCl_3$) δ 9.61 (s, 1H,), 8.27 (br d, 7.9 Hz, 1 H), 8.21 (dd, 7.9, 1.5 Hz, 1H), 8.0 (br s, 1H), 7.73 (m, 2H), 7.51 (dt, 8, 1.5 Hz, 1H), 7.50-7.38 (m, 2H), 7.34 (br d, 8.2 Hz, 1H) 7.23 (d, 7.3 Hz, 1H), 7.15 (dt, 6.9, 1.3 Hz, 1H), 7.05 (dt, 8.52, 1.2 Hz, 1H), 6.92 (br t, 8.7 Hz, 1H), 6.88 (m, 2H), 3.15 (dd, 9.9, 14.8 Hz, 1H), 3.1 (dd, 8.3, 14.8 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.5, 161.5, 151.0, 147.4, 135.9, 135.3, 134.7, 132.6, 132.1, 127.7, 127.4, 127.2, 127.0, 126.8, 125.6, 122.7, 122.2, 120.8, 119.5, 119.6, 118.3, 111.3, 109.0, 56.1, 24.2. ^{13}C NMR (DEPT-135) δ 134.7 (+), 132.6 (+), 132.2 (+), 12776 (+), 127.4 (+), 127.2 (+), 125.6 (+), 122.7 (+), 122.2 (+), 120.8 (+), 119.6 (+), 118.3 (+), 111.3 (+), 56.1 (+), 24.2 (-). CIMS $[M+K]^+$ 445 (calc $C_{25}H_{18}N_4O_2$ 406).

Acknowledgements

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Povzetek

Z lewisovimi kislinami ($MgCl_2$, $ZnCl_2$) katalizirano ciklodehidriranje linearnega tripeptida,sestavljenega iz treh aminokislinskih enot v zaporedju antranil-antranil-glicin,nudu možnost priprave tricikličnih kinozolino [3,2-d][1,4]benzodiazepinskih obročnih sistemov, ki jih najdemo v različnih biološko aktivnih naravnih alkaloidih. Ta metodologija tudi omogoča, s pomočjo tripeptida z aminokislinskim zaporedjem antranil-antranil-triptofan, prvo totalno sintezo asperlicina D.