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Total synthesis of asperlicin D

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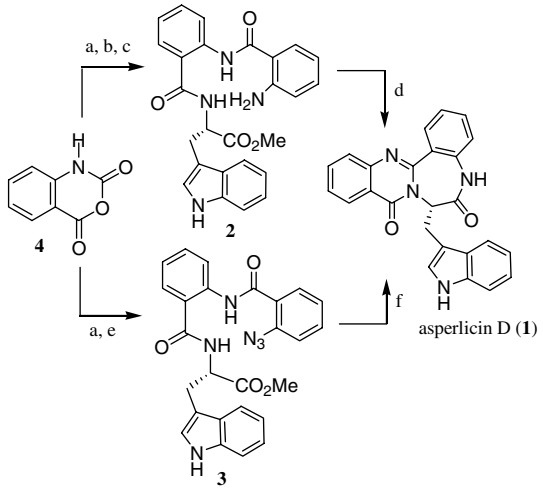
Abstract—Cyclodehydration of a linear tripeptide furnished the first total synthesis of asperlicin D in moderate yield. The cyclodehydration process was triggered by an intramolecular nucleophilic acyl substitution and an intramolecular aza-Wittig reaction.

Recently, several families of natural alkaloids, such as benzomalvins,[1] circumdatins,[2–4] asperlicins,[5,6] and scleraotigenin[7] incorporating two anthranilic acid units and an amino acid condensed together forming a quinazolino[1,4]-benzodiazepine system have been isolated from different sources. These naturally occurring alkaloids display important biological properties. Asperlicin A has antagonist activity against cholecystokinin. On the other hand, asperlicin C and asperlicin D (**1**) display lower biological activity.[5,6] All members of the asperlicin family have been synthesized except asperlicin D.[8] These alkaloids seem to be biosynthetically derivable from linear peptides. Retrosynthetically, cyclodehydration of a linear peptide precursor represents a concise and biomimetic route to the tetracyclic quinazolino[1,4]-benzodiazepine ring system.

In our continuing efforts to develop simple synthetic methods to biologically active compounds,[9] we report the first total synthesis of asperlicin D in a single step from a linear tripeptide. Our approach to asperlicin D was based on cyclization of the corresponding linear tripeptide analogues **2** and **3**. Amine **2** was conveniently prepared by a one-pot reaction in good yield (75–85%) by condensation of isatoic anhydride (**4**) with L-tryptophan methyl ester in dry acetonitrile followed by acylation with freshly prepared 2-nitrobenzoyl chloride and finally reduction of the nitro group to the corresponding amine employing $SnCl_2$ as described in Scheme 1.



Scheme 1. Reagents and conditions: (a) L-tryptophan methyl ester. Et_3N, CH_3CN, 93%; (b) 2-NO_2-PhCOCl, Et_3N, 78%; (c) $SnCl_2$, MeOH, 80%; (d) $MgCl_2$, DMF, 130 °C, 35%; (e) 2-N_3-PhCOCl, Et_3N, 78%; (f) Bu_3P, mesitylene, 150 °C, then H_2O–THF, $PhSO_3H$, 62%.

With a convenient access to **2**, we focused on the completion of the synthesis of targeted natural product. Towards this end, the cylcodehydration of **2** to asperlicin D was investigated.

Implementation of Wipf methodology ($Ph_3P/I_2/R_3N$)[10] to cyclodehydrate **2** afforded an inseparable mixture of products. After several attempts, the desired natural product **1** was isolated in low yield (<20%) contaminated with some impurities upon heating amine **2** at 180–200 °C for 2 h. Fortunately, when the reaction was conducted at 130–135 °C in DMF in the presence of anhydrous $MgCl_2$ or $ZnCl_2$, asperlicin D (**1**) was

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isolated in moderate yield (30–40%).[11] The isolated product showed spectral properties identical to those previously described for the natural product.[6] However, in the absence of salts ($MgCl_2$ or $ZnCl_2$) the starting material remained intact in DMF under reflux. On the other hand, attempts to promote cyclodehydration of **2** using $CaCl_2$ and $AlCl_3$ failed, even at reflux after long periods of time.

Since the yield of the targeted natural product was only moderate, an alternative route to its synthesis was investigated. Thus, a tandem aza-Wittig mediated annulation was studied.[12] The azido derivative **3** was the starting point for the second route. It was prepared in a one-pot reaction in good yield (>70%) by condensation of isatoic anhydride (**4**) with L-tryptophan methyl ester followed by acylation with freshly prepared 2-azidobenzoyl chloride. The Staudinger iminophosphorane intermediate[12] was generated in situ by stirring **3** with Ph_3P at room temperature until the evolution of nitrogen gas ceased (2 h).[13] Initial attempts to promote cyclization of the iminophosphorane in refluxing benzene or xylene were unsuccessful even after an extended reaction time. However, TLC indicated consumption of the starting material when the reaction was conducted in boiling mesitylene for 40 h. This reaction afforded two products (by TLC). Fortunately, after hydrolysis (H_2O, THF, and $PhSO_3H$) the crude reaction mixture furnished the natural product **1** in 40–50% yield and amine **2**. These two products were formed in variable proportions depending on the reaction time and temperature. The yield of **1** was improved to 62% by switching to Bu_3P in mesitylene at reflux.

In summary, we have found that linear tripeptide analogues **3** can be converted to the tetracyclic natural product asperlicin D (**1**) in a one-pot process. Furthermore, we have demonstrated that iminophosphorane intermediates having secondary amide protons can be employed in an intramolecular aza-Wittig reaction to provide a one step entry to the quinazolino[1,4]-benzodiazepine ring system found in asperlicin D.

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11. (a) Typical experimental procedure for the cyclization of **2**: A mixture of $MgCl_2$ (0.43 g, 4.5 mmol) and **2** (1.37 g, 3 mmol) in DMF (20 mL) was heated at 135 °C for 36 h, then the solvent was evaporated. The residue 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 **1** (0.24 g, 30%); mp 120–121 °C; IR (KBr disk, cm^{-1}) 3340 and 3237, 3045, 2975, 2904, 1681; ^1H NMR (250 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.27 (br d, $J = 7.9$ Hz, 1H), 8.21 (dd, $J = 7.9$, $J' = 1.5$ Hz, 1H), 8.00 (br s, 1H), 7.73 (m, 2H), 7.51 (dt, $J = 8$, $J' = 1.5$ Hz, 1H), 7.50–7.38 (m, 2H), 7.34 (br d, $J = 8.2$ Hz, 1H) 7.23 (d, $J = 7.3$, 1H), 7.15 (dt, $J = 6.9$, $J' = 1.3$ Hz, 1H), 7.05 (dt, $J = 8.52$, $J' = 1.2$ Hz, 1H), 6.92 (bt, $J = 8.7$ Hz, 1H), 6.88 (m, 2H), 3.15 (dd, $J = 9.85$, $J' = 14.8$ Hz, 1H), 3.10 (dd, $J = 8.28$, $J' = 14.8$ Hz, 1H); ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ 170.5, 161.5, 151.1, 147.4, 135.9, 135.3, 134.7, 132.6, 132.1, 127.7, 127.4, 127.2, 127.0, 126.8, 125.6, 123.0, 122.2, 120.8, 119.6, 119.6, 118.2, 111.3, 109.0, 56.1, 24.2; CIMS $[M+K]^+$ 445 (calcd $C_{25}H_{18}N_4O_2$ 406). (b) Typical procedure for the cyclization of **3**: A mixture of **3** (0.468 g, 1 mmol) and Bu_3P (0.202 g, 1 mmol) in mesitylene (10 mL) was heated at 150 °C for 16 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 purified as in part a to afford **1** (0.251 g, 62%).
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