First Total Synthesis of (–)-Circumdatin H, a Novel Mitochondrial NADH Oxidase Inhibitor

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Abstract: An efficient and highly convergent synthesis of the mitochondrial NADH oxidase inhibitor (–)-circumdatin H is described. The strategy employs the intramolecular Eguchi aza-Wittig protocol as a key step to install the crucial central core BC ring system, leading to the first total synthesis of the target molecule.

Key words: benzodiazepine alkaloids, circumdatin H, mitochondrial NADH oxidase, intramolecular aza-Wittig reaction, Eguchi protocol, quinazolin-4(3*H*)-ones

Benzodiazepine-fused quinazolinone alkaloids occupy an important place in the realm of natural and synthetic organic chemistry because of their therapeutic and pharmacological properties.¹ Naturally occurring alkaloids belonging to this class include compounds such as sclerotigenin (1), which was isolated from organic extracts of sclerotia of *Penicillium sclerotigenum* (NRRL 3461)² and shows promising antiinsectan activity, asperlicin, which is produced by Aspergillus alliaceus and is a potent cholecystokinin antagonist,³ and benzomalvin A (2), which was isolated from a fungal culture of Penicillium sp. and shows inhibitory activity against human neurokinin NK1 receptors.⁴ Related alkaloids have been isolated from a terrestrial isolate of the fungus Aspergillus ochraceus. Circumdatin C $(3)^5$ and circumdatin F $(4)^6$ are prototypical members, while other members such as circumdatin D (5),⁶ circumdatin E (6)⁶ and circumdatin H (7)⁷ have an additional tetrahydropyrrole ring (Figure 1). The compounds of this group are considered to be useful chemotaxonomic markers. Among these compounds, circumdatin H (7) and circumdatin E (6) are able to inhibit the mitochondrial respiratory chain in submitochondrial particles from beef heart, presumably by interfering with NADH oxidase activity (IC50 1.5 µM and 2.5 µM, respectively). Similar molecules, circumdatins A-H, have recently been reported by Kusumi and co-workers from the marine-derived fungus Aspergillus ostianus strain 01F313, together with a new compound, named circumdatin J (8), and a revision of the structures of circumdatin A and B from the previously reported betaine structures to unique oxepinones based on X-ray crystallography.8 These alkaloids are often biosynthetically derived from two appropriately substituted anthranilic acid units and chiral amino acids, and as a result contain a chiral center



Figure 1 Chemical structures of circumdatins and related natural products

in the α -position of the 2-substituent on the quinazolin-4-one.

Due to their interesting biological activity, limited availability from natural sources and fascinating molecular architecture, these compounds have attracted immediate attention and have become attractive synthetic targets. To the best of our knowledge, however, the synthesis of circumdatins 5-8 is not known. In this communication, we report the first efficient and convergent synthesis of 7, featuring the construction of the pentacyclic ring system, which can be easily adopted for the synthesis of various analogues.

Our synthetic plan for the synthesis of (-)-circumdatin H (7) is outlined in Scheme 1. Two adaptable and useful strategies for the present purpose were explored: i) synthesis of the substituted quinazoline ring system 11 either by cyclodehydration of benzoxazinone 10 or the tripeptide precursor 9 and ii) an exceptionally mild route via intramolecular aza-Wittig cyclization (Eguchi protocol) of precursor 12 to form the imine functionality while preserving the neighboring chiral center as a critical step in the synthesis.

In an effort to develop a more widely applicable methodology for **11**, we chose to evaluate one of the most commonly employed synthetic strategies via benzoxazinone **10** as an intermediate⁹ (Scheme 2). Our synthesis started with the condensation of methyl anthranilate (**13**) with *N*-(*tert*-butoxycarbonyl)-L-proline (**14**) under standard coupling conditions,¹⁰ *N*,*N'*-dicyclohexylcarbodiimide (DCC) and *N*-hydroxybenzotriazole (HOBt), which resulted in a 73% yield of the corresponding amide **15a**. Selective hydrolysis of the ester functionality under mild conditions using lithium hydroxide yielded the acid **15b** in

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Scheme 1 Retrosynthetic analysis of (-)-circumdatin H

94% yield. To find a rapid and elegant method for the formation of benzoxazinone **10**, intramolecular cyclodehydration of **15b** was carried out under various reaction conditions.¹¹ Of the commonly available coupling agents screened for the cyclization (DCC/HOBt, Boc_2O), the use of 1,1'-carbonyldiimidazole (CDI) in tetrahydrofuran at room temperature was found to be most suitable for this reaction in terms of yield (95%), reaction time and workup.

Reaction of benzoxazin-4-ones with anilines containing a reactive functional group at the *ortho* position adds another dimension to the basic transformation, in that further cyclization to more complex heterocyclic systems is possible.^{12a} We considered this strategy would be useful for the synthesis of circumdatin H (7), to induce cyclization involving one six-membered ring and one seven-

membered ring. Based on the literature reports,⁹ a mixture of benzoxazinone 10 and methyl anthranilate (13) was refluxed in pyridine or in the presence of zinc chloride for the transformation to the target molecule circumdatin; however, this procedure led to a complex mixture of products, necessitating chromatographic separation. In order to circumvent this problem, the reactants 10 and 13 were heated under solvent-free conditions using molten tetrabutylammonium bromide at 160 °C, which afforded the expected pentacyclic 13-desmethoxycircumdatin H (16) along with the tricyclic dilactam 17 in 62% and 12% isolated yield, respectively, after separation on silica gel (Scheme 2). To our surprise, enantiomeric erosion was encountered during the course of the reaction^{12b-d} and resulted in the racemic form (\pm) -16. To overcome the drawback of racemization, a new approach for 7 was formulated which is disclosed below.

In this new approach, N-sulfinylanthraniloyl chloride (18),¹³ prepared from anthranilic acid and thionyl chloride, was treated with methyl anthranilate (13) to yield methyl 2-(2-aminobenzoylamino)benzoate $(19)^{14}$ (Scheme 3). Treatment of the latter with N-(tert-butoxycarbonyl)-L-proline (14) using DCC and HOBt afforded the tripeptide 9 in 65% yield. Recently, intramolecular dehydrative cyclization of diamides to various quinazolinone scaffolds by employing 1,1,1,3,3,3-hexamethyldisilazane with iodine under mild conditions has been reported.¹⁵ When similar conditions were applied for the cyclization of 9 with the hope of obtaining quinazolinone 11, however, the sole product was identified as the N-Bocdeprotected tripeptide 20, which may be due to the sterically hindered cyclic nature of L-prolinamide. Hence, we devised an alternative route.



Scheme 2 Preparation of (±)-13-desmethoxycircumdatin H (16)



Scheme 3

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As we were searching for an alternative, more efficient strategy, our attention was drawn towards the tandem intramolecular aza-Wittig reaction (Eguchi protocol),¹⁶ which is devoid of a protection and deprotection sequence of reactions (Scheme 4). As part of our ongoing efforts devoted to the development of novel pyrrolobenzodiazepine DNA-interactive ligands,¹⁷ we explored the opportunity to utilize dilactam **23** for the synthesis of circumdatin H (**7**).



Scheme 4 Intramolecular aza-Wittig reaction to form (–)-circumdatin H (7)

Reaction of anthranilic acid (21a) with either ethyl chloroformate and triethylamine at room temperature for 18 hours followed by reflux for 4 hours or triphosgene at room temperature generated isatoic anhydride $(22)^{18}$ in 78% and 90% yield, respectively. Treatment of the latter with L-proline in dimethyl sulfoxide at 120 °C afforded dilactam 23.¹⁹ 2-Azido-5-methoxybenzoyl chloride (25b) is an important intermediate which was required for the construction of the quinazolinone system (C and D rings). Thus, 25b was prepared from 2-amino-5-methoxybenzoic acid (21b) via a sequence which involved diazotization (NaNO₂, HCl, -5 to 0 °C; liberated excess nitrous acid was destroyed by adding urea), nucleophilic substitution with sodium azide to give 24b and, finally, treatment with thionyl chloride. The next step was the acylation of dilactam 23 with the 2-azidobenzoyl chloride 25b, in the presence of 4-(dimethylamino)pyridine and triethylamine in tetrahydrofuran, to give 12b in quantitative yield. Having useful quantities of tetracyclic precursor 12b in hand, the stage was then set for the investigation of the crucial ringclosure reaction to establish the pentacyclic framework of circumdatin H (7). To this end, Staudinger reaction of the aryl azide 12b with tributylphosphine in benzene at 60 °C for one hour generated the corresponding iminophosphorane intermediate ($N_3 \rightarrow N=PBu_3$), and concomitant aza-Wittig cyclization with the imide carbonyl functionality afforded circumdatin H [(-)-7] in high yield. We were delighted to note that **12b** was smoothly cyclized and furnished a single compound, the expected imine 7. All of the spectroscopic data for the synthetic compound (–)-7 were in good agreement with the literature data⁷ for natural (–)-circumdatin H. The specific optical rotation of the synthetic circumdatin H { $[\alpha]_D^{20}$ –35.4 (*c* 0.1, MeOH)} differs from the reported value for natural circumdatin H { $[\alpha]_D^{20}$ –26.33 (*c* 0.078, MeOH)}. Since there is no ambiguity about the structure of the synthetic compound, we assume that the optical rotation of the natural product was lowered by minor impurities. Although the melting point of natural circumdatin H (7) was not determined due to the small amount of material isolated, the melting point of the synthetic circumdatin H is 218–219 °C.

The preparation and transformation of azide **12a** was carried out under an identical sequence of reactions as described above for **12b** in order to obtain synthetic pentacyclic (–)-13-desmethoxycircumdatin H (**7a**) whose specific rotation was observed as $[\alpha]_D^{20}$ –124.60 (*c* 0.5, MeOH), which is very close to other natural circumdatins.

In summary, we have accomplished a highly efficient synthesis of (–)-circumdatin H in four steps and 46% overall yield starting from anthranilic acid. Notable features of our synthetic approach include an efficient intramolecular aza-Wittig cyclization of a highly strained tetracyclic derivative and no protection and deprotection sequence of reactions. This effort also documents the first enantiospecific total synthesis of the pentacyclic circumdatin H. The convergent approach reported here provides a foundation for the future synthesis of other natural quinazolinobenzodiazepine alkaloids and synthetic analogues of circumdatin H for SAR studies and lead optimization, which will be reported in due course.

All moisture-sensitive reactions were carried out under N2 atmosphere in flame-dried glassware sealed by rubber septa. Unless otherwise specified, materials were obtained from commercial sources and used without purification. All solvents were dried according to standard procedures and purified by distillation prior to use. Addition of chemicals was performed using disposable plastic syringes. Column chromatography was performed using Acme silica gel (60-120 mesh). Solvents for chromatography (n-hexane, CH₂Cl₂, EtOAc) were distilled prior to use. For analytical TLC, Merck precoated silica gel 60 F-254 plates were used with UV light (254 nm) as visualizing agent. Melting points were obtained using a Veego VMP-DS precision digital melting point apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1030 polarimeter. IR spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR spectrophotometer. ¹H and ¹³C NMR spectra were recorded in CDCl₃ on either a Bruker Avance 300 (300.132 MHz for ¹H, 75.473 MHz for ¹³C) or a Varian FT-200 MHz (Gemini) spectrometer. Chemicals shifts are reported in parts per million (δ) relative to tetramethylsilane ($\delta = 0.0$) as an internal standard. Elemental analyses were performed on an Elementar Vario EL microanalyzer. Lowresolution mass spectra (ESI-MS) and HRMS were recorded on Micromass Quattro LC and Applied Biosystems QSTAR XL spectrometers, respectively.

Methyl Anthranilate (Methyl 2-Aminobenzoate, 13)

A mixture of anthranilic acid (**21a**; 10.0 g, 72.99 mmol), dimethyl sulfate (9.20 g, 72.99 mmol) and K_2CO_3 (25.22 g, 182.48 mmol) in anhyd acetone (200 mL) was heated under reflux for 3 h. After com-

pletion of the reaction, H_2O (300 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (2 × 25 mL), dried (Na₂SO₄) and filtered, and the solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (hexane–EtOAc, 7:3) to give **13** as a thick syrup; yield: 8.476 g (77%).

¹H NMR (300 MHz, CDCl₃): δ = 3.85 (s, 3 H, CO₂CH₃), 5.70 (br s, 2 H, NH₂), 6.55–6.62 (m, 2 H, H-5,6), 7.18–7.26 (m, 1 H, H-4), 7.80 (dd, *J* = 2.26, 1.51 Hz, 1 H, H-3).

ESI-MS: $m/z = 152 [M^+ + H]$.

Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00. Found: C, 63.61; H, 5.92.

N-(tert-Butoxycarbonyl)-L-proline (14)

L-Proline (3.45 g, 30 mmol) was suspended in THF–H₂O (2:1, 45 mL), and then 10% aq NaOH (15 mL) was added. To the resultant biphasic mixture was added Boc₂O (6.54 g, 30 mmol) in THF–H₂O (2:1, 45 mL). The reaction was stirred at r.t. overnight, and then the THF was removed by evaporation under reduced pressure. The residual aqueous solution was adjusted to pH 2 by the addition of 10% aq KHSO₄ (ca. 50 mL). The acidic solution was extracted with EtOAc (2×40 mL). The combined organic extracts were washed with H₂O (30 mL) and brine (30 mL), and then dried (Na₂SO₄). Removal of the desiccant and evaporation of the solvent under reduced pressure afforded a solid residue (7.25 g), which was recrystallized (EtOAc) to give 4.52 g of **14**. An additional 0.65 g (total yield: 80%) was recovered from the filtrate in two crops; mp 133–135 °C (dec with effervescence).

 $[\alpha]_{D}^{20}$ –59.7 (*c* 1.0, AcOH) {Lit.¹⁰ $[\alpha]_{D}^{20}$ –61 (*c* 1.0, AcOH)}.

¹H NMR (200 MHz, CDCl₃): δ = 1.38–1.54 [br s, 9 H, CO₂C(CH₃)₃], 1.83–2.38 (m, 4 H, H-3,4), 3.30–3.62 (m, 2 H, H-5), 4.18–4.39 (m, 1 H, H-2).

ESI-MS: $m/z = 216 [M^+ + H]$.

Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96. Found: C, 55.88; H, 7.90.

Methyl 2-{[*N*-(*tert*-Butoxycarbonyl)-L-prolyl]amino}benzoate (15a)

To a stirred soln of methyl anthranilate (**13**; 3.00 g, 19.86 mmol), HOBt (3.22 g, 23.84 mmol) and *N*-(*tert*-butoxycarbonyl)-L-proline (**14**; 4.27 g, 19.86 mmol) in anhyd THF (60 mL) at 0 °C under N₂ atmosphere was added DCC (4.91 g, 23.84 mmol), and the mixture was maintained at 0 °C for 1 h and at r.t. overnight. After completion of the reaction, the separated *N*,*N'*-dicyclohexylurea was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in a mixture of EtOAc (300 mL) and 10% aq NaHCO₃ (150 mL). The organic layer was separated and washed with 10% aq citric acid (150 mL), followed by 10% aq NaHCO₃ (150 mL) and H₂O (150 mL). Then, the organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to obtain **15a** as a syrup; yield: 5.1 g (73%).

¹H NMR (300 MHz, CDCl₃): δ = 1.25–1.58 [br s, 9 H, CO₂C(CH₃)₃], 1.95–1.98 (m, 2 H, H-3'), 2.06–2.22 (m, 2 H, H-4'), 3.40–3.78 (m, 2 H, H-5'), 3.94 (s, 3 H, CO₂CH₃), 4.20–4.42 (m, 1 H, H-2'), 6.99–7.06 (m, 1 H), 7.49–7.52 (m, 1 H), 7.88–8.01 (m, 1 H), 8.75–8.78 (m, 1 H), 11.44 (br s, 1 H, CONH).

ESI-MS: $m/z = 349 [M^+ + H]$.

Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94. Found: C, 62.12; H, 7.04.

2-{[*N***-(***tert***-Butoxycarbonyl)-L-prolyl]amino}benzoic Acid (15b) To a stirred soln of methyl 2-{[***N***-(***tert***-butoxycarbonyl)-L-prolyl]amino}benzoate (15a**; 4.50 g, 12.9 mmol) in a 2:1 mixture of MeOH (65 mL) and THF (32 mL) at r.t. was added 10% aq LiOH (8.13 mL), and the reaction mixture was maintained at r.t. for 4 h. After completion of the reaction, the mixture was diluted with H₂O (100 mL) and acidified with 10% aq KHSO₄ to pH 2–3 at 5 °C. The mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine (2 × 50 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (hexane–EtOAc, 1:1) to give **15b** as a syrup; yield: 4.1 g (94%).

IR (KBr): 3195, 2979, 2621 (acid), 1686, 1646 (amide), 1585, 1521, 1451 (aromatic C=C), 1411, 1366, 1303, 1257, 1236, 1161, 1133, 890, 852, 795, 758 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): $\delta = 1.35-1.49$ [br s, 9 H, CO₂C(CH₃)₃], 1.92–2.41 (m, 4 H, H-3',4'), 3.32–3.90 (m, 2 H, H-5'), 4.28–4.62 (m, 1 H, H-2'), 6.74 (br s, 1 H, CO₂H), 7.10 (t, *J*_{ortho} = 7.5 Hz, 1 H), 7.53 (t, *J*_{ortho} = 8.3 Hz, 1 H), 8.12 (d, *J* = 7.5 Hz, 1 H), 8.74 (dd, *J* = 7.5, 8.3 Hz, 1 H), 11.52 and 11.76 (2 × s, 1 H, CONH).

ESI-MS: $m/z = 335 [M^+ + H]$.

Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63. Found: C, 61.15; H, 6.67.

2-[(2S)-N-(tert-Butoxycarbonyl)pyrrolidin-2-yl]-4H-3,1-benzoxazin-4-one (10)

CDI (0.485 g, 3 mmol) was added to a stirred soln of $2-\{[N-(tert-butoxycarbonyl)-L-prolyl]amino\}$ benzoic acid (**15b**; 1.0 g, 3 mmol) in anhyd THF (28 mL) under N₂ atmosphere at r.t. The mixture was stirred at the same temperature for 1 h. After completion of the reaction, the solvent was evaporated and the crude product was purified by silica gel column chromatography (hexane–EtOAc, 9:1) to give **10** as a syrup; yield: 0.886 g (94%).

 $[\alpha]_{D}^{20}$ –130.77 (*c* 1.3, CHCl₃) {Lit.^{11a} $[\alpha]_{D}^{20}$ –131.3 (*c* 1.3, CHCl₃)}.

¹H NMR (300 MHz, CDCl₃): δ = 1.42–1.50 [br s, 9 H, CO₂C(CH₃)₃], 1.89–2.50 (m, 4 H, H-3',4'), 3.45–3.79 (m, 2 H, H-5'), 4.23–4.52 (m, 1 H, H-2'), 7.42–7.60 (m, 2 H, H-7,8), 7.78–7.80 (m, 1 H, H-6), 8.05–8.20 (m, 1 H, H-5).

ESI-MS: $m/z = 317 [M^+ + H]$.

Anal. Calcd for $C_{17}H_{20}N_2O_4{:}$ C, 64.54; H, 6.37. Found: C, 64.61; H, 6.40.

(±)-13-Desmethoxycircumdatin H (16)

To freshly prepared 2-[(2*S*)-*N*-(*tert*-butoxycarbonyl)pyrrolidin-2yl]-4*H*-3,1-benzoxazin-4-one (**10**; 0.452 g, 1.45 mmol) and methyl anthranilate (**13**; 0.218 g, 1.45 mmol) under N₂ atmosphere was added TBAB (0.466 g, 1.45 mmol), and the mixture was stirred at 120 °C for 3 h and at 160 °C for 3 h. After completion of the reaction (based on TLC), the mixture was cooled, dissolved in EtOAc (2 × 50 mL), and washed with 2% aq NaOH (2 × 50 mL), followed by H₂O (2 × 50 mL) and brine (25 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (hexane–EtOAc, 7:3). A higher *R_f* spot of the target 13-desmethoxycircumdatin H (**16**) was isolated as a pale yellow solid; yield: 0.283 g (62%); mp 283–284 °C.

 $[\alpha]_{D}^{20}$ –1.00 (*c* 0.1, MeOH).

¹H NMR (300 MHz, $CDCl_3$): $\delta = 2.03-2.45$ (m, 3 H, H-20b,21a,21b), 3.18–3.20 (m, 1 H, H-20a), 3.53–3.86 (m, 2 H, H-22a,22b), 4.58 (d, J = 5.9 Hz, 1 H, H-19), 7.47–7.58 (m, 4 H, H-5,6,7,14), 7.65–7.81 (m, 2 H, H-13,15), 8.00 (d, J = 6.6 Hz, 1 H, H-12), 8.31 (d, J = 8.1 Hz, 1 H, H-4).

ESI-MS: $m/z = 318 [M^+ + H]$.

Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76. Found: C, 71.85; H, 4.70.

Upon further elution (hexane–EtOAc, 6:4), a lower R_f spot of the homocoupled compound (±)-2,3-dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-dione (**17**) was isolated as a cream-white solid; yield: 0.037 g (12%); mp 244–246 °C.

 $[\alpha]_{D}^{20}$ +2.00 (*c* 0.30, MeOH).

IR (KBr): 3438, 3248 (amide NH), 2975, 2945, 1677, 1629 (amide), 1481, 1444, 1414 (aromatic C=C), 1392, 1287, 1264, 846, 798, 759, 700 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 1.98–2.04 (m, 3 H), 2.75–2.77 (m, 1 H), 3.60–3.82 (m, 2 H), 4.07 (d, *J* = 6.0 Hz, 1 H), 7.03 (d, *J* = 8.3 Hz, 1 H), 7.27 (t, *J* = 8.3 Hz, 1 H), 7.46 (t, *J* = 9.1 Hz, 1 H), 7.98 (d, *J* = 8.3 Hz, 1 H).

ESI-MS: $m/z = 217 [M^+ + H]$.

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59. Found: C, 66.61; H, 5.63.

N-Sulfinylanthraniloyl Chloride (18)

To a stirred suspension of anthranilic acid (**21a**; 4.11 g, 30 mmol) in anhyd toluene (60 mL) under N_2 atmosphere was added freshly distilled SOCl₂ (8.75 mL, 120 mmol), and the mixture was refluxed for 3 h. The excess SOCl₂ and toluene were distilled off by codistillation with toluene (10 mL) and the resulting residue (6.027 g) of compound **18** was dissolved in toluene and was immediately used in the next step.

Methyl 2-(2-Aminobenzoylamino)benzoate (19)

To a stirred soln of freshly prepared *N*-sulfinylanthraniloyl chloride (**18**; 6.027 g, 30 mmol) in toluene (60 mL) at r.t. under N₂ atmosphere was added methyl anthranilate (**13**; 3.48 g, 23.1 mmol) in toluene (60 mL) dropwise over 10 min, and the mixture was maintained at r.t. for 48 h. After completion of the reaction, the mixture was diluted with cold H₂O (150 mL) and extracted with CH₂Cl₂ (2 × 150 mL). The combined organic phases were washed with 10% aq NaHCO₃ (2 × 75 mL), followed by H₂O (50 mL) and brine (30 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford a solid residue, which was purified by column chromatography on silica gel (hexane–EtOAc, 98:2) to give **19** as a light yellow solid; yield: 3.241 g (40%); mp 115–116 °C (Lit.^{11b} 116–117 °C).

IR (KBr): 3472, 3356 (amine), 3028, 2940, 1727, 1668 (amide), 1582, 1520, 1444 (aromatic C=C), 1301, 1258, 1164, 1095, 968, 899, 753, 651 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 3.95 (s, 3 H, CO₂CH₃), 5.78 (br s, 2 H, NH₂), 6.63–6.75 (m, 2 H), 6.98–7.05 (m, 1 H), 7.17–7.24 (m, 1 H), 7.53–7.59 (m, 1 H), 7.68–7.71 (dd, *J* = 1.5, 1.5 Hz, 1 H), 8.01–8.04 (dd, *J* = 1.5, 1.5 Hz, 1 H), 8.24–8.87 (dd, *J* = 1.5, 1.5 Hz, 1 H), 11.83 (s, 1 H, CONH).

ESI-MS: $m/z = 271 [M^+ + H]$.

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22. Found: C, 66.68; H, 5.18.

Methyl 2-(2-{[*N*-(*tert*-Butoxycarbonyl)-L-prolyl]amino}benzoylamino)benzoate (9)

To a stirred soln of methyl 2-(2-aminobenzoylamino)benzoate (**19**; 0.650 g, 2.41 mmol), HOBt (0.390 g, 2.89 mmol) and *N*-(*tert*-but-oxycarbonyl)-L-proline (**14**; 0.517 g, 2.41 mmol) in anhyd THF (25 mL) at 0 °C under N₂ atmosphere was added DCC (0.596 g, 2.89 mmol), and the mixture was maintained at 0 °C for 1 h and at r.t. for 8 h. After completion of the reaction, the separated *N*,*N*'-dicyclohexylurea was filtered off and the filtrate was concentrated. The resulting residue was dissolved in a mixture of EtOAc (100 mL) and

10% aq NaHCO₃ (50 mL). The organic layer was separated and washed with 10% aq citric acid (50 mL), followed by 10% aq NaHCO₃ (50 mL) and H₂O (50 mL), then dried (Na₂SO₄), concentrated and purified by column chromatography on silica gel (hexane–EtOAc, 8:2) to give **9** as a syrup; yield: 0.733 g (65%).

 $[\alpha]_{D}^{20}$ –101.36 (*c* 2.43, CHCl₃).

IR (KBr): 3262 (amide NH), 2975, 1702 (amide), 1585, 1520, 1438 (aromatic C=C), 1384, 1266, 1163, 1128, 1049, 957, 894, 756, 696, 665 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 1.30–1.46 [br s, 9 H, CO₂C(CH₃)₃], 1.82–2.40 (m, 4 H, H-3',4'), 3.42–3.62 (m, 1 H, H-5'), 3.76–3.78 (m, 1 H, H-5'), 3.98 (s, 3 H, CO₂CH₃), 4.21–4.43 (m, 1 H, H-2'), 7.18–7.21 (m, 2 H), 7.50–7.70 (m, 2 H), 7.84–7.86 (m, 1 H), 8.08 (d, *J* = 7.5 Hz, 1 H), 8.73–8.96 (m, 2 H), 11.80 (s, 1 H, NH), 12.10 (br s, 1 H, NH).

ESI-MS: $m/z = 468 [M^+ + H]$.

Anal. Calcd for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25. Found: C, 64.15; H, 6.18.

Methyl 2-[2-(L-Prolylamino)benzoylamino]benzoate (20)

To a stirred soln of methyl 2-(2-{[N-(*tert*-butoxycarbonyl)-L-prolyl]amino}benzoylamino)benzoate (**9**; 0.234 g, 0.5 mmol) in anhyd CH₂Cl₂ (10 mL) was added I₂ (0.380 g, 1.5 mmol), followed by HMDS (0.242 g, 1.5 mmol, 3.0 equiv), under N₂ atmosphere at r.t. The reaction mixture was stirred at the same temperature for 48 h. After completion of the reaction, the mixture was diluted with CH₂Cl₂ (50 mL) and the organic layer was washed with 5% aq Na₂S₂O₃·5H₂O (3 × 25 mL), followed by H₂O (25 mL) and brine (25 mL), and then dried (Na₂SO₄). Then, the organic layer was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (EtOAc) to give **20** as a brownish yellow solid; yield: 0.168 g (90%); mp 119–120 °C. (The expected quinazolinone derivative **11**, however, was not obtained.)

IR (KBr): 3317, 3264, 3211 (amide NH), 2947, 2869, 1693, 1664 (amide), 1584, 1509, 1437 (aromatic C=C), 1296, 1268, 747, 691, 660 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): $\delta = 1.69-1.85$ (m, 2 H, H-3'), 2.00–2.24 (m, 2 H, H-4'), 3.12–3.14 (m, 2 H, H-5'), 3.84–3.87 (m, 1 H, H-2'), 3.95 (s, 3 H, CO₂CH₃), 7.09–7.20 (m, 2 H), 7.50 (t, *J* = 8.3 Hz, 1 H), 7.60 (t, *J* = 9.1 Hz, 1 H), 7.81 (dd, *J* = 6.0, 1.5 Hz, 1 H), 8.06 (dd, *J* = 6.0, 1.5 Hz, 1 H), 8.70 (d, *J* = 8.3 Hz, 1 H), 8.87 (d, *J* = 8.3 Hz, 1 H), 11.96 (br s, 2 H).

¹³C NMR (75 MHz, CDCl₃): δ = 26.06, 31.11, 47.32, 52.48, 61.69, 99.93, 120.52, 121.66, 122.85, 123.26, 127.12, 130.93, 132.57, 134.63, 139.17, 141.38, 167.21, 174.69, 175.07.

ESI-MS: $m/z = 368 [M^+ + H]$.

Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76. Found: C, 65.45; H, 5.84.

Isatoic Anhydride (22)

To a stirred suspension of anthranilic acid (**21a**; 5.0 g, 36.5 mmol) in ethyl chloroformate (35.181 mL, 368.28 mmol), Et₃N (5.09 mL, 36.50 mmol) was added dropwise over 10 min at r.t. The reaction mixture was stirred at the same temperature for 18 h and then refluxed at 100 °C for 4 h. After completion of the reaction, the mixture was cooled and the clear solution was diluted with benzene (30 mL). The separated solid was collected by filtration and recrystallized (EtOH, 40 mL) to afford **22** as a white solid; yield: 4.643 g (78%); mp 232–233 °C (Lit.^{18a} 233 °C).

¹H NMR (200 MHz, CDCl₃ + DMSO- d_6): δ = 7.18 (t, J = 8.0 Hz, 2 H), 7.61 (t, J = 7.3 Hz, 1 H), 7.95 (dd, J = 6.5, 1.4 Hz, 1 H), 11.67 (br s, 1 H, NH).

ESI-MS: $m/z = 164 [M^+ + H]$.

Anal. Calcd for $C_8H_5NO_3$: C, 58.90; H, 3.09. Found: C, 58.82; H, 3.15.

(+)-2,3-Dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-dione (23)

A mixture of isatoic anhydride (**22**; 2.0 g, 12.26 mmol) and L-proline (1.552 g, 13.49 mmol) in DMSO (6.5 mL) was heated in an oil bath at 120 °C for 4 h. After completion of the reaction, the clear mixture was cooled to r.t. and diluted with H₂O (200 mL). The separated solid was collected by filtration and washed with H₂O (2×10 mL) to give **23** as a cream white solid; yield: 2.171 g (82%); mp 220–222 °C (Lit.¹⁹ 220–222 °C).

 $[\alpha]_{D}^{20}$ +524.10 (c 1.0, MeOH) {Lit.¹⁹ [α]_D +523.00 (c 1.0, MeOH)}.

 $R_f = 0.50 (CH_2Cl_2 - EtOAc, 5:1).$

IR (KBr): 3438, 3248 (amide NH), 2975, 2945, 2870, 1677, 1629 (amide), 1481, 1444, 1414 (aromatic C=C), 1392, 1287, 1264, 846, 798, 759, 700, 663 cm⁻¹.

¹H NMR (300 MHz, $CDCl_3$): $\delta = 2.01-2.04$ (m, 3 H), 2.75–2.77 (m, 1 H), 3.60–3.82 (m, 2 H), 4.07 (d, J = 6.0 Hz, 1 H), 7.05 (d, J = 8.3 Hz, 1 H), 7.29–7.31 (m, J = 8.3 Hz, 1 H), 7.49 (t, J = 9.1 Hz, 1 H), 8.01 (d, J = 8.3 Hz, 1 H), 9.00 (s, 1 H, NH).

¹³C NMR (75 MHz, CDCl₃): δ = 23.42, 26.16, 47.23, 56.64, 121.08, 124.85, 126.97, 130.96, 132.31, 135.44, 165.40, 171.38.

ESI-MS: $m/z = 217 [M^+ + H]$.

HRMS (ESI): m/z calcd for $C_{12}H_{13}N_2O_2$: 217.0977 [M⁺ + H], $C_{12}H_{12}N_2NaO_2$: 239.0796 [M⁺ + Na]; found: 217.0972 [M⁺ + H], 239.0788 [M⁺ + Na].

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59. Found: C, 66.72; H, 5.68.

2-Azido-5-methoxybenzoic Acid (24b)

To a stirred suspension of 2-amino-5-methoxybenzoic acid (**21b**; 1.00 g, 5.98 mmol) in a mixture of concd HCl (1.25 mL) and H₂O (5 mL) at -5 °C was added a precooled soln of NaNO₂ (0.450 g, 6.52 mmol) in H₂O (1.2 mL) dropwise over 5 min. The mixture was stirred at -5 to 0 °C for 30 min, and then urea (0.450 g, 7.5 mmol) was added to destroy the excess nitrous acid. After 3 min at 0 °C, a precooled soln of NaN₃ (0.460 g, 7.08 mmol) in H₂O (1.25 mL) was added dropwise over 5 min at -5 to 0 °C. After 10 min at -5 to 0 °C, stirring of the clear reaction mixture was continued at r.t. overnight. The precipitated solid was collected by filtration, washed with cold H₂O (2 × 5 mL) and dried to give **24b** as a cream white solid; yield: 1.095 g (95%); mp 107–108 °C.

IR (KBr): 2943, 2658 (acid), 2125 (azide), 2086, 1703, 1672, 1610 (acid), 1571, 1499, 1449 (aromatic C=C), 1301, 1272, 1228 (ether), 1074, 1034, 913, 881, 814, 750, 658 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 3.86 (s, 3 H, OCH₃), 7.10–7.19 (m, 2 H, H-3,4), 7.58 (d, J_{meta} = 2.26 Hz, 1 H, H-6).

¹³C NMR (75 MHz, CDCl₃): δ = 55.73 (OCH₃), 116.60 (C-2), 120.81, 121.40, 132.48, 156.60, 168.23 (CO₂H).

EI-MS: m/z (%) = 193 (4.3) [M⁺], 165 (20.43), 149 (9.67), 134 (6.45), 121 (60.21), 106 (100), 85 (9.67), 78 (38.70), 63 (23.65), 43 (96.77), 41 (27.95), 40 (10.75).

Anal. Calcd for $C_8H_7N_3O_3$: C, 49.74; H, 3.65. Found: C, 49.66; H, 3.72.

10-(2-Azido-5-methoxybenzoyl)-2,3-dihydro-1*H*-benzo[*e*]pyr-rolo[1,2-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-dione (12b)

To a soln of Et_3N (0.524 g, 5.18 mmol, 1.25 equiv) and DMAP (0.354 g, 2.90 mmol, 0.7 equiv) in anhyd THF (8.0 mL) was slowly added dilactam **23** (0.895 g, 4.14 mmol, 1.0 equiv) at 0 °C under N₂ atmosphere. The mixture was stirred at the same temperature for 1

h. To the reaction mixture was added 2-azido-5-methoxybenzoyl chloride (**25b**; 1.093 g, 5.18 mmol, 1.25 equiv), which was prepared from 2-azido-5-methoxybenzoic acid (**24b**; 1.0 g, 5.18 mmol) and SOCl₂ (3.16 mL, 43.4 mmol) at 80 °C for 2 h, in THF (5 mL) at 0 °C. The mixture was stirred at the same temperature for 30 min and then at r.t. for 1 h. The solvent was evaporated and the resulting residue was dissolved in CH₂Cl₂ (100 mL). The organic layer was washed with H₂O (2×60 mL), dried (Na₂SO₄) and concentrated under reduced pressure to give **12b** (1.793 g) as a gummy brownish yellow syrup, which was dissolved in anhyd benzene (25 mL) and immediately used for the next step.

 $R_f = 0.61$ (CH₂Cl₂-EtOAc, 5:1).

(5b*S*)-2-Methoxy-5b,6,7,8-tetrahydro-10*H*,16*H*-pyrrolo[2,1*c*]quinazolino[3,2-*a*][1,4]benzodiazepine-10,16-dione [(*S*)-(-)-Circumdatin H, 7]

To a stirred soln of imide derivative **12b** (1.793 g) in anhyd benzene (25 mL) was added Bu₃P (0.889 g, 4.397 mmol) in one portion under N₂ atmosphere at r.t. The mixture was refluxed at 60 °C for 1 h and then left at r.t. overnight. After completion of the reaction, the solvent was evaporated and the resulting residue was dissolved in CH₂Cl₂ (150 mL). The organic layer was washed with 0.5 N aq HCl (3×60 mL) followed by brine (2×30 mL), and then dried (Na₂SO₄) and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (CH₂Cl₂-EtOAc, 5:1) to give (-)-**7** as a cream white solid; yield: 1.047 g (73% over two steps starting from **23**); mp 218–219 °C.

 $[\alpha]_{D}^{20}$ –35.4 (*c* 0.1, MeOH) {Lit.⁷ $[\alpha]_{D}^{20}$ –26.33 (*c* 0.078, MeOH)}.

 $R_f = 0.56 (CH_2Cl_2 - EtOAc, 5:1).$

IR (KBr): 3066, 2972, 1690, 1648, 1617 (amide), 1491, 1457, 1420 (aromatic C=C), 1361, 1275, 1235 (ether), 1023, 875, 832, 785, 759, 705 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): $\delta = 1.98-2.40$ (m, 3 H, H-20b,21a,21b), 3.14–3.16 (m, 1 H, H-20a), 3.60–3.62 (m, 1 H, H-22a), 3.77–3.79 (m, 1 H, H-22b), 3.93 (s, 3 H, OCH₃), 4.50 (d, J = 6.2 Hz, 1 H, H-19), 7.32 (dd, J = 6.2, 2.3 Hz, 1 H, H-14), 7.46–7.58 (m, 4 H, H-5,6,7,15), 7.61 (d, J = 3.1 Hz, 1 H, H-12), 7.98 (d, J = 6.2 Hz, 1 H, H-4).

¹³C NMR (75 MHz, CDCl₃): δ = 23.62 (C-21), 26.93 (C-20), 46.42 (C-22), 55.77 (OCH₃), 58.71 (C-19), 106.88 (C-12), 122.25 (C-11), 124.70 (C-14), 128.34 (C-7), 128.53 (C-5), 129.09 (C-15), 129.82 (C-4), 130.61 (C-6), 132.36 (C-3), 133.33 (C-8), 140.49 (C-16), 151.43 (C-18), 158.89 (C-13), 161.54 (C-10), 164.42 (C-2).

DEPT-¹³C NMR (75 MHz, CDCl₃): $\delta = 23.62$ (*C*H₂-21), 26.93 (*C*H₂-20), 46.42 (*C*H₂-22) (below the base line), 55.77 (OCH₃), 58.71 (*C*H-19), 106.88 (*C*H-12), 124.70 (*C*H-14), 128.34 (*C*H-7), 128.53 (*C*H-5), 129.09 (*C*H-15), 130.61 (*C*H-6) (above the base line).

EI-MS: m/z (%) = 347 (93.54) [M⁺], 322 (3.22), 306 (3.22), 280 (21.50), 279 (100), 263 (16.12), 236 (8.60), 221 (3.22), 207 (11.82), 179 (8.60), 160 (2.68), 149 (13.97), 139 (25.80), 120 (10.75), 102 (15.05), 90 (10.75), 77 (16.66), 63 (16.13), 45 (32.25), 41 (23.11), 40 (3.76).

ESI-MS: $m/z = 348 [M^+ + H]$.

HRMS (ESI): m/z calcd for $C_{20}H_{18}N_3O_3$: 348.1348 [M⁺ + H], $C_{20}H_{17}N_3NaO_3$: 370.1168 [M⁺ + Na]; found: 348.1328 [M⁺ + H], 370.1150 [M⁺ + Na].

Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93. Found: C, 69.08; H, 4.97.

2-Azidobenzoic Acid (24a)

To a stirred suspension of anthranilic acid (**21a**; 5.0 g, 36.5 mmol) in a 1:1 mixture of H_2O (63 mL) and concd HCl (63 mL) at -5 °C

was added a precooled soln of NaNO₂ (2.375 g, 34.42 mmol) in H₂O (32 mL) dropwise over 5 min, and the mixture was maintained at -5 to 0 °C for 15 min. The cold reaction mixture was filtered on a precooled Büchner funnel at -10 °C and the clear filtrate was added to a magnetically stirred soln of NaN₃ (2.10 g, 32.30 mmol) and NaOAc·3H₂O (52.5 g, 385.8 mmol) in H₂O (63 mL) at -5 °C over 5 min. After 10 min at -5 °C, the reaction mixture was allowed to attain r.t. over 90 min and the separated solid was collected by filtration, washed with H₂O (2 × 25 mL) and dried to give **24a** as a white solid; yield: 4.57 g (77%); mp 144–145 °C.

IR (KBr): 2962, 2821, 2646 (acid), 2105 (azide), 1696 (acid), 1595, 1574, 1485, 1454, 1410 (aromatic C=C), 1268, 1074, 918, 748, 688 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.21–7.25 (m, 2 H), 7.58 (t, *J* = 7.3 Hz, 1 H), 8.08 (d, *J* = 7.3 Hz, 1 H).

EI-MS: m/z (%) = 163 (2.68) [M⁺], 149 (2.15), 135 (19.35), 119 (6.98), 107 (16.12), 90 (9.67), 79 (100), 63 (45.16), 52 (67.74), 40 (6.98).

Anal. Calcd for $C_7H_5N_3O_2$: C, 51.54; H, 3.09. Found: C, 51.57; H, 3.05.

10-(2-Azidobenzoyl)-2,3-dihydro-1*H*-benzo[*e*]pyrrolo[1,2*a*][1,4]diazepine-5,11(10*H*,11a*H*)-dione (12a)

To a soln of Et₃N (0.585 g, 5.79 mmol, 1.25 equiv) and DMAP (0.395 g, 3.24 mmol, 0.7 equiv) in anhyd THF (8.0 mL) was slowly added dilactam **23** (1.0 g, 4.63 mmol, 1.0 equiv) at 0 °C under N₂ atmosphere. The mixture was stirred at the same temperature for 1 h. To the reaction mixture was added 2-azidobenzoyl chloride (**25a**; 1.05 g, 5.79 mmol, 1.25 equiv), which was prepared from 2-azidobenzoic acid (**24a**; 0.943 g, 5.79 mmol) and SOCl₂ (3.536 mL, 48.48 mmol) at 80 °C for 2 h, in THF (5 mL) at 0 °C. The mixture was stirred at the same temperature for 30 min and then at r.t. for 1 h. The solvent was evaporated and the resulting residue was dissolved in CH₂Cl₂ (100 mL). The organic layer was washed with H₂O (2 × 60 mL), dried (Na₂SO₄) and concentrated under reduced pressure to give **12a** (1.80 g) as a gummy brownish yellow syrup, which was dissolved in anhyd benzene (25 mL) and immediately used for the next step.

 $R_f = 0.61 \text{ (CH}_2\text{Cl}_2\text{-EtOAc}, 5:1).$

(S)-(-)-13-Desmethoxycircumdatin H (7a)

To a stirred soln of imide derivative **12a** (1.803 g) in anhyd benzene (25 mL) was added Bu₃P (0.889 g, 4.397 mmol) in one portion under N₂ atmosphere at r.t. The mixture was refluxed at 60 °C for 1 h and then left at r.t. overnight. After completion of the reaction, the solvent was evaporated and the resulting residue was dissolved in CH₂Cl₂ (150 mL). The organic layer was washed with 0.5 N aq HCl (3×40 mL) followed by brine (2×25 mL), and then dried (Na₂SO₄) and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (CH₂Cl₂–EtOAc, 5:1) to give (–)-**7a** as a cream white solid; yield: 1.139 g (78% over two steps starting from **23**); mp 250–251 °C.

 $[\alpha]_{D}^{20}$ –124.60 (*c* 0.5, MeOH).

 $R_f = 0.55 (CH_2Cl_2 - EtOAc, 5:1).$

IR (KBr): 2924, 2878, 1689, 1641, 1610 (amide), 1448, 1410 (aromatic C=C), 1360, 1334, 1293, 1210, 1154, 1112, 1082, 1082, 1020, 966, 876, 827, 780, 699 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): $\delta = 1.98-2.45$ (m, 3 H, H-20b,21a,21b), 3.12–3.15 (m, 1 H, H-20a), 3.50–3.86 (m, 2 H, H-22a,22b), 4.53 (d, J = 5.9 Hz, 1 H, H-19), 7.46–7.59 (m, 4 H, H-5,6,7,14), 7.74–7.80 (m, 2 H, H-13,15), 7.98 (d, J = 6.6 Hz, 1 H, H-12), 8.29 (d, J = 8.1 Hz, 1 H, H-4).

¹³C NMR (75 MHz, CDCl₃): δ = 23.61, 29.57, 46.42, 58.82 (C-19), 121.42, 127.32, 127.44, 127.53, 128.29, 129.83, 130.64, 132.30, 133.14, 134.66, 146.04, 153.53 (C-18), 161.59 (C-2), 164.30 (C-10).

ESI-MS: $m/z = 318 [M^+ + H]$.

HRMS (ESI): m/z calcd for $C_{19}H_{16}N_3O_2$: 318.1243 [M⁺ + H], $C_{19}H_{15}N_3NaO_2$: 340.1062 [M⁺ + Na]; found: 318.1247 [M⁺ + H], 340.1037 [M⁺ + Na].

Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76. Found: C, 71.85; H, 4.82.

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