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Low-Valent Titanium-Mediated Enantioselective Synthesis of Quinazolinone Alkaloids Circumdatins F, H, and Analogs

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We report the concise and protecting-group-free enantioselective total syntheses of circumdatins F and H. In view of the extreme importance of analogs of quinazolinone alkaloids in drug research and discovery, four analogs of bioactive quinazolinobenzodiazepine alkaloids, including demethoxycircumdatin H (**12**) and *N*-demethylbenzomalvin A (**13**), have been synthesized. The method is based on the low-valent titanium-promoted intramolecular reductive coupling of imides with *o*-nitrobenzimides, which yielded quinazolino[3,2-*a*][1,4]benzodiazepines under mild conditions. In addition, heptacyclic dehydraasperlicin E (**16**) has been synthesized from asperlicin C by a NCS-mediated dehydra-cyclization reaction.

Keywords synthetic methods, natural products, low-valent titanium, protecting-group-free, total synthesis

Introduction

Since the isolation of (+)-febrifugine (**1**) (Figure 1) from Chinese medicinal plant *Dichroa febrifuga* Lour. (Chang Shan) in the late 1940s,[1] the chemical and medicinal studies towards quinazolinone alkaloids have attracted considerable attention.[2] About 250 quinazolinone alkaloids have been isolated from natural sources.[2c] Among them, a sub-class are characterized by the fused quinazolinobenzodiazepine ring system, which include asperlicins A−E[3] [cf. Figure 1 for asperlicins C (**2**) and E (**3**)], benzomalvins A−C [cf. Figure 1 for benzomalvin A (**4**)],[4] and circumdatins A−H [cf. Figure 1 for circumdatins F (**5**) and H (**6**)].[5] Asperlicin E (**3**) is a non-peptidal antagonist of the gastrointestinal hormone neurotransmitter cholecystokinin (CCK) isolated from the fermentation broths produced by *Aspergillus alliaceus*.[3c-3e] Benzomalvin A (**4**) is a substance P inhibitor isolated from the culture broth of a *Penicillium* sp.[4] Circumdatin F[5a] (**5**) and circumdatin H[5d] (**6**) are two quinazolinobenzodiazepine alkaloids isolated from culture extracts of a terrestrial strain of the fungus *Aspergillus ochraceus*. Circumdatin H (**6**) showed slightly higher biological activity than circumdatin E (**7**) as inhibitor of the mammalian mitochondrial respiratory chain, with an IC_{50} value of (1.5±0.1) μmol/L in inhibiting the integrated electron transfer chain (NADH oxidase activity), and with an IC_{50} of 4.4 nmol/L as a respiratory inhibitor.[5d] Structurally, this class of natural products are quite interesting because they combine two pharmacophores into a molecule, namely, quinazoline and [1,4]-benzodiazepine.[6] [1,4]-Benzodiazepines are among the most commonly

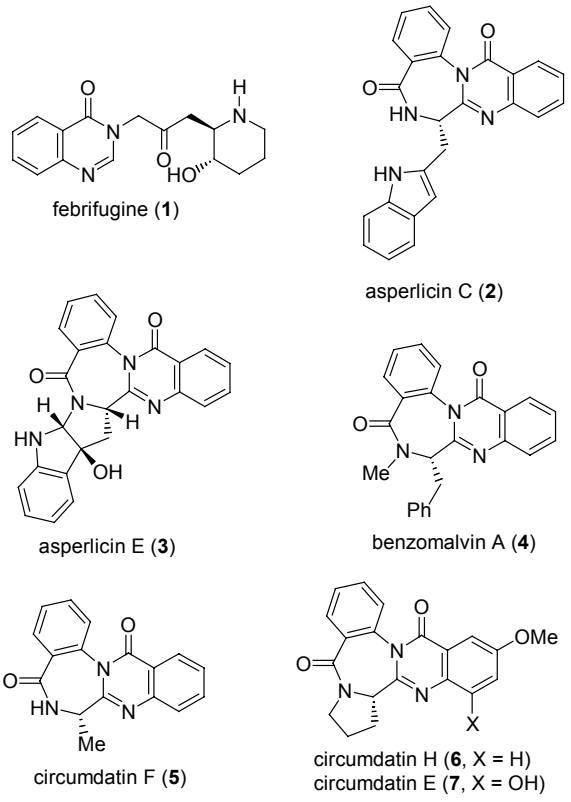

Figure 1 Some quinazolinone alkaloids.

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prescribed depressant medications in the United States today. It is not surprising that quinazolinobenzodiazepine alkaloids exhibit diverse biological profile including CCK receptor antagonism,[3] inhibition of substance P[4] and mitochondrial NADH oxidase.[5d] The unique structural feature and important biological activities of these alkaloids have attracted the attention of chemists and medicinal chemists, which resulted in a number of elegant enantioselective total syntheses,[7-12] and resulted in the development of more than 50 quinazolinone derivatives with diverse bioactivities for clinical use.[2c]

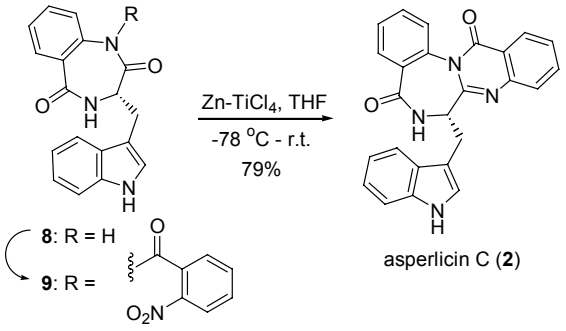
In connection with our interest in the syntheses of bioactive natural products and analogs,[13] and in the development of step economical synthetic methodologies,[14] we recently accomplished two enantioselective total syntheses[15] of the hexacyclic quinazolinone alkaloids (−)-chaetominine, asperlicin C (**2**), and heptacyclic alkaloid asperlicin E (**3**).[16] In view of the importance of analogs of quinazolinone alkaloids in drug R & D, and as an extension of the abovementioned work,[16] we undertook an investigation on the low-valent titanium-mediated reductive cyclization reaction-based enantioselective total syntheses of circumdatin F (**5**), circumdatin H (**6**), and five analogs, including demethoxycircumdatin H (**12**), *N*-demethyl-benzomalvin A (**13**) and dehydra-asperlicin E (**16**).

Results and Discussion

One of the most popular method for the construction of [1,4]benzodiazepine skeleton resides in the condensation of isatoic anhydride **10** with an *α*-amino acid to produce the benzodiazepinedione **11**.[2c,7a,17] For the implementation of the fused quinazolino moiety,[18] three tactics were adopted, namely, (1) the stepwise method via thioamide intermediates,[7a] (2) the intramolecular aza-Wittig reaction of an azidobenzene precursor (the Eguchi method),[7b,9a,10a,11,19] and (3) the reductive cyclization of an imido nitrobenzene using the modern version[20] of the Asahina/Ohta[21]-Levy/Stephen[22]-Mumm method.[23] Although the reductive cyclization using Zn/AcOH gave excellent enantioselectivity in the total syntheses of circumdatins E, H and J,[10c] it led to complete racemization in an attempted total syntheses of (−)-auranomide C.[12g] On the other hand, the same transformation by Pd/C-catalyzed hydrogenation has also been reported. Curiously, optical rotation data of the products have not been reported.[7e] Thus, the problem of racemization became the major concern for the total syntheses of quinazolinone alkaloids.

In our previous syntheses of asperlicins C (**2**) and E (**3**),[16] racemization-free conditions have been established for both the regio- and chemoselective acylation of **8** to give **9**, and the low-valent titanium (LVT)[24,25]-based reductive cyclization of **9** to give asperlicin C (**2**) (Scheme 1). Thus, this approach was adopted for the syntheses of quinazolinone alkaloids circumdatin F (**5**), circumdatin H (**6**), and analogs.

Scheme 1 The key steps in the synthesis of asperlicin C (**2**)

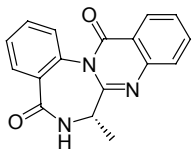
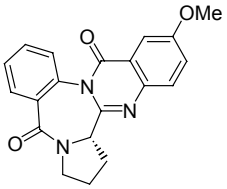
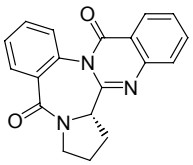
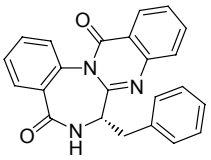
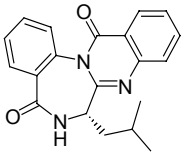
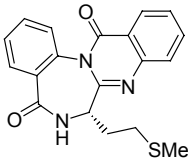


Our synthesis started with the known condensation reaction of isatoic anhydride **10** with L-amino acids.[7a,16] Treatment of commercially available isatoic anhydride **10** with different L-amino acids (L-Ala: Entry 1; L-Pro: Entries 2, 3; L-Phe: Entry 4; L-Leu, Entry 5; L-Met: Entry 6) in the presence of triethylamine followed by refluxing the resulting intermediates in glacial acetic acid produced, in one-pot, the corresponding benzodiazepines **8a**—**8f** in 63%—94% yields (Scheme 2, Table 1, column 2). For the selective *o*-nitrobenzoylation at the more acidic N^1 position,[7b,9a,26] the conditions that we established previously[16] were adopted. In the event, treatment of benzodiazepine **11a** with 2.0 equiv. of Et_3N, a catalytic amount of DMAP (＜5% equiv.) and 1.3 equiv. of *o*-nitrobenzoyl chloride at −20 ℃ for 24 h, gave the imide **9a** in 83% yields. It is worth noting that the acylation of compound **9b** [R^1, R^2=$(CH_2)_3$, R^3= OMe, Entry 2] needed to be run at −5 ℃, while the reactions of benzodiazepines **8bc**—**8f** proceeded smoothly at −20 ℃ to give the corresponding imides **9c**—**9f** in 76%—93% yields.

We next addressed the key reductive cyclization reaction. Our first targets were circumdatin F[5a] (**5**) and circumdatin H[5d] (**6**). According to the LVT-mediated reductive cyclization procedure established for the synthesis of asperlicin C (**2**),[16] compound **9a** was treated with 4.0 molar equiv. of $TiCl_4$/Zn at −78 ℃ for 6 h, then at r.t. for 48 h, which yielded circumdatin F (**5**) in an 86% yield (Entry 1). The spectral data of our synthetic products are in agreement with those reported.[9,27] Following the same procedure, compound **9b** was converted into circumdatin H (**6**) in an 83% yield (Entry 2). The spectral data (^{1}H and ^{13}C NMR) of our synthetic product matched those reported for circumdatin H (**6**).[5d,10]

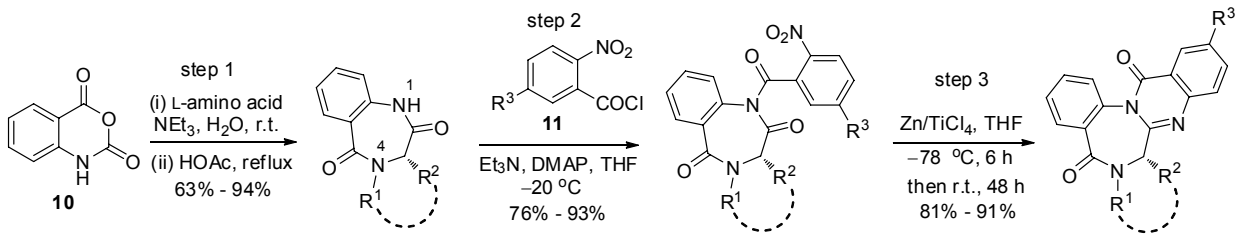
In view of the exhibited higher inhibitory activity of circumdatin H (**6**), which can be viewed as a dehydroxy analog of circumdatin E (**7**), towards mitochondrial NADH oxidase compared with that of the latter,[5d] the synthesis of the demethoxy analog of circumdatin E (**12**) was envisaged. Thus, compound **9c** was subjected to the LVT-mediated reductive cyclization reaction, which afforded demethoxycircumdatin E (**12**) in 90% (Entry 3).

Table 1 Results of the syntheses of quinazolino [3,2-*a*][1,4]benzodiazepine natural products and analogs

Entry	Amino acid (product **8**, yield/%)[a]	Product **9** (R^3, yield/%)[a]	Quinazolinobenzodiazepine (yield/%)[a]
1	**8a** (L-Ala, R^1=H, R^2=CH_3, 68)	**9a** (R^3=H, 83)	 circumdatin F (**5**) (86)
2	**8bc** (L-Pro, R^1, R^2=$CH_2CH_2CH_2$, 94)	**9b** (R^3=OMe, 76)	 circumdatin H (**6**) (83)
3	**8bc** (L-Pro, R^1, R^2=$CH_2CH_2CH_2$, 94)	**9c** (R^3=H, 93)	 demethoxy-circumdatin H (**12**) (90)
4	**8d** (L-Phe, R^1=H, R^2=Bn, 81%)	**9d** (R^3=H, 84)	 *N*-demethyl-benzomalvin A (**13**) (85)
5	**8e** (L-Leu, R^1=H, R^2=*i*-Bu, 63)	**9e** (R^3=H, 78)	 **14** (91)
6	8f (L-Met, R^1=H, R^2=$CH_2CH_2SCH_3$, 93)	**9f** (R^3=H, 76)	 **15** (81)

[a] Isolated yield.

Scheme 2 Synthetic approach to quinazolinobenzodiazepines



a, **c** - **f**: L-amino acid: **a**. Ala; **c**. Pro; **d**. Phe; **e**. Leu; **f**. Met; with **11a** (R = H); **b**: L-amino acid = Pro with **11b** (R = OMe)

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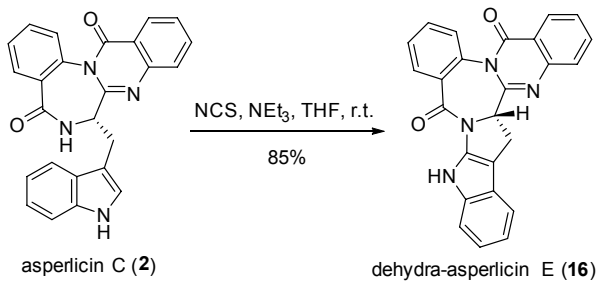
Next, we addressed the synthesis of *N*-demethylbenzomalvin A (**13**), an analog of benzomalvin A.[4] By following the same procedure, compound **9d** was converted to *N*-demethylbenzomalvin A (**13**) in a good yield of 85% (Entry 4). By the same procedure, two other analogs of quinazolinobenzodiazepine alkaloids **14** and **15** were prepared from **9e** and **9f** in 91% (Entry 5) and 81% yield (Entry 6), respectively.

Finally, we were interested in the synthesis of structurally complex heptacyclic dehydraasperlicin E (**16**) as an analog of asperlicin E (**3**). To this end, asperlicin C (**2**)[16] was treated with NCS-NEt_3 in THF at r.t.,[28] which produced regioselectively compound **16** in 85% yield (Scheme 3).

Scheme 3 Synthesis of dehydraasperlicin E (**16**)



asperlicin C (**2**) dehydra-asperlicin E (**16**)

Conclusions

In summary, on the basis of the LVT-mediated reductive cyclization reaction, we have achieved the highly enantioselective three-step syntheses of two natural products circumdatin F, circumdatin H, and four analogs of quinazolino[3,2-*a*][1,4]benzodiazepine alkaloids. In addition, on the basis of our previous synthesis of asperlicin C (**2**), the synthesis of compound **16** has been achieved in four steps from L-Trp. Through this work, it is reasonable to assume that the racemization-free LVT-mediated reductive cyclization reaction is applicable to the syntheses of quinazolino[3,2-*a*][1,4]-benzodiazepine alkaloids and analogs.

Experimental

General methods

Optical rotations were measured with a Perkin-Elmer 341 automatic polarimeter or an Anton Paar MCP 500 polarimeter. Melting points were determined on a Büchi M560 Automatic Melting Point apparatus. Infrared spectra were recorded with a Nicolet Avatar 330 FT-IR spectrometer using film or KBr pellet technique. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Silica gel (300－400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60－90 ℃) mixture. DMSO was pre-dried over calcium hydride. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

General procedure (A) for the preparation of compounds 8a－8f

To a mixture of isatoic anhydride (5.19 g) and 30.0 mmol of an L-amino acid were added 4.2 mL of practical-grade triethylamine and 30 mL of water. The reaction mixture was stirred at room temperature for 5 h and then concentrated under reduced pressure. The residue was dissolved in 60 mL of glacial acetic acid and refluxed for 4.5 h. After being cooled, the acetic acid was removed under reduced pressure, and the resulting residue was neutralized with a saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with EtOAc (30 mL× 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was recrystallized with EtOAc/hexane and washed with ether, which gave the desired compound.

(*S*)-3-Methyl-3,4-dihydro-1*H*-benzo[1,4]diazepine-2,5-dione (8a) Following the general procedure A, the reaction of isatoic anhydride **10** with L-Ala gave the known compound[1b] **8a** (yield: 68%) as a white solid. m.p. 276－279 ℃ (EtOAc); the aged sample has a m.p. 334－335 ℃ (EtOAc) [lit. 336－337 ℃,[1e] 332 ℃,[1g] 275－278 ℃[17c]]; $[\alpha]_D^{20}$ +468.7 (*c* 1.0, DMSO); $[\alpha]_D^{26}$ +426.1 (*c* 0.5, MeOH) {lit. $[\alpha]_D^{26}$ +421 (*c* 0.5, MeOH)[1f]}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.37 (s, 1H, PhN**H**CO), 8.39 (d, J=5.1 Hz, 1H, PhCON**H**), 7.76－7.72 (m, 1H, Ar**H**), 7.53－7.46 (m, 1H, Ar**H**), 7.24－7.06 (m, 2H, Ar**H**), 3.80 (dq, J=6.8, 5.1 Hz, 1H, COC**H**N), 1.23 (d, J=6.8 Hz, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 173.1, 168.6, 137.7, 133.1, 131.3, 127.2, 124.7, 121.8, 48.2, 14.7; IR (film) ν_{max}: 3255, 2967, 1693, 1624, 1480, 1446, 1413, 1259, 1064, 761, 701 cm^{-1}; MS (ESI) *m/z* 213 (M+Na$^+$, 100%).

(*S*)-2,3-Dihydro-1*H*-benzopyrrolo[1,2][1,4]diazepine-5,11(10*H*,11a*H*)-dione (8bc) Following the general procedure A, the reaction of isatoic anhydride **10** with L-Pro gave the known compound[1b] **8bc** (yield: 94%) as a white solid. m.p. 216－218 ℃ (EtOAc); the aged sample has a m.p. 219－221 ℃ (EtOAc) [lit. 218－219 ℃,[18n] 220－222 ℃[1b]]; $[\alpha]_D^{20}$ +550.8 (*c* 1.0, DMSO); the aged sample has a $[\alpha]_D^{25}$ +524.2 (*c* 1.0, MeOH) {lit. $[\alpha]_D^{25}$ +524.1 (*c* 1.0, MeOH)[10a]}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.49 (s, 1H, PhN**H**CO), 7.82－7.76 (m, 1H, Ar**H**), 7.53－7.47 (m, 1H, Ar**H**), 7.24－7.12 (m, 2H, Ar**H**), 4.13－4.08 (m, 1H, COC**H**N), 3.63－3.55 (m, 1H, NC**H**$_2$), 3.49－3.41 (m, 1H, NC**H**$_2$), 2.54－2.45 (m, 1H, NCH$_2$C**H**$_2$), 2.01－1.72 (m, 3H, C**H**$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 171.7, 165.5, 137.3, 133.0, 131.2, 127.5, 124.8, 122.2, 57.2, 47.8, 26.7, 24.0; IR (film) ν_{max}: 3255, 2967, 1693, 1624, 1480, 1446, 1413, 1259, 1064, 761, 701 cm^{-1}; MS (ESI) *m/z* 239 (M+Na$^+$, 100%).

(*S*)-3-Benzyl-3,4-dihydro-1*H*-benzo[1,4]diazepine-2,5-dione (8d) Following the general procedure A, the

reaction of isatoic anhydride **10** with L-Phe gave the known compound[1c] **8d** (yield: 81%) as a white solid. m.p. 236−238 ℃ (EtOAc); the aged sample has a m.p. 270−272 ℃ (EtOAc)] [lit. 235−237 ℃,[1c] 275−278 ℃,[1i] 245 ℃,[1g] 278−280 ℃[1e]]; $[\alpha]_D^{20}$ +302.5 (*c* 1.0, DMSO); the aged sample has a $[\alpha]_D^{26}$ +232.5 (*c* 0.5, MeOH) {lit. $[\alpha]_D^{26}$ +175 (*c* 0.5, MeOH)[1f]}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.44 (s, 1H, PhN**H**CO), 8.54 (d. *J*=5.9 Hz, 1H, PhCON**H**), 7.72−7.66 (m, 1H, Ar**H**), 7.53−7.46 (m, 1H, Ar**H**), 7.35−7.09 (m, 7H, Ar**H**), 3.95−3.88 (m, 1H, COC**H**N), 3.15 (dd, *J*=14.1, 4.8 Hz, 1H, PhC$\mathbf{H}_2$), 2.88 (dd, *J*=14.1, 9.4 Hz, 1H, PhC$\mathbf{H}_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.3, 168.7, 138.9, 137.7, 133.2, 131.3, 130.3 (2C), 129.1 (2C), 127.3 (2C), 124.9, 121.9, 54.8, 34.3; IR (film) ν_{max}: 3218, 2926, 1687, 1657, 1606, 1481, 1443, 1402, 1068, 759, 701 cm^{-1}; MS (ESI) *m/z* 273 (M+Na$^+$, 100%).

(*S*)-3-Isobutyl-3,4-dihydro-1*H*-benzo[1,4]diazepine-2,5-dione (8e) Following the general procedure A, the reaction of isatoic anhydride **10** with L-Leu gave the known compound[1c] **8e** (yield: 63%) as colorless crystals. m.p. 251−253 ℃ (EtOAc) {lit. 252 ℃[1c]}; $[\alpha]_D^{20}$ +308.0 (*c* 1.0, DMSO); $[\alpha]_D^{26}$ +285.4 (*c* 0.5, MeOH) {lit. $[\alpha]_D^{26}$ +221 (*c* 0.5, MeOH)[1f]}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.36 (s, 1H, PhN**H**CO), 8.43 (d, *J*=5.7 Hz, 1H, PhCON**H**), 7.78−7.73 (m, 1H, Ar**H**), 7.53−7.47 (m, 1H, Ar**H**), 7.24−7.08 (m, 2H, Ar**H**), 3.64−3.56 (m, 1H, COC**H**N), 1.76−1.64 (m, 1H, CHC$\mathbf{H}_2$), 1.59−1.53 (m, 2H, CHC$\mathbf{H}_2$ and C**H**CH$_3$), 0.84 (d, *J*=6.6 Hz, 3H, C$\mathbf{H}_3$), 0.76 (d, *J*=6.6 Hz, 3H, C$\mathbf{H}_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.6, 168.7, 137.7, 133.1, 131.3, 127.2, 124.8, 121.8, 51.2, 24.8, 23.7, 22.5; IR (film) ν_{max}: 3217, 2957, 1687, 1657, 1607, 1481, 1403, 1229, 1059, 761 cm^{-1}; MS (ESI) *m/z* 255 (M+Na$^+$, 100%).

(*S*)-3-[2-(Methylthio)ethyl]-3,4-dihydro-1*H*-benzo-[1,4]diazepine-2,5-dione (8f) Following the general procedure A, the reaction of isatoic anhydride **10** with L-Met gave the compound **8f** (yield: 93%) as a white solid. m.p. 180−183 ℃ (EtOAc); $[\alpha]_D^{20}$ +312.3 (*c* 1.0, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.35 (s, 1H, PhN**H**CO), 8.48 (d, *J*=4.7 Hz, 1H, PhCON**H**), 7.74−7.66 (m, 1H, Ar**H**), 7.50−7.41 (m, 1H, Ar**H**), 7.20−7.03 (m, 2H, Ar**H**), 3.79−3.70 (m, 1H, COC**H**N), 2.58−2.43 (m, 2H, SC$\mathbf{H}_2$), 2.03−1.79 (m, 2H, CHC$\mathbf{H}_2$), 1.98 (s, 3H, SC$\mathbf{H}_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.3, 168.8, 137.6, 133.2, 131.3, 127.2, 124.9, 121.9, 51.5, 30.4, 28.2, 15.4; IR (film) ν_{max}: 3216, 2917, 1684, 1653, 1607, 1480, 1441, 1402, 1259, 1026, 761 cm^{-1}; MS (ESI) *m/z* 273 (M+Na$^+$, 100%); HRMS-ESI calcd for $C_{23}H_{22}N_4O_5$ (M+H$^+$): 251.0854; found: 251.0857.

General procedure (B) for the preparation of compounds 9a−9f

To a solution of **8** (2.0 mmol) and DMAP (24 mg, 0.10 equiv.) in dry THF (40 mL) was added 0.56 mL of Et$_3$N (4.0 mmol, 2.0 equiv.) at room temperature. The resulting mixture was stirred for 15 min and then cooled to –20 ℃ before dropwise addition of 2-nitrobenzoyl chloride (**11a**) in dry THF (2 mL). After being stirred for 24 h at the same temperature, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with ether (10 mL×3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc∶CH_2Cl_2=1∶5) on silica gel to afford the desired compound **9**.

(*S*)-3-Methyl-1-(2-nitrobenzoyl)-3,4-dihydro-1*H*-benzo[1,4]diazepine-2,5-dione (9a) Following the general procedure B, the reaction of **8a** with **11a** gave the compound **9a** (yield: 82%) as a white solid. m.p. 110−113 ℃ (EtOAc); $[\alpha]_D^{20}$ –139.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.28−8.24 (m, 1H, Ar**H**), 7.94−7.91 (m, 1H, Ar**H**), 7.78−7.53 (m, 5H, Ar**H**), 7.41 (d, *J*=5.0 Hz, 1H, CON**H**), 7.37−7.33 (m, 1H, Ar**H**), 4.13 (dq, *J*=6.8, 5.0 Hz, 1H, C**H**), 1.33 (d, *J*=6.8 Hz, 3H, CHC$\mathbf{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.4, 168.7, 167.5, 145.0, 134.6, 134.2, 133.9, 132.0, 130.1, 129.8, 129.6, 129.04, 129.0 (2C), 126.5, 124.2, 50.9, 13.8; IR (film) ν_{max}: 3268, 1658, 1528, 1450, 1348, 1293, 1203, 1049, 765 cm^{-1}; MS (ESI) *m/z* 340 (M+H$^+$, 100%); HRMS-ESI calcd for $C_{23}H_{22}N_4O_5$ (M+H$^+$): 340.0933; found: 340.0920.

(*S*)-10-(5-Methoxy-2-nitrobenzoyl)-2,3-dihydro-1*H*-bezo-pyrrolo[1,2][1,4]diazepine-5,11(10*H*,11a*H*)-dione (9b) Following the general procedure B, the reaction of **8bc** with **11b** gave the compound **9b** (yield: 76%) as a white solid. m.p. 165−167 ℃ (EtOAc); $[\alpha]_D^{20}$ –12.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26−8.22 (m, 1H, Ar**H**), 7.98−7.93 (m, 1H, Ar**H**), 7.75−7.50 (m, 3H, Ar**H**), 7.02−6.98 (m, 1H, Ar**H**), 6.74−6.71 (m, 1H, Ar**H**), 4.20 (dd, *J*=8.0, 1.6 Hz, 1H, C**H**), 3.90 (s, 3H, OC$\mathbf{H}_3$), 3.84−3.77 (m, 1H, NC$\mathbf{H}_2$), 3.61−3.52 (m, 1H, CHC$\mathbf{H}_2$), 2.51−2.52 (m, 1H, CHC$\mathbf{H}_2$), 1.98−1.87 (m, 2H, CHC$\mathbf{H}_2$ and CH$_2$C$\mathbf{H}_2$), 1.85−1.75 (m, 1H, CH$_2$C$\mathbf{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.5, 167.1, 165.1, 164.5, 138.1, 136.8, 133.4, 132.0, 131.5, 129.7, 128.9, 128.8, 126.8, 114.2, 111.6, 59.9, 56.3, 46.4, 26.1, 23.5; IR (film) ν_{max}: 1738, 1704, 1646, 1582, 1514, 1457, 1415, 1339, 1299, 1253, 1209, 1049, 759 cm^{-1}; MS (ESI) *m/z* 328 (M+Na$^+$, 100%); HRMS-ESI Calcd for $C_{20}H_{17}N_3O_6$ (M+H$^+$): 396.1196; found: 396.1193.

(*S*)-10-(2-Nitrobenzoyl)-2,3-dihydro-1*H*-benzo-pyrrolo[1,2][1,4]diazepine-5,11(10*H*,11a*H*)-dione (9c) Following the general procedure B, the reaction of **8bc** with **11a** gave the compound **9c** (yield: 93%) as a white solid. m.p. 194−196 ℃ (EtOAc); $[\alpha]_D^{20}$ –74.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30−8.21 (m, 1H, Ar**H**), 7.97−7.91 (m, 1H, Ar**H**), 7.74−7.66 (m, 2H, Ar**H**), 7.65−7.56 (m, 2H, Ar**H**), 7.55−7.48 (m, 1H, Ar**H**), 7.33−7.27 (m, 1H, Ar**H**), 4.19 (dd, *J*=8.0, 1.6 Hz, 1H, C**H**), 3.83−3.74 (m, 1H, NC$\mathbf{H}_2$), 3.59−3.43 (m, 1H, CHC$\mathbf{H}_2$), 2.47−2.37 (m, 1H, CHC$\mathbf{H}_2$), 1.96−

1.84 (m, 2H, CHC**H**$_2$ and CH$_2$C**H**$_2$), 1.79－1.64 (m, 1H, CH$_2$C**H**$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 171.6, 167.3, 165.0, 144.9, 134.5, 134.2, 133.2, 132.0, 131.4, 129.8, 129.5, 128.9, 128.8, 126.3, 124.1, 59.8, 46.3, 26.0, 23.4; IR (film) ν_{max}: 1738, 1704, 1645, 1527, 1456, 1347, 1293, 1209, 1055, 756, 710 cm^{-1}; MS (ESI) *m*/*z* 366 (M＋H$^+$, 100%); HRMS-ESI calcd for $C_{19}H_{15}N_3O_5$ (M＋H$^+$): 366.1090; found: 366.1080.

(*S*)-3-Benzyl-1-(2-nitrobenzoyl)-3,4-dihydro-1*H*-benzo[1,4]diazepine-2,5-dione (9d) Following the general procedure B, the reaction of **8d** with **11a** gave the compound **9d** (yield: 84%) as a white solid. m.p. 104－106 ℃ (EtOAc); $[\alpha]_D^{20}$ –82.5 (*c* 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.31－8.27 (m, 1H, Ar**H**), 7.87－7.51 (m, 6H, Ar**H**), 7.39－7.34 (m, 2H, CON**H** and Ar**H**), 7.25－7.18 (m, 3H, Ar**H**), 7.13－7.08 (m, 2H, Ar**H**), 4.14 (dt, *J*＝8.9, 5.3 Hz, 1H, C**H**), 3.21 (dd, *J*＝14.8, 5.0 Hz, 1H, C**H**$_2$), 2.88 (dd, *J*＝14.8, 9.0 Hz, 1H, C**H**$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 171.8, 168.6, 167.5, 145.0, 135.5, 134.6, 134.1, 133.7, 132.0, 130.0, 129.9, 129.6 (2C), 129.1 (2C), 129.0 (2C), 128.8, 127.2, 126.5, 124.2, 56.2, 33.9; IR (film) ν_{max}: 3169, 2934, 1740, 1705, 1666, 1528, 1456, 1347, 1260, 1181, 1051, 756, 699 cm^{-1}; MS (ESI) *m*/*z* 416 (M＋H$^+$, 100%); HRMS-ESI calcd for $C_{23}H_{17}N_3O_5$ (M＋H$^+$): 416.1246; found: 416.1228.

(*S*)-3-Isobutyl-1-(2-nitrobenzoyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (9e) Following the general procedure B, the reaction of **8e** with **11a** gave the compound **9e** (yield: 78%) as a white solid. m.p. 105－107 ℃ (EtOAc); $[\alpha]_D^{20}$ –106.2 (*c* 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.28－8.24 (m, 1H, Ar**H**), 7.93－7.89 (m, 1H, Ar**H**), 7.80－7.66 (m, 4H, CON**H** and Ar**H**), 7.61－7.53 (m, 2H, Ar**H**), 7.36－7.33 (m, 1H, Ar**H**), 3.87 (dt, *J*＝8.9, 5.3 Hz, 1H, C**H**), 1.75－1.66 (m, 1H, C**H**$_2$), 1.65－1.54 (m, 2H, C**H**$_2$ and C**H**), 0.90 (d, *J*＝5.4 Hz, 3H, C**H**$_3$), 0.75 (d, *J*＝5.4 Hz, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 172.2, 169.0, 167.6, 144.9, 134.6, 134.2, 134.0, 132.0, 130.1, 129.8, 129.4, 129.1, 128.9, 126.4, 124.2, 53.3, 36.6, 24.1, 22.9, 21.4; IR (film) ν_{max}: 3274, 2963, 1706, 1663, 1529, 1348, 1498, 1194, 1055, 757 cm^{-1}; MS (ESI) *m*/*z* 382 (M＋H$^+$, 100%); HRMS-ESI calcd for $C_{23}H_{22}N_4O_5$ (M＋H$^+$): 382.1403; found: 382.1391.

(*S*)-7-[2-(Methylthio)ethyl]-6,7-dihydrobenzo[6,7][1,4]diazepino[2,1]quinazoline-5,13-dione (9f) Following the general procedure B, the reaction of **8f** with **11a** gave the compound **9f** (yield: 76%) as a white solid. m.p. 112－114 ℃ (EtOAc); $[\alpha]_D^{20}$ –101.9 (*c* 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.28－8.24 (m, 1H, Ar**H**), 7.96 (d, *J*＝5.5 Hz, 1H, CON**H**), 7.93－7.89 (m, 1H, Ar**H**), 7.78－7.66 (m, 3H, Ar**H**), 7.62－7.53 (m, 2H, Ar**H**), 7.39－7.35 (m, 1H, Ar**H**), 4.13 (dt, *J*＝8.2, 5.5 Hz, 1H, C**H**), 2.62－2.51 (m, 2H, C**H**$_2$S), 2.19－2.09 (m, 1H, CHC**H**$_2$), 2.00 (s, 3H, SC**H**$_3$), 1.97－1.89 (m, 1H, CHC**H**$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 171.9, 169.2, 167.5, 144.9, 134.7, 134.1, 133.9, 132.1, 130.0, 129.9, 129.6, 129.2, 129.0, 126.6, 124.2, 53.7, 29.7, 27.4, 15.3; IR (film) ν_{max}: 3336, 1738, 1660, 1528, 1454, 1347, 1293, 1261, 1055, 764, 658 cm^{-1}; MS (ESI) *m*/*z* 400 (M＋H$^+$, 100%); HRMS-ESI calcd for $C_{19}H_{17}N_3O_5S$ (M＋H$^+$): 400.0967; found: 400.0958.

General procedure (C) for the preparation of compounds 5, 6, 12, 13, 14 and 15

To a suspension of zinc powder (200 mg, 3.08 mmol) in THF (5 mL) was added $TiCl_4$ (0.22 mL, 2.59 mmol). The reaction mixture was stirred for 1 h at 50 ℃. After being cooled to –78 ℃, a solution of **10** (0.42 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred for 6 h at –78 ℃, then slowly warmed up to r.t. and stirred for another 48 h at r.t. The reaction mixture (pre-cooled to 0 ℃) was quenched with brine (5 mL) and stirred for another 2 h at 0 ℃. After separating the organic phase, the aqueous phase was extracted with EtOAc (2 mL×3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc∶CH_2Cl_2＝1∶5) to afford the desired quinazolino-[3,2-*a*][1,4]benzodiazepine compound.

Circumdatin F (5) Following the general procedure C, the reaction of **9a** gave circumdatin F[5a,5c] **5** (yield: 63%) as colorless crystals. m.p. 248－250 ℃ (EtOAc) {lit. 249.2－250.1[9a]}; $[\alpha]_D^{20}$ –204.2 (*c* 1.0, CHCl$_3$); $[\alpha]_D^{20}$ –191.1 (*c* 1.0, CHCl$_3$) {lit. $[\alpha]_D^{20}$ –121.5 (*c* 1.0, CHCl$_3$),[7c] $[\alpha]_D$ –18.9 (*c* 0.11, MeOH)[5c]}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.11－8.06 (m, 1H, Ar**H**), 7.97－7.93 (m, 1H, Ar**H**), 7.0 (br s, 1H, CON**H**), 7.65－7.49 (m, 5H, Ar**H**), 7.40－7.34 (m, 1H, Ar**H**), 4.32 (dq, *J*＝6.6, 6.6 Hz, 1H, C**H**), 2.11 (d, *J*＝6.6 Hz, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 168.2, 161.4, 154.9, 145.9, 134.5, 133.4, 131.1, 130.6, 129.7, 128.8, 128.2, 127.5, 127.3, 127.1, 121.1, 49.9, 15.1; IR (film) ν_{max}: 3336, 1689, 1664, 1618, 1388, 1299, 1250, 1059, 768 cm^{-1}; MS (ESI) *m*/*z* 314 (M＋Na$^+$, 100%).

Circumdatin H (6) Following the general procedure C, the reaction of **9b** gave circumdatin H[5d] **6** (yield: 83%) as colorless crystals. m.p. 215－217 ℃ (EtOAc) {lit. 216－217[10e]}; $[\alpha]_D^{20}$ –102.0 (*c* 1.0, CHCl$_3$) {lit. $[\alpha]_D^{25}$ –57.2 (*c* 0.36, CHCl$_3$),[10d] $[\alpha]_D^{29}$ –106 (*c* 0.82, MeOH),[10e] $[\alpha]_D^{25}$ –123.6 (*c* 0.80, MeOH),[10c] $[\alpha]_D$ –26.3 (*c* 0.078, MeOH)[5d]}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.01－7.97 (m, 1H, Ar**H**), 7.68－7.48 (m, 5H, Ar**H**), 7.39－7.34 (m, 1H, Ar**H**), 4.53 (dd, *J*＝8.0, 1.6 Hz, 1H, NC**H**), 3.91 (s, 3H, C**H**$_3$), 3.77 (ddd, *J*＝12.0, 8.3, 2.7 Hz, 1H, NC**H**$_2$), 3.60 (ddd, *J*＝12.0, 9.7, 7.2 Hz, 1H, NCHC**H**$_2$), 3.20－3.11 (m, 1H, NCHC**H**$_2$), 2.37－2.23 (m, 1H, NCHC**H**$_2$), 2.19－2.02 (m, 2H, CH$_2$C**H**$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 164.5, 161.6, 159.0, 151.5, 140.6, 133.4, 132.5, 130.7, 129.9, 129.2, 128.6, 128.4, 124.8, 122.3, 107.0, 58.8, 55.8, 46.5, 27.0, 23.7; IR (film) ν_{max}: 1687, 1482, 1435, 1199, 1128, 833, 743, 695, 511 cm^{-1}; MS (ESI) *m*/*z* 348 (M＋H$^+$, 100%); HRMS-ESI calcd for $C_{23}H_{22}N_4O_5$ (M＋H$^+$): 348.1348; found: 348.1332.

(*S*)-5b,6,7,8-Tetrahydrobenzo[6,7]pyrrolo[2',1':3,4][1,4]diazepino[2,1]quinazoline-10,16-dione (12) Following the general procedure C, the reaction of **9c** gave demethoxycircumdatin H[7d] **12** (yield: 90%) as colorless crystals. m.p. 227−229 ℃ (EtOAc) {lit. 228−230[7d]}; $[\alpha]_D^{20}$ −148.9 (*c* 1.0, $CHCl_3$) {lit. $[\alpha]_D^{20}$ −109.4 (*c* 1.0, $CHCl_3$),[7c] $[\alpha]_D^{20}$ −77.2 (*c* 0.30, $CHCl_3$)[10d]}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.31−8.27 (m, 1H, Ar**H**), 8.00−7.96 (m, 1H, Ar**H**), 7.80−7.68 (m, 2H, Ar**H**), 7.60−7.47 (m, 4H, Ar**H**), 4.54 (dd, *J*=7.8, 1.5 Hz, 1H, C**H**), 3.82−3.74 (m, 1H, NC$\mathbf{H}_2$), 3.65−3.55 (m, 1H, NC$\mathbf{H}_2$), 3.22−3.13 (m, 1H, CHC$\mathbf{H}_2$), 2.38−2.24 (m, 1H, CHC$\mathbf{H}_2$), 2.20−2.03 (m, 2H, $CH_2C\mathbf{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 164.4, 161.7, 153.6, 146.1, 134.7, 133.2, 132.4, 130.7, 129.9, 128.6, 128.3, 127.6, 127.5, 127.4, 121.5, 58.8, 46.5, 27.0, 23.6; IR (film) ν_{max}: 1691, 1646, 1616, 1454, 1411, 1296, 1250, 1064, 769, 699 cm^{-1}; MS (ESI) *m/z* 330 (M+Na$^+$, 100%).

(*S*)-7-Benzyl-6,7-dihydrobenzo[6,7][1,4]diazepino-[2,1-*b*]quinazoline-5,13-dione (13) Following the general procedure C, the reaction of **9d** gave *N*-demethylbenzomalvin A[7d] **13** (yield: 85%) as a white solid. m.p. 139−141 ℃ (EtOAc) {lit. 140−142 ℃[7d]}; $[\alpha]_D^{20}$ −101.5 (*c* 1.0, $CHCl_3$) {lit. $[\alpha]_D^{20}$ −103.7 (*c* 1.0, $CHCl_3$)[7c]}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.28−8.24 (m, 1H, Ar**H**), 7.92−7.88 (m, 1H, Ar**H**), 7.80−7.47 (m, 6H, Ar**H**), 7.35−7.21 (m, 5H, Ar**H**), 7.12 (d, *J*=6.0 Hz, 1H, CON**H**), 4.47 (dt, *J*=8.1, 6.0 Hz, 1H, C**H**), 3.76 (dd, *J*=14.6, 6.0 Hz, 1H, C$\mathbf{H}_2$), 3.60 (dd, *J*=14.6, 8.2 Hz, 1H, C$\mathbf{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.8, 161.5, 154.1, 146.1, 136.6, 134.8, 133.3, 131.3, 130.4, 129.9, 129.5 (2C), 129.0, 128.7 (2C), 128.4, 127.7, 127.6, 127.1, 121.4, 55.3, 35.4; IR (film) ν_{max}: 3067, 1689, 1664, 1615, 1454, 1384, 765, 697 cm^{-1}; MS (ESI) *m/z* 390 (M+Na$^+$, 100%).

(*S*)-7-Isobutyl-6,7-dihydrobenzo[6,7][1,4]diazepino[2,1]quinazoline-5,13-dione (14) Following the general procedure C, the reaction of **9e** gave the known compound[7d] **14** (yield: 91%) as colorless crystals. m.p. 228−230 ℃ (EtOAc) {lit. 227−229[7d]}; $[\alpha]_D^{20}$ −121.5 (*c* 1.0, $CHCl_3$) {lit. $[\alpha]_D^{20}$ −171.3 (*c* 1.0, $CHCl_3$)[7c]}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.25−8.20 (m, 1H, Ar**H**), 7.98−7.94 (m, 1H, Ar**H**), 7.75−7.42 (m, 5H, Ar**H**), 7.49−7.42 (m, 2H, CON**H** and Ar**H**), 4.19 (dt, *J*=8.6, 5.8 Hz, 1H, C**H**), 2.18−2.08 (m, 1H, C$\mathbf{H}_2$), 2.05−1.96 (m, 1H, C$\mathbf{H}_2$), 1.96−1.86 (m, 1H, C**H**), 1.00 (d, *J*=6.6 Hz, 3H, C$\mathbf{H}_3$), 0.88 (d, *J*=6.6 Hz, 3H, C$\mathbf{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.2, 161.6, 154.7, 146.1, 134.7, 133.5, 131.2, 130.6, 129.7, 128.9, 128.3, 127.7, 127.4, 127.3, 121.3, 52.4, 37.9, 24.3, 23.0, 21.9; IR (film) ν_{max}: 3210, 2955, 1666, 1614, 1454, 1384, 1296, 1248, 1068, 770, 756 cm^{-1}; MS (ESI) *m/z* 356 (M+Na$^+$, 100%).

(*S*)-7-[2-(Methylthio)ethyl]-6,7-dihydrobenzo[6, 7]-[1,4]diazepino[2,1]quinazoline-5,13-dione (15) Following the general procedure C, the reaction of **9f** gave the compound **15** (yield: 81%) as a white solid. m.p. 169−171 ℃ (EtOAc); $[\alpha]_D^{20}$ −101.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.26−8.22 (m, 1H, Ar**H**), 7.94−7.76 (m, 2H, Ar**H**), 7.67−7.53 (m, 5H, Ar**H** and CON**H**), 7.50−7.45 (m, 1H, Ar**H**), 4.42 (dt, *J*=7.3, 6.3 Hz, 1H, C**H**), 2.82−2.73 (m, 2H, SC$\mathbf{H}_2$), 2.71−2.61 (m, 1H, CHC$\mathbf{H}_2$), 2.31−2.41 (m, 1H, CHC$\mathbf{H}_2$), 2.11 (s, 3H, SC$\mathbf{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.5, 161.5, 154.1, 146.0, 134.7, 133.4, 131.3, 130.4, 129.8, 128.9, 128.3, 127.6, 127.5, 127.3, 121.3, 52.7, 30.2, 28.6, 15.4; IR (film) ν_{max}: 3256, 2921, 1690, 1662, 1617, 1598, 1455, 1385, 1251, 1021, 768 cm^{-1}; MS (ESI) *m/z* 352 (M+H$^+$, 100%); HRMS-ESI calcd for $C_{19}H_{17}N_3O_2S$ (M+H$^+$): 352.1120; found 352.1121.

(*S*)-18,18a-Dihydro-5*H*-benzo[6,7]indolo[3'',2'':4',5']pyrrolo[2',1':3,4][1,4]diazepino[2,1-*b*]quinazoline-5,11(13*H*)-dione (16) To a solution of (−)-asperlicin C (**2**)[16] (203 mg, 0.50 mmol) in THF (20 mL) at 0 ℃ was added a solution of NCS (134 mg, 0.50 mmol) in THF (5 mL). The mixture was stirred for 5 min at 0 ℃ before addition of Et_3N (0.21 mL, 1.5 mmol). After being stirred for 30 min at that temperature, a solution of NCS (134 mg, 0.50 mmol) in THF (5 mL) was added. The resulting mixture was warmed up to r.t. and stirred for 16 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) at 0 ℃. The aqueous phase was extracted with EtOAc (5 mL×3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc∶CH_2Cl_2=1∶20) to give dehydra-asperlicin E (**16**) (173 mg, yield: 85%) as a pale yellow solid. m.p. 269−271 ℃ (EtOAc); $[\alpha]_D^{20}$ +134.0 (*c* 0.5, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.15 (s, 1H, N**H**), 8.32−8.28 (m, 1H, Ar**H**), 8.11−8.06 (m, 1H, Ar**H**), 7.80−7.49 (m, 7H, Ar**H**), 7.35−7.31 (m, 1H, Ar**H**), 7.20−7.10 (m, 2H, Ar**H**), 5.53 (dd, *J*=9.3, 2.4 Hz, 1H, NC**H**CN), 4.66 (dd, *J*=14.3, 2.4 Hz, 1H, C$\mathbf{H}_2$), 3.41 (dd, *J*=14.3, 9.3 Hz, 1H, C$\mathbf{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 161.8, 160.9, 151.2, 145.8, 139.7, 137.6, 134.9, 133.2, 131.4, 130.7, 130.2, 129.1 (2C), 128.1, 128.0, 127.4, 123.3, 121.6, 121.0, 120.7, 118.1, 112.2, 102.8, 66.6, 24.8; IR (film) ν_{max}: 1692, 1651, 1609, 1525, 1453, 1353, 1076, 745 cm^{-1}; MS (ESI) *m/z* 405 (M+H$^+$, 100%); HRMS-ESI calcd for $C_{25}H_{16}N_4O_2$ (M+H$^+$): 405.1352; found: 405.1351.

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