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Microwave-Assisted Concise Total Syntheses of Quinazolinobenzodiazepine Alkaloids

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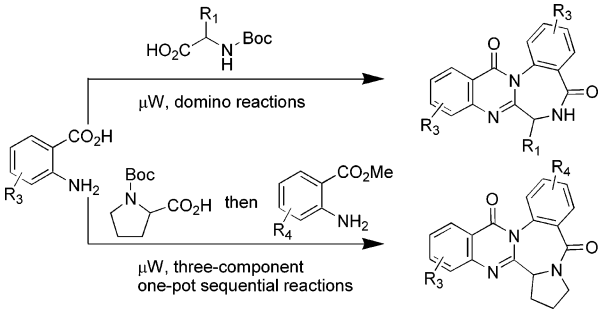

One-pot total syntheses of the quinazolinobenzodiazepine alkaloids sclerotigenin (**1**), (±)-circumdatin F (**2**), and (±)-asperlicin C (**3**) via novel microwave-assisted domino reactions were achieved in 55%, 32%, and 20% yields, respectively, from commercially available starting materials. A two-step total synthesis of (±)-benzomalvin A (**4**) was accomplished with an overall yield of 16%. Additionally, analogues of circumdatin E were synthesized via the three-component one-pot sequential reactions promoted by microwave irradiation. Finally, a two-step formal total synthesis of (±)-asperlicin E (**5**) was also realized by using this microwave-assisted protocol.

Introduction

A wide variety of quinazolinobenzodiazepine alkaloid natural products have been reported in recent years (Figure 1).[1] Circumdatins A−G were obtained from a terrestrial isolate of the fungus *Aspergillus ochraceus* and are suggested to be suitable chemotaxonomic markers for this species.[2] Sclerotigenin (**1**), an antiinsectant, was isolated from organic extracts of sclerotia of *Penicillium sclerotigenum* (NRRL 3461).[3] Asperlicin C (**3**) and asperlicin E (**5**), of the asperlicin family of CCK antagonists, were isolated from the fermentation broths produced by *Aspergillus alliaceus*.[4] Benzomalvin A (**4**) was isolated from a fungus culture of *Penicillium* sp and showed inhibitory activity against substance P at neurokinin NK1 receptor in the guinea pig, rat, and human.[5]

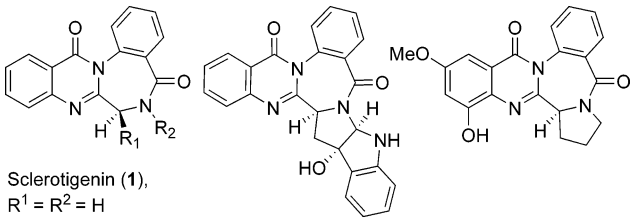

FIGURE 1. Structures of various quinazolinobenzodiazepine alkaloids.

There have been three general methodologies reported for the total syntheses of these natural products. Snider,

(1) For recent reviews on quinazoline alkaloids, see: (a) Michael, J. P. *Nat. Prod. Rep*. **2004**, *21*, 650−668. (b) Johne, S. *Rodd's Chemistry of Carbon Compounds*, Supplements to the 2nd ed.; Ansell, M. F., Ed.; Elsevier: Amsterdam, The Netherlands, 1995; Vol. IV I/J, pp 223−240.

(2) (a) Dai, J.-R.; Carte, B. K.; Sidebottom, P. J.; Yew, A. L.; Ng, S.-W.; Huang, Y.; Butler, M. S. *J. Nat. Prod.* **2001**, *64*, 125−126. (b) Rahbæk, L.; Breinholt, J.; Frisvad, J. C.; Christophersen, C. *J. Org. Chem.* **1999**, *64*, 1689−1692. (c) Rahbæk, L.; Breinholt, J. *J. Nat. Prod.* **1999**, *62*, 904−905.

(3) Joshi, B. K.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod.* **1999**, *62*, 650−652.

(4) Goetz, M. A.; Monaghan, R. L.; Chang, R. S. L.; Ondeyka, J.; Chen, T. B.; Lotti, V. J. *J. Antibiot.* **1988**, *41*, 875−877.

(5) Sun, H. H.; Barrow, C. J.; Sedlock, D. M.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1994**, *47*, 515−522.

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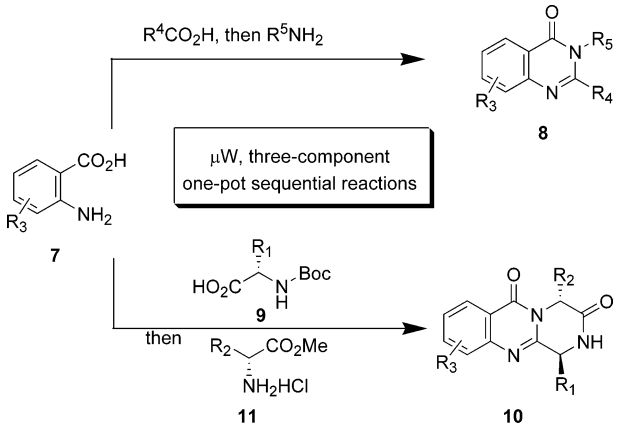
SCHEME 1. One-Pot Syntheses of 2,3-Disubstituted Quinazolin-4-ones and Pyrazino[2,1-*b*]quinazoline-3,6-diones



Thomas, and Eguchi respectively reported the synthesis of sclerotigenin,[6a,7] circumdatin F,[6a] asperlicin C,[6b] and benzomalvin A[8] via an aza-Wittig protocol. Bergman reported the synthesis of both circumdatin C and F with a Ganesan−Mazurkiewicz cyclization to form an iminobenzoxazine intermediate as a key step.[9] In addition, Bock completed the first total syntheses of asperlicin C and asperlicin E featuring a regioselective annulation of benzodiazepinedione with anthranilic acid for both syntheses.[10] All of these methodologies required multiple synthetic steps that proceed in low to moderate yields.

We recently reported an efficient microwave-assisted one-pot methodology for the synthesis of various 2,3-disubstituted quinazolin-4-ones **8** from commercially available starting materials.[11] On the basis of this approach, we achieved a one-pot total synthesis of pyrazino[2,1-*b*]quinazoline-3,6-dione cores and corresponding natural products represented by **10** (Scheme 1).[12,13]

To further extend the application of our new methodology, we investigated the total syntheses of quinazolinobenzodiazepine alkaloids, another important class in the quinazolinone alkaloid family.[14] Herein, we describe a novel domino process[15] for the synthesis of quinazolinobenzodiazepine alkaloids including sclerotigenin (**1**), (±)-circumdatin F (**2**), and (±)-asperlicin C (**3**). The new method sets a new standard for the synthesis of these quinazolinobenzodiazepine alkaloids as it uses only one reagent and one protecting group for the entire synthesis from readily available anthranilic acids and Boc-amino acids with only one step. With this new concise method, we have realized a two-step total synthesis of (±)-benzomalvin A (**4**). Finally, we also detail herein a concise synthesis of two differentially substituted analogues of circumdatin E (**6**) via one-pot reactions.[16]

Results and Discussion

Attempts for Three-Component One-Pot Sequential Synthesis of 1. Initially, we envisioned that our three-component one-pot, *sequential*, synthetic strategy[12] for the synthesis of the pyrazino[2,1-*b*]quinazoline-3,6-dione core could be useful for the synthesis of quinazolinobenzodiazepines. However, instead of creating two fused six-membered rings, we sought a six-membered ring fused to a seven-membered ring via similar one-pot MAOS (microwave-assisted organic synthesis).[17] Therefore, we chose sclerotigenin (**1**), the simplest alkaloid of this type, as a synthetic target on which to test our design. The total synthesis of **1** was achieved via a three-component one-pot reaction with 60% yield (Scheme 2) by coupling anthranilic acid (**7a**) with *N*-Boc-glycine (**9a**) in the presence of triphenyl phosphite ($P(OPh)_3$) in pyridine under microwave irradiation at 150 °C for 10 min, followed by the addition of methyl anthranilate (**12a**) and microwave irradiation at 250 °C for 15 min.[18] It is noteworthy that although a homo-coupling-dehydration pathway to form byproducts such as **13** and **14** was possible, in practice, we observed that the formation of desired **1** was dominant, while the presence of byproducts was in fact negligible.[19] This may be attributed to the coupling reaction of anthranilic acid **7a** with *N*-Boc amino acid **9a** being faster than the homo-coupling reaction of anthranilic acid **7a** under the reaction conditions.

Plan of the Modified Synthetic Route. The important observation of the dominance of Path B in Scheme 2 drove us to redesign the synthetic route and further simplify what was operationally a *sequential process* by

(6) (a) Snider, B. B.; Busuyek, M. V. *Tetrahedron* **2001**, *57*, 3301−3307. (b) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417−6418.

(7) Grieder, A.; Thomas, A. W. *Synthesis* **2003**, 1707−1711.

(8) Sugimori, T.; Okawa, T.; Eguchi, S.; Kakehi, A.; Yashima, E.; Okamoto, Y. *Tetrahedron* **1998**, *54*, 7997−8008.

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(11) Liu, J.-F.; Lee, J.; Dalton, A. M.; Bi, G.; Yu, L.; Baldino, C. M.; McElory, E.; Brown, M. *Tetrahedron Lett.* **2005**, *46*, 1241−1244.

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(13) For recent applications of microwave technology in natural product synthesis, see: (a) Baxendale, I. R.; Ley, S. V.; Piutti, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2194−2197. (b) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481−4484. (c) Grainger, R. S.; Patel, A. *Chem. Commun.* **2003**, 1072−1073 (d) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706−707. (e) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674−2677. (f) Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *Chem. Commun.* **2004**, 946−948. (g) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453−1456. (h) Lépine, R.; Zhu, J. *Org. Lett.* **2005**, *7*, 2981−2984.

(14) Our one-pot microwave methodology has been applied successfully in the total syntheses of pyrrolo[2,1-*b*]quinazoline alkaloids and their derivatives; see: Liu, J.-F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C. M.; Wilson, C. J.; Ng, S.-C. *Org. Lett.* **2005**, *7*, 3363−3366.

(15) According to Tietze, a "Domino reaction is a process involving two or more bond forming transformations which takes place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step." See: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vögtle, F., Eds.; Wiley-VCH: Weinheim, Germany, 2000.

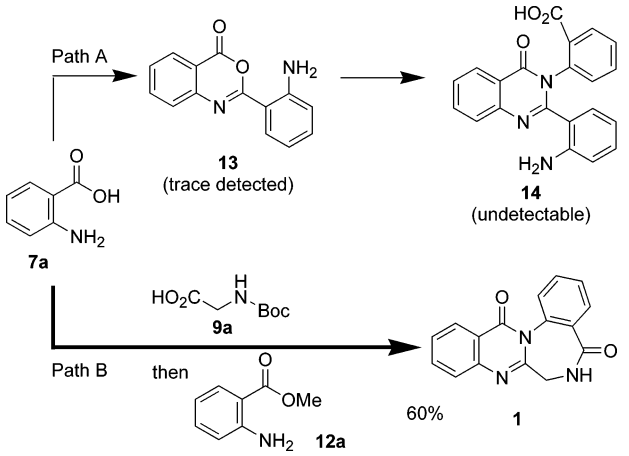
(16) For multicomponent reactions, see: (a) *Multicomponent Recations*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005.

(17) For a recent review of microwave-assisted organic synthesis (MAOS), see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6285. (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (c) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199−9223.

(18) It was found that both triphenyl phosphite and pyridine are essential for dehydration−cyclization.

(19) The reactions were monitored by LC-MS.

SCHEME 2. Initial Attempts for the One-Pot Sequential Synthesis of 1[a]



[a] Reagents and conditions: **7a** (1.0 equiv), **9a** (1.0 equiv), and $P(OPh)_3$ (1.2 equiv), pyridine, microwave heating, 150 °C, 10 min; then **12a** (1.0 equiv), microwave heating, 250 °C, 15 min.

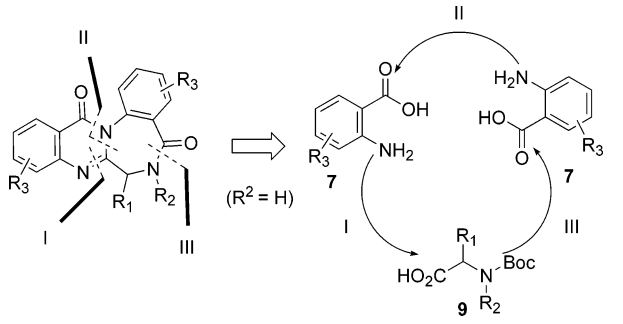
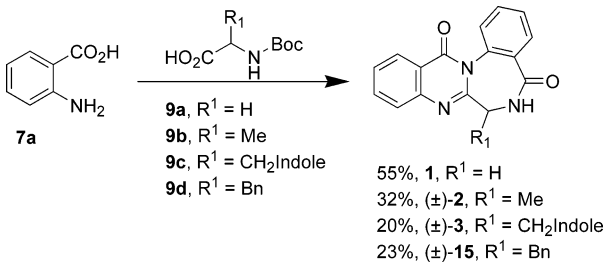


FIGURE 2. Retrosynthetic strategy for the "symmetric" quinazolinobenzodiazepine alkaloids via domino reactions.

carrying out a series of transformations via a *domino process* to make the "symmetric" quinazolinobenzodiazepine alkaloids (R^3 on both phenyl rings).[20] The modified retrosynthetic strategy is depicted in Figure 2. We postulated that due to the differential reactivities of the coupling partners, the reaction sequence would be I, II, and III to yield the desired products, rather than II, I, then III to form the byproducts, for example.[21] This new design allows access to the natural products **1**, **2**, **3**, and other "symmetric" quinazolinobenzodiazepines in a one-step operation.

One-Step Total Syntheses of 1, (±)-(2), and (±)-(3) and Synthesis of (±)-(15). Toward this end, we employed the following modified reaction process aimed at achieving an operationally simplified synthesis (Scheme 3). Reaction of anthranilic acid (**7a**, 2.0 equiv) with *N*-Boc-glycine **9a** (1.0 equiv) in the presence of $P(OPh)_3$ in pyridine under microwave irradiation at 230 °C for 20 min yielded the desired product **1** in a yield of 55%. When compared to the six-membered ring, the seven-membered ring benzodiazepine analogue is much more challenging to close owing to the stronger reaction conditions (i.e., higher temperature and longer reaction time) required to drive the reaction to completion.[12] The success of the synthesis of **1** via the domino process encouraged us to pursue the syntheses of (±)-(**2**), (±)-(**3**), and (±)-**15** (a precursor of **4**) employing the same strategy.[22] As expected, under the same reaction conditions used for the synthesis of **1**, reaction of anthranilic acid (**7a**, 2.0 equiv) with the corresponding racemic *N*-Boc amino acids **9b**, **9c**, and **9d** (1.0 equiv) provided (±)-(**2**), (±)-(**3**), and (±)-**15** in yields of 32%, 20%, and 23%, respectively.[23]

SCHEME 3. One-Step Total Syntheses of 1, (±)-(2), and (±)-(3) and Synthesis of (±)-(15)[a]



[a] Reagents and conditions: for **1**, **2**, **3**, and **15**, mixture of **7a** (2.0 equiv), the corresponding **9a**−**d** (1.0 equiv), and $P(OPh)_3$ (1.2 equiv) in pyridine, microwave heating, 230 °C, 20 min.

Synthesis of (±)-Asperlicin E (5) and (±)-Benzomalvin A. Given that asperlicin C (**3**) has been described as a precursor of asperlicin E (**5**) in Bock's total synthesis,[10] we have, with the achievement of the one-step synthesis of (±)-asperlicin C (**3**), completed the formal total synthesis of (±)-asperlicin E (**5**) in only two steps from commercially available starting materials (Scheme 4). Furthermore, methylation of (±)-**15** with MeI in the presence of LiHMDS allowed us to complete the total synthesis of (±)-benzomalvin A (**4**) in two steps with an overall yield of 16%.[24,25]

The conformational dynamic behavior of benzomalvin A (**4**) has been extensively investigated by Sun[26] and Eguchi.[8] Benzomalvin A (**4**), despite being separable from the other conformer (benzomalvin D) on the HPLC, can isomerize and approach a 4:1 (A:D) ratio at room temperature in hours (Figure 3). The *N*-Me amide in **4** was claimed to be responsible for this equilibrium behavior.[8,25] However, we observed that (±)-**15**, the precursor of **4** having amide *N*-H, also exists as two conformers. These two conformers could not remain conformationally pure even after separation by HPLC due to the lower rotational energy barrier of amide *N*-H compared to amide *N*-Me. The 3:1 conformer ratio as determined by ^1H NMR immediately after HPLC separation came to equilibrium (in $CDCl_3$) as a 1.5:1 mixture at room tempera-

(20) "Symmetric" quinazolinobenzodiazepine alkaloids here refer to alkaloids originating from two identical 2-aminobenzoic acids, while "nonsymmetric" quinazolinobenzodiazepine alkaloids here refer to alkaloids originating from the two *different* 2-aminobenzoic acids.

(21) The domino process requires 2 equiv of anthranilic acids **7** and 1 equiv of *N*-Boc amino acids **9** in the reaction mixture.

(22) Since we encountered enantiomeric erosion in the synthesis of quinazolinone alkaloids with the pyrazino[2,1-*b*]quinazoline-3,6-dione core (ref 12), we elected to perform the syntheses of the racemates of the quinazolinobenzodiazepine alkaloids in the work described herein.

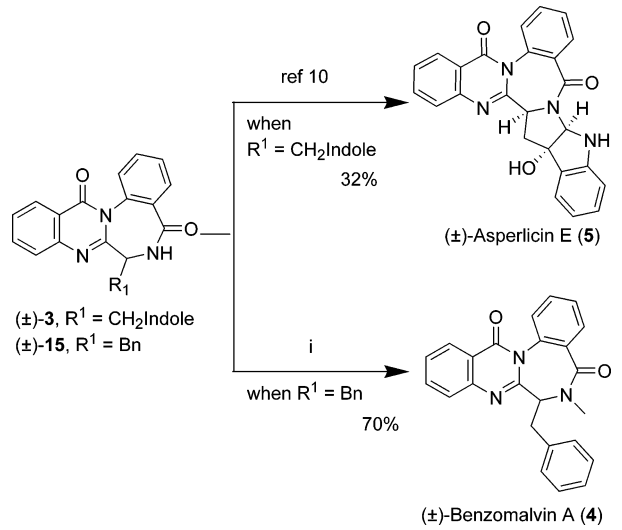
(23) Although the yields are relatively low, they are still comparable or better than that of reported multistep syntheses (refs 6−10). The low yields may be attributed to the inefficient formation of the fused seven-membered rings, which resulted in the decomposion of the intermediates and generation of side products.

(24) The first total synthesis of **4** was accomplished in six steps from **9d**, see ref 8.

(25) The *O*-methylation product was also isolated in 12% yield in an alkylation step, see the Experimental Section.

(26) Sun, H. H.; Barrow, C. J.; Cooper, R. *J. Nat. Prod.* **1995**, *58*, 1575−1580.

SCHEME 4. Formal Total Syntheisis of (±)-(5) and Total Synthesis of (±)-(4)[a]



[a] Reagents and conditions: (i) **15** (1.0 equiv), LiHMDS (2.5 equiv), THF, −78 °C, 15 min, and 0 °C, then MeI (1.5 equiv), rt, 30 min.

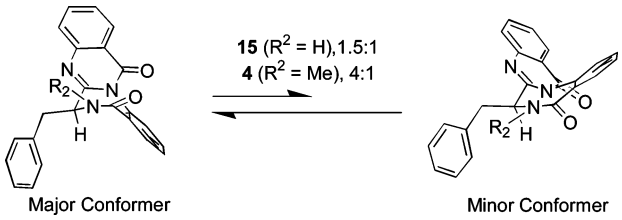
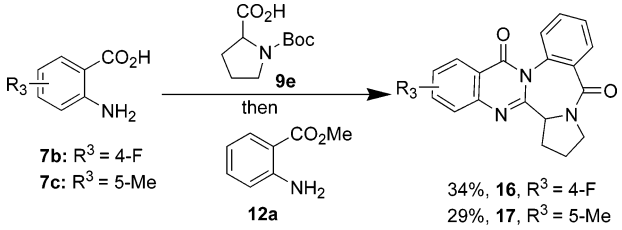


FIGURE 3. Conformational isomers of **4** and **15**.

SCHEME 5. Three-Component One-Pot Syntheses of Analogues of Circumdatin E (6)[a]



[a] Reagents and conditions: mixture of corresponding **7** (1.0 equiv), **9e** (1.0 equiv), and $P(OPh)_3$ (1.2 equiv), pyridine, microwave heating, 150 °C, 10 min; then **12a** (1.0 equiv), microwave heating, 230 °C, 15 min.

ture within several hours. Synthesis of (±)-benzomalvin A (**4**) from this conformer mixture of (±)-**15** provided the same ratio as the two conformers of **4** that was reported previously.[8]

Three-Component One-Pot Sequential Synthesis of Circumdatin E Analogues. While the domino approach is applicable to the syntheses of the "symmetric" quinazolinobenzodiazepine alkaloids, the three-component one-pot sequential synthesis strategy was used for the synthesis of the "nonsymmetric" quinazolinobenzodiazepine alkaloids (different substituents on the two phenyl rings).[20] As shown in Scheme 5, the reaction of anthranilic acids **7b** and **7c** with *N*-Boc-proline (**9e**) in the presence of $P(OPh)_3$ in pyridine under microwave irradiation at 150 °C for 10 min, followed by the addition of methyl anthranilate (**12a**) and further microwave irradiation at 230 °C for 15 min, afforded **16** and **17**, analogues of circumdatin E (**6**), in yields of 34% and 29%, respectively.[23]

Summary

Microwave-assisted one-pot total syntheses of the quinazolinobenzodiazepine alkaloids sclerotigenin (**1**), (±)-circumdatin F (**2**), and (±)-asperlicin C (**3**) have been achieved via novel domino reactions. Efficient two-step total synthesis of (±)-benzomalvin A (**4**) and formal total synthesis of (±)-asperlicin E (**5**) have been completed. Analogues of circumdatin E possessing differentially substituted aryl rings have also been prepared via the three-component one-pot sequential reactions promoted by microwave irradiation. The one-pot synthetic approaches developed herein to access both "symmetric" and "nonsymmetric" quinazolinobenzodiazepine alkaloids employ commercially available inputs and only one reagent, one protecting group, and one solvent. These combined advantages offer great opportunities to rapidly synthesize quinazolinone natural product-templated libraries for phenotypic screening as well as other screening paradigms. Further application of this methodology to the total syntheses of other scaffolds as well as to the construction of natural product-templated screening libraries will be reported in due course.

Experimental Section

Sclerotigenin (1): (a) Three-Component One-Pot Procedure (Scheme 2). To a conical-bottomed Smith Process vial were added anthranilic acid (**7a**) (28 mg, 200 μmol), *N*-Boc-glycine (**9a**) (35 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave on a Biotage Smith Synthesizer for 10 min at 150 °C. After the mixture was cooled to room temperature, methyl anthranilate (**12a**) (30 mg, 200 μmol) was added and the resulting mixture was heated in the microwave at 250 °C for 15 min. The reaction mixture was then concentrated in vacuo, and the residue was purified by preparative HPLC (ProntoSIL 120-10-C18 column (50 × 20 mm^2) with a flow rate at 44 mL/min utilizing an acetonitrile/water mobile phase) to afford **1** as a light yellow solid (33 mg, 60%); mp 270−273 °C (lit.[6a] mp 277−280 °C; lit.[3] mp 235−238 °C); ^1H NMR (400 MHz) δ 8.32 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.81 (t, J = 8.6 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.67−7.61 (m, 2H), 7.60−7.47 (m, 2H), 7.23 (br s, NH), 4.27 (dd, J = 15.2, 6.4 Hz, 1H); ^{13}C NMR (100 MHz) δ 168.0, 161.4, 153.5, 146.2, 135.1, 133.4, 131.5, 130.4, 129.7, 129.1, 128.1, 127.9, 127.6, 127.3, 121.5 47.1; MS *m/z* 278.20 (M + H); HRMS calcd for ($C_{16}H_{11}N_3O_2$ + Na) 300.0743, found 300.0743.

(b) One-Step Procedure (Scheme 3). To a conical-bottomed Smith Process vial were added anthranilic acid (**7a**) (56 mg, 400 μmol), *N*-Boc-glycine (**9a**) (35 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave on a Biotage Smith Synthesizer for 20 min at 230 °C. The reaction mixture was then concentrated in vacuo, and the residue was purified by preparative HPLC (ProntoSIL 120-10-C18 column (50 × 20 mm^2) with a flow rate at 44 mL/min utilizing an acetonitrile/water mobile phase) to afford **1** as a light yellow solid (30.5 mg, 55%) with identical spectral data as the above procedure.

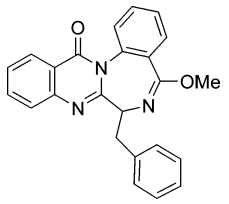
Circumdatin F (2). To a conical-bottomed Smith Process vial were added anthranilic acid (**7a**) (56 mg, 400 μmol), *N*-Boc-

alanine (**9b**) (38 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave on a Biotage Smith Synthesizer for 20 min at 230 °C. The reaction mixture was then concentrated in vacuo, and the residue was purified by preparative HPLC (ProntoSIL 120-10-C18 column (50 × 20 mm^2) with a flow rate at 44 mL/min utilizing an acetonitrile/water mobile phase) to afford (±)-**2** as light yellow crystals (19 mg, 32%); mp 245−247 °C (lit.[6a] mp 249.2−250.1 °C); ^{1}H NMR (400 MHz) δ 8.33 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.82 (t, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.68−7.52 (m, 4H), 6.32 (br s, NH), 4.42 (dq, *J* = 6.6, 6.6 Hz, 1H), 1.73 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 167.5, 161.6, 154.9, 146.1, 134.9, 133.5, 131.4, 130.5, 129.9, 129.0, 128.4, 128.7, 127.6, 127.5, 121.5, 49.8, 15.5; MS *m/z* 292.14 (M + H); HRMS calcd for ($C_{17}H_{13}N_3O_2$ + Na) 314.0900, found 314.0901.

Asperlicin C (3). To a conical-bottomed Smith Process vial were added anthranilic acid (**7a**) (56 mg, 400 μmol), 2-*tert*-butoxycarbonylamino-3-(1*H*-indol-3-yl)propionic acid (**9c**) (61 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave on a Biotage Smith Synthesizer for 20 min at 230 °C. The reaction mixture was then concentrated in vacuo, and the residue was purified by preparative HPLC (ProntoSIL 120-10-C18 column (50 × 20 mm^2) with a flow rate at 44 mL/min utilizing an acetonitrile/water mobile phase) to afford (±)-**3** as a light yellow solid after being dried with a freeze dryer (16.5 mg, 20%); ^{1}H NMR of major conformer (400 MHz, DMSO-*d*$_6$) δ 10.84 (br s, 1H), 8.87 (d, *J* = 6.4 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.90 (t, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.68−7.45 (m, 6H), 7.35−7.25 (m, 2H), 7.01 (t, *J* = 8 Hz, 1H), 6.89 (t, *J* = 8 Hz, 1H), 4.37 (m, 1H), 3.61 (dd, *J* = 15.2, 5.2 Hz, 1H), 3.40−3.30 (m, 1H); ^{13}C NMR of major conformer (100 MHz, DMSO-*d*$_6$) δ 161.94, 161.23, 156.27, 146.17, 136.2, 135.45, 133.18, 131.30, 130.09, 129.0, 127.8, 127.5, 127.27, 127.11, 124.72, 121.19, 121.10, 118.56, 111.62, 109.93. 54.75, 24.55; MS *m/z* 407.20 (M + H); HRMS calcd for ($C_{25}H_{18}N_4O_2$ + Na) 429.1322, found 429.1328.

6,7-Dihydro-7-benzylquinazolino[3,2-*a*][1,4]-benzodiazepine-5,13-dione ((±)-15). To a conical-bottomed Smith Process vial were added anthranilic acid (**7a**) (56 mg, 400 μmol), 2-*tert*-butoxycarbonylamino-3-phenylpropionic acid (**9d**) (53 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave on a Biotage Smith Synthesizer for 20 min at 230 °C. Using this procedure, two copies of the reaction were run, the combined reaction mixture was then concentrated in vacuo, and the residue was purified by preparative HPLC (ProntoSIL 120-10-C18 column (50 × 20 mm^2) with a flow rate at 44 mL/min utilizing an acetonitrile/water mobile phase and 0.1% trifluoroacetic acid as a modifier) to afford a conformer mixture (3:1 soon after the HPLC separation; 1.5:1 when NMR was recorded) of (±)-**15** as a light yellow solid TFA salt (44 mg, 23%); ^{1}H NMR (400 MHz) δ 8.32 (d, *J* = 8.0 Hz, 0.6H), 8.27 (d, *J* = 7.2 Hz, 0.4H), 8.23 (d, *J* = 8.0 Hz, 0.4H), 7.90 (d, *J* = 7.6 Hz, 0.6H), 7.84−7.71 (m, 1.8H), 7.66−7.43 (m, 4.2H), 7.30−7.10 (m, 4.4H), 6.99 (d, *J* = 7.8 Hz, 0.6H), 6.76 (t, *J* = 9.2 Hz, 0.4H), 6.42 (d, *J* = 6.0 Hz, NH), 4.48 (q, *J* = 8.0 Hz, 0.6H), 3.76 (dd, *J* = 14.8, 6.0 Hz, 0.6H), 3.28 (dd, *J* = 14.8, 8.0 Hz, 0.6H), 3.03 (dd, *J* = 14.0, 8.0 Hz, 0.4H), 2.80 (dd, *J* = 14.0, 9.2 Hz, 0.4H); ^{13}C NMR (100 MHz) δ 169.7, 167.5, 161.5, 161.2, 154.1, 150.9, 147.2, 146.1, 136.2, 135.2, 134.9, 134.7, 134.5, 133.2, 132.7, 132.1, 131.4, 130.3, 130.0, 129.6, 129.4, 129.0, 128.8, 128.6, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 127.0, 125.8, 121.7, 121.5, 120.6, 56.6, 55.2, 35.5, 34.1; MS *m/z* 368.16 (M + H); HRMS calcd for ($C_{23}H_{17}N_3O_2$ + Na) 390.1213, found 390.1212.

Benzomalvin A (4). To a solution of **15** (96 mg, 200 μmol, TFA salt) in THF (2 mL) at −78 °C under N_2 atmosphere was added LiHMDS (1 M solution in THF, 0.5 mL). The reaction mixture was stirred at −78 °C for 15 min and then stirred at 0 °C for another 15 min. The mixture was cooled to −78 °C, and MeI (20 μL, 300 μmol) was then added. After being stirred at room temperature for 2 h, the reaction mixture was quenched with two drops of saturated aqueous NH_4Cl, and then concentrated in vacuo. The residue was purified by preparative TLC (hexane/ethyl acetate = 1/1) to afford **4** as a light yellow solid (53 mg, 70%); mp 97−100 °C (lit.[8] mp 98−101 °C); ^{1}H NMR (400 MHz) δ 8.32 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.94 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.84−7.81 (m, 2H), 7.65−7.50 (m, 4H), 7.30−7.16 (m, 5H), 4.88 (dd, *J* = 8.0, 7.0 Hz, 1H), 3.80 (dd, *J* = 14.6, 8.0 Hz, 1H), 3.42 (dd, *J* = 14.6, 7.0 Hz, 1H), 3.10 (s, 3H); ^{13}C NMR (100 MHz) δ 167.3, 161.2, 151.8, 145.9, 136.6, 134.8, 132.9, 131.4, 130.9, 129.9, 129.0, 128.9, 128.8, 128.7, 127.7, 127.5, 126.9, 121.7, 58.2, 33.1, 27.9; MS *m/z* 382.22 (M + H); HRMS calcd for ($C_{24}H_{19}N_3O_2$ + Na) 404.1369, found 404.1366.



The *O*-methylation product was also isolated as a light yellow solid (9 mg, 12%); ^{1}H NMR (400 MHz) δ 8.23 (dd, *J* = 7.8, 0.8 Hz, 1H), 8.12 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.78−7.68 (m, 4H), 7.51−7.44 (m, 3H), 7.35 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.20−7.10 (m, 2H), 6.94 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.80 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.39 (s, 3H), 2.85 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.60 (dd, *J* = 14.0, 10.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 168.3, 160.8, 151.3, 147.3, 140.7, 134.8, 134.6, 132.5, 131.9, 128.7, 128.6, 127.54, 127.51, 127.3, 127.2, 126.2, 121.4, 57.3, 36.2, 34.5; MS *m/z* 382.20 (M + H); HRMS calcd for ($C_{24}H_{19}N_3O_2$ + Na) 404.1369, found 404.1369.

Analogue of Circumdatin E, 16. To a conical-bottomed Smith Process vial were added 2-amino-4-fluorobenzoic acid (**7b**) (31 mg, 200 μmol), *N*-Boc-proline (**9e**) (43 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave on Biotage Smith Synthesizer for 10 min at 150 °C. After the mixture cooled to room temperature, methyl anthranilate (**12a**) (30 mg, 200 μmol) was added and the resulting mixture was heated in the microwave at 230 °C for 15 min. The reaction mixture was concentrated in a Savant, and the residue was separated by preparative HPLC (ProntoSIL 120-10-C18 column (50 × 20 mm^2) with a flow rate at 44 mL/min utilizing an acetonitrile/water mobile phase and 0.1% trifluoroacetic acid as a modifier) to afford **16** as a light yellow solid TFA salt (30.5 mg, 34%); ^{1}H NMR (400 MHz) δ 2.24−2.32 (m, 2H), 2.48 (s, 3H), 3.16 (t, *J* = 7.8 Hz, 2H), 4.20 (t, *J* = 7.2 Hz, 2H), 7.53 (br s, 2H), 8.06 (s, 1H); ^{13}C NMR (100 MHz) δ 19.8, 21.4, 32.6, 46.7, 120.4, 126.0, 126.8, 135.8, 136.5, 147.3, 158.8, 161.2; MS *m/z* 336.18 (M + H); HRMS calcd for ($C_{19}H_{14}FN_3O_2$ + H) 336.1143, found 336.1143.

Analogue of Circumdatin E, 17. To a conical-bottomed Smith Process vial were added 2-amino-5-methylbenzoic acid (**7c**) (30 mg, 200 μmol), *N*-Boc-proline (**9e**) (43 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave on a Biotage Smith Synthesizer for 10 min at 150 °C. After the mixture cooled to room temperature, methyl anthranilate (**12a**) (30 mg, 200 μmol) was added and the resulting mixture was heated in the microwave at 230 °C for 15 min. The reaction mixture was concentrated in a Savant, and the residue was separated by preparative HPLC (ProntoSIL 120-10-C18 column (50 × 20 mm^2) with a flow rate at 44 mL/min utilizing an acetonitrile/water mobile phase and

0.1% trifluoroacetic acid as a modifier) to afford **17** as a light yellow solid TFA salt (26 mg, 29%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.19−2.26 (m, 1H), 2.54−2.64 (m, 1H), 3.04−3.20 (m, 2H), 5.03 (dd, J = 10, 2.6 Hz, 1H), 7.51 (td, J = 7.6, 1.1 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.82 (td, J = 8.0, 1.2 Hz, 1H), 8.11 (dd, J = 8.2, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.2, 31.3, 59.8, 120.7, 126.5, 127.0, 127.5, 135.2, 149.7, 160.3, 160.6, 172.1; MS *m/z* 332.18 (M + H); HRMS calcd for ($C_{20}H_{17}N_3O_2$ + H) 332.1394, found 332.1395.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1**−**4** and **15**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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