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Fluorous synthesis of sclerotigenin-type benzodiazepine–quinazolinones

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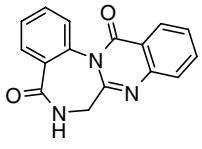
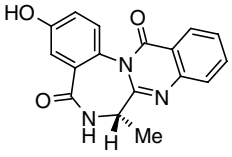
Abstract—A new synthetic protocol for sclerotigenin-type benzodiazepine–quinazolinone library scaffold is introduced. A fluorous benzyl protecting group is used for the synthesis of 4-benzodiazepine-2,5-dione intermediate and also as a phase tag for fluorous solid-phase extraction (F-SPE).

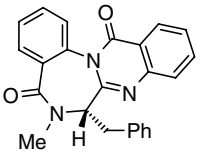
Sclerotigenin was isolated from the sclerotia of *Penicillium sclerotigenum* and has shown a promising anti-insectan activity.[1] It is the simplest member of the benzodiazepine–quinazolinone natural alkaloid family. Other members in this family such as circumdatins A–G isolated from terrestrial fungus *Aspergillus ochraceus*[2] and benzomalvins A–C isolated from fungus *Penicillium* sp. also possess interesting biological activities.[3]



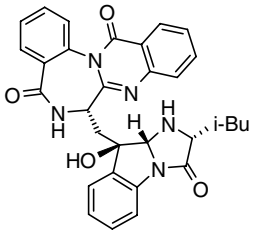
sclerotigenin



circumdatin C



benzomalvin A



(-) asperlicin

Privileged 1,4-benzodiazepine-2,5-dione ring systems are the key intermediates for the synthesis of benzodiazepine–quinazolinone alkaloids.[4] As part of our continuous effort on the development of fluorous synthetic protocols, we have employed a series of fluorous protecting groups for library synthesis.[5,6] Reported here is a new approach to synthesize benzodiazepinedione scaffold using fluorous benzyl as a protecting group and also as a phase tag for fluorous solid-phase extraction (F-SPE).[7] Further derivatization of benzodiazepinediones leads to the formation of sclerotigenin ring skeleton.

Taking the advantage that the numbers of conventional solution-phase and solid-phase synthetic methods for benzodiazepine have been reported in the literature,[8] we adopted Ellman's solid-phase method for fluorous synthesis (Scheme 1).[9] Fluorous benzaldehyde **1** prepared by the reaction of 2,6-dimethoxy-4-hydroxybenzaldehyde with 3-(perfluorooctyl)propanol was used as the starting material. Compound **2** was produced by reductive amination of **1** with an amino ester. Compound **2** reacted with an anthranilic acid in the presence of 1-ethyl-3,3-(dimethylaminopropyl)carbodiimide (EDCI) and *N*-methylpyrrolidine (NMP). The 1,4-benzodiazepine-2,5-dione ring formation was accomplished by base-promoted cyclization of **3**. Compounds **2**–**4** generated in this reaction sequence were purified by simple workup or F-SPE with Fluoro*Flash*®

Keywords: Sclerotigenin; Benzodiazepine–quinazolinone; 1,4-Benzodiazepine-2,5-dione; Fluorous synthesis; Solid-phase extraction.
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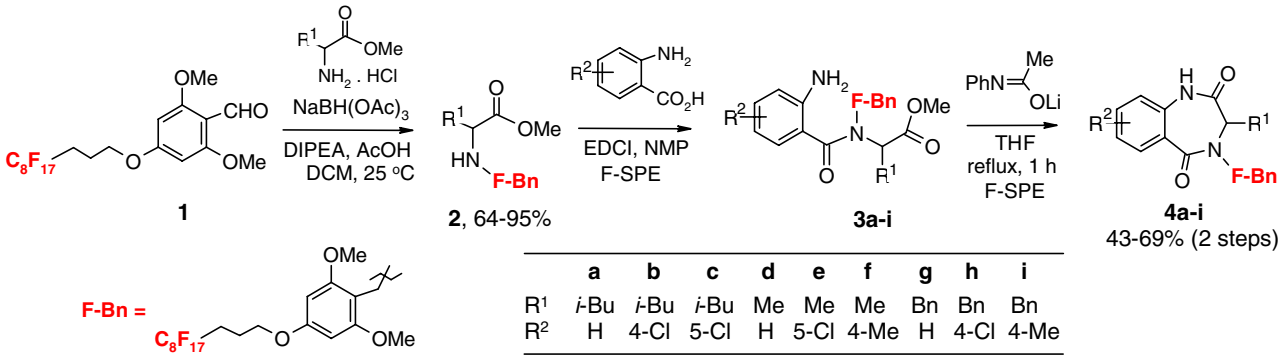
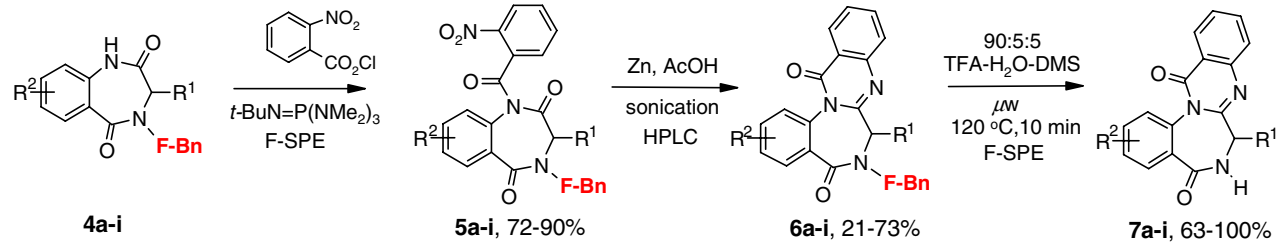


Scheme 1. Fluorous synthesis of benzodiazepinediones **4**.



Scheme 2. Parallel synthesis of nine benzodiazepine–quinazolinones **7**.

Table 1. Yields for the analogs of compounds **5**–**7**

	a	b	c	d	e	f	g	h	i
R^1	*i*-Bu	*i*-Bu	*i*-Bu	Me	Me	Me	Bn	Bn	Bn
R^2	H	4-Cl	5-Cl	H	5-Cl	4-Me	H	4-Cl	4-Me
5a–**i** (%)	82	80	90	75	94	90	75	72	81
6a–**i** (%)	44	50	67	21	51	62	70	65	73
7a–**i** (%)	83	86	91	91	63	71	100	89	97

cartridges.[10] In F-SPE, the first wash with 80:20 MeOH–H_2O eluted the non-fluorous components. The desired fluorous compound was eluted with 100% MeOH. A total of nine analogs of compound **4** with substitution variations (R^1 and R^2) were prepared.[11]

With nine different benzodiazepinediones **4** in hand, we then conducted parallel synthesis to construct the quinazolinone ring skeleton (Scheme 2).[1c] Compound **4** was acylated with 2-nitrobenzoyl chloride in the presence of *t*-BuN=P(NMe_2)$_3$ as a base to give compound **5** (Table 1). If substituted 2-nitrobenzoyl chloride was employed for acylation, the third diversity point (R^3) could be introduced. Compounds **5** were purified by automated RapidTrace® F-SPE.[12] The nitro group of **5** was reduced with zinc dust in acetic acid under sonication conditions. Resulted amino group simultaneously underwent cyclization to form the quinazolinone ring of **6**. The parallel sonication reactions of **5** gave the reduction/cyclization products **6** in a broad range of yield (21–73%). Since some reactions had low yields, F-SPE was not sufficient for purification. Reverse-phase chromatography was applied to purify compounds **6**. The capability to purify fluorous compounds by non-fluorous technique is a useful option. It could be a difficult task in solid-phase synthesis to separate resin-bound impurities. At the last step, F-benzyl tags of compounds **6** were removed by treating with 90:5:5 TFA–H_2O–dimethylsulfide (DMS) under microwave radiation, followed by F-SPE on RapidTrace® workstation to give the final product **7** with the sclerotigenin ring skeleton.[13]

In summary, we have developed a new approach for the synthesis of fluorous 1,4-benzodiazepine-2,5-diones. The key intermediates can be readily converted to sclerotigenin ring skeleton. The new method which produces the library scaffold with substitution variation coupled with the simple F-SPE separation provides an alternative for solution-phase parallel synthesis of benzodiazepine–quinazolinone analogs.

Acknowledgments

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10. Fluoro*Flash*® SPE cartridges are available from Fluorous Technologies, Inc. (www.fluorous.com).
11. *A general procedure for the synthesis of compounds* **2** *and* **4**. To a solution of leucine methyl ester hydrochloride (7.6 g, 42 mmol), 2,6-dimethoxy-4-[3-(perfluorooctyl)propyloxy]-benzaldehyde **1** (26 g, 40 mmol), and *N*,*N*-diisopropylethylamine (7 mL, 0.04 mol) in CH_2Cl_2 (0.3 L) was added 4 Å molecular sieves (3 g) at 23 °C. $NaBH(OAc)_3$ (13 g, 60 mmol) was added after 4 h, then water was added after additional 3 h. The CH_2Cl_2 layer was washed with aq NH_4Cl and brine. After most of the solvent was removed using a rotary evaporator, the residue was passed through a pad of silica gel (50 mL). The product was eluted with hexanes–EtOAc (1:1, 300 mL). The concentrated product was further triturated with hexanes–Et_2O to give the desired compound **2** (R^1 = *i*-Bu, 3.9 g, 95% yield). ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.08 (s, 2H), 4.02 (t, 2H, J = 5.8 Hz), 3.78 (s, 6H), 3.59 (s, 3H), 3.26 (t, 1H, J = 7.1 Hz), 2.45–2.00 (m, 5H), 1.82–1.35 (m, 3H), 0.88 (d, 3H, J = 6.5 Hz), 0.81 (d, 3H, J = 6.4 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.4, 159.3, 108.9, 90.7, 66.3, 59.0, 55.5, 51.3, 42.8, 39.9, 28.2, 27.9, 27.5, 24.8, 22.6, 22.0, 20.5. LC–MS (APCI+) m/z 772 $[M+1]^+$. To a solution of **2** (R^1 = *i*-Bu, 4.3 g, 5.6 mmol) in *N*-methylpyrrolidine (30 mL), 4-chloroanthranilic acid (1.9 g, 11 mmol) and EDCI–HCl (2.1 g, 11 mmol) were added as solids at 23 °C. The same amounts of the acid and EDCI–HCl were added after 2 h and 4 h. One day after the final addition, the reaction mixture was diluted with DMSO (300 mL), and was loaded onto an F-SPE cartridge (50 g), and the flask was rinsed with DMSO (100 mL), and was loaded to the silica gel. The non-fluorous components were eluted with MeCN–H_2O (1:1, 300 mL, and 4:1, 200 mL), and then most of the solvent was drained from the cartridge. The amide coupling product was eluted with MeCN (0.4 L). The MeCN solution was concentrated in a rotary evaporator, and the residue was treated with a solution of lithium acetanilide (0.33 M in THF, 30 mL). The mixture was refluxed for 1 h. After cooling, AcOH (0.6 mL) was added, and the solvent was removed in a rotary evaporator. MeOH (30 mL) was added to the residue, and it was heated until the solvent started to boil. The mixture was left at 23 °C for 1 d, and product **4b** (R^1 = *i*-Bu, R^2 = 4-Cl) was collected as a solid by filtration (3.5 g, 69% yield based on the amount of **2**). ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.16 (dd, J = 7.1, 1.9 Hz 1H), 6.90 (d, J = 1.8 Hz, 1H), 6.09 (s, 2H), 5.23 (d, J = 13.8 Hz, 1H), 4.56 (d, J = 13.8 Hz, 1H), 4.15–3.85 (m, 3H), 3.75 (s, 6H), 2.45–2.00 (m, 4H), 1.60–1.45 (m, 1H), 1.35–1.15 (m, 2H), 0.80 (d, J = 6.4 Hz, 3H), 0.73 (d, J = 6.6 Hz, 3H). ^{13}C NMR (67.5 Hz, $CDCl_3$) δ 173.5, 165.1, 160.6, 160.1, 137.7, 136.2, 133.3, 125.5, 124.6, 119.4, 104.1, 90.6, 66.3, 59.5, 55.5, 42.0, 38.3, 27.9 (t, J = 22 Hz), 25.2, 22.3, 22.1, 20.5. LC–MS (APCI+) m/z 893 $[M+1]^+$.
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13. *A general procedure for the synthesis of compounds* **5**–**7**. To a solution of **4** in CH_2Cl_2 was added *t*-butyliminotris(dimethylamino)phosphorane (10 equiv) and 2-nitrobenzoic acid (2 equiv). The reaction mixture was stirred for 10 min and then concentrated in a rotary evaporator. The residue was dissolved in DMF (1 mL) and purified on RapidTrace® SPE workstation with 2 g cartridges to afford **5** in 72–90% yield. A solution of **5** in acetic acid (1 mL) was added Zn dust (20 equiv) and sonicated at room temperature for 2 h. The Zn was filtered and the filtrate was diluted with EtOAc and washed with $NaHCO_3$ and brine. The EtOAc solution was dried and concentrated in a rotary evaporator. The residue was dissolved in MeCN and purified by C18 HPLC to afford **6** in 21–73% yields. A solution of **6** in TFA–H_2O–DMS (90:5:5) was stirred for 3 days before being concentrated in a rotary evaporator. The residue was dissolved in DMF (1 mL) and purified by RapidTrace® SPE workstation to afford **7** in 63–100% yields. Analytical date for compound **7b** (R^1 = *i*-Bu, R^2 = 4-Cl): ^{1}H NMR (275 Hz, $CDCl_3$) δ 0.90 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 6.5 Hz, 3H), 1.80–2.05 (m, 2H), 2.05–2.25 (m, 1H), 4.10–4.35 (m, 1H), 6.66 (d, J = 6.2 Hz, 1H), 7.45-7.59 (m, 2H), 7.67 (d, J = 1.9 Hz, 1H), 7.70–7.85 (m, 2H), 7.91 (d, J = 8.4 Hz, 1H), 8.31 (dd, J = 1.4, 8.0 Hz, 1H); ^{13}C NMR (67.5 Hz, $CDCl_3$) δ 22.0, 23.1, 24.3, 38.0, 52.4, 121.3, 127.5, 127.8, 127.9, 128.7, 128.9, 129.5, 131.0, 134.3, 135.2, 137.4, 146.0, 154.1, 161.5, 167.1; LCMS (APCI+) 368 $[M+1]^+$.