Oxygen Analogues of the Benzodiazepine Alkaloids Sclerotigenin and Circumdatin F

Anette Witt and Jan Bergman*

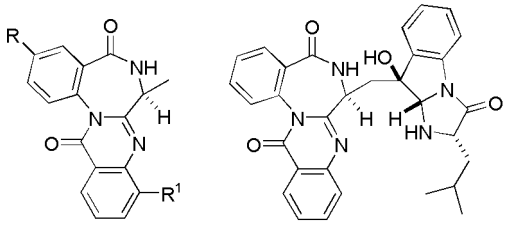
Unit for Organic Chemistry, Department of Biosciences, Karolinska Institute and
Södertörn University College, Novum Research Park, SE-141 57 Huddinge, Sweden
Received July 30, 2001

A new type of fused oxazepinones **9a** and **9b**, which are analogues of sclerotigenin and circumdatin F, were obtained in a two step synthesis from 2-(2-amino-benzoylamino)-benzoic acid or the corresponding methyl ester. Secondly a new synthesis of circumdatin F arose from this work, where 2-(2-propionylamino-benzoylamino)-benzoic acid methyl ester was used as an intermediate.

J. Heterocyclic Chem., **39**, 351 (2002).

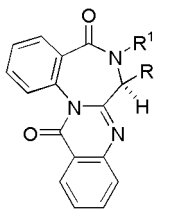
Introduction.

In 1999, several new fused benzodiazepine alkaloids were isolated from a terrestrial isolate of the fungus *Aspergillus ochraceus*. Circumdatin F (**1**) and C (**2**) are two prototypical members (Figure 1) [1]. Recently, a new metabolite, circumdatin G (**3**), has been isolated from the same fungus [2]. The related alkaloid, asperlicin (**4**), produced by *Aspergillus alliaceus*, is a potent cholecystokinin antagonist [3], and benzomalvin A (**5**), isolated from a fungus culture of *Penicillium* sp, showed inhibitory activity against substance P of the guinea pig, rat and human neurokinin NK1 receptors, respectively [4]. Sclerotigenin (**6**) was recently isolated from organic extracts of sclerotia of *Penicillium sclerotigenum* (NRRL 3461) [5], a potential antiinsectan benzodiazepine alkaloid. The total syntheses of circumdatin F (**1**) [6,7], circumdatin C (**2**) [6], asperlicin (**4**) [8] and benzomalvin A (**5**) [9], have been reported and the synthesis of sclerotigenin (**6**) [10] was reported already 20 years ago, *i.e* before its identification as a natural product. No synthesis of circumdatin G (**3**) has yet been published. Now we wish to report a synthesis of oxygen analogues of circumdatin F (**1**) and sclerotigenin (**6**). Furthermore one of the intermediates **8a** could be used in a synthesis of sclerotigenin (**6**) and also a new approach was used in a synthesis of circumdatin F (**1**).



1: R = R^1 = H
2: R = OH, R^1 = H
3: R = H, R^1 = OH

4



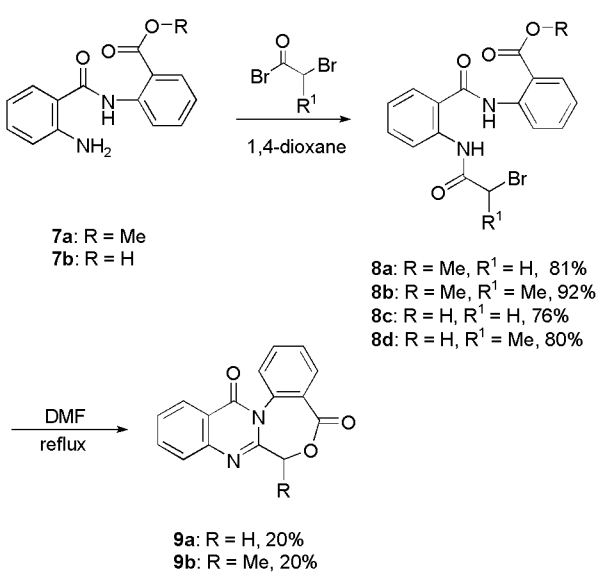
5: R = Bn, R^1 = Me
6: R = R^1 = H

Figure 1

Results and Discussion.

The ester **7a** [11], readily obtained from methyl anthranilate and *N*-sulfinylanthraniloyl chloride [12], was used as a key intermediate. The sulfinyl chloride, previously incorrectly described as a sulfinamide [13], was prepared from anthranilic acid and thionyl chloride. The acid **7b** [14] was synthesised from isatoic anhydride and anthranilic acid. When compounds **7a,b** were treated with bromoacetyl bromide in dioxane the corresponding bromoacetyl compounds **8a,c** were isolated in 81% and 76% yield, respectively (Scheme 1). Analogously with the latter compounds **8b,d** were isolated in 92% and 80% yield, when compounds **7a,b** were treated with 2-bromopropionyl bromide. When the acids **8c,d** were heated at reflux in DMF for 3 hours and overnight, the *O*-sclerotigenin **9a** and *O*-circumdatin F **9b** were isolated after recrystallisation from ethanol in 20% yields, respectively. A reasonable mechanism, using compounds **8c,d**, involves an initial cyclisation to the quinazolinone followed by an intramolecular *O*-alkylation.

Scheme 1



7a: R = Me
7b: R = H

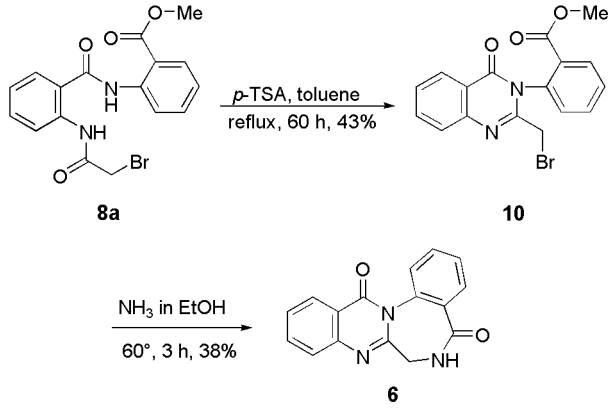
8a: R = Me, R^1 = H, 81%
8b: R = Me, R^1 = Me, 92%
8c: R = H, R^1 = H, 76%
8d: R = H, R^1 = Me, 80%

9a: R = H, 20%
9b: R = Me, 20%

When compounds **8a,b** were heated overnight at reflux in DMF, the *O*-sclerotigenin **9a** was only isolated in 1–2% yield and *O*-circumdatin F **9b** was isolated in 15% yield. Addition of base such as triethylamine did not improve the yields for the reaction with the methyl esters **8a,b**.

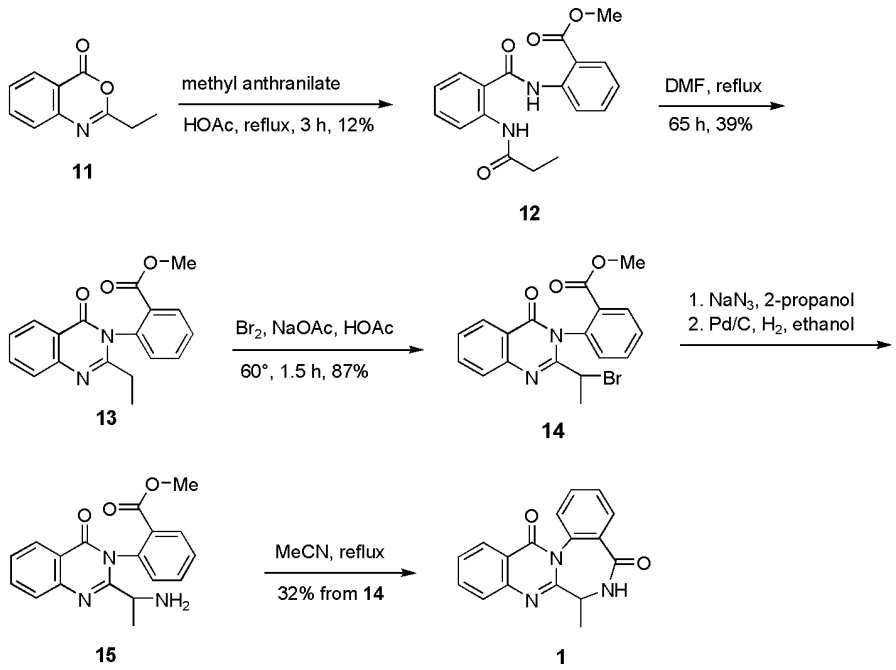
If compounds **8a,b** could be specifically cyclised to the quinazolinone adducts **10** or **14**, these latter compounds could serve as precursors for sclerotigenin (**6**) and circumdatin F (**1**). Compound **8a** could be cyclised using *p*-TSA in toluene at reflux to the quinazolinone **10** [10] in 43% yield (Scheme 2), previously synthesised *via* bromination of the 2-methyl analogue of compound **10**. The quinazolinone **10** when treated with ammonia in ethanol at 60° gave **6** [10] in 38% yield. Compound **8b** could not analogously be cyclised to the quinazolinone **14**, and therefore an alternative approach towards compound **14** was investigated starting with the benzoxazinone **11** [15].

Scheme 2



The benzoxazinone **11** [15], was heated at reflux with methyl anthranilate in acetic acid for 3 hours and compound **12** could be isolated in 12% yield (Scheme 3). The low yield might be due to hydrolysis of the starting material **11**, but the cyclised adduct **13** [16] could also be isolated as a co-product in 5% yield. Optimisation assays towards direct cyclisation from **11** to the quinazolin-4-one **13** gave no satisfactory results in our hands. Instead was compound **12** then heated at reflux in DMF for 65 hours and the quinazolinone adduct **13** was isolated in 39% yield. The total yield was only 4.7% yield in two steps, but prior synthesis of compound **13** has been obtained by allowing the appropriate imidate ester to stand for 15 months [16]. Introduction of an α-bromine atom in 2-ethylquinazolinone using bromine and NaOAc in acetic acid is known [17]. When using this methodology on compound **13** the expected product **14** was isolated in 87% yield, as a diastereomeric mixture (7:3) according to ^{1}H NMR. The interesting stereochemistry of compound **14** is probably due to the chiral axis, which arises from restricted rotation about the amide nitrogen to aryl methyl ester bond. This phenomenon was not further investigated at this point. It is well known that chiral axes are important in asymmetric catalysis [18]. The diastereomeric mixture was separated by flash chromatography in 47% and 32% yield, respectively. The total yield decreased, because the separation was not complete between the diastereomers. When the quinazolinone **14** was treated with ammonia in ethanol, no clean reaction could be observed. Instead the purified quinazolinone **14** was allowed to react with NaN_3 in 2-propanol at reflux overnight and subsequently hydrogenated using 5% Pd/C in ethanol for 7 hours to compound

Scheme 3



15, which could be cyclised without purification in refluxing acetonitrile overnight and after treatment with diethyl ether circumdatin F (**1**) was isolated in 32% yield (3 steps). The synthesis was completed with both diastereomers separately and **1** was isolated as racemate. The amine **15** was not characterised, because it could not be subjected to purification such as chromatography.

In conclusion, a synthesis of a new type of fused oxazepinones **9a,b** has been attained in 2 steps and 15–16% overall yield from **7a,b**. A new synthesis of circumdatin F (**1**) has been achieved in 6 steps in an overall yield of 1% from **11**.

EXPERIMENTAL

General Aspects. NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer, operating at 300 MHz for ^{1}H-nmr and 75 MHz for ^{13}C-nmr respectively; δ values are given in ppm. *J*-Values are given in Hz. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument. Mass spectra were recorded on a Hewlett-Packard GC/MS system (HP 6890 series GC system / HP 5973 mass selective detector) equipped with a capillary column (HP-5MS column with 5% phenyl methyl siloxane) operating in the electron impact (EI) mode at 70 eV. Only fragments larger than 20% of the base peak are given. Element analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. HRMS analyses were performed by E. Nilsson, University of Lund, Sweden. Melting points were determined on a Büchi Melting Point B-545 (capillary method) and are uncorrected. All solvents were purified by distillation or were HPLC grade. Flash chromatography was carried out on silica gel 60 (230–400 mesh ASTM, Merck), TLC analyses were run on Merck Silica Gel 60 F_{254} plates.

2-[2-(2-Bromo-ethanoyl)-benzoylamino]-benzoic Acid Methyl Ester (**8a**).

Bromoacetyl bromide (3.01 g, 15 mmol) was added to a solution of compound **7a** (2.70 g, 10 mmol) in dioxane (55 mL) at 0° under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 hours and then diluted with water until a precipitate appeared, which was collected and washed with water to give compound **8a** (3.17 g, 81%) as a white solid, mp 145–146°; ir (KBr): 3305, 3116, 2957, 1687, 1665, 1608, 1586, 1540, 1450, 1275, 757 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.86 (s, 3H, OC*H*$_3$), 4.16 (s, 2H, C*H*$_2$), 7.28 (ddd, 1H, J = 8.1, 7.2, 0.9), 7.35 (ddd, 1H, J = 8.1, 7.1, 0.9), 7.61 (ddd, 1H, J = 8.5, 7.1, 1.4), 7.69 (ddd, 1H, J = 8.6, 7.1, 1.6), 7.85 (dd, 1H, J = 7.8, 1.4), 7.99 (dd, 1H, J = 7.9, 1.6), 8.12 (d, 1H, J = 8.3), 8.39 (d, 1H, J = 8.3), 10.99 (s, 1H, N*H*), 11.34 (s, 1H, N*H*); ^{13}C-nmr (DMSO-d_6): δ 30.3 (t), 52.5 (q), 118.4 (s), 121.8 (d), 122.2 (d), 123.9 (d), 124.5 (d), 124.7 (s), 128.1 (d), 130.6 (d), 132.2 (d), 134.0 (d), 137.0 (s), 139.4 (s), 164.9 (s), 166.2 (s), 167.6 (s).

Anal. Calcd. for $C_{17}H_{15}BrN_2O_4$: C, 52.19; H, 3.86; N 7.16. Found: C, 52.28; H, 3.88; N, 7.12.

2-[2-(2-Bromo-propanoyl)-benzoylamino]-benzoic Acid Methyl Ester (**8b**).

Compound **8b** was prepared similarly to compound **8a** using 2-bromopropionyl bromide. Yield; 92% as a light yellow solid, mp 144–145°; ir (KBr): 3307, 3103, 1689, 1586, 1535, 1432, 1269, 1096, 757 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.74 (d, 3H, J = 6.8, C*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 4.79 (d, 1H, J = 6.8, C*H*), 7.27 (ddd, 1H, J = 8.0, 7.0, 1.0), 7.34 (ddd, 1H, J = 8.1, 7.1, 1.0), 7.61 (ddd, 1H, J = 8.5, 7.1, 1.4), 7.69 (ddd, 1H, J = 8.6, 7.0, 1.6), 7.85 (dd, 1H, J = 7.8, 1.3), 7.99 (dd, 1H, J = 7.9, 1.6), 8.10 (d, 1H, J = 8.2), 8.40 (d, 1H, J = 8.3), 10.99 (s, 1H, N*H*), 11.33 (s, 1H, N*H*); ^{13}C-nmr (DMSO-d_6): δ 21.6 (q), 44.7 (d), 52.6 (q), 118.2 (s), 121.7 (d), 122.3 (d), 123.9 (d), 124.5 (d), 124.8 (s), 128.1 (d), 130.6 (d), 132.3 (d), 134.1 (d), 137.0 (s), 139.5 (s), 166.2 (s), 167.6 (s), 167.7 (s).

Anal. Calcd. for $C_{18}H_{17}BrN_2O_4$: C, 53.35; H, 4.23; N, 6.91. Found: C, 53.46; H, 4.27; N, 6.82.

2-[2-(2-Bromo-ethanoyl)-benzoylamino]-benzoic Acid (**8c**).

Compound **8c** was prepared similarly to compound **8a** using 2-(2-benzoylamino)-benzoic acid **7b** [14]. Yield; 76 % as a white solid, mp 180–182°; ir (KBr): 3017, 2967, 1666, 1606, 1583, 1532, 1450, 1406, 1253, 1229, 750 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 4.19 (s, 2H, C*H*$_2$), 7.24 (ddd, 1H, J = 8.2, 7.1, 1.1), 7.33 (ddd, 1H, J = 8.1, 7.1, 0.9), 7.60 (ddd, 1H, J = 8.5, 7.1, 1.4), 7.67 (ddd, 1H, J = 8.7, 7.0, 1.6), 7.84 (dd, 1H, J = 7.9, 1.4), 8.04 (dd, 1H, J = 7.9, 1.6), 8.12 (d, 1H, J = 8.3), 8.58 (dd, 1H, J = 8.3, 0.6), 11.00 (s, 1H, N*H*), 11.89 (s, 1H, N*H*), 13.67 (br s, 1H, COO*H*); ^{13}C-nmr (DMSO-d_6): δ 30.33 (t), 117.5 (s), 120.6 (d), 122.4 (d), 123.4 (d), 124.5 (d), 124.9 (s), 128.0 (d), 131.1 (d), 132.2 (d), 134.1 (d), 137.0 (s), 140.4 (s), 164.9 (s), 166.1 (s), 169.7 (s).

Anal. Calcd. for $C_{16}H_{13}BrN_2O_4$: C, 50.95; H, 3.47; N, 7.43. Found: C, 50.76; H, 3.42; N, 7.28.

2-[2-(2-Bromo-propanoyl)-benzoylamino]-benzoic Acid (**8d**).

Compound **8d** was prepared similarly to compound **8a** using 2-bromopropionyl bromide and compound **7b** [14]. Yield; 80% as a light beige solid, mp 192–193°; ir (KBr): 2982, 1683, 1583, 1535, 1450, 1230, 758; ^{1}H-nmr (DMSO-d_6): δ 1.74 (d, 3H, J = 6.7, C*H*$_3$), 4.78 (q, 1H, J = 6.7, C*H*), 7.23 (dd, 1H, J = 7.8, 7.3), 7.33 (dd, 1H, J = 7.7, 7.4), 7.60 (ddd, 1H, J = 8.3, 7.4, 1.0), 7.67 (ddd, 1H, J = 8.5, 7.3, 1.4), 7.83 (dd, 1H, J = 7.8, 0.9), 8.04 (dd, 1H, J = 7.9, 1.4), 8.09 (d, 1H, J = 8.2), 8.58 (d, 1H, J = 8.3), 10.97 (s, 1H, N*H*), 11.87 (s, 1H, N*H*), 13.70 (br s, 1H, COO*H*); ^{13}C-nmr (DMSO-d_6): δ 21.6 (q), 44.7 (d), 117.4 (s), 120.6 (d), 122.4 (d), 123.4 (d), 124.5 (d), 125.1 (s), 128.1 (d), 131.1 (d), 132.2 (d), 134.1 (d), 137.0 (s), 140.5 (s), 166.1 (s), 167.7 (s), 169.6 (s).

7,7-Dihydro-quinazolino[3,2-*a*][4,1]benzoxazepine-5,13-dione (**9a**).

Compound **8c** (570 mg, 1.5 mmol) was heated at reflux for 3 hours in dry DMF (12.5 mL). The solution was poured into water (~20 mL) and a yellow precipitate was collected after 1 hour, which was recrystallised from ethanol to give compound **9a** (83 mg, 20%) as a yellow solid, mp 233–235°; ir (KBr): 1739, 1697, 1650, 1448, 1350, 1107, 785, 764 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 5.01 and 5.26 (AB q, 2H, J = 13.3, C*H*$_2$), 7.60–7.69 (m, 2H), 7.73–7.84 (m, 3H), 7.86 (dd, 1H, J = 7.7, 1.4), 7.93 (ddd, 1H, J = 8.4, 6.9, 1.5), 8.22 (dd, 1H, J = 7.9, 1.2); ^{13}C-nmr (DMSO-d_6): δ 69.7 (t), 121.5 (s), 125.9 (s), 126.9 (d), 127.4 (d), 128.1 (d), 128.5 (d), 129.0 (d), 131.2 (d), 132.5 (d), 133.3 (s), 135.2 (d), 145.8 (s), 150.9 (s), 160.4 (s), 167.0 (s); gc/ms (EI) *m/z* (rel.intensity) 279 (M^++1, 18%), 278 (M^+, 100), 277 (47), 249 (49), 221 (24).

HRMS (EI) for $C_{16}H_{10}N_2O_3$ requires *M*, 278.0691. Found: *m/z* 278.0694.

Anal. Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 69.16; H, 3.74; N, 10.15.

7-Methyl-7*H*-quinazolino[3,2-*a*][4,1]benzoxazepine-5,13-dione (**9b**).

Compound **8d** (400 mg, 1.0 mmol) was heated at reflux overnight in dry DMF (12 mL). The solution was poured into water (~20 mL). The resulting precipitate was collected and recrystallised from ethanol to give compound **9b** (60 mg, 20%) as light brown crystals, mp 224–225°; ir (KBr): 3001, 2941, 1723, 1698, 1619, 1313, 1262, 774, 760 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.69 (d, 3H, J = 6.2, CH_3), 5.43 (q, 1H, J = 6.2, C*H*), 7.59–7.83 (m, 5H), 7.86 (dd, 1H, J = 7.7, 1.5), 7.93 (ddd, 1H, J = 8.3, 6.9, 1.4), 8.21 (dd, 1H, J = 7.9, 1.3); ^{13}C-nmr (DMSO-d_6): δ 15.8 (q), 73.9 (d), 121.5 (s), 126.6 (s), 126.9 (d), 127.7 (d), 128.1 (d), 128.8 (d), 129.0 (d), 130.7 (d), 132.4 (d), 132.9 (s), 135.2 (d), 145.5 (s), 152.2 (s), 160.6 (s), 166.8 (s); gc/ms (EI) *m/z* (rel.intensity) 293 (M^++1, 6%), 292 (M^+, 33), 248 (26), 247 (100).

HRMS (EI) for $C_{17}H_{12}N_2O_3$ requires *M*, 292.0848. Found: *m/z* 292.0843.

Anal. Calcd. for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.74; H, 4.22; N, 9.62.

2-(2-Bromomethyl-4-oxo-4*H*-quinazolin-3-yl)-benzoic Acid Methyl Ester (**10**).

Compound **8a** (850 mg, 2.2 mmol) and a catalytic amount of *p*-TSA were dissolved in toluene (15 mL) and heated at reflux in a Dean-Stark for 60 hours. The solution was concentrated to an oily residue and purified by flash chromatography (gradient from 25–40% ethyl acetate in hexane as eluent) to give compound **10** (350 mg, 43%) as a yellow solid, mp 198–201° (lit. [10] 200–203°); ir (KBr): 3059, 2996, 1716, 1679, 1604, 1593, 1278, 775 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.62 (s, 3H, OCH_3) 4.11 and 4.25 (AB q, 2H, J = 11.0, CH_2) 7.61 (ddd, 1H, J = 7.9, 7.1, 0.8), 7.67–7.81 (m, 3H), 7.83–7.97 (m, 2H), 8.12 (dd, 1H, J = 7.9, 1.4), 8.18 (dd, 1H, J = 7.8, 1.5); ^{13}C-nmr (DMSO-d_6): δ 30.3 (t), 52.3 (q), 120.6 (s), 126.5 (d), 127.3 (d), 127.6 (s), 127.7 (d), 130.2 (d), 131.2 (d), 131.5 (d), 134.0 (d), 135.0 (d), 136.0 (s), 146.8 (s), 151.8 (s), 161.3 (s), 164.2 (s).

6,7,7-Trihydro-quinazolino[3,2-*a*][1,4]benzodiazepine-5,13-dione (**6**).

Compound **10** (210 mg, 0.56 mmol) was heated at 60° with presaturated NH_3 in ethanol (10 mL). After 3 hours the solution was cooled at 0° and a precipitate was collected. The mother liquid was allowed to stand and yellow crystals were collected to give sclerotigenin (**6**) (60 mg, 38%), mp 310–313° (lit. [10], 312–315 °C); ir (KBr): 3317, 1668, 1610, 1350, 1230, 760 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 4.00 (dd, 1H, J = 15.0, 6.7, CH_2), 4.19 (dd, 1H, J = 15.0, 5.2, CH_2), 7.53–7.68 (m, 4H), 7.72 (d, 1H, J = 8.1), 7.80 (d, 1H, *J* 7.2), 7.90 (dd, 1H, *J* 8.2, 7.0), 8.19 (d, 1H, *J* 7.3), 8.96 (br t, 1H, J = 5.8, N*H*); ^{13}C-nmr (DMSO-d_6): δ 46.2 (t), 121.0 (s), 126.9 (d), 127.1 (d), 127.6 (d), 128.5 (d), 128.8 (d), 129.3 (d), 130.6 (s), 130.7 (d), 133.4 (s), 135.2 (d), 146.1 (s), 154.8 (s), 161.0 (s), 167.0 (s); gc/ms (EI) *m/z* (rel.intensity) 278 (M^++1, 18%), 277 (M^+, 100), 276 (53), 249 (27), 248 (23).

2-(2-Propionylamino-benzoylamino)-benzoic Acid Methyl Ester (**12**).

Compound **11** [15] (1.78 g, 10 mmol) and methyl anthranilate (1.69 g, 11 mmol) were heated at reflux in acetic acid (40 mL) for 3 hours. The cooled solution was poured into water (~100 mL). The resulting precipitate was collected and purified by flash chromatography (33% ethyl acetate in hexane as eluent, r_f = 0.42) to give compound **12** (410 mg, 12%) as a white solid, mp 133–136°; ir (KBr): 3269, 3204, 1700, 1583, 1540, 1261, 753 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.05 (t, 3H, J = 7.5, CH_3), 2.33 (q, 2H, J = 7.5, CH_2), 3.85 (s, 3H, OCH_3), 7.23–7.32 (m, 2H), 7.56 (ddd, 1H, J = 8.5, 7.1, 1.4), 7.68 (ddd, 1H, J = 8.6, 7.0, 1.6), 7.81 (dd, 1H, J = 7.8, 1.4), 7.99 (dd, 1H, J = 7.9, 1.5), 8.14 (d, 1H, J = 8.3), 8.39 (d, 1H, J = 8.3), 10.51 (s, 1H, N*H*), 11.31 (s, 1H, N*H*); ^{13}C-nmr (DMSO-d_6): δ 9.4 (q), 30.0 (t), 52.5 (q), 118.3 (s), 121.7 (d), 122.1 (d), 123.6 (d), 123.8 (d), 124.1 (s), 128.0 (d), 130.6 (d), 132.2 (d), 134.1 (d), 137.9 (s), 139.5 (s), 166.6 (s), 167.7 (s), 171.9 (s).

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.17; H, 5.49; N, 8.50.

2-(2-Ethyl-4-oxo-4*H*-quinazolin-3-yl)-benzoic Acid Methyl Ester (**13**).

Compound **12** (1.16 g, 3.6 mmol) was heated at reflux in dry DMF (35 mL) for 65 hours. The dark solution was poured into water (~50 mL) and a precipitate was collected after 1 hour to give compound **13** (430 mg, 39%) as a yellow solid, mp 151–152° (lit. [16] 146.5–147°); ir (KBr): 2981, 2938, 1720,1677, 1604, 1595, 1275, 1084, 780, 766 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.13 (t, 3H, J = 7.3, CH_3), 2.13-2.45 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 7.51 (dd, 1H, J = 7.8, 7.2), 7.62 (d, 1H, J = 7.8), 7.66–7.75 (m, 2H), 7.81–7.89 (m, 2H), 8.08 (d, 1H, J = 7.8), 8.14 (d, 1H, J = 7.5); ^{13}C-nmr (DMSO-d_6): δ 10.4 (q), 28.4 (t), 52.3 (q), 120.3 (s), 126.2 (d), 126.3 (d), 126.9 (d), 127.5 (s), 129.7 (d), 130.7 (d), 131.4 (d), 134.2 (d), 134.6 (d), 137.3 (s), 147.3 (s), 157.3 (s), 161.4 (s), 164.4 (s).

2-[2-(1-Bromo-ethyl)-4-oxo-4*H*-quinazolin-3-yl]-benzoic Acid Methyl Ester (**14**).

Bromine (400 mg, 2.5 mmol) in acetic acid (5 mL) was added during 15 minutes to a solution of compound **13** (780 mg, 2.5 mmol) and NaOAc (220 mg, 2.7 mmol) in acetic acid (20 mL) at 60°. The reaction mixture was stirred for 1.5 hours. Whereupon the reaction mixture was slowly poured into cold water and the precipitate formed was collected, washed with water to give compound **14** (850 mg, 87%) as a yellow solid; diastereomeric mixture (7:3) according to ^{1}H NMR. The diastereomeric mixture of compound **14** (530 mg, 1.4 mmol) was separated by flash chromatography (60% ethyl acetate in hexane as eluent).

The First Diastereoisomer.

This compound (r_f = 0.42), 250 mg (47%) was obtained as a white solid, mp 149–150°; ir (KBr): 2950, 1724, 1680, 1595, 1275, 1064, 780 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.94 (t, 3H, J = 6.5, CH_3), 3.63 (s, 3H, OCH_3), 4.49 (q, 1H, J = 6.5, C*H*), 7.54–7.67 (m, 2H), 7.69–7.83 (m, 2H), 7.83–7.96 (m, 2H), 8.10 (dd, 1H, J = 7.9, 1.0), 8.14 (dd, 1H, J = 7.8, 1.4); ^{13}C-nmr (DMSO-d_6): δ 22.8 (q), 43.8 (d), 52.5 (q), 120.7 (s), 126.5 (d), 127.5 (d), 127.6 (s), 127.7 (d), 130.3 (d), 131.6 (2 × d), 133.9 (d), 135.1 (d), 135.4 (s), 146.6 (s), 155.4 (s), 161.1 (s), 164.7 (s).

The Second Diastereoisomer.

This compound (r_f = 0.30), 170 mg (32%) was obtained as a white solid, mp 176–178°; ir (KBr): 2951, 1723, 1681, 1592, 1265, 1092, 776, 695 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.96 (d, 3H, J = 6.5, CH_3), 3.56 (s, 3H, OCH_3), 4.57 (q, 1H, J = 6.5, C*H*), 7.59 (dd, 1H, J = 7.9, 7.1), 7.67–7.81 (m, 3H), 7.81–7.96 (m, 2H),

8.13 (dd, 1H, J = 7.9, 0.8), 8.17 (d, 1H, J = 7.8); ^{13}C-nmr (DMSO-d_6): δ 23.3 (q), 43.0 (d), 52.1 (q), 120.7 (s), 126.5 (d), 127.4 (d), 127.6 (d), 128.0 (s), 130.1 (d), 130.9 (d), 131.6 (d), 134.2 (d), 134.9 (d), 136.1 (s), 146.7 (s), 153.9 (s), 161.4 (s), 163.9 (s).

Anal. Calcd. for $C_{18}H_{15}BrN_2O_3$: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.79; H, 3.89; N, 7.15.

6,7-Dihydro-7-methyl-quinazolino[3,2-*a*][1,4]benzodiazepine-5,13-dione (**1**).

Sodium azide (100 mg, 1.5 mmol) dissolved in water (2 mL) was added to a mixture of compound **14** (285 mg, 0.74 mmol) in 2-propanol (10 mL). The mixture was heated at reflux overnight. The solution was concentrated to an oily residue and treated with water/ethyl acetate (1:1). The aqueous phase was extracted with ethyl acetate (25 mL×2), the combined organic phases were dried ($MgSO_4$) and concentrated to give an yellow oil. The crude oil was dissolved in ethanol (20 mL) and hydrogenated in a Parr apparatus with 220 psi at room temperature using 5% Pd/C as catalyst for 7 hours. After solvent concentration, the crude amino compound **15** was dissolved in acetonitrile (10 mL) and heated at reflux overnight. The solution was concentrated and treated with diethyl ether. The resulting precipitate was collected to give circumdatin F (**1**) (69 mg, 32%) as a light grey solid. The spectral data of **1** were identical with those previously published [1,6,7].

Acknowledgement.

We thank Mr. Patrik Rhönnstad, a student from Södertörn University College, for his help with part of the synthetic work.

REFERENCES AND NOTES

[1a] L. Rahbæk, J. Breinholt, J. C. Frisvad and C. Christophersen, *J. Org. Chem.*, **64**, 1689 (1999); [b] L. Rahbæk and J. Breinholt, *J. Nat. Prod.*, **62**, 904 (1999).

[2] J-R. Dai, B. K. Carté, P. J. Sidebottom, A. Lee Sek Yew, S-B. Ng, Y. Huang and M. S. Butler, *J. Nat. Prod.*, **64**, 125 (2001).

[3a] M. A. Goetz, M. Lopez, R. L. Monaghan, R. S. L. Chang, V. J. Lotti and T. B. Chen, *J. Antibiot.*, **38**, 1633 (1985); [b] J. M. Liesch, O. D. Hensens, J. P. Springer, R. S. L. Chang and V. J. Lotti, *J. Antibiot.*, **38**, 1638 (1985); [c] H. H. Sun, S. J. Byard and R. Copper, *J. Antibiot.*, **47**, 599 (1994).

[4] H. H. Sun, C. J. Barrow, D. M. Sedlock, A. M. Gillum and R. Copper, *J. Antibiot.*, **47**, 515 (1994).

[5] B. K. Joshi, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *J. Nat. Prod.*, **62**, 650 (1999).

[6] A. Witt and J. Bergman, *J. Org. Chem.*, **66**, 2784 (2001).

[7] B. B. Snider and M. V. Busuyek, *Tetrahedron*, **57**, 3301 (2001).

[8] F. He, B. M. Foxman and B. B. Snider, *J. Am. Chem. Soc.*, **120**, 6417 (1998).

[9] T. Sugimori, T. Okawa, S. Eguchi, A. Kakehi, E. Yashima and Y. Okamoto, *Tetrahedron*, **54**, 7997 (1998).

[10] D. R. Harrison, P. D. Kennewell and J. B. Taylor, *J. Heterocyclic Chem.*, **14**, 1191 (1977).

[11] V. P. Kamat and J. K. Kirtany, *Org. Prep. Proced. Int.*, **26**, 494 (1994).

[12] J. Garín, P. Merino, J. Orduna, T. Tejero and S. Uriel, *Tetrahedron Lett.*, **32**, 3263 (1991).

[13] T. Kametani, T. Higa, C. Van Loc, M. Ihara, M. Koizumi and K. Fukumoto, *J. Am. Chem. Soc.*, **98**, 6186 (1976).

[14a] A. Hoorfar, W. D. Ollis, J. A. Price, J. Stephanidou Stephanatou and J. F. Stoddart, *J. Chem. Soc., Perkin Trans 1*, 1649 (1982); [b] R. P. Staiger and E. B. Miller, *J. Org. Chem.*, **24**, 1214 [1959]; [c] A. Mohr, *J. Prakt. Chem.*, **79**, 281 (1909).

[15] A. O. Fitton and R. K. Smalley, Practical Heterocyclic Chemistry, Academic Press, London, 1968, pp 121−122.

[16] R. W. Leiby, *J. Org. Chem.*, **50**, 2926 (1985).

[17] I. Hermecz, J. Kökösi, B. Podányi and G. Szász, *Heterocycles*, **37**, 903 (1994).

[18] For recent review, see: M. McCarthy and P. J. Guiry, *Tetrahedron*, **57**, 3809 (2001).