A concise synthesis of enantiopure circumdatins E, H and J†

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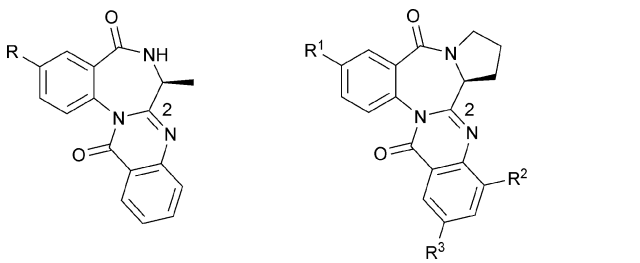
A concise total synthesis of enantiopure circumdatins E, H and J has been developed using a reductive cyclization of chiral *N*-prolinoyl-2-nitrobenzamides to construct the core quinazolinone ring.

Circumdatins, a sub-group of fused quinazolinobenzodiazepine alkaloids, were first isolated by Rahbæk *et al.* from a marine fungus *Aspergillus ochraceus* (subgenus Circumdati).[1] Biologically derived from the fusion of an amino acid and two molecules of anthranilic acids, these compounds possess an asymmetric substituent in the 2-position of the quinazolinone ring (Fig. 1). Owing to the diverse biochemical activity of quinazolinobenzodiazepine alkaloids and their derivatives, which includes, for instance, cholecystokinin antagonism[2] and inhibition of substance P[3] and mitochondrial NADH oxidase,[4] they have been firmly in the sights of the organic chemistry community.[5] However, publications on the synthesis of enantiopure circumdatins are sparse and, except for one publication on circumdatin C, are limited to circumdatin F.[6] The synthesis of other circumdatins is not known. In this Communication we would like to report the first concise total synthesis of enantiopure circumdatins E, H and J.



1: R = OH (circumdatin C)
2: R = H (circumdatin F)

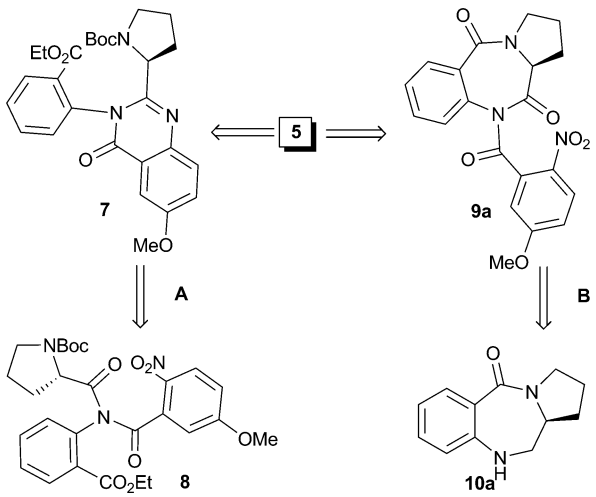
3: R^1, R^3 = OMe; R^2 = OH (circumdatin D)
4: R^1 = H, R^2 = OH, R^3 = OMe, (circumdatin E)
5: R^1, R^2 = H; R^3 = OMe (circumdatin H)
6: R^1, R^3= OMe; R^2 = H (circumdatin J)

Fig. 1 Structures of known circumdatins.

In the total synthesis of quinazolinobenzodiazepine alkaloids, the formation of the quinazolinone ring, while preserving the chiral integrity of the substituents, is a critical step. Traditionally, this cyclization has been done *via* the aza-Wittig reaction.[6b,7] However, this reaction has a downside of using explosive and commercially unavailable 2-azidobenzoic acids. The alternative Mazurkiewicz–Ganesan protocol, generally, requires longer synthetic sequences.[6a] Thermal cyclization of the corresponding amides usually brings about epimerization,[6d,8] although lately progress has been made using Lewis acid-catalyzed conditions.[6c–e]

Recently, we discovered that the reductive cyclization of the chiral amino acid-derived 2-nitrobenzamides cleanly affords quinazolinones with a chiral substituent in the 2-position.[9] We envisioned that this reaction would make possible a short synthesis of enantiopure pentacyclic circumdatins (the right structure on Fig. 1) whose common core can be conceived as formed from the fusion of L-proline and two molecules of substituted anthranilic acids.

Two synthetic strategies towards circumdatin H, which we chose as the first example, are shown on Scheme 1. In the first approach A, the synthesis is concluded with the formation of the benzodiazepine ring, while in the second approach B, it is the quinazolinone ring that forms last.



Scheme 1 Retrosyntheses of circumdatin H (**5**).

In order to prepare intermediate **8** for the approach A, we planned to employ the Mumm reaction of Boc-L-proline[9,10] with the recently reported *N*-(2-benzoate)-substituted imidoyl chlorides **14** (Scheme 2).[11] However, in our hands, the recommended heating of **12** with thionyl chloride led to a gradual formation of benzoxazine **13**. At no point during this heating could the desired imidoyl chloride **14** be detected. Our result is consistent with an earlier report from a different group of researchers that similar imidoyl chlorides were unstable, forming oxazines on heating.[12] The activation of the amide bond of **12** under milder

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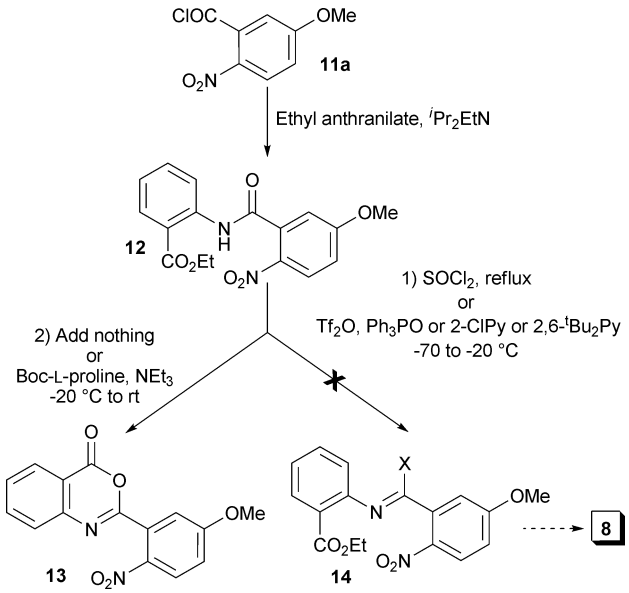
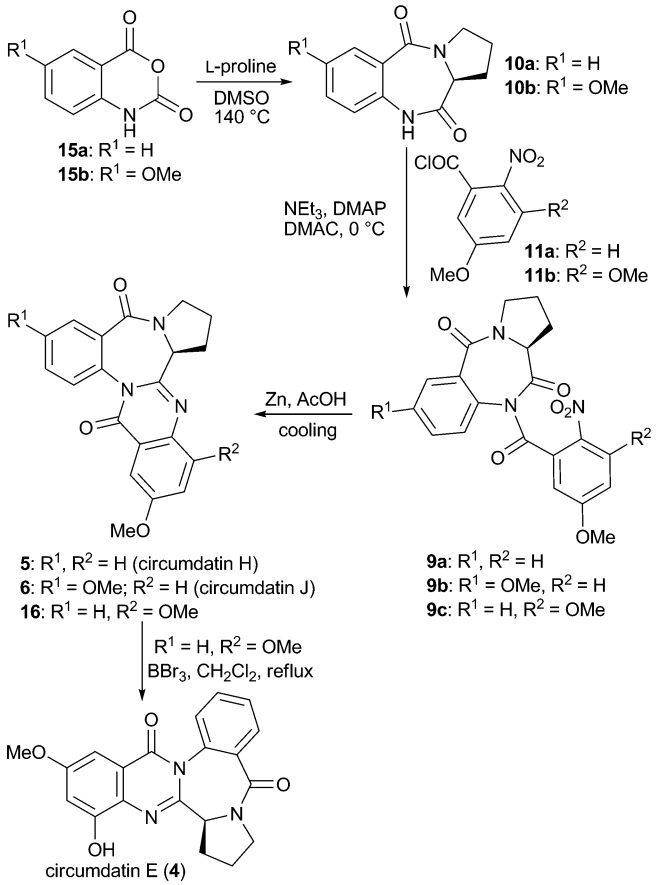


Scheme 2 Attempted synthesis of intermediate **8**.



Scheme 3 Preparation of circumdatins E, H and J.

conditions,[13] using Hendrickson reagent or triflic anhydride/2,6-di-*tert*-butylpyridine, or triflic anhydride/2-chloropyridine followed by the addition of Boc-L-proline and triethylamine also afforded **13**.

At this point we turned to the second approach (see disconnection B, Scheme 1 and Scheme 3), inspired by Snider's work on circumdatin F[6b] and asperlicin C[7a] and by the fact that intermediate **10a** could be obtained with high chiral purity in one step by simply heating isatoic anhydride with L-proline.[14]

After the first step smoothly afforded a 91% yield of **10a**, we began exploring the conditions for the following reaction with acid chloride **11a**.[15] Because of the poor solubility of **10a** in most organic solvents, the reactions conducted in THF employing NaH[14] or NaHMDS as a base were sluggish and accompanied by side reactions, required large excess of **11a** and prolonged reaction time, and afforded only moderate conversion to **9a**. Similarly disappointing results were obtained with DMAP in THF[6b] or CH_2Cl_2.[7a] In the search for an alternative solvent, we decided to try *N*,*N*-dimethylacetamide (DMAC), a solvent similar to DMF but more stable, which has been successfully used in the formation of amides from acid chlorides.[16]

To our satisfaction, the reaction of **10a** and **11a** in DMAC in the presence of DMAP and triethylamine resulted in 82% conversion to the desired 2-nitrobenzamide **9a**. Unlike the previously described analogues,[9] **9a** has proved to be quite unstable to water: it partially decomposed during an aqueous work-up and on a silica gel column, during an attempt to purify it. Taking this into account, the decision was made to proceed with the reductive cyclization step without isolating **9a**.

Thus, the reaction mixture containing **9a** was cooled and treated with excess acetic acid and zinc smoothly affording the desired circumdatin H (**5**) in 70–72% yield.‡[17] During this step, it is important to keep the temperature as low as possible to avoid a partial loss of chiral purity: when the reductive cyclization was conducted at 18 °C the product's enantiomeric excess (*ee*) was 87%; when the temperature was held at –20 °C during the addition of acetic acid and zinc and then was slowly raised to –5 °C the product had 98% *ee*.[18]

Encouraged by this result we set upon the preparation of the next target, circumdatin J (**6**) whose molecule contains an additional methoxy-substituent. The synthesis proceeded uneventfully. The reaction of commercially available 5-methoxyisatoic anhydride (**15b**) with L-proline afforded the desired benzodiazepinone **10b** in 88% yield. The following two-step one-pot acylation–reductive amination sequence conducted as described above, afforded a 70% yield of circumdatin J with higher than 99% *ee*.

The same general reaction sequence has successfully led to circumdatin E. Benzodiazepinone **10a** and acid chloride **11b**[19] smoothly gave rise to intermediate 2-nitrobenzamide **9c**. After some experimentation, we found that the best yield of **16** (50%) was achieved when the reductive cyclization was carried out in THF/acetic acid and used crude **9c** isolated after a brief aqueous work-up. Several sets of conditions such as treating **16** with excess BBr_3 or BCl_3, or heating with hydrobromic acid resulted in an unselective deprotection of the methoxy-groups in the molecule. Fortunately, heating **16** with 1.1 equivalent of BBr_3 in methylene chloride afforded circumdatin E in a moderate yield (46%). The reaction had to be stopped before it reached the completion to avoid the double deprotection.[20] To our delight, the chirality was preserved even under the strongly acidic conditions applied, and the final material possessed >99% *ee*.

In summary, we have developed a novel and concise entry into the chiral quinazolinobenzodiazepine alkaloids *via* a reductive

cyclization of 2-nitrobenzamides. This simple 2–3 step approach has enabled us to carry out the first synthesis of enantiopure circumdatins E, H and J in 21–65% overall yield from commercially available starting materials.

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Notes and references

‡ Representative procedure for the synthesis of circumdatin H (**5**). (*S*)-2,3-Dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-dione (**10a**) (500 mg, 2.31 mmol), DMAP (113 mg, 0.924 mmol) and Et_3N (0.64 mL, 470 mg, 4.62 mmol) were dissolved in anhydrous *N*,*N*-dimethylacetamide (5 mL). Acid chloride **11a** (0.43 mL, 600 mg, 2.78 mmol) was added while keeping temperature below 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. Acetic acid (5 mL) was added, and the reaction mixture was cooled to −30 °C. Zinc dust (3.00 g, 46.2 mmol) was added, and the reaction was stirred at −20 °C for 1.5 h and then slowly warmed to −5 °C over 2 h. The reaction mixture was poured into 10% aqueous K_2CO_3 (60 mL) and extracted with EtOAc (2 × 100 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes/EtOAc gradient from 50 to 100% EtOAc) to afford **5** in 72% yield (582 mg) as a yellow solid: mp 171–172 °C; $[\alpha]_D^{25}$ −123.6 (*c* 0.8, MeOH) (lit.[4] $[\alpha]_D$ −26.3 (*c* 0.078, MeOH)). 97.9% *ee* was determined by HPLC analysis using Chiralpak AD-H column (4.6 × 250 mm, 60% heptane: 40% *i*-PrOH with 0.1% TFA at 1 mL min^{-1}, wavelength 235 nm), retention time: *t*S= 12.7 min, and *t*R= 15.6 min. NMR data are consistent with the literature:[4] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.4, 1.2 Hz, 1H), 7.68 (d, J = 2.9 Hz, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.60–7.55 (m, 2H), 7.52 (ddd, J = 7.8, 6.2, 2.5, 1H), 7.38 (dd, J = 8.0, 3.0 Hz, 1H), 4.54 (dd, J = 8.0, 1.6 Hz, 1H), 3.93 (s, 3H), 3.79 (ddd, J = 11.5, 8.4, 2.7 Hz, 1H), 3.64–3.68 (m, 1H), 3.16 (m, 1H), 2.31 (sextet, J = 9.4 Hz, 1H), 2.18–2.12 (m, 1H), 2.11–2.03 (m, 1H).

1 (*a*) L. Rahbæk, J. Breinholt, J. C. Frisvad and C. Christophersen, *J. Org. Chem.*, 1999, **64**, 1689; (*b*) L. Rahbæk and J. Breinholt, *J. Nat. Prod.*, 1999, **62**, 904; (*c*) the structure of circumdatins A and B was recently revised, see: R. Ookura, K. Kito, T. Ooi, M. Namikoshi and T. Kusumi, *J. Org. Chem.*, 2008, **73**, 4245.

2 M. G. Bock, R. M. DiPardo, K. E. Rittle, B. E. Evans, R. M. Freidinger, D. F. Veber, R. S. L. Chang, T. B. Chen, M. E. Keegan and V. J. Lotti, *J. Med. Chem.*, 1986, **29**, 1941; M. G. Bock, R. M. DiPardo, S. M. Pitzenberger, C. F. Homnick, J. P. Springer and R. M. Freidinger, *J. Org. Chem.*, 1987, **52**, 1644.

3 H. H. Sun, C. J. Barrow, D. M. Sedlock, A. M. Gillum and R. Cooper, *J. Antibiot.*, 1994, **47**, 515.

4 M. P. Lopez-Gresa, M. C. Gonzalez, J. Primo, P. Moya, V. Romero and E. Estornell, *J. Antibiot.*, 2005, **58**, 416.

5 For a review, see: S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787.

6 (*a*) A. Witt and J. Bergman, *J. Org. Chem.*, 2001, **66**, 2784; (*b*) B. B. Snider and M. V. Busuyek, *Tetrahedron*, 2001, **57**, 3301; (*c*) U. A. Kshirsagar, S. B. Mhaske and N. P. Argade, *Tetrahedron Lett.*, 2007, **48**, 3243; (*d*) M.-C. Tseng, C.-Y. Lai, Y.-W. Chu and Y.-H. Chu, *Chem. Commun.*, 2009, 445; (*e*) M.-C. Tseng, H.-Y. Yang and Y.-H. Chu, *Org. Biomol. Chem.*, 2010, **8**, 419.

7 (*a*) F. He, B. M. Foxman and B. B. Snider, *J. Am. Chem. Soc.*, 1998, **120**, 6417; (*b*) T. Sugimori, T. Okawa, S. Eguchi, A. Kakehu, E. Yashima and Y. Okamoto, *Tetrahedron*, 1998, **54**, 7997.

8 J.-F. Liu, M. Kaselj, Y. Isome, J. Chapnick, B. Zhang, G. Bi, D. Yohannes, L. Yu and C. M. Baldino, *J. Org. Chem.*, 2005, **70**, 10488.

9 P. Zhichkin, E. Kesicki, J. Treiberg, L. Bourdon, M. Ronsheim, H. C. Ooi, S. White, A. Judkins and D. Fairfax, *Org. Lett.*, 2007, **9**, 1415.

10 For the first report of the Mumm reaction of imidoyl chlorides with amino acids, see: W. Gruszecki, M. Gruszecka and H. Bradaczek, *Liebigs Ann. Chem.*, 1988, 331.

11 A. Kalusa, N. Chessum and K. Jones, *Tetrahedron Lett.*, 2008, **49**, 5840.

12 N. D. Adams, S. J. Schmidt, S. D. Knight and D. Dhanak, *Tetrahedron Lett.*, 2007, **48**, 3983.

13 (*a*) J. B. Hendrickson and M. S. Hussoin, *J. Org. Chem.*, 1989, **54**, 1144; (*b*) A. G. Myers, N. J. Tom, M. E. Fraley, S. B. Cohen and D. J. Madar, *J. Am. Chem. Soc.*, 1997, **119**, 6072.

14 This intermediate is also commercially available; however, it is very simple to make following S. MacQuarrie-Hunter and P. R. Carlier, *Org. Lett.*, 2005, **7**, 5305. See the Supplementary Material for details.

15 **11a** was prepared by heating 5-methoxy-2-nitrobenzoic acid with thionyl chloride and used crude. See the Supplementary Material for details.

16 R. J. Cvetovich and L. DiMichelle, *Org. Process Res. Dev.*, 2006, **10**, 944.

17 The spectra of synthesized circumdatins E, H and J and their rotation signs match the ones reported for the corresponding natural materials. See the Supplementary Material for details.

18 The chiral purity of all products was determined by comparing the HPLC traces of the product and of the racemic material independently synthesized from racemic proline. For the HPLC conditions, see the Supplementary Material for details.

19 **11b** was prepared by reacting 2-nitro-3,5-dimethoxybenzoic acid with oxalyl chloride and used crude. The synthesis of the acid itself was based on F. Roblot, R. Hocquemiller and A. Cavé, *Bull. Soc. Chim. Fr.*, 1990, **127**, 258. See the Supplementary Material for details.

20 The yield given takes into account the recovered amount of starting material **16**.