Models of the BC ring systems of MPC1001 and MPC1001F†

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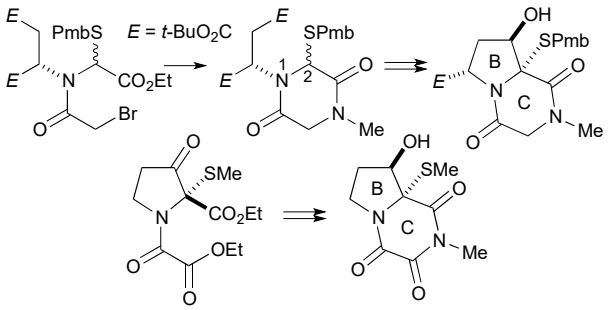
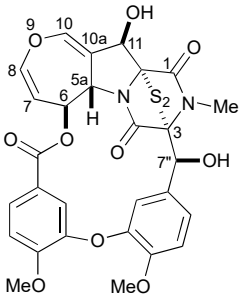
ABSTRACT: Piperazinedione **13**, representing the BC ring system of the anti-prostate cancer fungal metabolite MPC1001 was prepared by a route in which a sulfur-stabilized carbanion derived from **22** cyclizes onto the terminal ester of the chain attached to N^1. Another model, **14**, was synthesized by cyclization of an α-ketoamide nitrogen onto an ester; **14** represents the BC rings of MPC1001F.

Diagrams for the Table of contents graphic:



Abstract for the table of contents: Synthetic routes were developed to bicyclic piperazinedione and piperazinetrione systems that represent the BC rings of several members of the MPC1001 family of fungal metabolites.

MPC1001 (**1**),[1] MPC1001B-H (**2**–**4**, **6**–**9**)[1] and emestrin (**5**)[2,3] comprise a group of fungal metabolites of very complex structure. Emestrin possesses strong antifungal activity[2] while some of the others have biological properties relevant to the treatment of prostate cancer[1] and, in this respect, MPC1001 appears to be the most significant because in vitro tests show that, compared with currently used drugs, it has exceptionally strong activity against the DU145 prostate cancer cell line.[1] MPC1001B is slightly less potent.[1a] All of the compounds present formidable synthetic challenges, partly because of their structural complexity, partly as a result of stereochemical features and, to an appreciable extent, because their chemical reactivity pattern is largely uncharted. In each compound many carbon atoms are functionalized, with several examples of contiguous functionalization. No biological properties have been reported for MPC1001F but the compound shares many of the synthetic challenges of other members of the MPC family. One synthesis of MPC1001B has been published[4] but no member of the family with the seriously complicating presence of a C-11 hydroxyl, such as MPC1001, has been synthesized, although a number of impressive achievements in the synthesis of natural products also having dihydrooxepin and piperazine-1,4-dione subunits have been reported.[5]



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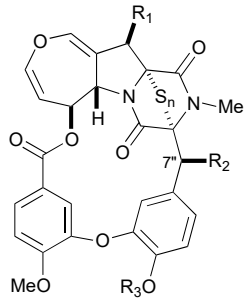
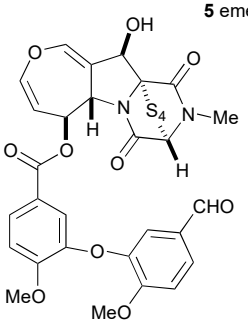
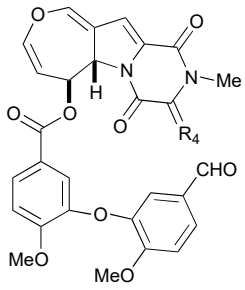


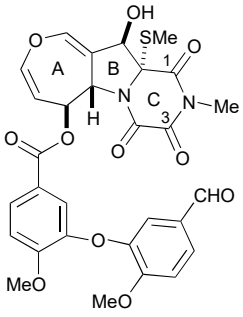
2 MPC1001B, n = 2, R_1 = H, R_2 = OH, R_3 = Me
3 MPC1001C, n = 2, R_1 = OH, R_2 = H, R_3 = Me
4 MPC1001D, n = 3, R_1 = OH, R_2 = OH, R_3 = Me
5 emestrin, n = 2, R_1 = OH, R_2 = OH, R_3 = H



6 MPC1001E

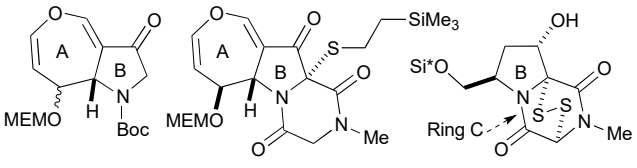


7 MPC1001G, R_1 = S
8 MPC1001H, R_1 = O



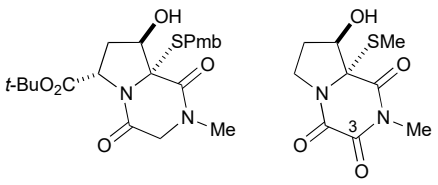
9 MPC1001F

Previous publications from this laboratory have described[6] exploratory synthetic studies related especially to MPC1001 in the form of routes to the model compounds **10**-**12** which were



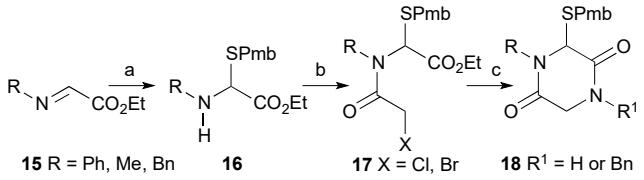
10 **11** **12** R = *t*-$BuMe_2Si$

synthesized from 4-hydroxy-L-proline. Here we describe a completely different approach to bicyclic piperazines that are BC ring models.[7] The particular compounds we have now made are **13** and **14** which are related to several members of the MPC series.



13 **14**

The approach to **13** is based on prior literature summarized in Scheme 1.[8] Several amines were condensed with ethyl glyoxylate to generate the corresponding imines **15**, and these were found to react in situ with PmbSH to produce the amines **16**. The nitrogen of **16** could be acylated with $ClCH_2COCl$ and with $BrCH_2COBr$ in the presence of aqueous $NaHCO_3$ under



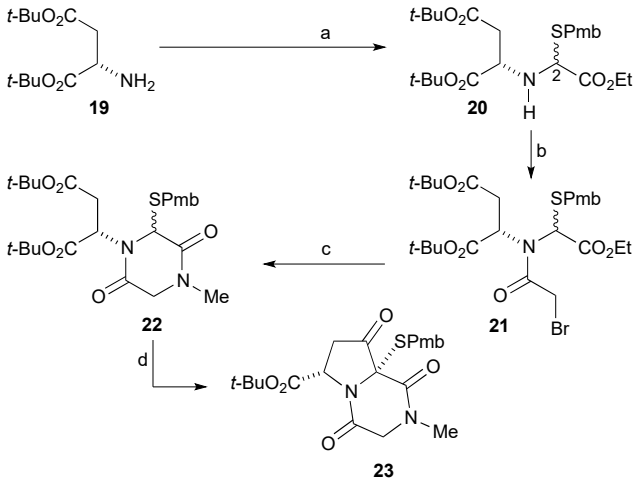
15 R = Ph, Me, Bn **16** **17** X = Cl, Br **18** R^1 = H or Bn

Scheme 1. General approach to piperazinediones with a sulfur substituent. Reagents and conditions. (a) EtO_2CCHO. (b) PmbSH. (c) $ClCH_2COCl$ or $BrCH_2COBr$. (d) NH_3 or $BnNH_2$.

Schotten-Baumann conditions, and then reaction with ammonia or $BnNH_2$ generated a piperazinedione bearing a PmbS group (**17**→**18**). We thought that this sequence, with a proper choice of RNH_2, would provide a general approach to bicyclic piperazinediones that are

appropriately substituted to represent informative models for the challenge of constructing the BC rings of MPC compounds that bear a C-11 hydroxyl.

To examine this possibility, as well as its stereochemical consequences, a solution of EtO_2CCHO (50%w/w in PhMe) was added to a solution of **19**,[9] followed, after 15 min, by *p*-$MeOC_6H_4CH_2SH$[13] in order to trap the intermediate imine (Scheme 2). This experiment provided the desired mixture of C-2 epimeric adducts **20** (in a ratio of ca 2:1). The next step (**20**→**21**),



Scheme 2. Preparation of ketone precursor to first MPC1001 model **13**. Reagents and conditions. (a) EtO_2CCHO, PmbSH, PhMe, 4 h, 99%. (b) $BrCH_2COBr$, CH_2Cl_2, –78 °C, 20 h, 88%. (c) $MeNH_2$, THF-MeCN, –30 °C to room temp. during 6 h, 80%. (d) LDA, HMPA, THF, –78 °C, 42% or 64% corrected for recovered **22**.

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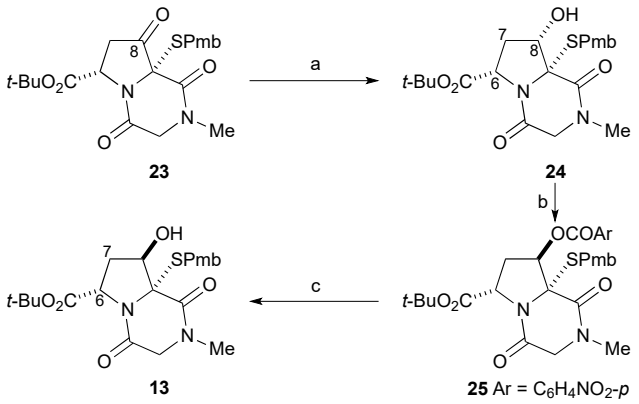
under the conditions reported[8a] by Hilton, Motherwell and Selwood, resulted in very little reaction, but a simple test with $BnNH_2$ (one of the compounds they used) immediately confirmed the perfect correctness of their results,[8a] and so the failure of our reaction was clearly due to

interference by the functionality in our particular amine. After several experiments under different conditions we found that treatment of **20** with $BrCH_2COBr$ (2 equiv) at –30 °C *without any base*, and workup with water provides the chromatographable amides **21** in good yield (88%). Conversion of **21** to **22** also required different conditions from those appropriate for **17→18**; in our case, reaction in the *absence* of Et_3N, using THF-MeCN as solvent at –30 °C, was most effective (80%).

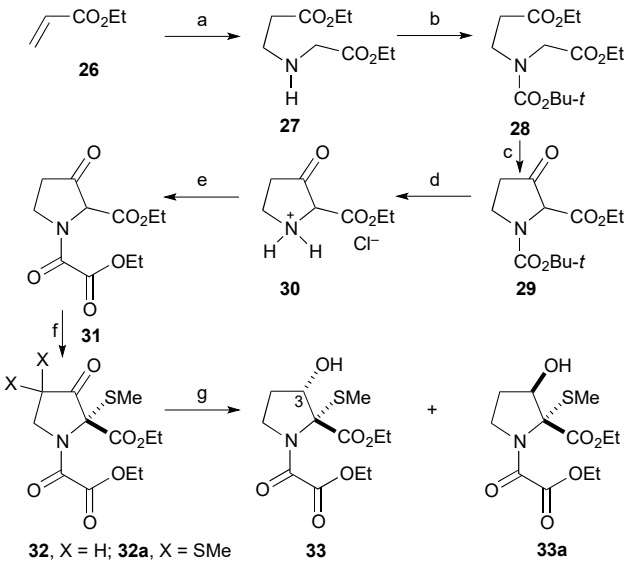
The next task was to generate ring B, and to this end the diesters **22** were treated with LDA at –78 °C to give the desired bicyclic product **23** (42% or 64% corrected for recovered **22**). The presence of HMPA (we used 3 equiv) is important, as is control of the reaction time (< 2.5 h). A curious additional requirement was the need for quenching the reaction mixture with an excess of AcOH at –78 °C. In studying this cyclization we examined the use of other bases [NaH, DBU, $(Me_3Si)_2NK$, $(Me_3Si)_2NLi$], but LDA was best.

Reduction of the C-8 ketone (Scheme 3) with $NaBH_4$ in THF-MeOH at 0 °C was stereoselective and gave alcohol **24** with *syn* OH and SPmb groups. This stereochemical assignment was based on 2D T-ROESY measurements which showed strong correlations between the β-hydrogens on C-6 and C-7 and also between the C-7 and C-8 β-hydrogens. A correlation was also observed between the benzylic protons of the Pmb group and the hydroxyl hydrogen. Mitsunobu inversion[14] gave the expected *p*-nitrobenzoate **25**, which was hydrolyzed by brief exposure to LiOH in THF-water to release **13**. For this compound a 2D T-ROESY experiment showed, as expected, a strong correlation between the C-6 and C-7 β-hydrogens and only a weak correlation between the C-7 β-hydrogen and the C-8 hydrogen. A strong C-7 α-hydrogen/C-8 α-hydrogen correlation was observed and no OH/CH_2Ar correlation.



Scheme 3. Preparation of first MPC1001 model **13**. (a) $NaBH_4$, THF-MeOH, 0 °C, 99%. (b) Ph_3P, *p*-$O_2NC_6H_4CO_2H$, THF, *i*-$PrO_2CN{=}NCO_2Pr$-*i*, –20 °C to room temp., 69% or 97% corrected for recovered **24**. (c) $LiOH.H_2O$, 2:1 THF-water, 10 min, 79%.

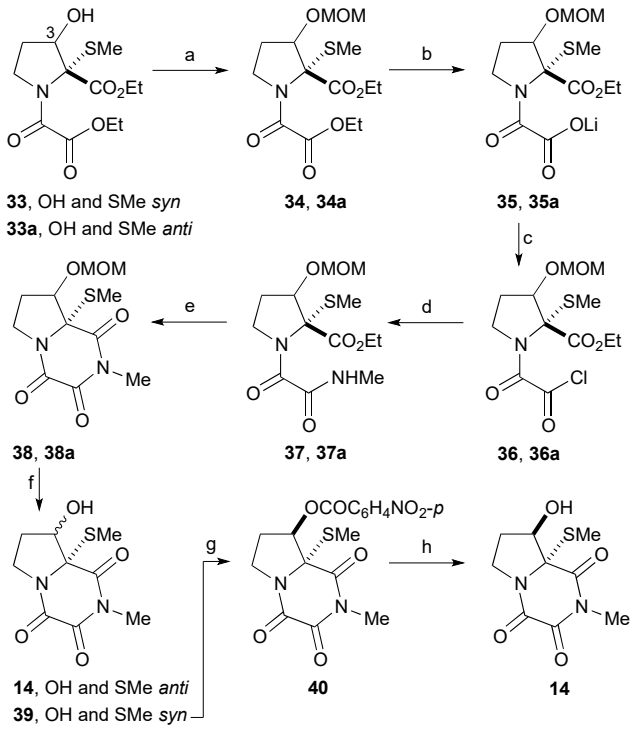
The other model we have made (**14**) corresponds to MPC1001F. The route to this model starts with the known[15] pyrrolidinone ester **29** (Scheme 4), which was easily prepared in three steps. Michael addition of glycine ethyl ester (generated in situ from its hydrochloride) to ethyl acrylate (**26**→**27**, 78%) and *N*-protection with Boc_2O gave the *N*-Boc bis ethyl ester **28** (92%), from which the desired pyrrolidinone **29** was obtained by Dieckmann cyclization (**28**→**29**), using



Scheme 4. Preparation of diastereoisomeric alcohols **33** and **33a**. Reagents and conditions. (a) Glycine ethyl ester hydrochloride, Et_3N, EtOH, 2 days, 78%. (b) Boc_2O, $CHCl_3$, aq NaOH, 0 °C then room temp overnight, 92%. (c) $(Me_3Si)_2NLi$, THF, –78 °C then warm to –30 °C over 4 h, 89%. (d) concentrated hydrochloric acid, 3:1 $CHCl_3$-Et_2O, 8 h. (e) Et_3N, EtO_2CCOCl, CH_2Cl_2, 0 °C, 14 h, 64–78%. (f) Na_2CO_3, 1-(methylthio)pyrrolidine-2,5-dione, MeCN, 63%. (g) $NaBH_4$, EtOH, –78 °C, 2 h, 67.7% of **33** and 14.5% of **33a**.

$(Me_3Si)_2NLi$ as the base (89%). Removal of the *N*-Boc protecting group was best done in a two-phase system consisting of CH_2Cl_2-Et_2O and concentrated hydrochloric acid. The resulting hydrochloride salt was directly treated with EtO_2CCOCl and Et_3N to afford amide **31** in 64–78% yield from **29**. For the sulfenylation (**31**→**32**) we tried $TolSO_2SMe$,[16] MeSCl[17] and the succinimido reagent 1-(methylthio)pyrrolidine-2,5-dione.[18] The first two gave very low yields, but the succinimido reagent immediately appeared promising and its performance was examined in detail using different solvents and temperatures, and with a variety of bases (Cs_2CO_3, *i*-Pr_2NEt, Et_3N, K_2CO_3, $NaHCO_3$ and Na_2CO_3). The best procedure called for the use of Na_2CO_3 in MeCN

at room temperature (6 h). Under these conditions it was possible to obtain the desired sulfide **32** in 61–66% yield on a gram-scale. We were unable to completely suppress formation of the trisulfenylated byproduct **32a**, which was formed in 17–19% yield. Reduction of the ketone carbonyl of **32** with $NaBH_4$ gave the two alcohols **33** and **33a** in 67% and 14.5% yield, respectively, the stereochemical assignments being made initially on the basis of 1D selective T-ROESY measurements. The major product has the unnatural C-2/C-3 relative stereochemistry (OH and SMe syn), but this is of little consequence as the C-3 center was easily inverted at a later stage.



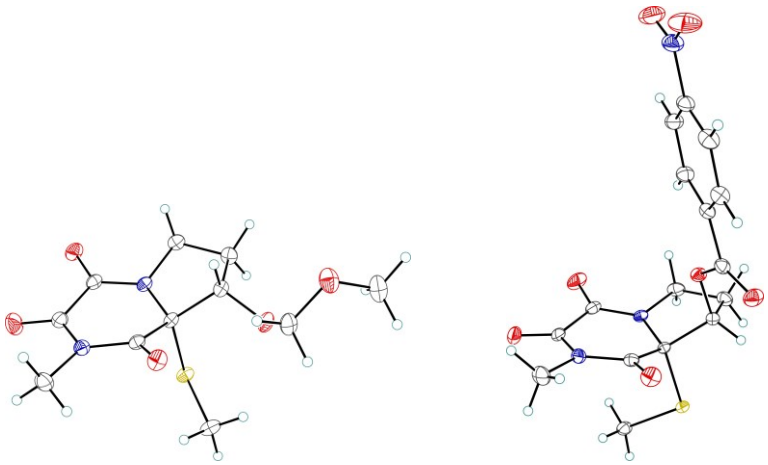
Scheme 5. Formation of MPC1001F model, **14**. "a"-Series: sulfur and oxygen anti. Reagents and conditions. (a) MOMBr, *i*-Pr_2NEt, Bu_4NI, CH_2Cl_2, 0 °C then room temp ca 16 h, 93% for **34**, 91% for **34a**. (b) $LiOH.H_2O$, aq THF, 0 °C, close TLC monitoring. (c) THF-DMF, $(COCl)_2$, 0 °C to room temp. (d) $MeNH_2$, THF, –78 °C, 73% for **37** from **34**; 64% for **37a** from **34a**. (e)

Et_3N, MeOH, 45 °C, 1 h, 91% for **38**; Et_3N, MeOH, room temp., 4 days, 64% (100% after correction for recovered **37a**) for **38a**. (f) Conc. HCl, MeOH, 60 °C, 1 h, 94% for **39**; 40 min for **14**, 85%. (g) Ph_3P, *p*-$O_2NC_6H_4CO_2H$, THF, –78 °C, *i*-$PrO_2CN{=}NCO_2Pr$-*i*, 12 h at room temp., 79%. (h) NaN_3, MeOH, 50 °C, 12 h, 76% or 87% corrected for recovered **40**.

Protection of the C-3 hydroxyl of **33** (93%) and **33a** (91%) as a MOM ether was achieved by treatment with MOMBr in the presence of Bu_4NI and Hünig's base (2 equiv of each) (Scheme 5). We then studied methods for constructing the piperazinedione ring, using **34** as the substrate. The initial plan was to hydrolyze *both* ester groups, form an anhydride, and treat that with $MeNH_2$.[19] It was hoped that cyclization of the resulting amide-acids could then be effected by the action of DCC. In the event, this approach gave a low yield and it was far better to treat the diester with 1 equiv of $LiOH.H_2O$ and to use the resulting mono lithium salt directly for conversion to the corresponding acid chloride. We assume that these intermediates have the indicated structures **35**, **35a** and **36**, **36a**, resulting from preferential hydrolysis of the less hindered and more electron-deficient ester. Reaction of **36** with $MeNH_2$ (initially ca 1 equiv) in THF with close TLC monitoring and addition of more $MeNH_2$, as required, gave amide-ester **37** in 75% overall yield from the parent diester **34**. Similarly, the minor isomer **34a** gave **37a** in 64% overall yield.

The next step called for cyclization to generate the piperazinetrione subunit. Using **37a** as the test substrate attempts at thermal cyclization in refluxing PhMe or DMF were unsuccessful, and so we examined the result of treating the compound with Et_3N. With this approach we observed a slow (4 days), but clean, reaction at room temperature in MeOH, affording the desired piperazinetrione **38a** (64% yield or ca 100% after correction for recovered

37a). When the temperature was raised to 45 °C the yield was lower. In contrast, the major isomer **37** cyclized much more easily (Et_3N, MeOH) and gave **38** in 91% yield after a reaction time of 1 h at 45 °C. Single crystal X-ray analysis of **38a** (Figure 1) verified the relative stereochemical assignments that had been based on NMR measurements on the much earlier precursors **33** and **33a**.



38a **40**

Figure 1. ORTEP diagrams of **38a** and **40**.

In the minor isomer series we now removed the MOM group, and this was readily done by adding 10 equiv of concentrated hydrochloric acid to a hot (60 °C) solution of the compound in MeOH (85% yield). Protecting group removal in the major isomer series (**38**→**39**) was carried out in the same way (94% yield). Finally, the stereochemistry of the hydroxyl of **39** was inverted by Mitsunobu reaction[14] via the *p*-nitrobenzoate **40**. This compound was nicely crystalline and the assigned structure was confirmed by single crystal X-ray analysis (Figure 1). Attempted hydrolysis of the nitrobenzoate (**40**→**14**) with LiOH caused complete decomposition but the nitrobenzoyl group was removed by heating with NaN_3[20] in 2:1 MeOH-THF (76% yield or 87%

after correction for recovered **40**) to afford **14**, so that now both alcohols **33** and **33a** had been converted to the desired hydroxy sulfide **14**.

The final product **13** of Scheme 3 represents the BC ring system of several of the MPC1001 group that bear an oxygen at C-8, and compound **14** is the corresponding model for MPC1001F. As far as we can establish, **14** is the only synthetic representative of the natural bicyclic sulfide-bearing piperazinetrione system.[21]

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References and footnotes

1 (a) H. Onodera, A. Hasegawa, N. Tsumagari, R. Nakai, T. Ogawa and Y. Kanda, *Org. Lett*., 2004, **6**, 4101–4104. (b) N. Tsumagari, R. Nakai, H. Onodera, A. Hasegawa, E. S. Rahayu, K. Ando and Y. Yamashita, *J. Antibiot*., 2004, **57**, 532–534.

2 (a) H. Seya, S. Nakajima, K. Kawai and S. Udagawa, S. *J. Chem. Soc., Chem. Commun*., 1985, 657–658. (b) H. Seya, K. Nozawa, S. Nakajima, K. Kawai and S. Udagawa, *J. Chem. Soc., Perkin Trans 1*, 1986, 109–116.

3 There are several emestrins, differing mainly in the number of bridging sulfur atoms (1–4) and in the presence or absence of a hydroxyl group at C-7": (a) K. B. Herath, H. Jayasuriya, J. G. Ondeyka, J. D. Polishook, G. F. Bills, A. W. Dombrowski, A. Cabello, P. P. Vicario, H. Zweerink, Z. Guan, and S. B. Singh, *J. Antibiotic*., 2005, **58**, 686–694 [emestrin, emestrin C (= MPC1001), emestrin D (= MPC1001D), emestrin E, secoemestrin C_1]. (b) H. M. T. B. Herath, M. Jacob, A. D. Wilson, H. K. Abbas and N. P. D.

Nanayakkara, *Nat. Prod. Res*., 2013, **27**, 1562–1568 (emestrins F and G). (c) K. Nozawa, S. Udagawa, S. Nakajima and K. Kawai, *Chem. Pharm. Bull*., 1987, **35**, 3460–3463 (emestrin B). (d) M. OOike, K. Nozawa and K. Kawai, *Phytochemistry*, 1997, **46**, 123–126 (secoemestrin C).

4 T. Kurogi, S. Okaya, H. Fujiwara, K. Okano and H. Tokuyama, *Angew. Chem. Int. Ed*., 2015, **54**, 283–287.

5 (a) J. A. Codelli, A. L. A. Puchlopek and S. E. Reisman, *J. Am. Chem. Soc*., 2012, **134**, 1930–1933. (b) H. Fujiwara, T. Kurogi, S. Okaya, K. Okano and H. Tokuyama, H. *Angew. Chem. Int. Ed*., 2012, **51**, 13062–13065.

6 (a) J. Peng and D. L. J. Clive, *Org. Lett*., 2007, **9**, 2939-2941. (b) J. Peng and D. L. J. Clive, *J. Org. Chem*., 2009, **74**, 513-519. (c) L. Wang and D. L. J. Clive, *Tetrahedron Lett.*, 2012, **53**, 1504-1506.

7 Review of the chemistry and medicinal chemistry of piperazine-2,5-diones: A. D. Borthwick, *Chem. Rev*. 2012, **112**, 3641–3716.

8 (a) S. T. Hilton, W. B. Motherwell and D. L. Selwood, *Synlett*, 2004, 2609–2611. (b) Cf. A. E. Aliev, S. T. Hilton, W. B. Motherwell and D. L. Selwood, *Tetrahedron Lett*., 2006, **47**, 2387–2390.

9 Aspartic acid was converted into its *N*-Cbz derivative (reference 10) and then treated with isobutylene in the presence of catalytic H_2SO_4 (reference 11). The product, without need for any purification, was then hydrogenolyzed (reference 12) to give **19**.

10 S. J. Choi, B. G. Lee, S. S. Oh, Y. T. Kim, J. Y. Eo and H. S. Kim. H. S. 2012 WO Patent 2012148246 A2, 2012.

11 Cf. M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, Springer-Verlag, New York, 2nd edn, 1994, p. 38.

12 A. Nortcliffe, I. N. Fleming, N. P. Botting and D. O'Hagan, *Tetrahedron*, 2014, **70**, 8343–8347.

13 H. Tanaka and A. Yokoyama, *Chem. Pharm. Bull*., 1960, **8**, 280–283.

14 (a) S. F. Martin and J. A. Dodge, *Tetrahedron Lett*., 1991, **32**, 3017–3020. (b) S. F. Martin, J. A. Dodge, L. E. Burgess, C. Limberakis and M. Hartmann, *Tetrahedron*, 1996, **52**, 3229–3246.

15 (a) T. J. Greshock and R. M. Williams, *Org. Lett*., 2007, **9**, 4255–4258. (b) R. M. Williams, J. Cao, H. Tsujishima and R. J. Cox., *J. Am. Chem. Soc.*, 2003, **125**, 12172–12178.

16 K. Fujiki, N. Tanifuji, Y. Sasaki and T. Yokoyama, *Synthesis*, 2002, 343–348.

17 J.-K. Son and R. W. Woodard, *J. Am. Chem. Soc*., 1989, **111**, 1363–1367.

18 Prepared from Me_2S_2, SO_2Cl_2 and succinimide. Cf. (a) T. Hostier, V. Ferey, G. Ricci, D. G. Pardo and J. Cossy, *Org. Lett.*, 2015, **17**, 3898–3901. (b) D. N. Harpp, B. Friedlander, D. Mullins and S. M. Vines, *Tetrahedron Lett*. 1977, **18**, 963–966.

19 Cf. A. Leonardi, D. Barlocco, F. Montesano, G. Cignarella, G. Motta, R. Testa, E. Poggesi, M. Seeber, P. G. De Benedetti and F. Fanelli, *J. Med. Chem*., 2004, **47**, 1900–1918.

20 J. A. Gómez-Vidal, M. T. Forrester and R. B. Silverman, *Org. Lett.*, 2001, **3**, 2477–2479.

21 We can find no synthetic routes even to corresponding *monocyclic* piperazinetriones having a sulfur substituent. In one of the only two reported examples the trione was formed as a byproduct (7.8% yield, reference 22) and in the other, trione formation is the result of degradation of a more complex structure (reference 23).

22 T. Sato and T. Hino, *Chem. Pharm. Bull*. 1976, **24**, 285–293.

23 J. Honzl, M. Šorm and V. Hanuš, *Tetrahedron* 1970, **26**, 2305–2319.