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COMMUNICATION

Synthesis of the ABH rings of ecteinascidin 597 using a connective Pummerer-type cyclisation†

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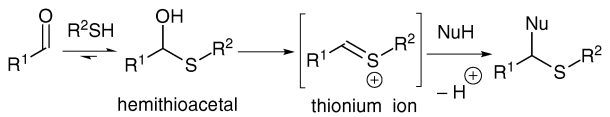
A connective Pummerer-type cyclisation involving a cysteine derivative and an *N*-benzyl glyoxamide 3 has been applied in an asymmetric synthesis of the protected ABH rings 2 of the antitumour and antimicrobial natural product ecteinascidin 597.

Thionium ions are important electrophiles in organic chemistry.[1] These intermediates are most often encountered in the Pummerer reaction of sulfoxides,[2] a process that is now firmly established as an important tool for organic synthesis.

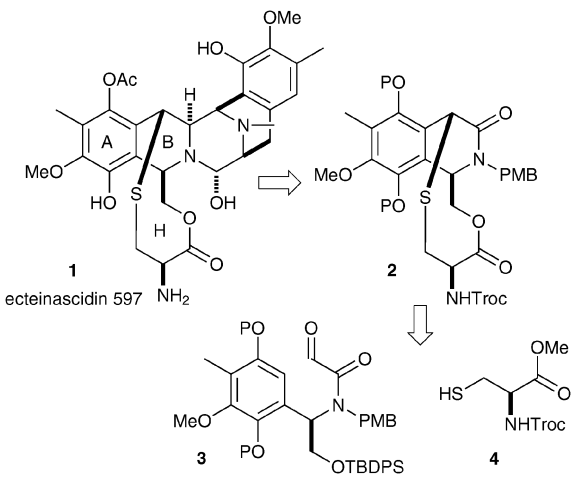
We have recently exploited a convergent approach to thionium ions from aldehyde and thiol starting materials that proceeds *via* hemithioacetal intermediates (Scheme 1).[3] The *connective* Pummerer-type reaction has a number of attractive features: it uses readily available starting materials, does not require the synthesis of sulfides and sulfoxides and is useful for convergent synthesis, as the structural features of the aldehyde, thiol and nucleophile are incorporated into the product. We have exploited the connective Pummerer reaction in a fluorous synthesis of *N*-heterocycles, in which the introduction of the tag through the addition of a fluorous thiol triggers *N*-heterocycle formation,[4] and in a dearomatising route to azaspirocycles.[5]



Scheme 1 A convergent route to thionium ions.

Here we describe the application of the connective Pummerer process to the construction of the ABH rings of the biologically-active natural product ecteinascidin 597 **1**. The ecteinascidins are a family of tetrahydroisoquinoline alkaloids isolated from the Caribbean tunicate *Ecteinascidia turbinata*.[6]

Members of the family display a wide range of antitumour and antimicrobial activities. For example, ecteinascidin 743 is licensed as Yondelis®/trabectidin for the treatment of advanced soft tissue sarcoma and is undergoing further clinical trials for the treatment of breast, prostate, and paediatric sarcomas. The limited availability of the ecteinascidins from natural sources and their intriguing properties have prompted studies that have culminated in a number of elegant syntheses and synthetic approaches to members of the family.[7] We have focused our synthetic studies on ecteinascidin 597 **1** (Scheme 2), a family member that was recently synthesised for the first time by Zhu.[8] We proposed that a connective Pummerer-type cyclisation involving glyoxamide **3** and cysteine derivative **4** could be used to assemble the ABH rings of **1** (and of analogues) (Scheme 2). Our convergent approach would negate the need to form sulfides and sulfoxides as precursors to the requisite thionium ions for Pummerer cyclisation.[9]



Scheme 2 Retrosynthetic analysis of the ABH rings of Et 597 (P = protecting group).

As our previous studies had shown that tetrahydroisoquinolinone formation using the connective Pummerer cyclisation could be problematic,[4,5] conditions for the efficient cyclisation of the electron-rich benzyl amine systems present in the ecteinascidins were developed. The use of $ZnCl_2$ or $Sc(OTf)_3$, without addition of an electrophile to activate the

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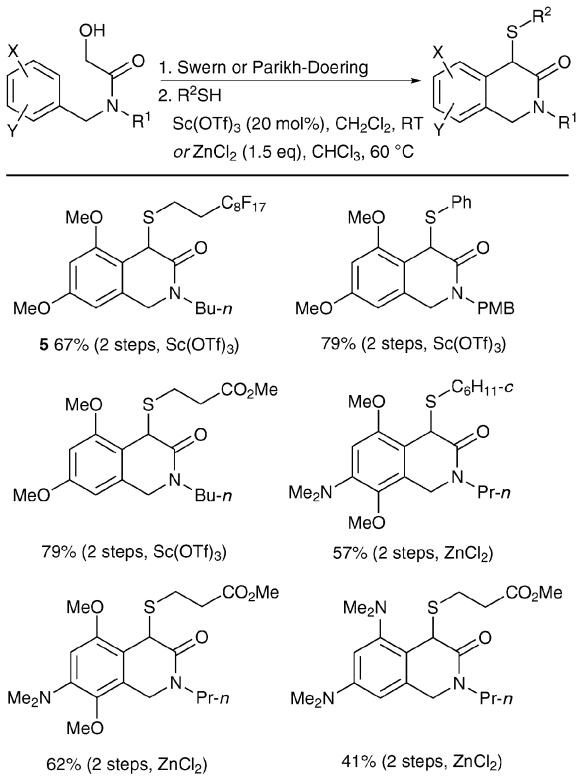
† Electronic supplementary information (ESI) available: Additional experiments, details of substrate synthesis, full experimental details, characterisation data and ^1H and ^{13}C NMR spectra for all new compounds, chiral HPLC analyses and the X-ray crystal structure of **11**. CCDC 808088. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc13992d

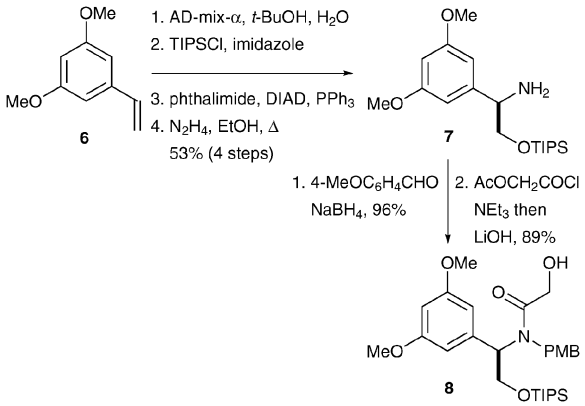


Scheme 3 Cyclisations of electron-rich *N*-benzyl glyoxamides.

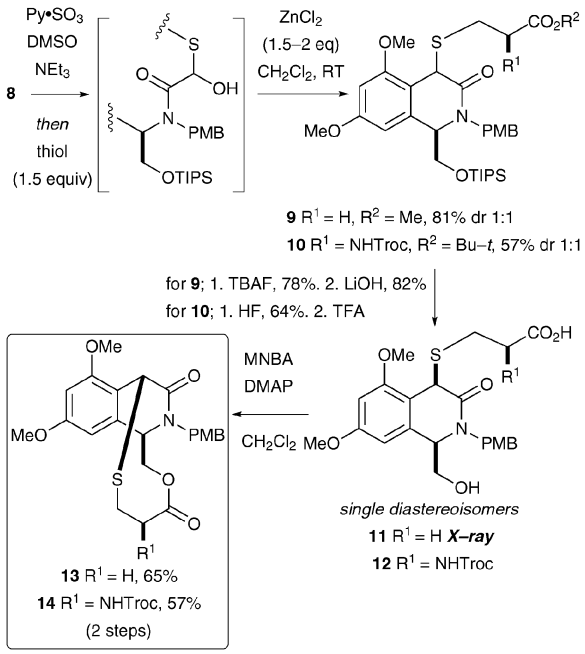
hemithioacetal intermediate, gave the desired tetrahydroisoquinolinones in acceptable overall yield (Scheme 3).[10] The competency of hemithioacetals as intermediates in the cyclisation was confirmed by *in situ* trapping of a glyoxamide from a Swern oxidation with thiol to give the corresponding hemithioacetal prior to the addition of $ZnCl_2$ and cyclisation (75% yield of **5**). Trifluoroacetylation of the same hemithioacetal prior to the addition of $ZnCl_2$ and cyclisation gave similar yields of **5**.[11] The cyclisations of substrates bearing amino groups were more efficient when warmed to 60 °C in the presence of stoichiometric $ZnCl_2$.[12]

We next prepared enantiomerically pure hydroxyamide **8**, a model compound for our approach to the ABH rings of ecteinascidin 597, from styrene **6** using Sharpless asymmetric dihydroxylation[13] followed by a Mitsunobu sequence[14] to give **7** (>84% ee by HPLC)[15] (Scheme 4). Reductive amination and coupling with acetoxy acetyl chloride and *in situ* removal of the acetate protecting group gave **8** in 85% overall yield. Pleasingly, oxidation of **8**, *in situ* trapping of the glyoxamide with methyl 3-mercaptopropanoate or *N*-Troc cysteine *t*-butyl ester and treatment with $ZnCl_2$ gave **9** and **10** respectively in good overall yield as inconsequential mixtures of diastereoisomers. Epimerisation occurred during silyl ether deprotection and ester hydrolysis to give *cis* diastereoisomers **11** and **12**. The stereochemistry of **11** was confirmed by X-ray crystallographic analysis.[16] Treatment of **11** and **12** with the Shiina reagent (MNBA, 2-methyl-6-nitrobenzoic anhydride)[17] gave ABH ring analogues **13** and **14** in moderate yield (Scheme 5).

We next prepared glyoxamide **3** (P = Me) possessing the substituted A-ring of ecteinascidin 597. We chose to prepare a



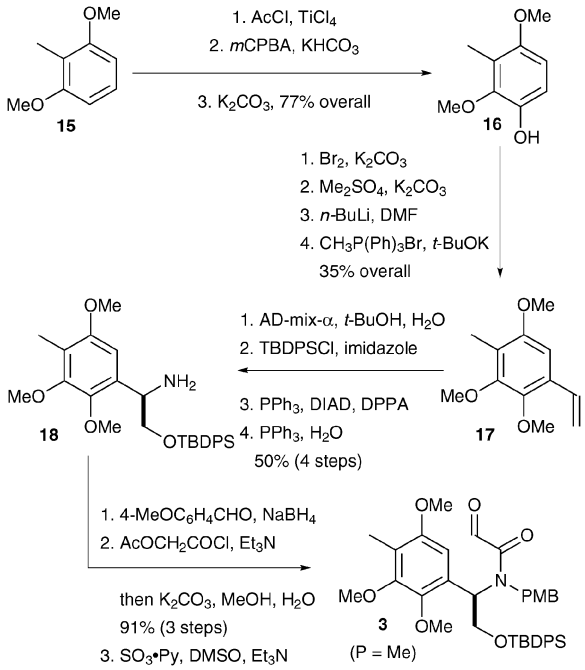
Scheme 4 Asymmetric synthesis of hydroxyamide **8**.



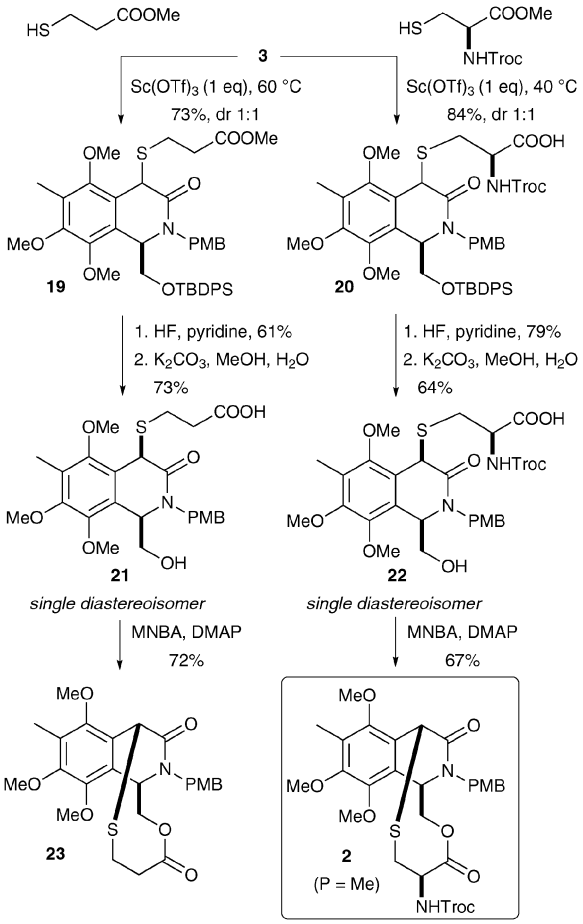
Scheme 5 Asymmetric synthesis of model ABH ring systems.

simple trimethoxy A-ring derivative at this stage although a derivative with the necessary orthogonal protection is also accessible using our approach. Substituted styrene **17** was prepared in seven steps from **15** *via* the corresponding benzaldehyde.[18] Sharpless asymmetric dihydroxylation[13] followed by a Mitsunobu sequence gave **18** (95% ee by HPLC).[15] Reductive amination, coupling with acetoxy acetyl chloride, *in situ* acetate hydrolysis and oxidation then gave glyoxamide **3** (Scheme 6).

Treatment of glyoxamide **3** with methyl 3-mercaptopropanoate or *N*-Troc cysteine methyl ester formed the corresponding hemithioacetals (observed by ^1H NMR) and subsequent exposure to $Sc(OTf)_3$ gave **19** and **20** respectively in good overall yield and as inconsequential mixtures of diastereoisomers (Scheme 7). As seen previously, epimerisation occurred during silyl ether deprotection and ester hydrolysis to give *cis* hydroxyacids **21** and **22**. Finally, macrolactonisation using Shiina's reagent[17] gave the protected ABH ring system of ecteinascidin 597 **2** (P = Me) and additional analogue **23** in good yield (Scheme 7).



Scheme 6 Asymmetric synthesis of the protected ABH ring system.



Scheme 7 Completing the asymmetric synthesis of the ABH ring system.

In summary, a connective Pummerer-type cyclisation of thiols and *N*-benzyl glyoxamides has been studied and applied in an asymmetric approach to the protected ABH ring system of the antitumour and antimicrobial natural product ecteinascidin 597. Studies aimed at completing the synthesis of the natural product and its analogues are underway.

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Notes and references

1 For a recent, overview of this area, see: L. H. S. Smith, S. C. Coote, H. F. Sneddon and D. J. Procter, *Angew. Chem., Int. Ed.*, 2010, **49**, 5832.

2 (*a*) R. Pummerer, *Ber. Dtsch. Chem. Ges.*, 1909, **42**, 2282; (*b*) R. Pummerer, *Ber. Dtsch. Chem. Ges.*, 1910, **43**, 1401; (*c*) S. Akai and Y. Kita, *Top. Curr. Chem.*, 2007, **274**, 35; (*d*) K. S. Feldman, *Tetrahedron*, 2006, **62**, 5003; (*e*) S. K. Bur and A. Padwa, *Chem. Rev.*, 2004, **104**, 2401; For applications of the Pummerer reaction in solid-phase synthesis, see: (*f*) L. A. McAllister, S. Brand, R. de Gentile and D. J. Procter, *Chem. Commun.*, 2003, 2380; (*g*) L. A. McAllister, K. L. Turner, S. Brand, M. Stefaniak and D. J. Procter, *J. Org. Chem.*, 2006, **71**, 6497.

3 (*a*) M. Miller, W. Tsang, A. Merritt and D. J. Procter, *Chem. Commun.*, 2007, 498; (*b*) M. Miller, J. C. Vogel, W. Tsang, A. Merrit and D. J. Procter, *Org. Biomol. Chem.*, 2009, **7**, 589.

4 (*a*) L. A. McAllister, R. A. McCormick, S. Brand and D. J. Procter, *Angew. Chem., Int. Ed.*, 2005, **44**, 452; (*b*) L. A. McAllister, R. A. McCormick, K. M. James, S. Brand, N. Willetts and D. J. Procter, *Chem.–Eur. J.*, 2007, **13**, 1032; (*c*) K. M. James, N. Willetts and D. J. Procter, *Org. Lett.*, 2008, **10**, 1203; (*d*) R. A. McCormick, K. M. James, N. Willetts and D. J. Procter, *QSAR Comb. Sci.*, 2006, **25**, 709. See also ref. 3 and 5; (*e*) S. C. Coote, S. Quenum and D. J. Procter, *Org. Biomol. Chem.*, 2011, **9**, 5104.

5 (*a*) C. Ovens, N. G. Martin and D. J. Procter, *Org. Lett.*, 2008, **10**, 1441; (*b*) C. Ovens, J. C. Vogel, N. G. Martin and D. J. Procter, *Chem. Commun.*, 2009, 3101.

6 K. Suwanborirux, K. Charupant, S. Amnuoypol, S. Pummangura, A. Kubo and N. Saito, *J. Nat. Prod.*, 2002, **65**, 935 and references therein.

7 For reviews of synthetic approaches to the ecteinascidins, see: (*a*) C. Avendaño and E. de la Cuesta, *Chem.–Eur. J.*, 2010, **16**, 9722; (*b*) C. Cuevas and A. Francesch, *Nat. Prod. Rep.*, 2009, **26**, 322.

8 J. Chen, X. Chen, M. Willot and J. Zhu, *Angew. Chem., Int. Ed.*, 2006, **45**, 8028.

9 Cysteine *S*-oxides can be prone to elimination: M. C. Aversa, A. Barattucci, P. Bonaccorsi and P. Giannetto, *J. Org. Chem.*, 2005, **70**, 1986.

10 Conditions using Lewis acids and hemithioacetals, with no electrophilic activator of the hemithioacetals, were ineffective for the cyclisation of *N*-benzyl glyoxamides lacking electron-releasing groups on the benzene rings.

11 See the ESI† for partial characterisation of the hemithioacetal and trifluoroacetylated hemithioacetal intermediates.

12 It appears likely that more Lewis acid and more forcing conditions were required for the cyclisation of these substrates as they contain alternative sites on the aromatic ring for Lewis acid coordination and deactivation.

13 For reviews of the Sharpless asymmetric dihydroxylation: (*a*) A. B. Zaitsev and H. Adolfsson, *Synthesis*, 2006, 1725; (*b*) H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.

14 P. Wipf and C. R. Hopkins, *J. Org. Chem.*, 2001, **66**, 3133.

15 See the ESI† for further details and HPLC traces.

16 See the ESI† for X-ray structure and CCDC number.

17 I. Shiina, M. Kubota and R. Ibuka, *Tetrahedron Lett.*, 2002, **43**, 7535.

18 (*a*) B. Zhou, J. Guo and S. J. Danishefsky, *Org. Lett.*, 2002, **4**, 43; (*b*) H.-J. Knölker, W. Fröhner and K. R. Reddy, *Synthesis*, 2002, 557.