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A Unified Strategy to 6–5–6–5–6-Membered Epipolythiodiketopiperazines: Studies towards the Total Synthesis of Scabrosin Diacetate and Haematocin

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Abstract: The family of epipolythiodiketopiperazine (ETP) natural products consists of over 200 members possessing a wide diversity of structures and biological activity. Recently, the subgroup of 6–5–6–5–6-membered ETPs has gained substantial attention, which has resulted in several total syntheses. Despite all the efforts that have been invested into accessing these complex structures, no synthesis of scabrosin diacetate (**1a**) and its related esters has been reported. Herein, our attempts towards scabrosin diacetate (**1a**) and haematocin (**3**) starting from diketopiperazine **12a** as a late-stage intermediate are presented. Diketopiperazine **12a** can be conveniently accessed in multigram quantities from aldehyde **18** and diketopiperazine **21** and was envisioned to serve as a general platform for the synthesis of 6–5–6–5–6-membered ETPs.

Introduction

The 2,5-diketopiperazine (2,5-DKP) scaffold is a privileged structural motif found in numerous natural products and therapeutic agents.[1] Epipolythiodiketopiperazines (ETPs) are 2,5-DKPs sulfenylated at the 3- and 6-position (for selected examples, see Figure 1). In the wake of the broad range of interesting biological activities, ranging from anticancer and antiviral to antifungal,[2] several syntheses of members from this class of natural products have been reported since the first isolation of an ETP, gliotoxin (**4**), in 1936.[2d,3]

The scabrosin esters (**1a**,**b**) were isolated in 1978 from the lichen *Xanthoparmelia scabrosa* by Elix and Jones, but their original structural assignment (**2**) was incorrect.[5] Twenty years later, Andersen reported the isolation of ambewelamides A (**1c**) and B (**1d**) from lichen of the *Usnea* species.[6] After this discovery, in 1999, new efforts by Elix et al. resulted in structural revision of the scabrosin esters based on multidimensional NMR spectroscopic techniques and single-crystal X-ray diffraction. These studies led to the conclusion that the ambewelamides (**1c**,**d**) and scabrosin esters (**1a**,**b**) are the same molecular entity.[7]

The scabrosin esters display potent anticancer activity down to the low nanomolar range.[6–8] Their high biological activity is thought to be mediated mostly by two distinct mechanisms:

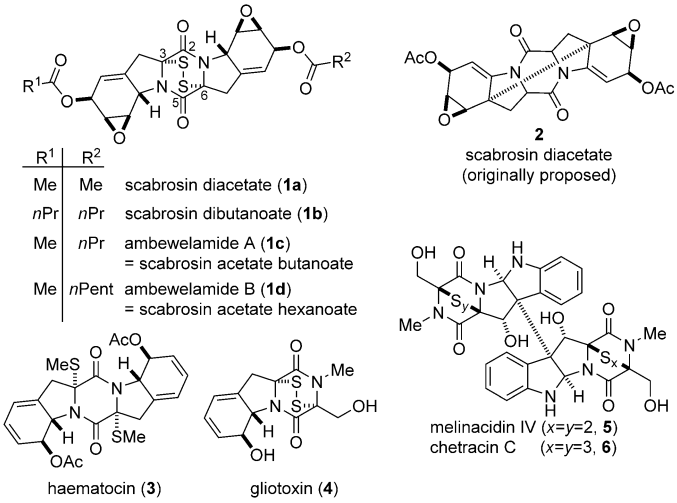

Figure 1. Selected ETPs.

Catalytic generation of reactive oxygen species by redox cycling, and mixed disulfide formation by thiol-disulfide exchange with cysteine residues of vital proteins.[2,4,8] Despite their intriguing structural features and potent cytotoxicity, only one synthetic study on the scabrosin esters has been reported to date.[9]

Biosynthetically, the ETPs are derived from aromatic amino acids by oxidative dearomatization. The scabrosin esters (**1**) have been proposed to arise from phenylalanine anhydride epoxidation to give **8**, followed by S_N2' epoxide opening (Scheme 1). Further epoxidation, esterification, and sulfenylation is then thought to take place.[6] In contrast to this hypothesis, recent insight into the biosynthesis of the related ETP aranotin showed that sulfur introduction takes place prior to the

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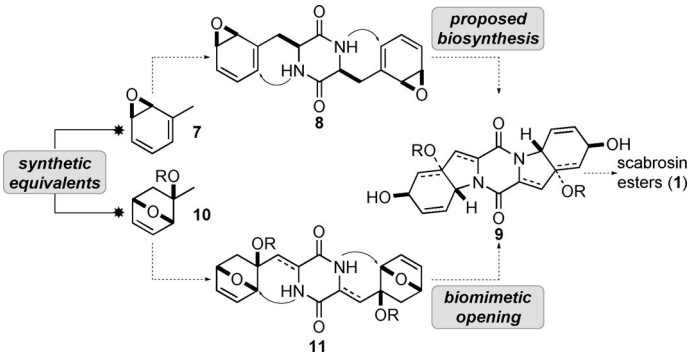


Scheme 1. Proposed biosynthesis and our biomimetic approach to the scabrosin esters (**1**).

initial arene epoxidation step.[10] This pathway may also be possible for the scabrosin esters.

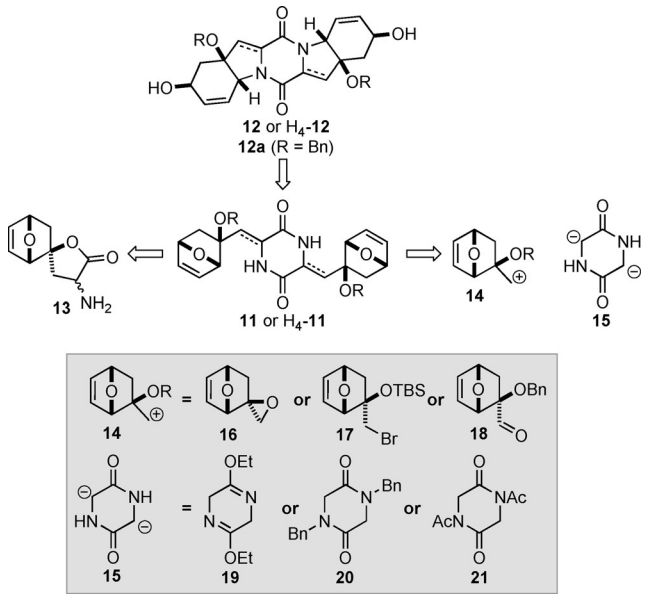
In addition to our efforts in using oxabicyclo[2.2.1]heptenes as valuable intermediates in organic synthesis,[11,12a] we recently reported a novel strategy to rapidly assemble functionalized 6–5–6-fused and 6–5–6–5–6-fused diketopiperazines.[12b] Herein we present our efforts towards synthesizing scabrosin diacetate (**1a**) and haematocin (**3**). The strategy relies on the previously established opening of the oxabicyclo[2.2.1]heptenes in diketopiperazine **11**. This reaction resembles the proposed biosynthetic pathway to the scabrosin esters in that the oxabicyclo[2.2.1]heptenes in intermediate **11** serve as surrogates for the epoxybenzene moieties of diketopiperazine **8**. The strategy is different from previous approaches to construct 6–5–6–5–6-fused ETP natural products,[3b–e] in that a two-directional approach is followed:[13] The core structure **9** is constructed first and is then functionalized on both symmetry equivalent sides of the molecule.

Results and Discussion

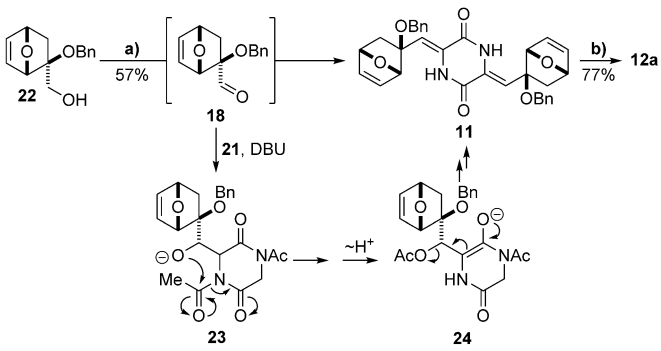
In a first generation synthetic approach we aimed at converting α-aminolactone **13** into the dimeric symmetrical diketopiperazine H_4-**11** (Scheme 2). Conditions known to be effective in the formation of diketopiperazines were unsuccessful.[14] Moreover, the tendency of lactone **13** to cyclize rapidly after hydrolysis or alcoholysis precluded the use of standard peptide coupling techniques to access diketopiperazine H_4-**11**. As an alternative, we envisioned using double alkylation of the bis(enolate)synthon **15** with electrophile **14**.

The use of epoxide **16** and bromide **17** as electrophilic components was first investigated in the alkylation reaction with Schöllkopf-type dihydropyrazine **19**, *N*,*N*′-dibenzyl-diketopiperazine **20**, and *N*,*N*′-diacetyldiketopiperazine **21** in the presence or absence of Lewis acids.[15] Neither of the attempts showed any trace of alkylated product H_4-**11**. This might be due to the high steric hindrance of alkylating agents **16** and **17**, and as a result, a more reactive electrophile was investigated.

We were intrigued by the findings of Loughlin et al. who reported the potassium *tert*-butoxide mediated condensation of *N*,*N*′-diacetyldiketopiperazine **21** with aliphatic aldehydes to yield bis(alkylidene)diketopiperazine fragments.[16a] Although the condensation of **21** with (electron-poor) aromatic aldehydes has been known since 1939, it was not until 2000 that Loughlin reported its double condensation with aliphatic aldehydes.[16b–e] Following this strategy, we prepared alcohol **22** (Scheme 3). However, oxidation to the corresponding aldehyde **18** under numerous conditions such as DMP,[17] PCC,[18] $PhI(OAc)_2$/TEMPO,[19] and Swern oxidation[20] failed. After careful investigation, we found that the corresponding aldehyde was unstable at ambient temperature. Consequently, trapping of the transient aldehyde was attempted in situ at low temperature with diketopiperazine **21** and base. In an initial attempt, the use of NEt_3 or *t*BuOK did not allow for any isolation of the desired product **11**. In the end, DBU was found to mediate both the Swern oxidation of **22** and the condensation of the transient aldehyde **18** with diketopiperazine



Scheme 2. Retrosynthetic strategy towards key intermediate (H_4)-**12**.

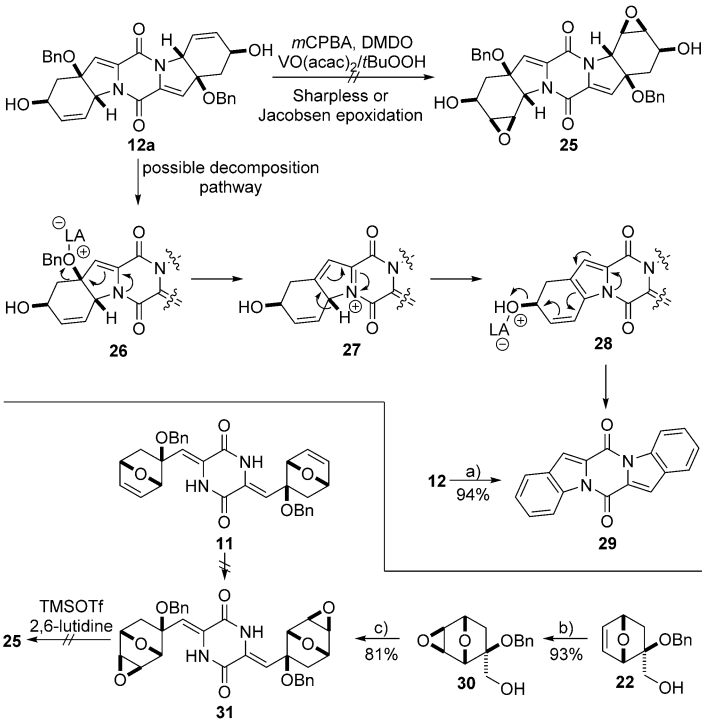


Scheme 3. Synthesis of diketopiperazine **11**:[12b] a) $(COCl)_2$ (1.5 equiv), DMSO (2.0 equiv), CH_2Cl_2, −78 °C; then **22** (1.0 equiv), 30 min; then **21** (0.38 equiv), DBU (15 equiv), −78 to 0 °C, 2 d, 57% (based on **21**); b) 2,6-lutidine (8.0 equiv), TMSOTf (6.0 equiv), CH_2Cl_2, 0 to 23 °C, 16 h; then K_2CO_3 (8.0 equiv), MeOH/THF (4:1), 23 °C, 30 min, 77% (2 steps). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TMS = trimethyl-silyl; Tf = trifluoromethanesulfonyl.

21. Hence, bis(alkylidene)diketopiperazine **11** could be obtained in 57% yield and >20:1 diastereoselectivity with respect to olefin geometrical isomers. The transformation is believed to be initiated by addition of the enolate of **21** to aldehyde **18** to give alkoxide **23**. Acetyl migration furnishes **24** and elimination completes the condensation process to give **11**. TMSOTf-mediated ring opening followed by in situ silyl deprotection completed the synthesis of intermediate **12a**.

With the completed pentacyclic core **12a** in hand, the route to scabrosin diacetate (**1a**) called for double epoxidation of the allylic alcohols. Subjection of diketopiperazine **12a** to $[VO(acac)_2]$/*t*BuOOH lead to complete decomposition of the starting material and trace amounts of fully aromatized diketopiperazine **29** were identified in the mixture of products (Scheme 4). Decomposition was also observed under conditions of the Sharpless and Jacobsen epoxidations as well as with peracids such as *m*CPBA or AcOOH. Under buffered conditions (*m*CPBA/$NaHCO_3$ or F_3CCO_3H/Na_2HPO_4) and neutral conditions (DMDO, TFDO), competing oxidation of the dihydropyrrole precluded the isolation of desired epoxide **25**.

We believe that trace amounts of (Lewis)acid catalyze the elimination of benzyl alcohol from **26** to give protonated pyrrole **27**. Proton loss followed by elimination then gives the fully aromatized diketopiperazine **29**. In order to support this hypothesis, we treated pentacyclic intermediate **12a** with 10 mol% of MsOH in CH_2Cl_2 and indeed obtained the highly insoluble elimination product **29** in 94% yield.

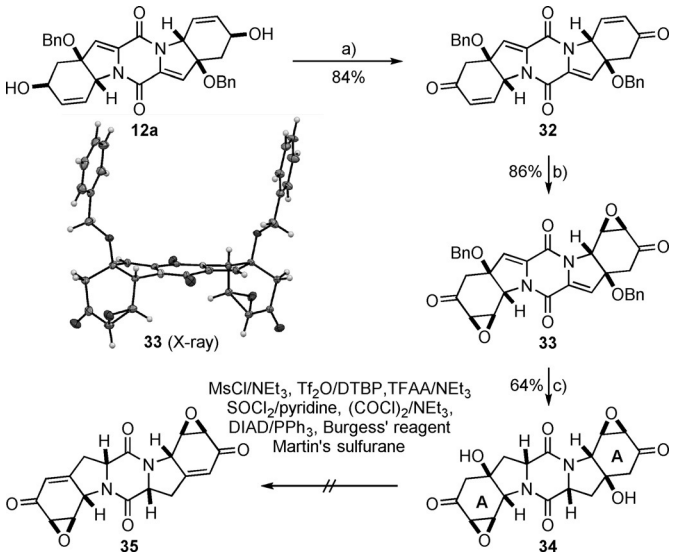


Scheme 4. Attempted synthesis of bis(epoxide) **25**: a) MsOH (10 mol%), CH_2Cl_2, 23 °C, 1 h, 94%; b) *m*CPBA (1.5 equiv), CH_2Cl_2, 23 °C, 16 h, 93%; c) $COCl)_2$ (1.5 equiv), DMSO (2.0 equiv), CH_2Cl_2, −78 °C; then **30** (1.0 equiv), 45 min; then **21** (0.4 equiv), DBU (15 equiv), −78 to 23 °C, 16 h, 81% (based on **21**); DMDO = dimethyldioxirane, Ms = methanesulfonyl; *m*CPBA = 3-chloroperoxybenzoic acid; DMSO = dimethylsulfoxide; DBU = 1,8-diaza-bicyclo[5.4.0]undec-7-ene.

Focus was therefore set onto introducing the epoxides at an earlier stage of the synthesis: It was not possible to epoxidize the bis(oxabicyclo[2.2.1]heptene) **11** to furnish heptacycle **31** directly (Scheme 4, bottom). The reason for this may be the acid sensitivity of the alkylidenediketopiperazine, as was the case for diketopiperazine **12a**. Fortunately, it was feasible to access the desired epoxide **31** in two steps by epoxidation of alcohol **22** and subsequent subjection of alcohol **30** to the previously developed oxidation/condensation sequence with *N*,*N*′-diacetyldiketopiperazine (**21**).

All attempts to employ the bis(epoxide) **31** in further transformations to give the fully assembled 6–5–6–5–6-core of diketopiperazine **25** failed. Although competing epoxide opening was anticipated under the ring-opening conditions, we found that epoxide **31** did not undergo any reaction at all. Upon heating of the reaction mixture, slow decomposition was observed.

We subsequently examined a sequence involving allylic oxidation and nucleophilic epoxidation of **12a** (Scheme 5). Because of its acid sensitivity, we investigated the use of neutral MnO_2 for its oxidation to bis(enone) **32**. The use of activated MnO_2 and short exposure to the oxidant were essential to obtain good yields. Enone **32** was rather unstable and, therefore, used directly after its preparation in the following epoxidation step. Initial attempts to epoxidize enone **32** under

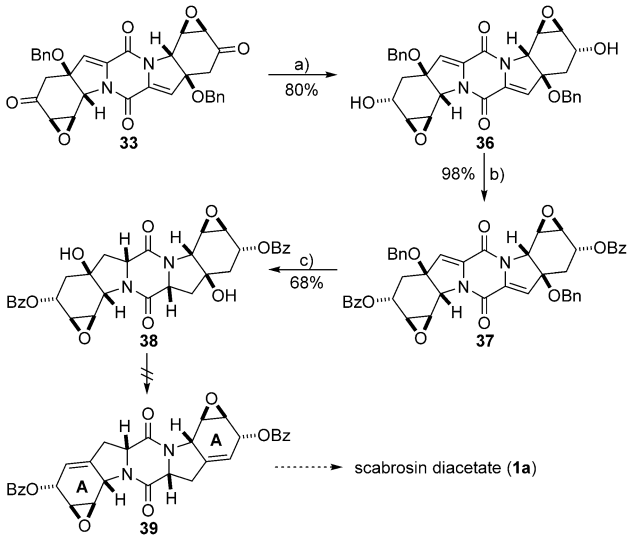


Scheme 5. Attempted synthesis of bis(epoxide) **35**: a) MnO_2 (35 equiv), 23 °C, 30 min, 84%; b) *t*BuOOH (10 euqiv.), DBU (2.0 equiv), CH_2Cl_2, −50 °C, 90 min, 86%; c) H_2, (1 bar) Pd/C (2.5 equiv), AcOEt, 23 °C, 30 min, 64%; Ms = methanesulfonyl; Tf = trifluoromethanesulfonyl; DTBP = 2,6-di-*tert*-butylpyridine; DIAD = diisopropyl azodicarboxylate; Burgess' reagent = 1-methoxy-*N*-triethylammoniosulfonyl-methanimidate; Martin's sulfurane = *bis*[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulfur; TFAA = trifluoroacetic anhydride; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

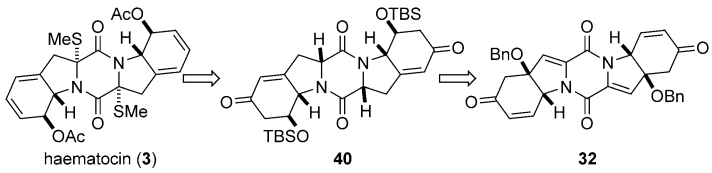
Weitz–Scheffer conditions (H_2O_2/NaOH)[21] or Meth–Cohnm conditions (*t*BuOOH/*n*BuLi and Ph_3COOH/KHMDS)[22] failed possibly because of the sensitivity of both **32** and **33** to base. An organocatalytic approach reported by List et al.,[23] which was anticipated to be less basic, did not give any of the desired product. Eventually, treatment of enone **32** at −50 °C with *t*BuOOH/DBU[24] and quenching of the mixture with acetic acid at low temperature allowed the isolation of bis(epoxide) **33** in 86% yield. Single-crystal X-ray crystallographic analysis unambiguously confirmed the assignment of the structure.[25]

Subsequent hydrogenation of the double bonds with concomitant removal of the benzyl ethers to give diol **34** proved to be troublesome. With catalytic amounts of hydrogenation catalysts, such as Pd/C, $Pd(OH)_2$/C,[26] Pd-black,[27] or Rh/Al_2O_3[28] in various solvents (AcOEt, MeOH, THF and AcOH) it was impossible to drive the reaction to full conversion—even under increased pressure of hydrogen (up to 10 bar).[29] Transfer hydrogenation with different hydrogen sources, such as $HCOONH_4$,[30a] *i*PrOH,[30b] or 1,4-cyclohexadiene[30c] also failed to give more than trace amounts of the desired product **34**. In the end, the use of 2.5 equivalents of Pd/C allowed for the selective conversion of benzyl ether **33** to bis(hydroxyketone) **34** in 64% yield.

With key intermediate **34** in hand, elimination of the tertiary alcohol was investigated. Dehydrations of similar systems have previously been reported with $Al_2O_3/MgSO_4$ or Tf_2O/DIPEA/DMAP.[31] With β-hydroxyketone **34**, however, these conditions as well as numerous other elimination protocols investigated mostly led to complete decomposition. Only in a few cases, aromatization of the **A**-ring was observed by analysis of the NMR spectra of the unpurified reaction mixtures. This observation suggested that **33** was highly prone to further elimination. To avoid this problem, an alternative strategy was attempted. Ketone reduction and protection of the resulting diol **36** gave benzoate **37** (Scheme 6). Then, debenzylation and hydrogenation of the double bonds yielded diol **38**. Yet again, under a variety of conditions, elimination of the tertiary alcohols to give diene **39** was unsuccessful. This was observed independently of the elimination mode (attempted *syn*- or *anti*-elimination and E_1- or E_2-elimination conditions respectively). We reasoned that ring strain in the **A**-rings of heptacycle **39** renders elimination difficult.



Scheme 6. Synthesis of diol **38** and attempted elimination to diene **39**: a) $LiHB(sBu)_3$ (4.0 equiv), THF, −78 °C, 10 min, 80%; b) BzCl (10 equiv), NEt_3 (10 equiv), DMAP (10 equiv), CH_2Cl_2, 0 to 23 °C, 4 h, 98%; c) H_2 (1 bar), Pd/C (2.5 equiv), AcOEt, 23 °C, 2 h, 68%; Bz = benzoyl; DMAP = 4-(dimethylamino)-pyridine.

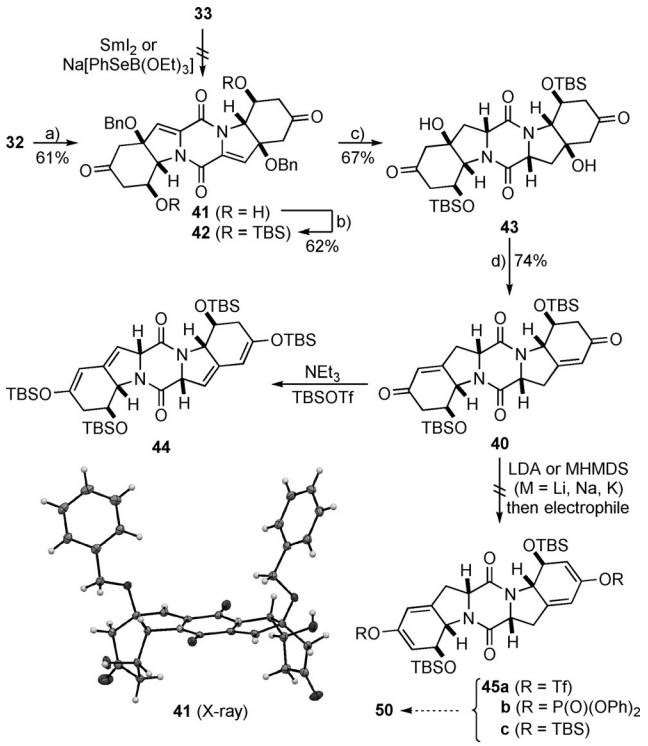


Scheme 7. Retrosynthetic strategy towards haematocin (**3**).

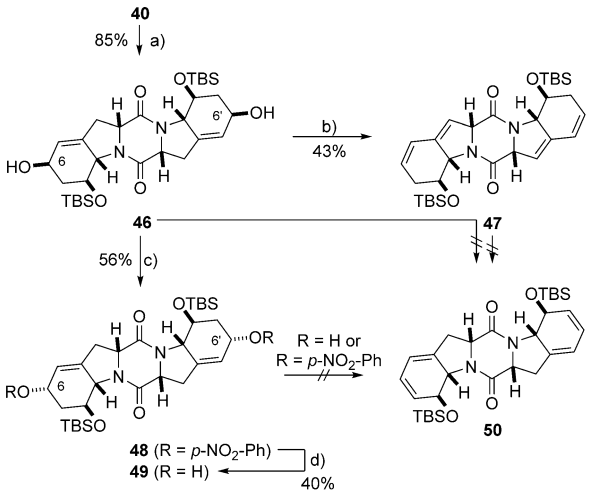
After having developed a fast and scalable synthesis of advanced intermediate enone **32**, we planned to use a similar synthetic strategy to access the haematocin (**3**) core (Scheme 7). Key intermediate **41** was first thought to be accessible by reduction of bis(epoxyketone) **33**, but neither SmI_2[32a] nor $(PhSe)_2/NaBH_4$[32b,c] gave diol **41** (Scheme 8). In the former case, SmI_2 also led to partial reduction of the enamides and gave a complex mixture of products.[33] In the latter case we observed no reaction. We believe that steric hindrance renders nucleophilic attack highly disfavored.

Bis(enone) **32** could be subjected to a sequence consisting of Cu-catalyzed 1,4-borylation[34] and an oxidation of the intermediate boronate with neutral H_2O_2 to give diol **41** in 61% yield. Single-crystal X-ray analysis unambiguously confirmed the relative configuration of the product.[35] TBS-protection and hydrogenation with excess Pd/C proceeded uneventfully to yield bis(β-hydroxyketone) **43**. In contrast to the unsuccessful elimination of the tertiary alcohols in diol **34** (Scheme 5), the dehydration of diol **43** proceeded smoothly at 0 °C and in 15 min with Martin's sulfurane to give bis(enone) **40**. The same conditions only led to decomposed starting material in the case of bis(epoxyketone) **34**. This suggests the strained epoxides as the main reason for the failed dehydration.

After the preparation of enone **40**, we attempted to convert it into bis(diene) **50** by means of deprotonation and trapping of the kinetic enolate with Comins' reagent[36a] or $(RO)_2P(O)Cl$[36b,c] followed by reductive defunctionalization. Several bases such as LDA, LiHMDS, NaHMDS, and KHMDS with and without solvent additives, such as HMPA or DMPU, were examined, but none of the conditions successfully gave **45**. Inspired by the work of Corey, we tried to convert diketone **40** into silylenol ether **45c** as a precursor for the corresponding bis(vinyl triflate) **45a**.[37] Utilizing Corey's[38] internal quench procedure (TBSCl and LDA) for silyl enol ether formation failed to give any **45c**. Treatment of **40** with TBSOTf and NEt_3 yielded exclusively the isomeric bis(enol ether) **44**, which suggests that



Scheme 8. Synthesis of diketone **40** and attempted conversion into tetraene **50**: a) B_2pin_2 (2.5 equiv), MeOH (4.0 equiv), CuCl (20 mol%), (*S*)-BINAP (20 mol%), *t*BuONa (20 mol%), THF, 1 h; then 30% H_2O_2 (20 equiv), THF, 3 h, 61%; b) TBSOTf (4.0 equiv), 2,6-lutidine (6.0 equiv), CH_2Cl_2, 0 to 23 °C, 1 h, 62%; c) H_2 (1 bar), Pd/C (2.0 equiv), AcOEt, 23 °C, 1 h, 67%; d) Martin's sulfurane (2.2 equiv), CH_2Cl_2, −78 to 0 °C, 15 min, 74%; LDA = lithium diisopropylamide; HMDS = *bis*(trimethylsilyl)amide; Tf = trifluoromethane-sulfonyl; B_2pin_2 = bis(pinacolato)diboron; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, Martin's sulfurane = bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulfur.



Scheme 9. Attempted synthesis of tetraene **50**: a) $NaBH_4$ (5.0 equiv), $CeCl_3 \cdot 7H_2O$ (6.0 equiv), MeOH, −78 to 0 °C, 85%; b) $(CF_3CO)_2O$ (5.0 equiv), NEt_3 (10 equiv), CH_2Cl_2, 23 °C, 30 min; then $[Pd(PPh_3)_4]$ (30 mol%), NEt_3 (10 equiv), THF, 60 °C, 2 h, 43% (2 steps); c) 4-nitrobenzoic acid (6.0 equiv), PPh_3 (8.0 equiv), DIAD (6.0 equiv), CH_2Cl_2, 0 to 23 °C, 15 min, 56%; d) LiOH (4.0 equiv), THF/MeOH (5:1), 23 °C, 10 min, 40%; DIAD = diisopropyl azodicarboxylate.

deprotonation at the γ-position is favored under these conditions.

Inspired by Nicolaou's synthesis of haematocin (**3**),[3e] we explored accessing diene **50** by Luche-reduction of the bis(enone) **40** followed by palladium-catalyzed elimination of the corresponding bis(trifluoroacetate) (Scheme 9). Accordingly, reduction of enone **40** gave diol **46** in 85% yield; however, trifluoroacetylation followed by treatment with $[Pd(PPh_3)_4]$ and NEt_3 exclusively produced tetraene **47** instead of **50**. Moreover, direct elimination of the hydroxyl groups of **46** with Burgess' reagent also resulted in formation of **47**.

The same results were obtained when the configuration at C6 and C6′ was inverted by use of Mitsunobu reaction to give **48**: If nitrobenzoate **48** was subjected to $NEt_3/[Pd(PPh_3)_4]$ or if alcohol **49** was treated with Burgess' reagent we could only obtain small amounts of tetraene **47** instead of **50**. These observations suggest that formation of the desired cyclohexa-1,3-diene motif of pentacycle **50** is kinetically unfavored.

Conclusion

In summary, we have devised a concise and scalable route to the core structure of 6–5–6–5–6-fused ETP natural products. The key bidirectional opening of bis(oxabicyclo[2.2.1]heptane) **11** enabled the rapid construction of the bis(tetrahydroindole) core **12a** and simultaneously installed the functional groups necessary for further elaboration. Although it was not possible to transform the late-stage intermediate **12a** into either scabrosin diacetate (**1a**) or haematocin (**3**), it was possible to access a wide diversity of functionalized 6–5–6–5–6-membered diketopiperazines. These results should encourage the future use of this strategy to access highly functionalized diketopiperazines for SAR studies or natural products synthesis.

Additionally, we have reported the first detailed study towards scabrosin diacete (**1a**), an ETP natural product that has not been synthesized previously despite considerable efforts towards the total syntheses of other family members. The results presented herein provide insight that should be helpful in devising synthetic strategies.

Acknowledgements

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Keywords: amides · epipolythiodiketopiperazines · epoxidation · haematocin · scabrosin diacetate

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