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A Unified Strategy Targeting the Thiodiketopiperazine Mycotoxins Exserohilone, Gliotoxin, the Epicoccins, the Epicorazines, Rostratin A and Aranotin

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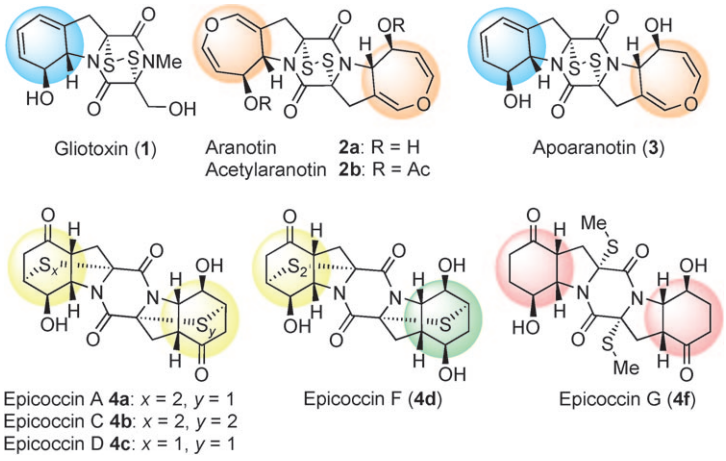
Abstract: A unified synthetic strategy directed towards mycotoxins belonging to the thiodiketopiperazine family is reported. The building blocks for a number of natural products—including exserohilone, gliotoxin, the epicoccins, the epicorazines, rostratin A and aranotin—have been synthesised stereoselectively from a common precursor. This key intermediate was constructed through an efficient and highly diastereoselective [2+2] cycloaddition between a ketene and an enecarbamate derived from L-pyroglutamic acid. The annelation of the second ring was accomplished through ring-closing metathesis and enol ether–olefin ring-closing metathesis to provide both *cis*- and *trans*-annelated azabicyclic cyclohexenones, as well as an annelated seven-membered cyclic enol ether. A Pd-catalysed elimination of allyl acetate gave rise to the cyclohexadienol structure of gliotoxin. Dimerisation of one building block to afford the diketopiperazine core was demonstrated.

Keywords: cycloaddition · epithiodiketopiperazines · metathesis · natural products · stereoselective synthesis

Introduction

Most fungal toxins are secondary metabolites, so-called mycotoxins.[1] Well-known classes of these include polyketides, cyclic peptides, alkaloids and sesquiterpenoids. Another class, the thiodiketopiperazines, are diketopiperazines containing thio functionality in bridged or open form. All of these thiodiketopiperazines exhibit important biological characteristics, attributed in many cases to the sulfur moiety.[2]

Out of this vast class of thiodiketopiperazines we have investigated the synthesis of a variety of natural products, all with the same absolute configurations at their C2, C8 and C9 carbon atoms (Scheme 1 and Scheme 2, below). They differ in the sulfur functionality, which can be either bridged or open, incorporating one, two or more sulfur atoms, and/or in the positions of these functionalities. The A/B (and D/E) ring systems are *cis*- or *trans*-annelated, thus differing in their configurations at C4 (and C4′) (Scheme 2, see numbering scheme **A**). In most of the natural products the A and E



Scheme 1. Structures of the mycotoxins gliotoxin (**1**), the aranotins (**2**), apoaranotin (**3**) and the epicoccins (**4**).

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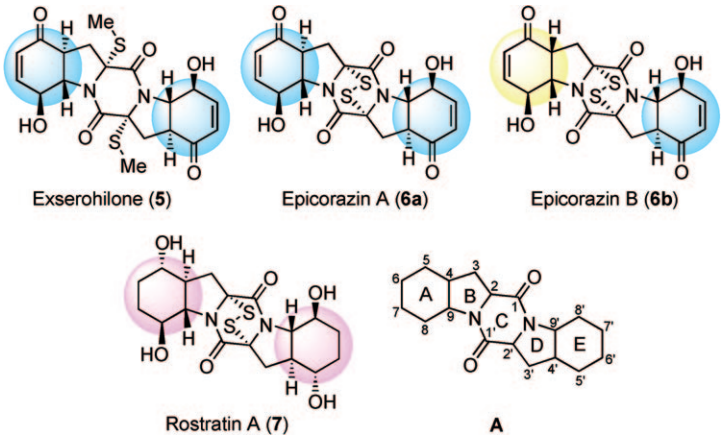


Scheme 2. Structures of the mycotoxins exserohilone (**5**), epicorazine A (**6a**), epicorazine B (**6b**) and rostratin A (**7**), together with the numbering scheme (**A**).

rings are substituted six-membered cyclohexane units, although aranotin (**2a**) features an oxygen-containing seven-membered heterocycle, a dihydrooxepine moiety.

Gliotoxin (**1**, Scheme 1) was the first thiodiketopiperazine to be reported and is the best characterised. It was isolated from culture broths of *Gliocladium fimbriatum*[3] and later also from other microorganisms such as *Trichoderma, Aspergillus* and *Penicillium*. It shows strong antibacterial and antiviral activity,[4] is immunosuppressive[5] and causes apoptotic and necrotic cell death.[6]

Aranotin (**2a**) and acetylaranotin (**2b**) are biosynthetically closely related to gliotoxin.[7] They have been isolated from *Arachniotus aureus* and *Aspergillus terreus*[7,8] and show in vitro and in vivo activities against polio (types 1, 2 and 3), Coxsackie (A21) and rhino- and parainfluenza (types 1 and 3) viruses.[7–9] The antiviral properties of the metabolites are of particular interest because of their ability to inhibit virus multiplication in tissue culture, with relatively low toxicities against mammalian cells.

Other members of the aranotin family, such as apoaranotin (**3**), are hybrids of gliotoxin (AB rings) and aranotin (DE rings) or are their 2,2′-$(SMe)_2$ forms.[7,10] The emethallicins, the phenylacetic ester and mandelic ester derivatives of aranotin and apoaranotin, show potent inhibitory activity of compound 48/80-induced histamine release from mast cells.[11] SCH 64874, another ester derivative, is the first example of a thiodiketopiperazine as an epidermal growth factor receptor antagonist. Other examples of thiodiketopiperazines with dihydrooxepine cores are emestrin and its methyl derivative MPC1001, exhibiting anti-cancer activity.[12,13]

The epicoccins (**4**, Scheme 1), which are all *cis*-annelated and contain the quite unusual sulfur bridge between C2 and C7, have only recently been isolated from a *Cordyceps*-colonising isolate of *Epicoccum nigrum*.[14,15] Epicoccin A (**4a**) shows modest antimicrobial activities, whereas epicoccin G (**4f**) effectively inhibits HIV-1 replication in C8166 cells.

Exserohilone (**5**, Scheme 2), with *trans* fusion of the A,B and D,E ring systems, isolated from *Exserohilum holmii*, exhibits phytotoxic activity.[16] The 2,2′-disulfide derivatives the epicorazines (**6**, again isolated from *Epicoccum nigrum*) show antibacterial activity against *Staphylococcus aureus*.[17] Closely related is rostratin A (**7**),[18] the only member of the rostratin family with this specific configuration. It was isolated from *Exserohilum rostratum* and shows in vitro cytotoxicity against the human colon carcinoma cell-line HCT-116.

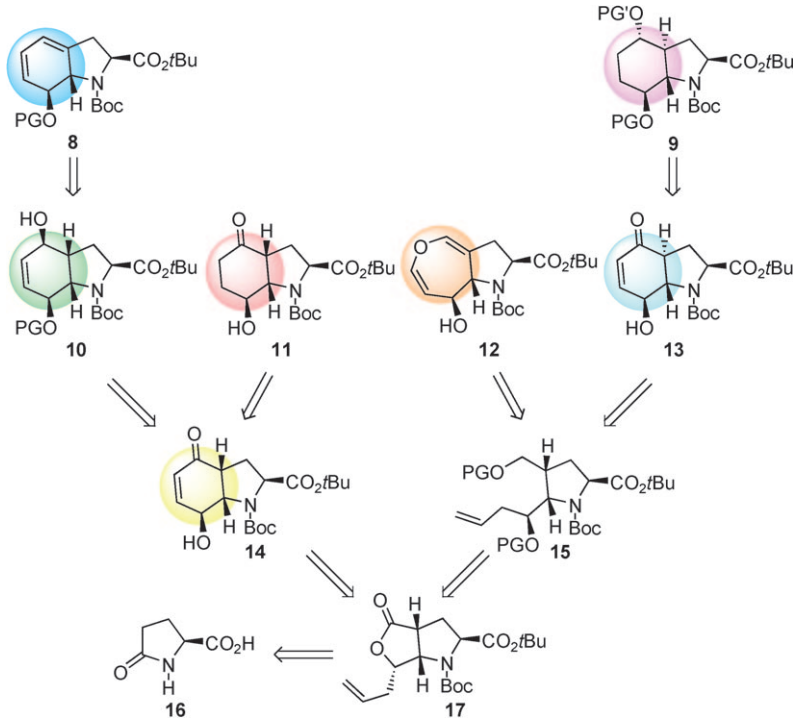
The complex structures and important biological activities of these thiodiketopiperazines clearly mark them as interesting synthetic targets. To the best of our knowledge, however, only gliotoxin has so far been produced by total synthesis,[19] although other synthetic strategies directed towards some of the thiodiketopiperazines, including rostratin C,[20] the epicoccins A, C and D (**3a–c**),[21] gliotoxin (**1**)[22] and MPC1001,[23] have been reported. Our results in the construction of C_2-symmetrical and unsymmetrical diketopiperazines in a one-step procedure from proline-type amino acids,[24] as well as the impressive thiolation results of Movassaghi and co-workers,[25] prompted us to target the synthesis of these thiodiketopiperazines. Our preliminary results relating to the construction of the scaffold of epicoccins A, C and D were published earlier.[21] We now wish to report our overall strategy directed towards gliotoxin (**1**), the aranotins (**2**), the epicoccins (**4**), exserohilone (**5**), the epicorazines (**6**) and rostratin A (**7**).

Results and Discussion

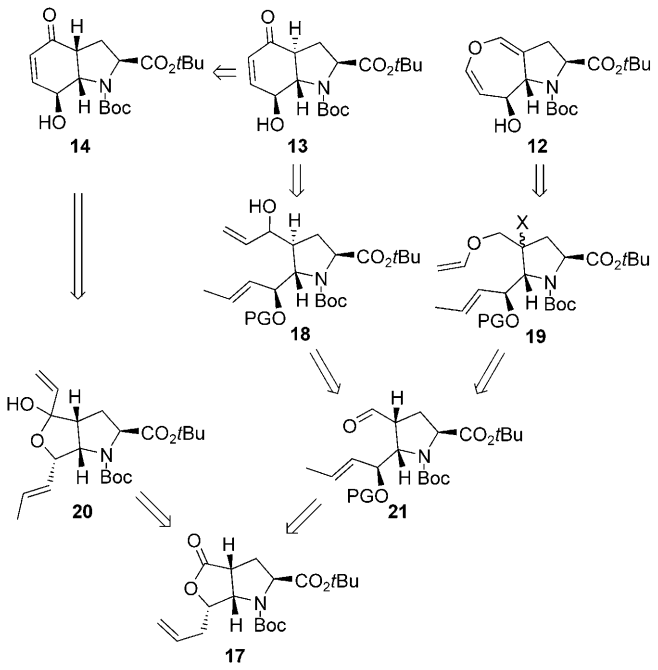
Retrosynthetic analysis: We envisaged a versatile and stereoselective synthesis of the building blocks of gliotoxin (**1**), the aranotins (**2**), the epicoccins (**4**), exserohilone (**5**), the epicorazines (**6**) and rostratin A (**7**) and others starting from one common precursor: the azabicyclic lactone **17** (Scheme 3). The lactone **17** was to be synthesised through a [2+2] cycloaddition between a ketene and an enecarbamate derived from L-pyroglutamic acid (**16**). The *cis*-annelated series, the cyclohexane **11** and the bisalcohol **10**, as well as the gliotoxin monomer **8**, were to be obtained from the *cis*-annelated cyclohexenone **14**.

Retrosynthetically, **14** was to be constructed from the azabicyclic lactone **17** in a three-step sequence involving a ring-closing metathesis (RCM) of the intermediate lactol **20**, generated by isomerisation of the terminal double bond and subsequent vinylation (Scheme 4). It was thought that the *trans*-fused series (the cyclohexenone **13** and the bisalcohol **9**) should be accessible either by epimerisation of the *cis*-annelated cyclohexenone **14** or by epimerisation of the aldehyde **21**. The key steps of the construction of the six-membered ring involve isomerisation of the double bond in **15** (Scheme 3), 1,2-addition of a vinyl Grignard to the aldehyde **21** and RCM (Scheme 4).

The aldehyde **21** is also an intermediate in our synthetic strategy for aranotin (**2a**). The key step of this approach is an enol ether–olefin RCM, providing a seven-membered tet-



Scheme 3. Retrosynthetic analysis of the building blocks for gliotoxin (**1**), the epicoccins (**4**), the aranotins (**2**), exserohilone (**5**), the epicorazines (**6**) and rostratin A (**7**). PG = protecting group.

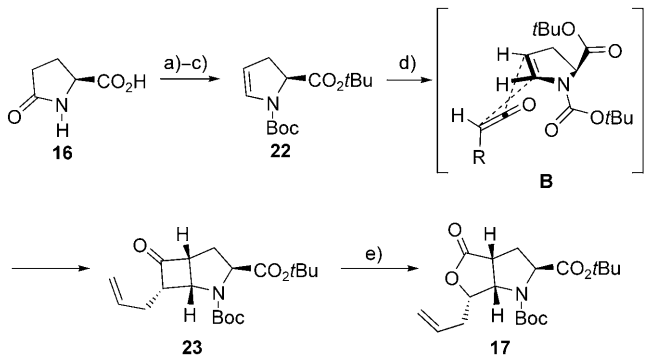


Scheme 4. Retrosynthetic approach to the *cis*- and *trans*-annelated cyclohexenonenes **14** and **13**, as well as to the annelated dihydrooxepine **12**.

rahydrooxepine ring. The second double bond of the aranotin building block **12** would have to be installed through an elimination reaction.

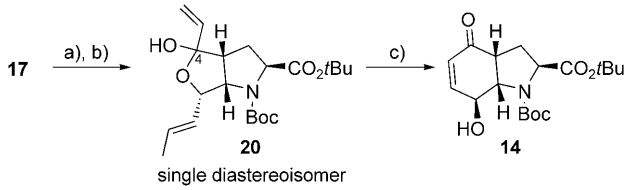
Synthesis: We achieved the synthesis of the azabicyclic lactone **17**, the key intermediate of our synthetic strategy, in five steps starting from L-pyroglutamic acid (**16**, Scheme 5).[21] The key step for the stereoselective construction of the azabicyclic lactone core was a highly diastereoselective [2+2] cycloaddition between a ketene, generated in situ from pent-4-enoyl chloride, and the enecarbamate **22**.[26–28] The azabicyclic cyclobutanone **23** was isolated as a single diastereoisomer in good yield.[29] A proposed explanation of the obtained diastereoselectivity is shown in Scheme 5 (**B**).[27b,30] Baeyer–Villiger oxidation of **23** with complete regio- and chemoselectivity gave the azabicyclic lactone **17** in good yield.

The terminal double bond was subsequently isomerised in the presence of the second-generation Grubbs catalyst[31] and vinyloxytrimethylsilane, giving



Scheme 5. Synthesis of the key intermediate azabicyclic lactone **17**: a) *t*BuOAc, $HClO_4$, RT; b) Boc_2O, DMAP (14 mol%), CH_3CN, 0°C→RT, 61% (two steps); c) $LiBHEt_3$, toluene, −78°C; DMAP (10 mol%), trifluoroacetic anhydride (TFAA), Hünig base (DIPEA), −78°C→RT, 77%; d) pent-4-enoyl chloride, NEt_3, cyclohexane, reflux, 75%; e) *m*CPBA, $NaHCO_3$, CH_2Cl_2, RT, 78%. Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, DIPEA = diisopropylethylamine.

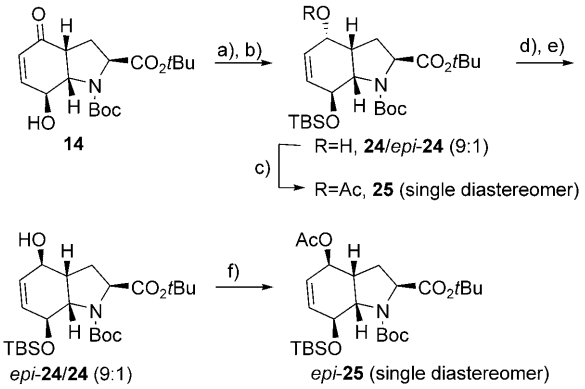
rise to the corresponding product, exclusively in the *E* configuration (Scheme 6). This isomerisation method, employing a ruthenium hydride as the active species, has been widely used in syntheses, in which the introduction of allyl groups proved to be more efficient compared with the introduction of vinyl or propenyl groups.[32] This was also the case in our synthetic strategy, because the [2+2] cycloaddition with but-3-enoyl chloride (instead of the utilised pent-4-enoyl chloride) did not give any cycloaddition product. In contrast with other catalytic systems, isomerisation occurs reliably only to the adjacent position. A 1,2-addition of



Scheme 6. Synthesis of the *cis*-annelated cyclohexenone **14**: a) vinyloxytrimethylsilane, second-generation Grubbs catalyst (3 mol%), toluene, reflux, 88% (99% based on recovered starting material (brsm)); b) vinyl Grignard, THF, −78°C, 80%; c) second-generation Grubbs catalyst (3 mol%), toluene, reflux, 72%.

vinyl Grignard reagent to the lactone gave the lactol **20** as a single diastereoisomer (of unknown configuration at C4). We were pleased that **20** underwent RCM in the presence of the second-generation Grubbs catalyst[31] to afford the *cis*-annelated cyclohexenone **14** as the building block for the epicoccins A, C and D (**4a**–**c**). The absolute configuration could be confirmed by crystal structure analysis.[21]

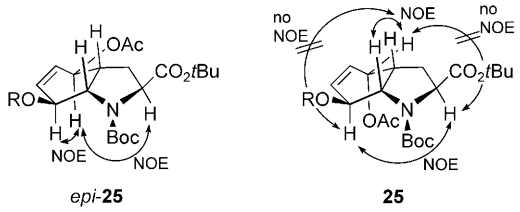
tert-Butyldimethylsilyl (TBS) protection of the hydroxy function in **14** and subsequent reduction (Scheme 7) gave



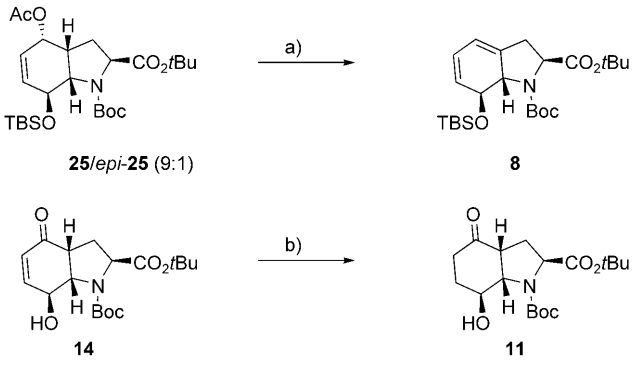
Scheme 7. Synthesis of the acetate **25** and the epicoccin F building block *epi*-**25** (**4d**): a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 73%; b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C, quant (**24**/*epi*-**24** 9:1); c) Ac_2O, DMAP, CH_2Cl_2, RT, 65% (**25**) and 18% (**25**/*epi*-**25** 1:1); d) DIAD, PPh_3, *p*-nitrobenzoic acid, THF, 0°C → RT, 65% (9:1); e) K_2CO_3, MeOH, RT, 82% (*epi*-**24**/**24** 9:1); f) Ac_2O, DMAP, CH_2Cl_2, RT, 81% (*epi*-**25**) and 11% (*epi*-**25** and **25**). DIAD = diisopropyl azodicarboxylate.

the alcohol **24** with good diastereoselectivity (9:1), with the hydride nucleophile attacking from the convex side of the molecule. Mitsunobu inversion[33] and subsequent hydrolysis of the benzoic ester gave rise to a 9:1 mixture of *epi*-**24** and **24**. The epimers could be separated as the acetates *epi*-**25** and **25**. The relative configurations of **25** and *epi*-**25** could be established by NOESY experiments (Scheme 8). The epicoccin F (**4d**) building block *epi*-**25** was thus synthesised stereoselectively in 13 steps.

A 9:1 mixture of the allylic acetates **25** and *epi*-**25** was subjected to the Pd^0-catalysed elimination conditions of Tsuji and Trost (Scheme 9).[34] The building block **8** for gliotoxin (**1**) could thus be synthesised effectively in 12 steps and 7.7% overall yield from L-pyroglutamic acid (**16**).[35] Hydrogenation of the *cis*-annelated cyclohexenone **14** with hydrogen on Pd/C gave rise to the building block **11** for epicoccin G (**4f**).



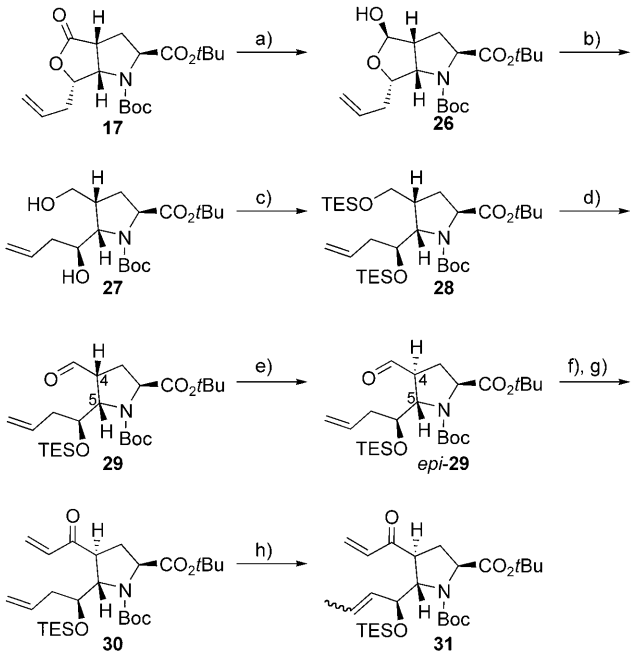
Scheme 8. NOE correlations in *epi*-**25** and **25** (R = OTBS).



Scheme 9. Synthesis of the building blocks **8** (for gliotoxin (**1**)) and **11** (for epicoccin G (**4f**)): a) $Pd(OAc)_2$ (20 mol%), PPh_3, NEt_3, toluene, 110°C, 58% (81% brsm); b) H_2, Pd/C (10 mol%), EtOAc, RT, 82%.

To give access to the *trans*-annelated series based on the azabicyclic cyclohexenone **13** (present in even more natural products than that based on the *cis*-annelated **14**) we performed epimerisation experiments with the *cis*-annelated TBS-protected cyclohexenone **14** and various bases and solvents. In all cases, however, only the starting material could be recovered, which is probably due to the *cis*-annelated cyclohexenone **14** being the thermally more stable epimer. This could later be demonstrated with the partial epimerisation of the *trans* isomer **13** to its *cis* isomer **14** under metathesis and basic conditions. We reasoned that epimerisation might be possible with a proline derivative such as **29** (Scheme 10), without an annelated second ring, with which the thermodynamically more stable product should be the one with its substituents at C4 and C5 in an *anti* relationship.

Initial experiments to synthesise the aldehyde **29** in a two-step procedure,[36] involving opening of the lactone **17** to give the corresponding amides or thioesters and subsequent reduction, failed as a result of the low reactivity of **17**. We therefore decided to reduce the lactone completely to the bisalcohol **27**, in a stepwise protocol via the lactol **26**. A crystal structure of **26** verified the assigned configuration of our compounds (Figure 1).



Scheme 10. Attempted synthesis of the *trans*-annelated cyclohexenone **13**: a) DIBAL, THF, −78 °C, 99 %; b) $NaBH_4$, MeOH, RT, 91 %; c) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 98 %; d) DMSO, $(COCl)_2$, −78 °C→−40 °C; NEt_3, −78 °C→0 °C; e) DBU, THF, RT, 76 % (2 steps); f) vinyl Grignard, THF, −78 °C, 84 %; g) Dess–Martin periodinane, CH_2Cl_2, RT, 96 %; h) vinyloxytrimethylsilane, second-generation Grubbs catalyst (5 mol %), toluene, 110 °C, 36–47 % with impurities of unknown structures. DIBAL = diisobutylaluminium hydride.

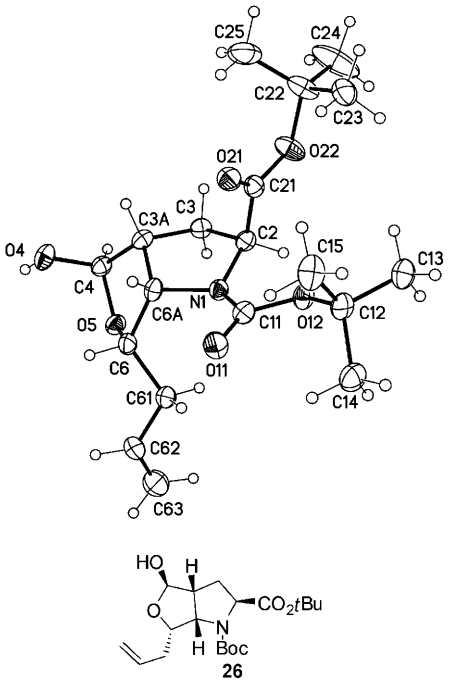
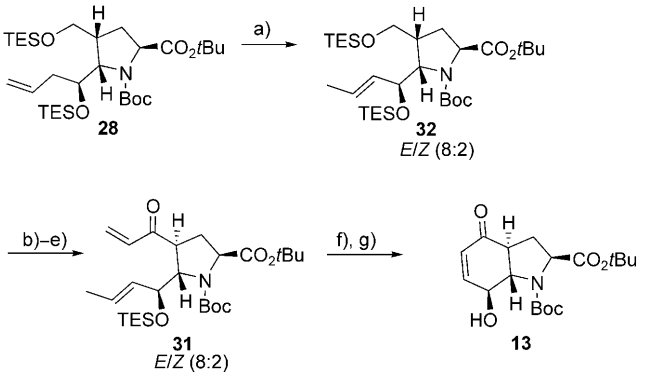


Figure 1. Crystal structure of lactol **26** (one independent molecule is shown, displacement parameters are drawn at 50 % probability level).

Both hydroxy functions were subsequently protected as triethylsilyl (TES) ethers. The primary TES-protected alcohol in **28** was then chemoselectively oxidised under Swern conditions to afford the corresponding aldehyde **29**, without oxidisation of the protected secondary alcohol (Scheme 10).[37] Sometimes, epimerisation of the aldehyde **29** (→*epi*-**29**) to a small degree (up to 20 %) was already observable under the Swern conditions. Complete epimerisation occurred upon treatment with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in THF at room temperature, to give *epi*-**29** as a single diastereoisomer. The 1,2-addition of vinyl Grignard reagent to the aldehyde function and subsequent oxidation to the vinyl ketone **30** was accomplished in good yields. Unfortunately, subsequent isomerisation of the terminal double bond proved difficult with this system. The allylic TES-alcohol **31** could be obtained only in low to moderate yield and with major impurities, which could not be separated. We reasoned that the Michael system of **30** could be responsible for the encountered problems and so we decided to perform the isomerisation on an earlier precursor.

Isomerisation of the double bond proceeded smoothly with the bistriethylsilyl ether **28**, to give the corresponding product as a mixture of *E* and *Z* isomers in a ratio of 8:2 (Scheme 11). Again, use of Swern conditions resulted in the

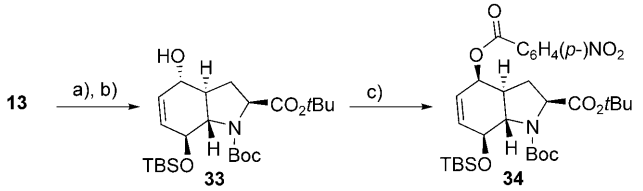


Scheme 11. Successful synthesis of the *trans*-annelated cyclohexenone **13**: a) vinyloxytrimethylsilane, second-generation Grubbs catalyst (5 mol %), toluene, reflux, quant. (*E*/*Z* 8:2); b) DMSO, $(COCl)_2$, −78 °C → −40 °C; NEt_3, −78 °C→0 °C; c) DBU, THF, RT, 87 % (2 steps, *E*/*Z* 8:2); d) vinyl Grignard, THF, −78 °C, 79 % (2 epimers 8:2, *E*/*Z* 8:2); e) Dess–Martin periodinane, CH_2Cl_2, RT, 92 % (*E*/*Z* 8:2); f) PPTS, CH_2Cl_2, RT, 80 % (*E*/*Z* 9:1); g) second-generation Grubbs catalyst (5 mol %), toluene, reflux, 56 % (**13**) and 29 % (**14**/**13** 3:1).

selective oxidation of the primary TES-protected alcohol in the presence of the secondary one. Epimerisation of the aldehyde, 1,2-addition and oxidation were accomplished in good to excellent yields as before. Unfortunately, we observed no conversion of the allylic TES-alcohol **31** in our attempted RCM reaction in the presence either of the second-generation Grubbs catalyst[31] or of the second-generation Grubbs–Hoveyda catalyst.[38] We reasoned that carbene formation next to the bulky triethylsilyl group might be too sterically hindered and indeed, after removal of the protect-

ing group on the allylic alcohol with pyridinium *para*-toluenesulfonate (PPTS), RCM could be accomplished in good yields. We have thus been able to synthesise the *trans*-annelated cyclohexenone **13**, representing the building block of epicorazines A (**6a**) and B (**6b**), as well as exserohilone (**5**), stereoselectively in 15 steps. We observed slow epimerisation under the RCM conditions, resulting in the additional isolation of the *cis* isomer **14** (22%).

Protection of the hydroxy function[39] and subsequent reduction with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ gave the allylic alcohol **33** with perfect diastereoselectivity (Scheme 12). To

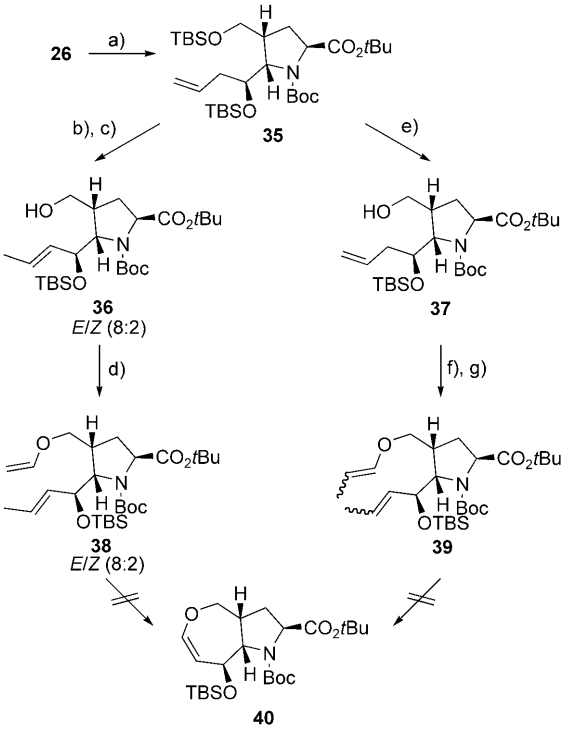


Scheme 12. Diastereoselective reduction of the *trans*-annelated cyclohexenone **13**: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, **33** (70%) and **33**/*epi*-**33** 1:1 (20%); b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C, 73%; c) DIAD, PPh_3, *p*-nitrobenzoic acid, THF, 0°C→RT, 98%.

assign the configuration at the newly established stereogenic centre, we also synthesised the epimer **34** through a Mitsunobu inversion. The coupling constants and NOESY data clearly verified the attributed configuration of **33**, which therefore represents the building block for rostratin A (**7**).

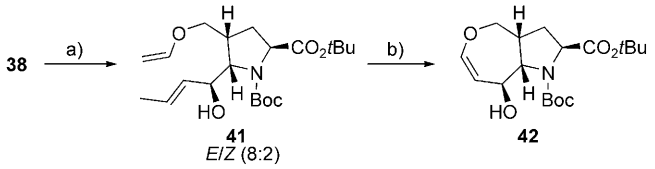
To assess the feasibility of enol ether–olefin RCM for the construction of our annelated oxepines (**19**→**12**, Scheme 4), we opted first to carry out the synthesis on an elaborated model substrate, lacking the leaving group for the construction of the second double bond. The bisalcohol **26** was doubly TBS-protected (→**35**) and the terminal double bond could again efficiently be isomerised (Scheme 13, left). After extensive screening for selective deprotection of the primary alcohol function, we identified HF/pyridine as the reagent of choice,[40] giving the monoprotected bisalcohol **36** in excellent yield. The hydroxy function was vinylated in the presence of an iridium catalyst, as reported by Okimoto et al.[41] Treatment of **36** with vinyl acetate in the presence of $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadiene) as the catalyst provided the enol ether **38**. We then attempted the enol ether–olefin RCM for the preparation of the oxepine ring in **40**. Our approach was guided by the success of RCM for the preparation of seven-membered cyclic enol ethers.[42] Unfortunately though, we observed no conversion either with the second-generation Grubbs catalyst[31] or with the second-generation Grubbs–Hoveyda[38] catalyst (25 mol%). Use of the Schrock catalyst,[43] reported to be more active and more successful than the ruthenium catalysts for enol ether–olefin RCM,[42a,44] led to decomposition.

In the proposed mechanism for enol ether–olefin RCM the Grubbs catalyst can react first either with the olefinic moiety or alternatively with the enol ether, forming a



Scheme 13. Synthesis of the precursors **38** and **39** for enol ether–olefin RCM: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 95%; b) vinyloxytrimethylsilane, second-generation Grubbs catalyst (5 mol%), toluene, reflux, quant (*E*/*Z* 8:2); c) HF/pyridine, THF, 0°C, 91% (*E*/*Z* 8:2); d) $[Ir(cod)Cl]_2$ (10 mol%), Na_2CO_3, vinyl acetate, toluene, 100°C, 95% (*E*/*Z* 8:2); e) HF/pyridine, THF, 0°C, 93%; f) allyl bromide, NaH, DMF, 0°C→RT, 70%; g) vinyloxytrimethylsilane, second-generation Grubbs catalyst (10 mol%), toluene, reflux, 62%.

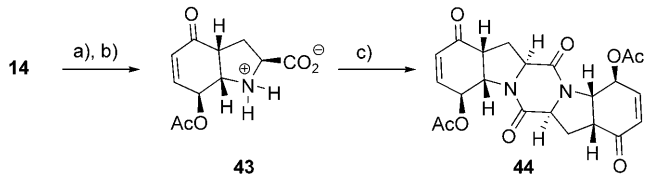
Fisher-type carbene. It has been reported that the formation of the Fisher-type carbene is critically detrimental, because it has proved to be significantly less reactive or even unreactive for further metathesis reaction in some cases.[42a,44b,45] Decreased accessibility of the vinyl ether should therefore favour cyclisation. To reduce this accessibility of the enol ether we opted for the installation of a propenyl substituent instead of the vinyl one (Scheme 13, right). The previously synthesised bis-TBS-ether **35** was therefore selectively monodeprotected with HF/pyridine (→**37**). The propenyl group was installed through isomerisation of the corresponding allyl ether. Guided by recent reports that a ruthenium hydride catalyst, generated from the second-generation Grubbs catalyst and vinyloxytrimethylsilane, also efficiently isomerises allyl ethers to their enol ether analogues,[46] we decided to carry out both allyl isomerisation and the isomerisation of the terminal double bond in one-pot fashion, and were indeed able to synthesise the doubly isomerised product **39** in good yield. Unfortunately, subsequent RCM in the presence of ruthenium and molybdenum catalysts was again unsuccessful. We then moved on to facilitate access to the olefin part by removal of the TBS protecting group on the allylic alcohol in **38** (Scheme 14). Gratifyingly the enol ether–olefin RCM proceeded smoothly with



Scheme 14. Enol ether–olefin RCM to afford the tetrahydrooxepine **42**: a) TBAF, THF, RT, 87% (*E*/*Z* 8:2); b) second-generation Grubbs catalyst (20 mol%), toluene, 110°C, quant. TBAF = tetra *n*-butylammonium fluoride.

the allylic alcohol **41** in the presence of the second-generation Grubbs[31] catalyst to afford the oxepine **42**, representing the dihydro building block for aranotin (**2a**) and related natural products. The second double bond of the oxepine moiety is to be incorporated through an elimination of a leaving group, to be installed on an earlier precursor such as aldehyde **21** (Scheme 4).

As proof of principle we had already tested our reported dimerisation conditions[24] on one of the synthesised building blocks. The *cis*-annelated cyclohexenone **14** was therefore protected as an acetate and the free amino acid **43** was obtained in neat trifluoroacetic acid (TFA) (Scheme 15). With methyl dichlorophosphite and triethylamine the diketopiperazine **44** could be isolated in modest yield over two steps as a single diastereoisomer. It represents the dethio analogue of the epicoccins A, C and D (**4a–c**).



Scheme 15. Final assembly of the core **44** in epicoccins A, C and D (**4a–c**): a) Ac_2O, DMAP, CH_2Cl_2, RT, 92%; b) TFA, RT; c) $MeOPCl_2$, NEt_3, toluene, 40°C→110°C, 18% (2 steps).

Conclusion

We have developed a unified synthetic strategy directed towards a number of natural products of the thiodiketopiperazine family, including gliotoxin (**1**), the aranotins (**2**), the epicoccins (**4**), exserohilone (**5**), the epicorazines (**6**) and rostratin A (**7**). This stereoselective and versatile synthetic strategy gives access to the *cis*- and *trans*-annelated series of azabicyclic cyclohexenones, the annelated cyclohexadienol structure of **1** and to the fused seven-membered cyclic enol ethers, the so-called oxepins. In all cases the annelation of the second ring to a proline ring system has been accomplished through RCM in the presence of the second-generation Grubbs catalyst. We have been able to demonstrate that the synthesised building blocks can be dimerised in a one-step protocol to afford the corresponding diketopiperazine cores, present in all of the natural products.

The completion of the dihydrooxepine building block **10**, present in aranotin (**2a**), as well as thiolation on advanced model diketopiperazines, are currently being pursued in our laboratories and will be reported in due course.

Experimental Section

For full experimental details see the Supporting Information.

Crystal structure determination of 26: The single-crystal X-ray diffraction study was carried out with a Bruker–Nonius Kappa-CCD diffractometer at 123(2) K with use of $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Direct Methods (SHELXS-97) were used for structure solution and refinement was carried out by use of SHELXL-97[47] (full-matrix, least-squares on F^2). Non-hydrogen atoms were refined anisotropically; hydrogen atoms were localised by difference electron density determination and refined with the aid of a riding model (H(O) free). The absolute configuration could not be determined reliably by refinement of Flack's *x*-parameter ($x = 0.0(10)$).[48] The absolute configuration was assigned by reference to the unchanging chiral centre of L-pyroglutamic acid (**16**) in the synthetic procedure. Refinement of Hooft's FLEQ parameter[49] confirmed the assigned absolute configuration (FLEQ = −0.01(24)). In one of the two independent molecules the allyl group and one *tert*-butyl carboxylate group were disordered. The crystals were pseudo-merohedral twins.

Compound 26: colourless crystals, ($C_{19}H_{31}NO_6$), $M = 369.45$, crystal size $0.35 \times 0.25 \times 0.15$ mm, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 10.157(1)$, $b = 10.186(1)$, $c = 40.645(4)$ Å, $V = 4205.1(7)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.167$ Mg m^{-3}, $F(000) = 1600$, $\mu = 0.086$ mm^{-1}, 40207 reflections ($2\theta_{max} = 55°$), 9168 unique [$R_{int} = 0.047$], 457 parameters, 214 restraints, $R1$ ($I > 2\sigma(I)$) = 0.051, $wR2$ (all data) = 0.120, $S = 1.03$, largest diff. peak and hole 0.425 and −0.420 e Å^{-3}.

CCDC-773914 (**26**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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