# An organocatalytic approach to the core of eunicellin†

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**A stereocontrolled synthesis of the core of eunicellin is described featuring a Claisen rearrangement and a diastereoselective organocatalytic Diels–Alder reaction as the key steps.**

Eunicellin **1** was isolated from *Eunicella stricta* in 1968 and its structure was determined by spectroscopic methods and X-ray crystal structure analysis of a dibromide derivative.[1] Since this initial report a wide variety of structurally related diterpenes (the cladiellins) have been isolated, many of which have now succumbed to total synthesis.[2] Eunicellin itself has yet to be synthesised in the laboratory and, as with many of the other cladiellins, possesses several challenging structural features including a *cis*-fused hexahydroisobenzofuran moiety flanked by a characteristic nine-membered ether. Such medium ring oxacycles form the core of many natural products,[3] but are often difficult to construct due to the associated unfavourable enthalpic ($\Delta H^{\ddagger}$) and entropic ($\Delta S^{\ddagger}$) factors, including transannular crowding, angle and eclipsing strain.[4] Current methods available for the synthesis of this common structural motif include direct cyclisation of an acyclic precursor, and ring expansion by fragmentation or rearrangement.[5]

Our own approach to medium-ring oxygen and nitrogen heterocycles involves the Claisen rearrangement of a suitably substituted vinyl ketene acetal,[6,7] a reaction first reported by Petrzilka[8] for the synthesis of a ten-membered lactone. We have successfully applied this methodology in the synthesis of natural products and related compounds.[9] Herein we report the stereocontrolled synthesis of the core tricyclic framework of eunicellin **1**, which features a Claisen-rearrangement and an organocatalysed Diels–Alder reaction as key steps, building on our previous work in this area.[9d] Crimmins and co-workers have demonstrated the power of the intramolecular Diels–Alder approach for the construction of a variety of cladiellins.[2k–m]

The retrosynthetic analysis of eunicellin **1** is shown in Scheme 1. An *exo*-selective Diels–Alder reaction of the α,β-unsaturated aldehyde **3** would deliver the tricyclic core of eunicellin **2** containing all the requisite functionality to allow synthesis of the natural product. The thermodynamically favoured 2,9-*cis* disubstituted $\Delta^5$-hexahydro-oxonin **3** would be derived from the lactone **4**, which in turn would be synthesised using a Claisen-rearrangement of an appropriately substituted ketene acetal **5**.‡

In a forward sense, the synthesis of the lactone **4** began with the conversion of 2-deoxy-D-ribose **6** into the corresponding methyl glycosides with subsequent silylation giving the diastereomeric acetals **7** (Scheme 2).[9a,g] Protection of the secondary alcohols in **7** as benzyl ethers, followed by hydrolysis, gave the lactols **9**.§ Treatment of the lactols **9** with excess ethynylmagnesium bromide furnished the expected diols **10**. Hydrosilylation of the diastereomeric mixture of alkynes **10** with phenyldimethylsilane in the presence of a platinum(0) catalyst[10,11] furnished the (*E*)-vinylsilanes **11** exclusively in 97% yield following the protocol described by Panek *et al.* (Scheme 3).[12] Transacetalisation of the diols **11** with the phenylselenyl acetaldehyde diethyl acetal[8] in toluene in the presence of an acid catalyst, gave the selenoacetals **12** as a mixture of a number of diastereomers. Oxidation of the selenides gave the corresponding selenoxides which, on heating in basic toluene under reflux, delivered the nine-membered lactone **4** as a single diastereomer in good overall yield. The stereochemistry at 4-C of the lactone **4** was assigned on the basis of $^1$H NMR NOE experiments and can be rationalised by invoking a chair-like transition state for the Claisen rearrangement.[9a,b] Methylenation of the lactone **4** with the Tebbe reagent[6,13] gave the desired enol ether **13** in excellent yield. Regioselective reductive phenylselenenylation of the enol ether then delivered the selenide **14** as a single diastereomer.¶[9b,d] Selenoxide formation, using buffered sodium periodate, followed by Pummerer rearrangement and subsequent methanolysis gave the 2,9-*cis*-disubstituted $\Delta^5$-hexahydro-oxonin **15**. A clear $^1$H NMR NOE between 2-H and 9-H of **15** confirmed the stereochemistry (Scheme 3). Two Wittig olefinations[14,15] gave the diene **16** in good yield as a single stereoisomer. Protecting group removal, Swern oxidation and a further Wittig olefination efficiently delivered the enal **3**.

We have reported previously that the thermal Diels–Alder cycloaddition of a related substrate bearing an (*S*)-configured 8-C carbinol centre gave predominantly the *endo*-cycloadduct corresponding to ***endo*-2**.‖ In related work Crimmins *et al.*[2l] have demonstrated that the stereochemical outcome of the thermal Diels–Alder reaction of a similar substrate bearing an (*R*)-configured 8-C silyloxy substituent delivers the desired *exo*-cycloadduct corresponding to the natural cladiellin stereochemistry. Here we demonstrate that an enantiopure organocatalyst may be employed to allow the synthesis of either the *exo* or the *endo* cycloadduct in good yield and high selectivity. Treatment of the triene **3** with **(*S*)-18**[16] (5 mol%) in a mixture of MeCN–$H_2O$ (95 : 5 v/v) generated the desired cycloadduct ***exo*-2** in good yield as a single diastereomer (Scheme 4).[17] The stereochemistry of ***exo*-2** was verified by X-ray crystal structure analysis of the

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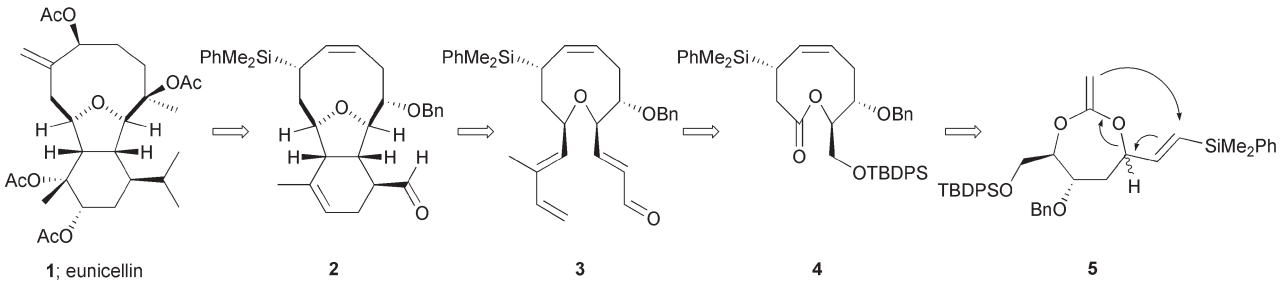
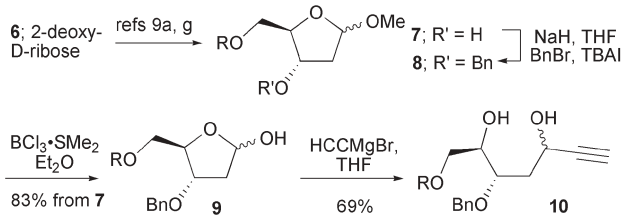
† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data, selected $^1$H and $^{13}$C NMR spectra, the cif file for ***exo*-2** See DOI: 10.1039/b709322e



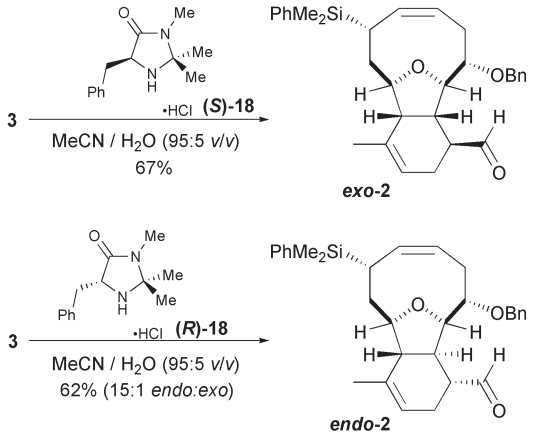

**Scheme 1** Retrosynthetic analysis of eunicellin **1**.




**Scheme 2** R = *t*BuPh$_2$Si (TBDPS).

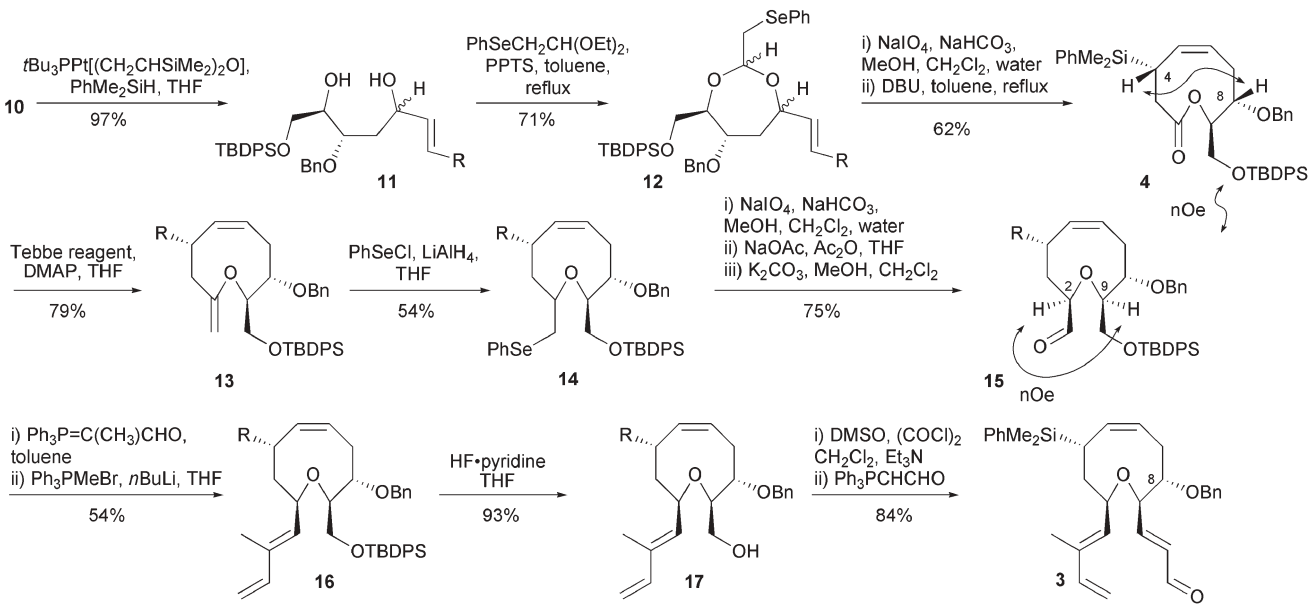
semicarbazone derivative **19** (Scheme 5, Fig. 1).** The X-ray crystal structure of **19** clearly shows the *cis–anti–cis* stereochemistry around the core hexahydroisobenzofuran, which is a characteristic feature of the eunicellins and also confirmed the relative stereochemistry at the phenyldimethylsilyl-bearing stereocentre.

Exposure of the α,β-unsaturated aldehyde **3** to the imidazolidinone catalyst **(*R*)-18**, delivered a 15 : 1 mixture of the cycloadducts ***endo*-2** and ***exo*-2** (Scheme 4), again in good yield. The stereochemistry of ***endo*-2** was established by $^1$H NMR NOE experiments (see ESI†). Attempts to effect the thermal cycloaddition of the diene **3** (heating in toluene at reflux for 24 h) resulted in quantitative recovery of starting material, indicating that the imidazolidinone-mediated reactions are indeed organocatalytic.

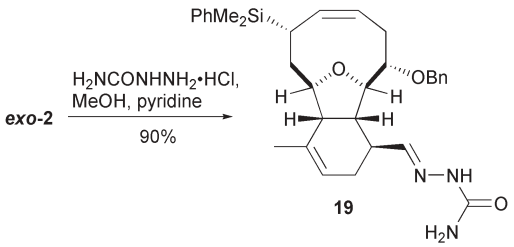



**Scheme 4**

In summary, a concise synthesis of the eunicellin core has been achieved. Key steps include the Claisen rearrangement to construct the medium-ring ether, and an organocatalyst-controlled Type I intramolecular Diels–Alder reaction. The diastereoselectivity of the cycloaddition reaction is highly dependent on the enantiomer of the organocatalyst used; the (*S*)-enantiomer of **18** affords predominantly the *exo*-adduct ***exo*-2** whereas the (*R*)-enantiomer




**Scheme 3** R = PhMe$_2$Si.




**Scheme 5**

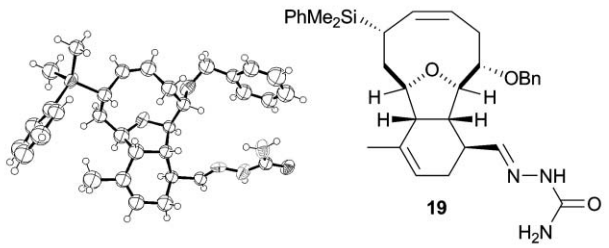



**Fig. 1** X-Ray crystal structure of the semicarbazone **19** showing 50% probability ellipsoids.

of **18** favours ***endo*-2**. The cycloadducts **2** contain the complete carbon framework of eunicellin **1** and work is ongoing to complete the total synthesis of members of this class of natural product and to understand the origin of the diastereoselectivity of the organocatalytic Diels–Alder reaction.

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## Notes and references

‡ For related work on the synthesis of nine-membered lactones starting from 2-deoxy-D-ribose see ref. 9*a*,*g*.

§ See ref. 9*a* and 9*g* for synthesis of the bis(TBDPS) protected analogues of **8**.

¶ The stereochemistry at the phenylselenylmethyl carbon in **14** was not determined.

‖ The substrate used for this thermal reaction was the corresponding α,β-unsaturated methyl ketone which had a *tert*butyldiphenylsilyloxy group in the place of a benzyloxy group and lacked the phenyldimethylsilyl group (see ref. 9*d*).

** Crystals of the semicarbazone **19** were extremely weakly diffracting but despite the limited data obtained from the synchrotron source at CCLRC, Daresbury Laboratory, it was possible to solve the structure by direct methods; the w$R_2$ factor was 0.251. CCDC 637637. For crystallographic data in CIF format see DOI: 10.1039/b709322e.

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