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Stereoselective synthesis of the octahydroisobenzofuran skeleton of the eunicellins

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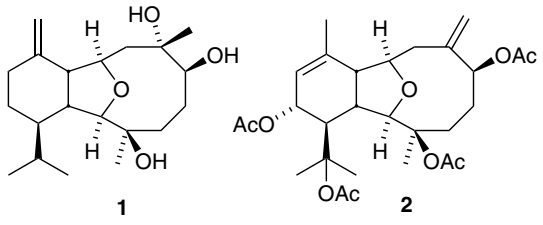
Abstract—A de novo asymmetric synthesis of the octahydroisobenzofuran skeleton contained within the eunicellin family of natural products has been completed. The key transformations involve the convergent assembly of a tetrasubstituted tetrahydrofuran by condensation of a functionalised allylsiloxane with an aldehyde; controlled epimerisation of a C4 aldehyde by intramolecular trapping; installation of the isopropyl substituent by stereoselective Michael addition to a 5,5-bicyclic enone; and ring expansion of the 5,5-system to the target structure by radical-mediated cyclopropane fragmentation.

The eunicellins are marine natural products with an oxygenated 2,11-cyclised cembranoid structure.[1] The key structural feature of the eunicellins is an unusual oxatricylic ring system in which is embedded an octahydroisobenzofuran core. Members of the family exhibit a diverse range of biological activities, for example, sclerophytin A **1** is cytotoxic against L1210 leukaemia cell lines at a concentration of 1 ng/mL,[2] while astrogorgin **2** inhibits cell division in fertilised starfish eggs.[3]



To date, four groups have completed the total synthesis of eunicellin natural products. The Overman group has been most active in the area, completing the syntheses of 6-acetoxycladiell-7(16),11-dien-3-ol,[4–6] cladiell-11-ene-3,6,7-triol[6,7] and sclerophytin A.[6,7] They have also disclosed the first syntheses of members of the related briarellin family.[8] Other groups to complete syntheses are those of Paquette (sclerophytins A and B),[7,9] Molander (6-acetoxycladiell-7(16),11-dien-3-ol)[10] and Crimmins (ophirin B).[11] The routes adopted by the first three groups proceed by the way of octahydroisobenzofuran intermediates, to which the final ring is annealed in the later stages of the synthesis. Overman and Molander both elected to construct this core by elaboration of chiral pool materials (carvone and α-phellandrene, respectively), whereas Paquette opted to prepare this unit directly by Diels–Alder cycloaddition to a chiral butenolide. Several approaches to subunits of the natural products have been reported.[12–15]

Given our previous endeavours in the stereoselective construction of polysubstituted tetrahydrofurans,[16–19] we were interested in applying this work to the preparation of functionalised octahydroisobenzofurans of potential use in the synthesis of eunicellins. Such an approach would be complementary to the chiral pool approaches, offering the potential for late-stage functionalisation to lead to members of the natural product family containing more highly oxygenated cyclohexane rings than those that have previously been prepared. In light of the preceding work, it seems highly likely that an appropriately functionalised bicyclic core could indeed be elaborated to construct the final ring of the eunicellins. We report herein a stereocontrolled approach to octahydroisobenzofurans.

Keywords: Eunicellin; Allylsiloxane; Cyclopropane; Ring expansion.
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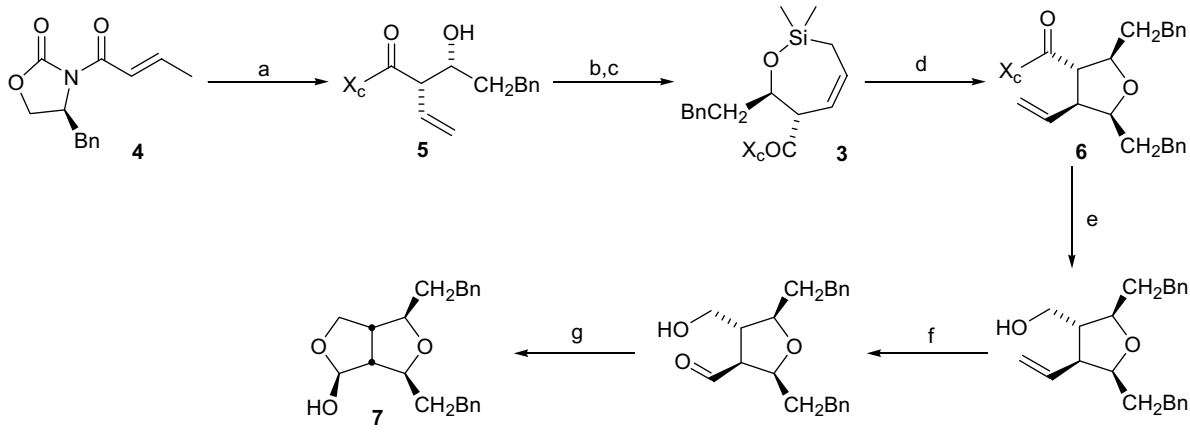


Scheme 1. Reagents and conditions: (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, $PhCH_2CH_2CHO$, −78 to 0 °C (85%); (b) $CH_2{=}CHCH_2SiMe_2Cl$, imidazole, DMF, rt (91%); (c) 3% $(Pcy_3)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, reflux (92%); (d) $PhCH_2CH_2CHO$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C to rt (91%); (e) $NaBH_4$, THF/H_2O, rt (89%); (f) O_3, CH_2Cl_2, −78 °C, then PPh_3; (g) DBU, toluene, rt (47%, two steps).

Our synthesis commenced with the stereoselective construction of a tetrasubstituted tetrahydrofuran. Cyclic allylsiloxane **3** was prepared in three steps from (*E*)-crotonyloxazolidinone **4** as shown in Scheme 1. Deconjugative aldol reaction of **4** with 3-phenylpropanal gave *syn*-aldol **5** as a single diastereoisomer.[20] Silylation with allylchloro-dimethylsilane and subsequent ring-closing olefin metathesis gave **3**. Lewis acid-mediated condensation of **3** with 3-phenylpropanal gave tetrahydrofuran **6** as a single diastereoisomer in 91% yield. The stereochemical outcome of this reaction can be rationalised by assuming that the key intramolecular Sakurai reaction proceeds by a chair-like transition state with an *E*-configured oxocarbenium ion and all substituents equatorially disposed (Fig. 1).

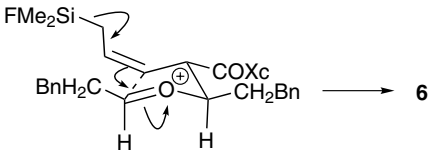


Figure 1. Model explaining the stereoselective formation of **6**.

Comparing the structure of **6** with the core of the eunicellins, it is clear that the stereocentre at C4 requires inversion to allow progression to the *cis*-fused 6,5-ring system. Attempted base-mediated epimerisation of the aldehyde derived from ozonolysis of the C4 ethenyl substituent was unsuccessful, leading to a mixture of products (including cleavage of the oxazolidinone auxiliary). Although epimerisation of similar aldehydes has previously been achieved in less substituted systems,[16,21] the system here will suffer destabilising steric interactions with an adjacent *cis*-substituent (phenethyl group or acyl oxazolidinone) regardless of the C4 stereochemistry, which removes the driving force for the epimerisation. In the event, we exploited the neighbouring C3 substituent to trap the desired C4 epimer by reduction of the acyl oxazolidinone to a hydroxymethyl group prior to oxidative cleavage of the olefin. Treatment with DBU now led cleanly to a single diastereoisomeric lactol

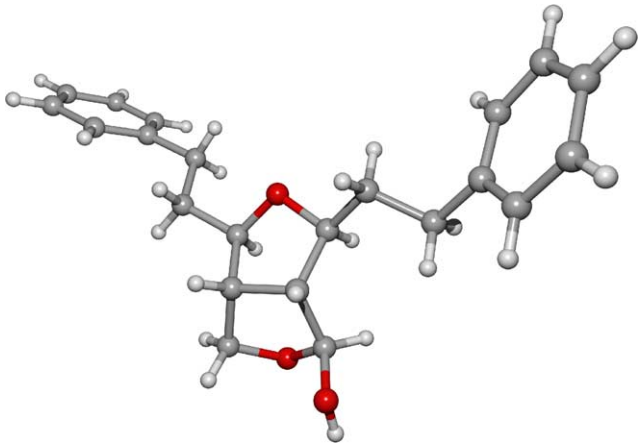
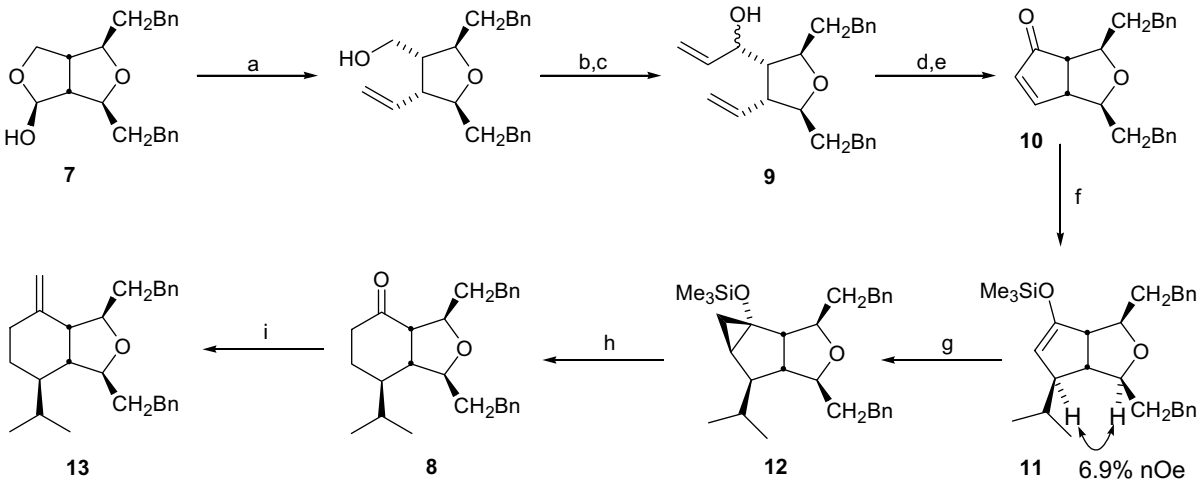


Figure 2. POV-ray representation of the X-ray crystal structure confirming the identity of **7**.

7, whereby the strong preference for a *cis*-fused 5,5-ring system selectively trapped the desired C4 epimer and prevented further decomposition. The constitution of **7** was unambiguously established by X-ray crystallography (Fig. 2). This epimerisation process may be of more general utility than solely the present application, since tetrasubstituted tetrahydrofuran lignans with 3,4-*cis* stereochemistry are well documented.[22,23]

With lactol **7** in hand, we turned our attention to the elaboration of the carbocyclic ring and stereoselective installation of the isopropyl substituent. Examination of the eunicellin structures suggested to us that a ketone of type **8** would be a versatile precursor to a number of the possible substitution patterns found in the eunicellins, which include *exo*-methylene groups, methyl-substituted cyclohexenes, and α-methylcyclohexanols. In principle, the reactivity of the ketone or a derivative could be used to install the isopropyl group; however, the 1,4-disposition of the two groups did not suggest any convincing methods for achieving this directly. Instead, we elected to employ a conjugate addition to a rigid, 5,5-bicyclic enone to control the stereochemistry of the installation of the



Scheme 2. Reagents and conditions: (a) $MePPh_3Br$, *n*-BuLi, THF, 0 °C to rt (76%); (b) PCC, CH_2Cl_2, rt (81%); (c) CH_2=CHMgBr, THF, 0 °C to rt (83%); (d) 5% $(Pcy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, rt (86%); (e) PCC, CH_2Cl_2, rt (99%); (f) ^iPrMgCl, LiCl, CuI, TMSCl, Et_3N, THF, −78 °C to rt (71%); (g) Et_2Zn, CH_2I_2, toluene, rt (20%); (h) $Fe(NO_3)_3$, 1,4-cyclohexadiene, DMF, rt; (i) $MePPh_3Br$, *n*-BuLi, THF, 0 °C to rt (20%, two steps).

isopropyl group, and subsequently to perform a ring expansion to furnish the desired ketone **8**.

Methylenation of lactol **7** with methylenetriphenylphosphorane was followed by oxidation of the primary alcohol and addition of vinylmagnesium bromide to give diene **9** (Scheme 2). Ring-closing olefin metathesis, followed by oxidation of the allylic alcohol, gave the target enone **10**. Copper-catalysed addition of isopropylmagnesium chloride to **10** in the presence of chlorotrimethylsilane gave direct access to enol ether **11** as a single diastereoisomer. The addition reaction is presumed to take place by addition to the convex face of the oxabicyclo[3.3.0]octene ring system, an assignment supported by a strong (6.9%) NOE enhancement between the allylic CH adjacent to the isopropyl group and the proton at position 2 of the tetrahydrofuran. To effect ring expansion, we employed the radical fragmentation of siloxycyclopropanes popularised by Booker-Milburn and Thompson.[24] Simmons–Smith cyclopropanation of silyl enol ether **11** gave a single diastereoisomer of the target cyclopropane **12**, which was treated with iron(III) nitrate and 1,4-cyclohexadiene to give ketone **8**. Finally, methylenation of **8** gave the core *exo*-methylene octahydroisobenzofuran **13** contained within eunicellins such as sclerophytin.[25]

In summary, a stereocontrolled synthesis of the bicyclic core of the eunicellins has been achieved in 16 steps from crotonyl oxazolidinone **4**. The extension of this work to encompass a total synthesis of the eunicellins can readily be envisaged by the use of appropriately substituted allylsiloxanes and aldehydes in the tetrahydrofuran-forming condensation sequence. Further studies in this area will be reported in full in due course.

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25. Physical and spectroscopic data for **13**: $[\alpha]_D^{24}$ +1.3 (*c* 0.24 CH_2Cl_2); ν_{max}/cm^{-1} (neat); 2961 w, 2928 w, 1640 w, 1511 m, 1454 s, 1261 s, 1094 and 1029 s; δ_H (500 MHz, $CDCl_3$) 7.23–7.09 (10H, m, ArH), 4.71 (1H, s), 4.64 (1H, s), 3.90 (1H, app t, *J* 7.0), 3.82 (1H, td, *J* 10.5, 3.0), 2.83 (1H, ddd, *J* 13.5, 11.5, 5.0), 2.71 (1H, ddd, *J* 13.5, 11.0, 5.5), 2.63–2.51 (3H, m), 2.19 (1H, m), 1.97 (1H, m), 1.94–1.57 (7H, m), 0.96 (1H, m), 0.89 (3H, d, *J* 7.0), 0.78 (1H, m) and 0.68 (3H, d, *J* 7.0); δ_C (75 MHz, $CDCl_3$); 145.4, 141.6, 141.3, 127.4, 127.33, 127.3, 124.7, 124.6, 109.8, 81.6, 78.5, 50.8, 48.2, 41.8, 38.3, 36.1, 31.7, 31.5, 30.7, 26.9, 24.4, 20.9 and 14.5 (1 × Ar–C signal overlapped); *m*/*z* (ES+) 389 (15%, $[M+H]^+$) 343 (66), 311 (100, $[M-Ph]^+$), 298 (45, $[M-Bn]^+$), 255 (38), 243 (44) and 215 (60); HRMS (ES+) found $[M+H]^+$ 389.2836, $C_{28}H_{37}O$ requires 389.2844.