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The first total synthesis of (+)-mucosin†‡

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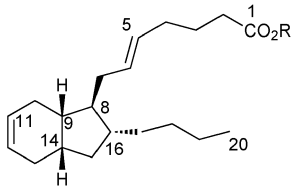
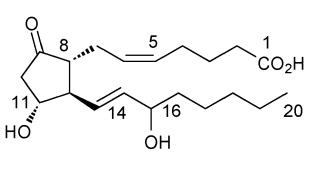
The first total synthesis of (+)-mucosin has been completed allowing assignment of the absolute stereochemistry of the natural product. A zirconium induced co-cyclisation was utilised to install the correct stereochemistry of the four contiguous stereocentres around the unusual bicyclo[4.3.0]nonene core.

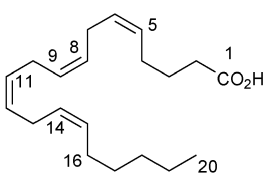
In 1997 (−)-mucosin **1**, a novel bicyclic eicosanoid was isolated from the marine sponge *Reniera mucosa* in the Mediterranean.[1] The structure of its methyl ester **2** was determined using mass, infrared and high field NMR spectroscopy. The relative stereochemistry was determined using a series of 2D NMR experiments. Mucosin is an interesting synthetic target given its unusual bicyclo [4.3.0]nonene core and close structural relation to the biologically important leukotrienes and prostanoids, including PGE_2 (**3**), thromboxane and prostacyclin, with which it presumably shares a common precursor in arachidonic acid (**4**).[2] The only similar structure of which we are aware is the C22 compound dictyosphaerin (**5**).[3] Herein we report the first total synthesis of (+)-mucosin and hence establish the absolute stereochemistry of the natural product.



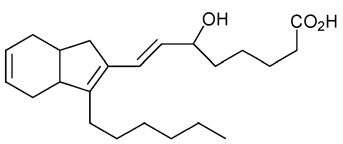
1 R = H, Mucosin
2 R = Me.



3 PGE_2



4 Arachidonic Acid



5 Dictyosphaerin

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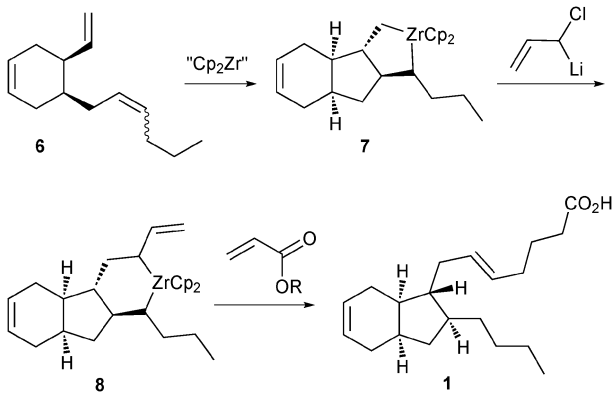
† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for all new compounds; comparison of data with that reported for the natural product; and additional crystallographic evidence for the relative stereochemistry of the major isomer formed. See DOI: 10.1039/c2cc17915f

‡ Dedicated to Prof. Phil Parsons on the occasion of his 60th birthday.

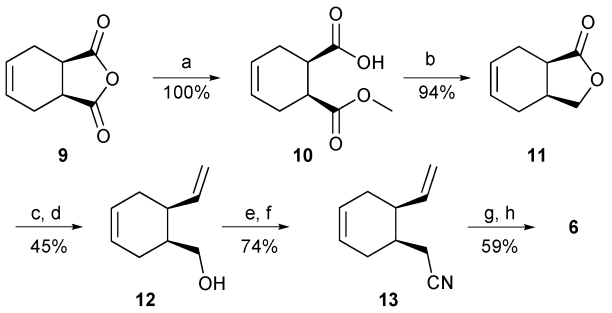
Our synthetic strategy (Scheme 1) was to use the zirconocene-(1-butene) induced co-cyclisation of triene **6** to zirconacycle **7** to control the relative stereochemistry of the four contiguous chiral centres in mucosin.[4] Further elaboration of the zirconacycle through allyl carbenoid insertion to afford **8** followed by 1,4-addition to an acrylate equivalent should provide a concise completion of the synthesis with control of the alkene stereochemistry.[5]

The synthesis of triene **6** was achieved in eight steps from the commercially available tetrahydrophthalic acid anhydride **9** (Scheme 2). The first step was the asymmetric ring opening of anhydride **9** for which there are wide variety of methods.[6] We found that catalysis of methanolysis with a chiral amine (alkaloid) as established by Bolm to be the simplest and cheapest.[7] Use of quinidine gave the (1*R*,6*S*) enantiomer of acid ester **10** in 100% yield and 90% ee. To obtain the opposite enantiomer quinine could have been used as the catalyst.[7] The selective reduction of acid ester **10** using Super-Hydride® furnished lactone **11**.[8] Partial reduction of **11** using DIBAL-H gave a lactol which underwent Wittig methylenation to yield alcohol **12**.[9] The second alkene branch was installed by conversion of **12** to its mesylate followed by cyanide displacement to give nitrile **13**. DIBAL-H reduction and treatment of the resultant aldehyde with butylidenetriphenylphosphorane gave triene **6** as a 4 : 1 mixture of *Z* : *E* isomers.

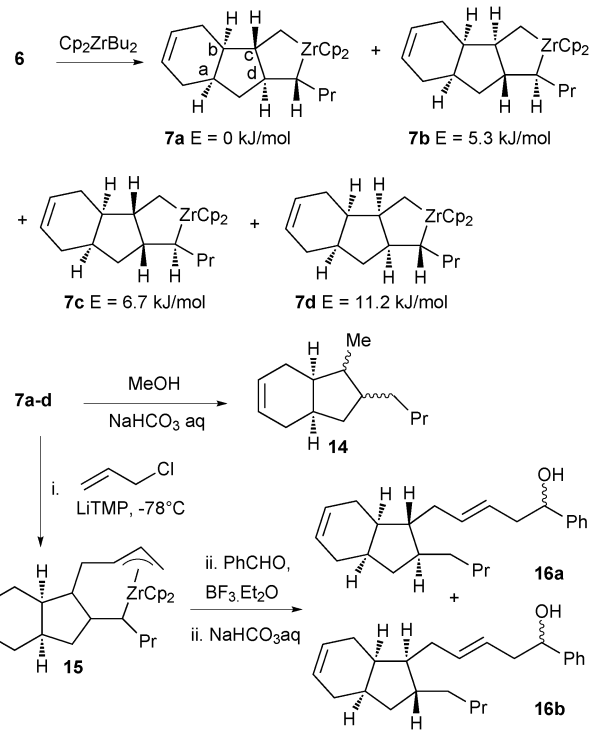
Control of the four contiguous stereocentres of mucosin is challenging, but precedent is that 3-zirconabicyclo[3.3.0]octanes form with *trans*-ring junction stereochemistry (thus controlling the relative stereocentres c and d—Scheme 3), and there is generally good *trans*-1,2-control between adjacent substituents and the zirconacyclopentane ring, which would give the correct



Scheme 1 Synthetic strategy for the synthesis of mucosin.



Scheme 2 Synthesis of triene **6**. *Reagents and Conditions*: (a) MeOH, quinidine, PhMe, −55 °C, 8 h, then −18 °C, 3 days then 2.0 M HCl; (b) $Li(Et)_3BH$, THF, 0 °C, 1 h then rt, 15 h then 2.0 M HCl; (c) DIBAL-H (fast addition), PhMe, −78 °C, 1 h, then 3.0 M HCl; (d) $MePh_3P^+Br^-$, *n*-BuLi, THF, 0 °C → rt, 2 h, then 1.0 M HCl; (e) MsCl, Et_3N, DMAP, THF, 0 °C, 2 h; (f) KCN, NaI, 18-crown-6, 90 °C, 66 h; (g) DIBAL-H (dropwise addition), THF, −78 °C → rt, 2 h, then MeOH, aq $NaHCO_3$; (h) $BuPh_3P^+Br^-$, *n*-BuLi, THF, 0 °C → rt, 2 h, then 1.0 M HCl.



Scheme 3 Zirconocene induced co-cyclisation of **6** and synthesis of alcohols **16**.

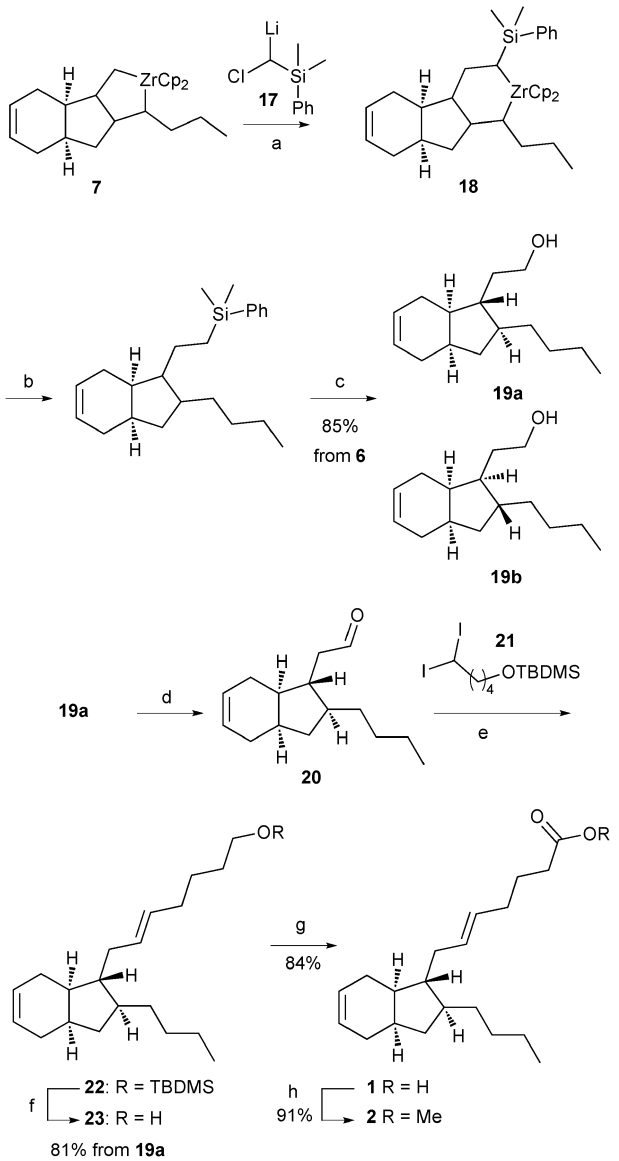
relative stereochemistry at centres b and c.[4] The effect of the stereocentre at a, and indeed of the fused 6-member ring was harder to predict.[10] Energies from Density Function Theory calculations have been shown to be useful in predicting the relative stability of zirconacycles.[11] The four most stable zirconacycle structures **7a–d**, which should form from **6** are shown in Scheme 3 with their calculated relative energies and indicate that the desired isomer **7a** is favoured. There are four additional stereoisomers differing in the configuration of the propyl-substituent, but we have shown in other systems that this centre is independent of the stereochemistry of the starting alkene due to rapid epimerisation *via* exocyclic β-hydride elimination/readdition.[12] Only the more stable epimers are shown as the energy differences were calculated to be >16 kJ mol^{-1}.

It is known that the formation of zirconacyclopentanes is reversible and heating is sometimes needed to form the thermodynamically more stable product.[13] Zirconium induced co-cyclisation of triene **6** was monitored by quenching aliquots to give the protonated compounds **14**, which were assayed by GC. After 1.25 h at room temperature we observed a 26 : 68 : 4 : 2 ratio, in order of GC retention times, of isomers formed with around 34% of **6** uncyclised, whereas after heating for 0.5 h at 65 °C the cyclisation was complete and the corresponding isomer ratio was 63 : 24 : 11 : 2. Further heating did not change the ratio significantly and additional products started to form. In order to identify if the kinetic or thermodynamic isomer was needed for mucosin we further elaborated the zirconacycles formed under each condition by insertion of 1-lithio-1-chloro-2-propene. The insertion occurred exclusively into the unsubstituted C–Zr bond to afford **15**, followed by the $BF_3{\cdot}Et_2O$ promoted addition of benzaldehyde to give the alcohols **16**.[14] Chromatography gave samples of **16** comprising 3.1 : 1 and 1 : 1.5 of major diastereoisomers (ignoring the hydroxyl stereochemistry) from the thermodynamic and kinetic conditions, respectively. By comparing the spectral data of the obtained alcohols **16** with those of mucosin **1**, we were able to establish that the major product obtained under thermodynamic conditions was **16a** derived from zirconacycle **7a** with the desired stereochemistry. We speculate, but have not proven, that the major isomer under kinetic conditions is the zirconacycle **7b**.

With reasonable conditions for predominant formation of the correct stereoisomer we examined introduction of the carboxy containing side chain. We have previously shown that allyl-zirconacycles similar to **15** react with the diethylacetal of acrolein to afford around 20% of the 1,4-addition product.[15] However, despite extensive investigation of different acrylate equivalents and conditions on model systems we were unable to achieve good yields of selective 1,4-addition.

An alternative stepwise approach was developed to complete the total synthesis. Insertion of the silyl carbenoid **17**[16] into zirconacycle mixture **7** formed under thermodynamic conditions gave the zirconacyclohexane **18**. Subsequent protonation and the Woerpel modification of the Fleming–Tamao oxidation[17] yielded alcohol **19** as a 2.7 : 1 mixture of diastereoisomers in 75% overall yield from triene **6**. The pure desired diasteroisomer **19a** could be seperated by HPLC. Removal of the minor diastereoisomer was also achieved by refluxing the mixture with iodine in benzene then purification by normal chromatography. We assume that the unwanted diastereoisomer was removed *via* iodoetherification although such a product was not isolated. Unfortunately the pure alcohol **19a** was only recovered in 39% yield. Despite the low recovery this method provided further evidence for the relative stereochemistry of the major diastereoisomer given that alcohol **19a** cannot undergo iodoetherification, and some evidence that the minor isomer is **19b** which can.

Oxidation of the alcohol **19a** to aldehyde **20** followed by Takai olefination[18] with diiodide **21** and removal of the silicon protecting group with TBAF gave the alcohol **23** in 81% overall yield. Finally alcohol **23** was oxidised to mucosin **1** in 84% yield using PDC in DMF (Scheme 4).[19] Conversion of acid **1** to its



Scheme 4 Completion of the synthesis of mucosin. *Reagents and conditions*: (a) THF, −78 °C, 45 mins; (b) $NaHCO_3$, MeOH, −78 °C → rt, 15 h; (c). KH, NMP, t-BuOOH, 0 °C → rt, 10 mins then TBAF, 70 °C, 14 h. (d) Me_2SO, CH_2Cl_2, oxalyl chloride, −60 °C, 15 min then Et_3N, −60 °C → rt, 1 h; (e) $CrCl_2$, DMF, THF, rt, 2.5 h; (f) TBAF, THF, rt, 3 h; (g) PDC, DMF, 0 °C → rt, 15 h. (h) CH_2N_2, Et_2O, −78 °C → rt, 1 h.

methyl ester **2** using diazomethane allowed comparison with the reported data demonstrating excellent agreement.[1] The optical rotation of the synthetic mucosin methyl ester (90% ee) was $[\alpha]_D^{26} = +38.2°$ ($c = 0.8$, *n*-hexane) compared with that reported for the methyl ester of the natural product of $[\alpha]_D^{26}$ −35.5 °C (*n*-hexane, $c = 0.8$) proving that the natural product is (*E*)-7-((1*S*,2*R*,3a*S*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)-hept-5-enoic acid.

In conclusion the absolute stereochemistry of the natural product (−)-mucosin has been established and the first total synthesis of its enantiomer (+)-mucosin has been completed in 14 steps and 7% overall yield. (−)-Mucosin could easily be made by using quinine in the enantioselective ring opening of **9**.

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