A formal synthesis of (+)-pyripyropene A using a biomimetic epoxy-olefin cyclisation

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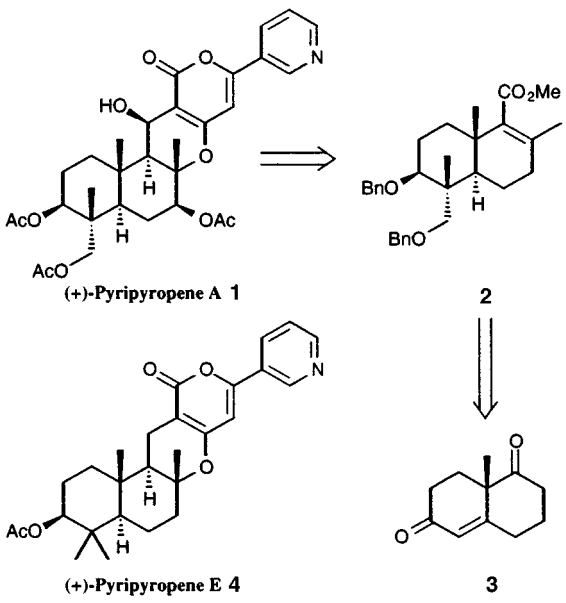
Bicyclic ester 2, a key intermediate in the first total synthesis of (+)-pyripyropene A 1, was synthesised from geraniol in 11 steps, utilising an epoxy-olefin biomimetic cyclisation as the key step.

Pyripyropenes A–L, isolated by Õmura and co-workers[1] from a fermentation broth of *Aspergillus fumigatus*, are the most effective naturally occurring inhibitors of acyl-CoA: cholesterol acyltransferase (ACAT), the enzyme responsible for intracellular esterification of cholesterol. Inhibition of the ACAT enzyme represents a new approach to the prevention and treatment of atherosclerosis and hypercholesterolemia[2] since evidence suggests that ACAT inhibitors may lower plasma cholesterol levels and prevent the accumulation of cholesteryl esters in arterial lesions.

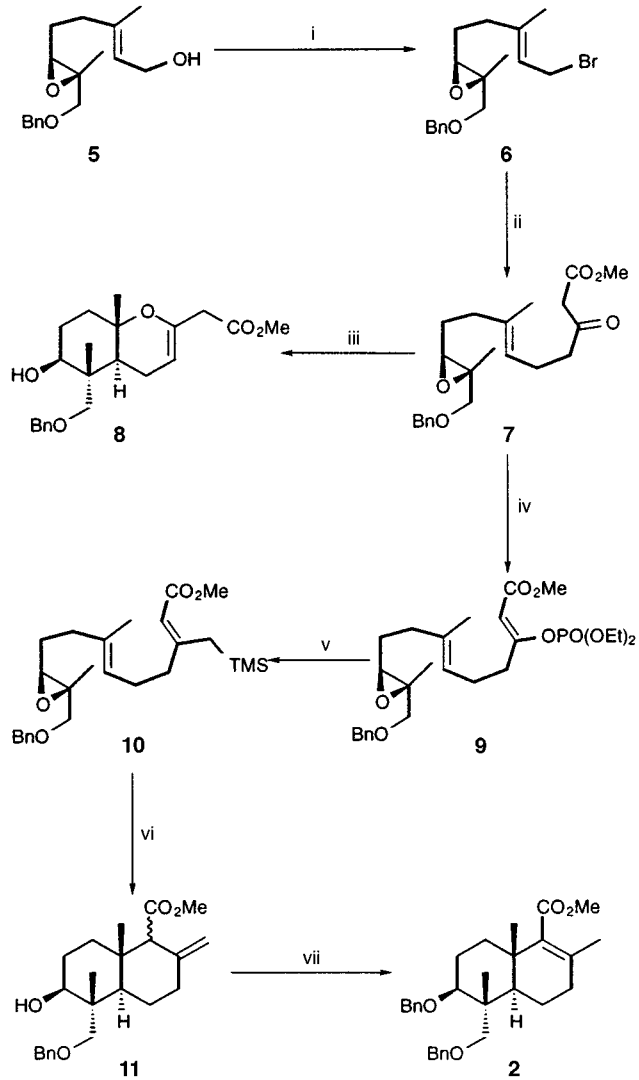
The most active member of the family, (+)-pyripyropene A **1**, was synthesised by Õmura and Smith from (+)-Wieland–Miescher ketone **3** in 19 steps[3] (Scheme 1).

We envisioned a short biomimetic route to the decalin subunit **2**, a key intermediate in the Õmura–Smith synthesis (prepared in 10 steps from **3**), utilising an epoxy-olefin cyclisation[4] of allyl silane **10**. Although a biomimetic polyene cyclisation has been used to prepare the simplest member of the family, pyripyropene E **4**,[5] it was surprising that this strategy had not been adopted for pyripyropene A **1** as the required epoxide contains a neighbouring alcohol group and as such could be easily obtained in enantiomerically pure form by Sharpless epoxidation.[6] Such epoxy alcohols (protected as ethers) have been successfully employed in epoxy-olefin cyclisations.[7]

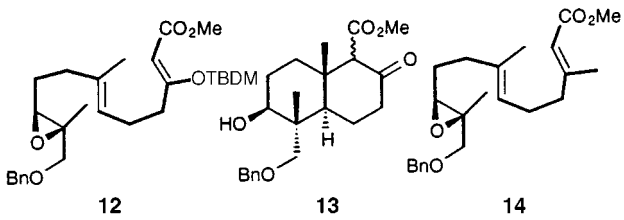
The known allylic alcohol **5**, derived from geraniol in 5 steps,[7] was converted to bromide **6** upon treatment with MsCl/Et_3N followed by LiBr at −78 °C. (Scheme 2).[8] Low temperature and a controlled amount of LiBr were required to minimise opening of the epoxide. The relatively unstable bromide **6** was then employed in the alkylation step with the dianion of methyl acetoacetate[9] to afford β-keto ester **7** in 78% yield. Upon treatment of β-keto ester **7** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2, epoxy-olefin cyclisation ensued but the oxabicycle **8** was formed exclusively.[10] To promote carbon over oxygen cyclisation, the carbonyl group had to be masked or removed and several possibilities were apparent from the literature. (i) Conversion of β-keto ester **7** into the silyl enol ether **12**.[11]



Scheme 1



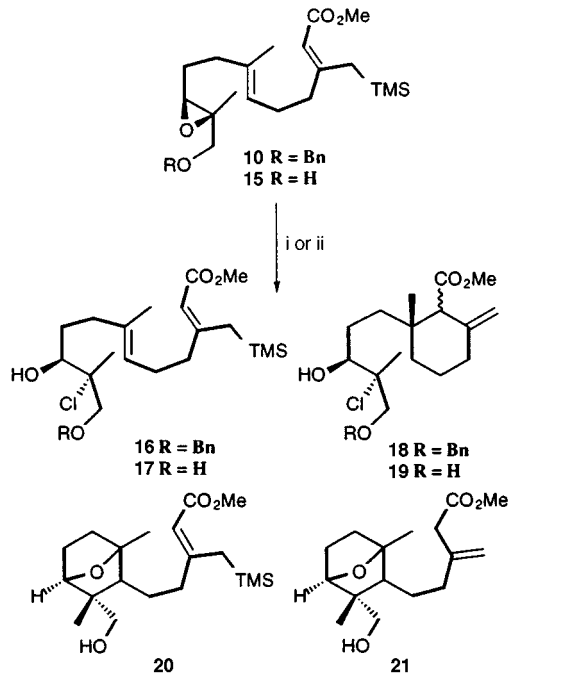
Scheme 2 *Reagents and conditions*: i, MsCl, Et_3N, THF, −78 °C, then LiBr (3 equiv.), acetone, −78 °C, 50 min, 87%; ii, methyl acetoacetate, NaH, Bu^nLi, THF, 0 °C, then **6**, 78%; iii, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 60%; iv, NaH, $(EtO)_2POCl$, Et_2O, 93%; v, $TMSCH_2MgCl$, $Ni(acac)_2$ (cat.), Et_2O, 0 °C, 54%; vi, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 54%; vii, NaH, BnBr, THF, reflux, 51%.



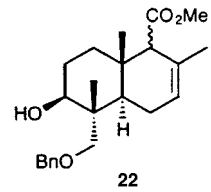
However, cyclisation of this substrate only provided a low yield (26% from **7**) of **13**. (ii) Conversion of β-keto ester **7** into the unsaturated ester **14**.[12] However, it is known that unsaturated esters are poor terminating groups for polyolefin cyclisation.[13] (iii) Conversion of β-keto ester **7** into allylsilane **10**.[14] Weiler had shown that allylsilanes bearing ester groups were sufficiently nucleophilic to undergo epoxy-olefin cyclisation.[14] This route was eventually successful. Thus, conversion of β-keto ester **7** to *Z*-enol phosphate **9** [NaH, $(EtO)_2POCl$, Et_2O] followed by coupling with $TMSCH_2MgCl$ in the presence of nickel(II) bisacetylacetonate furnished the cyclisation substrate, *Z*-allylsilane **10**.

Both the nature of the protecting group on oxygen[15] and cyclisation conditions were critical to the success of the key step. Treatment of the allylsilane **10** with $BF_3{\cdot}OEt_2$ at room temperature gave the required decalin in 54% yield as a 3:2 mixture of epimeric hydroxy esters **11**. In contrast, the use of $SnCl_4$ or $MeAlCl_2$ (Corey's preferred cyclisation catalyst)[4b–d] resulted in chlorohydrins **16** and **18** (Scheme 3). Attempts to cyclise the unprotected epoxy alcohol **15** failed;[16] only mixtures of unidentifiable acyclic and monocyclic products were observed with $BF_3{\cdot}OEt_2$ and the use of $MeAlCl_2$ resulted in the formation of chlorohydrins **17** and **19** as shown in Scheme 3. The use of $SnCl_4$ yielded bicyclic ethers **20** and **21** along with chlorohydrin **17**.

All that remained to complete the formal synthesis was isomerisation of the exocyclic double bond and benzylation of the free alcohol. However, attempts to isomerise the alkene **11** into conjugation with the ester using $RhCl_3$[17] resulted in the formation of the trisubstituted alkene **22** instead.[18] Fortuitously,



Scheme 3 *Reagents and conditions*: i, $MeAlCl_2$, CH_2Cl_2, room temp.; ii, $SnCl_4$, CH_2Cl_2, room temp.



benzylation of alcohol **11** using an excess of NaH in THF and BnBr[19] resulted in concomitant isomerisation of the alkene and provided **2** directly in 51% yield. Decalin **2** was spectroscopically identical[20] to that reported by Ōmura and Smith.[3]

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Notes and references

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19 The optimised procedure required refluxing **11** with NaH (5 equiv.) in THF for 4 h followed by addition of BnBr and refluxing for a further 2 h. Less isomerisation was observed if **11** was refluxed with NaH for a shorter time.

20 By ^1H NMR, ^{13}C NMR, mass and IR analyses.

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