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1,8-Stereocontrol by 1,5-Induction using an Allylstannane followed by a 2,3-Wittig Rearrangement: Diastereoselective Total Synthesis of (±)-Epipatulolide C

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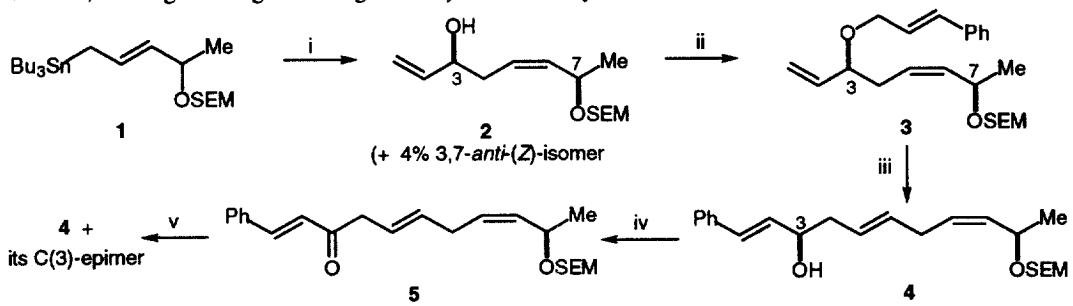
Abstract: The relative configurations of 1,8-stereogenic centres can be controlled by coupling the tin(IV) chloride promoted reactions of aldehydes with 4-alkoxypent-2-enylstannanes, which proceed with excellent 1,5-induction, with a 2,3-Wittig rearrangement: this approach has been used to complete a diastereoselective synthesis of (±)-epipatulolide C **16**.

In the accompanying paper,[1] the reaction of a 4-alkoxypent-2-enylstannane with an aldehyde followed by an Ireland-Claisen rearrangement was used to introduce 1,8-stereogenic centres diastereoselectively as exemplified by a synthesis of (±)-patulolide C. We now report that the combination of the allyltin - aldehyde reaction with a 2,3-Wittig rearrangement[2] can also be used to control the relative configurations of 1,8-stereogenic centres as illustrated by a stereoselective synthesis of (±)-epipatulolide C.

The racemic *syn*-(*Z*)-homoallylic alcohol **2**[1] was prepared stereoselectively from the 4-alkoxypent-2-enylstanne **1** and acrolein, 3,7-*syn* : 3,7-*anti* = 96 : 4, and *O*-alkylation using cinnamyl bromide gave the ether **3**. On treatment with butyllithium this ether, containing *ca.* 4% of its 3,7-*anti*-diastereoisomer, underwent a stereoselective 2,3-Wittig rearrangement to give the *syn*-3,10-alkoxyalcohol **4**.



Scheme 1 ***Reagents and conditions:*** i, $SnCl_4$, -78 °C, 10 min then acrolein, -78 °C,10 min (77%; *syn* : *anti* = 96 : 4); ii, NaH, cinnamyl bromide, NBu_4I, THF, 15 h (70%); iii, BuLi, -78 °C, 3 h (74%); iv, DMSO, $(COCl)_2$ (70%); v, $NaBH_4$ (75%).

The stereoselectivity of the Wittig rearrangement was established by oxidation of the rearranged product to the ketone **5** followed by non-stereoselective reduction. This gave a mixture of the 3,10-*syn*-alcohol **4** and its C(3)-epimer which, although they could not be separated, were distinguishable by ^1H NMR. Comparison of the ^1H NMR spectrum of the mixture of alcohols with that of the rearrangement product showed that the Wittig

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rearrangement had given a *ca.* 90 : 10 mixture of C(3)-epimeric alcohols. Structure **4** was assigned to the major alcohol on the basis that the rearrangement had proceeded *via* an envelope conformation of the lithiated ether with the cinnamyl group in a pseudo-equatorial position,[2] see Figure 1, and was confirmed by conversion into epipatulolide C **16**, see Scheme 2.

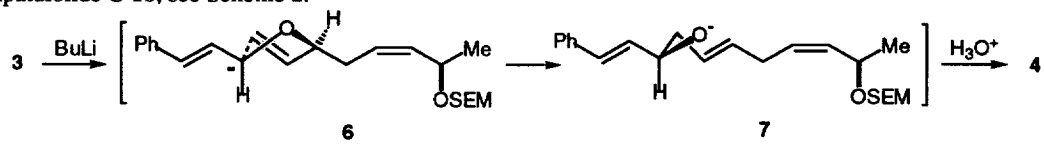
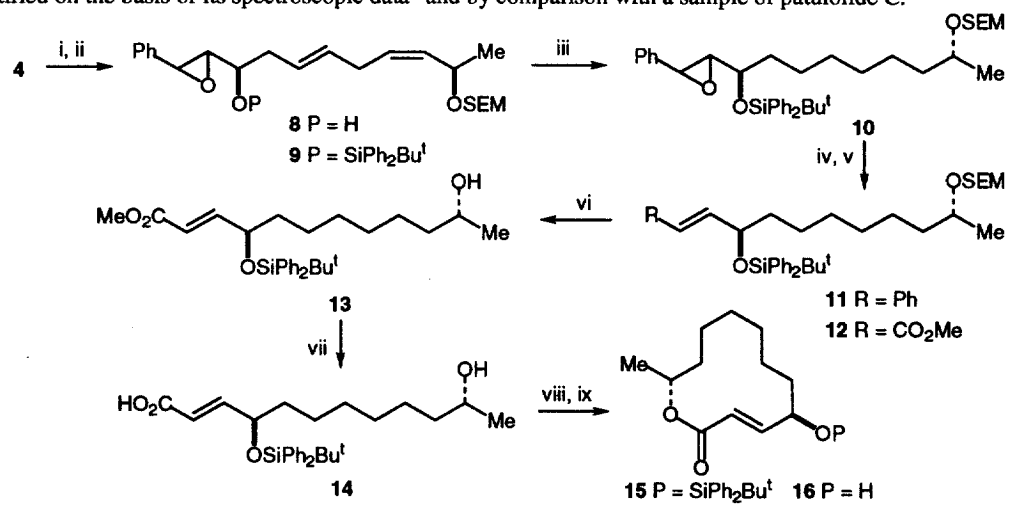


Figure 1,3-Chirality transfer by rearrangement of the lithiated cinnamyl ether **3**

To complete a synthesis of a patulolide, it was necessary to distinguish between the double-bonds of the Wittig rearrangement product **4**. This was achieved by regioselective epoxidation using *tert*-butyl hydroperoxide and $VO(acac)_2$ which gave the mono-epoxide **8** as a mixture of diastereoisomers. After alcohol protection, reduction using diimide gave the saturated epoxide **10** which was taken through to the protected hydroxyester **12** by deoxygenation using samarium diiodide,[3] ozonolysis and Wittig condensation. Selective deprotection and saponification gave the hydroxyacid **14** which was cyclised by the modified Yamaguchi method to give a mixture of the silylated epipatulolide C **15** and its epimer, ratio 93 : 7. Desilylation of **15** gave (±)-epipatulolide C **16** identified on the basis of its spectroscopic data[4] and by comparison with a sample of patulolide C.[1]



Scheme 2 ***Reagents and conditions:*** i, $VO(acac)_2$, ^tBuOOH (89%); ii, $^tBuPh_2SiCl$, imidazole (93%); iii, NaOAc, toluene *p*-sulfonylhydrazide, heat under reflux 3 h (84%); iv, SmI_2, THF (56%); v, O_3 then Me_2S followed by $Ph_3P{=}CHCO_2Me$ (61%); vi, $MgBr_2.Et_2O$, BuSH, K_2CO_3 (79%); vii, LiOH, $MeOH\text{-}H_2O$ (82%); viii, 2,6-dichlorobenzoyl chloride, Et_3N, r.t. 2 h then DMAP, toluene, heat under reflux, 8 h (56%); ix, TBAF, THF (61%).

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