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1,8-Stereocontrol by 1,5-Induction using an Allylstannane followed by Ireland-Claisen Rearrangement: Diastereoselective Total Synthesis of (±)-Patulolide C

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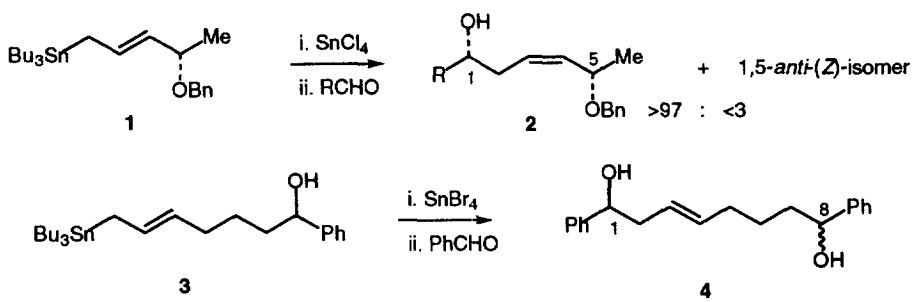
Abstract: The relative configurations of 1,8-stereogenic centres can be controlled by coupling the tin(IV) chloride promoted reactions of aldehydes with 4-alkoxypent-2-enylstannanes, which proceed with excellent 1,5-induction, with an Ireland-Claisen rearrangement: this approach has been used to complete a diastereoselective synthesis of (±)-patulolide C **29**. © 1998 Elsevier Science Ltd. All rights reserved.

Tin(IV) halide promoted reactions of alkoxyalk-2-enylstannanes with aldehydes have been shown to proceed with useful levels of 1,5-, 1,6- and 1,7-asymmetric induction.[1] For example, treatment of the 4-benzyloxypent-2-enylstannane **1** with tin(IV) chloride generates an allyltin trichloride which reacts with both aromatic and aliphatic aldehydes with stereoselectivity usually better than 97 : 3 in favour of the 1,5-*syn*-(*Z*)-products **2**.[2] However, preliminary investigations into 1,8-stereocontrol using this chemistry were not encouraging since a mixture, ratio *ca.* 60 : 40, of the 1,8-*syn*- and 1,8-*anti*-(*E*)-products **4** was obtained from the 7-hydroxyhept-2-enylstannane **3**, tin(IV) bromide and benzaldehyde. We now report procedures for effective 1,8-stereocontrol by combining the 1,5-induction from an allylstannane reaction with an Ireland-Claisen rearrangement[3] and the application of this procedure to complete a diastereoselective synthesis of patulolide C **29**.[4,5]



1 **2** **3** **4**

The racemic 4-(2-trimethylsilylethoxy)methoxypent-2-enylstannane **8** was prepared from propenyl phenyl sulfone by addition to ethanal, free-radical displacement using tributyltin hydride and protection, see Scheme 1, and was treated with acrolein to give the 1,5-*syn*-product **9** (77%) containing *ca.* 4% of its *anti*-diastereoisomer **10**. Mitsunobu inversion of the 1,5-*syn*-alcohol **9** using *p*-nitrobenzoic acid followed by saponification gave the

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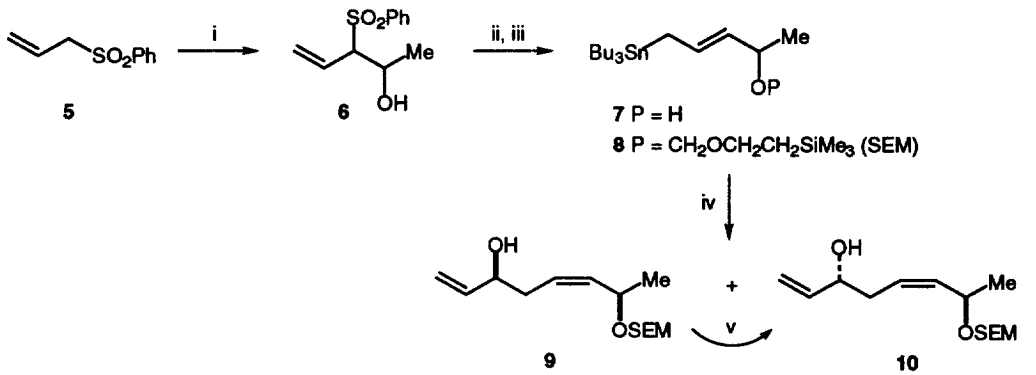
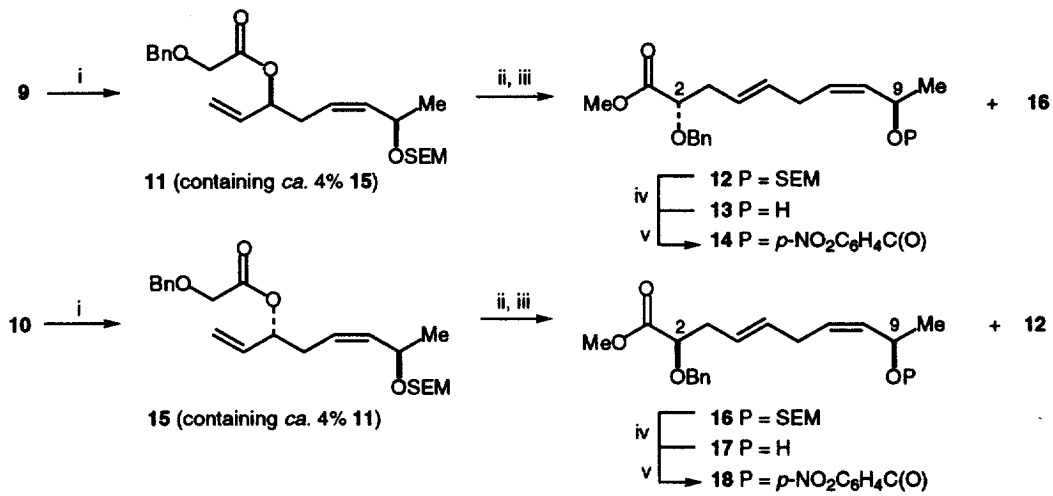
1,5-*anti*-product **10** which was identical to the minor product from the reaction of the stannane with acrolein. The 1,5-*syn*-configuration was assigned to the major product from the aldehyde - stannane reaction by analogy with earlier work[1,2] and was supported by spectroscopic data.



Scheme 1 ***Reagents and conditions:*** i, BuLi, -78 °C, 30 min then CH_3CHO (97%); ii, Bu_3SnH, AIBN, benzene, 65 °C, 2 h (89%); iii, SEMCl, $^iPr_2NEt$, 6 h, room temp. (93%); iv, $SnCl_4$, -78 °C, 10 min then acrolein, -78 °C, 10 min (77%); v, a. 4-nitrobenzoic acid, Ph_3P, diethyl azodicarboxylate, benzene, 2 h (60%); b. LiOH, MeOH - H_2O (89%).

The *syn*- and *anti*-alcohols **9** and **10** were converted into their benzyloxyacetates **11** and **15** and the Ireland-Claisen rearrangements[6] carried out by deprotonation of the esters using an amide base and silylation of the enolates using trimethylsilyl chloride. Although slightly better yields and stereoselectivities could be obtained by adding the amide base to a solution of the ester and trimethylsilyl chloride in tetrahydrofuran, more reliable results were obtained by adding the trimethylsilyl chloride to the preformed enolate. After warming to room temperature for 20 min and treatment with trimethylsilyl diazomethane, the esters **12**[7] and **16** were isolated in yields of *ca.* 80%.



Scheme 2 ***Reagents and conditions:*** i, $BnOCH_2COCl$, Et_3N, DMAP (cat), CH_2Cl_2, heat under reflux 2 h (84%); ii, $LiN(SiMe_3)_2$, -78 °C, Me_3SiCl, THF, -78 °C, 20 min, then warm to room temperature, 20 min; iii, Me_3SiCHN_2, 1 h (*ca.* 80% of **12** and **16** based on **11** and **15**, respectively); iv, HF, MeCN, 4 h (75%); v, 4-nitrobenzoyl chloride, Et_3N, DMAP (cat.), CH_2Cl_2, 2 h (90%).

The 2,9-*anti*- and *syn*-esters **12** and **16** could not be distinguished spectroscopically. However, comparison of the ^{1}H NMR spectra of the 4-nitrobenzoates **14** and **18** indicated that the rearrangements of the 1,5-*syn*- and -*anti*-esters **11** and **15** had proceeded to give mixtures of diastereoisomeric products typically in ratios of 86 : 14[8] and 11 : 89,[9] respectively. The relative configurations of the rearranged products were assigned on the basis of participation of (*Z*)-silylketene acetals, derived from chelated lithium enolates of the esters **11** and **15**, reacting through chair-like transition states, as indicated in Figure 1 for the 1,5-*syn*-ester **11**.[6]

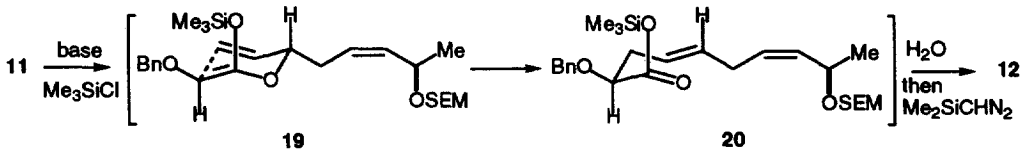
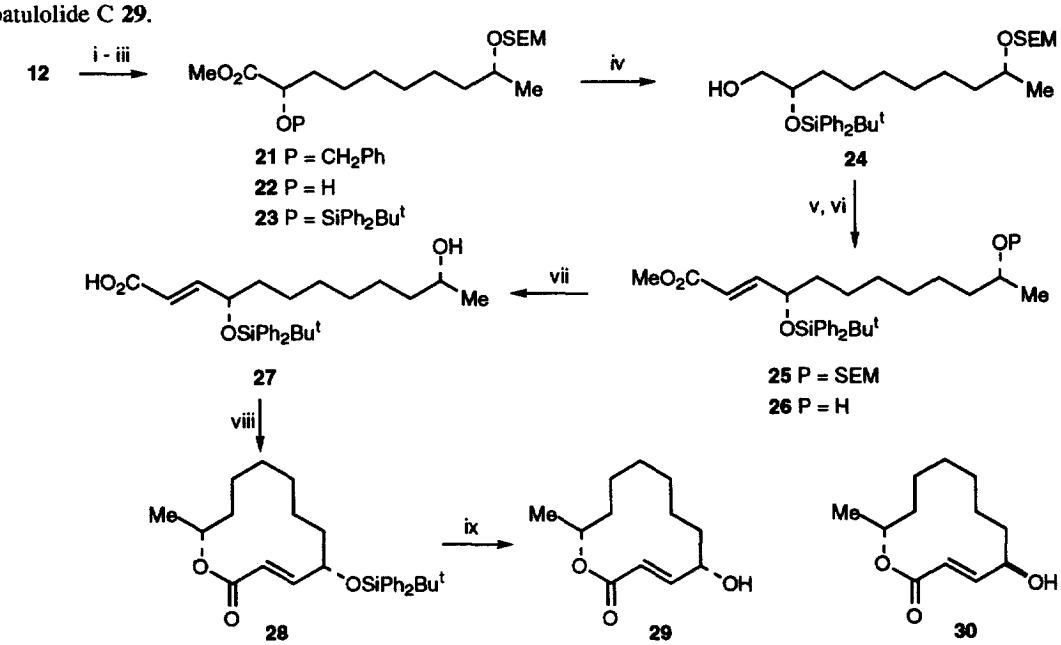


Figure 1 1,3-Chirality transfer by rearrangement of the silyl ketene acetal **19** derived from the 1,5-*syn*-ester **11**

The stereochemical assignments made to the rearranged esters **12** and **16** were confirmed by conversion of the 2,9-*anti*-diastereoisomer **12** (containing *ca.* 11% of its *syn*-diastereoisomer **16**[9]) into (±)-patulolide C **29**, see Scheme 3. Reduction of **12** using diimide, to avoid hydrogenolysis of the allylic oxygen functionality, gave the saturated ester **21**. After exchange of the benzyl protecting group for a *tert*-butyldiphenylsilyl group, reduction[10] of the ester gave the alcohol **24**. This was oxidised and a Wittig condensation of the aldehyde so obtained gave the unsaturated ester **25**. Selective deprotection and saponification gave the hydroxy acid **27** which was lactonised using the modified Yamaguchi procedure to give the macrolide **28**. Desilylation then gave patulolide C **29**.



Scheme 3 ***Reagents and conditions:*** i, NaOAc, toluene *p*-sulfonylhydrazide, DME, heat under reflux (85%); ii, H_2, Pd/C (89%); iii, ^{t}BuPh$_2$SiCl, imidazole (94%); iv, DIBAL-H (33%); v, DMSO, $(COCl)_2$ then $Ph_3P{=}CHCO_2Me$, CH_2Cl_2 (72% from **24**); vi, $MgBr_2.Et_2O$, BuSH, K_2CO_3 (89%); vii, LiOH, MeOH - H_2O (91%); viii, 2,6-dichlorobenzoyl chloride, Et_3N, 2 h, then DMAP, toluene, heat under reflux, 8 h (50%); ix, TBAF, THF (53%).

The structure of synthetic patulolide C **29** was assigned from its spectroscopic data[11] and comparison with a sample of synthetic epipatulolide C **30**.[12] The *O*-silylated patulolide C **28** could be separated from its C(4)-epimer by chromatography; at this stage the two diastereoisomers were present in a ratio of *ca.* 93 : 7.

This work shows how the combination of allyltin chemistry and a sigmatropic rearrangement can be used to prepare stereoselectively compounds with really remote stereogenic centres. As one stereogenic centre is being used to influence the introduction of the second, this approach can be used to synthesize *racemic* compounds diastereoselectively, as well as enantiomerically enriched compounds. In the accompanying paper,[12] a 2,3-Wittig rearrangement following the allyltin - aldehyde reaction is used to complete a stereoselective synthesis of epipatulolide C **30**. The diastereoselective preparation of compounds with 1,9-stereogenic centres using a 1,7-*syn*-selective allylstannane reaction followed by a [3,3]-sigmatropic rearrangement has also been described.[13]

Acknowledgements

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7 Selected data for **12**: colourless oil (Found: $M^+ + NH_4$, 452.2832. $C_{24}H_{42}NSiO_5$ requires *M*, 452.2832) υ_{max}/cm^{-1} 3009, 1752, 1451, 1438, 1249, 1202, 1104, 1025, 859, 836, 743 and 697; δ_H 0.00 (9 H, s, 3 x $SiMe_3$), 0.91 (2 H, t, *J* 8.5, CH_2Si), 1.20 (3 H, d, *J* 6.5, 10-H_3), 2.45 (2 H, t, *J* 5.5, 3-H_2), 2.78 (2 H, m, 6-H_2), 3.50 and 3.69 (each 1 H, m, O*H*CH_2), 3.71 (3 H, s, OMe), 3.95 (1 H, t, *J* J 6, 2-H), 4.41 (1 H, d, *J* 13, O*H*CHPh), 4.52 (1 H, dq, *J* 9, 6.5, 9-H), 4.55 and 4.62 (each 1 H, d, *J* 7, O*H*CHO), 4.67 (1 H, d, *J* 13, OHC*H*Ph), 5.3 (1 H, m, 8-H), 5.46 (3 H, m, 4-, 5- and 7-H) and 7.32 (5 H, m, ArH); δ_C -1.5, 18.1, 21.4, 30.7, 36.1, 51.7, 64.9, 66.6, 72.2, 78.1, 91.7, 125.2, 127.8, 127.9, 128.3, 129.8, 131.6, 131.9, 137.4 and 172.6; *m/z* (C.I.) 452 (M^+ + 18, 100%) and 412 (13).

8 Ratio from addition of trimethylsilyl chloride to preformed lithium enolate of ester **11** in THF.

9 Ratio from addition of lithium hexamethyldisilazide to a mixture of ester **15** and trimethylsilyl chloride in solution in THF

10 A better yield (89%) for the reduction of ester **23**, albeit on a mixture of 2,9-diastereoisomers, was obtained using $LiBHEt_3$.

11 Selected data for patulolide C **29**: colourless oil (Found: $M^+ + NH_4$, 230.1751. $C_{12}H_{24}NO_3$ requires *M*, 230.1756) υ_{max}/cm^{-1} 3413b, 1717, 1645, 1263, 1161 and 992; δ_H 0.86-1.88 (12 H, m, 5-, 6-, 7-, 8-, 9-, 10-H_2), 1.33 (3 H, d, *J* 6.5, 12-H_3), 4.54 (1 H, q, *J* 6, 4-H), 5.11 (1 H, m, 11-H), 6.13 (1 H, dd, *J* 1, 15.5, 2-H), and 6.89 (1 H, dd, *J* 6.5, 16, 3-H); δ_C 19.3, 20.7, 22.1, 27.8, 28.2, 32.8, 35.9, 70.9, 73.1, 121.5, 149.5, and 168.0; *m/z* (C.I.) 230 (M^+ + 18, 100%) and 213 (M^+ + 1, 32).

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