Stereoselective Synthesis of *cis*-2,5-Disubstituted Tetrahydrofurans: An Approach to Pamamycins

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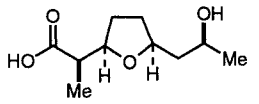
Abstract: A stereoselective synthesis of 2,5-*cis*-disubstituted tetrahydrofurans has been devised based on the epoxidation and rearrangement of products prepared from aldehydes with remote induction using allylstannanes and tin(IV) halides. This chemistry has been applied to synthesize the tetrahydrofuran containing fragments of (-)-nonactic acid and the pamamycins.

Considerable effort has been devoted to the synthesis of structurally complex tetrahydrofurans since they are important components of many natural products.[1] 2,5-*cis*-Disubstituted tetrahydrofurans adjacent to alkyl-substituted, stereogenic centres are found, for example, in (-)-nonactic acid **1**[2] and the pamamycins **2** - **6**.[3] The latter compounds are complex macrodiolides which exhibit autoregulatory, antifungal, antibacterial, and anion-transferring activities. We now report preliminary results on a stereoselective synthesis of such 2,5-*cis*-disubstituted tetrahydrofurans with adjacent alkyl-bearing stereogenic centres. Our approach is based on reactions of allylstannanes with aldehydes which proceed with remote asymmetric induction[4] followed by stereoselective epoxidation and rearrangement of the epoxides.



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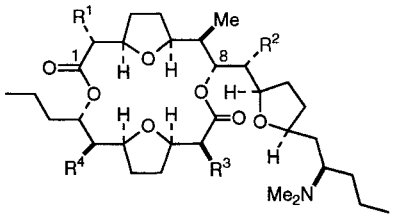
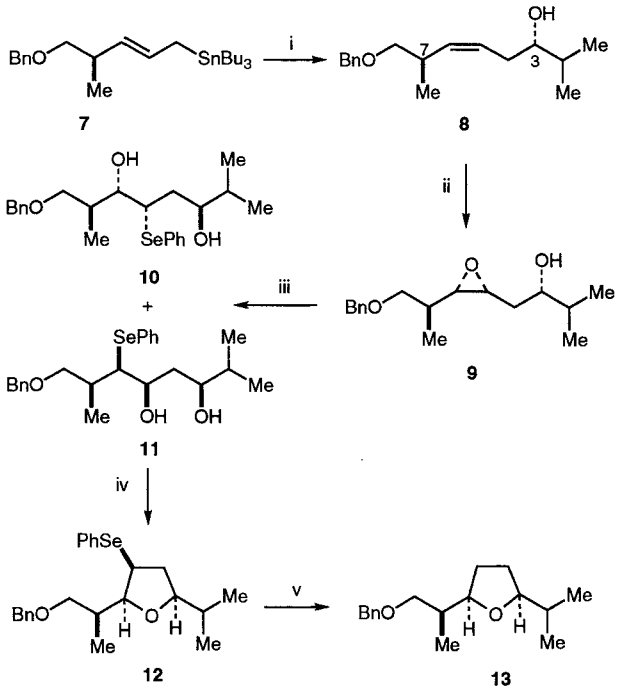


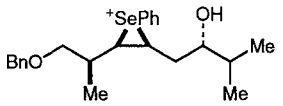
	R^1	R^2	R^3	R^4	
2	Me	Me	Me	H	pamamycin 607
3	Me	Et	Me	Me	pamamycin 635A
4	Me	Me	Et	Me	pamamycin 635 B
5	Et	Et	Et	H	pamamycin 649A
6	Et	Et	Me	Me	papamycin 649B

2-Methylpropanal reacts with the allyltin trichloride prepared by transmetallation of the 5-benzyloxy-4-methylpent-2-enylstannane **7** using tin(IV) chloride, to give the 8-benzyloxy-2,7-dimethyloct-5-en-3-ol **8** with excellent stereoselectivity, 3,7-*anti* : 3,7-*syn* ≥ 95:5, see **Scheme 1**.[5] Preliminary attempts to convert the alkenol **8** into a tetrahydrofuran directly by electrophile induced cycloetherification[1,6] were unsuccessful. For example, iodine in aqueous acetonitrile buffered with sodium hydrogen carbonate led to the formation of a complex mixture of products, and cyclisation using phenylselenenyl chloride was sluggish and inefficient. However, conversion to the tetrahydrofuran **13** was achieved by epoxidation, epoxide-ring opening and subsequent cyclisation.[7]

Epoxidation using *tert*-butyl hydroperoxide and $VO(acac)_2$ gave the *syn*-hydroxyepoxide **9** (83%) with useful stereoselectivity (93 : 7), the configuration of the major epoxide being assigned by analogy with the



Scheme 1. ***Reagents:*** i, $SnCl_4$, *i*-PrCHO, -78 °C (75%); ii, *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2 (83%); iii, $(PhSe)_2$, $NaBH_4$, EtOH (81%); iv, $HClO_4$ (cat.), CH_2Cl_2 (60%); v, Bu_3SnH (88%).



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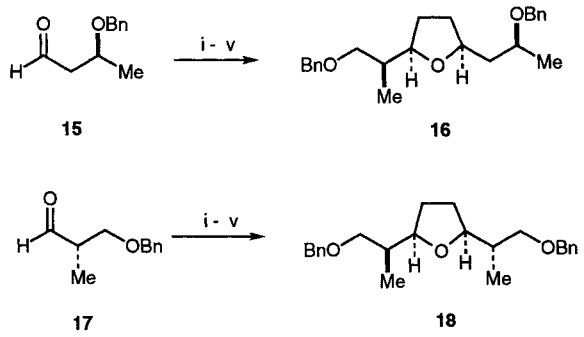
literature.[8] Ring-opening with sodium phenylselenide gave a mixture of the hydroxyselenides **10** and **11** which were not separated. Instead the mixture was treated with a catalytic amount of perchloric acid which converted both of the hydroxyselenides into the 2,5-*cis*-substituted tetrahydrofuran **12**, perhaps *via* participation of the intermediate selenonium ion **14**, together with a small amount of the (*Z*)-alkenol **8**.[7] Reduction using tributyltin hydride then removed the phenylselenenyl residue to give the disubstituted tetrahydrofuran **13**. The structure of this tetrahydrofuran was consistent with its spectroscopic data and mode of synthesis from the epoxide **9**.[9] The *cis*-disposition of the 2- and 5-substituents was confirmed by n.O.e. experiments.

Following these procedures, (*S*)-3-benzyloxybutanal **15** and (*S*)-3-benzyloxy-2-methylpropanal **17** were converted into the tetrahydrofurans **16** and **18** with excellent overall stereoselectivity so showing that the stereogenic centres in these aldehydes do not interfere with the reactions with the stannane or with the subsequent modifications of the products. Tetrahydrofurans **16** and **18** have the same configurations at all four of their stereogenic centres as (-)-

nonactic acid **1** and the C(1)-C(8) fragment of the pamamycins **2** - **6**, respectively.



Scheme 2. ***Reagents:*** i, 7.$SnCl_4$, -78 °C (75- 78%;); ii, *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2 (73-77%); iii, $(PhSe)_2$, $NaBH_4$, EtOH (75-84%); iv, $HClO_4$ (cat.), CH_2Cl_2 (30%); v, Bu_3SnH (88-90%).

This chemistry is being applied to complete syntheses of tetrahydrofuran containing natural products.

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References and Notes

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(9) All new compompounds were fully characterised by spectroscopic methods including accurate mass data: spectroscopic data for **13**: (Found: M^++H, 263.2011. $C_{17}H_{27}O_2$ requires *M*, 263.2011) υ_{max} /cm^{-1} 3063, 3030, 1467, 1454, 1382, 1364, 1099, 1071, 1029; δ_H ($CDCl_3$) 0.89 (3 H, d, *J* 7, CH_3), 0.98 and 1.00 (each 3 H, d, *J* 5, CH_3), 1.57 (2 H, m, 3-H and 4-H), 1.68 [1 H, m, C*H*(CH_3)$_2$], 1.92 (3 H, m, C*H*CH_3, 3-H' and 4-H'), 3.41 (1 H, dd, *J* 9, 7, C*H*HO), 3.54 (1 H, m), 3.67 (1 H, dd, *J* 9, 4.5, CH*H*O), 3.74 (1 H, m), 4.55 and 4.56 (each 1 H, d, *J* 12, PhC*H*H) and 7.34 (5 H, m, aromatic H); m/z (CI) 263 (M^+ + 1, 100%).