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Total synthesis of pamamycin 607: applications of remote asymmetric induction in organic synthesis

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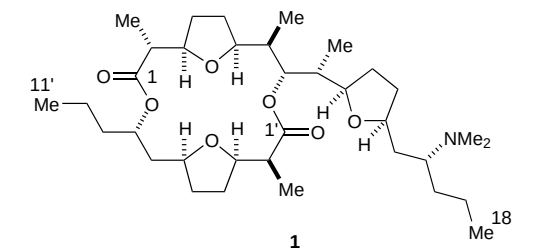
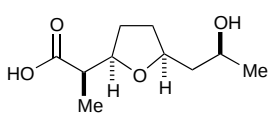
Abstract—A total synthesis of pamamycin 607 **1** is described. The synthesis of the C(1)–C(18) fragment involved the tin(IV) chloride-promoted reaction between (3*R*)-3-(*N*-methyl)tosylaminohexanal **18** and the allylstannane **4** followed by cyclisation and reductive removal of the phenylselanyl group to give the tetrahydrofuran **20** which was taken through to the aldehyde **21**. Aldol addition of the lithium enolate derived from 2,6-dimethylphenyl propanoate to this aldehyde followed by *O*-silylation gave the silyl ether **25** as the major product. This was converted into the aldehyde **31** which gave the bis-tetrahydrofuran **33** on reaction with the stannane **4**, cyclisation and reduction. Exchange of the *N*-protecting group, hydrogenolysis and oxidation then gave the acid **34**. This was esterified using the alcohol **42**, which had been prepared from the aldehyde **35** and the stannane *ent*-**4** using similar chemistry, to give the ester **43**. Deprotection gave the *seco*-acid **44** and cyclisation, *N*-deprotection and *N*-methylation gave pamamycin 607 **1**.

The pamamycins are a group of macrodiolides, exemplified by pamamycin 607 **1**, isolated from *Streptomyces alboniger*, which possess interesting antifungal activities.[1,2] Considerable interest has been shown in the synthesis of these compounds and syntheses of both the C(1)–C(18) and C(1′)–C(11′) fragments have been described.[3] A structural feature of the pamamycins is the presence of methyl substituted stereogenic centres adjacent to 2,5-*cis*-disubstituted tetrahydrofurans. This feature is also present in (−)-nonactic acid **2**.[4]

We now describe total syntheses of pamamycin 607 **1** and the methyl ester of nonactic acid **2**. Our approach is based on the stereoselective cyclisation, to 2,5-*cis*-disubstituted tetrahydrofurans, of homoallylic alcohols **3**, which are available stereoselectively from tin(IV) halide-promoted reactions between 5-alkoxypent-2-enylstannanes and aldehydes.[5,6]



1



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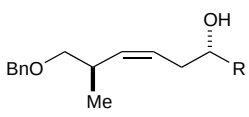

3

Several procedures have been reported for the stereoselective cyclisation of (*Z*)-homoallylic alcohols to 2,5-*cis*-disubstituted tetrahydrofurans including those using iodine under buffered conditions[7] and phenylselenenyl chloride[8] and phenylselenenyl phthalimide[9] under both acidic and basic conditions. In our hands, iodine induced cyclisations of alcohol **5**, prepared stereoselectively (1,5-*anti*:1,5-*syn* = 96:4) from butanal using the (4*R*)-5-benzyloxypent-2-enylstannane **4** [(*E*):(*Z*) = 70:30] and tin(IV) chloride[6] (see Scheme 1) gave only low yields of the required cyclised product due to competing debenzylation. However, cyclisations using phenylselenenyl electrophiles were much more promising and reasonable yields of the trisubstituted tetrahydrofuran **6** were obtained using either phenylselenenyl chloride or phthalimide in the presence of ca. 20 mol% of tin(IV) chloride. Only the all-*cis*-trisubstituted tetrahydrofuran **6** was isolated from these reactions consistent with participation of the transition state outlined in Fig. 1,[7–9] together with minor side-products formed by competing debenzylation. Reduction of the tetrahydrofuran **6** using tributyltin hydride gave the *cis*-2,5-disubstituted tetrahydrofuran **7**.[10]

A synthesis of methyl nonactate **13** was then developed as a model for the proposed pamamycin synthesis (see

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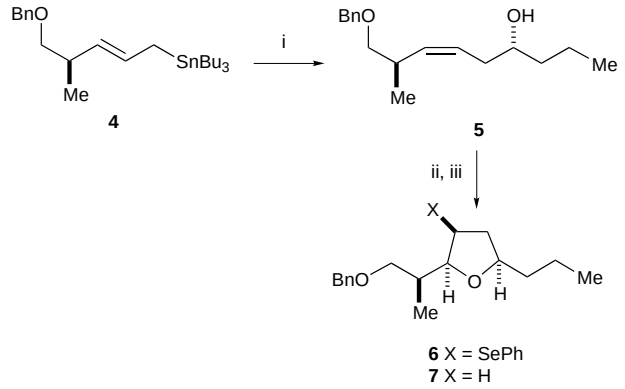


Scheme 1. *Reagents and conditions*: (i) $SnCl_4$, 5 min, −78°C, then ^{n}PrCHO, −78°C, 1 h (75%); (ii) PhSeCl or PhSePhth, 20 mol% $SnCl_4$, rt, 4 h (50–60%); (iii) Bu_3SnH, AIBN (85%).

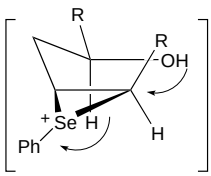


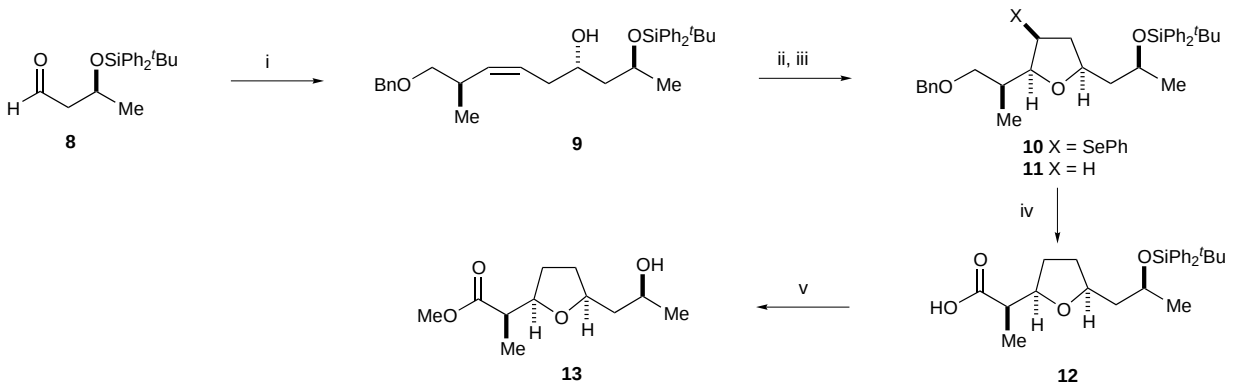
Figure 1.

Scheme 2). The protected hydroxyaldehyde **8**[11] was converted into the (*Z*)-1,5-*anti*-alkenol **9** (82%, 1,5-*anti*:1,5-*syn* >96:4) using the stannane **4**, and reaction of **9** with phenylselenenyl phthalimide followed by reduction gave the tetrahydrofuran **11** as a single stereoisomer (>95:5) after chromatography. Hydrogenolysis and oxidation using pyridinium dichromate in *N*,*N*-dimethyl formamide led to the acid **12**, and esterification using trimethylsilyl diazomethane and desilylation gave methyl nonactate **13**[12] which was identical with a sample prepared from nonactin.

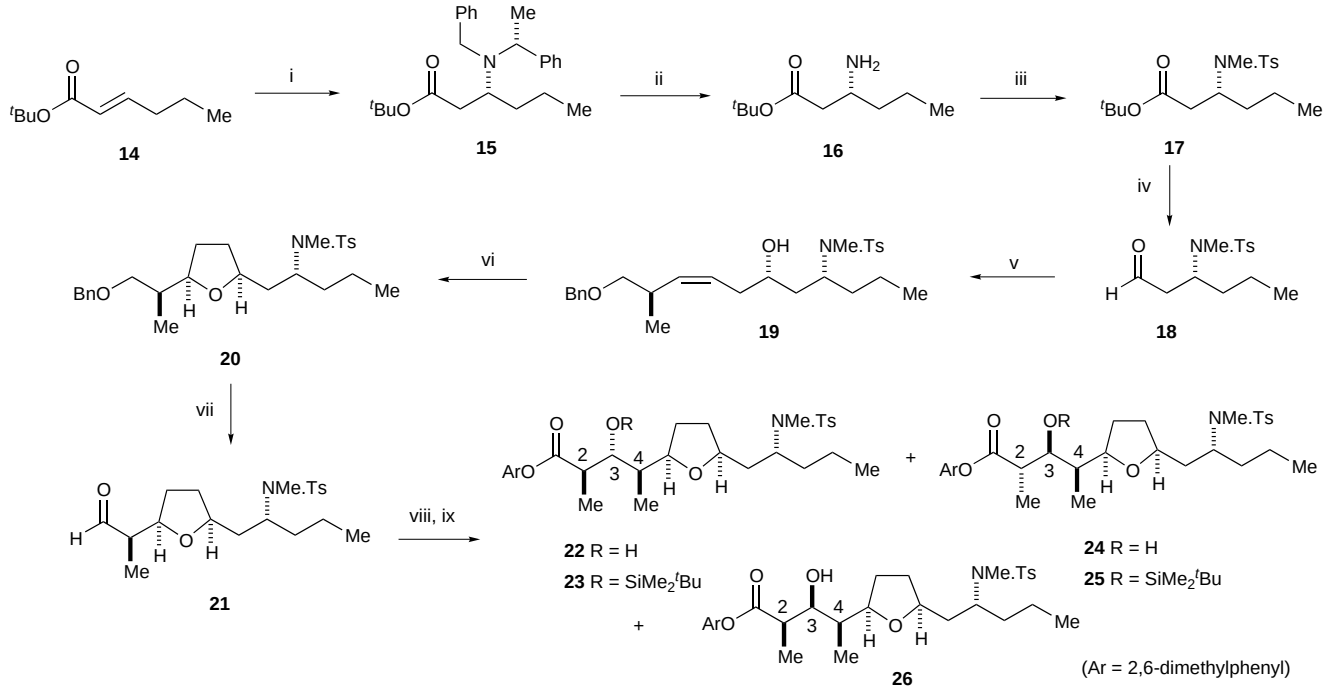
This synthesis of methyl nonactate confirmed the stereoselectivity of cyclisation of (*Z*)-homoallylic alcohols and indicated that the reaction conditions required for the cyclisation were compatible with silyl and benzyl ether protecting groups.

In planning the synthesis of the C(1)–C(18) fragment of pamamycin 607 **1**, it was decided to start at the C(18) end and to incorporate the amino group at C(15), albeit in a protected form, early in the synthesis (see Scheme 3). Conjugate addition of lithium (*R*)-(α-methylbenzyl)benzylamide to *tert*-butyl (*E*)-hex-2-enoate **14**[13] followed by transfer hydrogenolysis gave the β-amino-ester **16** with excellent enantiomeric excess.[14] Protection of the nitrogen as its toluene *p*-sulfonyl derivative and methylation gave the amido-ester **17** which was converted into the aldehyde **18** by reduction followed by oxidation. This aldehyde reacted with the allyltin trichloride generated by transmetallation of the stannane **4** to give the alcohol **19**, less than 4% of any other diastereoisomer being detected in the product by ^{1}H and ^{13}C NMR. Cyclisation of **19** using phenylselenenyl chloride and 20 mol% of tin(IV) chloride gave the 2,5-*cis*-disubstituted tetrahydrofuran **20**[15] after reductive removal of the phenylselanyl group although the yield of this cyclisation was only ca. 43% because of competing *O*-debenzylation and participation by the tosylamino group to give mixtures of side-products which were not fully identified.[16] Hydrogenolysis and oxidation then gave the aldehyde **21** which was treated with the lithium enolate derived from 2,6-dimethylphenyl propanoate[17] to give a mixture of the aldol products **22**, **24** and **26**, ratio 19:72:9, respectively. The 2,3-*syn*-3,4-*syn*-isomer **26** could be separated directly from this mixture by column chromatography. The other two isomers were separated as their *tert*-butyldimethylsilyl ethers **23** and **25**. The structure of the silyl ether **25** prepared from the major aldol product was established as the required 2,3-*anti*-3,4-*syn*-diastereoisomer by reduction and deprotection to give the diol **27** which was converted into the carbonate **28** (Scheme 4). The diol and carbonate were also prepared from the aldehyde **21** by lithium dimethyl cuprate ring-opening of the epoxide **30** prepared by Sharpless epoxidation of the alkenol **29** using (+)-diethyl tartrate.[18] The diol and carbonate prepared by the two routes were identical.

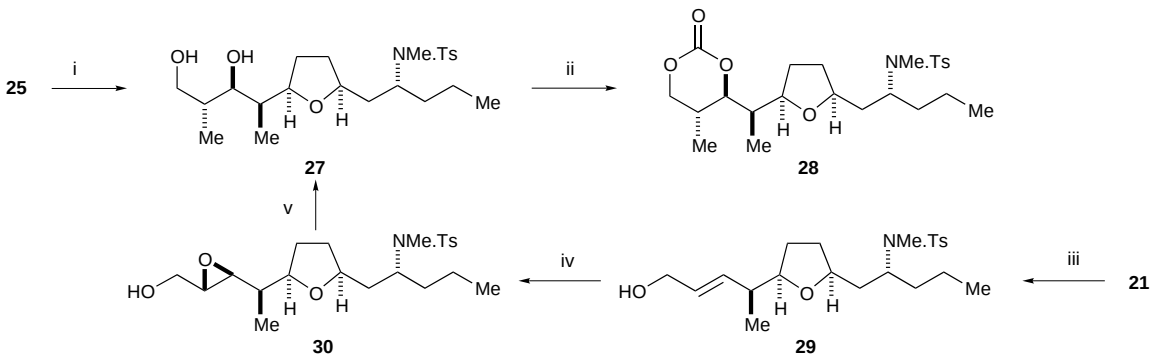
The preferred formation of the 2,3-*anti*-3,4-*syn*-isomer in the aldol reaction is consistent with addition of the (*Z*)-enolate[17] of the 2,6-dimethylphenyl ester to the aldehyde according to the Felkin–Anh model.[19]



Scheme 2. *Reagents and conditions*: (i) **4**, $SnCl_4$, −78°C, 1 h (82%); (ii) PhSePhth, 20% $SnCl_4$ (62%); (iii) Bu_3SnH, AIBN (85%); (iv) (a) 10% Pd/C, H_2 (73%), (b) PDC, DMF (82%); (v) (a) Me_3SiCHN_2 (78%), (b) Bu_4NF, THF (78%).



Scheme 3. *Reagents and conditions*: (i) (*R*)-BnNH·CHMePh, ^{n}BuLi, −78°C (89%); (ii) $Pd(OH)_2/C$, HCO_2NH_4, HCO_2H (100%); (iii) (a) TsCl, Et_3N, DMAP (91%), (b) NaH, MeI (100%); (iv) (a) $LiAlH_4$, Et_2O (94%), (b) $(COCl)_2$, DMSO, Et_3N (95%); (v) **4**, $SnCl_4$, −78°C (64%); (vi) (a) PhSeCl, 20 mol% $SnCl_4$ (43%), (b) Bu_3SnH, AIBN (94%); (vii) (a) H_2, Pd/C, EtOH (98%), (b) $(COCl)_2$, DMSO, Et_3N (90%); (viii) 2,6-dimethylphenyl propanoate, $LiN^{i}Pr_2$, −78°C (**22**+**24**, 63%; **26**, 7%); (ix) $^{t}BuMe_2SiOTf$ (**23**, 17%; **25**, 66%).

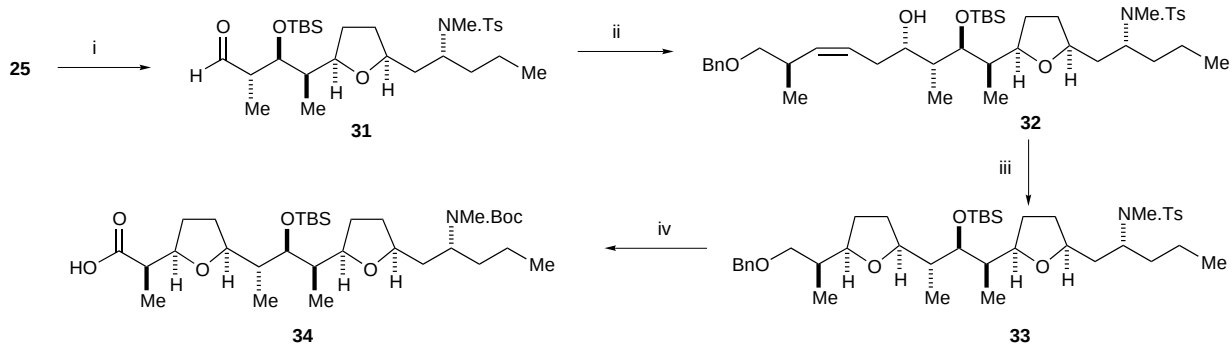


Scheme 4. *Reagents and conditions*: (i) (a) DIBAL-H (80%), (b) TBAF (89%); (ii) $(imid)_2CO$ (87%); (iii) (a) Ph_3PCHCO_2Me (81%), (b) DIBAL-H (74%); (iv) $Ti(O^{i}Pr)_4$, L-(+)-DET, TBHP (70%); (v) $LiCuMe_2$ (57%).

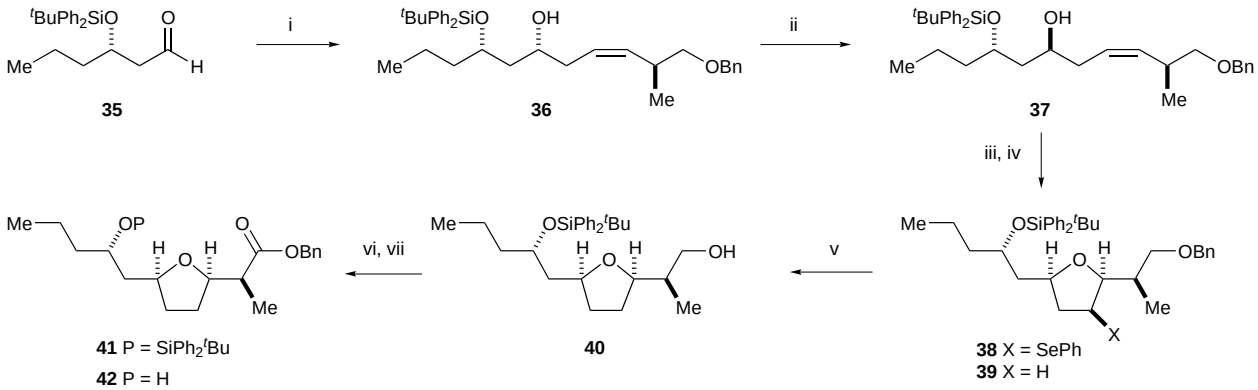
Reduction and oxidation of the protected major aldol product **25** gave the aldehyde **31** which reacted with the allyltin trichloride generated from the allylstannane **4** to give the (*Z*)-1,5-*anti*-product **32**[5,6] (Scheme 5). Cyclisation in this case was best achieved using phenylselenenyl phthalimide in the presence of zinc(II) chloride and gave the bis-tetrahydrofuran **33**[20] in ca. 50% yield from the homoallylic alcohol after reductive removal of the phenylselanyl group. The benzyl ether **33** was taken through to the acid **34** corresponding to the C(1)–C(18) fragment of pamamycin 607 by removal of the tosyl group, reprotection of the nitrogen as its *tert*-butoxycarbonyl derivative, hydrogenolysis, and oxidation.

This approach was now applied to synthesise the C(1′)–C(11′) fragment of pamamycin 607. In this case, it was necessary to invert the configuration of the hydroxyl bearing stereogenic centre introduced during the allylstannane reaction before cyclisation (see Scheme 6).

The tin(IV) chloride-promoted reaction between the protected hydroxyaldehyde **35**[21] and the allylstannane *ent*-**4** gave the (*Z*)-1,5-*anti*-product **36** (1,5-*anti*:1,5-*syn* ca. 87:13). This was converted into its 1,5-*syn*-diastereoisomer **37** by Mitsunobu inversion using 4-nitrobenzoic acid followed by saponification. Cyclisation of the 1,5-*syn*-alcohol **37** using phenylselenenyl phthalimide in the presence of 20 mol% tin(IV) chloride then gave the tetrahydrofuran **38** (ca. 60%) together with inseparable side-products (10–15%) which were believed to be diastereoisomers of **38**. Reduction of this mixture by tributyltin hydride gave the 2,5-*cis*-



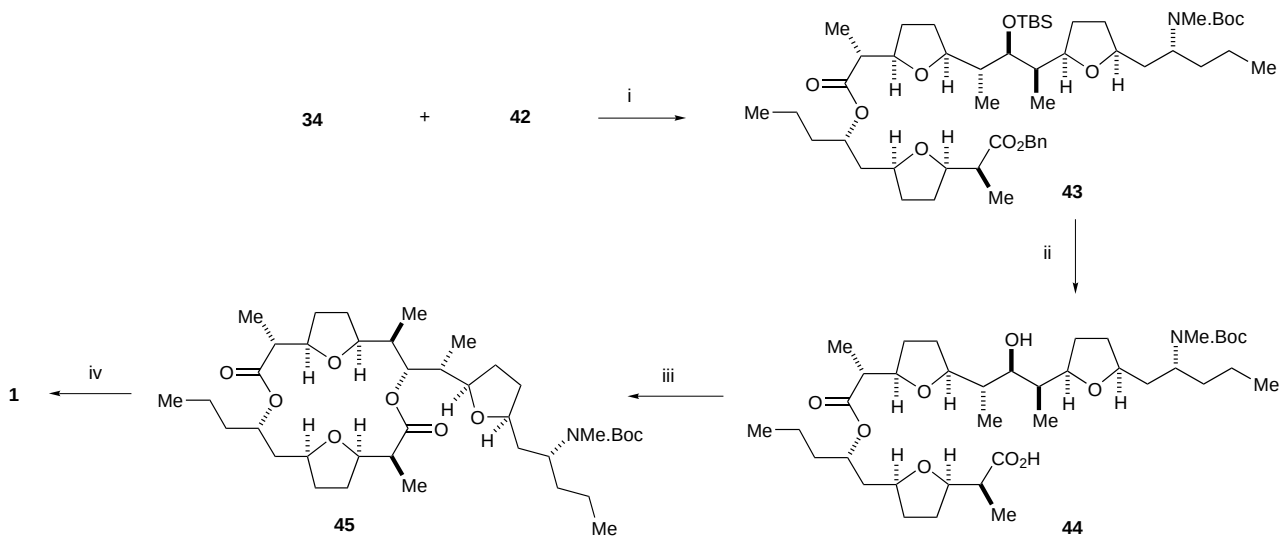
Scheme 5. *Reagents and conditions*: (i) (a) DIBAL-H (82%), (b) $(COCl)_2$, DMSO, Et_3N, (95%); (ii) **4**, $SnCl_4$ (83%); (iii) (a) PhthSePh, $ZnCl_2$, CH_2Cl_2 (54%), (b) Bu_3SnH, AIBN (85%); (iv) (a) Na naphth, −60°C (84%), (b) Boc_2O, Et_3N (80%), (c) H_2, Pd/C, (d) Dess–Martin periodane, (e) $NaOCl_2$, NaH_2PO_4 (85% over the last three steps).



Scheme 6. *Reagents and conditions*: (i) *ent*-**4**, $SnCl_4$ (80%); (ii) (a) Ph_3P, *p*-nitrobenzoic acid, DEAD (68%), (b) NaOH (94%); (iii) PhSePhth, $SnCl_4$ (74% including 60% of **38**); (iv) Bu_3SnH, AIBN (89%); (v) 10% Pd/C, H_2 (70%); (vi) (a) Dess–Martin periodane, (b) $NaOCl_2$, NaH_2PO_4, (c) $^iPr_2NEt$, BnBr (81% from **40**); (vii) conc. aq. HCl, MeOH (49%).

disubstituted tetrahydrofuran **39** which was converted into the alcohol **40** by hydrogenolysis, the side-products being removed at this stage by column chromatography.

Oxidation and carboxylate alkylation then gave the benzyl ester **41** which was desilylated to give the free alcohol **42** corresponding to the C(1′)–C(11′) fragment of pamamycin 607 **1**.



Scheme 7. *Reagents and conditions*: (i) 2,4,6-trichlorobenzoyl chloride, DMAP, CH_2Cl_2, 3 h, rt (63%); (ii) (a) HCl, EtOH, 40–50°C, 3 h, followed by Boc_2O, Et_3N (80%), (b) H_2, Pd/C, EtOH; (iii) 2,4,6-trichlorobenzoyl chloride, Et_3N, 24 h, rt, then DMAP, 24 h, rt (25%); (iv) (a) TFA, CH_2Cl_2, 45 min, rt (82%), (b) CH_2O, $NaBH_3CN$, AcOH, (60%).

The completion of the synthesis of pamamycin 607 **1** is outlined in Scheme 7. The acid **34** and alcohol **42** were coupled using 2,4,6-trichlorobenzoyl chloride[23] to give the ester **43**. Attempted desilylation using tetrabutylammonium fluoride was accompanied by eliminative tetrahydrofuran opening and so the *tert*-butyldimethylsilyl group was removed using aqueous hydrogen chloride in ethanol. This also removed the *tert*-butyloxycarbonyl group which had to be reinstated. Hydrogenolysis then gave the *seco*-acid **44** which was cyclised using 2,4,6-trichlorobenzoyl chloride[23] to give the macrodiolide **45** in 25% yield accompanied by a dimer. Finally, removal of the *tert*-butyloxycarbonyl group and *N*-methylation gave pamamycin 607 **1**, characterised as its trifluoroacetate salt, which had spectroscopic data (^{1}H and ^{13}C NMR, MS) identical to those of the natural product.[24]

This total synthesis of pamamycin 607 exemplifies the synthesis of tetrahydrofurans using reactions between allylstannanes and aldehydes followed by phenylselenenyl induced cyclisation, and demonstrates that this chemistry can be used for the synthesis of complex natural products. In this synthesis, all the stereogenic centres, apart from that at C(15), were introduced either during the allylstannane–aldehyde reactions or were induced by centres which had been introduced during the allylstannane–aldehyde reactions. The application of this strategy, for the synthesis of other tetrahydrofuran containing natural products, is under investigation.

Acknowledgements

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15. The 2,5-*cis*-configuration assigned to the tetrahydrofuran **20** was established by NOE studies and confirmed by correlation with known compounds.[3]
16. Lower yields were obtained for cyclisation if the nitrogen was protected as its Cbz-derivative due to increased participation of the *N*-substituent. Difficulties were

encountered when the nitrogen was protected using a very electron withdrawing group, e.g. triflate. The introduction of the C(15)-amino group at the end of the synthesis, e.g. from a hydroxyl group, was less efficient overall.

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19. The structure of the 2,3-*anti*-3,4-*anti*-isomer **23** was similarly confirmed using (–)-diethyl tartrate for the epoxidation of the alkene **29**.
20. The stereo- and regioselectivity of cyclisation of **32** were confirmed by NOE and 2D NMR studies together with chemical correlations.
21. The aldehyde **35** was prepared from (*S*)-2-hydroxypentanoic acid.[22]
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24. Pamamycin 607 trifluoroacetate[25] (acetone-d_6): δ_C 175.0 (C-1), 173.7 (C-1′), 83.2 (C-3), 81.1 (C-10), 80.0 (C-13), 79.2 (C-3′), 77.3 (C-6), 75.2 (C-6′), 75.2 (C-8), 71.5 (C-8′), 68.7 (C-15), 47.9 (C-2), 43.7 (C-23), 42.1 (C-2′), 41.5 (C-9), 39.4 (C-7′), 37.9 (C-7), 37.9 (C-9′), 36.5 (C-22), 34.2 (C-14), 32.1 (C-5′), 31.6 (C-12), 31.1 (C-4), 30.3 (C-11), 29.0 (C-16), 28.1 (C-5), 27.9 (C-4′), 20.3 (C-17), 18.8 (C-10′), 14.3 (C-11′), 14.0 (C-18), 14.0 (C-19), 10.4 (C-21), 9.8 (C-20) and 8.7 (C-12′).
25. Assignments by comparison with data of Natsume and collaborators.