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Stereocontrolled total synthesis of (+)-concanamycin F: the strategic use of boron-mediated aldol reactions of chiral ketones

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Dedicated to Professor Gilbert Stork with respect and admiration on the occasion of his 90th birthday

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ABSTRACT

A highly stereocontrolled total synthesis of the 18-membered macrolide (+)-concanamycin F, a potent inhibitor of vacuolar ATPases, is described that proceeds in 5.8% yield over 26 steps. The three key fragments, C1–C13 vinyl iodide, C14–C22 vinyl stannane and C23–C28 aldehyde, were efficiently constructed using asymmetric boron-mediated aldol reactions of appropriate chiral ketone building blocks. The nature of the silyl protection of the C7/C9 hydroxyls proved to be critical for achieving macrocyclisation, with TES ethers being superior to a cyclic silylene derivative. Following a Liebeskind-Stille cross-coupling reaction between the C1–C13 vinyl iodide and C14–C22 vinyl stannane fragments to assemble the (12*E*,14*E*)-diene, a modified Yamaguchi macrolactonisation delivered the requisite 18-membered macrocyclic core. This advanced intermediate was also obtained by an alternative sequence using an esterification step to connect the C1–C13 and C14–C22 fragments followed by a Pd-catalysed intramolecular Stille reaction to install the (12*E*,14*E*)-diene. Conversion of the resulting macrocyclic intermediate into a methyl ketone then enabled a highly diastereoselective Mukaiyama aldol coupling of the derived silyl enol ether with the C13–C28 aldehyde fragment to install the fully elaborated side chain, whereby subsequent global deprotection of the resulting β-hydroxyketone under suitable conditions (TASF followed by *p*-TsOH) afforded (+)-concanamycin F.

1. Introduction

The concanamycins (**1**–**6**, Fig. 1) are important members of the plecomacrolide antibiotic family of microbial secondary metabolites.[1-3] Concanamycin A (**1**) was first isolated in 1960 from the fermentation broth of the soil microbe *Streptomyces neyagawaensis* nov. sp.[2a] It was later re-isolated along with concanamycins B (**2**) and C (**3**),[2b] and the gross structural features were elucidated by NMR analysis and chemical degradation.[2c,d] Subsequently, the full stereochemistry of concanamycin A was determined by single crystal X-ray diffraction analysis of its 3′,9-di-*O*-acetate derivative, which also revealed the presence of a characteristic internal hydrogen bond network within the side chain.[2e,f] More recently, concanamycin F (**6**) was isolated from a culture of *Streptomyces* sp. A1509,[2g] and has also been obtained from concanamycin C by controlled glycosidic cleavage.[2h] Structurally, the concanamycins are characterised by a highly substituted 18-membered macrocyclic core containing four alkenes, and a side chain attached at C17 containing a six-membered hemiacetal ring and a further alkene, arising from cyclisation of a 28-carbon polyketide-derived backbone. The main structural variations evident across the congeners **1**–**6** are the nature of the substitution at C8 (R^1=Et, Me or H) and the presence or absence at C23 of a 2′-deoxy-D-rhamnose sugar residue (R^2=H or $CONH_2$).

The concanamycin macrolides all exhibit potent biological activity through inhibition of vacuolar (H^+) ATPases.[1a,3] Vacuolar ATPases are proton pumps, which occur in all eukaryotic cells as part of the endomembrane system. Inhibition of vacuolar ATPase activity by the concanamycins leads to disruption of cellular acidification, which in turn results in antiviral and immunosuppressant activity, as well as the attenuation of resistance in MDR tumour cell lines. While the concanamycins have been used extensively as biological tools for investigating V-ATPase inhibition, their development as a drug candidate has been thwarted due to the toxicity of the unmodified natural products.[2d] However, this general class of V-ATPase inhibiting plecomacrolides, which includes the bafilomycins, has served as a template for the design of novel therapeutic agents for the treatment of osteoporosis by selectively targeting the proton ATPase responsible for bone resorption,[4] while derivatives of the concanamycins have recently been described in the patent literature as lead structures for anti-inflammatory diseases as well as oncology indications.

The therapeutic potential of the concanamycins as lead structures, along with their fascinating structural features and complex array of 14 stereogenic centres, has stimulated considerable interest

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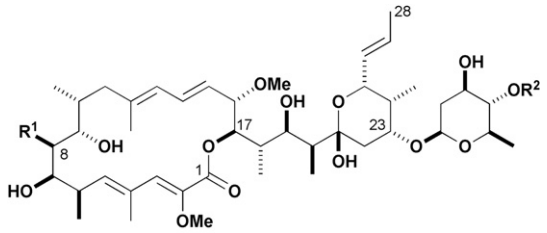
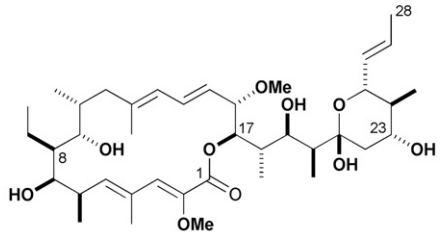


1: Concanamycin A (R^1 = Et, R^2 = $CONH_2$)
2: Concanamycin B (R^1 = Me, R^2 = $CONH_2$)
3: Concanamycin C (R^1 = Et, R^2 = H)
4: Concanamycin D (R^1 = Me, R^2 = H)
5: Concanamycin E (R^1 = H, R^2 = $CONH_2$)



6: Concanamycin F

Fig. 1. The concanamycin family of 18-membered plecomacrolides.

in pursuing their chemical synthesis. Building on their elegant synthetic studies in the area, the first total synthesis of concanamycin F was achieved by the Toshima group.[5,6] As part of our ongoing interest in the total synthesis of important bioactive macrolides,[7] we also identified the concanamycins as attractive targets and have communicated some of our preliminary results.[8] Herein, we provide a full account of an expedient aldol-based strategy for the modular assembly of the concanamycins, culminating in a highly stereocontrolled total synthesis of (+)-concanamycin F that proceeds in 26 steps and 5.8% overall yield. As well as the strict requirement for efficient installation of the 14 stereogenic centres and five alkenes, the choice of suitable protecting groups proved to be critical for successful macrocyclisation to construct the 18-membered macrolactone core and introduce the labile side chain.

2. Retrosynthetic analysis and general synthetic strategy

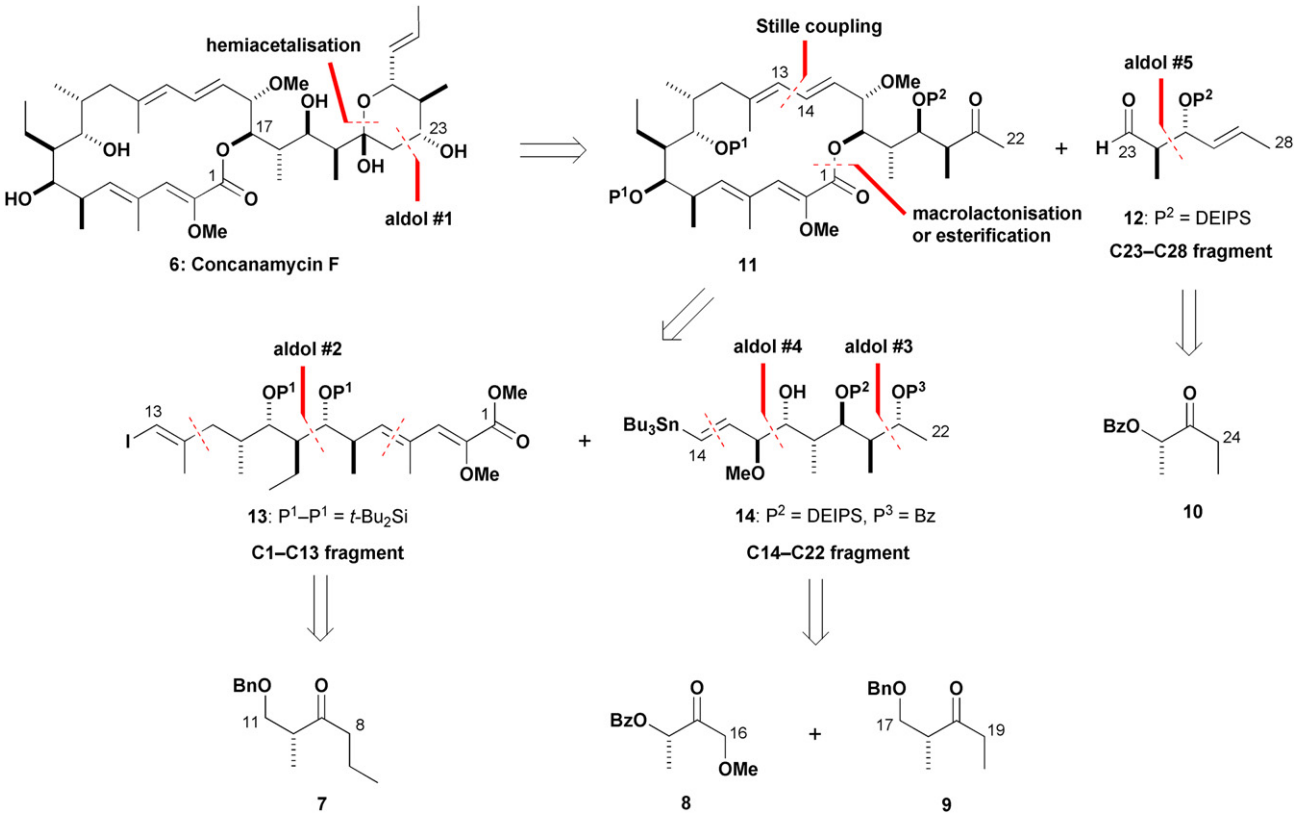
Our retrosynthetic analysis for concanamycin F (**6**) is summarised in Scheme 1, where the pivotal carbon–carbon bond disconnections are highlighted. Five strategic aldol disconnections were selected, leading back to the four chiral ketones **7**–**10** as building blocks. Opening the hemiacetal ring in **6** identifies the key C22–C23 scission, leading back to the macrocyclic methyl ketone **11** and the aldehyde **12**, corresponding to a C23–C28 subunit. The precedent set in our total synthesis of swinholide A[9] suggested that such a C22–C23 aldol coupling would likely proceed with high selectivity. Based on a C13–C14 bond cleavage in **11**, we next identified the two major fragments, i.e., vinyl iodide **13** (C1–C13) and vinyl stannane **14** (C14–C22). The construction of the 18-membered macrocycle was then planned to occur by a Stille cross-coupling reaction[10] followed by macrolactonisation.[11] Alternatively, an esterification to connect the fragments followed by an intramolecular Stille coupling reaction might be employed to close the macrocyclic ring. Advantageously, this modular plan would give useful flexibility in the late stages of the synthesis, as was also recognised by the Toshima group.[5d] The two major intermediates in the synthesis plan are of similar complexity, where vinyl iodide fragment **13** contains five contiguous stereocentres, while the stannane **14** has six contiguous stereocentres (C21 would be carried forward as a hydroxyl-bearing stereocentre and later oxidised to generate a methyl ketone). Based on detailed stereochemical analysis of these elaborate sequences, an aldol disconnection of fragment **12** led us back to the chiral ketone **7**, while the two aldol disconnections indicated in fragment **14** were traced back to the building blocks **8** and **9**. The unsaturated aldehyde subunit **12** (C23–C28) should be accessible by one further aldol reaction, involving the ethyl ketone **10**.

Notably, the foregoing synthetic blueprint for constructing the concanamycins is dependent on achieving a series of boron-mediated *anti*-selective aldol reactions[12] using the chiral ketones **7**–**10**. In practice, this would allow us to further showcase the versatility of this aldol methodology for complex polyketide synthesis.[13] A glycolate-type aldol reaction would employ the ketone **8** for introduction of the methoxy- and hydroxy-bearing stereocentres at C16 and C17, respectively. The two building blocks **7** and **9** are readily prepared from methyl (*R*)-3-hydroxy-2-methylpropionate (Roche ester),[14] while **8** and **10** are available from ethyl (*S*)-lactate.[15] In this way, all 14 of the stereocentres present within concanamycin F were planned to originate solely from these two chiral starting materials in combination with suitable means of substrate-based stereoinduction.

Having considered how to tackle the stereochemical issues, where the correct introduction of the geometry of the five alkenes will also need to be addressed, the choice of appropriate protecting groups was considered. Due to the sensitivity of the hemiacetal-containing side chain in the concanamycins, we elected to use silyl protecting groups throughout, which would then need to be removed under especially mild conditions. Previous model studies[8a] had indicated that the selection of P^2=DEIPS (*i*-$PrEt_2Si$), as introduced by Toshima et al.,[5a] in **12** and **14** would be appropriate. At the outset, we elected to initially introduce a cyclic silylene protecting group on the C7 and C9 hydroxyls (i.e., P^1–P^1=*t*-Bu_2Si in **13**). Examination of the X-ray crystal structure of concanamycin A[2f] suggested that the presence of such a cyclic protecting group would not unduly perturb the preferred conformation of the macrocyclic core, i.e., we hypothesised that it would not interfere with macrocyclisation. Finally, P^3=Bz was chosen as a suitably orthogonal protecting group in the C14–C22 subunit **14** relative to the silyl ethers. This initial synthetic strategy was designed to provide a highly convergent route to concanamycin F (**6**), and other congeners including concanamycin A (**1**) may also be accessible by suitable glycosylation.

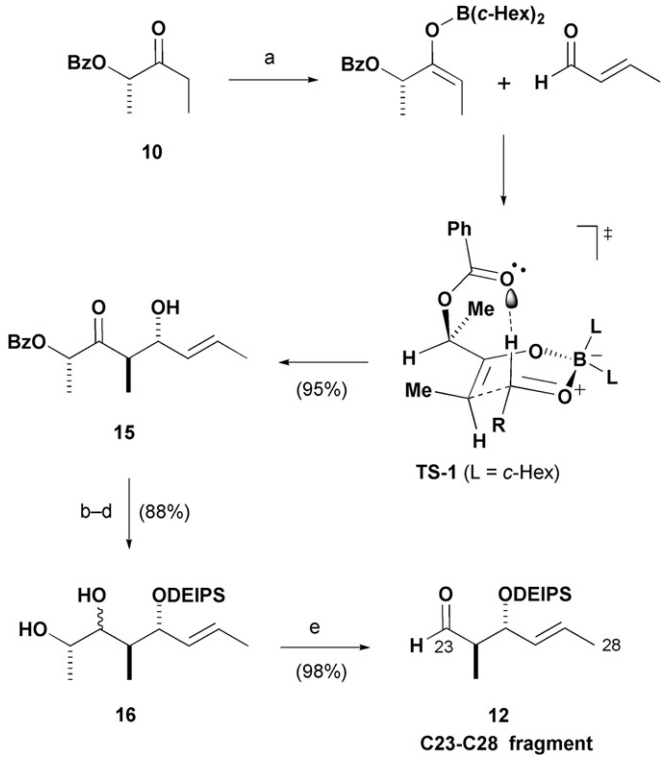
3. Results and discussion

In pursuing our synthetic efforts towards the concanamycins, we first prepared the C23–C28 fragment **12** (Scheme 2), which was also used in model studies for exploring the introduction of the side chain and β-glycosylation at the C23 alcohol.[8a] The aldehyde **12**, incorporating the C24 and C25 stereocentres along with the (*E*)-alkene, was conveniently obtained by a boron aldol reaction of the lactate-derived ethyl ketone **10** and crotonaldehyde. Employing our standard conditions for generating the (*E*)-enolate (*c*-Hex_2BCl, Me_2NEt),[15b] the *anti*-aldol reaction of **10** afforded **15** in excellent yield and diastereoselectivity (95%, >95:5 dr). The high π-facial bias in this boron aldol addition is rationalised by the bicyclic twist-boat transition state **TS-1**, involving participation of the benzoate carbonyl in a stabilising formyl hydrogen bond whilst avoiding A(1,3) strain within the enolate component. Conversion of adduct **15** into the glycol **16** was then achieved in a straightforward manner by DEIPS ether formation (*i*-$PrEt_2SiCl$, imid), followed by reduction with $NaBH_4$ and hydrolysis of the benzoate (K_2CO_3, MeOH). Oxidative glycol cleavage using $NaIO_4$ then gave the aldehyde **12** in



Scheme 1. Retrosynthetic analysis of concanamycin F with five strategic aldol disconnections indicated, leading to key fragments and associated building blocks.

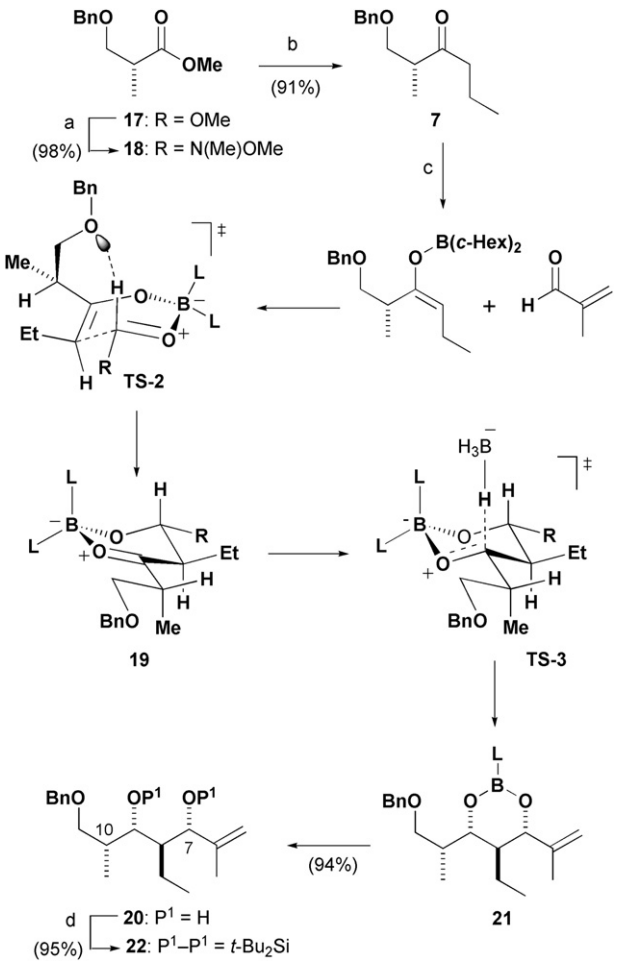
high yield (98%). This first key fragment would be employed later for the controlled attachment of the side chain to the fully elaborated macrocyclic core of concanamycin.



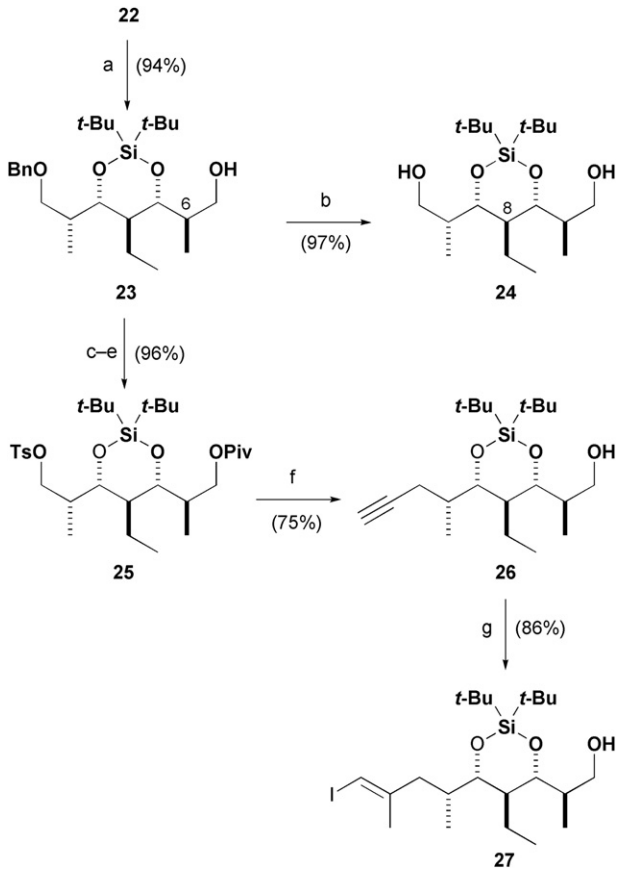
Scheme 2. (a) *c*-Hex$_2$BCl, Me$_2$NEt, Et$_2$O, 0 °C; crotonaldehyde, −78 °C→−20 °C, 16 h; H$_2$O$_2$, MeOH, pH 7 buffer, 0 °C, 1 h; (b) DEIPSCl, imid, CH$_2$Cl$_2$, 0 °C→rt, 30 min; (c) NaBH$_4$, MeOH, 0 °C→rt, 30 min; (d) K$_2$CO$_3$, MeOH, rt, 4 h; (e) NaIO$_4$, MeOH, H$_2$O, rt, 1 h.

As the C1–C13 fragment identified for construction of the macrocyclic core, the vinyl iodide **13** contains all of the structural features contained within the western hemisphere. This major fragment was constructed by adapting our general aldol-based methodology for stereopentad synthesis.[16] In this case, an ethyl substituent at C8 was required instead of the methyl group arising from a more standard propionate-type polyketide biosynthesis, as featured in concanamycins B and D. Following our standard experimental procedure, the required propyl ketone **7** was prepared in two steps from the benzyl-protected Roche ester **17** (Scheme 3).[14b] Merck conditions[17] were employed for formation of the Weinreb amide **18**, involving the in situ generation of the magnesium amide (MeON(Me)MgCl) using *i*-PrMgCl as base. This convenient protocol gave the amide **18** in excellent yield (98%), which was then smoothly converted into the ketone **7** (91%) by a Grignard addition using *n*-PrMgCl.

The construction of the correctly configured C7–C10 stereotetrad was now addressed. In this situation, a 1,4-*syn*-aldol reaction of ketone **7** with methacrolein would be followed by a diastereoselective reduction of the intermediate boron aldolate **19** in a one-pot process. This highly selective transformation has also featured in the context of the total synthesis of the denticulatins[18] and reidispongiolide A.[19] In practice, (*E*)-selective enolisation of **7** (*c*-Hex$_2$BCl, Et$_3$N) and addition of methacrolein at −20 °C gave the aldolate **19**, which was followed by treatment with LiBH$_4$ at −78 °C (in the presence of excess Et$_3$N as a trap for BH$_3$ to avoid any competing hydroboration of the alkene). Work-up involving oxidative removal of boron then gave the 1,3-*syn* diol **20** in excellent yield and selectivity (94%, >95:5 dr) for the installation of the three new stereocentres. This highly versatile and general 1,4-*syn* aldol addition is considered to proceed through the preferred bicyclic transition structure **TS-2**, involving a stabilising formyl hydrogen bond with the benzyl ether oxygen whilst minimising A(1,3)-strain within the enolate, as supported by the recent DFT computational



Scheme 3. (a) MeNHOMe·HCl, *i*-PrMgCl, CH_2Cl_2, −15 °C, 50 min; (b) *n*-PrMgCl, THF, 0 °C, 1 h; (c) *c*-Hex_2BCl, Et_3N, Et_2O, 0 °C, 2 h; methacrolein, −20 °C, 1.5 h; $LiBH_4$, Et_3N, −78 °C, 1.5 h; H_2O_2, MeOH, NaOH, 0 °C, 1 h; (d) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine, THF, 0 °C→rt, 2.5 h.



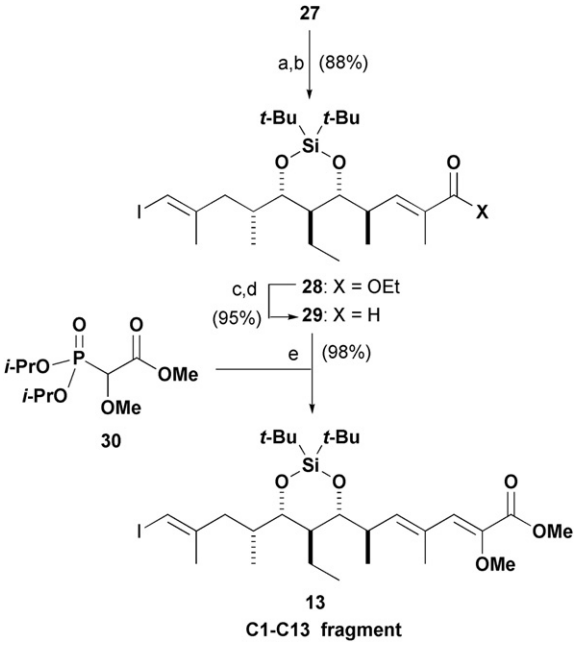
Scheme 4. (a) 9-BBN, THF, 0 °C→rt, 3 h; H_2O_2, NaOH, MeOH, 0 °C, 1 h; (b) 10% Pd/C, H_2, THF, rt; (c) $Me_3C(O)Cl$, DMAP, Et_3N, CH_2Cl_2, rt, 18 h; (d) 10% Pd/C, H_2, THF, rt, 3 h; (e) TsCl, pyr, rt, 16 h; (f) lithium acetylide·ethylenediamine, HMPA, DMSO, rt, 2.5 h; (g) Cp_2ZrCl_2, $AlMe_3$, $(CH_2Cl)_2$, 40 °C, 16 h; I_2, THF, −20 °C→rt, 20 min.

studies of Paton and Goodman.[20] In the subsequent reduction step, preferential *axial* attack of borohydride proceeds through **TS-3**, and the resulting boronic ester **21** can be isolated if required. Silylation of the 1,3-diol **20** with *t*-$Bu_2Si(OTf)_2$/lutidine then gave the corresponding di-*tert*-butylsilylene derivative **22**.

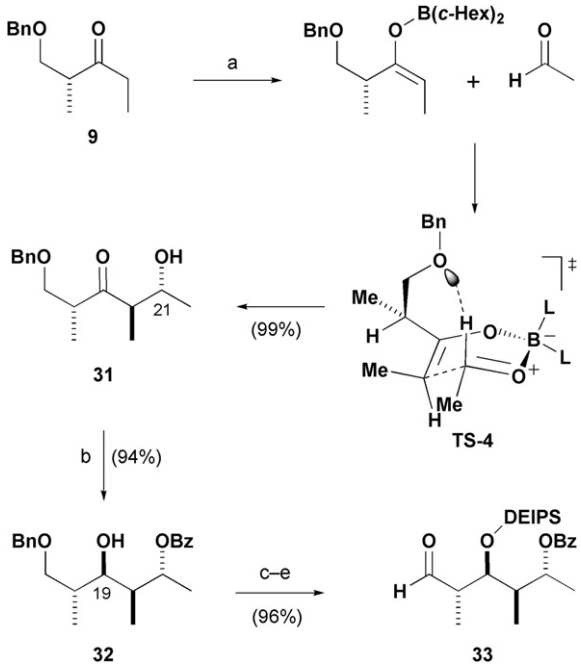
Completion of the stereopentad sequence contained within the C1–C13 region of concanamycin now required installation of the final C6 methyl-bearing stereocentre. This was to be achieved by a diastereoselective hydroboration of the terminal 1,1-disubstituted alkene in **22** (Scheme 4). It was anticipated that high π-facial selectivity would be secured here by the combined influence of the allylic stereocentre[21] and the bulky silyl protecting group with the use of a suitable borane. In the event, hydroboration of the 1,1-disubstituted alkene **21** using 9-BBN afforded the alcohol **22** as a single isomer in 94% yield. At this stage, the expected (6*R*)-configuration was confirmed by hydrogenolysis of the benzyl ether in **23** to give the corresponding 1,7-diol **24**, which had ^1H and ^{13}C NMR spectra and a measurable optical rotation in accord with the lack of symmetry about C8.

The alcohol **23** was then converted into the tosylate **25** in three straightforward steps, by a sequence involving formation of the pivaloate, hydrogenolysis of the benzyl ether and tosylation of the resulting alcohol (96% overall). Chain extension of **25** then was effected through displacement at C11 with lithium acetylide as its ethylene diamine complex, to give the terminal alkyne **26**. Conveniently, this substitution reaction was accompanied by concomitant cleavage of the pivaloate group to liberate the primary alcohol at the other end of the chain. At this point, the (*E*)-vinyl iodide required for the projected fragment assembly by a Stille cross-coupling reaction could be installed by a Negishi carbometallation[22] of the alkyne **26** (Cp_2ZrCl_2, $AlMe_3$) and quenching the intermediate organoalane with iodine to give **27** (86%). Reassuringly, the stereopentad sequence with its attendant bulky silyl protection did not interfere with this organometallic addition to the alkyne as this can often be a problem in the sterically hindered situations encountered in polypropionate fragment construction.[23]

Having installed the vinyl iodide functionality needed for fragment coupling, our attention turned to elaborating the other end of the stereopentad segment **27** to build in the unsaturated ester terminus (Scheme 5). After some exploratory studies, it was found that the conjugated 2-methoxydienoate moeity within **13** could be installed with efficient control over the olefin geometry (Scheme 5). Firstly, oxidation of alcohol **27** and Wittig olefination of the resulting aldehyde with $Ph_3P{=}C(Me)CO_2Et$ gave the corresponding enoate **28** (4*E*/4*Z*=97:3), which was transformed into the enal **29** by DIBAL reduction followed by oxidation of the intermediate alcohol. Controlled introduction of the methoxy-bearing alkene in **13** proved to be more challenging, requiring careful optimisation of the Horner–Wadsworth–Emmons reaction conditions. Variables investigated included the size of the phosphonate alkyl group, the reaction temperature and the choice of counter ion.[8b,24] This study culminated in the use of the phosphonate **30** in conjunction with KHMDS and 18-crown-6[25] at 0 °C. These preferred conditions gave the desired (2*Z*,4*E*)-diene ester **13** in 98% yield, as a 94:6 ratio of geometric isomers, completing the construction of the fully elaborated C1–C13 fragment.



Scheme 5. (a) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C→rt, 30 min; (b) $Ph_3P{=}C(Me)CO_2Et$, PhMe, 110 °C, 6 h; (c) DIBAL, CH_2Cl_2, −78 °C, 30 min; (d) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C→rt, 1 h; (e) **30**, KHMDS, 18-crown-6, THF, 0 °C, 30 min; **29**, 0 °C, 4 h.



Scheme 6. (a) *c*-Hex_2BCl, Et_3N, Et_2O, 0 °C, 2 h; MeCHO, −78→rt, 16 h; H_2O_2, MeOH, pH 7 buffer, 0 °C, 1 h; (b) PhCHO, SmI_2, THF, −10 °C, 1 h; (c) DEIPSCl, imid, DMF, rt, 16 h; (d) $Pd(OH)_2$, H_2, rt, 3 h; (e) DMSO, $(COCl)_2$, CH_2Cl_2; Et_3N, −78→0 °C, 30 min.

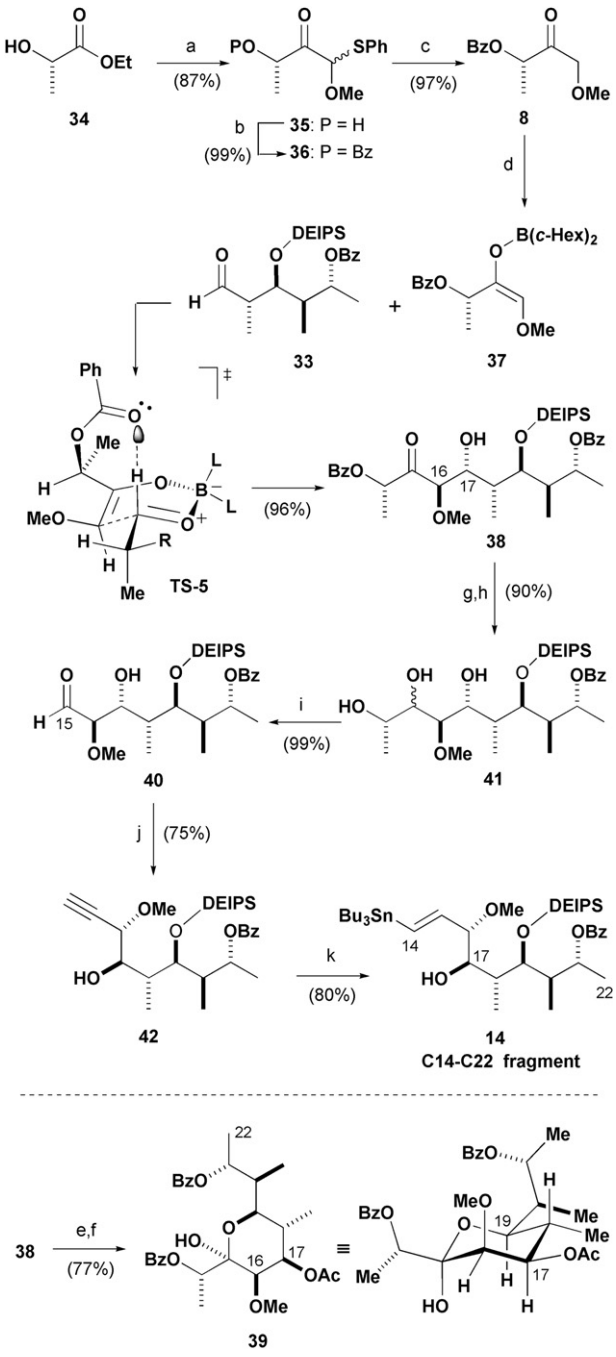
Based on our original synthesis plan (Scheme 1), the remaining major fragment required was the C14–C22 vinyl stannane **14** for a projected Stille cross-coupling reaction with vinyl iodide **13**. Assembly of the carbon chain in fragment **14** with controlled introduction of the six contiguous stereocentres required two consecutive boron-mediated *anti*-aldol reactions using the ketones **8** and **9**. In an analogous manner to the preparation of ketone **7** (Scheme 3), the ethyl ketone **9** was obtained from the same Roche ester-derived amide **18**.[14] By using our standard enolisation conditions (*c*-Hex_2BCl, Et_3N), the (*E*)-enolate derived from **9** was added to acetaldehyde to give the adduct **31** in excellent yield (99%), as essentially a single diastereomer (Scheme 6). The temporary introduction of the C21 hydroxyl group now enabled access to the desired C19–C20 *syn* relationship by employing a suitable hydroxyl-directed reduction. In the event, an Evans–Tischenko[26] 1,3-*anti* reduction of the β-hydroxyketone **31** was performed (SmI_2, PhCHO), leading to formation of the benzoate **32** as a single diastereomer (94%). After silyl protection of the resulting C19 hydroxyl group as the DEIPS ether and subsequent hydrogenolysis of the benzyl group, a Swern oxidation of the ensuing primary alcohol then gave aldehyde **33** (96% overall).

We were now ready to tackle the second aldol addition to introduce the *anti*-related oxygen-bearing stereocentres at C16 and C17. This first required the synthesis of the methoxymethyl ketone **8** (Scheme 7), which was obtained by a sequence involving lithiation of $MeOCH_2SPh$ with *t*-BuLi to generate MeOCH(Li)SPh, followed by its addition to ethyl (*S*)-lactate (**34**) to give sulfide **35**. After formation of the corresponding benzoate, **35**→**36**, Raney nickel mediated reductive desulfurisation then gave the required ketone **8**. Following the conditions developed for the analogous benzyloxymethyl ketone,[15b] enolisation of **8** (*c*-Hex_2BCl, Me_2NEt, Et_2O) generated the (*E*)-enolate **37** and addition to aldehyde **33** gave exclusively the *anti*-α-methoxy-β-hydroxy ketone **38** in excellent yield (96%). In this double stereodifferentiating aldol reaction, the dominant π-facial bias of the enolate component **37** is presumably matched with the Felkin–Anh preference of the chiral aldehyde **33**, as indicated in the preferred transition state **TS-5** (cf. **TS-1** in Scheme 2 for addition to a prochiral aldehyde). The expected configuration at C19 in **38** was determined by ^1H NMR analysis of the derived (*R*)- and (*S*)-MTPA esters based on application of the advanced Mosher method.[27] In addition, the silyl group was removed from **38** with concomitant cyclisation to give a six-membered hemiacetal, followed by acetylation to give **39**. Detailed ^1H NMR analysis of **39** revealed diagnostic vicinal coupling constants within the ring and a NOE correlation between H17 and H19, consistent with a 1,3-diaxial relationship.

Formation of the C15 aldehyde **40** was now required. Initially, an in situ reduction of the cyclic intermediate obtained in the boron aldol reaction was carried out by treatment with an excess of $LiBH_4$ in a similar fashion to that employed earlier for **14**→**20** (cf. Scheme 3). While the ketone functionality was reduced as expected, this was accompanied by the selective reductive cleavage of the C14 benzoate over that at C21, leading to the isolation of the triol **41** in 71% yield. Following some optimisation, we found that **41** could be obtained in improved yield (90%) by $NaBH_4$ reduction of the aldol adduct **38** obtained after oxidative work-up, followed by treatment with K_2CO_3 in MeOH. Controlled oxidative glycol cleavage of triol **41** was then achieved by brief treatment with buffered $Pb(OAc)_4$ to give the aldehyde **40** cleanly (99%).

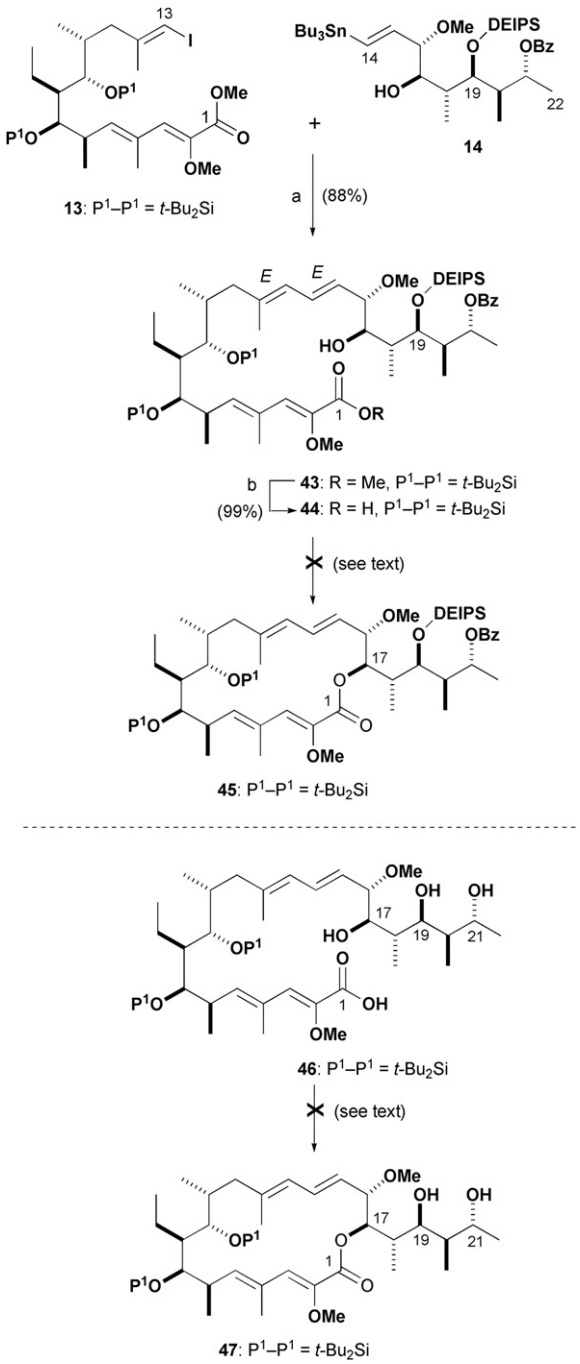
Following the efficient aldol-based construction of the advanced aldehyde intermediate **40**, elaboration into the (*E*)-vinyl stannane **14** was now addressed. After obtaining unsatisfactory yields for Takai olefination[28] on this sensitive substrate, the desired transformation was achieved by using the Ohira–Bestmann alkynation protocol[29] followed by hydrostannylation. In the event, the aldehyde **40** was first treated with dimethyl-1-diazo-2-oxopropyl phosphonate and K_2CO_3 in MeOH to give alkyne **42**. Reassuringly, this reaction proceeded without any competing hydrolysis of the benzoate group. Next, the alkyne **42** was converted into the (*E*)-vinyl stannane **14** by a Pd-catalysed *syn*-hydrostannylation[30] using Bu_3SnH. Notably, this scaleable 11-step sequence provided the C14–C22 fragment **14** in 45.8% overall yield from **9**, with complete control over the installation of the six stereocentres.

At this stage of our synthetic campaign, the three key fragments **12**, **13** and **14** had each been prepared efficiently on a gram scale



Scheme 7. (a) $MeOCH_2SPh$, *t*-BuLi, −78 °C, 2 h; **34**, 40 min; (b) Bz_2O, *i*-Pr_2NEt, DMAP, CH_2Cl_2, rt, 2 h; (c) W-2 Ra–Ni, H_2, EtOH, rt, 30 min; (d) *c*-Hex_2BCl, Et_3N, Et_2O, 0 °C, 3 h; **33**, Et_2O, −78→−20 °C, 16 h; H_2O_2, MeOH, pH 7 buffer, 0 °C, 1 h; (e) aq HCl, THF, rt, 4 h; (f) Ac_2O, pyr, rt, 3 h; (g) $NaBH_4$, MeOH, rt, 30 min; (h) K_2CO_3, MeOH, rt, 2 h; (i) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, rt, 10 min; (j) $MeCOC(=N_2)PO(OMe)_2$, K_2CO_3, MeOH, rt, 16 h; (k) $PdCl_2(PPh_3)_2$, Bu_3SnH, CH_2Cl_2, rt, 10 min.

from the chiral ketones **10**, **7**, **8** and **9**, respectively. At this juncture, we moved forward to explore the pivotal cross-coupling and macrocyclisation steps en route to concanamycin F. The Stille cross-coupling reaction[10] between the stannane **14** and the iodide **13** was first attempted (Scheme 8) using catalytic $Pd(PPh_3)_4$ in DMF with CuI as an additive, affording the diene **43** in modest yield (32%, 55% brsm). Detailed ^1H NMR analysis of the coupled product confirmed the integrity of the olefin geometry and that the (12*E*,14*E*)-diene had been introduced cleanly. After further experimentation, Cu(I)-promoted conditions for Stille cross-coupling reactions[31] in the absence of any palladium catalysts, as developed by Allred and Liebeskind,[32] were found to give much improved yields of **43**. Thus, the use of stoichiometric copper(I) thiophene-2-carboxylate (CuTC) in NMP provided coupled product **43** in high yield (88%). A three-fold excess of the iodide partner **13** was used to achieve complete consumption of the more valuable vinyl stannane **14**, with all the unreacted iodide recovered after the reaction. With the key fragment coupling step achieved, the hydrolysis of the methyl ester in **43** was now required to give the *seco*-acid for macrolactonisation. To avoid competing hydrolysis of the benzoate, nucleophilic displacement of the methyl group was employed. Treatment of **43** with potassium trimethylsilanolate (TMSOK)[33] in Et_2O led to rapid consumption of the methyl ester and isolation of the corresponding carboxylic acid **44** in excellent yield (99%).



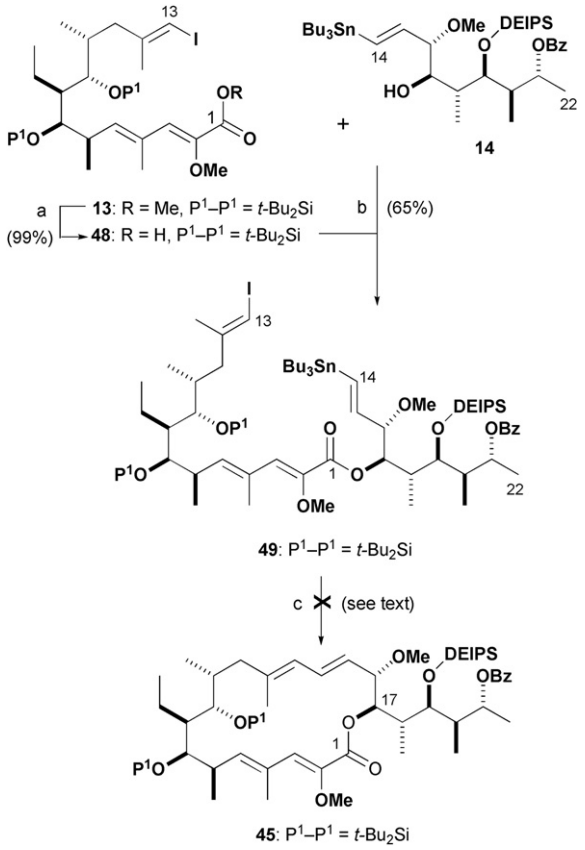
Scheme 8. (a) CuTC, NMP, rt, 1 h; (b) TMSOK, Et_2O, rt, 30 min; (c) Et_3N, 2,4,6-$Cl_3(C_6H_2)COCl$, DMAP, PhMe.

We now could now move forward to examine macrolactonisation[11] of the *seco*-acid **44** to construct the macrocyclic core of concanamycin. Initially, the classical Yamaguchi procedure (2,4,6-$Cl_3(C_6H_2)$COCl, Et_3N, PhMe; DMAP),[34] and variations on it,[35] were attempted but no cyclised product **45** could be identified. Despite many macrolactonisation attempts, performed under a variety of reaction conditions and using elevated temperatures, no indication of any macrocycle **45** could be obtained by NMR analysis of the product mixture before and after purification. Achieving this key transformation, in which we have gained considerable confidence over the years with a variety of elaborate *seco*-acid substrates being cyclised without incident, was now proving to be our Achilles heel! Reasoning that the relatively bulky DEIPS protecting at C19 in **44** might be sterically hindering the C17 alcohol for acylation, we next prepared the triol *seco*-acid **46**. Following the precedent set in our scytophycin C synthesis,[36] this triol acid was subjected directly to Yonemitsu's variation of the Yamaguchi conditions.[35] However, neither the desired 18-membered macrocycle **47** nor even the isomeric 20- or 22-membered macrocycles resulting from acylation at the C19 or C21 hydroxyls were obtained. Frustratingly, from this additional failed macrocyclisation, it was concluded that the presence of the DEIPS group in **44** was probably not the problem. Nevertheless, some unfavourable conformational constraint must exist that was interfering with the activated acid intermediate from being able to acylate any of the C17, C19 and C21 hydroxyls. At this stage, a revised strategy based on an intramolecular Stille coupling reaction to forge the C13–C14 bond and construct the macrocycle was examined.

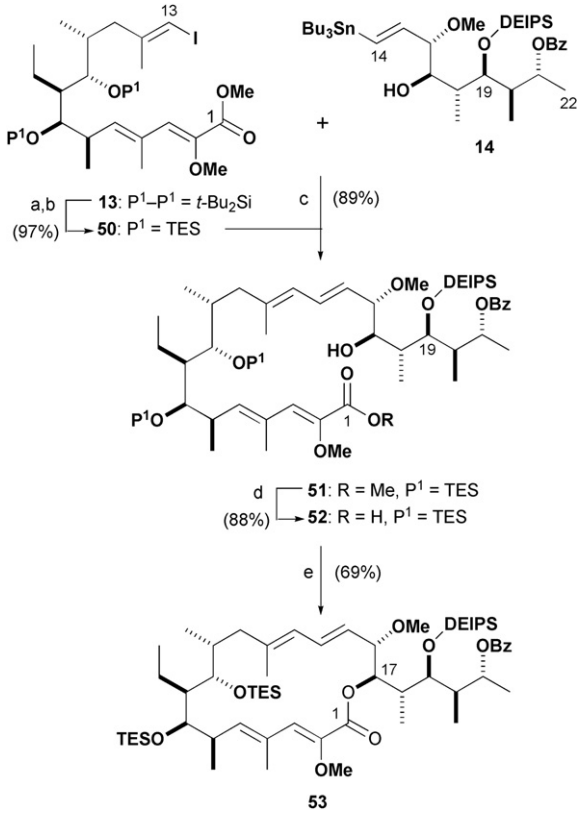
In order to assemble a suitable substrate to examine the intramolecular Stille reaction, the ester linkage at C17 needed to be introduced first. To this end, hydrolysis of the methyl ester **13** using TMSOK gave the corresponding acid **48** cleanly (Scheme 9). Successful acylation of the C17 hydroxyl in the vinyl stannane **14** to give ester **49** under Yamaguchi conditions required the use of a large excess of reagents in toluene.[36] With a view to forging the C13–C14 bond, the intramolecular Stille reaction of **49** was first attempted employing the CuTC conditions that had worked well for the preparation of **43**. However, this only led to the isolation of the C14 protodestannylation product with the vinyl iodide at C13 remaining intact. Frustratingly, the use of more traditional Pd-catalysed Stille conditions, e.g., $Pd(PPh_3)_4$ in DMF at 50 °C with CuI as an additive, resulted in the formation of only non-cyclised products and decomposition.

At this juncture, these failures suggested that all of the cyclisation substrates examined so far cannot easily adopt a suitable conformation which brings the termini sufficiently close to react. One site of conformational constraint was the cyclic di-*tert*-butylsilylene group protecting the C7/C9 hydroxyls. Therefore, the silylene protecting group in **13** was cleaved by extended treatment with HF·Et_3N in THF (99%) and the resulting diol was reprotected as the C7/C9 bis-TES ether **50** (Scheme 10). The Stille cross-coupling reaction with vinyl stannane **13** was carried out using 3.4 equiv of vinyl iodide **50** and 1.5 equiv CuTC, giving the desired diene product **51** in excellent yield (89% with full recovery of unreacted **50**). The methyl ester was then hydrolysed using TMSOK in Et_2O to give acid **52** (88%). After some optimisation, it was found that the macrolactonisation of *seco*-acid **52** could now be achieved by the Yonemitsu modification[35,36] of the Yamaguchi method, employing a large excess of reagents[37] (11 equiv 2,4,6-$Cl_3(C_6H_2)$COCl, 12 equiv Et_3N, 25 equiv DMAP) in dilute toluene. Gratifyingly, this procedure now afforded the desired 18-membered macrocycle **53** in a satisfactory 69% yield after 18 h at room temperature. This indicated that the sterically demanding di-*tert*-butylsilylene cyclic protecting group was indeed the cause of our earlier macrocyclisation failures.

Having accomplished the synthesis of macrocycle **53** in the TES ether series using a macrolactonisation, its alternative preparation

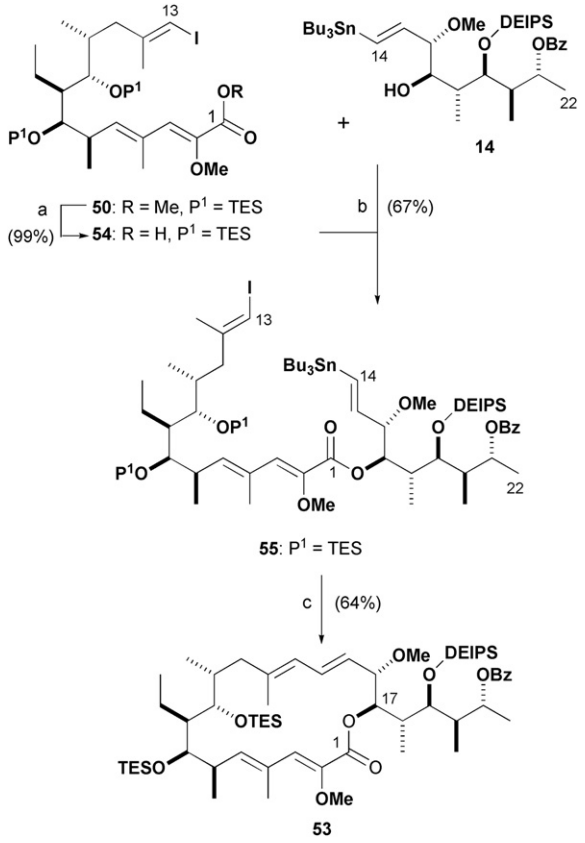


Scheme 9. (a) TMSOK, Et_2O, rt, 30 min; (b) Et_3N, 2,4,6-$Cl_3(C_6H_2)$COCl, DMAP, PhMe, rt, 18 h; (c) CuTC, NMP, rt, 1 h; or $Pd(PPh_3)_4$, CuI, DMF, 50 °C 16 h; or $Pd(CH_3CN)_2Cl_2$, *i*-Pr_2NEt, DMF, THF, rt, 16 h.



Scheme 10. (a) HF·Et_3N, THF, rt, 7 days; (b) TESOTf, 2-6-lutidine, CH_2Cl_2, −78→0 °C, 10 min; (c) CuTC, NMP, rt, 1 h; (d) TMSOK, Et_2O, rt, 30 min; (e) Et_3N, 2,4,6-$Cl_3(C_6H_2)$COCl, DMAP, PhMe, rt, 18 h.

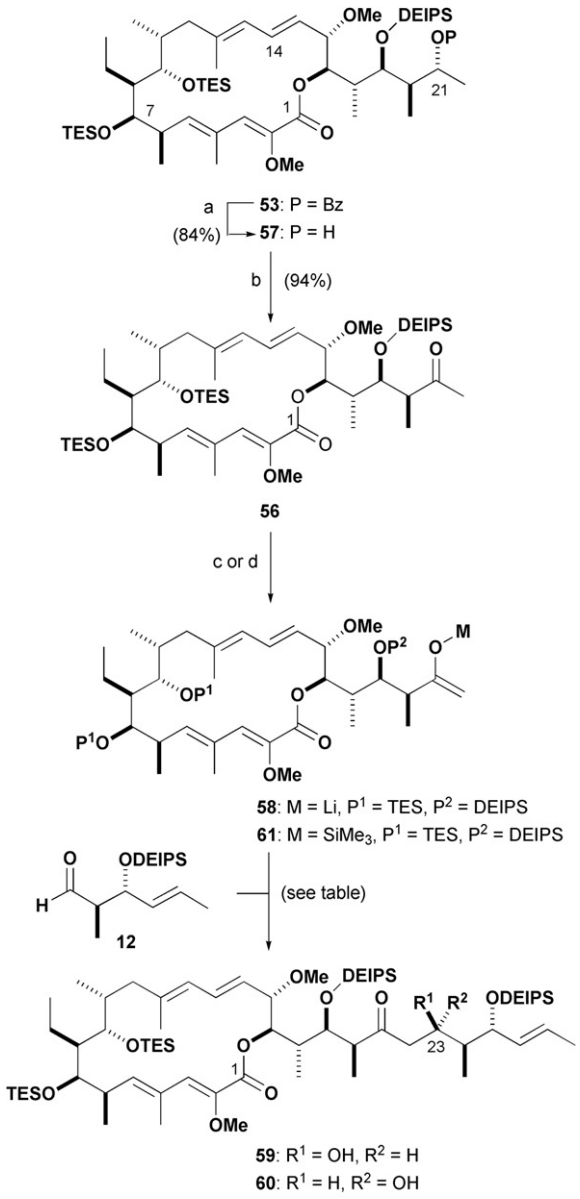
using an intramolecular Stille reaction was now explored. Hydrolysis of the methyl ester **50** using TMSOK gave the corresponding acid **54** in essentially quantitative yield (Scheme 11). The esterification of acid **54** and alcohol **14** was then carried out using modified Yamaguchi conditions to yield the desired ester **55** (67%). An attempted intramolecular Stille reaction using CuTC[32] resulted in only protodestannylation and recovered starting material. However, it was then found that Pd-catalysed coupling conditions were now superior, as treatment of **55** with $Pd_2(dba)_3$, Ph_3As and *i*-Pr_2NEt gave the desired macrocycle **53** (64%). We had therefore moved forward and now had two workable routes to the macrocyclic core of concanamycin and chose to concentrate on the higher yielding macrolactonisation route to advance material towards the proposed endgame.



Scheme 11. (a) TMSOK, Et_2O, rt, 30 min; (b) Et_3N, 2,4,6-$Cl_3(C_6H_2)COCl$, DMAP, PhMe, rt, 18 h; (c) $Pd_2(dba)_3$, Ph_3As, *i*-Pr_2NEt, DMF, THF, 60 °C, 16 h.

In order to elaborate **53** into the target macrocyclic methyl ketone **56**, a selective cleavage of the benzoate in the presence of the macrolactone linkage was required. Inspection of the structure of macrolide **53** suggested that the lactone was in a relatively hindered environment compared to the benzoate located near the terminus of the side chain. Therefore, it was decided to use a bulky reducing agent in order to differentiate between the two esters. In practice, brief treatment of **53** with DIBAL at low temperature (−78 °C, 1 min) led to the desired site-selective reduction to give the macrocyclic alcohol **57** (84%) (Scheme 12). Oxidation of secondary alcohol **57** using Dess–Martin periodinane[38] then afforded the methyl ketone **56** in high yield (94%). Following the preferred Stille coupling/macrolactonisation route, the synthesis of the advanced intermediate **56** was carried out in five steps and 43% overall yield from the vinyl iodide **50** and the vinyl stannane **14**.

At this point, we could now move forward to investigate the introduction of the full side chain of concanamycin by a complex aldol coupling between methyl ketone **56** and the already prepared



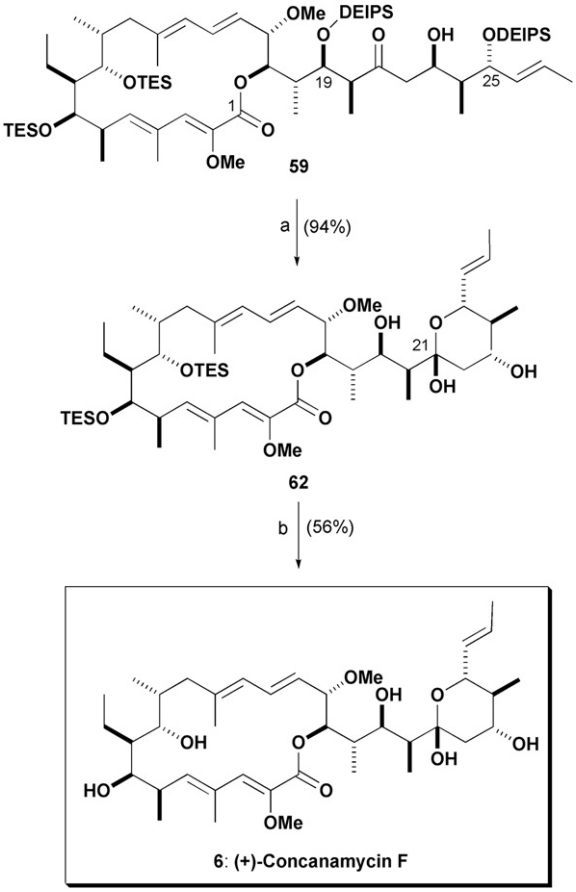
enolate (M)	conditions	**59** : **60**	yield (%)
58 (Li)	c	73 : 27	44
61 ($SiMe_3$)	d	>97 : 3	81

Scheme 12. (a) DIBAL, CH_2Cl_2, −78 °C, 1 min; (b) DMP, CH_2Cl_2, rt, 2 h; (c) LDA, THF, −78 °C, 1 h; **12**, −78 °C, 1 h; (d) Me_3SiCl, Et_3N, THF, −78 °C; LiHMDS, 10 min; $BF_3{\cdot}OEt_2$, **12**, CaH_2, CH_2Cl_2, −100 °C, 2 min.

aldehyde **12** corresponding to the C23–C28 fragment. This was initially explored using the lithium enolate **58** obtained by deprotonation of **56** with LDA, based on a protocol used in our synthesis of elaiolide.[39] In the event, this gave a disappointing 44% yield (61% brsm) of a 73 : 27 mixture of adducts in favour of the desired β-hydroxyketone **59**, resulting from the expected Felkin–Anh attack, and the epimeric β-hydroxyketone **60**. Following our success in achieving highly diastereoselective complex aldol couplings in the synthesis of swinholide A using Mukaiyama conditions with $BF_3{\cdot}OEt_2$ as the preferred Lewis acid,[9] we next turned to generating the silyl enol ether from **56**. Treatment of ketone **56** at −78 °C in THF with a premixed solution of TMSCl and Et_3N, followed by addition of LiHMDS, gave the required silyl enol ether **61**, which underwent smooth aldol coupling with **12**, when carried out using

$BF_3{\cdot}OEt_2$ in the presence of CaH_2. Gratifyingly, this reaction proceeded rapidly at −100 °C (2 min) in excellent yield (81%) and with complete selectivity for the desired adduct **59**. The inclusion of the CaH_2 as a drying agent was key to avoid competing hydrolysis of the silyl enol ether **61** back to **56**. In this pivotal fragment coupling, the high selectivity for **59** can be accounted for by the cooperative interplay between preferred Felkin–Anh attack for 1,2-stereoinduction and the Evans polar model[40] for 1,3-*anti* induction in the open transition state associated with this Lewis acid-promoted aldol addition.

Having successfully forged the C22–C23 bond in **59**, we anticipated that a final silyl deprotection step would then install the required 6-membered hemiacetal ring and afford concanamycin F (Scheme 13). Initially, the deprotection of **59** was attempted using TASF, as employed by Roush and co-workers in their total synthesis of bafilomycin A_1.[41] However, this only led to the formation of the C21 hemiacetal **62** in 94% yield, with both TES groups still remaining in place. Extended reaction times and elevated temperatures resulted in only decomposition. Next, an attempt using TBAF (as used by the Toshima group on an analogous intermediate with DEIPS ethers at C7 and C9)[5d] to deprotect the residual TES groups in **62** led to the isolation of impure concanamycin F (**6**) in unacceptably low yield (22%). Pleasingly, the use of *p*-TsOH in MeCN/H_2O/CH_2Cl_2 proved to be much more proficient in cleaving the TES ethers from **62**, affording after purification a 56% yield of (+)-concanamycin F (**2**), $[\alpha]_D^{22}$ +10.6 (*c* 0.32, $CHCl_3$) versus lit.[42] +11.0 (*c* 0.3, $CHCl_3$). The resulting synthetic material was rigorously authenticated by spectroscopic correlation with that of a sample of concanamycin F prepared by controlled glycosidic cleavage of concanamycin A,[2h] as well as by comparison with an ^1H NMR spectrum of natural concanamycin F provided by Prof. Zeeck.



Scheme 13. (a) TASF, DMF, H_2O, rt, 16 h; (b) *p*-TsOH, MeCN, CH_2Cl_2, H_2O, rt, 3 h.

4. Conclusions

In summary, we have completed a highly stereocontrolled synthesis of (+)-concanamycin F, which proceeds in 26 steps (longest linear sequence from Roche ester) and 5.8% overall yield. This work further demonstrates the versatility of substrate-based aldol stereocontrol using the readily available chiral ketone building blocks **7**–**10** in complex polyketide synthesis. Here the C10 and C18 methyl-bearing stereocentres contained in concanamycin F originate from the ketones **7** and **9**, respectively, while the remaining 12 stereocentres were introduced efficiently using versatile aldol methodology, in combination with diastereoselective ketone reductions and an alkene hydroboration. The present work also makes feasible the designed chemical synthesis of novel concanamycin analogues having modified biological activity,[43] and glycosylation to access concanamycin A may also be possible.[8a]

While our initial synthetic blueprint, as outlined in Scheme 1, served reasonably well for constructing the three key fragments **12**, **13** and **14**, it required some revision along the way to successfully access the characteristic 18-membered macrolactone of the concanamycins. Initially, the key ring-forming step was beset with problems and required extensive troubleshooting to identify a viable route. Fortunately, our strategy proved sufficiently flexible in refining a workable ordering of the steps and for accessing the substrates **52** and **55**, both having TES ethers at C7 and C9, for achieving macrocyclisation either by Yamaguchi macrolactonisation or a Stille coupling reaction to give the pivotal intermediate **53**. As in other complex polyoxygenated natural products, identifying the optimum protecting group strategy is often still a matter of trial and error, and becomes clearer as one has to circumvent various unanticipated problems that arise in progressing the synthetic route. From a personal perspective, protecting groups often interfere in unexpected ways with key transformations and avoiding them completely is a highly attractive proposition.[44] Although this is difficult to realise in archetypal macrolides having multiple hydroxyl groups, limiting their deployment and making sure they do not obstruct the critical macrocyclic ring formation must be paramount concerns. In the case in hand, the nature of the protection of the C7/C9 hydroxyls proved to be especially critical for achieving macrocyclisation, directly enabling our successful completion of the total synthesis of (+)-concanamycin F.

5. Experimental and data for compounds

See the electronic Supplementary data.

Acknowledgements

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Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.012.

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