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# Stereocontrolled Aldol Additions to α-Methylene-β-Alkoxy Aldehydes: Application to the Synthesis of a $C_{13}$–$C_{25}$ Segment of Bafilomycin $A_1$.

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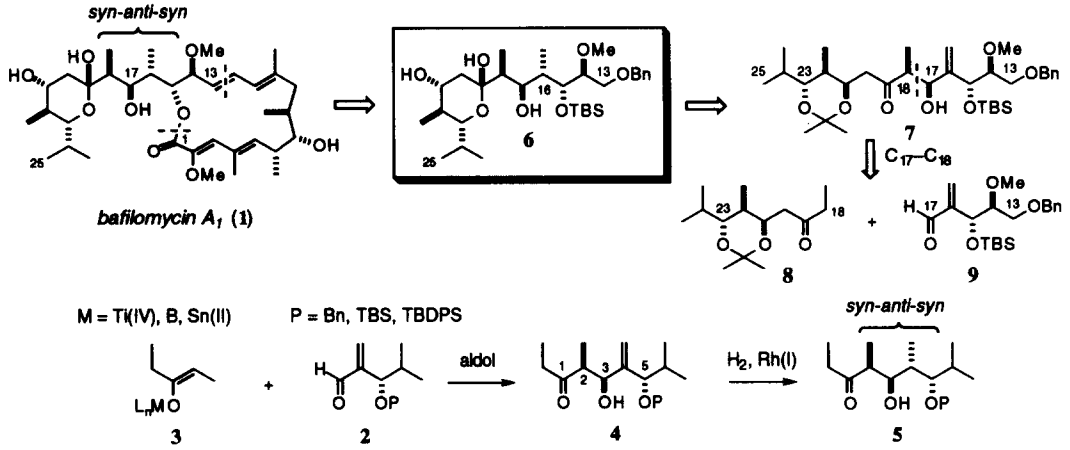
**Abstract:** A boron-mediated, *syn*-aldol coupling between ethyl ketone **8** and aldehyde **9**, followed by directed hydrogenation at $C_{16}$ and acetonide hydrolysis, gives the $C_{13}$–$C_{25}$ segment **6** of bafilomycin $A_1$.

Bafilomycin $A_1$ (**1** in **Scheme 1**) belongs to a family of structurally related polyketide macrolide antibiotics, which include other bafilomycins,[1] the concanamycins[2] and the hygrolidins.[3] First isolated in 1983 by Werner *et al.*,[1a,b] bafilomycin $A_1$ is a potent and specific ATPase inhibitor[4] which shows broad spectrum antibiotic activity. The stereochemistry, originally proposed by Corey[5] from NMR analysis in combination with molecular modelling, was determined to be as shown in **1** by X-ray crystallography.[1c] The first total synthesis of bafilomycin $A_1$ was recently completed by Evans and Calter,[6] whilst a synthesis of a $C_{13}$–$C_{25}$ segment has been reported by the Roush group.[7]

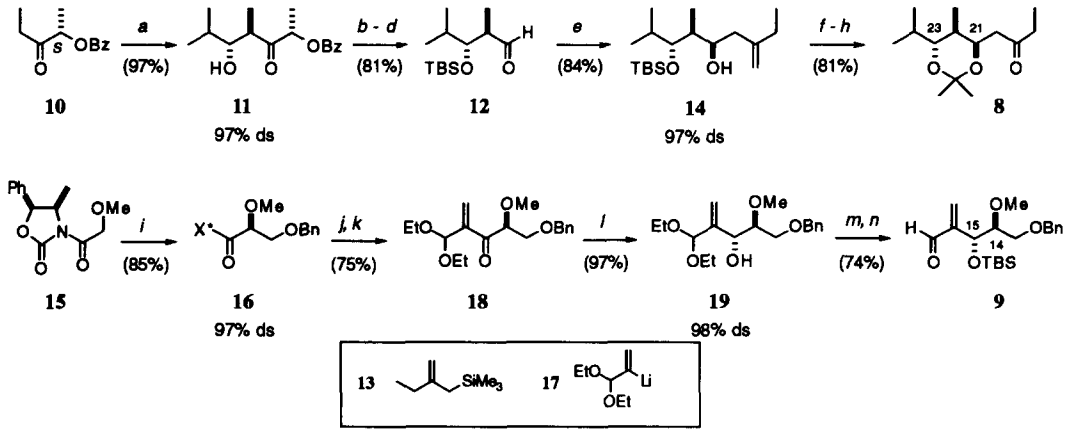



**Scheme 1**

As part of our work on polypropionate synthesis,[8] we recently found that α-methylene-β-alkoxy aldehydes such as **2** produce useful levels of 1,3-asymmetric induction in aldol reactions with simple ketones. For example, Ti(IV), B and Sn(II) enolates **3** gave the 2,3-*syn*-3,5-*anti* adduct **4** preferentially, which can be stereoselectively hydrogenated, as in **4** → **5**.[8a] The macrolide bafilomycin $A_1$ appeared to be an ideal target to test this methodology, due to the occurrence of the same *syn-anti-syn* stereotetrad spanning $C_{15}$–$C_{18}$ (*cf.* **5**). We now report a novel aldol construction of the $C_{13}$–$C_{25}$ bafilomycin $A_1$ segment **6** based on this approach.

Our synthetic strategy (**Scheme 1**) relied on: (*i*) introduction of the $C_{16}$ stereocentre in **6** by hydroxyl-directed hydrogenation of alkene **7**; (*ii*) $C_{17}$–$C_{18}$ bond formation by aldol coupling between ketone **8** and aldehyde **9**. Achieving a useful level of remote stereocontrol (by 1,3-induction from **9** and/or 1,4-induction from **8**) was an essential requirement for the aldol step.

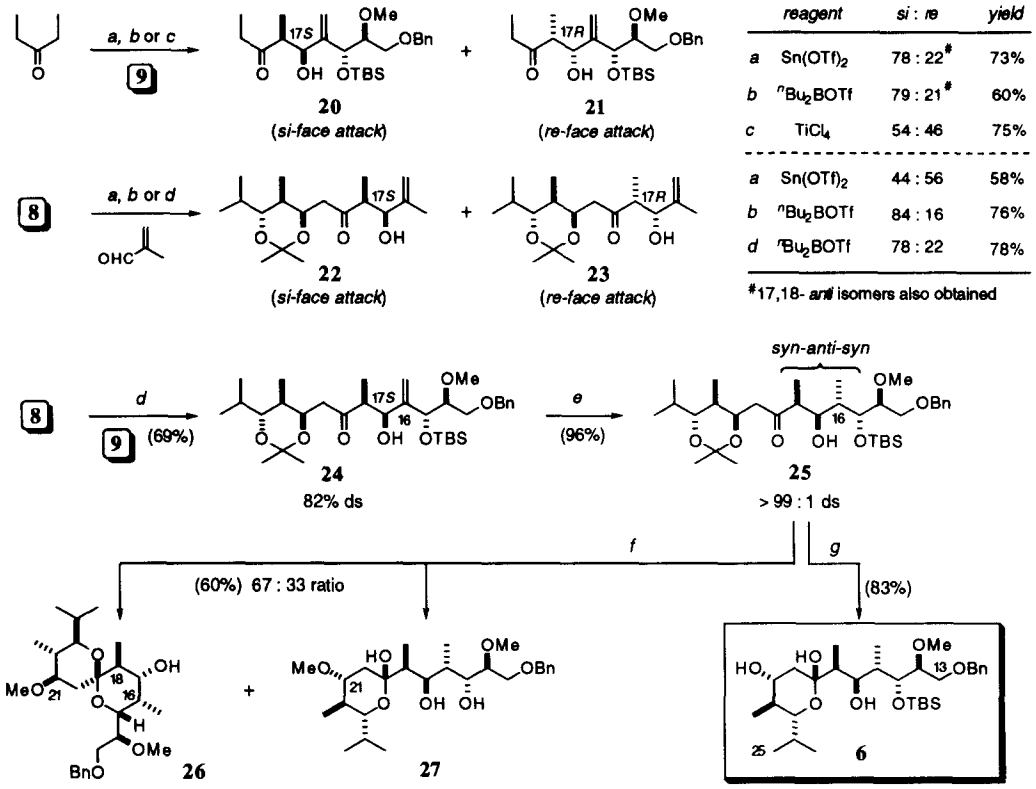
The synthesis of the coupling partners chosen for the critical $C_{17}$–$C_{18}$ aldol connection is summarised in **Scheme 2**. Ketone **8**,[9] with acetonide protection across the $C_{21}$ and $C_{23}$ hydroxyls, was efficiently prepared using an *anti* aldol reaction between the (*S*)-lactate-derived ketone **10** and isobutyraldehyde. Using our standard conditions,[10a] the *E*-enol dicyclohexylborinate derived from **10** gave the *anti-anti* adduct **11** in 97% yield with 97% ds. After conversion[10b] into aldehyde **12** (81%), a Felkin-Anh controlled addition of the allylsilane **13**,[11] promoted by $TiCl_4$, gave an 84% yield of **14** with 97% ds. Alkene **14** then led to ketone **8**, $[\alpha]_D^{20} = -9.1°$ (*c* 3.0, $CHCl_3$), *via* a 3-step sequence (81% overall) of silyl ether deprotection, acetonide formation, and oxidative double bond cleavage. The synthesis of the aldehyde **9** relied on the Evans alkylation of the chiral glycolate **15**.[12] Alkylation of the Ti(IV) enolate of **15** with $BnOCH_2Cl$ gave **16** (85%) with high selectivity (97% ds). Transamination to the Weinreb amide,[13] followed by addition of the organolithium reagent **17**,[14] then gave the enone **18** (75%). Luche reduction ($NaBH_4$, $CeCl_3$)[15] of **18** proceeded with 98% ds in favour of the *anti* glycol derivative **19** (97%). Finally, silyl protection and acetal hydrolysis gave a 74% yield of the enal **9**, $[\alpha]_D^{20} = +17.6°$ (*c* 1.6, $CHCl_3$).




**Scheme 2** (*a*) $^cHex_2BCl$, $Me_2NEt$, $Et_2O$, 0 °C, 3 h; $^iPrCHO$, –78 → –20 °C, 15 h; aq. MeOH, $H_2O_2$, 0 °C, 1 h. (*b*) TBSOTf, 2,6-lutidine, $CH_2Cl_2$ –78 °C, 2 h. (*c*) $NaBH_4$, MeOH, 0 °C, 30 min; $K_2CO_3$, MeOH, 20 °C, 3 h. (*d*) $NaIO_4$, aq. MeOH, 20 °C, 30 min. (*e*) **13**, $TiCl_4$, $CH_2Cl_2$, –94 °C, 10 min. (*f*) TBAF, THF, 20 °C, 30 min. (*g*) $(MeO)_2CMe_2$, PPTS, $CH_2Cl_2$, 20 °C, 4 h. (*h*) $OsO_4$, NMO, $^tBuOH/THF/H_2O$, 20 °C, 4 h; $NaIO_4$, pH 7 buffer, 10 min. (*i*) $TiCl_4$, $^iPr_2NEt$, $CH_2Cl_2$, 0 °C, 1 h; $BnOCH_2Cl$, 0 °C, 16 h. (*j*) MeONHMe.HCl, $Me_3Al$, $CH_2Cl_2$, –15 → 20 °C, 20 h. (*k*) **17**, THF, –78°C, 2 h. (*l*), $CeCl_3.7H_2O$, $NaBH_4$, EtOH, –78 °C, 1.5 h. (*m*) TBSOTf, 2,6-lutidine, THF, 0 °C, 20 min; EtOH. (*n*) $(CO_2H)_2$, aq. THF, 20 °C, 20 h.

The π-facial selectivities of the ketone **8** and aldehyde **9** in aldol reactions were investigated separately (**Scheme 3**). As in our previous study,[8a] the 1,3-asymmetric induction arising from the chiral aldehyde **9** was examined in reactions with the Sn(II), B and Ti(IV) enolates of diethylketone. In all cases, the major *syn* adduct **20**, corresponding to *si*-face attack on the aldehyde was obtained,[16] with good selectivity for both the Sn(II) and B enolates (**20** : **21** = *ca.* 4 : 1). Minor amounts of *anti* adducts were also obtained. The sense of induction agreed with that from our earlier work (*cf.* **2** + **3** → **4**).[8a] Contrary to our previous results, the $TiCl_4$-mediated reaction provided low facial selectivity here (**20** : **21** = 1.2 : 1). The 1,4-induction in the *syn* aldol reaction of chiral ketone **8** with methacrolein was examined next. The Sn(II) enolate derived from **8** showed little selectivity for **22** *vs* **23**. However, the corresponding *Z*-enol di-*n*-butylborinate gave improved results. With $CH_2Cl_2$ or $Et_2O$ as solvent, the *syn* adduct **22**, again corresponding to *si*-face attack on the aldehyde,[16] predominated (**22** : **23** = 5 : 1 in $Et_2O$). Cyclic protection of the 1,3-diol in **8** proved essential for good aldol stereocontrol.[17]

These studies suggested that matched double diastereodifferentiation should result from a boron-mediated *syn* aldol coupling at $C_{17}$–$C_{18}$ of the two components. The desired (17*S*)-adduct **24** was accordingly obtained, with 82% ds, from addition of the *Z*-enol di-*n*-butylborinate of ketone **8** to aldehyde **9**. Hydroxyl-directed hydrogenation of alkene **24** using $(Ph_3P)_3RhCl$[8a,18] introduced the $C_{16}$ stereocentre with excellent selectivity (>99 : 1 ds), giving **25** in 96% yield. This has the required *syn-anti-syn* $C_{15}$–$C_{18}$ stereotetrad of bafilomycin $A_1$. Under acidic conditions in methanol, the acetonide and silyl ether in **25** were removed and cyclisation occurred to give a 2 : 1 mixture of the spiroacetal **26**[9] and the hemiacetal **27** (a $C_{13}$-$C_{25}$ segment of L681,110 $B_1$)[19] in 60% yield. Note that both these compounds had incorporated methanol at $C_{21}$ (presumably by dehydration to the enone and conjugate addition of MeOH).[20] NOE studies performed on **26** served to confirm the stereochemistry at $C_{16}$, $C_{17}$ and $C_{18}$. Careful acetonide hydrolysis and cyclisation of **25** under aqueous acidic conditions, however, provided an 83% yield of **6**[9], $[\alpha]_D^{20}$ = +8.0° (*c* 0.25, $CHCl_3$), corresponding to the required $C_{13}$-$C_{25}$ segment of bafilomycin $A_1$.




**Scheme 3** (*a*) $Sn(OTf)_2$, $Et_3N$, $CH_2Cl_2$, –78 °C, 2 h; RCHO, –78 → –25 °C, 3 h. (*b*) $^nBu_2BOTf$, $^iPr_2NEt$, $Et_2O$, –78°C, 2 h; RCHO, –78 → –25 °C, 16 h. (*c*) $TiCl_4$, $CH_2Cl_2$, –78 °C, 30 min; $^iPr_2NEt$, 1 h; RCHO, 1 h. (*d*) as for *b*, except reaction in $CH_2Cl_2$. (*e*) $H_2$ (15 bar), PhH, $(Ph_3P)_3RhCl$, 16 h. (*f*) conc. HCl, MeOH (1:10), –7 °C, 1.5 h. (*g*) 40% aq. HF, 4:1 MeCN:$H_2O$, 20 °C, 1 h.

In conclusion, the hemiacetal **6**, which contains the $C_{13}$–$C_{25}$ subunit of the macrolide bafilomycin $A_1$, has been synthesised in 11 steps and 22% overall yield starting from ketone (*S*)-**10**. Largely due to the efficiency of the key aldol coupling/hydrogenation sequence, **8** + **9** → **24** → **25**, a high level of stereocontrol is realised (73% overall ds for the introduction of 9 stereocentres).

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