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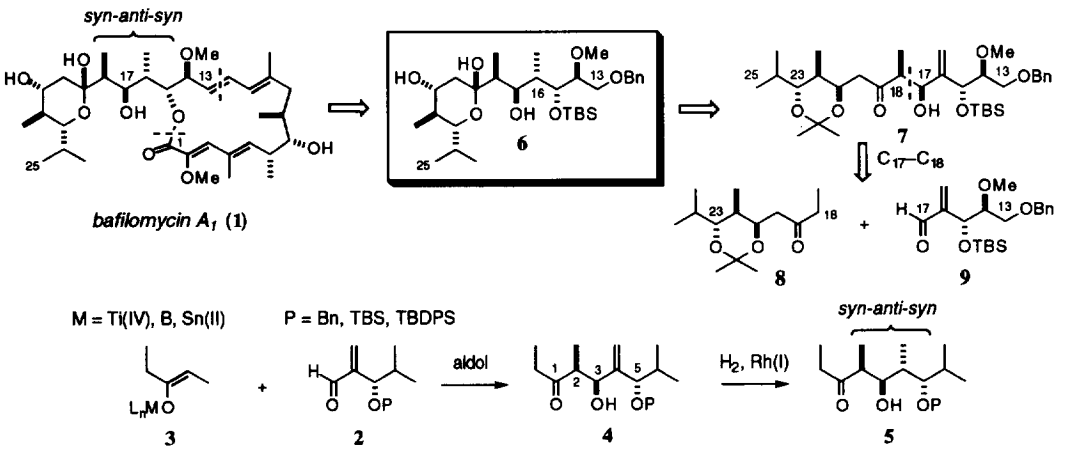
Abstract: A boron-mediated, *syn*-aldol coupling between ethyl ketone **8** and aldehyde **9**, followed by directed hydrogenation at C_{16} and acetonide hydrolysis, gives the C_{13}–C_{25} segment **6** of bafilomycin A_1.

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]

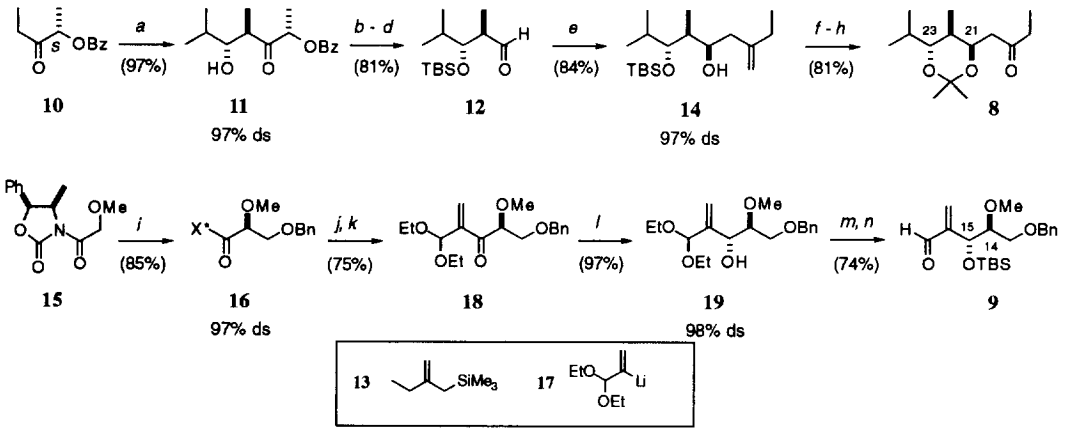


Scheme 1

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.

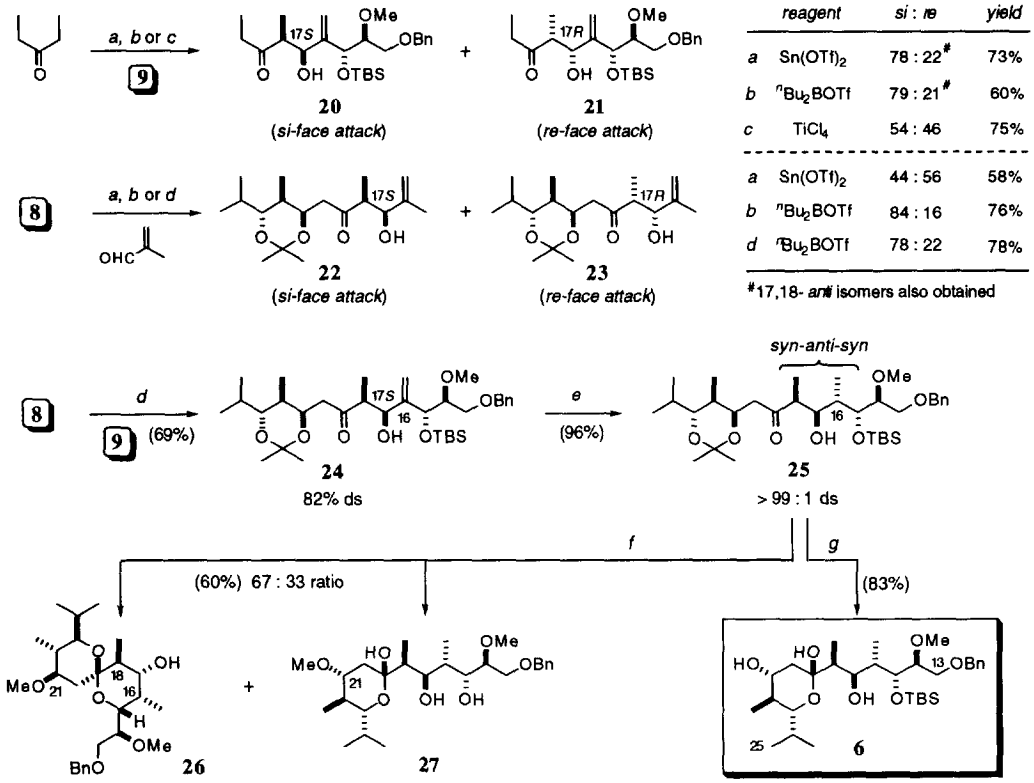
The synthesis of the coupling partners chosen for the critical C_{17}–C_{18} aldol connection is summarised in **Scheme 2**. Ketone **8**,[9] with acetonide protection across the C_{21} and C_{23} hydroxyls, was efficiently prepared using an *anti* aldol reaction between the (*S*)-lactate-derived ketone **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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9. All new compounds gave spectroscopic data in agreement with the assigned structures. Compound **6** had ^{1}H NMR δ(400 MHz, $CDCl_3$) 7.27 - 7.35 (5H, m, Ph), 5.00 (1H, d, J = 1.9 Hz, CHO$\underline{H}$), 4.57 (1H, d, J = 12.0 Hz, C$\underline{H}_A$H$_B$Ph), 4.52 (1H, m, H_{17}), 4.49 (1H, d, J = 12.0 Hz, CH$_A\underline{H}_B$Ph), 4.04 (1H, br d, CHO$\underline{H}$), 3.96 (1H, dd, J = 6.1, 2.6 Hz, H_{15}), 3.75 (1H, d, J = 8.2 Hz, H_{13A}), 3.68 (1H, ddd, J = 10.8, 9.9, 4.7 Hz, H_{21}), 3.43 - 3.56 (3H, m, H_{13B}, H_{14}, H_{23}), 3.42 (3H, s, OMe), 2.25 (1H, dd, J = 11.9, 4.7 Hz, H_{20A}), 1.93 (1H, m, H_{16}), 1.91 (1H, m, H_{24}), 1.61 (1H, m, H_{18}), 1.32 (1H, m, H_{22}), 1.16 (1H, dd [partially obscured], H_{20B}), 1.02 (3H, d, J = 6.8 Hz, C_{24}-Me$_A$), 0.94 (3H, d, J = 6.5 Hz, C_{22}-Me), 0.93 (3H, d, J = 7.1 Hz, C_{18}-Me), 0.86 (9H, s, Me_3CSi), 0.84 (3H, d, J = 7.0 Hz, C_{16}-Me), 0.82 (3H, d, J = 6.8 Hz, C_{24}-Me$_B$), 0.11 (3H, s, Me$_A$Si), 0.05 (3H, s, Me$_B$Si); HRMS (CI, NH_3) calc. for $C_{31}H_{57}O_7Si$ $(M + H)^+$ 569.38736 found 569.3870. Compound **26** had ^{1}H NMR δ(500 MHz, $CDCl_3$) 7.27 - 7.36 (5H, m, Ph), 4.60 (1H, d, J = 12.2 Hz, C$\underline{H}_A$H$_B$Ph), 4.48 (1H, d, J = 12.2 Hz, CH$_A\underline{H}_B$Ph), 3.98 (1H, dd, J = 9.5, 2.3 Hz, H_{15}), 3.87 (1H, dd, J = 10.5, 2.2 Hz, H_{13A}), 3.79 (1H, m, H_{17}), 3.53 (1H, dd, J = 10.5, 6.0 Hz, H_{13B}), 3.45 (3H, s, OMe), 3.40 (1H, obscured, H_{14}), 3.28 (3H, s, OMe), 3.07 (1H, m, H_{21}), 3.03 (1H, dd, J = 11.0, 2.2 Hz, H_{23}), 2.17 (1H, m, H_{16}), 2.05 (1H, dd, J = 15.1, 7.4 Hz, H_{20A}), 1.86 (1H, m, H_{22}), 1.77 (1H, dd, J = 15.1, 1.1 Hz, H_{20B}), 1.75 (1H, m, H_{24}), 1.54 (1H, m, H_{18}), 0.98 (3H, d, J = 6.8 Hz, C_{24}-Me$_A$), 0.93 (3H, d, J = 6.5 Hz, C_{18}-Me), 0.90 (3H, d, J = 6.9 Hz, C_{16}-Me), 0.89 (3H, d, J = 6.7 Hz, C_{22}-Me), 0.79 (3H, d, J = 6.8 Hz, C_{24}-Me$_B$); HRMS (CI, NH_3) calc. for $C_{26}H_{46}O_6N$ $(M + NH_4)^+$ 468.33251 found 468.3325.
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17. The use of ketone **8**, having PMB and silyl ether protecting groups at C_{21} and C_{23}, in analogous Ti-, Sn(II)- and B-mediated aldol reactions with methacrolein led to reduced selectivity for the 17,18-*syn*-18,21-*syn* isomer corresponding to **22** (significant amounts of 17,18-*anti* isomers were also formed). These findings are also in agreement with those of Evans (ref. 6), where cyclic protection at C_{21} and C_{23} (using a di-*t*-butylsilylene group) was required for a high level of aldol stereocontrol.
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