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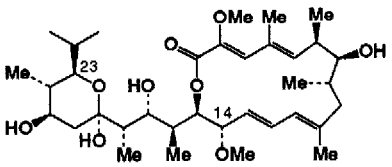
# Stereoselective Synthesis of the C(13)-C(25) Segment of Bafilomycin A1

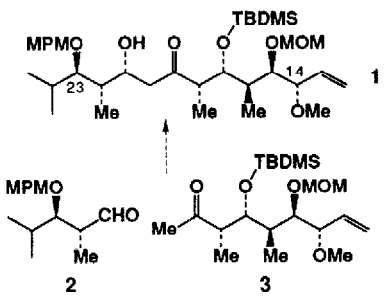
William R Roush* and Thomas D. Bannister
Department of Chemistry, Indiana University, Bloomington, IN 47405

*Abstract.* The aldol reaction of **2** and the lithium enolate of **3** provides the bafilomycin C(13)-C(25) fragment **1** with 8 · 1 stereoselectivity.

Bafilomycin $A_1$, a member of the hygrolide family of macrolide antibiotics,[1,2] is a potent, relatively specific membrane ATPase inhibitor that displays broad spectrum antibacterial and antifungal activity, and also has been reported to have immunosuppressive activity.[3] The stereochemistry of bafilomycin $A_1$, assigned originally by Corey on the basis of NMR data and molecular modelling studies,[2] has been verified by X-ray crystallography [4] To the best of our knowledge, no reports have yet appeared concerning the synthesis of bafilomycin or any of the structurally related hygrolides [5]



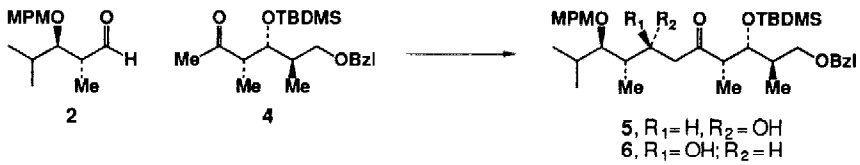

bafilomycin $A_1$



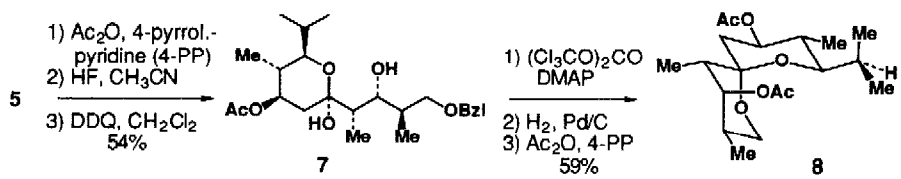

Our synthetic strategy focused on the aldol coupling of **2** and **3** for construction of the C(13)-C(25) fragment **1**. While highly diastereo- and enantioselective aldol reactions have been used in many natural products syntheses,[6] the coupling of **2** and **3** is complicated by the fact that both components are chiral. Consequently, the stereochemical outcome will depend on the intrinsic diastereofacial preference of each.[7] The literature reveals examples of fragment assembly[8] steps that proceed with excellent diastereoselectivity, in which the intrinsic diastereofacial preferences of the two components appear to be matched,[8,9] but also others in which stereoselectivity is poor possibly due to the dissonant pairing of diastereofacial preferences.[3,10] At the outset of these investigations, it was not possible to predict the success of this coupling, since information concerning the diastereofacial selectivity of enolates of chiral methyl ketones like **3** was not available.[11,12] We are pleased to report, therefore, that the aldol reaction of **2** and the lithium enolate of **3** provides the bafilomycin C(13)-C(25) fragment **1** with 8 · 1 selectivity. However, diastereoselectivity in this reaction is strikingly dependent on the type of enolate employed, as well as on the nature of the C(15)-alkoxy substituent.

We began by examining the aldol reaction of **2**[13] and the readily available model methyl ketone **4**.[14] The lithium enolate of **4**, prepared by treatment of **4** with $LiN(TMS)_2$ in THF at -78°C, underwent a highly diastereoselective reaction with **2** under kinetically controlled conditions (THF, -78°C, 30 sec before $NH_4Cl$ quench), providing a 10 . 1 mixture of the desired 21(R)-aldol **5** and its epimer **6** in 90% yield.[15] The

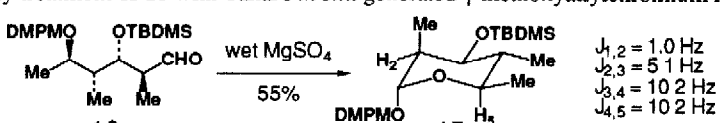
stereochemistry of **5** was confirmed by several techniques, including the conversion to spiro acetal **8** which permitted the complete assignment of all stereocenters via $^1$H NMR J analysis and NOE studies. Interestingly, the stereoselectivity of the aldol coupling of **2** and **4** was highly dependent on the reaction conditions, as experiments performed using the sodium enolate or the lithium enolate in a THF-HMPA mixture provided roughly 1 : 1 mixtures of the two aldols. Stereoselectivity was also poor in the dibutylboron enolate mediated aldol reaction (a 1.2 · 1 mixture of **5** and **6**) In addition, attempts to improve the stereoselectivity via the triple asymmetric synthesis ploy,[8] using the boron enolate generated from **4** and (-)-Ipc$_2$BOTf,[11d] provided the unwanted 21(S)-aldol **6** as the major component of a 2 · 1 mixture.

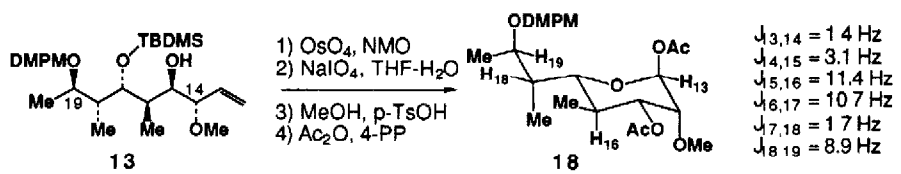


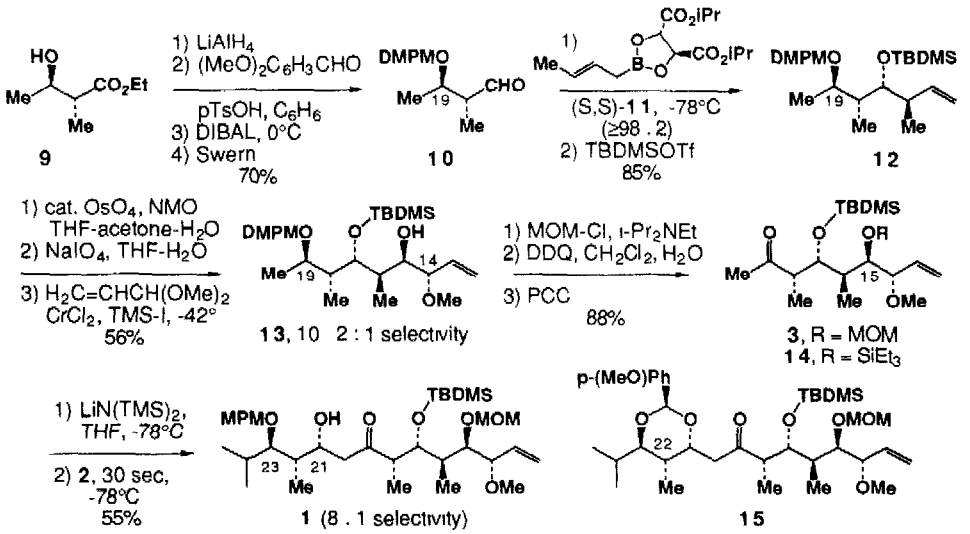

| Conditions | Yield | Selectivity (5 : 6) |
|---|---|---|
| $LiN(TMS)_2$, THF, -78°C, 30 sec | 90% | 10 : 1 |
| $LiN(TMS)_2$, THF-HMPA, -78°C, 30 sec | 66% | 1 . 1.2 |
| $NaN(TMS)_2$, THF, -78°C, 30 sec | 51% | 1 : 1 |
| $Bu_2BOTf$, $Et_3N$, $CH_2Cl_2$, -40°C | 65% | 1.2 : 1 |
| (-)-$Ipc_2BOTf$, $Et_3N$, $CH_2Cl_2$ -40°C | 72% | 1 . 2 |
| (+)-$Ipc_2BOTf$, $Et_3N$, $CH_2Cl_2$, -40°C | -- | *No Reaction* |




Encouraged by these results, we turned to the synthesis of **3**. β-Hydroxy-α-methylbutyrate **9**, readily available with 20 : 1 stereoselectivity via the alkylation of ethyl (R)-β-hydroxybutyrate,[16] was smoothly elaborated to aldehyde **10** by a sequence involving the DIBAL reduction of an intermediate 3,4-dimethoxybenzylidene acetal.[17] The reaction of **10** and (S,S)-tartrate modified (E)-crotylboronate **11** provided, after hydroxyl protection, TBDMS ether **12** with ≥98 : 2 selectivity (only one isomer detected) [18] The stereochemistry of **12** was verified by the accidental conversion of the derived aldehyde **16** to the pyranose **17** upon exposure to wet $MgSO_4$. The C(14) and C(15) stereocenters were then introduced with 10 : 2 : 1 selectivity treatment of **16** with Takai's *in situ* generated γ-methoxyallylchromium reagent.[19]






The stereochemistry of the major diastereomer **13**, isolated chromatographically in 67% yield, was verified by conversion to pyranose **18**.

Homoallylic alcohol **13** was then protected as a MOM ether (MOM-Cl, i-$Pr_2NEt$ as solvent, 50°C), the 3,4-dimethoxybenzyl ether was removed[20] and the resultant alcohol oxidized with PCC to provide methyl ketone **3** in 88% overall yield. The lithium enolate generated from **3** in THF at -78°C was then treated with aldehyde **2** to give an 8 : 1 mixture of the desired aldol **1** and its 21(S)-diastereomer. Finally, the C(21)-C(23) anti relationship of **1** was verified by DDQ oxidation ($CH_2Cl_2$, 4Å sieves)[20] to p-methoxybenzylidene acetal **15**, that showed a doublet of doublets (J = 10.1 and 5.4 Hz) for H(22) in the $^1H$ NMR spectrum.

We conclude by noting that while the aldol reaction of **2** and **3** proceeds with synthetically useful levels of diastereoselection, the stereochemical course is surprisingly dependent on the protecting group of the remote C(15)-alkoxy group: the aldol reaction of **2** and the lithium enolate [$LiN(TMS)_2$, THF, 90 sec reaction with **2**] of **14**, which has a C(13) triethylsilyl ether, provided a 55 : 45 mixture of the two aldols (72% yield). This unexpected observation, along with further progress towards the completion of a total synthesis of bafilomycin $A_1$, will be the topics of subsequent reports from our laboratory.

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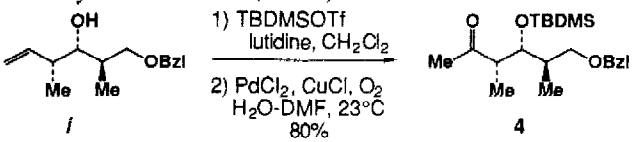
13. (a) The synthesis of aldehyde **2** will be reported in our full paper. (b) The intrinsic diastereofacial selectivity of **2** was established in aldol reactions with isopropyl methyl ketone The reaction with the lithium enolate [LiN(TMS)$_2$] in THF at -42°C provided a 3 : 1 mixture favoring the Felkin diastereomer while the boron enolate generated with $Bu_2BOTf$ and $Et_3N$ in $CH_2Cl_2$ provided the same mixture but with only 1.4 : 1 selectivity.
14 Methyl ketone **4** was synthesized from ***i*** (ref. 18) as shown below




*i* **4**

15. All new compounds were fully characterized by high field $^1$H NMR, IR, and mass spectroscopy. In addition, satisfactory C,H combustion analyses (±0.4%) were obtained for **1**, **3**, **4**, **5**, **6**, **8**, the primary alcohol precursor to **10**, **12-14**, and **17**
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