Studies on the Synthesis of Bafilomycin A_1: Stereochemical Aspects of the Fragment Assembly Aldol Reaction for Construction of the C(13)−C(25) Segment

William R. Roush,*[,1] Thomas D. Bannister,[2] Michael D. Wendt,[2] Jill A. Jablonowski,[2] and Karl A. Scheidt[3]

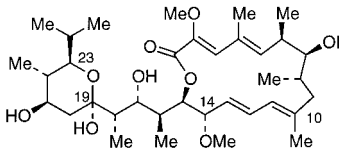
Departments of Chemistry, Indiana University, Bloomington, Indiana 47405, and University of Michigan, Ann Arbor, Michigan 48109

roush@umich.edu

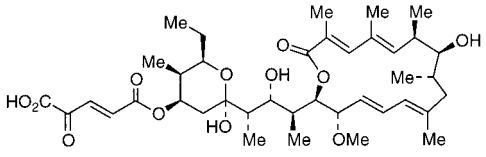
Received December 28, 2001

Highly stereoselective syntheses of aldols **8a**−**c** corresponding to the C(13)−C(25) segment of bafilomycin A_1 were developed by routes involving fragment assembly aldol reactions of chiral aldehyde **6a** and the chiral methyl ketones **7.** A remote chelation effect plays a critical role in determining the stereoselectivity of the key aldol coupling of **6a** and the lithium enolate of **7b**. The protecting group for C(23)−OH of the chiral aldehyde fragment also influences the selectivity of the lithium enolate aldol reaction. In contrast, the aldol reaction of **6a** and the chlorotitanium enolates of **7a,c** were much less sensitive to the nature of the C(15)-hydroxyl protecting group. Studies of the reactions of chiral aldehydes with Takai's (γ-methoxyallyl)chromium reagent **40** are also described. The stereoselectivity of these reactions is also highly dependent on the protecting groups and stereochemistry of the chiral aldehyde substrates.

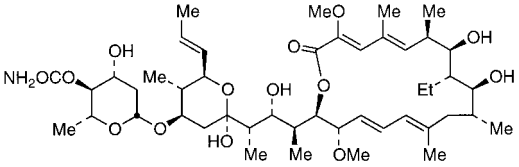
Bafilomycin A_1 (**1**),[4] a member of the hygrolide family of macrolide antibiotics,[5] is a potent vacuolar H^+-ATPase inhibitor that displays broad antibacterial and antifungal activity.[6] The stereochemistry of bafilomycin A_1, and of the hydrolide family in general, was initially assigned by Corey on the basis of a molecular modeling analysis of published NMR data.[5] The stereostructural assignment of **1** was subsequently verified by X-ray crystallography.[7,8] Other members of this family include the hygrolidins (e.g., hygrolidin, **2**), which are active against SV-40 transformed C-3H-2K cells,[9,10] leucanicidin, which has antifungal and insecticidal activity,[11] L-681,110A_1, an inhibitor of Na^+/K^+-ATPase,[12] and L-155,175, which has antiparasitic activity.[13] The concanamycins (e.g., concanomycin A, **3**), are 18-membered lactone congeners which also are potent vacuolar H^+-ATPase inhibitors.[14] The newest member of this family is formamicin, **4**, which displays significant cytotoxicity against murine tumor cell lines in vitro, particularly leukemia cells.[15,16]



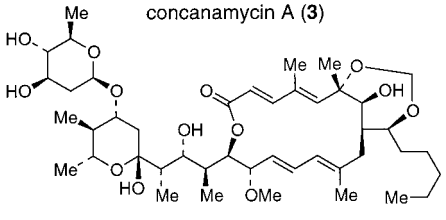
bafilomycin A_1 (**1**)



hygrolidin (**2**)



concanamycin A (**3**)



formamicin (**4**)

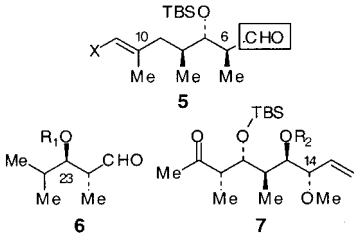
The interesting biological activity of this group of compounds has stimulated interest both in the semisynthesis of analogues,[17−19] as well as the chemical synthesis

(1) Address correspondence to this author at the Department of Chemistry, University of Michigan, Ann Arbor, MI 48109-1055.
(2) Indiana University.
(3) University of Michigan.
(4) Werner, G.; Hagenmaier, H.; Drautz, H.; Baumgartner, A.; Zähner, H. *J. Antibiot.* **1984**, *37*, 110.
(5) Corey, E. J.; Ponder, J. W. *Tetrahedron Lett.* **1984**, *25*, 4325.
(6) Bowman, E. J.; Siebers, A.; Altendorf, K. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7972.
(7) Baker, G. H.; Brown, P. J.; Dorgan, R. J. J.; Everett, J. R.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1987**, *28*, 5565.
(8) Baker, G. H.; Brown, P. J.; Dorgan, R. J. J.; Everett, J. R. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1073 and references therein.
(9) Seto, H.; Tajima, I.; Akao, H.; Furihata, K.; Otake, N. *J. Antibiot.* **1984**, *37*, 610.
(10) Seto, H.; Akao, H.; Furihata, K.; Otake, N. *Tetrahedron Lett.* **1982**, *23*, 2667.
(11) Isogai, A.; Sakuda, S.; Matsumoto, S.; Ogura, M.; Furihata, K.; Seto, H.; Suzuki, A. *Agric. Biol. Chem.* **1984**, *48*, 1379.
(12) Hensens, O. D.; Monaghan, R. L.; Huang, L. Y.; Albers-Schönberg, G. *J. Am. Chem. Soc.* **1983**, *105*, 3672.
(13) Goetz, M. A.; McCormick, P. A.; Monaghan, R. L.; Ostlind, D. A.; Hensens, O. D.; Liesch, J. M.; Albers-Schönberg, G. *J. Antibiot.* **1985**, *38*, 161.
(14) Kinashi, H.; Someno, K.; Sakaguchi, K.; Higashijima, T.; Miyazawa, T. *Tetrahedron Lett.* **1981**, *22*, 3861.

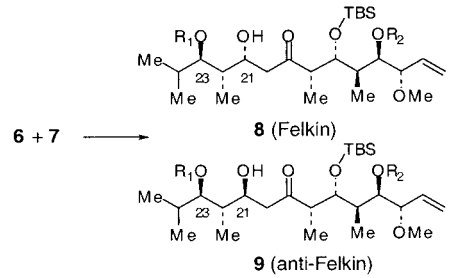
10.1021/jo016413f CCC: $22.00
Published on Web 05/21/2002

of the natural products themselves. Total syntheses of bafilomycin A_1 have been recorded by Evans,[20] Toshima,[21−23] Hanessian,[24] and also our laboratory.[25,26] Several other studies on the synthesis of the bafilomycin have been reported,[27,28] including a very recent total synthesis of bafilomycin V_1 by Marshall and co-workers.[29] A total synthesis of hygrolidin has been accomplished by Yonemitsu,[30,31] and total syntheses of concanamicin F (the aglycone of concanamicin A) have been recorded by both the Toshima and Paterson groups.[32,33] We report here the details of our synthesis of the C(13)−C(25) segment of **1** via a fragment assembly aldol sequence, preliminary accounts of which have been reported previously.[34,35] These studies strongly influenced the evolution of the strategy for our ultimately successful bafilomycin total synthesis.[25,26]

From the outset, our strategy for the synthesis of bafilomycin A_1 focused on the assembly of three key fragments: stereotriad **5**, corresponding to the C(5)−C(11) segment of the natural product; aldehyde **6**, the C(21)−C(25) fragment; methyl ketone **7**, the C(13)−C(20) unit. We anticipated that the C(10)−C(14) diene unit spanning fragments **5** and **7** could be introduced by a Wittig- or Horner-type olefination sequence, or via a Pd(0) mediated cross coupling reaction, and that a diastereoselective aldol reaction would be used in the union of the chiral methyl ketone (deriving from fragment **7**) with the chiral aldehyde **6**. However, it was not obvious at the outset what the preferred order of fragment coupling would be, nor was it apparent what the stereochemical control opportunities would be for the proposed aldol coupling of fragments **6** and **7**.



The aldol reaction has been studied extensively during the past decade, and numerous applications of this process have now been recorded in the synthesis of natural (and unnatural) products.[36] However, in 1989 when our studies on this problem were initated, relatively little information was available that would allow us to predict with confidence the outcome of the proposed aldol coupling. Because both fragments **6** and **7** are chiral, we expected that the stereochemical course of this reaction would depend on the intrinsic diastereofacial preference of each.[37] While it was reasonable to expect that the aldehyde fragment would favor production of the desired C(21,22)-syn diastereomer **8** by application of the Felkin−Anh paradigm,[38−41] assuming that the reaction did not proceed by way of a chelate-controlled pathway,[42] less certain was the diastereofacial selectivity preference of the chiral methyl ketone fragment **7**.[43−48] Although a considerable body of information existed concerning aldol reactions of chiral ethyl ketone enolates, there were indications that the diastereofacial selectivity of chiral ethyl ketone enolates is dependent on the metal counterion.[49−52] Moreover, evidence also existed that aldol reactions of methyl ketone enolates are often less diastereofacial selective than the corresponding ethyl ketone enolates.[36f] Accordingly, we decided to address the stereochemistry of the proposed aldol coupling as the first step in the development of our strategy for the total synthesis of bafilomycin A_1.

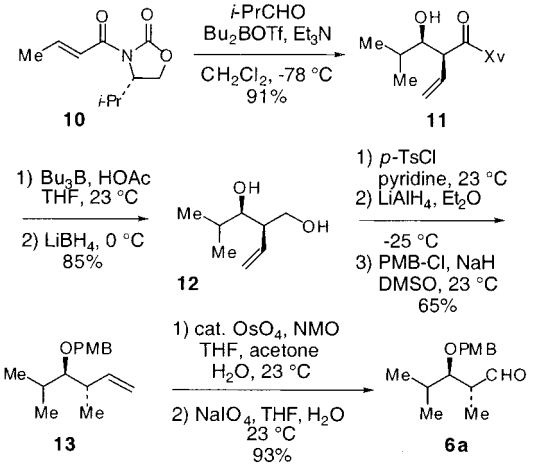


The results of this study, preliminary accounts of which were published in 1992 and 1993,[34,35] served to define the protecting groups that would be used for the R_1 and R_2 positions of **6** and **7**, as well as the preferred order of

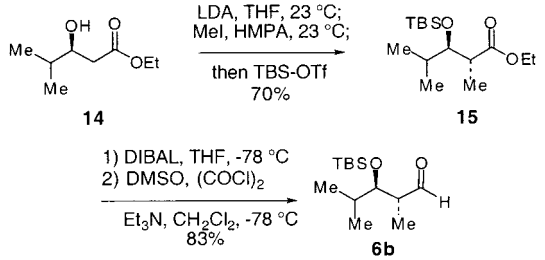
(15) Igarashi, M.; Kinoshita, N.; Ikeda, T.; Nakagawa, E.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 926.
(16) Igarashi, M.; Nakamura, H.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 932.
(17) Hanessian, S.; Tehim, A.; Meng, Q. C.; Grandberg, K. *Tetrahedron Lett.* **1996**, *37*, 9001.
(18) Gatti, P. A.; Gagliardi, S.; Cerri, A.; Visconti, M.; Farina, C. *J. Org. Chem.* **1996**, *61*, 7185.
(19) Gagliardi, S.; Gatti, P. A.; Belfiore, P.; Zocchetti, A.; Clarke, G. D.; Farina, C. *J. Med. Chem.* **1998**, *41*, 1883.
(20) Evans, D. A.; Calter, M. A. *Tetrahedron Lett.* **1993**, *34*, 6871.
(21) Toshima, K.; Jyojima, T.; Yamaguchi, H.; Murase, H.; Yoshida, T.; Matsumura, S.; Nakata, M. *Tetrahedron Lett.* **1996**, *37*, 1069.
(22) Toshima, K.; Yamaguchi, H.; Jyojima, T.; Noguchi, Y.; Nakata, M.; Matsumura, S. *Tetrahedron Lett.* **1996**, *37*, 1073.
(23) Toshima, K.; Jyojima, T.; Yamaguchi, H.; Noguchi, Y.; Yoshida, T.; Murase, H.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1997**, *62*, 3271.
(24) Hanessian, S.; Ma, J.; Wang, W.; Gai, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10200.
(25) Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed.* **1999**, *38*, 1652.
(26) Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, in press.
(27) Paterson, I.; Bower, S.; McLeod, M. D. *Tetrahedron Lett.* **1995**, *36*, 175.
(28) Marshall, J. A.; Adams, N. D. *Org. Lett.* **2000**, *2*, 2897.
(29) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **2002**, *67*, 733.
(30) Makino, K.; Kimura, K.; Nakajima, N.; Hashimoto, S.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 9073.
(31) Makino, K.; Nakajima, N.; Hashimoto, S.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 9077.
(32) Jyojima, T.; Miyamoto, N.; Katohno, M.; Nakata, M.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **1998**, *39*, 6007.
(33) Paterson, I.; Doughty, V. A.; McLeod, M. D.; Trieselmann, T. *Angew. Chem., Int.* **2000**, *39*, 1308.
(34) Roush, W. R.; Bannister, T. D. *Tetrahedron Lett.* **1992**, *33*, 3587.
(35) Roush, W. R.; Bannister, T. D.; Wendt, M. D. *Tetrahedron Lett.* **1993**, *34*, 8387.
(36) Reviews of the aldol reaction: (a) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. (b) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317. (c) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: New York, 1991; Vol. 2, p 181. (d) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: New York, 1991; Vol. 2, p 239. (e) Paterson, I. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: New York, 1991; Vol. 2, p 301. (f) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24. (g) Heathcock, C. H. *Asymmetric Synth.* **1984**, *3*, 111. (h) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.
(37) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(38) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.
(39) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.
(40) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.
(41) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.
(42) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

coupling of fragments **5**−**7** in the ultimately successful total synthesis.[25] Stereochemical studies of aldol reactions of chiral methyl ketone[20,53−58] and ethyl ketone metal enolates[58−60] subsequently published from several laboratories, including our own,[53−55,59] have now defined a significant number of the stereochemical features of fragment assembly aldol reactions that can be used for predictive purposes in designing efficient syntheses of complex target molecules.

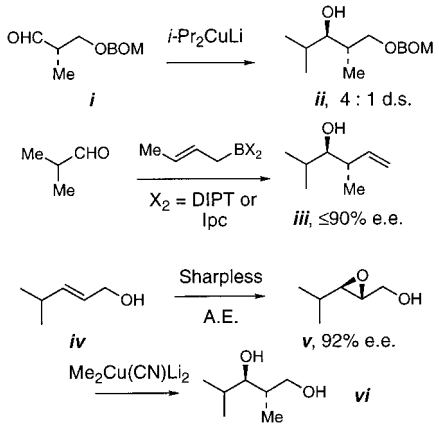
Synthesis of Aldehyde 6. Because the stereochemistry (and the stereoselectivity) of the fragment assembly aldol coupling of **6** and **7** would depend on the diastereofacial preferences of each component,[37] it was necessary that both fragments be synthesized with high enantiomeric purity. After several inital routes were rejected owing to poor diastereo- and/or enantioselectivity,[61,62] our first workable synthesis of **6** was developed on the basis of an Evans' asymmetric aldol reaction of chiral crotonate imide **10**.[63] Thus, asymmetric aldol reaction of **10** with isobutyraldehyde provided syn aldol **11** in 91% yield as the only observed isomer. Reduction of the borate ester regenerated from **11** with $LiBH_4$ produced diol **12** in 85% yield. Tosylation of the primary hydroxyl group under standard conditions followed by reduction of the tosylate using $LiAlH_4$ in Et_2O and then protection of the secondary alcohol as a *p*-methoxybenzyl (PMB) ether[64] gave **13** in 65% overall yield. Oxidative cleavage[65] of the vinyl group then completed the synthesis of aldehyde **6a**.



Ultimately, the preferred method for synthesis of 2,3-anti aldehyde **6** originated from from *β*-hydroxy ester **14**, which is easily prepared by enantioselective reduction of ethyl isobutyrylacetate.[66] Fráter anti alkylation[67] of the lithium enolate of **14** with MeI followed by in situ silylation of the alkoxide with TBS−OTf provide ester **15** in 70% yield with >95:5 diastereoselectivity. Reduction of the ester to the primary alcohol with DIBAL-H and subsequent Swern oxidation[68] of the alcohol afforded aldehyde **6b** in 83% overall yield.

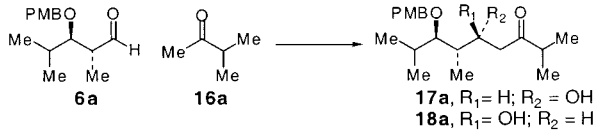


Aldol Reactions of 6: Initial Studies. The aldol reaction of **6a** and isopropyl methyl ketone (**16a**) was

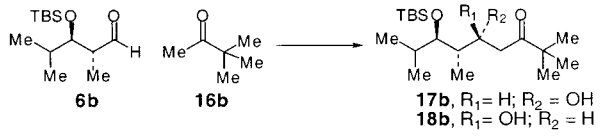


(43) Seebach, D.; Chow, H. F.; Jackson, R. F. W.; Lawson, K.; Sutter, M. A.; Thaisrivongs, S.; Zimmermann, J. *J. Am. Chem. Soc.* **1985**, *107*, 5292.
(44) Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357.
(45) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997.
(46) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.
(47) Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982.
(48) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129.
(49) McCarthy, P. A.; Kageyama, M. *J. Org. Chem.* **1987**, *52*, 4681.
(50) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866.
(51) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.
(52) Martin, S. F.; Lee, W.-C. *Tetrahedron Lett.* **1993**, *34*, 2711.
(53) Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3443.
(54) Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95.
(55) Roush, W. R.; Dilley, G. J. *Tetrahedron Lett.* **1999**, *40*, 4955.
(56) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537.
(57) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585.
(58) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
(59) Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3447.
(60) Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1996**, *37*, 1957.
(61) Bannister, T. D. Ph.D. Thesis, Indiana University, 1991.
(62) (a) One route to **6** based on the addition of diisopropylcuprate to *β*-alkoxy aldehyde **i** was abandoned since the key carbonyl addition step proceeded with only 4:1 diastereoselectivity (cf.: Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035). (b) A second route based on the asymmetric (*E*)-crotylboration of isobutyraldehyde was abandoned since the volatile homoallylic alcohol **iii** was obtained with ≤90% ee (Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339. Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919). (c) A third route to **6** involving the Sharpless asymmetric epoxidation of **iv** also was abandoned as epoxy alcohol **v** was obtained with only 92% ee (Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1). (d) A route involving the Heathcock−Evans anti aldol reaction of isobutyraldehyde and the L-valine-derived acyloxazolidinone was also discarded, as in our hands the desired anti aldol (corresponding to **15**) was obtained with only 4:1 diastereoselectivity and in moderate yield (cf.: Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747).
(63) Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957.
(64) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
(65) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(66) Genêt, J. P.; Ratovelomanana-Vidal, V.; Caño de Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, *36*, 4801 and references therein.
(67) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269.
(68) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.

examined to assess the diastereofacial preference of the chiral aldehyde. Treatment of the lithium enolate of **16a**, generated by using $LiN(TMS)_2$ in THF, with **6a** for 1 min[21] at −78 °C provided a 3:1 mixture of diastereomeric aldols **17a**, **18a** in 94% yield. The stereochemistry of each aldol was verified by treatment with 1.0 equiv of DDQ, which effected oxidative cyclization to the corresponding *p*-methoxybenzylidene acetals, the stereostructures of which were easily confirmed by ^1H NMR analysis (see Supporting Information).[69] The aldol reaction of **6a** and **16a** was less selective (1.4:1 in favor of **17a**) by using the boron enolate generated by treatment of **16a** with Bu_2BOTf and Et_3N but improved to 4.2:1 by using the chiral boron enolate prepared from **16a** and (−)-Ipc_2BOTf according to Paterson's protocol.[46] The aldol reactions of aldehyde **6b** and the lithium and dibutylboron enolates of pinacalone (**16b**) were also examined and were found to be less selective than the corresponding reactions of **6a**. Comparable results for the aldol reactions of **6a,b** have been reported by Evans.[58]



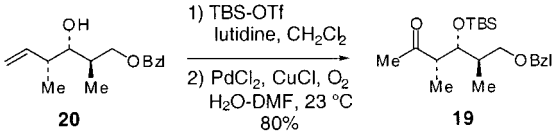
Conditions	Yield	17 : 18
$LiN(TMS)_2$, THF, -78 °C, 1 min	94%	3 : 1
Bu_2BOTf, Et_3N, CH_2Cl_2, -40 °C	82%	1.4 : 1
(-)-Ipc_2BOTf, Et_3N, CH_2Cl_2, -40 °C	51%	4.2 : 1



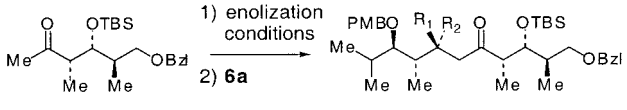
Conditions	17 : 18
$LiN(TMS)_2$, THF, -78 °C, 1 min	2 : 1
Bu_2BOTf, Et_3N, CH_2Cl_2, -40 °C	1 : 1.2

These studies showed that the intrinsic diastereofacial preference of **6a,b** favors the naturally occurring C(21) bafilomycin stereochemistry, when the aldol reaction is performed with a lithium enolate. Because the selectivity of the aldol reactions was modestly better using **6a** with a PMB protecting group rather than **6b** with a TBS ether, we concentrated on **6a** in the studies which follow.

The aldol reaction of **6a** and the model chiral methyl ketone **19** was next examined. Methyl ketone **19** was synthesized from the readily available homoallylic alcohol **20**[70] by protection of the hydroxyl group as a TBS ether and Wacker oxidation[71] of the vinyl group.

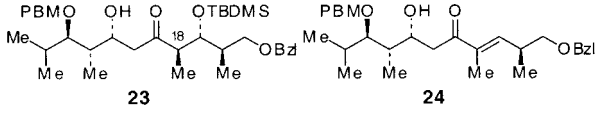


The lithium enolate of **19** underwent a highly diastereoselective reaction with **6a** under kinetically controlled conditions (THF, −78 °C, 30 s before NH_4Cl quench). Under these conditions, the desired aldol **21** predominated over diastereomer **22** by a ratio of 10:1. Interestingly, the stereoselectivity of the aldol coupling of **6a** and **19** was dependent on the reaction conditions. When the lithium enolate of **19** was treated with **6a** for a longer time (30 min) at −78 °C or at higher temperatures (−40 °C, 5 min), substantial amounts of the C(18)-epimer **23** (up to 50% of **23**) and enone **24** (from the −40 °C experiment only) were also obtained. These products presumably arise by intramolecular abstraction of the C(18)−H by the intermediate C(21) lithium alkoxide. Moreover, if the lithium enolate aldol reaction was performed in the presence of HMPA, selectivity dropped to 1:1.2 with the undesired epimer **22** predominating. Use of the sodium enolate and the dibutylboron enolate generated from **19** each gave ca. 1:1 mixtures of the two aldols. Attempts to improve the stereoselectivity of the boron aldol reaction via triple asymmetric synthesis,[44] by using the boron enolate generated from **6a** and (−)-Ipc_2BOTf,[46] were also unsuccessful, as this experiment provided the unwanted aldol **22** as the major component of a 2:1 mixture. No reaction was observed in attempts to couple **19** and **6a** using enol borane intermediate from **19** and the enantiomeric (+)-Ipc_2BOTf.



Conditions	Yield	Selectivity (21 : 22)
$LiN(TMS)_2$, THF, -78 °C; (a)	90%	10 : 1
$LiN(TMS)_2$, THF-HMPA, -78 °C; (a)	66%	1 : 1.2
$NaN(TMS)_2$, THF, -78 °C; (a)	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*

(a) The reaction of the enolate and **6a** was quenched after 30 sec at -78 °C by addition of aq. NH_4Cl.



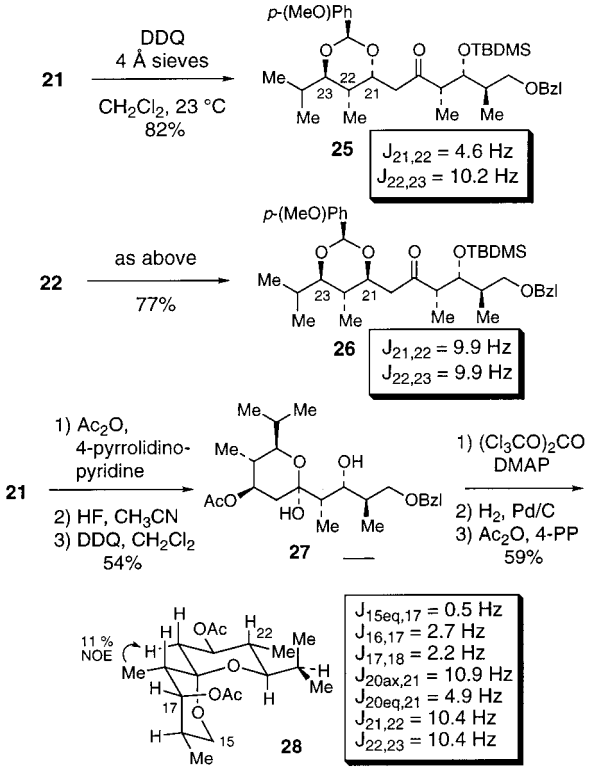
The stereochemistry of the new hydroxyl groups in **21** and **22** was assigned by conversion of each compound to the corresponding *p*-methoxybenzylidene acetals **25** and **26**. In view of concerns raised by the isolation of the C(18)-epimer **23**, the C(18) stereochemistry of **21** was assigned by conversion to the spiroketal **28**, the stereochemistry of which follows unambiguously from the ^1H NMR NOE and coupling constant (*J*) data that are shown. The stereochemical assignment of C(18) of **22** is more involved and is summarized in the Supporting Information.

The dependence of aldol stereoselectivity on reaction conditions and especially on the nature of the metal enolate was curious. (Subsequent studies from our laboratory have established that the dependence of aldol stereoselectivity on metal enolate is general for methyl ketone aldol reactions.[53−55,59]) To determine if the product distribution reflected kinetic or thermodynamic control, we treated aldol **22**, the minor product of the aldol reaction of **6a** and **19**, with 1.1 equiv of $LiN(TMS)_2$ in THF at −78 °C for 15 min and also with $Li(NTMS)_2$ in THF−HMPA at −78 °C for 15 min, to regenerate the lithium aldolate. Diastereomer **21** was not observed in

(69) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

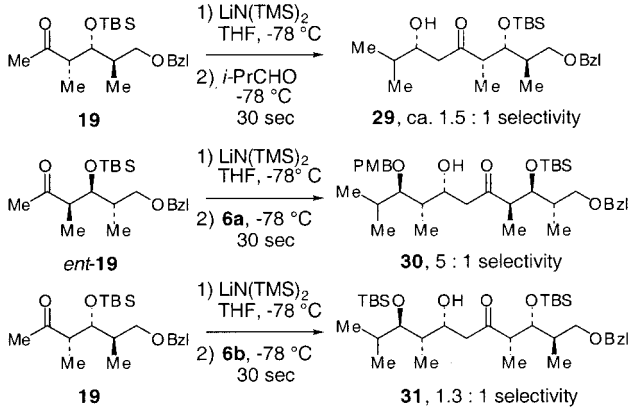
(70) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(71) Hegedus, L. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4; p 551.

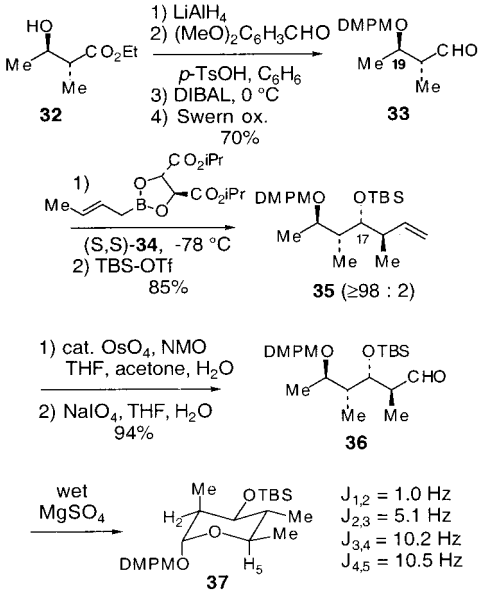


either case, indicating that the aldol reaction of **6a** and the lithium enolate of **19** is kinetically controlled under the conditions specified above.

To gain additional insight into the factors that control the stereoselectivity of the aldol reaction of **6a** and **19**, we examined the aldol coupling of **19** with isobutyraldehyde and also the reaction of **6a** and the enantiomeric methyl ketone, *ent*-**19**. The reaction of the lithium enolate of **19** and isobutyraldehyde provided a ca. 1.5:1 mixture of aldols, while the reaction of **6a** and *ent*-**19** gave a 5:1 mixture favoring aldol **30**. These results, in concert with the data presented previously for the reaction of aldehyde **6a** and methyl ketones **16** (3:1 ds favoring **17a)** and **19** (10:1 ds favoring **21**), indicate that Masamune's multiplicativity rule does not apply rigorously to these double asymmetric fragment assembly aldol reactions.[37] Although the stereochemistry of aldol **29** was not assigned rigorously, we have tentatively assigned the major distereomer as the 1,4-syn isomer depicted for **29** by application of the ^{1}H NMR analysis of the characteristic ABX pattern for the methylene α-to the ketone carbonyl.[72] This assignment indicates that the lithium enolate of **19** exhibits a *re*-diastereofacial preference, which in turn is consistent with the diminished selectivity observed in the aldol reaction of *ent*-**19** and **6a** (5:1), compared to the 10:1 selectivity for the reaction of **19** and **6a**. We believe that the lithium enolate of **19** and **6a** represents the matched case, while the combination of **6a** and *ent*-**19** represents the mismatched pair in these fragment assembly aldol reactions.[37] Because the selectivity of the reaction of **19** and isobutyraldehyde is very modest, it appears that the stereochemical course of these reactions is dominated by the diastereofacial preference of the chiral aldehyde component. This conclusion is reinforced by the observation that the aldol reaction of **19** and TBS-protected chiral aldehyde **6b** (which is less diastereofacial selective than **6a** in reactions with achiral methyl ketone enolates; vide supra) is virtually nonselective.[73]

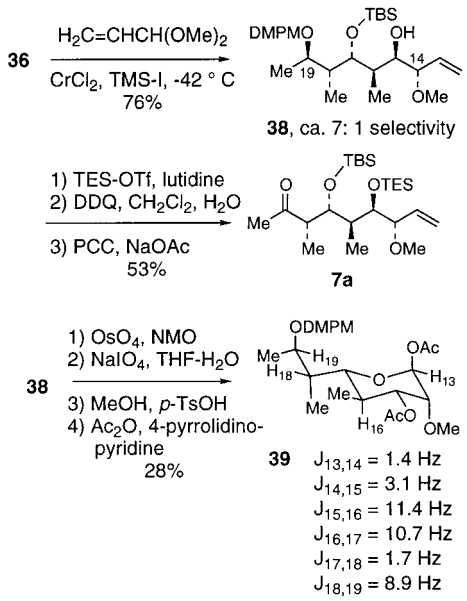


Synthesis of Chiral Methyl Ketone 7. The excellent stereoselectivity of the aldol reaction of **6a** and the lithium enolate of **19** encouraged us to proceed with the synthesis of the originally targeted methyl ketone **7**. We elected to synthesize **7a** with the C(15)-hydroxyl protected as a triethylsilyl (TES) ether, in anticipation that this protecting group would be suitable for use in the total synthesis. The synthesis of **7a** began with ethyl β-hydroxy-α-methylbutyrate **32**, which we prepared with 20:1 stereoselectivity via the Frater−Seebach alkylation of ethyl (*R*)-β-hydroxybutyrate.[67] Aldehyde **33** was prepared from **32** by a four-step sequence involving DIBAL reduction of an intermediate 3,4-dimethoxybenzylidene acetal.[74,75] Treatment of aldehyde **33** with the diisopropyl (*S,S*)-tartrate modified (*E*)-crotylboronate **34**[76] in toluene at −78 °C in the presence of activated 4 Å molecular sieves provided a single homoallylic alcohol (via a matched double asymmetric transformation)[70] with ≥98:2 selectivity by ^{1}H NMR analysis. Protection of the C(17) hydroxyl as a TBS ether then provided **35** in 85% yield for the two steps. The stereochemistry of **35** was verified by the accidental conversion of the derived aldehyde **36** to the pyranose **37** upon exposure to wet $MgSO_4$.

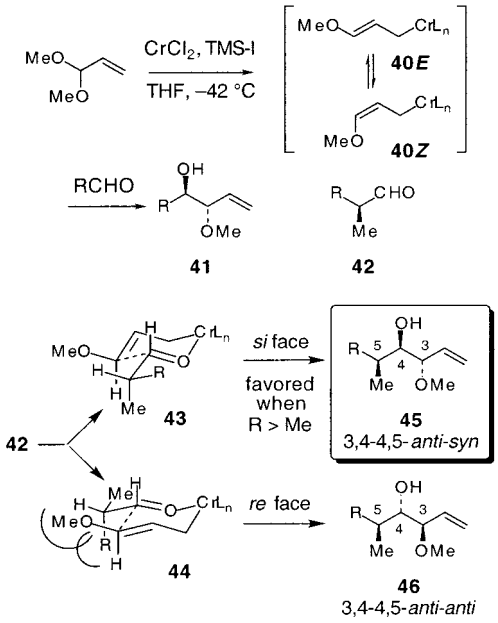


(72) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; VanNieuwehnze, M. S.; Gustin, D. J.; Dilley, G. D.; Lane, G. D.; Scheidt, K. A.; Smith, W. J. *J. Org. Chem.* **2002**, *67*, 4284.

We were now ready to introduce the C(14) and C(15) stereocenters of the targeted methyl ketone **7a**. Hoffmann had developed an (*E*)-(γ-methoxyallyl)boronate reagent that in principle could be used for the present purposes.[77] However, in view of the difficulties associated with the synthesis of Hoffmann's (*E*)-(γ-methoxyally)lboronate, we elected to explore use of Takai's (γ-methoxyallyl)chromium reagent which is generated in situ from acrolein dimethyl acetal, TMS−I, and $CrCl_2$.[78] We were delighted to find that subjecting aldehyde **36** to Takai's reaction conditions provided homoallylic alcohol **38** with ca. 7:1 selectivity; the isolated yield of **38** was 76%. Multiple gram quantities (>10 g) of allyl methyl ether **38** were synthesized by using this procedure. The stereochemistry of **38** was assigned by conversion to the pyranose derivative **39**, which exhibited $J_{14,15} = 3.1$ Hz and $J_{15,16} = 11.4$ Hz in the ^{1}H NMR spectrum. These data are unambiguously consistent with the 14,15-anti-15,16-syn stereochemical relationship in **38**. Finally, the synthesis of **7a** was completed by protection of C(15)−OH as a TES ether, DDQ oxidative deprotection of the DMPM ether,[64] and PCC oxidation of the resulting C(19)−OH.



The Takai methoxyallylation protocol is mechanistically related to the reactions of the Hiyama−Nozaki crotylchromium reagent with aldehydes[79,80] in which chairlike transition states similar to **43** and **44** are thought to be involved.[81] It is known that substituted allylchromium reagents equilibrate between (*E*) and (*Z*) isomers at rates faster than carbonyl addition and that the (*E*) isomer (cf. **40***E*) is more reactive than the (*Z*)-isomer.[81] Application of the Felkin−Anh model for nucleophilic addition to α-methyl chiral aldehydes,[38,39] or our "gauche pentane" model of asymmetric induction,[41,70,81] leads to the prediction that transition state **43** should be favored in reactions of the (methoxyallyl)-chromium reagent **40***E* with chiral aldehydes **42**. Takai, however, favors a mechanism involving the intermediacy of an internally chelated (*Z*)-(methoxyallyl)chromium species, which would require that the major product **45** be produced through a boatlike transition state (not shown).[78,82]



Because there were no other examples of reactions of chiral aldehydes with Takai's reagent **40** at the time that our synthesis of **7a** was developed, we examined the reactions of **40** with several other chiral aldehydes. After our report of the conversion of **36** to **38**, several additional examples of the reactions of the (γ-alkoxyallyl)chromium species have appeared.[23,82,83] The additional results summarized here indicate the reaction diastereoselectivity is sensitive to the nature of the protecting groups and the stereochemistry of the aldehyde substrate. Surprisingly, the reaction of **40** with aldehyde **6a** (with a β-*p*-methoxybenzyl ether protecting group) gives a 60:40 mixture of products in which the anti-Felkin isomer **46** predominates. However, when the β-alkoxy protecting group is switched to a TBS ether, as in **47**, the Felkin diastereomer **45** is the major component of a 62:38 mixture. On the other hand, the reaction of the 2,3-syn aldehyde **48** with a β-alkoxy PMB ether protecting group provides the Felkin isomer **45** as the major product (ds = 72:28). The most selective substrate of those examined is **49**, which gave a 9:1 mixture favoring the Felkin isomer **45**.

(73) The diminished selectivity of the aldol reaction of **19** and the TBS protected aldehyde **6b**, compared to the reaction with the PMB-protected **6a** and **19**, is consistent with our observations that the stereoselectivities of methyl ketone fragement assembly aldol reactions are highly dependent on the aldehyde β-protecting group and especially that TBS-ether-protected β-alkoxy aldehydes are much less Felkin selective in reactions with chiral methyl ketone lithium enolates than are analogous β-alkoxy aldehydes bearing alkyl ether protecting groups (see refs 53 and 55).

(74) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595.

(75) The more direct sequence involving conversion of **32** to the corresponding dimethoxybenzyl (DMPM) ether via treatment with the DMPM-imidate reagent followed by DIBAL reduction of the ester to the aldehyde was less efficient and more difficult to perform on large scale.

(76) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.

(77) Hoffmann, R. W.; Kemper, B.; Metternich, R.; Lehmeier, T. *Liebigs Ann. Chem.* **1985**, 2246.

(78) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5263.

(79) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179.

(80) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, *19*, 1685.

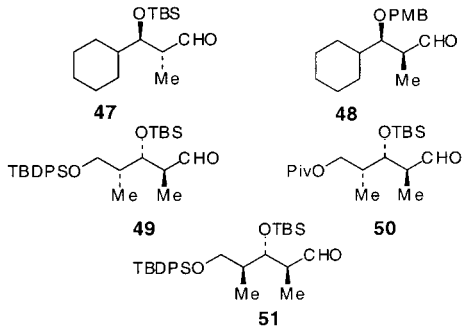
(81) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, p 1.

(82) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.

(83) Boeckman, R. K., Jr.; Hudack, R. A., Jr. *J. Org. Chem.* **1998**, *63*, 3524.

Surprisingly, however, changing the terminal TBDPS ether protecting group to a pivaloate ester in **50**, or by changing the stereochemistry of the C(4)-methyl group as in **51**, gave substrates that exhibited very poor selectivity in reactions with the (methoxyallyl)chromium reagent **40**. While the factors that govern the diastereoselectivity of these reactions are not readily apparent, one can speculate that chelate pathways involving either the *Z*-isomer of the reagent[78] or the substrate [42] may be competitive in some of these cases. It is indeed fortuitous that aldehyde **36** that we targeted for the bafilomycin A_1 synthesis is one of the more selective substrates for the Cr(II)-mediated methoxyallylation reaction.

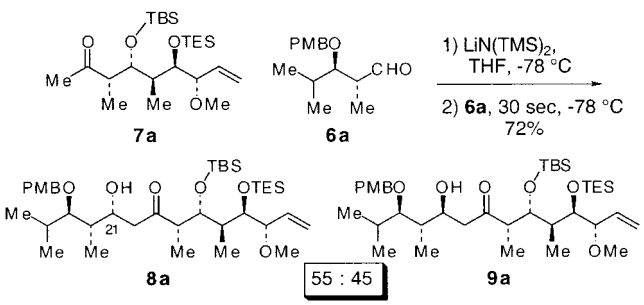
Substrates for the Takai Methoxyallylation Reaction[a,b]



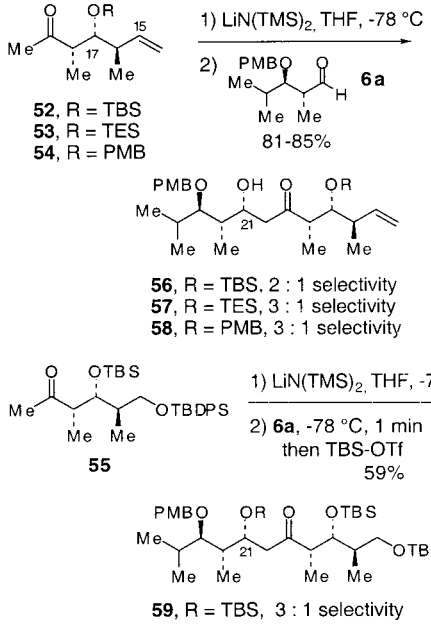
Substrate	Yield	Product Ratio, 45 : 46
6a	83%	40 : 60
36	87%	85 : 15
47	78%	62 : 38
48	72%	72 : 28
49	90%	90 : 10
50	–	66 : 34
51	–	60 : 40

(a) All reactions were performed using the procedure described in the Experimental Section for the methoxyallylation of **36**.
(b) The stereochemistry of the products of the methoxyallylation reactions have been assigned as described in the Supporting Information.

Aldol Reactions of 6a and 7a. The aldol reaction of **6a** and **7a** was performed by using the conditions that gave the optimal 10:1 selectivity in the aldol reaction of **6a** and **19**. Thus, treatment of **7a** with $LiN(TMS)_2$ in THF at −78 °C gave the lithium enolate, to which was added a solution of aldehyde **6a** in THF. The reaction was quenched 30 s later by addition of aqueous NH_4Cl. *To our considerable surprise, this reaction gave a 55:45 mixture of aldols* **8a** *and* **9a**. The stereochemistry at C(21) of both diastereomers was verified by DDQ oxidation to the corresponding *p*-methoxybenzylidene acetals (see Supporting Information).[69]



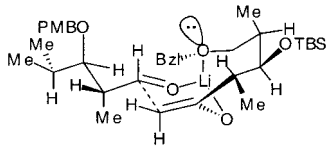
The lack of stereoselectivity in the aldol reaction of **6a** and **7a** prompted us to examine several additional substrates (**52**−**55**) in an attempt to uncover the factor(s) responsible for the aberrant behavior of methyl ketone **7a**. The lithium enolates of **52**−**55** were generated by treatment with $LiN(TMS)_2$ in THF at −78 °C and allowed to react with **6a** for ≤1 min at −78 °C. These reactions also proved to be only moderately selective (2−3:1) for the 21(*R*) aldol stereoisomers **56**−**59**. Aldol **59** (R = H) was unstable to chromatography, so in this case the lithium aldolate was treated with TBS−OTf before reaction workup, thereby permitting aldol **59** (R = TBS) to be isolated. Control experiments established that the reaction of **53** and **6a** is kinetically controlled, as regeneration of the lithium aldolate from the minor aldol diastereomer ($LiN(TMS)_2$, THF, −78 °C, 15 min) failed to result in its equilibration with **57**.



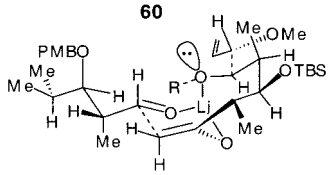
These results established that the C(17) alkoxy protecting group of the methyl ketone fragment has an insignificant influence on the reaction diastereoselectivity, as ketones **52**−**54** with TBS, TES, and PMB protecting groups at this position gave essentially identical results in the aldol reactions with **6a**. However, comparison of the results of reaction of **6a** with **19** (10:1 selectivity) and **55** (3:1 selectivity), which have C(15)−OBzl and C(15)−OTBDPS groups, respectively, indicates that a C(15)-alkoxy group is needed to achieve good diastereoselectivity in this aldol reaction. On the basis of these data, we speculated that the aldol reaction of **6a** and **19** proceeds by way of a chelated transition state such as **60**. Although remote chelation effects are rarely observed,[42,84,85] this hypothesis is consistent with the observations that enolates deriving from **56**−**58** with vinyl substituents, rather than C(15)-alkoxy groups, give low selectivity in the aldol reactions with **6a**. This transition state model also explains the behavior of methyl ketone **7a** with a C(15)-triethylsilyl ether which also should be precluded from participation in a chelated

(84) Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6335.
(85) Frenette, R.; Monette, M.; Bernstein, M. A.; Young, R. N.; Verhoeven, T. R. *J. Org. Chem.* **1991**, *56*, 3083.

transition state such as **61**.[86] Finally, this hypothesis is also consistent with the results of the aldol reactions of **6a** and the sodium enolate of **19**, and also of the lithium enolate of **19** in the presence of HMPA, since chelates involving the C(15)-alkoxy group should be less likely under these conditions.

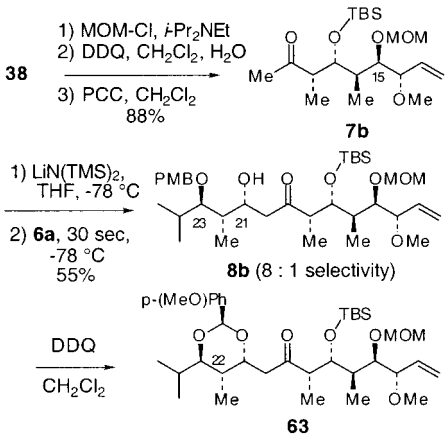


60

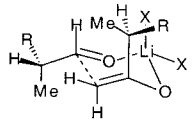


61, R = TES
62, R = MOM

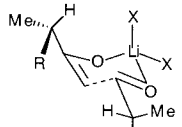
It is well appreciated that lithium enolates are aggregated in solution[87,88] and that the dimeric forms are believed to be the most reactive species.[87] Accordingly, it may well be that transition structure **60** is overly simplified and that the C(15)-alkoxy substituent of **19** is actually chelated to a second lithium cation in an aggregate.[89] Nevertheless, the hypothesis that chelation involving the C(15)-alkoxy group is essential for high stereoselection is easily tested experimentally: synthetically useful stereoselectivity should be restored if the C(15)-alcohol protecting group of **7a** is changed from a triethylsilyl ether to a protecting group (cf. the MOM ether protecting group of **7b**) that can more easily participate in a chelate. We were most pleased to find, therefore, that the kinetically controlled aldol reaction of aldehyde **6a** and methyl ketone **7b** provided **8b** with 8:1 selectivity. The stereochemistry of the newly formed hydroxyl center was assigned by conversion to the *p*-methoxybenzylidene acetal **63**.[69]



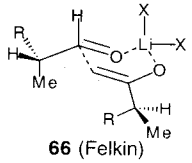
Transition State Analysis. The synthetically useful stereoselectivity of the aldol reaction of **6a** and **7b** is consistent with the particpation of the C(15)-alkoxy group in the chelated transition state **62**. However, the results of aldol reactions of methyl ketones **7a** and **52**−**55**, which are incapable of participating in such highly organized, chelated transition structures, indicate that several less diastereoselective transition states must also be accessible. It is conceivable that both chairlike (**64**, **65**) and boatlike (**66**, **67**) transition states could be involved. Several computational studies indicate that chairlike and boatlike transition states in methyl ketone aldol reactions are relatively close in energy.[90,91] Moreover, some data exist in the boron aldol area indicating that methyl ketone aldol reactions that proceed by way of boatlike transition states exhibit opposite enolate face selectivity compared to the pathways involving chairlike transition structures.[36f,46] Therefore, both the chairlike and boatlike transition structures must be considered in any transition state analysis.



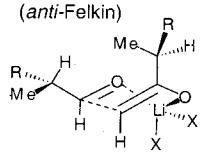
64 (Felkin)



65 (*anti*-Felkin)



66 (Felkin)



67 (*anti*-Felkin)

We expect that the diastereofacial selectivity of aldol reactions that proceed via nonchelated chairlike transition states should favor the Felkin diastereomers (e.g., **56**−**58** from **52**−**54**), in view of Evans' observation that the aldol reactions of chiral ethyl ketone Z(O)-enolates are highly diastereoselective by way of chairlike transition states analogous to **64**.[51,60] However, to account for the modest selectivity of these fragment assembly methyl ketone aldol reactions, we must invoke either the alternative chairlike transition state **65**, in which the enolate adds in an anti-Felkin sense to the chiral aldehyde or the anti-Felkin boatlike transition structure **67**. Further analysis of **65** and **67** reveals that the enolate α-stereocenter adopts a sterically disfavored rotamer with the "R" group eclipsing the enolate double bond in **65**, whereas the enolate α-stereocenter adopts a more favorable rotamer with the medium-sized methyl group eclipsing the enolate double bond in **67**. On the assumption that the chairlike and boatlike transition structures should be comparable in energy (in the absence of overriding steric effects),[90] and because the foregoing analysis suggests that **67** might have fewer destabilizing interactions than **65**, we have invoked **67** to explain the significant production of anti-Felkin diastereomers in the aldol reactions of **7a** and **52**−**55**. Studies designed to probe this hypothesis are in progress and will be reported in due course.

(86) For studies on the influence of protecting groups on chelate controlled carbonyl additions: (a) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847. (b) Frye, S. V.; Eliel, E. L.; Cloux, R. *J. Am. Chem. Soc.* **1987**, *109*, 1862. (c) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279. (d) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281. (e) Keck, G. E.; Castellino, S.; Wiley: M. R. *J. Org. Chem.* **1986**, *51*, 5478. (f) Reetz, M. T.; Hüllmann, M.; Seitz, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 477.

(87) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(88) Williard, P. G.; Liu, Q. Y. *J. Am. Chem. Soc.* **1993**, *115*, 3380.

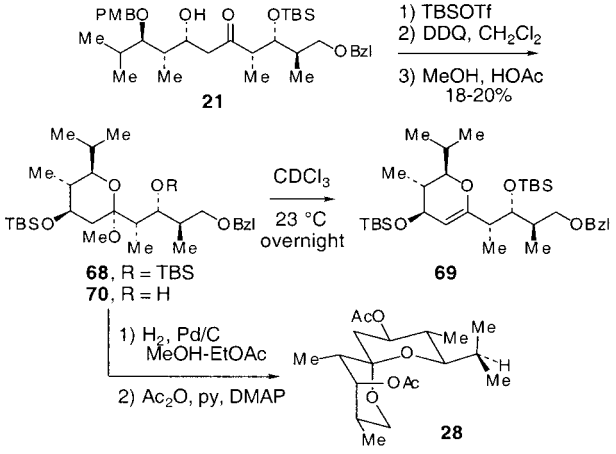
(89) For the disclosure of an aldol reaction of a lithium enolate in the solid state: Wei, Y.; Bakthavatchalam, R. *Tetrahedron Lett.* **1991**, *32*, 1535.

(90) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481.

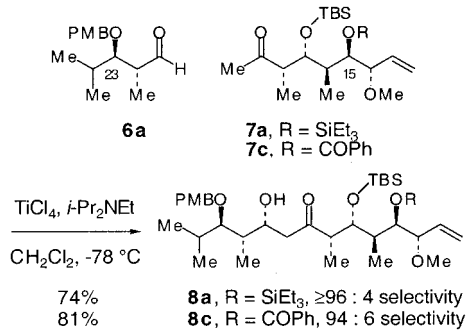
(91) Bernardi, F.; Robb, M. A.; Suzzi-Valli, G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1991**, *56*, 6472.

Implications for the Projected Bafilomycin A_1 Total Synthesis. Our goal at the outset of these studies was to define the opportunities for use of the fragment assembly aldol reaction for synthesis of the C(13)−C(25) segment of bafilomycin A_1. While the synthesis of **8b** via the aldol reaction of **6a** and **7b** satisfied this inital goal, it was readily apparent that **8b** would not be a viable intermediate for the total synthesis. First, the C(15)-MOM ether is too robust a protecting group for the deprotection sequence planned for later in the synthesis. However, given the sensitivity of aldol selectivity on the C(23) and C(15) protecting groups in **6a** and **7b**, as well as the senstivity of the Takai methoxyallylation reaction to the nature of protecting groups on the aldehyde substrate, we were unable to identify a workable revision of the protecting group scheme that would be compatible with use of the lithium enolate fragment assembly aldol reaction as a key step in the projected total synthesis. (Additional constraints on the nature of the C(15)-hydroxyl protecting group became apparent as the total synthesis progressed toward completion.[25,26]) Second, even if a solution to the protecting group/reaction selectivity problem had been achieved, it would have been necessary to devise a strategy for protecting the C(19) ketone to prevent intramolecular hemiketalization by the C(15)−OH during the subsequent macrolactonization reaction.

Several studies addressing the latter issue were performed using aldol **21** as a model system. However, we found that the methyl hemiketal **68** was very sensitive to elimination of methanol, leading to glycal **69**. Glycal **69** was produced during the DDQ deprotection of **21**, as well as during the acid-catalyzed reaction of the hemiacetal with MeOH. Moreover, an NMR sample of **68** readily eliminated MeOH when allowed to stand in $CDCl_3$ overnight. Similar problems have been encountered by Marshall in his studies directed toward the bafilomycin synthesis.[28] In addition, spiroketalization of **68** occurred readily during the catalytic debenzylation reaction (leading to **28**). Although we found that hemiketal **70** was much more stable when the C(17)−OH was deprotected, this also did not appear to be a synthetically useful solution to the problem at hand.



On the basis of these results, we concluded that it would be appropriate to perform the key fragment assembly aldol reaction at the very end of the synthesis, after the macrocycle was assembled. In this scenerio, C(15)−OH would be "protected" by the C(1)-acyl unit of the natural product. It was not obvious, however, that a C(15) acyloxy unit would be compatible with the conditions of a lithium enolate aldol reaction. Because a chlorotitanium enolate should be compatible with the C(15)-acyloxy substituent of the methyl ketone, we explored the aldol reaction of **6a** with the titanium enolate of methyl ketone **7c**. To our considerable delight, the aldol reactions of aldehyde **6a** with the chlorotitanium enolates of both **7a,c** each provided the desired Felkin diastereomers **8a,c** with ≥94:6 selectivity. Chelated transition states analogous to **62** seem unlikely under these conditions, so the excellent diastereoselectivity may be a consequence of the shorter Ti−O bond lengths that maximize nonbonded interactions in the boatlike transition state (i.e., analogous to **67**),[52] thereby raising the energy of the competitive boatlike transition state so that the vast majority of the reaction proceeds via the chairlike transition structure analogous to **64**.



Summary. We have developed highly stereoselective syntheses of aldols **8a**−**c** corresponding to the C(13)−C(25) segment of bafilomycin A_1. In the course of these investigations we discovered that a remote chelation effect plays a critical role in determining the stereoselectivity of the key coupling of aldehyde **6a** and the lithium enolate of **7b** and also that the C(23) protecting group of the chiral aldehyde fragment influences the selectivity of the lithium enolate aldol reaction. In contrast, the aldol reaction of **6a** and the titanium enolates of **7a,c** proved to be much less sensitive to the nature of the C(15)-hydroxyl protecting group. The latter results defined an important technology platform that permitted us to initiate efforts to complete the total synthesis of bafilomycin A_1.[25,26]

Acknowledgment. Support provided the National Institute of General Medical Sciences (Grant GM 38436) is gratefully acknowledged. We also thank Dr. Akihiro Tasaka for helping to optimize the synthesis of **38**.

Supporting Information Available: Complete experimental details and stereochemical assignments of all aldol products and products of the Takai γ-methoxyallylation reactions of chiral aldehydes and selected ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO016413F