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Synthesis of C13−C25 Fragment of 24-Demethylbafilomycin C_1 via Diastereoselective Aldol Reactions of a Ketone Boron Enolate as the Key Step

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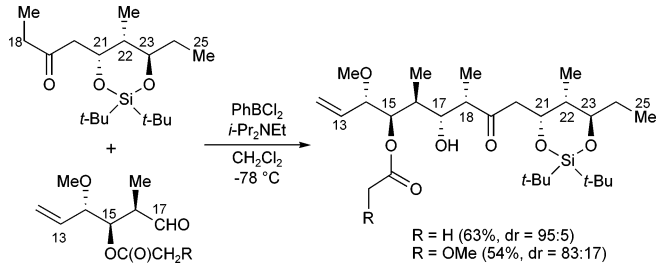
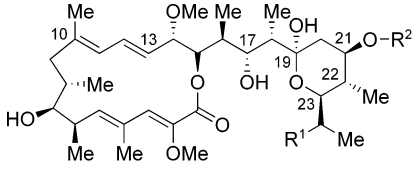


An efficient synthesis of the C13−C25 fragment is described for 24-demethylbafilomycin C_1, a new member of the plecomacrolide family isolated from fermentation broth of *Streptomyces* sp. CS which is a commensal microbe of *Maytenus hookeri*. The targeted C13−C25 fragment possesses five oxygenated and three methyl-substituted stereogenic centers. It is obtained through formation of the C17−C18 syn aldol by using an ethyl ketone boron enolate with diastereomeric ratios of 95:5 and 83:17, respectively, for the chiral aldehydes substituted with acetoxy and methoxyacetoxy groups at C15. The results confirm the observation that the stereochemistry at C22 of the ketone is determinant to the diastereoselectivity of the aldol reaction. The synthesized C13−C25 fragment having a methoxyacetoxy group at C15 is considered as a useful precursor for construction of the 16-membered ring lactone of 24-demethylbafilomycin C_1 through an aldol condensation of the methoxyacetate followed by formation of the C12−C13 double bond via a diene−ene RCM reaction.

Introduction

Bafilomycin A_1 (**1**, Chart 1)[1] is the representative structure of the class B subgroup of the plecomacrolides.[2,3] It features both a unique folding hemiacetal structure in the side chain and an intramolecular hydrogen-bonding network among the macrolactone carbonyl oxygen and the two hydroxyl groups at C17 and C19. The latter is believed to be critically important for the biological function of the plecomacrolides as specific vacuolar H^+-ATPase (V-ATPase) inhibitors.[4−6] A model was recently proposed for the binding site of bafilomycin A_1 on V-ATPase of *Neurospora crassa*.[7] A number of other findings indicate that a high rate of proton transport by V-ATPase seems closely associated with development of diseases such as

CHART 1. Structures of Bafilomycin A_1 (1) and 24-Demethylbafilomycin C_1 (2)



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† Zhejiang University.
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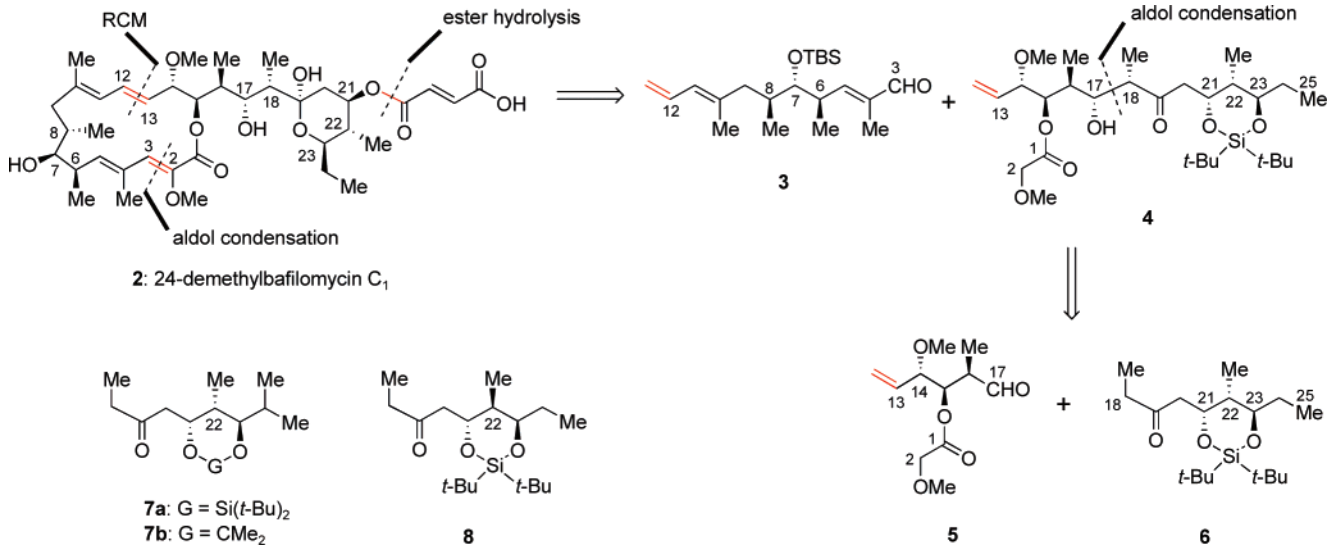
SCHEME 1. Key Retrosynthetic Bond Disconnections of 2 via RCM and Aldol Condensation



osteoporosis and cancer. Therefore inhibitors of V-ATPase are considered as promising therapeutic drugs.[8,9] Recently, Lu and Shen reported 24-demethylbafilomycin C_1 (**2**)[10a] and related macrolides[10b] isolated from the fermentation broth of *Streptomyces* sp. CS, a commensal microbe of *Maytenus hookeri*. The macrolide **2** exhibits strong cytotoxicity against P388 and A549 tumor cell lines with ca. 80% and 90% inhibitions at 10^{-6}–10^{-8} M concentrations, respectively. Structurally, **2** has one methyl group less than bafilomycin C_1 at C24[1] while it is a homologue to PD118,576 A_1 (C23-Et vs C23-Me).[11] Total syntheses of bafilomycin A_1 and other plecomacrolides have been extensively studied by many research groups.[12,13] Macrolactonization[14] was generally used for ring closure while the C10−C13 diene unit assembled via Pd-catalyzed cross-coupling reactions.[15]

In connection with our ongoing research program on formation of macrolides via RCM strategies,[16,17] we envisaged a retrosynthetic analysis of 24-demethylbafilomycin C_1 (**2**) as outlined in Scheme 1. Critical bond disconnections between C12−C13 and C2−C3 according to the diene−ene RCM[18] and an aldol condensation−β-elimination sequence[12g] disassemble **2** into the C3−C12 and C13−C25 fragments **3** and **4**. Although direct formation of the 16-membered macrolactone possessing the tetraene functionality via the diene−ene RCM was not possible,[18a] we have successfully tackled this issue in a model system by using a sequence of aldol condensation (C2−C3 single bond formation) → diene−ene RCM (C12−C13 double bond formation) → β-elimination (C2−C3 double bond formation).[19] We planned to synthesize the C13−C25 fragment **4** by employing a diastereoselective aldol reaction between the chiral aldehyde **5** and the chiral ethyl ketone **6**. Similar aldol reactions between the chiral ketone **7a** and the macrolactone-derived aldehydes or simple achiral aldehydes were reported to afford the desired syn-aldol products in high diastereoselectivity (>95:5).[12a,d] In contrast, the C22 epimer **8** of our chiral ketone **6** gave remarkably reduced diastereoselectivity of 75:25 in an analogous aldol reaction used for the total synthesis of hygrolidin.[20] It

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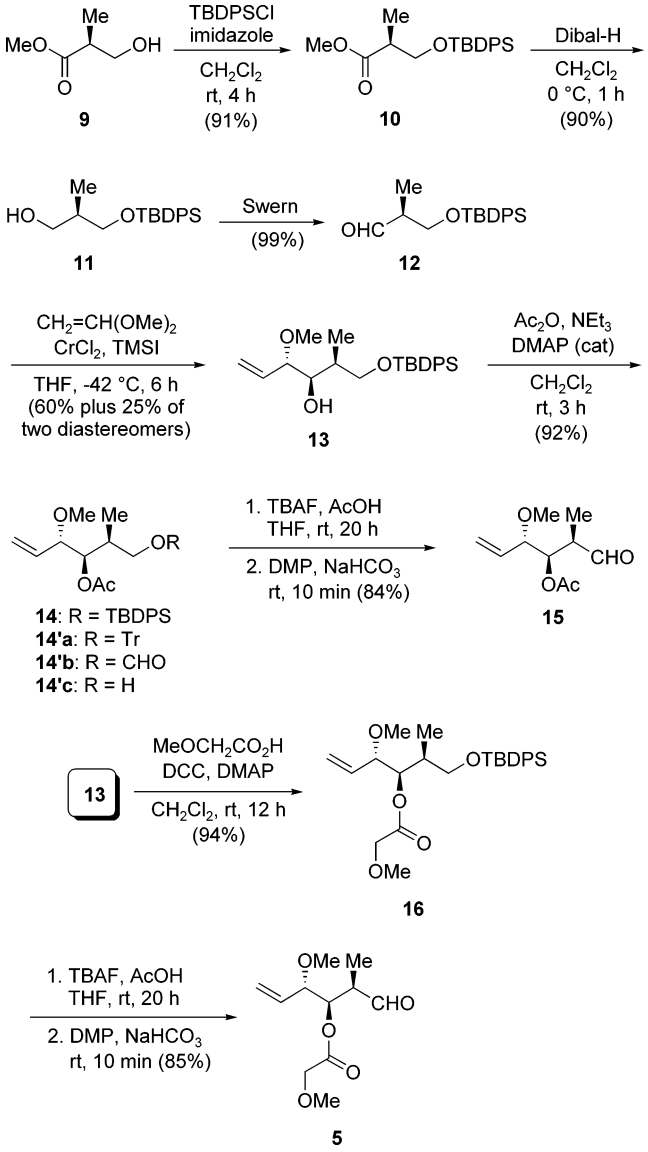
seems that the stereochemistry at C22 of the chiral ethyl ketones **7a** and **8** significantly influences the stereochemical course of the aldol reaction.[12a] Moreover, the cyclic silyl ether motif in **7a** is crucial for high diastereoselectivity because the related cyclic acetal **7b** gave ca. 80:20 ratio of diastereomeric aldols formed from α,β-unsaturated aldehydes.[12h] In this article, we describe our original results on the synthesis of the C13−C25 fragment **4** by employing a diastereoselective aldol reaction between the chiral aldehyde **5** and the chiral ethyl ketone **6** as well as the effect of the methoxyacetate moiety of **5** on diastereoselectivity in formation of the C17−C18 bond.

Results and Discussion

Synthesis of Chiral Aldehydes 5 and 15. Our synthesis started from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (**9**) (Scheme 2). Initially we prepared the known trityl-protected acetate **14′a** from **9**[12d] and removed the trityl group by stirring in HCO_2H−EtOAc at room temperature to give a mixture of the formate **14′b** and the desired alcohol **14′c**. Treatment of the mixture in refluxing MeOH converted **14′b** into **14′c**, which was obtained in 78% overall yield from **14′a**. For a scale-up synthesis, we changed the trityl protection group to TBDPS ether. Thus, protection of **9** as the TBDPS ether **10** was followed by Dibal-H reduction to furnish the alcohol **11** in 82% overall yield. Swern oxidation converted **11** into the aldehyde **12** which was then subjected to the Takai's (γ-methoxyallyl)chromium reagent[21] prepared in situ from $CrCl_2$ and acrolein dimethyl acetal in the presence of trimethylsilyl iodide to afford the homoallyl alcohol **13** in 60% yield along with 25% of two minor diastereomers.[22] The desired diastereomer **13** was transformed

SCHEME 2. Synthesis of Chiral Aldehydes 5 and 15



into the corresponding acetate **14** and methoxyacetate **16** in 92% and 94% yields, respectively, which were isolated in isomeric pure forms. Desilylation of **14** with TBAF−AcOH followed by oxidation of the primary alcohol with Dess−Martin periodinane (DMP)[23] provided the acetoxy-substituted chiral aldehyde **15** in 84% overall yield from **14**. Similarly, the methoxyacetate-substituted chiral aldehyde **5** was obtained from **16** in 85% overall yield.

Synthesis of Chiral Ethyl Ketone 6. Several approaches have been reported for controlling the three consecutive stereogenic centers at C21−C23 of bafilomycin A_1. Toshima and co-workers prepared the chiral ketone **7a** (Scheme 1) starting from a sugar derivative obtainable from D-glucose.[12d] In Hanessian's total synthesis of bafilomycin A_1, the C20−C25 fragment (as the iodide) was assembled from D-valine by utilizing a highly stereoselective conjugate addition−hydroxylation protocol.[12g] Cossy and co-workers synthesized the same

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(21) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5263−5266.

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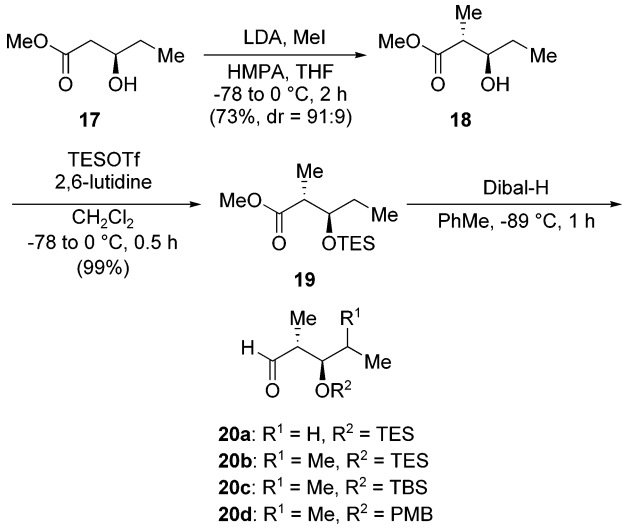
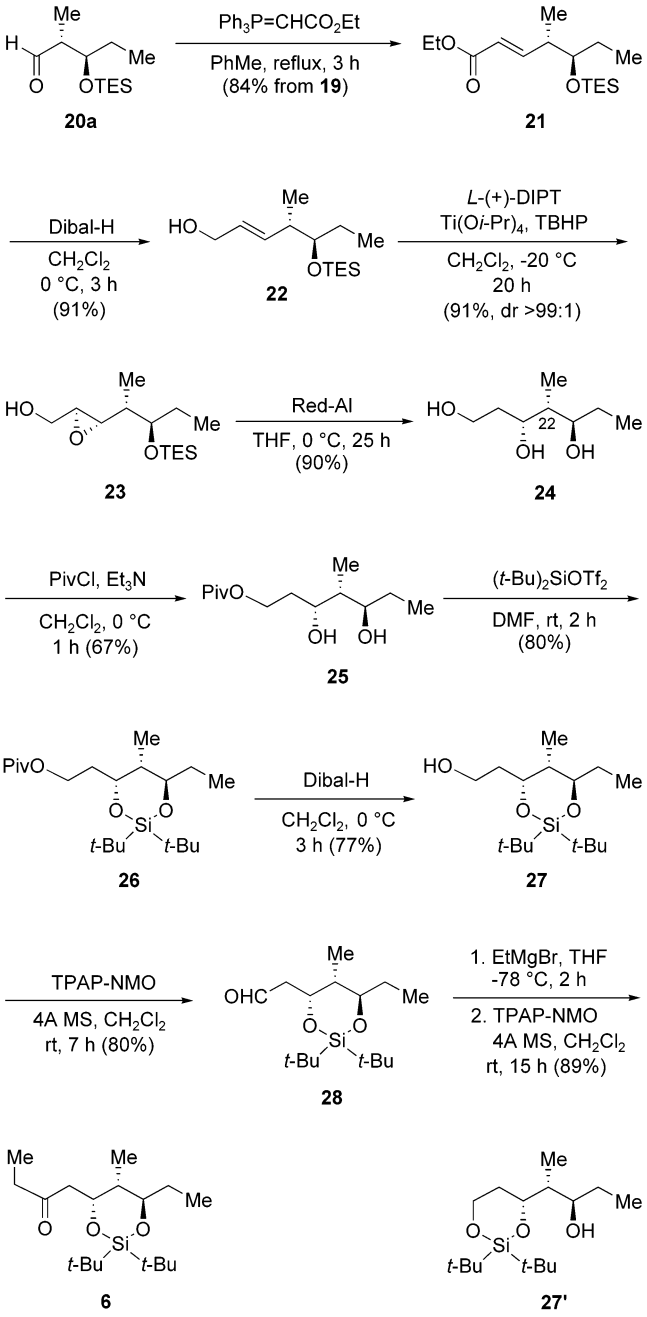
SCHEME 3. Synthesis of Chiral Aldehyde 20a



iodide based on sequential enantioselective monoreduction of 2-alkyl 1,3-diketone and stereoselective reduction of the chiral β-hydroxyketone.[12j] Marshall and Adams secured the C22−C23 anti aldol stereochemistry by addition of a chiral allenylzinc reagent with isobutyraldehyde and then installed the C21 chiral hydroxyl group through Sharpless asymmetric epoxidation and regioselective reductive epoxide ring opening.[12i] Roush and coworkers used the chiral aldehydes **20c**,**d** (Scheme 3) in their fragment assembly aldol coupling reactions of various methyl ketones.[12f,24] Diastereoselectivity was found to be dependent on reaction conditions. In the total synthesis of bafilomycin A_1, the aldol reaction of **20c** with the macrolactone-derived methyl ketone afforded >95:5 diastereomer ratio.[12f] Evans and coworkers systematically examined the merged 1,2- and 1,3-asymmetric induction in Mukaiyama aldol reactions with methyl ketone derived enol silyl ethers and found that **20c**,**d** gave high diastereoselectivity of >95:5 in most cases.[25] Diastereoselectivity of 95:5 was also reported for the Mukaiyama-type aldol reaction of **20b** with 3-methyl-2,4-bis(trimethylsilyloxy)penta-1,3-diene.[12] We selected a practical approach for gram-scale preparation of the chiral aldehyde **20a** according to a similar sequence used by Roush for accessing **20c**.[24] As shown in Scheme 3, the chiral alcohol **17**, readily prepared from enantioselective hydrogenation of methyl 3-oxo-pentanoate using (*R*)-binap and (COD)Ru(2-methylallyl)$_2$ as the catalyst precursors,[26] was subjected to Fráter−Seebach anti alkylation[27] to give **18** in 73% yield with a diastereomer ratio of 91:9. The minor diastereomer could not be separated by column chromatographic purification, and the mixture was carried forward in the following reactions up to the alcohol **27** (Scheme 4). Protection of the hydroxyl group in **18** with TESOTf and 2,6-lutidine afforded the TES ether **19**, which was directly converted into the aldehyde **20a** by controlled reduction of the ester group with Dibal-H at −89 °C.

Scheme 4 illustrates the synthesis of the chiral ethyl ketone **6**. The aldehyde **20a** was subjected to Wittig olefination with

SCHEME 4. Synthesis of Chiral Ketone 6



the stabilized phosphorus ylide in refluxing toluene to produce the α,β-unsaturated ester **21** in 84% overall yield from **19**. The ester **21** was then reduced using Dibal-H at 0 °C to the allyl alcohol **22** (91%), which underwent the Sharpless asymmetric allylic epoxidation with L-(+)-DIPT as the chiral ligand to furnish the epoxide **23** in 91% yield and in >99:1 diastereomer ratio. A regioselective reductive epoxide ring opening[12i] was carried out with Red-Al at 0 °C to form the triol **24** after unexpected removal of the TES ether under the reaction conditions, presumably due to the Lewis acidity of Red-Al. Selective monoprotection of the triol **24** gave the desired pivalate **25** in 67% yield along with other undesired pivalates. Treatment of the diol **25** with (*t*-Bu)$_2$SiOTf$_2$ in DMF resulted in formation of the cyclic silyl ether **26** (80%). We found that at one time Dibal-H reduction of **26** afforded the second alcohol **27′** which gave the corresponding ketone after PCC oxidation. Fortunately,

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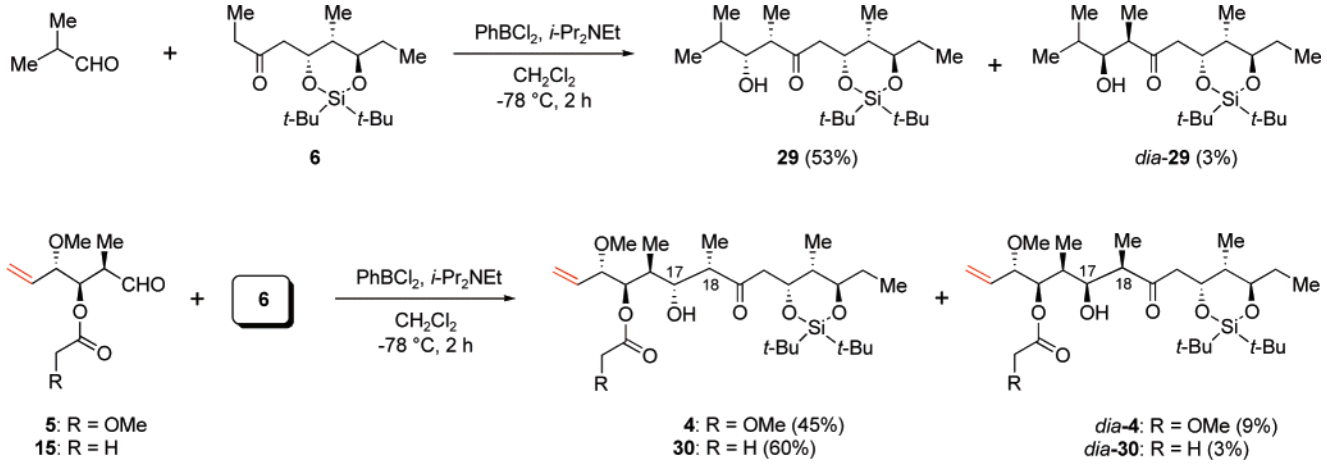
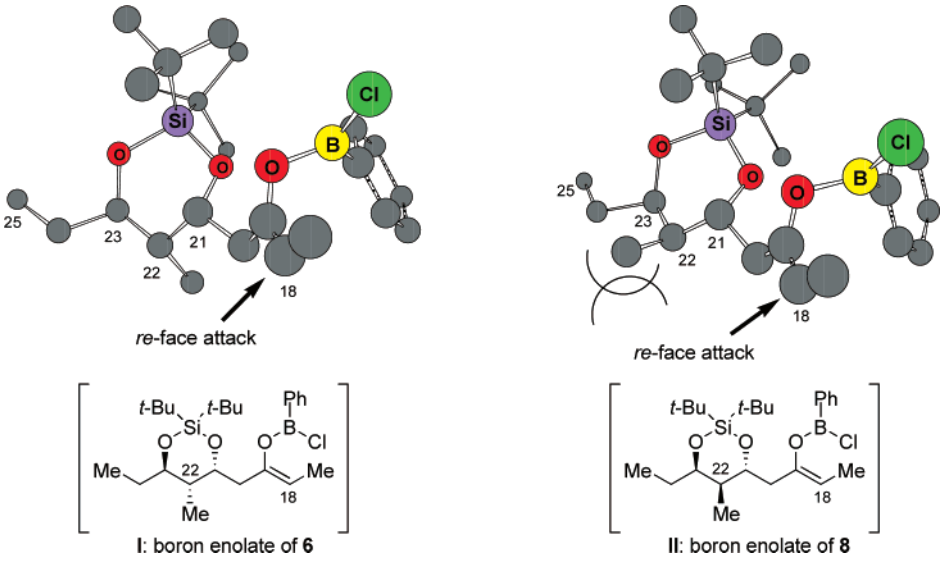
SCHEME 5. Aldol Reactions of Chiral Ketone 6 with Chiral and Achiral Aldehydes



the rearrangement product **27′** could be suppressed with precaution during Dibal-H reductive cleavage of the pivalate **26**, and the alcohol **27** was isolated in an isomeric pure form in 77% yield. Oxidation of **27** with TPAP−NMO in the presence of 4 Å molecular sieves afforded the aldehyde **28** (80%). Addition of EtMgBr with **28** followed by TPAP−NMO oxidation furnished the chiral ethyl ketone **6** in 89% overall yield from **28**. The ketone **6** has an optical rotation value of $[\alpha]^{20}_D$ +80.2 (*c* 1.75, $CHCl_3$), which is consistent with $[\alpha]^{20}_D$ +85.2 (*c* 0.89, $CHCl_3$) reported for the homologous ketone **7a**.[12d]

Aldol Reactions of Boron Enolate of Chiral Ethyl Ketone 6. With both the chiral aldehydes **5** and **15** and the chiral ketone **6** in hand, we performed the aldol reactions as shown in Scheme 5. As mentioned above, Evans and Calter examined the aldol stereoselectivity of α-unsubstituted-*β*-silyloxy ethyl ketones related to the total synthesis of bafilomycin A_1.[12a] In the presence of $PhBCl_2$ and *i*-Pr_2NEt in CH_2Cl_2, the chiral ethyl ketone **7a** was converted into the (*Z*)-boron enolate (−78 °C, 30 min; 0 °C, 30 min).[28] The latter reacted with both isobutyraldehyde and several chiral aldehydes to afford exclusively the syn aldols. Moreover, anti-Felkin[29] selectivity was observed for the aldol reactions of chiral *syn*-α-alkyl-*β*-oxygen-substituted aldehydes in a matched double stereodifferentiating manner.[30] We carried out the aldol reaction of **6** with isobutyraldehyde under similar conditions used for **7a** and obtained the syn-aldol products **29** (53%) and *dia*-**29** (3%) in 95:5 diastereomer ratio. As compared to >99:1 diastereomer ratio reported for the same aldol reaction of **7a**,[12a] the ethyl ketone **6** afforded slightly reduced diastereoselectivity. The *β*,*γ*-bisoxygenated aldehydes **5** and **15** have not been examined in the aldol reactions with **7a**. We were pleased to find out that the analogous aldol reaction between **15** and **6** gave **30** and *dia*-**30** in 95:5 diastereomer ratio.[30] The major isomer **30** was isolated in 60% yield and in isomeric pure form. The result is consistent with the diastereoselectivity observed for the reaction of the macrolactone-derived aldehyde with **7a** used for the total synthesis of bafilomycin A_1.[12a,d] To our delight, the aldol reaction between the *β*-methoxyacetoxy-substituted aldehyde **5** and the chiral ethyl ketone **6** took place under the same boron enolate conditions ($PhBCl_2$, *i*-$PrNEt_2$, CH_2Cl_2, −78 °C) to furnish the target C13−C25 fragment **4** of 24-demethylbafilomycin C_1. The product **4** was obtained in 45% isolated yield along with a minor isomer *dia*-**4** (9%).[31] The diastereoselectivity for **4** and *dia*-**4** is 83:17, suggesting that the *β*-methoxyacetoxy group in **5** diminishes preference for *anti*-Felkin selectivity in stereochemical communication among the boron enolate and the aldehyde. Although the detail is not clear, it appears that the methoxyacetoxy group in **5** might interact with the boron enolate in the transition state, resulting in lower

CHART 2. Chem3D Structures of the Preferred Boron Enolates I and II of Ethyl Ketones 6 and 8



anti-Felkin/Felkin selectivity. For addressing the enolate face selectivity, Evans and Calter constructed a model favored for *re*-face attack based on the ground-state conformational preference of the enol form of **7a**.[12a] According to the preferred conformation analogous to **7a**, we illustrate the Chem3D-derived boron enolate structures **I** and **II** of the ethyl ketones **6** and **8** in Chart 2.[32] The *re*-face of enolate C18−C19 double bond is much more open for approaching the aldehydes in both **I** and **II**. In the latter case, the *re*-face is suffered from unfavorable steric interaction with the C22-methyl group, which accounts for the 75:25 diastereoselectivity in the aldol reaction of **8** with the macrolactone-derived aldehyde used in the Yonemitsu and Hashimoto's total synthesis of hygrolidin.[20]

Conclusion

In summary, we have established an efficient synthesis of the C13−C25 fragments **4** and **30** of 24-demethylbafilomycin C_1 by using a key aldol reaction of the chiral aldehydes **5** and **15** with the boron enolate derived from chiral ethyl ketone **6**. The chiral aldehydes **5** and **15** possess both β,γ-bisoxygenated functionalities and an α-alkyl group, and they were readily prepared by diastereoselective reaction of the chiral aldehyde **12** with the Takai's (γ-methoxyallyl)chromium reagent.[21] On the other hand, the three consecutive stereogenic centers in the ethyl ketone **6** were assembled by Fráter−Seebach anti alkylation[27] followed by a sequence of Sharpless asymmetric allylic epoxidation and regioselective reductive epoxide ring opening. The aldol reaction between the β-acetoxy-substituted aldehyde **15** and the chiral ketone **6** gave 95:5 diastereoselectivity favored for the anti-Felkin aldol **30** in 60% isolated yield. Similarly, the analogous aldol reaction of the β-methoxyacetoxy-substituted aldehyde **5** afforded the desired anti-Felkin aldol **30** in 45% isolated yield and in isomeric pure form albeit in a slightly diminished diastereomer ratio of 83:17. These results are consistent with the diastereoselectivity reported for the C24-homologous ethyl ketone **7a**. Our study on the aldol reaction also suggests that the poor diastereoselectivity of 75:25 recorded for C22-epimeric ketone **8** originates from the unfavorable orientation of the C22-methyl group as shown in **II** of Chart 2. Moreover, our successful synthesis of the C13−C25 fragment provides the basis for further study toward total synthesis of 24-demethylbafilomycin C_1.

Experimental Section

(3*S*,4*R*,5*S*)-6-[(*tert*-Butyldiphenyl)silyloxy]-3-methoxy-5-methylhex-1-en-4-ol (13). To a stirred suspension of $CrCl_3$ (4.020 g, 25.40 mmol) in dry THF (100 mL) cooled in an ice-water bath (0 °C) was added slowly $LiAlH_4$ (0.507 g, 12.70 mmol). After stirring for 20 min at the same temperature, the resultant mixture was cooled to −42 °C followed by sequential addition of acrolein dimethyl acetal (1.0 mL, 8.46 mmol), iodotrimethylsilane (1.2 mL, 8.46 mmol), and a solution of the aldehyde **12** (1.380 g, 4.23 mmol) in dry THF (5.0 mL) via syringes. After stirred for 6 h at −42 °C, the reaction was quenched by 1 M aqueous HCl (50 mL) with ice-cooling, and the resultant mixture was then extracted with Et_2O (60 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexane) to give the alcohol **13** (1.000 g, 60%) along with a mixture of two diastereomers (0.410 g, 25%). **13**: a colorless oil; R_f = 0.38 (10% EtOAc in hexane); $[\alpha]^{20}_D$ +16.4 (*c* 0.25, $CHCl_3$); IR (film) 3500 (br), 2931, 1112 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.66 (m, 4H), 7.48−7.36 (m, 6H), 5.80 (ddd, J = 17.4, 10.5, 8.4 Hz, 1H), 5.36 (dd, J = 10.5, 1.8 Hz, 1H), 5.26 (ddd, J = 17.4, 1.8, 0.9 Hz, 1H), 3.86 (dd, J = 6.6, 3.9 Hz, 1H), 3.74 (dd, J = 9.9, 4.5 Hz, 1H), 3.68 (dd, J = 9.9, 5.1 Hz, 1H), 3.53 (dd, J = 7.6 Hz, 1H), 3.27 (s, 3H), 2.79 (br s, 1H, O*H*), 2.05−1.95 (m, 1H), 1.06 (s, 9H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.86 (×2), 135.8, 135.78 (×2), 133.4, 133.3, 129.94, 129.92, 127.92 (×2), 127.90 (×2), 119.9, 84.0, 75.3, 68.6, 56.6, 36.2, 27.3 (×3), 19.6, 11.4; HRMS (+ESI) calcd for $C_{24}H_{34}O_3SiNa$ (M + Na^+), 421.2169; found, 421.2155.

(3*S*,4*R*,5*S*)-6-[(*tert*-Butyldiphenyl)silyloxy]-3-methoxy-4-methoxyacetoxy-5-methylhex-1-ene (16). To a solution of the alcohol **13** (220.0 mg, 0.55 mmol) in dry CH_2Cl_2 (5 mL) cooled in an ice-water bath (0 °C) was added methoxyacetic acid (65 μL, 0.83 mmol), DCC (344.0 mg, 1.65 mmol), and DMAP (204.0 mg, 1.65 mmol). The resultant mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to give the methoxyacetate **16** (243.0 mg, 94%) as a colorless oil. R_f = 0.55 (10% EtOAc−hexane); $[\alpha]^{20}_D$ +28.3 (*c* 0.30, $CHCl_3$); IR (film) 2933, 1759, 1192, 1108 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.62 (μ, 4H), 7.45−7.34 (m, 6H), 5.70 (ddd, J = 17.2, 10.0, 7.6 Hz, 1H), 5.32 (dd, J = 6.0, 4.8 Hz, 1H), 5.27 (dd, J = 10.4, 1.6 Hz, 1H), 5.18 (dd, J = 17.2, 1.2 Hz, 1H), 3.94 (s, 2H), 3.64 (dd, J = 8.4, 6.4 Hz, 1H), 3.51 (dd, J = 10.4, 7.2 Hz, 1H), 3.44 (dd, J = 10.0, 6.4 Hz, 1H), 3.39 (s, 3H), 3.25 (s, 3H), 2.23−2.13 (m, 1H), 1.05 (s, 9H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 135.56 (×2), 135.55 (×2), 135.1, 133.6, 133.4, 129.52, 129.50, 127.5 (×4), 199.8, 82.5, 74.1, 69.7, 65.7, 59.2, 56.4, 35.9, 26.8 (×3), 19.1, 11.5; MS (+ESI) *m*/*z* 493 (M + Na^+, 100); HRMS (+ESI) calcd for $C_{27}H_{38}O_5SiNa$ (M + Na^+), 493.2381; found, 493.2367.

(2*S*,3*R*,4*S*)-4-Methoxy-3-methoxyacetoxy-2-methylhex-5-en-1-ol. To a solution of **16** (230.0 mg, 0.49 mmol) in THF (4 mL) cooled in an ice-water bath (0 °C) was added TBAF (1.0 mL, 1.0 mmol, 1 M in THF) and acetic acid (58 μL, 1.0 mmol) followed by stirring for 20 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, and the reaction mixture was extracted with EtOAc (5 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 30% EtOAc in hexane) to give the alcohol (99.0 mg, 86%) as a colorless oil. R_f = 0.22 (30% EtOAc−hexane); $[\alpha]^{20}_D$ +41.9 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (ddd, J = 17.2, 10.8, 8.4 Hz, 1H), 5.35−5.25 (m, 2H), 5.13 (dd, J = 8.0, 4.0 Hz, 1H), 4.03 and 3.97 (ABq, J = 16.4 Hz, 2H), 3.66 (dd, J = 8.0, 8.0 Hz, 1H), 3.51 (dd, J = 11.6, 5.6 Hz, 1H), 3.42 (s, 3H), 3.33 (dd, J = 11.2, 8.8 Hz, 1H), 3.28 (s, 3H), 2.39 (br s, 1H, O*H*), 2.27−2.16 (m, 1H), 0.88 (d, J =

(27) (a) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269−1277. (b) Zuger, M.; Weller, T.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2005−2009.

(28) Hamana, H.; Sasakura, K.; Sugasawa, T. *Chem. Lett.* **1984**, 1729−1732.

(29) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204; 2205−2208.

(30) Diminished anti-Felkin selectivity was reported for an achiral ethyl ketone lithium enolate, see: Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1996**, *37*, 1957−1960.

(31) The syn-aldol structures were assigned according to the small coupling constants of 1.6−4.4 Hz between C17 and C18 methine protons as listed in Table S1 in Supporting Information.

(32) The enolate structures **I** and **II** are used only for illustrative purpose. The coordinates are found in Tables S2 and S3 in Supporting Information. There are several enolate structures of similar stabilities minimized at MM2 level by Chem3D. All of them favor for *re*-face attack to the aldehydes.

7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 135.4, 120.2, 81.8, 74.3, 69.5, 64.5, 59.2, 56.3, 36.0, 10.5; MS (+ESI) *m*/*z* 255 (M + Na^+, 100); HRMS (+ESI) calcd for $C_{11}H_{20}O_5Na$ (M + Na^+), 255.1208; found, 255.1202.

(2*R*,3*R*,4*S*)-4-Methoxy-3-methoxyacetoxy-2-methylhex-5-enal (5). To a solution of the previous alcohol (90.0 mg, 0.38 mmol) in dry CH_2Cl_2 (4 mL) was added powdered $NaHCO_3$ (65.0 mg, 0.80 mmol) and Dess−Martin periodinane (1.7 mL, 0.51 mmol, 0.3 M in CH_2Cl_2) at room temperature. The resultant mixture was stirred for 10 min, and the reaction was quenched with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$. The reaction mixture was extracted with Et_2O (3 mL × 3), and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexane) to give the aldehyde **5** (86.0 mg, 99%) as a colorless oil. R_f = 0.50 (30% EtOAc−hexane); $[\alpha]^{20}_D$ +11.2 (*c* 0.60, $CHCl_3$); IR (film) 3021, 2936, 1758, 1720, 1192, 1127 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, *J* = 1.6 Hz, 1H), 5.66 (ddd, *J* = 17.2, 10.0, 8.0 Hz, 1H), 5.42 (dd, *J* = 8.0, 5.6 Hz, 1H), 5.35 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.30 (m, 1H), 3.99 and 3.94 (ABq, *J* = 16.4 Hz, 2H), 3.61 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.40 (s, 3H), 3.26 (s, 3H), 2.90−2.82 (m, 1H), 1.12 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 169.4, 134.7, 121.1, 82.3, 72.5, 69.5, 59.3, 56.4, 48.0, 8.5; MS (+ESI) *m*/*z* 253 (M + Na^+, 100); HRMS (+ESI) calcd for $C_{11}H_{18}O_5Na$ (M + Na^+), 253.1046; found, 253.1048.

(2*S*,3*S*,4*S*,5*R*)-2,3-Epoxy-4-methyl-5-[(triethylsilyl)oxy]heptan-1-ol (23). To a suspension of anhydrous powdered 4 Å molecular sieves (2.80 g) in dry CH_2Cl_2 (120 mL) was added l-(+)-diisopropyl tartrate (6.0 mL, 27.2 mmol). The mixture was cooled to −20 °C and Ti(O*i*-Pr)$_4$ (7.0 mL, 22.7 mmol) was added via a syringe. After stirring for 10 min at −20 °C, tert-butyl hydroperoxide (8.4 mL, 5−6 M in decane, 42.0 mmol) was added dropwise. The mixture was stirred for 30 min and then the allyl alcohol **22** (4.900 g, 18.9 mmol) in dry CH_2Cl_2 was added dropwise over a period of 10 min. The resultant mixture was stirred at −20 °C for 20 h followed by quenching with a minimal amount of H_2O (10 mL). After warming to room temperature, the heterogeneous mixture was stirred vigorously for 20 min and filtered through a pad of Celite with rinsing by CH_2Cl_2. Then 30% NaOH (100 mL, in brine) was added to the filtrate, and the mixture was stirred for 2 h. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexane) to afford **23** (4.700 g, 91%) as a colorless oil. R_f = 0.58 (20% EtOAc−hexane); IR (film) 3444 (br), 2959, 2872, 1008 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 3.79−3.64 (μ, 3H), 3.47−3.42 (μ, 1H), 2.86−2.84 (μ, 1H), 2.84 (σ, 1H), 2.71 ($\delta\delta$, *J* = 7.2, 2.2 Hz, 1H), 1.53−1.44 (m, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.6 Hz, 3H), 0.59 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 86.5, 72.8, 69.1, 67.6, 50.7, 37.4, 22.7, 19.7, 17.0 (×3), 15.4 (×3); HRMS (+ESI) calcd for $C_{14}H_{30}O_3$-SiNa (M + Na^+), 297.1856; found, 297.1849.

(3*R*,4*R*,5*R*)-4-Methylheptane-1,3,5-triol (24). To a solution of the epoxy alcohol **23** (4.000 g, 14.4 mmol) in dry THF (150 mL) cooled in an ice-water bath (0 °C) was added Red-Al (26.4 mL, 65+ wt %, 87.0 mmol) dropwise. The resultant mixture was stirred at 0 °C for 25 h followed by quenching with saturated aqueous sodium potassium tartrate (Rochelle's salt) (100 mL) carefully. Et_2O (100 mL) was added to the reaction mixture which was allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide the triol **24** (2.100 g, 90%) as a colorless oil. R_f = 0.42 (10% MeOH−CH_2Cl_2); IR (film) 3354 (br), 2964, 1051 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 ($\delta\tau$, *J* = 10.4, 2.0 Hz, 1H), 3.87−3.77 (m, 5H), 3.54 (dt, *J* = 7.2, 3.6 Hz, 1H), 1.86−1.78 (m, 1H), 1.63−1.44 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.2, 61.8, 41.5, 34.6, 28.0, 12.0, 9.6; HRMS (+ESI) calcd for $C_8H_{18}O_3Na$ (M + Na^+), 185.1148; found, 185.1142.

(3*R*,4*R*,5*R*)-3,5-Dihydroxy-4-methylheptan-1-yl Trimethylacetate (25). To a solution of the triol **24** (1.800 g, 10.8 mmol) in dry CH_2Cl_2 (60 mL) cooled in an ice-water bath (0 °C) was added dropwise pyridine (1.3 mL, 16.2 mmol) and trimethylacetyl chloride (1.3 mL, 10.8 mmol). The resultant mixture was stirred for 1 h at the same temperature followed by quenching with saturated aqueous NH_4Cl (60 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (60 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2-SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide **25** (1.800 g, 67%) as a colorless oil. R_f = 0.55 (10% MeOH−CH_2Cl_2); IR (film) 3418 (br), 2971, 1729, 1712, 1186 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (ddd, *J* = 10.8, 8.4, 5.2 Hz, 1H), 4.16 (dt, *J* = 10.8, 5.6 Hz, 1H), 3.98 (dt, *J* = 9.6, 2.8 Hz, 1H), 3.57−3.52 (m, 1H), 3.07 (br s, 2H, O*H*), 1.87−1.77 (m 1H), 1.73−1.46 (m, 4H), 1.18 (s, 9H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 76.9, 69.4, 61.9, 40.9, 38.7, 32.9, 28.1, 27.1 (×3), 11.7, 9.8; HRMS (+ESI) calcd for $C_{13}H_{26}O_4Na$ (M + Na^+), 269.1723; found, 269.1716.

Compound 26. To a stirred solution of the diol **25** (1.500 g, 6.2 mmol) in dry DMF (40 mL) cooled in an ice-water bath (0 °C) was added dropwise *t*-$Bu_2Si(OTf)_2$ (3.2 mL, 9.4 mmol). The resultant mixture was stirred for 2 h at room temperature followed by quenching with ice-cold water (40 mL). The mixture was extracted with EtOAc (50 mL × 3), and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatograph (silica gel, 2% EtOAc in hexane) to provide **26** (2.100 g, 84%) as a colorless oil. R_f = 0.91 (10% EtOAc−hexane); IR (film) 2963, 2935, 2859, 1732, 1158, 1132, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (ddd, *J* = 11.6, 7.2, 4.4 Hz, 1H), 4.24 (ddd, *J* = 8.4, 8.0, 6.8 Hz, 1H), 4.07 (ddd, *J* = 8.8, 5.6, 3.2 Hz, 1H), 3.77 (ddd, *J* = 10.8, 7.6, 3.2 Hz, 1H), 2.14−2.08 (m, 1H), 1.82−1.46 (m, 3H), 1.40−1.30 (m, 1H), 1.20 (s, 9H), 0.99−0.95 (m, 18H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 74.2, 73.1, 62.1, 40.4, 38.7, 30.2, 28.2, 27.6 (×3), 27.3 (×3), 27.2 (×3), 21.3, 20.6, 13.5, 8.7; HRMS (+ESI) calcd for $C_{21}H_{42}O_4SiNa$ (M + Na^+), 409.2745; found, 409.2730.

Alcohol 27. To a solution of the ester **26** (2.000 g, 5.2 mmol) in dry CH_2Cl_2 (50 mL) cooled in an ice-water bath (0 °C) was added Dibal-H (12.0 mL, 1.0 M in hexane, 12.0 mmol) followed by stirring at the same temperature for 3 h. The reaction was carefully quenched with MeOH (10 mL), and then saturated aqueous sodium potassium tartrate (Rochelle's salt) (100 mL) and Et_2O (100 mL) were added with vigorous stirring till the mixture became clear. The organic layer was separated, and the aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc in hexane) afforded **27** (1.200 g, 77%). R_f = 0.27 (10% EtOAc−hexane); IR (film) 3358 (br), 2962, 2934, 2859, 1131, 1063 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (ddd, *J* = 5.6, 4.4, 1.2 Hz, 1H), 3.94−3.86 (m, 2H), 3.78 (td, *J* = 9.0, 3.0 Hz, 1H), 2.15−2.08 (m, 1H), 1.88−1.80 (m, 1H), 1.64−1.57 (m, 2H), 1.41−1.32 (m, 1H), 1.26 (s, 1H, O*H*), 1.01 (s, 18H), 0.96 (t, *J* = 7.0 Hz, 3H), 0.77 (d *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 75.3, 74.8, 60.1, 41.6, 34.6, 28.9, 28.1 (×3), 27.8 (×3), 21.9, 21.2, 13.9, 9.2; HRMS (+ESI) calcd for $C_{16}H_{34}O_3SiNa$ (M + Na^+), 325.2169; found, 325.2162.

Aldehyde 28. To a suspension of powdered 4 Å molecular sieves (1.80 g) in dry CH_2Cl_2 (18 mL) was added the alcohol **27** (1.100

g, 3.6 mmol) in dry CH_2Cl_2 (3 mL), NMO (660.0 mg, 5.4 mmol), and TPAP (60.0 mg, 0.15 mmol). The resultant mixture was stirred for 7 h at room temperature, and the reaction mixture was filtrated through a pad of Celite with rinsing by EtOAc. The combined filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to afford **28** (868.0 mg, 80%) as a colorless oil. $R_f = 0.55$ (10% EtOAc−hexane); IR (film) 2964, 2935, 2860, 1716, 1131, 1063 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.73 (dd, J = 4.4, 0.8 Hz, 1H), 4.74 (ddd, J = 8.8, 5.2, 3.2 Hz, 1H), 3.80 (ddd, J = 10.8, 8.0, 3.2 Hz, 1H), 2.56−2.50 (m, 2H), 2.23−2.17 (m, 1H), 1.65−1.58 (m, 1H), 1.37−1.29 (m, 1H), 0.96−0.91 (m, 21H), 0.75 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 202.3, 74.8, 73.6, 46.2, 41.2, 28.6, 27.9 (×3), 27.6 (×3), 22.0, 21.1, 13.6, 9.0; HRMS (+ESI) calcd for $C_{16}H_{32}O_3SiNa$ ($M + Na^+$), 323.2013; found, 323.2014.

Ketone 6. To a solution of the aldehyde **28** (810.0 mg, 2.7 mmol) in dry THF (25 mL) cooled at −78 °C was added dropwise EtMgBr (5.6 mL, 1.0 M in Et_2O, 5.6 mmol) followed by stirring at the same temperature for 2 h. The reaction mixture was allowed to warm to room temperature and quenched with saturated aqueous NH_4Cl (10 mL). The resultant mixture was extracted with EtOAc (30 mL × 3), and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to give the corresponding alcohol which was used in the next step without further purification.

To a suspension of powdered 4 Å molecular sieves (1.20 g) in dry CH_2Cl_2 (12 mL) was added the above alcohol (750.0 mg, 2.3 mmol) in dry CH_2Cl_2 (3 mL), NMO (552.0 mg, 4.6 mmol), and TPAP (90.0 mg, 0.24 mmol) followed by stirring for 15 h at room temperature. The reaction mixture was filtrated through a pad of Celite with rinsing by EtOAc. The combined filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexane) to afford **6** (671.0 mg, 89% overall yield from **28**) as a colorless oil. R_f = 0.81 (10% EtOAc−hexane); $[\alpha]^{20}_D$ +80.2 (c 1.75, $CHCl_3$); IR (film) 2963, 2935, 2859, 1717, 1474, 1131, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (ddd, J = 10.0, 5.2, 3.2 Hz, 1H), 3.75 (dt, J = 8.4, 3.2 Hz 1H), 2.69 (dd, J = 14.4, 10.4 Hz, 1H), 2.60−2.47 (m, 2H), 2.38 (dd, J = 14.4, 3.2 Hz, 1H), 2.16−2.11 (m, 1H), 1.62−1.59 (m, 1H), 1.36 (dq, J = 14.4, 7.6 Hz, 1H), 1.06 (t, J = 7.2 Hz, 3H), 0.98 (s, 9H), 0.97 (s, 9H), 0.95 (t, J = 7.2 Hz, 3H), 0.73 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 74.1, 73.3, 45.4, 40.3, 36.1, 28.1, 27.5 (×3), 27.2 (×3), 21.4, 20.7, 13.5, 8.7, 7.6; HRMS (+ESI) calcd for $C_{18}H_{36}O_3SiNa$ ($M + Na^+$), 351.2326; found, 351.2314.

Aldol Reaction of Aldehyde 5 with Ethyl Ketone 6. Aldols 4 and *dia*-4. To a stirred solution of the ethyl ketone **6** (37.0 mg, 0.11 mmol) in dry CH_2Cl_2 (2.0 mL) cooled at −78 °C was added dropwise $PhBCl_2$ (30 μL, 0.22 mmol) and i-Pr_2NEt (47 μL, 0.28 mmol) followed by stirring at the same temperature for 30 min. The resultant mixture was allowed to warm slowly to 0 °C and was stirred for another 20 min. To the solution cooled again at −78 °C was added the aldehyde **5** (12.0 mg, 0.05 mmol) in dry CH_2Cl_2 (0.3 mL) followed by stirring at −78 °C for 2 h. The reaction was quenched with pH 7 phosphate buffer (2 mL). The resultant mixture was then extracted with Et_2O (2 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 25% EtOAc in hexane) to afford **4** (28.0 mg, 45%) and its diastereomer *dia*-**4** (5.5 mg, 9%). **4**: a colorless oil; $R_f = 0.49$ (33% EtOAc−hexane); $[\alpha]^{20}_D$ +38.1 (c 0.40, $CHCl_3$); IR (film) 3511 (br), 2966, 2934, 2859, 1758, 1706, 1197, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 (ddd, J = 17.2, 10.0, 8.0 Hz, 1H), 5.44 (dd, J = 8.0, 1.6 Hz, 1H), 5.30 (dd, J = 10.0, 1.2 Hz, 1H), 5.27 (dd, J = 17.2, 0.8 Hz, 1H), 4.64 (ddd, J = 8.8, 5.6, 3.2 Hz, 1H), 3.98 and 3.92 (ABq, J = 18.4 Hz, 2H), 3.75 (td, J = 8.0, 3.2 Hz, 1H), 3.69 (dd, J = 10.0, 2.0 Hz, 1H), 3.65 (t, J = 8.0 Hz, 1H), 3.41 (s, 3H), 3.26 (s, 3H), 3.20 (br s, 1H, O*H*), 2.87 (qd, J = 7.2, 2.0 Hz, 1H), 2.74 (dd, J = 15.2, 10.4 Hz, 1H), 2.47 (dd, J = 15.2, 3.2 Hz, 1H), 2.16−2.07 (m, 2H), 1.67−1.55 (m, 1H), 1.44−1.33 (m, 1H), 1.14 (d, J = 7.2 Hz, 3H), 0.98−0.94 (m, 21H), 0.87 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3, 167.0, 136.0, 120.1, 82.2, 74.5, 73.4, 73.1, 71.0, 69.7, 59.3, 56.4, 46.4, 44.1, 40.3, 35.4, 28.2, 27.4 (×3), 27.2 (×3), 21.4, 20.7, 13.5, 9.9, 8.7, 8.4; HRMS (+ESI) calcd for $C_{29}H_{54}O_8SiNa$ ($M + Na^+$), 581.3480; found, 581.3506. *dia*-**4**: a colorless oil; $R_f = 0.45$ (33% EtOAc−hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.62 (ddd, J = 16.8, 10.4, 8.0 Hz, 1H), 5.31 (δ, J = 10.4, 1.6 Hz, 1H), 5.28 (dd, J = 16.8, 1.6 Hz, 1H), 4.98 (dd, J = 8.0, 4.0 Hz, 1H), 4.62 (ddd, J = 9.2, 5.2, 3.6 Hz, 1H), 3.98 and 3.90 (ABq, J = 16.4 Hz, 2H), 3.77 (dd, J = 7.2, 4.4 Hz, 1H), 3.73 (dd, J = 8.0, 4.4 Hz, 1H), 3.63 (t, J = 8.0 Hz, 1H), 3.40 (s, 3H), 3.28 (s, 3H), 3.04 (qd, J = 7.2, 4.4 Hz, 1H), 2.72 (dd, J = 15.2, 10.0 Hz, 1H), 2.54 (dd, J = 15.6, 3.6 Hz, 1H), 2.18−2.08 (m, 2H), 1.63−1.54 (m, 2H), 1.41−1.34 (m, 1H), 1.19 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 7.2 Hz, 3H), 0.98 (s, 18H), 0.95 (t, J = 7.2 Hz, 3H), 0.76 (d, J = 7.2 Hz, 3H); HRMS (+ESI) calcd for $C_{29}H_{54}O_8SiNa$ ($M + Na^+$), 581.3480; found, 581.3454.

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Supporting Information Available: General methods, procedures, compound characterizations, and copies of ^1H and ^{13}C NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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