Synthesis of C3–C12 Fragment of 24-Demethylbafilomycin C_1 via *anti*-Selective Aldol Condensation as the Key Stereocontrol Step

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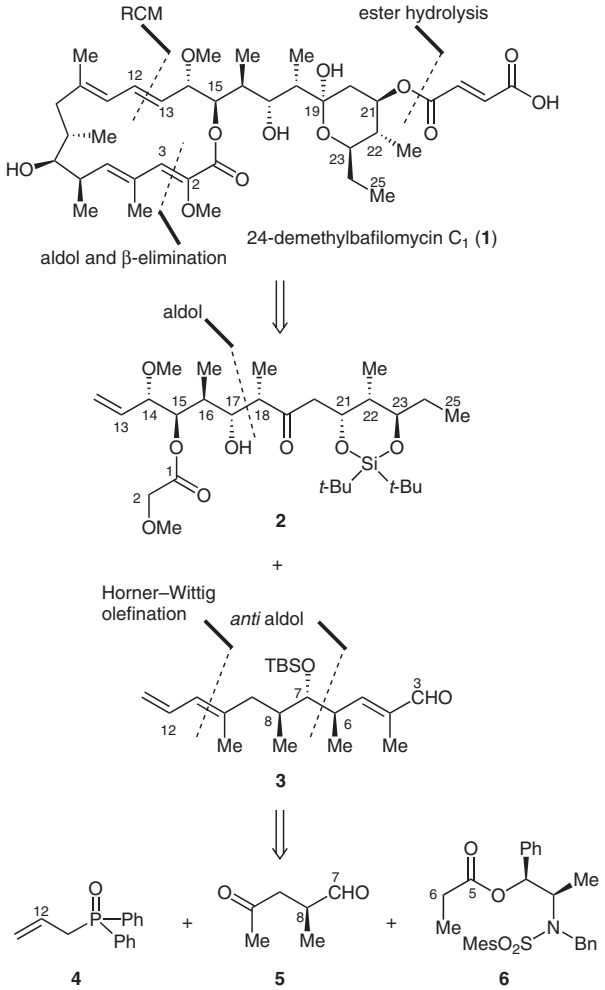
Abstract: An efficient synthesis of the C3–C12 aldehyde fragment of 24-demethylbafilomycin C_1 was accomplished for assembling the 16-membered plecomacrolide skeleton according to a 1,3-diene–ene ring-closing metathesis (RCM) strategy. A boron-mediated *anti*-selective aldol condensation of Abiko's chiral propionate was used to secure the C6 and C7 stereogenic centers while the C8 chirality was introduced from a chiral building block. The dithiane alkylation and the methyl ketone Horner–Wittig olefination using allyldiphenylphosphine oxide were employed for construction of the requisite (*E*)-1,3-diene subunit.

Key words: *anti*-selective aldol, 1,3-diene, dithiane, Horner–Wittig olefination, α,β-unsaturated aldehyde

The plecomacrolides are a family of unique secondary metabolites possessing a 16- or 18-membered ring macrolactone and a folding hemiacetal subunit on the side chain.[1,2] 24-Demethylbafilomycin C_1 (**1**, Scheme 1)[3a] is a new member of the class B subgroup of the plecomacrolides. It is produced together with other related compounds by a commensal microbe *Streptomyces* sp. CS associated with *Maytenus hookeri*.[3] 24-Demethylbafilomycin C_1 was reported to exert strong cytotoxicity at 10^{-6} to 10^{-8} M concentrations against P388 and A549 tumor cell lines by ca. 80% and 90% inhibitions, respectively. The parent antibiotic, bafilomycin A_1, does not have the fumaric acid monoester moiety attached to the oxygen atom at C21.[4] It is the most investigated class B plecomacrolide as the specific vacuolar H^+-ATPase (V-ATPase) inhibitor.[5–8] Since Evans and Calter[9a] reported the first total synthesis of bafilomycin A_1 in 1993, a number of laboratories has dedicated efforts to construct this complex and highly functionalized target.[9–11] In general, the palladium-catalyzed cross-coupling reactions of vinyl boron or tin derivatives with vinyl iodides were used for installation of the 1,3-diene functionality via formation of the C11–C12 bond. We designed a different approach toward assembling the tetraene macrolactone embedded in a 16-membered ring by employing a 1,3-diene–ene ring-closing metathesis (RCM).[12,13] According to the findings by Yang and co-workers,[14] the 16-membered ring macrolactone with the tetraene in place could not be directly constructed via 1,3-diene–ene RCM. Therefore, we focused our effort on alternative solutions to meet this synthetic challenge.[15] We have successfully prepared a model macrolactone lacking the C6–C8 stereotriad via sequential formation of the C2–C3 single bond by aldol condensation, the C12–C13 double bond by 1,3-diene–ene RCM, and finally the C2–C3 double bond by β-elimination.[15a,b] We have recently accomplished synthesis of the C13–C25 fragment **2** by a diastereoselective aldol condensation of the ketone boron enolate as the key step.[16] We report here on synthe-



Scheme 1 Retrosynthetic bond disconnections of 24-demethylbafilomycin C_1 (**1**) yielding the C13–C25 side chain **2** and the C3–C12 aldehyde fragment **3**

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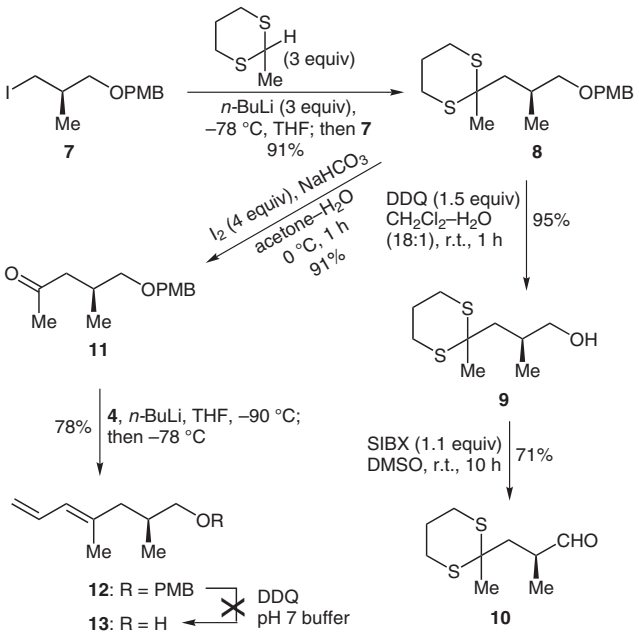
sis of the C3–C12 aldehyde fragment **3** via a highly *anti*-selective aldol condensation of a derivative of the keto aldehyde **5** with Abiko's chiral propionate **6**.[17]

The C6–C8 stereotriad[18] in the bafilomycin-type plecomacrolides has been synthesized in various manners. Toshima and co-workers[9d] used the chiral intermediate obtained from Felkin–Anh-selective Hiyama addition of crotyl–chromium species to O-protected lactaldehyde[19] for installation of the C6/C7 *anti* stereochemistry. It was followed by a substrate-controlled hydroboration to secure the C8 stereogenic center. Roush's total synthesis[9f] employed a diastereoselective crotylboration of the chiral aldehyde derived from methyl (*R*)-(–)-3-hydroxy-2-methylpropionate to control the C6–C8 *anti*/*anti* stereotriad. Hanessian's strategy[9g] relied on the stereocontrolled cuprate additions in a two-directional mode. Marshall's total synthesis[10b] of bafilomycin V_1 utilized stereoselective addition of chiral nonracemic allenylzinc reagent to a chiral aldehyde for formation of the C7–C8 bond. In addition, an interesting desymmetrization of a cyclohexanone derivative was developed for accessing the *anti*/*anti* stereotriad.[10d] According to our synthetic strategy in Scheme 1, the 1,3-diene moiety of **3** could be installed by the Horner–Wittig olefination of the methyl ketone **5** with allyldiphenylphosphine oxide **4**.[20] The aldehyde functionality in **5** was expected to undergo an *anti*-selective aldol reaction with the (*E*)-boron enolate generated from Abiko's chiral propionate **6**. Thus, our first task was to search for a suitable synthetic equivalent of **5** for easy differentiation of the two carbonyl groups.

As given in Scheme 2, we prepared the dithiane derivative **8** from the known chiral iodide **7** readily available from methyl (*R*)-(–)-3-hydroxy-2-methylpropionate.[21] Hydrolysis of the dithiane **8** by treating with I_2 and $NaHCO_3$ in aqueous acetone afforded the ketone **11** (91%) which was subjected to the Horner–Wittig olefination with **4**[20] to form the 1,3-diene **12** in 78% yield. We tried removal of the PMB group in **12** with DDQ but the desired alcohol **13** was not obtained due to decomposition under the reaction conditions. On checking the crude product by ^{1}H NMR spectroscopy, only 4-methoxybenzaldehyde could be assigned along with some unidentified materials. We turned our attention to the dithiane aldehyde **10** as the masked ketone aldehyde **5**. Removal of the PMB group in **8** with DDQ gave a 95% yield of the alcohol **9**. It was followed by a selective oxidation of the primary alcohol in the presence of the dithiane moiety. After screening for different oxidants, we managed to obtain **10** in 60–70% yields from **9** by using stabilized IBX[22] (1.1 equiv; added in portions),[23] Dess–Martin periodinane (DMP),[24] or TPAP–NMO.[25] It is worthy mentioning that IBX was reported to remove a 1,3-dithinyl group in aqueous DMSO.[26]

We performed the *anti*-selective aldol condensation of the chiral aldehyde **10** with the (*E*)-boron enolate derived from **6** to secure the *anti*/*anti* stereotriad in **14** (Scheme 3). The latter was prepared on a 3 gram scale in high diastereoselectivity of 95:5[27] and in the desired absolute configuration as predicted by the chiral auxiliary in **6**.[17]

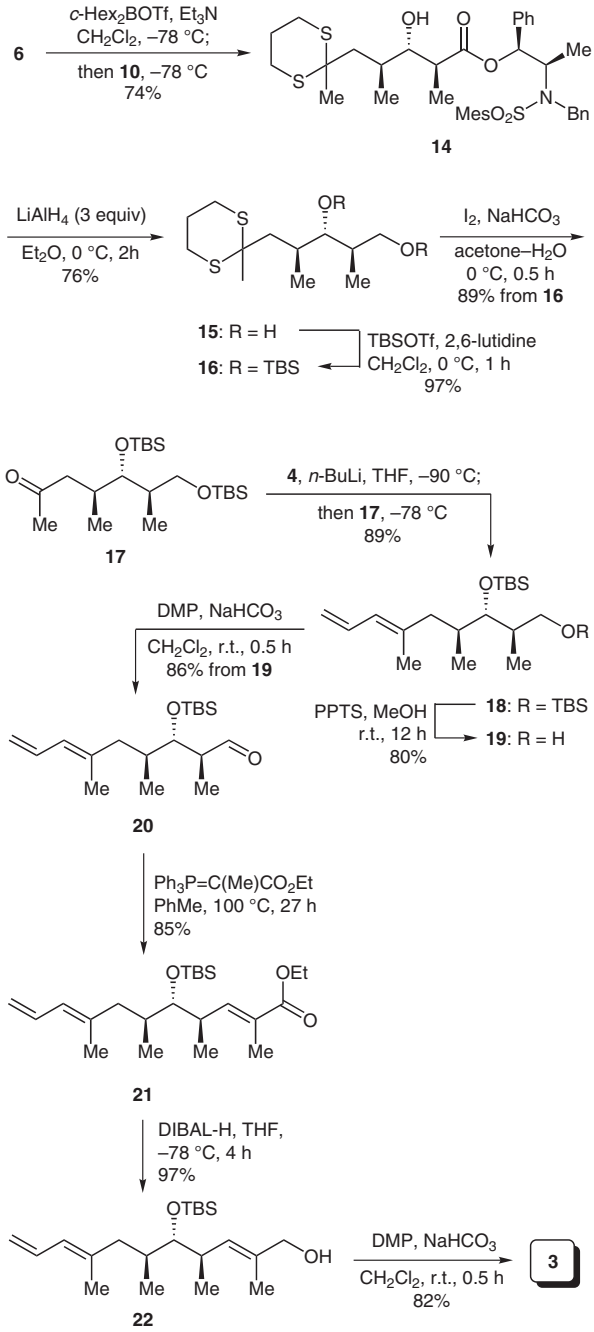


Scheme 2 Synthesis of the dithiane aldehyde **10** as the masked **5**

Influence of the stereogenic center of the aldehyde **10** on the stereochemical course of the aldol reaction was not observed. Reduction of **14** with $LiAlH_4$ gave the diol **15** in 76% isolated yield. Protection of **15** as the bis-TBS ether **16** (97%) and subsequent hydrolysis of the dithianyl moiety afforded the methyl ketone **17** in 89% yield from **16**. The Horner–Wittig olefination of **17** with allyldiphenylphosphine oxide **4**[20] furnished the (*E*)-1,3-diene **18** in 89% yield. It was found that addition of the reagents at –90 °C was essential for achieving high diastereoselectivity for the Horner–Wittig olefination. Selective removal of the primary TBS ether in **18** by treating with a catalytic amount of PPTS in MeOH at room temperature gave the alcohol **19** in 80% yield. DMP oxidation in the presence of $NaHCO_3$ converted **19** into the corresponding aldehyde **20** (86%)[28] whose 1,3-diene moiety remained intact under the oxidation conditions. The aldehyde **20** was subjected to the Wittig olefination with the ylide, $Ph_3P{=}C(Me)CO_2Et$, in toluene at 100 °C for 27 hours to produce the α,β-unsaturated ester **21** in 85% yield with exclusive *E* configuration for the newly formed trisubstituted double bond. Reduction of the ester moiety in **21** by DIBAL-H afforded the alcohol **22** (97%) which was then oxidized with DMP to furnish the target C3–C12 aldehyde fragment **3** in 82% yield.[29]

In summary, we have developed a concise synthesis of the C3–C12 fragment **3** of 24-demethylbafilomycin C_1 and the related 16-membered class B plecomacrolides. The readily available dithiane aldehyde **10** was confirmed to be an appropriate synthon to the ketone aldehyde **5**. The *anti*-selective aldol reaction of **10** with the (*E*)-boron enolate derived from Abiko's chiral propionate **6** afforded the desired *anti*/*anti* stereotriad in high diastereoselectivity presumably attained via a reagent control process. Finally, the (*E*)-1,3-diene functionality was installed at –90 °C by

the Horner–Wittig olefination of the methyl ketone **17** with allyldiphenylphosphine oxide **4**. Therefore, the target molecule **3** could be prepared from the chiral iodide **7** by a 13-step sequence in an overall yield of 12.3%. Moreover, our findings on selective oxidation of an alcohol with stabilized IBX, DMP, or TPAP–NMO in the presence of a dithianyl moiety may be useful for application in multistep syntheses.



Scheme 3 Synthesis of the C3–C12 aldehyde fragment **3**

Acknowledgment

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(23) **Procedure for Oxidation of the Alcohol 9 with Stabilized IBX to Form Aldehyde 10**
To a solution of the alcohol **9** (1.990 g, 9.66 mmol) in DMSO (40 mL; without drying) was added stabilized IBX in six portions (45 wt%, 1.002 × 6 g, 9.66 mmol). After each addition of stabilized IBX, the resultant mixture was stirred for 2 h at r.t. The reaction was quenched by aq $Na_2S_2O_3$ followed by addition of sat. aq $NaHCO_3$. The aqueous mixture was extracted with EtOAc (100 × 2 mL) and the combined organic layer was dried over anhyd Na_2SO_4, filtrated, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 14% EtOAc in hexane) to provide the aldehyde **10** (1.399 g, 71% yield).
Compound **10**: yellow oil; $[\alpha]_D^{20}$ –2.2 (*c* 1.35, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.71 (d, *J* = 1.8 Hz, 1 H), 2.94–2.60 (m, 6 H), 2.10–1.80 (m, 2 H), 1.70 (dd, *J* = 14.7, 3.0 Hz, 1 H), 1.56 (s, 3 H), 1.15 (d, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.4, 48.3, 43.2, 42.5, 28.3, 26.5 (×2), 24.6, 16.2. HRMS (ESI$^+$): *m/z* calcd for $C_9H_{17}OS_2$ [M + H$^+$]: 205.0721; found: 205.0729.

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(27) We checked the diastereomeric ratio of the isolated aldol products prepared in several runs by ^1H NMR spectroscopy and found that the ratio is about 95:5 in all cases. We did not obtain any separable minor diastereomers on the 3-gram-scale reaction, implying that the minor diastereomer is not separable from the major isomer.

(28) Epimerization of the aldehyde **20** obtained from both the DMP (aq $NaHCO_3$, CH_2Cl_2, r.t.) and SIBX (DMSO, r.t.) oxidation was observed. The diastereomeric ratios are about 95:5. We are not sure whether the epimerization occurred during the oxidation or over silica gel during column chromatographic separation.

(29) **Physical and Spectroscopic Data of 3**
Colorless oil; $[\alpha]_D^{20}$ 31.9 (*c* 0.73, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 6.72 (dd, *J* = 9.9, 1.2 Hz, 1 H), 6.61–6.48 (m, 1 H), 5.81 (d, *J* = 11.4 Hz, 1 H), 5.09 (dd, *J* = 16.8, 1.8 Hz, 1 H), 4.99 (d, *J* = 10.2 Hz, 1 H), 3.54 (dd, *J* = 4.5, 3.0 Hz, 1 H), 2.95–2.85 (m, 1 H), 2.19 (d, *J* = 8.4 Hz, 1 H), 1.85–1.64 (m, 2 H), 1.76 (s, 3 H), 1.71 (s, 3 H), 1.04 (d, *J* = 7.5 Hz, 3 H), 0.92 (s, 9 H), 0.74 (d, *J* = 6.3 Hz, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.6, 157.6, 137.3, 137.2, 133.0, 127.4, 115.0, 79.4, 43.7, 36.9, 35.9, 26.0 (×3), 18.6, 18.3, 16.3, 15.3, 9.3, –3.9, –4.0. HRMS (ESI$^+$): *m/z* calcd for $C_{21}H_{39}O_2Si$ [M + H$^+$]: 351.2719; found: 351.2729.