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Synthetic studies on bafilomycin A_1: stereoselective synthesis of the enantiopure C_1–C_{11} fragment

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Abstract—The synthesis of the enantiopure C_1–C_{11} fragment of bafilomycin A_1 has been achieved with a 4% overall yield over 18 steps from (*R*)-(+)-citronellol. Key steps involve Sharpless asymmetric epoxidation, Miyashita reaction of a γ,δ-epoxymethacrylate with trimethylaluminum in the presence of water, bis-OTMS selective Swern oxidations, Corey–Fuchs alkyne formation, Negishi's carbometalation, and stereoselective formation of the C_2–C_3 trisubstituted bond of the conjugated diene by a Wittig-type olefination of the α,β-unsaturated C_3–C_{11} aldehyde with the ylide derived from the readily available phosphonium salt [Cl^-, $Ph_3P^+CH(OMe)COOMe$].

1. Introduction

Bafilomycins and concanamycins are related macrolides (16- and 18-membered lactones, respectively), which are highly selective inhibitors of vacuolar proton ATPases (V-ATPases) at the nanomolar concentration and therefore they are important tools allowing the distinction with other types of ATPases.[1] V-ATPases are multisubunit protein complexes, composed of two functional domains, which are ubiquitous in eukaryotic organisms,[2] and much effort is still undertaken in order to identify the mechanism of action and the binding site(s) of bafilomycins and concanamycins to the V-ATPases.[3] Much effort has also been done to examine the structure–activity relationships of these macrolides.[4] However bafilomycins or concanamycins are not selective for any particular type of V-ATPases and consequently are highly toxic when administered to animals. In quest of new leads for the treatment of osteoporosis, considerable efforts have been achieved in order to find smaller and simpler molecules, mimicking some structural features of bafilomycins or concanamycins, which might be more selective for the V-ATPase of human osteoclasts with respect to the V-ATPases of other human tissues.[4a,5] The stereochemistry and absolute configuration of bafilomycin and some related macrolides have been first assigned by Corey and Ponder on the basis of an analysis of the published ^{1}H NMR data coupled with extensive computer modeling,[6] and were further confirmed by X-ray crystallography.[7]

The first total synthesis of bafilomycin A_1 has been achieved by Evans and Calter,[8] and subsequently were reported the syntheses of Toshima,[9] Roush,[10] Hanessian,[11] and their co-workers. Yonemitsu and co-workers also accomplished the total synthesis of the related macrolide hygrolidin,[12] whereas Marshall and Adams disclosed that of bafilomycin V_1, an open chain *seco*-methyl ester.[13] The syntheses of structural subunits of bafilomycin A_1 have also been reported by the groups of Paterson,[14] Férézou and Prunet,[15] Cossy.[16] On the other hand, total syntheses of concanamycin F have also been completed by Paterson,[17] Toshima[18] and their co-workers. We wish to now report our synthetic approach to bafilomycin A_1 **1**,[19] based on the retrosynthetic analysis described in Scheme 1 for the 16-membered macrolide substructure **A**, corresponding to Evans and Calter's intermediate,[8] which might be obtained from intermediates **B** and **C** either via a lactonization using an acyl activation, or via an intramolecular Stille coupling.

Keywords: Epoxides; Aluminium and compounds; Alkynes; Zirconium and compounds; Silyl ether selective oxidation; Wittig reactions.
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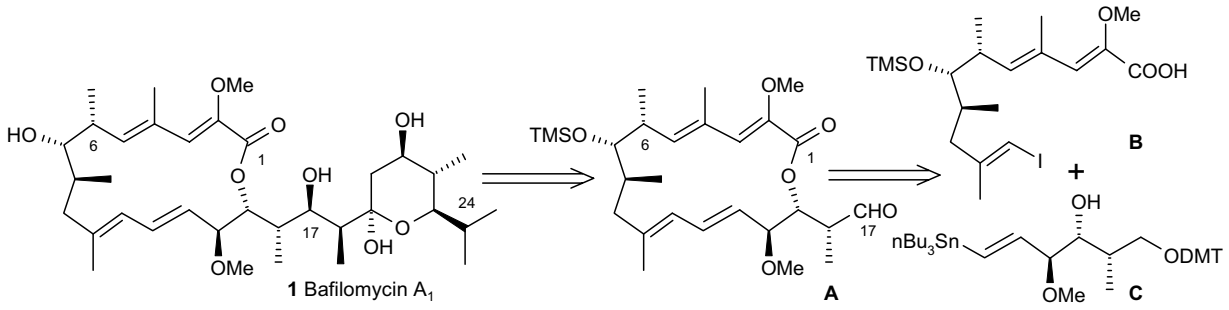
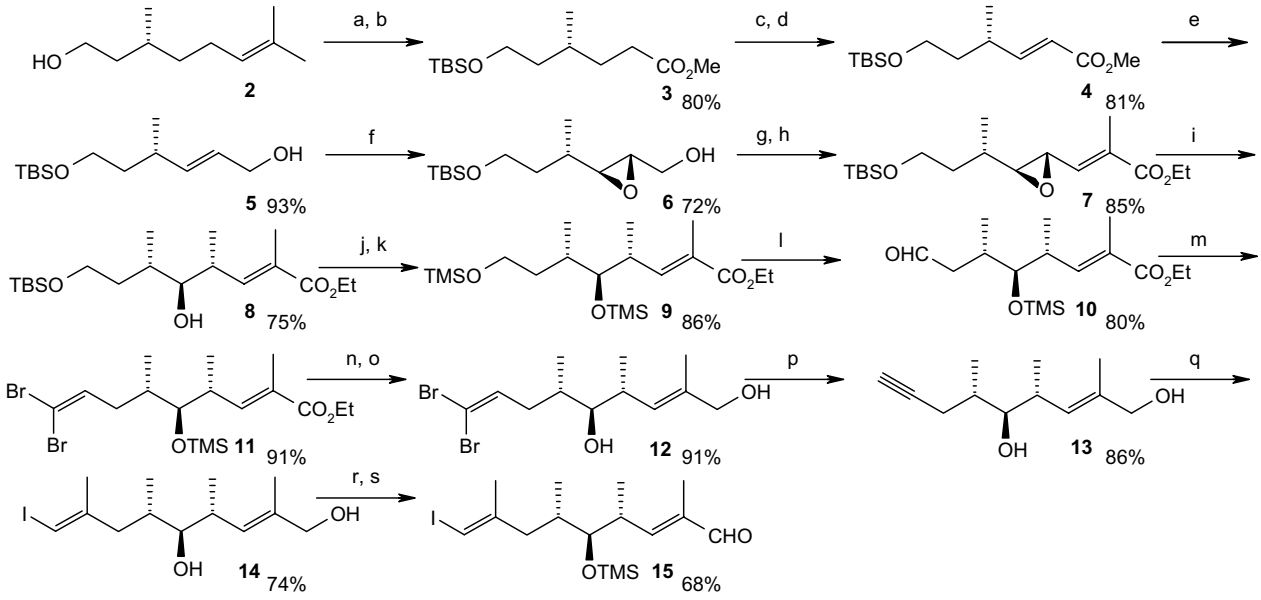


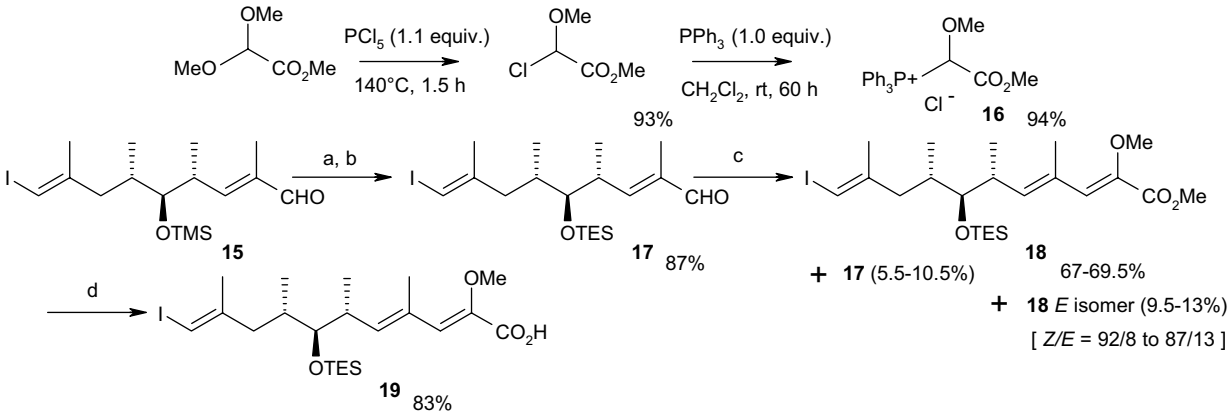
Scheme 1.



Scheme 2. Reagents and conditions: (a) TBSCl (1.2 equiv), imidazole (2.2 equiv), DMF, rt, quant.; (b) NaOH 2.5 M in MeOH (5 equiv)/CH_2Cl_2 (1/4), −78 °C, ozone, 80%; (c) LDA (1.2 equiv), THF, −78 °C, 30 min, then PhSeSePh (1.5 equiv), −78 °C, 1 h, −78 °C to rt in 1 h, 88%; (d) 30% H_2O_2 (4 equiv), CH_2Cl_2, pyridine (2 equiv), 0 °C, 92%; (e) DIBAH (5 equiv), toluene, −78 °C, 3 h; (f) $Ti(OiPr)_4$ (1.3 equiv), (+)-DET (1.3 equiv), anhyd CH_2Cl_2, *t*-BuOOH (−3 M in isooctanes, 2.2 equiv), −30 °C, 16 h; (g) oxalyl chloride (1.2 equiv), DMSO (2.4 equiv), CH_2Cl_2, −78 °C, 10 min, then **6**, 30 min and then NEt_3 (5.0 equiv), −78 °C to rt, 1 h; (h) crude aldehyde, $Ph_3P{=}C(Me)CO_2Et$ (2.0 equiv), THF, rt, 3 h; (i) **7** in $ClCH_2CH_2Cl$, H_2O (6.0 equiv), rt, then −30 °C, $AlMe_3$ 2 M in hexanes (10 equiv), 4 h; (j) TBAF 1 M (1.1 equiv), THF, rt, 2 h; (k) TMSCl (5 equiv), NEt_3 (8 equiv), DMF, rt, 2 h; (l) oxalyl chloride (1.1 equiv), DMSO (2.2 equiv), CH_2Cl_2, −78 °C, 15 min, then **9**, 45 min and NEt_3 (5.0 equiv), −78 °C to rt, 30 min; (m) PPh_3 (4 equiv), CBr_4 (2 equiv), CH_2Cl_2, then NEt_3 (8 equiv), rt, 15 min, then −78 °C, **10** and −78 °C to rt, 7 h; (n) DIBAH (3 equiv), toluene, −78 °C, 3 h; (o) TBAF 1 M (1.1 equiv), THF, rt, 2 h; (p) **12**, THF, −78 °C, then *n*-BuLi 1.6 M in hexanes (5 equiv), 1 h and −78 °C to rt, 2 h; (q) $AlMe_3$ 2 M in hexanes (6 equiv) added to Cp_2ZrCl_2 (2 equiv), anhyd $ClCH_2CH_2Cl$, rt, 1.5 h, then **13**, rt, 20 h, and subsequently −30 °C, I_2 (1.2 equiv) in THF, −30 °C to rt, 1 h; (r) TMSCl (5 equiv), NEt_3 (10 equiv), DMF, rt, 1.5 h, 91%; (s) oxalyl chloride (1.1 equiv), DMSO (2.2 equiv), CH_2Cl_2, −78 °C, 15 min, then bis-OTMS ether, 1 h and NEt_3 (5 equiv), −78 °C to rt, 45 min, 75%.

2. Synthesis of the C_3–C_{11} fragment (Scheme 2)

Synthesis started from commercial (*R*)-(+)-citronellol ($[\alpha]_D$ +5.3 (neat), 96% optical purity) and the methyl ester **3** was isolated in 80% overall yield after ozonolysis of the intermediate TBS ether, using Marshall's conditions.[20] The allylic alcohol **5** was then obtained in 75% yield from **3** (three steps); further Sharpless asymmetric epoxidation[21] afforded, after chromatography, the epoxy alcohol **6** as a pure enantiomer in 72% yield and 1% of a diastereoisomeric epoxy alcohol. Swern oxidation and further stereoselective Wittig olefination (*E*/*Z* = 94/6) gave, after chromatography, the required *E*-γ,δ-epoxymethacrylate **7** and its *Z* isomer, isolated in 85% and 4% yield, respectively. Highly regio- and stereoselective opening of **7** with $AlMe_3$–H_2O, in the conditions developed by Miyashita and co-workers,[22] gave the desired intermediate **8**, isolated in 75% yield; the best results were here obtained with a normal addition.[19] It was then converted into the bis-OTMS derivative **9** for a selective Swern oxidation,[23] which provided the aldehyde **10**, isolated in 69% overall yield from **8**. Conversion of **10** into the alkyne **13** was achieved by the methodology of Corey and Fuchs,[24] and the best conditions for obtaining the intermediate dibromoolefin **11** were found with the use of a preformed mixture[25] of Ph_3P (4 equiv), CBr_4 (2 equiv), and NEt_3 (8 equiv), in order to avoid deprotection of the silylether and further conversion of the corresponding alcohol into the bromide.[19] After DIBAH reduction of **11**, we chose to



Scheme 3. Reagents and conditions: (a) HF·pyridine (3.3 equiv), pyridine (10 equiv), THF, rt, 4 h; (b) TESOTf (6 equiv), *i*-Pr_2NEt (10 equiv), DMF, rt, 3 h; (c) **16** (3.0 equiv), NEt_3 (3.5 equiv), CH_2Cl_2, rt, 15 min, then addition of **17** in CH_2Cl_2, reflux, 4 days and again **16** (3.0 equiv), NEt_3 (3.5 equiv), reflux, 2 days; (d) 1 N aq NaOH (5 equiv)/THF (1/1), reflux, 24 h and then 1 N aq NaOH (5 equiv), reflux, 6 h.

deprotect the TMS ether for avoiding partial deprotection and intermolecular *trans*-silylation in the next step, due to our preliminary experiments.[19] The dibromoolefin **12** was then converted into **13**, isolated in 71% overall yield from **10** (four steps). The alkyne **13** gave stereospecifically the vinyl iodide **14**, isolated in 74% yield, using Negishi's carbometalation conditions;[26] use of the conditions developed by Wipf and Lim,[27] in the presence of 1 or 2 equiv of H_2O, in order to increase the rate of the carbometalation, led here to complex mixtures. Further selective Swern oxidation of the corresponding bis-OTMS ether afforded the desired aldehyde **15** in 68% overall yield from **14**.

Concerning that part, it is also worth to point out that when we compared different sequences, we isolated some unexpected products resulting from the participation of the triple bond or the dibromoolefin in the reaction of the corresponding *E*-γ,δ-epoxymethacrylate with $AlMe_3$ in the presence of water.[19]

3. The C_1–C_{11} fragment by a Wittig-type olefination (Scheme 3)

Toshima and co-workers tried a number of phosphonates and conditions in order to improve the stereoselectivity of the formation of the particular C_2–C_3 trisubstituted double bond; however, even in the final state of their synthesis, if the olefination was achieved in 89% yield, it afforded a *Z*/*E* mixture of 2/1.[9] Analogous results were also previously obtained with a phosphonate by Evans and Calter.[8a] Concerning that specific problem, the best solution was reported in 1997 by Paterson and co-workers in their studies related to concanamycins, with $(i\text{-PrO})_2P(O)$–CH(OMe)–COOMe/KHMDS/[18-6] crown in THF at 0 °C, conditions that provided the olefination product in 98% yield with a *Z*/*E* ratio of 94/6;[28] the Paterson conditions were later employed by Roush,[10] Marshall,[13] Toshima,[18b] and their co-workers. During completion of the present work, another original solution was developed by Férézou and co-workers, which was highly stereoselective, but was more complex and less efficient.[15a,c] In order to find another solution, we decided to examine Wittig-type olefinations with the phosphonium salt **16**, which is easy to prepare (Scheme 3).[29] Indeed the corresponding stabilized ylide should allow less basic conditions than those employed with the phosphonates. We first examined the reactions of this phosphonium salt with α,β-unsaturated aldehydes, which to our knowledge (except *trans*-cinnamaldehyde[29e]) were never examined before,[29] and among them more precisely α- or β-substituted by a methyl group, in different conditions (base, solvent, temperature, added salts). With these models, the best results with respect to yield and stereoselectivity (*Z*/*E* = 92/8 to 94/6) were obtained with NEt_3 in CH_2Cl_2, $ClCH_2CH_2Cl$, or toluene, at room temperature or 35–40 °C.[19] Higher temperatures in toluene, or use of more polar solvents like THF, were detrimental (stereoselectivity, yield, isomerization of the starting aldehyde).[19]

However, the same best olefination conditions applied to the aldehyde **15** led to partial deprotection for the starting material and the products, and therefore the 7-OTMS group was found here to be unsatisfactory; moreover the 7-OTMS group showed also to be too labile further in the synthesis.[19] Therefore, after deprotection of the silyl ether with [HF·pyridine] in the presence of pyridine to avoid any epimerization at C_6, and subsequent formation of the 7-OTES ether, **17** was obtained in 87% overall yield from **15**. After still some optimization with the aldehyde **17**, the required C_1–C_{11} fragment **18** was obtained with the desired *Z,E* geometry of the diene unit, with quite reproducible yields (67–69.5%) and stereoselectivity (92/8 to 87/13) (at a scale of 0.2–1 mmol).[30] No epimerization at C_6 or loss of stereochemistry of the conjugated double bond of the aldehyde **17** were observed. The stereochemistry of the *Z* and *E* olefins were unambiguously determined by NMR (NOE, chemical shifts, $^3J[C_1\text{–}H_3]$). After completion of this work, Hanessian et al. reported another efficient two-step solution for the stereospecific conversion of **17** into the required diene **18** in 69% overall yield.[11]

Finally the corresponding acid **19** was isolated in 83% yield after saponification of **18** with 1 N aqueous NaOH, in THF at reflux, and purification by chromatography over silica gel; no isomerization or epimerization were observed.[19]

The enantiopure C_1–C_{11} fragment **19** of bafilomycin is thus obtained with a 4% overall yield over 18 steps from commercially available (*R*)-(+)-citronellol.

Acknowledgements

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30. Compound **18**: colorless oil; $[\alpha]_D$ −45 (*c* 0.1, $CHCl_3$); IR (cm^{-1}, $CHCl_3$): 1713 (C=O), 1621 (C=C); ^1H NMR (400 MHz, $CDCl_3$): δ/TMS 6.60 (s, 1H, H_3), 5.92 (dq, 1H, H_5, $J_{5,6} = 10$, $J_{CH_3,5} = 1$), 5.83 (s, 1H, H_{11}), 3.79 (s, 3H, CO_2CH_3), 3.65 (s, 3H, OCH_3), 3.40 (dd, 1H, H_7, $J_{6,7} = 3.5$, $J_{7,8} = 5.5$), 2.68 (m, 1H, H_6), 2.43 (dd, 1H,

H_{9a}, $J_{9a,9b} = 13$, $J_{9a,8} = 3$), 1.97 (d, 3H, CH_3, $J_{CH_3,5} = 1$), 1.92 (dd, 1H, H_{9b}, $J_{9a,9b} = 13$, $J_{9b,8} = 10, 5$), 1.77 (s, 3H, CH_3), 1.68 (m, 1H, H_8), 0.96 (d, 3H, CH_3, $J_{6,CH_3} = 7$), 0.96 (t, 9H, CH_3CH_2Si, $J_{CH_3,CH_2Si} = 8$), 0.73 (d, 3H, CH_3, $J_{8,CH_3} = 7$), 0.60 (q, 6H, CH_3CH_2Si, $J_{CH_3,CH_2Si} = 8$); ^{13}C NMR (50.3 MHz, $CDCl_3$): 165.5 (C_1), 147.0 (C_{10}), 142.7 and 130.3 (C_2, C_4), 141.7 (C_5), 130.1 (C_3), 80.6 (C_7), 75.3 (C_{11}), 60.3 (OCH_3), 52.0 (CO_2CH_3), 43.1 (C_9), 36.1 (C_6, C_8), 23.6, 18.5, 15.8 and 14.7 (CH_3), 7.2 (CH_3CH_2Si), 5.5 (CH_3CH_2Si); $C_{23}H_{41}IO_4Si = 536.56$; MS (EI, m/z): 536 (M^+), 537 ($MH)^+$, 507, 115 ($Si(C_2H_5)_3^+$).

18 (*E*,*E*) isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ/TMS 5.84 (s, 1H, H_{11}), 5.62 (s, 1H, H_3), 5.40 (dq, 1H, H_5, $J_{5,6} = 10$, $J_{CH_3,5} = 1$), 3.76 (s, 3H, CO_2CH_3), 3.65 (s, 3H, OCH_3), 3.36 (dd, 1H, H_7, $J_{6,7} = 4$, $J_{7,8} = 5$), 2.60 (m, 1H, H_6), 2.46 (dd, 1H, H_{9a}, $J_{9a,9b} = 13$, $J_{9a,8} = 3$), 1.93 (dd, 1H, H_{9b}, $J_{9a,9b} = 13$, $J_{9b,8} = 10$), 1.81 (s, 3H, CH_3), 1.74 (d, 3H, CH_3, $J_{CH_3,5} = 1$), 1.70 (m, 1H, H_8), 0.97 (d, 3H, CH_3, $J_{6,CH_3} = 7$), 0.97 (t, 9H, CH_3CH_2Si, $J_{CH_3,CH_2Si} = 8$), 0.75 (d, 3H, CH_3, $J_{8,CH_3} = 7$), 0.61 (q, 6H, CH_3CH_2Si, $J_{CH_3,CH_2Si} = 8$); $C_{23}H_{41}IO_4Si = 536.56$; MS (EI, m/z): 536 (M^+), 507, 475, 115 ($Si(C_2H_5)_3^+$).

19: pale yellow oil; IR (cm^{-1}, $CHCl_3$): 1723 and 1686 (C=O), 1614 (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ/TMS 6.73 (s, 1H, H_3), 6.00 (dq, 1H, H_5, $J_{5,6} = 10$, $J_{CH_3,5} = 1$), 5.84 (br s or q, 1H, H_{11}, $J_{CH_3,11} = 1$), 3.69 (s, 3H, OCH_3), 3.41 (dd, 1H, H_7, $J_{6,7} = 3.5$, $J_{7,8} = 5.5$), 2.70 (m, 1H, H_6), 2.44 (dd, 1H, H_{9a}, $J_{9a,9b} = 13$, $J_{9a,8} = 4$), 1.99 (d, 3H, CH_3, $J_{CH_3,5} = 1$), 1.93 (dd, 1H, H_{9b}, $J_{9a,9b} = 13$, $J_{9b,8} = 10.5$), 1.79 (d, 3H, CH_3, $J_{CH_3,11} = 1$), 1.70 (m, 1H, H_8), 0.99 (d, 3H, CH_3, $J_{6,CH_3} = 7$), 0.97 (t, 9H, CH_3CH_2Si, $J_{CH_3,CH_2Si} = 8$), 0.74 (d, 3H, CH_3, $J_{8,CH_3} = 7$), 0.61 (q, 6H, CH_3CH_2Si, $J_{CH_3,CH_2Si} = 8$); ^{13}C NMR (50.3 MHz, $CDCl_3$): 170.2 (C_1), 146.7 (C_{10}), 143.0 and 132.0 (C_2, C_4), 141.6 (C_5), 130.1 (C_3), 80.4 (C_7), 75.0 (C_{11}), 60.2 (OCH_3), 42.7 (C_9), 35.8 (C_6, C_8), 23.3, 18.2, 15.6 and 14.3 (CH_3), 6.8 (CH_3CH_2Si), 5.3 (CH_3CH_2Si); $C_{22}H_{39}IO_4Si = 522.53$; MS (SIMS, m/z): 545 (MNa^+).