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Enantioselective monoreduction of 2-alkyl 1,3-diketones using chiral ruthenium catalysts. Synthesis of the C14–C25 fragment of bafilomycin A_1

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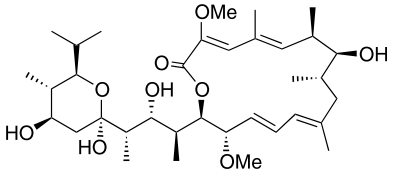
Abstract—The enantioselective monoreduction of 2-alkyl 1,3-diketones by dynamic kinetic resolution using optically active ruthenium catalysts allowed the preparation of the C14–C25 fragment of bafilomycin A_1.

Bafilomycin A_1 is a polyketide isolated from the fermentation broth of *Streptomyces griseus* in 1983[1] (Scheme 1). The natural product is a member of the plecomacrolide family of macrolide antibiotics that includes the hygrolidins,[2,3] the concanamycins[4] and formamicin.[5,6]

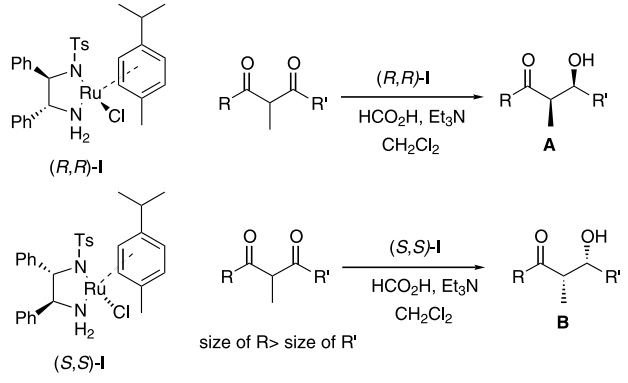


Scheme 1. Bafilomycin A_1.

Bafilomycin A_1 is a potent and specific inhibitor of vacuolar ATPases (V-ATPases) in vitro and in vivo[7] and displays broad antibacterial and antifungal activity.[8] The stereochemistry of bafilomycin A_1 was initially assigned on the basis of molecular modelling and conformational analysis of published NMR data,[9] and was confirmed by X-ray analysis.[10,11]

The natural compound contains twelve stereogenic centers, two diene units, an acid- and base-sensitive six-membered hemiketal unit, which participates in the hydrogen-bonding network with the C17 hydroxyl group and the 16-membered lactone carbonyl. By virtue of the challenging chemical structure and biological properties, considerable effort has been devoted to the development of efficient syntheses of bafilomycin A_1 and its analogues.[7b,12,13]

Recently, we reported that the enantioselective monoreduction of 2-alkyl 1,3-diketones by dynamic kinetic resolution mediated by chiral ruthenium catalysts (*R*,*R*)-**I** and (*S*,*S*)-**I** afforded, respectively, and selectively 2-alkyl 3-hydroxyketones of type **A** and **B** in high diastereo- and enantioselectivity[14] (Scheme 2). As an extension of this work, we report herein the application of this enantioselective monoreduction of diketones to the synthesis of the C14–C25 fragment of bafilomycin A_1.



Scheme 2. Enantioselective monoreduction of 2-alkyl 1,3-diketones.

The retrosynthetic analysis of bafilomycin A_1 was envisaged by assembling fragments **C** and **D** using a Stille coupling reaction followed by a macrolactonization.

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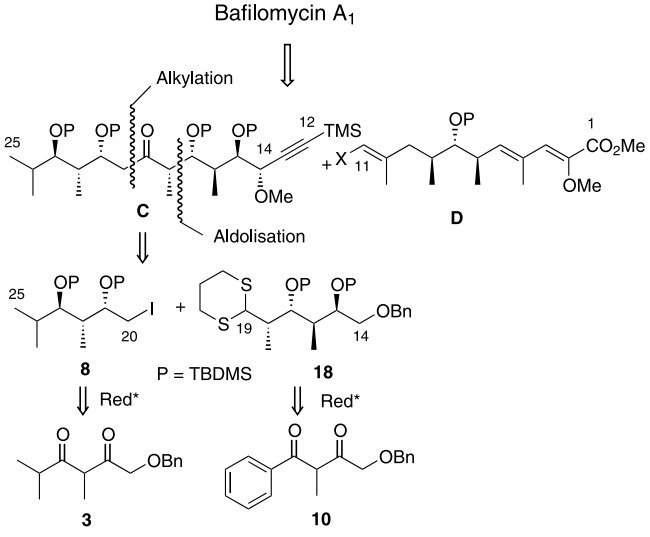
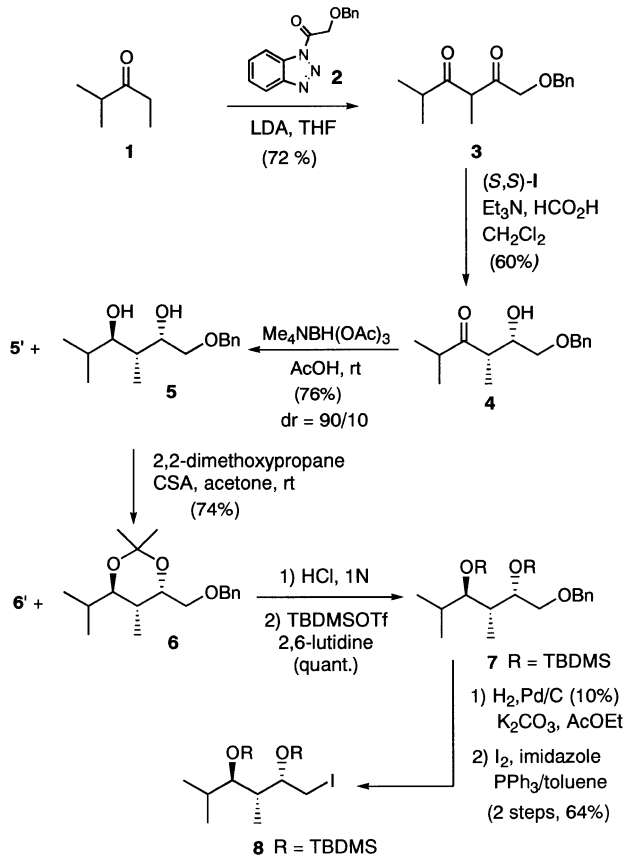
The C12–C25 fragment (fragment **C**) could be synthesized by alkylation of dithiane **18** with iodide **8**. The stereotriad **8** and the stereotetrad **18** could be obtained by enantioselective monoreduction of diketones **3** and **10**, using the optically active ruthenium catalysts (*S*,*S*)-**I** and (*R*,*R*)-**I**, respectively (Scheme 3).

The synthesis of the C20–C25 segment of bafilomycin A_1, iodide **8**, began with the preparation of diketone **3**. This compound was obtained by condensation of the kinetic enolate of 2-methylpentan-3-one **1** (LDA, THF, −78°C) with acylbenzotriazole **2** (72% yield). The enantioselective monoreduction of **3**, accomplished using ruthenium complex (*S*,*S*)-**I** in the presence of Et_3N and HCO_2H in refluxing CH_2Cl_2, afforded the β-hydroxyketone **4** in 60% yield[14] and 94% ee.[15] Hydroxyketone **4** was reduced with $Me_4NBH(OAc)_3$ in acetic acid[16] to give the *syn*,*anti*-stereotriad **5**. Under these conditions, a mixture of two isomers **5** and **5′**[17] was obtained in a ratio of 90/10 in 76% yield. The separation of the two isomers was tedious and, in order to overcome this difficulty, the mixture of the two isomers was converted to the corresponding acetonides[18] **6** and **6′** (dimethoxypropane, CSA in acetone, 74% yield) which were then separated. As the ketal protecting group proved to be troublesome for further operations, compound **6** was transformed to the bis-*t*-butyldimethylsilyl (TBDMS) ether **7** in a two-step sequence in quantitative yield (HCl 1N, THF then TBDMSOTf, 2,6-lutidine, CH_2Cl_2). The conversion of **7** into iodide **8** was achieved in 64% yield after selective cleavage of the benzyl protecting group [H_2, Pd/C (10%), K_2CO_3, AcOEt, 71% yield] followed by iodination (I_2, PPh_3, imidazole in refluxing toluene).[19] Iodide **8** was obtained in eight steps from 2-methylpentan-3-one **1** with an overall yield of 15.5% (Scheme 4).

The synthesis of dithiane **18**, which represents the C14–C19 fragment, was realized from diketone **10**. Diketone **10** was prepared in 72% yield by condensation of the lithium enolate of propiophenone **9** with



Scheme 3. Retrosynthetic analysis of bafilomycin A_1.



Scheme 4. Synthesis of the C20–C25 fragment.

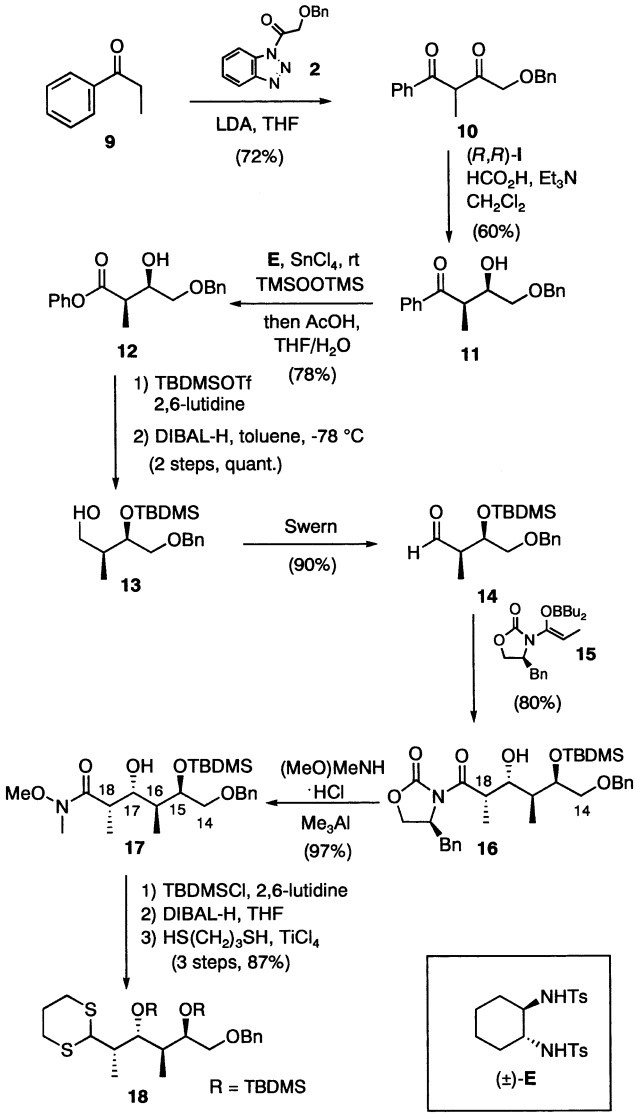
acylbenzotriazole **2**. The enantioselective monoreduction of **10**, with ruthenium complex (*R*,*R*)-**I**, under the previously developed conditions[14] led to β-hydroxyketone **11** in 93% ee.[14]

For the construction of the *syn*,*anti*,*syn*-stereotetrad, the β-hydroxyketone **11** was transformed to aldehyde **14** via ester **12** using a regioselective Baeyer–Villiger oxidation. The Baeyer–Villiger oxidation of the unprotected β-hydroxyketone **11** was achieved with bis(trimethylsilyl) peroxide in the presence of $SnCl_4$ and (±)-1,2-bis(tosylamido)cyclohexane **E** in CH_2Cl_2 at rt.[20] After treatment with $NaHCO_3$ followed by acidic treatment for 24 h, the β-hydroxy ester **12** was isolated in 78% yield, and transformed into the desired aldehyde **14** in a three-step sequence. The hydroxy group in **12** was protected as a TBDMS ether and, after reduction with DIBAL-H (toluene, −78°C), alcohol **13** was oxidized to aldehyde **14** (Swern oxidation) with a 90% yield for the overall process (Scheme 5).

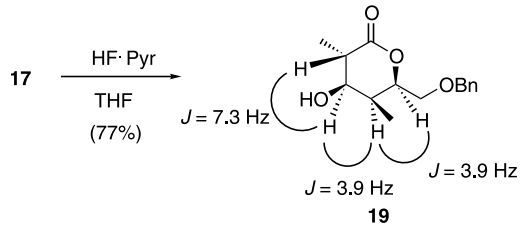
The required configuration at C17 and C18 was set with an anti-Felkin–*anti*-selective aldol reaction.[21] Addition of (*Z*)-oxazolidinone boron enolate **15** to aldehyde **14** led to **16** in 80% yield as a single diastereomer. The relative stereochemistry in **16** was confirmed by transformation of **16** into lactone **19** via amide **17** (cf. vide infra). The value of the ^1H NMR coupling constants in **19** ($J_{H15\text{-}H16}=3.9$ Hz, $J_{H16\text{-}H17}=$

3.9 Hz and $J_{H17\text{-}H18}=7.3$ Hz) were in accordance with the *syn*,*anti*,*syn* relative stereochemistry in stereotetrad **16** (Scheme 6).

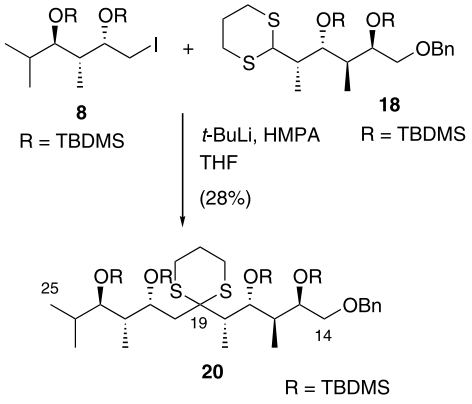
Transformation of **16** to dithiane **18** was achieved in a four-step sequence via amide **17**. After conversion of oxazolidinone **16** to amide **17** using *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminium (3 equiv.) in CH_2Cl_2[22] (97% yield), the hydroxy group at C17 was protected as a TBDMS ether, and the amide was reduced with DIBAL-H (THF, −78°C). The resulting aldehyde was directly treated with propane-1,3-dithiol in the presence of $TiCl_4$ to produce dithiane **18** in 87% overall yield. The C14–C19 fragment, dithiane **18**, was obtained in 11 steps from propiophenone with a 20.5% overall yield (Scheme 5).



Scheme 5. Synthesis of the C14–C19 fragment.



Scheme 6. Synthesis of lactone **19** to determine the relative configuration in **16**.



Scheme 7. Synthesis of the C14–C25 unit.

Finally, the assembly of the C14–C19 and C20–C25 fragments of bafilomycin A_1 was realized by alkylation of the lithiated dithiane **18** (*t*-BuLi, HMPA, THF) with iodide **8**,[12c] which led to the formation of compound **20** in a 28% non-optimized yield (Scheme 7).

In summary, a convergent route to prepare the C14–C25 fragment of bafilomycin A_1 was achieved. The sequence involves two dynamic kinetic resolution steps of 2-alkyl 1,3-diketones using optically active ruthenium complexes, which set the correct configuration at C15, C16, C21 and C22. To control the C23 stereogenic center, an *anti*-selective directed reduction of a β-hydroxyketone was used. The introduction of the C17 and the C18 stereogenic centers was realized by an anti-Felkin–*anti*-aldol reaction. With fragment C14–C25 in hand, progress toward the total synthesis of bafilomycin A_1 continues and will be reported in due course.

Acknowledgements

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