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A total synthesis of (–)-antimycin A_{3b}

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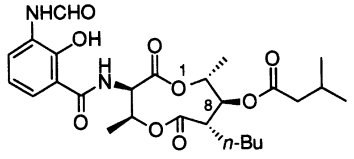
Abstract

(–)-Antimycin A_{3b}, the antipode of natural antibiotic antimycin A_{3b}, was synthesized utilizing the asymmetric aza-Claisen rearrangement.

Keywords: asymmetric synthesis; aza-Claisen rearrangements; amides; antibiotics; lactonization.

(+)-Antimycin A_3 was isolated from *streptomyces* sp.[1] as a component of antimycin A complex (a mixture of A_1–A_8), which inhibited specifically the electron transfer activity of ubiquinol-cytochrome *c* oxidoreductase.[2] Among the components of antimycin A complex, A_3, which is available from Sigma Co., is one of the most active agents and has been widely used in biological and biochemical investigations.[3]



(-)-Antimycin A_{3b} ((-)-**1**)

Although the structure of antimycin A_3 had been established as 3-methylbutanoate (+)-**1** with a unique nine-membered dilactone structure, recent analytical investigations using HPLC disclosed that antimycin A_3 was in fact a mixture of (+)-**1**, now renamed antimycin A_{3b}, and its acyloxy isomer at the 8-position, which is 2-methylbutanoate, named antimycin A_{3a}.[3b,4] Since the separation of A_{3a} and A_{3b} is possible only with enormous effort, pure material of each component is practically available for biological and biochemical investigations.[5,6]

Antimycin A_{3b} (previous name A_3) has been an attractive target of synthetic efforts and a total synthesis[7] and its formal syntheses[8] have been accomplished. However, further effort to a

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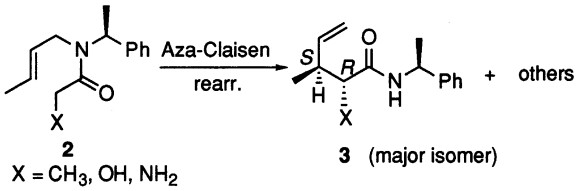
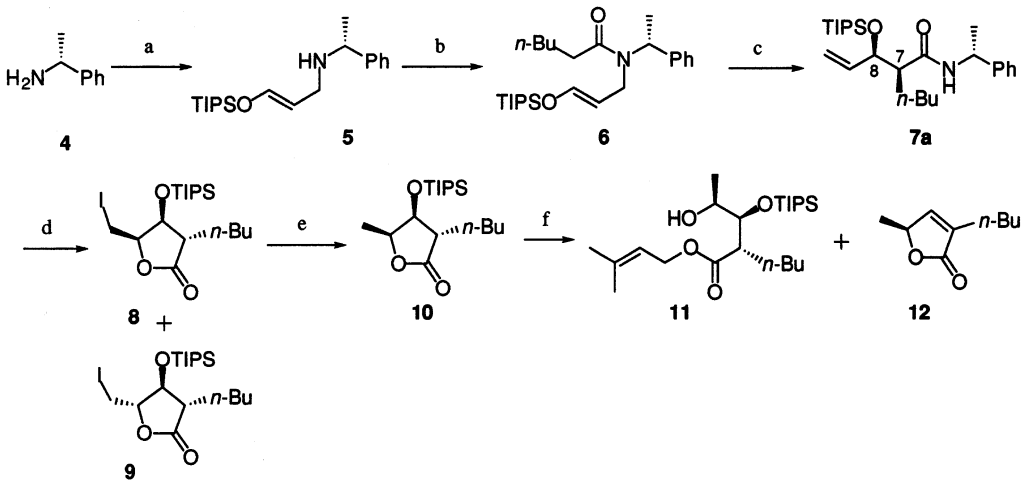
practical and economical synthesis is still needed to supply sufficient amounts of pure antimycin A_{3b} for biological or biochemical studies.

We have developed the asymmetric aza-Claisen rearrangement,[9] the thermal [3,3] sigmatropic rearrangement of the enolate of carboxamides **2** to **3** (Scheme 1), and demonstrated its applicability to straightforward short-step syntheses of natural products, including (–)-verrucarinolactone,[10] *D-allo*-isoleucine,[10] (–)-isoiridomyrmecin,[11] and (+)-α-skytanthine.[12] We applied the methodology to the synthesis of (–)-antimycin A_{3b}, the antipode of this naturally occurring antibiotic, taking development of a practical synthetic route into consideration and having an interest in biological activities.[13] The result is reported herein.



Scheme 1.

(*R*)-(+)-Methylbenzylamine (**4**) was silylated with 1.0 equiv. of Me_3SiOTf/DBU at 0°C. To the resulting mixture were added $[(CH_3)_2CH]_3SiOTf$ (TIPSOTf, 1.0 equiv.) and acrolein (1.0 equiv.) simultaneously to give the amine **5** (Scheme 2), in which the *E*-configuration of the olefinic double bond was verified by NMR spectroscopy. Acylation of **5** afforded the amide **6**, the precursor of the proposed aza-Claisen rearrangement. The rearrangement was carried out under standard conditions[9] to give the amides as a four stereoisomeric mixture, from which the major (7*S*,8*R*)-isomer **7a** was obtained by SiO_2 column chromatography as an inseparable 82:18 mixture with its (7*R*,8*S*)-isomer **7b** (78% combined yield).

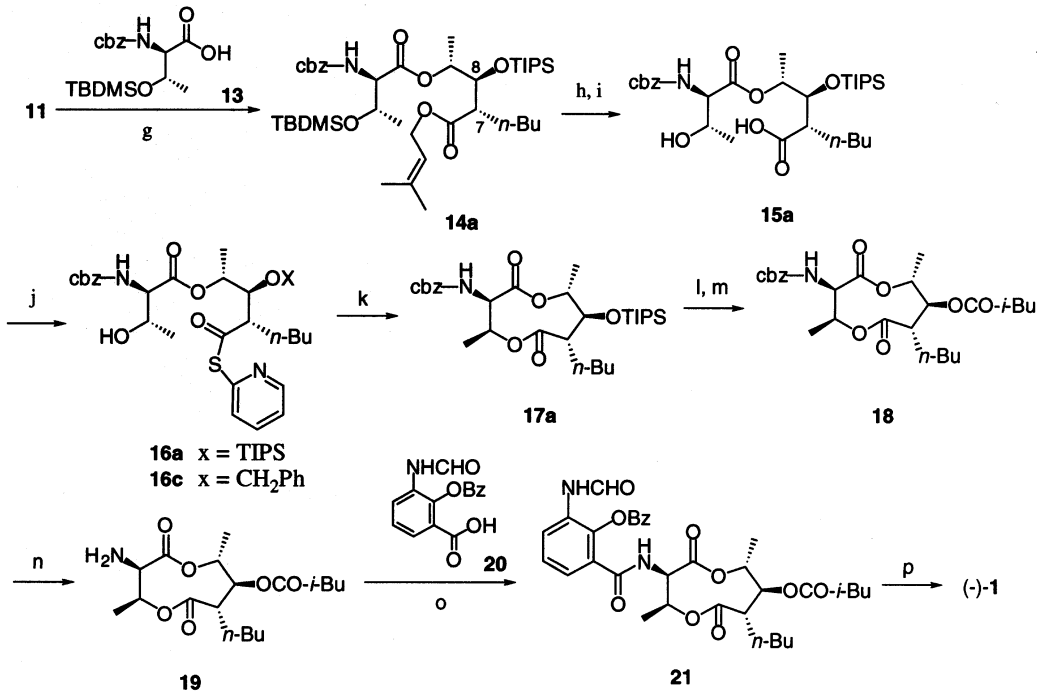


Scheme 2. (a) (i) TMSOTf, DBU, ether, 0°C, 1 h; (ii) TIPSOTf, acrolein, ether, 0°C–rt, 6 h, 64%; (b) hexanoyl chloride, NEt_3, CH_2Cl_2, 0°C, 98%; (c) (i) LHMDS, tol, –78°C; (ii) 120°C, 6 h, 78%; (d) I_2, *N*,*N*-dimethyl-*p*-nitroaniline, DME–H_2O (3:2), rt, 3 days, 78%; (e) Bu_3SnH, PhH, reflux, 91%; (f) (i) CsOH, *t*-BuOH, 0°C; (ii) prenyl bromide, Py, ether, 0°C, 24 h, 40%

The iodolactonization[14] of the mixture **7a**,**b** afforded the iodo-lactone **8** (78%, enantiomeric mixture derived from **7a**,**b**) along with the stereoisomer **9** (4%), whose stereochemistry were

determined by NOE experiments. The lactone **8** was reduced with Bu_3SnH (2.4 equiv.) to **10**. After hydrolysis of **10** with 1 N CsOH aq. (1.0 equiv.) in *t*-BuOH, the solvent was evaporated and the residue was dried in a desiccator (P_2O_5) under reduced pressure for 2 days. The resulting gummy oil was treated with prenyl bromide (3.0 equiv.) and pyridine (3.0 equiv.) in ether at 0°C[15] to yield the prenyl ester **11** (40%) along with the butenolide **12** (40%).

The Mitsunobu reaction[16] of the hydroxy ester **11** with *N*,*O*-protected *D*-threonine **13** gave a diastereomeric mixture of the diester **14a** and its (7*R*,8*R*)-isomer **14b**[17] (Scheme 3). The TBDMS and the prenyl groups on the mixture **14a**,**b** were removed by acidic treatment, followed by a palladium-catalyzed reaction, affording the seco acids **15a**,**b**. The acids were converted into the dilactones **17a**,**b** in only 36% yield via the formation of the 2-pyridinethiol esters[18] **16a**,**b** and their treatment with $AgClO_4$ at ambient temperature (the method of Gerlach)[19]. However, when the reaction mixture was heated under reflux for 2 h the yield increased dramatically to 82%. The diastereomer **17a** and **17b** were separated by SiO_2 column chromatography.



Scheme 3. (g) **13**, DEAD–PPh_3, PhH, rt, 24 h, 100%; (h) 6N HCl, EtOH, rt, 24 h, 95%; (i) $Pd(OAc)_2$, PPh_3, NEt_3, HCOOH, dioxane, 100°C, 1 h, 85%; (j) 2,2′-dipyridyl disulfide, PPh_3, PhH, rt, 3 h, 99%; (k) $AgClO_4$, PhH, 80°C, 2 h, 82%; (l) TBAF, THF, 0°C, 5 min, 85%; (m) isovaleric anhydride, Py, 53%; (n) H_2, Pd–C, AcOEt, 67%; (o) **20**, WSC, HOBt, NMM, DMF, rt, 95%; (p) H_2, Pd–C, AcOEt, 89%

The *O*-isovaleryate **18** was obtained by quick treatment of **17a** with Bu_4NF at 0°C, followed by acylation with isovaleric anhydride. The cbz group of **18** was removed by the hydrogenolysis (Pd–C in ethyl acetate) to the amine **19**, which was successfully acylated with **20**, water-soluble carbodiimide (WSC), 1-hydroxybenzotriazole hydrate (HOBt), and *N*-methylmolpholine (NMM) in DMF to give the benzyl ether **21**. Hydrogenolysis of **21** with Pd–C in ethyl acetate led cleanly to (–)-antimycin A_{3b} [(–)-**1**][20] in good yield, mp 183.5–184.0°C, $[\alpha]_D^{21}$ –74.2 (*c* 0.98, $CHCl_3$), whose physical properties compared well with those in the literature[7b] [mp 183–185°C, $[\alpha]_D^{24}$ +80 (*c* 0.2, $CHCl_3$)].

Thus, the usefulness of the aza-Claisen rearrangement was amply demonstrated by the efficient synthesis of (−)-antimycin A_{3b} [(−)-**1**]. Further synthetic studies of not only (−)-**1** analogs but also (+)-**1** analogs and the investigation of their biological activities are now in progress.

Acknowledgements

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20. (–)-Antimycin A_{3b}: colorless needles (rotamer mixture): mp 183.5–184.0°C (ether/pet. ether); $[\alpha]_D^{21}$ –74.2 (*c* 0.98, $CHCl_3$): ^1H NMR (300 MHz, $CDCl_3$) δ 12.63 and 12.47 (total integr. 1H, s and br.s), 8.56 (1H, br.dd, $J=8.1$, 1.3 Hz), 8.52 (1H, d, $J=1.8$ Hz), 8.02 (1H, br.s), 7.25 (1H, dd, $J=8.1$, 1.3 Hz), 7.09 and 7.07 (total integr. 1H, br.d, $J=7.8$ Hz and br.d, $J=7.8$ Hz), 6.92 and 6.90 (total integr. 1H, t, $J=8.1$ Hz and t, $J=7.8$ Hz), 5.76 (1H, dq, $J=7.8$, 6.6 Hz), 5.32 and 5.29 (total integr. 1H, t, $J=7.8$ Hz and t, $J=7.8$ Hz), 5.12 and 5.16 (total integr. 1H, t, $J=9.9$ Hz and t, $J=9.9$ Hz), 4.98 (1H, dq, $J=9.9$, 6.3 Hz), 2.52 (1H, ddd, $J=11.7$, 9.9, 2.7 Hz), 2.26 (2H, d, $J=7.8$ Hz), 2.15 (1H, septet d, $J=7.8$, 6.3 Hz), 1.78–1.63 (1H, m), 1.43–1.04 (5H, m), 1.32 (3H, d, $J=6.6$ Hz), 1.30 (3H, d, $J=6.3$ Hz), 0.99 (6H, d, $J=6.3$ Hz), 0.87 (3H, t, $J=7.8$ Hz); IR (neat) 3370, 1750, 1692, 1644, 1611 cm^{-1}; MS (CI) *m/z* 520 (M+), 458, 418, 264, 236, 220, 202 (bp); HMRS *m/z* 520.2454 (520.24206 calcd for $C_{26}H_{36}N_2O_9$).