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Tetrahedron Letters 44 (2003) 7829–7832

TETRAHEDRON LETTERS

Total synthesis of the (+)-antimycin A_3 family: structure elucidation of (+)-antimycin A_{3a}

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Received 16 July 2003; revised 4 August 2003; accepted 11 August 2003

Abstract—(+)-Antimycin A_{3a} (AA_{3a}), one component of the natural antibiotic antimycin A_3, was synthesized using an asymmetric aza-Claisen rearrangement. The stereochemistry at the 2′ position on the acyloxy side chain of AA_{3a} was established as *S*-configuration by comparison of the synthetic AA_{3a} and the natural AA_{3a}.
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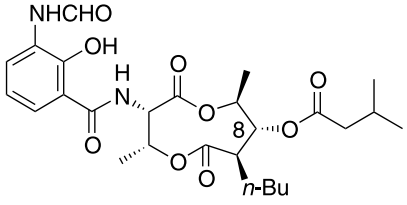
Antimycin A (AA) complex was isolated from *Streptomyces* sp. as antibiotics possessing antifungal activity.[1] Among the components of AA complex, AA_3, available from Sigma Co., is one of most active agents and has been widely used in biological and biochemical studies[2] because of its unique inhibitory activity against ubiquinol-cytochrome *c* oxidoreductase.[3]

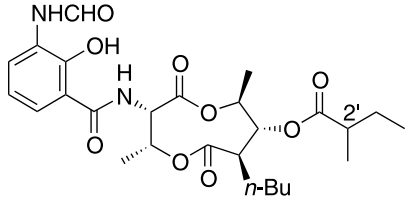
Recently, we disclosed that this enchanting agent purchased from Sigma Co. was a 6:4 mixture of AA_{3a} and AA_{3b},[4] whose separation was possible only with enormous effort.[5] For precise biological and biochemical investigations, the supply of each pure component seems to be very important. Although AA_{3b} has been synthesized by several groups,[6] further effort to a practical synthesis is still needed to supply sufficient amount of pure AA_{3b}. Furthermore, AA_{3a} has not been synthesized and the stereochemistry at the 2′ position on the acyloxy side chain of AA_{3a} has not yet been determined.

We have developed an asymmetric aza-Claisen rearrangement,[7] and applied the methodology to the synthesis of (−)-AA_{3b} taking development of a practical synthetic route into consideration and having an interest in biological activities.[4] As part of our continuing efforts toward antimycin chemistry, we synthesized the two possible isomers of (+)-AA_{3a}, which were (*S*)- and (*R*)-2-methylbutanoates, named (+)-AA_{3a}(*S*) and (+)-AA_{3a}(*R*), respectively in this paper. The synthesis elucidated the stereochemistry of the acyloxy side chain at the 8-position of the nine-membered dilactone ring in natural AA_{3a}. The results are reported herein.

Starting from (*S*)-(−)-phenethylamine (**1**), a diastereomeric mixture of *seco* acids (7*R*,8*R*)-isomer **8a** and (7*S*,8*S*)-isomer **8b** was obtained following the previous route[4] outlined in Scheme 1. In the previous synthesis of AA_{3b}, the mixture of **8a**,**b** was converted to the dilactones **10a**,**b** via the formation of the 2-pyridinethiol esters **9a**,**b** which were treated with $AgClO_4$ in benzene under reflux conditions. Although the lactonization proceeded in satisfactory yield (82%), we decided to abandon the use of explosive $AgClO_4$.[8] We tested the conditions for the cyclization of thiol esters with different metal salts. The best results were obtained when a



(+)-antimycin A_{3b}



(+)-antimycin A_{3a}

Keywords: asymmetric synthesis; antimycin A_{3a}; antibiotics; structure determination.
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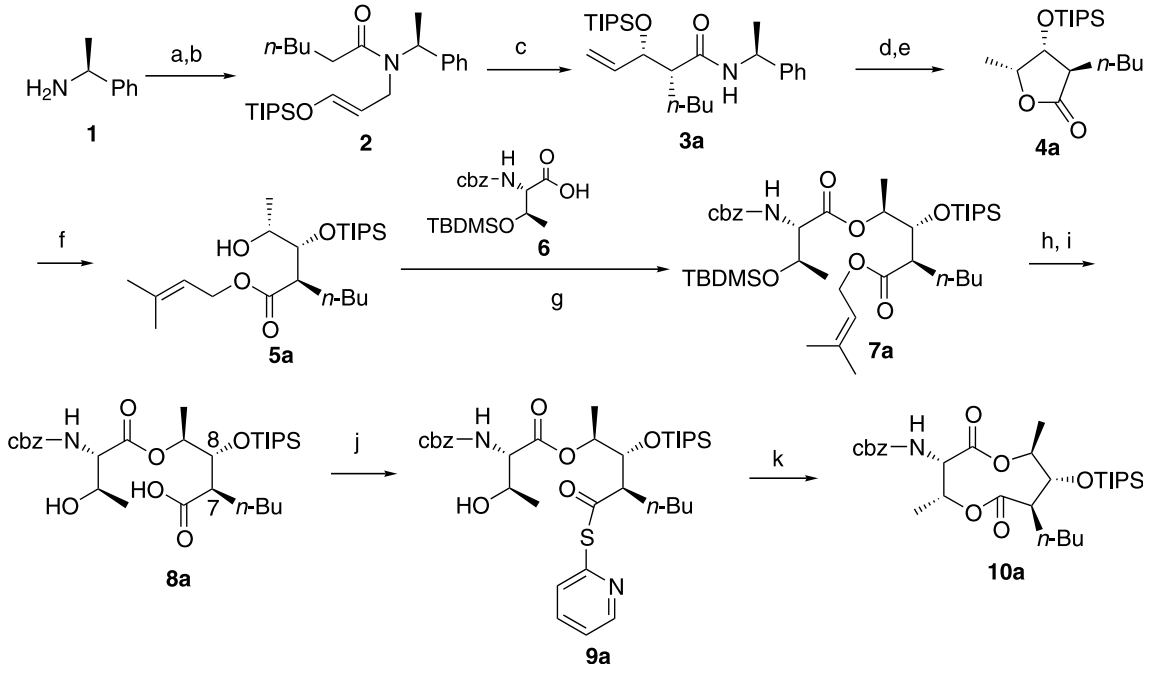
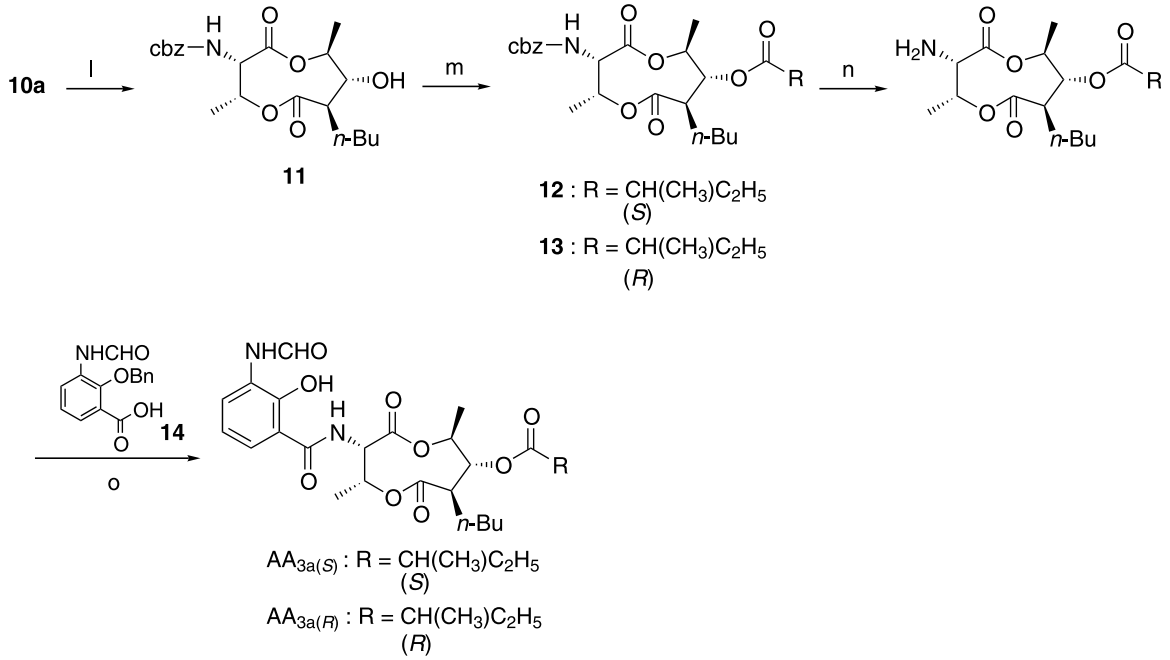
doi:10.1016/j.tetlet.2003.08.046



Scheme 1. *Reagents and conditions*: (a)~(i) Ref. 4; (j) 2,2′-dipyridyl disulfide, PPh_3, PhH, rt, 3 h, 99%; (k) $Cu(OTf)_2$·PhH, PhH, 80°C, 3 h, 88%.

solution of **9a**,**b** in benzene was added slowly over 2 h to a refluxing benzene solution of one equivalent of $Cu(OTf)_2$·PhH complex under high dilution conditions.[9] The yield was improved to 88% and the resulting dilactones **10a** and **10b** were separated by SiO_2 column chromatography.

The TIPS group of the lactone **10a** was removed smoothly using HF·Py at 0°C to provide the alcohol **11** without epimerization at the C7 position[10] (95% yield) (Scheme 2). Compound **11** was esterified with (*S*)- or (*R*)-2-methylbutanoic acid[11] in the presence of water-soluble carbodiimide (WSC) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in CH_2Cl_2 to provide the ester **12** or **13** in an unoptimized 60~72% yield. Following the previous procedure (hydrogenolysis of the Cbz group, acylation, and hydrogenolysis of the benzyl ether), the ester **12** or **13** was transformed into (+)-AA_{3a}(*S*) (72% yield from **12**) or (+)-AA_{3a}(*R*) (an unoptimized 47% yield from **13**).[12]



Scheme 2. *Reagents and conditions*: (l) HF·Py, THF, 32 h, 95%; (m) $C_2H_5C^*H(CH_3)COOH$, WSC, DMAP, CH_2Cl_2; (n) H_2, Pd/C, AcOEt; (o) (i) **14**, WSC, HOBt, NMM, DMF; (ii) H_2, Pd/C, AcOEt.

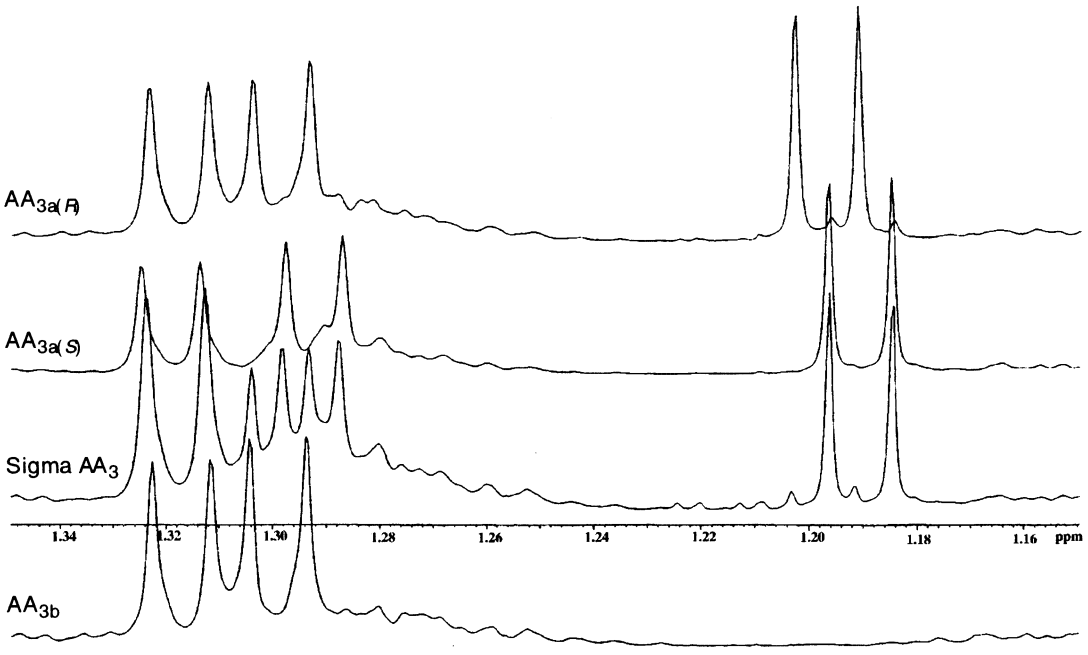


Figure 1. 600 MHz ^{1}H NMR spectra of AA_{3b}, sigma AA_3, $AA_{3a(S)}$ and $AA_{3a(R)}$.

In order to elucidate the stereochemistry of the 2-methylbutanoate moiety in the natural (+)-AA_{3a}, we carefully compared the 600 MHz ^{1}H NMR spectra of synthetic AA_{3b}, $AA_{3a}(S)$, $AA_{3a}(R)$ and AA_3 from Sigma Co. The spectra (from 1.34 to 1.16 ppm) are depicted in Figure 1.

The signal at 1.190 ppm (3H, d) in the spectrum of sigmas AA_3 is identical with the signal of $AA_{3a}(S)$, which is assigned to the 2-methyl group on the 2-methylbutanoate moiety. On the contrary, the signal for the methyl group of $AA_{3a}(R)$ appears at 1.197 ppm (3H, d). The signals of the methyl groups on the nine-membered dilactone ring of sigmas AA_3 are observed from 1.33 to 1.28 ppm. This signal pattern can be recognized as a superposition of the signal of AA_{3b} and $AA_{3a}(S)$. Consequently, the stereochemistry at the 2′ position on the acyloxy side chain of AA_{3a} was established as *S*-configuration.

Thus, we succeeded in synthesizing of AA_{3a} and determined the stereochemistry at the 2′ position on the acyloxy side chain of AA_{3a}. Further synthetic studies of AA_3 analogs and the investigation of their biological activities are now in progress.

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12. The physical properties were as follows:
(+)AA_{3a}(*S*): colorless needles (rotamer mixture): mp 173.1∼174.0°C (ether/pet. ether); $[\alpha]_D^{21}$ +91.6 (*c* 0.32, $CHCl_3$): ^1H NMR (600 MHz, $CDCl_3$) δ 12.63 and 12.47 (total integr. 1H, s and s), 8.79 and 8.51 (total integr. 1H, d, $J=11.4$ Hz and d, $J=1.2$ Hz), 8.55 and 7.38 (total integr. 1H, dd, $J=7.8$, 1.2 Hz and br.d, $J=7.2$ Hz), 7.98 and 7.78 (total integr. 1H, br.s and br.d, $J=11.4$ Hz), 7.30 and 7.25 (total integr. 1H, br.d, $J=7.2$ Hz and dd, $J=7.8$, 1.2 Hz), 7.09 and 7.07 (total integr. 1H, br.d, $J=7.2$ Hz and br.d, $J=7.2$ Hz), 6.92 and 6.90 (total integr. 1H, t, $J=7.8$ Hz and t, $J=7.8$ Hz), 5.75 (1H, dq, $J=7.8$, 6.6 Hz), 5.31 and 5.29 (total integr. 1H, t, $J=7.8$ Hz and t, $J=7.2$ Hz), 5.11 and 5.09 (total integr. 1H, t, $J=10.2$ Hz and t, $J=10.2$ Hz), 5.00 (1H, dq, $J=9.6$, 6.6 Hz), 2.53 (1H, ddd, $J=12$, 10.2, 3.6 Hz), 2.43 (1H, ddq, $J=7.8$, 7.2, 6.6 Hz), 1.75∼1.67 (1H, m), 1.74 (1H, ddq, $J=14.4$, 7.2, 7.8 Hz), 1.50 (1H, ddq, $J=14.4$, 7.8, 7.2 Hz), 1.39∼1.23 (4H, m), 1.32 (3H, d, $J=6.6$ Hz), 1.29 (3H, d, $J=6.6$ Hz), 1.21∼1.11 (1H, m), 1.19 (3H, d, $J=6.6$ Hz), 0.95 (3H, dd, $J=7.8$, 7.2 Hz), 0.87 (3H, t, $J=7.2$ Hz); IR (neat) 3370, 2963, 2875, 1747, 1684, 1644, 1604, 1537 cm^{-1}; MS (FAB) *m*/*z* 521 (M^++1), 419, 329, 278, 236, 91 (bp); HRMS *m*/*z* 521.2463 (521.2499 calcd for $C_{26}H_{37}O_9N_2$).
(+)-AA_{3a}(*R*): colorless needles (rotamer mixture): mp 156.5∼157.0°C (ether/pet. ether); $[\alpha]_D^{20}$ +74.4 (*c* 0.36, $CHCl_3$): ^1H NMR (600 MHz, $CDCl_3$) δ 12.63 and 12.47 (total integr. 1H, s and s), 8.79 and 8.51 (total integr. 1H, d, $J=12$ Hz and d, $J=1.8$ Hz), 8.56 and 7.38 (total integr. 1H, dd, $J=7.8$, 1.2 Hz and br.d, $J=7.8$ Hz), 7.95 and 7.76 (total integr. 1H, br.s and br.d, $J=11.4$ Hz), 7.29 and 7.25 (total integr. 1H, br.d, $J=7.2$ Hz and dd, $J=7.8$, 1.2 Hz), 7.08 and 7.06 (total integr. 1H, br.d, $J=7.2$ Hz and br.d, $J=7.2$ Hz), 6.93 and 6.90 (total integr. 1H, t, $J=7.8$ Hz and t, $J=7.8$ Hz), 5.74 (1H, dq, $J=7.8$, 6.6 Hz), 5.30 and 5.29 (total integr. 1H, t, $J=7.8$ Hz and t, $J=7.8$ Hz), 5.10 and 5.09 (total integr. 1H, t, $J=9.6$ Hz and t, $J=10.2$ Hz), 5.00 (1H, dq, $J=9.6$, 6.6 Hz), 2.54 (1H, ddd, $J=12.0$, 10.8, 3.0 Hz), 2.43 (1H, ddq, $J=7.8$, 7.2, 7.2 Hz), 1.75∼1.67 (1H, m), 1.74 (1H, ddq, $J=15.0$, 7.8, 7.8 Hz), 1.49 (1H, ddq, 15.0, 7.2, 7.8 Hz), 1.39∼1.23 (4H, m), 1.32 (3H, d, $J=6.6$ Hz), 1.30 (3H, d, $J=6.6$ Hz), 1.21∼1.11 (1H, m), 1.20 (3H, d, $J=7.2$ Hz), 0.94 (3H, dd, $J=7.8$, 7.2 Hz), 0.87 (3H, t, $J=7.2$ Hz); IR (neat) 3370, 2963, 2935, 2875, 1747, 1688, 1643, 1610, 1534 cm^{-1}; MS (FAB) *m*/*z* 521 (M^++1), 265, 237, 164, 136 (bp); HRMS *m*/*z* 521.2527 (521.2499 calcd for $C_{26}H_{37}O_9N_2$).