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Synthesis of novel analogues of antimycin A_3

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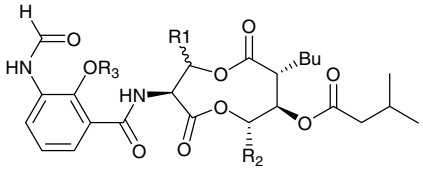
ABSTRACT

Four novel analogues of antimycin A_3, **1a–d**, were synthesized in good overall yields.

Antimycin A, a mixture of A_1–A_8, was isolated from *streptomyces species* as antibiotics possessing antifungal activity.[1] Among the components of antimycin A complex, antimycin A_3 is one of the most active agents that specifically inhibits the electron transfer activity of ubiquinol-cytochrome *c* oxidoreductase.[2] Antimycin A_3 also shows effects on mitochondrial function for the ability to selectively kill cells with high versus low Bcl-X_L expression in isogenic cell lines, which acted as selective apoptotic triggers in tumor cells.[3]

As part of our drug discovery program in oncology, we were interested in evaluating novel analogues of antimycin A_3. Specifically, we were interested in analogues varying at R1, R2, and R3 groups as shown in Figure 1 (**1a–d**). Although the synthesis of antimycin A_3 is known in the literature,[4] reports on analogues varying at the dilactone core are limited. In this Letter, we wish to report the synthesis of these four novel analogues of antimycin A_3 (**1a–d**).

The retrosynthetic analysis of analogue **1a** is outlined in Figure 2. As shown, **1a** can be envisioned from connection of dilactone **3** with 3-formamido-2-methoxybenzoic acid (**2**) and isovaleryl chloride. The nine-membered dilactone **3** can be constructed from



antimycin A_3: R_1 = (*R*)-Me, R_2 = Me, R_3 = H
1a: R_1 = (*R*)-Me, R_2 = H, R_3 = Me
1b: R_1 = H, R_2 = Me, R_3= Me
1c: R_1 = (*S*)-Me, R_2 = H, R_3 = Me
1d: R_1 = H, R_2 = H, R_3 = Me

Figure 1.

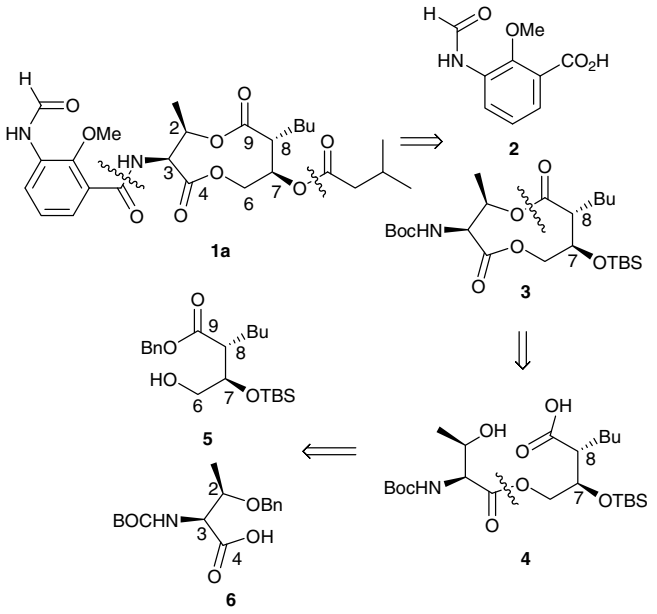


Figure 2.

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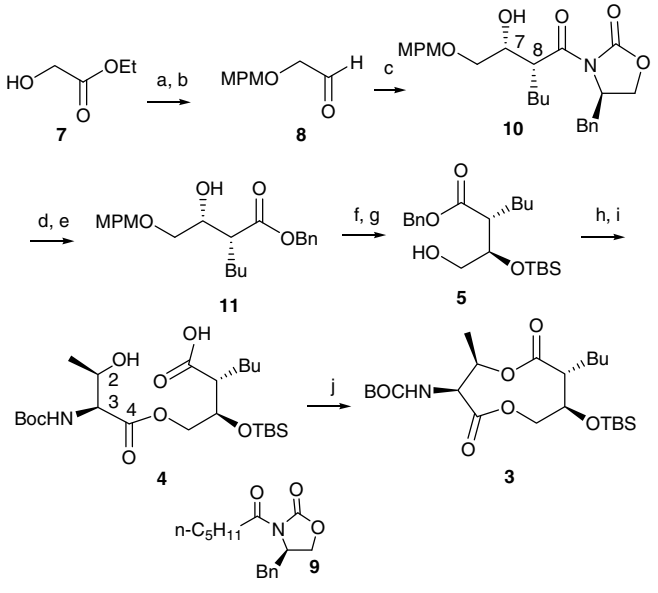
cyclization of hydroxy carboxylic acid **4**, which could be built from alcohol **5** and threonine derivative **6**.

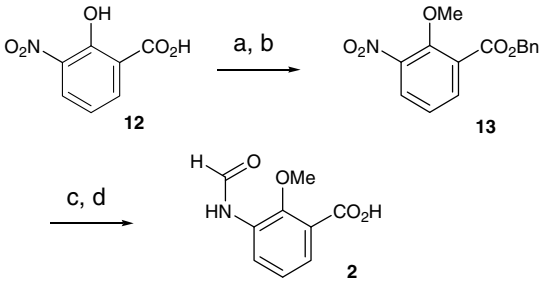
Scheme 1 outlines the synthesis of aminodilactone **3**. Starting from ethyl hydroxy acetate (**7**), protection of hydroxy group followed by reduction of ester provided aldehyde **8**. The stereochemistry of C_7 and C_8 in **1a** was then established via Evans aldol condensation using aldehyde **8** and (*R*)-4-benzyl-3-hexanoyl-oxazolidin-2-one (**9**), which was readily prepared from (*R*)-4-benzyloxazolidin-2-one and hexanoyl chloride. Under these conditions, alcohol **10** was obtained in 87% yield with high diastereoselectivity (>98% de).[5] Removal of chiral auxiliary under standard condition followed by protection of the acid provided **11** in 90% yield. The secondary hydroxy group in **11** was then protected as TBS ether, and the primary hydroxy group was freed using DDQ to give alcohol **5**. Coupling of **5** with threonine derivative **6** introduced C_2–C_4 fragment in **1a**, and provided the corresponding benzyl ester in 84% yield. Reductive removal of benzyl groups freed both hydroxy and carboxylic acid termini, and yielded hydroxy carboxylic acid **4**. Thus, intermediate **4** set up the stage for the nine-membered dilactone formation.

Macrocyclization of **4** was conducted under Corey–Nicolaou's condition promoted by silver ion.[6] To avoid dimerization, highly diluted reaction solution (~0.001 M) was used. Thus pre-formed thioester solution, obtained by refluxing **4** with triphenylphosphine and 2,2′-dipyridyl disulfide in toluene, was added to a solution of silver perchlorate in toluene at reflux for over 2 h. After stirring at reflux for an additional hour, dilactone **3**[7] was formed in 48% yield.

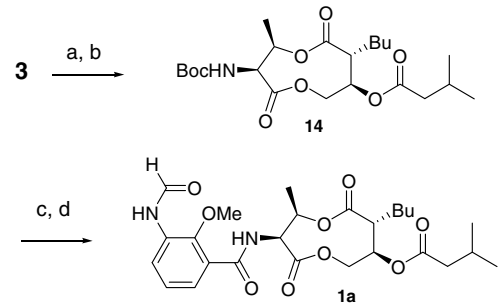
With the key intermediate **3** available, **1a** was constructed by installations of the two side chains as outlined in Scheme 2. First, the aromatic side chain 3-formamido-2-methoxybenzoic acid was prepared from commercially available material 2-hydroxy-3-nitrobenzoic acid (**12**). Protection of the carboxylic acid followed by conversion of the phenol to its methyl ether provided **13** in excellent yields. Hydrogenation of **13** gave 3-amino-2-methoxybenzoic acid, which was converted to 3-formamido-2-methoxybenzoic acid (**2**) upon treatment with acetic formic anhydride.



Scheme 1. Reagents and conditions: (a) MPM-Cl, NaH, DMF, Bu_4NI, 0 °C to rt (88%); (b) DiBALl, CH_2Cl_2, −78 °C (70%); (c) **9**, Bu_2BOTf, TEA, CH_2Cl_2 (87%); (d) LiOH, H_2O_2, 0 °C to rt; (e) BnOH, Ph_3P, DIAD, THF, rt (90% for two steps); (f) TBSCl, Im., DMF, rt (86%); (g) DDQ, CH_2Cl_2/H_2O (>95%); (h) Boc-Thr(OBn)-OH (**6**), EDCI DMAP, CH_2Cl_2, 0 °C to rt (84%); (i) H_2, Pd/C, EtOH, rt (>95%); (j) (1) $(C_5H_4NS)_2/Ph_3P$, tol., rt; (2) $AgClO_4$, tol., 120 °C (48%).



a: BnOH, H_2SO_4, toluene (>95%); b: MeI, K_2CO_3, DMF, rt, (>95%); c: H_2, Pd/C, EtOAc (>95%); d: MeC(O)-O-CHO, THF (90%)

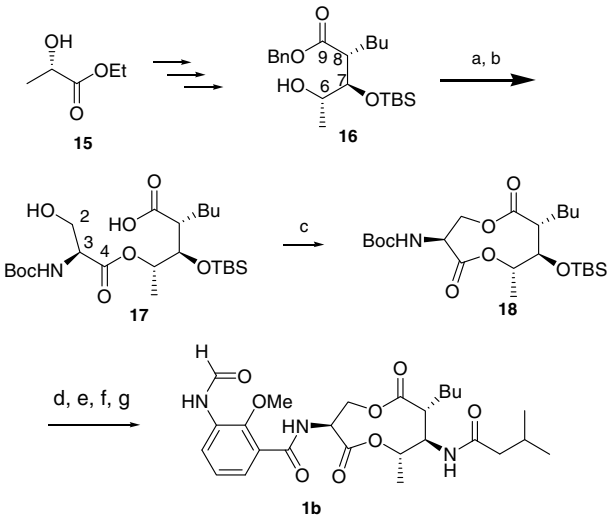


a: HF.Pyr., THF, rt, 3 days (95%); b: isovaleryl chloride, CH_2Cl_2, Pyr., 0 °C (88%); c: 50% TFA/CH_2Cl_2, rt (95%); d: **2,** EDCI, DMAP, CH_2Cl_2 (94%)

Scheme 2.

Removal of TBS group in intermediate **3** with HF/pyridine followed by treatment with isovaleryl chloride installed the isovaleryl side chain. Finally, deprotection of BOC group followed by coupling with 3-formamido-2-methoxybenzoic acid (**2**) completed the synthesis of **1a**[7] in high yield.

A similar synthetic route was applied to the synthesis of **1b.** Starting from (*S*)-ethyl 2-hydroxypropanoate (**15**) and applying the chemistry described in Scheme 1, steps a–g, C_6–C_8 chiral centers were established and alcohol **16** was obtained in 42% yield. Coupling of alcohol **16** with Boc-Ser(OBn)-OH introduced C_2–C_4 fragment and thus provided, after deprotection, the hydroxy carboxylic acid intermediate **17** (Scheme 3). In this case, macrocycli-

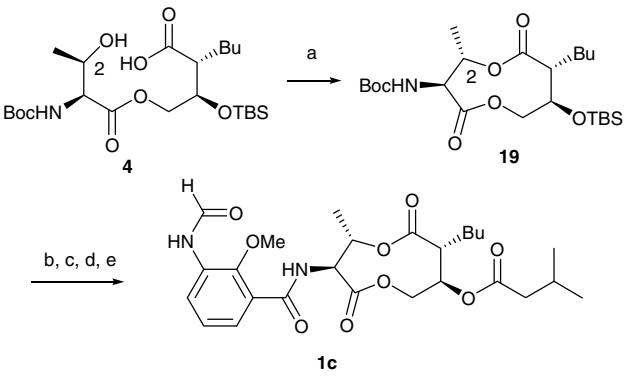


Scheme 3. Reagents and conditions: (a) Boc-Ser(OBn)-OH, EDCI, DMAP, DMF (89%); (b) H_2, Pd/C, EtOH (>95%); (c) Ph_3P, DIAD, CH_2Cl_2, (98%): (d) HF·Pyr., THF, rt (95%); (e) isovaleryl chloride, CH_2Cl_2, Pyr., 0 °C (82%); (f) 50% TFA/CH_2Cl_2, rt (95%); (g) **2**, EDCI, DMAP, CH_2Cl_2 (83%).

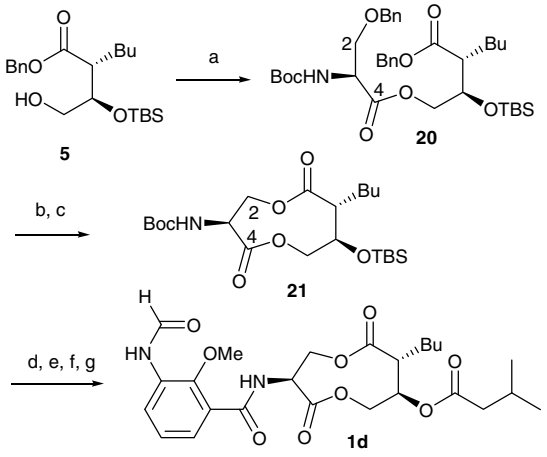
zation of **17** proceeded smoothly under Mitsunobu conditions to provide dilactone **18**[7] in excellent yield. Again, installations of the isovaleryl side chain and 3-formamido-2-methoxybenzoyl side chain, which were used in the synthesis of **1a**, completed the preparation of **1b**[7] in good overall yield.

The synthesis of analogues **1c** and **1d** adopted the intermediates **4** and **5**, respectively, from Scheme 1. As outlined in Scheme 4, the preparation of **1c** started from hydroxy carboxylic acid **4**. In this case, cyclization of **4** under Mitsunobu conditions proceeded smoothly with inversion of the stereo center at C_2 to give dilactone **19**[7] with desired stereochemistry in 91% yield. Again, coupling of the two side chains as described previously finished the synthesis of **1c**[7] in high yields.

The preparation of analogue **1d** was from intermediate **5** as shown in Scheme 5. Thus, coupling of alcohol **5** with Boc-Ser(OBn)-OH in the presence of EDCI and DMAP introduced the C_2–C_4 fragment and provided compound **20** in 91% yield. Then deprotection of the two benzyl groups followed by cyclization under Mitsunobu conditions yielded dilactone **21**.[7] Again, removal of the TBS group with HF/pyridine followed by treatment with isovaleryl chloride fixed the isovaleryl side chain, and deprotection of BOC group followed by coupling with 3-formamido-2-methoxybezoic acid completed the synthesis of analogue **1d**.[7]



Scheme 4. Reagents and conditions: (a) DIAD, Ph_3P, CH_2Cl_2, (91%); (b) HF·Pyr., THF, rt (90%); (c) isovaleryl chloride, Pyr. (89%); (d) TFA, CH_2Cl_2 (95%); (e) **2**, EDCI, DMAP (92%).



Scheme 5. Reagents and conditions: (a) Boc-Ser(OBn)-OH, EDCI, DMAP (91%); (b) H_2, Pd/C, EtOH (95%); (c) DIAD, Ph_3P, CH_2Cl_2 (92%); (d) HF·Pyr., THF, rt (90%); (e) isovaleryl chloride, Pyr. (87%); (f) TFA, CH_2Cl_2 (95%); (g) **2**, EDCI, DMAP (95%).

In summary, four novel analogues of antimycin A_3 (**1a–d**) were synthesized in good overall yields.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.050.

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7. Experimental data for intermediates **3**, **18**, **19**, **21**; and compounds **1a**, **1b**, **1c**, and **1d**.
   Compound **3**: ^{1}H NMR($CDCl_3$) δ ppm 5.51 (m, 1H), 5.26 (d, 1H), 4.94 (t, 1H), 4.50 (m, 1H), 3.96–3.88 (m, 2H), 2.26 (m, 1H), 1.78–1.55 (m, 2H), 1.45 (s, 9H), 1.29 (d, 2H), 1.25–1.00 (m, 4H), 0.89 (s, 9H), 0.88 (t, 3H), 0.04 (d, 6H).
   Compound **18**: ^{1}H NMR($CDCl_3$) δ ppm 5.2 (m, br, 2H), 4.6 (m, br, 2H), 3.5 (m, 2H), 2.2 (t, 1H), 1.6 (m, 1H), 1.3 (s, 9H), 1.2 (d, 3H), 1.2–1.0 (m, 5H), 0.8 (s, 9H), 0.76 (t, 3H), 0.03 (s, 3H), 0.00 (s, 3H). ^{13}C NMR($CDCl_3$) δ ppm 174.32, 170.62, 154.78, 80.39, 77.71, 77.42, 66.10, 53.05, 51.88, 29.40, 29.25, 28.23, 25.91, 22.44, 18.95, 18.15, 13.78, −3.11, −3.22. HRMS(ES$^+$) calcd for $C_{23}H_{43}NaSiNO_7$ (M+Na$^+$): 496.2719, found 496.2713.
   Compound **19**: ^{1}H NMR($CDCl_3$) δ ppm 5.44 (d, 1H), 4.94 (br s, 1H), 4.56 (m, 1H), 4.20 (d, 1H), 3.95 (dt, 1H), 3.62 (t, 1H), 2.26 (m, 1H), 1.65 (m, 1H), 1.40 (d, 2H), 1.32 (s, 9H), 1.25–1.00 (m, 5H), 0.79 (s, 9H), 0.78 (t, 3H), 0.02 (d, 6H). ^{13}C NMR($CDCl_3$) δ ppm 174.19, 168.57, 155.02, 80.26, 74.85, 69.85, 67.87, 60.87, 53.05, 28.92, 28.53, 28.25, 25.63, 22.32, 18.99, 17.88, 13.70, −4.46, −4.81. MS(ES$^+$) for (M+Na$^+$): 496.2. HRMS(ES$^+$) calcd for $C_{23}H_{44}NO_7Si$ (M+H$^+$): 474.2887, found 474.2897.
   Compound **21**: ^{1}H NMR($CDCl_3$) δ ppm 5.2 (m, 2H), 4.65 (m, 1H), 4.3 (b, 1H), 3.95 (b, 1H), 3.80 (dt, 1H), 3.60 (b, 1H), 2.24 (m, 1H), 1.65 (m, 1H), 1.48 (m, 1H), 1.38 (s, 9H), 1.25–1.00 (m, 4H), 0.80 (s, 9H), 0.76,(t, 3H), 0.03 (d, 6H). ^{13}C NMR($CDCl_3$) δ ppm 173.85, 170.76, 154.80, 80.51, 72.19, 68.68, 65.59, 52.67, 52.60, 29.19, 28.45, 28.22, 25.62, 22.40, 17.89, 13.73, −4.50, −4.78. MS(ES$^+$) for (M+Na$^+$): 482.2. HRMS(ES$^+$) calcd for $C_{22}H_{41}NO_7NaSi$ (M+Na$^+$): 482.2532, found 482.2541.
   Compound **1a**: ^{1}H NMR($CDCl_3$) δ ppm 8.82–8.30 (m, 3H), 7.88–7.72 (m, 2H), 7.40–7.24 (m, 1H), 5.70 (m, 1H), 5.39 (m, 1H), 5.15 (dt, 1H), 4.64 (t, 1H), 4.15 (m, 1H), 3.89 (s, 3H), 2.54 (m, 1H), 2.22 (d, 2H), 2.12 (m, 1H), 1.73–1.45 (m, 2H), 1.34 (d, 3H), 1.35–1.20 (m, 4H), 0.97 (d, 6H), 0.88 (t, 3H). ^{13}C NMR($CDCl_3$) δ ppm 172.98, 171.69, 170.64, 164.31, 161.33, 158.77, 147.27, 130.88, 127.78, 126.66, 125.68, 125.52, 125.28, 125.08, 121.66, 72.04, 71.33, 65.12, 62.84, 54.21, 49.54, 43.17, 29.18, 28.06, 25.66, 22.44, 22.36, 22.29, 15.23, 13.75. MS(ES$^+$) for (M+H$^+$): 521.2 (M+Na$^+$): 543.2. HRMS(ES$^+$) calcd for $C_{26}H_{37}N_2O_9$ (M+H$^+$): 521.2499, found: 521.2513. $[\alpha]_D$ +46.2 (0.360 g/dL, MeOH).
   Compound **1b**: ^{1}H NMR(DMSO-d_6) δ ppm 9.7 (s, 1H), 8.83 (d, 1H), 8.37 (s, 1H), 8.28 (d, 1H), 7.20 (d, 1H), 7.16 (t, 1H), 5.11 (t, 1H), 4.92 (q, 1H), 4.80 (m, 2H), 4.09 (t, 1H), 3.7 (s, 3H), 2.61 (t, 1H), 2.44 (m, 1H), 2.30 (d, 2H), 2.00 (m, 1H), 1.50 (m, 1H), 1.20 (d, 3H), 1.35–1.05 (m, 4H), 0.90 (d, 6H), 0.80 (t, 3H). ^{13}C NMR($CDCl_3$) δ ppm 172.81, 171.61, 170.50, 161.20, 158.74, 147.21, 130.85, 126.61, 125.53, 125.26, 125.04, 121.80, 75.46, 74.89, 66.00, 62.71, 51.12, 50.19, 43.22, 29.69, 29.21, 28.28, 25.47, 22.40, 17.87, 13.73. MS(ES$^+$) for (M+H$^+$): 521.2. HRMS(ES$^+$) calcd for $C_{26}H_{37}N_2O_9$ (M+H$^+$): 521.2499, found 521.2509.
   Compound **1c**: ^{1}H NMR($CDCl_3$) δ ppm 8.82–8.50 (m, 2H), 7.87–7.75 (m, 2H), 7.42–7.22 (m, 1H), 5.25–5.21 (m, 2H), 4.94–4.85 (m, 2H), 3.92 (s, 3H), 3.90 (m, 1H), 2.67 (m, 1H), 2.20 (d, 2H), 2.11 (m, 1H), 1.70–1.50 (m, 2H), 1.59 (d, 3H), 1.35–1.18 (m, 4H), 0.96 (d, 6H), 0.89 (t, 3H). ^{13}C NMR($CDCl_3$) δ ppm 172.90,

171.64, 167.68, 164.29, 158.75, 147.35, 130.86, 126.58, 125.36, 124.86, 121.28, 73.84, 70.93, 64.56, 62.84, 59.15, 49.84, 43.15, 29.09, 28.04, 25.62, 22.34, 22.28, 19.00, 13.72. MS(ES^+) for ($M+H^+$): 521.2. HRMS(ES^+) calcd for $C_{26}H_{37}N_2O_7$ ($M+H^+$): 521.2499, found: 521.2493. $[\alpha]_D$ +43.0 (0.320 g/dL, $CHCl_3$).

Compound **1d**: ^1H NMR($CDCl_3$) δ ppm 8.82–8.39 (m, 3H), 7.87–7.75 (m, 2H), 7.25 (t, 1H), 5.28–5.14 (m, 3H), 4.68 (m, br, 1H), 4.34 (br, 1H), 4.05 (br, 1H), 3.89 (s, 3H), 2.60 (m, 1H), 2.23 (d, 2H), 2.11 (m, 1H), 1.70–1.50 (m, 2H), 1.35–1.18 (m, 4H), 0.97 (d, 6H), 0.88 (t, 3H). ^{13}C NMR($CDCl_3$) δ ppm 172.80, 171.68, 164.32, 161.44, 158.85, 147.28, 130.88, 126.58, 125.48, 125.05, 121.58, 71.68, 65.59, 65.28, 62.70, 51.85, 49.57, 43.14, 29.15, 28.03, 25.64, 22.38, 22.35, 22.27, 13.73. MS(ES^+) for ($M+H^+$): 507.2. HRMS(ES^+) calcd for $C_{25}H_{35}N_2O_9$ ($M+H^+$): 507.2356, found: 507.2349. $[\alpha]_D$ +55.9 (0.470 g/dL, $CHCl_3$).