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3-*N*,*N*-Dimethylamino-3-deoxy lincomycin: A structure-based hybrid between lincomycin and the desosamine unit of erythromycin

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Dedicated to Professor Koji Nakanishi, chemist extraordinaire, wishing him the best in chemistry and in life.

Abstract—The observation that the desosamine sugar unit in erythromycin and the methyl thiolincosaminide portion of lincomycin occupy virtually identical sites on the 23S rRNA according to X-ray crystallographic data, instigated the synthesis of 3-*N*,*N*-dimethylamino-3-deoxy lincomycin as a hybrid structure. The synthesis in eight steps from lincomycin, involving a trans-diequatorial opening of an intermediate epoxide as the key step, is described.

1. Introduction

Lincomycin **1**, a broad spectrum antibiotic isolated from *Streptomyces lincolnensis*,[1] has been used to treat bacterial infections in humans for many years[2] (Fig. 1). Studies pertaining to structure elucidation,[3] NMR[4] and degradation[5,6] were elegantly done decades ago by scientists at the former Upjohn Company. Since then, numerous reports directed at the total synthesis[7] and chemical modifications have been documented.[8] Surprisingly, the seemingly simple replacement of the 7-hydroxyl group with inversion of configuration led to the semi-synthetic analogue 7-epichlorolincomycin (clindamycin),[9] with improved activity against Gram-positive bacteria compared to lincomycin. Many other analogues modified at C-7 have been synthesized and tested as inhibitors.[10] The displacement and proliferation of resistance mechanisms to a number of antibiotics[11] has generated much interest in the discovery of new entities from natural sources,[12] by chemical modification, or by genetic engineering.[13] A potentially lucrative source of new structures consists of hybrids between antibiotics of demonstrable activity.[14] Thus, by incorporating certain functional or structural features found in one class of antibiotic into another, the possibilities for discovering new active entities (hybrids) may increase substantially. In this regard, very few semi-synthetic hybrid antibiotic structures have been reported.[14] For example, the amide group present in chloramphenicol, sparsomycin, lincomycin, and puromycin have been interchanged.[15] However, only limited success was found in this approach to new hybrid antibiotics that act at the ribosomal level to inhibit bacterial protein biosynthesis. Utilizing a different design concept, we had conceived and synthesized

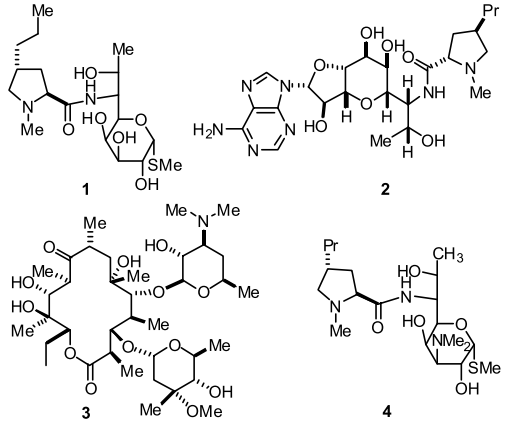

Figure 1. Structures of lincomycin **1**, quantamycin **2**, erythromycin **3**, and 3-*N*,*N*-dimethylamino-3-deoxylincomycin **4**.

Keywords: Lincomycin; Desosamine; 23S r-RNA; Hybrid structure.
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Quantamycin **2** (Fig. 1), a computer-simulated hybrid structure between lincomycin and the first nucleotide unit in a model t-Met tRNA.[16] In the absence of structural information on specific sites of binding on bacterial ribosomal subunits at the time, these were nevertheless new paradigms in testing approaches at 'rational' design of novel entities endowed with functional and/or structural features present in two natural products. With the advent of powerful crystallographic techniques showing details of X-ray complexes, new approaches can be envisaged. We have previously reported on the design, synthesis and activities of hybrid structures relating to quinolones,[17] β-lactams,[18] inhibitors of adenylosuccinate synthetase[19] and macrolide segment mimetics.[20]

Macrolides and lincomycin act by stimulating the dissociation of peptidyl tRNA from the bacterial ribosome during the translocation process, thereby inhibiting protein biosynthesis.[21] Both bind to the 23S rRNA of the 50S ribosomal subunit, in the vicinity of peptide exit channel.[22] In elegant X-ray crystallographic studies of complexes of several antibiotics, macrolides such as erythromycin **3** have shown that they bind at the peptide exit tunnel region.[22] Coincidentally, clindamycin also binds to the same subunit with a virtual overlap of the methyl thiolincosaminide portion with the desosamine sugar unit in erythromycin (Fig. 2). The interactions of the C-2 to C-4 hydroxyl group in clindamycin (or lincomycin) with A-2058, G-2505, PO^{4-}-2505 and PO^{4-}-2503 are matched by identical ones in desosamine at C-2 and C-3 (Fig. 3A and B).

We therefore hypothesized that a hybrid structure in which a dimethylamino group replaces the C-3 hydroxyl group in lincomycin would benefit from the same interactions, and possibly engage in a stronger PO^{4}-2505 charged interaction. Thus, we focused on 3-*N*,*N*-dimethylamino-3-deoxy lincomycin **4** as a hybrid target structure.

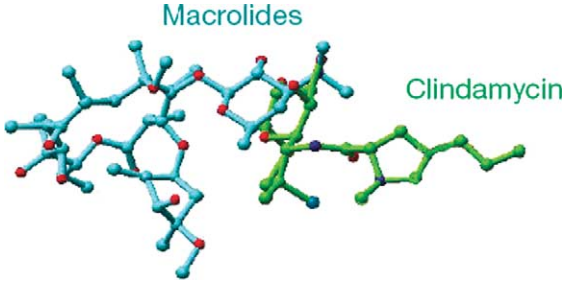


Figure 2. Virtual overlap region of methyl thiolincosamide unit of clindamycin (or lincomycin) with desosamine unit of erythromycin.[22]

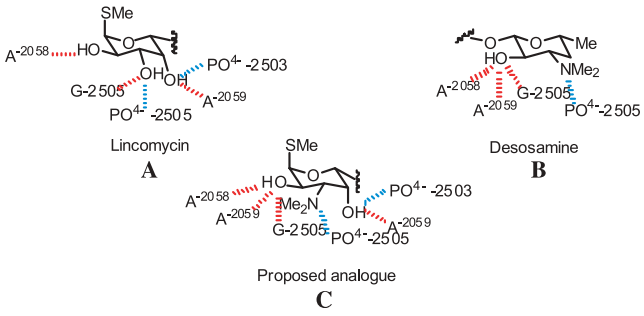
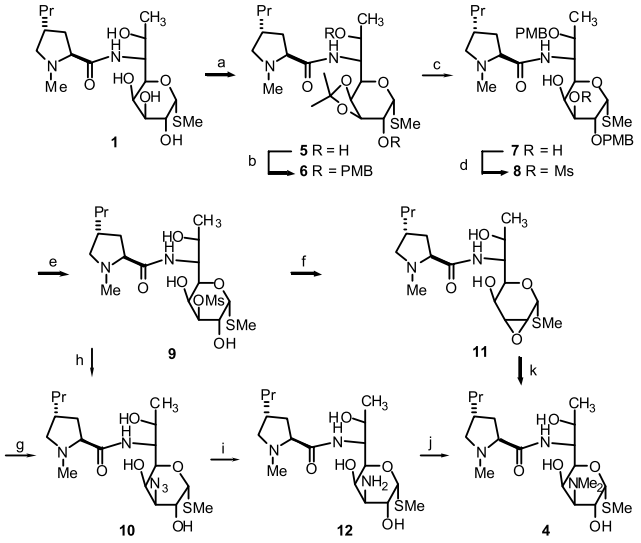


Figure 3. Interactions of lincomycin, desosamine unit, and proposed analogue with ribosomal units.



Scheme 1. Reagents and conditions: (a) acetone, *p*-TSA, 1 h, 74%; (b) PMB-Cl, NaH, DMF, 12 h, 35%; (c) 80:20 AcOH/H_2O, 70 °C, 24 h, 75%; (d) MsCl, Py/CH_2Cl_2, 0 °C, 3 h, 87%; (e) CAN, CH_3CN/H_2O, 2 h, 69%; (f) NaOMe/MeOH, reflux, 2.5 h, 63%; (g) NaN_3, DMF, 130 °C, 4 h, 62%; (h) NaN_3, $MeO(CH_2)_2OH$, 130 °C, 1.5 h, 84%; (i) Me_3P, THF/H_2O, reflux, 91%; (j) HCHO, $NaCNBH_3$, AcOH, MeOH, 3 h, 87%; (k) 40% aq Me_2NH, 12 h, 77%.

2. Results and discussion

Lincomycin **1**, was converted to the known 2,3-*O*-isopropylidene derivative **5**[5], then treated with *p*-methoxybenzyl chloride in the presence of NaH in DMF to give **6**, accompanied by the *N*-alkylated product (Scheme 1). Deprotection of the acetal in **6** with 80% aq acetic acid at 70 °C afforded the diol **7** in excellent yield. Selective mesylation at C-3 gave **8** in 87% yield. Our initial strategy was to displace the mesylate with a suitable oxygen nucleophile, with the intention of effecting a second inversion with azide ion. However, under a variety of conditions and nucleophiles no displacement could be achieved. We attributed this to the unfavourable trajectory of approach of the incoming nucleophile due to severe non-bonded 1,3-interaction with the axial anomeric thiomethyl group. We therefore adopted a different strategy. Cleavage of the PMB ethers in **8** with ceric ammonium nitrate gave the triol **9**, which was treated with NaN_3 in DMF at 130 °C.

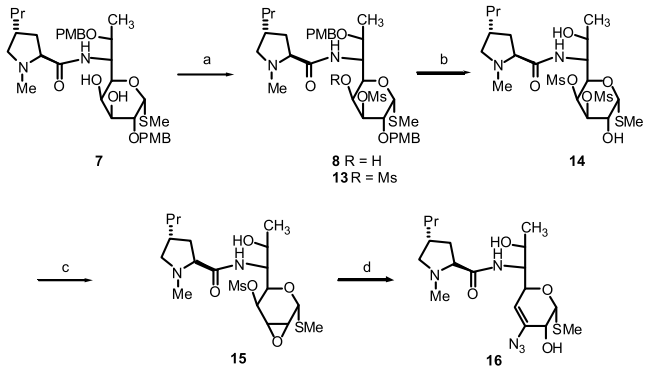
The resulting azido derivative was assigned structure **10** as intended in the target **4**. The regio- and stereochemistry at C-3 was confirmed by a series of homonuclear decoupling ^1H NMR experiments. Thus, irradiation of the signal of the anomeric carbon at δ 5.00 ppm caused the signal of the axial C-2 proton to appear as a doublet at δ 3.51 ppm ($J_{2,3}$ = 7 Hz), and the axial C-3 proton as

a doublet of doublets at δ 3.95 ppm ($J_{3,2}$ = 7 Hz, $J_{3,4}$ = 4.2 Hz). Irradiation of the C-2 proton signal at δ 3.51 ppm resulted in the anomeric proton to appear as a singlet at δ 5.00 ppm, and the C-3 proton as a doublet at δ 3.95 ppm $J_{3,4}$ = 3.9 Hz). Finally, irradiation of the C-3 proton at δ 3.95 ppm revealed the anomeric proton as a doublet at δ 5.00 ppm ($J_{1,2}$ = 5.0 Hz), and the C-2 proton as a doublet at δ 3.51 ppm ($J_{2,1}$ = 7 Hz)[23] As a test for the absence of a vicinal diol in **10**, it was found to be inert to the action of $NaIO_4$ (except for the conversion to a mixture of sulfoxides after 1 h). Upon treatment with acetone and *p*TSA, **10** was recovered unchanged, thus placing the azide group at C-3. The displacement with net retention of configuration at C-3 occurs via initial formation of the 'gulo' epoxide **11**, which undergoes a regioselective diequatorial opening at C-3 to give **10**. The expected trans-diaxial opening at C-2 is presumably retarded due to the presence of the bulky side-chain. There are several examples of diequatorial opening of epoxides due to steric factors and conformational effects.[24]

To validate the regiochemistry of **10** resulting from initial formation of an epoxide **11**, we prepared the epoxide from **9** by treatment with NaOMe in MeOH under reflux conditions. Opening of **11** with NaN_3 in 2-methoxyethanol at 130 °C gave **10**, which was identical to the sample obtained directly from **9**.

In order to probe the possibility of an in situ Payne rearrangement during the epoxide opening reaction, we treated the diol (**7**) with excess methanesulfonyl chloride, which gave the unseparable mixture of dimesylate **13** along with **8**. Cleavage of the PMB ethers with ceric ammonium nitrate afforded the diol (**14**), which on treatment with NaOMe in MeOH under reflux conditions gave the epoxide **15** (Scheme 2). Attempted selective opening of the epoxide **15** with NaN_3 in 2-methoxyethanol at 100 °C gave **16**. This can occur by initial diequatorial opening with azide, followed by β-elimination of the axial mesylate.[25]

Reduction of the azido group in **10** under Staudinger conditions[26] gave the amine **12**, which was treated with formaldehyde under conditions of reductive animation



Scheme 2. Reagents and conditions: (a) MsCl, Py/CH_2Cl_2 0 °C, 3 h; (b) CAN, CH_3CN/H_2O, 2 h; (c) NaOMe/MeOH, reflux, 2.5 h; (d) NaN_3, $MeO(CH_2)_2OH$, 100 °C, 1.5 h, 57%.

in the presence of $NaCNBH_3$[27] to give **4** in excellent overall yield (Scheme 1). Alternatively, treatment of the epoxide **11** with 40% aq dimethylamine[24a] afforded **4** in 77% yield, which was identical with the sample obtained from reductive animation route.

3. Conclusion

We have synthesized 3-*N*,*N*-dimethylamino-3-deoxy lincomycin as a structure-based inspired hybrid between lincomycin and the desosamine unit of erythromycin. Disappointingly, neither **4** nor the amino or azido precursors **10** and **12** displayed any inhibition of the growth *of E. coli* or *S. aureus* (MIC > 10 μM). Against the same strains, lincomycin showed MIC > 10 and 2.5 μ/mL, respectively. The lack of activity may be related to inefficient cell penetration, efflux, or no recognition at the ribosomal level for effective inhibition of protein biosynthesis. The development of cross-resistance in the macrolide-lincosamide-streptogramine B (MLS_B)[28] area warrants further studies to discover new entities with improved antibacterial profiles.

4. Experimental

4.1. General

Flash chromatography was carried out using 230–400 mesh silica gel. Mixtures of ethyl acetate and hexanes were used as the eluents, unless otherwise specified. Analytical thin layer chromatography (TLC) was performed on glass plates coated with a 0.02 mm layer of silica gel 60 F-254. Melting points were uncorrected. IR spectra were recorded as films. ^1H and ^{13}C NMR spectra were recorded at 300 and 400 MHz, respectively, and the chemical shifts are reported in parts per million (ppm) on the δ scale, with $CDCl_3$ as reference, unless otherwise specified. LCMS spectra were recorded using electron spray ionization technique. Optical rotations were measured in $CHCl_3$ or MeOH at 23 °C. All reactions were carried out under nitrogen or argon unless otherwise specified.

4.1.1. 3,4-*O*-Isopropylidene lincomycin (5). A solution of lincomycin (**1**) (1.5 g, 3.7 mmol) in 15 mL of acetone was added to a solution of 1.5 g of *p*-toluenesulfonic acid monohydrate in 15 mL of acetone with good stirring at room temperature. The mixture was stirred for 1 h, after which 10 mL of anhydrous ether was added and stirring was continued in an ice bath for 0.5 h. The resulting crystals were filtered off, washed with ether (2× 20 mL) and a second crop was recovered on cooling the mother liquor. Combined crops were suspended in 25 mL of ether and shaken vigorously with 5% $NaHCO_3$ solution to generate the free base. The organic layer was separated, the aqueous layer was back-extracted with 30 mL ether, and the combined extracts were washed with brine, dried over Na_2SO_4, after concentration under vacuum and the residue was purified by column chromatography (EtOAc) to give **5** as a sticky white solid (1.1 g, 74%): mp 125 °C; $[\alpha]_D$ +104 (*c* 1, CH_2Cl_2); IR

(neat) 3324, 2922, 1654 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.08–8.05 (1H, d, J = 7.9 Hz), 5.23 (1H, d, J = 5.0 Hz), 4.60–4.58 (1H, d, J = 6.6 Hz), 4.36–4.35 (1H, d, J = 4.2 Hz), 4.28–4.04 (4H, m), 3.15–2.98 (3H, m), 2.39 (3H, s), 2.2 (3H, s), 2.01–1.69, (3H, m), 1.55 (3H, s), 1.37 (3H, s), 1.30–1.23 (7H, m), 0.91 (3H, m); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 176.2, 110.1. 86.6, 76.7, 70.0, 69.1, 68.9, 67.7, 63.3, 56.3, 42.2, 38.4, 38.1, 28.1, 26.2, 21.9, 20.0, 14.6, 13.9; MS Calcd for $C_{21}H_{38}N_2O_6S$ (M^+): 446.6. Found: 447.4 (M+1).

4.1.2. 2,7-*O*-Di-*p*-methoxybenzyl-3,4-*O*-isopropylidene lincomycin (6). To a solution of compound **5** (0.6 g, 1.34 mmol) in anhydrous DMF (15 mL) 60% NaH in mineral oil (0.15 g, 4.04 mmol) was added at 0 °C under argon atmosphere and the mixture was stirred for 30 min. *p*-Methoxybenzyl chloride was added slowly at 0 °C and the mixture was stirred for 12 h at room temperature, then quenched with ice, diluted with ether (30 mL), washed with 5% $NaHCO_3$ solution and extracted with ether (2× 20 mL). Combined organic phase was washed with brine, dried over Na_2SO_4, concentrated under vacuum at low temperature and the residue was purified by column chromatography (EtOAc/hexanes, 45:55) to afford **6** (0.32 g, 35%) as a sticky solid: $[\alpha]_D$ +72.9 (*c* 1.3, MeOH); IR (neat) 3396, 2968, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.12–8.10 (1H, d, J = 8.9 Hz), 7.30–7.23 (4H, m), 6.87–6.84 (4H, m), 5.17 (1H, d, J = 5.1 Hz), 4.63–4.56 (4H, m), 4.39–4.35 (2H, m), 4.13–4.11 (1H, m), 4.09–3.97 (1H, m), 3.80–3.79 (6H, m), 3.68–3.62 (2H, s), 3.04–2.88, (3H, m), 2.31 (3H, s), 2.06–1.98 (4H, m), 1.79 (1H, m), 1.61 (1H, m) 1.37 (3H, s), 1.26 (7H, m), 1.16 (3H, s), 0.89 (3H, m); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 175.2, 159.7, 130.8, 130.3, 129.9, 129.7, 114.2, 114.1, 109.4, 84.2, 76.1, 75.9, 74.5, 74.1, 72.0, 70.2, 69.3, 65.8, 63.4, 55.7, 55.6, 54.3, 42.1, 38.2, 38.1, 36.2, 28.2, 26.2, 22.0, 16.7, 14.7, 13.2; MS Calcd for $C_{37}H_{54}N_2O_8S$ (M^+): 686.4. Found: 687.7 (M+1).

4.1.3. 2,7-*O*-Di-*p*-methoxybenzyl lincomycin (7). A solution of compound **6** (157 mg, 0.23 mmol) in AcOH:H_2O (8:2, 5 mL) was heated at 70 °C for 24 h. The reaction mixture was allowed to cool, neutralized with 5% $NaHCO_3$ solution and extracted with EtOAc (3× 20 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated under vacuum and the residue was purified by column chromatography (EtOAc/hexanes, 75:25) to afford **7** (100 mg, 75%) as a sticky solid: $[\alpha]_D$ +85.6 (*c* 1.7, MeOH); IR (neat) 3340, 2924, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.84–7.82 (1H, d, J = 8.1 Hz), 7.37–7.33 (2H, m), 7.21–7.18 (2H, d, J = 8.2 Hz), 6.91–6.84 (4H, m), 5.21 (1H, d, J = 5.3 Hz), 4.67–4.65 (2H, $_m$), 4.43–4.41 (3H, m), 3.98–3.92 (3H, m), 3.82–3.72 (9H, m), 3.16–3.15 (1H, d, J = 4.3 Hz), 2.94 (1H, m), 2.72–2.70, (1H, J = 6.8 Hz), 2.26 (3H, s), 2.10–1.95 (6H, m), 1.31–1.24 (7H, m), 0.91 (3H, m); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 178.2, 159.8, 159.5, 130.7, 130.4, 130.1, 129.7, 114.2, 114.1, 86.7, 76.1, 73.2, 72.5, 70.5, 70.4, 70.2, 69.0, 68.9, 63.1, 55.7, 50.3, 41.9, 38.2, 38.1, 36.2, 21.9, 15.1, 14.7, 14.1; MS Calcd for $C_{34}H_{50}N_2O_8S$ (M^+): 646.3. Found: 647.6 (M+1).

4.1.4. 2,7-*O*-Di-*p*-methoxybenzyl-3-*O*-methanesulfonyl lincomycin (8). Methanesulfonyl chloride (70 μL, 0.91 mmol) was added slowly to a mixture of **7** (390 mg, 0.6 mmol) in anhydrous pyridine/CH_2Cl_2 (1:1, 10 mL) at 0 °C. The reaction mixture was stirred for 3 h, quenched with ice, neutralized with 5% $NaHCO_3$ solution and extracted with EtOAc (3× 25 mL). Combined organic phase was washed with brine, dried over Na_2SO_4, concentrated under vacuum and the residue was purified by column chromatography (EtOAc/hexanes, 55:45) to afford **8** (380 mg, 87%) as a sticky solid: $[\alpha]_D$ +89.9 (*c* 1.5, MeOH); IR (neat) 3321, 2930, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.87–7.84 (1H, d, J = 9.1 Hz), 7.33–7.29 (2H, m), 7.23–7.21 (2H, d, J = 8.6 Hz), 6.91–6.85 (4H, m), 5.34 (1H, d, J = 5.5 Hz), 4.71–4.67 (2H, m), 4.66–4.33 (5H, m), 3.99–3.89 (3H, m), 3.83 (3H, s), 3.82 (3H, s), 3.17–3.15 (1H, m), 2.98–2.93 (5H, m), 2.27 (3H, s), 2.09–1.91 (6H, m), 1.37–1.27 (7H, m), 0.91 (3H, m); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 177.9, 159.9, 159.6, 150.1, 136.5, 130.5, 130.2, 129.7, 124.2, 114.2, 114.1, 86.4, 80.4, 73.4, 72.9, 72.4, 70.5, 70.2, 68.9, 63.2, 55.7, 50.3, 42.0, 38.8, 38.2, 38.1, 36.2, 21.9, 15.3, 14.7, 13.7; MS Calcd for $C_{35}H_{52}N_2O_{10}S_2$ (M^+): 724.3. Found: 725.5 (M+1).

4.1.5. 3-*O*-Methanesulfonyl lincomycin (9). Cerium ammonium nitrate (600 mg, 1.08 mmol) was added to a **8** (170 mg, 0.24 mmol) in MeCN/H_2O (9:1, 5 mL) at room temperature, and the mixture was vigorously stirred for 2 h at room temperature, then neutralized with 5% $NaHCO_3$ solution and extracted with EtOAc (5× 20 mL). Combined organic phase was washed with brine, dried over Na_2SO_4, concentrated under vacuum at low temperature and the residue was purified by column chromatography (MeOH/EtOAc, 5:95) to afford **9** (75 mg, 69%) as a white solid: mp 89 °C; $[\alpha]_D$ +141.5 (*c* 0.75, MeOH); IR (neat) 3369, 2929, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.88 (1H, s), 5.43–5.42 (1H, d, J = 5.3 Hz), 4.62–4.58 (1H, m), 4.52–4.50 (1H, m), 4.24–4.13 (3H, m), 4.04–3.99 (2H, m), 3.29–3.15 (6H, m), 2.46–2.42 (3H, s), 2.23 (3H, s), 2.26 (3H, s), 2.19–1.98 (3H, m), 1.33–1.20 (7H, m), 0.92 (3H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 177.7, 89.2, 81.4, 71.9, 68.8, 68.7, 66.1, 63.2, 53.5, 42.2, 39.2, 38.3, 38.1, 36.1, 31.3, 21.9, 18.1, 14.7, 14.4; MS Calcd for $C_{19}H_{36}N_2O_8S_2$ (M^+): 484.2. Found: 485.2 (M+1).

4.1.6. 2,3-Anhydro lincomycin (11). To a solution of **9** (30 mg, 0.06 mmol) in MeOH (3 mL) was added NaOMe solution (pH 9) under argon atmosphere and the solution was refluxed for 2.5 h. The reaction mixture was concentrated under vacuum at low temperature and the residue was purified by column chromatography (MeOH/CH_2Cl_2, 5:95) to afford **11** (15 mg, 63%): $[\alpha]_D$ +70.1 (*c* 0.8, MeOH); IR (neat) 3323, 2924, 1654 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.81–7.79 (1H, d, J = 5.2 Hz), 5.41 (1H, br s), 4.22–4.18 (1H, m), 4.16–4.09 (1H, m), 3.82 (1H, m), 3.76–3.73 (1H, d, J = 10.6 Hz), 3.52 (2H, s), 3.27–3.24 (1H, m), 3.19–3.09 (1H, m), 2.44 (3H, s), 2.23 (3H, s), 2.22–2.12 (2H, m), 2.06–1.92 (2H, m), 1.35–1.25 (7H, m), 0.92 (3H, m); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 177.8, 82.1, 69.4, 68.8, 67.4, 63.6, 63.1, 53.9, 53.8, 52.8, 42.2, 38.3, 38.1,

36.1, 21.9, 17.7, 14.7, 14.6; MS Calcd for $C_{18}H_{32}N_2O_5S$ (M^+): 388.2. Found: 389.2 (M+1).

4.1.7. 3-Azido-3-deoxy lincomycin 10 (from 11). Sodium azide (67 mg, 1 mmol) was added to a solution of **9** (33 mg, 0.09 mmol) in 2-methoxyethanol (5 mL) under argon atmosphere, and the mixture was heated at 130 °C for 1.5 h. Concentration and purification of the residue by column chromatography ($MeOH/CH_2Cl_2$, 6:94) afforded **10** (31 mg, 84%) as a sticky solid.

Compound **10** (From **9**): A mixture of **9** (40 mg, 0.08 mmol), NaN_3 (65 mg, 1 mmol) in anhydrous DMF (5 mL) was heated at 130 °C for 4 h, the reaction mixture was concentrated under vacuum and the residue was purified by column chromatography ($MeOH/CH_2Cl_2$, 6:94) to afford **10** (22 mg, 62%) as a sticky solid: $[\alpha]_D$ +68.8 (*c* 1, MeOH); IR (neat) 3340, 2926, 2109, 1659 cm^{-1}; ^1H NMR (CDC_3, 400 MHz) δ: 7.88–7.85 (1H, d, $J = 9$ Hz), 5.0–4.99 (1H, d, $J = 5.0$ Hz), 4.26–4.18 (2H, m), 4.08–4.04 (1H, dd, $J = 2.4$ Hz, 8.9 Hz), 3.95–3.93 (1H, dd, $J = 4.2$, 7.0 Hz), 3.59–3.58 (1H, dd, $J = 2.5$, 4.3 Hz), 3.52–3.49 (1H, dd, $J = 4.8$, 6.9 Hz), 3.19 (1H, d, $J = 2.8$ Hz), 3.03–2.99 (1H, dd, $J = 4.6$, 10.7 Hz), 2.39 (3H, s), 2.24 (3H, s), 2.19–2.05 (2H, m), 2.04–1.84 (2H, m), 1.32–1.24 (7H, m), 0.91 (3H, t, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 177.8. 85.9, 72.2, 70.5, 70.0, 68.8, 67.7, 62.9, 53.5, 42.1, 38.1, 37.5, 35.9, 30.1, 21.9, 18.1, 15.7, 14.6; MS Calcd for $C_{18}H_{33}N_5O_5S$ (M^+): 431.2. Found: 432.2 (M+1).

4.1.8. 3-Amino-3-deoxy lincomycin (12). To a solution of **10** (21 mg, 0.05 mmol) in THF was added trimethylphosphine (150 μL, 1 M in toluene) and the solution was stirred under argon atmosphere for 30 min. Water (10 μL) was added and the mixture, stirred under reflux for 45 min., then concentrated under vacuum and purified by column chromatography ($NH_4OH/MeOH/CH_2Cl_2$, 1:10:89) to afford **12** (18 mg, 91%): $[\alpha]_D$ +91.1 (*c* 0.9, MeOH); IR (neat) 3352, 2922, 1649 cm^{-1}; ^1H NMR ($CDCl_3$, + D_2O 5 μL, 400 MHz) δ: 5.01 (1H, br s), 4.23–4.17 (3H, m), 3.89–3.87 (1H, m), 3.56–3.54 (1H, d, $J = 3.4$ Hz), 3.17 (1H, m), 3.02–2.97 (2H, m), 2.39 (3H, s), 2.19 (3H, s), 2.07–1.94 (3H, m), 1.87–1.85 (1H, m), 1.32–1.23 (7H, m), 0.91–0.89 (3H, t, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$ + CD_3OD 5 μL, 400 MHz) δ: 177.4, 88.5, 70.7, 69.8, 69.4, 68.9, 67.2, 63.2, 54.6, 53.7, 42.3, 38.2, 38.1, 36.2, 22.0, 18.1, 16.1, 14.7; MS Calcd for $C_{18}H_{35}N_3O_5S$ (M^+): 405.2. Found: 406.2 (M+1).

4.1.9. 3-*N*,*N*-Dimethylamino-3-deoxy lincomycin 4 (from 12). To a mixture of **12** (20 mg, 0.05 mmol), formaldehyde (0.10 mmol, 37%) in MeOH (2 mL), was added AcOH (10 μL) then stirred for 1 h. $NaCNBH_3$ (20 mg, 0.3 mmol) was added to the mixture and stirred for 3 h at room temperature, then concentrated under vacuum and purified by column ($NH_4OH/MeOH/CH_2Cl_2$, 1:8:91) to afford **4** (19 mg, 87%).

Compound **4** (from **11**): A solution of **11** (14 mg, 0.036 mmol) and dimethylamine (1 mL, 40%) was stirred for 12 h at room temperature, then concentrated and the residue was purified by column chromatography ($NH_4OH/MeOH/CH_2Cl_2$, 1:8:91) to afford **4** (12 mg, 77%): $[\alpha]_D$ +72.5 (*c* 0.55, MeOH); IR (neat) 3321, 2927, 1656 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD 5 μL, 400 MHz) δ: 5.25–5.23 (1H, d, $J = 5.5$ Hz), 4.19–4.09 (3H, m), 3.93–3.88 (1H, dd, $J = 4.6$, 7.5 Hz), 3.69 (1H, m), 3.17 (1H, m), 3.02–2.98 (1H, dd, $J = 4.3$, 10.7 Hz), 2.49 (6H, br s), 2.38 (3H, s), 2.21 (3H, s), 2.08–1.95 (3H, m), 1.89–1.79 (2H m), 1.34–1.24 (7H, m), 0.91–0.87 (3H, t, $J = 6.1$ Hz); ^{13}C NMR ($CDCl_3$ + CD_3OD 5 μL, 400 MHz) δ: 170.2, 81.8, 72.3, 69.7, 68.1, 66.9, 65.9, 62.4,53.2, 41.9, 41.5, 37.5, 37.2, 35.4, 29.8, 21.2, 18.2, 14.7, 13.9; MS Calcd for $C_{20}H_{39}N_{30}O_5S$ (M_+): 433.3. Found: 434.2 (M+1).

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