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ORIGINAL ARTICLE

Synthesis and structure–activity relationships of novel lincomycin derivatives. Part 1. Newly generated antibacterial activities against Gram-positive bacteria with *erm* gene by C-7 modification

Yoshinari Wakiyama, Ko Kumura, Eijiro Umemura, Kazutaka Ueda, Satomi Masaki, Megumi Kumura, Hideki Fushimi and Keiichi Ajito

We synthesized 7(*S*)-7-deoxy-7-arylthiolincomycin derivatives possessing a heterocyclic ring at the C-7 position via sulfur atom by either Mitsunobu reaction of 2,3,4-tris-*O*-(trimethylsiliyl)lincomycin or S_N2 reaction of 7-*O*-methanesulfonyl-2,3,4-tri-*O*-trimethylsiliyllincomycin. As a result, 7(*S*)-7-deoxy-7-arylthiolincomycin derivatives 16, 21 and 27 exhibited antibacterial activities against respiratory infection-related Gram-positive bacteria with *erm* gene, although clindamycin did not have any activities against those pathogens. Furthermore, 7(*S*)-configuration of lincomycin derivatives was found to be necessary for enhancing antibacterial activities from the comparison results of configurations of 16 (*S*-configuration) and 30 (*R*-configuration) at the 7-position.

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INTRODUCTION

Macrolide antibiotics possess broad spectrum of antibacterial activity against Gram-positive bacteria (*Streptococcus pneumoniae*, *Streptococcus pyogenes*, etc.), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae* and *Neisseria gonorrhoeae* and also have a safety profile as oral drugs. Therefore, macrolide antibiotics have been used as chemotherapeutic agents in clinical sites over many years. Resistant bacteria, however, have markedly increased recently,[1–3] and this phenomenon has caused serious problems in the treatment of bacterial respiratory infections.

Macrolide antibiotics inhibit bacterial protein synthesis. Macrolide antibiotics have potent antibacterial activities through inhibiting elongation of an amino-acid sequence by binding to 23S ribosomal RNA.[4–6] The mechanisms of action for bacteria to gain resistance are manifold, but in general, these can be characterized as involving drug efflux, alterations in the drug target site or drug inactivation. Resistant mechanisms in macrolides have diversified recently. Notably, there are major bacterial strains in clinical site, with point mutation in the drug target site,[7,8] with methylase produced by *erm* gene and with efflux pump produced by *mef* gene.

The methylase of bacteria inhibits macrolide binding to 23S ribosomal RNA through either methylation or dimethylation at the N-6 position of the adenine residue (A2058Ec).[7,9,10] On the other hand, the efflux pump of bacteria is able to transport a variety of compounds, thus conferring resistance to a broad range of antibiotics.

Clarithromycin[11] and azithromycin[12] (Figure 1) are not effective enough against resistant bacteria (*S. pneumoniae* and *S. pyogenes*) with *erm* gene and influenced by *S. pneumoniae* with *mef* gene. On the other hand, telithromycin (TEL),[13] which was launched as the first ketolide antibiotic, is effective against resistant bacteria with *erm* and *mef* genes. X-ray crystallographic[6,14] and footprinting analysis[15–17] indicated that TEL would be capable to bind to not only domain V (A2058Ec, A2059Ec) of 23S rRNA but also to domain II (A752). TEL, however, has possibility to cause serious liver damage[18,19] and loss of consciousness,[20,21] and it is scarcely used in Japan. No oral antibiotic, which is effective against the resistant bacteria with *erm* and *mef* genes, with no problems in terms of safety or taste, has been launched so far.

Lincomycin (LCM)[22–25] was isolated as a secondary metabolite from the fermentation broth of *Streptomyces lincolnensis*. Clindamycin (CLDM)[26] was synthesized by chemical modification of LCM (Figure 1) and exhibited improved antimicrobial activities and pharmacokinetics compared with LCM. But they are not effective against resistant bacteria (*S. pneumoniae* and *S. pyogenes*) with *erm* gene (Table 1).

Chemical modifications at the C-7 positions of LCM (7-dehydrolincomycin (7-ketolincomycin),[27] 7-deoxylincomycin,[28] lincomycin-7-acylate[29] and lincomycin-7-carbonate,[29] 7(*R*)-7-azido-7-deoxylincomycin,[25] 7(*R*)-7-amino-7-deoxylincomycin,[25] 7(*R*)-7-cyano-7-deoxylincomycin,[25] 7(*R*)-7-deoxy-7-thiolincomycin,[30] 7(*S*)-7-deoxy-7-thiolincomycin,[30] 7(*S*)-7-bromo-7-deoxylincomycin,[26] 7(*S*)-7-deoxy-7-iodolincomycin,[26] 7(*R*)-7-chloro-7-deoxylincomycin,[26]

Pharmaceutical Research Center, Meiji Seika Pharma Co., Ltd, Kohoku-ku, Yokohama, Japan
Correspondence: Dr K Ajito, Pharmaceutical Research Center, Meiji Seika Pharma Co., Ltd, 760 Morooka-cho, Kohoku-ku, Yokohama 222–8567, Japan.
E-mail: keiichi.ajito@meiji.com

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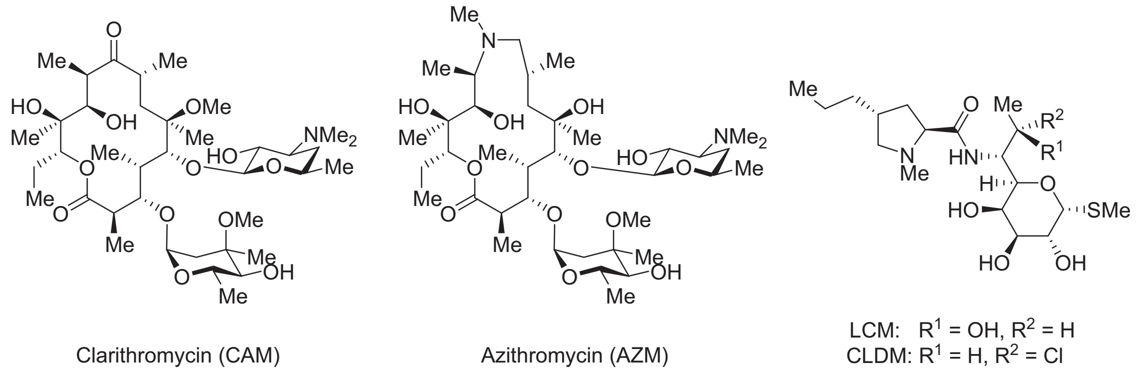

Clarithromycin (CAM) Azithromycin (AZM)

LCM: R^1 = OH, R^2 = H
CLDM: R^1 = H, R^2 = Cl

Figure 1 Chemical structures of the representative macrolides, lincomycin (LCM) and clindamycin (CLDM).

Table 1 Antibacterial activities (MIC, $\mu g\,ml^{-1}$) of the representative macrolides, lincomycin (LCM) and clindamycin (CLDM)

Test organism[a]	*Characteristics*[b]	*CAM*	*AZM*	*LCM*	*CLDM*
Streptococcus pneumoniae DP1 TypeI	susceptible	0.03	0.06	1	0.06
S. pneumoniae -2	susceptible	0.03	0.03	1	0.12
S. pneumoniae -3	susceptible	0.015	0.03	0.25	0.06
S. pneumoniae -4	*ermAM* methylase(c)	>128	>128	>128	>128
S. pneumoniae -5	*ermAM* methylase(c)	>128	>128	>128	>128
S. pneumoniae -6	*ermAM* methylase(c) + *mefE*	>128	>128	>128	>128
S. pneumoniae -7	*ermAM* methylase(i)	>128	>128	128	128
S. pneumoniae -8	*ermAM* methylase(i)	>128	>128	128	128
S. pneumoniae -9	*mefE* efflux	0.5	0.5	1	0.12
Streptococcus pyogenes Cook	susceptible	0.015	0.06	0.12	0.06
S. pyogenes -2	*ermAM* methylase(c)	>128	>128	>128	128
S. pyogenes -3	*mefE* efflux	8	8	0.25	0.12
Haemophilus influenzae	susceptible	2	0.25	8	16
H. influenzae -2	susceptible	4	1	16	8
H. influenzae -3	susceptible	8	2	16	16
H. influenzae -4	⊿acr	0.5	0.5	4	1

Abbreviations: AZM, azithromycin; CAM, clarithromycin.
[a] All strains except standard organisms were clinically isolated.
[b] (c): constitutive; (i): inducible.
Grey shading strains are target strains.

and 7-epilincomycin (7(*S*)-lincomycin),[26] 7-deoxy-7-methyllincomycin[31] and so on) have been investigated so far. In these compounds, 7(*S*)-7-bromo-7-deoxylincomycin and 7(*S*)-7-deoxy-7-iodolincomycin exhibited enhanced antibacterial activities in the same order of magnitude as CLDM, and 7(*R*)-7-azido-7-deoxylincomycin had the same antibacterial activities as LCM.

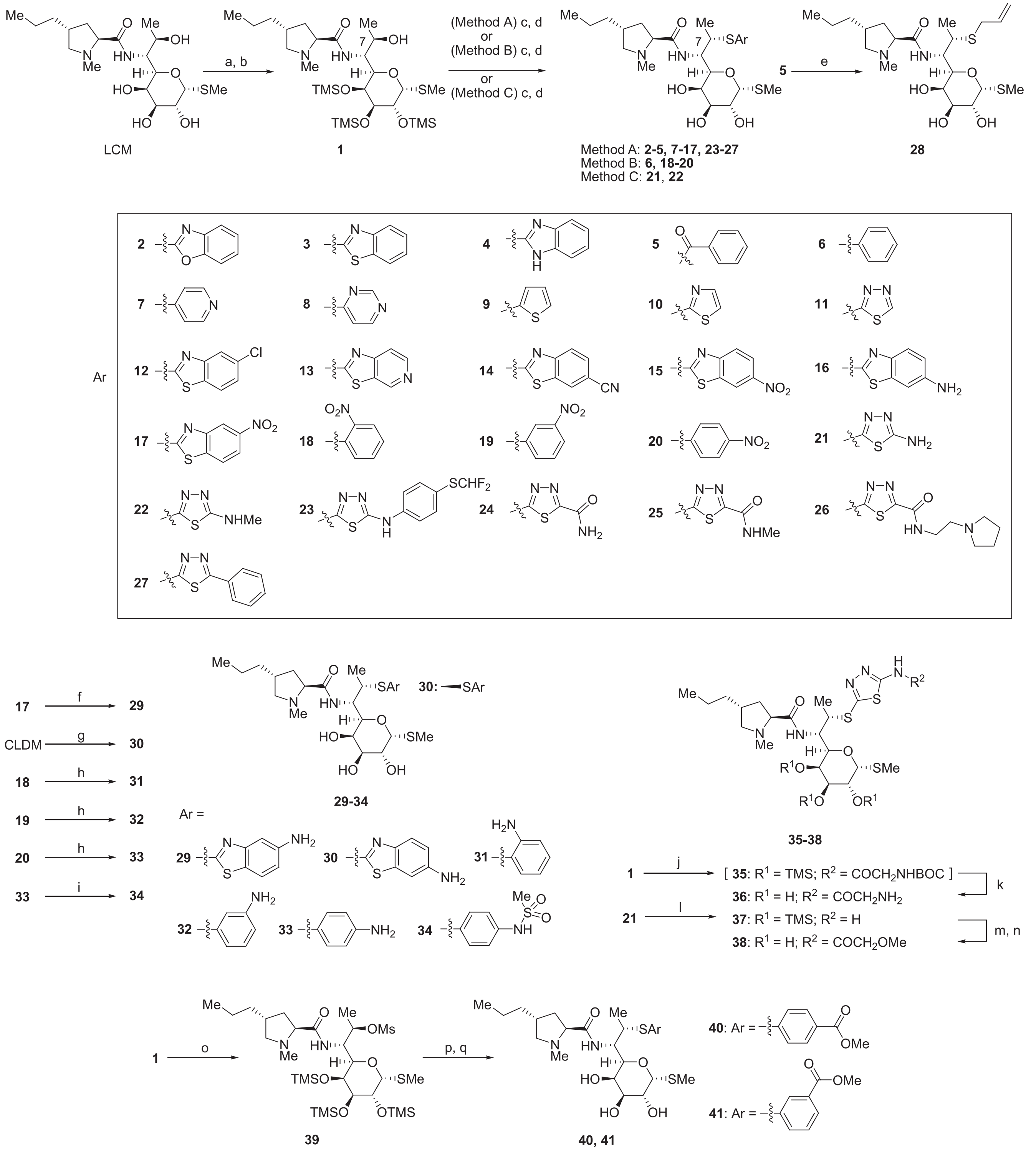
In the case of possessing a chlorine atom at the 7-position, CLDM (7(*S*)-Cl) had stronger antibacterial activities than 7-epiclindamycin (7(*R*)-Cl). 7-Epilincomycin (7(*S*)-lincomycin) had one-half of the potency of the LCM possessing 7(*R*)-configuration (7(*S*)-OH<7(*R*)-OH).

7(*R*)-7-*O*-methyllincomycin, of which 7-hydrolyl group was protected, showed improved potency, whereas 7(*S*)-7-*O*-methyllincomycin had stronger activities of 3.5 times the response of LCM against *Sarcina lutea* (7(*S*)-OMe>7(*R*)-OMe).[32,33] Unfortunately, both larger alkoxy groups and substituted alkoxy groups resulted in weaker antibacterial activities than those of LCM.

On the other hand, both 7(*S*)-7-deoxy-7-thiolincomycin and 7(*R*)-7-deoxy-7-thiolincomycin showed only 10% activity as compared with LCM. 7(*S*)-7-alkylthio-7-deoxylincomycin and 7(*S*)-7-substituted alkylthio-7-deoxylincomycin[34–38] were more active than LCM against Gram-positive or Gram-negative organisms, and 7(*R*)-7-deoxy-7-imidazol-2-yl-thiolincomycin, which had been reported by Sztaricskai *et al.*,[39] retained the same order of magnitude of antibacterial activities against tested organisms as those of LCM. Antibacterial activities were affected by both configuration and a structure of a substituent at the 7-position. 7(*S*)-7-deoxy-7-phenylthiolincomycin was reported by Bannister *et al.*[38] but no antibacterial activity of this compound was reported.

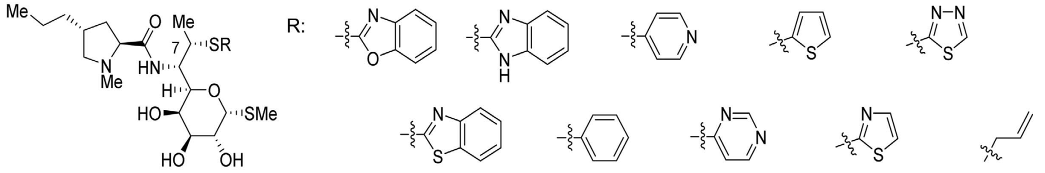
Thus we were interested in derivatives with a heterocyclic ring introduced via sulfur atom at the C-7 position with 7(*S*)-configuration. According to the above publications, LCM derivatives exhibited much stronger *in vitro* activities compared with LCM, but no LCM derivatives were effective against resistant bacteria with *erm* gene.

LCM and CLDM inhibited bacterial protein synthesis similar to macrolide antibiotics. The structures of lincomycin derivatives are different from those of macrolide antibiotics, but X-ray crystallographic analysis indicated that their binding sites to rRNA are closely located in a neighboring area.[4,6] According to the report,[4,6] there were several major interactions by hydrogen bonding between


LCM
a, b
1
(Method A) c, d
or
(Method B) c, d
or
(Method C) c, d
Method A: 2-5, 7-17, 23-27
Method B: 6, 18-20
Method C: 21, 22
5
e
28
Ar
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
17 f 29
CLDM g 30
18 h 31
19 h 32
20 h 33
33 i 34
29-34
30: SAr
Ar =
35-38
1 j [35: R¹ = TMS; R² = COCH₂NHBOC] k
36: R¹ = H; R² = COCH₂NH₂
21 l 37: R¹ = TMS; R² = H
38: R¹ = H; R² = COCH₂OMe
m, n
1 o
39
p, q
40, 41
40: Ar =
41: Ar =

Scheme 1 Synthesis of 7(*S*)-7-arylthio-7-deoxylincomycin derivatives. Conditions: a, TMSCl, HMDS, Py, r.t., 2 h; b, 80% AcOH, MeOH, r.t., 16 h; Method A: c, PPh_3, DEAD, the corresponding HS-Ar, THF or toluene, 0 °C to 50 °C, 16–18 h, d, 1–2 *N* HCl, MeOH, r.t., 30 min; Method B: c, PBu_3, DEAD, the corresponding Ar-S-S-Ar, THF, 0 °C to r.t., 19–25 h; d, 2 *N* HCl, r.t., 0.5–3 h; Method C: c, PPh_3, DEAD, *tert*-butyl 5-mercapto-1,3,4-thiadiazol-2-ylcarbamate or *tert*-butyl 5-mercapto-1,3,4-thiadiazol-2-yl(methyl)carbamate, THF, 0 °C to r.t., 17 h, d, TFA, r.t., 60 min; e, NaOMe, allyl iodide, MeOH, r.t.; f, $SnCl_2{\cdot}H_2O$, $NaBH_4$, EtOH, r.t., 3 h; g, 6-aminobenzo[*d*]thiazole-2-thiol, K_2CO_3, DMF, 100 °C, 16 h; h, $SnCl_2{\cdot}H_2O$, $NaBH_4$, EtOH, r.t., 3 h; i, MsCl, TEA, DMF, r.t., 20 min; j, PPh_3, DEAD, *tert*-butyl 2-(5-mercapto-1,3,4-thiadiazol-2-ylamino)-2-oxoethylcarbamate, THF, 0 °C to r.t., 17 h, k, TFA, r.t., 0.5 h; l, TMSCl, HMDS, Py, r.t., 2.5 h; m, 2-methoxyacetyl chloride, TEA, THF, 0 °C, 2 h; n, 1 *N* HCl, MeOH, r.t., 2 h; o, MsCl, TEA, $CHCl_3$, r.t., 3 h; p, the corresponding HS-Ar, K_2CO_3, DMF, 80 °C, 3–16 h, q, 1 *N* HCl, MeOH, r.t., 0.5–2 h.

Table 2 Antibacterial activities (MIC, $\mu g\,ml^{-1}$) of 7-thio-substituted LCM derivatives



Test organism[a]	*Characteristics*[b]	*CLDM*	***2***	***3***	***4***	***6***	***7***	***8***	***9***	***10***	***11***	***28***
Streptococcus pneumoniae DP1 TypeI	susceptible	0.06	0.06	0.25	0.06	0.25	0.12	0.12	0.12	0.12	0.12	0.06
S. pneumoniae -2	susceptible	0.12	0.06	0.25	0.12	0.25	0.25	0.25	0.25	0.25	0.25	0.12
S. pneumoniae -3	susceptible	0.06	0.06	0.25	0.03	0.12	0.12	0.12	0.12	0.12	0.12	0.06
S. pneumoniae -4	*ermAM* methylase(c)	>128	128	128	>128	128	>128	>128	128	>128	128	>128
S. pneumoniae -5	*ermAM* methylase(c)	>128	>128	128	>128	128	>128	>128	128	128	128	>128
S. pneumoniae -6	*ermAM* methylase(c) + *mefE*	>128	>128	128	>128	128	>128	>128	128	>128	128	>128
S. pneumoniae -7	*ermAM* methylase(i)	128	>128	128	>128	128	128	>128	128	64	128	128
S. pneumoniae -8	*ermAM* methylase(i)	128	64	128	>128	128	128	>128	128	64	128	>128
S. pneumoniae -9	*mefE* efflux	0.12	0.06	0.25	0.03	0.12	0.06	0.12	0.12	0.12	0.12	0.06
Streptococcus pyogenes Cook	susceptible	0.06	0.03	0.12	0.03	0.12	0.12	0.12	0.12	0.06	0.06	0.06
S. pyogenes -2	*ermAM* methylase(c)	128	64	16	64	128	64	64	64	128	128	>128
S. pyogenes -3	*mefE* efflux	0.12	0.06	0.25	0.12	0.12	0.25	0.25	0.25	0.12	0.25	0.12
Haemophilus influenzae	susceptible	16	8	64	32	16	32	32	32	64	16	16
H. influenzae -2	susceptible	8	4	16	32	8	8	16	8	32	16	8
H. influenzae -3	susceptible	16	16	64	64	32	32	64	64	128	32	32
H. influenzae -4	⊿acr	1	0.5	2	1	0.5	1	2	0.5	1	1	1

Abbreviations: CLDM, clindamycin; LCM, lincomycin.
[a] All strains except standard organisms were clinically isolated.
[b] (c): constitutive; (i): inducible.
Grey shading strains are target strains.

the peptidyl transferase cavities (A2058Ec, A2059Ec and G2520Ec) and hydroxyl groups at the sugar portion of CLDM. These data suggest that it is difficult for us to improve antibacterial activity by chemical modification at the sugar moiety. In fact, 2-deoxylincomycin[40] has been reported to show only 1% activity compared with LCM.

As we previously described, TEL has a risk of causing serious side effects[18–21] and it is rarely used in Japan. Furthermore, its production cost seems to be relatively high owing to its complicated structure. On the other hand, CLDM possessing a simple structure has similar antibacterial activity against susceptible strains such as clarithromycin and exhibits acceptable oral absorption in animals and humans. However, CLDM is not effective enough against resistant bacteria of *S. pneumoniae* or *S. pyogenes* with *erm* gene. So a novel oral lincomycin analog, which is effective against resistant bacteria with *erm* gene and/or *mef* gene and does not have any problems in safety, taste or pharmacokinetics, is strongly desired for treatment of respiratory infections in clinical sites.

On the other hand, 7(*S*)-7-azido-7-deoxylincomycin, CLDM, 7(*S*)-7-bromo-7-deoxylincomycin and 7(*S*)-7-alkylthio-7-deoxylincomycin had the same or stronger antibacterial activity compared with LCM. According to the relationships between configuration and a substituent (7(*S*)-Cl > 7(*R*)-Cl and 7(*S*)-OMe > 7(*R*)-OMe), enhancement of activities in 7(*S*)-configuration might require a hydrophobic substituent such as a chlorine atom or a methyl group, not as OH or SH (7(*S*)-OH < 7(*R*)-OH (LCM), 7(*S*)-SH≈7(*R*)-SH < LCM). Larger alkoxy groups and substituted alkoxy groups with 7(*S*)-configuration resulted in weaker antibacterial activities than those of LCM, while 7(*S*)-7-alkylthio-7-deoxylincomycin was more active than LCM against Gram-positive organisms. As a result, a sulfur atom might be preferable to an oxygen atom at the 7-position for enhancing antibacterial activities. 7(*R*)-7-deoxy-7-imidazol-2-yl-thiolincomycin had the same antibacterial activity as LCM. Here we planned synthesis of lincomycin analogs possessing a heterocyclic ring via sulfur atom focusing on the 7(*S*)-configuration at the 7-position, in order to generate unreported antibacterial activity against respiratory infection-related Gram-positive bacteria with *erm* gene.

RESULTS AND DISCUSSION

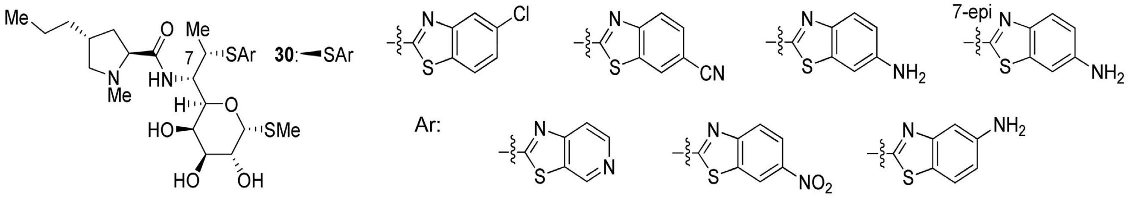
Design of LCM derivatives

The results of X-ray crystallographic analysis[4–6] have already been reported in application of CLDM. According to three-dimensional information around the 7-position of CLDM, we hypothesized that CLDM had enough three-dimensional space around the 7-position, and it might be able to enhance antibacterial activities by filling the space with an appropriate substituent. So we designed 7(*S*)-LCM derivatives possessing a hydrophobic heterocyclic ring via sulfur atom and practically synthesized 7(*S*)-7-arylthio-7-deoxylincomycin by Mitsunobu reaction.

Synthesis of 7(*S*)-7-arylthio-7-deoxylincomycin derivatives

Synthesis of 7(*S*)-7-arylthio-7-deoxylincomycin derivatives is outlined in Scheme 1. We first prepared a key intermediate **1**[41] derived from LCM in two steps in order to construct the same configuration at the 7-position as CLDM in final target molecules. Our synthesis began with silylation of all OH groups of LCM, and the 7-*O*-TMS group was selectively deprotected by AcOH to give the key intermediate (**1**) with an excellent yield. LCM derivatives (**2–5**, **7–17** and **21–27**), which possess a heterocyclic ring at the C-7 position via sulfur atom, were synthesized from **1** with the corresponding thiol under the Mitsunobu condition (Methods A and C).[42,43] Compounds **6**[38] and **18–20** possessing a phenyl thiol group were synthesized by Method B in application of the corresponding disulfide. Furthermore, compound **28**[38] was prepared by allylation of **5** under the NaOMe

Table 3 Antibacterial activities (MIC, $\mu g\,ml^{-1}$) of LCM derivatives possessing a substituted benzothiazol-2-ylthio group at the 7-position



Test organism[a]	*Characteristics*[b]	***12***	***13***	***14***	***15***	***16***	***29***	***30***
Streptococcus pneumoniae DP1 TypeI	susceptible	0.12	0.12	0.25	0.06	0.06	0.12	0.03
S. pneumoniae -2	susceptible	0.12	0.12	0.25	0.06	0.06	0.12	0.03
S. pneumoniae -3	susceptible	0.12	0.12	0.12	0.03	0.03	0.06	0.03
S. pneumoniae -4	*ermAM* methylase(c)	64	64	128	64	8	32	32
S. pneumoniae -5	*ermAM* methylase(c)	32	>128	128	64	32	64	32
S. pneumoniae -6	*ermAM* methylase(c) + *mefE*	64	>128	128	64	64	128	64
S. pneumoniae -7	*ermAM* methylase(i)	64	128	64	32	16	32	32
S. pneumoniae -8	*ermAM* methylase(i)	32	128	64	32	8	64	32
S. pneumoniae -9	*mefE* efflux	0.12	0.12	0.12	0.06	0.03	0.06	0.03
Streptococcus pyogenes Cook	susceptible	0.12	0.06	0.12	0.06	0.03	0.06	0.03
S. pyogenes -2	*ermAM* methylase(c)	16	32	16	16	4	32	16
S. pyogenes -3	*mefE* efflux	0.25	0.12	0.25	0.06	0.06	0.12	0.06
Haemophilus influenzae	susceptible	32	32	64	32	8	32	16
H. influenzae -2	susceptible	32	16	16	16	4	8	16
H. influenzae -3	susceptible	64	64	64	64	32	32	32
H. influenzae -4	⊿acr	2	1	1	0.25	0.25	0.5	0.5

Abbreviation: LCM, lincomycin.
[a] All strains except standard organisms were clinically isolated.
[b] (c): constitutive; (i): inducible.
Grey shading strains are target strains.

condition to investigate structure–activity relationship (SAR) of an allyl group. As a part of chemical modification of the benzothiazole group, **29** was also prepared by reduction of the nitro group of **17** using $SnCl_2{\cdot}H_2O$-$NaBH_4$. Next, **30** was synthesized by S_N2 reaction of CLDM with the corresponding thiol under the basic condition to confirm the effect on antibacterial activity by configuration at the C-7 position. On the other hand, the nitrophenyl derivatives (**18**–**20**), which were synthesized under the Mitsunobu condition, were reduced to give the corresponding aminophenyl derivatives (**31**–**33**). Because compound **33** was the most potent compared with **31** or **32**, **33** was converted to compound **34**. A Boc group and three trimethylsilyl (TMS) groups of **35** prepared by the Mitsunobu condition were simultaneously deprotected to give a desired compound **36**. TMS protection of **21** gave **37**, which was reacted with 2-methoxyacetyl chloride with triethylamine, and then deprotected to provide a methoxyacethyl derivative (**38**).

On the other hand, Mitsunobu conditions still had problems, and thus compounds **18**, **20** and **40** were synthesized in only low yields. So compounds **20**, **40** and **41** were synthesized by S_N2 reactions with the corresponding thiol in good yields under the basic conditions in application of a methanesulfonate **39** synthesized from **1**. SAR of novel LCM derivatives are shown in Tables 2–5.

SAR analysis of LCM derivatives possessing a heterocyclic ring at the C-7 position via sulfur atom

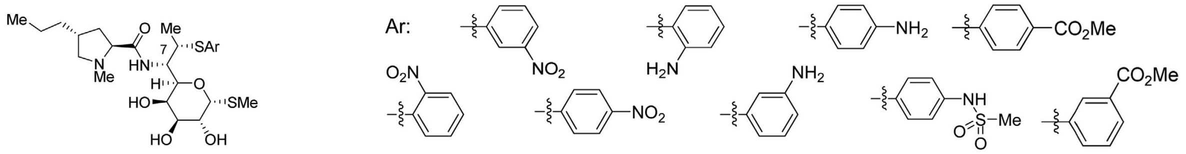
Antibacterial activity of LCM derivatives, which possessed a heterocyclic ring, the benzene ring or an allyl group at the C-7 position via sulfur atom, is shown in Table 2. Compound **2** was shown to be slightly more potent against *H. influenzae* than CLDM. Compound **3** had weak activity against *S. pyogenes* with *erm* gene, although CLDM did not have any activities against the pathogen. So we pursued further optimization at the 7-position. As a result, derivatives possessing a phenyl, thienyl or 1,3,4-thiadiazolyl group did not exhibit remarkable activity against *S. pyogenes* with *erm* gene.

Filling a space around the C-7 position might enhance antibacterial activities against resistant *S. pyogenes* with *erm* gene. Thus we selected **3** as a fundamental bicycle framework for further optimization. Additionally, **6** and **11** were selected as general examples of an isolated 6-membered ring and an isolated 5-membered ring, respectively. Next we tried to enhance antibacterial activities by introducing a substitute to the selected three frameworks.

SAR analysis of LCM derivatives possessing a benzothiazol-2-ylthio group at the 7-position

LCM derivatives having a benzothiazoyl or a thiazoropyridyl group at the 7-position were synthesized and their antibacterial activities are shown in Table 3. Notably, conversion of **3** to **12**, **15** or **16** at the 7-position improved antibacterial activity against *S. pneumoniae* with *erm* gene. Especially, antibacterial activity of **16** was significantly enhanced. An amino group might have a role to enhance antibacterial activity and may interact with a certain binding site on 23S rRNA. Compound **29** possessing an amino group at the 5-position in the benzothiazole ring generally exhibited improved antibacterial activity against *S. pneumoniae* with *erm* gene compared with **3**. On the other hand, we prepared **30** possessing the (*R*)-configuration at the

Table 4 Antibacterial activities (MIC, μg ml^{-1}) of LCM derivatives possessing a substituted phenylthio group at the 7-position



Test organism^a	*Characteristics*^{b}	***18***	***19***	***20***	***31***	***32***	***33***	***34***	***40***	***41***
Streptococcus pneumoniae DP1 TypeI	susceptible	1	0.25	0.25	0.5	0.25	0.12	0.03	0.25	0.12
S. pneumoniae -2	susceptible	1	0.25	0.25	1	0.25	0.25	0.03	0.25	0.25
S. pneumoniae -3	susceptible	0.5	0.25	0.12	0.5	0.25	0.12	0.03	0.06	0.06
S. pneumoniae -4	*ermAM* methylase(c)	>128	128	128	>128	>128	>128	64	32	128
S. pneumoniae -5	*ermAM* methylase(c)	>128	128	128	>128	>128	>128	128	64	128
S. pneumoniae -6	*ermAM* methylase(c) + mefE	128	128	>128	>128	>128	>128	128	128	128
S. pneumoniae -7	*ermAM* methylase(i)	128	128	128	>128	>128	128	16	32	128
S. pneumoniae -8	*ermAM* methylase(i)	128	128	128	>128	>128	128	16	32	128
S. pneumoniae -9	*mefE* efflux	0.5	0.25	0.12	0.25	0.25	0.06	0.03	0.06	0.06
Streptococcus pyogenes Cook	susceptible	0.5	0.12	0.12	0.12	0.25	0.06	0.03	0.25	0.06
S. pyogenes -2	*ermAM* methylase(c)	>128	128	128	>128	>128	>128	8	32	32
S. pyogenes -3	*mefE* efflux	1	0.25	0.25	0.25	0.25	0.12	0.03	0.25	0.25
Haemophilus influenzae	susceptible	>128	128	128	128	32	16	4	64	64
H. influenzae -2	susceptible	128	64	32	32	8	8	16	32	64
H. influenzae -3	susceptible	>128	128	>128	>128	32	32	32	128	128
H. influenzae -4	⊿acr	64	1	1	2	1	0.5	0.25	1	1

Abbreviation: LCM, lincomycin.
[a] All strains except standard organisms were clinically isolated.
[b] (c): constitutive; (i): inducible.
Grey shading strains are target strains.

7-position to confirm its potency. Based on comparison of antibacterial activities of compound **30** to those of compound **16**, we found that (*S*)-configuration at the 7-position was important for potent antibacterial activities.

SAR analysis of LCM derivatives possessing a phenylthio group at the 7-position

Next we consequently pursued modification of LCM derivatives possessing a substituted phenyl group at the C-7 position via sulfur atom and their antibacterial activities are shown in Table 4. The enhanced antibacterial activities by introducing an amino (**16**) or a nitro group (**15**) as shown in Table 3 encouraged us to further explore SAR through introducing an amino or a nitro group at the *o*-, *m*- and *p*-position on the phenyl ring. Unexpectedly, compounds **18–20** and **31–33** showed weaker antibacterial activities against resistant bacteria with *erm* gene than **15** or **16**. Among nitrophenyl and aminophenyl derivatives in Table 4, the *para*-amino derivative (**33**) exhibited relatively stronger activities against susceptible *S. pneumoniae and H. influenzae*. Conversion of the amino group to a methoxycarbonyl group (**33** to **40**) at the *p*-position on the phenyl ring improved antibacterial activities against bacteria with *erm* gene. Based on SAR analysis of compounds **18–20**, **31–33**, **40** and **41**, *para*-substituted analogs exhibited relatively stronger antibacterial activities against resistant bacteria than *o*-substituted or *m*-substituted analogs. Furthermore, **34** possessing a methanesulfonyl group at the amino group of **33** exhibited the most potent antibacterial activity in the phenylthio derivatives, except some strains belonging to *S. pneumoniae* with *erm* gene. These results suggest that (i) it is important for a substituent to keep a specific size, length and three-dimensional direction for appropriate binding to rRNA, and (ii) there are several important hydrogen bondings with some functional moieties, such as C = O, N = O, S = O or NH_2.

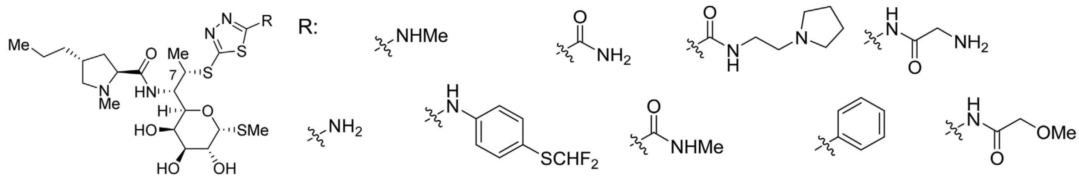
SAR analysis of LCM derivatives possessing a 1,3,4-thiadiazolylthio group at the 7-position

Next we pursued chemical modification of LCM derivatives possessing a substituted 1,3,4-thiadiazole at the C-7 position via sulfur atom and their antibacterial activities are shown in Table 5. We could find several important functional moieties for improvement of activity so far. Then we first introduced an amino group on the 1,3,4-thiadiazole ring. Compound **21** exhibited improved activities against both resistant bacteria with *erm* gene and *H. influenzae* compared with **11**. We synthesized several compounds **22**, **23**, **36** and **38**, which have an additional group introduced to the amino group of **21**. Compound **36** possessing a glycyl moiety as an aliphatic amine had weaker antibacterial activities than **21**. Conversion of the glycyl moiety to a methoxyacetyl moiety (**36** → **38**) improved antibacterial activities. Furthermore, derivatives **22** and **23** were synthesized and a difluoromethylthiophenyl analog (**23**) showed stronger activities against *S. pneumoniae* with *erm* gene than **21**. These results suggest that the phenyl moiety of **23** is an important group and that it enhances antibacterial activities against resistant bacteria with *erm* gene. We synthesized **27** in order to confirm this hypothesis. As expected, **27** showed relatively stronger antibacterial activities against bacteria with *erm* gene compared with **21**. Finally, we were interested in conversion of a NH-CO bonding to a CO-NH bonding (**36** and **38** → **24**–**26**). Compound **26** also exhibited effective antibacterial activities against bacteria with *erm* gene. These results suggest that filling a space around the 7-position of LCM has an important role to enhance antibacterial activities by hydrogen bonding, π-π stacking or CH–π interaction to undefined binding site on 23S rRNA.

CONCLUSION

With a purpose of generating new effective templates against bacteria, we first prepared the key intermediate **1**[41] derived from LCM with two

Table 5 Antibacterial activities (MIC, μg ml^{-1}) of LCM derivatives possessing a substituted 1, 3, 4-thiadiazolylthio group at the 7-position



Test organism[a]	*Characteristics*[b]	***21***	***22***	***23***	***24***	***25***	***26***	***27***	***36***	***38***
Streptococcus pneumoniae DP1 TypeI	susceptible	0.03	0.06	0.12	0.25	0.12	0.12	0.06	0.25	0.06
S. pneumoniae -2	susceptible	0.06	0.06	0.12	0.25	0.12	0.12	0.06	0.5	0.03
S. pneumoniae -3	susceptible	0.06	0.03	0.12	0.12	0.06	0.12	0.03	0.25	0.12
S. pneumoniae -4	*ermAM* methylase(c)	16	64	16	128	64	16	8	128	64
S. pneumoniae -5	*ermAM* methylase(c)	64	128	16	>128	64	16	8	>128	64
S. pneumoniae -6	*ermAM* methylase(c) + *mefE*	128	N.D.	32	>128	N.D.	128	64	>128	64
S. pneumoniae -7	*ermAM* methylase(i)	16	32	8	128	32	8	8	128	8
S. pneumoniae -8	*ermAM* methylase(i)	16	16	2	>128	32	16	8	128	8
S. pneumoniae -9	*mefE* efflux	0.03	0.03	0.12	0.25	0.12	0.12	0.06	0.25	0.06
Streptococcus pyogenes Cook	susceptible	0.03	0.06	0.12	0.12	0.12	0.12	0.06	0.25	0.06
S. pyogenes -2	*ermAM* methylase(c)	8	32	8	128	16	16	2	64	8
S. pyogenes -3	*mefE* efflux	0.06	0.06	0.12	0.25	0.12	0.25	0.12	1	0.06
Haemophilus influenzae	susceptible	8	8	16	64	8	32	16	64	32
H. influenzae -2	susceptible	4	8	8	64	8	64	8	64	16
H. influenzae -3	susceptible	8	16	32	64	32	128	32	128	32
H. influenzae -4	⊿acr	0.25	0.5	0.25	2	0.5	2	0.5	4	0.5

Abbreviations: LCM, lincomycin; ND, not detected.
[a] All strains except standard strains were clinically isolated.
[b] (c): constitutive; (i): inducible.
Grey shading strains are target strains.

steps to synthesize LCM analogs possessing the same configuration at the 7-position as CLDM in final target molecules. Our LCM derivatives were generally synthesized under Mitsunobu condition with the corresponding thiol from the key intermediate (**1**).

Compounds **16**, **21** and **27** exhibited antibacterial activities against respiratory infection-related Gram-positive bacteria with *erm* gene, although CLDM did not have any activities against those pathogens. Furthermore, we confirmed that 7(*S*)-configuration was necessary for enhancing antibacterial activities on the basis of comparison results of configurations of **16** and **30**. This work suggests that LCM derivatives may overcome resistant bacteria. SAR analysis, as indicated in this paper, would be useful for further medicinal chemistry in application of LCM derivatives. Our synthetic research in LCM derivatives is in progress.

EXPERIMENTAL PROCEDURE

General methods

^{1}H NMR spectra were measured with a BRUKER Ascend 400 NMR spectrometer (BRUKER corporation, Coventry, UK) for 400 MHz, JEOL JNM-GSX 400 NMR spectrometer (JEOL Ltd.,Tokyo, Japan) for 400 MHz or a Varian Gemini 300 NMR spectrometer (Varian Inc., Palo Alto, CA, USA) for 300 MHz in $CDCl_3$ or CD_3OD. TMS (0 p.p.m.) in $CDCl_3$ or CD_3OD was used as an internal reference standard. Mass spectra (MS) were obtained on a JEOL JMS-700 mass spectrometer (JEOL Ltd.) or Agilent Technologies 6530-Q-TOF LC/MS mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). The optical rotations were recorded with Jasco P-2300 digital polarimeter (Jasco corporation, Tokyo, Japan). Column chromatography was performed with silica gel (Wakogel C200, Wako Pure Chemical Industries Ltd., Osaka, Japan). Preparative thin layer chromatography was performed with silica gel (Merck, Darmstadt, Germany: TLC plates Silica gel 60 F254). All organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed with a rotary evaporator under reduced pressure.

*2,3,4-Tris-O-(trimethylsilyl)lincomycin (**1**).* To a solution of lincomycin (50 g, 123 mmol) in pyridine (200 ml) were added trimethylchlorosilane (90 ml, 704 mmol) and hexamethyldisilazane (65 ml, 310 mmol) and stirred at room temperature (RT) for 2 h, and then it was concentrated under reduced pressure. The residue was diluted with water, then extracted with hexane, washed with water and concentrated under reduced pressure. To a solution of the resulting residue in methanol (150 ml) was added 80% aqueous acetic acid (22.5 ml) stirred at RT for 16 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (30 ml) and concentrated under reduced pressure. The residue was diluted with water and hexane, then extracted with hexane, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The title compound was obtained as a colorless solid (69.5 g, 91%). ESI-MS (*m/z*) 623 $(M+H)^+$ as $C_{27}H_{58}N_2O_6SSi_3$; ^{1}H NMR (400 MHz, chloroform-*d*) δ 0.14 (s, 18 H), 0.18 (s, 9 H), 0.85–0.93 (m, 3 H), 1.14 (d, J=6.4 Hz, 3 H), 1.22–1.35 (m, 4 H), 1.79–1.90 (m, 1 H), 1.92–2.07 (m, 3 H), 2.09 (s, 3 H), 2.38 (s, 3 H), 3.00 (dd, J=10.9, 3.9 Hz, 1 H), 3.07 (br d, J=1.6 Hz, 1 H), 3.12–3.21 (m, 1 H), 3.59 (dd, J=9.5, 2.5 Hz, 1 H), 3.80 (br d, J=2.5 Hz, 1 H), 4.00 (d, J=9.5 Hz, 1 H), 4.04–4.13 (m, 1 H), 4.15 (dd, J=9.5, 5.6 Hz, 1 H), 4.27–4.33 (m, 1 H), 5.21 (d, J=5.6 Hz, 1 H), 7.42 (d, J=9.8 Hz, 1 H).

***7(S)**-7-(Benzo[d]oxazol-2-ylthio)-7-deoxylincomycin (**2**).* To a solution of compound **1** (240 mg, 0.39 mmol) in tetrahydrofuran (THF; 5 ml) at 0 °C were added triphenylphosphine (150 mg, 0.57 mmol), diethylazodicarboxylate (0.10 ml, 0.55 mmol) and benzo[d]oxazole-2-thiol (85 mg, 0.56 ml) and stirred at 0 °C for 1 h. The mixture was stirred at RT for 16 h. The mixture was diluted with 2 N HCl (1 ml)-MeOH (1 ml) and then stirred at RT for 30 min and concentrated under reduced pressure. The resulting residue was dissolved by water and washed with diethyl ether. The mixture was added to $NaHCO_3$ (150 mg), then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$/28% aq NH_4OH = 20/1/0.1) to obtain the title compound as a colorless solid (147.6 mg, 71%). $[\alpha]_D^{26}$ +77.6° (c 0.77, MeOH); ESI-MS (*m/z*) 540 $(M+H)^+$ as $C_{25}H_{37}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{37}N_3O_6S_2$: 540.2202, found: 540.2204; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.85–0.97 (m, 3 H), 1.26–1.40 (m, 4 H), 1.61

(d, $J=6.8$ Hz, 3 H), 1.77–1.85 (m, 1 H), 1.87 (s, 3 H), 1.97–2.09 (m, 2 H), 2.12–2.28 (m, 1 H), 2.35 (s, 3 H), 2.98 (dd, $J=10.5$, 5.2 Hz, 1 H), 3.21 (dd, $J=8.5$, 6.2 Hz, 1 H), 3.56 (dd, $J=10.2$, 3.2 Hz, 1 H), 3.83 (br d, $J=3.2$ Hz, 1 H), 4.10 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.43 (br d, $J=9.8$ Hz, 1 H), 4.45 (dq, $J=6.8$, 3.2 Hz, 1 H), 4.64 (dd, $J=9.8$, 3.2 Hz, 1 H), 5.24 (d, $J=5.6$ Hz, 1 H), 7.27–7.36 (m, 2 H), 7.49–7.60 (m, 2 H).

7(S)**-7-(Benzo[d]thiazol-2-ylthio)-7-deoxylincomycin* (3***). Compound **1** (320 mg, 0.51 mmol) and benzo[d]thiazole-2-thiol (250 mg, 1.49 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **3** (225.5 mg, 79%) as a colorless solid. $[\alpha]_D^{26}$ 74.1° (c 1.05, MeOH); ESI-MS (*m/z*) 556 $(M+H)^+$ as $C_{25}H_{37}N_3O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{37}N_3O_5S_3$: 556.1974, found: 556.1975; ^1H NMR (400 MHz, methanol-d_4) δ 0.85–0.98 (m, 3 H), 1.24–1.40 (m, 4 H), 1.59 (d, $J=6.8$ Hz, 3 H), 1.78–1.90 (m, 1 H), 1.83 (s, 3 H), 1.98–2.10 (m, 2 H), 2.12–2.27 (m, 1 H), 2.34 (s, 3 H), 3.01 (dd, $J=10.4$, 5.3 Hz, 1 H), 3.19 (dd, $J=8.6$, 6.1 Hz, 1 H), 3.58 (dd, $J=10.3$, 3.3 Hz, 1 H), 3.82 (br dd, $J=3.3$, 0.6 Hz, 1 H), 4.11 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.43 (br dd, $J=9.7$, 0.6 Hz, 1 H), 4.52 (dq, $J=6.8$, 3.1 Hz, 1 H), 4.62 (dd, $J=9.7$, 3.1 Hz, 1 H), 5.25 (d, $J=5.6$ Hz, 1 H), 7.35 (ddd, $J=8.1$, 7.2, 1.2 Hz, 1 H), 7.45 (ddd, $J=8.1$, 7.2, 1.2 Hz, 1 H), 7.81–7.89 (m, 2 H).

7(S)**-7-(**1H**-Benzo[d]imidazol-2-ylthio)-7-deoxylincomycin* (4***). Compound **1** (240 mg, 0.39 mmol) and 1*H*-benzo[d]imidazole-2-thiol (87.9 mg, 0.59 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **4** (157.7 mg, 76%) as a colorless solid. $[\alpha]_D^{27}$ +91.9° (c 1.06, MeOH); ESI-MS (*m/z*) 539 $(M+H)^+$ as $C_{25}H_{38}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{38}N_4O_5S_2$: 539.2362, found: 539.2361; ^1H NMR (400 MHz, methanol-d_4) δ 0.87–0.97 (m, 3 H), 1.25–1.38 (m, 4 H), 1.47 (d, $J=7.1$ Hz, 3 H), 1.72–1.83 (m, 1 H), 1.90–2.05 (m, 2 H), 1.93 (s, 3 H), 2.14–2.28 (m, 1 H), 2.24 (s, 3 H), 3.01 (dd, $J=10.3$, 5.4 Hz, 1 H), 3.13 (dd, $J=8.6$, 6.2 Hz, 1 H), 3.60 (dd, $J=10.3$, 3.4 Hz, 1 H), 3.84 (br d, $J=3.4$ Hz, 1 H), 4.12 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.16 (dq, $J=7.1$, 3.2 Hz, 1 H), 4.43–4.49 (m, 1 H), 4.51 (dd, $J=9.5$, 3.2 Hz, 1 H), 5.24 (d, $J=5.6$ Hz, 1 H), 7.19–7.26 (m, 2 H), 7.50 (br s, 2 H).

7(S)-S**-(7-Deoxylincomycin-7-yl)benzothioate* (5***). To a solution of compound **1** (500 mg, 0.8 mmol) in toluene (5 ml) at 0 °C were added triphenylphosphine (316 mg, 1.20 mmol), diethylazodicarboxylate (0.22 ml, 1.20 mmol) and benzothioic S-acid (172 mg, 1.24 mmol) and stirred at RT for 3 h. The mixture was diluted with 2 N HCl (2 ml) and concentrated under reduced pressure. The resulting residue was dissolved by water and washed with diethyl ether. The mixture was added $NaHCO_3$ (150 mg), then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$/28% aq $NH_4OH=9/1/0.1$) to obtain the title compound as a colorless solid (100 mg, 24%). ESI-MS (*m/z*) 527 $(M+H)^+$ as $C_{25}H_{38}N_2O_6S_2$; ^1H NMR (400 MHz, methanol-d_4) δ 0.85–0.98 (m, 3 H), 1.23–1.39 (m, 4 H), 1.44 (d, $J=6.8$ Hz, 3 H), 1.83–1.92 (m, 1 H), 1.88 (s, 3 H), 1.98–2.07 (m, 1 H), 2.07–2.15 (m,1 H), 2.15–2.28 (m, 1 H), 2.43 (s, 3 H), 3.07 (dd, $J=10.5$, 5.1 Hz, 1 H), 3.27 (dd, $J=8.3$, 5.8 Hz, 1 H), 3.55 (dd, $J=10.2$, 3.3 Hz, 1 H), 3.78–3.85 (m, 1 H), 4.11 (dd, $J=10.2$, 5.7 Hz, 1 H), 4.23–4.32 (m, 2 H), 4.58 (dd, $J=9.7$, 3.2 Hz, 1 H), 5.25 (d, $J=5.7$ Hz, 1 H), 7.42–7.55 (m, 2 H), 7.59–7.68 (m, 1 H), 7.91–8.00 (m, 2 H).

7(S)**-7-Deoxy-7-phenylthiolincomycin* (6***). To a solution of compound **1** (1.0 g, 1.6 mmol) in THF (15 ml) at 0 °C were added tributylphosphine (971 mg, 4.8 mmol), diethylazodicarboxylate (0.59 ml, 3.2 mmol) and 1,2-diphenyldisulfide (530 mg, 2.4 mmol) and stirred at RT for 24 h. The mixture was diluted with 2 N HCl (1 ml) and stirred at RT for 30 min and then concentrated under reduced pressure. The resulting residue was dissolved by water and washed with diethyl ether. The mixture was added to $NaHCO_3$ (150 mg), then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH$/28% aq $NH_4OH=20/1/0.1 \rightarrow 9/1/0.1$) to obtain the title compound as a colorless solid (724.0 mg, 91%). $[\alpha]_D^{26}$ +111.1° (*c* 0.63, MeOH); ESI-MS (*m/z*) 499 $(M+H)^+$ as $C_{24}H_{38}N_2O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{38}N_2O_5S_2$: 499.2300, found: 499.2304; ^1H NMR (400 MHz, methanol-d_4) δ 0.88–0.97 (m, 3 H), 1.29 (d, $J=6.9$ Hz, 3 H), 1.31–1.41 (m, 4 H), 1.80–1.90 (m, 1 H), 1.95–2.04 (m, 1 H), 2.00 (s, 3 H), 2.05–2.25 (m, 2 H), 2.39 (s, 3 H), 2.98 (dd, $J=10.7$, 4.6 Hz, 1 H), 3.24 (dd, $J=8.3$, 5.9 Hz, 1 H), 3.58 (dd, $J=10.2$, 3.3 Hz, 1 H), 3.74 (br d, $J=3.3$ Hz, 1 H), 3.86 (qd, $J=6.9$, 2.6 Hz, 1 H), 4.10 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.35 (dd, $J=9.7$, 0.6 Hz, 1 H), 4.41 (dd, $J=9.7$, 2.6 Hz, 1 H), 5.26 (d, $J=5.6$ Hz, 1 H), 7.22–7.28 (m, 1 H), 7.29–7.36 (m, 2 H), 7.40–7.46 (m, 2 H).

7(S)**-7-Deoxy-7-(pyridin-4-ylthio)lincomycin* (7***). Compound **1** (100 mg, 0.16 mmol) and pyridine-4-thiol (27.6 mg, 0.25 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **7** (99.8 mg, 40%) as a colorless solid. $[\alpha]_D^{26}$ +88.3° (*c* 0.94, MeOH); ESI-MS (*m/z*) 500 $(M+H)^+$ as $C_{23}H_{37}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{23}H_{37}N_3O_5S_2$: 500.2253, found: 500.2259; ^1H NMR (400 MHz, methanol-d_4) δ 0.87–0.98 (m, 3 H), 1.28–1.40 (m, 4 H), 1.46 (d, $J=7.0$ Hz, 3 H), 1.78 (s, 3 H), 1.79–1.89 (m, 1 H), 1.96–2.11 (m, 2 H), 2.13–2.25 (m, 1 H), 2.39 (s, 3 H), 2.98 (dd, $J=10.5$, 4.9 Hz, 1 H), 3.24 (dd, $J=8.4$, 5.9 Hz, 1 H), 3.57 (dd, $J=10.2$, 3.2 Hz, 1 H), 3.80 (br dd, $J=3.2$, 0.8 Hz, 1 H), 4.09 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.11 (dq, $J=7.0$, 2.9 Hz, 1 H), 4.37 (br dd, $J=9.6$, 0.8 Hz, 1 H), 4.59 (dd, $J=9.6$, 2.9 Hz, 1 H), 5.23 (d, $J=5.6$ Hz, 1 H), 7.33–7.39 (m, 2 H), 8.29–8.35 (m, 2 H).

7(S)**-7-Deoxy-7-(pyrimidin-4-ylthio)lincomycin* (8***). Compound **1** (100 mg, 0.16 mmol) and pyrimidine-4-thiol (27.9 mg, 0.25 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **8** (124 mg, 50%) as a colorless solid. $[\alpha]_D^{27}$ +85.0° (*c* 1.53, MeOH); ESI-MS (*m/z*) 501 $(M+H)^+$ as $C_{22}H_{36}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{22}H_{36}N_4O_5S_2$: 501.2205, found: 501.2208; ^1H NMR (400 MHz, methanol-d_4) δ 0.87–0.98 (m, 3 H), 1.26–1.41 (m, 4 H), 1.48 (d, $J=6.7$ Hz, 3 H), 1.79 (s, 3 H), 1.79–1.90 (m, 1 H), 1.97–2.12 (m, 2 H), 2.13–2.26 (m, 1 H), 2.37 (s, 3 H), 3.01 (dd, $J=10.5$, 5.1 Hz, 1 H), 3.24 (dd, $J=8.4$, 6.0 Hz, 1 H), 3.55 (dd, $J=10.2$, 3.2 Hz, 1 H), 3.80 (br dd, $J=3.2$, 0.7 Hz, 1 H), 4.10 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.34 (br dd, $J=9.5$ Hz, 0.7, 1 H), 4.49–4.60(m, 2 H), 5.23 (d, $J=5.6$ Hz, 1 H), 7.40 (dd, $J=5.6$, 1.5 Hz, 1 H), 8.36 (br dd, $J=5.6$, 0.4 Hz, 1 H), 8.87 (br dd, $J=1.5$, 0.4 Hz, 1 H).

7(S)**-7-Deoxyl-7-(thiophen-2-ylthio)lincomycin* (9***). Compound **1** (240 mg, 0.39 mmol) and thiophene-2-thiol (100 mg, 0.86 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **9** (19.4 mg, 10%) as a colorless solid. $[\alpha]_D^{26}$ +140.7° (*c* 0.47, MeOH); ESI-MS (*m/z*) 505 $(M+H)^+$ as $C_{22}H_{36}N_2O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{22}H_{36}N_2O_5S_3$: 505.1865, found: 505.1863; ^1H NMR (400 MHz, methanol-d_4) δ 0.89–0.98 (m, 3 H), 1.27 (d, $J=7.1$ Hz, 3H), 1.30–1.41 (m, 4 H), 1.78–1.89 (m, 1 H), 1.92–2.00 (m, 1 H), 2.01–2.08 (m, 1 H), 2.08–2.19 (m, 1 H), 2.21 (s, 3 H), 2.33 (s, 3 H), 2.96 (dd, $J=10.7$, 4.6 Hz, 1 H), 3.20 (dd, $J=8.1$, 5.6 Hz, 1 H), 3.54–3.65 (m, 2 H), 3.73 (br d, $J=2.8$ Hz, 1 H), 4.11 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.34 (dd, $J=9.8$, 2.9 Hz, 1 H), 4.37–4.43 (m, 1 H), 5.29 (d, $J=5.6$ Hz, 1 H), 7.06 (dd, $J=5.4$, 3.5 Hz, 1H), 7.22 (dd, $J=3.5$, 1.2 Hz, 1 H), 7.55 (dd, $J=5.4$, 1.2 Hz, 1 H).

7(S)**-7-Deoxy-7-(thiazol-2-ylthio)lincomycin* (10***). Compound **1** (240 mg, 0.39 mmol) and thiazole-2-thiol (43.0 mg, 0.37 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **10** (13.6 mg, 7%) as a colorless solid. $[\alpha]_D^{26}$ +109.5° (*c* 0.67, MeOH); ESI-MS (*m/z*) 506 $(M+H)^+$ as $C_{21}H_{35}N_3O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{21}H_{35}N_3O_5S_3$: 506.1817, found: 506.1802; ^1H NMR (400 MHz, methanol-d_4) δ 0.88–0.97 (m, 3 H), 1.27–1.40 (m, 4 H), 1.61 (d, $J=7.0$ Hz, 3 H), 1.79–1.92 (m, 1H), 1.95–2.14 (m, 2H), 2.01 (s, 3H), 2.15–2.29 (m, 1 H), 2.35 (s, 3 H), 3.01 (dd, $J=10.4$, 5.3 Hz, 1 H), 3.26 (dd, $J=8.6$, 6.1 Hz, 1 H), 3.57 (dd, $J=10.3$, 3.3 Hz, 1 H), 3.78 (br d, $J=3.3$ Hz, 1 H), 4.10 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.13 (dq, $J=7.0$, 3.1 Hz, 1 H), 4.39 (br d, $J=9.8$ Hz, 1 H), 4.51 (dd, $J=9.8$, 3.1 Hz, 1 H), 5.25 (d, $J=5.6$ Hz, 1 H), 7.54 (d, $J=3.5$ Hz, 1 H), 7.73 (d, $J=3.5$ Hz, 1 H).

7(S)**-7-Deoxy-7-(1,3,4-thiadiazol-2-ylthio)lincomycin* (11***). Compound **1** (240 mg, 0.39 mmol) and 1,3,4-thiadiazole-2-thiol (80.0 mg, 0.68 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **11** (121.0 mg, 62%) as a colorless solid. $[\alpha]_D^{27}$ +100.2° (*c* 2.03, MeOH); ESI-MS (*m/z*) 507 $(M+H)^+$ as $C_{20}H_{34}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{20}H_{34}N_4O_5S_3$: 507.1770, found: 507.1773; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.87–0.98 (m, 3 H), 1.26–1.42 (m, 4 H), 1.53 (d, *J* = 6.8 Hz, 3 H), 1.80–1.90 (m, 1 H), 1.93 (s, 3 H), 1.97–2.12 (m, 2 H), 2.15–2.28 (m, 1 H), 2.38 (s, 3 H), 3.03 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.27 (dd, *J* = 8.4, 6.1 Hz, 1 H), 3.57 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.81 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.37–4.46 (m, 2 H), 4.60 (dd, *J* = 9.8, 3.2 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 9.37 (s, 1H).

*7(S)-7-(5-Chlorobenzo[d]thiazol-2-ylthio)-7-deoxylincomycin (**12**).* Compound **1** (160 mg, 0.26 mmol) and 5-chlorobenzo[d]thiazole-2-thiol (160 mg, 0.79 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **12** (110.6 mg, 73%) as a colorless solid. $[\alpha]_D^{26}$ +52.8° (*c* 0.25, MeOH); ESI-MS (*m/z*) 590 $(M+H)^+$ as $C_{25}H_{36}ClN_3O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{36}ClN_3O_5S_3$: 590.1584, found: 590.1581; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.87–0.96 (m, 3 H), 1.27–1.39 (m, 4 H), 1.59 (d, *J* = 7.0 Hz, 3 H), 1.78–1.88 (m, 1 H), 1.86 (s, 3 H), 1.97–2.08 (m, 2 H), 2.13–2.27 (m, 1 H), 2.32 (s, 3 H), 2.98 (dd, *J* = 10.5, 5.2 Hz, 1 H), 3.20 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.82 (br dd, *J* = 3.2, 0.9 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.41 (br dd, *J* = 9.7, 0.9 Hz, 1 H), 4.53 (dq, *J* = 7.0, 3.3 Hz, 1 H), 4.61 (dd, *J* = 9.7, 3.3 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.35 (dd, *J* = 8.6, 2.1 Hz, 1 H), 7.81–7.87 (m, 2 H).

*7(S)-7-Deoxyl-7-(thiazolo[5,4-c]pyridin-2-ylthio)lincomycin (**13**).* Compound **1** (320 mg, 0.51 mmol) and thiazolo[5,4-*c*]pyridine-2-thiol (250 mg, 1.49 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **13** (205.9 mg, 72%) as a colorless solid. $[\alpha]_D^{26}$ +67.1° (*c* 0.50, MeOH); ESI-MS (*m/z*) 505 $(M+H)^+$ as $C_{24}H_{36}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{36}N_4O_5S_3$: 557.1926, found: 557.1924; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.87–0.98 (m, 3 H), 1.27–1.41 (m, 4 H), 1.62 (d, *J* = 6.7 Hz, 3 H), 1.82 (s, 3 H), 1.80–1.91 (m, 1 H), 1.98–2.13 (m, 2 H), 2.15–2.28 (m, 1 H), 2.38 (s, 3 H), 3.03 (dd, *J* = 10.4, 5.3 Hz, 1 H), 3.24 (dd, *J* = 8.6, 6.2 Hz, 1 H), 3.56 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.83 (br dd, *J* = 3.2, 0.73 Hz, 1 H), 4.11 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.43 (br dd, *J* = 9.5, 0.73 Hz, 1 H), 4.63–4.72 (m, 2 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.82 (dd, *J* = 5.6, 0.9 Hz, 1 H), 8.51 (d, *J* = 5.6 Hz, 1 H), 9.06 (d, *J* = 0.9 Hz, 1 H).

*7(**S**)-7-(6-Cyanobenzo[d]thiazol-2-ylthio)-7-deoxylincomycin (**14**).* Compound **1** (160 mg, 0.26 mmol) and 6-cyanobenzo[d]thiazole-2-thiol (55 mg, 0.29 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **14** (98.4 mg, 66%) as a colorless solid. $[\alpha]_D^{26}$ +73.0° (*c* 1.10, MeOH); ESI-MS (*m/z*) 581 $(M+H)^+$ as $C_{26}H_{36}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{36}N_4O_5S_3$: 581.1926, found: 581.1926; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.87–0.97 (m, 3 H), 1.25–1.41 (m, 4 H), 1.61 (d, *J* = 6.6 Hz, 3 H), 1.78–1.89 (m, 1 H), 1.82 (s, 3 H), 1.98–2.09 (m, 2 H), 2.14–2.26 (m, 1 H), 2.35 (s, 3 H), 2.98 (dd, *J* = 10.4, 5.1 Hz, 1 H), 3.21 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.82 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.7 Hz, 1 H), 4.42 (br dd, *J* = 9.5, 0.8 Hz, 1 H), 4.60–4.70 (m, 2 H), 5.24 (d, *J* = 5.7 Hz, 1 H), 7.76 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.94 (br dd, *J* = 8.5, 0.6 Hz, 1 H), 8.32 (br dd, *J* = 1.7, 0.6 Hz, 1 H).

*7(**S**)-7-Deoxy-7-(6-nitrobenzo[d]thiazol-2-ylthio)lincomycin (**15**).* Compound **1** (240 mg, 0.39 mmol) and 6-nitrobenzo[d]thiazole-2-thiol (180 mg, 0.85 mmol) were treated in toluene (5 ml) according to the similar procedure as described for the preparation of **2** to afford **15** (152.7 mg, 66%) as a colorless solid. $[\alpha]_D^{29}$ +67.6° (*c* 0.60, MeOH); ESI-MS (*m/z*) 601 $(M+H)^+$ as $C_{25}H_{36}N_4O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{36}N_4O_7S_3$: 601.1824, found: 601.1827; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.87–0.98 (m, 3 H), 1.28–1.40 (m, 4 H), 1.62 (d, *J* = 6.7 Hz, 3 H), 1.77–1.89 (m, 1 H), 1.83 (s, 3 H), 1.98–2.09 (m, 2 H), 2.14–2.27 (m, 1 H), 2.36 (s, 3 H), 2.99 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.22 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.56 (dd, *J* = 10.1, 3.2 Hz, 1 H), 3.83 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.10 (dd, *J* = 10.1, 5.6 Hz, 1 H), 4.43 (br dd, *J* = 9.5, 0.8 Hz, 1 H), 4.62–4.71 (m, 2 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.95 (d, *J* = 9.0, 1 H), 8.32 (dd, *J* = 9.0, 2.3, Hz, 1 H), 8.85 (d, *J* = 2.3 Hz, 1 H).

*7(**S**)-7-(6-Aminobenzo[d]thiazol-2-ylthio)-7-deoxylincomycin (**16**).* Compound **1** (630 mg, 1.01 mmol) and 6-aminobenzo[d]thiazole-2-thiol (300 mg, 1.65 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **16** (386.7 mg, 67%) as a colorless solid. $[\alpha]_D^{26}$ +89.0° (*c* 1.11, MeOH); ESI-MS (*m/z*) 571 $(M+H)^+$ as $C_{25}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{38}N_4O_5S_3$: 571.2083, found: 571.2075; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.86–0.97 (m, 3 H), 1.26–1.38 (m, 4 H), 1.52 (d, *J* = 7.0 Hz, 3 H), 1.75–1.89 (m, 1 H), 1.94 (s, 3 H), 1.95–2.11 (m, 2 H), 2.12–2.25 (m, 1 H), 2.32 (s, 3 H), 3.03 (dd, *J* = 10.4, 5.3 Hz, 1 H), 3.17 (dd, *J* = 8.6, 6.2 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.81 (br dd, *J* = 3.2, 0.7 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.27 (dq, *J* = 7.0, 3.1 Hz, 1 H), 4.43 (br dd, *J* = 9.8, 0.7 Hz, 1 H), 4.55 (dd, *J* = 9.8, 3.1 Hz, 1 H), 5.25 (d, *J* = 5.5 Hz, 1 H), 6.85 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.08 (dd, *J* = 2.3, 0.25 Hz, 1 H), 7.59 (dd, *J* = 8.7, 0.25 Hz, 1 H).

*7(**S**)-7-Deoxy-7-(5-nitrobenzo[d]thiazol-2-ylthio)lincomycin (**17**).* Compound **1** (320 mg, 0.51 mmol) and 5-nitrobenzo[d]thiazole-2-thiol (120 mg, 0.57 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **17** (138.8 mg, 45%) as a colorless solid. $[\alpha]_D^{26}$ +58.2° (*c* 0.81, MeOH); ESI-MS (*m/z*) 601 $(M+H)^+$ as $C_{25}H_{36}N_4O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{36}N_4O_7S_3$: 601.1824, found: 601.1826; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.88–0.97 (m, 3 H), 1.30–1.40 (m, 4 H), 1.62 (d, *J* = 6.8 Hz, 3 H), 1.80–1.90 (m, 1 H), 1.85 (s, 3 H), 1.99–2.10 (m, 2 H), 2.16–2.30 (m, 1 H), 2.36 (s, 3 H), 3.01 (dd, *J* = 10.3, 5.3 Hz, 1 H), 3.25 (dd, *J* = 8.7, 6.2 Hz, 1 H), 3.57 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.84 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.11 (dd, *J* = 10.3, 5.7 Hz, 1 H), 4.42 (br dd, *J* = 9.6, 0.8 Hz, 1 H), 4.61 (dd, *J* = 6.8, 3.3 Hz, 1 H), 4.65 (dd, *J* = 9.6, 3.3 Hz, 1 H), 5.25 (d, *J* = 5.7 Hz, 1 H), 8.08 (d, *J* = 8.8, 1 H), 8.21 (dd, *J* = 8.8, 2.2, Hz, 1 H), 8.64 (br dd, *J* = 2.2, 0.24 Hz, 1 H).

*7(**S**)-7-Deoxy-7-(2-nitrophenylthio)lincomycin (**18**).* Compound **1** (200 mg, 0.32 mmol) and 1,2-bis(2-nitrophenyl)disulfide (148.5 mg, 0.48 mmol) were treated according to the similar procedure as described for the preparation of **6** to afford **18** (40.1 mg, 23%) as a colorless solid. $[\alpha]_D^{27}$ +69.9° (*c* 0.91, MeOH); ESI-MS (*m/z*) 544 $(M+H)^+$ as $C_{24}H_{37}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{37}N_3O_7S_2$: 544.2151, found: 544.2157; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.86–0.99 (m, 3 H), 1.29–1.38 (m, 4 H), 1.38 (d, *J* = 6.8 Hz, 3 H), 1.79 (s, 3 H), 1.81–1.92 (m, 1 H), 1.98–2.14 (m, 2 H), 2.14–2.26 (m, 1 H), 2.42 (s, 3 H), 3.01 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.28 (dd, *J* = 8.7, 6.1 Hz, 1 H), 3.57 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.79 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.06 (dq, *J* = 6.8, 2.7 Hz, 1 H), 4.08 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.37 (br dd, *J* = 9.8, 0.8 Hz, 1 H), 4.57 (dd, *J* = 9.8, 2.7 Hz, 1 H), 5.21 (d, *J* = 5.6 Hz, 1 H), 7.38 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1 H), 7.64 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 1 H), 7.70 (br dd, *J* = 8.2, 1.2 Hz, 1 H), 8.05 (dd, *J* = 8.3, 1.4 Hz, 1 H).

*7(**S**)-7-Deoxy-7-(3-nitrophenylthio)lincomycin (**19**).* Compound **1** (1.0 g, 1.6 mmol) and 1,2-bis(3-nitrophenyl)disulfide (742 mg, 2.4 mmol) were treated according to the similar procedure as described for the preparation of **6** to afford **19** (366.5 mg, 42%) as a colorless solid. $[\alpha]_D^{29}$ +75.2° (*c* 0.48, MeOH); ESI-MS (*m/z*) 544 $(M+H)^+$ as $C_{24}H_{37}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{37}N_3O_7S_2$: 544.2151, found: 544.2148; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.89–0.97 (m, 3 H), 1.30–1.37 (m, 4 H), 1.38 (d, *J* = 6.8 Hz, 3 H), 1.80–1.91 (m, 1 H), 1.93 (s, 3 H), 1.97–2.12 (m, 2 H), 2.13–2.24 (m, 1 H), 2.40 (s, 3 H), 2.99 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.24 (dd, *J* = 8.3, 5.9 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.79 (br dd, *J* = 3.3, 0.8 Hz, 1 H), 3.99 (dq, *J* = 6.8, 2.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.36 (br dd, *J* = 9.5, 0.8 Hz, 1 H), 4.52 (dd, *J* = 9.5, 2.8 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.55–7.61 (m, 1 H), 7.81 (ddd, *J* = 7.9, 1.8, 0.9 Hz, 1 H), 8.09 (br ddd, *J* = 8.2, 2.2, 0.9 Hz, 1 H), 8.21–8.23 (m, 1 H).

*7(**S**)-7-Deoxy-7-(4-nitrophenylthio)lincomycin (**20**).* Compound **1** (200 mg, 0.32 mmol) and 1,2-bis(4-nitrophenyl)disulfide (148.5 mg, 0.48 mmol) were treated according to the similar procedure as described for the preparation of **6** to afford **20** (29.7 mg, 17%) as a colorless solid. $[\alpha]_D^{26}$ +67.1° (*c* 0.29, MeOH); ESI-MS (*m/z*) 544 $(M+H)^+$ as $C_{24}H_{37}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{37}N_3O_7S_2$: 544.2151, found: 544.2151; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.87–0.98 (m, 3 H), 1.30–1.39 (m, 4 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 1.79–1.90 (m, 1 H), 1.81 (s, 3 H), 1.97–2.12 (m, 2 H), 2.13–2.26 (m, 1 H), 2.40 (s, 3 H), 3.00 (dd, *J* = 10.6, 5.0 Hz, 1 H), 3.25 (dd, *J* = 8.4, 6.1 Hz, 1 H), 3.57 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.80 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.09 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.03–4.16 (m, 1 H), 4.37 (br dd, $J=9.7$, 0.8 Hz, 1 H), 4.58 (dd, $J=9.7$, 2.9 Hz, 1 H), 5.24 (d, $J=5.6$ Hz, 1 H), 7.51–7.57 (m, 2 H), 8.13–8.19 (m, 2 H).

7(S)-7-(5-Amino-1,3,4-thiadiazol-2-ylthio)-7-deoxylincomycin (21). To a solution of compound **1** (240 mg, 0.39 mmol) in THF (5 ml) at 0 °C were added triphenylphosphine (150 mg, 0.57 mmol), diethylazodicarboxylate (0.1 ml, 0.55 mmol) and *t*-butyl (5-mercapto-1,3,4-thiadiazol-2-yl)carbamate (130 mg, 0.56 mmol) and stirred at RT for 17 h. The mixture was concentrated under reduced pressure and diluted with saturated aqueous $NaHCO_3$ (10 ml), extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to obtain 7(*S*)-7-(5-amino-1,3,4-thiadiazol-2-ylthio)-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin as a colorless solid (271.3 mg, 84%). 7(*S*)-7-(5-Amino-1,3,4-thiadiazol-2-ylthio)-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (271.3 mg, 0.32 mmol) in 90% aqueous trifluoroacetic acid (5 ml) was kept at RT for 1 h. The mixture was concentrated under reduced pressure and diluted with saturated aqueous $NaHCO_3$ (10 ml) and then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$/28% aq NH_4OH = 5/1/0.1) to obtain the title compound as a colorless solid (111.4 mg, 66%). $[\alpha]_D^{26}$ +139.8° (*c* 0.28, MeOH); ESI-MS (*m/z*) 520 $(M+H)^+$ as $C_{20}H_{35}N_5O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{20}H_{35}N_5O_5S_3$: 522.1879, found: 522.1877; ^1H NMR (400 MHz, methanol-d_4) δ 0.87–0.97 (m, 3 H), 1.27–1.38 (m, 4 H), 1.41 (d, $J=7.0$ Hz, 3 H), 1.76–1.90 (m, 1 H), 1.92–2.07 (m, 2 H), 2.11 (s, 3 H), 2.14–2.26 (m, 1 H), 2.33 (s, 3 H), 2.97 (dd, $J=10.5$, 4.9 Hz, 1 H), 3.26 (dd, $J=8.6$, 6.2 Hz, 1 H), 3.57 (dd, $J=10.3$, 3.2 Hz, 1 H), 3.74–3.78 (m, 1 H), 3.94 (dq, $J=7.0$, 2.9 Hz, 1 H), 4.10 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.39 (br dd, $J=9.8$, 0.5 Hz, 1 H), 4.45 (dd, $J=9.8$, 2.9 Hz, 1 H), 5.26 (d, $J=5.6$ Hz, 1 H). For the qualified analytical purpose, the above colorless solid was further purified by reverse-phase column chromatography (YMC triart C18, 20 × 250 mm, RT, 18.9 ml min^{-1}, 50 mM $AcONH_4/CH_3CN=70/30$) and precipitated (MeOH/ethyl acetate) to obtain the highly purified title compound as a colorless solid.

7(S)-7-Deoxy-7-(5-methylamino-1,3,4-thiadiazol-2-ylthio)lincomycin (22). Compound **1** (240 mg, 0.39 mmol) and *t*-butyl (5-mercapto-1,3,4-thiadiazol-2-yl)(methyl)carbamate (100 mg, 0.40 mmol) were treated according to the similar procedure as described for the preparation of **21** to afford **22** (147.1 mg, 71% (two steps)) as a colorless solid. $[\alpha]_D^{26}$ +118.4° (*c* 0.27, MeOH); ESI-MS (*m/z*) 534 $(M+H)^+$ as $C_{21}H_{37}N_5O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{21}H_{37}N_5O_5S_3$: 536.2035, found: 536.2039; ^1H NMR (400 MHz, methanol-d_4) δ 0.87–0.98 (m, 3 H), 1.27–1.38 (m, 4 H), 1.41 (d, $J=7.0$ Hz, 3 H), 1.77–1.88 (m, 1 H), 1.93–2.01 (m, 1 H), 2.04 (dd, $J=10.1$, 8.7 Hz, 1 H), 2.12 (s, 3 H), 2.14–2.26 (m, 1 H), 2.33 (s, 3H), 2.93–3.01 (m, 1 H), 2.97 (s, 3 H), 3.25 (dd, $J=8.4$, 6.2 Hz, 1 H), 3.57 (dd, $J=10.3$, 3.2 Hz, 1 H), 3.78 (br dd, $J=3.2$, 0.7 Hz, 1 H), 3.94 (dq, $J=7.0$, 2.9 Hz, 1 H), 4.10 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.38 (br dd, $J=9.8$, 0.7 Hz, 1 H), 4.46 (dd, $J=9.8$, 2.9 Hz, 1 H), 5.26 (d, $J=5.6$ Hz, 1 H).

7(S)-7-Deoxy-7-(5-(4-(difluoromethylthio)phenylamino)-1,3,4-thiadiazol-2-ylthio)lincomycin (23). Compound **1** (240 mg, 0.39 mmol) and 5-(4-(difluoromethylthio)phenylamino)-1,3,4-thiadiazole-2-thiol (120 mg, 0.41 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **23** (99.5 mg, 38%) as a colorless solid. $[\alpha]_D^{24}$ +96.7° (*c* 0.78, MeOH); ESI-MS (*m/z*) 680 $(M+H)^+$ as $C_{27}H_{39}F_2N_5O_5S_4$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{39}F_2N_5O_5S_4$: 680.1880, found: 680.1876; ^1H NMR (400 MHz, methanol-d_4) δ 0.85–0.95 (m, 3 H), 1.26–1.39 (m, 4 H), 1.46 (d, $J=7.0$ Hz, 3 H), 1.78–1.88 (m, 1 H), 1.93–2.06 (m, 2 H), 2.12 (s, 3 H), 2.14–2.28 (m, 1 H), 2.33 (s, 3 H), 2.95–3.02 (m, 1 H), 3.26 (dd, $J=8.4$, 6.2 Hz, 1 H), 3.59 (dd, $J=10.3$, 3.3 Hz, 1 H), 3.79 (br d, $J=3.3$ Hz, 1 H), 4.02–4.10 (m, 1 H), 4.12 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.41 (br d, $J=9.8$ Hz, 1 H), 4.49 (dd, $J=9.8$, 3.6 Hz, 1 H), 5.28 (d, $J=5.6$ Hz, 1 H), 7.00 (t, $J=56.8$ Hz, 1 H), 7.52–7.58 (m, 2 H), 7.64–7.70 (m, 2 H).

7(S)-7-(5-Carbamoyl-1,3,4-thiadiazol-2-ylthio)-7-deoxylincomycin (24). Compound **1** (240 mg, 0.39 mmol), and 5-mercapto-1,3,4-thiadiazole-2-carboxamide (95 mg, 0.59 mmol) were treated at 50 °C according to the similar procedure as described for the preparation of **2** to afford **24** (67.8 mg, 32%) as a colorless solid. $[\alpha]_D^{26}$ +83.6° (*c* 0.69, MeOH); ESI-MS (*m/z*) 550 $(M+H)^+$ as $C_{21}H_{35}N_5O_6S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{21}H_{35}N_5O_6S_3$: 550.1828, found: 550.1829; ^1H NMR (400 MHz, methanol-d_4) δ 0.86–0.97 (m, 3 H), 1.30–1.41 (m, 4 H), 1.57 (d, $J=7.0$ Hz, 3 H), 1.78–1.89 (m, 1 H), 1.94 (s, 3 H), 1.97–2.09 (m, 2 H), 2.13–2.26 (m, 1 H), 2.37 (s, 3 H), 2.99 (dd, $J=10.5$, 5.1 Hz, 1 H), 3.24 (dd, $J=8.5$, 6.2 Hz, 1 H), 3.56 (dd, $J=10.3$, 3.2 Hz, 1 H), 3.81 (br dd, $J=3.2$, 0.8 Hz, 1 H), 4.10 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.40 (br dd, $J=9.7$, 0.8 Hz, 1 H), 4.49 (dq, $J=7.0$, 3.1 Hz, 1 H), 4.61 (dd, $J=9.7$, 3.1 Hz, 1 H), 5.25 (d, $J=5.6$ Hz, 1 H). For the qualified analytical purpose, the above colorless solid was further purified by reverse-phase column chromatography (YMC triart C18, 20 × 250 mm, RT, 18.9 ml min^{-1}, 50 mM $AcONH_4/CH_3CN=50/50$) to obtain the highly purified title compound as a colorless solid.

7(S)-7-Deoxy-7-(5-methylcarbamoyl-1,3,4-thiadiazol-2-ylthio)lincomycin (25). Compound **1** (240 mg, 0.39 mmol) and 5-mercapto-*N*-methyl-1,3,4-thiadiazole-2-carboxamide (100 mg, 0.57 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **25** (26.1 mg, 12%) as a colorless solid. $[\alpha]_D^{26}$ +81.8° (*c* 1.29, MeOH); ESI-MS (*m/z*) 564 $(M+H)^+$ as $C_{22}H_{37}N_5O_6S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{22}H_{37}N_5O_6S_3$: 564.1984, found: 564.1977; ^1H NMR (400 MHz, methanol-d_4) δ 0.85–0.98 (m, 3 H), 1.26–1.42 (m, 4 H), 1.56 (d, $J=6.8$ Hz, 3 H), 1.78–1.89 (m, 1 H), 1.94 (s, 3 H), 1.97–2.12 (m, 2 H), 2.13–2.27 (m, 1 H), 2.38 (s, 3 H), 2.94 (s, 3 H), 3.00 (dd, $J=10.5$, 5.1 Hz, 1 H), 3.25 (dd, $J=8.6$, 6.1 Hz, 1 H), 3.56 (dd, $J=10.2$, 3.2 Hz, 1 H), 3.79–3.84 (m, 1 H), 4.10 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.40 (br d, $J=9.8$ Hz, 1 H), 4.48 (dq, $J=6.8$, 3.1 Hz, 1 H), 4.62 (dd, $J=9.8$, 3.1 Hz, 1 H), 5.25 (d, $J=5.6$ Hz, 1 H). For the qualified analytical purpose, the above colorless solid was further purified by reverse-phase column chromatography (YMC triart C18, 20 × 250 mm, RT, 11.3 ml min^{-1}, 0.1% aq. $TFA/CH_3CN=60/40$) to obtain the highly purified title compound as a colorless solid.

7(S)-7-Deoxy-7-(5-(2-(pyrrolidin-1-yl)ethylcarbamoyl)-1,3,4-thiadiazol-2-ylthio) lincomycin (26). Compound **1** (240 mg, 0.39 mmol) and 5-(2-(pyrrolidin-1-yl)ethylcarbamoyl)-1,3,4-thiadiazole-2-thiol (130 mg, 0.50 mmol) were treated according to the similar procedure as described for the preparation of **2** to afford **26** (69.8 mg, 28%) as a colorless solid. $[\alpha]_D^{27}$ +78.0° (*c* 0.54, MeOH); ESI-MS (*m/z*) 647 $(M+H)^+$ as $C_{27}H_{46}N_6O_6S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{46}N_6O_6S_3$: 647.2719, found: 647.2716; ^1H NMR (400 MHz, methanol-d_4) δ 0.87–0.97 (m, 3 H), 1.28–1.39 (m, 4 H), 1.56 (d, $J=7.0$ Hz, 3 H), 1.77–1.90 (m, 5 H), 1.94 (s, 3 H), 1.97–2.12 (m, 2 H), 2.13–2.26 (m, 1 H), 2.37 (s, 3 H), 2.57–2.67 (m, 4 H), 2.73 (t, $J=6.7$ Hz, 2 H), 2.98 (dd, $J=10.5$, 5.1 Hz, 1 H), 3.24 (dd, $J=8.5$, 6.2 Hz, 1 H), 3.51–3.60 (m, 3 H), 3.81 (br dd, $J=3.2$, 0.8 Hz, 1 H), 4.10 (dd, $J=10.2$, 5.6 Hz, 1 H), 4.40 (br dd, $J=9.7$, 0.8 Hz, 1 H), 4.48 (dq, $J=7.0$, 3.1 Hz, 1 H), 4.62 (dd, $J=9.7$, 3.1 Hz, 1 H), 5.25 (d, $J=5.6$ Hz, 1 H).

7(S)-7-Deoxy-7-(5-phenyl-1,3,4-thiadiazol-2-ylthio)lincomycin (27). Compound **1** (240 mg, 0.39 mmol) and 5-phenyl-1,3,4-thiadiazole-2-thiol (100 mg, 0.51 mmol) in toluene (5 ml) were treated according to the similar procedure as described for the preparation of **2** to afford **27** (46.5 mg, 21%) as a colorless solid. $[\alpha]_D^{27}$ +157.2° (*c* 1.47, $CHCl_3$); ESI-MS (*m/z*) 583 $(M+H)^+$ as $C_{26}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{38}N_4O_5S_3$: 583.2083, found: 583.2086; ^1H NMR (400 MHz, methanol-d_4) δ 0.86–0.97 (m, 3 H), 1.26–1.38 (m, 4 H), 1.57 (d, $J=7.0$ Hz, 3 H), 1.79–1.91 (m, 1 H), 1.96–2.11 (m, 2 H), 2.03 (s, 3 H), 2.15–2.28 (m, 1 H), 2.38 (s, 3 H), 3.03 (dd, $J=10.5$, 5.1 Hz, 1 H), 3.27 (dd, $J=8.5$, 6.1 Hz, 1 H), 3.58 (dd, $J=10.3$, 3.2 Hz, 1 H), 3.83 (br dd, $J=3.2$, 0.7 Hz, 1 H), 4.12 (dd, $J=10.3$, 5.6 Hz, 1 H), 4.36–4.46 (m, 2 H), 4.60 (dd, $J=9.7$, 3.2 Hz, 1 H), 5.27 (d, $J=5.6$ Hz, 1 H), 7.49–7.58 (m, 3 H), 7.89–7.95 (m, 2 H).

7(S)-7-Allylthio-7-deoxylincomycin (28). To a solution of compound **5** (83.2 mg, 0.16 mmol) in methanol (1 ml) were added allyl iodide (26.5 mg, 0.16 mmol) and 28% sodium methoxide in mehtanol (0.56 ml) and stirred at RT for 14 h. The mixture was diluted with 1 N HCl (1 ml) and concentrated under reduced pressure. The resulting residue was dissolved by water and washed with diethyl ether. The mixture was added to $NaHCO_3$ (150 mg) and then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$/28% aq $NH_4OH = 20/1/0.1$) to obtain the title compound as a colorless solid (22.0 mg, 30%). $[\alpha]_D^{25}$ +115.3° (*c* 0.34, MeOH); ESI-MS (*m/z*) 463 $(M+H)^+$ as $C_{21}H_{38}N_2O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{21}H_{38}N_2O_5S_2$: 463.2300, found: 463.2295; ^1H NMR (400 MHz, methanol-d_4) δ 0.89–0.96 (m, 3 H), 1.27–1.40 (m, 4 H), 1.31 (d, $J = 7.0$ Hz, 3 H), 1.82–1.92 (m, 1 H), 2.00 (ddd, $J = 12.5$, 7.6, 4.7 Hz, 1 H), 2.08–2.27 (m, 2 H), 2.19 (s, 3 H), 2.44 (s, 3 H), 3.05 (dd, $J = 10.5$, 4.4 Hz, 1 H), 3.23–3.39 (m, 4 H), 3.56 (dd, $J = 10.2$, 3.3 Hz, 1 H), 3.67–3.74 (m, 1 H), 4.09 (dd, $J = 10.2$, 5.6 Hz, 1 H), 4.21 (br d, $J = 9.8$ Hz,1 H), 4.27 (dd, $J = 9.8$, 2.4 Hz, 1 H), 5.04–5.11 (m, 1 H), 5.19 (dq, $J = 17.0$, 1.4 Hz, 1 H), 5.25 (d, $J = 5.6$ Hz, 1 H), 5.85 (ddt, $J = 17.0$, 10.7, 1.0 Hz, 1 H).

*7(**S**)-7-(5-Aminobenzo[d]thiazol-2-ylthio)-7-deoxylincomycin (**29**).* To a solution of compound **17** (75.0 mg, 0.12 mmol) in ethanol (3.0 ml) were added $SnCl_2 \cdot H_2O$ (140 mg, 0.62 mmol) and $NaBH_4$ (6.5 mg, 0.17 mmol) and stirred at RT for 3 h. The mixture was concentrated under reduced pressure. The resulting residue was dissolved by ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$/28% aq $NH_4OH = 20/1/0.1$) to obtain the title compound as a colorless solid (34.2 mg, 48%). $[\alpha]_D^{25}$ +59.4° (*c* 0.58, MeOH); ESI-MS (*m/z*) 571 $(M+H)^+$ as $C_{25}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{38}N_4O_5S_3$: 571.2083, found: 571.2090; ^1H NMR (400 MHz, methanol-d_4) δ 0.87–0.96 (m, 3 H), 1.25–1.39 (m, 4 H), 1.55 (d, $J = 7.0$ Hz, 3 H), 1.76–1.86 (m, 1 H), 1.88 (s, 3 H), 1.96–2.08 (m, 2 H), 2.12–2.24 (m, 1 H), 2.32 (s, 3 H), 2.99 (dd, $J = 10.5$, 5.2 Hz, 1 H), 3.18 (dd, $J = 8.5$, 6.2 Hz, 1 H), 3.57 (dd, $J = 10.1$, 3.2 Hz, 1H), 3.81 (br dd, $J = 3.2$, 0.7 Hz, 1 H), 4.10 (dd, $J = 10.1$, 5.6 Hz, 1 H), 4.39 (dq, $J = 7.0$, 3.1 Hz, 1 H), 4.42 (br dd, $J = 9.7$, 0.7 Hz, 1 H), 4.58 (dd, $J = 9.7$, 3.1 Hz, 1 H), 5.24 (d, $J = 5.6$ Hz, 1 H), 6.81 (dd, $J = 8.6$, 2.2 Hz, 1H), 7.16–7.18 (m, 1 H), 7.52 (dd, $J = 8.6$, 0.2 Hz, 1 H).

*7(**R**)-7-(6-Aminobenzo[d]thiazol-2-ylthio)-7-deoxylincomycin (**30**).* To a solution of clindamycin hydrochloride (460 mg, 1.0 mmol) in DMF (5 ml) were added K_2CO_3 (152 mg, 1.1 mmol) and 6-aminobenzo[d]thiazole-2-thiol (200 mg, 1.1 mmol) and stirred at 100 °C for 16 h. Then it was concentrated under reduced pressure. The residue was diluted with water and then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$/28% aq $NH_4OH = 20/1/0.1$) to obtain the title compound as a colorless solid (233.3 mg, 41%). $[\alpha]_D^{27}$ +129.5° (*c* 0.45, MeOH); ESI-MS (*m/z*) 571 $(M+H)^+$ as $C_{25}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{38}N_4O_5S_3$: 571.2083, found: 571.2079; ^1H NMR (400 MHz, methanol-d_4) δ 0.87–0.96 (m, 3 H), 1.27–1.39 (m, 4 H), 1.50 (d, $J = 7.1$ Hz, 3 H), 1.75–1.87 (m, 1 H), 1.95–2.01 (m, 1 H), 2.05 (dd, $J = 10.2$, 8.9 Hz, 1 H), 2.17 (s, 3 H), 2.13–2.26 (m, 1 H), 2.39 (s, 3 H), 2.98 (dd, $J = 10.4$, 5.0 Hz, 1 H), 3.21 (dd, $J = 8.5$, 6.2 Hz, 1 H), 3.54 (dd, $J = 10.2$, 3.3 Hz, 1 H), 3.80–3.84 (m, 1 H), 4.11 (dd, $J = 10.2$, 5.6 Hz, 1 H), 4.28 (br dd, $J = 9.2$, 0.6 Hz, 1 H), 4.30 (dq, $J = 7.1$, 3.9 Hz, 1 H), 4.65 (dd, $J = 9.2$, 3.9 Hz, 1 H), 5.29 (d, $J = 5.6$ Hz, 1 H), 6.84 (dd, $J = 8.7$, 2.3 Hz, 1 H), 7.08 (dd, $J = 2.3$, 0.4 Hz, 1 H), 7.57 (dd, $J = 8.7$, 0.4 Hz, 1 H). For the qualified analytical purpose, the above colorless solid was further purified by reverse-phase column chromatography (YMC triart C18, 20 × 250 mm, RT, 18.9 ml min^{-1}, 50 mM $AcONH_4/CH_3CN = 35/65$) to obtain the highly purified title compound as a colorless solid.

*7(**S**)-7-(2-Aminophenylthio)-7-deoxylincomycin (**31**).* To a solution of compound **18** (39.6 mg, 0.07 mmol) in ethanol (2 ml) were added $SnCl_2 \cdot H_2O$ (82.1 mg, 0.36 mmol) and $NaBH_4$ (13.7 mg, 5.0 mmol) and stirred at RT for 3 h. To the mixture was added aq $NaHCO_3$ and then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$/28% aq $NH_4OH = 9/1/0.1$) to obtain the title compound as a colorless solid (10.9 mg, 29%). $[\alpha]_D^{28}$ +74.5° (*c* 0.33, MeOH); ESI-MS (*m/z*) 514 $(M+H)^+$ as $C_{24}H_{39}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{39}N_3O_5S_2$: 514.2409, found: 514.2412; ^1H NMR (400 MHz, methanol-d_4) δ 0.89–0.97 (m, 3 H), 1.17 (d, $J = 7.1$ Hz, 3 H), 1.28–1.40 (m, 4 H), 1.75–1.85 (m, 1 H), 1.89–1.98 (m, 1 H), 2.04–2.12 (m, 1 H), 2.14–2.23 (m, 1 H), 2.19 (s, 3 H), 2.32 (s, 3 H), 3.01 (dd, $J = 10.6$, 5.0 Hz, 1 H), 3.25 (dd, $J = 8.3$, 5.9 Hz, 1 H), 3.58 (dd, $J = 10.2$, 3.2 Hz, 1 H), 3.67 (dq, $J = 7.1$, 2.8 Hz, 1 H), 3.74 (br dd, $J = 3.2$, 0.5 Hz, 1 H), 4.11 (dd, $J = 10.2$, 5.6 Hz, 1 H), 4.31 (dd, $J = 9.8$, 2.8 Hz, 1 H), 4.38 (br dd, $J = 9.8$, 0.5 Hz, 1 H), 5.27 (d, $J = 5.6$ Hz, 1 H), 6.61–6.67 (m, 1 H), 6.81 (dd, $J = 8.1$, 1.1 Hz, 1 H), 7.13 (ddd, $J = 8.8$, 7.2, 1.5 Hz, 1 H), 7.34 (dd, $J = 7.7$, 1.5 Hz, 1 H).

*7(**S**)-7-(3-Aminophenylthio)-7-deoxylincomycin (**32**).* Compound **19** (238.2 mg, 0.44 mmol), $SnCl_2 \cdot H_2O$ (494.4 mg, 2.19 mmol) and $NaBH_4$ (82.9 mg, 2.19 mmol) were treated according to the similar procedure as described for the preparation of **31** to afford **32** (36.0 mg, 16%) as a colorless solid. $[\alpha]_D^{29}$ +91.0° (*c* 0.60, MeOH); ESI-MS (*m/z*) 514 $(M+H)^+$ as $C_{24}H_{39}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{39}N_3O_5S_2$: 514.2409, found: 514.2408; ^1H NMR (400 MHz, methanol-d_4) δ 0.89–0.98 (m, 3 H), 1.31 (d, $J = 7.0$ Hz, 3 H), 1.30–1.40 (m, 4 H), 1.79–1.92 (m, 1 H), 1.93–2.10 (m, 2 H), 2.02 (s, 3 H), 2.11–2.23 (m, 1 H), 2.38 (s, 3 H), 2.97 (dd, $J = 10.7$, 4.6 Hz, 1 H), 3.25 (dd, $J = 8.1$, 5.6 Hz, 1 H), 3.59 (dd, $J = 10.2$, 3.3 Hz, 1 H), 3.72 (br d, $J = 3.3$ Hz, 1 H), 3.75–3.83 (m, 1 H), 4.10 (dd, $J = 10.2$, 5.5 Hz, 1 H), 4.33–4.40 (m, 2 H), 5.26 (d, $J = 5.5$ Hz, 1 H), 6.59 (ddd, $J = 8.0$, 2.2, 0.9 Hz, 1 H), 6.71 (ddd, J = 7.7, 1.7, 0.9 Hz, 1 H), 6.78–6.82 (m, 1 H), 6.99–7.06 (m, 1 H).

*7(**S**)-7-(4-Aminophenylthio)-7-deoxylincomycin (**33**).* Compound **20** (29.3 mg, 0.054 mmol), $SnCl_2 \cdot H_2O$ (60.8 mg, 0.27 mmol) and $NaBH_4$ (10.0 mg, 0.26 mmol) were treated according to the similar procedure as described for the preparation of **31** to afford **33** (9.7 mg, 35%) as a colorless solid. $[\alpha]_D^{28}$ +142.0° (*c* 0.51, MeOH); ESI-MS (*m/z*) 514 $(M+H)^+$ as $C_{24}H_{39}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{39}N_3O_5S_2$: 514.2409, found: 514.2411; ^1H NMR (400 MHz, methanol-d_4) δ 0.89–0.98 (m, 3 H), 1.20 (d, $J = 7.1$ Hz, 3 H), 1.30–1.41 (m, 4 H), 1.80–1.90 (m, 1 H), 1.92–2.00 (m, 1 H), 2.04–2.21 (m, 2 H), 2.17 (s, 3 H), 2.34 (s, 3 H), 2.98 (dd, $J = 10.6$, 4.6 Hz, 1 H), 3.24 (dd, $J = 8.2$, 5.6 Hz, 1 H), 3.53 (dq, $J = 7.1$, 2.8 Hz, 1 H), 3.60 (dd, $J = 10.3$, 3.3 Hz, 1 H), 3.68–3.72 (m, 1 H), 4.10 (dd, $J = 10.3$, 5.6 Hz, 1 H), 4.25 (dd, $J = 9.9$, 2.8 Hz, 1 H), 4.38 (br d, $J = 9.9$ Hz, 1 H), 5.27 (d, $J = 5.6$ Hz, 1 H), 6.62–6.68 (m, 2 H), 7.20–7.26 (m, 2 H).

*7(**S**)-7-(4-Methanesulfonamidophenylthio)-7-deoxylincomycin (**34**).* To a solution of compound **33** (83.8 mg, 0.16 mmol) in DMF (1 ml) were added triethylamine (0.027 ml, 0.2 mmol) and methanesulfonyl chloride (0.015 ml, 0.2 mmol) and stirred at RT for 20 min. To the mixture was added saturated aqueous $NaHCO_3$ (10 ml) and then extracted with ethyl acetate, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$/28% aq $NH_4OH = 9/2/0.2$) to obtain the title compound as a colorless solid (28.0 mg, 29%). $[\alpha]_D^{26}$ +94.2° (*c* 1.01, MeOH); ESI-MS (*m/z*) 592 $(M+H)^+$ as $C_{25}H_{41}N_3O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{41}N_3O_7S_3$: 592.2185, found: 592.2180; ^1H NMR (400 MHz, methanol-d_4) δ 0.89–0.98 (m, 3 H), 1.28 (d, $J = 7.0$ Hz, 3 H), 1.31–1.41 (m, 4 H), 1.78–1.92 (m, 1 H), 1.99 (ddd, $J = 12.9$, 7.9, 5.0 Hz, 1 H), 2.04 (s, 3 H), 2.05–2.11 (m, 1 H), 2.11–2.23 (m, 1 H), 2.38 (s, 3 H), 2.94–3.03 (m, 1 H), 2.97 (s, 3 H), 3.25 (dd, $J = 8.1$, 5.6 Hz, 1 H), 3.58 (dd, $J = 10.2$, 3.2 Hz, 1 H), 3.74 (br d, $J = 3.2$ Hz, 1 H), 3.78 (dq, $J = 7.0$, 2.5 Hz, 1 H), 4.10 (dd, $J = 10.2$, 5.6 Hz, 1 H), 4.31–4.36 (m, 1 H), 4.38 (dd, $J = 9.7$, 2.5 Hz, 1 H), 5.26 (d, $J = 5.6$ Hz, 1 H), 7.18–7.25 (m, 2 H), 7.40–7.48 (m, 2 H).

*7(**S**)-7-(5-(2-Aminoacetamido)-1,3,4-thiadiazol-2-ylthio)-7-deoxylincomycin (**36**).* To a solution of compound **1** (240 mg, 0.39 mmol) in THF (5 ml) at 0 °C were added triphenylphosphine (150 mg, 0.57 mmol), diethylazodicarboxylate (0.1 ml, 0.55 mmol) and *t*-butyl (2-((5-mercapto-1,3,4-thiadiazol-2-yl) amino)-2-oxoethyl)carbamate (150 mg, 0.52 mmol) and stirred RT for 17 h. The mixture was concentrated under reduced pressure, and the resulting residue (compound **35**) in 90% aqueous trifluoroacetic acid (5 ml) was stirred at RT for 30 min. The mixture was concentrated under reduced pressure. The resulting residue was purified by preparative reverse-phase column chromatography (YMC triart C18, 20 × 250 mm^2, RT, 18.9 ml min^{-1}, 0.1% aq TFA/$CH_3CN = 85/15$). This trifluoroacetate was desalted by preparative reverse-phase column chromatography (YMC triart C18, 20 × 250 mm^2, RT, 18.9 ml min^{-1}, H_2O/MeOH = 100/0 (15 min) → 0/100 (15–40 min)) to obtain the highly purified title compound as a colorless solid (54.0 mg, 24%). $[\alpha]_D^{25}$ +100.4° (*c* 0.29, MeOH); ESI-MS (*m/z*) 578 $(M+H)^+$ as $C_{22}H_{38}N_6O_6S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{22}H_{38}N_6O_6S_3$: 579.2093, found: 579.2095; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.86–0.97 (m, 3 H), 1.29–1.39 (m, 4 H), 1.42 (d, *J* = 7.0 Hz, 3 H), 1.77–1.87 (m, 1 H), 1.93–2.09 (m, 2 H), 2.06 (s, 3 H), 2.13–2.25 (m, 1 H), 2.32 (s, 3 H), 2.98 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.26 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.57 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.54–3.62 (m, 2 H), 3.78 (br dd, *J* = 3.2, 0.5 Hz, 1 H), 4.08 (dq, *J* = 7.0, 2.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.40 (br dd, *J* = 9.8, 0.5 Hz, 1 H), 4.47 (dd, *J* = 9.8, 2.8 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H).

*7(**S**)-7-(5-Amino-1,3,4-thiadiazol-2-ylthio)-7-deoxy-2,3,4-tris-O-(trimethylsilyl) lincomycin (**37**).* To a solution of compound **21** (403 mg, 0.77 mmol) in pyridine (8 ml) were added trimethylchlorosilane (0.61 ml, 4.8 mmol) and hexamethyldisilazane (1.05 ml, 5.0 mmol) and stirred at RT for 2.5 h, and then it was concentrated under reduced pressure. The residue was diluted with saturated aqueous NH_4Cl and extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1) to obtain the title compound as a colorless solid (467 mg, 82%). ESI-MS (*m/z*) 738 $(M+H)^+$ as $C_{29}H_{59}N_5O_5S_3Si_3$; ^{1}H NMR (400 MHz, chloroform-*d*) δ 0.13 (s, 18H), 0.17 (s, 9 H), 0.79–0.97 (m, 3 H), 1.15–1.37 (m, 4 H), 1.42 (d, *J* = 6.9 Hz, 3 H), 1.71–1.90 (m, 2 H), 1.91–2.06 (m, 2 H), 2.08 (s, 3 H), 2.40 (s, 3 H), 2.99 (dd, *J* = 10.7, 3.6 Hz, 1 H), 3.12–3.23 (m, 1 H), 3.61 (dd, *J* = 9.6, 2.5 Hz, 1 H), 3.74 (br d, *J* = 2.2 Hz, 1 H), 4.04–4.24 (m, 3 H), 4.60–4.70 (m, 1 H), 5.23 (d, *J* = 5.5 Hz, 1 H), 5.50 (s, 2 H), 7.59 (d, *J* = 10.7 Hz, 1 H).

*7(**S**)-7-Deoxy-7-(5-(2-methoxyacetamido)-1,3,4-thiadiazol-2-ylthio)lincomycin (**38**).* To a solution of compound **37** (104 mg, 0.14 mmol) in THF (3 ml) were added triethylamine (0.06 ml, 0.43 mmol) and 2-methoxyacetyl chloride (0.02 ml, 0.22 mmol) and stirred at 0 °C for 2 h. The mixture was diluted with saturated aqueous NH_4Cl and extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$ = 19/1) to obtain 7 (*S*)-7-deoxy-7-(5-(2-methoxyacetamido)-1,3,4-thiadiazol-2-ylthio)-2,3,4-tris-*O*-(trimethylsilyl)lincomycin as a colorless solid (109.8 mg, 96%). 7(*S*)-7-Deoxy-7-(5-(2-methoxyacetamido)-1,3,4-thiadiazol-2-ylthio)-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (109.8 mg, 0.14 mmol) in 1 N HCl (1 ml)–MeOH (1 ml) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure. The resulting residue was dissolved by water and washed with diethyl ether. The mixture was added $NaHCO_3$ (150 mg) and then extracted with ethyl acetate, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$/28% aq NH_4OH = 5/1/0.1) to obtain the title compound as a colorless solid (37.8 mg, 47%). $[\alpha]_D^{26}$ +98.3° (*c* 0.65, MeOH); ESI-MS (*m/z*) 594 $(M+H)^+$ as $C_{23}H_{39}N_5O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{23}H_{39}N_5O_7S_3$: 594.2090, found: 594.2095; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.88–0.97 (m, 3 H), 1.30–1.41 (m, 4 H), 1.46 (d, *J* = 7.0 Hz, 3 H), 1.82–1.92 (m, 1 H), 1.97–2.08 (m, 1 H), 2.04 (s, 3 H), 2.08–2.15 (m, 1 H), 2.15–2.27 (m, 1 H), 2.39 (s, 3 H), 3.08 (dd, *J* = 10.4, 5.0 Hz, 1 H), 3.25–3.34 (m, 1 H), 3.48 (s, 3 H), 3.57 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.77–3.81 (m, 1 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.16–4.24 (m, 1 H), 4.21 (s, 2 H), 4.39 (br dd, *J* = 9.8, 0.6 Hz, 1 H), 4.53 (dd, *J* = 9.8, 3.1 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H).

*7-O-Methanesulfonyl-2,3,4-tris-O-(trimethylsilyl)lincomycin (**39**).* To a solution of compound **1** (5.0 g, 8.0 mmol) in chloroform (25 ml) were added triethylamine (2.79 ml, 20.1 mmol) and methanesulfonyl chloride (1.24 ml, 16.1 mmol) and stirred at RT for 3 h. The mixture was dissolved by chloroform (60 ml), washed with saturated aqueous $NaHCO_3$ (50 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1) to obtain the title compound as a colorless solid (5.50 g, 98%). ESI-MS (*m/z*) 701 $(M+H)^+$ as $C_{28}H_{60}N_2O_8S_2Si_3$; ^{1}H NMR (400 MHz, chloroform-*d*) δ 0.13 (s, 9 H), 0.14 (s, 9 H), 0.17 (s, 9 H), 0.89 (br t, *J* = 6.9 Hz, 3 H), 1.21–1.36 (m, 4 H), 1.40 (d, *J* = 6.6 Hz, 3 H), 1.79–1.89 (m, 1 H), 1.92–2.09 (m, 3 H), 2.11 (s, 3 H), 2.40 (s, 3 H), 2.99 (dd, *J* = 10.7, 3.7 Hz, 1 H), 3.09 (s, 3 H), 3.14–3.21 (m, 1 H), 3.52 (dd, *J* = 9.5, 2.4 Hz, 1 H), 3.75 (br d, *J* = 2.4 Hz, 1 H), 3.90 (d, *J* = 9.7 Hz, 1 H), 4.15 (dd, *J* = 9.5, 5.6 Hz, 1 H), 4.70–4.78 (m, 1 H), 5.09–5.15 (m, 1 H), 5.16 (d, *J* = 5.6 Hz, 1 H), 7.61 (d, *J* = 10.7 Hz, 1 H).

*7(**S**)-7-Deoxy-7-(4-methoxycarbonylphenylthio)lincomycin (**40**).* To a solution of compound **39** (100 mg, 0.14 mmol) in DMF (1.0 ml) were added K_2CO_3 (59.8 mg, 0.43 mmol) and methyl 4-mercaptobenzoate (48.9 mg, 0.29 mmol) and stirred at 80 °C for 3 h. The mixture was cooled down to RT, diluted with 1 N HCl (2 ml)–MeOH (1 ml), stirred at RT for 2 h and concentrated under reduced pressure. The resulting residue was dissolved by water, washed with diethyl ether. To the mixture was added $NaHCO_3$ (150 mg) and then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$/28% aq NH_4OH = 5/1/0.1) to obtain the title compound as a colorless solid (58.0 mg, 73%). $[\alpha]_D^{24}$ +84.6° (*c* 0.97, MeOH); ESI-MS (*m/z*) 557 $(M+H)^+$ as $C_{26}H_{40}N_2O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{40}N_2O_7S_2$: 557.2355, found: 557.2359; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.88–0.96 (m, 3 H), 1.29–1.37 (m, 4 H), 1.40 (d, *J* = 6.8 Hz, 3 H), 1.79–1.91 (m, 1 H), 1.84 (s, 3 H), 1.96–2.05 (m, 1 H), 2.05–2.12 (m, 1 H), 2.12–2.25 (m, 1 H), 2.40 (s, 3 H), 3.00 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.24 (dd, *J* = 8.2, 5.7 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.78 (br dd, *J* = 3.2, 0.7 Hz,1 H), 3.89 (s, 3 H), 4.03 (dq, *J* = 6.8, 2.8 Hz,1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.37 (br dd, *J* = 9.7, 0.7 Hz, 1 H), 4.52 (dd, *J* = 9.7, 2.8 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.42–7.49 (m, 2 H), 7.90–7.97 (m, 2 H).

*7(**S**)-7-Deoxy-7-(3-methoxycarbonylphenylthio)lincomycin (**41**).* Compound **39** (200 mg, 0.29 mmol) and methyl 3-mercaptobenzoate (95.9 mg, 0.57 mmol) were treated according to the similar procedure as described for the preparation of **40** to afford **41** (101.6 mg, 64%) as a colorless solid. $[\alpha]_D^{29}$ +93.6° (*c* 2.37, MeOH); ESI-MS (*m/z*) 557 $(M+H)^+$ as $C_{25}H_{37}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{37}N_3O_6S_2$: 557.2355, found: 557.2355; ^{1}H NMR (400 MHz, methanol-d_4) δ 0.88–0.97 (m, 3 H), 1.29–1.40 (m, 4 H), 1.33 (d, *J* = 7.0 Hz, 3 H), 1.78–1.91 (m, 1 H), 1.95–2.04 (m, 1 H), 1.97 (s, 3 H), 2.04–2.11 (m, 1 H), 2.11–2.23 (m, 1 H), 2.39 (s, 3 H), 2.99 (dd, *J* = 10.7, 4.7 Hz, 1 H), 3.23 (dd, *J* = 8.2, 5.7 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.74–3.79 (m, 1 H), 3.87–3.96 (m, 1 H), 3.91 (s, 3 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.36 (br dd, *J* = 9.7, 0.6 Hz, 1 H), 4.48 (dd, *J* = 9.7, 2.8 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.42–7.49 (m, 1 H), 7.67 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1 H), 7.87–7.92 (m, 1 H), 8.02–8.06 (m, 1 H).

In vitro antibacterial activity

MIC, μg ml^{-1} was determined by the agar dilution method, which was described in Clinical and Laboratory Standards Institute (M7-A5 in 2000). Test strains of *S. pneumoniae* and *S. pyogenes* were subjected to seed culture using brain heart infusion agar (Becton Dickinson and Company, Tokyo, Japan) and 5% defibrinated horse blood. Test strains of *H. influenzae* were subjected to seed culture using sensitivity disk agar-N 'Nissui' (SDA; Nissui, Tokyo, Japan), 5% defibrinated horse blood, 5 μg ml^{-1} Hemin and 15 μg ml^{-1} NAD. A 5-μl portion of cell suspension of the test strains having about 10^6 CFU per ml was inoculated into SDA supplemented with 5% defibrinated horse blood, 5 μg ml^{-1} Hemin and 15 μg ml^{-1} NAD and incubated at 37 °C for 18–22 h. Then MIC was measured.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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