Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 1483–1487

An efficient entry to new sugar modified ketolide antibiotics

Alex Romero, Chang-Hsing Liang, Yu-Hung Chiu, Sulan Yao, Jonathan Duffield, Steven J. Sucheck, Ken Marby, David Rabuka, Po Yee Leung, Youe-Kong Shue, Yoshi Ichikawa and Chan-Kou Hwang*

Department of Chemistry, Optimer Pharmaceuticals, Inc., 10110 Sorrento Valley Road, Suite C, San Diego, CA 92121, USA

Received 16 September 2004; revised 5 January 2005; accepted 7 January 2005
Available online 22 January 2005

Abstract—A new and efficient route to a ketolide aglycon served as a basis for the unprecedented 5-*O*-glyco-modification of ketolide antibiotics. Combined with an effective copper-catalyzed triazole-forming reaction a series of novel and potent ketolide antibiotics were synthesized.

Macrolide antibiotics, including erythromycin A (**1**), clarithromycin (**2**), and azithromycin (**3**) (Fig. 1), are important therapeutic agents for the treatment of respiratory tract infections (RTIs) due to their broad spectrum of activity against several dominant respiratory pathogens and their excellent safety profile. However, the widespread use of antibiotics over the past decades has increased the prevalence of macrolide antibiotic-resistant pathogens. It is estimated that by this year, nearly 40% of all *Streptococcus* strains, the major causative pathogen for RTIs, will be resistant to both penicillin and macrolide antibiotics in the US.[1]

Ketolides, a new class of macrolides, have recently been developed having improved antibacterial activities.

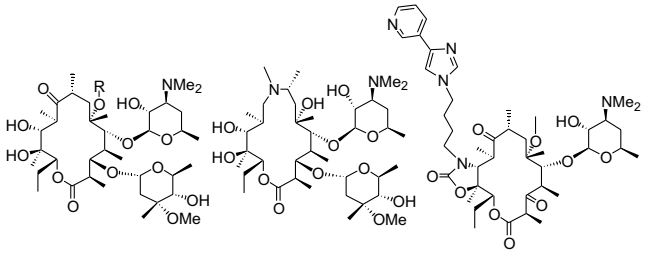


Figure 1. Macrolide and ketolide antibiotics.

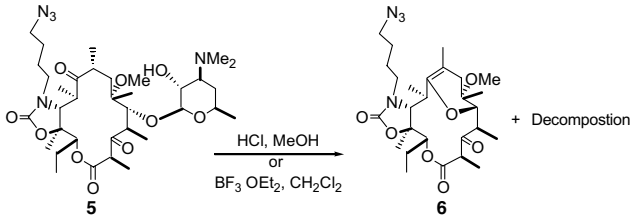
Their structural features are: (1) lack of 3-*O*-cladinose, (2) presence of 3-keto group, and (3) presence of aromatic functionality to interact with domain II of the bacterial rRNA, as seen in telithromycin (**4**).[2] Although ketolides demonstrate excellent antibacterial activities, they are still prone to ubiquitous resistance mechanisms developed by bacteria; *Erm*-mediated methylation of the bacterial ribosomal RNA whereby the 5-*O*-desosamine plays a key role.[3,4a–c]

We initiated our macrolide discovery program based on the hypothesis that if we could establish a technology by which the 5-*O*-desosamine residue of a ketolide can be replaced with an optimized sugar motif, effective macrolide-based antibiotics could be discovered that are active against these resistant pathogens. We embarked on developing conditions for the following chemical transformations: (1) an efficient procedure for aglycon preparation, (2) facile glycosylation of the 5-OH group, and (3) effective procedure for introducing aromatic functionality for interacting with domain II.

The 5-*O*-desosamine residue has been considered to be critical for the antibacterial activity of macrolide/ketolide antibiotics and there have been only few reports describing the removal or modification of this sugar.[4,5] Attempted forcing acidic conditions to remove the 5-*O*-desosamine commonly results in elimination side products or decomposition of the macrolide core. For example, when ketolide **5** was submitted to HCl in MeOH or $BF_3{\cdot}OEt_2$ in CH_2Cl_2, ketolide **6** was the only identifiable side product isolated (Scheme 1). Due to the acid sensitivity of the ketolide core and the difficulty

Keywords: Ketolide aglycon; Glycosylation; Triazole formation; Antibiotics.
* Corresponding author. Tel.: +1 858 909 0736; fax: +1 858 909 0737; e-mail: jhwang@optimerpharma.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.023



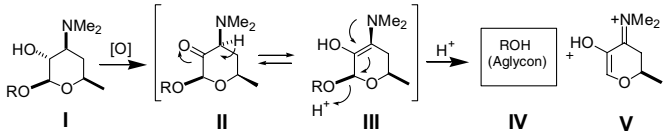
Scheme 1. Attempted acidic removal of 5-*O*-desosamine.

associated with removing the 5-*O*-desosamine sugar from macrolide antibiotics, we focused on developing a new procedure for the efficient removal of the 5-*O*-desosamine from ketolide derivatives. By identifying the unique structural features of desosamine, namely, the 3′-dimethylamino-2′-hydroxy sugar motif (**I**) (Scheme 2), we speculated that the oxidation of the 2′-OH group to the 2′-keto group (**II**) would facilitate tautomerization to generate the 2′,3′-enol form (**III**). Subsequent elimination of the glycoside under mild acidic hydrolysis would then generate the desired ketolide aglycon (**IV**). In order to initiate this investigation, we prepared the versatile azide containing synthetic intermediate **5** (Scheme 3), which could be easily transformed into a substituted-triazole containing ketolide, via a [3+2] cycloaddition reaction between an azide and an alkyne.

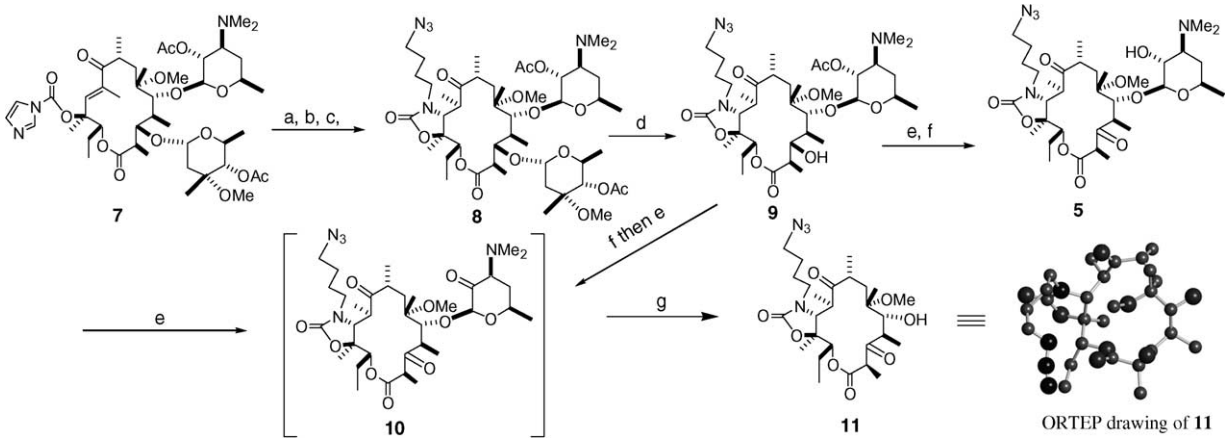
The synthesis of **5** began with the reaction of the known acylimidazole intermediate **7**[6] with 4-amino-1-butanol in DMF to generate a cyclic carbamate (Scheme 3). As previously described,[7] the reaction of **7** with amines is selective and produces a major isomer. Tosylation of the primary alcohol and subsequent displacement of the tosylate group with NaN_3 in DMF afforded azidomacrolide **8** in 88% overall yield. Removal of the 3-*O*-cladinose residue was accomplished using 1 N HCl to give compound **9** in 92% yield. The resulting 3-OH group was oxidized using Swern conditions[8] to give the ketolide and then treated with MeOH to afford **5**.

Ketolide **5** was subjected again to Swern oxidation. Although we had confirmed that the reaction took place by observing an additional carbonyl signal in the ^{13}C NMR spectrum, surprisingly, we were unable to isolate **10** in pure form by a silica gel chromatography due to gradual degradation to the expected ketolide aglycon product. Indeed, upon heating **10** in MeOH in the presence of silica gel generated ketolide aglycon **11** in 55%. The structure of **11** was further confirmed by X-ray crystallography.[9] To our delight, we have also found that the one-step bis-Swern oxidation of the diol derivative (deacetylated product of **9**), following methanolysis in silica gel, also effectively afforded the ketolide aglycon **11**.[10]

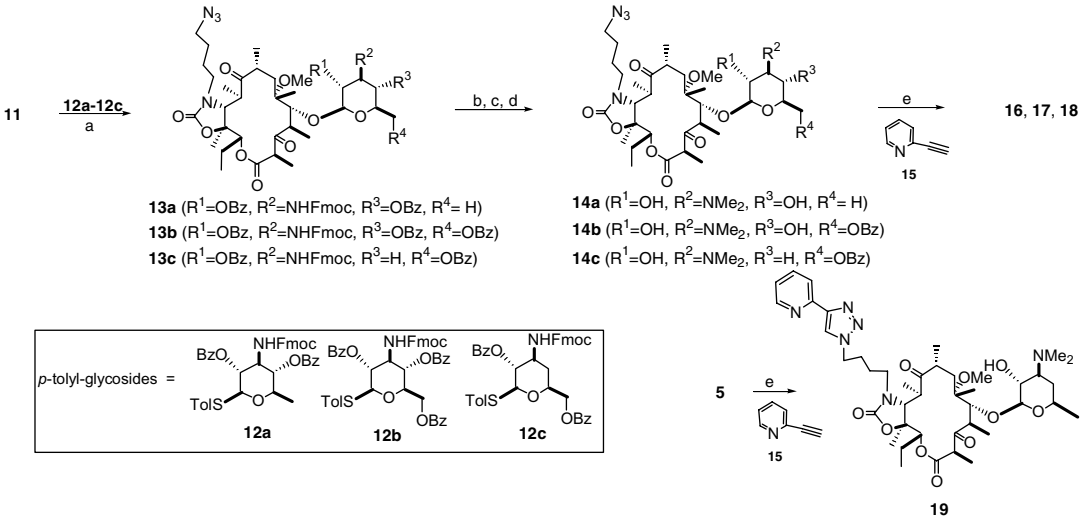
The glycosylation of **11** with sugar derivative **12a–c** (Scheme 4) using NIS/AgOTf afforded the protected glycosylated products **13a–c** in 65–70% yield in ~10:1 anomeric mixture in which the desired β-form was the predominant isomer.[11,12] The Fmoc protecting group was removed by treating with 10% piperidine in DMF and reductive amination was accomplished with $NaBH(OAc)_3$ and formaldehyde in THF to give the requisite *N*,*N*-dimethylamine. The glycosylated products having the 2′-OBz and/or 4′-OBz groups were selectively removed by heating in MeOH to give the deprotected adducts **14a–c** in 65–75% yield for the combined three steps. For each of the glycosylated deprotected ketolides, the azide group was reacted with 2-pyridyl acety-



Scheme 2. Proposed mechanism for deglycosylation.



Scheme 3. Reagents and conditions: (a) 4-amino-1-butanol, DMF, 95%; (b) TsCl, pyridine, 93%; (c) NaN_3, DMF, 80 °C, 100%; (d) 1 N HCl, MeOH, 92%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 95%; (f) MeOH, 65 °C, 98%; (g) silica gel, MeOH, N_2, 65 °C, 55%.



Scheme 4. Reagent and conditions: (a) NIS, AgOTf, 2,6-di-*tert*-butylpyridine, 65%; (b) 10% piperidine, 83%; (c) HCHO, $NaBH(OAc)_3$, 85%; (d) MeOH, 70 °C, 92%; (e) cat. CuI, toluene, 75 °C, 98%.

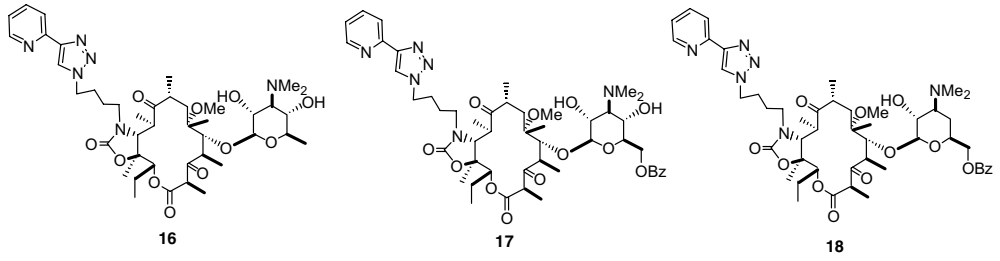


Figure 2. Newly synthesized ketolides.[14–19]

lene **15** in the presence of catalytic amount of CuI to give a single regioisomer of the triazole adducts, **16**, **17**, and **18** in >95% yield.[13] Similarly, ketolide **5** was converted to **19**, having the natural 5-*O*-desosamine, in 98% yield. Employing this strategy, novel ketolide antibiotics containing new 5-*O*-sugars and having a unique hetero-aromatic triazole substituent were assembled (Fig. 2) and tested for antimicrobial activity. Ketolides **17** and **18** were active against sensitive *S. pneumoniae* (ATCC 49619) (both <0.125 μg/mL) and macrolide resistant *S. pyogenes* (3029, erm) (2 and 0.5 μg/mL, respectively). Ketolide **16** and **19**, containing the naturally occurring sugars, mycaminose and desosamine, respectively, were active against *S. pneumoniae* (both <0.125 μg/mL), although they were devoid of activity against *S. pyogenes* (3029, erm) (both >64 μg/mL). From this initial screening, we have identified ketolides having the novel 5-*O*-sugar motif containing an additional 6′-OBz group (**17** and **18**) exhibited excellent antibacterial activities. The results of these microbiological studies will be reported elsewhere.

In summary, mild conditions for preparing ketolide aglycons have been developed, which served as a basis for the unprecedented 5-*O*-glyco-modification of ketolide antibiotics. This work may provide significant opportunities for the design of a new class of macrolide/ketolide-based antibiotics.

Acknowledgements

This work was partially supported by SBIR research grant 1R43 AI058395-01, awarded by the National Institute of Allergy and Infectious Diseases, National Institute of Health. We thank Dr. Pamela Sears, Mrs. Niki Robert, and Mrs. Jamie Seddon for the biological evaluation of these compounds. We also thank Professors Chi-Huey Wong, Samuel J. Danishefsky, and K. Barry Sharpless for helpful discussions.

References and notes

1. McCormick, A. W.; Whitney, C. G.; Farley, M. M.; Lynfield, R.; Harrison, L. H.; Bennet, N. M.; Schaffner, W.; Reingold, A.; Hadler, J.; Cieslak, P.; Samore, M. H.; Lipsitch, M. *Nat. Med.* **2003**, 1–7.
2. Agouridas, C.; Chantot, J.-F.; Denis, A.; Solange, G. D.; Odile, L. M. U.S. Patent 5,635,485, 1997.
3. Schmitz, F.-J.; Petridou, J.; Jagusch, H.; Astfalk, N.; Scheuring, S.; Schwarz, S. *J. Antimicrob. Chemother.* **2002**, *49*, 611–617.
4. (a) Omura, S. *Macrolide Antibiotics Chemistry, Biology, and Practice*; Academic: London, 2002; (b) Zhanel, G. G.; Walters, M.; Noreddin, A.; Vercaigne, L. M.; Wierzbowski, A.; Embil, J. M.; Gin, A. S.; Douthwaite, S.; Hoban, D. J. *Drugs* **2002**, *62*, 1771–1804; (c) Asaka, T.; Manaka, A.; Sugiyama, H. *Curr. Top. Med. Chem.*

2003, *3*, 961–989; (d) Jones, P. H.; Powley, E. K. *J. Org. Chem.* **1968**, *33*, 665–670; (e) LeMahieu, R. A.; Carson, M.; Kierstead, R. W. *J. Med. Chem.* **1974**, *17*, 953–956.
5. Djokic, S.; Kobrehel, G.; Lazarevski, G.; Lopotar, N.; Tamburasev, Z. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1881.
6. Baker, W. R.; Clark, J. D. U.S. Patent 4,742,049, 1988.
7. Or, Y.; Clark, R.; Wang, S.; Chu, D.; Nilius, A.; Flamm, R.; Mitten, M.; Ewing, P.; Alder, J.; Ma, Z. *J. Med. Chem.* **2000**, *43*, 1045–1049.
8. Swern, D. *J. Org. Chem.* **1976**, *41*, 957–962.
9. Crystallographic data for structure **11** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 250316.
10. We have applied this procedure (Swern oxidation then methanolysis) to telithromycin. The telithromycin aglycon was successfully obtained in 55% yield.
11. The *p*-tolyl glycosides were designed and synthesized in-house. The protecting group scheme (i.e., 2-OBz) was chosen in order to direct the β-configuration at the anomeric center resulting from the glycosylation reaction.
12. General procedure for the glycosylation of aglycon **11**: *N*-Iodosuccinimide (1.5 equiv) was added to a mixture of 11-*N*-(4-azido-butyl)-6-*O*-methyl-5-hydroxy-3-oxo-erythronolide A, 11,12-carbamate **11** (1.0 equiv, 1 mmol), thioglycoside (1.3 equiv), molecular sieves (250 mg), and CH_2Cl_2 (10 mL) at −78 °C. After 10 min, AgOTf (1.7 equiv) and 2,6-di-*tert*-butyl-pyridine (1.8 equiv) were added and the mixture was gradually allowed to warm to rt. After 6–18 h, a 1:1 mixture of satd aq $NaHCO_3$ and Na_2SO_3 (50 mL) was added and the mixture was diluted with CH_2Cl_2 (150 mL) and the resulting layers were separated. The organic layer was dried with Na_2SO_4 and concentrated. Purification by silica gel chromatography (toluene–acetone) afforded glycosylated compounds.
13. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, B. *Angew. Chem., Int. Ed.* **2002**, *114*, 2596–2599; (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
14. Spectroscopic data for compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.52 (dd, J = 7.9, 4.2 Hz, 1H), 4.07–4.04 (m, 1H), 3.85 (q, J = 6.8 Hz, 1H), 3.70–3.61 (m, 1H), 3.47–3.38 (m, 3H), 3.22 (s, 3H), 3.09–3.00 (m, 2H), 4.30 (dq, J = 10.5, 7.0 Hz, 1H), 2.15 (d, J = 17.9 Hz, 1H), 2.03 (d, J = 17.9 Hz, 1H), 1.90–1.79 (m, 1H), 1.62 (s, 3H), 1.73–1.48 (m, 4H), 1.33 (d, J = 7.0 Hz, 3H), 1.33 (s, 3H), 1.30 (d, J = 6.6 Hz, 3H), 1.26 (s, 3H), 1.28–1.24 (m, 1H), 1.12 (d, J = 7.1 Hz, 3H), 0.97 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.04, 168.76, 157.56, 148.75, 102.38, 83.67, 78.79, 77.91, 72.31, 60.13, 51.19, 50.79, 49.05, 47.67, 45.69, 38.02, 36.68, 26.57, 24.37, 23.18, 22.84, 17.50, 17.23, 14.99, 14.76, 11.37, 9.65. MS: Calcd for $C_{27}H_{42}N_4O_7Na$ (M+Na): 557.30, found: 557.22.
15. Spectroscopic data for compound **11**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.93 (dd, J = 10.5, 2.3 Hz, 1H), 4.20 (d, J = 9.4 Hz, 1H), 3.84 (q, J = 7.0 Hz, 1H), 3.72–3.61 (m, 2H), 3.59 (s, 1H), 3.38–3.28 (m, 2H), 3.15 (q, J = 7.0 Hz, 1H), 2.91 (m, 1H), 2.71 (s, 3H), 2.67–2.62 (m, 1H), 1.97 (ddt, J = 7.6, 5.3, 2.3 Hz, 1H), 1.80 (dd, J = 14.6, 2.6 Hz, 1H), 1.70–1.52 (m, 6H), 1.50 (s, 3H), 1.41 (d, J = 7.0 Hz, 3H), 1.39 (s, 3H), 1.22 (d, J = 7.0 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.1, 203.8, 169.3, 157.2, 82.2, 78.4, 77.2, 74.3, 60.3, 51.6, 51.0, 49.7, 47.1, 44.7, 42.9, 39.1, 38.3, 26.2, 24.3, 22.2, 19.9, 18.2, 16.7, 14.7, 14.4, 13.8, 10.4. HRMS (ES): Calcd for $C_{27}H_{45}N_4O_8$ (M+H): 553.3232, found: 553.3222.
16. Spectroscopic data for compound **16**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (ddd, J = 4.8, 1.3, 0.8 Hz, 1H), 8.17 (s, 1H), 8.16 (ddd, J = 7.6, 1.3, 0.8 Hz, 1H), 7.77 (ddd, J = 7.6, 7.6, 1.3, Hz, 1H), 7.21 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 4.94 (dd, J = 10.7, 2.4 Hz, 1H), 4.46 (t, J = 7.3 Hz, 2H), 4.33 (d, J = 7.3 Hz, 1H), 4.26 (d, J = 8.3 Hz, 1H), 3.83 (q, J = 6.8 Hz, 1H), 3.79–3.56 (m, 3H), 3.46 (dd, J = 10.4, 7.4 Hz, 1H), 3.39–3.30 (m, 1H), 3.18–3.02 (m, 3H), 2.62 (s, 3H), 3.65–2.58 (m, 1H), 2.51 (s, 6H), 2.37 (dd, J = 10.4, 9.9 Hz, 1H), 2.11–1.50 (m, 8H), 1.35 (d, J = 6.8 Hz, 3H), 1.32 (d, J = 7.6 Hz, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 1.24 (d, J = 7.6 Hz, 3H), 1.17 (d, J = 7.1 Hz, 3H), 1.02 (d, J = 7.1 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.0, 203.6, 169.9, 157.5, 150.7, 149.6, 148.5, 137.0, 122.9, 122.2, 120.4, 103.6, 82.4, 79.3, 78.3, 78.0, 73.6, 71.3, 70.4, 66.7, 60.6, 51.4, 50.2, 50.1, 47.2, 45.0, 42.9, 41.9, 39.7, 39.3, 28.0, 24.4, 22.5, 19.9, 18.6, 18.06, 15.7, 14.9, 14.8, 14.2, 10.7. MS: Calcd for $C_{42}H_{65}N_6O_{11}$ (M+H): 829.5, found: 829.4.
17. Spectroscopic data for compound **17**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.18 (s, 1H), 8.19–8.15 (m, 1H), 8.10–8.00 (m, 2H), 7.77 (td, J = 7.8, 1.8 Hz, 1H), 7.61–7.55 (m, 1H), 7.49–7.43 (m, 2H), 7.21 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 4.93 (dd, J = 10.6, 2.3 Hz, 1H), 4.68 (dd, J = 11.9, 5.8 Hz, 1H), 4.56 (dd, J = 11.9, 2.5 Hz, 1H), 4.49–4.40 (m, 3H), 4.29 (d, J = 8.1 Hz, 1H), 3.84 (q, J = 6.8 Hz, 1H), 3.76–3.54 (m, 4H), 3.46–3.36 (m, 2H), 3.13–3.04 (m, 2H), 2.58–2.51 (m, 1H), 2.51 (s, 6H), 2.48 (s, 3H), 2.47 (dd, J = 10.1, 10.1 Hz, 1H), 2.03–1.41 (m, 8H), 1.47 (s, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 7.0 Hz, 3H), 1.26 (s, 3H), 1.14 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 7.1 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.82, 203.49, 169.90, 167.05, 157.25, 150.40. 149.34, 148.30, 136.84, 133.46, 129.78, 129.68, 128.55, 122.71, 122.00, 120.21, 103.44, 82.21, 77.93, 77.47, 76.71, 75.77, 70.37, 70.14, 66.24, 63.94, 60.39, 51.19, 49.93, 49.58, 46.87, 44.83, 42.62, 41.70, 39.36, 38.97, 27.70, 24.19, 22.63, 19.65, 18.39, 15.42, 14.65, 14.41, 13.94, 10.43. HRMS (ES): Calcd for $C_{49}H_{69}N_6O_{13}$ (M+H): 949.4917, found: 949.4902.
18. Spectroscopic data for compound **18**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (dd, J = 4.8, 1.8 Hz, 1H), 8.18 (s, 1H), 8.17 (dd, J = 7.6, 1.0 Hz, 1H), 8.08 (dd, J = 8.0, 1.3 Hz, 2H), 7.78 (ddd, J = 7.6, 7.6, 1.8 Hz, 1H), 7.59 (tt, J = 7.3, 1.3 Hz, 1H), 7.47 (dd, J = 8.0, 7.3 Hz, 2H), 7.22 (ddd, J = 7.6, 4.8, 1.0 Hz, 1H), 4.95 (dd, J = 10.5, 2.0 Hz, 1H), 4.47 (t, J = 7.4 Hz, 2H), 4.39 (m, 3H), 4.27 (d, J = 8.3 Hz, 1H), 3.86 (q, J = 6.8 Hz, 1H), 3.78–3.63 (m, 4H), 3.57 (s, 1H), 3.28 (dd, J = 10.0, 7.1 Hz, 1H), 3.19–3.05 (m, 2H), 2.60–2.50 (m, 2H), 2.47 (s, 3H), 2.32 (s, 6H), 2.05–1.52 (m, 10H), 1.49 (s, 3H), 1.36 (d, J = 6.8 Hz, 3H) 1.32 (d, J = 7.3 Hz, 3H), 1.28 (s, 3H), 1.16 (d, J = 6.8 Hz, 3H) 1.02 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.2, 203.8, 169.9, 166.5, 157.5, 150.7, 149.6, 148.6, 137.0, 133.6, 129.9, 129.8, 128.7, 122.9, 122.2, 120.4, 104.2, 82.4, 79.8, 78.2, 77.4, 71.8, 70.5, 66.5, 65.9, 60.6, 51.4, 50.2, 49.7, 47.5, 45.1, 42.8, 40.4, 39.6, 39.2, 27.9, 24.4, 23.1, 22.4, 20.0, 18.6, 15.8, 14.8, 14.5, 14.1, 10.7. MS: Calcd for $C_{49}H_{69}N_6O_{12}$ (M+H): 933.5, found: 933.4.
19. Spectroscopic data for compound **19**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H), 8.17 (s, 1H), 8.16 (ddd, J = 7.8, 1.3, 1.0 Hz, 1H), 7.77 (ddd, J = 7.8, 7.6, 1.8 Hz, 1H), 7.21 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 4.93 (dd, J = 10.6, 2.3 Hz, 1H), 4.46 (t, J = 7.6 Hz, 2H), 4.30 (d, J = 7.3 Hz, 1H), 4.23 (d, J = 8.8 Hz, 1H), 3.84 (q, J = 6.8 Hz, 1H), 3.81–3.53 (m, 3H), 3.57 (s, 1H), 3.31–3.23 (m, 1H), 3.16–3.02 (m, 2H), 2.95–2.90 (m, 1H), 2.78 (s, 1H, –OH), 2.62 (s, 3H), 2.63–2.56 (m, 1H), 2.37 (s, 6H), 2.10–1.50 (m, 10H), 1.47 (s, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.33 (s, 3H), 1.29 (d,

J = 7.6 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H), 1.16 (d, J = 7.1 Hz, 3H), 1.01 (d, J = 7.1 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.6, 203.7, 169.7, 157.3, 150.1, 149.3, 148.3, 136.8, 122.7, 122.0, 120.2, 103.9, 82.2, 79.7, 78.2, 76.7, 70.3, 69.6, 65.9, 60.4, 51.2, 50.0, 49.9, 47.6, 44.9, 42.7, 40.2, 39.6, 39.0, 28.2, 27.7, 24.2, 22.2, 21.2, 19.8, 18.4, 15.8, 14.7, 14.4, 13.9, 10.5. MS: Calcd for $C_{42}H_{65}N_6O_{10}$ (M+H):813.48, found: 813.48.