Articles

Nonpeptide Luteinizing Hormone-Releasing Hormone Antagonists Derived from Erythromycin A: Design, Synthesis, and Biological Activity of Cladinose Replacement Analogues

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The design and synthesis of a series of 11,12-cyclic carbamate derivatives of 6-*O*-methylerythromycin A that are novel, nonpeptide LHRH antagonists, is described. The macrolide antagonist **1**, discovered during a screen of our chemical repository, was compared to a macrocyclic peptide antagonist **2** using molecular modeling, thus providing a model for the design of more potent antagonists. Medicinal chemistry efforts to find a replacement for cladinose at position 3 of the erythronolide core provided a series of oxazolidinone carbamates that were equally as active as the cladinose-containing parent macrolides. The descladinose LHRH antagonist **14** has 1−2 nM affinity for both rat and human LHRH receptors and is a potent inhibitor of LH release ($pA_2 = 8.76$) in vitro. In vivo, **14** was found to produce a dose-dependent suppression of LH in male castrate rats via both iv and po dosing.

Introduction

Luteinizing hormone-releasing hormone (LHRH), secreted from the hypothalamus, binds to the LHRH receptor in the pituitary gland, thereby stimulating the release of gonadotropins, luteinizing hormone, and follicle-stimulating hormone. LHRH antagonists inhibit gonadal functions and are useful for the treatment of endocrine-based conditions such as endometriosis, uterine fibroids, and precocious puberty, as well as several steroid-dependent malignancies, including cancers of the prostate and breast.[1,2] A number of peptidic LHRH antagonists have been reported that are potent inhibitors of gonadal function, several of which have been studied clinically.[2−6] In general, these compounds have presented development problems typical of large peptides, notably poor oral bioavailability resulting in difficult or complex methods of administration, short duration of action, and many have been found to be potent inducers of histamine-release.[2] Peptide LHRH antagonists have been approved as injectable drugs for use in the treatment of female infertility.[3,4] More recently, reports of potent, nonpeptidic antagonists of the LHRH receptor have shown promise for overcoming many of the shortcomings of the peptides, which may result in better success in the clinic.[7,8]

A screen of our chemical repository resulted in the discovery of macrolides derived from 6-*O*-methylerythromycin A that bound to the rat LHRH receptor with submicromolar affinity. The most potent antagonists were 11,12-cyclic carbamate derivatives, having a carbamate side-chain consisting of a 2- or 3-atom chain terminating in an aromatic ring. One of the most active antagonists identified was the anilinoethyl derivative **1**, shown in Figure 1. In an effort to understand the activity of these compounds, we compared the structure of **1** to that of the potent cyclic decapeptide antagonist **2** (Figure 1).[9] We were intrigued by the possibility that the aryl side-chain of the 11,12-cyclic carbamate could be mimicking an aromatic side-chain in the peptide, most likely either the 4-Cl-Phe at position 2 or the Tyr at position 5, and that the 3′-amino group of desosamine

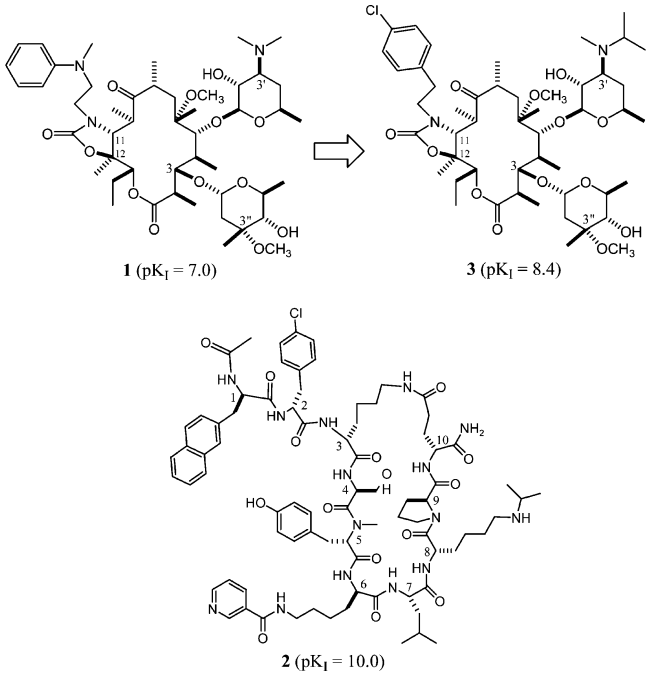

Figure 1. Macrocyclic LHRH antagonists.

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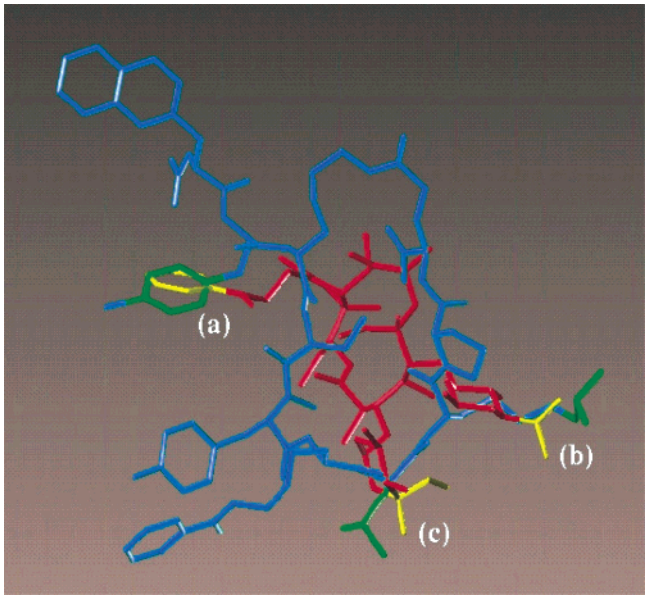
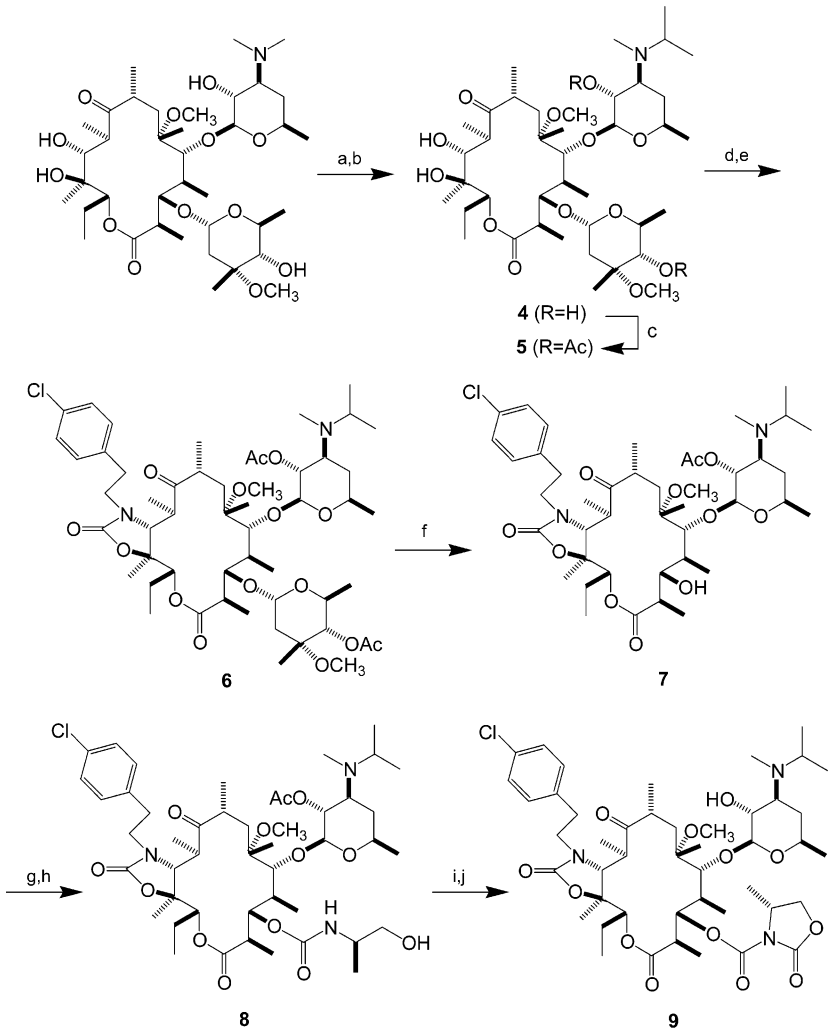


Figure 2. Overlay of **1** (red) and **2** (light blue) showing key points of comparison. Important groups for comparison are highlighted yellow for **1** and green for **2**: (a) overlay of phenyl group of 1 with 4-Cl-Phe of **2**; (b) overlay of dimethylamine of **1** with Isp(Lys) of **2**; (c) overlay of cladinose of **1** with Leu of **2**.

could be mimicking the isopropyl lysine (Isp-Lys) side-chain at position 8. In a molecular modeling comparison, the cyclic carbamate side-chain gave a best fit with the 4-Cl-Phe at position 2. Compound **3** (Figure 1),[10] in which both the cyclic carbamate side-chain as well as the alkyl substituent on the 3′-amine have been modified to match the peptide substituents, demonstrated a 20-fold improvement in activity relative to **1**.

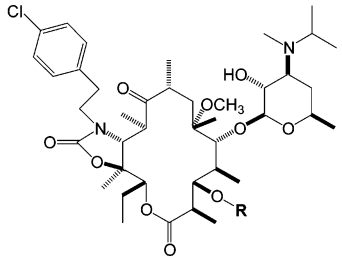
Figure 2 shows an overlay of the X-ray crystal structure of **1** with a model for **2** derived from NMR studies.[11] In addition to the comparison of aromatic side-chains (a) and alkylamine groups (b), a third point of comparison was identified in which position 3″ of cladinose gave a close fit with the Leu side chain at position 7 of the peptide (c). This model suggested an additional site for chemical modification by replacing the cladinose group at position 3 of the erythronolide core of the macrocyclic antagonists. It was hoped that, by replacing cladinose, we might arrive at compounds with improved activity as well as improved pharmacokinetic properties, such as solubility and acid stability,[12,13] which could result in increased bioavailability. Furthermore, it was anticipated that cladinose removal might result in compounds having decreased antibacte-

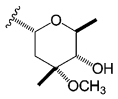
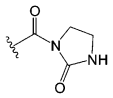
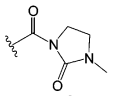
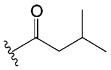
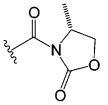
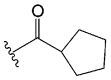
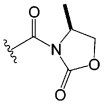
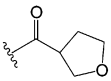
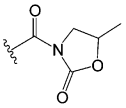
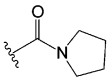
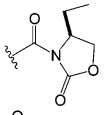
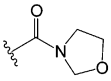
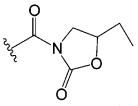
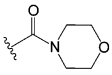
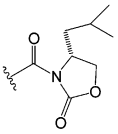
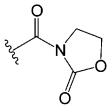
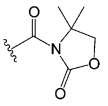
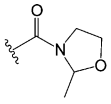
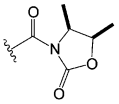
Scheme 1[a]



[a] Reagents: (a) I_2, NaOAc, MeOH; (b) acetone, $NaCNBH_3$, AcOH, MeOH; (c) Ac_2O, TEA, DMAP, CH_2Cl_2; (d) sodium hexamethyldisialazide, 1,1′-carbonyldiimidazole (CDI), THF, DMF; (e) 4-chlorophenethylamine, CH_3CN; (f) HCl, EtOH; (g) CDI, DMAP, CH_2Cl_2; (h) (*R*)-alaninol, THF; (i) CDI, DMAP, TEA, CH_2Cl_2; (j) AcOH, MeOH.

Table 1. Receptor Binding Data for Descladinose Macrolide LHRH Antagonists[a]



compd	R	rat pK_I	human pK_I	compd	R	rat pK_I	human pK_I
3		8.35	7.65	**24**		6.66	5.69
15	H	5.60	~5	**25**		5.91	5.33
16		6.85	5.69	**9**		8.28	7.31
17		7.30	6.20	**26**		8.54	7.73
18		7.85	6.67	**27**		8.10	7.44
19		6.95	5.79	**28**		8.20	7.18
20		7.29	6.70	**29**		7.74	6.25
21		6.37	5.25	**30**		6.16	6.56
22		8.67	6.94	**31**		8.05	7.10
23		6.92	6.10	**32**		8.54	<7

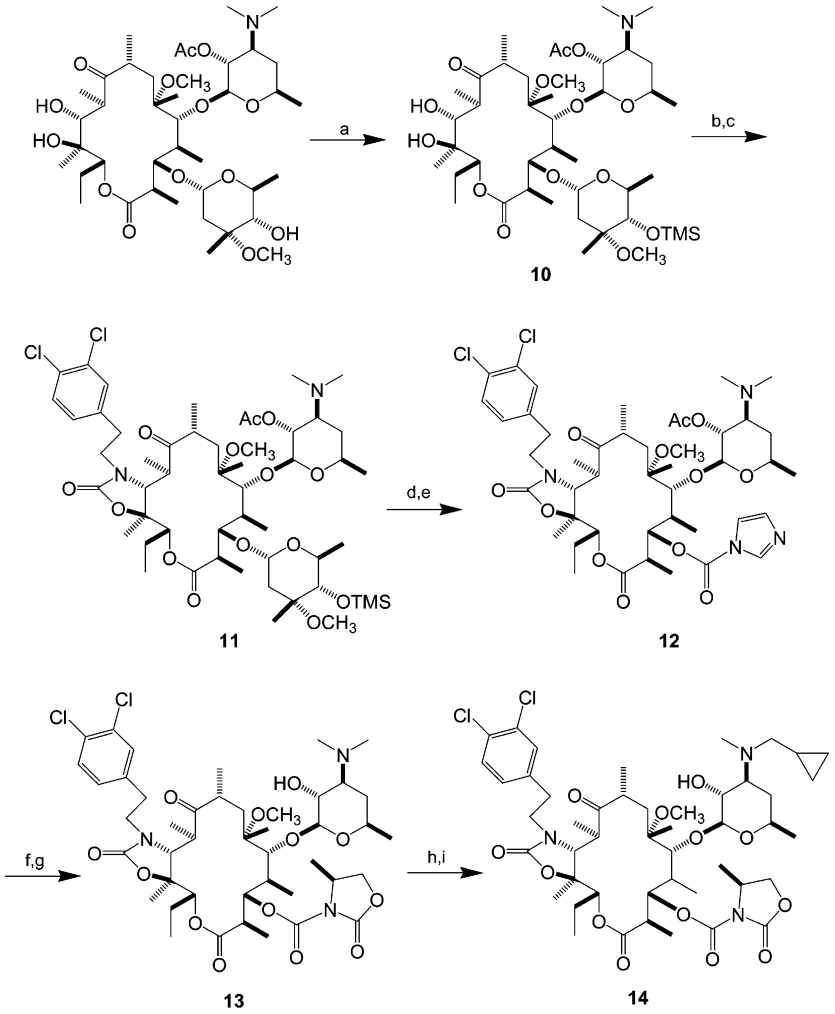
[a] Reported pK_I values are an average of two or more measurements, with standard error ≤ ±0.35 pK_I units.

rial activity,[14] a property of this class of compounds undesirable to our purposes.

Biological Testing. The in vitro receptor-binding assay for LHRH antagonists was conducted using rat and human receptors cloned in CHO cells.[15] The binding affinities for both rat and human LHRH receptors are reported as pK_I values. An in vitro assay for the abilities of test compounds to function as antagonists of LH release was performed using cultured rat pituitary cells, and results are reported as pA_2 values.[16] Compounds tested in vivo for their abilities to affect plasma LH levels in castrate male rats were dosed via either an intravenous bolus or an oral gavage.[15]

Chemical Synthesis. Synthesis of descladinose macrolide LHRH antagonists is accomplished as shown in Scheme 1. The starting material, 6-*O*-methylerythromycin A,[17] is demethylated at the 3′-amino position,[18,19] followed by reductive alkylation with acetone to give the isopropylamino derivative **4**. Selective acetylation of the 2′ and 4″ hydroxyl groups gives diacetate **5**. The known two-step procedure for preparing the 11,12-cyclic carbamate,[20] using 4-chlorophenethylamine, gives **6**. Cladinose removal is effected by hydrolysis with HCl in aqueous EtOH to give **7**, an intermediate useful for preparing all of the descladinose analogues listed in Table 1. Ester derivatives are prepared by acetylation

Scheme 2[a]



[a] Reagents: (a) TMSCl, pyridine, CH_2Cl_2; (b) NaH, CDI, THF, DMF; (c) 3,4-dichlorophenethylamine, CH_3CN; (d) HCl, EtOH; (e) CDI, DMAP, CH_2Cl_2; (f) 4-(*S*)-methyl-oxazolidinone, lithium hexamethyldisialazide, THF, DMF; (g) AcOH, MeOH; (h) I_2, NaOAc, MeOH; (i) cyclopropanecarboxaldehyde, $NaCNBH_3$, AcOH, MeOH.

with an acid anhydride reagent. Alternatively, carbamates are prepared via the acylimidazole intermediate derived by reaction with 1,1′-carbonyldiimidazole (CDI). Thus, reaction of **7** with CDI in the presence of DMAP, followed by (*R*)-alaninol, gives carbamate **8**. Further reaction of the hydroxycarbamate with CDI gives the 4-(*R*)-methyloxazolidinone carbamate, which is deacetylated to give **9**.

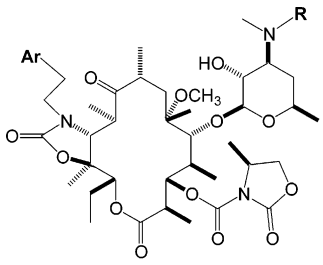
A useful alternative procedure for preparing oxazolidin-2-one carbamates is shown in Scheme 2. Compound **10**, prepared by selective TMS protection of 2′-*O*-acetyl-6-*O*-methylerythromycin A, is converted to dichlorophenethyl 11,12-cyclic carbamate **11**. Hydrolytic removal of the cladinose, followed by reaction with CDI, gives acylimidazole intermediate **12**. Reaction of **12** with the anion generated from 4-(*S*)-methyloxazolidin-2-one[21] using lithium hexamethyldisialazide, followed by deacetylation, gives oxazolidinone carbamate **13**. Demethylation of the 3′-amino group, followed by reductive alkylation with cyclopropanecarboxaldehyde, affords **14**.

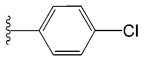
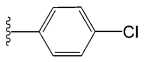
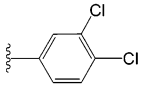
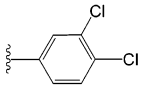
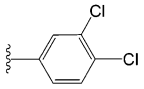
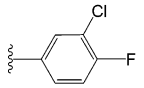
Results and Discussion

A summary of medicinal chemistry efforts to find a replacement for cladinose can be found in Table 1. Removal of cladinose (**15**) resulted in a large (∼3 log) loss in binding to both the rat and human receptors, further supporting our model predicting an important contribution from the cladinose substituent. To probe the SAR at position 3 of the erythronolide core, a series of simple esters was prepared. An isovaleryl group (**16**), designed as a mimic of the Leu side-chain, resulted in modest restoration of activity (∼2 log less active than the parent **3**). However, the more active esters were cycloalkyl carbonyl derivatives, of which the most active was the cyclopentyl derivative **17**. Further improvement in binding affinity was obtained in the tetrahydrofuranyl derivative **18**. This simple 3-*O*-acyl derivative had affinity for both rat and human receptors within 10-fold that of the cladinose parent **3**. Although not shown, several aromatic esters were also prepared (i.e., benzoyl, furanoyl, etc.), and were found to be significantly less active than the corresponding saturated esters.

Encouraged by results in the ester series, a series of carbamates was prepared. Not only were carbamates expected to have improved properties in vivo over their ester counterparts, but this strategy also allowed for a more thorough investigation of the SAR by utilizing the diverse set of commercially available amines. In general, SAR in the carbamate series mirrored closely that of the ester series, such that the most active simple

Table 2. Biological Data for Descladinose Macrolide LHRH Antagonists[a]



compd	Ar	R	rat pK_I	human pK_I	pA_2
26			8.54	7.73	ND
33			8.93	7.42	ND
34			9.63	7.82	7.85
35			9.16	8.24	8.97
14			9.17	8.73	8.76
36			9.97	9.48	9.32

[a] Reported pK_I and pA_2 values are an average of 2 or more measurements, with standard error $\leq \pm 0.35$ pK_I units and $< \pm 0.25$ pA_2 units.

carbamate prepared was the pyrrolidine derivative, **19**. Furthermore, the oxazolidine derivative **20** had 10-fold greater affinity for the human receptor than **19**. As a rule, the carbamates tended to be 2−3-fold less active than the esters, as is evident with these two examples (compare **19** with **17** and **20** with **18**). The importance of the position of the ring oxygen to the receptor affinities of **18** and **20** can be seen by comparing these compounds with the morpholine derivative **21**. This compound, which is 10-fold less active than the oxazolidine analogue **20**, is also significantly less active than the non-oxygen-containing pyrrolidine carbamate **19**.

Replacement of the methylene at position 2 with a carbonyl group, to give **22**, resulted in an oxazolidinone derivative that had much improved affinity for both rat and human receptors. Simply substituting position 2 with a methyl group (**23**) resulted in a loss in receptor binding relative to the unsubstituted oxazolidine derivative **20**. Taken together, these results indicated that the oxazolidinone carbamate, having the carbonyl oxidation state at position 2, was a significant advance for the series. The imidazolidinone derivative **24** was greater than 10-fold less active than oxazolidinone **22**, further establishing the importance of the ring oxygen. Substituting the imidizolidinone nitrogen (**25**) resulted in additional loss in receptor affinity.

In an attempt to further improve the series, the oxazolidinone ring was substituted at positions 4 and 5. It was found that a single methyl group at either position resulted in an improvement in binding to the human receptor (compare compounds **9**, **26**, and **27** to the unsubstituted analogue **22**). Of these, the most active compound was the 4-(*S*)-methyl derivative, **26**, which bound to both the rat and human receptors with equal affinity to the cladinose parent **3**. However, simply increasing the size of the alkyl substituent by a single carbon resulted in a significant loss in binding affinity (compare **28** with **26**, and **29** with **27**). This effect is particularly pronounced in the case of the 5-ethyl derivative **29**, which is much less active than the unsubstituted derivative, **22**. The isobutyl derivative **30** demonstrates the limits of substituent size at position 4. Furthermore, increasing the number of methyl substituents on the oxazolidinone ring also resulted in a loss in binding to the LHRH receptor (compare **31** and **32** with **26**).

Having identified a substituent for position 3 of the erythronolide core that could be used in replacement of cladinose without a loss in binding to the LHRH receptor, further efforts to increase overall receptor affinity were focused on modifying other sites of the molecule. Taking advantage of SAR developed in a series of compounds having cladinose at position 3,[10] it was anticipated that improvements in binding could be made by altering the aryl substituent on the 11,12-cyclic carbamate, and by changing the alkyl substituents on the 3′-amino group of desosamine. A brief summary of results can be found in Table 2. Attempts to optimize the 3′-amine alkyl substituent in the 4-chlorophenethyl cyclic carbamate series resulted in no significant im-

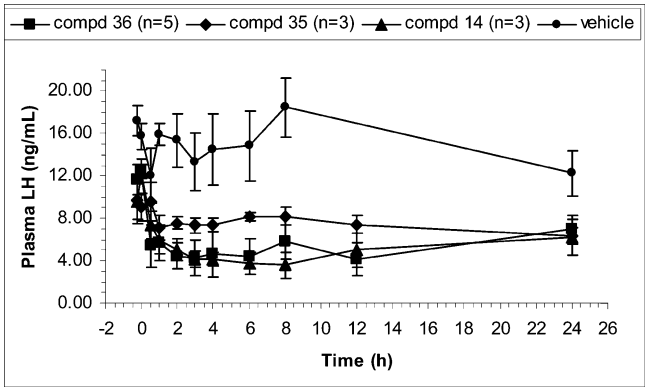


Figure 3. Plasma LH responses (mean ± SEM) to intravenous dosing of LHRH antagonists at 2 mg/kg in castrate male rats.

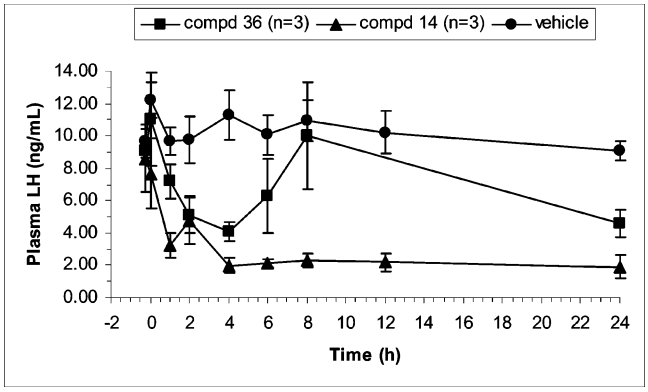


Figure 4. Plasma LH responses (mean ± SEM) to oral dosing of LHRH antagonists at 24 mg/kg in castrate male rats.

provements in binding (for example, see **33**). However, modification of the cyclic carbamate substituent to give the 3,4-dichloro derivative (**34**) resulted in a significant increase in affinity for the rat receptor. Furthermore, in the 3,4-dichlorophenethyl cyclic carbamate series, replacement of the isopropyl substituent of the 3′-amine led to significant improvements in binding to the human receptor (see **35** and **14**). The most active compound in the dichloro series, **14**, has 1−2 nM affinity for both the rat and human LHRH receptors. Finally, replacement of one of the chlorine atoms with a fluorine (see **36**) resulted in a compound with subnanomolar affinity for both rat and human receptors. Table 2 also presents data on the abilities of these compounds to antagonize the agonist-induced release of LH from cultured rat pituitary cells. Results of this functional assay (reported as pA_2 values) are in good agreement with receptor binding data.

Several descladinose macrolide LHRH antagonists were evaluated in vivo for their abilities to suppress LH release in castrated male rats. Compounds **14**, **35**, and **36** were each tested in vivo for their abilities to effect plasma LH levels in castrate male rats via administration of a single 2 mg/kg iv bolus dose (Figure 3). All three compounds caused a significant, sustained lowering of plasma LH levels at this dose, with the *N*-cyclopropylmethyl analogues, **14** and **36**, being somewhat more effective than the *N*-cyclopentyl analogue, **35**. When **14** and **36** were administered to castrate male rats as a 24 mg/kg oral dose (Figure 4), **14** gave a much more profound effect on lowering plasma LH, which was sustained out to 24 h. The oral activity of **14** for LH

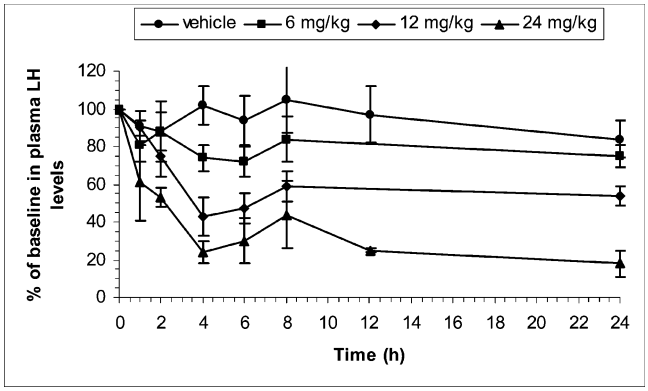


Figure 5. Plasma LH responses (mean ± SEM) to oral dosing of compound **14** in castrate male rats expressed as a percentage of baseline LH levels ($n = 3$ for each dose group).

suppression was also found to be dose dependent (Figure 5). A significant effect on plasma LH was observed with oral administration of **14** in castrate male rats at 12 mg/kg (40% suppression relative to vehicle) and 24 mg/kg (80% suppression relative to vehicle). The LH lowering effect was sustained for up to 24 h with both dosing groups. Compound **14** was found to be the most effective analogue tested in the macrolide LHRH antagonist series, including compounds containing cladinose at the 3-position of the erythronolide core, at lowering plasma LH via oral administration.

The antibacterial activities of macrolide LHRH antagonists was also found to differ somewhat between the cladinose and descladinose series. In general, compounds having a small alkyl substituent on the 3′-amine were found to be significantly less active against most bacterial strains in the descladinose series (for example, **26** was >10-fold less active than **3** against several strains of staphylococci). However, increasing the size of the 3′-amine alkyl substituent (i.e. cyclopropylmethyl or cyclopentyl) greatly reduced the antibacterial activities of both cladinose and descladinose macrolide antagonists, such that there were only marginal differences in antibacterial activities between the two series. Compound **14** was found to be inactive (MIC >100 μg/mL) against all test strains of *S. aureus*, *E. coli*, and *P. aeruginosa* and was >10-fold less active than erythromycin A against all test strains of streptococci and micrococci.[22]

Conclusion

Molecular modeling studies comparing screening lead **1** with cyclic peptide antagonist **2** provided a model that was used to identify sites of the nonpeptide LHRH antagonist for structural modification, including the cladinose at position 3 of the erythronolide core. Medicinal chemistry efforts to find a replacement group for cladinose resulted in the identification of a 5-(*S*)-methyloxazolidin-2-one carbamate group that could be used to substitute position 3 of the erythronolide core, resulting in a novel class of potent LHRH antagonists. These compounds are synthesized in a straightforward manner starting with the known 11,12-cyclic carbamates of 6-*O*-methylerythromycin A. Optimization of the descladinose macrolide LHRH antagonist series gave **14**, which binds to both rat and human LHRH receptors with ∼1 nM affinity and is a potent inhibitor of LH release, in vitro. In vivo, compound **14** demonstrated

dose-dependent suppression of LH in castrated male rats via both iv and po dosing. The oral activity of **14** provided an advantage for this descladinose macrolide over cladinose-containing macrolide LHRH antagonists, which did not significantly effect plasma LH levels in rats when administered orally.

Experimental Section

General Procedures. Molecular modeling studies were performed on a Silicon Graphics Octane UNIX computer using the Sybyl[23] molecular modeling software. Melting points were measured with an oil bath melting point apparatus and are uncorrected. IR spectra were obtained using either a Nicolet 5SXC FT-IR (KBr) or a Nicolet 750 FT-IR (microscope) spectrometer. ^{1}H NMR spectra were recorded at 300 MHz using a Bruker ARX 300 NMR spectrometer or at 500 MHz using a Varian UNITY 500 NMR spectrometer. ^{13}C NMR spectra were recorded at 75 MHz using a Bruker ARX 300 NMR spectrometer or at 125 MHz using a Varian UNITY 500 NMR spectrometer. Chemical shifts are in ppm (δ) relative to TMS. Mass spectra were recorded using either a Finnigan Navigator AQA (APCI), Finnigan SSQ7000 (ESI), or JEOL JMS−SX102A-Hybrid (FAB) mass spectrometer. Combustion analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Thin-layer chromatography (TLC) was performed using E. Merck SG-60F plates. Flash chromatography was performed on silica gel 60 (230−400 mesh) from E. Merck. Solvents (including anhydrous) and reagents were used as supplied by commercial sources. 4-(*S*)-methyloxazolidin-2-one was prepared by the literature procedure.[21]

3′-*N*-Desmethyl-3′-*N*-isopropyl-6-*O*-methylerythromycin A (4). To a solution of 6-*O*-methylerythromycin A (40.0 g, 53.5 mmol) in MeOH (120 mL) were added $NaOAc{\cdot}3H_2O$ (36.4 g, 267.5 mmol) and I_2 (13.7 g, 54.0 mmol). The dark colored reaction mixture was heated to reflux with stirring for 4 h, after which time the solution was colorless. More I_2 (2.7 g, 10.6 mmol) was added, and reflux was continued an additional 4 h until TLC (90:10:1 $CHCl_3$:MeOH:NH_4OH) indicated the reaction was complete. The mixture was concentrated to ca. 20 mL, diluted with $CHCl_3$ (500 mL), washed with 0.2 M $Na_2S_2O_3$ (2 × 500 mL) and brine (500 mL), and dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product as an amorphous solid. To a solution of this compound in MeOH (500 mL) and acetone (100 mL) were added AcOH (3.1 mL, 54.2 mmol) and $NaCNBH_3$ (6.8 g, 108.2 mmol), and the reaction mixture was stirred at room temperature 2 days, after which time TLC (90:10:1 $CHCl_3$:MeOH:NH_4OH) indicated the reaction was complete. The mixture was concentrated and partitioned between H_2O (500 mL) and $CHCl_3$ (3 × 400 mL), and the combined organics were dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product that was crystallized from aq CH_3CN to give **4** as large colorless prisms (21.2 g). The filtrate was concentrated and purified by column chromatography on silica gel (97:3 $CHCl_3$:MeOH) to give additional **4** as a colorless, crystalline solid (14.5 g, total yield = 35.7 g, 86%): mp = 200−203 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.9, 175.8, 102.9, 96.1, 80.8, 78.5, 78.0, 76.7, 74.3, 72.7, 70.5, 69.1, 68.8, 65.8, 62.9, 52.6, 50.6, 49.5, 45.3, 45.1, 39.4, 39.3, 37.3, 35.0, 33.2, 30.8, 21.5, 21.1, 20.5, 19.8, 18.7, 18.0, 16.0, 12.3, 10.6, 9.0; MS (CI) *m*/*z* 776 $(M + H)^+$.

2′,4″-Di-*O*-acetyl-3′-*N*-desmethyl-3′-*N*-isopropyl-6-*O*-methylerythromycin A (5). To a solution of **4** (32.12 g, 41.39 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C under dry N_2 were added triethylamine (14.0 mL, 100.44 mmol), Ac_2O (9.00 mL, 95.39 mmol), and DMAP (0.10 g, 0.82 mmol). The reaction mixture was allowed to warm to room temperature and stir for 20 h, after which time TLC (9:1 $CHCl_3$:MeOH) indicated the reaction was complete. The mixture was partitioned between 0.5 M NaH_2PO_4 (300 mL) and $CHCl_3$ (3 × 300 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product that was crystallized from CH_3CN to give **5** as small colorless needles (24.9 g). The filtrate was concentrated and purified by column chromatography on silica gel (1:2 EtOAc:hexanes) to give additional **5** as a colorless, crystalline solid (5.7 g, total yield = 30.6 g, 86%): mp = 230−231 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.1, 175.5, 170.3, 169.8, 100.0, 95.8, 80.4, 78.6, 78.3, 77.8, 76.6, 74.2, 72.7, 71.8, 69.1, 67.3, 63.1, 59.1, 53.1, 50.5, 49.3, 45.3, 44.9, 38.7, 38.6, 37.2, 35.2, 34.9, 31.6, 21.6, 21.3, 21.2, 21.1, 20.8, 20.6, 19.7, 18.3, 18.0, 16.1, 16.0, 14.2, 12.3, 10.6, 9.0; MS (APCI) *m*/*z* 860 $(M + H)^+$.

2′,4″-Di-*O*-acetyl-11-deoxy-11-[carboxy(4-chlorophenethyl)amino]-3′-*N*-desmethyl-3′-*N*-isopropyl-6-*O*-methylerythromycin A 11,12-(cyclic carbamate) (6). To a solution of **5** (27.87 g, 32.40 mmol) in anhydrous THF (300 mL) at −40 °C under dry N_2 was added a solution of sodium bis(trimethylsilyl)amide (1.0 M in THF, 35.0 mL). The resulting solution was stirred at −40 °C 2 h, after which time a solution of 1,1′-carbonyldiimidazole (18.40 g, 113.5 mmol) in anhydrous 2:3 DMF:THF (200 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stir 16 h, after which time TLC (9:1 $CHCl_3$:MeOH) indicated the reaction was complete. The mixture was poured into 0.5 M NaH_2PO_4 (500 mL) and extracted with EtOAc (3 × 400 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give an amorphous solid. To a solution of this compound in CH_3CN (30 mL) was added 4-chlorophenethylamine (14.0 mL, 100.0 mmol), and the reaction mixture was stirred at room temperature for 18 h, after which time TLC (9:1 $CHCl_3$:MeOH) indicated the reaction was complete. The mixture was poured into 0.5 M NaH_2PO_4 (500 mL) and extracted with EtOAc (3 × 300 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product that was crystallized from $CHCl_3$/hexanes to give **6** as large, colorless prisms (21.15 g). The filtrate was concentrated and purified by column chromatography on silica gel (1:1 EtOAc:hexanes) to give additional **6** as a colorless, crystalline solid (3.20 g, total yield = 24.35 g, 73%): mp = 135−142 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 176.0, 170.3, 169.7, 157.2, 137.4, 131.9, 130.3, 128.5, 100.2, 95.9, 82.7, 79.8, 78.8, 78.6, 77.4, 76.3, 72.7, 71.9, 67.4, 63.2, 60.4, 59.1, 53.2, 50.6, 49.3, 45.6, 45.1, 45.0, 39.0, 38.5, 35.2, 34.9, 32.8, 31.5, 22.0, 21.6, 21.3, 21.2, 20.8, 20.6, 20.1, 18.9, 18.3, 16.0, 14.4, 14.2, 10.2, 8.9; MS (APCI) *m*/*z* 1023 $(M + H)^+$.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(2′-*O*-acetyl-3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (7). A solution of **6** (23.25 g, 22.7 mmol) in 1:1 N HCl:EtOH (800 mL) was stirred at room temperature 4 days, after which time TLC (9:1 $CHCl_3$:MeOH) indicated the reaction was complete. NaOH (2 N) was carefully added to adjust to pH 4, and the resulting solution was extracted with $CHCl_3$ (3 × 400 mL). The combined organic layers were dried over Na_2SO_4 and then filtered and concentrated to give a crude product which was purified by column chromatography on silica gel (1:1 EtOAc:hexanes) to give **7** as a colorless, amorphous solid (15.9 g, 85%): ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 175.1, 169.8, 157.1, 137.3, 131.9, 130.3, 128.5, 100.2, 82.8, 80.9, 78.5, 77.6, 76.3, 71.5, 69.0, 60.7, 59.5, 53.1, 49.9, 45.8, 45.0, 44.2, 38.9, 38.4, 35.9, 34.9, 32.8, 31.3, 22.2, 21.3, 21.2, 21.0, 20.7, 19.4, 18.9, 15.2, 14.3, 10.1, 7.7; MS (FAB) *m*/*z* 823 $(M + H)^+$.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-3-*O*-[2-(*R*)-amino-1-propanol]carbamoyl-5-*O*-(2′-*O*-acetyl-3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (8). To a solution of **7** (5.00 g, 6.07 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C under dry N_2 were added 1,1′-carbonyldiimidazole (2.00 g, 12.33 mmol) and 4-(dimethylamino)pyridine (0.75 g, 6.14 mmol). The reaction mixture was allowed to warm to room temperature and stir 3 days, after which time TLC (9:1 $CHCl_3$:MeOH) indicated the reaction was complete. The mixture was partitioned between 0.5 M NaH_2PO_4 (200 mL) and $CHCl_3$ (3 × 150 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product which was purified

by column chromatography on silica gel (3:1 EtOAc:hexanes) to give the 3-*O*-acylimidazole derivative of **7** as a colorless, amorphous solid (4.64 g, 83%). To a solution of this compound (1.00 g, 1.09 mmol) in anhydrous THF (2 mL) was added D-alaninol (0.2 mL, 25.7 mmol). The reaction mixture was stirred at room temperature for 2 days, after which time TLC (9:1 $CHCl_3$:MeOH) indicated the reaction was complete. The mixture was partitioned between saturated aq NH_4Cl (100 mL) and $CHCl_3$ (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product which was purified by column chromatography on silica gel (97:3 $CHCl_3$:MeOH) to give **8** as a colorless, amorphous solid (0.64 g, 63%): ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.7, 174.2, 169.7, 157.1, 156.5, 137.3, 131.9, 130.3, 128.5, 100.7, 82.8, 79.6, 78.4, 78.1, 76.5, 71.5, 69.2, 66.7, 60.6, 59.8, 53.0, 50.2, 48.9, 45.7, 45.0, 43.3, 38.9, 38.3, 35.6, 34.8, 32.7, 31.4, 22.1, 21.3, 21.1, 20.6, 19.4, 19.0, 17.3, 14.8, 14.3 (2C), 10.1, 8.7; MS (APCI) *m/z* 924 $(M + H)^+$.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-[4-(*R*)-methyl-oxazolidin-2-one-3-yl]carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (9). To a solution of **8** (270 mg, 0.29 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C under dry N_2 were added 1,1′-carbonyldiimidazole (100 mg, 0.62 mmol) and DMAP (36 mg, 0.29 mmol). The reaction mixture was allowed to warm to room temperature and stir 8 h, after which time TLC (9:1 $CHCl_3$:MeOH) indicated complete conversion to a less polar product. Triethylamine (0.20 mL, 1.43 mmol) was added, and the reaction flask was sealed and warmed to 40 °C with stirring for 2 days, after which time TLC (9:1 $CHCl_3$:MeOH) indicated the reaction was complete. The mixture was partitioned between saturated aq NH_4Cl (40 mL) and $CHCl_3$ (3 × 30 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product which was purified by column chromatography on silica gel (1:1 EtOAc:hexanes) to give the 2′-*O*-acetate of **9** as a colorless, amorphous solid (205 mg, 74%). A solution of this compound (180 mg, 0.19 mmol) in MeOH (5 mL) and AcOH (10 μL) was stirred at room temperature 16 h, after which time TLC (9:1 $CHCl_3$:MeOH) indicated the reaction was complete. The solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel (97:3 $CHCl_3$:MeOH) to give **9** as a colorless, amorphous solid (165 mg, 96%): IR (microscope) υ 3475, 2980, 1825, 1760, 1735, 1715, 1460, 1385, 1355, 1280, 1235, 1170, 1105, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.21 (m, 4H), 5.13 (d, J = 10.8 Hz, 1H), 5.01 (dd, J = 11.1, 2.6 Hz, 1H), 4.61−4.51 (m, 1H), 4.38 (ψt, J = 8.3 Hz, 1H), 4.05 (d, J = 7.1 Hz, 1H), 3.97 (dd, J = 8.7, 4.3 Hz, 1H), 3.88−3.75 (m, 4H), 3.43−3.35 (m, 1H), 3.17−2.83 (m, 9H), 2.65−2.53 (m, 1H), 2.53−2.42 (m, 1H), 2.26−2.14 (m, 4H), 1.90 (m, J = 7.6, 2.5 Hz, 1H), 1.79−1.48 (m, 5H), 1.47 (d, J = 6.1 Hz, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.27−1.10 (m, 15H), 1.10−1.01 (m, 6H), 0.81 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.7, 173.8, 157.0, 150.8, 137.1, 131.8, 130.3, 128.5, 104.3, 82.7, 82.4, 81.2, 78.5, 76.9, 70.0, 69.6, 68.5, 64.0, 60.7, 52.7, 51.1, 50.1, 45.6, 45.0, 43.1, 38.9, 38.7, 36.3, 32.8 (2C), 30.9, 22.1, 21.2, 20.8, 20.0, 19.6, 18.9, 15.3, 14.3 (2C), 10.1, 9.0; MS (FAB) *m/z* 908 $(M + H)^+$; Anal. ($C_{46}H_{70}ClN_3O_{13}\cdot H_2O$) C, H, N.

2′-*O*-Acetyl-4″-*O*-trimethylsilyl-6-*O*-methylerythromycin A (10). To a solution of 2′-*O*-acetyl-6-*O*-methylerythromycin A (45 g, 57 mmol) in anhydrous CH_2Cl_2 (450 mL) at 0 °C under a drying tube was added pyridine (13.8 mL, 171 mmol), followed by the dropwise addition of chlorotrimethylsilane (14.5 mL, 114 mmol) over 15 min. The reaction mixture was stirred at 0 °C for 1 h, after which time TLC (9:1 CH_2Cl_2:MeOH) indicated the reaction was complete. The mixture was washed with 0.5 M NaH_2PO_4 (500 mL), H_2O (300 mL), saturated aq $NaHCO_3$ (300 mL), H_2O (300 mL), and brine (100 mL) and dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product that was crystallized from CH_3CN to give **10** as colorless crystals (48 g, 98%): mp = 235−237 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.0, 175.6, 169.9, 100.0, 96.0, 80.5, 80.3, 78.3, 77.8, 76.4, 74.1, 73.2, 72.0, 69.0, 67.1, 65.2, 62.7, 50.3, 49.4, 45.1, 44.9, 40.5, 38.7, 38.6, 37.1, 35.6, 30.9, 22.1, 21.5, 21.4, 20.9, 19.7, 19.2, 17.8, 15.9, 15.8, 12.1, 10.4, 8.9, 0.8; MS (ESI) *m/z* 862 $(M + H)^+$.

2′-*O*-Acetyl-4″-*O*-trimethylsilyl-11-deoxy-11-[carboxy-(3,4-dichlorophenethyl)amino]-6-*O*-methylerythromycin A 11,12-(cyclic carbamate) (11). To a solution of **10** (20.40 g, 24.2 mmol) in anhydrous THF (20 mL) and anhydrous DMF (200 mL) at 0 °C under dry N_2 was added 1,1′-carbonyldiimidazole (19.6 g, 120.9 mmol), followed by the portionwise (∼0.2 g each) addition of NaH (60% suspension in mineral oil, 1.16 g, 29.0 mmol). The reaction mixture was allowed to warm to room temperature and stir 1 h, after which time TLC (17:3 EtOAc:*i*-PrOH indicated the reaction was complete. The reaction was carefully quenched with H_2O and partitioned between H_2O (500 mL) and EtOAc (3 × 300 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give the crude acylimidazolide. To a solution of this compound (10.00 g, 10.7 mmol) in CH_3CN (30 mL) was added 3,4-dichlorophenethylamine (8.00 g, 42.1 mmol), and the reaction mixture was stirred at room temperature for 72 h, during which time the product slowly precipitated. TLC (17:3 EtOAc:*i*-PrOH) indicated only a trace of unreacted compound remained. The solvent was removed in vacuo, the residue was partitioned between H_2O (200 mL) and EtOAc (3 × 200 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product that was crystallized from hot CH_3CN to give **11** as colorless crystals (6.5 g). The filtrate was concentrated and purified by column chromatography on silica gel (23:2 EtOAc:*i*-PrOH) to give additional **11** as a colorless, crystalline solid (3.7 g, total yield = 10.2 g, 90%): mp = 169−173 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.4, 176.3, 170.0, 157.2, 139.3, 132.2, 131.0, 130.2, 130.1, 128.4, 100.1, 96.3, 82.8, 80.6, 79.8, 78.9, 76.2, 73.2, 71.8, 67.3, 65.3, 62.8, 60.3, 50.5, 49.6, 45.5, 45.3, 44.8, 40.6, 39.0, 38.7, 38.5, 35.7, 32.6, 31.1, 22.2, 21.9, 21.6, 20.2, 19.3, 18.8, 16.1, 14.3, 14.1, 10.2, 9.1, 0.9; MS (ESI) *m/z* 1059 $(M + H)^+$.

11-Deoxy-11-[carboxy(3,4-dichlorophenethyl)amino]-3-*O*-(imidazole)carbamoyl-5-*O*-(2′-O-acetyl)desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (12). A solution of **11** (9.40 g, 8.87 mmol) in 1:1 N HCl:EtOH (600 mL) was stirred at room temperature 16 h, after which time TLC (19:1 $CHCl_3$:MeOH) indicated the reaction was complete. NaOH (2 N) was carefully added to adjust to pH 5, and the resulting solution was extracted with $CHCl_3$ (3 × 300 mL). The combined organic layers were dried over Na_2SO_4 and then filtered and concentrated to give a crude product which was purified by column chromatography on silica gel (19:1 $CHCl_3$:MeOH) to give a colorless, amorphous solid (6.97 g, 95%). To a solution of this compound in anhydrous CH_2Cl_2 (50 mL) under dry N_2 were added 1,1′-carbonyldiimidazole (2.00 g, 12.33 mmol) and DMAP (0.75 g, 6.14 mmol). The reaction mixture was stirred at room temperature 3 days, after which time TLC (9:1 $CHCl_3$:MeOH) indicated the reaction was complete. The mixture was partitioned between 0.5 M NaH_2PO_4 (200 mL) and $CHCl_3$ (3 × 200 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product which was purified by column chromatography on silica gel (9:1 $CHCl_3$:*i*-PrOH) to give **12** as a colorless, amorphous solid (7.00 g, 85% from **11**): ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.5, 173.5, 169.6, 157.0, 148.6, 139.1, 136.9, 132.3, 131.4, 131.0, 130.3, 128.3, 116.9, 100.3, 82.7, 82.6, 78.5, 78.0, 77.2, 71.2, 69.3, 63.1, 60.8, 50.3, 45.7, 44.9, 42.7, 40.5, 39.0, 38.2, 36.1, 32.6, 30.4, 22.0, 21.3, 20.9, 19.3, 18.9, 14.9, 14.3, 10.1, 8.7; MS (APCI) *m/z* 923 $(M + H)^+$.

11-Deoxy-11-[carboxy(3,4-dichlorophenethyl)amino]-3-*O*-[4-(*S*)-methyloxazolidin-2-one-3-yl]carbamoyl-5-*O*-desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (13). To a solution of **12** (1.00 g, 1.08 mmol) and 4-(*S*)-

methyl-oxazolidin-2-one[21] (0.33 g, 3.25 mmol) in anhydrous THF (20 mL) at −78 °C under dry N_2 was added a solution of lithium bis(trimethylsilyl)amide (1.0 M in hexanes, 1.10 mL), dropwise. The mixture was stirred at −78 °C 30 min, and then anhydrous DMF (10 mL) was slowly added over ca. 5 min. The reaction mixture was allowed to warm to −40 °C and stir 8 h, after which time TLC (1:1 $CHCl_3$:acetone) indicated the reaction was complete. The reaction was quenched cold with saturated aq NH_4Cl (2 mL) and partitioned between H_2O (100 mL) and EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and then filtered and concentrated to give a crude product which was purified by column chromatography on silica gel (7:3 $CHCl_3$:acetone) to give the 2′-*O*-acetate of **13** as a colorless, amorphous solid (0.77 g, 74%). This compound was dissolved in MeOH (20 mL) and AcOH (75 μL) and stirred at room temperature 24 h, after which time TLC (4:1 CH_2Cl_2:*i*-PrOH) indicated the reaction was complete. The solvent was removed in vacuo to give a crude product which was purified by column chromatography on silica gel (9:1 CH_2Cl_2:*i*-PrOH) to give **13** as a colorless, amorphous solid (0.69 g, 70% from **12**): ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 174.1, 157.1, 151.4, 151.1, 139.2, 132.2, 131.0, 130.3, 130.2, 128.4, 103.0, 82.8, 81.3, 79.5, 78.6, 76.8, 70.5, 69.7, 68.6, 65.8, 60.7, 51.5, 50.3, 45.7, 44.9, 42.9, 40.3, 38.9, 38.6, 36.4, 32.6, 28.7, 22.0, 21.2, 19.6, 19.5, 18.9, 15.0, 14.3, 14.2, 10.1, 8.8; MS (APCI) *m/z* 914 $(M + H)^+$; Anal. ($C_{44}H_{65}Cl_2N_3O_{13}$) C, H, N.

11-Deoxy-11-[carboxy(3,4-dichlorophenethyl)amino]-3-*O*-[4-(*S*)-methyloxazolidin-2-one-3-yl]carbamoyl-5-*O*-(3′-*N*-desmethyl-3′-*N*-cyclopropylmethyl)desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (14). To a solution of **13** (1.00 g, 1.10 mmol) in *i*-PrOH (50 mL) were added I_2 (0.31 g, 1.20 mmol) and $NaOAc·3H_2O$ (0.75 g, 5.51 mmol). The reaction vessel was equipped with a reflux condenser, and the dark colored mixture was stirred under a 500 W lamp 1 h, after which time the dark color was dissipated and TLC (9:1 $CHCl_3$:MeOH) indicated the reaction was complete. The cooled mixture was partitioned between 0.5 M $Na_2S_2O_3$ (100 mL) and $CHCl_3$ (3 × 100 mL), and the combined organic layers were washed with H_2O (100 mL) and brine (100 mL) and dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product which was precipitated from Et_2O to give the 3′-*N*-desmethyl derivative of **13** as an off white powder (0.95 g, 96%). To a solution of this compound (202 mg, 224 μmol) in *i*-PrOH (7 mL) were added cyclopropanecarboxaldehyde (0.17 mL, 2.24 mmol), AcOH (25 μL), and $NaCNBH_3$ (28 mg, 448 μmol). The reaction mixture was stirred at room temperature 16 h, after which time TLC (9:1 EtOAc:MeOH) indicated the reaction was complete. The mixture was diluted with EtOAc (100 mL) and washed with saturated NH_4Cl (50 mL), saturated aq $NaHCO_3$ (2 × 50 mL), H_2O (2 × 50 mL), and brine, and the organic phase was dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product which was purified by column chromatography on silica gel (EtOAc) to give **14** as a colorless, amorphous solid (140 mg, 66%): IR (microscope) *υ* 3445, 2980, 2945, 1825, 1800, 1760, 1740, 1460, 1380, 1350, 1310, 1235, 1170, 1110, 1070, 1055 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.1 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.19 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.09 (d, *J* = 11.2 Hz, 1H), 4.97 (dd, *J* = 10.8, 2.4 Hz, 1H), 4.45−4.35 (m, 2H), 4.15 (d, *J* = 7.2 Hz, 1H), 4.04−3.96 (m, 1H), 3.90−3.79 (m, 3H), 3.74 (s, 1H), 3.37−3.25 (m, 1H), 3.24−2.83 (m, 9H), 2.67−2.55 (m, 2H), 2.48−2.35 (m, 1H), 2.33 (br s, 3H), 2.26−2.18 (m, 1H), 1.95−1.87 (m, 1H), 1.79−1.52 (m, 6H), 1.51 (d, *J* = 6.4 Hz, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.27−1.11 (m, 15H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H), 0.63−0.44 (m, 2H), 0.20−0.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 174.1, 157.1, 151.4, 151.2, 139.2, 132.2, 131.0, 130.3, 130.2, 128.4, 102.9, 82.8, 81.2, 79.1, 78.5, 76.8, 70.1, 69.7, 68.6, 64.4, 60.6, 58.5, 51.5, 50.3, 45.7, 44.9, 42.9, 38.9, 38.5, 36.9, 36.4, 32.6, 29.3, 22.0, 21.2, 19.7, 19.6, 18.9, 15.1, 14.3, 14.2, 10.1, 8.9, 4.4, 3.6; MS (APCI) *m/z* 954 $(M + H)^+$; Anal. ($C_{47}H_{69}Cl_2N_3O_{13}$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (15). This compound was prepared by stirring a solution of **7** (50 mg, 0.06 mmol) in MeOH (2 mL) for 16 h. Concentration in vacuo gave **15** as a colorless solid: IR (KBr) *υ* 3440, 2970, 2940, 1760, 1735, 1710, 1455, 1420, 1380, 1230, 1165, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.20 (m, 4H), 5.03 (dd, *J* = 10.9, 2.7 Hz, 1H), 4.40 (d, *J* = 7.5 Hz, 1H), 3.97 (br s, 1H), 3.92−3.71 (m, 4H), 3.64−3.53 (m, 2H), 3.23 (dd, *J* = 10.2, 7.5 Hz, 1H), 3.17−3.07 (m, 1H), 3.02 (s, 3H), 3.02−2.84 (m, 3H), 2.80−2.59 (m, 2H), 2.20 (s, 3H), 2.12−2.02 (m, 1H), 1.98−1.78 (m, 2H), 1.73−1.47 (m, 4H), 1.46 (s, 3H), 1.41 (s, 3H), 1.34−1.26 (m, 6H), 1.19−1.13 (m, 6H), 1.11−1.03 (m, 9H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.6, 175.6, 157.1, 137.2, 132.0, 130.3, 128.5, 107.2, 88.3, 82.9, 78.8, 78.7, 76.3, 70.5 (2C), 62.7, 60.9, 53.3, 49.7, 45.5, 44.9, 44.7, 39.2, 38.4, 36.2, 32.8 (2C), 30.5, 22.2, 21.3, 20.8, 20.6, 18.9, 18.5, 15.2, 14.3, 14.1, 10.1, 8.3; MS (DCI) *m/z* 781 $(M + H)^+$; Anal. ($C_{41}H_{65}ClN_2O_{10}·H_2O$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-(isovaleroyl)-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (16). This compound was prepared following the procedure described for **18**, substituting isovaleric acid for tetrahydro-3-furoic acid, to give **16** as a colorless amorphous solid: IR (KBr) *υ* 3450, 2970, 1760, 1740, 1710, 1455, 1420, 1375, 1230, 1165, 1060 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.20 (m, 4H), 5.07 (d, *J* = 11.0 Hz, 1H), 5.00 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.98 (d, *J* = 7.0 Hz, 1H), 3.90−3.77 (m, 2H), 3.78 (s, 1H), 3.72 (d, *J* = 4.1 Hz, 1H), 3.44−3.32 (m, 1H), 3.18−3.07 (m, 2H), 3.08 (s, 3H), 3.07−2.83 (m, 4H), 2.67−2.46 (m, 2H), 2.38−2.08 (m, 6H), 1.99−1.82 (m, 1H), 1.80−1.47 (m, 4H), 1.43 (s, 3H), 1.32 (s, 3H), 1.30−0.98 (m, 28H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 174.4, 172.7, 157.1, 137.3, 131.9, 130.3, 128.5, 103.7, 82.8, 81.1, 78.5, 77.1, 69.9, 69.7, 63.1, 60.6, 52.7, 50.2, 45.7, 45.0, 43.6, 43.0, 38.9, 38.6, 36.4, 33.0, 32.8, 30.9, 25.2, 22.7, 22.1, 21.2, 21.1, 20.4, 19.6, 18.9, 15.3, 14.3 (2C), 10.1, 8.9; MS (FAB) *m/z* 865 $(M + H)^+$; Anal. ($C_{46}H_{73}ClN_2O_{11}$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-(cyclopentylcarbonyl)-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (17). This compound was prepared following the procedure described for **18**, substituting cyclopentylcarboxylic acid for tetrahydro-3-furoic acid, to give **17** as a colorless, amorphous solid: IR (KBr)*υ* 3440, 2970, 1760, 1735, 1710, 1460, 1420, 1380, 1230, 1170, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.22 (m, 4H), 5.05 (d, *J* = 11.0 Hz, 1H), 5.00 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.99 (d, *J* = 7.3 Hz, 1H), 3.90−3.77 (m, 2H), 3.75 (d, *J* = 4.1 Hz, 1H), 3.45−3.32 (m, 1H), 3.18−3.07 (m, 2H), 3.08 (s, 3H), 3.06−2.75 (m, 5H), 2.72−2.50 (m, 2H), 2.27−2.10 (m, 4H), 2.08−1.47 (m, 13H), 1.43 (s, 3H), 1.32 (s, 3H), 1.32−1.02 (m, 24H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 176.3, 174.4, 157.1, 137.3, 131.9, 130.3, 128.5, 103.4, 82.8, 80.9, 78.5, 77.1, 69.9, 69.5, 63.0, 60.6, 52.8, 50.2, 45.7, 45.0, 44.3, 43.2, 38.9, 38.6, 36.5, 33.0, 32.8, 31.0, 29.6, 27.1, 25.8, 25.6, 22.1, 21.2, 21.0, 20.3, 19.6, 18.9, 15.2, 14.3 (2C), 10.1, 8.9; MS (ESI) *m/z* 877 $(M + H)^+$; Anal. ($C_{47}H_{73}ClN_2O_{11}·0.5H_2O$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-(tetrahydro-3-furoyl)-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (18). To a solution of tetrahydro-3-furoic acid (0.12 mL, 1.25 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C under dry N_2 were added trimethylacetyl chloride (0.16 mL, 1.30 mmol) and triethylamine (0.18 mL, 1.30 mmol), and the resulting solution was stirred at 0 °C 1 h. This mixture was transferred via cannula to a flask containing a solution of **7** (250 mg, 0.30 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C under dry N_2. The reaction mixture was allowed to warm to room temperature and stir 16 h, after which time TLC (19:1 $CHCl_3$:MeOH) indicated the reaction was complete. The mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated aq NH_4-

Cl (20 mL), saturated aq $NaHCO_3$ (20 mL), and brine (20 mL), and dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product which was purified by column chromatography on silica gel (98:2 $CHCl_3$:MeOH) to give a colorless, amorphous solid. A solution of this compound (233 mg, 0.25 mmol) in MeOH (10 mL) was stirred at room temperature 16 h, after which time TLC (9:1 $CHCl_3$:MeOH) indicated the reaction was complete. The solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel (97:3 $CHCl_3$:MeOH) to give **18** as a colorless, amorphous solid (110 mg, 50%): IR (KBr) υ 3445, 2980, 1760, 1740, 1715, 1460, 1380, 1235, 1170, 1105, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.22 (m, 4H), 5.07 (d, J = 11.0 Hz, 1H), 5.00 (dd, J = 11.0, 2.2 Hz, 1H), 4.04−3.73 (m, 8H), 3.45−3.34 (m, 1H), 3.24−2.84 (m, 11H), 2.68−2.52 (m, 2H), 2.45−2.06 (m, 5H), 1.97−1.82 (m,1H), 1.77−1.45 (m, 4H), 1.42 (s, 3H), 1.33 (s, 3H), 1.30−1.03 (m, 24H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 174.2, 173.6, 173.4, 157.1, 137.3, 131.9, 130.3, 128.5, 103.7, 82.7, 81.1, 78.6, 78.2, 76.8, 70.4, 70.1, 70.0, 68.2, 68.0, 63.1, 62.6, 60.7, 52.8, 50.2, 45.6, 45.0, 44.3, 44.2, 43.2, 43.1, 38.9, 38.6, 36.5, 33.0, 32.9, 32.8, 31.0, 22.1, 21.2, 19.7, 18.9, 15.3, 14.3 (2C), 10.1, 8.9; MS (APCI) m/z 879 $(M + H)^+$; Anal. ($C_{46}H_{71}ClN_2O_{12}$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-3-*O*-(1-pyrrolidinylcarbonyl)-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (19). This compound was prepared following the procedure described for **8**, substituting pyrrolidine for D-alaninol, to give the 2′-*O*-acetate of **19**, which was stirred in MeOH at room temperature 24 h and concentrated in vacuo to give **19** as a colorless, amorphous solid: IR (KBr)υ 3450, 2970, 2880, 1760, 1735, 1710, 1460, 1420, 1380, 1230, 1170, 1105, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.22 (m, 4H), 5.03 (dd, J = 10.9, 2.4 Hz, 1H), 4.95 (d, J = 11.2 Hz, 1H), 3.98 (d, J = 7.1 Hz, 1H), 3.88 (d, J = 3.1 Hz, 1H), 3.88−3.79 (m, 1H), 3.79 (s, 1H), 3.56−3.22 (m, 5H), 3.17−3.07 (m, 1H), 3.08 (s, 3H), 3.05−2.84 (m, 4H), 2.67−2.55 (m, 1H), 2.48−2.38 (m, 1H), 2.20 (s, 3H), 2.20−2.10 (m, 1H), 2.02−1.78 (m, 5H), 1.78−1.46 (m, 4H), 1.43 (s, 3H), 1.31 (s, 3H), 1.31−1.00 (m, 24H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 215.8, 174.5, 157.1, 154.5, 137.3, 131.9, 130.3, 128.5, 103.2, 103.5, 82.9, 80.3, 78.3, 77.9, 76.3, 69.8, 69.6, 63.6, 60.6, 52.6, 50.2, 46.4, 45.8, 45.7, 45.0, 43.2, 38.9, 38.5, 36.0, 33.0, 32.8, 31.0, 25.9, 25.1, 22.1, 21.2, 21.1, 20.4, 19.5, 18.9, 15.1, 14.3, 14.2, 10.1, 9.0; MS (FAB) m/z 878 $(M + H)^+$; Anal. ($C_{46}H_{72}ClN_3O_{11}\cdot 0.5H_2O$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-(oxazolidine-3-yl)carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (20). 11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-[ethanolamine]carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) was prepared using the procedure described for **8** substituting ethanolamine for D-alaninol. To a solution of this compound (0.20 g, 0.22 mmol) and paraformaldehyde (10 mg, 0.33 mmol) in benzene (4 mL) was added camphorsulfonic acid (60 mg, 0.26 mmol), and the resulting mixture was stirred at reflux in a flask equipped with a Dean−Stark apparatus. After 2 h, TLC (19:1 $CHCl_3$:MeOH) indicated the reaction was complete. The mixture was partitioned between saturated aq $NaHCO_3$ (20 mL) and $CHCl_3$ (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo to give a crude product that was purified by column chromatography on silica gel (2:1 EtOAc:hexanes) to give the 2′-*O*-acetate of **20** as a colorless, amorphous solid (132 mg, 65%). A solution of this compound (110 mg, 0.12 mmol) in MeOH (5 mL) was stirred at room temperature 24 h, after which time TLC (19:1 $CHCl_3$:MeOH) indicated the reaction was complete. The solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel (97:3 $CHCl_3$:MeOH) to give **20** as a colorless, amorphous solid (105 mg, quant.): IR (KBr) υ 3450, 2970, 2880, 1760, 1735, 1710, 1460, 1420, 1380, 1230, 1170, 1105, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.22 (m, 4H), 5.03 (dd, J = 11.1, 2.6 Hz, 1H), 4.97 (d, J = 10.1 Hz, 1H), 4.13−3.95 (m, 2H), 3.95 (d, J = 7.4 Hz, 1H), 3.89−3.74 (m, 3H), 3.62 (m, 1H), 3.49 (m, 1H), 3.32 (m, 1H), 3.16−3.08 (m, 2H), 3.07 (s, 3H), 3.05−2.84 (m, 4H), 2.60 (m, 1H), 2.49 (m, 1H), 2.23−2.13 (m, 4H), 1.90 (m, J = 7.4, 2.4 Hz, 1H), 1.80−1.43 (m, 4H), 1.43 (s, 3H), 1.32 (s, 3H), 1.32−1.00 (m, 24H), 0.81 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.7, 174.3, 157.1, 153.2, 137.3, 131.9, 130.3, 128.5, 103.5, 82.8, 81.1, 79.0, 78.9, 78.4, 78.2, 77.2, 76.5, 69.8, 69.7, 67.6, 66.8, 60.7, 52.7, 50.1, 45.8, 45.0, 44.3, 43.2, 38.9, 38.6, 36.0, 32.9, 32.8, 30.8, 22.1, 21.2, 20.9, 19.5, 18.9, 15.1, 14.3 (2C), 10.1, 9.0; MS (FAB) m/z 880 $(M + H)^+$; Anal. ($C_{45}H_{70}ClN_3O_{13}$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-3-*O*-(4-morpholinylcarbonyl)-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (21). This compound was prepared following the procedure described for **8**, substituting morpholine for D-alaninol, to give the 2′-*O*-acetate of **21**, which was stirred in MeOH at room temperature 24 h and concentrated in vacuo to give **21** as a colorless, amorphous solid: IR (KBr) υ 3420, 2960, 1790, 1735, 1705, 1455, 1420, 1380, 1275, 1240, 1170, 1110, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.23 (m, 4H), 5.02 (dd, J = 11.0, 2.2 Hz, 1H), 4.98 (d, J = 11.0 Hz, 1H), 3.97 (d, J = 7.4 Hz, 1H), 3.88−3.78 (m, 3H), 3.77 (s, 1H), 3.75−3.57 (m, 6H), 3.55−3.30 (m, 3H), 3.18−3.06 (m, 5H), 3.06−2.84 (m, 4H), 2.67−2.47 (m, 2H), 2.21 (s, 3H), 2.21−2.13 (m, 1H), 1.90 (m, J = 7.4, 2.3 Hz, 1H), 1.82−1.45 (m, 5H), 1.43 (s, 3H), 1.32 (s, 3H), 1.24−1.02 (m, 21H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 215.7, 174.2, 157.1, 155.1, 137.3, 131.9, 130.3, 128.5, 103.2, 82.8, 80.1, 78.8, 78.4, 76.5, 69.9, 69.7, 66.7, 66.6, 63.6, 60.6, 52.7, 50.2, 45.7, 45.0, 44.4, 44.3, 43.2, 43.1, 38.9, 38.6, 36.0, 33.0, 32.8, 30.9, 22.1, 21.2, 20.6, 19.5, 18.9, 15.1, 14.3, 14.2, 10.1, 9.0; MS (APCI) m/z 894 $(M + H)^+$; Anal. ($C_{46}H_{72}ClN_3O_{12}\cdot 0.5H_2O$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-(oxazolidin-2-one-3-yl)carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (22). This compound was prepared following the procedure described for **9**, substituting ethanolamine for D-alaninol, to give **22** as a colorless, amorphous solid: IR (KBr) υ 3440, 2975, 1825, 1760, 1740, 1460, 1385, 1325, 1310, 1235, 1170, 1070, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.23 (m, 4H), 5.09 (d, J = 11.2 Hz, 1H), 5.01 (dd, J = 10.8, 2.2 Hz, 1H), 4.42−4.32 (m, 2H), 4.27−4.19 (m, 1H), 4.08−3.74 (m, 6H), 3.48−3.33 (m, 1H), 3.16−2.83 (m, 9H), 2.68−2.43 (m, 2H), 2.26−2.15 (m, 4H), 1.89 (m, J = 7.4, 2.3 Hz, 1H), 1.77−1.47 (m, 4H), 1.43 (s, 3H), 1.36 (s, 3H), 1.29−1.11 (m, 12H), 1.11−1.01 (m, 9H), 0.81 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.6, 173.8, 157.1, 150.8, 137.3, 132.0, 130.3, 128.5, 104.5, 82.7, 82.2, 81.4, 78.6, 77.0, 69.9, 69.6, 63.6, 61.6, 60.8, 53.0, 50.1, 50.3, 45.7, 45.0, 43.3, 43.0, 39.0, 38.7, 38.6, 36.4, 32.8, 30.6, 22.1, 21.2, 19.6, 19.5, 18.9, 15.2, 14.4, 14.3, 10.1, 8.9; MS (APCI) m/z 894 $(M + H)^+$; Anal. ($C_{45}H_{68}ClN_3O_{13}$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-(2-methyloxazolidin-3-yl)carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (23). This compound was prepared following the procedure described for **20**, substituting acetaldehyde for paraformaldehyde, to give **23** as a colorless, amorphous solid: IR (KBr) υ 3440, 2975, 1760, 1735, 1710, 1460, 1415, 1380, 1330, 1235, 1170, 1110, 1090, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.22 (m, 4H), 5.53−5.46 (m, 0.3H), 5.33−5.22 (m, 0.7H), 5.05−4.89 (m, 2H), 4.17−3.71 (m, 7H), 3.70−3.29 (m, 2H), 3.18−2.82 (m, 9H), 2.66−2.41 (m, 2H), 2.23−2.12 (m, 4H), 1.97−1.82 (m, 1H), 1.80−1.37 (m, 11H), 1.32 (s, 3H), 1.24−1.11 (m, 12H), 1.10−1.00 (m, 9H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 215.7, 174.2, 157.1, 137.3, 131.9, 130.3, 128.5, 103.8, 86.5, 85.5, 82.8, 81.4, 78.4, 77.2, 69.7, 65.3, 64.6, 63.8, 63.3, 60.7, 52.6, 50.1 (2C), 45.7, 45.0, 44.7, 43.3, 43.2, 38.9, 38.6, 36.0, 35.9, 32.7, 30.7, 22.1,

21.2, 20.5, 20.4, 19.6, 19.5, 18.9, 15.1, 14.9, 14.3, 14.2, 10.1, 9.1; MS (APCI) *m/z* 894 (M + H)$^+$; Anal. ($C_{46}H_{72}ClN_3O_{12}$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-(imidazolidin-2-one-1-yl)carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (24). This compound was prepared following the procedure described for **9**, substituting ethylenediamine for D-alaninol, to give **24** as a colorless, amorphous solid: IR (microscope) υ 3330, 2980, 1790, 1760, 1715, 1460, 1380, 1330, 1235, 1170, 1110, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31−7.22 (m, 4H), 5.44 (br s, 1H), 5.06 (d, J = 11.2 Hz, 1H), 5.02 (dd, J = 10.9, 2.4 Hz, 1H), 4.20−4.07 (m, 2H), 3.95−3.79 (m, 4H), 3.78 (s, 1H), 3.56−3.39 (m, 3H), 3.30−3.17 (m, 1H), 3.12 (q, J = 7.1 Hz, 1H), 3.07 (s, 3H), 3.07−2.82 (m, 4H), 2.67−2.54 (m, 1H), 2.33 (br s, 3H), 2.19 (m, J = 7.1, 2.4 Hz, 1H), 1.90 (m, J = 7.4, 2.3 Hz, 1H), 1.79−1.44 (m, 4H), 1.44 (s, 3H), 1.34 (s, 3H), 1.33−1.10 (m, 18H), 1.05 (d, J = 6.8 Hz, 3H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 215.6, 174.0, 157.1, 155.7, 151.5, 137.2, 132.0, 130.3, 128.5, 104.1, 82.7, 79.9, 78.4, 77.2, 76.7, 69.4, 67.7, 60.8, 50.0, 45.7, 45.0, 43.2, 43.1, 38.9, 38.6, 36.7, 36.3, 32.9, 32.8, 22.1, 21.1, 19.5, 18.9, 15.2, 14.3, 10.0, 9.0; MS (ESI) *m/z* 893 (M + H)$^+$; Anal. ($C_{45}H_{69}ClN_4O_{12}$·2.5 H_2O) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′−N-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-(3-methylimidazolidin-2-one-1-yl)carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (25). This compound was prepared following the procedure described for **9**, substituting *N*-methylethylenediamine for D-alaninol, to give **25** as a colorless, amorphous solid: IR (KBr) υ 3420, 2975, 1790, 1760, 1715, 1460, 1380, 1330, 1265, 1170, 1110, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31−7.22 (m, 4H), 5.04 (d, J = 11.5 Hz, 1H), 5.01 (dd, J = 11.2, 2.4 Hz, 1H), 4.16 (d, J = 6.7 Hz, 1H), 4.07−3.96 (m, 1H), 3.90 (d, J = 2.8 Hz, 1H), 3.88−3.70 (m, 4H), 3.51−3.33 (m, 2H), 3.33−3.18 (m, 1H), 3.12 (q, J = 7.1 Hz, 1H), 3.07 (s, 3H), 3.06−2.87 (m, 3H), 2.86 (s, 3H), 2.66−2.54 (m, 1H), 2.37 (br s, 3H), 2.18 (m, J = 7.3, 2.9 Hz, 1H), 1.90 (m, J = 7.4, 2.4 Hz, 1H), 1.79−1.47 (m, 5H), 1.43 (s, 3H), 1.33 (s, 3H), 1.28−1.08 (m, 18H), 1.05 (d, J = 7.1 Hz, 3H), 0.81 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 215.7, 174.1, 157.1, 154.1, 151.6, 137.3, 132.0, 130.3, 128.5, 103.8, 82.8, 79.9, 78.5, 77.2, 76.7, 69.5, 68.8, 63.3, 60.8, 50.1, 45.7, 45.0, 43.4, 43.2, 40.5, 38.9, 38.6, 36.2, 33.0, 32.8, 31.7, 30.8, 22.1, 21.1, 19.5, 18.9, 15.2, 14.3, 10.1, 9.0; MS (ESI) *m/z* 907 (M + H)$^+$; Anal. ($C_{46}H_{71}ClN_4O_{12}$·H_2O) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-[4-(S)-methyloxazolidin-2-one-3-yl]carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (26). This compound was prepared following the procedure described for **9**, substituting L-alaninol for D-alaninol, to give **26** as a colorless, amorphous solid: IR (KBr) υ 3430, 2965, 1820, 1795, 1750, 1730, 1455, 1380, 1350, 1305, 1165, 1100, 1060, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.22 (m, 4H), 5.10 (d, J = 11.2 Hz, 1H), 5.01 (dd, J = 10.9, 2.4 Hz, 1H), 4.45−4.36 (m, 2H), 4.18−4.10 (m, 1H), 4.05−3.96 (m, 1H), 3.88−3.80 (m, 3H), 3.76 (s, 1H), 3.40−3.28 (m, 1H), 3.13−2.82 (m, 9H), 2.66−2.48 (m, 2H), 2.29−2.15 (m, 4H), 1.90 (m, J = 7.4, 2.3 Hz, 1H), 1.79−1.45 (m, 5H), 1.51 (d, J = 6.1 Hz, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.27−1.11 (m, 15H), 1.10−1.00 (m, 6H), 0.82 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 174.0, 157.1, 151.3, 137.3, 131.9, 130.3, 128.5, 103.0, 82.7, 81.3, 79.6, 78.5, 76.8, 70.0, 69.7, 68.6, 62.9, 60.6, 52.6, 51.5, 50.3, 45.7, 45.0, 43.0, 38.9, 38.5, 36.4, 33.1, 32.8, 30.9, 22.0, 21.2, 19.8, 19.6, 18.9, 15.1, 14.3, 10.1, 8.9; MS (ESI) *m/z* 908 (M + H)$^+$; Anal. ($C_{46}H_{70}ClN_3O_{13}$·H_2O) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-(5-methyloxazolidin-2-one-3-yl)carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (27). This compound was prepared following the procedure described for **9**, substituting 1-amino-2-propanol for D-alaninol, to give **27** as a colorless, amorphous solid: IR (microscope) υ 3435, 2970, 1820, 1760, 1740, 1715, 1460, 1380, 1350, 1305, 1170, 1105, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.23 (m, 4H), 5.11 (d, J = 11.2 Hz, 0.5H), 5.09 (d, J = 11.2 Hz, 0.5H), 5.01 (dd, J = 10.8, 2.5 Hz, 0.5H), 4.99 (dd, J = 10.9, 2.4 Hz, 0.5H), 4.63−4.54 (m, 0.5H), 4.46−4.37 (m, 1H), 4.19−4.11 (m, 1H), 4.04−3.98 (m, 0.5H), 3.95−3.75 (m, 4H), 3.75−3.45 (m, 2H), 3.42−3.25 (m, 1H), 3.20−2.82 (m, 9H), 2.68−2.54 (m, 2H), 2.38 (br s, 1.5H), 2.29−2.15 (m, 2.5H), 1.96−1.84 (m, 1H), 1.78−1.45 (m, 6H), 1.43 (s, 3H), 1.35 (s, 1.5H), 1.34 (s, 1.5H), 1.28−1.02 (m, 21H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 215.7, 174.0, 173.7, 157.1, 151.4, 137.3, 137.2, 132.0, 130.3, 128.5, 104.8, 103.1, 82.8, 82.7, 81.5, 78.6, 76.9, 69.9, 68.6, 62.9, 60.9, 60.7, 52.6, 51.5, 51.1, 50.2, 50.0, 45.7, 45.6, 45.0, 43.2, 43.0, 38.9, 38.7, 38.6, 36.4, 33.2, 32.8, 31.2, 22.1 (2C), 21.2, 21.1, 20.3, 19.7, 19.6, 18.9, 18.8, 15.4, 15.1, 14.4, 14.3, 10.1 (2C), 9.2, 8.9; MS (APCI) *m/z* 908 (M + H)$^+$; Anal. ($C_{46}H_{70}ClN_3O_{13}$·H_2O) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-[4-(S)-ethyl-oxazolidin-2-one-3-yl]carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (28). This compound was prepared following the procedure described for **9**, substituting (*S*)-2-amino-1-butanol for D-alaninol, to give **28** as a colorless, amorphous solid: IR (KBr) υ 3440, 2965, 1825, 1795, 1760, 1740, 1460, 1380, 1365, 1310, 1170, 1110, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.22 (m, 4H), 5.08 (d, J = 10.9 Hz, 1H), 5.01 (dd, J = 10.9, 2.4 Hz, 1H), 4.36 (ψt, J = 8.4 Hz, 1H), 4.30−4.20 (m, 1H), 4.17 (d, J = 7.4 Hz, 1H), 4.13 (dd, J = 8.5, 3.2 Hz, 1H), 3.89−3.80 (m, 3H), 3.76 (s, 1H), 3.41−3.29 (m, 1H), 3.22−2.83 (m, 10H), 2.65−2.52 (m, 2H), 2.33−2.17 (m, 4H), 2.03−1.48 (m, 7H), 1.43 (s, 3H), 1.34 (s, 3H), 1.28−1.08 (m, 18H), 1.05 (d, J = 6.7 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 174.0, 157.0, 151.4, 137.3, 131.8, 130.3, 128.5, 102.8, 82.7, 81.3, 79.6, 78.5, 76.8, 70.0, 69.7, 69.2, 66.3, 62.9, 60.6, 56.1, 50.3, 45.7, 45.0, 43.0, 38.9, 38.5, 36.4, 33.2, 32.8, 31.1, 22.0, 21.2, 19.6, 18.9, 15.1, 14.3, 10.1, 8.9, 8.1; MS (APCI) *m/z* 922 (M + H)$^+$; Anal. ($C_{47}H_{72}ClN_3O_{13}$·1.5 H_2O) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-(5-ethyl-oxazolidin-2-one-3-yl)carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (29). This compound was prepared following the procedure described for **9**, substituting 1-amino-2-butanol for D-alaninol, to give **29** as a colorless, amorphous solid: IR (KBr) υ 3440, 2970, 1825, 1760, 1740, 1715, 1460, 1380, 1320, 1170, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.23 (m, 4H), 5.07 (d, J = 10.8 Hz, 1H), 5.02 (dd, J = 10.8, 2.0 Hz, 1H), 4.54−4.42 (m, 0.6H), 4.31−4.22 (m, 0.4H), 4.13−4.02 (m, 0.6H), 4.02−3.93 (m, 0.4H), 3.93−3.71 (m, 4H), 3.62−3.35 (m, 2H), 3.17−2.82 (m, 11H), 2.68−2.53 (m, 2H), 2.28−2.13 (m, 4H), 1.96−1.45 (m, 6H), 1.43 (s, 3H), 1.35 (2s, 3H), 1.28−1.00 (m, 24H), 0.81 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.6, 173.8, 157.1, 150.8, 137.2, 132.0, 130.3, 128.5, 104.5, 82.7, 82.7, 81.2, 78.5, 77.2, 74.7, 69.6, 60.8, 50.0, 48.2, 45.6, 45.0, 43.0, 38.9, 38.5, 36.4, 32.9, 32.8, 27.9, 22.1, 21.1, 20.4, 19.6, 18.8, 15.2, 14.4, 14.3, 10.0, 8.9, 8.6; MS (ESI) *m/z* 922 (M + H)$^+$; Anal. ($C_{47}H_{72}ClN_3O_{13}$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-[4-(*R*)-isobutyl-oxazolidin-2-one-3-yl]carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (30). This compound was prepared following the procedure described for **9**, substituting D-leucinol for D-alaninol, to give **30** as a colorless, amorphous solid: IR (KBr) υ 3430, 2965, 1820, 1760, 1740, 1715, 1460, 1380, 1365, 1305, 1170, 1100, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.22 (m, 4H), 5.11 (d, J = 11.2 Hz, 1H), 5.00 (dd, J = 10.9, 2.4 Hz, 1H), 4.55−4.41 (m, 2H), 4.16−4.01 (m, 2H), 3.88−3.76 (m, 4H), 3.54−3.40 (m, 1H), 3.32−3.20 (m, 1H), 3.15−2.82 (m, 9H), 2.65−2.54 (m, 1H), 2.34 (br s, 3H), 2.25−2.14 (m, 1H), 1.99 (s, 1H), 1.90 (m, J = 7.4, 2.3 Hz, 1H), 1.80−1.49 (m, 6H), 1.43 (s, 3H), 1.35 (s, 3H), 1.27−1.16 (m, 15H), 1.14 (d, J = 7.1 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 1.00 (s, 3H), 0.98 (s, 3H), 0.82 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 215.6, 173.7, 157.1, 150.7, 137.2, 132.0, 130.3,

128.5, 104.6, 82.7, 81.4, 77.2, 69.4, 68.8, 67.5, 64.2, 60.9, 53.7, 50.0, 45.6, 45.0, 43.2, 42.9, 38.9, 38.6, 36.4, 32.8, 32.7, 31.0, 24.8, 23.7, 22.1, 21.5, 21.1, 19.8, 19.7, 18.8, 15.4, 14.4, 14.2, 10.1, 9.1; MS (APCI) *m/z* 950 $(M + H)^+$; Anal. ($C_{49}H_{76}ClN_3O_{13}$·$0.5H_2O$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-(4,4-dimethyloxazolidin-2-one-3-yl)carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (31). This compound was prepared following the procedure described for **9**, substituting 2-amino-2-methyl-1-propanol for D-alaninol, and the product crystallized upon concentration in vacuo to give **31** as a colorless, crystalline solid: mp = 144−148 °C; IR (KBr) υ 3435, 2965, 1815, 1790, 1755, 1735, 1460, 1380, 1315, 1285, 1230, 1170, 1070, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.22 (m, 4H), 5.12 (d, J = 11.2 Hz, 1H), 5.01 (dd, J = 11.2, 2.4 Hz, 1H), 4.28 (d, J = 7.4 Hz, 1H), 4.03 (s, 2H), 3.85 (t, J = 8.3 Hz, 2H), 3.77 (s, J = 4.4 Hz, 1H), 3.75 (d, J = 4.4 Hz, 1 H), 3.40−3.29 (m, 1H), 3.20−2.96 (m, 7H), 2.96−2.83 (m, 2H), 2.67−2.54 (m, 2H), 2.28−2.16 (m, 4H), 1.90 (m, J = 7.3, 2.2 Hz, 1H), 1.81−1.48 (m, 4H), 1.58 (2s, 6H), 1.43 (s, 3H), 1.34 (s, 3H), 1.30−1.23 (m, 4H), 1.19−1.02 (m, 18H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.9, 174.1, 157.1, 151.6, 137.3, 131.7, 130.3, 128.5, 102.5, 82.8, 80.8, 79.2, 78.5, 76.8, 74.8, 70.1, 69.4, 62.6, 60.5, 59.9, 52.6, 50.4, 45.7, 45.0, 43.0, 38.9, 38.6, 36.3, 33.2, 32.8, 30.9, 25.1, 24.8, 22.0, 21.3, 20.9, 20.4, 19.6, 19.0, 15.0, 14.3, 14.2, 10.1, 9.0; MS (APCI) *m/z* 922 $(M + H)^+$; Anal. ($C_{47}H_{72}ClN_3O_{13}$·$2.0H_2O$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-3-*O*-[4,5-(S,R)-dimethyloxazolidin-2-one-3-yl]carbamoyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (32). This compound was prepared following the procedure described for **9**, substituting 3-(*S*)-amino-2-(*R*)-butanol for D-alaninol, to give **32** as a colorless, amorphous solid: IR (KBr) υ 3440, 2970, 1820, 1795, 1760, 1740, 1460, 1365, 1170, 1105, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31−7.22 (m, 4H), 5.07 (d, J = 11.0 Hz, 1H), 5.01 (dd, J = 11.0, 2.4 Hz, 1H), 4.66 (m, J = 6.7 Hz, 1H), 4.14 (d, J = 7 Hz, 1H), 3.92 (d, J = 2 Hz, 1H), 3.89−3.79 (m, 1H), 3.77 (s, 1H), 3.45−3.35 (m, 1H), 3.22−3.14 (m, 1H), 3.13 (q, J = 6.7 Hz, 1H), 3.09 (s, 3H), 3.08−2.98 (m, 3H), 2.94−2.85 (m, 1H), 2.70−2.56 (m, 2H), 2.27 (br s, 3H), 2.26−2.18 (m, 1H), 1.90 (m, J = 7.3, 2.2 Hz, 1H), 1.77−1.62 (m, 3H), 1.60−1.51 (m, 1H), 1.43 (s, 3H), 1.41 (d, J = 6.1 Hz, 3H), 1.36 (d, J = 6.8 Hz, 3H), 1.34 (s, 3H), 1.25−1.18 (m, 6H), 1.18−1.07 (m, 12H), 1.05 (d, J = 6.7 Hz, 3H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8, 174.0, 157.1, 151.2, 151.0, 137.2, 131.9, 130.3, 128.4, 103.1, 82.7, 81.3, 80.3, 78.5, 76.8, 74.0, 69.6, 69.2, 63.0, 60.6, 55.1, 50.1, 45.6, 45.0, 43.0, 38.9, 38.5, 36.4, 33.1, 32.7, 31.3, 22.0, 21.1, 20.3, 19.8, 19.5, 18.8, 15.1, 14.2 (2C), 13.6, 10.1, 8.9; MS (ESI) *m/z* 922 $(M + H)^+$; Anal. ($C_{47}H_{72}ClN_3O_{13}$·$0.5H_2O$) C, H, N.

11-Deoxy-11-[carboxy(4-chlorophenethyl)amino]-3-*O*-[4-(S)-methyloxazolidin-2-one-3-yl]carbamoyl-5-*O*-(3′-*N*-desmethyl-3′-*N*-cyclopentyl)desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (33). This compound was prepared following the procedure described for **35**, substituting 4-chlorophenethylamine for 3,4-dichlorophenethylamine, to give **33** as a colorless, amorphous solid: IR (KBr) υ 3445, 2970, 1825, 1800, 1760, 1740, 1460, 1385, 1350, 1310, 1170, 1110, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.22 (m, 4H), 5.10 (d, J = 11.2 Hz, 1H), 5.02 (dd, J = 11.0, 2.5 Hz, 1H), 4.45−4.35 (m, 2H), 4.10 (d, J = 7.1 Hz, 1H), 4.04−3.94 (m, 1H), 3.90−3.78 (m, 3H), 3.76 (s, 1H), 3.35−3.25 (m, 1H), 3.18−2.95 (m, 7H), 2.95−2.82 (m, 2H), 2.66−2.54 (m, 2H), 2.29−2.15 (m, 1H), 2.16 (s, 3H), 1.95−1.47 (m, 13H), 1.43 (s, 3H), 1.34 (s, 3H), 1.27−1.11 (m, 14H), 1.04 (d, J = 6.8 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.7, 174.0, 157.1, 151.4, 151.1, 137.3, 132.0, 130.3, 128.5, 103.1, 82.7, 81.4, 79.6, 78.5, 76.9, 69.9, 69.8, 68.6, 63.7, 63.2, 60.6, 51.4, 50.2, 45.7, 45.0, 43.0, 38.9, 38.5, 36.4, 33.2, 32.8, 31.6, 31.0, 30.7, 30.2, 23.7, 22.1, 21.2, 19.8, 19.5, 18.9, 15.1, 14.3, 14.2, 10.1, 8.9; MS (APCI) *m/z* 934 $(M + H)^+$; Anal. ($C_{48}H_{72}ClN_3O_{13}$·H_2O) C, H, N.

11-Deoxy-11-[carboxy(3,4-dichlorophenethyl)amino]-3-*O*-[4-(S)-methyloxazolidin-2-one-3-yl]carbamoyl-5-*O*-(3′-*N*-desmethyl-3′-*N*-isopropyl)desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (34). This compound was prepared following the procedure described for **14**, substituting acetone for cyclopropanecarboxaldehyde, to give **34** as a colorless, amorphous solid: IR (microscope) υ 3440, 2970, 2940, 1820, 1800, 1755, 1735, 1460, 1380, 1350, 1305, 1170, 1105, 1065, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 2.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.19 (dd, J = 8.1, 2.0 Hz, 1H), 5.09 (d, J = 11.1 Hz, 1H), 4.98 (dd, J = 11.0, 2.2 Hz, 1H), 4.46−4.36 (m, 2H), 4.18−4.10 (m, 1H), 4.03−3.96 (m, 1H), 3.91−3.81 (m, 3H), 3.74 (s, 1H), 3.39−3.27 (m, 1H), 3.18−2.83 (m, 9H), 2.67−2.50 (m, 2H), 2.26−2.15 (m, 4H), 1.97−1.83 (m, 1H), 1.79−1.48 (m, 8H), 1.43 (s, 3H), 1.34 (s, 3H), 1.29−1.02 (m, 21H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 174.1, 157.1, 151.4, 151.1, 139.2, 132.2, 131.0, 130.3, 130.2, 128.4, 125.0, 103.0, 82.8, 81.3, 79.7, 79.6, 78.6, 76.8, 70.0, 69.7, 68.6, 62.9, 60.7, 51.5, 50.3, 45.7, 44.9, 43.0, 38.9, 38.5, 36.4, 33.1, 32.6, 30.9 (2C), 29.7, 22.0, 21.2, 21.0, 20.9, 20.4, 19.7, 19.6, 18.9, 15.1, 14.3, 14.2, 10.1, 8.9; MS (ESI) *m/z* 942 $(M + H)^+$; Anal. ($C_{46}H_{69}Cl_2N_3O_{13}$) C, H, N.

11-Deoxy-11-[carboxy(3,4-dichlorophenethyl)amino]-3-*O*-[4-(S)-methyloxazolidin-2-one-3-yl]carbamoyl-5-*O*-(3′-*N*-desmethyl-3′-*N*-cyclopentyl)desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (35). This compound was prepared following the procedure described for **14**, substituting cyclopentanone for cyclopropanecarboxaldehyde, to give **35** as a colorless, amorphous solid: IR (KBr) υ 3440, 2970, 1820, 1800, 1755, 1735, 1460, 1380, 1350, 1305, 1230, 1170, 1105, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.19 (dd, J = 8.4, 2.0 Hz, 1H), 5.10 (d, J = 11.2 Hz, 1H), 4.97 (dd, J = 11.0, 2.2 Hz, 1H), 4.47−4.35 (m, 2H), 4.11 (d, J = 7.5 Hz, 1H), 4.06−3.97 (m, 1H), 3.91−3.79 (m, 3H), 3.74 (s, 1H), 3.38−3.26 (m, 1H), 3.23−2.83 (m, 9H), 2.74−2.60 (m, 2H), 2.25−2.14 (m, 4H), 2.00−1.48 (m, 14H), 1.43 (s, 3H), 1.34 (s, 3H), 1.32−1.12 (m, 15H), 1.04 (d, J = 6.8 Hz, 3H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 174.0, 157.1, 151.4, 151.2, 139.2, 132.2, 131.0, 130.3, 130.2, 128.4, 103.0, 82.8, 81.3, 79.7, 78.5, 76.8, 69.8, 69.7, 68.6, 64.1, 63.3, 60.7, 51.5, 50.2, 45.7, 44.9, 43.0, 38.9, 38.5, 36.4, 33.4, 32.6, 31.4, 30.9, 30.3, 29.7, 23.7, 23.2, 22.0, 21.2, 19.7, 19.5, 18.9, 15.1, 14.3, 14.2, 10.1, 8.9; MS (APCI) *m/z* 968 $(M + H)^+$; Anal. ($C_{48}H_{71}Cl_2N_3O_{13}$) C, H, N.

11-Deoxy-11-[carboxy(3-chloro-4-fluorophenethyl)amino]-3-*O*-[4-(S)-methyloxazolidin-2-one-3-yl]carbamoyl-5-*O*-(3′-*N*-desmethyl-3′-*N*-cyclopropylmethyl)desosaminyl-6-*O*-methylerythronolide A 11,12-(cyclic carbamate) (36). This compound was prepared following the procedure described for **14**, substituting 3-chloro-4-fluorophenethylamine for 3,4-dichlorophenethylamine, to give **36** as a colorless, amorphous solid: IR (microscope) υ 3449, 2975, 2941, 1824, 1801, 1758, 1738, 1502, 1458, 1380, 1350, 1307, 1271, 1169, 1106, 1063 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 2.4 Hz, 1H), 7.23−7.19 (m, 1H), 7.05 (ψt, J = 8.8, 1H), 5.09 (d, J = 11.0 Hz, 1H), 4.99 (d, J = 9.1 Hz, 1H), 4.44−4.35 (m, 2H), 4.13 (d, J = 6.7 Hz, 1H), 4.03−3.97 (m, 1H), 3.89−3.81 (m, 3H), 3.74 (s, 1H), 3.33−3.25 (m, 1H), 3.23−2.96 (m, 7H), 2.92−2.83 (m, 1H), 2.66−2.51 (m, 2H), 2.39 (dd, J = 10.8, 6.7 Hz, 1H), 2.29 (s, 3H), 2.26−2.18 (m, 2H), 1.95−1.86 (m, 1H), 1.77−1.48 (m, 8H), 1.43 (s, 3H), 1.34 (s, 3H), 1.27−1.13 (m, 15H), 1.05 (d, J = 6.7 Hz, 3H), 0.82 (t, J = 7.3 Hz, 3H), 0.59−0.45 (m, 2H), 0.13−0.06 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8, 174.1, 157.1, 156.8 (d, J = 247 Hz), 151.3, 151.0, 135.9 (d, J = 4 Hz), 131.0, 128.5 (d, J = 7 Hz), 120.5 (d, J = 17 Hz), 116.3 (d, J = 21 Hz), 102.9, 82.8, 81.2, 79.3, 78.5, 76.7, 70.1, 69.8, 68.6, 64.8, 60.5, 58.7, 51.4, 50.3, 45.7, 45.0, 42.9, 38.9, 38.5, 36.9, 36.3, 32.4, 29.5, 21.9, 21.2, 19.7, 19.5, 18.9, 15.0, 14.3, 14.2, 10.1, 9.9, 8.8, 4.3, 3.4; MS (ESI) *m/z* 938 $(M + H)^+$; Anal. ($C_{47}H_{69}ClFN_3O_{13}$) C, H, N.

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