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Bioorganic & Medicinal Chemistry 12 (2004) 3503–3519
Bioorganic & Medicinal Chemistry

Novel ketolide antibiotics with a fused five-membered lactone ring—synthesis, physicochemical and antimicrobial properties

Daniel Hunziker,[a,*] Pierre-C. Wyss,[a] Peter Angehrn,[a] Aranka Mueller,[a] Hans-Peter Marty,[a] Remy Halm,[a] Laurenz Kellenberger,[b] Veronique Bitsch,[b] Gerard Biringer,[b] Wolf Arnold,[a] Andreas Stämpfli,[a] Anne Schmitt-Hoffmann[b] and Denis Cousot[b]

[a]*F. Hoffmann-La Roche Ltd, Discovery Research, CH-4070 Basel, Switzerland*
[b]*Basilea Pharmaceutica Ltd, PO Box, CH-4005 Basel, Switzerland*

Received 14 October 2003; accepted 27 April 2004

Abstract—In an effort to find novel semisynthetic macrolides with extended antibacterial spectrum and improved activity we prepared a series of compounds based on commercially available clarithromycin, a potent and safe antimicrobial agent of outstanding clinical and commercial interest. According to the literature, improvement of antibacterial activity of erythromycin type antibiotics can be achieved by introduction of fused heterocycles such as cyclic carbonates or carbamates at positions 11 and 12 (such as in telithromycin). In the course of the work presented here, a similar, hitherto unprecedented set of compounds bearing a five-membered lactone ring fused to positions 11 and 12 was prepared based on carbon–carbon bond formation via intramolecular Michael addition of a [(hetero)arylalkylthio]acetic acid ester enolate to an α,β-unsaturated ketone as the key step. Some of the ketolide compounds described in this paper were highly active against a representative set of erythromycin sensitive and erythromycin resistant test strains. The best compound showed a similar antimicrobial spectrum and comparable activity in vitro as well as in vivo as telithromycin. Furthermore, some physicochemical properties of these compounds were determined and are presented here. On the basis of these results, the novel ketolide lactones presented in this paper emerged as valuable lead compounds with comparable properties as the commercial ketolide antibacterial telithromycin (Ketek™).

1. Introduction

The macrolide antibiotic erythromycin A (**1**) has been in successful clinical use as an agent against Gram-positive pathogens for several decades.[1] Due to its limited chemical stability and its gastro-intestinal side effects it has been gradually replaced by very effective and safe semisynthetic second generation derivatives such as clarithromycin (**2**),[2] roxithromycin (**3**)[3] and azithromycin (**4**)[4] in the last decades (Fig. 1). Very recently however, extensive spread of erythromycin A resistance among Gram-positive cocci isolates has raised the urgent need for novel derivatives with improved activity, stability and antimicrobial spectrum. Yet, clarithromycin (**2**) and azithromycin (**4**)—while featuring improved pharmacokinetics as compared to **1**—did not show any significant activity against bacterial isolates showing macrolide-lincosamide-streptogramine B (MLS_B) cross-resistance.

During the last years, industrial researchers from Aventis and Abbott Laboratories reported two novel semisynthetic macrolides belonging to the ketolide class[5] named telithromycin or HMR3647 (**5**)[6] and ABT773 (**6**)[7] (Fig. 1). These compounds showed significantly improved activities against macrolide-resistant isolates of important pathogens such as *Staphylococcus aureus* and *Streptococcus pneumoniae*. Both compounds comprise two key structural features: an 11,12-cyclic carbamate moiety and a 3-oxo group (refer to the erythromycin numbering in Fig. 1). In both cases, antimicrobial activity is further modulated by attachment of an additional (hetero)arylalkyl side chain to either the carbamate nitrogen (such as in **5**) or O(6) (such as in **6**).

Keywords: Ketolide; Macrolide; Ketolide antibiotic; Macrolide antibiotic; Antiinfective; Antibiotic.
* Corresponding author. Tel.: +41-61-688-95-39; fax: +41-61-688-83-67; e-mail: daniel.hunziker@roche.com

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doi:10.1016/j.bmc.2004.04.039

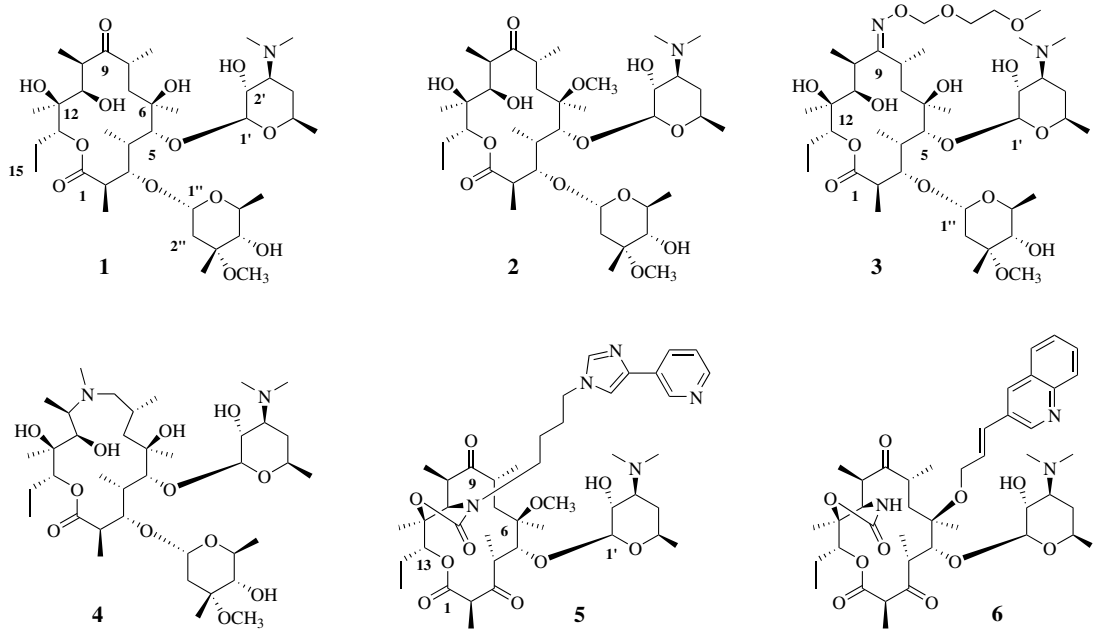


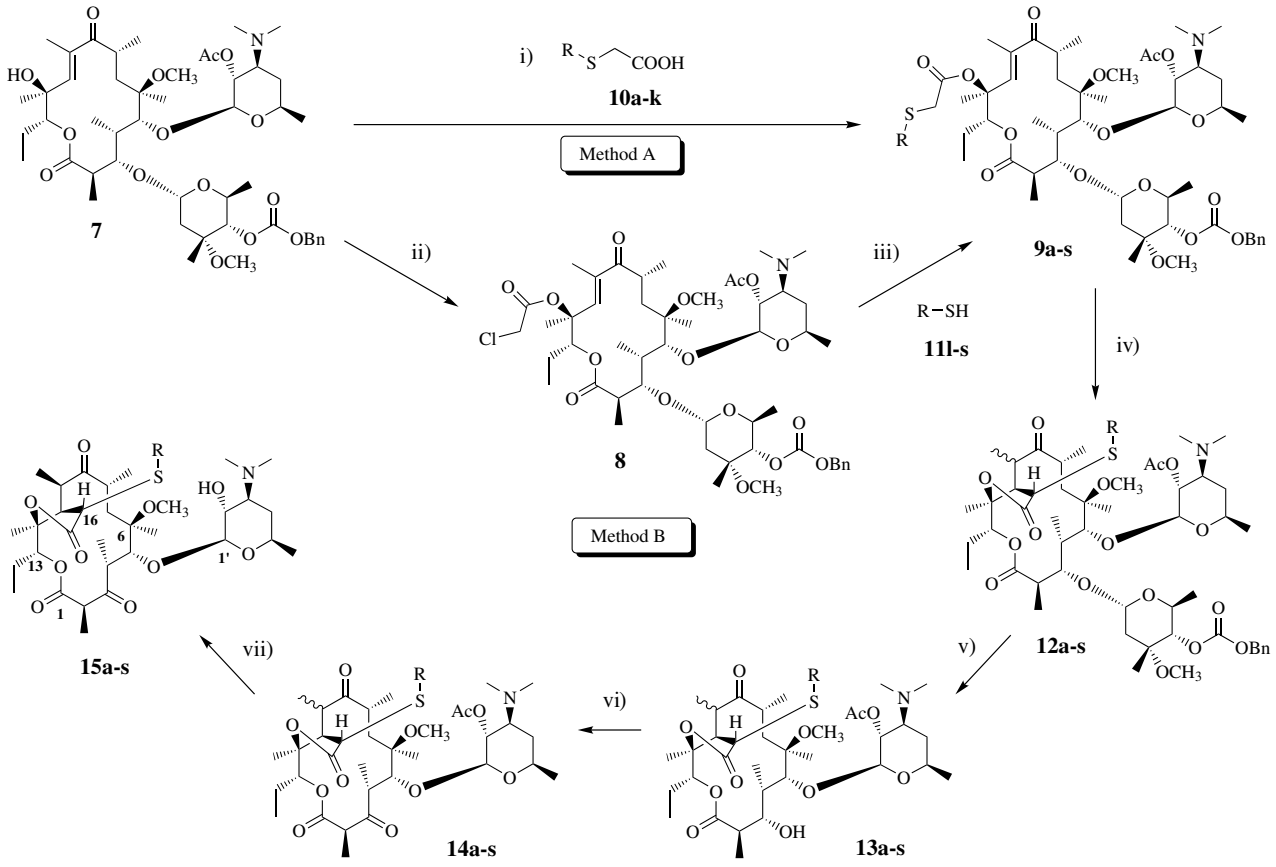
Figure 1. Structure and numbering scheme of the macrolide antibiotic erythromycin (**1**). Erythromycin derived semisynthetic macrolides comprise: clarithromycin (**2**), roxithromycin (**3**), azithromycin (**4**), telithromycin (**5**) and ABT773 (**6**).

Telithromycin has been introduced to the market while ABT773 is reported to be in late stage clinical trials. Additional possibilities to further enhance antimicrobial activities of the ketolide class of antibiotics such as replacement of the hydrogen at C(2) by a fluorine atom are reported in the literature.[8] Many excellent reviews about the most recent semisynthetic macrolide antibiotics have been published by various authors.[9]

2. Results and discussion

2.1. Chemistry and structural analysis

Although much work had been invested towards the development of novel semisynthetic derivatives of **1** or its chemically more stable homologue **2** in the last decades, we felt that innovation in this field might still be possible especially in the eastern part of the macrocyclic ring comprising positions C(10) to C(12). It has been shown earlier that introduction of fused heterocycles such as carbonates[10] and carbamates[11] at these positions lead to improvement of the antimicrobial potency. As a consequence, we considered 10,11-anhydroclarithromycin (**7**) initially reported by Baker and co-workers[11] as an ideal starting material for our own chemical programme. In analogy to the findings made earlier by others[5,11] we envisioned the introduction of a novel ring fused to the 11,12-positions of the macrocycle as well, however, with a clear focus towards the formation of new carbon–carbon bonds. Similar independent work along these lines has been published recently.[12] We quickly realized that acylation of the tertiary hydroxy group at C(12) of **7** can be easily achieved in high yield by treatment with DCC, DMAP and α-halo-substituted carboxylic acids such as chloroacetic acid to give, for example, chloroacetyl derivative **8**. Similarly, treatment of **7** with *S*-alkyl- or aryl substituted α-thio acetic acids, DCC and DMAP in CH_2Cl_2 gave clean reactions and high yields of the corresponding esters **9** (Scheme 1). These substituted α-thio ester derivatives **9** were considered to be of particular interest since we felt that—due to the anion stabilizing effect of the sulfur that should facilitate deprotonation in α-position of the critical ester carbonyl group—an intramolecular Michael reaction should now be possible under milder conditions. In addition, we expected an enhanced selectivity against proton abstraction at the α-positions of other carbonyl groups present in the macrocyclic backbone of **9** which—on the other hand—was found not to take place that easily. Synthesis of the desired cyclization precursors **9** by this method (Scheme 1, method A) required suitable [[(hetero)arylalkyl]thio]acetic acids **10a–k** (Table 1) as starting materials. Compounds of this type were either commercially available or were prepared according to literature procedures.[13] Yet, the scope of this formal ester formation was significantly limited since it could not be performed with most of the more interesting α-thio acetic acids carrying more polar, nitrogen containing heterocyclic substituents due to limited solubility in CH_2Cl_2. No reaction took place if CH_2Cl_2 was substituted with other solvents such as DMF.[14] Nevertheless, this drawback could be easily circumvented by treatment of chloroacetyl derivative **8** with a suitable [(hetero)arylalkyl]thiol **11** in the presence of a base such as DBU (Scheme 1, method B), a process that again resulted in the desired cyclization precursor **9**. The use of this alternative method required the adequate side chain precursors in form of their thiols **11l–s** (Table 1). Synthesis of side chain precursors **10** and **11** will be discussed in more detail below.



Scheme 1. Synthesis of ketolides **15** via intramolecular Michael reaction. See Table 1 for definition of side chains R. Reagents and conditions: (i) DCC, DMAP, CH_2Cl_2, RT, 48 h; (ii) DCC, DMAP, chloroacetic acid, CH_2Cl_2, RT, 48 h; (iii) DBU, cat. NaI, acetone, RT; (iv) NaH, DMF, 0 °C, 2 h (or KO^{t}Bu, DMF, 0 °C, 2 h); (v) 3% HCl in MeOH; (vi) EDC*HCl, DMSO, pyridinium trifluoroacetate, CH_2Cl_2, 5 °C, 2 h; (vii) MeOH, 48 h, RT.

Table 1. Ketolide lactones **15a–s**: structures, synthetic methods and starting materials

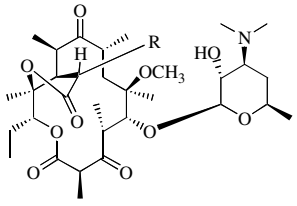
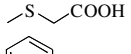
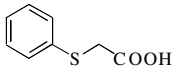
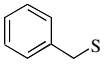
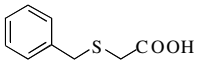
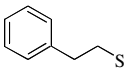
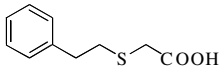
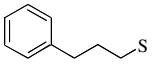
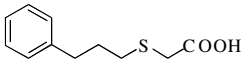
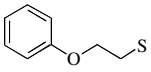
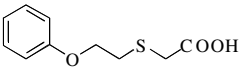
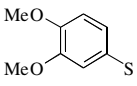
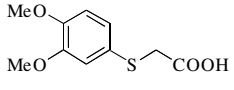
Ketolide	 R =	Method	Side chain building block	Source
15a	CH_3S	A	**10a** 	Commercial
15b	PhS	A	**10b** 	Commercial
15c		A	**10c** 	Commercial
15d		A	**10d** 	Lit.[a]
15e		A	**10e** 	Lit.[a]
15f		A	**10f** 	Commercial
15g		A	**10g** 	Commercial

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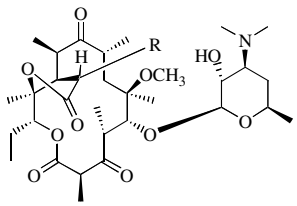
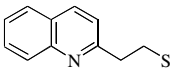
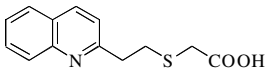
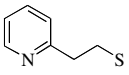
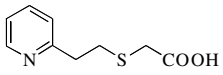
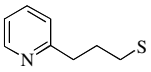
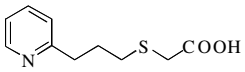
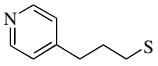
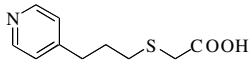
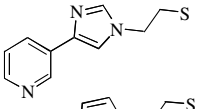
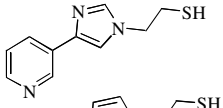
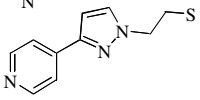
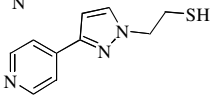
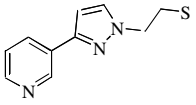
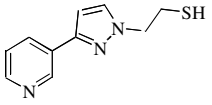
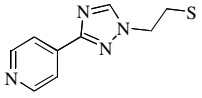
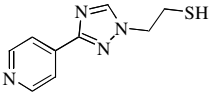
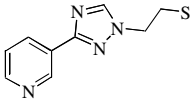
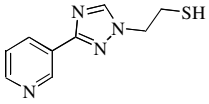
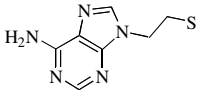
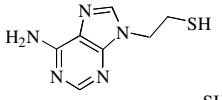
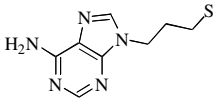
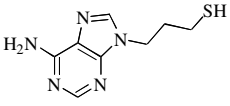
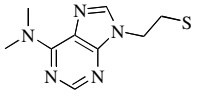
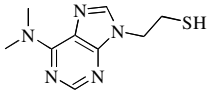
Table 1 (*continued*)

Ketolide	 R =	Method	Side chain building block	Source
15h		A	**10h** 	Lit.[b]
15i		A	**10i** 	Lit.[b]
15j		A	**10j** 	This paper
15k		A	**10k** 	This paper
15l		B	**11l** 	This paper
15m		B	**11m** 	This paper
15n		B	**11n** 	This paper
15o		B	**11o** 	This paper
15p		B	**11p** 	This paper
15q		B	**11q** 	This paper
15r		B	**11r** 	This paper
15s		B	**11s** 	This paper
16	H	na[c]	na	This paper

[a] Prepared according to Von Braun and Weissbach.[13a]
[b] Prepared according to Il'ichev et al.[13b]
[c] na: not applicable.

With these substituted α-thio ester derivatives **9** in hand we turned our attention to the key step of our reaction sequence being the intramolecular 1,4-addition. To our delight, treatment of the starting materials **9** with NaH or KO^{t}Bu in DMF resulted in the formation of the desired cyclization product—the corresponding five-membered lactone **12**—in modest to excellent yields. THF proved to be a poorer solvent for this reaction since a substantial amount of deacylated material **7**—the initial starting material—was observed under these reaction conditions. The cyclization step generally remained somewhat capricious despite some further optimization work. Yields for **12** ranged from 20% to 80% depending on the starting material used and only pure starting materials led to good yields. The use of starting materials with lower purity required addition of excess base in the cyclization process, leading to side reactions. In this cyclization process **9** → **12**, three adjacent

stereocentres (C(10), C(11) and C(16)) are generated in a single reaction step (see Scheme 1 for numbering). Since the pre-existing configuration at carbon C(12) leads to an attack of the enolate anion to the *trans* double bond from the *Si*-face and the resulting absolute configuration at C(11) is thus tightly controlled, four diastereomeric products are expected to be formed in this transformation. In reality, the course of the reaction turned out to be less complex since the desired products **12** were obtained as a mixture of two diastereomers at most, as judged by ^{1}H NMR. In the case of example **15k** that is presented in detail in the experimental section, intermediate **12k** consisted of a single epimer. Nevertheless, the diastereomeric ratio of the reaction products **12** obtained for the various examples proved to be very variable. We assumed that it was dependent on the reaction time, the amount and type of base added (e.g., NaH vs KO^{t}Bu) and—last but not least—on the work up and purification conditions.[15] It turned out that separation of this epimeric mixture was not necessary since—most intriguingly, as outlined in more detail below—epimerization in the process of the final deprotection step turned out to be feasible and the target ketolide could be obtained as a single diastereoisomer. In addition, the Z-protecting group in the cladinose moiety proved to be somewhat labile under these reaction conditions and in some cases a side product with a deprotected cladinose sugar could be isolated. For the time being, this could be tolerated since the side product was also a suitable starting material for the next reaction step.

Lactone **12** obtained from the cyclization step was usually used without rigorous purification and characterization. Treatment of **12** with 3% HCl in methanol resulted in selective removal of the cladinose moiety.[16] 3-Hydroxy derivative **13** thus obtained was oxidized under modified Pfitzner–Moffatt conditions as described by others[5] to furnish the corresponding ketolide **14** in high yield. This compound was deacetylated simply by treatment with pure methanol to give the target ketolide **15** in excellent yield. To our surprise, if starting material **14** was an epimeric mixture, one diastereomer cleanly isomerized under these conditions and the final product was obtained as a single isomer. Spectroscopic evidence for this isomerization process in the final deprotection step is presented in Figure 2 with (phenylpropylthio)ketolide **15e**. The ^{1}H NMR spectrum of starting material **14e** (Fig. 2, spectrum A) revealed two sets of signals in an approximate ratio of 1.5:1 (with both isomers having identical masses as indicated by MS, data not shown). We assumed that these compounds were epimers at position C(10). Stirring of mixture **14e** in methanol for 48 h without any additional reagent followed by subsequent removal of the solvent resulted in the formation of product **15e** whose spectrum is depicted in Figure 2 (spectrum B). This material consisted obviously of a single stereoisomer and—as expected—deacetylation had occurred. More detailed proton NMR analysis (chemical shifts and coupling constants) suggested natural configuration at C(10) as judged by comparison of the spectra with those reported for the

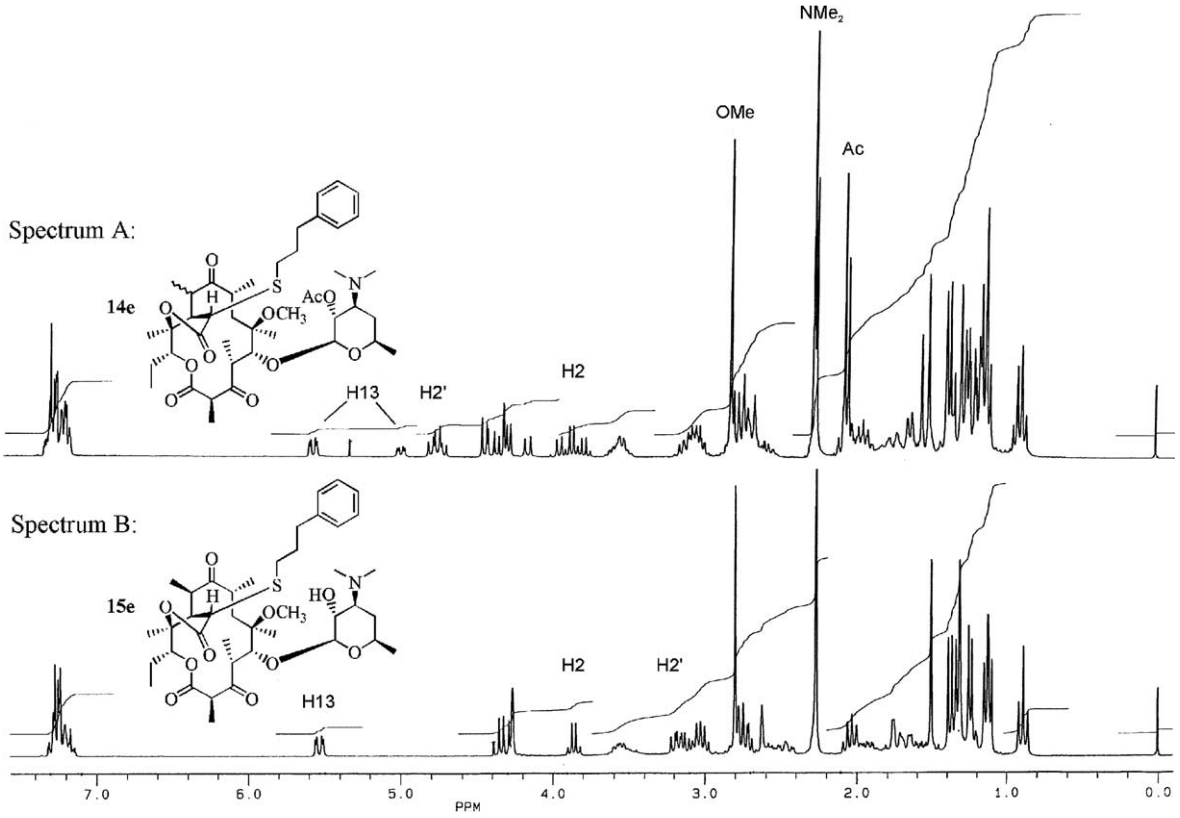


Figure 2. Spectroscopic evidence for the facile epimerization process that was observed during ketolide synthesis. Epimerization of the undesired epimer at C(10) resulted in the formation of a single stereoisomer with the natural configuration at all carbons (shown here with example **15e**).

references clarithromycin (**2**), erythromycin (**1**) and telithromycin (**5**) (see below for a more detailed discussion).

Synthesis of derivatives bearing a (heteroarylalkylthio) side chain with a free NH_2-group such as adenine derivative **15q** followed essentially the same synthetic pathway. Yet, synthesis was somewhat less straightforward, since we omitted the use of protecting groups in the first attempt. Treatment of the precursor **9q** under standard cyclization conditions resulted in the formation of a more complex mixture of products according to TLC analysis. Mass spectrometry suggested the two main products to be the desired cyclization product **12q-A** and a DMF condensation product **12q-B** (Fig. 3). Due to the complexity of the mixture and insignificant R_f differences of these products on TLC, further purification was not anticipated. Luckily, acidic methanolysis performed in the subsequent cladinose cleaving step also led to cleavage of the DMF adduct and the desired 3-hydroxy derivative **13q** was obtained as the main product in 61% yield over two steps. Oxidation of the hydroxyl group of **13q** under the conditions described earlier again led to partial formation of an unexpected product that was identified as the corresponding sulfilimine derivative **14q-A** of the desired O(2′)-protected ketolide by MS and proton NMR. Again, sulfilimine derivative **14q-A** was cleaved in the subsequent reaction step to give the desired deprotected ketolide **15q** as the main product and as a single diastereomer. Despite this somewhat more complex reaction procedure, compounds of this type could be prepared on a 500 mg scale in essentially pure form.

Absolute configuration of the final ketolide products was investigated by proton NMR with compound **15b** (R = phenylthio, see Table 1) based on coupling constants and NOE patterns. Investigation of crystal structures obtained from the Cambridge Structural Database of erythromycin (**1**), clarithromycin (**2**) and a 11,12-cyclic carbamate revealed the striking fact that the conformation of the macrocyclic backbone is almost identical in all three cases (data not shown). We therefore assumed that this should also be the case for our lactones since the absolute configuration of the stereocentres C(10), C(11) and C(12) in the macrocyclic backbone was not expected to be different from those in a cyclic carbamate. This assumption was supported by the fact that proton–proton coupling constants within characteristic spin systems of the eastern part of the macrocycle of selected examples were essentially the same as those reported for the cyclic carbamates.[5] A representative sketch of this common backbone conformation is presented in Figure 4 with a view along the axis of the C(10)–C(11) bond of **15b** (erythromycin numbering). Indicative NOE crosspeaks in the eastern part of the molecule are also given. NOE crosspeak between C(10)-Me and H(16) was considered as the most indicative signal since it clearly suggested an (*S*)-configuration for C(16) and an (*R*)-configuration for C(10) (which is the 'natural' configuration). This conclusion was supported by the following spectroscopic observations: vicinal coupling constants between the proton pairs H(16)–H(11) and H(10)–H(11) are very small and the multiplicities observed are singlet for H(16), singlet for H(11) and quartet for H(10). These ^{1}H NMR data suggested dihedral angles for H(16)–H(11) and H(11)–H(10) in the range of 90°, which is in accordance with the structural model depicted in Figure 4. Further support for this analysis might be found in the absence of a NOE crosspeak between H(16) and H(13). Since the essential features in the ^{1}H NMR spectra of the final products **15** were always extremely similar, we assumed that the conclusions drawn here for **15b** are also valid for all other examples.

Syntheses of side chain precursors **10** and **11** that were not commercially available and unknown in the literature were performed according to Scheme 2. Synthesis of **10j** and **10k** started with the corresponding commercially available 3-pyridylpropanols **16** that were converted to thioesters **17** by treatment with DIAD, PPh_3

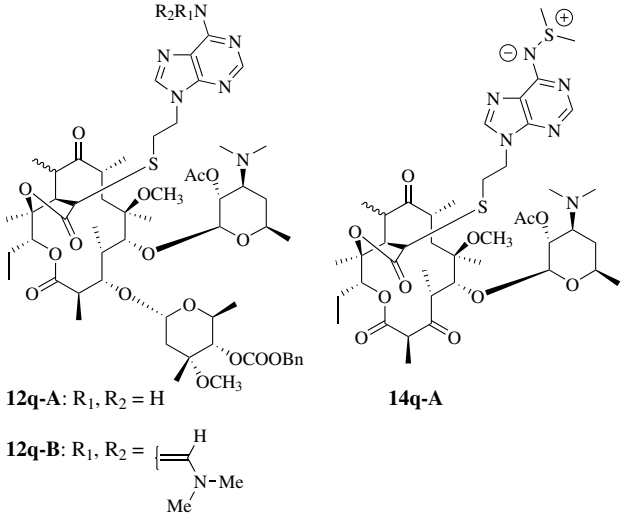


Figure 3. Synthesis of derivatives **15q** and **15r** containing an adenine moiety. Due to the presence of the unprotected aromatic NH_2 function, two additional intermediates **12q-B** and **14q-A** are formed in the course of the synthetic process according to Scheme 1.

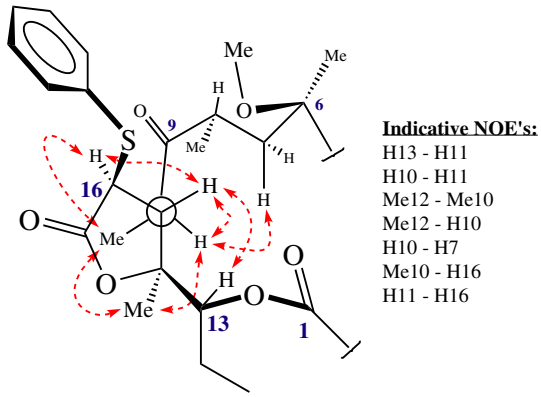
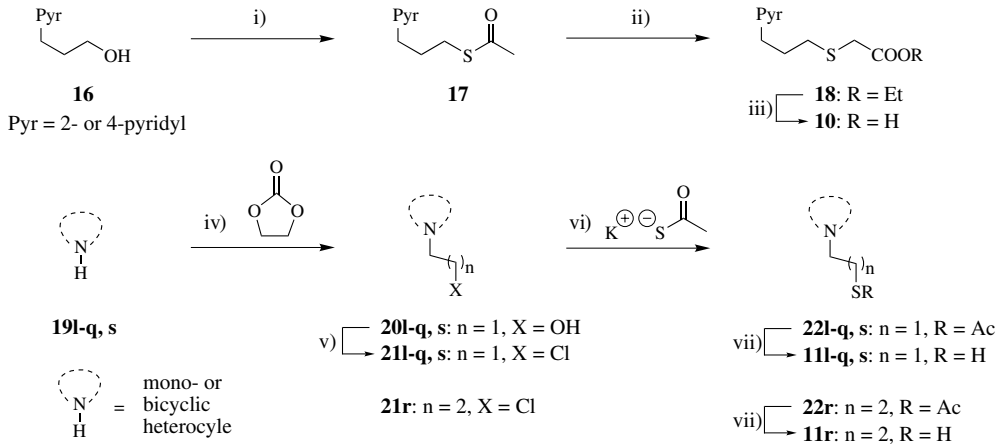


Figure 4. Stereochemical analysis of ketolides **15**. NOE pattern analysis was done with phenylthio derivative **15b**.



Scheme 2. Syntheses of side chain precursors **10** and **11**. Reagents and conditions: (i) DIAD, PPh_3, thioacetic acid, 0 °C to RT; (ii) $NaBH_4$, EtOH then NaOEt, ethyl bromoacetate; (iii) NaOH, dioxane, then HCl; (iv) NaOH (cat.), DMF, 160 °C; (v) $SOCl_2$, reflux; (vi) acetone, reflux, 12 h; (vii) NH_3 gas, MeOH.

and thioacetic acid according to Mitsunobu. Compounds **17** were reduced with $NaBH_4$ in ethanol and the resulting thiolate anions were alkylated in situ with ethyl bromoacetate to give esters **18**. Saponification of **18** resulted in the formation of the desired carboxylic acids **10**.

Thiol side chain synthesis was based on the mono- or bicyclic aromatic heterocycles being available in all cases either commercially or according to literature procedures (see experimental part). Treatment of the suitable heterocycles **19l–q,s** with ethylene carbonate and a catalytic amount of NaOH in DMF at 160 °C directly led to hydroxyethylated compounds **20l–q,s** in good yields. Regioselectivity was excellent in all cases and products **20l–q,s** were obtained as single regioisomers after purification. NOE experiments confirmed the structures of all these intermediates. Subsequently, $SOCl_2$ treatment of **20l–q,s** at 70 °C resulted in formation of chlorides **21l–q,s**. Chloropropyl intermediate **21r** was made directly in modest yield from adenine by treatment with base and 1-bromo-3-chloropropane. Chloroalkyl compounds **21** were treated with potassium thioacetate to give thioesters **22** and thiols **11** were then liberated from their precursors **22** by treatment with gaseous NH_3 in oxygen-free methanol. Free thiols **11** proved to be very susceptible to oxidation and in most cases the corresponding disulfide was an impurity. However, disulfide formation could be essentially suppressed if proper precautions such as exclusion of oxygen were taken and further purification steps such as silica gel chromatography were omitted.

For the sake of completeness, the basic, unsubstituted lactone **16** was also prepared. This material was obtained in 90% yield from phenyl–propyl derivative **15e** by treatment with Raney nickel in ethyl acetate. Based on these approaches, about 20 compounds with different side chains (see Table 1 for an overview) were prepared initially. Biological data and some physicochemical properties of these compounds will be discussed in the following section.

2.2. Biological and physicochemical properties

Solubilities of ketolide lactones were generally in the range of 3.0–7.0 mg/mL at pH 6.7 and generally exceeded the solubility of clinically used clarithromycin (**2**) (experimental value: 1.5 mg/mL). Thus, this parameter was not considered as a critical issue for the current lead series. Lipophilicities (determined as logD values at pH 7.4) were in the range of 1.2–2.7 for all compounds, depending on the nature of the alkylthio or (hetero)arylalkylthio side chain. Within the lactone series, logD values were found to be in good agreement with calculated lipophilicities ClogP (data not shown). Overall, lipophilicity was considered to be a very important parameter since membrane impairing properties appeared with compounds bearing a very lipophilic arylalkyl side chain. An example for this effect can be found in Table 1, example **15e**, where the MIC value of 16 μg/mL against the constitutively resistant strain *S. aureus* 745 is most probably due to cytotoxic effects. With this example in mind, an estimation of the cytotoxic potential of selected examples of **15** was attempted with determination of the IC_{50} values against HeLa cells (Table 2). Chart 1 confirms an apparent correlation

Table 2. Cytotoxic potential of ketolides **15** and references **1**, **2** and **5** (see Chart 1 for a graphical representation)

Macrolide	ClogP/logD	IC_{50} HeLa (μg/mL)	pIC_{50}
1	2.48/1.26	45.7	4.34
2	3.18/1.57	24.9	4.60
5	4.08/1.75	23.3	4.63
15a	1.70/nd[a]	18.5	4.73
15d	3.90/nd	1.30	5.89
15e	4.40/nd	1.10	5.96
15h	4.06/nd	2.40	5.62
15i	2.70/nd	8.40	5.08
15j	3.21/nd	7.80	5.11
15l	2.55/2.16	13.5	4.87
15n	2.55/2.62	10.3	4.99
15p	1.73/2.25	25.4	4.60
15q	1.19/1.68	34.4	4.46

[a] nd: not determined.

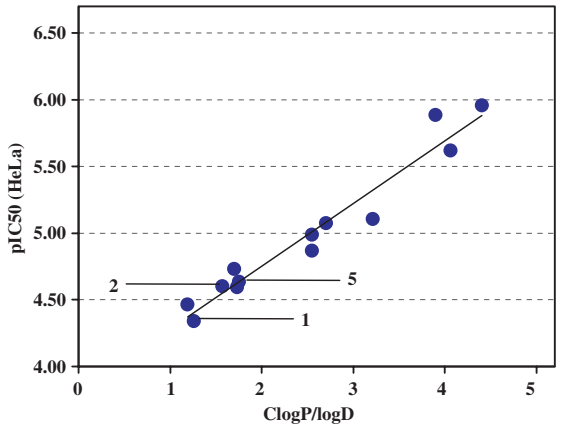


Chart 1. Apparent correlation between macrolide/ketolide lipophilicity (ClogP/logD) and cytotoxic potential (pIC_{50}).

between ClogP/logD of different compounds **15** and their pIC_{50} against HeLa cells. An IC_{50} value of 10 μg/mL was considered as an acceptable limit for the cytotoxic potential and therefore only compounds with a calculated ClogP value of less than about 2.5 were considered to be acceptable for synthesis in the later stage of the project.

Generally, ketolide lactones **15** proved to be very effective antimicrobial agents and all compounds were highly active against macrolide sensitive strains of *S. aureus* and *S. pneumoniae* (Table 3). Similar to other known ketolide series such as the carbamates that include telithromycin (**5**), replacement of the cladinose sugar by a keto group resulted in high activity against erythromycin-resistant but josamycin-sensitive *S. aureus* 1086 as exemplified in Table 3 with basic, unsubstituted ketolide lactone **16**. All compounds including **5** remained, however, inactive against the constitutively resistant strain *S. aureus* 745. Generally, the lactones **15** seemed to be slightly more active against *S. aureus* than **5**. Activity against *S. pneumoniae* with various degrees of macrolide resistance was strongly dependent on the nature of the side chain attached to the five-membered lactone ring via the sulfide bridge. Examples of **15** comprising a bicyclic (hetero)aryl moiety in the side chain were generally more active against highly macrolide-resistant *S. pneumoniae* such as strains SL199T and 12288 than compounds containing monocyclic aryl moieties. The influence of chain length of the thioether linker was investigated within the phenyl series comprising compounds **15b**–**15e**. Here, the most active compound against *S. aureus* was phenethyl derivative **15d**, while homologous compounds with either a shorter or longer side chain showed decreased activity (see Table 3). This fact led us to focus on compounds carrying an aryl–ethyl side chain in the initial phase of the programme; however, with compounds bearing more complex side chains such as **15q** and **15r** this effect was less dramatic or even absent. Within the series presented in Table 3, the most active and the most balanced compounds in terms of antimicrobial spectrum proved to be [3-(6-amino-9*H*-purine-9-yl)propyl]thio derivative **15r** and [3-(6-amino-9*H*-purine-9-yl)ethyl]thio derivative **15q**. Both compounds showed high activity against macrolide-sensitive and resistant Gram-positive bacteria—in about the same range as telithromycin (**5**). They also showed some

Table 3. Antimicrobial properties of ketolides **15** and**16** against various bacterial isolates [references: erythromycin (**1**), clarithromycin (**2**), telithromycin (**5**) and josamycin]

Macrolide	Minimum inhibitory concentration (MIC, μg/mL)							
	S. aureus ATCC29213	*S. aureus* 1086	*S. aureus* 745	*E. coli* ATCC25922	*S. pneumoniae* 1/1	*S. pneumoniae* 1/4	*S. pneumoniae* SL199T	*S. pneumoniae* 12288
15a	0.5	0.5	>16	>16	⩽0.5	32	16	>32
15b	0.5	0.5	>16	>16	⩽0.5	2	16	16
15c	1	1	>16	>16	⩽0.5	8	16	16
15d	⩽0.25	⩽0.25	>16	>16	⩽0.5	1	4	32
15e	1	1	16	>16	⩽0.5	1	8	16
15f	⩽0.25	⩽0.25	>16	>16	⩽0.5	4	4	8
15g	0.5	0.5	>16	>16	⩽0.5	1	8	16
15h	0.25	0.25	>16	>16	⩽0.12	0.25	0.5	2
15i	⩽0.25	⩽0.25	>16	16	⩽0.5	1	2	8
15j	⩽0.12	⩽0.12	>16	>16	⩽0.12	0.25	2	8
15k	⩽0.12	⩽0.12	>16	>16	⩽0.12	⩽0.12	2	8
15l	0.25	0.25	>16	>16	⩽0.12	⩽0.12	2	2
15m	⩽0.12	⩽0.12	>16	>16	⩽0.12	⩽0.12	1	4
15n	⩽0.12	⩽0.12	>16	>16	⩽0.12	⩽0.12	0.5	0.5
15o	0.25	⩽0.12	>16	>16	⩽0.12	1	4	>16
15p	⩽0.12	⩽0.12	>16	>16	⩽0.12	⩽0.12	1	1
15q	⩽0.12	⩽0.12	>16	8	⩽0.12	0.25	0.25	0.25
15r	⩽0.12	⩽0.12	>16	16	⩽0.25	⩽0.25	⩽0.25	0.25
15s	0.25	1	>16	>16	⩽0.25	⩽0.25	1	2
16	0.5	0.5	>16	>16	⩽0.12	16	>16	>16
1	0.5	>32	>64	>16	⩽0.12	32	>32	>32
2	0.25	16	>16	>16	⩽0.12	16	16	>16
5	⩽0.12	⩽0.12	>64	16	⩽0.12	⩽0.12	⩽0.12	0.25
Josamycin	2	2	>16	>16	⩽0.12	⩽4	>16	>16

activity against selected Gram-negatives such as *Escherichia coli* (MIC = 8 μg/mL for **15q**) but were inactive against *Pseudomonas aeroguinosa*. Interestingly, ketolide **15l** with a 'telithromycin-like' side chain was only moderately active against both macrolide sensitive and resistant strains.

As compound **15q** was one of the most active and most balanced compounds of the series presented in Table 3, it was further tested against various isolates of the important respiratory tract pathogen *Haemophilus influenzae* (Table 4). Among the reference compounds, azithromycin (**4**) was clearly the most active compound if all MIC values were considered. Telithromycin (**5**) was less active than **4** but more powerful than **1** and **2**. To our delight, ketolide **15q** seemed to be slightly more active than **5** on the basis of all MIC values. On the other hand, **15q** remained somewhat less effective than **4**.

As a summary, the best compounds **15n**, **15q** and **15r** out of the lactone series presented in this paper showed a similar antimicrobial spectrum as the reference ketolide telithromycin (**5**). They were slightly less active against macrolide resistant strains of *S. pneumoniae* but seemed to be more active against the important respiratory tract pathogen *H. influenzae*. In addition, **15q** seemed to be slightly more potent against selected Gram-negative bacteria such as *E. coli* (MIC = 8 μg/mL).

Pharmacokinetic properties of **15n** and **15q** were determined in mice and compared to reference compounds **1** and **2**. As expected, erythromycin (**1**) showed the poorest properties with oral bioavailabilities (*F*%) below 10% resulting in very low plasma levels and short plasma half life of 0.4 h in vivo. Clarithromycin (**2**) exhibited better properties (*F*% = 13%) and higher plasma levels, but still in vivo half life remained quite short (0.6 h). In contrast, both ketolide lactones investigated in this model showed markedly higher oral bioavailabilities around 60% and low total clearances and therefore, plasma levels were found to be significantly higher. In vivo half lives in plasma were found to be in the range of 1.1–1.2 h in mice; values that would allow to predict a half life in humans suitable for once a day dosing. Based on these preliminary pharmacokinetic results an in vivo experiment with compounds **15n** and **15q** as well as with other examples seemed to be justified.

Table 4. Inhibitory activity of ketolide **15q** and of selected reference compounds against *H. influenzae* (erythromycin (**1**); clarithromycin (**2**); azithromycin (**4**); telithromycin (**5**))

H. influenzae	Minimum inhibitory concentration (MIC, μg/mL)				
	1	**2**	**4**	**5**	**15q**
H. influenzae 1	4	8	2	4	1
3201	4	16	2	4	4
3457	0.5	1	0.5	0.25	0.25
3640	2	4	1	2	2
12214	4	8	2	4	2
23145	4	8	2	4	4
23369	4	16	4	4	4
H20 HDL	2	4	1	2	1
H28 HEL	2	4	1	2	2
4139	1	4	0.5	2	2
H36 ODL	4	16	2	4	2
11	4	16	2	4	4
QK 12/87	2	2	0.5	1	0.5
2947	4	16	2	4	2
ATCC 9334	4	8	2	2	4
QK 50	4	8	2	2	2
B 1501	4	8	1	2	1
H13 LAH	4	8	2	2	2
ATCC 49247	4	8	2	4	1
Rd KW20	4	8	2	4	4
Christy	4	8	2	4	2

Table 5. In vivo efficacies of selected ketolides **15** in mice

Macrolide	ED_{50} (mg/kg)	
	po[a]	sc[b]
Erythromycin (**1**)	20.0	~1.5
Telithromycin (**5**)	5.0	1.2
15n	7.1	2.5
15q	12.0	1.2
15r	7.1	<1.5

[a] Oral administration (gavage).
[b] Subcutaneous administration.

Subsequently, compounds **15n**, **15q** and **15r** were tested in vivo in a mouse infection model with erythromycin sensitive *Streptococcus pyogenes* as the pathogen. Compounds were administered both per os and subcutaneously and compared to placebo, **1** and **5**, respectively. ED_{50} values determined in this experiment are presented in Table 5. Telithromycin (**5**) was the most potent compound after oral administration, while **15n** and **15r** were slightly less active but nevertheless in the same range as **5**. Adenyl-ethyl derivative **15q** was about twofold less active than **5** but significantly more potent than erythromycin (**1**). These data are in reasonable agreement with the pharmacokinetic properties presented above. All compounds exhibited similar in vivo efficacies in terms of ED_{50} after subcutaneous administration.

3. Conclusion

The novel semisynthetic ketolide lactones **15** presented in this paper contain a fused five-membered lactone ring unprecedented so far. The aforementioned ring has been formed via intramolecular 1,4-addition of an [(hetero)arylalkylthio]acetic acid ester enolate to an α,β-unsaturated ketone. While the formation of four diastereomers had to be expected principally in this reaction, only two of them were observed by proton NMR and the minor isomer was converted into the other one later in the reaction sequence. Final ketolide products—obtained as single diastereoisomers—exhibited excellent antimicrobial properties against both erythromycin sensitive and resistant strains of Gram-positive pathogens such as *S. aureus* and *S. pneumoniae* with the exception of constitutively resistant *S. aureus*. In

addition, efficacy has been proven in vivo in a mouse infection model with *S. pyogenes* as the pathogen and compounds were active both per os and after subcutaneous administration. In vitro activities as well as in vivo efficacies of the best compounds were in the same range as the reference ketolide telithromycin. On the basis of these synthetic efforts, other novel classes of macrolides seem to be accessible as well. For example, the sulfur atom presented in **15a**–**s** may be oxidized to give the corresponding sulfone, a process that alters the lipophilicity of the side chain and therefore of the entire molecule while activity is retained. First steps along these lines showed promising results and further data are presented elsewhere.[17] As a summary, the novel class of ketolides presented in this paper emerged as a valuable lead series that might be useful in the fight against spreading pathogens showing resistance against the common macrolide antibiotics that are currently in clinical use.

4. Experimental section

Certain abbreviations are used repeatedly in the following specification. These include: TLC for thin layer chromatography; HPLC for high performance liquid chromatography; DMSO for dimethylsulfoxide; DBU for 1,8-diazabicyclo[5,4,0]undec-7-ene; DIPEA for diisopropylethylamine (Huenig's base); DIAD for diisopropyl azodicarboxylate; DMF for dimethylformamide; THF for tetrahydrofuran; DCC for *N*,*N*′-dicyclohexylcarbodiimide; DMAP for 4-dimethylaminopyridine; EDC*HCl for *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; MS for mass spectrometry; NMR for nuclear magnetic resonance; RT for room temperature; HRMS for high resolution mass spectrometry; EI for electron impact ionization; ESI for electrospray ionization. Other abbreviations are defined consecutively in the text.

Minimum inhibitory concentrations (MIC values) were determined by broth microdilution in 96-well plates. Mueller–Hinton broth (Difco) was used for *staphylococci*, *E. coli* and *P. aeruginosa*, while iso-sensitest broth (Oxoid) supplemented with 3% laked horse blood (Oxoid) was used for *S. pneumoniae*. The final inoculum was approx 10^6 colony forming units (CFU) per mL for *S. pneumoniae* and 10^5 CFU's for all other organisms. Plates were incubated for 24 h at 35 °C and then read for turbidity. The lowest compound concentration that showed no turbidity was taken as the MIC value.

In vivo mouse infection experiments were conducted as follows: mice (five animals per dose) were infected ip (intraperitoneally) with erythromycin susceptible *S. pyogenes* β15 and solutions of macrolide antibiotics were administered per os (gavage) or subcutaneously at different dosages 1 and 3 h post-infection. Erythromycin (**1**) and telithromycin (**5**) were used as reference compounds in these experiments. ED_{50} values (mg/kg) were calculated from the survival rates of infected and treated animals at day 3 after infection.

To determine pharmacokinetic properties, aqueous solutions of ketolides **15** were applied orally by gavage (at 30 mg/kg) or injected iv (at 10 mg/kg) to mice and plasma levels (ng/mL) were determined by LC–MS at 0.08, 0.25, 0.5, 0.75, 1, 2, 4 and 6 h post-administration. Some standard parameters calculated from these raw data sets (data not shown) are presented in the main section of this paper.

Thermodynamic solubilities were determined at the pH indicated in the text (mostly at pH 6.7) in 0.05 M phosphate buffer with photometric quantification of the amount of dissolved compound. Lipophilicities (logD values, distribution coefficients) were determined photometrically at pH 7.4 in 1-octanol/50 mM TAPSO buffer in the presence of 5% (v/v) DMSO. Octanol/water partition coefficients ClogP were calculated using the kowClogP software KOW 1.57, which is commercially available.

TLC was performed on Merck TLC plates with the solvent system indicated in the experimental section. Compounds were visualized using either UV at 254 nm, 1% aqueous $KMnO_4$ solution or cer-ammonium-molybdate solution (20 g $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 4 g $Ce(SO_4)_2{\cdot}4H_2O$, 360 mL water, 40 mL H_2SO_4 concd). Merck silica gel 60 (0.040–0.063 mesh) was used for flash chromatography. ^{1}H NMR spectra were measured on a Bruker DPX NMR-spectrometer at 250 and 400 MHz, respectively, in the solvent indicated. Chemical shifts are given in ppm relative to TMS; coupling constants are given in Hz. Assignments of resonances (where possible) were made based on chemical shifts and by comparison with completely assigned spectra of **1** and **2**[18] and based on two-dimensional COSY and HSQC spectra. MS spectra were taken with the ionization method indicated in the experimental part on API 365 (ESI) or Finnegan MAT 95 (EI, ESI) mass spectrometers.

Reagents were generally purchased in the highest purity available and used without further purification except where indicated in the text. Doubly protected 10,11-didehydroclarithromycin derivative **7** was synthesized in four steps from commercially available clarithromycin (**2**) (obtained from Senn Chemicals, Switzerland) according to literature procedures by Baker and coworkers.[11]

The numbering convention for ketolide lactones **15** used in the text is based on the numbering for erythromycin (**1**) as indicated in Figure 1 and Scheme 1, respectively. Note however, that the systematic names in the experimental part are based on CA nomenclature and *not* on **1**.

4.1. Synthesis of ketolides 15 via method A

4.1.1. Ethanethioic acid, *S*-[3-(pyridin-4-yl)propyl]ester (17k). Diisopropyl azodicarboxylate (DIAD) (9.8 mL, 51 mmol) was added dropwise to a solution of 13.3 g (51 mmol) triphenylphosphine in 125 mL THF kept at 0 °C. The mixture was stirred for 30 min and then a

solution of 3.47 g (25 mmol) 3-pyridin-4-yl-propanol (**16k**) and 3.6 mL (51 mmol) thioacetic acid in 50 mL THF was added. Stirring was continued for 12 h and the mixture was allowed to warm to room temperature. The yellow solution was concentrated in vacuo and the residue was purified by flash chromatography (ethyl acetate/hexanes 1:1) to give 3.2 g (65%) of the desired product **17k** as a yellow liquid. This material was used without in depth characterization. R_f: 0.20 (ethyl acetate/hexanes 1:1). MS (ESI): 196.3 (MH^+).

4.1.2. [[3-(Pyridin-4-yl)propyl]thio]acetic acid ethyl ester (18k). Compound **17k** (3.2 g, 16.4 mmol) was dissolved in 50 mL ethanol and 620 mg (16.4 mmol) $NaBH_4$ was added in one portion. The mixture was stirred at room temperature overnight and then 377 mg (17.4 mmol) NaOEt and 1.81 mL (16.4 mmol) ethyl bromoacetate were added. Stirring was continued until TLC analysis showed the presence of a single new product. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give 3.4 g (87%) of a crude product **18k** that was used without further purification.

4.1.3. [[3-(Pyridin-4-yl)propyl]thio]acetic acid (10k). Compound **18k** (3.4 g, 14.3 mmol) was dissolved in dioxane (40 mL) and 7.9 mL (15.05 mmol) of 2 N NaOH was added. The mixture was allowed to stir at room temperature for 12 h and 7.9 mL (15.1 mmol) 2 N HCl was added until the pH was about 7.0. Water was added and the aqueous phase was extracted continuously with ethyl acetate to give—after removal of the solvent in vacuo—704 mg (23%) of the desired product **10k** as a white powder. ^{1}H NMR ($CDCl_3$): 9.20 (br s, 1H), 8.35 (m, 2H), 7.27 (m, 2H), 3.26 (s, 2H), 2.83 (t, 2H, $J = 7.2$), 2.64 (t, 2H, $J = 7.2$), 2.02 (m, 2H). MS (EI): 212.2 (MH^+).

4.1.4. [[3-(Pyridin-2-yl)propyl]thio]acetic acid (10j). Was obtained in analogy to the previous reaction sequence **16k** → **10k** from 3-(pyridin-2-yl)-propanol (**16j**): ^{1}H NMR ($CDCl_3$): 13.60 (s (br), 1H), 8.60 (m, 1H), 7.73 (m, 1H), 7.26 (m, 2H), 3.31 (s, 2H), 2.98 (t, 2H, $J = 7.6$), 2.77 (t, 2H, $J = 7.6$), 2.07 (m, 2H). MS (EI): 212.2 (MH^+).

4.1.5. (10*E*)-10,11-Didehydro-11-deoxy-6-*O*-methyl-erythromycin 2′-acetate 4″-(phenylmethyl carbonate) 12-[[[3-(pyridin-4-yl)propyl]thio]acetate] (9k). Starting material **7** (400 mg, 0.441 mmol) was dissolved in CH_2Cl_2 (15 mL) and 210 mg (1.32 mmol) [[3-(pyridin-4-yl)propyl]thio]acetic acid (**10k**) and DMAP (10 mg, 0.81 mmol) were added. DCC (275 mg, 1.32 mmol) was added in one portion and the initially clear solution turned into a yellow suspension within 5 min. The mixture was allowed to stir for 48 h and was then filtered. The filtrate was diluted with CH_2Cl_2, washed with 5% aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated in vacuo. Purification of the residue by flash chromatography gave 413 mg (85%) of the desired product **9k** as a foam. R_f: 0.26 (CH_3CN/CH_2Cl_2/NH_4OH 1:1:0.1). ^{1}H NMR ($CDCl_3$): 8.51 (m, 2H, pyridine Hα), 7.36 (m, 5H, phenyl), 7.12 (m, 2H, pyridine Hβ), 6.62 (s, 1H, H11), 5.73 (dd, 1H, $J_1 = 10.8$, $J_2 = 2.4$, H13), 5.26 (d, 1H, $J = 12.5$, OCH_2Ph), 5.13 (d, 1H, $J = 12.5$, OCH_2Ph), 4.98 (m, 1H, H1″), 4.68 (dd, 1H, $J_1 = 10.8$, $J_2 = 6.6$, H2′), 4.56 (d, 1H, $J = 7.2$, H1′), 4.47 (d, 1H, $J = 9.0$, H4″), 4.36 (m, 1H, H5″), 3.91 (m, 1H, H3), 3.52–3.70 (m, 2H, H5, H5′), 3.33 (s, 3H, OMe), 3.25 (m, 1H, H8), 3.16 (s, 3H, OMe), 3.13 (s, 2H, SCH_2CO), 2.88 (m, 1H, H2), 2.70 (t, 2H, $J = 6.6$) and 2.60 (t, 2H, $J = 6.6$, S$CH_2CH_2CH_2$pyr), 2.60 (m, 2H, H3′), 2.41 (d, 1H, $J = 15.0$, H2″), 2.23 (s, 6H, NMe_2), 2.00 (s, 2H, CH_3COO), 1.88 (s, 3H, 10Me), 2.00–1.80 (m, 4H, $SCH_2CH_2CH_2$pyr, H4, H7), 1.59 (s, 3H, quart. CCH_3), 1.40–1.00 (m, ~22H, H4′, 7*CH_3), 0.93 (d, 3H, CHCH_3), 0.88 (t, 3H, CH_3CH_2). HRMS: Calcd for MH^+ ($C_{58}H_{87}O_{16}N_2S$): 1099.5771; found: 1099.5776.

4.1.6. (3*S*,3a*R*,4*R*,6*R*,8*R*,9*R*,10*S*,11*S*,12*R*,15*R*,15a*S*)-9-[[2-*O*-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-11-[[2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-4-*O*-[(phenylmethoxy)carbonyl]-α-L-*ribo*-hexopyranosyl]oxy]-15-ethyldecahydro-8-methoxy-4,6,8,10,12,15a-hexamethyl-3-[[3-(pyridin-4-yl)propyl]thio]-2*H*-furo[2,3-*c*]oxacyclotetradecin-2,5,13 (3*H*,6*H*)-trione (12k). Compound **9k** (413 mg, 0.376 mmol) was dissolved in DMF (11 mL) and cooled to 0 °C by means of an ice bath. A 1 M solution of potassium *tert*-butylate in THF (0.564 mL, 0.564 mmol) was added dropwise over a period of 50 min and the resulting mixture was allowed to stir at 0 °C for 3 h. The resulting mixture was partitioned between aqueous 0.5 M KH_2PO_4 and diethyl ether. The organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (silica gel, CH_3CN/CH_2Cl_2/NH_4OH 1:1:0.01 and ethyl acetate/MeOH 20:1) to give the desired product **12k** (88 mg, 21%) as a single diastereomer as a foam. R_f: 0.12 (CH_3CN/CH_2Cl_2/NH_4OH 1:1:0.1). ^{1}H NMR ($CDCl_3$, measured at 2 °C): 8.51 (m, 2H, pyridine Hα), 7.37 (m, 5H, phenyl), 7.22 (m, 2H, pyridine Hβ), 5.48 (dd, $J_1 = 10.0$, $J_2 = 2.4$, H13), 5.26 (d, 1H,$J_1 = 12.0$, OCH_2Ph), 5.12 (d, 1H, $J = 12.0$, OCH_2Ph), 4.95 (d, 1H, $J = 4.8$, H1″), 4.73 (dd, 1H, $J_1 = 10.0$, $J_2 = 7.6$, H2′), 4.63 (d, 1H, $J = 7.6$, H1′), 4.47 (d, 1H, $J = 9.6$, H4″), 4.38 (s, 1H, SCHCOO), 2.29 (m, 1H, H5″), 3.89 (d, 1H, $J = 8.8$, H3), 3.65 (m, 1H, H5′), 3.57 (d, 1H, $J = 6.8$, H5), 3.34 (s, 3H, OMe), 3.09 (s, 3H, OMe), hidden below (m, 1H), 2.99 (br q, 1H, $J = 6.4$, H10), 2.86 (m, 2H) and 2.70 (m, 3H, pyr$CH_2CH_2CH_2$S) and H2, 2.57 (s, 1H, H11), 2.53 (m, 1H, H3′), 2.42 (m, 1H, H2″), 2.24 (s, 6H, NMe_2), 2.15–2.00 (m, 1H), 2.07 (s, 3H, CH_3COO), 1.95–1.80 (m, 3H), 1.80–1.50 (m, ~10H), 1.44, 1.32, 1.12 3*(s, 3H, quart. CCH_3), 1.23, 1.16, 1.13, 1.10, 1.07, 0.93 6*(d, 3H, CHCH_3), hidden below (m, 1H, H4′), 0.88 (t, 3H, CH_3CH_2). MS (ESI): 1099.5 (MH^+), 550.6 ($[MH_2]^{++}$). HRMS: Calcd for MH^+ ($C_{58}H_{87}O_{16}N_2S$): 1099.5771; found: 1099.5776.

4.1.7. (3*S*,3a*R*,4*R*,6*R*,8*R*,9*R*,10*S*,11*S*,12*R*,15*R*,15a*S*)-9-[[2-*O*-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-15-ethyldecahydro-11-hydroxy-8-methoxy-4,6,8,10,12,15a-hexamethyl-3-[[3-(pyridin-4-yl)-propyl]thio]-2*H*-furo[2,3-*c*]oxacyclotetradecin-2,5,13 (3*H*,6*H*)-trione (13k). Compound **12k** (200 mg, 0.182 mmol) was subjected to acidic methanolysis in 3% HCl in methanol (2 mL) at RT for 48 h. The mixture was then diluted with CH_2Cl_2 and washed with 5% aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated to give the crude product. This was purified by flash chromatography (silica gel, $CHCl_3$/MeOH/NH_4OH 9:1:0.1) to give 109 mg (74%) of the desired product **13k** as a single diastereomer according to NMR. R_f: 0.43 ($CHCl_3$/MeOH/NH_4OH 9:1:0.1). ^1H NMR ($CDCl_3$, measured at 2 °C): 8.49 (m, 2H, pyridine Hα), 7.21 (m, 2H, pyridine Hβ), 5.58 (dd, 1H, $J_1 = 10.0$, $J_2 = 2.4$, H13), 4.77 (dd, 1H, $J_1 = 10.4$, $J_2 = 7.6$, H2′), 4.65 (d, 1H, $J = 7.6$, H1′), 4.48 (s, 1H, S*CH*COO), 3.74 (s, 1H, H3), 3.49 (m, 2H, H5, H5′), 3.13–3.00 (m, 2H, H10), 3.03 (s, 3H, OMe), 2.90–2.70 (m, 5H, S*CH*$_2$CH$_2$*CH*$_2$pyr), 2.67 (s, 1H, H11), 2.51 (m, 1H, H8), 2.26 (s, 6H, NMe_2), hidden below (m, 1H), 2.09 (s, 3H, CH_3COO), hidden below (m, 3H, SCH$_2$*CH*$_2$CH$_2$pyr), 1.91 (m, 1H), 1.80–1.20 (m, ∼9H, aliphatic H), 1.51, 1.27 2*(s, 3H, quart. CCH_3), 1.28, 1.23, 1.12, 1.10, 0.98 5*(s, 3H, CH*CH*$_3$), 0.86 (t, 3H, *CH*$_3$CH$_2$). MS (ESI): 807.4 (MH^+), 404.8 ($[MH_2]^{++}$). HRMS: Calcd for MH^+ ($C_{42}H_{67}N_2O_{11}S$): 807.4465; found: 807.4466.

4.1.8. (3*S*,3a*R*,4*R*,6*R*,8*R*,9*R*,10*R*,12*R*,15*R*,15a*S*)-9-[[2-*O*-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-15-ethyloctahydro-8-methoxy-4,6,8,10,12,15a-hexamethyl-3-[[3-(pyridin-4-yl)propyl]-thio]-2*H*-furo[2,3-*c*]oxacyclotetradecin-2,5,11,13 (3*H*,6*H*,12*H*)-tetrone (14k). Intermediate **13k** (100 mg, 0.124 mmol) was dissolved in CH_2Cl_2 (4.5 mL) and EDC*HCl (158 mg, 0.826 mmol) and DMSO (173 mg, 2.22 mmol) were added. The mixture was cooled to 5 °C by means of a water bath and a solution of pyridinium trifluoroacetate (158 mg, 0.826 mmol) in CH_2Cl_2 (4.5 mL) was added slowly. The resulting mixture was allowed to stir at 5 °C for 45 min. Water was added and the resulting mixture was partitioned between ether and 3% aqueous $NaHCO_3$ solution. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (silica gel, $CH_3CN/CH_2Cl_2/NH_4OH$ 1:1:0.01) to yield the desired protected ketolide **14k** (59 mg, 59%) as a single diastereomer as a foam. R_f: 0.60 ($CHCl_3$/MeOH/NH_4OH 9:1:0.1). ^1H NMR ($CDCl_3$, measured at 2 °C): 8.50 (m, 2H, pyridine Hα), 7.19 (m, 2H, pyridine Hβ), 5.50 (dd, 1H, $J_1 = 10.4$, $J_2 = 2.4$, H13), 4.75 (dd, $J_1 = 10.4$, $J_2 = 7.6$, H2′), 4.40 (d, 1H, $J = 7.6$, H1′), 4.28 (s, 1H, S*CH*COO), 4.24 (d, 1H, $J = 6.8$, H5), 3.85 (q, 1H, $J = 6.8$, H2), 3.56 (m, 1H, H5′), 3.11–3.00 (m, 3H, H4, H10, SC*H*$_2$CH$_2$CH$_2$pyr), 2.82–2.62 (m, 4H, H8, SC*H*$_2$CH$_2$*CH*$_2$pyr), 2.78 (s, 3H, OMe), 2.61 (s, 1H, H11), 2.57 (m, 1H, H3′), 2.25 (s, 6H, NMe_2), 2.07 (s, 3H, CH_3COO), hidden below (m, 2H, SCH$_2$*CH*$_2$CH$_2$pyr), 1.94 (m, 1H, CH$_3$C*H*$_2$CH), 1.80–1.55 (m, ∼4H, aliphatic H), 1.51, 1.31 2*(s, 3H, quart. C*CH*$_3$), 1.40, 1.26, 1.18, 1.16, 1.11 5*(d, 3H, CH*CH*$_3$), hidden below (m, 1H, H4′), 0.89 (t, 3H, *CH*$_3$CH$_2$). MS (ESI): 805.4 (MH^+), 403.8 ($[MH_2]^{++}$). HRMS: Calcd for MNa^+ ($C_{42}H_{64}N_2O_{11}SNa$): 827.4128; found: 827.4128.

4.1.9. (3*S*,3a*R*,4*R*,6*R*,8*R*,9*R*,10*R*,12*R*,15*R*,15a*S*)-15-Ethyloctahydro-8-methoxy-4,6,8,10,12,15a-hexamethyl-3-[[3-(pyridin-4-yl)propyl]thio]-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-2*H*-furo[2,3-*c*]oxacyclotetradecin-2,5,11,13 (3*H*,6*H*,12*H*)-tetrone (15k). Protected ketolide **14k** (59 mg, 0.073 mmol) was dissolved in methanol (2.0 mL) and allowed to stir for 48 h. The solution was then concentrated in vacuo and the residue was purified by flash chromatography (silica gel, $CH_3CN/CH_2Cl_2/NH_4OH$ 1:1:0.01) to give the desired deprotected ketolide **15k** as a single diastereomer. Colorless foam: 48 mg (86%). R_f: 0.10 ($CHCl_3$/MeOH/NH_4OH 9:1:0.1). ^1H NMR ($CDCl_3$): 8.49 (m, 2H, pyridine Hα), 7.18 (m, 2H, pyridine Hβ), 5.50 (dd, 1H, $J_1 = 10.0$, $J_2 = 2.4$, H13), 4.33 (d, 1H, $J = 7.2$, H1′), 4.28 (d, 1H, $J = 7.2$, H5), 4.26 (s, 1H, S*CH*COO), 3.86 (q, 1H, $J = 6.8$, H2), 3.56 (m, 1H, H5′), 3.50 (br, 1H, OH), 3.18 (dd, 1H, $J_1 = 10.0$, $J_2 = 7.2$, H2′), 3.14–3.00 (m, 3H, H4, H10, SC*H*$_2$CH$_2$CH$_2$pyr), 2.79 (s, 3H, OMe), 3.88–2.65 (m, 3H, SC*H*$_2$CH$_2$*CH*$_2$pyr), 2.63 (s, 1H, H11), 2.57 (m, 1H, H8), 2.47 (m, 1H, H3′), 2.27 (s, 6H, NMe_2), 2.05 (m, 2H, SCH$_2$CC*H*CH$_2$pyr), 1.94 (m, 1H, CHC*H*$_2$CH$_3$ (H14)), 1.80–1.63 (m, 3H, H7, H7, H4′), 1.59 (m, 1H, CHC*H*$_2$CH$_3$ (H14)), 1.52, 1.32 2*(s, 3H, quart. CCH_3), 1.38, 1.33, 1.24, 1.14, 1.12 5*(d, 3H, CH*CH*$_3$), hidden below (m, 1H, H4′), 0.89 (t, *CH*$_3$CH$_2$). MS (ESI): 763.3 (MH^+), 382.3 ($[MH_2]^{++}$). HRMS: Calcd for MNa^+ ($C_{40}H_{63}N_2O_{10}SNa$): 785.4021; found: 785.4023.

4.2. Synthesis of ketolides 15 via method B

4.2.1. (10*E*)-10,11-Didehydro-11-deoxy-6-*O*-methyl-erythromycin 2′-acetate 12-[chloroacetate] 4″-(phenyl-methyl carbonate) (8). 10,11-Anhydroclarithromycin (**7**) (250 mg, 0.276 mmol) synthesized according to Baker and co-workers[11] was dissolved in CH_2Cl_2 (5 mL) under argon and chloroacetic acid (156 mg, 1.66 mmol) and DMAP (5 mg, 0.16 mmol) were added. *N*,*N*-Dicyclohexylcarbodiimide (341 mg, 1.65 mmol) was added in one portion and the clear solution turned into a suspension within 5 min. The resulting mixture was allowed to stir for $1\frac{1}{2}$ days. The reaction mixture was filtered and the filtrate was diluted with CH_2Cl_2, washed with 5% aqueous $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash chromatography on silica gel using $CH_3CN/CH_2Cl_2/NH_4OH$ 1:1:0.01 as an eluent. Evaporation of the fractions containing the desired product gave 213 mg (79%) of a brownish foam. R_f: 0.61 (CH_2Cl_2/MeOH/NH_4OH 100:10:1). ^1H NMR ($CDCl_3$): 7.36 (m, 5H, phenyl), 6.60 (s, 1H, H11), 5.71 (dd, 1H, $J_1 = 10.4$, $J_2 = 2.4$, H13), 5.25 (d, 1H, $J = 12.4$, OC*H*$_2$Ph), 5.14 (d, 1H, $J = 12.4$, OC*H*$_2$Ph), 4.97 (m, 1H, H1″), 4.68 (m, 1H, H2′), 4.56 (d, 1H, $J = 7.2$, H1′), 4.45 (d, 1H, $J = 9.6$, H4″), 4.35 (m, 1H, H5″), 3.99 (s, 2H, ClC*H*$_2$CO), 3.81 (m, 1H, H3), 3.60 (m, 1H, H5′),

3.55 (d, 1H, $J = 6.8$, H5), 3.32 (s, 3H, OCH_3), 3.20 (m, 1H, H8), 3.12 (s, 3H, OCH_3), 2.87 (m, 1H, H2), 2.66 (m, 1H, H3′), 2.40 (d, 1H, $J = 15.2$, H2″), 2.23 (s, 6H, NMe_2), 2.01 (s, 3H, CH_3COO), 1.86 (s, 3H, C10-CH_3), 1.93–1.80 (m, 2H, H4, H7), 1.78–1.50 (m, 4H, H20, H20, H4′, H2″), 1.65 (s, 3H, quart. C–CH_3), 1.42 (m, 1H, H7), 1.40–1.10 (m, ~10H, H4′, 3CH_3), 1.08, 0.92 2*(d, 3H, CHCH_3), 0.89 (t, 3H, $J = 7.2$, CH_3CH_2). MS (ESI): 982.4 (MH^+). HRMS: Calcd for MH^+ ($C_{50}H_{77}NO_{16}Cl$): 982.4934; found: 982.4932.

4.2.2. 9-(2-Hydroxyethyl)-6-amino-9*H*-purine (20q). Adenine (**19q**, 2.7 g, 20 mmol) was suspended in DMF (100 mL) and 1.76 g (20 mmol) ethylene carbonate was added. After addition of a catalytic amount of NaOH (15 mg), the mixture was stirred at 160 °C for 2 h. DMF was removed in vacuo and the residue was crystallized from EtOH (350 mL) to give 2.1 g (59%) of **20q** as a brownish solid. ^{1}H NMR (DMSO-d_6): 3.74 (q, 2H, CH_2OH), 4.18 (t, 2H, NCH_2), 4.99 (t, 1H, OH), 7.16 (br s, 2H, NH_2), 8.07 (s, 1H, adenine H), 8.13 (s, 1H, adenine H). MS (EI): 179.1 (M^+).

4.2.3. 9-(2-Chloroethyl)-6-amino-9*H*-purine (21q). Compound **20q** (1.97 g, 11 mmol) was suspended in 20 mL thionyl chloride and heated at 70 °C for 45 min. Excess thionyl chloride was removed in vacuo and the residue was dissolved in water (100 mL). The aqueous solution was basified with $NaHCO_3$ solution (10%) and the resulting slurry was stirred for 15 min. The product was isolated by filtration, washed with water and dried to give 1.25 g of a brownish solid. The crystallization step was repeated to give another 220 mg of product **21q**. Total yield: 1.47 g (68%). ^{1}H NMR (DMSO-d_6): 4.07 (t, 2H), 4.50 (t, 2H), 7.23 (br s, 2H), 8.15 (s, 1H), 8.17 (s, 1H). MS (EI): 197.1 (M^+).

4.2.4. Ethanethioic acid, *S*-[[6-amino-9*H*-purine-9-yl]-ethyl]ester (22q). Compound **21q** (1.2 g, 6.07 mmol) was suspended in acetone (30 mL). After addition of solid potassium thioacetate (870 mg, 7.6 mmol), the mixture was heated to reflux for 12 h. The suspension was concentrated in vacuo, suspended in CH_2Cl_2 and chromatographed on 120 g of silica gel, eluting with a gradient of 0–9% methanol in CH_2Cl_2. The appropriate fractions were combined and evaporated to give 1.4 g (97%) of **22q** as a brownish solid. ^{1}H NMR (DMSO-d_6): 2.30 (s, 3H), 3.40 (t, 2H), 4.32 (t, 2H), 7.20 (br s, 2H), 8.11 (s, 1H), 8.14 (s, 1H). MS (EI): 237.1 (M^+).

4.2.5. (6-Amino-9*H*-purine)-1-ethanethiol (11q). Compound **22q** (1.3 g, 5.5 mmol) was suspended in 50 mL degassed methanol, kept under argon. Gaseous ammonia was bubbled through the solution for 5 min and the internal temperature rose to 40 °C. The resulting solution was stirred for 60 min and a colorless precipitate was observed. The suspension was filtered and the filtrate was concentrated and the fluffy solid thus obtained was dried at 60 °C in vacuo. Yield of **11q**: 850 mg (79%). ^{1}H NMR (DMSO-d_6): 2.50 (1H, covered by DMSO), 2.96 (br q, 2H), 4.30 (t, 2H), 7.20 (br s, 2H), 8.14 (s, 2H). MS (EI): 195.1 (M^+). The product was contaminated with approx. 5% of the corresponding disulfide.

In a similar fashion, the following side chain building blocks **11** were obtained:

[4-(Pyridin-3-yl)-1*H*-imidazole]-1-ethanethiol (**11l**) from 4-(pyridin-3-yl)-1*H*-imidazole (**19l**):[19] ^{1}H NMR ($CDCl_3$): 1.44 (br t, 1H), 2.94 (br q, 2H), 4.20 (t, 2H), 7.31 (dd, 1H), 7.32 (s, 1H), 7.62 (s, 1H), 8.11 (m, 1H), 8.49 (m, 1H), 8.97 (d, 1H). MS (EI): 206.0 (MH^+).

[3-(Pyridin-4-yl)-1*H*-pyrazole]-1-ethanethiol (**11m**) from 3-(pyridin-4-yl)-1*H*-pyrazole (**19m**):[12] ^{1}H NMR ($CDCl_3$): 1.38 (t, 1H), 3.05 (td, 2H), 4.36 (t, 2H), 6.65 (d, 1H), 7.52 (d, 1H), 7.67 (m, 2H), 8.62 (m, 2H). MS (EI): 205.1 (M^+).

[3-(Pyridin-3-yl)-1*H*-pyrazole]-1-ethanethiol (**11n**) from 3-(pyridin-3-yl)-1*H*-pyrazole (**19n**):[20] ^{1}H NMR (DMSO-d_6): 2.41 (br t, 1H), 2.96 (br q, 2H), 4.32 (t, 2H), 6.83 (d, 1H), 7.42 (m, 1H), 7.87 (d, 1H), 8.14 (m, 1H), 8.49 (m, 1H), 9.01 (d, 1H). MS (ESI): 206.2 (MH^+).

[3-(Pyridin-4-yl)-1*H*-1,2,4-triazole-1-yl]-1-ethanethiol (**11o**) from 3-(pyridin-4-yl)-1*H*-1,2,4-triazole (**19o**): ^{1}H NMR (DMSO-d_6): 2.51 (br t, 1H), 2.99 (br q, 2H), 4.43 (t, 2H), 7.91 (m, 2H), 8.68 (m, 2H), 8.71 (s, 1H). MS (EI): 206.1 (M^+).

[3-(Pyridin-3-yl)-1*H*-1,2,4-triazole-1-yl]-1-ethanethiol (**11p**) from 3-(pyridin-3-yl)-1*H*-1,2,4-triazole (**19p**):[21] ^{1}H NMR (DMSO-d_6): 2.50 (br t, 1H), 2.98 (br q, 2H), 4.41 (t, 2H), 7.51 (m, 1H), 8.31 (m, 1H), 8.62 (m, 1H), 8.67 (s, 1H), 9.17 (s, 1H). MS (EI): 206.1 (M^+).

(6-Amino-9*H*-purine)-1-propanethiol (**11r**) from 9-(3-chloropropyl)-6-amino-9*H*-purine (**21r**) (made according to the literature[22] from adenine and 1-bromo-3-chloropropane) in analogy to the procedure outlined in Scheme 2. ^{1}H NMR (DMSO-d_6): 8.14 (s, 2H), 7.20 (br s, 2H), 4.24 (t, 2H), 2.56 (br t, 1H), 2.31 (br q, 2H), 2.08 (m, 2H). MS (ESI): 210.2 (MH^+).

(*N*,*N*-Dimethyl-6-amino-9*H*-purine)-1-ethanethiol (**11s**) from *N*,*N*-dimethyl-6-amino-9*H*-purine (**19s**): ^{1}H NMR ($CDCl_3$): 8.34 (s, 1H), 7.80 (s, 1H), 4.37 (t, H), 3.54 (br s, 6H), 3.01 (m, 2H), 1.37 (t, 1H). MS (EI): 223.1 (M^+).

4.2.6. (10*E*)-10,11-Didehydro-11-deoxy-6-*O*-methyl-erythromycin 2′-acetate 12-[[[2-[6-amino-9*H*-purine-9-yl]-ethyl]thio]acetate] 4″-(phenylmethyl carbonate) (9q). To a solution of 214 mg (218 μmol) **8** in 8 mL acetone were added 36 μL DBU and a catalytic amount of NaI. (6-Amino-9*H*-purine)-1-ethanethiol (**11q**, 45 mg, 230 μmol) was added in one portion and the resulting suspension was allowed to stir at room temperature. The suspension gradually cleared to give a slightly hazy solution. The reaction mixture was diluted with CH_2Cl_2, extracted with 5% aqueous $NaHCO_3$, dried over Na_2SO_4 and evaporated. The crude product was purified by flash

chromatography on silica gel (ethyl acetate/methanol/NEt_3 9:1:0.1) to give 193 mg (76%) of the desired product **9q** as a glass. R_f: 0.37 ($CHCl_3$/MeOH/NH_4OH 9:1:0.1). ^1H NMR ($CDCl_3$): 8.35 (s, 1H, adenine H), 7.86 (s, 1H, adenine H), 7.36 (m, 5H, phenyl), 6.60 (s, 1H, H11), 5.71 (dd, 1H, $J_1 = 10.0$, $J_2 = 2.4$, H13), 5.51 (br s, 2H, NH_2), 5.24 (d, 1H, $J = 12.4$, OCH_2Ph), 5.13 (d, 1H, $J = 12.4$, OCH_2Ph), 4.97 (m, 1H, H1″), 4.68 (dd, 1H, $J_1 = 10.4$, $J_2 = 1.8$, H2′), 4.56 (d, 1H, $J = 7.2$, H1′), 4.45 (d, 1H, $J = 9.6$, H4″), 4.40 (t, 2H, $J = 6.4$, NCH_2CH$_2$S), 4.37 (m, 1H, H5″), 3.79 (m, 1H, H3), 3.60 (m, 1H, H5′), 3.56 (d, 1H, $J = 6.8$, H5), 3.32 (s, 3H, OMe), 3.24 (m, 1H, H8), 3.16 (s, 2H, SCH_2COO), 3.15 (s, 3H, OCH_3), 3.09 (t, 2H, $J = 6.8$, NCH$_2$CH_2S), 2.88 (m, 1H, H2), 2.67 (m, 1H, H3′), 2.40 (d, 1H, $J = 15.2$, H2″), 2.23 (s, 6H, NMe_2), 2.00 (s, 3H, CH_3COO), 1.87 (s, 3H, C10-CH_3), hidden below (m, 3H, H4, H7, H7), 1.61 (s, 3H, quart. CCH_3), 1.75–1.45 (m, 4H, aliphatic H), 1.40–1.05 (m, ~22H, H4′ and 7*CH_3), 0.92 (d, 3H, CHCH_2), 0.87 (t, 3H, CH_3CH$_2$). MS (ESI): 1141.5 (MH^+), 571.3 ($[MH_2]^{++}$). HRMS: Calcd for MH^+ ($C_{57}H_{85}N_6O_{16}S$): 1141.5743; found: 1141.5739.

4.2.7. (3*S*,3a*R*,4*R*,6*R*,8*R*,9*R*,10*S*,11*S*,12*R*,15*R*,15a*S*)-9-[[2-*O*-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-3-[[2-[6-amino-9*H*-purine-9-yl]ethyl]-thio]-11-[[2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-4-*O*-[(phenylmethoxy)carbonyl]-α-L-*ribo*-hexopyranosyl]oxy]-15-ethyldecahydro-8-methoxy-4,6,8,10,12,15a-hexamethyl-2*H*-furo[2,3-*c*]oxacyclotetradecin-2,5,13 (3*H*,6*H*)-trione (12q-A) and corresponding DMF condensation product (12q-B). Sodium hydride dispersion (approx. 55% in oil, 77 mg, 1.6 mmol) was suspended in DMF (4 mL) and cooled to 0 °C by means of an ice bath. A solution of **9q** in 10 mL DMF was added slowly by syringe and the resulting mixture was allowed to stir for 90 min. TLC analysis revealed the complete consumption of the starting material and three major new product spots were observed. The reaction mixture was partitioned between 0.5 M KH_2PO_4 and diethyl ether. The organic layer was separated, washed with water and brine, dried over $MgSO_4$ and evaporated to give 641 mg (88%) of crude product that was used without further purification. Mixture of two compounds **12q-A** and **12q-B** with different molecular weight: **12q-A**; MS (ESI): 1141.4 (MH^+), 571.8 ($[MH_2]^{++}$), **12q-B**; 1196.2 ([MH+DMF−H_2O]$^+$), 599.1 ([MH_2+DMF−H_2O]$^{++}$). R_f values: three major spots at R_f 0.50–0.65 ($CHCl_3$/MeOH/NH_4OH 9:1:0.1).

4.2.8. (3*S*,3a*R*,4*R*,6*R*,8*R*,9*R*,10*S*,11*S*,12*R*,15*R*,15a*S*)-9-[[2-*O*-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-3-[[2-[6-amino-9*H*-purine-9-yl]ethyl]-thio]-15-ethyldecahydro-11-hydroxy-8-methoxy-4,6,8,10,12,15a-hexamethyl-2*H*-furo[2,3-*c*]oxacyclo-tetradecin-2,5,13 (3*H*,6*H*)-trione (13q). Compound mixture **12q-A/12q-B** obtained in the previous step (640 mg, 0.561 mmol) was subjected to acidic methanolysis in 20 mL methanol containing 3% HCl at RT for 20 h. The reaction mixture was concentrated in vacuo, taken up in 5% $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography on silica gel (5 g cartridge) using ethyl acetate/MeOH/NEt_3 9:1:0.1 as an eluent. The product **13q** was obtained as a slightly yellow solid. Yield: 407 mg (85%). R_f: 0.40 ($CHCl_3$/MeOH/NH_4OH 9:1:0.1). ^1H NMR ($CDCl_3$): 8.32 (s, 1H, adenine H), 8.21 (s, 1H, adenine H), 5.54 (br s, 2H, NH_2), 5.45 (dd, 1H, $J_1 = 10.0$, $J_2 = 1.5$, H13), 4.47 (dd, 1H, $J_1 = 10.0$, $J_2 = 8.0$, H2′), 4.71 (m, 1H, NCH_2CH$_2$S), 4.68 (d, $J = 4.0$, H1′), 4.59 (s, 1H, SCHCOO), 4.55 (m, 1H, NCH_2CH$_2$S), 3.77 (s, 1H), 3.62 (m, 1H, NCH$_2$CH_2S), 3.50 (m, 1H), 3.43 (m, 1H, NCH$_2$CH_2S), 3.20–3.05 (m, 3H, H4, H10 and ?), 2.97 (s, 3H, OMe), 2.77–2.65 (m, 2H, H2, H8), 2.65 (s, 1H, H11), 2.60–2.50 (m, 2H, H3′, OH?), 2.26 (s, 6H, NMe_2), 2.06 (s, 3H, CH_3COO), 1.90 (m, 1H, CH_2CH$_3$), 1.80–1.50 (m, several aliphatic H), 1.47, 1.33 2*(s, 3H, quart. CCH_3), 1.25, 1.20, 1.16, 1.14, 0.98 5*(d, 3H, CHCH_3), 8.82 (t, 3H, CH_2CH_3). MS (ESI): 849.3 (MH^+), 425.7 ($[MH_2]^{++}$). HRMS: Calcd for MH^+ ($C_{41}H_{65}N_6O_{11}S$): 849.4436; found: 849.4432.

4.2.9. (3*S*,3a*R*,4*R*,6*R*,8*R*,9*R*,10*R*,12*R*,15*R*,15a*S*)-9-[[2-*O*-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-3-[[2-[6-amino-9*H*-purine-9-yl]ethyl]thio]-15-ethyloctahydro-8-methoxy-4,6,8,10,12,15a-hexamethyl-2*H*-furo[2,3-*c*]oxacyclotetradecin-2,5,11,13 (3*H*,6*H*,12*H*)-tetrone-sulfilimine derivative (14q-A). To a suspension of **13q** (390 mg, 0.459 mmol), EDC*HCl (587 mg, 3.06 mmol) and DMSO (0.587 mL, 8.27 mmol) in 4.5 mL CH_2Cl_2 was added a solution of pyridinium trifluoroacetate (592 mg, 3.06 mmol) in 12 mL in CH_2Cl_2 slowly at 5 °C. The mixture gradually cleared and stirring was continued at 5 °C for 30 min and then for two hours at RT. The mixture was poured into 5% $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give a crude product. The product was purified on silica gel (10 g cartridge) using ethyl acetate/MeOH/NEt_3 as an eluent. The fractions containing the product were combined and evaporated to give the desired compound as the sulfilimine derivative **14q-A**. Yield: 348 mg (89%). R_f: 0.44 ($CHCl_3$/MeOH/NH_4OH 9:1:0.1). ^1H NMR ($CDCl_3$): 8.24 (s, 1H, adenine H), 8.04 (s, 1H, adenine H), 5.38 (dd, 1H, $J_1 = 10.0$, $J_2 = 2.0$, H13), 4.77 (m, 1H, H2′), 4.63 (m, 1H, NCH_2CH$_2$S), 4.48 (m, 1H, NCH_2CH$_2$S), 4.43 (d, 1H, $J = 7.6$, H1′), 4.41 (s, 1H, SCHCOO), 4.26 (d, 1H, $J = 5.6$, H5), 3.80 (q, 1H, $J = 6.8$, H2), 3.65–3.50 (m, 2H, H5′, NCH$_2$CH_2S), 3.18–3.04 (m, ~7H), 2.84 (s, 6H, NSMe_2), 2.72 (s, 3H, OMe), hidden below (m, 1H, H8), 2.65 (s, 1H, H11), 2.60 (m, 1H, H3′), 2.29 (br s, 6H, NMe_2), 2.05 (s, 3H, CH_3COO), 1.93 (m, 1H, CH_3CH_2), 1.71–1.52 (m, ~7 aliphatic H), 1.52 (s, 3H, quart. CCH_3), 1.40–1.10 (m, ~19H, 6*CH_3, 1 aliphatic H), 0.86 (t, 3H, CH_3CH_3). MS (ESI): 907.6 (MH^+).

4.2.10. (3*S*,3a*R*,4*R*,6*R*,8*R*,9*R*,10*R*,12*R*,15*R*,15a*S*)-3-[[2-[6-Amino-9*H*-purine-9-yl]ethyl]thio]-15-ethyloctahydro-8-methoxy-4,6,8,10,12,15a-hexamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-2*H*-furo-[2,3-*c*]oxacyclotetradecin-2,5,11,13 (3*H*,6*H*,12*H*)-tetrone (15q). Protected compound **14q-A** (340 mg, 0.4 mmol)

was dissolved in methanol (50 mL) and allowed to stir at RT for 48 h. After completion of the reaction, the mixture was concentrated in vacuo. The residue was taken up in CH_2Cl_2 and the organic layer was washed with 3% aqueous $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (10 g silica gel cartridge) using ethyl acetate/MeOH/NEt_3 9:1:0.1 as an eluent. Fractions containing pure product were combined and evaporated to give 205 mg (63%) of the desired product **15q** as a foam. R_f: 0.4 ($CHCl_3$/MeOH/NH_4OH 9:1:0.1). ^1H NMR ($CDCl_3$): 8.34 (s, 1H, adenine H), 8.22 (s, 1H, adenine H), 5.48 (br s, 2H, NH_2), 5.38 (dd, 1H, $J_1 = 10.0$, $J_2 = 2.4$, H13), 4.68 (m, 1H, NCH_2CH$_2$S), 4.51 (m, 1H, NCH_2CH$_2$S), 4.39 (s, 1H, S*CH*COO), 4.33 (d, 1H, $J = 7.2$, H1′), 4.29 (d, 1H, $J = 6.8$, H5), 3.84 (q, 1H, $J = 6.8$, H2), 3.60–3.52 (m, 2H, H5′, NCH$_2$CH_2S), 3.50 (br, 1H, OH), 3.19 (dd, 1H, $J_1 = 10.4$, $J_2 = 7.2$, H2′), 3.17–3.05 (m, 3H, H4, H10, NCH$_2$CH_2S), 2.70 (s, 3H, OMe), 2.62 (s, 1H, H11), hidden below (m, 1H, H8), 2.45 (m, 1H, H3′), 2.27 (6H, NMe_2), 1.92 (m, 1H, CH_3CH_2), 1.72–1.50 (m, 5 aliphatic H), 1.53, 1.38 2*(s, 3H, quart. CCH_3), 1.33, 1.32, 1.26, 1.17, 1.16 5*(d, 3H, CHCH_3), hidden below (m, 1H, H4″), 0.85 (t, 3H, CH_2CH_3). MS (ESI): 805.5 (MH^+), 403.7 ($[MH_2]^{++}$). HRMS: Calcd for MH^+ ($C_{39}H_{61}N_6O_{10}S$): 805.4170; found: 805.4166.

4.2.11. (3a*R*,4*R*,6*R*,8*R*,9*R*,10*R*,12*R*,15*R*,15a*S*)-15-Ethyloctahydro-8-methoxy-4,6,8,10,12,15a-hexamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]-oxy]-2*H*-furo[2,3-*c*]oxacyclotetradecin-2,5,11,13 (3*H*,6*H*,12*H*)-tetrone (16). To a solution of 20 mg (26.7 μmol) **15e** in 1.0 mL ethyl acetate was added Raney nickel (previously washed successively with water, methanol and ethyl acetate). The mixture was stirred vigorously for 12 h and filtered. Removal of the solvent in vacuo gave 15 mg (92%) of a colorless solid. ^1H NMR ($CDCl_3$, diagnostic signals only): 0.86 (t, 3H), 1.06 (d, 3H), 1.13 (d, 3H), 1.24 (d, 3H), 1.31 (s, 3H), 1.32 (d, 3H), 1.37 (d, 3H), 1.49 (s, 3H), 2.27 (s, 6H), 2.62 (s, 3H), 3.02 (br q, 1H), 3.49 (br s, 1H), 3.56 (m, 1H), 3.88 (q, 1H), 4.25 (d, 1H), 4.32 (d, 1H), 4.88 (dd, 1H). MS (ESI): 612.3 (MH^+).

All ketolides that were synthesized in analogy to the examples **15k** and **15q**, respectively, are summarized in Table 6. The synthetic method is indicated. Structures of all compounds are confirmed by selected spectroscopic properties.

Table 6. Spectroscopic properties of ketolides **15a–s**

Ketolide	Method	MS (ESI) MH^+ found	HRMS (ESI, MH^+)		^1H NMR (δ, $CDCl_3$), representative signals only
			Calcd	Found	
15a	A	658.2	658.3625	658.3622	0.88 (t, 3H), 1.11 (d, 3H), 1.13 (d, 3H), 1.25 (d, 3H), 1.31 (s, 3H), 1.32 (d, 3H), 1.37 (d, 3H), 1.51 (s, 3H), 2.27 (s, 6H), 2.41 (s, 3H), 2.58 (s, 1H), 2.77 (s, 3H), 3.03 (q, 1H), 3.11 (m, 1H), 3.19 (dd, 1H), 3.58 (m, 1H), 3.85 (q, 1H), 4.16 (s, 1H), 4.27 (d, 1H), 4.33 (d, 1H), 5.58 (dd, 1H)
15b	A	720.5	720.3781	720.3790	0.93 (t, 3H), 1.09 (t, 3H), 1.13 (t, 3H), 1.26 (t, 3H), 1.34 (d, 3H), 1.35 (s, 3H), 1.40 (d, 3H), 1.52 (s, 3H), 2.27 (s, 6H), 2.82 (s, 1H), 2.86 (s, 3H), 3.08 (q, 1H), 3.10–3.22 (m, 2H), 3.57 (m, 1H), 3.87 (q, 1H), 4.30 (d, 1H), 4.35 (d, 1H), 4.62 (s, 1H), 5.38 (dd, 1H), 7.28–7.37 (m, 3H), 7.70 (dd, 2H)
15c	A	734.4	nd[a]		0.88 (t, 3H), 1.03 (d, 3H), 1.09 (d, 3H), 1.24 (d, 3H), 1.30 (s, 3H), 1.31 (d, 3H), 1.49 (s, 3H), 2.26 (s, 6H), 2.59 (s, 1H), 2.75 (s, 3H), 3.57 (m, 1H), 4.83 (q, 1H), 4.02 (d, 1H), 4.15 (d, 1H), 4.18 (s, 1H), 4.25 (d, 1H), 4.33 (d, 1H), 5.53 (dd, 1H), 7.20–7.43 (m, 5H)
15d	A	748.5	748.4094	748.4100	0.88 (t, 3H), 1.14 (2d, 6H), 1.25 (d, 3H), 1.32 (s, 3H), 1.33 (d, 3H), 1.37 (d, 3H), 1.51 (s, 3H), 2.26 (s, 6H), 2.62 (s, 1H), 2.73 (s, 3H), 3.86 (q, 1H), 4.27 (d, 1H), 4.34 (d, 1H), 4.35 (s, 1H), 5.53 (dd, 1H), 7.13–7.28 (m, 5H)
15e	A	762.4	762.4251	762.4246	0.89 (t, 3H), 1.11 (d, 3H), 1.13 (d, 3H), 1.24 (d, 3H), 1.32 (s, 3H), 1.33 (d, 3H), 1.38 (d, 3H), 1.51 (s, 3H), 2.03 (m, 2H), 2.27 (s, 6H), 2.62 (s, 1H), 2.80 (s, 3H), 3.86 (q, 1H), 4.26 (s, 1H), 4.28 (d, 1H), 4.33 (1H), 5.53 (dd, 1H), 7.12–7.32 (m, 5H)
15f	A	764.3	nd		0.88 (t, 3H), 1.10 (d, 3H), 1.13 (d, 3H), 1.23–1.40 (3d, 1s), 1.51 (s, 3H), 2.26 (s, 6H), 2.67 (s, 1H), 2.75 (s, 3H), 3.58 (m, 1H), 3.87 (q, 1H), 4.23–4.38 (m, 5H), 5.47 (dd, 1H), 6.89–7.00 (m, 3H), 7.21–7.32 (m, 2H)
15g	A	780.5	nd		0.93 (t, 3H), 1.07 (d, 3H), 1.13 (d, 3H), 1.27 (d, 3H), 1.34 (d, 3H), 1.36 (s, 3H), 1.40 (d, 3H), 1.51 (s, 3H), 2.27 (s, 6H), 2.82 (s, 1H), 2.88 (s, 3H), 3.58 (m, 1H), 3.87 (s, 3H), 3.88 (q, 1H), 3.93 (s, 3H), 4.31 (d, 1H), 4.35 (d, 1H), 4.51 (s, 1H), 5.36 (dd, 1H), 6.84 (d, 1H), 7.28 (d, 1H), 7.30 (s, 1H)
15h	A	799.4	799.4203	799.4197	0.86 (t, 3H), 1.51 (s, 3H), 2.27 (s, 6H), 2.63 (s, 1H), 2.65 (s, 3H), 3.83 (q, 1H), 4.25 (d, 1H), 4.33 (d, 1H), 4.41 (s, 1H), 5.50 (dd, 1H), 7.46 (t, 1H), 7.49 (d, 1H), 7.68 (td, 1H), 7.77 (d, 1H), 8.03 (d, 1H), 8.05 (d, 1H)
15i	A	749.5	749.4047	749.4049	0.87 (t, 3H), 1.13 (2d, 6H), 1.25 (d, 3H), 1.31 (s, 3H), 1.32 (d, 3H), 1.35 (d, 3H), 1.50 (s, 3H), 2.27 (s, 6H), 2.62 (s, 1H), 2.67 (s, 3H), 3.57 (m, 1H), 3.84 (q, 1H), 4.27 (d, 1H), 3.33 (d, 1H), 4.35 (s, 1H), 5.48 (dd, 1H), 7.08 (dd, 1H), 7.35 (d, 1H), 7.57 (td, 1H), 8.52 (d, 1H)

(*continued on next page*)

Table 6 (*continued*)

Ketolide	Method	MS (ESI) MH^+ found	HRMS (ESI, MH^+)		^1H NMR (δ, $CDCl_3$), representative signals only
			Calcd	Found	
15j	A	763.3	nd		0.89 (t, 3H), 1.10 (d, 3H), 1.13 (d, 1H), 1.24 (d, 3H), 1.32 (s, 3H), 1.33 (d, 3H), 1.37 (d, 3H), 1.50 (s, 3H), 2.26 (s, 6H), 2.63 (s, 1H), 2.80 (s, 3H), 3.56 (m, 1H), 3.86 (q, 1H), 4.27 (s, 1H), 4.28 (d, 1H), 4.35 (d, 1H), 5.53 (dd, 1H), 7.09 (dd, 1H), 7.22 (d, 1H), 7.58 (td, 1H), 8.52 (d, 1H)
15k	A	763.1	763.4203	763.4199	See experimental part for a full description
15l	B	815.3	nd		0.87 (t, 3H), 1.14 (2 overlapping d, 6H), 1.53 (s, 3H), 2.32 (s, 6H), 2.61 (s, 1H), 2.64 (s, 3H), 3.83 (q, 3H), 4.24 (d, 1H), 4.30–4.40 (m, 4H), 5.43 (dd, 1H), 7.27 (m, 1H), 7.54 (s, 1H), 7.69 (s, 1H), 8.07 (m, 1H), 8.44 (m, 1H), 9.00 (d, 1H)
15m	B	815.4	815.4265	815.4262	0.86 (t, 3H), 1.15 (2d, 6H), 1.26 (d, 3H), 1.31 (d, 3H), 1.33 (s, 3H), 1.35 (d, 3H), 1.52 (s, 3H), 2.27 (s, 6H), 2.61 (s, 1H), 2.68 (s, 3H), 3.84 (q, 1H), 4.28 (s, 1H), 4.33 (s, 1H), 4.33 (d, 1H), 4.56 (m, 2H), 5.41 (dd, 1H), 6.57 (d, 1H), 7.66 (m, 2H), 7.79 (d, 1H), 8.60 (m, 2H)
15n	B	815.6	815.4265	815.4270	0.87 (t, 3H), 1.15 (2d, 6H), 1.27 (d, 3H), 1.32 (d, 3H), 1.33 (s, 3H), 1.34 (d, 3H), 1.52 (s, 3H), 2.29 (s, 6H), 2.63 (s, 1H), 2.67 (s, 3H), 2.84 (q, 1H), 4.28 (d, 1H), 4.34 (s, 1H), 4.35 (d, 1H), 4.45–4.51 (m, 2H), 5.42 (dd, 1H), 6.50 (d, 1H), 7.29 (m, 1H), 7.78 (d, 1H), 8.08 (m, 1H), 8.52 (m, 1H), 8.98 (d, 1H)
15o	B	816.2	816.4217	816.4218	0.86 (t, 3H), 1.16 (2d, 6H), 1.53 (s, 3H), 2.29 (s, 6H), 2.61 (s, 1H), 2.65 (s, 3H), 3.84 (q, 1H), 4.22–4.38 (m, 3H), 4.62 (m, 2H), 5.33 (dd, 1H), 7.93 (br m, 2H), 8.54 (s, 1H), 8.68 (br m, 2H)
15p	B	816.4	816.4217	816.4223	0.86 (t, 3H), 1.16 (2d, 6H), 1.26 (d, 3H), 1.53 (s, 3H), 2.29 (s, 6H), 2.61 (s, 1H), 2.66 (s, 3H), 3.83 (q, 1H), 4.29 (d, 1H), 4.33 (s, 1H), 4.33 (s, 1H), 4.61 (m, 2H), 5.36 (dd, 1H), 7.36 (m, 1H), 8.33 (m, 1H), 8.53 (s, 1H), 8.62 (m, 1H), 9.29 (s, 1H)
15q	B	805.5	805.4170	805.4166	See experimental part for a full description
15r	B	819.4	nd		0.90 (t, 3H), 1.14 (2d, 6H), 1.25 (d, 3H), 1.32 (s, 3H), 1.33 (d, 3H), 1.38 (d, 3H), 1.59 (s, 3H), 2.35 (s, 6H), 2.81 (s, 3H), 3.05–3.18 (m, 3H), 3.23 (dd, 1H), 3.57 (m, 1H), 3.86 (q, 1H), 4.27 (s, 1H), 4.28 (d, 1H), 4.34 (d, 1H), 4.32–4.50 (m, 2H), 5.53 (dd, 1H), 5.51 (br s, 2H), 8.15 (s, 1H), 8.36 (s, 1H)
15s	B	833.5	nd		0.87 (t, 3H), 1.15 (2d, 6H), 1.16 (d, 3H), 1.33 (2d, 6H), 1.36 (s, 3H), 1.52 (s, 3H), 2.27 (s, 6H), 2.46 (m, 1H), 2.62 (s, 1H), 2.69 (s, 3H), 3.07–3.13 (m, 2H), 3.15–3.25 (m, 2H), 3.40–3.62 (m, 10H), 3.83 (q, 1H), 4.28 (d, 1H), 4.33 (d, 1H), 4.37 (s, 1H), 4.48 (m, 1H), 4.63 (m, 1H), 5.38 (dd, 1H), 8.10 (s, 1H), 8.31 (s, 1H)

[a] nd: not determined.

Acknowledgements

We thank Mrs. Veronique Schirmer for excellent technical assistance with the investigation of in vitro activities and in vivo efficacies of our ketolides. Dr. Cornelia Zumbrunn-Acklin is greatly acknowledged for the synthesis of basic ketolide lactone **16**. Furthermore, we are indebted to the laboratory of Walter Meister for the measurement of mass spectra and to Mr. Louis Allemann for the determination of HR-mass spectra. Prof. Sir Jack Baldwin, Prof. Elias J. Corey and Prof. Andrea Vasella are greatly acknowledged for many fruitful and helpful discussions in the course of this project.

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14. It has been brought to our attention that this apparent ester formation might actually be the result of a ketene addition to the tertiary hydroxy group at position C(12).
15. In the initial phase of the project, chromatographic purifications were performed in all steps with $CHCl_3$/MeOH/NH_4OH solvent systems. In these cases, mixtures of diasteromers for products **12**, **13** and **14** were obtained. In the later stage, some chromatographic purification steps were made using ethyl acetate/MeOH/NEt_3 mixtures as eluents and in these cases, usually, only one diastereomer was observed by NMR. We therefore concluded that this isomerization process can also be initiated on the level of lactones **12**, **13** or **14** by treatment with NEt_3.
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