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Novel 6-position modified 1-thioalkyl-lincosamines

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Abstract

A general method for the synthesis of 6-position modified lincosamines via stereospecific nucleophilic addition to readily available galactose 6-nitrone has been developed. A new route for the stereospecific installation of thioalkyl groups at the 1-position was also developed. These methods allow access to a variety of new derivatives of antibacterial lincosamides.

Keywords: Lincosamides; Thiogalactosides; Nitrones; Aminosugars; Diastereoselective addition

The lincosamide class of antibiotics is best represented by clindamycin (CLI), which consists of two distinct structural subunits: *N*-methyl-4′*R*-propyl-L-proline amino acid (or 4-*n*-propylhygric acid) and an amino sugar, 7-chloro-methylthio-lincosamine (7-Cl-MTL) fragment.[1,2] Our medicinal chemistry program targeting the next generation of lincosamide antibacterial agents has identified the 7-position of the lincosamine sugar as a site that is amenable to modification. 7-Methyl-methylthio-lincosamine (7-Me-MTL, see Fig. 1) shows similar antibacterial activity to the 7-Cl-MTL progenitor[3] when coupled to a suitable cyclic amino acid.[4] Reported herein is a general stereospecific route to 6-position modified thiolincosamine sugars.

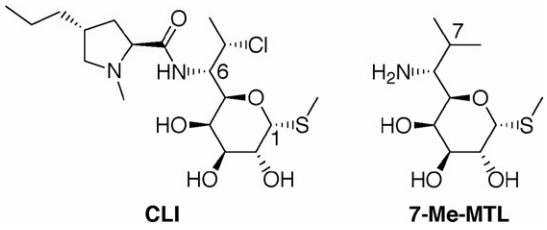

Fig. 1. Clindamycin and 7-Me-MTL.

The Dondoni group has reported the stereospecific addition of 2-lithiothiazole to protected galactose nitrone **1**,[5] en route to formal syntheses of lincosamine and destomic acid.[6] We sought to broaden the scope of this reaction in order to access a range of novel lincosamines modified at the 6-position. In our hands, a variety of organometallic nucleophiles have shown equally high selectivity for the natural 6(*R*)-diastereomer; in all cases, the undesired diastereomer was not detected. By way of example, Scheme 1 shows the addition of cyclopropyl magnesium bromide to nitrone **1** and subsequent conversion to trifluoroacetamide **5a**. Applying the reported methods of unmasking the amino-functionality of **2a** gave unsatisfactory results: treatment of hydroxylamine **2a** in methanol with aqueous $TiCl_3$ (20 wt %, freshly prepared)[6,7] provided a mixture of the desired imine **3a**, and the undesired reduced benzyl amine; whereas reacting **2a** with anhydrous $TiCl_3$ in THF[8] gave a mixture of imine **3a**, amine **4a**, and undesired reduced benzyl amine. A superior method for the dehydration of **2**→**3** was found to be the treatment of **2a** with methanesulfonyl chloride and triethylamine in methylene chloride. Liberation of imine **3a** to amine **4a** was accomplished by transimination with Girard's reagent T ((carboxymethyl)trimethylammonium chloride hydrazide),[9] which added the convenience of partitioning the reaction byproducts into the aqueous layer upon workup. This two-step process represents a generally applicable strategy

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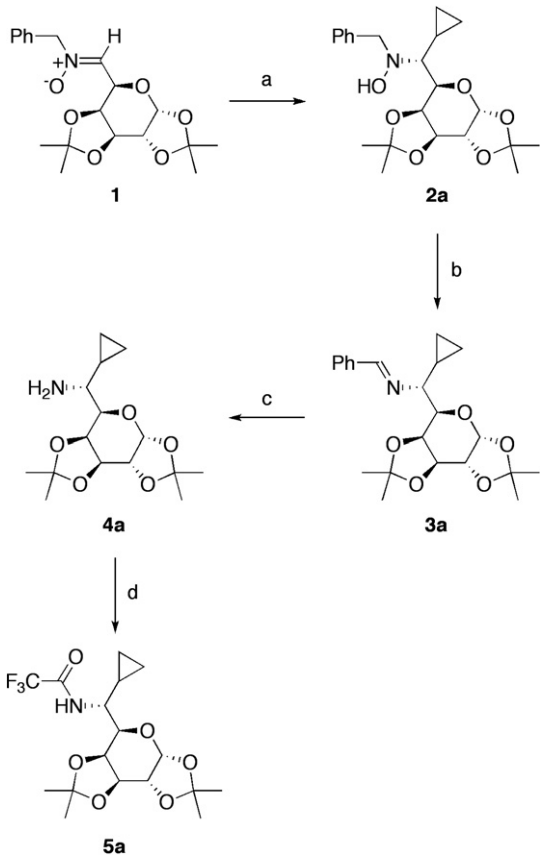
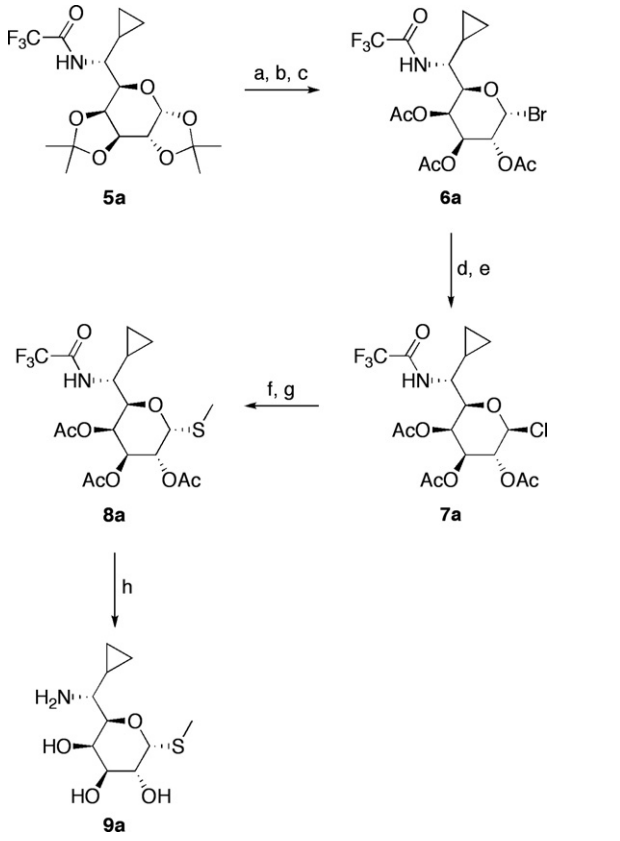


Scheme 1. Preparation of trifluoroacetamide **5a**. Reagents and conditions: (a) C_3H_5MgBr (0.5 M in THF), Et_2AlCl (1.0 M in heptane), Et_2O, −78 °C, 89%; (b) MsCl, Et_3N, CH_2Cl_2, 0–23 °C; (c) Girard's reagent T, MeOH, 23 °C; (d) TFAA, 2,6-lutidine, CH_2Cl_2, 0–23 °C, 78% (three steps).



Scheme 2. Installation of α-thiomethyl group. Reagents and conditions: (a) TFA, H_2O, 0–23 °C; (b) Ac_2O, Et_3N; DMAP, CH_2Cl_2, 23 °C; (c) HBr, AcOH, 0–23 °C, 74% (three steps); (d) AgOAc, AcOH, 23 °C; (e) $BF_3{\cdot}OEt_2$, PCl_5, CH_2Cl_2, 23 °C, 91% (two steps); (f) MeSNa, HMPA, DMF, 23 °C; (g) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 23 °C, 53% (two steps); (h) NaOH aq, MeOH, 23 °C, 97%.

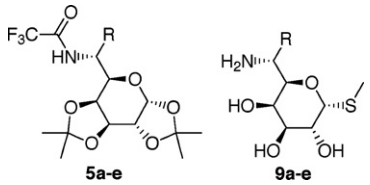
for the conversion of benzylhydroxylamines to primary amines. Crude amine **4a** was protected as trifluoroacetamide **5a**. At this stage, the trifluoroacetamide was subjected to the first chromatographic purification of the sequence.

The lincosamine thiomethyl substituent and its configuration are known to be important for antibacterial activity.[1] The stereospecific introduction of the C1-thiomethyl group is a largely unaddressed issue in lincosamine synthesis.[2,10] Scheme 2 details our approach to the installation of the requisite thioalkyl group to our 6-position modified lincosamine sugars. The acidic deprotection of diacetonide **5a** with aqueous trifluoroacetic acid was followed by global acetylation to provide a mixture of α/β/pyranose/furanose tetraacetates. This isomeric mixture of four compounds was converted to α-bromopyranose triacetate **6a** as a single major isomer via treatment with hydrogen bromide in acetic acid. α-Bromide **6a** was transformed first to the 1,2-*trans*-tetraacetate with silver acetate/acetic acid, then to the β-chloride **7a** using phosphorus pentachloride/boron-trifluoride diethyletherate.[11] Chloride **7a** was subjected to nucleophilic displacement with sodium thiomethoxide, avoiding the β-directing effect of the 2-position acetate observed under Lewis acid-catalyzed glycosylation conditions. Partial deacetylation was observed under the reaction conditions, the crude product was subjected to reacylation prior to undergoing the second chromatographic purification of the synthetic sequence.

The global deprotection of trifluoroacetamide triacetate **8a** was effected with aqueous sodium hydroxide in methanol. Isolation of **9a** was achieved via first acidifying the basic reaction mixture with aqueous hydrochloric acid; then concentrating the resulting solution. The resulting hydrochloride salt was dissolved in ethanol and filtered to remove the precipitated NaCl. The resulting ethanolic solution of the hydrochloride salt was then neutralized with Amberlite IRA-400 resin (OH form); the free base **9a** was obtained (>95% pure) upon concentrating the liquid phase.

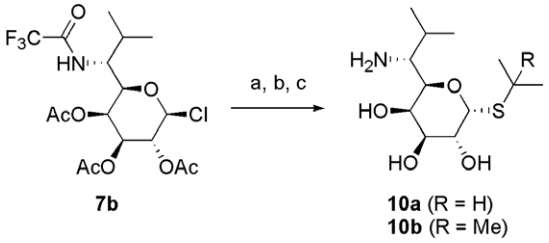
In addition to C-6 cyclopropyl thiomethyl lincosamine, isopropyl, cyclopentyl, allyl, and 4-chlorophenyl C-6 analogs were also prepared via this route. Table 1 shows the overall yields of trifluoroacetamides **5a**–**e** from galactose nitrone **1**, and the yields obtained in each case for the conversion of trifluoroacetamide diacetonides **5** to their respective thiomethyl lincosamines **9**. The selectivity for the desired 6-*R* and 1-*R* stereochemistry was confirmed by comparison of **9b** to an authentic sample obtained via our previously established route from 1-thiomethyl-lincosamine.[4] It should be noted that the efficiency of the route is

Table 1
Yields obtained for analog synthesis via Schemes 1 and 2



R Entry	*c*-Propyl **a**	*i*-Propyl **b**	*c*-Pentyl **c**	Allyl **d**	4-Cl–Ph **e**
Yield of **5**[a] (%)	69	74	82	78	81
Yield of **9**[b] (%)	36	48	39	31	33

[a] Overall yield from nitrone (**1**→**5**).
[b] Overall yield from diacetonide (**5**→**9**).



Scheme 3. Installation of alternative α-thioalkyl groups. Reagents and conditions: (a) Me_2RCSNa, HMPA, DMF, 23 °C; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 23 °C; (c) NaOH aq, MeOH, 23 °C, 58–61% (three steps).

such that gram-quantities of the amino sugars **9** are readily obtained from 5 to 6 g of nitrone **1**.

This new route also provides stereoselective access to additional 1-thioalkyl analogs via the β-chlorogalactose intermediate **7**. The synthesis of *tert*-butylthio- and isopropylthio-lincosamines (**10a**,**b**) is shown in Scheme 3.

In summary, we have developed a novel route to thiolincosamine sugars featuring access to structural diversity at both the 6- and 1-positions.[12] While consisting of several individual synthetic steps, the basic route requires just two chromatographic purifications, highlighting the high average yield-per-step and the excellent stereoselectivity for the desired isomer. These methods can be employed to synthesize a variety of novel lincosamides with potential for antibacterial therapy.

Supplementary data

Detailed experimental procedures for the conversion of **1**→**5a**→**9a** and copies of ^{1}H NMR spectra for **5a**–**e**, **9a**–**e**, **10a**,**b** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.167.

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12. ^{1}H NMR data (300 MHz, CD_3OD) **9a**: δ 5.28 (d, $J = 5.7$ Hz, 1H), 4.13–4.06 (m, 2H), 3.97 (d, $J = 6.6$ Hz, 1H), 3.59 (dd, $J = 3.3$, 9.9 Hz, 1H), 2.33 (dd, $J = 6.9$, 9.0 Hz, 1H), 2.05 (s, 3H), 0.91–0.77 (m, 1H), 0.58–0.43 (m, 2H), 0.39–0.31 (m, 1H), 0.28–0.19 (m, 1H). Compound **9b**: δ 5.24 (d, $J = 5.7$ Hz, 1H), 4.04 (dd, $J = 6.0$, 10.8 Hz, 1H), 4.02 (dd, $J = 1.2$, 3.3 Hz, 1H), 3.93 (dd, $J = 1.5$, 8.7 Hz, 1H), 3.54 (dd, $J = 3.3$, 10.5 Hz, 1H), 2.91 (dd, $J = 3.6$, 8.1 Hz, 1H), 2.08–1.96 (m, 1H), 2.06 (s, 3H), 0.99 (d, $J = 6.9$ Hz, 3H), 0.88 (d, $J = 6.9$ Hz, 3H). Compound **9c**: δ 5.28 (d, $J = 5.7$ Hz, 1H), 4.16–4.08 (m, 2H), 3.93 (dd, $J = 0.9$, 6.6 Hz, 1H), 3.54 (dd, $J = 3.0$, 10.2 Hz, 1H), 2.99 (t, $J = 6.6$ Hz, 1H), 2.17–2.04 (m, 1H), 2.07 (s, 3H), 1.88–1.51 (m, 6H), 1.42–1.26 (m, 2H). Compound **9d**: δ 5.94–5.78 (m, 1H), 5.27 (d, $J = 5.7$ Hz, 1H), 5.20–5.10 (m, 2H), 4.09 (dd, $J = 5.7$, 10.2 Hz, 1H), 4.04 (dd, $J = 1.5$, 3.3 Hz, 1H), 3.82 (dd, $J = 0.9$, 8.1 Hz, 1H), 3.57 (dd, $J = 3.3$, 9.9 Hz, 1H), 3.13 (dt, $J = 3.9$, 8.4 Hz, 1H), 2.57–2.47 (m, 1H), 2.14–2.02 (m, 1H), 2.07 (s, 3H). Compound **9e**: δ 7.37 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 9.0$ Hz, 2H), 5.09 (d, $J = 6.0$ Hz, 1H), 4.13–4.03 (m, 4H), 3.58 (dd, $J = 3.3$, 10.2 Hz, 1H), 1.41 (s, 3H). Compound **10a**: δ 5.36 (d, $J = 6.0$ Hz, 1H), 4.05 (dd, $J = 5.7$, 10.2 Hz, 1H), 4.01 (dd, $J = 1.5$, 3.3 Hz, 1H), 3.95 (dd, $J = 1.2$, 8.7 Hz, 1H), 3.48 (dd, $J = 3.3$, 10.5 Hz, 1H), 3.04–2.93 (m, 1H), 2.89 (dd, $J = 3.6$, 8.4 Hz, 1H), 2.07–1.95 (m, 1H), 1.30 (d, $J = 6.9$ Hz, 3H), 1.26 (d, $J = 6.9$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J = 6.6$ Hz, 3H). Compound **10b**: δ 5.39 (d, $J = 5.7$ Hz, 1H), 4.05 (dd, $J = 6.0$, 10.8 Hz, 1H), 4.01 (dd, $J = 1.2$, 3.3 Hz, 1H), 3.90 (dd, $J = 1.5$, 8.7 Hz, 1H), 3.39 (dd, $J = 3.3$, 10.5 Hz, 1H), 2.88 (dd, $J = 3.6$, 8.1 Hz, 1H), 2.08–1.95 (m, 1H), 1.36 (s, 9H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 3H).