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Preliminary studies on the synthesis of rancinamycins from nitrosugars

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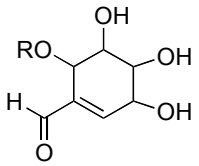
INTRODUCTION

Rancinamycins (**1a**-**d**)[1] are a group of secondary metabolites which are produced by *Streptomyces lincolnensis* in a sulphur-depleted culture medium and have important antibiotic activity in vitro against *Proteus vulgaris*, *Proteus rettgeri* and *Staphylococcus aureus*.



1 a) R=CO*i*-Pr
b) R=CO*n*-Pr
c) R=CO*n*-Bu
d) R=H

Figure 1

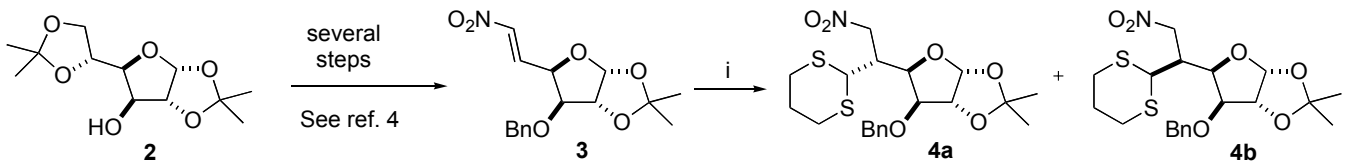
The structures (except stereochemistry) of the main components of the rancinamycin complex were determined with IR, UV, and NMR spectra. Rancinamycin I is a mixture of 5 isomeric components, designated Ia, Ib, Ic, Id and Ie. Rancinamycin II is also a mixture of 5 isomeric compounds, designated rancinamycins IIa-IIe. Differences in the acyl group or in stereochemistry probably account for the isomers. Rancinamycin III is a mixture of 4 isomeric components. The differences between the 4 isomers is unknown. Rancinamycin IV is 3,4-dihydroxybenzaldehyde.

Here we describe the first total synthesis of a racinamycin analogue (**1e**) from nitrosugars,[2] following a route which includes an improvement of the previously described[3] transformation of nitrosugar **4b** into cyclitol **6b** prior to a new nitro removal in nitrocarbasugars (Scheme 2).

RESULTS AND DISCUSSION

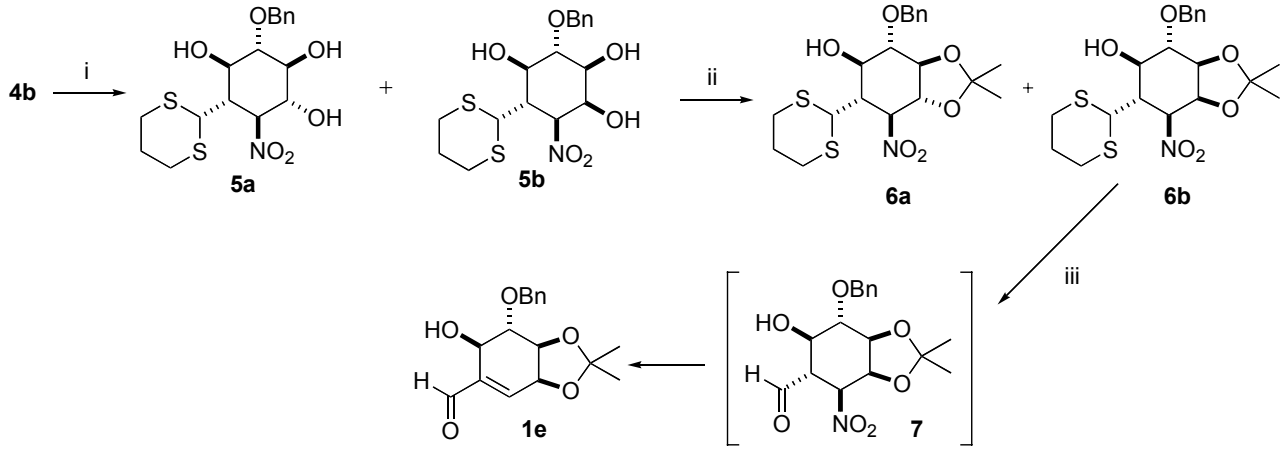
Nitroolephin **3**[4] obtained from diacetone-D-glucose (**2**) was allowed to react with 1.2 equiv. of 2-lithio-1,3-dithiane (DTN) at –78 ºC for two hours, the result being a 78% yield of a 1:3 mixture for compounds **4a** and **4b**

(Scheme 1), a ratio established by NMR (comparison of the intensity of H_1 protons). The major component **4b** was easily isolated by crystallization.



Scheme 1.- i) 2-Lithio-1,3-dithiane, THF, -78°C, 2 h, (4a:4b-1:3), 78% yield

The next step was the removal of the 1,2-*O*-isopropylidene group of the major component **4b** with acetic acid and the resulting free sugar was directly treated with 2.5 equiv. of sodium hydrogen carbonate in aqueous methanol at room temperature for 12 h, giving a 87% yield of an unisolable syrupy mixture of **5a** and **5b** (t.l.c.). Refluxing of a solution of this mixture with 2-methoxypropene and PPTS in methylene chloride for 3 hours allowed isopropylidene nitrocyclohexanes **6a** (not previously described) and **6b**[5] to be isolated from the reaction mixture in 24% and 61% yields, respectively (Scheme 2).



Scheme 2.- i) a. $AcOH_{(aq)}$ (75%), ref, 3 h; b. $NaHCO_{3(aq)}$ (2%), MeOH, r.t., 12 h, (5a:5b-1:2.5), 87% yield;
ii) $CH_3OC(CH_3)CH_2$, PPTS, CH_2Cl_2, ref, 3 h, 24% yield of 6a, 61% yield of 6b; iii) MeI, $NaHCO_{3(aq)}$, CH_3CN, 35°C, 36 h, 53% yield

The *myo* configuration assigned to previously uncharacterized inositol derivative **6b** was easily established taking into account that configurations of stereogenic centres of C_1, C_4, C_5 and C_6 are the same as those of its precursor **4b** and presupposing that this compound predominatly adopts the thermodynamically prefered chair-like conformation **6b** (Figure 2) where H_3 adopts an equatorial disposition and the rest of the hydrogens on the ring adopt axial dispositions. This was easily confirmed from its ^1H NMR spectrum, since all the coupling constants of the ring protons are 7.5-10 Hz, except coupling constants of H_2 and H_3 ($J_{2,3}$=4.3 Hz) and H_3 and H_4 ($J_{3,4}$=7.0 Hz).

The *scyllo* configuration of the new minor inositol derivative **6a** was also established from its ^{1}H NMR parameters, which reveal that H_1, H_2, H_3, H_4, H_5 and H_6 are all axial (Figure 2).

Figure 2: R_1+R_2=-CMe_2

Finally, treatment of compound **6b** with MeI and aqueous hydrogen sodium carbonate produced compound **1e**, which was easily identified from its analytical and spectroscopical data. Formation of this compound is probably the result of the liberation of the masked carbonyl group of **6b** followed by a kinetically and thermodynamically favoured E_1cB elimination of the nitro group of the resulting b-nitro cyclohexanecarbaldehyde **7** in the basic reaction conditions.[6]

CONCLUSION

In conclusion, we have developed the first total synthesis of a rancinamycin like compound from nitrosugars, following a route which includes the enantioselective tranformation of nitrosugar **4b** into carbasugar derivative **6b**.

Work is now in progress to extend this route to the panel of hexoses in order to prepare a wide range of rancinamicyns (**1**) for chemical and biological studies, including determination of the stereochemistry of all its 14 described isomers.

ACKNOWLEDGEMENTS

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