

Sophorolipids: Renewable resources for chemical derivatization

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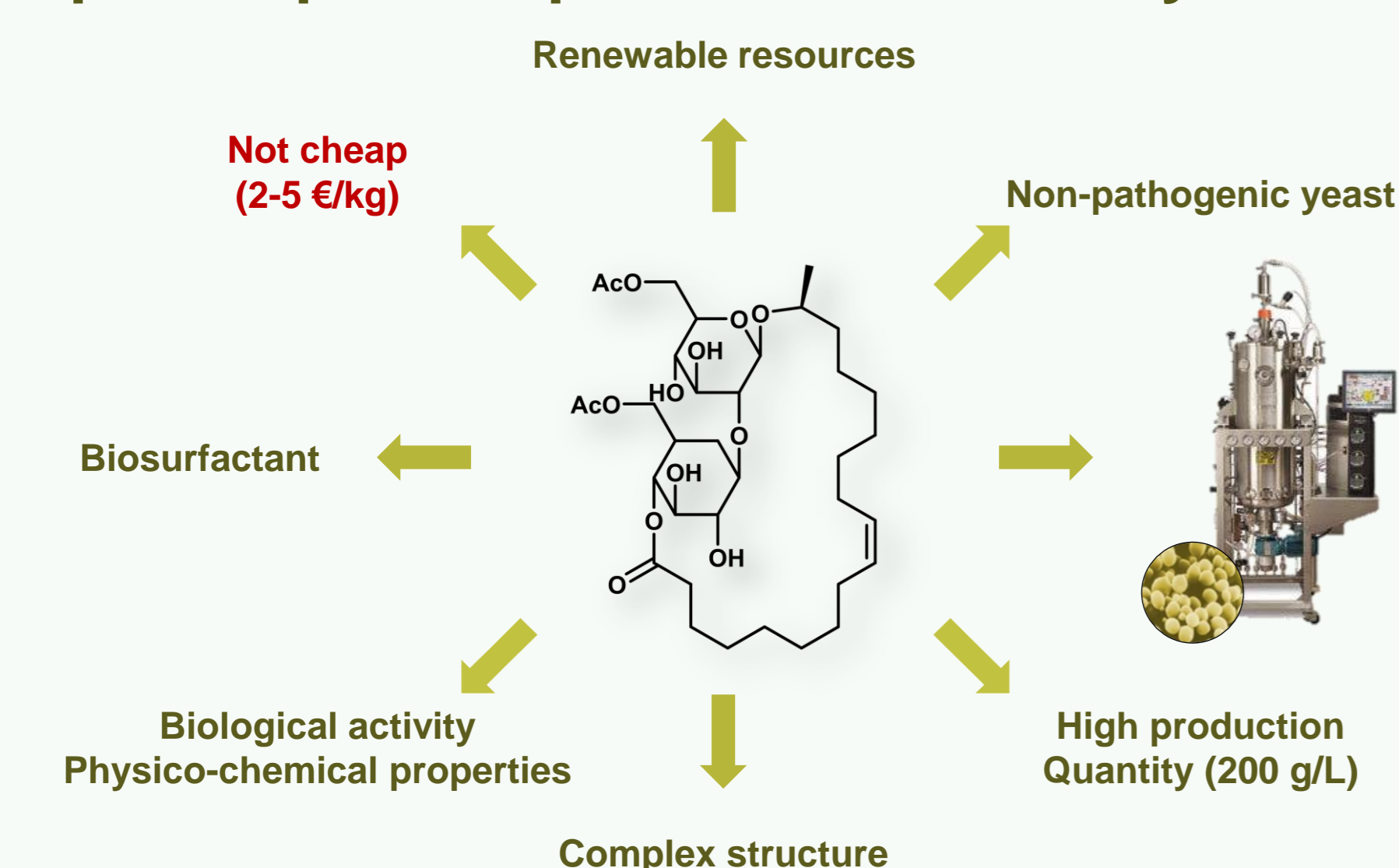
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Introduction

Sophorolipid = sophorose head + fatty acid tail



Biological activity:

- Dermatological
- Antimicrobial
- Anticancer
- Immunoregulatory
- Sporicidal and antiviral

Self-assembly properties:

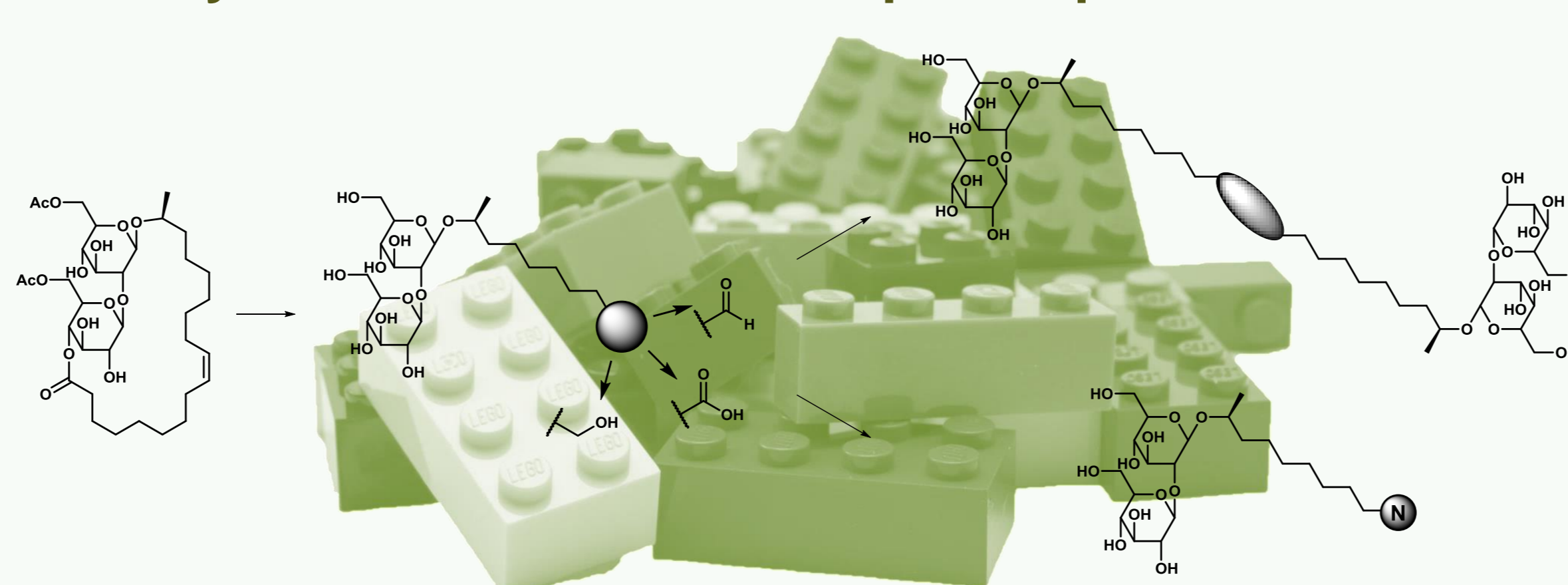
- Nanostructures with supramolecular chirality
- Capping of nanoparticles



Interesting building blocks for chemical derivatization

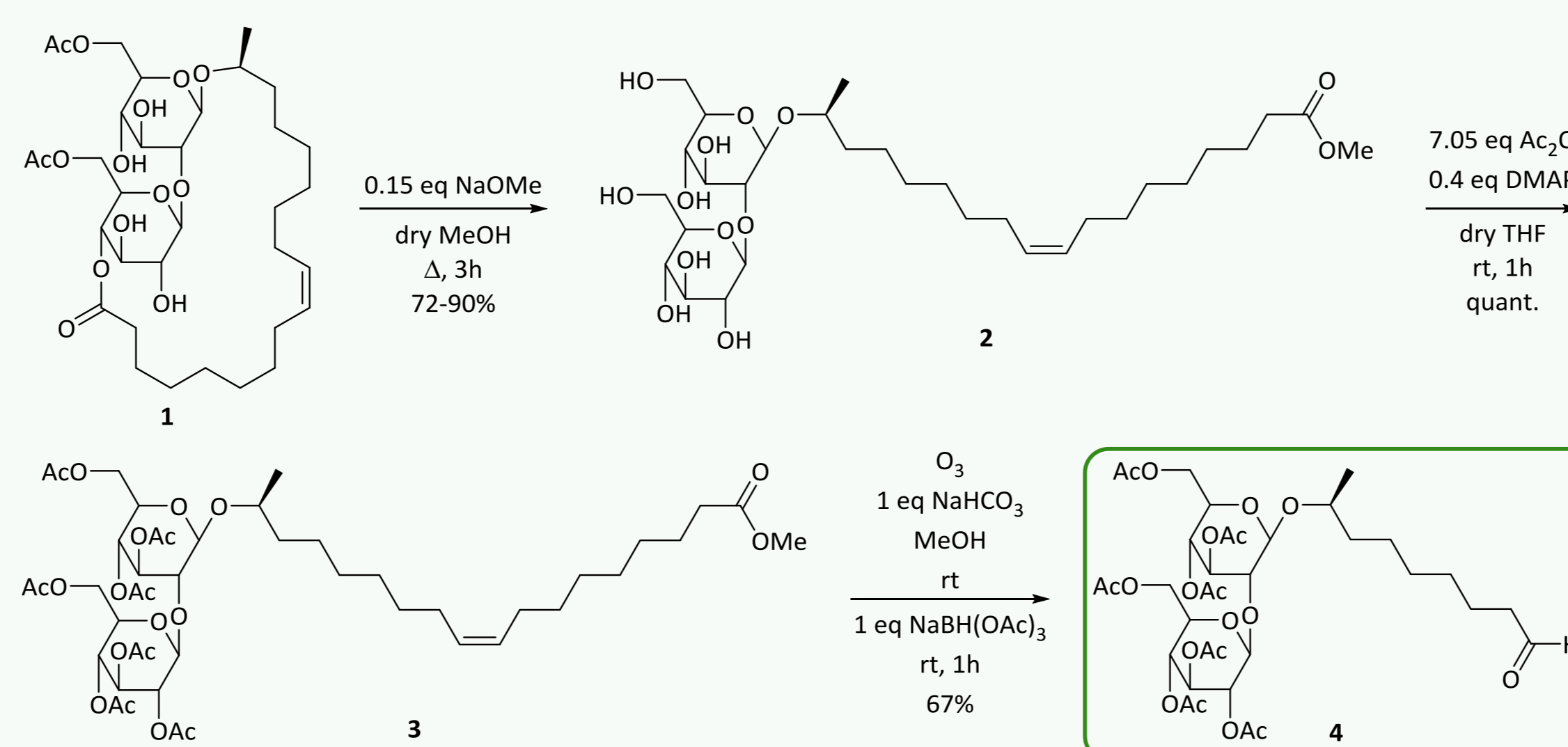
Objectives

Synthesis of innovative sophorolipid derivatives

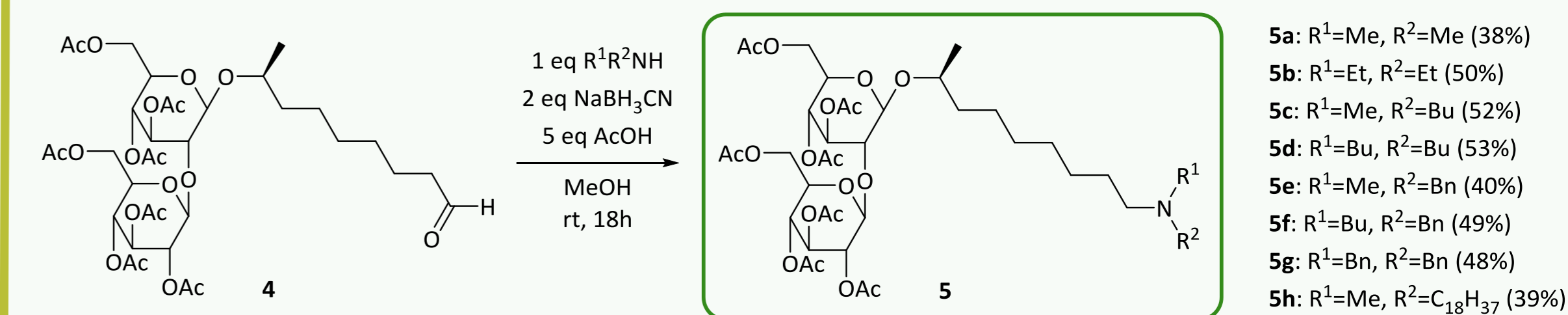


→ High added-value products for the pharmaceutical sector

Sophorolipid aldehyde intermediate

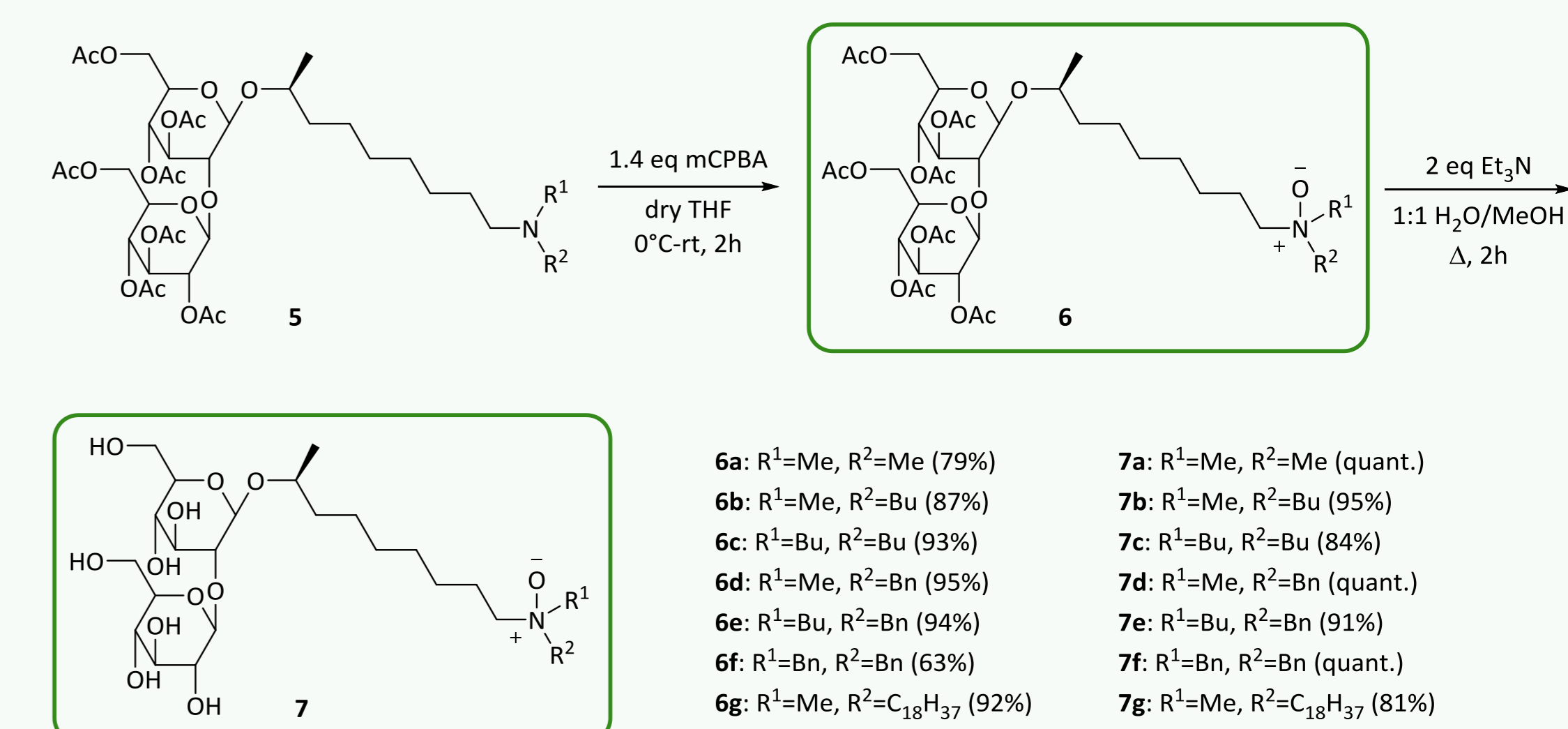


Sophorolipid amines



- No antimicrobial activity against *E. coli* LMG 8063, *K. pneumoniae* LMG 2095, *S. aureus* LMG 8064 and *B. subtilis* LMG 13579

Sophorolipid amine oxides



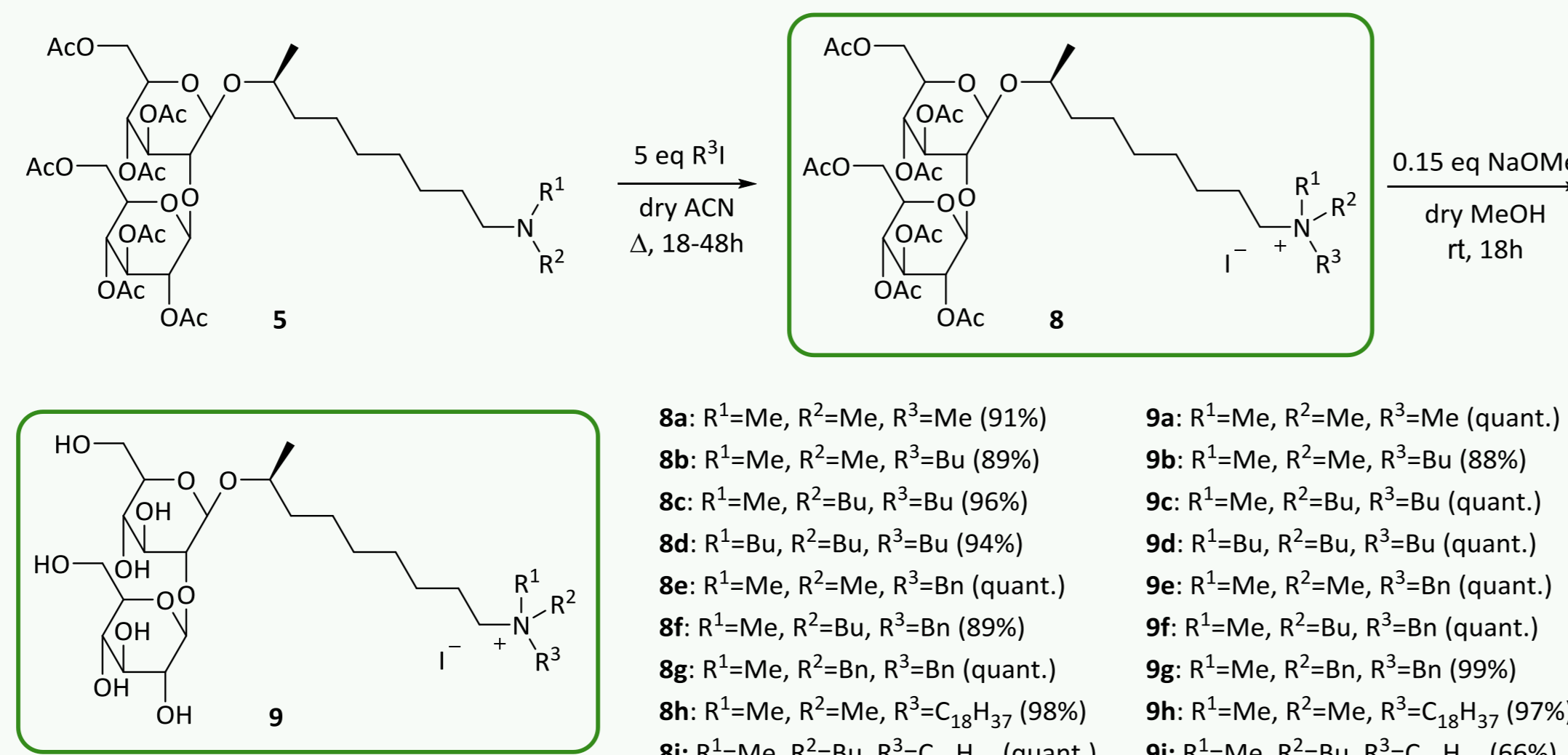
- Evaluation antimicrobial activity against *E. coli* LMG 8063, *K. pneumoniae* LMG 2095, *P. aeruginosa* PAO1, *S. aureus* ATCC 6538 and *S. aureus* Mu50
- Only weak activity for **7f** against *P. aeruginosa* PAO1 (MIC_{1/2} = 1000 µg/mL)

E.I.P. Delbeke, S.L.K.W. Roelants, N. Matthijs, B. Everaert, W. Soetaert, T. Coenye, K.M. Van Geem, C.V. Stevens, *Ind. Eng. Chem. Res.*, 2016, 55, 7273-7281.

Quaternary ammonium sophorolipids

Antimicrobial evaluation

- Evaluation antimicrobial activity against *E. coli* LMG 8063, *K. pneumoniae* LMG 2095, *S. aureus* LMG 8064 and *B. subtilis* LMG 13579
- Significant growth inhibition against **Gram-positive** strains for 13 derivatives
- Minimum inhibitory concentration (MIC) determination for active derivatives
- **Control antibiotic:** Gentamicin sulfate



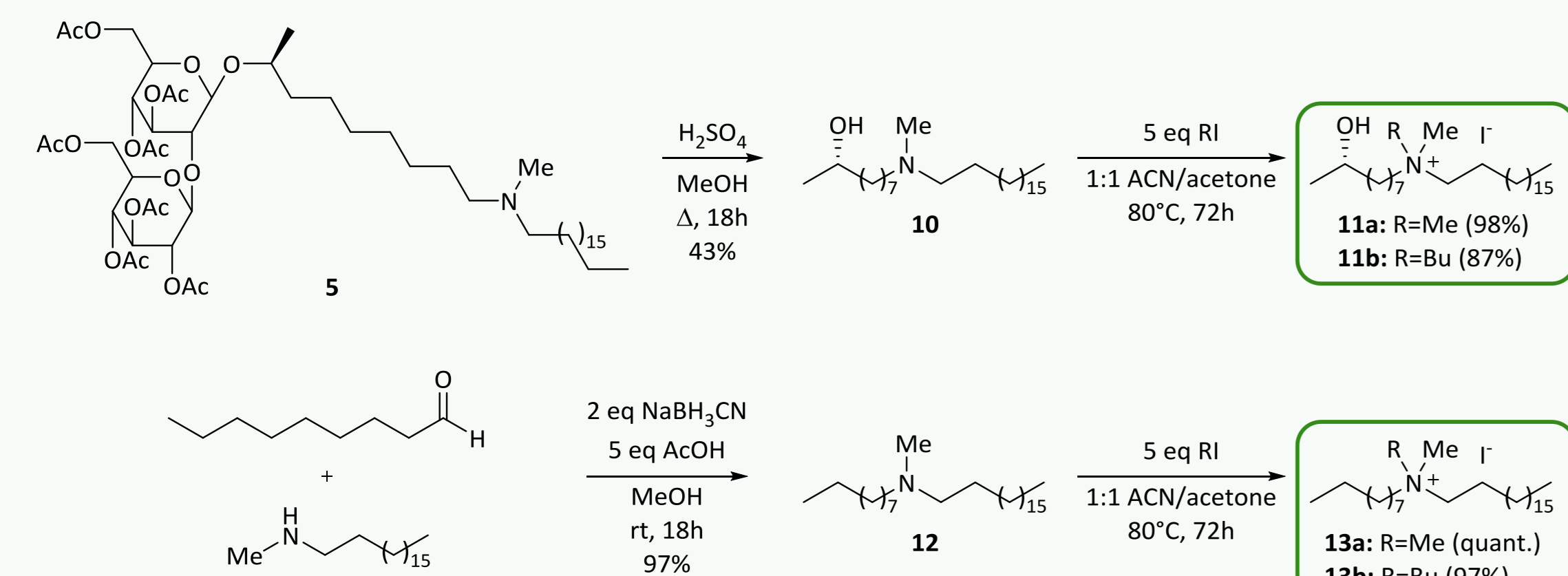
- 8a: R¹=Me, R²=Me, R³=Me (91%)
- 8b: R¹=Me, R²=Me, R³=Bu (89%)
- 8c: R¹=Me, R²=Bu, R³=Bu (96%)
- 8d: R¹=Bu, R²=Bu, R³=Bu (94%)
- 8e: R¹=Me, R²=Me, R³=Bn (quant.)
- 8f: R¹=Me, R²=Bu, R³=Bn (89%)
- 8g: R¹=Me, R²=Bn, R³=Bn (99%)
- 8h: R¹=Me, R²=Me, R³=C₁₈H₃₇ (98%)
- 8i: R¹=Me, R²=Bu, R³=C₁₈H₃₇ (quant.)
- 9a: R¹=Me, R²=Me, R³=Me (quant.)
- 9b: R¹=Me, R²=Me, R³=Bu (88%)
- 9c: R¹=Me, R²=Bu, R³=Bu (quant.)
- 9d: R¹=Bu, R²=Bu, R³=Bu (quant.)
- 9e: R¹=Me, R²=Me, R³=Bn (quant.)
- 9f: R¹=Me, R²=Bu, R³=Bn (99%)
- 9g: R¹=Me, R²=Bn, R³=Bn (97%)
- 9h: R¹=Me, R²=Me, R³=C₁₈H₃₇ (97%)
- 9i: R¹=Me, R²=Bu, R³=C₁₈H₃₇ (66%)

E.I.P. Delbeke, B.I. Roman, G.B. Marin, K.M. Van Geem, C.V. Stevens, *Green Chem.*, 2015, 17, 3373-3377.

Minimum inhibitory concentration (MIC) values

	(µM)	8b	8c	8d	8e	8f	8g	8h	8i	9b	9h	9i	Gentamicin sulfate
<i>S. aureus</i>	>101	>97	>93	489	>94	45	8	8	>144	6	5	10	
<i>E. faecium</i>	>101	>97	>93	>977	>94	>91	8	8	>144	6	5	21	
<i>B. subtilis</i>	>101	24	>93	977	>94	45	8	8	>144	6	5	10	
<i>S. pneumoniae</i>	>101	97	>93	977	>94	91	8	8	>144	6	5	52	

Synthesis deglycosylated derivatives



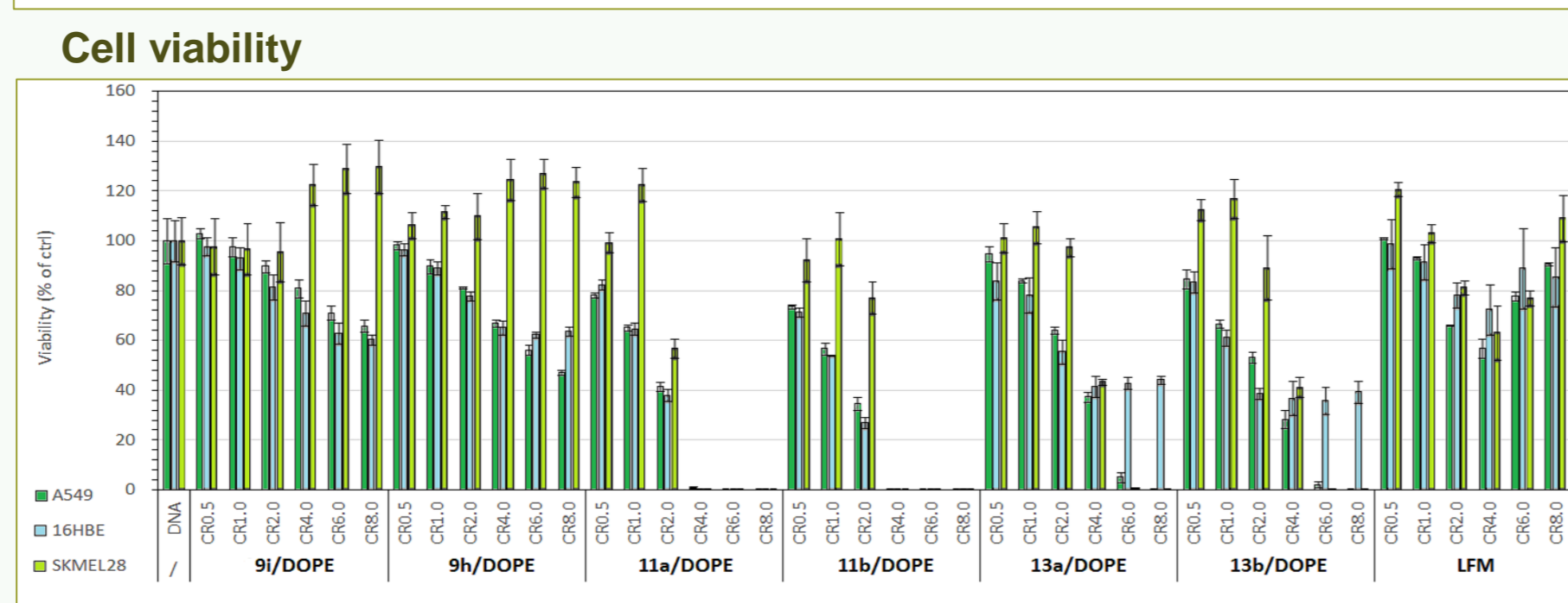
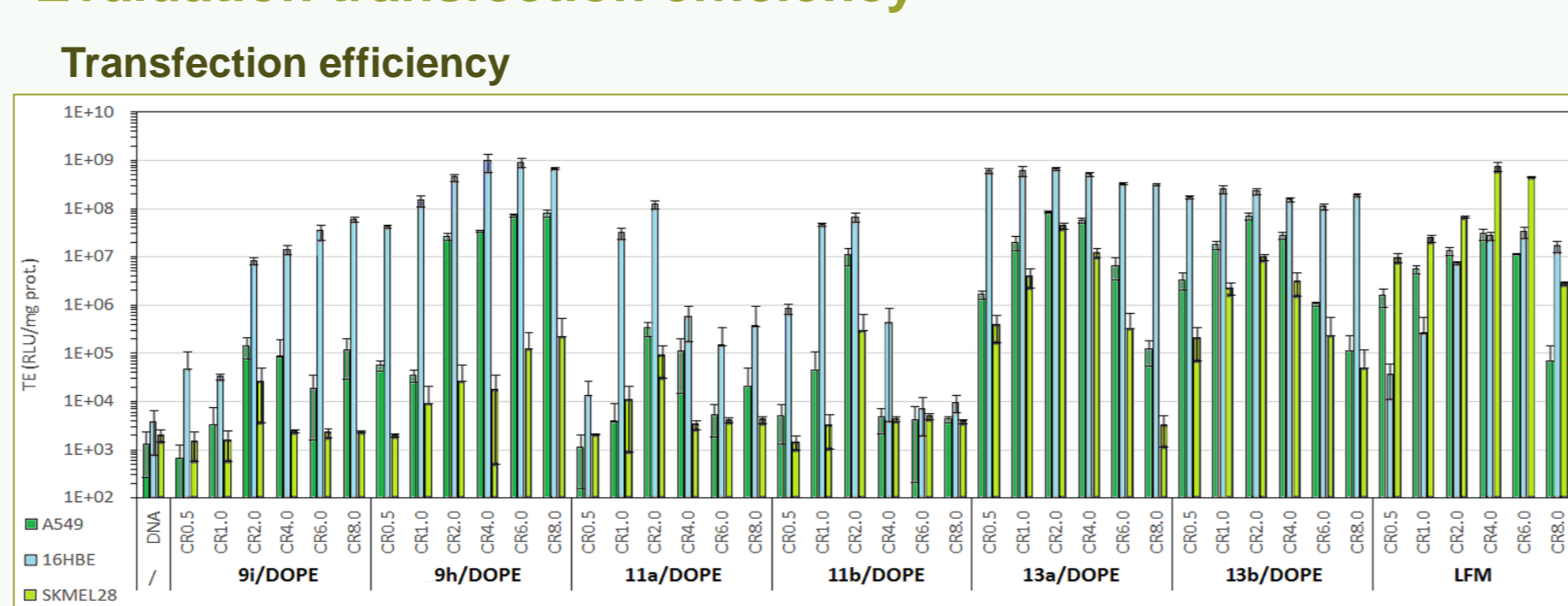
- Hydroxylated and non-hydroxylated quaternary ammonium salts with an octadecyl chain
- Evaluation influence carbohydrate head on antimicrobial activity and transfection efficiency

Minimum inhibitory (MIC) and bactericidal (MBC) concentrations

	<i>S. Aureus</i> ATCC 6538		<i>S. aureus</i> Mu50	
(µM)	MIC	MBC	MIC	MBC
SL lactone	182	363	363	1453
SL acid	>1607	>1607	>1607	>1607
8h	6,6	6,6	26,4	52,7
8i	6,4	204	50,9	204
9h	2,2	8,8	4,4	17,5
9i	2,1	2,1	4,2	16,7
11a	3,4	55,1	110	110
11b	3,2	51,3	103	103
13a	56,7	56,7	227	227
13b	26,3	26,3	105	211

- Only **9h** and **9i** good candidates for *in vitro* testing
- Good transfection for both quaternary ammonium sophorolipids in some cell lines
- High toxicity for deglycosylated derivatives in transfection assay

Evaluation transfection efficiency

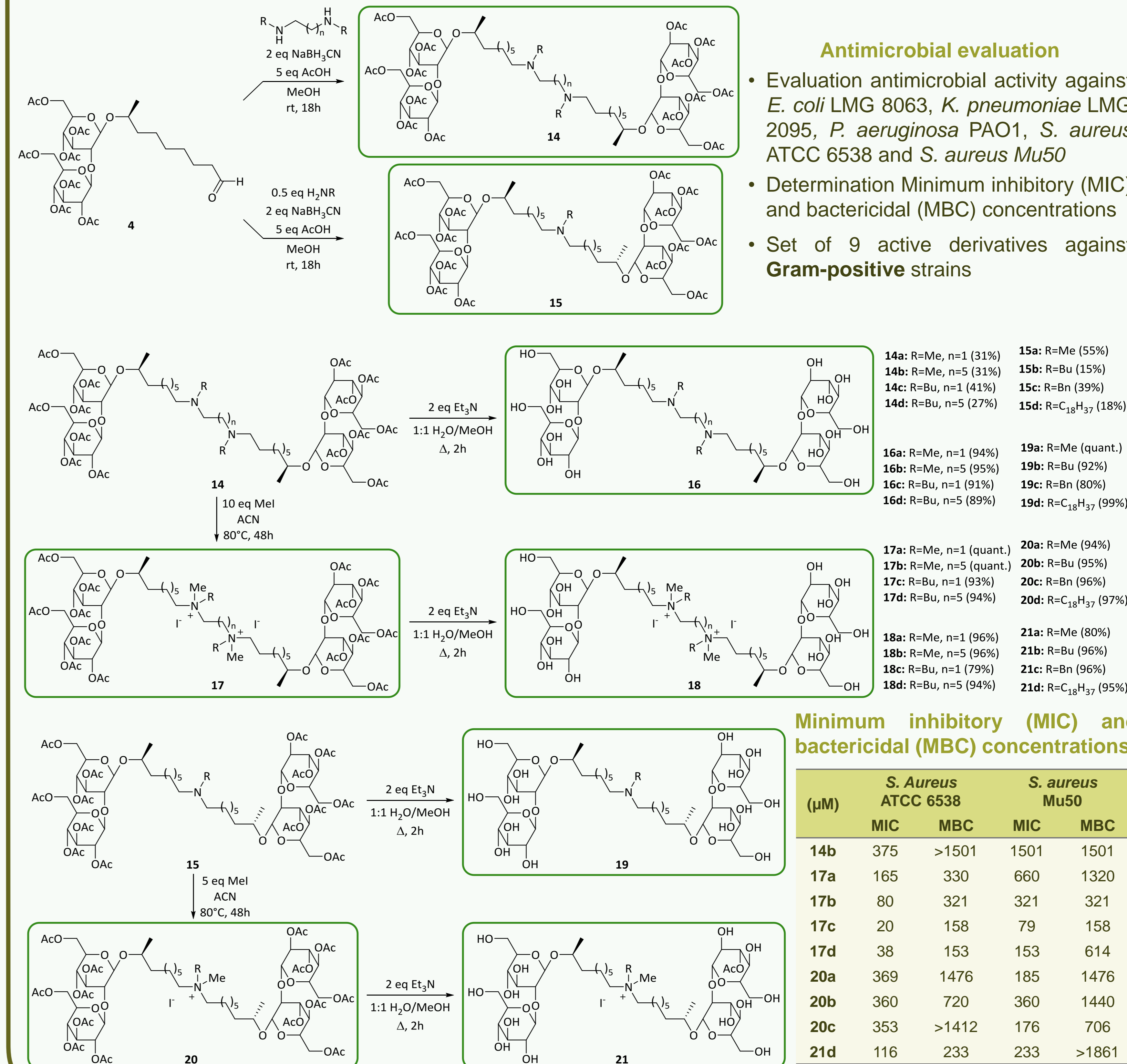


E.I.P. Delbeke, O. Lozach, T. Le Gall, M. Berchel, T. Montier, P.-A. Jaffrès, K.M. Van Geem, C.V. Stevens, *Org. Biomol. Chem.*, 2016, 14, 3744-3751.

Bolaamphiphilic sophorolipids

Antimicrobial evaluation

- Evaluation antimicrobial activity against *E. coli* LMG 8063, *K. pneumoniae* LMG 2095, *P. aeruginosa* PAO1, *S. aureus* ATCC 6538 and *S. aureus* Mu50
- Determination Minimum inhibitory (MIC) and bactericidal (MBC) concentrations
- Set of 9 active derivatives against **Gram-positive** strains



- 14a: R=Me, n=1 (31%)
- 14b: R=Me, n=5 (31%)
- 14c: R=Bu, n=1 (41%)
- 14d: R=Bu, n=5 (27%)
- 15a: R=Me (55%)
- 15b: R=Bu (15%)
- 15c: R=Bn (39%)
- 15d: R=C₁₈H₃₇ (18%)
- 16a: R=Me, n=1 (94%)
- 16b: R=Me, n=5 (95%)
- 16c: R=Bu, n=1 (91%)
- 16d: R=Bu, n=5 (89%)
- 17a: R=Me, n=1 (quant.)
- 17b: R=Me, n=5 (quant.)
- 17c: R=Bu, n=1 (93%)
- 17d: R=Bu, n=5 (94%)
- 18a: R=Me, n=1 (96%)
- 18b: R=Me, n=5 (96%)
- 18c: R=Bu, n=1 (79%)
- 18d: R=Bu, n=5 (94%)
- 19a: R=Me (quant.)
- 19b: R=Bu (92%)
- 19c: R=Bn (80%)
- 19d: R=C₁₈H₃₇ (99%)
- 20a: R=Me (94%)
- 20b: R=Bu (95%)
- 20c: R=Bn (96%)
- 20d: R=C₁₈H₃₇ (97%)
- 21a: R=Me (80%)
- 21b: R=Bu (96%)
- 21c: R=Bn (96%)
- 21d: R=C₁₈H₃₇ (95%)

Minimum inhibitory (MIC) and bactericidal (MBC) concentrations

	<i>S. Aureus</i> ATCC 6538		<i>S. aureus</i> Mu50	
(µM)	MIC	MBC	MIC	MBC
14b	375	>1501	1501	1501
17a	165	330	660	1320
17b	80	321	321	321
17c	20	158	79	158
17d	38	153	153	614
20a	369	1476	185	1476
20b	360	720	360	1440
20c	353	>1412	176	706
21d	116	233	233	>1861

Conclusion

- Quaternary ammonium sophorolipids with octadecyl chain are most interesting derivatives
- High antimicrobial activity and transfection efficiency
- Positive influence of carbohydrate head

Acknowledgement

The research leading to these results has received funding from the Long Term Structural Methusalem Funding by the Flemish Government (grant number BOF09/01M00409)