Tetrahedron Letters 56 (2015) 1159–1161

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A stereocontrolled synthesis of the hydrophobic moiety of rhamnolipids

Boudjema Menhour [a], Patrick Mayon [a], Karen Plé [b], Sandrine Bouquillon [a], Stéphan Dorey [c], Christophe Clément [c], Magali Deleu [d], Arnaud Haudrechy [a,*]

[a] Institut de Chimie Moléculaire de Reims, UMR CNRS 7312, Université de Reims, 51687 Reims Cedex, France
[b] Institut de Chimie Organique et Analytique, UMR CNRS 7311, Université d'Orléans, 45067 Orleans Cedex, France
[c] Unité de Recherche Vignes et Vins de Champagne, EA 4707, Université de Reims, 51687 Reims Cedex, France
[d] Centre de Biophysique Moléculaire Numérique, Université de Liège, Passage des Déportés, 2, 5030 Gembloux, Belgium

ARTICLE INFO

Article history:
Received 19 December 2014
Revised 11 January 2015
Accepted 13 January 2015
Available online 19 January 2015

Keywords:
Rhamnolipids
Enzymatic resolution
Mitsunobu reaction
Cross metathesis reaction

ABSTRACT

A new approach toward the synthesis of the hydrophobic moiety of rhamnolipid derivatives has been developed, involving two key cross-metatheses and an unusual Mitsunobu reaction. Small structural variations of the side chains should enable a better understanding of the role of the lipid moiety in immunostimulatory and plant defense eliciting properties.

Introduction

Bacterial rhamnolipids,[1] especially those produced by *Pseudomonas aeruginosa*[2] and *Burkholderia plantarii*[3] have shown a great deal of promise for the environmental remediation of oil spills[4] and toxic metals.[5] They have also been described as immunostimulators[6] and have been reported for their antibacterial, mycoplasmacidal, and antiviral activities.[7] More recently, rhamnolipids have been shown to efficiently induce a local resistance against *Botrytis cinerea* and are promising as potential elicitors (Fig. 1).[8]

Typically, rhamnolipids are bioproduced as a mixture of compounds with various chain lengths.[9] Synthetic approaches are scarce in the literature.[6c,10] Most of them involve a selective reduction of a β-ketoester using Noyori conditions,[6c,10c] appearing early in the overall synthesis, which can be a serious drawback in gaining access to a wide range of compounds.

In a previous study, a smart solid phase strategy was used to produce a glycolipid library. Immunostimulatory structure–activity relationship analysis indicated a specific recognition based mode of action.[6c] Encouraged by a synthesis of (−)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid by Sabitha et al.[11], we investigated a different approach with a common key intermediate subsequently submitted to cross-metathesis conditions in order to produce a versatile library of derivatives (Scheme 1).

Results and discussion

We focused on the use of the well-known acetoxyester **5**,[12] easily prepared on a convenient scale (more than five grams, with a 94% ee, measured by chiral HPLC with an IC column) using PS Amano lipase as a biocatalyst for an enantioselective acetylation (Scheme 2). The loss of half of the starting material, inherent with an enzymatic resolution, was an initial drawback, but this fact later proved beneficial.

Selective deprotection of the acetate group of compound **5** was then accomplished using standard conditions to give the **4**(***S***) hydroxyester while treatment with trifluoroacetic acid gave the carboxylic acid **6** in nearly quantitative yields (Scheme 3).

All our attempts to couple **4**(*S*) and **6** via diverse esterification procedures were unsuccessful (DCC/DMAP, EDCI, and TBTU with diverse solvents). Surprisingly, compound **5** was the only observed product as previously described by Duynstee et al.,[10b] While attempting various coupling reactions, work was also in progress to recycle the unwanted enantiomer **4**(***R***). Reviewing the literature showed that Mitsunobu reactions on allylic alcohols can be performed with 'non-aryl' carboxylic acids.[13] One particularly interesting case was reported with a more complex structure.[13c]

* Corresponding author. Tel.: +33 (0)326913236; fax: +33 (0)326913166.
E-mail address: arnaud.haudrechy@univ-reims.fr (A. Haudrechy).

http://dx.doi.org/10.1016/j.tetlet.2015.01.091
0040-4039/

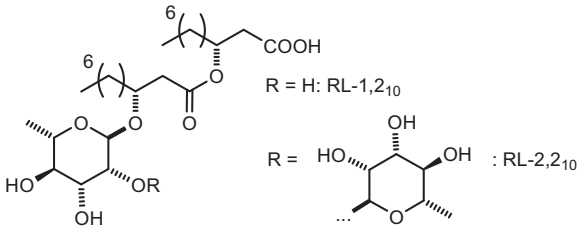
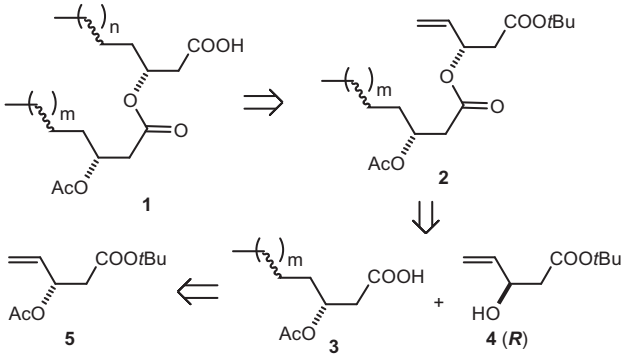
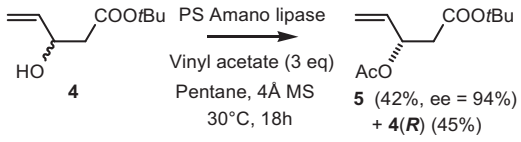


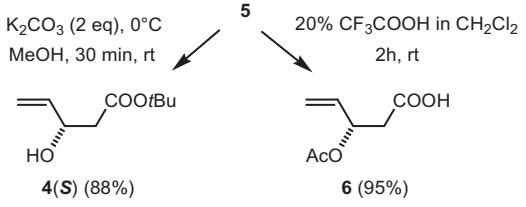
Figure 1. Two examples of natural rhamnolipids used as elicitors.[8]



Scheme 1. Retrosynthetic approach to the hydrophobic moiety of rhamnolipid derivatives **1** (m and n varying from 2 to 17).



Scheme 2. Enzymatic resolution using PS Amano lipase.

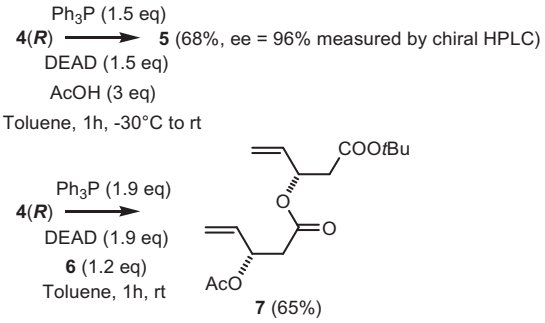


Scheme 3. Orthogonal deprotection of acetoxyester **5**.

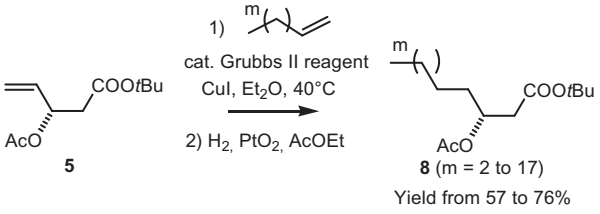
Two preliminary tests gave very promising results (Scheme 4). The first one allowed us to recycle the undesired enantiomer **4**(***R***), while the second one solved two problems, the desired inversion of configuration and coupling to furnish compound **7**, a precursor of double chain derivatives **1**. This second example proved to be an esthetic alternative to the desired previously unsuccessful coupled reaction.

We then tested the cross-metathesis conditions on the pivotal substrate **5**[14] with sixteen different alkenes using conditions recently described by Voigtritter et al.[15] (Scheme 5). As the separation of *Z* and *E*-alkenes proved to be difficult in certain cases, we decided to directly hydrogenate the crude mixture in a one-pot sequence.

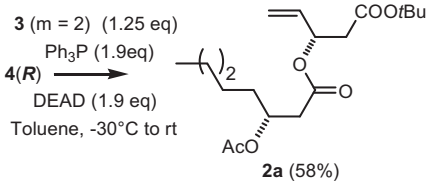
Deprotection of derivative **8** ($m = 2$) with CF_3COOH in CH_2Cl_2 gave the carboxylic acid **3** ($m = 2$ in 89% yield) which was subjected to a Mitsunobu coupling with hydroxylester **4**(***R***) giving the expected compound **2** ($m = 2$) in 58% yield (Scheme 6).



Scheme 4. Mitsunobu reactions on hydroxylester **4**(***R***) (1).

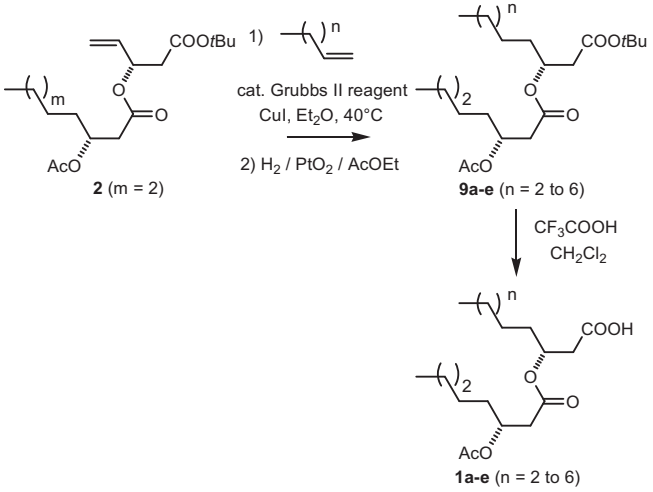


Scheme 5. Cross metathesis-hydrogenation of double ester **5**.



Scheme 6. Mitsunobu reactions on hydroxylester **4**(***R***) (2).

Table 1
Cross metathesis of ester **2** ($m = 2$)



n	2	3	4	5	6
Yield in **9** (%)	60	53	48	54	52
Yield in **1a–e** (%)	76	86	70	73	88

Finally, to demonstrate the generality of our approach, a second cross-metathesis reaction was performed on derivative **2** ($m = 2$) with five different alkenes, followed by direct hydrogenation of the reaction mixture (Table 1). In all cases, dimeric structures coming from the alkenes and approximately 15% of starting materials could be easily removed by silica gel column chromatography. Acid hydrolysis then gave the desired acids in yields varying between 70% and 88%.

Conclusion

We have developed a short and efficient strategy for the synthesis of the hydrophobic moiety of rhamnolipids. A first metathesis/hydrogenation sequence gives access to a large number of functionalized alkyl side chains. Mitsunobu conditions were then used to couple the acid and the alcohol fragments. A second metathesis/hydrogenation sequence was then applied to give the desired lipid esters which were hydrolyzed to give the corresponding acids. Subsequent rhamnosylation will then allow us to obtain hybrid structures, in order to better understand the structure–activity relationships of this fascinating class of elicitors. Work is in progress toward this goal.

Acknowledgments

Financial support from the CNRS (Centre National de la Recherche Scientifique), the Ministry of Higher Education and Research (MESR: Ministère de l'Enseignement Supérieur et de la Recherche) are gratefully acknowledged.

References and notes

1. Abdel-Mawgoud, A. M.; Lépine, F.; Déziel, E. *Appl. Microbiol. Biotechnol.* **2010**, *86*, 1323–1336. and references cited therein.
2. (a) Jarvis, F. G.; Johnson, M. J. *J. Am. Chem. Soc.* **1949**, *71*, 4124–4126; (b) Hauser, G.; Karnovsky, M. L. *J. Bacteriol.* **1954**, *68*, 645–655; (c) Edwards, J. R.; Hayashi, J. A. *Arch. Biochem. Biophys.* **1965**, *111*, 415–421; (d) Johnson, M. K.; Boese-Marazzo, D. *Infect. Immunol.* **1980**, *29*, 1028–1033; (e) Hirayama, T.; Kato, I. *FEBS Lett.* **1982**, *139*, 81–85; (f) Syldatk, C.; Lang, S.; Wagner, F.; Wray, V.; Witte, L. Z. *Naturforsch., Teil C* **1985**, *40*, 51–60.
3. (a) Häussler, S.; Nimtz, M.; Domke, T.; Wray, V.; Steinmetz, I. *Infect. Immunol.* **1998**, *66*, 1588–1593; (b) Andrä, J.; Rademann, J.; Howe, J.; Koch, M. H. J.; Heine, H.; Zähringer, U.; Brandenburg, K. *Biol. Chem.* **2006**, *387*, 301–310.
4. (a) Zhang, Y.; Miller, R. M. *Appl. Environ. Microbiol.* **1992**, *58*, 3276–3282; (b) Mulligan, C. N.; Yong, R. N.; Gibbs, B. F. *Eng. Geol.* **2001**, *60*, 193–207.
5. (a) Desai, J. D.; Banat, I. M. *Microbiol. Mol. Biol. Rev.* **1997**, *61*, 47–64; (b) Ochoa-Loza, F. J.; Artiola, J. F.; Maier, R. M. *J. Environ. Qual.* **2001**, *30*, 479–485.
6. (a) Goran, P.; Visnja, P. *Chem. Abstr.* **1996**, *124*, 106658; (b) Schwichtenberg, L. Doctoral Thesis, Christian-Albrechts University Kiel, 2003, http://e-diss.uni-kiel.de/diss 809/.; (c) Bauer, J.; Brandenburg, K.; Zähringer, U.; Rademann, J. *Chem. Eur. J.* **2006**, *12*, 7116–7124.
7. Leisinger, T.; Margraff, R. *Microbiol. Rev.* **1979**, *43*, 422–442.
8. (a) Varnier, A. L.; Sanchez, L.; Vatsa, P.; Boudesocque, L.; Garcia-Brugger, A.; Rabeoelina, F.; Sorokin, A.; Renault, J.-H.; Kauffmann, S.; Pugin, A.; Clément, C.; Baillieul, F.; Dorey, S. *Plant Cell Environ.* **2009**, *32*, 178–193; (b) Vatsa, P.; Sanchez, L.; Clément, C.; Baillieul, F.; Dorey, S. *Int. J. Mol. Sci.* **2010**, *11*, 5095–5108; (c) Sanchez, L.; Courteaux, B.; Hubert, J.; Kauffmann, S.; Renault, J.-H.; Clément, C.; Baillieul, F.; Dorey, S. *Plant Physiol.* **2012**, *160*, 1630–1641; (d) Delaunois, B.; Farace, G.; Jeandet, P.; Clément, C.; Baillieul, F.; Dorey, S.; Cordelier, S. *Environ. Sci. Pollut. Res.* **2014**, *21*, 4837–4846.
9. (a) Koch, A. K.; Kappeli, O.; Fiechter, A.; Reiser, J. *J. Bacteriol.* **1991**, *173*, 4212–4219; (b) Bodour, A. A.; Drees, K. P.; Maier, R. M. *Appl. Environ. Microbiol.* **2003**, *69*, 3280–3287.
10. (a) Westerduin, P.; de Haan, P. E.; Dees, M. J.; van Boom, J. H. *Carbohydr. Res.* **1988**, *180*, 195–205; (b) Duynstee, H. I.; Van Vliet, M. J.; van der Marel, G. A.; van Boom, J. H. *Eur. J. Org. Chem.* **1998**, *2*, 303–307; (c) Coss, C.; Carrocci, T.; Maier, R. M.; Pemberton, J. E.; Polt, R. *Helv. Chim. Acta* **2012**, *95*, 2652–2659.
11. Sabitha, G.; Reddy, S. S. S.; Bhaskar, V.; Yadav, J. S. *Synthesis* **2010**, *7*, 1217–1222.
12. (a) Tan, C.-H.; Holmes, A. B. *Chem. Eur. J.* **2001**, *7*, 1845–1854; (b) Souto, J. A.; Vaz, E.; Lepore, I.; Pöppler, A.-C.; Franci, G.; Alvarez, R.; Altucci, L.; de Lera, A. R. *J. Med. Chem.* **2010**, *53*, 4654–4667; (c) Kaji, E.; Komori, T.; Yokoyama, M.; Kato, T.; Nishino, T.; Shirahata, T. *Tetrahedron* **2010**, *66*, 4089–4100.
13. (a) Kwon, Y.-U.; Chung, S.-K. *Org. Lett.* **2001**, *3*, 3013–3016; (b) Kobayashi, Y.; Matsuumi, M. *Tetrahedron Lett.* **2002**, *43*, 4361–4364; (c) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr *J. Am. Chem. Soc.* **2003**, *125*, 7889–7901; (d) Ainai, T.; Matsuumi, M.; Kobayashi, Y. *J. Org. Chem.* **2003**, *68*, 7825–7832; (e) Alvarez, L. D.; Veleiro, A. S.; Baggio, R. F.; Garland, M. T.; Edelsztein, V. C.; Coirini, H.; Burton, G. *Bioorg. Med. Chem.* **2008**, *16*, 3831–3838.
14. Wohlrab, A.; Lamer, R.; VanNieuwenhze, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 4175–4177.
15. Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697–4702
Spectral data of selected new compounds:
(*R*)-3-(((*R*)-3-acetoxyoctanoyl)oxy)octanoic acid **1a**: $[\alpha]_D^{20}$ −1.0° (*c* 0.25, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 5.24–5.16 (m, 2H, 2*CH*-O), 2.66–2.50 (m, 4H, α-CH_2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.68–1.52 (m, 4H, $2CH_2$), 1.38–1.19 (m, 12H, $6CH_2$), 0.87 (t, 6H, $2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.6, 170.6, 169.9, 70.8, 70.7, 39.4, 38.4, 34.0, 33.9, 31.7, 31.6, 24.9, 22.6, 21.2, 14.1; HRMS (ESI^+) *m*/*z* calcd for $C_{18}H_{32}O_6Na$ $[M+Na]^+$ 367.2097, found 367.2079.
(*R*)-3-(((*R*)-3-acetoxyoctanoyl)oxy)nonanoic acid **1b**: $[\alpha]_D^{20}$ +1.1° (*c* 0.9, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.75 (br s, 1H, OH), 5.26–5.15 (m, 2H, 2*CH*-O), 2.66–2.49 (m, 4H, α-CH_2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.69–1.50 (m, 4H, $2CH_2$), 1.38–1.18 (m, 14H, $7CH_2$), 0.87 (t, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.3, 170.6, 169.9, 70.9, 70.7, 39.4, 38.8, 34.0, 31.8, 31.7, 29.1, 25.2, 24.9, 22.7, 22.6, 21.2, 14.2, 14.1; HRMS (ESI^+) *m*/*z* calcd for $C_{19}H_{34}O_6Na$ $[M+Na]^+$ 381.2253, found 381.2249.
(*R*)-3-(((*R*)-3-acetoxyoctanoyl)oxy)decanoic acid **1c**: $[\alpha]_D^{20}$ −1.4° (*c* 0.85, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.38 (br s, 1H, OH), 5.25–5.15 (m, 2H, 2*CH*-O), 2.66–2.50 (m, 4H, α-CH_2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.68–1.50 (m, 4H, $2CH_2$), 1.38–1.20 (m, 16H, $8CH_2$), 0.87 (t, 6H, $2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.9, 170.8, 170.0, 70.9, 70.8, 39.4, 38.8, 34.0, 31.9, 31.7, 29.4, 29.3, 25.2, 24.9, 22.7, 22.6, 21.2, 14.2, 14.1; HRMS (ESI^+) *m*/*z* calcd for $C_{20}H_{36}O_6Na$ $[M+Na]^+$ 395.2410, found 395.2404.
(*R*)-3-(((*R*)-3-acetoxyoctanoyl)oxy)undecanoic acid **1d**: $[\alpha]_D^{20}$ +2.2° (*c* 1.25, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 8.0 (br s,1H, OH), 5.25–5.16 (m, 2H, 2*CH*-O), 2.66–2.50 (m, 4H, α-CH_2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.68–1.51 (m, 4H, $2CH_2$), 1.38–1.19 (m, 18H, $9CH_2$), 0.87 (t, 6H, $2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.9, 170.7, 169.9, 70.9, 70.7, 39.4, 38.8, 34.0, 31.9, 31.7, 29.6, 29.5, 29.3, 25.2, 24.8, 22.8, 22.6, 21.2, 14.2, 14.1; HRMS (ESI^+) *m*/*z* calcd for $C_{21}H_{38}O_6Na$ $[M+Na]^+$ 409.2566, found 409.2570.
(*R*)-3-(((*R*)-3-acetoxyoctanoyl)oxy)dodecanoic acid **1e**: $[\alpha]_D^{20}$ −1.6° (*c* 0.65, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 5.25–5.16 (m, 2H, 2*CH*-O), 2.66–2.49 (m, 4H, α-CH_2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.68–1.50 (m, 4H, $2CH_2$), 1.38–1.19 (m, 20H, $10CH_2$), 0.87 (t, 6H, $2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.4, 170.6, 169.9, 70.9, 70.7, 39.4, 38.8, 34.0, 32.0, 31.7, 29.7, 29.6, 29.5, 29.4, 25.2, 24.9, 22.8, 22.6, 21.2, 14.2, 14.1; HRMS (ESI^+) *m*/*z* calcd for $C_{22}H_{40}O_6Na$ $[M+Na]^+$ 423.2712, found 423.2723.