

## Minimally Competent *Lewis* Acid Catalysts: Indium(III) and Bismuth(III) Salts Produce Rhamnosides (= 6-Deoxymannosides) in High Yield and Purity

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This paper is dedicated to *Dieter Seebach* for the wonderful science that he has showed us all as a chemist, and for the kindness he has showed me as a person

Glycosylation of decan-1-ol (**2**), (±)-decan-2-ol (**3**), and (±)-methyl 3-hydroxydecanoate (**4**) with L-rhamnose peracetate **5** to produce rhamnosides (= 6-deoxymannosides) **6**, **7**, and **8** in the presence of *Lewis* acids BF<sub>3</sub>·Et<sub>2</sub>O, Sc(OTf)<sub>3</sub>, InBr<sub>3</sub>, and Bi(OTf)<sub>3</sub> was studied (*Table 1*). While the strong *Lewis* acids BF<sub>3</sub>·Et<sub>2</sub>O and Sc(OTf)<sub>3</sub> were effective as glycosylation promoters, they had to be used in excess; however, glycosylation required careful control of reaction times and temperatures, and these *Lewis* acids produced impurities in addition to the desired glycosides. Enantiomerically pure rhamnosides (*R*)-**1** and (*S*)-**1** (*Fig.*) were obtained from L-rhamnose peracetate **5** and (±)-benzyl 3-hydroxydecanoate (**9**) via the diastereoisomeric rhamnosides **10** (*Table 2*; *Scheme 3*). The much weaker *Lewis* acids InBr<sub>3</sub> and Bi(OTf)<sub>3</sub> produced purer products in high yield under a wider range of conditions (higher temperatures), and were effective glycosylation promoters even when used catalytically (<10% catalyst; *Table 2*). We refer to these *Lewis* acids as ‘minimally competent *Lewis* acids’ (*cf. Scheme 4*).

**Introduction.** – Earlier studies [1] directed toward the glycosylation of serine and threonine [2] with readily available sugar peracetates [3] for the efficient production of O-linked glycopeptides [4–6] led us to explore the use of weaker rather than stronger *Lewis* acids in conjunction with higher temperatures with these relatively unreactive per-*O*-acetylated glycosyl donors [7]. The discovery that the weak *Lewis* acid InBr<sub>3</sub> was effective led us explore this approach in the synthesis of rhamnolipids [8]. *Rademann* and co-workers’ synthesis was quite elegant for the production of a rhamnolipid library [9] but did not provide a robust, scalable approach that could be used to produce larger amounts for the study of their surfactant properties [10].

We required rhamnoside diastereoisomers, (*R*)-**1** and (*S*)-**1** (*Fig.*), as well as the ability to produce various chain lengths at will. These single-chain glycosides are related to bacterial rhamnolipids [8][9], which are typically produced as mixtures of various chain lengths [10][11]. Bacterial rhamnolipids, particularly those produced by *Pseudomonas aeruginosa* show a great deal of promise for the environmental remediation of oil spills [12][13] and toxic metals [14][15].

**Results.** – The first glycosylation reactions were performed with decan-1-ol (**2**) as a model glycosyl acceptor and β-lactose peracetate as a model glycosyl donor. Heating

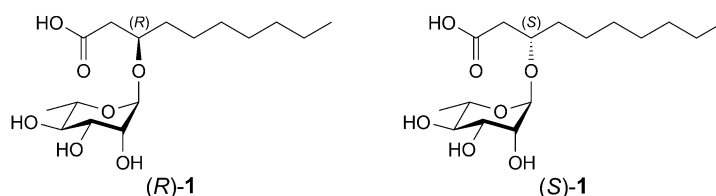
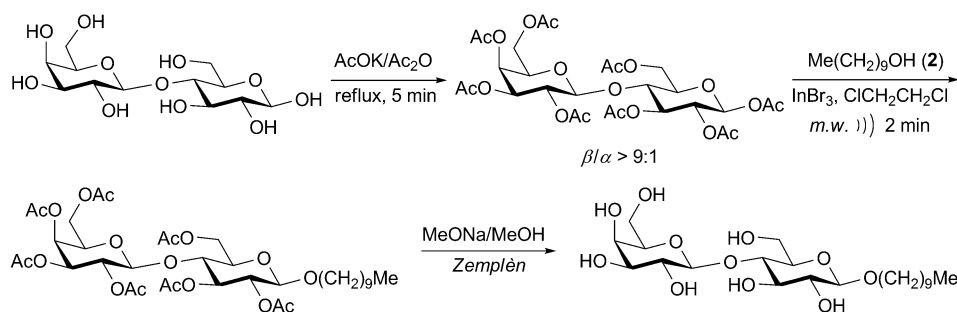


Figure. Diastereoisomeric glycolipids (rhamnolipid analogues) (R)- and (S)-1

mixtures of the donor and acceptor in a sealed tube (by means of microwaves) in  $\text{ClCH}_2\text{CH}_2\text{Cl}$  as solvent in the presence of  $\text{InBr}_3$  or other *Lewis* acids was used to define reaction conditions (Scheme 1). The classical *Zemplén* deacetylation methodology ( $\text{MeONa}/\text{MeOH}$   $\text{pH} \approx 9$ ) was used to remove the acetate protecting groups to provide the nonionic surfactant  $\beta$ -decyl lactoside in 50% yield. Higher temperatures ( $> 80^\circ$ ) or longer reaction times for the glycosylation resulted in the formation of  $\alpha$ -lactoside and product degradation.

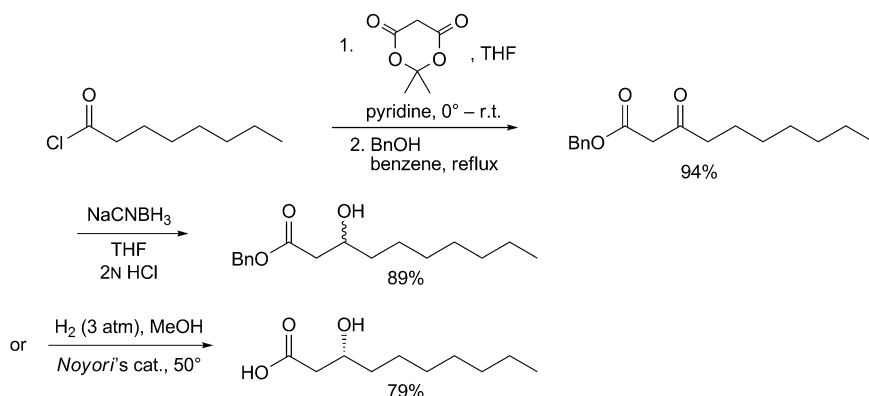
Scheme 1. Synthesis of  $\beta$ -Decyl Lactoside from the Peracetate of  $\beta$ -Lactose

These were the initial conditions used for the synthesis of L-rhamnosides. The requisite fatty acid was prepared from the corresponding  $\beta$ -keto ester by simple reduction with  $\text{NaCNBH}_3$  [16][17], or by enantioselective reduction by means of *Noyori's* method [18]. The  $\beta$ -keto ester in turn was prepared from the appropriate acyl chloride and *Meldrum's* acid [19] as depicted in Scheme 2.

L-Rhamnose (= 6-deoxy-L-mannose) was converted to the peracetate donor **5** with  $\text{Ac}_2\text{O}$  and pyridine, and subjected to glycosylation conditions (microwaves) in the presence of one of three different *Lewis* acids. Initially, the  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $\text{Sc}(\text{OTf})_3$  ( $\text{Tf} = \text{CF}_3\text{SO}_2$ ), and  $\text{InBr}_3$  in  $\text{ClCH}_2\text{CH}_2\text{Cl}$  were examined as promoters in conjunction with the three acceptors decan-1-ol (**2**), ( $\pm$ )-decan-2-ol (**3**), and methyl ( $\pm$ )-3-hydroxydecanoate (**4**) to produce glycosides **6**, **7**, and **8**, respectively (Table 1). Other solvent systems were explored:  $\text{CH}_2\text{Cl}_2/\text{PhMe}$  1 : 5;  $\text{CHCl}_3$ , and  $\text{CCl}_4$  were found to be effective, but several other solvents were not useful, *i.e.*, in  $\text{Et}_2\text{O}$ , THF, and DMF, was formed no product. Temperatures above  $80^\circ$  resulted in product mixtures.

Further studies indicated that, similar to  $\text{InBr}_3$ , the bismuth(III) salt  $\text{Bi}(\text{OTf})_3$  [20] was also a minimally competent *Lewis* acid, but with properties that were superior to  $\text{InBr}_3$  for these reactions, as shown in Table 2. In addition to being less hygroscopic than

Scheme 2. Synthesis of Benzyl 3-Hydroxydecanoates from Meldrum's Acid

Table 1. Synthesis of Glycosides from L-Rhamnose Peracetate **5** and Decanols **2–4** in  $\text{ClCH}_2\text{CH}_2\text{Cl}$ , in the Presence of Different Lewis Acids<sup>a)</sup>

| Decanol                                    | Yield <sup>b)</sup> [%]                              |                                        |                              |
|--------------------------------------------|------------------------------------------------------|----------------------------------------|------------------------------|
|                                            | $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (5.0 equiv.) | $\text{Sc}(\text{OTf})_3$ (1.0 equiv.) | $\text{InBr}_3$ (0.1 equiv.) |
| Decan-1-ol ( <b>2</b> )                    | 52                                                   | 39                                     | 39                           |
| (±)-Decan-2-ol ( <b>3</b> )                | 71                                                   | 33                                     | 50                           |
| Methyl (±)-3-hydroxydecanoate ( <b>4</b> ) | 43                                                   | 16                                     | 34                           |

<sup>a)</sup> Conditions: 2.2 equiv. of L-rhamnose peracetate **5** and 1 equiv. of decanol **2**, **3**, or **4** in  $\text{ClCH}_2\text{CH}_2\text{Cl}$  at 60° in a sealed tube. <sup>b)</sup> Yield of **6** (from **2**), **7** (from **3**), and **8** (from **4**).

indium(III) compounds, bismuth(III) salts are generally regarded as nontoxic, and are much cheaper than the corresponding indium(III) salts [21]. Additionally it was discovered that MeCN was the best solvent for rhamnoside formation [22], and that conventional reflux conditions with this solvent were ideal. The methyl ester **8** was replaced by benzyl ester **9** to permit hydrogenolysis and UV monitoring. The minimally competent  $\text{Bi}(\text{OTf})_3$  provided higher yields than  $\text{InBr}_3$ , and conventional heating conditions with MeCN as the solvent was reproducible, forming the rhamnosides **6**, **7**, and **10** from decan-1-ol (**2**), (±)-decan-2-ol (**3**), and benzyl (±)-3-hydroxydecanoate (**9**).

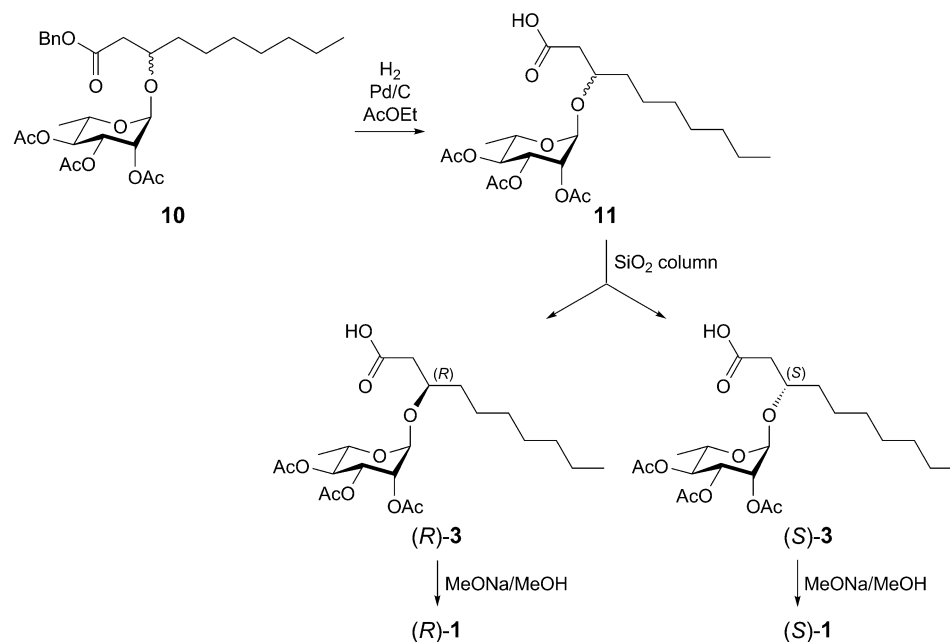
Hydrogenolysis of the diastereoisomer mixture of benzyl esters **10** produced a mixture of acids **11** in which the L-rhamnoside head group functioned as a very effective

Table 2. Comparison of Lewis Acids  $\text{InBr}_3$  and  $\text{Bi}(\text{OTf})_3$  in the Glycosylations of L-Rhamnose Peracetate **5** with Decanols **2**, **3**, or **9** in  $\text{MeCN}^a$ )

| Decanol                                    | Yield <sup>b)</sup> [%]      |                                        |
|--------------------------------------------|------------------------------|----------------------------------------|
|                                            | $\text{InBr}_3$ (0.1 equiv.) | $\text{Bi}(\text{OTf})_3$ (0.1 equiv.) |
| Decan-1-ol ( <b>2</b> )                    | 89                           | 91                                     |
| (±)-Decan-2-ol ( <b>3</b> )                | 83                           | 89                                     |
| Benzyl (±)-3-hydroxydecanoate ( <b>9</b> ) | 38                           | 60                                     |

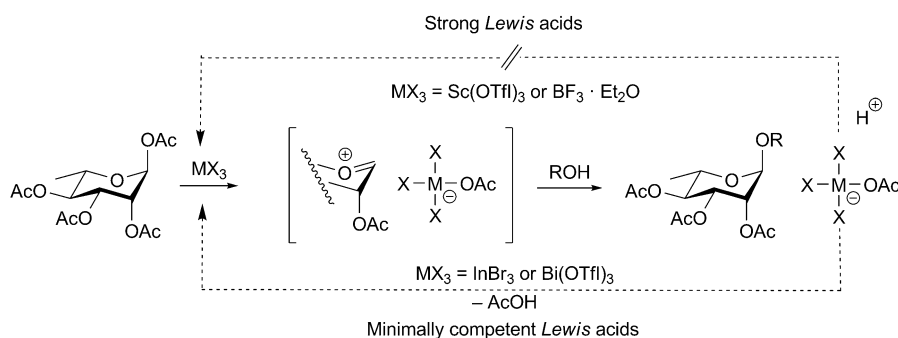
<sup>a)</sup> Conditions: 2.2 equiv. of L-rhamnose peracetate **5** and 1 equiv. of **2**, **3**, or **9** in  $\text{MeCN}$  under reflux, 2.5 h. <sup>b)</sup> Yield of **6** (from **2**), **7** (from **3**), and **10** (from **9**).

chiral auxiliary during chromatography (Scheme 3), permitting facile separation of the diastereoisomeric acids (*R*)-**11** and (*S*)-**11**. Subsequent *Zemplén* deacylation of the purified diastereoisomers provided the corresponding rhamnosides (*R*)-**1** and (*S*)-**1** in excellent yield and purity.

 Scheme 3. Chromatographic Separation of Diastereoisomeric Monolipids **11**


**Discussion.** – A major benefit of minimally competent *Lewis* acid is the fact that it can be used as a true catalyst, rather than stoichiometrically as a promoter of glycosylation. Stronger *Lewis* acids will retain the acetate leaving group from the donor, essentially becoming *Brønsted* acids as the glycosylation reaction proceeds. The minimally competent *Lewis* acids release the acetate to form acetic acid during the reaction, with concomitant regeneration of the catalyst (*Scheme 4*). Thus, the use of an ‘H-atom acceptor’ such as tetramethylurea [23] is not necessary or even desirable for such glycosylations.

Scheme 4. *Minimally Competent Lewis Acids Releasing the Acetate Moiety to Regenerate the Active Lewis acid.* Stronger *Lewis* acids retain the acetate to produce strong *Brønsted* acids.



Discovery of a second minimally competent *Lewis* acid,  $\text{Bi}(\text{OTf})_3$ , augers well for the discovery of more catalysts for glycosylation. It is noteworthy that the use of the relatively simple and robust sugar peracetates in conjunction with these mild *Lewis* acids allows for considerable leeway in the development of glycosylation conditions. Thus, the use of highly reactive glycosyl donors (*e.g.*, bromides, trichloroacetimidates, sulfoxides) for use with stoichiometric or even excess amounts of expensive, unstable, and/or exotic promoters ( $\text{Ag}^+$ ,  $\text{Hg}^{2+}$  salts,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  [ $\text{Me}_2\text{SSMe}](\text{OTf})$ , *etc.*), and long reaction times are no longer required. Although above-described reactions were performed with 10%  $\text{Bi}(\text{OTf})_3$  and nominally dry MeCN so that the reactions go to completion within a few hours, scrupulously dry conditions permit the use of much smaller amounts of catalyst. Further experimentation with more complex glycosides, polysaccharides, and glycolipids is clearly warranted.

### Experimental Part

1. *General.* All glassware was flame-dried prior to reactions, and all reactions were done under Ar. Microwave: 900 W Emerson MW8992SB microwave oven, purchased from a Target department store. Flash chromatography (FC): silica gel 60 ( $\text{SiO}_2$ , 200–400 mesh; Geduran No. EM-11567-1); Horizon HPFC system (Biotage, Inc.). HPLC: Varian-Prostar HPLC system, with a Prostar-330 photodiode array detector and a Phenomenex-Jupiter (250 mm  $\times$  21.2 mm, 15  $\mu\text{m}$ )  $C_{18}$  semi-prep. column. M.p.: uncorrected.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR Spectra: Bruker-DRX-400 (400 MHz), -DRX-500 (500 MHz), and -DRX-600 (600 MHz) spectrometers; in  $\text{CDCl}_3$ ,  $(\text{D}_6)\text{DMSO}$ , or  $\text{CD}_3\text{OD}$ ;  $\delta$  in ppm rel. to  $\text{Me}_4\text{Si}$  as internal standard,  $J$  in Hz; all NMR spectra were analyzed and interpreted with the MestReNova® software. ESI-MS: Thermo-Finnigan LCQ Deca with pos. and neg. detection,  $\text{MeOH}/\text{H}_2\text{O}$  1:1 solvent system; in  $m/z$  (rel. %).

2. *Decyl  $\beta$ -Lactoside*. A mixture of AcOK (6.56 g, 66.8 mmol) and Ac<sub>2</sub>O (21 ml, 220 mmol) was heated under reflux, followed by slow addition of lactose (1.01 g, 2.79 mmol) to the boiling mixture. The mixture was stirred for 5 min and allowed to cool to r.t., where it was then diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with ice-cold H<sub>2</sub>O, 1% NaHCO<sub>3</sub>, sat. NaHCO<sub>3</sub>, and sat. NaCl soln. The org. layer was dried (MgSO<sub>4</sub>) and concentrated to a colorless oil which was then dissolved in a minimal amount of CH<sub>2</sub>Cl<sub>2</sub> and recrystallized by addition of Et<sub>2</sub>O:  *$\beta$ -lactose peracetate* (58%). White, crystalline solid. M.p. 104–106°.

The  *$\beta$ -lactose peracetate* (1.78 g, 2.62 mmol), decan-1-ol (**2**; 0.50 ml, 2.62 mmol), and InBr<sub>3</sub> (0.093 g, 0.262 mmol) were added to a 50 ml triple-walled resealable vessel (internally threaded with a *Teflon* plug), dissolved in ClCH<sub>2</sub>CH<sub>2</sub>Cl (3–4 ml), and irradiated in a 900 W *Emerson-MW8992SB* microwave oven (power level 6) for 2 min. The crude yellow oil was purified by FC (gradient AcOEt/hexanes 1:9 → 2:8 → 3:7 → 4:6): *decyl  $\beta$ -lactoside peracetate* (60%). White foam. M.p. 94–99°. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): 5.31 (*d*, *J* = 3.2, 1 H); 5.16 (*t*, *J* = 9.3, 1 H); 5.07 (*dd*, *J* = 10.4, 7.9, 1 H); 4.92 (*dd*, *J* = 10.4, 3.4, 1 H); 4.85 (*dd*, *J* = 9.5, 8.0, 1 H); 4.49–4.38 (*m*, 3 H); 4.15–4.01 (*m*, 3 H); 3.87–3.72 (*m*, 3 H); 3.56 (*ddd*, *J* = 9.8, 5.0, 1.9, 1 H); 3.41 (*dt*, *J* = 9.6, 6.8, 1 H); 2.12 (*s*, *J* = 2.9, 3 H); 2.09 (*s*, *J* = 7.8, 3 H); 2.06–1.97 (*m*, 12 H); 1.93 (*s*, *J* = 5.9, 3 H); 1.58–1.45 (*m*, 2 H); 1.33–1.16 (*m*, 14 H); 0.85 (*t*, *J* = 6.9, 3 H). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): 170.2; 170.2; 170.0; 169.9; 169.6; 169.4; 168.9; 101.0; 100.6; 76.3; 72.9; 72.6; 71.8; 71.0; 70.7; 70.2; 69.2; 66.7; 62.1; 60.8; 31.9; 29.6; 29.5; 29.4; 29.3; 25.8; 22.7; 20.8; 20.8; 20.7; 20.6; 20.5; 14.1. ESI-MS (*pos.*): 815.1 (17, [*M* + *K*]<sup>+</sup>), 799.2 (99, [*M* + *Na*]<sup>+</sup>), 794.1 (53, [*M* + *NH*]<sup>+</sup>).

The *decyl  $\beta$ -lactoside peracetate* (2.93 g, 3.77 mmol) was dissolved in dry MeOH (30 ml) under Ar, and a 25% (wt./v) MeONa/MeOH soln. (0.5 ml) was added dropwise until the soln. reached pH 9–10. The mixture was stirred for 24 h (TLC monitoring) and then neutralized by *Dowex*® 50WX8–100 ion-exchange resin. The mixture was filtered and the filtrate concentrated: *decyl  $\beta$ -lactoside* (72%). White solid. M.p. 140–160° (*dec.*). <sup>1</sup>H-NMR (500 MHz, (D<sub>6</sub>)DMSO): 6.04 (*s*, 1 H); 5.84–5.31 (*m*, 4 H); 5.17 (*dd*, *J* = 19.1, 7.5, 2 H); 4.73 (*dt*, *J* = 6.6, 5.8, 2 H); 4.67–4.14 (*m*, 19 H); 3.99 (*t*, *J* = 8.2, 1 H); 3.50 (*dt*, *J* = 3.6, 1.8, 1 H); 2.37–2.13 (*m*, 14 H); 1.85 (*t*, *J* = 6.9, 3 H). <sup>13</sup>C-NMR (125 MHz, (D<sub>6</sub>)DMSO): 103.8; 102.5; 80.8; 75.5; 75.0; 74.8; 73.2; 73.1; 70.6; 68.7; 68.1; 60.6; 60.4; 31.3; 29.3; 29.0; 29.0; 28.9; 28.7; 25.5; 22.1; 14.0. ESI-MS (*pos.*): 987.0 (100, [2 *M* + *Na*]<sup>+</sup>), 964.9 (13, [2 *M* + *H*]<sup>+</sup>), 505.4 (12, [*M* + *Na*]<sup>+</sup>), 482.9 (10, [*M* + *H*]<sup>+</sup>).

3. *Microwave Procedure for Rhamnosides 6–8 (Table I)*. Rhamnose peracetate **5** (1.2 equiv.), alcohol (1 equiv.), and Sc(OTf)<sub>3</sub> (1 equiv.), InBr<sub>3</sub> (0.1 equiv.), or BF<sub>3</sub>·Et<sub>2</sub>O (5 equiv.) were dissolved in dry ClCH<sub>2</sub>CH<sub>2</sub>Cl (1.5 ml) in a flame-dried triple-walled resealable vessel (internally threaded with a *Teflon* plug), and the vessel was microwave-irradiated (900 W *Emerson MW8992SB*) for 2 min on power level 6. The slightly yellow mixture was neutralized with sat. NaHCO<sub>3</sub> soln., the org. layer washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>), and concentrated, and the obtained oil purified by FC (20% AcOEt/hexanes). Yields of **6–8** in Table I.

*Decyl 6-Deoxy- $\alpha$ -L-mannopyranoside Triacetate (6)*: Colorless oil. *R*<sub>f</sub> (30% AcOEt/hexanes) 0.64. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): 5.28 (*dd*, *J* = 10.1, 3.5, 1 H); 5.20 (*dd*, *J* = 3.5, 1.7, 1 H); 5.03 (*t*, *J* = 9.9, 1 H); 4.68 (*d*, *J* = 1.5, 1 H); 3.84 (*dq*, *J* = 9.9, 6.3, 1 H); 3.63 (*dt*, *J* = 9.5, 6.8, 1 H); 3.39 (*dt*, *J* = 9.6, 6.6, 1 H); 2.12 (*s*, 3 H); 2.02 (*s*, 3 H); 1.96 (*s*, 3 H); 1.59–1.53 (*m*, 2 H); 1.35–1.21 (*m*, 14 H); 1.19 (*d*, *J* = 6.3, 3 H); 0.86 (*t*, *J* = 6.9, 3 H). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): 170.2; 170.0; 169.9; 97.4; 71.3; 70.0; 69.2; 68.2; 66.2; 31.9; 29.6; 29.5; 29.4; 29.3; 26.1; 22.7; 20.9; 20.8; 20.7; 17.4; 14.1.

*(1R)- and (1S)-1-Methylnonyl 6-Deoxy- $\alpha$ -L-mannopyranoside Triacetate (7)*: diastereoisomer mixture 1:1: Colorless oil. *R*<sub>f</sub> (30% AcOEt/hexanes) 0.68. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): 5.28 (*dd*, *J* = 10.1, 3.5, 1 H); 5.25 (*dd*, *J* = 10.1, 3.5, 1 H); 5.15–5.11 (*m*, 2 H); 5.02 (*t*, *J* = 9.9, 1 H); 5.01 (*t*, *J* = 10.0, 1 H); 4.79 (*d*, *J* = 1.7, 1 H); 4.77 (*d*, *J* = 1.7, 1 H); 3.92 (*dq*, *J* = 9.8, 6.3, 1 H); 3.89 (*dq*, *J* = 9.8, 6.3, 1 H); 3.70 (*dt*, *J* = 11.8, 6.0, 1 H); 3.64 (*dt*, *J* = 12.4, 6.1, 1 H); 2.11 (*s*, 6 H); 2.01 (*s*, 3 H); 2.01 (*s*, 3 H); 1.95 (*s*, 6 H); 1.60–1.44 (*m*, 2 H); 1.44–1.30 (*m*, 2 H); 1.26 (*dd*, *J* = 26.5, 8.0, 24 H); 1.16 (*d*, *J* = 6.3, 9 H); 1.08 (*d*, *J* = 6.1, 3 H); 0.84 (*t*, *J* = 6.9, 3 H); 0.84 (*t*, *J* = 7.0, 3 H). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): 170.2; 170.1; 170.0; 169.9; 169.9; 97.0; 94.9; 75.8; 73.1; 71.4; 71.2; 70.6; 70.4; 69.2; 69.2; 66.4; 66.2; 36.9; 36.2; 31.8; 31.8; 29.6; 29.5; 29.5; 29.5; 29.2; 29.2; 25.6; 25.3; 22.6; 21.1; 20.9; 20.8; 20.7; 18.9; 17.3; 17.3; 14.1.

*Methyl (3R)- and (3S)-3-[(2,3,4-Tri-O-acetyl-6-deoxy- $\alpha$ -L-mannopyranosyl)oxy]decanoate (8)*: diastereoisomer mixture 1:1: Colorless oil. *R*<sub>f</sub> (pair of diastereoisomers) 0.45 and 0.40. <sup>1</sup>H-NMR

(500 MHz,  $\text{CDCl}_3$ ): 5.21 (*d*,  $J = 3.4$ , 1 H); 5.19 (*d*,  $J = 3.4$ , 1 H); 5.11 (*dd*,  $J = 3.4$ , 1.8, 1 H); 5.07 (*dd*,  $J = 3.4$ , 1.8, 1 H); 5.01 (*t*,  $J = 9.9$ , 1 H); 4.99 (*t*,  $J = 10.0$ , 1 H); 4.83 (*d*,  $J = 1.5$ , 1 H); 4.80 (*d*,  $J = 1.5$ , 1 H); 4.10–3.97 (*m*, 2 H); 3.94–3.82 (*m*, 2 H); 3.66 (*s*, 3 H); 3.65 (*s*, 3 H); 2.54 (*dd*,  $J = 15.3$ , 8.1, 1 H); 2.50 (*dd*,  $J = 15.5$ , 7.5, 1 H); 2.44 (*dd*,  $J = 15.4$ , 6.4, 1 H); 2.43 (*dd*,  $J = 15.4$ , 6.9, 1 H); 2.10 (*d*,  $J = 2.8$ , 6 H); 2.00 (*d*,  $J = 3.0$ , 6 H); 1.93 (*d*,  $J = 1.9$ , 6 H); 1.63–1.40 (*m*, 4 H); 1.36–1.17 (*m*, 16 H); 1.16 (*d*,  $J = 6.3$ , 1 H); 1.15 (*d*,  $J = 6.2$ , 1 H); 0.83 (*td*,  $J = 6.9$ , 3.5, 6 H).  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ): 171.7; 171.6; 170.1; 170.0; 169.9; 169.9; 169.9; 97.5; 95.9; 76.3; 74.9; 71.1; 70.3; 70.2; 69.1; 69.0; 66.7; 66.6; 51.7; 51.6; 39.9; 39.3; 35.0; 33.3; 31.7; 31.7; 29.4; 29.4; 29.1; 29.1; 25.1; 24.7; 22.6; 22.6; 20.9; 20.9; 20.8; 20.7; 17.2; 17.2; 14.0.

4. *Conventional Reflux Procedure for Rhamnosides 6, 7, and 10* (Table 2). To a soln. of rhamnose peracetate **5** (2.2 equiv.) in dry MeCN, the alcohol (1 equiv.) and either  $\text{Bi}(\text{OTf})_3$  (0.10 equiv.) or  $\text{InBr}_3$  (0.10 equiv.) were added. The mixture was refluxed under a *Liebig* condenser for 2.5 h and then allowed to cool to r.t. For  $\text{Bi}(\text{OTf})_3$ , the yellow-brown mixture was diluted with  $\text{CH}_2\text{Cl}_2$ , *Celite*<sup>®</sup> was added, the mixture filtered, and the filtrate concentrated to a yellow-brown syrup. For  $\text{InBr}_3$ , the yellow mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and neutralized with sat.  $\text{NaHCO}_3$  soln., and the org. layer washed with  $\text{H}_2\text{O}$ , dried ( $\text{MgSO}_4$ ), and concentrated. Purification was achieved by FC (gradient hexanes/AcOEt 0 → 20%). Yields of **6**, **7**, and **10** in Table 2.

*Phenylmethyl (3R)- and (3S)-3-[(2,3,4-Tri-O-acetyl-6-deoxy- $\alpha$ -L-mannopyranosyl)oxy]decanoate (10)*: diastereoisomer mixture 45 : 55). Colorless oil.  $R_f$  (30% AcOEt/hexanes) 0.55.  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ ): 7.36–7.27 (*m*, 10 H); 5.23 (*ddd*,  $J = 10.1$ , 3.4, 1.0, 2 H); 5.14 (*dt*,  $J = 4.4$ , 2.2, 1 H); 5.13–5.10 (*m*, 5 H); 5.02 (*td*,  $J = 10.0$ , 5.9, 2 H); 4.87 (*d*,  $J = 1.6$ , 1 H); 4.83 (*d*,  $J = 1.6$ , 1 H); 4.14–4.02 (*m*, 2 H); 3.95–3.86 (*m*, 2 H); 2.66–2.46 (*m*, 4 H); 2.12 (*d*,  $J = 5.9$ , 6 H); 2.04–1.99 (*m*, 6 H); 1.96 (*d*,  $J = 1.5$ , 6 H); 1.63–1.43 (*m*, 4 H); 1.37–1.19 (*m*, 23 H); 1.18 (*d*,  $J = 6.3$ , 3 H); 1.15 (*d*,  $J = 6.3$ , 3 H); 0.85 (*td*,  $J = 6.9$ , 3.7, 6 H).  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ): 171.1; 170.9; 170.1; 170.0; 169.9; 135.7; 135.7; 128.5; 128.5; 128.2; 128.2; 97.4; 96.2; 76.1; 75.1; 71.1; 70.3; 70.2; 69.1; 69.1; 66.7; 66.7; 66.5; 66.4; 40.2; 39.5; 35.0; 33.4; 31.7; 29.5; 29.4; 29.1; 29.1; 25.1; 24.7; 22.6; 22.6; 20.9; 20.8; 20.7; 17.3; 14.1.

5. *(3R)- and (3S)-3-[(2,3,4-Tri-O-acetyl-6-deoxy- $\alpha$ -L-mannopyranosyl)oxy]decanoic Acid ((R)-11 and (S)-11, resp.)*. To a soln. of **10** (8.57 g, 15.6 mmol) in dry THF (100 ml) at r.t., a small amount of 10% (wt.) Pd/C was added under Ar. By means of a balloon, the flask was filled with  $\text{H}_2$  gas (1 atm) and the mixture stirred vigorously at r.t. for 24 h. Then the mixture was purged with Ar, diluted with  $\text{CH}_2\text{Cl}_2$ , and filtered through *Celite*<sup>®</sup>, the filtrate concentrated, and the resulting oil purified by FC ( $\text{Et}_2\text{O}$ /hexanes 1 : 1 with 1% AcOH): (*R*)-**11** (38%) and (*S*)-**11** (33%).

*Data of (R)-11*: Colorless oil.  $[\alpha]_D = -30.6$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).  $R_f$  ( $\text{Et}_2\text{O}$ /hexanes 1 : 1 with 1% (v/v) AcOH) 0.26.  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ): 5.24 (*dd*,  $J = 10.1$ , 3.5, 1 H); 5.12 (*dd*,  $J = 3.4$ , 1.8, 1 H); 5.03 (*t*,  $J = 9.9$ , 1 H); 4.89 (*d*,  $J = 1.8$ , 1 H); 4.04 (*dq*,  $J = 11.7$ , 5.9, 1 H); 3.93 (*dq*,  $J = 9.8$ , 6.3, 1 H); 2.57 (*dd*,  $J = 15.8$ , 7.5, 1 H); 2.49 (*dd*,  $J = 15.8$ , 5.3, 1 H); 2.11 (*s*, 3 H); 2.03 (*s*, 3 H); 1.96 (*s*, 3 H); 1.65–1.50 (*m*, 2 H); 1.32–1.22 (*m*, 10 H); 1.18 (*d*,  $J = 6.3$ , 3 H); 0.89–0.84 (*m*, 3 H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ): 176.2; 170.2; 170.1; 170.1; 97.5; 76.2; 71.1; 70.3; 69.1; 66.8; 39.3; 35.0; 31.7; 29.4; 29.1; 25.1; 22.6; 20.9; 20.8; 20.7; 17.3; 14.0.

*Data of (S)-11*: Clear oil.  $[\alpha]_D = -47.9$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).  $R_f$  ( $\text{Et}_2\text{O}$ /hexanes 1 : 1 with 1% (v/v) AcOH) 0.38.  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ): 5.23 (*dd*,  $J = 10.1$ , 3.4, 1 H); 5.14 (*dd*,  $J = 3.4$ , 1.8, 1 H); 5.02 (*t*,  $J = 9.9$ , 1 H); 4.82 (*d*,  $J = 1.7$ , 1 H); 4.07 (*dq*,  $J = 7.5$ , 5.9, 1 H); 3.93 (*dq*,  $J = 9.9$ , 6.3, 1 H); 2.63 (*dd*,  $J = 15.9$ , 7.6, 1 H); 2.52 (*dd*,  $J = 15.9$ , 4.8, 1 H); 2.12 (*s*, 3 H); 2.02 (*s*, 3 H); 1.96 (*s*, 3 H); 1.52 (*ddd*,  $J = 23.0$ , 14.2, 5.3, 2 H); 1.32–1.21 (*m*, 10 H); 1.15 (*d*,  $J = 6.3$ , 3 H); 0.87–0.82 (*m*, 3 H).  $^{13}\text{C}$ -NMR (101 MHz,  $\text{CDCl}_3$ ): 176.7; 170.2; 170.1; 170.0; 96.4; 75.1; 71.1; 70.3; 69.1; 66.8; 39.9; 33.6; 31.7; 29.5; 29.1; 24.8; 22.6; 20.9; 20.8; 20.7; 17.2; 14.0.

6. *(3R)- and (3S)-3-(6-Deoxy- $\alpha$ -L-mannopyranosyloxy)decanoic Acid ((R)-1 and (S)-1, resp.)*. To a soln. of (*R*)-**11** (5.77 g, 12.5 mmol) in dry MeOH (50 ml) at r.t., MeONa was added while stirring to achieve a pH 9–10 (monitoring by a drop of the mixture onto a moistened pH-indicator strip). The mixture was stirred at r.t. for 3.5 h and then quenched with *Dowex*  $\text{H}^+$  resin. The resin was removed by filtration and the filtrate concentrated to an oil. No further purification was required. However, redissolving of the product in a minimal amount of hexanes, followed by filtration, was occasionally required to remove residual  $\text{Na}^+$  salts: (*R*)-**1** (99%). Colorless oil.  $[\alpha]_D = -34.8$  ( $c = 1.0$ , MeOH).  $R_f$  (10% MeOH/ $\text{CH}_2\text{Cl}_2$  with 1% (v/v) AcOH) 0.20.  $^1\text{H}$ -NMR (400 MHz,  $\text{CD}_3\text{OD}$ ): 4.75 (*d*,  $J = 1.7$ , 1 H);

3.96–3.89 (*m*, 1 H); 3.65 (*dd*,  $J = 3.4, 1.7, 1\text{ H}$ ); 3.61–3.53 (*m*, 1 H); 3.51 (*dd*,  $J = 9.5, 3.4, 1\text{ H}$ ); 3.29–3.24 (*m*, 1 H); 2.34 (*qd*,  $J = 15.0, 6.4, 2\text{ H}$ ); 1.54–1.43 (*m*, 2 H); 1.26–1.17 (*m*, 10 H); 1.14 (*d*,  $J = 6.3, 3\text{ H}$ ); 0.80 (*dd*,  $J = 7.9, 6.0, 3\text{ H}$ ).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CD}_3\text{OD}$ ): 176.2; 101.6; 76.9; 73.9; 72.7; 72.4; 70.2; 41.2; 36.4; 33.0; 30.7; 30.3; 26.3; 23.7; 17.9; 14.4. ESI-MS (neg.): 334.1 (12,  $M^-$ ), 333.1 (99,  $[M - \text{H}]^-$ ).

Glycolipid (*S*)-**1** was obtained in the same fashion: Yield 99%. Colorless oil.  $[\alpha]_D = -47.0$  ( $c = 1.0$ , MeOH).  $R_f$  (10% MeOH/ $\text{CH}_2\text{Cl}_2$  with 1% (*v/v*) AcOH) 0.25.  $^1\text{H}$ -NMR (400 MHz,  $\text{CD}_3\text{OD}$ ): 4.66 (*d*,  $J = 1.7, 1\text{ H}$ ); 3.93 (*dq*,  $J = 7.5, 5.7, 1\text{ H}$ ); 3.62 (*dd*,  $J = 3.4, 1.7, 1\text{ H}$ ); 3.58–3.45 (*m*, 2 H); 3.20 (*t*,  $J = 9.5, 1\text{ H}$ ); 2.33 (*ddd*,  $J = 20.4, 14.8, 6.6, 2\text{ H}$ ); 1.42 (*dt*,  $J = 9.1, 6.2, 2\text{ H}$ ); 1.21–1.13 (*m*, 10 H); 1.09 (*d*,  $J = 6.2, 3\text{ H}$ ); 0.77–0.73 (*m*, 3 H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CD}_3\text{OD}$ ): 176.5; 100.3; 75.9; 74.0; 72.7; 72.3; 70.1; 42.2; 34.5; 33.0; 30.7; 30.3; 25.9; 23.7; 17.9; 14.4. ESI-MS (neg.): 334.1 (12,  $M^-$ ), 333.1 (99,  $[M - \text{H}]^-$ ).

## REFERENCES

- [1] R. Polt, L. Z. Szabo, J. Treiberg, Y. Li, V. J. Hruby, *J. Am. Chem. Soc.* **1992**, *114*, 10249.
- [2] S. A. Mitchell, M. R. Pratt, V. J. Hruby, R. Polt, *J. Org. Chem.* **2001**, *66*, 2327.
- [3] C. M. Keyari, R. Polt, *J. Carbohydr. Chem.* **2010**, *29*, 181.
- [4] M. M. Palian, V. I. Boguslavsky, D. F. O'Brien, R. Polt, *J. Am. Chem. Soc.* **2003**, *125*, 5823.
- [5] M. Dhanasekaran, M. M. Palian, I. Alves, L. Yeomans, C. M. Keyari, P. Davis, E. J. Bilsky, R. D. Egleton, H. I. Yamamura, N. E. Jacobsen, G. Tollin, V. J. Hruby, F. Porreca, R. Polt, *J. Am. Chem. Soc.* **2005**, *127*, 5435.
- [6] Y. Li, M. R. Lefever, D. Muthu, J. M. Bidlack, E. J. Bilsky, R. Polt, *Future Med. Chem.* **2012**, *4*, 205.
- [7] M. R. Lefever, L. Z. Szabó, B. Anglin, J. Hogan, L. Cooney, R. Polt, *Carbohydr. Res.* **2012**, *351*, 121.
- [8] F. G. Jarvis, M. J. Johnson, *J. Am. Chem. Soc.* **1949**, *71*, 4124.
- [9] J. Bauer, K. Brandenburg, U. Zähringer, J. Rademann, *Chem. – Eur. J.* **2006**, *12*, 7116.
- [10] A. A. Bodour, K. P. Drees, R. M. Maier, *Appl. Environ. Microbiol.* **2003**, *69*, 3280.
- [11] A. K. Koch, O. Kappeli, A. Fiechter, J. Reiser, *J. Bacteriol.* **1991**, *173*, 4212.
- [12] Y. Zhang, R. M. Miller, *Appl. Environ. Microbiol.* **1992**, *58*, 3276.
- [13] C. N. Mulligan, R. N. Yong, B. F. Gibbs, *Eng. Geol.* **2001**, *60*, 193.
- [14] J. D. Desai, I. M. Banat, *Microbiol. Mol. Biol. Rev.* **1997**, *61*, 47.
- [15] F. J. Ochoa-Loza, J. F. Artiola, R. M. Maier, *J. Environ. Qual.* **2001**, *30*, 479.
- [16] D. Sames, R. Polt, *Synlett* **1995**, *SI*, 552.
- [17] C. F. Lane, *Synthesis* **1975**, 135.
- [18] M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Org. Synth.* **1998**, *9*, 589.
- [19] Y. Oikawa, K. Sugano, O. Yonemitsu, *J. Org. Chem.* **1978**, *43*, 2087.
- [20] N. M. Leonard, L. C. Wieland, R. S. Mohan, *Tetrahedron* **2002**, *58*, 8373.
- [21] K. Dill, E. L. McGowan, in 'The Chemistry of Organic Arsenic, Antimony and Bismuth Compounds', Ed. S. Patai, Wiley & Sons, New York, 1994, p. 695–713.
- [22] R. R. Schmidt, *Angew. Chem., Int. Ed.* **1986**, *25*, 212.
- [23] S. Hanessian, J. Banoub, *Carbohydr. Res.* **1977**, *53*, C13.

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