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# Sulfone and phosphinic acid analogs of decaprenolphosphoarabinose as potential anti-tuberculosis agents

Charla A. Centrone and Todd L. Lowary*

*Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, OH 43210, USA*

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**Abstract**—Mycobacteria biosynthesize a cell wall structure that is rich in polysaccharides containing arabinofuranose residues. The source of these arabinofuranose residues is decaprenolphosphoarabinose (**1**), the donor substrate for mycobacterial arabinosyltransferases. We have previously demonstrated that an analog of **1**, *C*-phosphonate **7**, prevented the growth of mycobacteria and this compound is currently undergoing testing for efficacy in tuberculosis-infected mice. We describe here the synthesis and testing of additional analogs of **1** that contain either a sulfone (**8**–**14**) or phosphinic acid (**15**–**19**) moiety in place of the phosphodiester functionality. Screening of these compounds in vitro against *Mycobacterium tuberculosis* strain $H_{37}Rv$ revealed that while some of these compounds possessed low to modest activity, none was as potent as **7**.


## 1. Introduction

All mycobacteria, including the human pathogen *Mycobacterium tuberculosis*, produce a cell wall structure that fulfills an important role in protecting these organisms from their environment.[1,2] Two polysaccharides, arabinogalactan (AG) and lipoarabinomannan (LAM), are major structural components of the cell wall in these organisms. An unusual structural feature of these glycans is that all of the arabinose and galactose residues exist in the furanose ring form. The arabinan component of AG and LAM is biosynthesized by a family of arabinosyltransferases (AraT's) that use decaprenolphosphoarabinose (DPA, **1**, Fig. 1) as the donor of the arabinofuranose residues.[3–6]

Mycobacteria require an intact cell wall for viability and therefore compounds that inhibit the enzymes responsible for biosynthesizing this structure have potential as anti-mycobacterial agents.[7,8] Of particular note are the enzymes that introduce the galactofuranose and arabinofuranose residues into AG and LAM. Polysaccharides containing furanose residues are unknown in mammals and the enzymes that are involved in the biosynthesis of these glycans are therefore ideal targets for drug action.[9,10] The emergence of drug resistant strains of mycobacteria[11,12] and the resurgence of these diseases, in particular in immunocompromised individuals,[13] has prompted increasing interest in the identification of new anti-mycobacterial drugs.

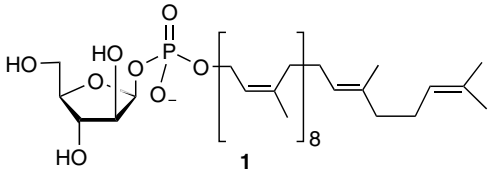


**Figure 1.** Decaprenolphosphoarabinose, DPA.

We have a long-standing interest in inhibitors of mycobacterial AraT's given their demonstrated suitability as targets for drug action. Previous studies[14–16] have shown that ethambutol, a drug used in the treatment of tuberculosis, inhibits the AraT's that produce the arabinan component of AG and LAM. In an earlier report,[17] we described the synthesis of a panel of *C*-phosphonate-based DPA analogs (**2**–**7**, Chart 1) and their subsequent evaluation as anti-tuberculosis agents. It was

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* Corresponding author at present address: Alberta Ingenuity Centre for Carbohydrate Science, Department of Chemistry, The University of Alberta, Gunning–Lemieux Chemistry Centre, Edmonton, AB T6G 2G2, Canada. Tel.: +78 0492 1861; fax: +78 0492 7705; e-mail: tlowary@ualberta.ca

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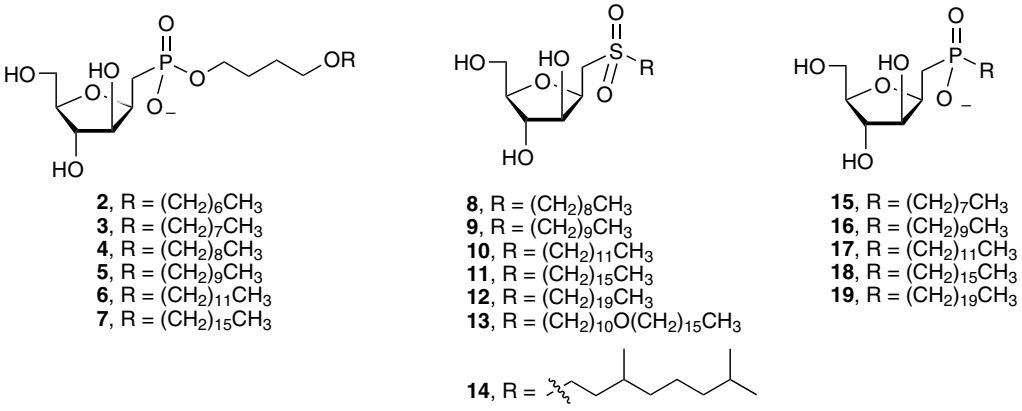


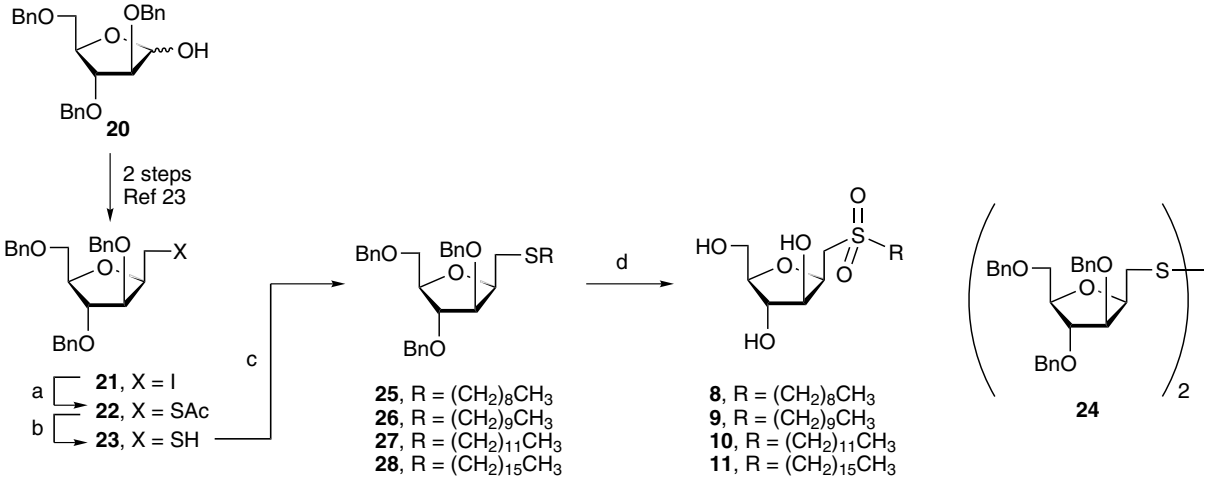

**Chart 1.**

expected that replacement of the glycosidic oxygen in **1** with a methylene group would provide compounds that would be bound by mycobacterial AraT's, but that could not turn over therefore blocking cell wall biosynthesis and killing the organism. When tested against *M. tuberculosis* strain $H_{37}Rv$, only one of these *C*-phosphonates, **7**, was shown to prevent the growth of the organism in vitro, with an MIC value of 3.13 μg/mL. Further studies[18] revealed that **7** had an $IC_{50}$ against Vero cells of 36.4 μg/mL and thus the selectivity index[19] was 11.6. Based on these results, *C*-phosphonate **7** is currently being tested for efficacy in tuberculosis-infected mice. Given this success, we chose to prepare additional DPA analogs in which the phosphate group was replaced with other isosteres. We describe here the synthesis of a series of glycosyl sulfone[20,21] DPA analogs (**8**–**14**) and their evaluation as potential anti-tuberculosis agents. We also describe the results of screening a panel of phosphinic acid-containing DPA analogs (**15**–**19**) against *M. tuberculosis*. The synthesis of these phosphinic acids has been previously reported.[22]

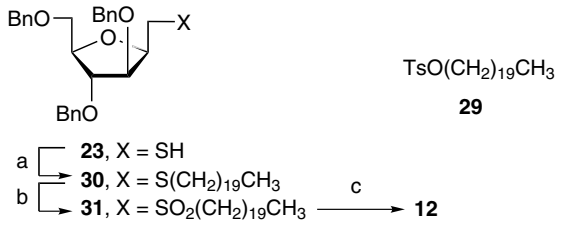
## 2. Results and discussion

### 2.1. Synthesis of glycosyl sulfones

The synthesis of the glycosyl sulfones **8**–**11** (Scheme 1) began with iodide **21**, which was prepared in two steps from commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranose, **20**.[23] Reaction of **21** with potassium thioacetate afforded **22** in 94% yield and conversion to thiol **23** was achieved with lithium aluminum hydride (97%). We also attempted this deacylation under milder reaction conditions (e.g., sodium borohydride, or sodium methoxide), however the yields were lower due to the formation of significant amounts of a byproduct. The spectral data for this byproduct was consistent with it being disulfide **24**. Alkylation of **23** with sodium hydride and commercially available linear alkyl iodides ($C_9$, $C_{10}$, $C_{12}$, and $C_{16}$) afforded sulfides **25**–**28** in 65–82% yield. Attempts to directly synthesize these sulfides by reaction of iodide **21** with various long-chain alkyl thiolate salts gave lower yields of the product, and thus we view the




**Scheme 1.** Reagents and conditions: (a) KSAc, DMF, rt, 94%; (b) $LiAlH_4$, $Et_2O$, rt, 97%; (c) for synthesis of **25**: $CH_3(CH_2)_8I$, NaH, DMF, rt, 72%; for synthesis of **26**: $CH_3(CH_2)_9I$, *n*-BuLi, $Et_2O$, 0 °C → rt, 65%; for synthesis of **27**: $CH_3(CH_2)_{11}I$, NaH, DMF, rt, 82%; for synthesis of **28**: $CH_3(CH_2)_{15}I$, NaH, DMF, rt, 74%; (d) *m*-CPBA, $CH_2Cl_2$, rt, followed by workup and then $H_2$, Pd/C, $CH_3OH$, HOAc, rt, yields of: **8**—79%, **9**—85%, **10**—76%, and **11**—49%.




**Scheme 2.** Reagents and conditions: (a) **29**, *n*-BuLi, THF, 0 °C → rt; (b) *m*-CPBA, $CH_2Cl_2$, rt, 30% from **23**; (c) $H_2$, Pd/C, $CH_3OH$, HOAc, rt, 80%.

indirect approach via **23** as superior. Oxidation of **25**–**28** with *m*-chloroperoxybenzoic acid yielded the corresponding benzylated sulfones, which were then deprotected by hydrogenolysis yielding **8**–**11** in 49–85% yield over the two steps.

The synthesis of sulfone **12** (Scheme 2) involved the coupling of **23** with 1-*p*-toluenesulfonyloxyeicosane, **29**, which was prepared from 1-eicosanol and *p*-toluenesulfonyl chloride.[22] The product sulfide, **30**, was impossible to separate from **29** and thus the crude product was oxidized affording, after purification, sulfone **31** in 50% yield from **23**. Hydrogenolysis provided target **12** in 80% yield.

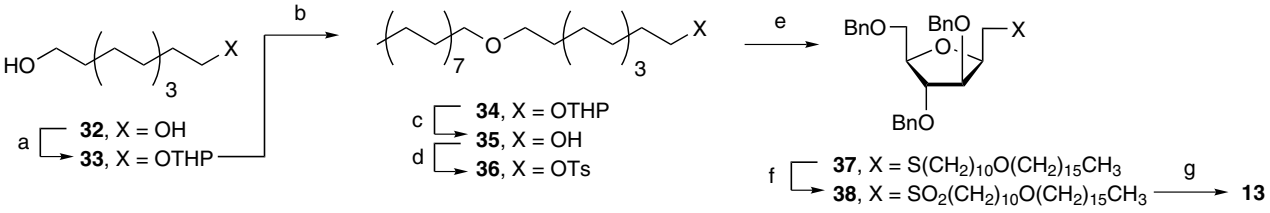
We endeavored to prepare a sulfone with a longer (>$C_{20}$) alkyl group and therefore explored the preparation of a tosylate from 1-triacontanol ($CH_3(CH_2)_{29}OH$). However, the extreme insolubility of this $C_{30}$ alcohol in essentially all common organic solvents (e.g., hexanes, THF, pyridine, glacial acetic acid, $CHCl_3$, and mixtures of these and other solvents), made this impractical. Instead, we opted to prepare a long-chain alkylating agent containing an ether linkage, which we anticipated would increase solubility in organic solvents. Because **7**, which is active against *M. tuberculosis*, has an oxygen atom in the linear chain, we did not anticipate that the inclusion of an ether moiety into a sulfone analog would abrogate activity. Thus, commercially available 1,10-decanediol, **32**, was reacted (Scheme 3) with 3,4-dihydropyran and a catalytic amount of *p*-toluenesulfonic acid. The monoprotected alcohol, **33**, was obtained in 53% yield along with the corresponding bis-tetrahdropyranyl acetal and unreacted **32**. Alcohol **33** was then alkylated with 1-iodohexadecane to afford **34** in low (21%) yield. Attempts to improve the yield by increasing the reaction temperature, led only to elimination of the iodide to form 1-hexadecene. Deprotection of the tetrahydropyranyl ether was achieved by heating **34** in a mixture of acetic acid, tetrahydrofuran, and water at 65 °C, yielding **35** in 84% yield. Conversion of **35** into the corresponding tosylate, **36**, required comparably vigorous conditions (potassium hydride, 18-crown-6, *p*-toluenesulfonyl chloride) and provided the product in only low (26%) yield. More conventional methods for preparation of this tosylate (*p*-toluenesulfonyl chloride, pyridine) failed. With **36** in hand, it was coupled with **23** in the presence of potassium hydride and 18-crown-6 providing the thioether, **37**, which could not be separated from unreacted **36**. Therefore, the crude mixture of **36** and **37** was oxidized with *m*-chloroperoxybenzoic acid to afford, after purification, sulfone **38** in 30% overall yield from **23**. In an effort to improve the coupling yield of **36** and **23**, the use of *n*-BuLi in THF and NaH in DMF was explored, but under these conditions the major product was disulfide **24** (see Scheme 1). Hydrogenolysis of **38** yielded **13** in 60% yield.

The final target, **14**, was synthesized as outlined in Scheme 4 in a manner analogous to the other compounds. Thiol **23** was alkylated with geranyl tosylate, **39**, generated in situ from gerianol, to afford **40** in 76% yield. Oxidation of **40** provided **41** in 53% yield, which was then deprotected yielding **14** in 64% yield.

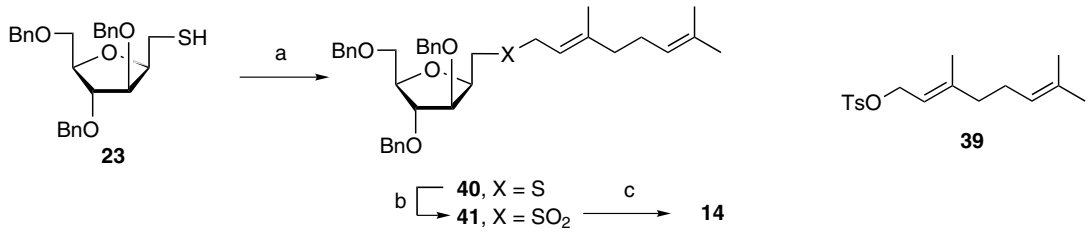
### 2.2. Screening of compounds as potential anti-mycobacterial agents

DPA analogs **8**–**20** were screened for their ability to prevent the growth of *M. tuberculosis* strain $H_{37}Rv$ using the fluorescence-based Alamar Blue microplate assay.[24] This assay makes use of the Alamar Blue dye that changes from blue (and non-fluorescent) to pink (and fluorescent) in the presence of the growing bacteria. Compounds that prevent the growth of the organism thus result in a decrease in fluorescence, which is quantitated. The results obtained when compounds **8**–**20** were tested in this assay are presented in Table 1. For purposes of comparison, the data previously obtained for **7** is also included.

From the results presented in the table, it is clear that none of the sulfone (**8**–**14**) or phosphinic acid (**15**–**20**) DPA analogs were as potent inhibitors of mycobacterial growth as *C*-phoshonate **7**. Although some compounds did show some activity, the amount of growth inhibition is low to modest and not at a level that warrants further




**Scheme 3.** Reagents and conditions: (a) 3,4-dihydropyran, *p*-TsOH, THF, rt, 53%; (b) $CH_3(CH_2)_{15}I$, NaH, DMF, rt, 21%; (c) AcOH, THF, $H_2O$, 65 °C, 84%; (d) *p*-TsCl, KH, 18-crown-6, THF, rt, 26%; (e) **23**, KH, 18-crown-6, THF, rt; (f) *m*-CPBA, $CH_2Cl_2$, rt, 45% from **36**; (g) $H_2$, Pd/C, $CH_3OH$, AcOH, 60%.




**Scheme 4.** Reagents and conditions: (a) **39**, *n*-BuLi, THF −78 °C, 76%; (b) $NaIO_4$, $CH_3OH$, $H_2O$, 70 °C, 53%; (c) $H_2$, Pd/C, $CH_3OH$, AcOH, 64%.

**Table 1.** Activity of **7**–**20** against *M. tuberculosis* strain $H_{37}Rv$[a]

| Compound | % Inhibition |
|---|---|
| **7**[b] | 92 |
| **8** | 0 |
| **9** | 21 |
| **10** | 45 |
| **11** | 0 |
| **12** | 4 |
| **13** | 0 |
| **14** | 20 |
| **15** | 0 |
| **16** | 0 |
| **17** | 17 |
| **18** | 0 |
| **19** | 0 |

[a] All compounds were screened at a concentration of 6.25 μg/mL using the Alamar Blue assay.[24]
[b] Taken from Ref. 17; **7** has a MIC of 3.13 μg/mL.

screening of these compounds as potential anti-tuberculosis agents. Moreover, the results demonstrate that no clear correlation exists between structure and biological activity. For example, in our previous studies with *C*-phosphonates **2**–**7**, it was demonstrated that only the analog with the longest alkyl chain was active. However, the same trend is not observed with these sulfone and phosphinic acid-containing compounds.

To the best of our knowledge, no previous phosphinic-acid containing DPA analogs have been synthesized or tested for anti-mycobacterial activity. In contrast, a previous report,[25] has described the preparation and testing of five sulfone DPA analogs (**42**–**46**, Fig. 2) as anti-mycobacterial agents. None of these compounds was shown to have appreciable activity. However, it is interesting to note that the most active of these compounds, azasugars **45** and **46**, contain a $C_{12}$ alkyl chain, as does the most active of our sulfone and phosphinic acid analogs (**10** and **17**, respectively). The significance of this observation is unclear in view of the low anti-tuberculosis activity of these compounds.

The apparent failure of the phosphinic acid in the long-chain analogs (e.g., **18** and **19**) to serve as mimics of the phosphate group in **1** is somewhat surprising and could be due to the difference in $pK_a$ between the phosphate and phosphinic acid protons. The proton of a phosphoric acid diester (e.g., **1**) would be expected[26] to be more acidic than the proton in an analogous phosphinic acid and thus the former should be significantly more ionized at physiological pH. The degree of ionization of this moiety would likely influence the binding of these compounds to the enzyme and hence their inhibitory and anti-tuberculosis potential. Consistent with this hypothesis is the lack of activity of the sulfones, which cannot be ionized.

In summary, we have described the synthesis of analogs of decaprenolphosphoarabinose (**1**), the mycobacterial donor substrate of arabinofuranose residues. Screening of these compounds for anti-tuberculosis activity showed that although some compounds did inhibit the growth of the organism, the effects were low to modest. Therefore, more detailed study of these compounds, either in additional assays or in investigations to determine their mode of action (perhaps as inhibitors of

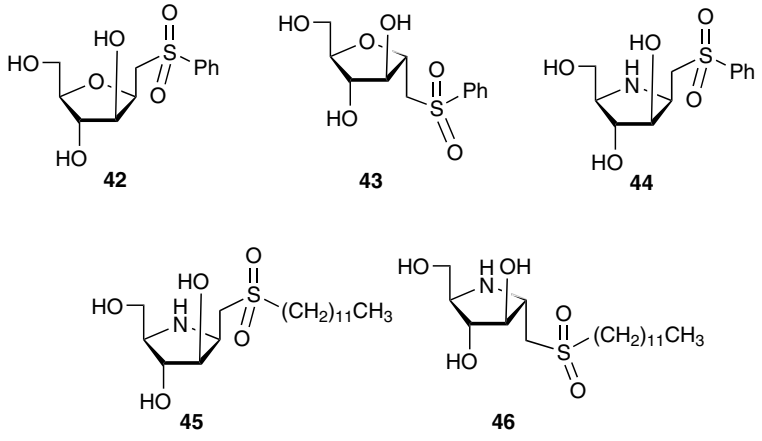



**Figure 2.** Previous sulfone-containing DPA analogs tested for anti-mycobacterial activity.

mycobacterial AraT's) is likely of only limited value in the context of drug development.

## 3. Experimental

### 3.1. General methods

Solvents were distilled from the appropriate drying agents before use. Unless stated otherwise, all reactions were carried out at room temperature under a positive pressure of argon and were monitored by TLC on silica gel 60 $F_{254}$. Spots were detected under UV light or by charring with 10% $H_2SO_4$ in ethanol. All hydrogenolysis reactions were carried out at atmospheric pressure. Solvents were evaporated under reduced pressure and below 40 °C (bath). Organic solutions of crude products were dried over anhydrous $Na_2SO_4$. Column chromatography was performed on silica gel 60 (40–60 μM). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 21 ± 2 °C. Melting points are uncorrected. $^1$H NMR spectra were recorded at 250, 400, or 500 MHz, and chemical shifts are referenced to either TMS (0.0, $CDCl_3$) or $CD_3OH$ (4.78, $CD_3OD$). $^{13}$C NMR spectra were recorded at 62.5, 100, or 125 MHz and chemical shifts are referenced to $CDCl_3$ (77.00, $CDCl_3$) or $CD_3OD$ (49.00, $CD_3OD$). Electrospray mass spectra were recorded on samples suspended in mixtures of THF and $CH_3OH$ with added trifluoroacetic acid or NaCl.

### 3.2. 1-(Nonyl)-2,5-anhydroglucityl sulfone (8)

Thioether **25** (91 mg, 0.16 mmol) was dissolved in $CH_2Cl_2$ (5 mL) and *m*-CPBA (117 mg, 0.47 mmol) was added and the mixture stirred for 20 min. The reaction mixture was neutralized with a saturated aqueous solution of sodium bicarbonate and diluted with $CH_2Cl_2$ (20 mL). The organic layer was washed with $H_2O$ (2 × 10 mL) and then dried. The solvent was evaporated to afford the crude sulfone as a white solid (200 mg) that was, without further purification, dissolved in $CH_3OH$ (5 mL) containing AcOH (10 μL). Palladium on carbon (10%, 25 mg) was added and the reaction mixture was stirred under $H_2$ overnight. After filtering the solid and evaporating the solvent, the residue was purified by chromatography (EtOAc) to afford **8** (42 mg, 79% over two steps) as a white solid: $R_f$ 0.21 (EtOAc); mp 101–103 °C; $[\alpha]_D$ +6.7 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 0.86 (t, 3H, *J* = 6.9 Hz), 1.33–1.19 (m, 10H), 1.45–1.35 (m, 2H), 1.83–1.75 (m, 2H), 3.16–3.03 (m, 2H), 3.32 (dd, 1H, *J* = 14.6, 3.6 Hz), 3.41 (dd, 1H, *J* = 14.8, 8.2 Hz), 3.78–3.68 (m, 2H), 3.91–3.87 (m, 1H), 4.06–4.01 (m, 1H), 4.17–4.10 (m, 2H), 4.36–4.32 (m, 1H), 4.51–4.45 (m, 1H), 4.74–4.69 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 14.1, 21.6, 22.6, 28.5, 29.1, 29.2, 29.3, 31.8, 52.8, 54.2, 62.1, 75.4, 78.0, 78.2, 86.1; HRMS calcd for $C_{15}H_{30}O_6SNa^+$: 361.1655. Found: 361.1654.

### 3.3. 1-(Decyl)-2,5-anhydroglucityl sulfone (9)

Thioether **26** (133 mg, 0.23 mmol) was dissolved in $CH_2Cl_2$ (5 mL) and *m*-CPBA (172 mg, 0.69 mmol) was added and the mixture stirred for 20 min. Workup as described for the oxidation of **25** yielded a crude sulfone (251 mg) that was, without further purification, dissolved in $CH_3OH$ (5 mL) containing AcOH (10 μL). Palladium on carbon (10%, 40 mg) was added and the mixture was stirred under $H_2$ overnight. After filtering the solid and evaporating the solvent, the residue was purified by chromatography (EtOAc) to afford **9** (92 mg, 85% over two steps) as a white solid: $R_f$ 0.25 (EtOAc); mp 88–89 °C; $[\alpha]_D$ +8.7 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 0.85 (t, 3H, *J* = 6.8 Hz), 1.34–1.18 (m, 12H), 1.43–1.35 (m, 2H), 1.83–1.73 (m, 2H), 3.15–3.03 (m, 2H), 3.32 (dd, 1H, *J* = 14.8, 4.6 Hz), 3.41 (dd, 1H, *J* = 14.8, 8.4 Hz), 3.79–3.68 (m, 2H), 3.92–3.87 (m, 1H), 4.07–3.99 (m, 2H), 4.17–4.13 (m, 1H), 4.27–4.22 (m, 1H), 4.51–4.45 (m, 1H), 4.71–4.67 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 14.1, 21.7, 22.7, 28.5, 29.2, 29.3, 29.4, 29.5, 31.9, 52.8, 54.2, 62.1, 75.4, 78.0, 78.3, 86.1; HRMS calcd for $C_{16}H_{32}O_6SNa^+$: 375.1812. Found: 375.1804.

### 3.4. 1-(Dodecyl)-2,5-anhydroglucityl sulfone (10)

Thioether **27** (140 mg, 0.23 mmol) was dissolved in $CH_2Cl_2$ (5 mL) and *m*-CPBA (167 mg, 0.68 mmol) was added and the mixture stirred for 20 min. Workup as described for the oxidation of **25** yielded a crude sulfone (181 mg) that was, without further purification, dissolved in $CH_3OH$ (5 mL) containing AcOH (10 μL). Palladium on carbon (10%, 40 mg) was added and the reaction mixture was stirred under $H_2$ overnight. After filtering the solid and evaporating the solvent, the residue was purified by chromatography (EtOAc) to afford **10** (65 mg, 76% over two steps) as a white solid: $R_f$ 0.26 (EtOAc); mp 94–95 °C; $[\alpha]_D$ +10.3 (*c* 0.8, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$ 0.86 (t, 3H, *J* = 6.8 Hz), 1.34–1.18 (m, 16H), 1.46–1.35 (m, 2H), 1.90–1.77 (m, 2H), 2.68 (br s, 3H), 3.15–3.03 (m, 2H), 3.30 (dd, 1H, *J* = 14.8, 3.8 Hz), 3.41 (dd, 1H, *J* = 14.8, 8.4 Hz), 3.87–3.75 (m, 2H), 3.98–3.95 (m, 1H), 4.04–4.00 (m, 1H), 4.24 (s, 1H), 4.57–4.52 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 14.1, 21.7, 22.7, 28.5, 29.2, 29.4, 29.4, 29.6, 29.7, 29.7, 31.9, 52.8, 54.2, 62.2, 75.5, 78.1, 78.3, 86.1; HRMS calcd for $C_{18}H_{36}O_6SNa^+$: 403.2125. Found: 403.2152.

### 3.5. 1-(Hexadecyl)-2,5-anhydroglucityl sulfone (11)

Thioether **28** (140 mg, 0.21 mmol) was dissolved in $CH_2Cl_2$ (5 mL) and *m*-CPBA (153 mg, 0.62 mmol) was added and the mixture stirred for 20 min. Workup as described for the oxidation of **25** yielded a crude sulfone (210 mg) that was, without further purification, dissolved in $CH_3OH$ (5 mL) containing AcOH (10 μL). Palladium on carbon (10%, 40 mg) was added and the mixture was stirred under $H_2$ overnight. After filtering the solid and evaporating the solvent, the residue was purified by chromatography (EtOAc/hexane, 5:1) to afford **11** (37 mg, 49% over two steps) as a white solid: $R_f$ 0.21 (5:1, EtOAc/hexane); mp 180–181 °C; $[\alpha]_D$ +3.6 (*c* 1.2, $CH_3OH$); $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$ 0.82 (t, 3H, *J* = 6.9 Hz), 1.31–1.17 (m, 24H), 1.41–1.33 (m, 2H), 1.78–1.68 (m, 2H), 3.25–3.02 (m, 3H), 3.35 (dd,

1H, $J = 15.2, 9.2$ Hz), 3.65–3.55 (m, 2H), 3.79–3.75 (m, 1H), 3.89–3.87 (m, 1H), 3.94–3.90 (m, 1H), 4.39–4.34 (m, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta_C$ 14.4, 22.8, 23.7, 29.5, 30.2, 30.5, 30.7, 30.8, 30.8, 33.1, 54.4, 55.0, 63.4, 77.2, 79.4, 79.5, 88.1; HRMS calcd for $C_{22}H_{44}O_6SNa^+$: 459.2751. Found: 459.2764.

### 3.6. 1-(Eicosyl)-2,5-anhydroglucityl sulfone (12)

Sulfone **31** (120 mg, 0.16 mmol) was dissolved in $CH_3OH$ (5 mL) containing AcOH (10 μL). Palladium on carbon (10%, 50 mg) was added and the mixture was stirred under $H_2$ overnight. After filtering the solid and evaporating the solvent, the residue was purified by chromatography (EtOAc/hexane, 5:1) to afford **12** (62 mg, 80%) as a white solid. $R_f$ 0.21 (5:1, EtOAc/hexane); mp 105–107 °C; $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$ 0.82 (t, 3H, $J = 6.8$ Hz), 1.30–1.10 (m, 32H), 1.42–1.32 (m, 2H), 1.79–1.68 (m, 2H), 3.19–3.01 (m, 2H), 3.35 (dd, 1H, $J = 15.0, 9.1$ Hz), 3.65–3.51 (m, 2H), 3.77–3.73 (m, 1H), 3.84–3.78 (m, 1H), 3.89–3.86 (m, 1H), 3.92–3.90 (m, 1H), 4.39–4.34 (m, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta_C$ 14.5, 22.9, 23.7, 29.5, 30.2, 30.5, 30.7, 30.8, 33.1, 54.4, 55.0, 63.4, 77.2, 79.4, 79.6, 88.1; HRMS calcd for $C_{26}H_{52}O_6SNa^+$: 515.3377. Found: 515.3348.

### 3.7. 1-(Decyl-10′-*O*-hexadecyl)-2,5-anhydroglucityl sulfone (13)

Sulfone **38** (40 mg, 0.048 mmol) was dissolved in a 5:1 mixture of $CH_3OH$ and AcOH (2 mL) and hydrogenolyzed as described for the preparation of **12** using palladium on carbon (10%, 20 mg). Purification by chromatography (EtOAc/hexane, 3:1) afforded **13** (17 mg, 60%) as a white solid: $R_f$ 0.12 (3:1, EtOAc/hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 0.86 (t, 3H, $J = 6.8$ Hz), 1.35–1.18 (m, 36H), 1.45–1.36 (m, 2H), 1.59–1.49 (m, 4H), 1.86–1.77 (m, 2H), 3.17–3.01 (m, 2H), 3.43–3.25 (m, 9H), 3.82–3.72 (m, 2H), 4.03–3.92 (m, 2H), 4.21 (s, 1H), 4.56–4.48 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 14.1, 21.8, 22.7, 26.1, 26.2, 28.4, 29.0, 29.1, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 31.9, 52.7, 54.3, 62.3, 71.0, 71.0, 75.8, 77.2, 78.2, 78.6, 86.2; HRMS calcd for $C_{32}H_{64}O_7SNa^+$: 615.4265. Found: 615.4259.

### 3.8. 1-(3,7-Dimethyloctyl)-2,5-anhydroglucityl sulfone (14)

Sulfone **41** (66 mg, 0.12 mmol) was dissolved in $CH_3OH$ (5 mL) containing AcOH (10 μL) and hydrogenolyzed as described for the preparation of **12** using palladium on carbon (10%, 30 mg). Purification by chromatography (EtOAc/hexane, 3:1) afforded **14** (24 mg, 64%) as a pale yellow oil that was a 3:1 mixture of diastereomers: $R_f$ 0.13 (5:1, EtOAc/hexane); $[\alpha]_D$ +13.7 (*c* 1.0, $CHCl_3$); Selected NMR data: $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$ 0.84 (s, 3H), 0.85 (s, 3H), 0.90–0.87 (m, 3H), 1.19–1.08 (m, 3H), 1.35–1.22 (m, 3H), 1.63–1.45 (m, 3H), 1.84–1.73 (m, 1H), 3.28–3.04 (m, 3H), 3.39 (dd, 1H, $J = 15.0, 9.1$ Hz), 3.67–3.55 (m, 2H), 3.81–3.77 (m, 1H), 3.93–3.90 (m, 1H), 3.98–3.96 (m, 1H), 4.42–4.38 (m, 1H); Selected NMR data: $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 20.0, 20.0, 23.4, 23.5, 26.1, 26.2, 29.5, 29.8, 29.9, 33.6, 33.7, 38.2, 38.3, 40.7, 53.6, 53.7, 54.7, 54.7, 57.2, 63.6, 63.8, 77.6, 77.6, 78.5, 79.8, 80.0, 82.2, 88.6; HRMS calcd for $C_{16}H_{32}O_6SNa^+$: 375.1818. Found: 375.1823.

### 3.9. 3,4,6-Tri-*O*-benzyl-2,5-anhydroglucityl thioacetate (22)

Iodide **21** (4.70 g, 8.63 mmol) was dissolved in dry DMF (30 mL) and potassium thioacetate (1.48 g, 12.9 mmol) was added and the reaction mixture stirred for 12 h. The solution was diluted with ether (250 mL), washed with $H_2O$ (3 × 100 mL), dried, and concentrated. The resulting residue was purified by chromatography (hexane/EtOAc, 5:1) affording **22** (3.98 g, 94%) as a pale yellow oil: $R_f$ 0.23 (hexane/EtOAc, 6:1); $[\alpha]_D$ +25.1 (*c* 1.1, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta_H$ 2.31 (s, 3H), 3.20 (d, 2H, $J = 6.9$ Hz), 3.50 (dd, 1H, $J = 9.9, 6.8$ Hz), 3.60 (dd, 1H, $J = 9.9, 5.6$ Hz), 3.93–3.89 (m, 2H), 3.98–3.95 (m, 2H), 4.60–4.36 (m, 6H), 7.38–7.22 (m, 15H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta_C$ 27.9, 30.4, 70.2, 71.4, 71.5, 73.2, 79.9, 82.9, 82.9, 83.2, 127.6, 127.6, 127.7, 127.7, 127.8, 127.8, 128.3, 128.4, 137.5, 137.6, 138.1, 195.4; HRMS calcd for $C_{53}H_{82}O_7SNa^+$: 515.1863. Found: 515.1867.

### 3.10. 3,4,6-Tri-*O*-benzyl-2,5-anhydroglucityl thiol (23)

Thioacetate **22** (170 mg, 0.35 mmol) was dissolved in anhydrous $Et_2O$ (7 mL) and lithium aluminum hydride (13 mg, 0.35 mmol) was added and the mixture stirred for 1 h. The solution was diluted with ethyl acetate (30 mL), and the organic layer was washed with $H_2O$ (10 mL) and brine (10 mL) before being dried and concentrated. The resulting residue was purified by chromatography (hexane/EtOAc, 6:1) affording **23** (151 mg, 97%) as a colorless oil: $R_f$ 0.44 (hexane/EtOAc, 4:1); $[\alpha]_D$ +44.3 (*c* 1.1, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta_H$ 1.39 (t, 1H, $J = 8.8$ Hz), 2.76 (d, 1H, $J = 7.2$ Hz), 2.80 (d, 1H, $J = 7.2$ Hz), 3.49 (dd, 1H, $J = 9.8, 6.7$ Hz), 3.59 (dd, 1H, $J = 9.9, 5.9$ Hz), 3.96–3.93 (m, 1H), 4.01–3.98 (m, 1H), 4.18–4.05 (m, 2H), 4.39 (d, 1H, $J = 11.8$ Hz), 4.60–4.47 (m, 5H), 7.38–7.21 (m, 15H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta_C$ 22.7, 70.4, 71.4, 73.3, 83.1, 83.1, 83.2, 83.2, 127.6, 127.7, 127.8, 127.8, 127.9, 128.3, 128.5, 137.6, 137.7, 138.1.

### 3.11. 1-(Nonyl)-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl sulfide (25)

Sodium hydride (19 mg, 0.80 mmol) was added to a solution of thiol **23** (120 mg, 0.27 mmol) in dry DMF (5 mL). After 5 min, 1-iodononane (0.16 mL, 0.80 mmol) was added and the mixture was stirred for 1 h before $CH_3OH$ (1 mL) and then $Et_2O$ (20 mL) were added. The organic layer was washed with $H_2O$ (2 × 40 mL), brine (15 mL), and then dried and concentrated. The resulting residue was purified by chromatography (hexane/EtOAc, 10:1) affording **25** (111 mg, 72%) as a colorless oil: $R_f$ 0.28 (hexane/EtOAc, 10:1); $[\alpha]_D$ +41.0 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 0.88 (t, 3H, $J = 6.9$ Hz), 1.39–1.22 (m, 12H), 1.61–1.52 (m, 2H), 2.53 (t, 2H,

$J$ = 7.4 Hz), 2.91–2.73 (m, 2H), 3.50 (dd, 1H, $J$ = 9.9, 6.8 Hz), 3.61 (dd, 1H, $J$ = 9.8, 5.8 Hz), 3.92–3.90 (m, 1H), 3.98–3.96 (m, 1H), 4.30–4.02 (m, 2H), 4.59–4.40 (m, 6H), 7.37–7.22 (m, 15H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 14.1, 22.6, 28.8, 29.2, 29.2, 29.5, 29.8, 30.1, 31.8, 32.9, 70.5, 71.4, 71.6, 73.3, 81.2, 82.5, 83.0, 83.6, 127.5, 127.6, 127.7, 127.7, 127.7, 127.8, 128.3, 128.3, 128.4, 137.8, 137.8, 138.2.

### 3.12. 1-(Decyl)-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl sulfide (26)

*n*-Butyl lithium (0.1 mL, 0.16 mmol) was added to a solution of thiol **23** (66 mg, 0.15 mmol) in anhydrous $Et_2O$ (5 mL) at 0 °C. After 5 min, 1-iododecane (38 μL, 0.18 mmol) was added and the solution was stirred for 12 h, while warming to room temperature. Workup as described for the preparation of **25** and purification by chromatography (hexane/EtOAc, 9:1) afforded **26** (56 mg, 65%) as a colorless oil: $R_f$ 0.35 (hexane/EtOAc, 10:1); $[\alpha]_D$ +31.3 ($c$ 1.0, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta_H$ 0.88 (t, 3H, $J$ = 6.6 Hz), 1.40–1.19 (m, 14H), 1.62–1.50 (m, 2H), 2.53 (t, 2H, $J$ = 7.4 Hz), 2.92–2.72 (m, 2H), 3.49 (dd, 1H, $J$ = 10.0, 6.8 Hz), 3.61 (dd, 1H, $J$ = 9.8, 6.0 Hz), 3.94–3.90 (m, 1H), 3.99–3.95 (m, 1 H), 4.29–4.00 (m, 2H), 4.61–4.40 (m, 6H), 7.39–7.18 (m, 15H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta_C$ 14.1, 22.6, 28.9, 29.2, 29.3, 29.5, 29.5, 29.8, 30.1, 31.9, 32.9, 70.6, 71.4, 71.7, 73.3, 81.3, 82.6, 83.0, 83.6, 127.6, 127.6, 127.7, 127.7, 127.7, 127.8, 128.3, 128.3, 128.4, 137.8, 137.8, 138.2.

### 3.13. 1-(Dodecyl)-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl sulfide (27)

Sodium hydride (40 mg, 1.00 mmol) was added to a solution of thiol **23** (150 mg, 0.33 mmol) in dry DMF (5 mL). After 5 min, 1-iodododecane (0.25 mL, 1.00 mmol) was added and the reaction mixture was stirred for 1 h before $CH_3OH$ (1 mL) and then $Et_2O$ (20 mL) were added. Workup as described for the preparation of **25** and purification by chromatography (hexane/EtOAc, 10:1) afforded **27** (168 mg, 82%) as a colorless oil: $R_f$ 0.45 (hexane/EtOAc, 9:1); $[\alpha]_D$ +28.9 ($c$ 1.0, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta_H$ 0.88 (t, 3H, $J$ = 6.6 Hz), 1.41–1.18 (m, 18H), 1.62–1.50 (m, 2H), 2.53 (t, 2H, $J$ = 7.4 Hz), 2.92–2.72 (m, 2H), 3.49 (dd, 1H, $J$ = 9.9, 6.8 Hz), 3.61 (dd, 1H, $J$ = 9.9, 5.9 Hz), 3.94–3.90 (m, 1H), 4.00–3.96 (m, 1H), 4.30–4.01 (m, 2H), 4.61–4.40 (m, 6H), 7.39–7.20 (m, 15H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta_C$ 14.1, 22.7, 28.9, 29.2, 29.3, 29.5, 29.6, 29.6, 29.7, 30.0, 70.5, 71.4, 71.6, 73.3, 81.2, 82.4, 83.0, 83.5, 127.6, 127.7, 127.7, 127.7, 128.3, 128.3, 128.4, 137.7, 137.8, 138.1.

### 3.14. 1-(Hexadecyl)-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl sulfide (28)

Sodium hydride (40 mg, 1.00 mmol) was added to a solution of thiol **23** (150 mg, 0.33 mmol) in dry DMF (5 mL). After 5 min, 1-iodohexadecane (350 mg, 1.00 mmol) was added and the reaction mixture stirred for 12 h before $CH_3OH$ (1 mL) and then $Et_2O$ (20 mL) were added. Workup as described for the preparation of **25** and purification by chromatography (hexane/EtOAc, 10:1) afforded **28** (167 mg, 74%) as a colorless oil: $R_f$ 0.56 (hexane/EtOAc, 9:1); $[\alpha]_D$ +28.2 ($c$ 1.1, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta_H$ 0.88 (t, 3H, $J$ = 6.6 Hz), 1.39–1.20 (m, 26H), 1.62–1.50 (m, 2H), 2.53 (t, 2H, $J$ = 7.4 Hz), 2.93–2.72 (m, 2H), 3.49 (dd, 1H, $J$ = 9.9, 6.8 Hz), 3.61 (dd, 1H, $J$ = 9.9, 5.9 Hz), 3.94–3.90 (m, 1H), 4.00–3.96 (m, 1H), 4.30–4.01 (m, 2H), 4.61–4.40 (m, 6H), 7.38–7.22 (m, 15H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta_C$ 14.1, 22.6, 28.8, 29.2, 29.3, 29.5, 29.6, 29.6, 29.6, 29.7, 30.0, 31.9, 70.5, 71.5, 71.6, 73.2, 81.2, 82.4, 83.0, 83.5, 127.5, 127.6, 127.6, 127.7, 127.7, 127.7, 128.3, 128.3, 128.4, 137.7, 137.7, 138.0.

### 3.15. 1-(Decadecyl)-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl sulfone (31)

Thiol **23** (291 mg, 0.65 mmol) was dissolved in THF (10 mL) at 0 °C. *n*-Butyl lithium (0.44 mL, 0.71 mmol) was added, followed by a solution of **29**[22] (400 mg, 0.88 mmol) in THF (15 mL). The mixture was warmed to rt and stirred for 4 h and then neutralized with AcOH, and diluted with EtOAc (40 mL). The organic layer was washed with $H_2O$ (15 mL), brine (15 mL), dried, and concentrated to afford an inseparable mixture of **29** and **30** (466 mg total). The crude mixture (413 mg) was dissolved in $CH_2Cl_2$ (10 mL) and *m*-CPBA (418 mg, 1.69 mmol) was added and the mixture stirred for 2 h. Workup as described for the oxidation of **25** yielded a crude product that was purified by chromatography (hexane/EtOAc, 4:1) to afford **31** (164 mg, 30% over two steps) as an amorphous white solid: $R_f$ 0.32 (hexane/EtOAc, 4:1); $[\alpha]_D$ +5.2 ($c$ 1.3, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 0.95 (t, 3H, $J$ = 6.8 Hz), 1.44–1.26 (m, 34H), 1.92–1.82 (m, 2H), 3.20–3.07 (m, 3H), 3.67–3.48 (m, 3H), 4.06–4.01 (m, 2H), 4.21–4.18 (m, 1H), 4.43–4.39 (m, 1H), 4.65–4.52 (m, 6H), 7.44–7.26 (m, 15H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 14.1, 21.7, 22.6, 28.4, 29.0, 29.2, 29.3, 29.5, 29.6, 29.6, 29.6, 31.9, 53.2, 54.1, 70.1, 71.5, 71.6, 73.3, 75.5, 82.5, 83.1, 83.2, 127.6, 127.6, 127.7, 127.7, 127.8, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5, 128.5, 137.1, 137.4, 137.9; HRMS calcd for $C_{47}H_{70}O_6SNa^+$: 785.4785. Found: 785.4781.

### 3.16. 10-Tetrahydropyranyloxy-1-decanol (33)

1,10-Decanediol, **32**, (2.0 g, 11.5 mmol) was dissolved in THF (50 mL) and 3,4-dihydropyran (1.15 mL, 12.6 mmol) added, followed by *p*-TsOH (328 mg, 1.73 mmol). The mixture was stirred for 2 h and then pyridine (2 mL) was added and the solvent evaporated. Purification by chromatography (hexane/EtOAc, 4:1) afforded **33** (1.56 g, 53%) as a colorless oil: $R_f$ 0.20 (4:1, hexane/EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$ 1.33–1.20 (m, 12H), 1.58–1.43 (m, 8H), 1.69–1.63 (m, 1H), 1.82–1.74 (m, 2H), 3.33 (dt, 1H, $J$ = 9.6, 6.7 Hz), 3.47–3.42 (m, 1H), 3.57 (t, 2H, $J$ = 6.7 Hz), 3.67 (dt, 1H, $J$ = 9.6, 6.9 Hz), 3.85–3.79 (m, 1H), 4.53–4.51 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta_C$ 19.6, 25.4, 25.7, 26.1, 29.3, 29.4, 29.4, 29.5, 29.7, 30.7, 32.7, 62.2, 62.8, 67.6, 98.8; HRMS calcd for $C_{15}H_{30}O_3Na^+$: 281.2087. Found: 281.2087.

### 3.17. 10-*O*-Hexadecyl-1-tetrahydropyranyloxydecane (34)

Alcohol **33** (517 mg, 2.00 mmol) was dissolved in dry DMF (10 mL) and sodium hydride (160 mg, 4.00 mmol) was added followed, after 10 min, by 1-iodohexadecane (1.06 g, 3.01 mmol) in DMF (5 mL). The reaction mixture was stirred for 12 h and then $CH_3OH$ (5 mL) and $Et_2O$ (50 mL) were added. The organic layer was washed with $H_2O$ (2 × 30 mL), brine (30 mL) and then dried and concentrated. Purification by chromatography (hexane/EtOAc, 7:1) gave **34** (204 mg, 21%) as a colorless oil: $R_f$ 0.58 (6:1, hexane/EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$ 0.86 (t, 3H, $J$ = 7.1 Hz), 1.39–1.19 (m, 38H), 1.60–1.45 (m, 10H), 1.72–1.66 (m, 1H), 1.85–1.76 (m, 1H), 3.38–3.33 (m, 5H), 3.50–3.45 (m, 1H), 3.70 (dt, 1H, $J$ = 9.6, 6.9 Hz), 3.87–3.82 (m, 1H), 4.56–4.54 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta_C$ 14.1, 19.7, 22.7, 25.5, 26.2, 26.2, 29.3, 29.5, 29.5, 29.5, 29.5, 29.6, 29.6, 29.7, 29.8, 29.8, 30.8, 31.9, 62.3, 67.7, 71.0, 71.0, 98.8; HRMS calcd for $C_{31}H_{62}O_3Na^+$: 505.4591. Found: 505.4584.

### 3.18. 10-*O*-Hexadecyl-1-decanol (35)

10-*O*-hexadecyl-1-tetrahydropyranyloxydecane, **34** (200 mg, 0.41 mmol), was dissolved in a 3:1:1 mixture of AcOH/THF/$H_2O$ (10 mL) and heated at 65 °C for 3 h. The mixture was diluted with $CH_2Cl_2$ (20 mL) and the organic layer was washed with $H_2O$ (2 × 10 mL), brine (10 mL), and then dried. The solvent was evaporated and the residue was purified by chromatography (hexane/EtOAc, 7:1) to afford **35** (139 mg, 84%) as a white solid: $R_f$ 0.25 (6:1, hexane/EtOAc); mp 67–68 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta_H$ 0.85 (t, 3H, $J$ = 6.9 Hz), 1.35–1.16 (m, 36H), 3.40–3.30 (m, 8H), 3.36 (t, 4H, $J$ = 6.7 Hz), 3.60 (t, 2 H, $J$ = 6.6 Hz); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta_C$ 14.1, 22.7, 25.7, 26.2, 29.4, 29.4, 29.5, 29.5, 29.6, 29.7, 29.8, 31.9, 32.8, 63.0, 70.9, 71.0; HRMS calcd for $C_{26}H_{54}O_2Na^+$: 421.4016. Found: 421.4015.

### 3.19. 10-*O*-Hexadecyl-1-*p*-toluenesulfonyloxydecane (36)

Alcohol **35** (139 mg, 0.35 mmol) and 18-crown-6 (127 mg, 0.42 mmol) were dissolved in THF (10 mL). Potassium hydride (17 mg, 0.42 mmol) was added, and after 5 min, *p*-TsCl (200 mg, 1.05 mmol). The mixture was stirred for 12 h at rt and then $CH_3OH$ (1 mL) and EtOAc (10 mL) were added. The organic layer was washed with $H_2O$ (10 mL), brine (10 mL), and then dried and concentrated. The resulting residue was purified by chromatography (hexane/EtOAc, 9:1) to afford **36** (50 mg, 26%) as a white solid: $R_f$ 0.44 (6:1, hexane/EtOAc); mp 71–72 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta_H$ 0.85 (t, 3H, $J$ = 6.8 Hz), 1.38–1.14 (m, 38H), 1.67–1.45 (m, 6H), 2.42 (s, 3H), 3.36 (t, 4H, $J$ = 6.7 Hz), 3.99 (t, 2H, $J$ = 6.5 Hz), 7.31 (d, 2H, $J$ = 8.0 Hz), 7.76 (d, 2H, $J$ = 8.3 Hz); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta_C$ 14.1, 22.7, 25.7, 26.2, 26.2, 29.4, 29.4, 29.5, 29.5, 29.6, 29.7, 29.8, 31.9, 32.8, 63.0, 70.6, 70.9, 71.0, 127.8, 129.7, 133.3, 144.5; HRMS calcd for $C_{33}H_{60}O_4SNa^+$: 575.4104. Found: 575.4119.

### 3.20. 1-(Decyl-10′-*O*-hexadecyl)-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl sulfone (38)

Thiol **23** (117 mg, 0.26 mmol) was dissolved in THF (5 mL) and 18-crown-6 (95 mg, 0.31 mmol) was added, followed by potassium hydride (12 mg, 0.31 mmol). A solution of **36** (59 mg, 0.11 mmol) in THF (15 mL) was added dropwise and the reaction stirred for 45 min. The mixture was then neutralized with AcOH, diluted with EtOAc (20 mL), washed with $H_2O$ (10 mL), brine (10 mL), and then dried. The solvent was evaporated to give sulfide **37** that was inseparable from **36** (50 mg total). The crude mixture (46 mg) was then dissolved in $CH_2Cl_2$ (3 mL) and *m*-CPBA (41 mg, 0.17 mmol) was added and the reaction mixture stirred for 30 min. Workup as described for the oxidation of **25** yielded a residue that was purified by chromatography (hexane/EtOAc, 6:1) to afford **38** (41 mg, 45% over two steps) as an amorphous white solid: $R_f$ 0.24 (hexane/EtOAc, 5:1); $[\alpha]_D$ +4.9 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 0.81 (t, 3H, $J$ = 7.0 Hz), 1.37–1.10 (m, 38H), 1.53–1.43 (m, 4H), 1.80–1.67 (m, 2H), 3.08–2.91 (m, 3H), 3.31 (overlapping t, 4H, $J$ = 6.8 Hz), 3.53–3.35 (m, 3H), 3.91–3.88 (m, 2H), 4.08–4.03 (m, 1H), 4.27 (d, 1H, $J$ = 11.7 Hz), 4.53–4.38 (m, 6H), 7.30–7.11 (m, 15H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 14.1, 21.7, 22.7, 26.2, 26.2, 28.4, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.7, 29.8, 31.9, 53.3, 54.2, 70.1, 70.9, 71.0, 71.6, 73.3, 75.5, 82.5, 83.2, 83.2, 127.7, 127.7, 127.7, 127.8, 127.8, 127.9, 128.1, 128.4, 128.5, 128.5, 128.6, 137.1, 137.5, 137.9; HRMS calcd for $C_{53}H_{82}O_7SNa^+$: 885.5673. Found: 885.5601.

### 3.21. 1-Geranyl-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl sulfide (40)

*n*-Butyl lithium (0.8 mL, 1.26 mmol) was added dropwise to a solution of **23** (515 mg, 1.14 mmol) dissolved in THF (10 mL) at −78 °C and geranyl tosylate (**39**) was added. Tosylate **39** was prepared by the addition of *n*-butyl lithium (3.9 mL, 6.20 mmol) to geraniol (870 mg, 5.64 mmol) in THF (15 mL) at −78 °C, followed by the addition of *p*-TsCl (1.40 g, 7.33 mmol); this solution was added directly to the alkylation reaction. The mixture was slowly warmed to rt over 2 h and then $H_2O$ (20 mL) and $Et_2O$ (30 mL) were added. The organic layer was separated, washed with brine (10 mL), dried, and concentrated. The residual oil was purified by chromatography (hexane/EtOAc, 9:1) to afford **40** (509 mg, 76%) as a colorless oil: $R_f$ 0.42 (6:1, hexane/EtOAc); $[\alpha]_D$ +22.4 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 1.58 (s, 3H), 1.62 (s, 3H), 1.67 (s, 3H), 2.10–1.97 (m, 4H), 2.85–2.75 (m, 2H), 3.26–3.11 (m, 2H), 3.49 (dd, 1H, $J$ = 9.8, 7.0 Hz), 3.60 (dd, 1H, $J$ = 9.8, 5.8 Hz), 4.18–3.91 (m, 2H), 4.20–4.09 (m, 2H), 4.59–4.39 (m, 6H), 5.10–5.03 (m, 1H), 5.27–5.20 (m, 1H), 7.35–7.20 (m, 15H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 16.0, 17.5, 25.5, 26.4, 29.0, 29.9, 39.5, 70.4, 71.2, 71.5, 73.1, 81.1, 82.5, 82.9, 83.4, 120.3, 123.8, 127.4, 127.5, 127.5, 127.5, 127.6, 127.7, 128.1, 128.2, 128.3, 129.6, 131.4, 137.7, 137.7, 138.1, 138.8; HRMS calcd for $C_{37}H_{46}O_4SNa^+$: 609.2919. Found: 609.2914.

### 3.22. 1-Geranyl-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl sulfone (41)

Sulfide **40** (116 mg, 0.23 mmol) was dissolved in a mixture of acetonitrile (8 mL) and $H_2O$ (0.3 mL). Sodium periodate (145 mg, 0.68 mmol) was added and the reaction mixture was heated at 70 °C. The reaction proceeded for 2 d and, during this time, three more portions of sodium periodate (145 mg, 0.68 mmol each) were added. After cooling to rt and evaporating the solvent, the crude mixture was purified by chromatography (hexane/EtOAc, 4:1) to afford **41** (65 mg, 53%) as a colorless oil: $R_f$ 0.33 (3:1, hexane/EtOAc); $[\alpha]_D$ +10.0 (*c* 1.1, $CHCl_3$); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta_H$ 1.58 (s, 3H), 1.67 (s, 6H), 2.08 (s, 4H), 2.86 (dd, 1H, $J = 13.3$, 3.4 Hz), 3.05 (dd, 1H, $J = 13.2$, 9.3 Hz), 3.66–3.44 (m, 4H), 3.94–3.91 (m, 1H), 4.01–3.97 (m, 1H), 4.17–4.07 (m, 1H), 4.36 (d, 1H, $J = 11.8$ Hz), 4.60–4.45 (m, 6H), 5.10–5.00 (m, 1H), 5.35–5.24 (m, 1H), 7.40–7.19 (m, 15H); $^{13}C$ NMR (62.5 MHz, $CDCl_3$) $\delta_C$ 16.9, 17.6, 25.6, 26.2, 39.7, 51.8, 52.4, 70.1, 71.4, 71.4, 73.2, 75.1, 82.9, 83.4, 83.6, 111.1, 123.5, 127.6, 127.7, 127.7, 127.7, 127.9, 128.3, 128.4, 128.4, 131.8, 137.4, 137.6, 138.0, 145.0; HRMS calcd for $C_{37}H_{46}O_6SNa^+$: 641.2907. Found: 641.2874.

### 3.23. Measurement of anti-tuberculosis activity of 8–20

Measurement of the anti-tuberculosis activity of the target compounds was carried out as previously reported using the fluorescence-based Alamar Blue microplate assay.[24] All compounds were tested against *Mycobacterium tuberculosis* strain $H_{37}Rv$ (ATCC 27294) at a concentration 6.25 μg/mL. The results of these assays, expressed as a percent inhibition of growth of the bacteria in provided in Table 1.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