Carbohydrate Research, 241 (1993) 117–129
Elsevier Science Publishers B.V., Amsterdam

Synthesis of mirror coryno cord factors

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(Received June 16th, 1992; accepted August 24th, 1992)

ABSTRACT

A protected bis-heptosiduronic acid, (2,3,4-tri-*O*-benzyl-6-deoxy-α-D-*gluco*-heptopyranosyluronic acid) 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-*gluco*-heptopyranosiduronic acid, was synthesized by the iron carbonyl method of chain elongation, starting from 2,3,4,2′,3′,4′-hexa-*O*-benzyl-6,6′-di-*O*-tosyl-α,α-trehalose. Its dimethyl ester was also prepared by acid-catalyzed methanolysis of its diamide, previously obtained by another route. Mitsunobu esterification of the diacid with (racemic) (2*RS*,3*SR*)- and (2*RS*,3*RS*)-3-*O*-benzylcorynomycolyl alcohols, obtained by reduction of synthetic, 3-*O*-benzylated methyl C_{32}-corynomycolates with lithium aluminum hydride, furnished the corresponding diesters in high yields. Hydrogenolytic debenzylation of the products led to "mirror" coryno cord factors.

INTRODUCTION

Cord factors (**1**) are 6,6′-diesters of α,α-trehalose with long-chain, 2-alkyl, 3-hydroxy fatty acids generically called mycolic acids. They are widely distributed in bacteria of the order Actinomycetales where they play important metabolic roles. Different bacterial genera are distinguished by different ranges of the number of carbon atoms in the fatty acids. Thus, mycobacteria produce, with some exceptions, cord factors containing C_{74}–C_{90} acids (mycolic acids proper), whereas nocardiae and corynebacteria produce analogous esters of C_{32}–C_{56} (nocardomycolic) and C_{20}–C_{36} (corynomycolic) acids, respectively[1–3]. A large variety of biological functions and bioactivities have been attributed to cord factors[1–4], and their study has consequently spawned the desire to make available, by chemical synthesis, various types of structural analogs (pseudo cord factors) for comparative biochemical and immunochemical investigations. Thus, Goren and Jiang[5] synthesized what they termed a "mirror" pseudo cord factor (**2**), which is a diester of trehalose dicarboxylic acid (trehalosuronic acid) with a long-chain alkoxyaryl alkanol. The essential constitutional difference between **1** and **2** is a regioinverted ester functionality, apart from the nature of the lipid chains. Whereas only one

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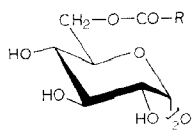
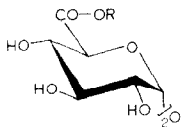
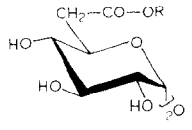


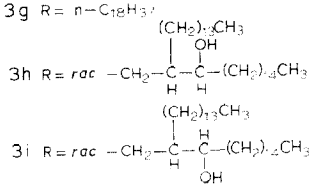
1 –CO–R = mycoloyl



2 R = $-(CH_2)_4C_6H_4OC_{16}H_{33}$



3a R = H
3b R = Me
3c R = n–C_8H_{17}
3d R = n–$C_{15}H_{31}$
3e R = n–$C_{15}H_{33}$
3f R = n–$C_{17}H_{35}$
3g R = n–$C_{18}H_{37}$



3h R = *rac* $-CH_2-CH(OH)-CH(H)-(CH_2)_{14}CH_3$

3i R = *rac* $-CH_2-CH(H)-CH(OH)-(CH_2)_{14}CH_3$

example of a "mirror" ester of type **2** appears to have been described (with R as indicated), several analogous "mirror" amide pseudo cord factors were prepared[3,5], having CONHR or $CONR_2$ groups in place of the ester functions. Among these were particularly interesting analogs wherein R represented spacer-borne corynomycolamido and mycolamido groups, and although details of preparation and physical constants for these compounds were not published, they were reported (ref. 3, pp 391–396) to show significantly lower toxicity in mice than true cord factors.

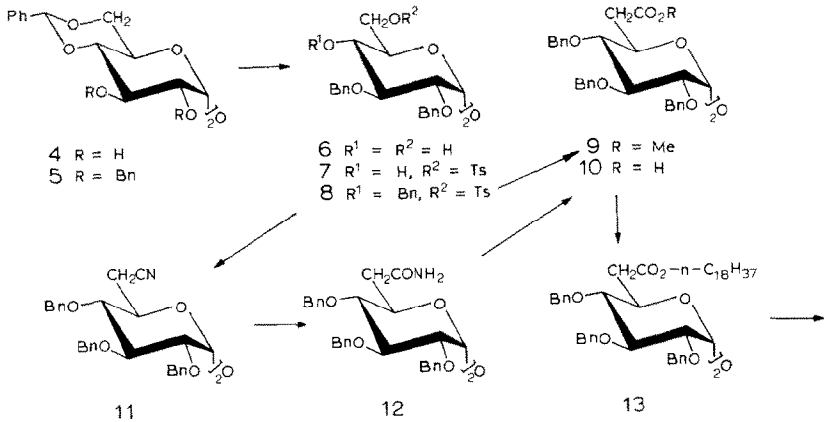
We recently synthesized a novel type of "mirror" pseudo cord factor, namely, diesters (**3b–3g**) of (6-deoxy-α-D-*gluco*-heptopyranosyluronic acid) 6-deoxy-α-D-*gluco*-heptopyranosiduronic acid (**3a**), a new homolog of trehalosuronic acid[6,7]. Unlike **2**, esters of type **1** and **3** have their functionalities (acyloxy and alkoxycarbonyl groups, respectively) attached to the same positions (C-6,6′) of the trehalose carbon skeleton. Some of the "mirror" esters with lipid chains of intermediate length (**3d–3g**) exhibited interesting antigenic properties in studies evaluating various synthetic cord factor analogs as immunoreactants for the serodiagnosis of tuberculosis[8,9], and they were found to inhibit the release of interleukin-6 induced in human blood mononuclear cells by mycobacterial antigens and bacterial endotoxins[10]. They also suppressed T-cell proliferation stimulated by mycobacterial antigens[10]. For use in further biochemical studies along these lines we decided to synthesize "mirror" cord factors containing corynomycolyl groups, both with 2*RS*,3*SR* stereochemistry (**3h**) (2*S*,3*R* is "natural") and with 2*RS*,3*RS* stereochemistry (**3i**).

RESULTS AND DISCUSSION

Before approaching the task of esterifying the diacid **3a** with corynomycolyl alcohols we considered it worthwhile to reassess the various synthetic procedures

that had led to **3a** and its esters **3b–3g**. Compound **3a** had been obtained[6] by application of the iron carbonyl method of chain extension[11] to 6,6′-di-*O*-tosyl-α,α-trehalose hexaacetate, followed by *O*-deacetylation, or alternatively, by nucleophilic displacement of triflate by potassium cyanide in 6,6′-di-*O*-triflyl-α,α-trehalose hexaacetate, followed by *O*-deacetylation and hydrolysis of the resulting dinitrile with alkaline hydrogen peroxide. Yields of **3a** were 22 and 73% in the first and second procedure, respectively, but the advantage of the latter was partly offset by the fact that the starting ditriflate is less readily accessible than the ditosylate. In view of Goren's advocacy of the use of partially benzyl-protected trehalose derivatives for efficient cord factor syntheses[12] we also sought[6] to obtain the hexabenzyl ether (**10**) of **3a** for possible use in ester synthesis. Although an attempted application (not reported[6]) of the iron carbonyl method with a benzyl-protected substrate had failed, the hexa-*O*-benzyl dinitrile **11** was in fact prepared in high yield by potassium cyanide displacement in 2,3,4,2′,3′,4′-hexa-*O*-benzyl-6,6′-di-*O*-triflyl-α,α-trehalose. Alkaline hydrolysis of **11** had given the crystalline diamide **12** but failed to proceed to the diacid stage under a variety of conditions. These difficulties have now been overcome in renewed efforts.

Thus, conditions were elaborated to synthesize the dimethyl ester **9** of the hexa-*O*-benzyl diacid **10** in good yield by application of the iron carbonyl method to 6,6′-di-*O*-tosyl-α,α-trehalose hexabenzyl ether (**8**). Known[12b] **8** was procured from trehalose essentially according to published directions, with some procedural variations and improvements. The 4,6:4′,6′-di-*O*-benzylidene derivative[13] **4** was benzylated ($PhCH_2Br$–NaH), and the product (**5**) deacetalated with iodine in methanol[14], to furnish 2,3,2′,3′-tetra-*O*-benzyl-α,α-trehalose[13b,15] (**6**). Selective tosylation of **6** yielded 85% of its crystalline 6,6′-ditosylate **7** (previously obtained[12f] as a syrup in 27% yield), which was benzylated to **8** (Scheme 1). Treatment[6,11] of **8** with sodium dicarbonylcyclopentadienyliron in oxolane effected displacement of



Scheme 1.

tosyloxy by $Fe(CO)_2Cp$, and reaction of the resulting sugar-iron intermediate with iodine and methanol caused oxidative carbonyl insertion followed by methanolysis, to afford **9** in 63% yield. The key to success in this step was the use of iodine as oxidant. In previous instances bromine was preferred as it reacts at a higher rate[6,11]; however, it appeared incompatible with benzyl groups present in the molecule. Saponification of **9** then gave the diacid **10** in an acceptable yield * of 72%.

The aforementioned problem of hydrolysis of the diamide **12** was solved when we became aware of the excellent method of Greenlee and Thorsett[16] for conversion of amides into methyl esters, consisting simply of treatment with boiling methanol in the presence of a cation-exchange resin. The diester **9** was thus obtained from **12** in 78% yield. A fresh supply of **12** required for these studies was prepared via the dinitrile **11** as described[6], and it was found in this connection that **11** can equally well be obtained (yield, 91%) from the ditosylate **8** instead of the corresponding ditriflate[6], by displacement with lithium cyanide in *N,N*-dimethylformamide solution.

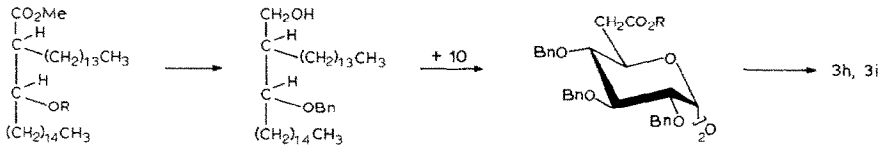
Having secured the sugar component **10**, we proceeded to examine its esterification with long-chain fatty alcohols. We first wished to establish, in a model experiment, the suitability of **10** for condensation with[7] alkyl mesylates, and to elaborate appropriate conditions for subsequent debenzylation. Reaction of the potassium salt of **10** with octadecyl mesylate gave a 77% yield of the protected distearyl ester **13**, which by hydrogenolytic debenzylation over Pd–C gave **3g** (70%), identical with the product synthesized previously. However, this mode of esterification was unsuccessful when tried with mycolyl mesylate **, and we therefore turned to other methods.

Having observed in TLC that **13** is also formed on reaction of **10** with octadecanol in the presence of dicyclohexylcarbodiimide (DCC) as the activating agent and 4-dimethylaminopyridine as catalyst, we applied this method[19] to a 3-*O*-benzylcorynomycolyl alcohol. To procure this, synthetic methyl C_{32}-corynomycolate[20] (**14a**) and its 2*RS*,3*SR* diastereomer **14b** were prepared following Datta et al.[21]. Both were benzylated by use of benzyl 2,2,2-trichloroacetimidate in the presence of trifluoromethanesulfonic acid[22], to give the protected esters **15a** and **15b** which were reduced by lithium aluminum hydride to the alcohols **16a** and **16b**. The alcohol **16b** (obtained in higher yield) was then condensed with **10** by DCC in toluene during 5 h at 70°C, giving a 52% yield of the fully benzylated dicorynomycolyl ester **17b** after chromatographic separation from unreacted mate-

* Some diminution in yield may have resulted from concomitant degradation of **9** through β-elimination of a ring oxygen.

** The mesylate was prepared in this laboratory[17] from mycolic acid (originating from natural cord factor "Peurois" and kindly donated by Dr. A. Liav), which was protected as the 3-*O*-(tetrahydro-2-pyranyl) derivative[18], reduced to the alcohol by $LiAlH_4$ or BH_3, conventionally mesylated, and deprotected.

rial and a byproduct that appeared to be a monoester bearing a DCC-related grouping on C-7′. Extension of the reaction time afforded no improvement.



14a R = H (2*RS*,3*RS*) 16a (2*RS*,3*SR*) 17a R = 3-*O*-benzyl-(2*RS*,3*SR*)-corynomycolyl
14b R = H (2*RS*,3*SR*) 16b (2*RS*,3*RS*) 17b R = 3-*O*-benzyl-(2*RS*,3*RS*)-corynomycolyl
15a R = Bn (2*RS*,3*RS*)
15b R = Bn (2*RS*,3*SR*)

Better results were achieved by Mitsunobu esterification[23], a method previously employed to advantage in cord factor syntheses[18]. Both alcohols **16a** and **16b** readily underwent condensation with the diacid **10**, mediated by diisopropyl azodicarboxylate (DIAD) and triphenylphosphine, to furnish high yields (~ 88%) of esters **17a** and **17b**. Hydrogenolytic debenzylation finally led to the target compounds **3h** and **3i** in yields of ~ 66%. These synthetic "mirror" coryno cord factors are, by necessity, diastereomeric mixtures as they were generated by combination of racemic alcohols with a chiral acid. This was reflected in certain features of the NMR spectra of the precursors **17a** and **17b**. Thus, their pyranosidic H-1 signals appeared as narrow multiplets (instead of doublets), and the H-2, H-6a, and H-6b signals were doublets of narrow multiplets (instead of doublets of doublets), owing to the slightly different shifts of corresponding signals from diastereomers. Similarly, ^{13}C signal duplications were discernible for C-6,6′ of the sugar and for the benzylic carbon atoms of the ester groups (see Experimental). Product **3h** must contain, as one of three components, the diester with two (2*S*,3*R*)-corynomycolyl groups, stereochemically corresponding to the naturally occurring corynomycolic[24a] and mycolic[24b] acids. The latter possess the 2*R*,3*R* configuration[24], as does one enantiomer[21] in racemic **14a** and **15a**. Reduction of the methyl carboxylate to a primary carbinol function, however, entails a reversal of sequence rule priorities for the C-2 substituents and hence requires the 2*S*,3*R* designation for that enantiomer in the resulting, racemic alcohol **16a**, even though bonding about the chiral centers remained the same as in **15a**.

EXPERIMENTAL

General methods.—Drying of nonpolar solutions during workup procedures was done with Na_2SO_4. Column chromatography was performed on Silica Gel 230–400 mesh with the following solvent combinations (v/v), also used for TLC on precoated silica gel plates: EtOAc–hexanes, (*A*) 1:100, (*B*) 1:50, (*C*) 1:30, (*D*)

1:20, (*E*) 1:10, (*F*) 1:6, (*G*) 1:4, (*H*) 1:3, and (*I*) 1:2; (*J*) 1:5 MeOH–EtOAc; (*K*) 1:10 MeOH–CH_2Cl_2; (*L*) 1:5 MeOH–$CHCl_3$; and (*M*) 4:5:30 H_2O–MeOH–EtOAc. Melting points were taken in glass capillaries in a Gallenkamp electrothermal apparatus and are uncorrected. Optical rotations were determined at room temperature with a Perkin–Elmer Model 241 polarimeter and refer to $CHCl_3$ solutions. Infrared data (ν_{max}) were recorded on a Bomen MB-100 instrument; normally, only bands of particular structural importance are listed. Most NMR data were obtained by use of a Varian Gemini 200 instrument, operating at 200 (^1H) and 50.3 (^{13}C) MHz; ^1H data referring to 300-MHz spectra (Varian XL-300 instrument) are so denoted. Samples were dissolved in $CDCl_3$, and δ values were measured from the internal chloroform signal at δ 7.24. For symmetrically substituted trehalose-type compounds the data given refer to a single glycosyl residue. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

2,3,2′,3′-Tetra-O-benzyl-4,6:4′,6′-di-O-benzylidene-α,α-trehalose (**5**). — The bisacetal[13c] **4** (7.7 g) and NaH (4.65 g of a 61% suspension in mineral oil, rinsed with toluene and added at 0°C) in dry *N*,*N*-dimethylformamide (100 mL) were stirred for 3 h at 25°C. Benzyl bromide (14 mL) was then added and stirring continued overnight. Some concd aq NH_3 was added to decompose residual NaH, and after 1 h the mixture was diluted with water (500 mL) and extracted several times with toluene. The extract was washed with satd aq $NaHCO_3$ and water, dried, and evaporated. The residue crystallized from ether–hexane, giving **5** (10.95 g, 89%); mp 151–152°C; $[\alpha]_D$ +51.3° (*c* 1). The compound has been described[13b] as a viscous syrup. ^1H NMR: δ 7.5–7.2 (m, Ph), 5.55 (s, PhC*H*), 5.11 (d, $J_{1,2}$ 3.7 Hz, H-1), 4.99–4.69 (6 equally spaced lines for 2 partially overlapping AB-q, 4 H, 2 PhCH_2), 4.30–4.08 (m, 3 H), and 3.71–3.55 (m, 3 H) for H-2,3,4,5,6a,6b; ^{13}C NMR: δ 138.8, 138.1, 137.6 (C-1 of 3 Ph), 128.9–126.2 (multiple peaks, Ph), 101.3 (PhCH), 95.0 (C-1), 82.4 (C-4), 78.8, 78.7 (C-2,3), 75.4, 73.8 (2 PhCH_2), 69.0 (C-6), and 63.0 (C-5).

2,3,2′,3′-Tetra-O-benzyl-α,α-trehalose (**6**). — Compound **5** (10.7 g) was dissolved in MeOH (200 mL) containing I_2 (2 g), with addition of Me_2CO (20 mL) for complete dissolution. The mixture was boiled under reflux for 1 h, cooled, and stirred with solid $Na_2S_2O_3$ (4 g) until it became colorless (~ 10 min). The residue obtained upon solvent evaporation was dissolved in CH_2Cl_2 and washed with aq $NaHCO_3$ and water. Evaporation of the dried solution gave **6** (7.13 g, 84%), crystallized from EtOAc–hexane; mp 199–200°C; $[\alpha]_D$ +121° (*c* 0.6); lit.[15] mp 186–188°C; $[\alpha]_D$ +120°; lit.[13b] mp 186–189°C; $[\alpha]_D$ +124°.

2,3,2′,3′-Tetra-O-benzyl-6,6′-di-O-p-tolylsulfonyl-α,α-trehalose (**7**). — Tosyl chloride (420 mg, 2.2 mmol) was added portionwise at 0°C to a solution of **6** (705 mg, 1.0 mmol) in pyridine (5 mL, dried over CaH_2). After it was stirred overnight at room temperature, the mixture showed a single spot for **7** (R_f 0.6) in TLC (solvent *H*). It was poured into ice–water, and the product was extracted with CH_2Cl_2. The washed (1 M HCl followed by water), dried, and concentrated extract gave **7**

(869 mg, 85%) upon crystallization by the addition of hexane; mp 146–147°C; $[\alpha]_D$ +83.7° (*c* 0.7); lit.[12f] $[\alpha]_D$ +70° for a syrupy product. ^{1}H NMR: δ 7.68 (d, *J* 8.4 Hz) and 7.32–7.22 (m) for aryl, 5.02 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.85 (center of AB-q, 2 H, *J* 11.4 Hz, PhCH_2), 4.495 (center of AB-q, 2 H, *J* 12.1 Hz, PhCH_2), ~4.0, 3.76, and 3.46 (3 m, 2 H each, H-2,3,4,5,6a,6b), 2.42 (s, 3 H, CH_3 of Ts), and 2.27 (d, $J_{4,OH}$ 3.2 Hz, O*H*-4); ^{13}C NMR: δ 144.8 (C-1 of Ts), 138.3 and 137.7 (C-1 of Ph), 132.7 (C-4 of Ts), 129.8–127.3 (multiple peaks, aryl), 94.2 (C-1), 80.0 and 78.8 (C-2,3), 75.3 and 72.7 (2 PhCH_2), 69.6 and 69.2 (C-4,5), 68.3 (C-6), and 21.7 (CH_3 of Ts). Anal. Calcd for $C_{54}H_{58}O_{15}S_2$ (1011.1): C, 64.14; H, 5.78; S, 6.32. Found: C, 64.08; H, 5.88; S, 6.07.

*2,3,4,2',3',4'-Hexa-*O*-benzyl-6,6'-di-*O*-*p*-tolylsulfonyl-α,α-trehalose* (**8**). — Compound **7** (5.0 g) was benzylated with benzyl bromide (2.4 mL) and NaH (780 mg of a 61% suspension in mineral oil) essentially as described for the benzylation of **4**, but in refluxing oxolane (200 mL) during 24 h. Complete consumption of **7** (R_f 0.3) and formation of **8** (R_f 0.5) was seen in TLC (solvent *1*). Decomposition of remnant NaH with some added MeOH, evaporation of the solvent, washing of a CH_2Cl_2 solution of the product with aq $NaHCO_3$ followed by water, and finally, column chromatography (solvent *H*) of the recovered crude product gave pure **8** as a colorless syrup (4.84 g, 82%); $[\alpha]_D$ +67.3° (*c* 0.5); lit.[12b] $[\alpha]_D$ +73°; ^{1}H NMR: δ 7.67 (d, *J* 8.4 Hz) and 7.28–7.06 (m) for aryl, 4.96 (d, $J_{1,2}$ 3.4 Hz, H-1), 4.87, 4.58, and 4.56 (centers of 3 AB-q, 2 H each, *J* 10.9, 11.9, and 10.8 Hz, 3 PhCH_2), 4.1–3.75 (m, 4 H) and 3.5–3.4 (m, 2 H) for H-2,3,4,5,6a,6b, and 2.37 (s, 3 H, CH_3 of Ts); ^{13}C NMR: δ 145.0 (C-1 of Ts), 138.6, 137.9, 137.8 (C-1 of 3 Ph), 132.7 (C-4 of Ts), 129.9–127.4 (multiple peaks, aryl), 94.2 (C-1), 81.5 and 79.2 (C-2,3), 76.9 (C-4), 75.6, 75.2, and 73.0 (3 PhCH_2), 69.0 (C-5), 68.3 (C-6), and 21.7 (CH_3 of Ts). Anal. Calcd for $C_{68}H_{70}O_{15}S_2$ (1191.4): C, 68.55; H, 5.92; S, 5.38. Found: C, 68.87; H, 5.97; S, 5.26.

*Methyl [(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosyluronate) 2,3,4-tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosid]uronate* (**9**). — *(a) From* **8**. Rigorously dried apparatus[11] and reagents, and careful exclusion of atmospheric moisture are crucial in this operation. The hexabenzyl ether **8** (3 g) was allowed to react under N_2 with sodium dicarbonyl-η^5-cyclopentadienyliron (NaFp) [prepared from 2.67 g of $Fe(CO)_2Cp$ dimer (Aldrich Chemical Co.) in dry[11] oxolane (150 mL)], exactly as detailed[6] for the corresponding hexa-*O*-acetyl derivative, except that a longer reaction time (20 h) was required for complete conversion of **8** (R_f 0.5) into the sugar-iron intermediate (R_f 0.7, yellow spot visible prior to spraying; TLC with solvent *1*). A stream of CO was then bubbled through the solution, a slurry of I_2 (10 g) in MeOH (100 mL) was added portionwise at room temperature, and the mixture was stirred under CO for 20 h. In TLC the yellow spot disappeared and a spot for **9** (R_f 0.55, visible upon spraying with 5% H_2SO_4 in EtOH, and heating) was seen. The solvent was evaporated and a solution of the residue in EtOAc was washed with satd aq $Na_2S_2O_3$ to remove I_2, followed by aq $NaHCO_3$ and water, dried, and concentrated. The material was chromatographed on SiO_2

(300 g) by use of solvent *G* to yield syrupy **9** (1.53 g, 63%); $[\alpha]_D$ +90.3° (*c* 0.8); ν_{max}^{film} 1738 cm^{-1} (ester CO); ^1H NMR: δ 7.4–7.15 (m, Ph), 5.39 (d, $J_{1,2}$ 3.4 Hz, H-1), 5.00–4.55 (3 AB-q, 6 H, 3 PhCH_2), 4.345 (dt, H-5), 4.14 (t, $J_{2,3} = J_{3,4} = 9.2$ Hz, H-3), 3.59 (s, 3 H, OMe, partly overlapping dd for H-2) , and 3.31 (t, $J_{3,4} \approx J_{4,5} \approx 9.4$ Hz, H-4), 2.70 (dd, $J_{5,6a}$ 3, $J_{6a,6b}$ 15.6 Hz, H-6a), 2.36 (dd, $J_{5,6b}$ 9.3, $J_{6a,6b}$ 15.6 Hz, H-6b); ^{13}C NMR: δ 138.9, 138.5, 138.5 (C-1 of Ph), 128.5–127.5 (multiple peaks, Ph), 90.6 (C-1), 81.4, 81.3, and 80.1 (C-2,3,4), 75.6, 74.9, and 73.0 (3 PhCH_2), 67.7 (C-5), 51.8 (OMe), and 37.1 (C-6). Anal. Calcd for $C_{58}H_{62}O_{13}$ (967.1): C, 72.03; H, 6.46. Found: C, 71.90; H, 6.42.

(b) From **12**. A solution of diamide **12** (1.10 g of trihydrate, prepared[6] from **11**) in MeOH (80 mL) was stirred with Amberlite IR-120(H^+) resin (30 g, washed with MeOH and dried prior to use), and gently boiled under reflux (oil bath, 80°C) for 4 days. The resin was filtered off and washed successively with MeOH and EtOAc, the filtrate concentrated, and applied to a column (SiO_2). Elution with solvent *G* gave pure **9** (838 mg, 78%), identical with **9** from **8** (^1H and ^{13}C NMR).

*(2,3,4,-Tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosyluronic acid) 2,3,4-tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosiduronic acid* (**10**). — A solution of diester **9** (1.00 g) in oxolane (20 mL), MeOH (10 mL), and aq 20% KOH (10 mL) was kept at room temperature for 8 h and then concentrated at reduced pressure (bath temperature, 40°C) to remove organic solvent. The remaining, largely aqueous solution was carefully acidified to pH 2 (indicator paper) at 0°C with 5% HCl and extracted with CH_2Cl_2. The extract was washed three times with water, dried, and evaporated, and the crude product purified by column chromatography (solvent *K*), to give syrupy **10** (960 mg) which from CH_2Cl_2–hexane gave crystalline **10** (697 mg, 72%); mp 142–143°C; $[\alpha]_D$ +96.7° (*c* 1); ν_{max}^{KBr} 1713 cm^{-1} (CO); ^1H NMR: δ 7.3–7.1 (m, Ph), 5.35 (d, $J_{1,2}$ 3 Hz, H-1), 4.98–4.52 (m, 6 H, 3 PhCH_2), 4.30 (dt, H-5), 4.13 (t, $J_{2,3} \approx J_{3,4} \approx 9.3$ Hz, H-3), 3.58 (dd, $J_{1,2}$ 3.1, $J_{2,3}$ 9.6 Hz, H-2), 3.27 (t, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4), 2.75 (dd, $J_{5,6a} \approx 2$, $J_{6a,6b} \approx 15$ Hz, H-6a), 2.30 (dd, $J_{5,6b}$ 10.4, $J_{6a,6b}$ 15.3 Hz, H-6b); ^{13}C NMR: δ 178.2 (*C*O), 138.7, 138.3, 138.3 (C-1 of Ph), 128.3–127.3 (multiple peaks, Ph), 90.1 (C-1), 81.1, 81.05, and 80.1 (C-2,3,4), 75.5, 74.8, and 72.9 (3 PhCH_2), 67.0 (C-5), and 37.1 (C-6). Anal. Calcd for $C_{56}H_{58}O_{13}$ (939.1): C, 71.63; H, 6.23. Found: C, 71.69; H, 6.23.

*2,3,4-Tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosyluronononitrile 2,3,4-tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosiduronononitrile* (**11**). — A solution of **8** (4.0 g) in 0.5 M LiCN in *N*,*N*-dimethylformamide (20 mL; Aldrich Chemical Co.) was kept under N_2 for 20 h at 85°C, cooled, diluted with water (100 mL), and extracted with 1:1 EtOAc–Et_2O (3 × 75 mL). The extract was washed with water (2 × 25 mL), dried, concentrated, and subjected to column chromatography (solvent *G*), affording syrupy **11** (2.73 g, 91%); $[\alpha]_D$ +135.6° (*c* 1); lit.[6] $[\alpha]_D$ +132°. The ^1H and ^{13}C NMR data were identical with those reported[6].

*Octadecyl [(octadecyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosyl-uronate) 2,3,4-tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosid]uronate* (**13**). — A mixture of diacid **10** (200 mg) in Me_2CO (2 mL) and K_2CO_3 (32.4 mg) in water (1

mL) was evaporated to dryness at 40°C, and the resulting salt was dried overnight in a high vacuum and then dissolved in dry Me_2SO (10 mL) together with octadecyl methanesulfonate[7] (221.4 mg). The mixture was heated under N_2 for 3 h at 70°C, then cooled, diluted with water, and extracted with ether (3 × 50 mL). The extract was washed with water, dried, concentrated, and purified by column chromatography (solvent *E*), to give **13** (236 mg, 77%) as a colorless syrup; $[\alpha]_D$ +62.5° (*c* 0.6); ν_{max}^{film} 1736 cm^{-1} (ester CO); ^1H NMR (300 MHz, assignments confirmed by COSY): δ 7.4–7.15 (m, Ph), 5.43 (d, $J_{1,2}$ 3.4 Hz, H-1), 5.00–4.55 (3 AB-q, 6 H, 3 PhCH_2), 4.34 (dt, H-5), 4.13 (t, $J_{2,3} + J_{3,4} = 18.5$ Hz, H-3), 3.99 (t, *J* 6.9 Hz, 2 H, H-1,1′ of alkyl), 3.62 (dd, $J_{1,2}$ 3.4, $J_{2,3}$ 9.5 Hz, H-2), 3.31 (t, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 2.69 (dd, $J_{5,6a}$ 3, $J_{6a,6b}$ 15.6 Hz, H-6a), 2.37 (dd, $J_{5,6b}$ 9.3, $J_{6a,6b}$ 15.9 Hz, H-6b), 1.54 (m, 2 H, H-2,2′ of alkyl), 1.25 (m, large peak, internal CH_2 of alkyl), and 0.86 (t, terminal CH_3); ^{13}C NMR: δ 171.1 (*C*O), 138.8, 138.5, and 138.5 (C-1 of Ph), 128.3–127.4 (multiple peaks, Ph), 90.5 (C-1), 81.3, 81.25, and 80.0 (C-2,3,4), 75.5, 74.8, and 72.8 (3 Ph*C*H_2), 67.5 (C-5), 64.8 (C-1 of alkyl), 37.0 (C-6), 32.0, 22.8, and 14.2 (terminal $CH_2CH_2CH_3$ of alkyl), 29.8–28.6 and 25.9 (internal CH_2 of alkyl). Anal. Calcd for $C_{92}H_{13}O_{13}$ (1444.0): C, 76.52; H, 9.07. Found: C, 76.47; H, 8.96.

*Octadecyl [(octadecyl 6-deoxy-α-*D*-gluco-heptopyranosyluronate) 6-deoxy-α-*D*-gluco-heptopyranosid]uronate* (**3g**). — The benzyl derivative **13** (100 mg) dissolved in 1:1 EtOAc–EtOH (12 mL) was hydrogenated over 10% Pd–C (100 mg) during 10 h at 3.5 kPa H_2 pressure and room temperature. The catalyst was filtered off and washed with oxolane, and the filtrate was evaporated. The product showed one major spot (R_f 0.45) in TLC (solvent *M*), identical with that of a cochromatographed authentic sample[7] of **3g**, and faster-moving trace contaminants. The latter were removed by column chromatography (solvent *J*), which gave solid **3g** (44 mg, 70%); $[\alpha]_D$ +62.7° (*c* 1); lit.[7] $[\alpha]_D$ +61°; IR spectrum identical with that of authentic **3g**.

*Methyl (2*RS*,3*RS*)- and (2*RS*,3*SR*)-3-hydroxy-2-tetradecyloctadecanoates* (**14a** *and* **14b**). — Claisen condensation of methyl palmitate was performed as described[21]. The resulting *keto ester* showed the following NMR data: ^1H, δ 3.69 (s, 3 H, OMe), 3.41 (t, *J* 7.4 Hz, H-2), 2.47 (m, 2 H) and 2.30 (m, 2 H) for H-4,4′ of main chain and H-1,1′ of 2-alkyl, 1.80 (m, 2 H), 1.60 (m, 2 H), and 1.22 (m, large peak) for internal CH_2 groups, and 0.85 (t, 2 terminal CH_3); ^{13}C: δ 205.5 (keto *C*O), 170.4 (ester *C*O), 59.0 (C-2), 52.2 (OMe), 41.9 (C-4), 31.9, 22.7, and 14.1 (terminal $CH_2CH_2CH_3$), 29.7–27.5 (multiple peaks), 24.7, and 23.5 (internal CH_2).

Borohydride reduction of the keto ester and chromatographic separation of the diastereomeric hydroxy esters[21] furnished **14a** (R_f 0.4) and **14b** (R_f 0.55, TLC with $CHCl_3$) in yields and with physical constants and ^1H NMR data in agreement with those reported; ^{13}C NMR for **14a**: δ 176.2 (*C*O), 72.3 (C-3), 51.5 (OMe), 50.9 (C-2), 35.7 (C-4), 31.9, 22.7, and 14.1 (terminal $CH_2CH_2CH_3$), 29.7–29.4, 27.4, and 25.7 (internal CH_2); for **14b**: δ 176.1 (*C*O), 72.1 (C-3), 51.6 (OMe), 51.0 (C-2),

34.3 (C-4), 31.9, 22.7, and 14.1 (terminal $CH_2CH_2CH_3$), 29.7–29.4, 27.8, 26.9, and 25.9 (internal CH_2).

Methyl (2RS,3RS)-3-benzyloxy-2-tetradecyloctadecanoate (**15a**). — To a stirred solution of **14a** (510 mg) in CH_2Cl_2 (5 mL) and cyclohexane (30 mL) was added benzyl trichloroacetimidate[22] (600 mg), followed by trifluoromethanesulfonic acid (0.2 mL). Upon overnight storage of the mixture, TLC (solvent *F*) indicated complete replacement of **14a** (R_f 0.4) by **15a** (R_f 0.67). The reaction was quenched by addition of pyridine (1 mL), and the solution washed with water, dried, and evaporated to a syrup. This was triturated with hexane, whereby a white solid was formed. The filtrate therefrom was evaporated to dryness with repeated additions of water followed by acetone. Purification of the crude product by column chromatography (solvents *A–E* in sequence) furnished syrupy **15a** (550 mg, 92%) which, although contaminated by a small proportion of dibenzyl ether (^{1}H NMR: δ 4.55, s, PhCH_2), was sufficiently pure for further use. An analytical sample was freed from the Bn_2O impurity by repeated chromatography. ^{1}H NMR: δ 7.30–7.26 (m, Ph), 4.47 (AB-q, 2 H, *J* 11.4 Hz, PhCH_2O-3), 3.64 (s, 3 H, OMe), 3.61 (m, 1 H, H-3), 2.65 (quintet, 1 H, H-2), ~ 1.5 (m) and 1.24 (large peak) for internal CH_2, and 0.86 (t, 6 H, *J* 6.3 Hz, 2 terminal CH_3); ^{13}C NMR: δ 175.3 (*C*O), 138.6 (C-1 of Ph), 128.4–127.5 (multiple peaks, Ph), 80.5 (C-3), 72.1 (Ph*C*H_2), 51.4 (OMe), 49.9 (C-2), 31.9, 22.7, and 14.1 (terminal $CH_2CH_2CH_3$), 30.9, 29.7–29.4, 27.9, 27.7, and 24.5 (internal CH_2). Anal. Calcd for $C_{40}H_{72}O_3$ (601.0): C, 79.94; H, 12.08. Found: C, 79.63; H, 11.92.

Methyl (2RS,3SR)-3-benzyloxy-2-tetradecyloctadecanoate (**15b**). — Prepared from **14b** in 93% yield as just described for **15a**, **15b** gave a ^{1}H NMR spectrum very similar to that of its diastereomer; ^{13}C NMR: δ 174.9 (*C*O), 138.4 (C-1 of Ph), 128.3, 127.8, and 127.6 (Ph), 80.0 (C-3), 72.0 (Ph*C*H_2), 51.4 (OMe), 49.7 (C-2), 31.9, 22.7, and 14.1 (terminal $CH_2CH_2CH_3$), 32.1, 29.7–29.4, 28.5, 27.9, and 25.3 (internal CH_2). Anal. Calcd as for **15a**. Found: C, 80.07; H, 11.89.

(2RS,3SR)-3-Benzyloxy-2-tetradecyl-1-octadecanol (**16a**). — Compound **15a** (300 mg) and $LiAlH_4$ (80 mg) were boiled for 4 h in refluxing oxolane (10 mL). To the cooled mixture was added EtOAc to decompose excess reductant, and the solution was filtered through Celite and evaporated to give a residue. This was triturated with hexane, insoluble parts were filtered off, and the filtrate was washed with water, dried, and concentrated for column chromatography, performed by sequential use of solvents *B–E*, to give oily **16a** (240 mg, 84%); ^{1}H NMR: δ 7.33–7.28 (Ph), 4.51 (AB-q, 2 H, *J* 11.3 Hz, PhCH_2), 3.83 and 3.55 (2 dd, 1 H each, H-1,1′), 3.51 (m, H-3), 2.81 (br s, O*H*), 1.89 (m, H-2), 1.62 (m), 1.25 (large peak), and 1.15 (m) for internal CH_2, and 0.87 (t, 6 H, *J* 6.1 Hz, 2 terminal CH_3); ^{13}C NMR: δ 138.3 (C-1 of Ph), 128.4, 127.8, and 127.7 (Ph), 83.3 (C-3), 72.2 (Ph*C*H_2), 63.3 (C-1), 42.6 (C-2), 32.0, 22.7, and 14.1 (terminal $CH_2CH_2CH_3$), 31.3, 29.9–29.4, 28.7, 27.4, and 25.2 (internal CH_2). Anal. Calcd for $C_{39}H_{72}O_2$ (573.0): C, 81.75; H, 12.67. Found: C, 81.63, H, 12.55.

(2RS,3RS)-3-Benzyloxy-2-tetradecyl-1-octadecanol (**16b**). — Compound **16b** was

prepared in 87% yield from **15b** as just described for **16a**; ^{1}H NMR (300 MHz): δ 7.34–7.24 (Ph), 4.55 (AB-q, 2 H, J 11.4 Hz, PhCH_2), 3.72 (dd, J 8.8 and 10.7 Hz, H-1), 3.57 (dd, J 4.0 and 10.7 Hz, H-1′), 3.51 (m, H-3), 2.96 (br, OH), 2.00 (m, H-2), 1.58 (m), 1.44 (m), 1.24 (large peak), and 1.15 (m) for internal CH_2, and 0.86 (t, 6 H, J 6.6 Hz, 2 terminal CH_3); ^{13}C NMR: δ 138.2 (C-1 of Ph), 128.4, 128.0, and 127.8 (Ph), 82.8 (C-3), 71.8 (PhCH_2), 64.3 (C-1), 41.2 (C-2), 32.0, 22.8, and 14.2 (terminal $CH_2CH_2CH_3$), 29.9-29.4, 27.8, 27.1, and 26.4 (internal CH_2). Anal. Calcd as for **16a**. Found: C, 81.88; H, 11.66.

*(2RS,3SR)-3-Benzyloxy-2-tetradecyloctadecyl {[(2RS,3SR)-3-benzyloxy-2-tetradecyloctadecyl 2,3,4,-tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosyluronate] 2,3,4-tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosid}uronate* (**17a**). — A flask was charged with diacid **10** (100 mg, 0.107 mmol), alcohol **16a** (147 mg, 0.256 mmol), and Ph_3P (112 mg, 0.43 mmol). The contents were thoroughly dried in a high vacuum and then dissolved in toluene (5 mL, dried over molecular sieves). Diisopropyl azodicarboxylate (87 mg, 0.085 mL, 0.43 mmol) was added by syringe at 0°C. After overnight storage of the mixture under N_2 at room temperature, a strong spot for **17a** (R_f 0.70) and a weak spot for unreacted **16a** (R_f 0.60) were seen in TLC (solvent *G*). The residue obtained upon solvent evaporation was triturated with hexane (30 mL); insoluble material was filtered off, washed with hexane (50 mL), and discarded. The hexane filtrates were evaporated and the residue was subjected to column chromatography. Initial elution with solvent *B* removed unreacted **16a**, and continued elution with solvent *D* gave **17a** as a homogeneous oil (193 mg, 88.5%); $[\alpha]_D$ +45.1° (c 0.7); ν_{max}^{film} 1735 (ester CO), 1458, 1325, 1175, 1095, 1070, and 1002, and bands typical for Bn at 735 and 696 cm^{-1}; ^{1}H NMR (300 MHz): δ 7.4–7.1 (Ph), 5.48 (nm, H-1), 5.0–4.4 (4 partially overlapping AB-q, 8 H, 4 PhCH_2), 4.35 (dt, H-5), 4.13 (t, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3), 4.05 (m, 2 H, H-1,1′ of octadecyl), 3.61 (dnm, H-2), 3.34–3.27 (m, 2 H, H-4 of sugar and H-3 of octadecyl), 2.65 (dnm, H-6a), 2.35 (dnm, H-6b), 1.82 (m, H-2 of octadecyl), and 1.6-0.8 (same pattern as in **16a**); ^{13}C NMR: δ 171.0 (*C*O), 138.9–138.5 (C-1 of Ph), 128.3–127.3 (Ph), 90.4 (C-1), 81.3 (C-3 of octadecyl), 81.1, 80.0, and 79.2 (C-2,3,4), 75.5, 74.7, and 72.8 (3 PhCH_2 on sugar), 71.8, 71.7 (PhCH_2 on alkyl), 67.3 (C-5), 64.9 and 40.3 (C-1 and C-2 of octadecyl), 36.75, 36.7 (C-6), 32.0, 22.8, and 14.2 (terminal $CH_2CH_2CH_3$), 30.6, 29.8–29.4, 27.5, and 25.7 (internal CH_2). Anal. Calcd for $C_{134}H_{198}O_{15}$ (2049.0): C, 78.55; H, 9.74. Found: C, 78.54; H, 9.77.

*(2RS,3RS)-3-Benzyloxy-2-tetradecyloctadecyl {[(2RS,3RS)-3-benzyloxy-2-tetradecyloctadecyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosyluronate] 2,3,4,-tri-*O*-benzyl-6-deoxy-α-*D*-gluco-heptopyranosid}uronate* (**17b**). — *(a) By the DIAD method.* Condensation of **10** (50 mg) with **16b** (73 mg) by the method just described for **17a** gave **17b** as an oil (96 mg, 88%); $[\alpha]$ +39.1° (c 0.8); ν_{max}^{film} 1736 (ester CO), 1460, 1324, 1175, 1095, 1070, 734, and 697 cm^{-1}. The ^{1}H NMR spectrum (300 MHz) was very similar to that of **17a**, although there were slight differences in the patterns of the benzylic resonances (δ 5.05–4.45), the H,H′ protons of octadecyl (δ 4.0–3.9) and the sugar H-6a and H-6b protons (δ 2.65 and 2.35). ^{13}C NMR: δ 171.1

(*C*O), 138.9–138.6 (C-1 of Ph), 90.4 (C-1), 81.3, 80.1, and 79.2 (C-2,3,4), 78.8 (unassigned), 75.5 74.7, and 72.8 (3 Ph*C*H$_2$ on sugar), 71.8, 71.6 (Ph*C*H$_2$ on alkyl), 67.3 (C-5), 65.0 (C-1 of octadecyl), 40.1, 40.0 (C-2 of octadecyl), 36.8 (C-6), 32.0, 22.8, and 14.2 (terminal *C*H$_2$*C*H$_2$*C*H$_3$), 30.7, 30.5, 30.0, 29.8–39.4, 27.8, and 27.0 (internal *C*H$_2$). Anal. Calcd as for **17a**. Found: C, 78.48; H, 9.71.

(b) By the DCC method. Thoroughly vacuum-dried **10** (150 mg, 0.16 mmol), **16b** (220 mg, 0.38 mmol), dicyclohexylcarbodiimide (78 mg, 0.38 mmol), and 4-dimethylaminopyridine (10 mg) were dissolved at 0°C in dry toluene (10 mL), under N_2. The mixture was kept for 4 h at room temperature and then for 5 h at 70°C. After cooling, filtration, and evaporation of the solution a residue was obtained which showed **17b** (R_f 0.75) and two less-mobile components (R_f 0.55 and 0.5) in TLC (solvent *G*). The products were separated by column chromatography. Initial elution with solvent *D* curiously produced first the component of intermediate TLC mobility, which proved to be unreacted **16b** (43 mg), followed by a small amount of a mixture of **16b** and **17b**. Continued elution with solvent *E* gave **17b** as an oil (171 mg, 52%), followed eventually by the unidentified, slow-moving by-product (96 mg). The ^{1}H NMR spectrum of **17b** was identical with that of **17b** formed by the DIAD method. The ^{1}H and ^{13}C NMR spectra of the by-product were exceedingly complex, suggestive of an unequally substituted disaccharide derivative, and exhibiting features tentatively attributable to cyclohexyl groups.

*(2*RS,*3*SR*)-3-Hydroxy-2-tetradecyloctadecyl {[(2*RS,*3*SR*)-3-hydroxy-2-tetradecyloctadecyl 6-deoxy-α-*D-gluco-*heptopyranosyluronate] 6-deoxy-α-*D-gluco-*heptopyranosid}uronate* (**3h**). — Compound **17a** (80 mg) dissolved in EtOAc (6 mL) and EtOH (6 mL) was hydrogenated over 10% Pd–C (100 mg) during 24 h at 3.5 kPa H_2 pressure and room temperature. A very strong spot for **3h** (R_f 0.4) appeared in TLC (solvent *L*), along with traces of faster moving, incompletely debenzylated products. The catalyst was removed and washed well with $CHCl_3$, and the solution evaporated. Column chromatography of the amorphous residue was started by elution with $CHCl_3$, which removed the minor impurities, and continued by elution with solvent *L*, which produced pure **3h** as an amorphous solid (34 mg, 65%); $[\alpha]_D$ +42.6° (*c* 0.4); ν_{max}^{KBr} 3348 (OH), 1728 (ester CO), 1461, 1149, 1074, 1044, and 989 cm^{-1} (benzyl bands at 735-696 cm^{-1} were absent). No well-resolved NMR spectra could be obtained. Anal. Calcd for $C_{78}H_{150}O_{15}$ (1328.0): C, 70.55; H, 11.38. Found: C, 70.76; H, 11.21.

*(2*RS,*3*RS*)-3-Hydroxy-2-tetradecyloctadecyl {[(2*RS,*3*RS*)-3-hydroxy-2-tetradecyloctadecyl) 6-deoxy-α-*D-gluco-*heptopyranosyluronate] 6-deoxy-α-*D-gluco-*heptopyranosid}uronate* (**3i**). — Compound **17b** (45 mg) was hydrogenated as just described for **17a**, to give **3i** as an amorphous solid (19.5 mg, 67% after chromatographic purification); R_f 0.45 (solvent *L*); $[\alpha]_D$ +39.8° (*c* 0.8); ν_{max}^{KBr} 3353 (OH), 1722 (ester CO), 1462, 1148, 1074, 1044, and 991 cm^{-1} (benzyl bands at 735–696 cm^{-1} were absent). No well-resolved NMR spectra could be obtained. Anal. Calcd as for **3h**. Found: C, 70.37; H, 11.42.

ACKNOWLEDGMENT

This work was supported financially by the Natural Sciences and Engineering Research Council of Canada.

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