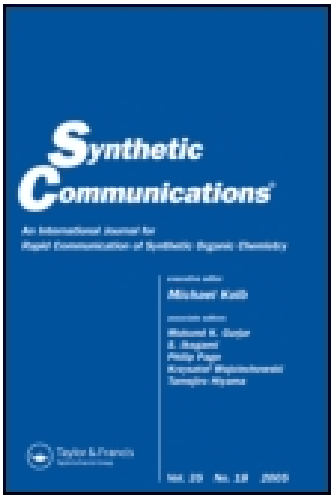

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Microwave-Assisted Protocols Applied to the Synthesis of 1′,2,3,3′,4,4′-Hexa-O-benzylsucrose

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MICROWAVE-ASSISTED PROTOCOLS APPLIED TO THE SYNTHESIS OF 1′,2,3,3′,4,4′-HEXA-*O*-BENZYLSUCROSE

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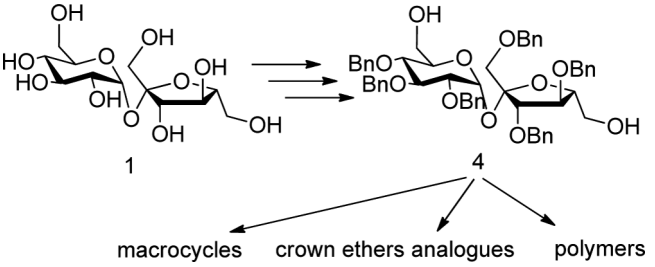
GRAPHICAL ABSTRACT



Abstract *The sucrose derivative 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose is a key intermediate for the chemoselective synthesis of various useful materials, such as macrocycles, crown ether analogs, and polymers. Several strategies for the synthesis of this compound were explored by applying microwave-assisted protocols, thus permitting significant reductions of time and energy compared to other routes. The outcomes of the different approaches were compared and the optimal one, in terms of yield and reproducibility, was found to be the initial protection at the positions 6 and 6′, with* tert*-butyldiphenylsilylchloride (TBDPSCl) in the presence of 4-(dimethylamino)pyridine (4-DMAP) and pyridine as a solvent, then perbenzylation of the remaining hydroxyl groups, followed by selective deprotection of the TBDPS groups to obtain the title compound.*

Keywords Carbohydrates; chemoselective synthesis; microwave chemistry; protection–deprotection strategies; sucrose derivatives

INTRODUCTION

Sugars are an important resource for the development of new materials owing to their low price.[1] Sucrose (**1**, Scheme 1) is a cheap bulk product and has great potential for this purpose. The potential value of sucrose as a raw material has been

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recognized for many years and has been the subject of considerable research.[2] Because sucrose has eight chemically active hydroxyl groups, regioselective derivatization is important for the selective synthesis of sucrose-containing linear polymers.[3] The methods used to produce and purify carbohydrate derivatives are often tedious and complex,[4] making the synthesis of selectively protected sucrose derivatives laborious. Clearly, there is a need for simpler procedures using faster and environmentally friendlier heating methods, and these are provided by the use of microwave (MW) techniques.[5] Microwave-enhanced synthesis has been extended to almost all areas of chemistry.[6] Carbohydrate chemistry has suffered a certain delay in adopting this technology, as documented by the limited number of applications.[7] It has been applied to sucrose chemistry only in our laboratory,[5,8] because the general opinion was that the method was hampered by the thermal instability of sucrose.[2]

We have been developing strategies to produce highly functional and biocompatible novel biomaterials in synthetically efficient ways from natural building blocks.[8–10] For this, our approach has been to synthesize regioselectively structurally well-defined bifunctional sucrose monomers for which the key intermediate was 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose **4**. This compound has been first reported by Jarosz et al.[4,11] and has found various applications for the synthesis of macrocycles, crown ether analogs, and polymers. To gain access to larger and affordable quantities of this intermediate, we have explored the various methods described in the literature for the synthesis of **4** under microwave irradiation and compared their outcomes and applicability. The protocols presented in this work have allowed significant reduction of time and energy compared with other routes[3,10] and have potential for the automatization of tedious multistep syntheses of useful sucrose derivatives. Another elegant method to obtain **4** was published by Yin et al., based on a regioselective conversion of terminal benzyl ethers into silyl ethers using $Co_2(CO)_8$-Et_3SiH under 1 atm of CO.[12] This protocol was not tested under microwave irradiation because of difficulties related to the use of CO.

RESULTS AND DISCUSSION

The key to successful synthesis under microwave irradiation is to use proper equipment designed especially for chemical laboratories. Monomodal microwave equipment has overcome the uncertainties associated with domestic and multimodal microwave ovens, as it offers precise control of temperature and pressure, and the software provides simplified process monitoring and control, which results in accurate and reproducible reaction conditions. In many cases a simple transposition of a reaction mixture from conventional conditions to a microwave reactor is not possible. There are many factors to be taken into consideration, such as the dipole moments of the components of the reaction mixture, their dielectric relaxation time, the dielectric constant (or relative permittivity) ε', the dielectric loss ε'' (complexed permittivity), and tangent delta (δ, loss tangent).[13] Sucrose is soluble in protic solvents such as water, methanol, and ethanol and reasonably soluble in dipolar aprotic solvents such as pyridine, dimethylformamide (DMF), and dimethylsulfoxide (DMSO), which are suitable as nucleophilic substitution media. Both pyridine and DMF have comparatively high boiling points (pyridine 115 °C and DMF 153 °C) and a dipolarity suitable for the absorption of microwave radiation,

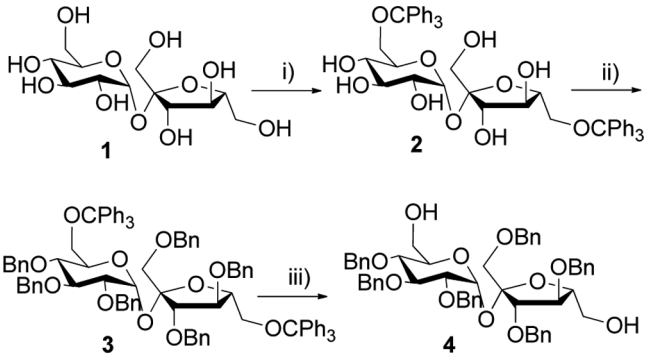
which is why these solvents were used as reaction media for all experiments where the substrate was sucrose. In these cases, room-temperature saturated solutions were used, 1 g sucrose/15 mL pyridine or DMF. In the case of sucrose functionalization the elimination of solvent is not recommended as this leads to significantly lower yields because of overheating.

The energy transfer in a microwave-assisted reaction is incredibly rapid, and only by programming temperature control could the decomposition of the substrates be avoided and comparatively good yields of product obtained in short reaction times. By this method, as the temperature reaches the set value, the power is reduced so that the reaction mixture does not overshoot. It then stays at a lower level to maintain the set temperature throughout the entire reaction. The maximum temperature that the reaction mixtures were allowed to reach was chosen in every case according to the boiling points and stabilities of the reagents and solvent. The maximum irradiation power was set to 300 W for all the reactions in order to obtain comparable results, and the reaction time was optimized with a view to the best yield. In some cases (for example, the formation of compound **4** by method IV), an attempt to increase the yields by increasing the reaction times lead to partial hydrolysis of the benzyl groups and the formation of several side products; while at lower reaction times and/or lower temperatures the conversion of the starting material was not complete.

Synthesis of 1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose 4 Under Microwave Irradiation via Di-trityl Derivative, Method I

To access the primary hydroxyls of sucrose selectively, the first step was always blocking of one, two, or all three primary positions of sucrose with bulky substituents. The groups most utilized for this purpose are triphenylmethyl- (trityl-, Tr) and *tert*-butyldiphenylsilyl- (TBDPS) chlorides. The advantage of using TrCl over TBDPSCl is that it is a relatively cheap reagent, but, on the other hand, it is thermally unstable and not selective for mono-protection. *tert*-Butyldimethylsilyl chloride (TBDMSCl) can also be used,[14] but as it is smaller than TBDPSCl, it is less selective. This reagent is very useful for distinguishing between the 1′ and 6,6′-positions of sucrose.[15]

Methods to prepare 6,6′-di-*O*-tritylsucrose **2** have been examined by Mach et al.[16] It has been used as a starting compound in many synthetic sequences. The optimized method to improve the yield up to 50% was to dissolve the sucrose in pyridine at room temperature, and to the saturated homogeneous solution add 2.2 equiv of trityl chloride in one portion, followed by stirring at rt for 48 h. Transposition of this reaction to the microwave reactor allowed us to increase the yield of crude product to 75% after only 5 min of irradiation (Scheme 1, Table 1). Although the reaction proceeded smoothly and with good yield, we found it very difficult to purify the resulting reaction mixture by conventional silica-gel chromatography. The product **2** was always mixed with triphenylmethanol, as evidenced by integration of the aromatic signals (7.00–8.00 ppm) of the proton NMR spectra. We have also tried the reported improved procedure,[17] consisting of a series of extractions and crystallization, but did not obtain pure compound. That is why the yield reported is to be considered of crude product, which was not isolated in pure form. We found this to be a great disadvantage of the method, as it was not



Method I

Scheme 1. Preparation of 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose **4** by method I. (i) TrCl, DMAP, pyridine, 90 °C, 300 W, 5 min, 75% (crude); (ii) BnBr, NaH, DMF, 145 °C, 300 W, 10 min, 72% (crude); and (iii) I_2, CH_2Cl_2/MeOH, 40 °C, 300 W, 20 min, 59%.

possible to prove the rate of substitution by NMR spectroscopy and the compounds mono-, di-, and tri-trityl sucroses can be distinguished only by thin-layer chromatography (TLC) using reliable reference samples.

The crude compound **2** was then benzylated using BnBr/NaH in DMF, leading to compound **3** in 10 min (145 °C, 300 W). Again **3** was isolated as a crude product with 72% yield (see ^{1}H NMR in the Supporting Information), which was somewhat lower than that obtained under conventional conditions (84%), probably because of the instability of the trityl group under microwave irradiation.

Table 1. Reaction conditions and experimental results under microwave heating compared with conventional conditions

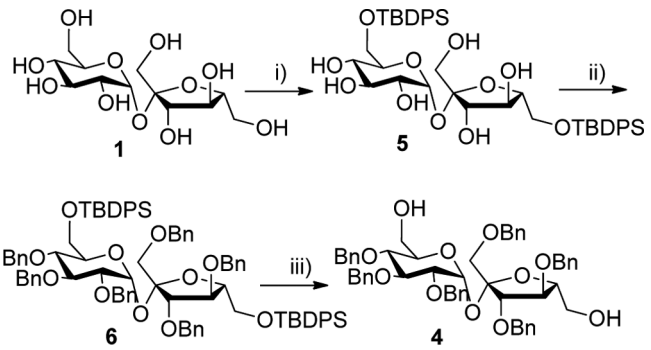
Method	Compound	Reagents, solvents	MW conditions, reaction time, yield, ref.	Conventional conditions, reaction time, yield, ref.
I	**2**	TrCl, DMAP, Pyr	90 °C, 300 W, 5 min, 75% (crude)	rt, 48 h, 50% (crude)[11]
	3	BnBr, NaH, DMF	145 °C, 300 W, 10 min, 72% (crude)	rt, 5 h, 84% (crude)[11]
	4	I_2, CH_2Cl_2/ MeOH	40 °C, 300 W, 20 min, 59%	reflux, 5 h, 58%[11]
II	**5**	TBDPSCl, Pyr	90 °C, 300 W, 5 min, 85%[5]	60 °C, 27 h, 78%[18]
	6	NaH, BnBr, DMF	145 °C, 300 W, 5 min, 50%[19]	rt, 2 h, 32%
	4	TBAF, THF	65 °C, 300 W, 5 min, 7%[19]	rt, 5 h, 65%
III	**7**	CBr_4, PPh_3, Pyr	90 °C, 300 W, 10 min, 76%[5]	70 °C, 2 h, 91%[22]
	8	BnBr, (NaH, KOH or Ag_2O), DMF	145 °C, 300 W, 15 min, 0%	rt, 2 h, 0%
	4	—	—	—
IV	**9**	CCl_4, PPh_3, Pyr	70 °C, 300 W, 10 min, 73%[5]	70 °C, 2 h, 65-75%[23]
	10	BnBr, KOH, DMF	145 °C, 300 W, 5 min, 14%	rt, 12 h, 77%[11]
	11	$Bu_4N^+CH_3COO^-$, toluene	105 °C, 300 W, 15 min, 59%	reflux (toluene), 2 h + rt, 12 h, 72%[11]
	4	MeONa, MeOH	50 °C, 300 W, 5 min, 32%	rt, 3 h, 82%[11]

Selective detritylation with iodine in dichloromethane/methanol required 20 min under microwave irradiation (40 °C, 300 W) to give **4** in a good yield (59% or 32% overall from sucrose).

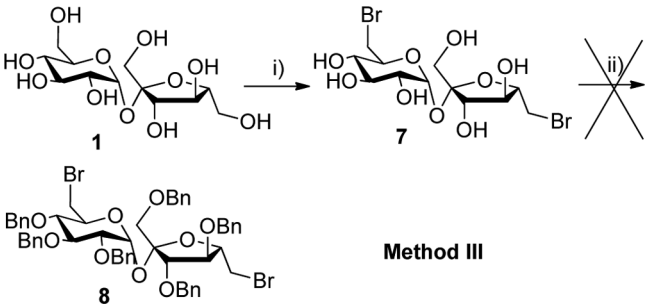
Synthesis of 1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose 4 Under Microwave Irradiation via Di-TBDPS Derivative, Method II

The introduction of *O*-*tert*-butyldiphenylsilyl group is the first step in many protection–deprotection sequences. When the silylation reaction of sucrose was performed with 3 molar equiv of *tert*-butyldiphenylsilyl chloride,[18] the crystalline 6,6′-di- and 6,l′,6′-tri-*O*-*tert*-butyldiphenylsilyl sucroses in yields of 78% and 18.7%, respectively, were obtained. This reaction was complete in 5 min under microwave irradiation (90 °C, 300 W) using 2.2 equiv of TBDPSCl in dry pyridine, to afford (85%) of 6,6′-di-*O*-*tert*-butyldiphenylsilylsucrose **5** (Scheme 2, Table 1).[5] The disilylated sucrose **5** was then perbenzylated using BnBr/NaH in DMF leading to compound **6** in 5 min (50%, 150 °C, 300 W). Chemoselective deprotection of the silyl group, using TBAF in THF, led to 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose **4** in a good 70% yield (30% overall from sucrose).[19]

All the intermediate compounds of this synthetic sequence have been readily isolated in pure form and their structures have been proven by conventional spectroscopic methods. The advantage of the method is the possibility to perform the reactions with the crude intermediate products, thus saving time and solvents. The disadvantage was the significantly lowered yield of the benzylation step, due to the relative instability of the *tert*-butyldiphenylsilyl protecting groups under the basic reaction conditions, which led to the formation of 6′-*O*-*tert*-butyldiphenylsilyl-1′,2,3,3′,4,4′,6-hepta-*O*-benzylsucrose (typically about 20%) and octabenzylated sucrose (about 15%) as by-products for this step. A strategy to improve the yield was to prepare the reaction mixture, perform the reaction, and do the workup as fast as possible.



Scheme 2. Preparation of 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose **4** by method II. (i) 2.2 eq TBDPSCl, DMAP, pyridine, 90 °C, 300 W, 5 min, 85%; (ii) BnBr/NaH, DMF, 145 °C, 300 W, 5 min, 50%; (iii) TBAF, THF, 65 °C, 300 W, 5 min, 70%.



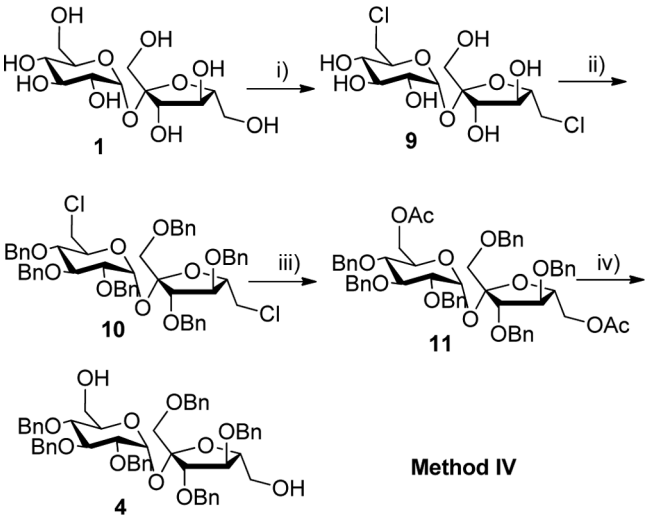
Scheme 3. (i) CBr_4, PPh_3, pyridine, 90 °C, 300 W, 10 min, 76%; (ii) BnBr, (NaH, KOH, or Ag_2O) $Bu_4N^+Br^-$, DMF, rt, 2 h or 145 °C, 300 W, 15 min, no product.

Synthesis of 1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose 4 Under Microwave Irradiation via 6,6′-Dibromo-6,6′-dideoxysucrose, Method III

The compound 6,6′-dibromo-6,6′-dideoxysucrose **7** is another bifunctionalized sucrose derivative, readily prepared under microwave irradiation and used as starting material in various synthetic sequences.[5,20] Unfortunately, being a very good leaving group, the dibromide proved very unstable under the basic benzylation conditions and we were not able to obtain the product **8** (Scheme 3, Table 1).

Synthesis of 1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose 4 Under Microwave Irradiation via 6,6′-Dichloro-6,6′-dideoxysucrose, Method IV

As the reaction sequence of method III was not successful, a starting compound with a poorer leaving group, 6,6′-dichloro-6,6′-dideoxysucrose **9**,[5,21]



Scheme 4. Preparation of 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose **4** by method IV: (i) CCl_4, PPh_3, pyridine, 70 °C, 300 W, 10 min, 73%; (ii) BnBr, KOH, $Bu_4N^+Br^-$, DMF, rt, 12 h, 77%; (iii) $Bu_4N^+CH_3COO^-$, toluene, 105 °C, 300 W, 15 min, 59%; and (iv) MeONa, MeOH, 50 °C, 300 W, 5 min, 32%.

was used (Scheme 4, Table 1). Perbenzylation of the remaining six hydroxyl groups was performed using potassium hydroxide as a base.[11] The attempt to perform this step under microwave irradiation (145 °C, 300 W, 5 min) led to a yield of **10** only 14%, and we were not able to optimize it to a greater value. Thus it was performed under conventional conditions, as previously described.[11] Subsequent reaction with tetrabutyl-ammonium acetate afforded the corresponding 6,6′-di-*O*-acetyl derivative **11** in 59% under microwave irradiation, which was followed by deacetylation to give **4**. The last step also did not afford better yield under microwave irradiation: 32% versus 82% at room temperature.

CONCLUSIONS

Four methods previously described in the literature for the synthesis of the key intermediate 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose **4** have been examined under microwave irradiation. The most reliable method was the reaction sequence starting from 6,6′-di-*O*-*tert*-butyldiphenylsilylsucrose **5** (method II). From **4**, various bifunctional derivatives such as esters and ethers substituted chemoselectively at 6 and 6′-position of sucrose could be obtained in good yields. The microwave-assisted protocols described here resulted in significant reduction of time (from 2–48 h to 5–20 min) and energy, and about a 50% reduction in the amount of solvents used, compared with conventional methods.

EXPERIMENTAL

Reagents and solvents were purified before use.[24] Solvents used as reaction media (pyridine, DMF, THF, toluene, CH_3OH, and CH_2Cl_2) were freshly distilled. The reactions under microwave irradiation were performed in open flasks equipped with a temperature control sensor and under magnetic stirring using a monomodal microwave reactor MicroSynth Labstation (MileStone, USA). This synthesizer has a single-mode cavity with temperature and pressure control. In this way, temperature runaway and explosion risks are avoided. The reaction conditions are expressed as a function of the reaction temperature and not the magnetron power. NMR spectra were recorded at 400 MHz in $CDCl_3$ or DMSO-d_6, with chemical shift values (δ) in ppm downfield from TMS (0 ppm) or the residual solvent peak of DMSO (2.50 ppm). The signals were assigned with the aid of distortionless enhancement polarization transfer (DEPT), correlation spectroscopy (COSY), and heteronuclear multiple quantum correlation (HMQC) experiments. Optical rotations were measured at 20 °C on an AA-1000 polarimeter (0.5 dm cell) at 589 nm. The concentrations (c) are expressed in $g/10^2$ mL. Melting points were determined with a capillary apparatus, and are uncorrected. Fourier transform infrared (FTIR) spectra were recorded on Perkin-Elmer Spectrum BX apparatus in KBr dispersions (solids) or on NaCl windows (liquids). Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) spectra were recorded on an Ultraflex III TOF/TOF Bruker equipped with laser type smartbeam and detecting system fast MCP-Gating. The synthesized compounds were purified by flash column chromatography using Merck silica gel 60 (230–400 mesh).

6,6′-Di-*O*-triphenylmethylsucrose, 2[11]

Sucrose (1.00 g, 2.92 mmol) was dissolved in pyridine (15 mL). DMAP (4 mg, 0.03 mmol) and TrCl (1.84 g, 6.61 mmol) were added. The mixture was placed in the microwave cavity and subjected to microwave irradiation of max 300 W at constant temperature of 90 °C for 5 min. The solvent was then evaporated at reduced pressure and the residue was chromatographed using hexane–ethyl acetate (EtOAc), 1:2, and then EtOAc–acetone-H_2O (10:10:1) to afford crude **2** as a white solid (2.42 g, 75%), mp 98–100 °C; lit.[11] mp 99–102 °C. $[\alpha]_D^{20} + 36.8$ (*c* 1.1, CH_3OH); lit.[11] $[\alpha]_D + 38.7$ (*c* 1.09, CH_3OH). The compound was identical in all respects with the substance previously described in the literature.[11]

1′,2,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-di-*O*-triphenylmethylsucrose, 3[11]

Sodium hydride, NaH (60% suspension in oil, 94 mg, 2.34 mmol) was added carefully at 0 °C to a stirred solution of **2** (200 mg, 0.24 mmol) in DMF (5 mL). After 20 min, benzyl bromide (12 equiv., 501 mg, 2.93 mmol) was added dropwise over 15 min. The reaction mixture was placed in the microwave cavity and subjected to microwave irradiation of max 300 W at constant temperature 145 °C for 10 min. TLC (EtOAc–acetone–H_2O, 10:10:1) showed that the starting material had been consumed. The mixture was poured into cold H_2O (20 mL) and the product was extracted with diethyl ether (4 × 15 mL). The combined organic layers were washed with H_2O (2 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was chromatographed (hexane–EtOAc, 10:1, then 5:1) to give compound **3** as a colorless solid. Yield 240 mg (72%), mp 97–100 °C; no report in lit. $[\alpha]_D^{20} + 17.6$ (*c* 0.8, $CHCl_3$); lit.[11] $[\alpha]_D + 20.6$ (*c* 1.0, $CHCl_3$). The compound was identical in all respects with the substance previously described in the literature.[11]

1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose, 4[19]

Method I. 6,6′-Di-*O*-trityl-1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (**3**, 1.00 g, 0.73 mmol) was dissolved in dichloromethane–methanol (1:3, 20 mL) to which iodine (185 mg, 0.73 mmol) was added; then the mixture was placed in the microwave cavity and subjected to microwave irradiation of max 300 W at constant temperature 40 °C for 20 min. A 10% aqueous solution of sodium thiosulfate was added until the mixture became colorless (60 mL), and the product was extracted with diethyl ether (4 × 30 mL). The combined organic extracts were washed with water and brine, dried, and concentrated. Chromatography (hexane–EtOAc, 3:2) of the residue afforded **4** as a colorless oil (380 mg, 59%), $[\alpha]_D^{20} + 37.6$ (*c* 0.9, $CHCl_3$); lit.[16] $[\alpha]_D + 40.8$ (*c* 1.0, $CHCl_3$). The compound was identical in all respects with the substance previously described in the literature.[11,19]

1′,2,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-dichloro-6,6′-dideoxysucrose, 10[11]

To a stirred solution of 6,6′-dichloro-6,6′-dideoxysucrose **9** (1.00 g, 2.63 mmol) in DMF (15 mL) was added powdered KOH (1.33 g, 23.7 mmol), tetrabutylammonium bromide (60 mg), and benzyl bromide (4.06 g, 2.82 mL, 23.7 mmol), and the

mixture was placed in the microwave cavity and subjected to microwave irradiation of max 300 W at constant temperature 145 °C for 5 min. The mixture was then partitioned between water (100 mL) and ether (100 mL); the organic phase was separated, washed with water, dried, and concentrated; and the residue was chromatographed (hexane–EtOAc, 7:1) to afford **10** as a colorless oil (340 mg, 14%), $[\alpha]_D^{20} + 31.5$ (*c* 0.9, $CHCl_3$); lit.[11] $[\alpha]_D + 32.0$ (*c* 1.0, $CHCl_3$). The compound was identical in all respects with the substance previously described in the literature.[11]

6,6′-Di-*O*-acetyl-1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose, 11[11]

Tetrabutylammonium acetate (3.25 g, 10.8 mmol) was added to a solution of **10** (500 mg, 0.54 mmol) in toluene (50 mL), and the mixture was placed in the microwave cavity and subjected to microwave irradiation of max 300 W at constant temperature 105 °C for 15 min. After concentration, the residue was dissolved in CH_2Cl_2 (50 mL), the solution was washed with water (3 × 50 mL), and the aqueous phase was extracted with CH_2Cl_2(2 × 25 mL). The organic phases were combined, dried, concentrated, and chromatographed (hexane–EtOAc, 3:1) to give **11** as a colorless oil (310 mg, 59%). $[\alpha]_D^{20} + 49.2$ (*c* 1.0, $CHCl_3$); lit.[11] $[\alpha]_D + 50.6$ (*c* 1.0, $CHCl_3$). The compound was identical in all respects with the substance previously described in the literature.[11]

1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose, 4[19]

Method IV. Compound **11** (500 mg, 0.52 mmol) was dissolved in methanol (40 mL) containing catalytic amounts of sodium methoxide, and the mixture was placed in the microwave cavity and subjected to irradiation of max 300 W at constant temperature 50 °C for 5 min. After concentration, the residue was chromatographed (hexane–EtOAc, 1:1) to give colorless oil (0.15 g, 32%), which was identical in all respect with the previously described substance **4** (see method I).

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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