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Sucrose Chemistry:
Fast and Efficient Microwave-
Assisted Protocols for the Generation
of Sucrose-Containing Monomer Libraries

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1. Introduction

Sucrose is a carbohydrate feedstock of low molecular weight which is ubiquitous in its availability and is of relatively low cost (Lichtenthaler and Mondel, 1997). The potential value of sucrose as a raw material has been recognized for many years and has been the subject of considerable research. The quest for novel, sustainable, but also structurally robust materials is gaining momentum as the pressure on our environment is building up and the progressive changeover of the chemical industry to renewable feedstock for their raw materials emerges as an inevitable necessity. Although extensive work has been done on the synthesis of glycopolymers, more research efforts are needed to bridge the conceptual, technological and economical gap between fossil hydrocarbons and renewable carbohydrates (Khan, 1984).

Sucrose is a particularly appropriate material for use in the formation of many products of commercial significance produced currently from petroleum-based materials, because: it is a naturally occurring, relatively abundant renewable resource; it is polyfunctional, with three reactive primary hydroxyl groups that can be readily and selectively derivatized; it is a 1-2′ linked disaccharide and therefore a nonreducing sugar and thus it does not have the potential for the wide variety of reactions that reducing sugars have; it is a naturally occurring carbohydrate, therefore products based on it are potentially biocompatible and biodegradable (Davis and Fairbanks, 2002).

As part of a program directed toward the valorization of sucrose by incorporating it into polymers, its conversion to natural compounds, and its possible application as a chiral auxiliary in selective asymmetric cycloaddition (Lichtenthaler and Peters, 2004), we needed to obtain derivatives of sucrose which could be functionalized easily and selectively at the primary hydroxyl groups (Fig. 1) (Jarosz and Mach, 2002). For this, the development of short and easy routes for the preparation of larger quantities of these target molecules was necessary.
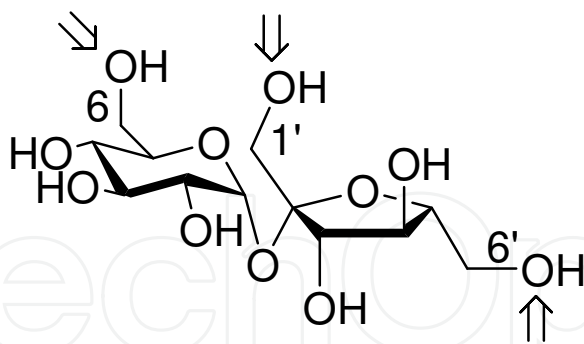
Fig. 1. The primary hydroxyl groups in the sucrose molecule can be selectively functionalized.

A high degree of regioselectivity can be achieved by the enzymatic approach (Patil et al., 1991; Potier et al., 2000), although some disadvantages and limitations can be found in the use of enzymes (low stability of the enzymes in organic solvents or the correct choice of reagents for introducing the unsaturation, (Chen and Park, 2000).

The functionalization of carbohydrates normally involves various protection-deprotection steps, which take a lot of experimental time (Jarosz and Mach, 2002). In order to access selectively specific positions with nonselective reagents, the first step would always be blocking of one, two, or all three primary positions of sucrose with bulky substituents. The groups most utilized for this purpose are triphenylmethyl- (trityl-) (Mach et al., 2001) and *tert*-butyldiphenylsilyl- (TBDPS) chlorides. The advantage of using trityl chloride over TBDPSCl is that it is a relatively cheap reagent, but unfortunately, it is not selective for mono-protection. Thus, the first step in many protection-deprotection sequences to obtain valuable monofunctionalized compounds often consists of a regioselective silylation of the 6'-hydroxyl group of the sucrose (Barros et al., 2000a; Barros et al., 2004b; Crucho et al., 2008) using 1.1 equiv. of *tert*-butyldiphenylchlorosilane (TBDPSCl) in dry pyridine. The methods have been described for sucrose first by Karl et al.,(Karl et al., 1982) to obtain a 49 % yield, and later (Barros et al., 2004b) optimized to 85 % by closely following the reaction by TLC and stopping it when di-*O*-TBDPS sucrose first appeared as a less polar product. A similar strategy has been applied to obtain 6,6'-di-*O*-TBDPS-sucrose, where 2.2 eq TBDPSCl were used (Karl et al., 1982). With the 6 and 6' positions blocked, regioselective access to the 1'-hydroxyl was gained, and the compound 1'-bromo-1'-deoxy-6,6'-di-*O*-TBDPS-sucrose has been reported (Andrade et al., 2007).

The first publications from our group on this topic (Barros et al., 2000a; Barros et al., 2000b) were directed to selective protection-deprotection of silyl ethers of sucrose, based on the fact that the primary alcohol groups are more reactive than the secondary and that between the primary hydroxyls there is a relatively well defined reactivity (Barros et al., 2001). Thus, 6'- or 1'-OH free heptabenzoyl sucrose derivatives (Fig. 2 and 6) have been obtained via a short sequence (three to five steps from sucrose) with good overall yields. The flexibility of this pathway allowed the facile exchange of the protecting groups, as has been shown by the preparation of the heptaacetate and heptabenzyl homologues, and made possible the selective preparation of several monohydroxy sucrose esters or ethers (Fig. 2).
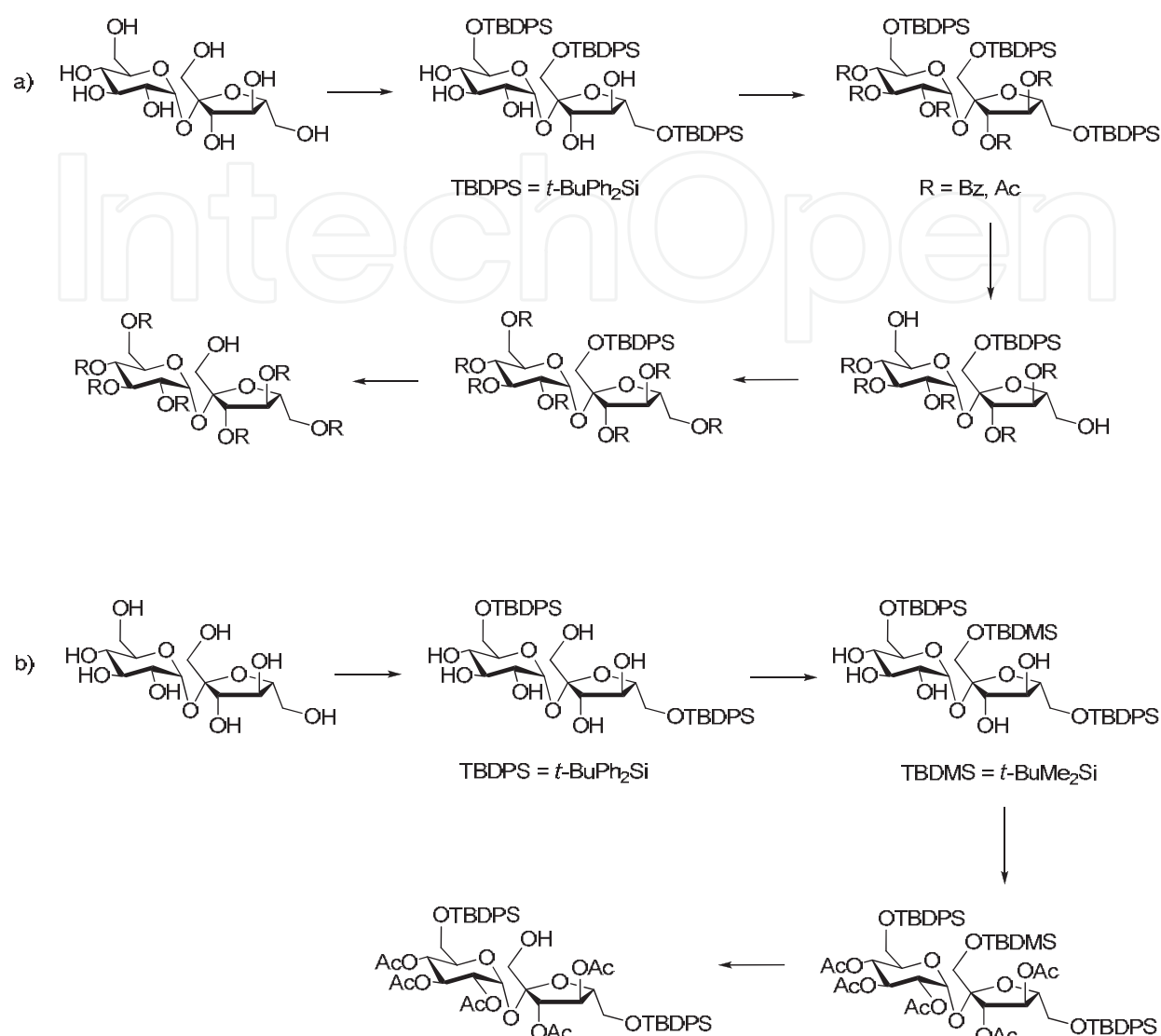
Fig. 2. Access to the 1'-position of the fructose moiety: a) via selective *O*-desilylation, 5 steps, 66 % overall yield (Barros et al., 2000b); b) via selective deprotection of *tert*-butyldimethylsilyl ether, 30 % overall yield (Barros et al., 2000a).

The potential applications of these compounds are numerous and thus several types of reactions involving the primary positions have been studied and various novel compounds prepared – by galloylation, three monogalloyl sucroses with antioxidant activity were prepared (Barros et al., 2000a); *O*-silyl protected sugars have been converted into their corresponding formates using the Vilmeier-Haack complex (Andrade and Barros, 2004); using Wittig olefination, branched-chain olefinic compounds have been obtained (Andrade et al., 2007), and their application as chiral auxiliaries in 1,3-dipolar cycloaddition to azides has been reported (Andrade and Barros, 2009). With the aim of developing cleaner and faster technologies, the latter two methods have been carried out using microwave-assisted synthesis (Fig. 3, 4).
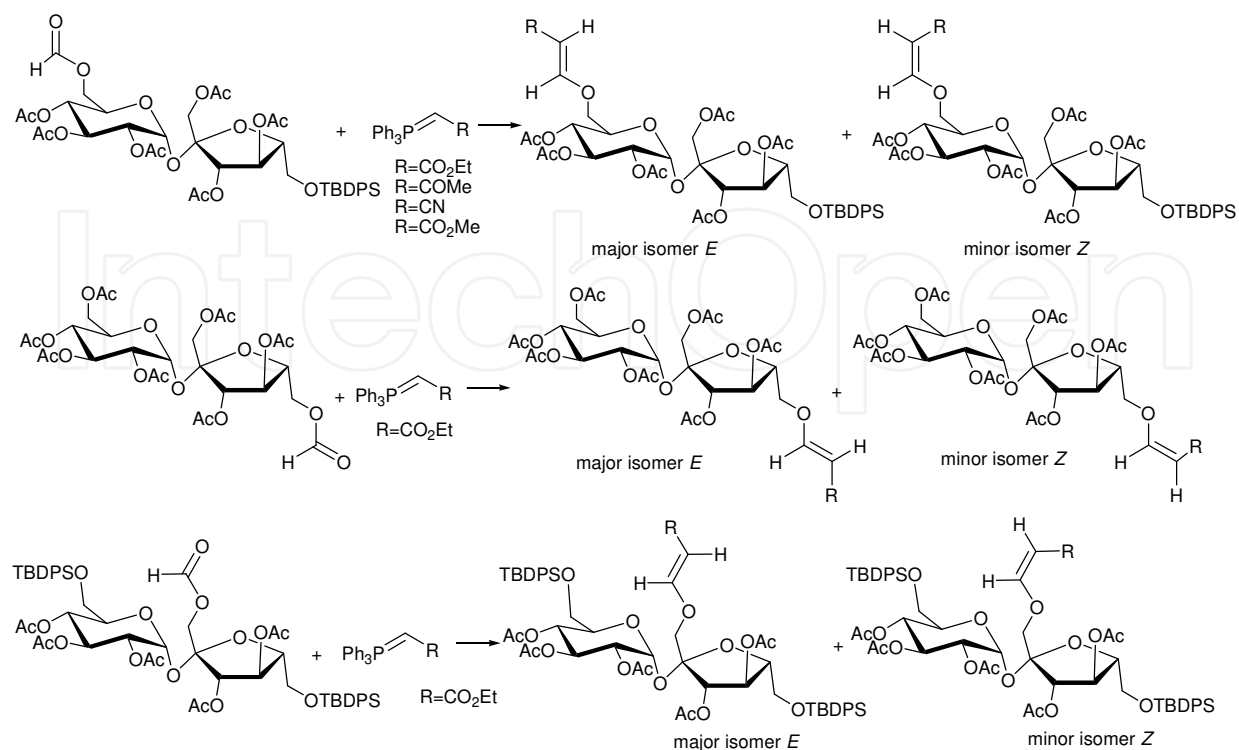
Fig. 3. Microwave assisted selective synthesis of sucrose derivatives containing unsaturated systems by Wittig reaction.
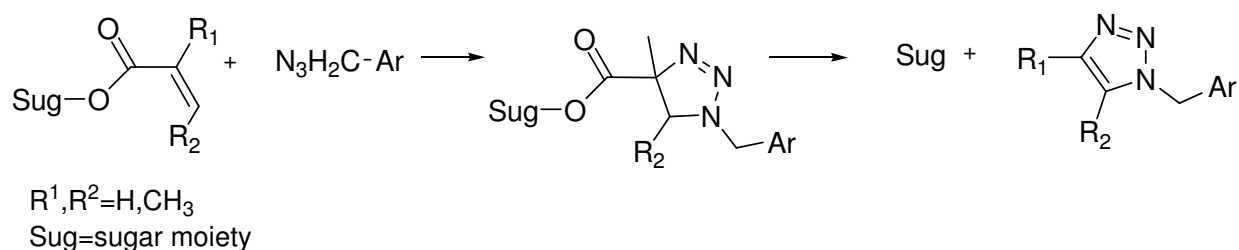

$R^1, R^2 = H, CH_3$
Sug = sugar moiety

Fig. 4. Microwave assisted 1,3-dipolar cycloaddition of vinylic sugars with aryl azides.

Petrochemical derived polymers (such as polystyrene), functionalized with sugar, to form biodegradable polymers is a recently discovered application of a sugar linked synthetic polymer (Galgali et al., 2002). The class of sugar based polymers, generally known as poly(vinylsaccharide)s, has also been investigated for a variety of applications, particularly in the biomedical field (Carneiro et al., 2001; Kobayashi et al., 1985). The most widely used method for the synthesis of poly (vinylsaccharide)s was based on the free radical polymerizations of vinyl sugars (Klein et al., 1990). An extensive review of the preparation and applications of this type of polymers is available (Varma et al., 2004). Kobayashi (Kobayashi, 2001) has described various applications of glyconjugate polymers in the biological and biomedical fields. Synthetic carbohydrate-based polymers having pendant sugar residues are of great interest, not only as simplified models for biopolymers bearing oligosacharides, but also as artificial glycoconjugates in biochemistry and medicine.

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The introduction of sugars into polymeric molecules can bestow new properties, such as increased polarity, chirality, biodegradability, and biocompatibility. Sucrose-containing polymers, having a polyvinyl backbone and pendant sucrose moieties, have been obtained by polymerization or copolymerization of sucrose derivatives – esters, ethers, and acetals, bearing a carbon-carbon double bond (Fig. 5), (Fanton et al., 1992; Ferreira et al., 2000; Jhurry et al., 1992; Patil et al., 1991). The monomers have been prepared either by multistep synthesis, leading to defined compounds and subsequently a well-defined polymerization processes (Fig. 6,7), (Barros et al., 2004b; Barros and Petrova, 2009; Barros et al., 2007; Barros and Sineriz, 2002; Crucho et al., 2008), or by direct functionalization of unprotected sucrose, leading to mixtures of isomers and therefore to more complex polymers (Barros et al., 2010b).

A number of monomers has been synthesized from sucrose during the last decades, as presented in Fig. 5. Nonselective derivatization of free sucrose to provide "statistical" mixtures that might find industrial applications were not of interest since undefined polymeric structures result. Also, the di- and tri- substituted derivatives were not of interest, as they result in cross-linked networks.

The first selectively obtained monomer described was the substituted derivative at the three primary positions, then there appeared substituted or hydrolized isopropylidene derivatives with free or acetylated hydroxyl groups, which were also a mixture of 2 isomers (Fanton et al., 1992). To the best of our knowledge, mono-unsaturated sucrose esters at the 1'-position were selectively obtained only with the aid of enzymes (Fig. 5) (Dordick et al., 1994; Potier et al., 2000).
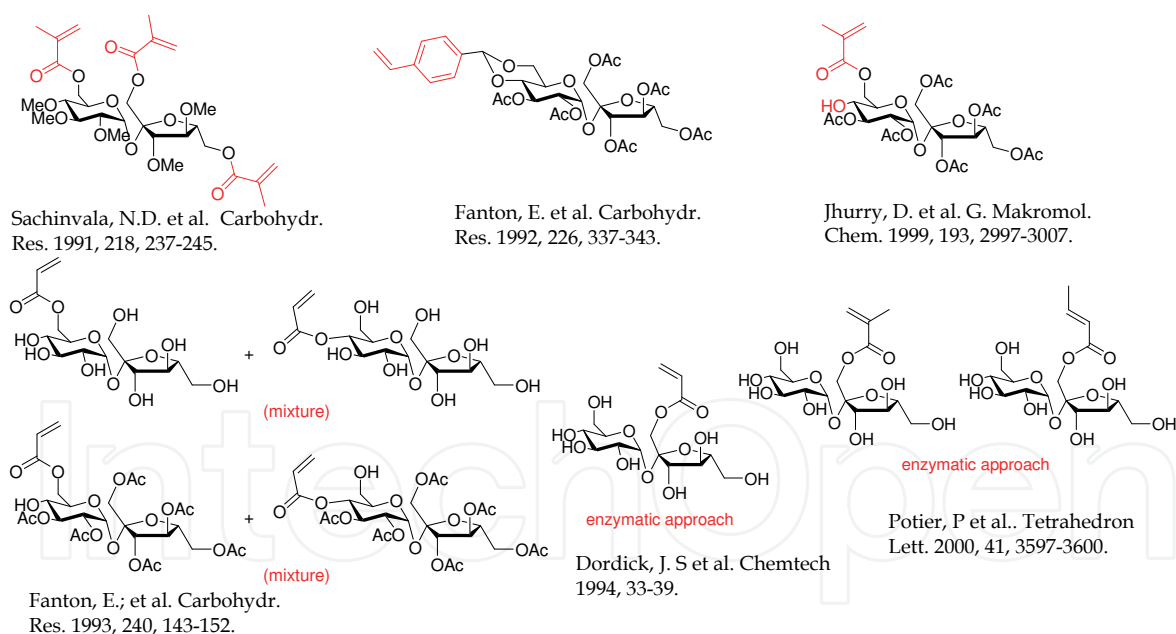

Fig. 5. Structures of some selectively obtained sucrose monomers.

The direct transformation of unprotected sucrose in the context of the preparation of derivatives of industrial interest is a challenging task (Queneau et al., 2004). In general, it is accepted that bulky substituents like *tert*-butyl-di-phenylsilyl (TBDPS), are introduced at the primary positions in the order 6-OH ≈ 6'-OH > 1'-OH (Lichtenthaler and Peters, 2004). Since sucrose has eight chemically active hydroxyl groups, regioselective derivatization is important in the selective synthesis of sucrose-containing linear polymers (Barros and Petrova, 2009; Barros et al., 2007; Barros et al., 2010a) and other new

compounds. The route to selective derivatization of the 6'-position of the sucrose, developed in our laboratory (Barros et al., 2004a; Barros et al., 2000a), allowed us to obtain the fully benzylated sucrose with only the 6'-hydroxyl unprotected **4** (Fig. 6) in three steps from sucrose and 58 % overall yield. We have prepared several unsaturated sucrose esters and ethers from this intermediate (Fig. 7). These monomers could be converted into pure linear polymers, avoiding the formation of mixtures of di- and higher substituted unsaturated esters, which results in cross-linked polymers (Chen and Park, 2000). Saccharide containing synthetic polymers have attracted great attention because of their potential as biotechnological, pharmacological, and medical materials (Varma et al., 2004).
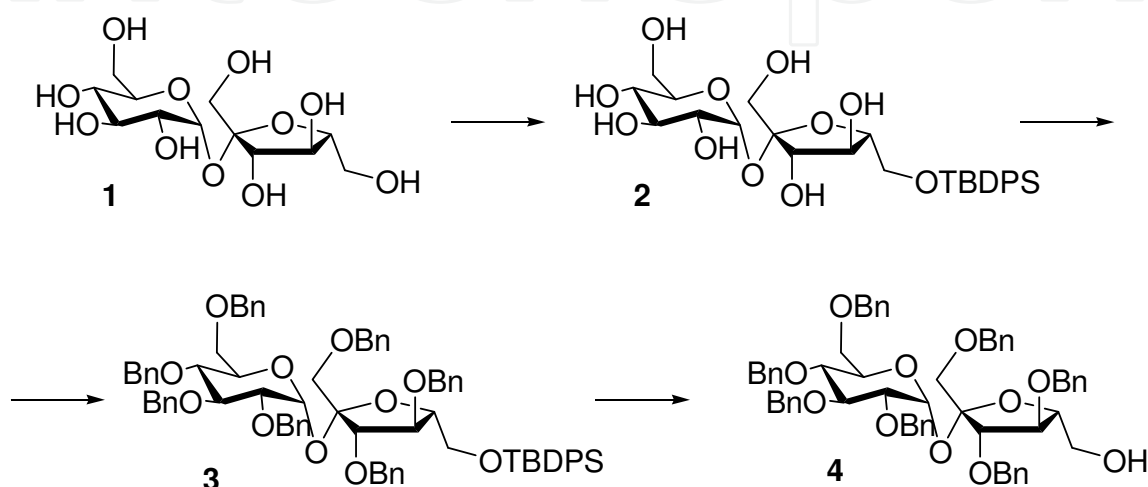

Fig. 6. Protection-deprotection sequence from sucrose.

Microwave-enhanced synthesis has been extended to almost all areas of chemistry (Lidstrom et al., 2001) with the exception of carbohydrate chemistry which has suffered a certain delay, as is testified by the limited number of applications (Corsaro et al., 2004; Soderberg et al., 2001). In particular, it had previously not been applied to sucrose chemistry, and the general opinion is that the method is hampered by competitive degradation of sucrose because of its thermal instability (Queneau et al., 2007). Herein, a method to overcome these limitations and to apply highly efficient and fast synthetic protocols for the synthesis of a series of sugar monomers under microwave irradiation is presented. These alternative protocols allowed a significant decrease of the reaction time to achieve useful sucrose derivatives, compared to other known routes (Barros et al., 2000a; Barros and Sineriz, 2002; Crucho et al., 2008). In all cases, a comparison was made between results obtained with conventional and microwave-assisted methods.

The key point to successful synthesis under microwave irradiation is to use proper equipment, especially designed for chemical laboratories. Monomodal microwave equipment has overcome the uncertainties associated with domestic microwave ovens, as it offers much more precise control over conditions of temperature and pressure than any previous technology and the software provides simplified process monitoring and control, which results in accurate, reproducible reaction conditions (www.milestonesrl.com). The energy transfer in a microwave-assisted reaction is incredibly quick, and only by programming temperature control the decomposition of the substrates has been avoided and comparatively high yields have been obtained in short reaction times. In this method, as

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the temperature reaches the input value, the power is reduced so that the reaction mixture does not exceed the set point. It then stays at a lower level in order to maintain the set temperature throughout the entire reaction.

The methods used to produce and purify carbohydrate derivatives are often tedious and complex, which makes the selective synthesis of sucrose derivatives laborious and new, simpler procedures are needed. In the development of new carbohydrates or in their transformations there is a need for faster and cleaner methods which can be provided by microwave heating. The library of microwave assisted protocols, presented in this chapter, allows significant reduction of time and energy and potential automatization of tedious multi-step synthesis.

Synthesis **2002**, *10*, 1407-1411.

J. Org. Chem. **2004**, *69*, 7772-7775.

Molecules **2008**, *13*, 762-770.

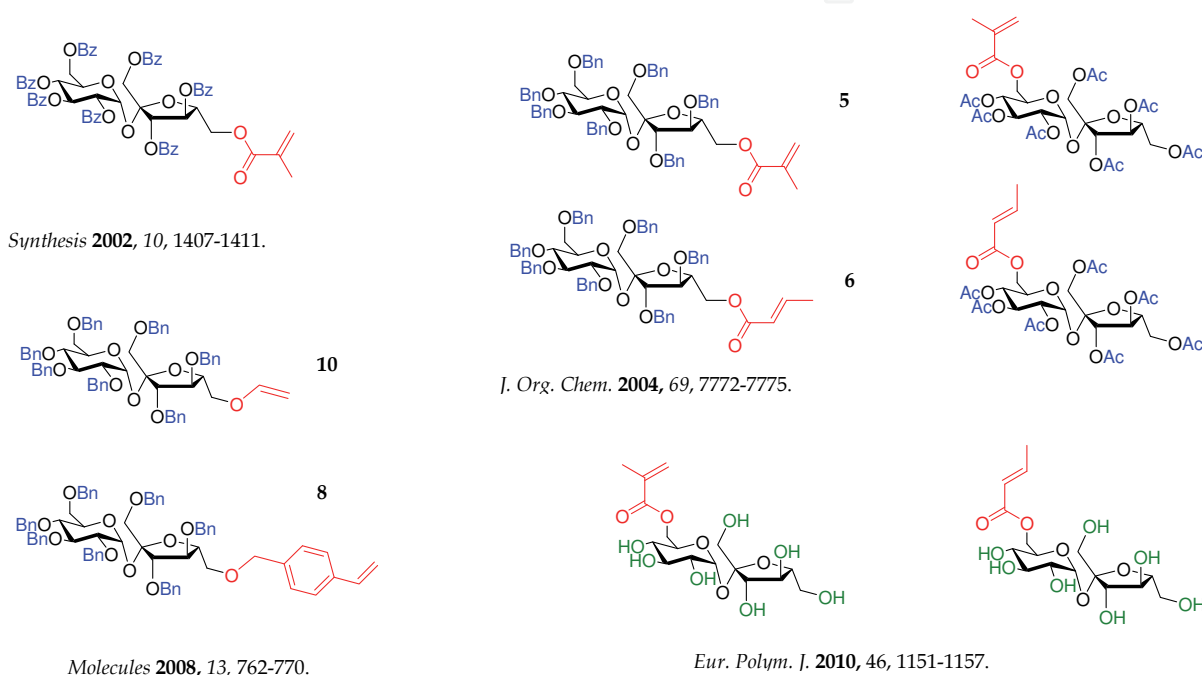*Eur. Polym. J.* **2010**, *46*, 1151-1157.

Fig. 7. Structures of some sucrose monomers synthesized in our group.

2. Methods

2.1 General

Reagents and solvents were purified by standard procedures (Perrin et al., 1980). Starting compound **4** (1′,2,3,3′,4,4′,6-hepta-*O*-benzyl sucrose) has been synthesized as previously reported (Barros et al., 2004b). NMR spectra were recorded at 400 MHz in CDCl$_3$, or D$_2$O, with chemical shift values (δ) in ppm downfield from TMS (0 ppm) or the solvent residual peak of D$_2$O (4.79 ppm) as internal standard. 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. FTIR spectra were recorded on Perkin-Elmer Spectrum BX apparatus in KBr dispersions. The yields are all isolated yields after silica gel chromatography. The reactions under microwave irradiation were performed using a monomodal microwave reactor MicroSynth Labstation (MileStone, USA)(www.milestonesrl.com) in open flasks equipped with temperature control sensor and magnetic stirring.
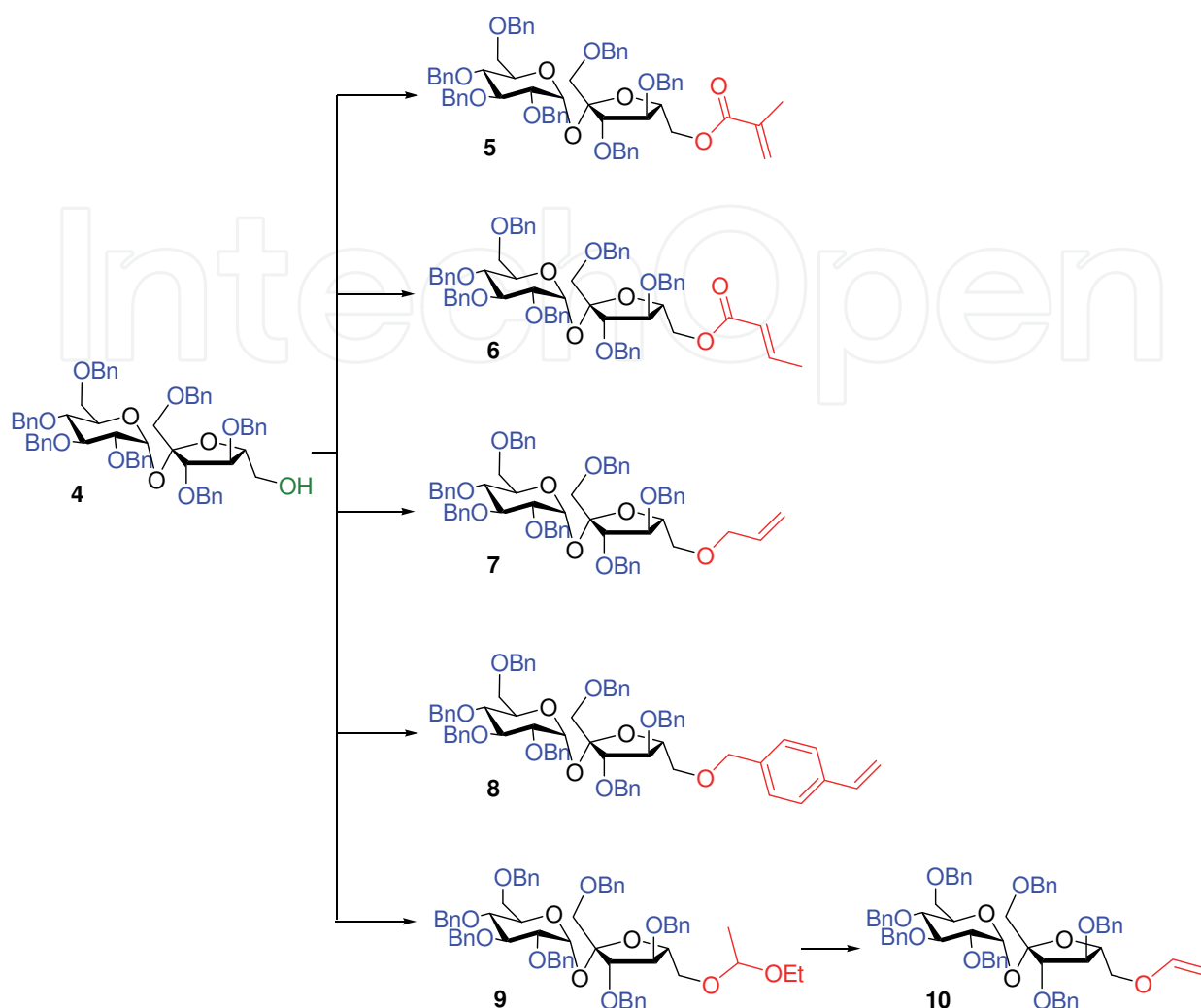
Fig. 8. Synthesis of benzylated sucrose monomers from **4**.

1′,2,3,3′,4,4′,6-Hepta-*O*-benzyl-6′-*O*-methacryloyl-sucrose (5)
and 1′,2,3,3′,4,4′,6-hepta-*O*-benzyl-6′-*O*-crotonyl-sucrose (6)

To a 0.1 M solution of **4** (500 mg, 0.514 mmol) in anhyd. CH_2Cl_2, Et_3N (130 mg, 1.286 mmol) and a catalytic amount of 4-DMAP was added. The mixture was cooled to 0 °C, and then 0.5 M solution of crotonic/ methacrylic anhydride (1.2 equiv.) in anhyd. CH_2Cl_2 was added. The reaction mixture was stirred at 0 °C for 10 min, and then placed in the microwave cavity and subjected to microwave irradiation (max 300W at constant temperature 35 °C) for 10 min. The mixture was diluted with more CH_2Cl_2 (40 ml) and washed with aq. 1.0 N HCl (8 ml), satd. aq. $NaHCO_3$, and dist. H_2O. The organic layer was dried (Na_2SO_4), and the solvent evaporated. Purification by flash column chromatography, eluent hexane-ethyl acetate, 5:1, yielded 0.273 g (51 %) of **5** and 0.348 g (65 %) of **6**.

5: $[\alpha]_D^{20}$ +46.9(*c* 1.2, $CHCl_3$); ${}^1H$ NMR ($CDCl_3$): δ 7.37-7.13 (m, 35H), 6.15 (d, *J* 3.6 Hz, 1H), 5.55 (d, *J* 3.6 Hz, 1H), 5.72 (d, *J* 3.7 Hz, 1H), 4.83 (d, *J* 11.0 Hz, 1H), 4.79 (d, *J* 11.0 Hz, 1H), 4.72-4.33 (m, 14H), 4.18 (d, *J* 12.0 Hz, 1H), 4.11 (dd, *J* 11.2, 5.5 Hz, 1H), 4.09-4.05 (m, 1H), 3.93 (t, *J* 9.2 Hz, 1H), 3.75-3.62 (m, 3H), 3.55-3.47 (m, 2H), 2.00 (s, 3H). Anal. Calcd for $C_{65}H_{68}O_{12}$: C, 74.98, H, 6.58. Found: C, 74.69; H, 6.88.

6: $[\alpha]_D^{20}$ +48.1 (*c* 1.3, CHCl$_3$); ^{1}H NMR (CDCl$_3$): δ 7.37-7.13 (m, 35H), 6.90 (dq, *J* 15.6, 6.8 Hz, 1H), 5.80 (d, *J* 15.6 Hz, 1H), 5.72 (d, *J* 3.7Hz, 1H), 4.83 (d, *J* 11.0 Hz, 1H), 4.79 (d, *J* 11.0 Hz, 1H), 4.72-4.33 (m, 14H), 4.18 (d, *J* 12.0 Hz, 1H), 4.11 (dd, *J* 11.2, 5.5 Hz, 1H), 4.09-4.05 (m, 1H), 3.93 (t, *J* 9.2 Hz, 1H), 3.75-3.62 (m, 3H), 3.55-3.47 (m, 2H), 1.75 (s, 3H). Anal. Calcd for C$_{65}$H$_{68}$O$_{12}$: C, 74.98; H, 6.58. Found: C, 74.74; H, 6.66.

1′,2,3,3′,4,4′,6-hepta-*O*-benzyl-6′-*O*-allyl sucrose (7)

Conventional synthesis

A solution of 1′,2,3,3′,4,4′,6-hepta-*O*-benzyl sucrose (**4**, 500 mg, 0.514 mmol) in DMF (6 mL) was added dropwise to a slurry of NaH (60% dispersion in mineral oil, 0.031 g, 0.77 mmol) in DMF (10 mL). The mixture was cooled to 0 °C in an ice bath and stirred with exclusion of moisture for 30 min. Allyl bromide (0.124 g, 1.03 mmol) was then added dropwise, the ice bath was removed and the reaction monitored by TLC (hexane-ethyl acetate, 5:1). When there was no more of the initial compound (2-3 hours), excess of the hydride was destroyed by careful addition of water, and the mixture was partitioned between water and ether (50 mL each). The organic phase was washed with water, dried, concentrated and the product **7** was isolated by column chromatography (5:1 hexane–EtOAc) as a colourless oil (0.312 g, 60%), which was in all aspects identical to the product obtained bellow.

Microwave synthesis

A solution of 1′,2,3,3′,4,4′,6-hepta-*O*-benzyl sucrose (**4**, 500 mg, 0.514 mmol) in DMF (6 mL) was added dropwise to a slurry of NaH (60% dispersion in mineral oil, 0.031 g, 0.77 mmol) in DMF (10 mL). The mixture was cooled to 0 °C in an ice bath and stirred with exclusion of moisture for 30 min, allyl bromide (0.124 g, 1.03 mmol) was then added dropwise, and the mixture was subjected to microwave irradiation (max 300W at constant temperature 145 °C) for 5 min. Excess of the hydride was destroyed by careful addition of water, the mixture was partitioned between water and ether (50 mL each), the organic phase washed with water, dried, concentrated and the product **7** was isolated by column chromatography (5:1 hexane–EtOAc) as a colourless oil (0.307 g, 59%), $[\alpha]_D^{20}$ +29.9 (*c* 1.1, CHCl$_3$). ^{1}H NMR (CDCl$_3$): δ 7.32 (m, 30H, Ar-H), 5.93 (m, 2H, H-1, C*H*-allyl group), 5.30 (dd, 2H, *J*$_{HA,HB}$ 17.3 Hz, C*H$_2$*-allyl group), 5.18 (t, 4H, *J*$_{3′,4′}$ 10.8 Hz, H-3′, H-4′, Ar-C*H$_2$*), 4.94 (t, 3H, *J*$_{3,4}$ 11.1 Hz, H-4, Ar-C*H$_2$*), 4.82 (dd, 3H, *J*$_{6A,6B}$ 10.9 Hz, H-6, Ar-C*H$_2$*), 4.72 (d, 1H, *J* 10.8 Hz, Ar-C*H$_2$*), 4.61 (d, 1H, *J* 10.8 Hz, Ar-C*H$_2$*), 4.44 (d, 4H, *J*$_{6′A,6′B}$ 7.7 Hz, H-6′, Ar-C*H$_2$*), 4.14 (dd, 1H, *J*$_{1,2}$ 5.7 Hz, *J*$_{2,3}$ 12.7 Hz, H-2), 4.03 (dd, 2H, *J*$_{CH2,CH}$ 5.4 Hz, *J*$_{CH2A,B}$ 11.2 Hz, OC*H$_2$*CH=CH$_2$), 3.70 (t, 1H, *J*$_{2,3,4}$ 10.4 Hz, H-3), 3.61 (m, 5H, H-1′, H-5 Ar-C*H$_2$*), 3.46 (m, 2H, H-5′, Ar-C*H$_2$*). ^{13}C NMR (CDCl$_3$): δ 138.6, 138.4, 138.2 (C$_q$ benzyl groups), 134.0 (*C*H allyl group), 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4 (C$_{Ar}$), 117.0 (*C*H$_2$, allyl group), 108.2 (C-2′), 102.7 (C-1), 84.7, 82.3, 77.9, 77.3, 77.0, 76.7 (C-2,3,3′,4,4′,5,5′), 75.7, 75.0, 74.8, 72.5, 70.3, 68.9 (C-1′,6,6′, O*C*H$_2$Ph, O*C*H$_2$CH=CH$_2$). Anal. Calcd for C$_{64}$H$_{68}$O$_{11}$: C, 75.87; H, 6.78. Found: C, 75.71; H, 6.86.

1′,2,3,3′,4,4′,6-hepta-*O*-benzyl-6′-*O*-vinylbenzyl sucrose (8)

To a solution of **4** (0.5 g, 0.514 mmol) in DMF (12.5 mL) was added NaH (0.07 g, 1.0 eq) at 0°C. After 20 min, 4-vinylbenzyl chloride (0.09 mL, 1.0 eq) was added, the ice-bath removed, and the reaction mixture was subjected to microwave irradiation (max 300W at constant temperature 145 °C) for 10 min. The reaction mixture was poured into cold H$_2$O (50 ml). The product was extracted with diethyl ether (4x30 ml), and the combined organic layers were washed with H$_2$O (2x20 ml), dried over Na$_2$SO$_4$ and concentrated. The residue was purified

by flash column chromatography on silica gel, eluent hex/EtOAc 3:1. Compound **8** was obtained as a light yellow oil (0.280 g, 50%); Rf 0.7 (hex/AcOEt 3:1); ^{1}H NMR (CDCl$_3$): δ 7.28-7.12 (m, 39H, Ar-H), 6.65 (dd, 1H, J 13.2, 8.2 Hz, PhCH=), 5.71- 5.66 (m, 2H, H-1, =CH$_{2trans}$), 5.20 (dd, 1H, J 10.8, 2.11 Hz, =CH$_{2cis}$), 4.86-4.35 (m, 16 H, H-5', CH$_2$-Ph), 4.22-3.84 (m, 4H, H-6'$_a$, H-6'$_b$, H-5, H-4', H-3), 3.71-3.25 (m, 7H, H-2, H-6$_a$, H-6$_b$, H-1'$_a$, H-1'$_b$, H-4, H-3'). ^{13}C NMR (CDCl$_3$): δ 138.9 (Ar-C), 138.6 (Ar-C), 138.2 (Ar-C), 138.0 (Ar-C), 137.9 (PhCH=), 136.8 (Ar-C), 136.5 (Ar-C), 128.3 (Ar-CH), 128.3 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 127.7 (Ar-CH), 127.6 (Ar-CH), 127.5 (Ar-CH), 126,2 (Ar), 113.7 (CH$_2$=), 104.6 (C-2'), 89.9 (C-1), 83.9 (C-5'), 82.4 (CH$_2$-Ph), 81.9 (C-3), 81.9 (C-4'), 79.8 (C-3'), 79.6 (C-5), 77.6 (C-2), 75.5 (CH$_2$-Ph), 74.8 (CH$_2$-Ph), 73.4 (CH$_2$-Ph), 73.0 (CH$_2$-Ph), 72.5 (CH$_2$-Ph), 72.2 (CH$_2$-Ph), 71.4 (C-6'), 71.2 (C-6), 70.6 (C-4), 68.4 (C-1'). Anal. Calcd for C$_{70}$H$_{72}$O$_{11}$: C, 77.18; H, 6.66. Found: C, 76.91; H, 6.78.

1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-(1-ethoxy)ethyl sucrose (9)

To a solution of **4** (1.00 g; 1.03 mmol) in dry CH$_2$Cl$_2$ (10 mL) were added PPTS (10 mg) and ethylvinyl ether (0.074 g; 1.55 mmol). The reaction mixture was subjected to microwave irradiation (max 300W at constant temperature 35 °C) for 10 min. NaHCO$_3$ (1 g) was added, stirred for 10 min more, filtered, concentrated and purified by flash column chromatography on silica gel 60 (0.04-0.06 mm), eluent: hex/EtOAc 3:1. Compound **9** was obtained as a light yellow oil (0.580 g, 54%); Rf 0.40 (hex/EtOAc 3:1); IR: ν$_{max}$ (CH$_2$Cl$_2$) 3088, 3040, 3030, 2976, 2897, 2867, 2000-1600, 1496, 1454, 1363, 1266, 1208, 1082, 1028, 736, 698 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 9.79 (qd, 1H, J 2.13 Hz, CH), 7.33-7.20 (m, 32H, Ar-H), 7.12-7.10 (m, 2H, Ar-H), 5.54 (d, 1H, J 2.5 Hz, H-1), 4.92-4.28 (m, 16H, CH$_2$-Ph, H-5' and H-3), 4.09-4.06 (m, 1H, H-6), 4.03-3.97 (m, 2H, H-4' and H-3'), 3.87-3.80 (m, 1H, H-6'), 3.73-3.63 (m, 4H, H-2, H-1' and OCH$_2$CH$_3$), 3.61-3.51 (m, 4H, H-5, H-1', H-6' and H-4), 3.48 (d, 1H, J 3.03 Hz, H-6), 2.20 (d, 1H, J 2.13 Hz, CHCH$_3$), 1.27-1.19 (m, 4H, CH$_2$CH$_3$). ^{13}C NMR(CDCl$_3$): δ 128.3 (Ph), 128.0 (Ph), 127.9 (Ph), 127.8 (Ph), 127.7 (Ph), 127.5 (Ph), 103.8 (C-2'), 91.1 (C-1), 83.6 (C-5'), 81.8 (C-3'), 81.2 (C-4'), 79.5 (C-3), 79.4 (C-5), 77.3 (C-2), 75.6 (CH$_2$-Ph), 74.9 (CH$_2$-Ph), 73.5 (CH$_2$-Ph), 73.4 (CH$_2$-Ph), 73.3 (CH$_2$-Ph), 72.9 (CH$_2$-Ph), 72.5 (CH$_2$-Ph), 71.3 (C-4), 71.2 (C-6'), 67.9 (C-1'), 61.2 (C-6), 60.6 (OCH$_2$CH$_3$), 20.0 (O$_2$CHCH3), 15.3 (OCH$_2$CH$_3$). Anal. Calcd for C$_{65}$H$_{72}$O$_{12}$: C, 74.69; H, 6.94. Found: C, 74.57; H, 7.08.

1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-vinyl sucrose (10)

To a solution of **9** (0.580 g, 0.555 mmol) in dry CH$_2$Cl$_2$ (7 mL) were added Et$_3$N (0.067 g, 0.666 mmol) and TMSOTf (trimethylsilyl trifluoromethanesulfonate) (0.148 g, 0.666 mmol) at 0°C. After 10 min it was allowed to warm to r.t. and subjected to microwave irradiation (max 300W at constant temperature 145 °C) for 5 min. The reaction mixture was neutralised with 1N NaOH (4 mL), and extracted with diethyl ether (3 x 20 mL). After drying and concentrating, it was purified by flash column chromatography on silica gel 60 (0.04-0.06 mm), eluent: hex/EtOAc 3:1. Compound **10** was obtained as a light yellow oil (0.166 g, 30%); Rf 0.5 (Hex/AcOEt 3:1); IR:ν$_{max}$ (CH$_2$Cl$_2$) 3088, 3064, 3030. 2909, 2869, 1737, 2000-1600, 1497, 1454, 1361, 1243, 1209, 1096, 910, 737, 698 cm^{-1}; ^{1}H NMR(CDCl$_3$): δ 7.31-7.26 (m, 35H, Ar-H), 7.16-7.14 (m, 1H, Ar-H), 6.49 (dd, 1H, J 10.73, 5.1 Hz, OCH=), 5.67 (d, 1H, J 2.6 Hz, H-1), 4.93 (d, 1H, J 8.16 Hz, CH$_2$-Ph), 4.83 (d, 1H, J 8.19 Hz, CH$_2$-Ph), 4.77 (d, 1H, J 8.16 Hz, CH$_2$-Ph), 4.68-4.38 (m, 12H, CH$_2$-Ph and H-5'), 4.20 (dd, 1H, J 10.8 and 1.41 Hz, =CH$_{2trans}$), 4.18-4.15 (m, 1H, H-3'), 4.10-4.05 (m, 1H, H-4), 4.01 (dd, 1H, J 5.1 and 1.44 Hz, =CH$_{2cis}$), 3.97-3.92 (m, 1H, H-4'), 3.86-3.81 (m, 1H, H-6), 3.75 (m, 1H, H-6), 3.64 (t, 1H, J 7.17 Hz, H-2), 3.56-3.49 (m,

3H, H-5, H-1' and H-6'), 3.42 (dd, 1H, J 7.1 and 1.2 Hz, H-6'). ^{13}C NMR (CDCl$_3$): δ 151.6 (OCH=), 128.3 (Ph), 128.3 (Ph), 127.9 (Ph), 127.8 (Ph), 127.7 (Ph), 127.6 (Ph), 127,5 (Ph), 104.6 (C-2'), 90.2 (C-1), 86.9 (=CH$_2$), 83.9 (C-5'), 81.8 (C-3'), 81.2 (C-4'), 79.5 (C-3), 79.4 (C-5), 77.3 (C-2), 75.6 (CH$_2$-Ph), 74.8 (CH$_2$-Ph), 73.4 (CH$_2$-Ph), 72.9 (CH$_2$-Ph), 72.6 (CH$_2$-Ph), 72.3 (CH$_2$-Ph), 71.0 (C-6'), 70.6 (C-4), 69.1 (C-1'), 69.5 (C-6). Anal. Calcd for C$_{63}$H$_{66}$O$_{11}$: C, 75.73; H, 6.66. Found: C, 75.67; H, 6.78.

General procedure for synthesis of sucrose monoesters 11-15

Conventional synthesis

Sucrose (1.00 g, 2.92 mmol) was dissolved in anhydrous DMF (50 ml), and triphenylphosphine (1.03 g, 3.90 mmol) and the corresponding acid (1.1 eq) were added at room temperature. After complete dissolution, the mixture was cooled to 0 °C and DIAD (diisopropyl azodicarboxylate) (95% in benzene, 0.82 ml, 3.90 mmol) was slowly introduced. TLC (ethyl acetate/MeOH/water 5/2/1) showed the appearance of two new compounds after 24 h stirring at room temperature. After removal of DMF under reduced pressure, the residue was purified by flash column chromatography, eluent ethyl acetate/acetone/water 100/100/1, then 10/10/1 to afford the 6,6'-disubstituted derivative as the faster moving fraction, and monosubstituted derivative as the slower moving fraction. Yields: 45-50 % (see Table 1) in the form of pale yellow oils, which were in all aspects identical to the products obtained bellow.
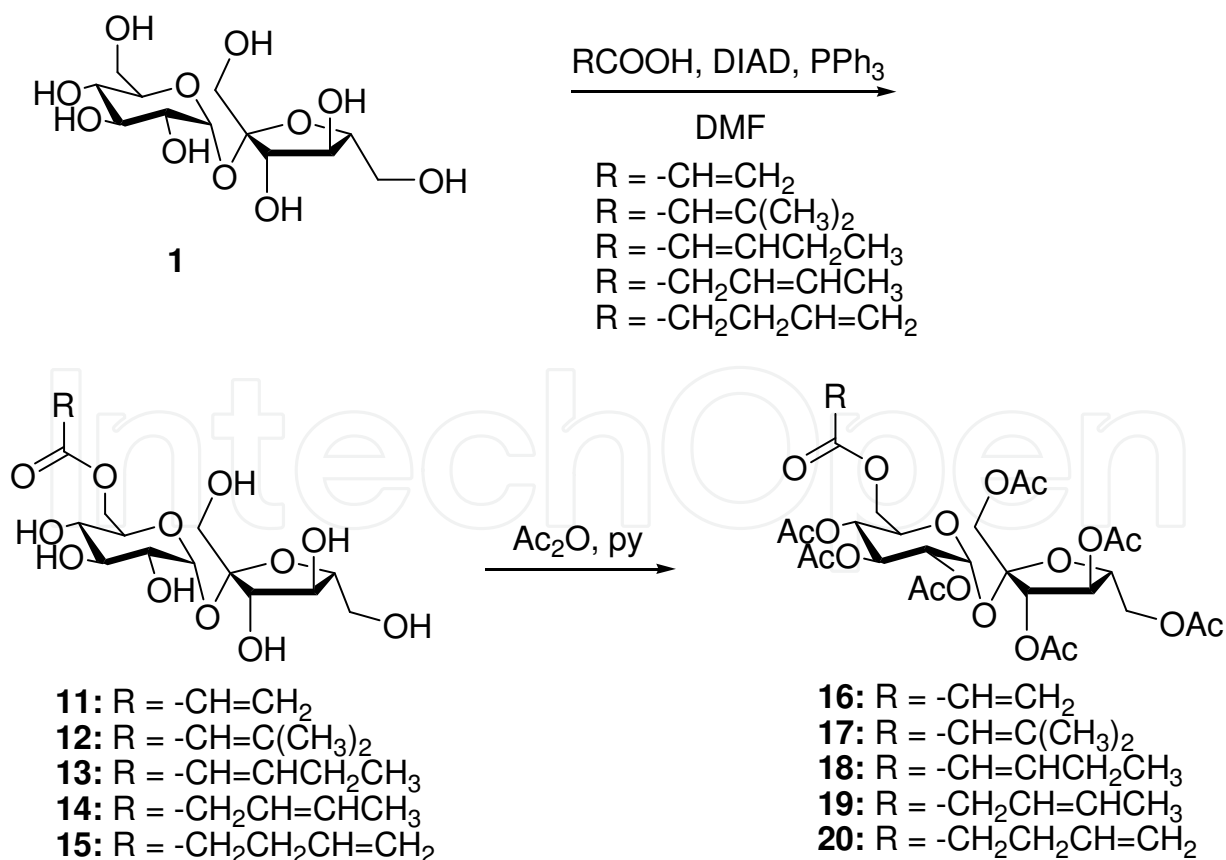

Fig. 9. Library of unprotected and acetylated double bond-containing sucrose monoesters.

Microwave synthesis

Sucrose (1.00 g, 2.92 mmol) was dissolved in anhydrous DMF (15 ml), and triphenylphosphine (1.03 g, 3.90 mmol) and the corresponding acid (1.1 eq) were added at room temperature. After complete dissolution, the mixture was cooled to 0 °C and DIAD (95% in benzene, 0.82 ml, 3.90 mmol) was slowly introduced. The reaction mixture was placed in the microwave cavity, and subjected to microwave irradiation (max 300W at constant temperature 145 °C) for 10 min. After removal of DMF under reduced pressure, the residue was purified by flash column chromatography, eluent ethyl acetate/acetone/water 100/100/1, then 10/10/1 to afford the corresponding disubstituted derivative as the faster moving fraction, and monosubstituted derivative as the slower moving fraction.

6-*O*-acryloyl sucrose 11

Yield: 51 %; ^{1}H NMR: δ_H(400 MHz, D_2O): 6.41-6.27 (1H, t, $J_{CH2b-CH2a=CH}$=16.7 Hz, =CH_{2a}), 6.19 (1H, m, =CH), 5.95-5.85 (1H, t, $J_{CH2a-CH2b=CH}$=11.4 Hz, =CH_{2b}), 5.32-5.25 (1H, d, J_{1-2}=3.5 Hz, H_1), 4.39-4.19 (2H, m, $H_{6a,b}$), 4.14-4.08 (1H, d, $J_{3'-4'}$=8.5 Hz, $H_{3'}$), 4.05-3.86 (2H, m+t, $J_{3'-4'-5'}$=8.7 Hz, H_5, $H_{4'}$), 3.84-3.75 (1H, m, $H_{5'}$), 3.75-3.61 (3H, m, $H_{6'a,b}$, H_3), 3.54 (2H, s, $H_{1'a,b}$), 3.49-3.41 (1H, dd, J_{1-2}=3.6 Hz, J_{2-3}=9.9 Hz, H_2), 3.38-3.30 (1H, t, J_{3-4-5}=9.9 Hz, H_4). ^{13}CNMR: δ_C(100 MHz, D_2O): 168.6 (-COO-), 133.0 (CH_2=), 127.7 (CH=), 104.1 ($C_{2'}$), 92.4 (C_1), 81.8 ($C_{5'}$), 76.7 ($C_{3'}$), 74.5 ($C_{4'}$), 72.7 (C_3), 71.3 (C_2), 70.6 (C_5), 69.8 (C_4), 63.9 (C_6), 62.9 ($C_{6'}$), 61.8 ($C_{1'}$). Anal. Calcd for $C_{15}H_{24}O_{12}$: C, 45.46; H, 6.10. Found: C, 45.27; H, 6.28.

6-*O*-(3,3-dimethylacryloyl) sucrose 12

Yield: 42 %; $[\alpha]_D$= +53.27 (c=0.81, $CHCl_3$). ^{1}HNMR: δ_H(400 MHz, D_2O): 5.69 (1H, s, $(CH_3)_2$C=CH-), 5.32-5.27 (1H, d, J_{1-2}=3.5 Hz, H_1), 4.39-4.16 (2H, dq, J_{6a-5}=5.1 Hz, J_{6a-6b}=12.1 Hz, J_{H6-COO}=53.4 Hz, H_6), 4.14-4.07 (1H, d, $J_{3'-4'}$=7.3 Hz, $H_{3'}$), 4.02-3.94 (1H, m, H_5), 3.93-3.85 (1H, t, $J_{3'-4'-5'}$=8.6 Hz, $H_{4'}$), 3.82-3.75 (1H, m, $H_{5'}$), 3.71-3.62 (3H, d+t, $J_{6'-5'}$=5.1 Hz, J_{2-3-4}=9.1 Hz, $H_{6'}$, H_3), 3.54 (2H, s, $H_{1'}$), 3.50-3.43 (1H, dd, J_{1-2}=3.6 Hz, J_{2-3}=9.4 Hz, H_2), 3.39-3.30 (1H, t, J_{3-4-5}=9.5 Hz, H_4), 2.03 (3H, s, -CH_3), 1.84 (3H, s, -CH_3). ^{13}CNMR: δ_C(100 MHz, D_2O): 168.9 (-COO-), 161.5 (($CH_3)_2$C=), 114.7 (-CH=), 104.1 ($C_{2'}$), 92.3 (C_1), 81.8 ($C_{5'}$), 76.8 ($C_{3'}$), 74.6 ($C_{4'}$), 72.8 (C_3), 71.3 (C_2), 70.8 (C_5), 70.2 (C_4), 63.2 (C_6), 63.1 ($C_{6'}$), 61.8 ($C_{1'}$), 27.1 (CH_3), 20.3 (CH_3). Anal. Calcd for $C_{17}H_{28}O_{12}$: C, 48.11; H, 6.65. Found: C, 47.97; H, 6.79.

6-*O*-(2-pentenoyl) sucrose 13

Yield: 47 %; $[\alpha]_D$= +52.70 (c=1.04, $CHCl_3$), ^{1}HNMR: δ_H(400 MHz, D_2O): 7.13-7.02 (1H, dt, J_{CH-CH2}=6.3 Hz, $J_{CH=CH}$=15.7 Hz, CH_2CH=CH), 5.90-5.80 (1H, d, $J_{CH=CH}$=15.8 Hz, CH=CH-COO), 5.33-5.29 (1H, d, J_{1-2}=3.7 Hz, H_1), 4.40-4.21 (2H, dq, J_{6a-5}=5.3 Hz, J_{6a-6b}=12.3 Hz, J_{H6-COO}=44.4 Hz, H_6), 4.14-4.09 (1H, d, $J_{3'-4'}$=8.7 Hz, $H_{3'}$), 4.04-3.97 (1H, m, H_5), 3.94-3.87 (1H, t, $J_{3'-4'-5'}$=8.6 Hz, $H_{4'}$), 3.84-3.76 (1H, m, $H_{5'}$), 3.72-3.64 (3H, d+t, $J_{6'-5'}$=4.1 Hz, J_{2-3-4}=10.0 Hz, $H_{6'}$, H_3), 3.56 (2H, s, $H_{1'}$), 3.51-3.45 (1H, dd, J_{1-2}=3.8 Hz, J_{2-3}=9.9 Hz, H_2), 3.40-3.32 (1H, t, J_{3-4-5}=9.6 Hz, H_4), 2.23-2.12 (2H, p, $J_{CH-CH2-CH3}$=6.9 Hz, CH_2), 1.00-0.92 (3H, t, $J_{CH2-CH3}$=7.4 Hz, CH_3). ^{13}CNMR: δ_C(100 MHz, D_2O): 169.3 (-COO-), 154.8 (CH_2CH=CH), 119.0 (-COO-CH=CH), 104.1 ($C_{2'}$), 92.3 (C_1), 81.8 ($C_{5'}$), 76.8 ($C_{3'}$), 74.6 ($C_{4'}$), 72.7 (C_3), 71.3 (C_2), 70.8 (C_5), 70.1 (C_4), 63.8 (C_6), 63.1 ($C_{6'}$), 61.8 ($C_{1'}$), 25.4 (CH_2), 11.6 (CH_3). Anal. Calcd for $C_{17}H_{28}O_{12}$: C, 48.11; H, 6.65. Found: C, 47.99; H, 6.74.

6-*O*-(3-pentenoyl) sucrose 14

Yield: 48 %, $[\alpha]_D^{25}$=+46.98 (c=0.94, $CHCl_3$); ^{1}HNMR: δ_H(400 MHz, D_2O): 5.64-5.53 (1H, m, J_{CH-CH3}=6.6 Hz, CH=CH-CH_3), 5.49-5.38 (1H, m, J_{CH-CH2}=7.0 Hz, CH=CH-CH_2), 5.32-5.27 (1H,

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d, J_{1-2}=3.2 Hz, H$_1$), 4.35-4.15 (2H, dq, J_{6a-5}=4.6 Hz, J_{6a-6b}=13.2 Hz, J_{H6-COO}=53.3 Hz, H$_{6a,b}$), 4.15-4.07 (1H, d, $J_{3'-4'}$=8.6 Hz, H$_{3'}$), 4.00-3.88 (2H, m+t, $J_{3'-4'-5'}$=8.8 Hz, H$_5$+H$_{4'}$), 3.84-3.76 (1H, m, H$_{5'}$), 3.74-3.69 (2H, d, $J_{6'-5'}$=6.7 Hz, H$_{6'}$), 3.69-3.61 (1H, t, J_{2-3-4}=9.7 Hz, H$_3$), 3.55 (2H, s, H$_{1'}$), 3.50-3.41 (1H, dd, J_{1-2}=3.6 Hz, J_{2-3}=9.7 Hz, H$_2$), 3.39-3.29 (1H, t, J_{3-4-5}=9.5 Hz, H$_4$), 3.03-3.00 (2H, m, J_{CH-CH2}=6.5 Hz, CH$_2$), 1.65-1.53 (3H, d, J_{CH-CH3}=6.0 Hz, CH$_3$). ^{13}CNMR: δ_C(100 MHz, D$_2$O): 175.5 (-COO-), 131.4 (CH$_3$CH=CH), 122.3 (-CH$_2$-CH=CH), 104.1 (C$_{2'}$), 92.4 (C$_1$), 81.8 (C$_{5'}$), 76.7 (C$_{3'}$), 74.5 (C$_{4'}$), 72.7 (C$_3$), 71.3 (C$_2$), 70.7 (C$_5$), 69.9 (C$_4$), 64.0 (C$_6$), 63.0 (C$_{6'}$), 61.7 (C$_{1'}$), 37.6 (CH$_2$), 17.6 (CH$_3$). Anal. Calcd for C$_{17}$H$_{28}$O$_{12}$: C, 48.11; H, 6.65. Found: C, 48.02; H, 6.88.

6-*O*-(4-pentenoyl) sucrose 15

Yield: 42 %,[α]$_D^{25}$=+54.64 (c=0.91, CHCl$_3$) ; ^{1}HNMR: δ_H(400 MHz, D$_2$O): 5.86-5.73 (1H, ddt, J_{CH-CH2}=6.6 Hz, $J_{CH=CH2cis}$=10.6 Hz, $J_{CH=CH2trans}$=16.8 Hz, CH$_2$=C*H*-CH$_2$), 5.32-5.28 (1H, d, J_{1-2}=3.5 Hz, H$_1$),5.05-4.91 (2H, dd, $J_{CH-CH2cis}$=10.2 Hz, $J_{CH=CH2trans}$=17.7 Hz, C*H*$_2$=CH-CH$_2$), 4.35-4.15 (2H, dq, J_{6a-5}=4.6 Hz, J_{6a-6b}=11.8 Hz, J_{H6-COO}=47.4 Hz, H$_{6a,b}$), 4.15-4.08 (1H, d, $J_{3'-4'}$=8.7 Hz, H$_{3'}$), 4.00-3.89 (2H, m+t, $J_{3'-4'-5'}$=8.6 Hz, H$_5$+H$_{4'}$), 3.84-3.76 (1H, m, H$_{5'}$), 3.74-3.70 (2H, d, $J_{6'-5'}$=6.3 Hz, H$_{6'}$), 3.70-3.63 (1H, t, J_{2-3-4}=9.6 Hz, H$_3$), 3.56 (2H, s, H$_{1'}$), 3.50-3.43 (1H, dd, J_{1-2}=3.6 Hz, J_{2-3}=9.9 Hz, H$_2$), 3.40-3.31 (1H, t, J_{3-4-5}=9.6 Hz, H$_4$), 2.50-2.42 (2H, t, $J_{CH2-CH2}$=7.1 Hz, C*H*$_2$-COO), 2.33-2.23 (2H, q, $J_{CH2-CH2-CH}$=6.5 Hz, CH$_2$-C*H*$_2$-CH). ^{13}CNMR: δ_C(100 MHz, D$_2$O): 176.2 (-COO-), 137.4 (CH$_2$=CH), 115.8 (CH$_2$=CH), 104.1 (C$_{2'}$), 92.3 (C$_1$), 81.8 (C$_{5'}$), 76.7 (C$_{3'}$), 74.5 (C$_{4'}$), 72.7 (C$_3$), 71.3 (C$_2$), 70.7 (C$_5$), 69.9 (C$_4$), 63.7 (C$_6$), 63.0 (C$_{6'}$), 61.7 (C$_{1'}$), 33.3 (COO-CH$_2$), 28.6 (CH$_2$-CH=). Anal. Calcd for C$_{17}$H$_{28}$O$_{12}$: C, 48.11; H, 6.65. Found: C, 48.20; H, 6.69.

General method for peracetylation

Corresponding sucrose ester (**11-15**) (500mg) was dissolved in pyridine (5 mL) and 2.5 mL of acetic anhydride was added. The reaction mixture was placed in the microwave cavity, and subjected to MW irradiation (max 300W) at constant temperature (90 °C) for 5 min. The method afforded, after removal of the solvent and purification by flash column chromatography (eluent hexane/ethyl acetate 3/1, then 1/1), the corresponding acetylated sucrose monoesters (**16-20**) in 96-98 % yield.

1′,2,3,3′,4,4′,6′-hepta-*O*-acetyl- 6-*O*-acryloyl sucrose 16

[α]$_D^{25}$= +45.96 (c=0.98, CHCl$_3$); ^{1}HNMR: δ_H(400 MHz, CDCl$_3$): 6.46-6.36 (1H, dd, $J_{CH2b-CH2a}$=5.3 Hz, $J_{CH2\ =CH}$=17.7 Hz, =C*H*$_{2a}$), 6.22-6.05 (1H, m, =C*H*), 5.88-5.80 (1H, t, $J_{CH2a-CH2b=CH}$=12.4 Hz, =C*H*$_{2b}$), 5.71-5.66 (1H, d, J_{1-2}=3.1 Hz, H$_1$), 5.49-5.40 (2H, m, H$_3$, H$_{3'}$), 5.38-5.33 (1H, t, $J_{3'-4'-5'}$=5.7 Hz, H$_{4'}$), 5.11-5.03 (1H, t, J_{3-4-5}=10.1 Hz, H$_4$), 4.90-4.83 (1H, dd, J_{1-2}=3.8 Hz, J_{2-3}=9.6 Hz, H$_2$), 4.35-4.24 (5H, m, H$_5$, H$_{6'a,b}$, H$_{6a,b}$), 4.24-4.08 (3H, m+s, H$_{5'}$, H$_{1'a,b}$), 2.18 (3H, s, CH$_3$O), 2.12 (9H, s, 3CH$_3$O), 2.10 (3H, s, CH$_3$O), 2.05 (3H, s, CH$_3$O), 2.02 (3H, s, CH$_3$O). ^{13}CNMR: δ_C(100 MHz, D$_2$O): 170.5-169.5 (8-COO-), 131.1 (CH$_2$=), 127.7 (*C*H=), 104.1 (C$_{2'}$), 89.9 (C$_1$), 79.1 (C$_{5'}$), 75.7 (C$_{3'}$), 75.0 (C$_{4'}$), 70.3 (C$_2$), 69.6 (C$_3$), 68.4 (C$_5$), 68.1 (C$_4$), 63.6 (C$_{6'}$), 62.8 (C$_{1'}$), 61.9 (C$_6$), 20.6 (7CH$_3$CO). Anal. Calcd for C$_{29}$H$_{38}$O$_{19}$: C, 50.44; H, 5.55. Found: C, 50.40; H, 5.51.

1′,2,3,3′,4,4′,6′-hepta-*O*-acetyl- 6-*O*-(3,3-dimethylacryloyl) sucrose 17

[α]$_D^{25}$= +40.27 (c=1.04, CHCl$_3$), ^{1}HNMR: δ_H(400 MHz, CDCl$_3$): 5.74 (1H, s, (CH$_3$)$_2$C=C*H*-), 5.71-5.68 (1H, d, J_{1-2}=3.7 Hz, H$_1$), 5.49-5.40 (2H, t+d, $J_{3'-4'}$=5.3 Hz, H$_3$, H$_{3'}$), 5.39-5.33 (1H, t, $J_{3'-4'-5'}$=5.7 Hz, H$_{4'}$), 5.13-5.08 (1H, t, J_{3-4-5}=9.7 Hz, H$_4$), 4.90-4.84 (1H, dd, J_{1-2}=3.7 Hz, J_{2-3}=10.3 Hz, H$_2$), 4.39-4.33 (1H, dd, J_{5-6}=4.0 Hz, J_{4-5}=11.9 Hz, H$_5$), 4.33-4.09 (7H, m, H$_{6'}$, H$_6$, H$_{5'}$, H$_{1'}$), 2.18 (3H, s, CH$_3$O), 2.16 (3H, s, -CH$_3$), 2.12 (6H, s, 2CH$_3$O), 2.11 (3H, s, CH$_3$O), 2.10 (3H, s, CH$_3$O),

2.04 (3H, s, CH$_3$O), 2.01 (3H, s, CH$_3$O), 1.90 (3H, s, -CH$_3$). ^{13}CNMR: δ_C(100 MHz, D$_2$O): 170.5-169.4 (8-COO-), 157.9 ((CH$_3$)$_2$$C$=), 115.3 (-$C$H=), 104.1 (C$_{2'}$), 90.0 (C$_1$), 79.2 (C$_{5'}$), 75.8 (C$_{3'}$), 75.1 (C$_{4'}$), 70.3 (C$_2$), 69.8 (C$_3$), 68.6 (C$_5$), 68.4 (C$_4$), 63.6 (C$_{6'}$), 62.9 (C$_{1'}$), 60.7 (C$_6$), 27.4 (CH$_3$), 20.6 (7$CH_3$CO). Anal. Calcd for C$_{31}H_{42}O_{19}$: C, 51.81; H, 5.89. Found: C, 51.75; H, 5.91.

1',2,3,3',4,4',6'-hepta-*O*-acetyl- 6-*O*-(2-pentenoyl) sucrose 18

$[\alpha]_D^{25}$= +76.47 (c=0.94, CHCl$_3$), ^{1}HNMR: δ_H(400 MHz, CDCl$_3$): 7.14-7.02 (1H, dt, J_{CH-CH2}=6.3 Hz, $J_{CH=CH}$=15.6 Hz, CH$_2$CH=CH), 5.91-5.82 (1H, d, $J_{CH=CH}$=15.7 Hz, CH=CH-COO), 5.73-5.68 (1H, d, J_{1-2}=3.7 Hz, H$_1$), 5.50-5.41 (2H, t+d, H$_3$, H$_{3'}$), 5.38-5.34 (1H, t, $J_{3'-4'-5'}$=5.5 Hz, H$_{4'}$), 5.15-5.08 (1H, t, J_{3-4-5}=9.8 Hz, H$_4$), 4.91-4.84 (1H, dd, J_{1-2}=3.5 Hz, J_{2-3}=10.3 Hz, H$_2$),4.38-4.32 (1H, dd, J_{5-6}=4.2 Hz, J_{4-5}=12.2 Hz, H$_5$), 4.32-4.14 (7H, m, H$_{6'}$, H$_6$, H$_{5'}$, H$_{1'}$), 2.30-2.20 (2H, p, $J_{CH-CH2-CH3}$=6.8 Hz, CH$_2$), 2.18 (3H, s, CH$_3$O), 2.12 (6H, s, 2CH$_3$O), 2.11 (3H, s, CH$_3$O), 2.10 (3H, s, CH$_3$O), 2.04 (3H, s, CH$_3$O), 2.02 (3H, s, CH$_3$O), 1.12-1.05 (3H, t, $J_{CH2-CH3}$=7.4 Hz, CH$_3$). ^{13}CNMR: δ_C(100 MHz, D$_2$O): 170.5 (CH$_3$$CO$), 170.1 (CH$_3$$CO$), 169.8 (CH$_3$$CO$), 169.6 (CH$_3$$CO$), 169.4 (CH$_3$$CO$), 166.3 (-COO-), 151.9 (CH$_2$CH=CH), 119.5 (-COO-CH=CH), 104.1 (C$_{2'}$), 90.0 (C$_1$), 79.2 (C$_{5'}$), 75.7 (C$_{3'}$), 75.1 (C$_{4'}$), 70.3 (C$_2$), 69.7 (C$_3$), 68.5 (C$_5$), 68.3 (C$_4$), 63.5 (C$_{6'}$), 62.8 (C$_{1'}$), 61.4 (C$_6$), 25.3 (CH$_2$), 20.6 (7CH$_3$CO), 12.0 (CH$_3$). Anal. Calcd for C$_{31}$H$_{42}$O$_{19}$: C, 51.81; H, 5.89. Found: C, 51.73; H, 5.92.

1',2,3,3',4,4',6'-hepta-*O*-acetyl- 6-*O*-(3-pentenoyl) sucrose 19

$[\alpha]_D^{25}$= +40.71 (c=1.11, CHCl$_3$), ^{1}HNMR: δ_H(400 MHz, CDCl$_3$): 5.72-5.67 (1H, d, J_{1-2}=3.5 Hz, H$_1$), 5.65-5.52 (2H, m, J_{CH-CH2}, J_{CH-CH3}=5.2 Hz, CH=CH), 5.48-5.41 (2H, t+d, $J_{3'-4'}$=6.2 Hz, H$_3$, H$_{3'}$), 5.40-5.34 (1H, t, $J_{3'-4'-5'}$=6.0 Hz, H$_{4'}$), 5.12-5.04 (1H, t, J_{3-4-5}=9.8 Hz, H$_4$), 4.91-4.83 (1H, dd, J_{1-2}=3.6 Hz, J_{2-3}=10.4 Hz, H$_2$), 4.39-4.33 (1H, dd, J_{5-6}=4.1 Hz, J_{4-5}=11.8 Hz, H$_5$), 4.33-4.09 (7H, m, H$_{6'}$, H$_6$, H$_{5'}$, H$_{1'}$), 3.11-3.02 (2H, d, J_{CH-CH2}=5.0 Hz, CH$_2$), 2.17 (3H, s, CH$_3$O), 2.12 (3H, s, CH$_3$O), 2.11 (3H, s, CH$_3$O), 2.10 (3H, s, CH$_3$O), 2.10 (3H, s, CH$_3$O), 2.04 (3H, s, CH$_3$O), 2.02 (3H, s, CH$_3$O), 1.75-1.67 (3H, d, J_{CH-CH3}=5.2 Hz, CH$_3$). ^{13}CNMR: δ_C(100 MHz, D$_2$O): 171.9 (-COO-), 170.7 (CH$_3$$CO$), 170.5 (CH$_3$$CO$), 170.1 (CH$_3$$CO$), 169.9 (CH$_3$$CO$), 169.6 (CH$_3$$CO$), 129.7 (CH=$C$H), 122.3 (CH=CH), 104.1 (C$_{2'}$), 89.9 (C$_1$), 79.2 (C$_{5'}$), 75.7 (C$_{3'}$), 75.0 (C$_{4'}$), 70.3 (C$_2$), 69.6 (C$_3$), 68.5 (C$_5$), 68.2 (C$_4$), 63.5 (C$_{6'}$), 62.8 (C$_{1'}$), 61.8 (C$_6$), 37.5 (CH$_2$), 20.6 (7CH$_3$CO), 17.9 (CH$_3$). Anal. Calcd for C$_{31}$H$_{42}$O$_{19}$: C, 51.81; H, 5.89. Found: C, 51.83; H, 5.95.

1',2,3,3',4,4',6'-hepta-*O*-acetyl- 6-*O*-(4-pentenoyl) sucrose 20

$[\alpha]_D^{25}$=+49.82(c=0.88, CHCl$_3$), ^{1}HNMR: δ_H(400 MHz, CDCl$_3$): 5.90-5.76 (1H, ddt, J_{CH-CH2}=6.4 Hz, $J_{CH=CH2cis}$=10.4 Hz, $J_{CH=CH2trans}$=16.5 Hz, CH$_2$=CH-CH$_2$), 5.71-5.67 (1H, d, J_{1-2}=3.6 Hz, H$_1$), 5.48-5.41 (2H, t+d, J_{2-3-4}=9.2 Hz, $J_{3'-4'}$=5.3 Hz, H$_3$, H$_{3'}$), 5.39-5.33 (1H, t, $J_{3'-4'-5'}$=5.7 Hz, H$_{4'}$), 5.12-5.06 (1H, t, J_{3-4-5}=9.5 Hz, H$_4$), 5.06-4.98 (2H, t, $J_{CH-CH2cis-CH2trans}$=9.6 Hz, CH_2=CH-CH$_2$), 4.89-4.84 (1H, dd, J_{1-2}=3.7 Hz, J_{2-3}=10.3 Hz, H$_2$), 4.38-4.32 (1H, dd, J_{5-6}=4.4 Hz, J_{4-5}=11.8 Hz, H$_5$), 4.32-4.28 (2H, t, $J_{6'a-6'b-5'}$=3.1 Hz, H$_{6'}$), 4.28-4.25 (2H, d, J_{5-6}=4.9 Hz, H$_6$), 4.23-4.19 (1H, t, $J_{4'-5'-6'}$=5.6 Hz, H$_{5'}$), 4.18 (2H, s, H$_{1'}$), 2.50-2.42 (2H, t, $J_{CH2-CH2}$=6.1 Hz, CH_2-COO), 2.42-2.34 (2H, q, $J_{CH2-CH2-CH}$=6.2 Hz, CH$_2$-CH_2-CH), 2.17 (3H, s, CH$_3$O), 2.12 (6H, s, 2CH$_3$O), 2.11 (3H, s, CH$_3$O), 2.10 (3H, s, CH$_3$O), 2.04 (3H, s, CH$_3$O), 2.02 (3H, s, CH$_3$O). ^{13}CNMR: δ_C(100 MHz, D$_2$O): 172.7 (-COO-), 170.5 (CH$_3$$CO$), 170.1 (CH$_3$$CO$), 169.9 (CH$_3$$CO$), 169.6 (CH$_3$$CO$), 169.5 (CH$_3$$CO$), 136.6 (CH$_2$=CH), 115.5 (CH$_2$=CH), 104.1 (C$_{2'}$), 90.0 (C$_1$), 79.2 (C$_{5'}$), 75.7 (C$_{3'}$), 75.0 (C$_{4'}$), 70.3 (C$_2$), 69.6 (C$_3$), 68.5 (C$_5$), 68.1 (C$_4$), 63.6 (C$_{6'}$), 62.8 (C$_{1'}$), 61.5 (C$_6$), 33.1 (COO-CH$_2$), 28.6 (CH$_2$-CH=), 20.6 (7$CH_3$CO). Anal. Calcd for C$_{31}H_{42}O_{19}$: C, 51.81; H, 5.89. Found: C, 51.92; H, 5.99.

3. Results and discussion

The synthesis of a library of new sucrose-containing monomers has been developed using microwave irradiation, focusing on the selectivity of the transformations. Synthesis of esters and ethers, substituted regioselectively at 6′-position of sucrose was achieved using protection-deprotection strategy. The regioselective formation of monounsaturated esters at 6-position, by applying the Mitsunobu conditions for esterification of sucrose has also been studied.

Sucrose is soluble in protic solvents such as water, methanol and ethanol, and reasonably soluble in dipolar aprotic solvents such as pyridine, DMF and DMSO, which are suitable as nucleophilic substitution media. DMF has comparatively high boiling point (153 °C) and a dipole suitable for the absorption of microwave radiation. Dichloromethane also proved suitable as a reaction media for the benzylated sucrose derivatives. The maximum temperature which 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.

The reactions under microwave irradiation were performed using a monomodal microwave reactor MicroSynth Labstation (MileStone, USA)(www.milestonesrl.com) in open flasks equipped with temperature control sensor and magnetic stirring. This microwave synthesizer has a single mode cavity with temperature regulation and pressure control, which means that temperature runaway and explosion risk are avoided. It should be noticed that the reaction conditions are not expressed as a function of the magnetron power, as for most microwave-assisted reactions published, but by the reaction temperature.

3.1 Synthesis of benzylated sucrose-containing monomers

With the purpose of comparing the polymerization ability of monomers, in which the vinyl group is adjacent to the sucrose moiety, or is located further away, a small library was generated, using compound **4** as starting material.

Esterifications of the free 6′-hydroxyl of **4** were carried out by treating it in a mixture of dichloromethane and triethylamine, with the appropriate anhydride, to afford the expected compounds **5** and **6** in good yields (Table 1). The ^{1}H NMR spectra of these compounds exhibit two signals which have been attributed to the double bond. For methacrylate **5** a singlet at 6.15 ppm and a doublet at 5.60 ppm and for crotonate **6** a mutiplet at 6.90 ppm and a doublet at 5.80 ppm. We assigned the allylic methyl groups of the molecules at 1.95 ppm for **5** and 1.70 ppm for **6**.

Conventional etherification was tested involving a primary halide, in our case allyl bromide or 4-vinylbenzyl chloride (Jhurry et al., 1992), optimizing the procedure for protected sucrose. In this case, the intermediate **4** was treated with NaH in DMF at 0°C, with the subsequent addition of the allyl bromide to form **7** in 59 % yield; or 4-vinylbenzyl chloride, to form **8** in 50 % yield under microwave irradiation (Fig. 8).

For obtaining vinyl sucrose ether **10**, we have adopted a two-step route via mixed acetals, based on the Gassman method, first reported in 1993 (Gassman et al., 1993), as it requires readily available reagents, mild conditions, and does not involve the use of heavy metal salt catalysts, such as mercury (Hughes et al., 2005). It consists in forming a vinyl group by the elimination of ethanol from mixed acetals with trimethylsilyl trifluoromethanesulfonate (TMS-triflate) in the presence of alkyl amines.

The mixed acetal **9** was prepared by treating **4** with ethyl vinyl ether in the presence of PPTS under microwave irradiation. No side products were observed and a mixture of diastereomers was produced, with no attempt at separation being made. After purification by flash column chromatography, the elimination reaction was performed by treating **9** with TMS-triflate and triethylamine under microwave irradiation, leading to **10** (Fig. 8). The yield of this step was decreased by the competing side reaction of formation of silyl ether, resulting of a complexation of the trimethylsilyl cation with the sucrose connected oxygen atom, as it was discussed by Gassman *et al.* (Gassman et al., 1993) and Hughes *et al.* (Hughes et al., 2005). Complexation of the trimethylsilyl cation with the ethoxy group oxygen produced the desired vinyl sucrose ether.

3.2 Functionalization of sucrose avoiding protecting group chemistry

The Mitsunobu reaction (Mitsunobu, 1981) is a convenient method for selective esterification. Such a process performed on free sucrose affords 6,1',6'-triesters or 6,6'-diesters (Beraud et al., 1989; Bottle and Jenkins, 1984), establishing the reactivity of hydroxy groups as 6-OH > 6'-OH >1'-OH > secondary OH groups. Several interesting esters of sucrose, such as derivatives of fatty acids (Molinier et al., 2004) and 6-perfluoroalkanoates for biomedical uses (Abouhilale et al., 1991) have been prepared by this method. Treatment of the free sucrose with phthalimide under Mitsunobu conditions afforded derivative, in which the primary 6-OH and 6'-OH groups were replaced with phthalimide moieties, while the secondary ones at the C-3' and C-4' positions were converted into an epoxide (Amariutei et al., 1988).

In contrast to many related condensation reactions (Gu et al., 2008), Mitsunobu reactions proceed under mild, essentially neutral conditions and exhibit stereospecificity, functional selectivity and regioselectivity. Because of these features the Mitsunobu reaction has been employed in synthesis of macrolide antibiotics, nucleosides, nucleoside phosphates, amino acids, amino sugars, steroids and other natural products (Brain et al., 2001; Chong and Chu, 2000). The mechanism of the Mitsunobu reaction involves the formation of a phosphonium intermediate that reacts with the alcohol oxygen atom and the selectivity observed in these reactions is presumably a result of the preferential attack at the primary hydroxy groups (Grochowski et al., 1982; Itzstein and Jenkins, 1983). In the case of sucrose, the 1'-position being neopentyl-like, is considerably more hindered than the 6- and 6'-positions. The product has been shown to be the 6-substituted rather than the 6'-substituted by hydrolysis with invertase (Bottle and Jenkins, 1984; Guthrie et al., 1979).

Mitsunobu esterification conditions (Mitsunobu, 1981) are known to provide good selectivity, even in the case of a complex polyol like sucrose, thus allowing a rapid and efficient synthesis of sucrose esters. Although the atom economy of the procedure was poor, it gave excellent results on a small scale and allowed us to avoid the use of protecting group chemistry and multi-step procedures. Applying microwave irradiation to this procedure allowed us to reduce the reaction time to 10 min instead of 30 h at r.t., and provided better selectivity towards the *6-O*-mono-ester over *6,6'-O*-diester. Subsequent conventional acetylation afforded the corresponding acetylated products in quantitative yields. In the case of the monomer **11**, the products obtained were very reactive and tended to polymerize spontaneously upon concentration. This difficulty was overcome by adding hydroquinone to the mixture (Russo et al., 2007).

Our goal was to obtain monoesters of sucrose selectively (Fig. 9), which is why only one equivalent of the corresponding acid was used, and the irradiation was not more than 10 min at 145 °C. Thus it was possible to optimize the yields to about 50 % of regioisomerically pure unsaturated monoesters of sucrose. The corresponding sucrose 6,6′-O-diesters were isolated in smaller amounts than the monoesters, and it was not possible to avoid their formation.

Comp. No.	Microwave conditions	Reagents	Time [min]	Yield [%]	Conventional conditions	Yield[a] [%], ref.
5	35°C/300W	$(CH_2=C(CH_3)CO)_2O$, NEt₃, CH_2Cl_2	10	51	r.t./ 4 h	73 (Barros et al., 2004b)
6	35°C/300W	$(CH_3CH=CHCO)_2O$, NEt₃, CH_2Cl_2	10	65	r.t./ 4 h	81 (Barros et al., 2004b)
7	145°C/300W	$CH_2=CHCH_2Br$, NaH, DMF	10	59	r.t./ 3 h	60
8	145°C/300W	$CH_2=CHC_6H_4CH_2Br$, NaH, DMF	10	50	70°C/ 4 h	46 (Crucho et al., 2008)
9	35°C/300W	$CH_2=CHOEt$, PPTS, CH_2Cl_2	10	54	r.t./ 2 h	56 (Crucho et al., 2008)
10	35°C/300W	TMSOTf, NEt₃, CH_2Cl_2	10	30	r.t./ 2 h	31 (Crucho et al., 2008)
11	145°C/300W	$H_2C=CHCO_2H$/PPh₃, DIAD, DMF	10	51	r.t./ 24 h	49
12	145°C/300W	$(CH_3)_2C=CHCO_2H$/PPh₃, DIAD, DMF	10	42	r.t./ 24 h	46
13	145°C/300W	$CH_3CH_2CH=CHCO_2H$/PPh₃, DIAD, DMF	10	47	r.t./ 24 h	50
14	145°C/300W	$CH_3CH=CHCH_2CO_2H$/PPh₃, DIAD, DMF	10	48	r.t./ 24 h	47
15	145°C/300W	$H_2C=CHCH_2CH_2CO_2H$/PPh₃, DIAD, DMF	10	42	r.t./ 24 h	45
16-20	90°C/300W	peracetylation $(CH_3CO)_2O$, pyridine	5	96-98	r.t./ 12 h	96-98

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

The differentiation between the regioisomeric esters of sucrose can be verified by several methods (Guthrie et al., 1979), (Chauvin et al., 1993). However, the most common assignment is by high-resolution NMR, supported by HMBC (Zoete et al., 1999). For all the monoesters of unprotected sucrose in the ¹H NMR, differences in the chemical shifts of the protons corresponding to the glucose ring, compared to the spectra of unsubstituted sucrose, were observed. The signal for H-5 was moved downfield from 3.72 to 4.00 ppm, and the signal for H-6 (a and b) from 3.69 to 4.31 ppm and split from a singlet to a duplet and duplet of duplets (Fig. 10 - comparison of the sucrose region signals in the ¹H NMR spectra of sucrose and sucrose 6-O-monoesters). In the ¹³C NMR spectrum a similar shift of the signals for the glucose ring was observed: C-4 from 69.6 in sucrose to 70.1 ppm in the ester, C-5 from 72.9 to 70.8 ppm, and most significantly, the C-6 from 60.4 to 63.8 ppm (Fig. 11). In the COSY spectrum, correlation between the proton at 4.02 ppm, which was assigned to H-5, and the methylene

protons at 4.31 ppm, was observed assigning them to H-6. In the HMQC spectrum, the signal at 63.8 ppm gave a crosspeak with the H at 4.31 ppm, confirming it is C-6. This differentiation between the glucose and fructose rings and the three methylene signals of the protons and carbons have been confirmed by DEPT, COSY (Fig. 12), and HMQC spectra, and places the acyl-substituent at the C-6 position, but it is most certainly proved by HMBC technique (Fig. 13). Thus, a crosspeak between the C of the carbonyl group and H-6 was observed, confirming the place of the substituent at C-6, as well as the long range couplings between C-4 and H-6, between C-6 and H-4, and C-5 and H-6, which were consistent with structures **11-15**.
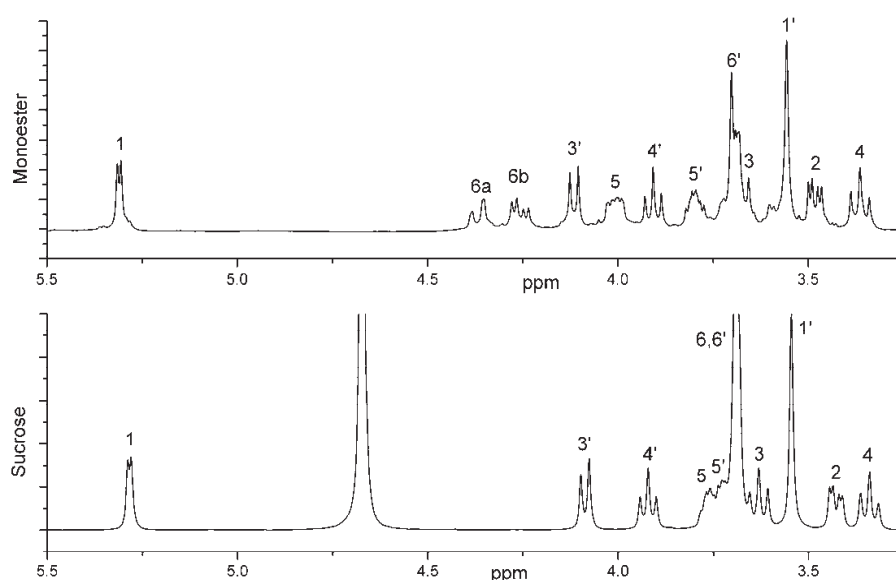

Fig. 10. Comparison of the sucrose region signals in the ¹H NMR spectra of sucrose and sucrose 6-*O*-mono-esters.

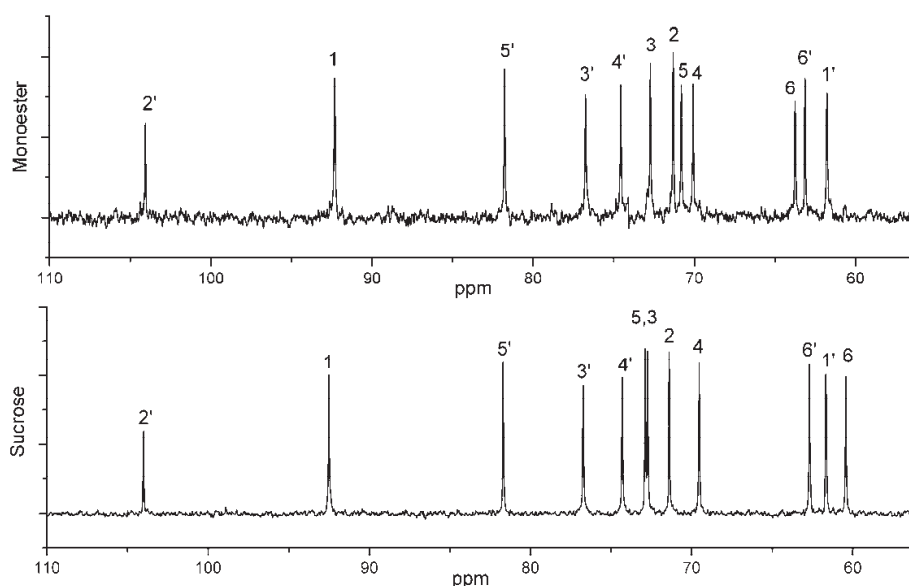Fig. 11. Comparison of the sucrose region signals in the ¹³C NMR spectra of sucrose and sucrose 6-*O*-mono-esters.
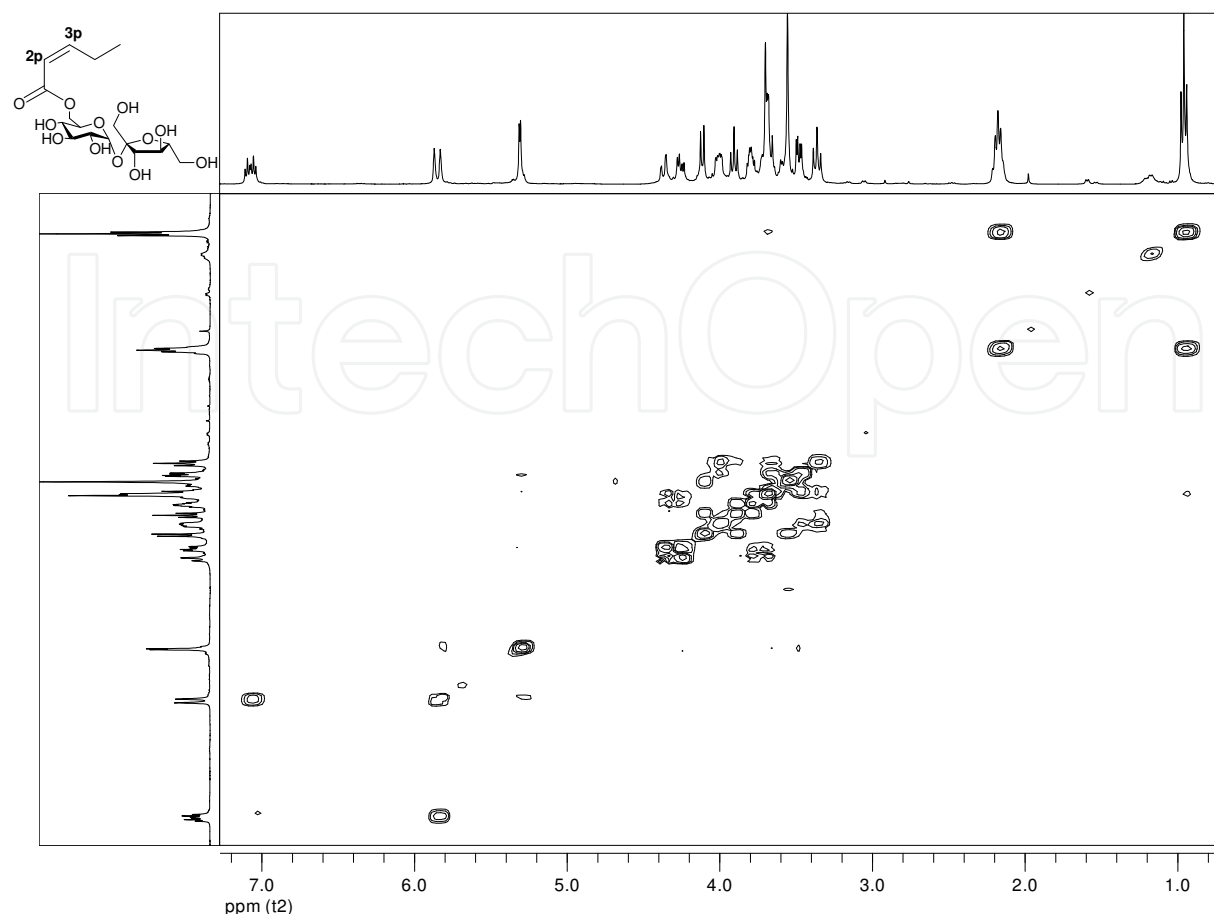
Fig. 12. COSY spectrum of 6-*O*-(2-pentenoyl) sucrose **13**.

To obtain the corresponding acetylated products **16-20**, conventional treatment with acetic anhydride in pyridine was performed. It is common opinion in the literature, that acetylation of the sugar derivatives facilitates and simplifies the NMR analysis (Jarosz and Mach, 2002; Zoete et al., 1999). However, in our case it proved impossible to distinguish the site of substitution in the acetylated products, as the attachment of an acyl group instead of an acetyl results in very small differences in chemical shifts for both the sugar proton and carbon signals, since both groups are connected through ester bonds. It was possible to obtain a complete assignment of the sugar signals (Sanders and Hunter, 1987), assuming the same position of the acyl substituents as in the unprotected derivatives – 6. In the HMBC spectrum all possible cross-peaks resulting from three-bond couplings between sugar protons and in the substituents groups are present. The possible cross-peaks between C-carbonyl groups and the sugar protons were observed, while the four-bond signals between the sugar carbons and acetyl CH_3 protons, reported in (Zoete et al., 1999), were not observed, and assignment for the site of the acyl substituent based on them was not possible.

3.2 Environmental assessment of the method

Two useful measures of the potential environmental acceptability of chemical processes are the *E* factor, defined as the mass ratio of waste to desired product, and the atom utilization, calculated by dividing the molecular weight of the desired product by the sum of the molecular weights of all substances produced in the stoichiometric equation (Table 2), (Sheldon, 2008). In this calculation the solvents were not taken into consideration as waste as

they were easily recovered and reused. According to a study presented by Sheldon (Sheldon, 2008), these values are in the range reported for bulk chemicals, i.e. are lower than for the fine chemical industry. We could see from table 2 that the reactions involving formation of phosphorous intermediates (**11-15**) are less economic than the straightforward substitution, but one has to take into account the formation of the starting material **4** in three steps from sucrose. On the other hand, the advantage of the direct method stems from the improved regioselectivity and the avoidance of protecting group chemistry. The data shows that the one-step methods for the valorization of sucrose as a renewable natural feedstock were beneficial over multistep protection-deprotection strategies.
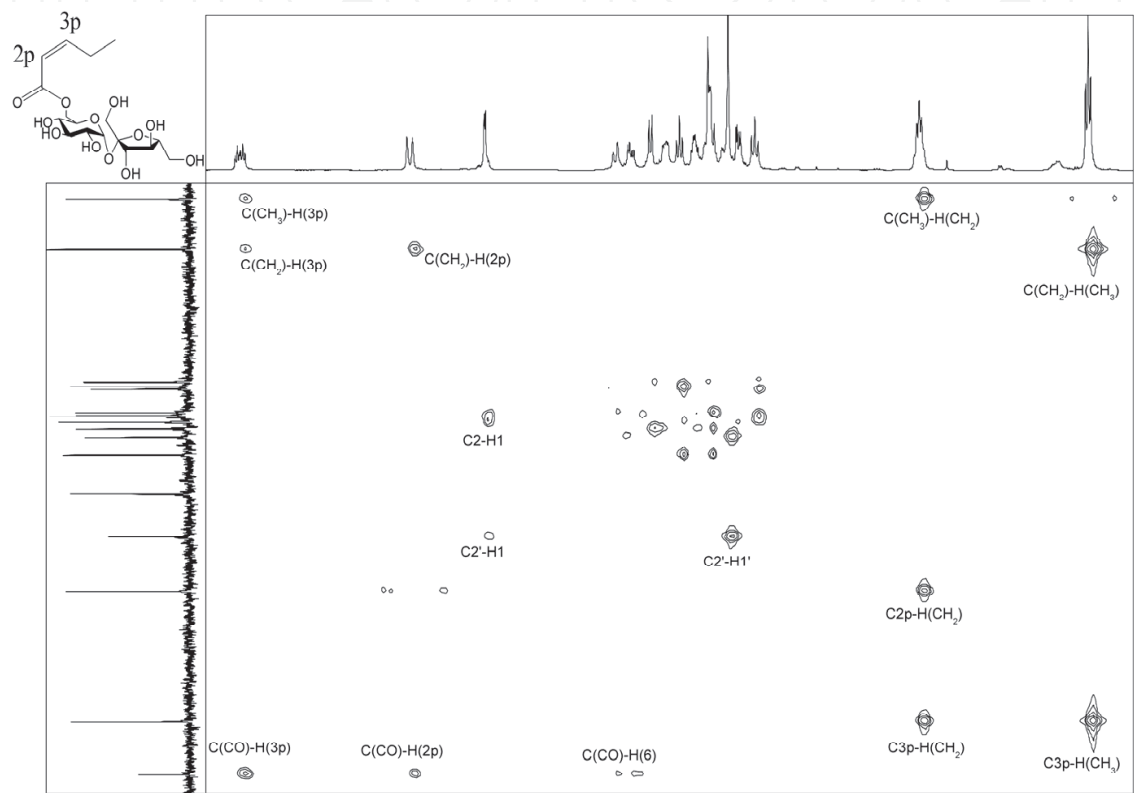

Fig. 13. HMBC spectrum of 6-*O*-(2-pentenoyl) sucrose **13**.

Comp. No.	E factor (g waste/ g product)	Atom Utilization (M product/ M all compounds formed), [%]
4 (from 1)	1.13	60
5	0.35	85
6	0.28	85
7	0.17	91
8	0.20	91
10	1.23	73
11	1.39	59
12	1.57	60
13	1.41	60
14	1.38	60
15	1.57	60

Table 2. Environmental acceptability and Percentage of atom utilization.

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4. Conclusion

This chapter provides a number of mild and effective protocols for the synthesis of diverse monomeric carbohydrate building blocks. The utilization of microwave irradiation as a more efficient mode of heating leading to shorter reaction periods was evaluated. It has been shown that microwave radiation efficiently promoted the reactions and allowed a great reduction in reaction times and at the same time improving or maintaining the good yields achieved by conventional conditions. In the case of sucrose functionalization the elimination of solvent is not recommended as it led to significantly lower yields because of overheating. Microwave-assisted carbohydrate chemistry is, at the present time, experiencing considerable growth and has the potential to greatly improve the image of carbohydrate chemistry. Short reaction times and large rate enhancements as compared to conventional methods are observed, notably in reactions using mild reagents or involving steric hindrance. Yields are comparable or better than when using conventional methods, and sometimes much higher in reactions where the short reaction time prevents decomposition. The short reaction times in combination with easy reproducibility and workup, make these methods suitable for automation.

5. Acknowledgment

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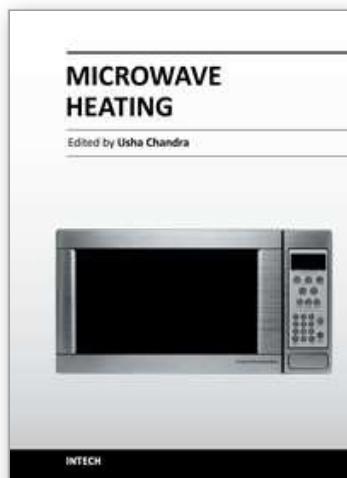
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