Microwave-assisted Chemistry of Carbohydrates

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Abstract: Microwave irradiation is becoming an increasingly popular method of heating which replaces the classical one because it proves to be a clean, cheap, and convenient method. Often, it affords higher yields and results in shorter reaction times. This method of heating has been extended to almost all areas of chemistry with the exception of the carbohydrate chemistry which has suffered a certain delay, as it is testified by the limited number of applications.

The aim of this review is to explore the variety of these applications in carbohydrate chemistry, even if in a limited number, which have been carried out with microwave irradiation as activating agent. Mainly, these concern the selective or unselective protection and deprotection of hydroxyl functionalities, and triglyceride alcoholysis and glycerolysis reactions of industrial interest since these lead to materials for the production of straining, emulsifying and softening agents and moreover for the production of an ecologic fuel (biodiesel). Other aspects of the carbohydrate chemistry such as the syntheses of monosaccharides containing heterocyclic nuclei, or unsaturations, or halogens are also included. Synthetically, the effect on the mutarotation phenomenon, polysaccharides, methanolysis and hydrolysis of saccharides, flavour formation deriving from the interactions of sugars with amino acids, and sterospecific activation of the C-H bond for the deuterium and tritium labelling are reported.

In several cases, a comparison is made between results obtained with conventional and microwave-assisted methods.

1. INTRODUCTION

In recent years, the electromagnetic energy in the range of microwaves have gained special attention as regards the most various fields of utilization such as the alimentary (domestic ovens), analytical (small ovens devoted to the mineralization), and that one of bio-medical applications.

In the field of organic synthetic chemistry, a certain delay has been suffered either in the base research for the clear improvements which can lead to higher yields of cleaner products, minor energy consumption, and environmental compatibility or in the industrial research, which requires new synthetic designs and then, above all, new designs of reactors necessary for the use, control, and containment of this type of electromagnetic energy. This delay, however, is rapidly reducing and the electromagnetic energy, caused by microwaves, used as an activating agent in chemistry, is generally adopted today for the synthesis of a large variety of compounds.

Numerous organic reactions assisted by microwave heating have been performed and reviewed in articles [1] or books [2]. These concern the acylation and alkylation reactions, aromatic and nucleophilic substitutions, condensations, cycloadditions, protection and deprotection reactions, esterifications and transesterifications, heterocyclizations, rearrangements, organometallic reactions, oxidations and reductions [1o]. The chief features, which appear from these micro-assisted reactions, are the enhanced selectivity, much improved reaction rates, milder reaction conditions and formation of cleaner products and then higher yields and minor wastes. It is not clear yet, whether these features derive from a superheating caused by microwaves or because these latter alter the transition state parameters of reactions. Moreover, an other feature is the possibility of carrying out reactions without solvent (or, anyway, with a strong reduction of solvents). These reactions are especially appealing as they can be carried out in open vessels, thus avoiding the risk of the development of high pressure in addition to the associated ease of manipulation. Furthermore, these reactions lead to a fall of costs and minor environmental impact.

However, a limited number of these reactions regard so far the carbohydrate chemistry, and since carbohydrates play an important role in a vast array of biological processes, and particularly there are many advantages, for example, in carbohydrate-based drugs such as low toxicity and immunogenicity, the interest in their preparation and reactivity by microwave heating is very high. 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.

We herein describe about these limited methods assisted by microwave heating for fast and high yielding processes, until today used in carbohydrate chemistry to our best knowledge. We hope that this review provides the organic chemist, who is interested in carbohydrates, an overview of already existing methodologies, as well as an outline of the benefits and limitations connected with microwave heating, especially today in the light of growing development of carbohydrate chemistry caused by the actual passage from petroleum, as material raw, to natural feedstock. In most cases a comparison is made with results obtained with classical methods.

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2. APPARATUS

Organic chemistry has achieved extensive improvements from microwave irradiation with the help of either domestic ovens [3] or, more recently, monomode reactors [4], which have allowed to conduct different reactions with noticeable success, but with the limit imposed by their size of using a maximum of reactants (30-40 g). Recently, commercial ovens have been designed for kilogram scale preparative reactions. Alternatively there are continuous flow systems [5] in which the reagents are pumped through the microwave cavity, allowing only a portion of the sample to be irradiated at a time and then the same heat profile to be exactly kept, even for large-scale synthesis. The main drawback is that, in some cases, not all the substance will be in solution prior to or after microwave irradiation and this can cause the flow to stop due to pipes becoming blocked.

Domestic ovens were the first to be used and their employment is still today exploited in relation, particularly, to Microwave Induced Organic Reaction Enhancement (MORE) [6]. This is a chemistry technique by which reactions are performed in unmodified domestic microwave ovens in a matter of minutes using very limited amounts of high boiling solvents or no solvents if one of the reactants is a suitable liquid.

Domestic ovens mainly use the radiation of 2450 MHz frequency, less frequently that one of 900 MHz frequency, which are directed into the oven. The level of the energy is controlled by an on-off cycle that can be adjusted for various levels of energy. Microwaves are non-ionizing radiations that are absorbed by ions in solution and by dipolar compounds. Since glass and many polymeric materials are nearly transparent to microwaves, advantage is taken by this property of microwaves to sharply reduce the amount of used organic solvents. The energy input is controlled so that the solvent and/or the reaction mixture is not allowed to approach the boiling point too closely. Thereby, the amount of vaporization is kept low and no reflux condenser is needed. A major advantage is given by the usual reaction time which is a few minutes even on a few hundred grams scale. The reduction of solvents and formation of lowered amounts of by-products decrease the pollution at the source and ensure high levels of "atom economy".

Another advantage of MORE chemistry techniques is the lowered energy consumption compared to conventional reactions performed under reflux which require also the latent heat of vaporization.

Monomode reactors are the best system able to allow measurements and control of temperature throughout the reaction which proceeds with a good homogeneity and high energetic yield. Due to the evident industrial interest, more convenient and new larger apparatus later on have been developed in order to increase the amounts of products especially for typical solvent-free organic reactions.

These reactors were essentially designed for scale-up with focused microwaves equipped with a one litre vessel, a mechanical stirrer for providing a good homogeneity and eventually a dropping funnel so that it makes possible to perform reactions under controlled atmospheres. These operate with an adjustable power between 40 and 800 W and may be monitored either in power or in temperature, or both. Automatic control of the irradiation (power and temperature) as well as data treatment could be followed by a computer system.

3. PROTECTION

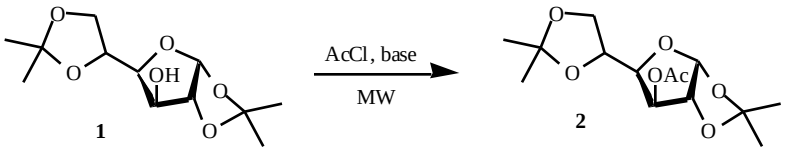
3.1 Acylation

Several methods have been described for fast and high yielding microwave-assisted protection of carbohydrate hydroxyl functionalities with acetic anhydride, acetyl, chloroacetyl, pivaloyl, dodecanoyl, and benzoyl chloride together either with a conventional base, such as pyridine and triethylamine, or with a polystyrene-linked alkyl amine. The use of solid supported reagent in these reactions resulted in a slightly slower reaction, but still comparable with conventional methods.

Also enzymes were proved to work well under the microwave irradiation for the regioselective acylations of sugar derivatives and, moreover, enhancements of the rate of reactions in non-aqueous solvents. Chen *et al*. [7], for example, reported a study devoted to investigate, through practical procedures for the screening of enzyme reactions, the initial, central and residual enzyme activity in organic solvents, and inversion of enantioselectivity by solvents.

3.1.1 Acetylation

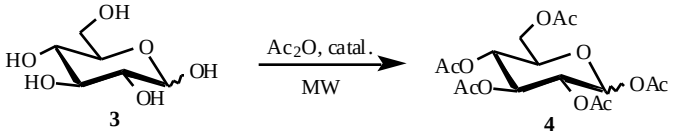
In a recent paper, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) was selected as carbohydrate model compound by Oscarson *et al*. [8] for its acetylation with acetyl chloride and pyridine, or *N*,*N*-(diisopropyl)amino-ethylpolystyrene (PS-DIEA) or *N*-(methylpolystyrene)-4-(methylamino)-pyridine (PDS-DMAP) as conventional base (monosaccharide:acetyl chloride = 1:2) to give the acetyl derivative **2** (Scheme 1, Table 1).



Scheme 1.

Table 1: Acetylation of 1 into 2 with acetyl chloride and a conventional base [8].

Reagent	Base	Temp. (°C)	Time (min)	Yield of 2 (%)
AcCl	Pyridine	170	12	80
AcCl	PS-DIEA	165	20	66
AcCl	PS-DMAP	180	15	88
ClAcCl	Pyridine	100	5	95

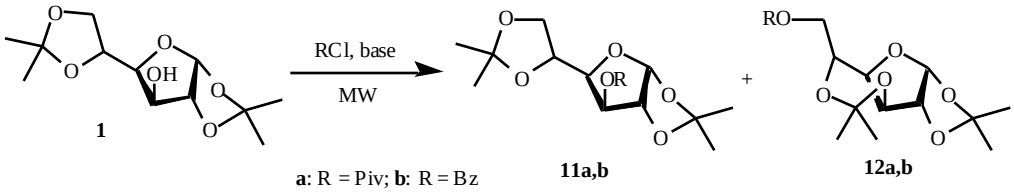


Scheme 2.

Table 2: Peracetylation of 3, 5, 7 and 9 with acetic anhydride and various catalysts [10].

Compd	Catalyst	Heating mode	Power (W)	Time (min)	Temp. (°C)	Yield (%)	Ratio α/β
3	$ZnCl_2$	MW[a]	50-20	6.5	125	**4** (98)	1/1
3	$ZnCl_2$	Δ[b]		6.5	125	**4** (83)	7/3
3	AcONa	MW[a]	80-20	10	106	**4** (90)	2/8
3	AcONa	Δ[b]		10	106	**4** (88)	2/8
3	AcOK	MW[a]	80-20	15	135	**4** (80)	3/7
3	AcOK	Δ[b]		15	135	**4** (98)	2/8
5	AcONa	MW[a]	80-20	11	140	**6** (97)	6/4
7	AcONa	MW[a]	80-20	11	137	**8** (90)	4/6
9	AcONa	MW[a]	80-20	11	127	**10** (87)	8/2

[a]MW = Microwave irradiation; [b]Δ = Conventional heating



a: R = Piv; **b**: R = Bz

Scheme 3.

Table 3: Pivaloylation of 1 with pivaloyl choride and a conventional base [8].

Reagent	Base	Temp. (°C)	Time (min)	Global yield[a] (%)
PivCl	Pyridine	170	15	85[a]
PivCl	PS-DMAP	160	20	79
PivCl	PS-DIEA	180	15	88

[a]Yields inclusive of **11a** + **12a** (**11a**:**12a** = 3:1).

Itonori *et al*. [9] described a technique for the microwave-mediated acetolysis of carbohydrates derived from glycosphingolipids using a mixture of hydrogen chloride, water and acetic acid, which proved to be a rapid, quantitative and useful method for structural analysis in the protostomia glycosphingolipids. The authors moreover showed that only by this method the detection of some sugar components or an improved recovery, for example, of xylose, was possible. For the acetolysis, which is important for the detection of the amount of sugar compounds and chemical sugar linkage in glycosphingolipids, the conventional method requires a time-consuming step which reaches 18 hours, against one minute of the microwave method.

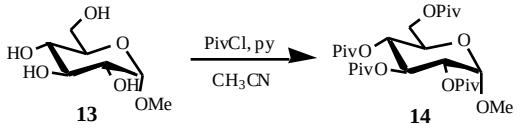
3.1.2 Peracetylation

Peracetylation of D-glucose (**3**) to give the acetyl derivative **4** with a small excess of acetic anhydride under catalysis of either anhydrous potassium or sodium acetate, or zinc chloride was found practically quantitative in less 15 min with microwave heating (Scheme 2, Table 2) by Limousin *et al*. [10]. As under classical conditions, reactions were highly β-selective with potassium or sodium acetate. With zinc dichloride, a 1:1 mixture of α/β pentacetates was obtained under microwave irradiation, whereas a ratio of 7:3 resulted under conventional oil bath heating. Attempts with D-galactose (**5**), D-mannose (**7**) or *N*-troc-D-glucosamine (**9**) and sodium acetate as a catalyst gave also excellent yields of acetyl derivates **6**, **8**, **10**, respectively, within 11 min (Table 2).

Loupy *et al*. [11] performed peracetylation of **3** into two experiments by using 11.1 or 200 mmoles with a slight excess of acetic anhydride and catalytic amounts of zinc dichloride, either under classical heating or under microwave activation, and obtained yields rather similar whatever were the conditions used.

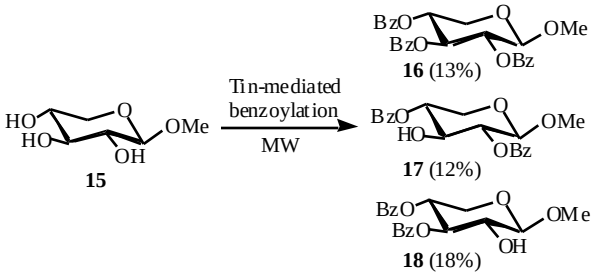
3.1.3 Pivaloylation

Of special interest are the formation of pivaloyl esters due to the steric bulk of the pivaloyl group. Oscarson *et al*. [8] found that these reactions are often very slow using conventional methods, but utilizing microwave heating the pivaloate formation (even multiple) is in the same range as acetate or benzoate formation with the α:β ratio of 1:2 (Scheme 3, Table 3).



13 **14**

Scheme 4.



15 **16** (13%) **17** (12%) **18** (18%)

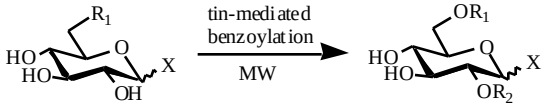
Scheme 5.

During pivaloylation of **1** with pyridine as base, the authors [8] isolated, along with **11a**, as a by-product, also 6-*O*-pivaloyl-1,2:3,5-di-*O*-isopropy1idene-α-D-glucofuranose (**12a**) in about 25% yield. This was shown to derive through a 5,6- to 3,5-acetal migration prior to acylation. Acetal migration was not observed for the acetylation and chloroacetylation reactions, indicating that acetylation is too rapid to allow for the acetal rearrangement. This migration, which has been observed earlier under Koenigs-Knorr and halogenation conditions [12], is probably catalyzed by the formed pyridinium chloride, since irradiation of **1** in pyridine with no acyl chloride added showed no migration. Furthermore, the use of a solid supported base, when the pyridinium chloride formed is bound to the resin and not free in solution, prevented the migration.

Pivaloylation of methyl α-D-glucopyranoside **13** in pyridine gave 68% of pivaloyl derivative 1**4** in 10 min (Scheme 4).

3.1.4 Benzoylation

In connection with their current endeavours towards the synthesis of polyoxygenated natural products and oligosaccharides [13], Herradòn *et al*. [14] examined the effect of microwave heating on the regio-selective benzoylation of different carbohydrate-derived polyols through the formation of not isolable dibutylstannylene acetals by using a commercial microwave oven. The interesting feature of this transformation is that the dibutylstannylene acetal is obtained by heating a mixture of the polyol and dibutyl tin oxide in a commercial oven for few minutes. This compares favourably with the standard method that requires heating for several hours. The benzoylation of methyl β-D-pyranoside **15**, as previously documented in literature [15], is not selective giving a mixture of tribenzoate **16** and dibenzoates **17** and **18** (Scheme 5), while that of derivatives **19**, **21** and **23** gave the selectively protected derivatives **20**, **22** and **24** (Scheme 6). Later, dibutyltin oxide was used as catalyst in the presence of an equivalent of a base obtaining from **21** the 26% of the monobenzoate **22** along with 40% of starting material.



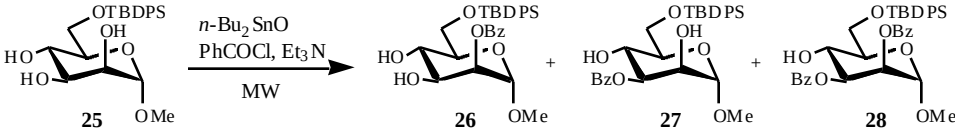
19 X = a-OMe, R_1 = H
21 X = a-OMe, R_1 = TBPS
23 X = b-SPh, R_1 = H

20 X = a-OMe, R_1 = R_2 = Bz
22 X = a-OMe, R_1 = TBPS, R_2 = Bz
24 X = b-SPh, R_1 = H, R_2 = Bz

Scheme 6.

In order to verify the possibility of modulating the selectivity in microwave-promoted protection of hydroxyl functionalities, Herradòn *et al*. [16] studied further the influences of both the solvent and the power output of the oven on the selectivity of dibutylstannylene acetal-mediated benzoylation of polyols among which some carbohydrates such as methyl α-D-mannopyranoside **25** (Scheme 7). Their studies led to the results given in Table 5.

Oscarson *et al*. [8] obtained the same results as those of the pivaloylation when **1** was subjected to the benzoylation (Scheme 3). Benzoylation of selected substrates, such as 1, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**29**), methyl 4,6-*O*-benzylidene-α-D-glucopyranose (**31**), which are not stable in acidic conditions, was performed by Clèophax *et al*. [17] in a monomode system with methyl benzoate by *trans*-esterification under basic conditions (K_2CO_3, KOH, K_3PO_4), using tetrabutyl-ammonium bromide as phase transfer agent, either in the absence of solvent or in the presence of small amounts of various solvents (dimethyl formamide, diglyme, mesytilene).

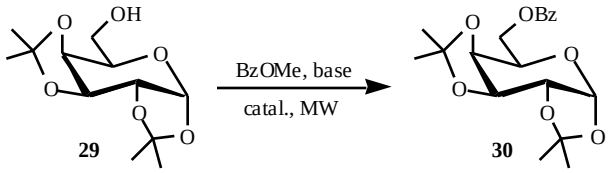


25 **26** **27** **28**

Scheme 7.

Table 4: Benzoylation of 25 with PhCOCl, *n*-Bu_2SnO and Et_3N [16].

Solvent, power	26 (%)	27 (%)	28 (%)
Toluene, maximum	35	25	10
Toluene, medium	18	57	2
Toluene, minimum	6	35	0
Acetonitrile, minimum	0	41	0
Blank, toluene, maximum	0	0	0
Blank, acetonitrile, minimum	0	0	0



29 **30**

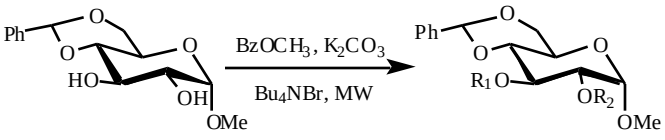
Scheme 8.

A weak and non nuclephilic base like potassium carbonate provided better yields of 3-*O*-benzoyl derivative **11b** than other stronger bases as potassium hydroxide, which probably induces the saponification of esters.

Longer reaction time and the use of tetrabutylammonium bisulfate as the catalyst did not improved the yield. Under solvent-free conditions the best results was limited to 44% in yield. The addition of small of dimethyl formamide led to a large improvement in yield which became nearly quantitative (96%).

The same conditions were applied to **29** which afforded a yield of 66% of benzoyl derivative **30** under solvent-free conditions within 4 minutes of irradiation. When 2 mL of dimethyl formamide were added, the yield was increased up to 76% within 15 minutes of irradiation (Scheme 8).

Several attempts towards selective mono-benzoylation as well as di-benzoylation were performed with sugar **31**, but no selectivity was observed for mono-benzoylation. Using 4 equiv of methyl benzoate, a 82% yield of di-benzoylated product **32** was obtained with 15 minutes of irradiation. Under classical heating, the yield was very low with principally the mono-benzoylated products **33** and **34** showing again a very significant specific microwave effect (Scheme 9).



31

32: $R_1 = R_2 = Bz$
33: $R_1 = Bz$; $R_2 = H$
34: $R_1 = H$; $R_2 = Bz$

Scheme 9.

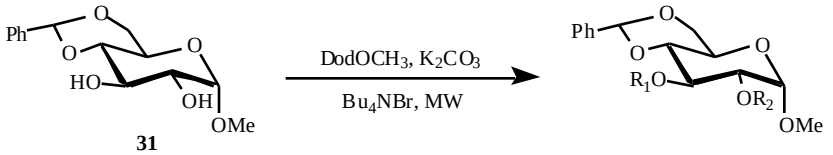
3.1.5 Dodecanoylation

Trans-esterification of **1** was achieved by Clèophax *et al*. [17] under treatment with methyl laurate, potassium carbonate as the base and tetrabutylammonium bromide as the phase transfer catalyst. The best yield (88%) was obtained in the presence of dimethylformamide with a very important specific effect of irradiation.

With **31**, selective di-esterification (product **35**) as well as mono-esterification (products **36** and **37**) were achieved (Scheme 10) and the main results are given in the Table 5.

Also isosorbide **38** was esterified with methyl laureate (Scheme 11) because of its importance as by-product of the starch industry, available in large quantities and low cost. Products of mono-esterification (**39** and **40**) were obtained in the presence of potassium carbonate and different phase transfer catalysis (4%) and solvents. The main results are given in Table 6.

Gelo-Pujic *et al*. [18] has studied the immobilized lipase-catalyzed esterification of **3** and **13** with dodecanoic acid in dry media under focused microwave irradiation using a



31

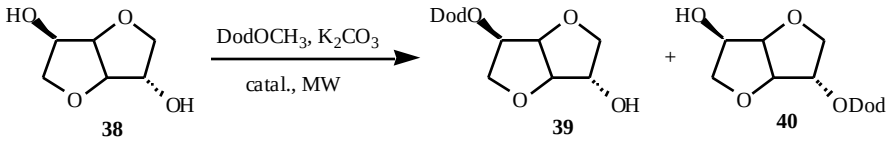
35: $R_1 = R_2 = Dod$
36: $R_1 = Dod$; $R_2 = H$
37: $R_1 = H$; $R_2 = Dod$

Scheme 10.

Table 5: *Trans*-esterification of 31 into di-ester 35 and mono-esters 36 and 37 in basic medium (K_2CO_3) with methyl dodecanolate in the presence of Bu_4NBr (4%) and DMF [17].

35 (%)	36 (%)	37 (%)	K_2CO_3 (equiv)	Methyl dodecanolate (equiv)	Time (min)	Temp. (°C)
27	23	22	3	4	9	147
56	21	19	3	4	15	151
77	12	11	3	4	30	147
0	2	1	3	4	9[a]	147
8	18	18	3	4	1620[a]	147
24	26	15	1.5	1.5	15	150

[a]Conventional heating (thermostated oil bath)



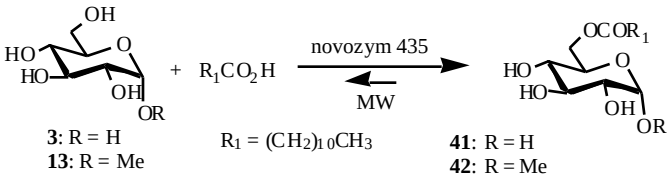
38 **39** **40**

Scheme 11.

Table 6: *Trans*-esterification of 38 into 39 and 40 with methyl dodecanolate in the presence of K_2CO_3 and a phase transfer catalyst (4%) [17].

Total Yield (%)	39/40 (%)	Catal.[a]	Solvent (2 mL)	Time (min)	Temp. (°C)
44	18/26	A	DMF	15	154
47	25/22	A	DMSO	15	174
63	38/25	B	DMF	15	159
44	24/20	B	DMSO	15	172
61	25/36	B	DMSO	30	164
< 5		B[b]	DMF	15	159
14	9/5			1200	159

[a]A: Aliquat 336; B: Bu_4NBr. [b]Conventional Heating (thermostated oil bath).

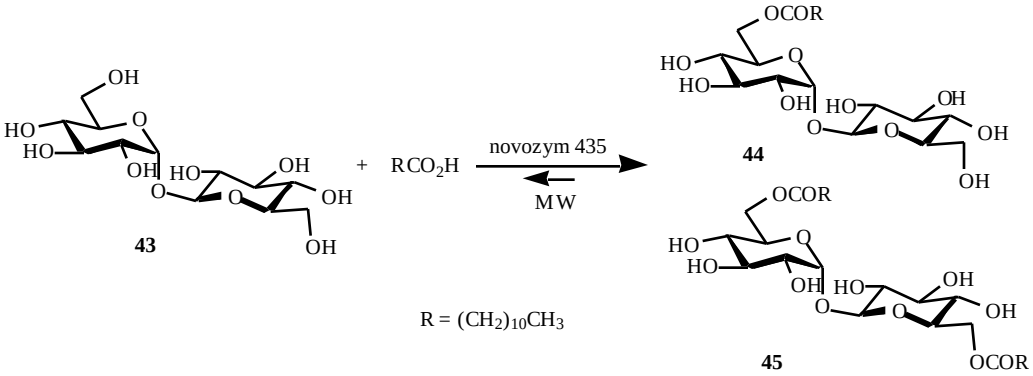


Scheme 12.

Table 7: Esterification of 3 with dodecanoic acid in the 1:3 ratio to give 41 [18].

Mode of sample preparation[a]	Time (h)	Temp. (°C)	Power range (W)	Yield of 41 (%)
A	2	95	120-60	62
A[b]	2	95	120-60	67
A	5	95	120-40	95
A	5	95	oil bath	55
B	3	95	120-60	95
B	2	110	120-60	97
A[c]	4.5	95	120-40	48
A[d]	5	110	120-90	81

[a]Mode A: Addition of the acid solution after the desiccation under vacuum. Mode B: Addition of the acid solution at the beginning of the reaction. [b]Reaction conducted with recovered enzyme. [c]A ratio of eq 1:1.5 was used. [d]Five-fold larger preparation.



Scheme 13.

Synthewave reactor and classical heating under the same conditions of time and temperature (Scheme 12). The advantages of performing these reactions in the microwave reactor are evident in all cases in terms of better regio-selectivity, higher yields and cleaner purities (Table 7).

Starting from α,α-trealose **43**, the mayor product obtained was the 6,6'-di-ester **45** accompanied by minor of 4% of 6-mono-ester **44** (Scheme 13, Table 8).

The esterification of sucrose and ascorbic acid with different fatty acids was performed by Bradoo *et al* [19] in a microwave oven using porcine pancreas, B. stearothermophilus SB-1 and B. cepacioa RGP-10 lipases within a screening procedure for characterization of lipase selectivities. Microwave-assisted enzyme catalysis resulted an attractive procedure for rapid characterization of a large number of enzyme samples and substrates, which otherwise resulted in a cumbersome and time-consuming exercise.

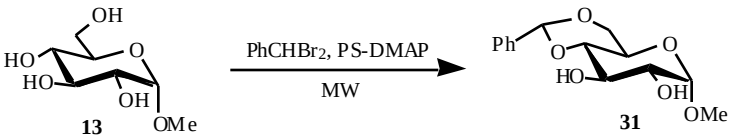
3.2 Acetal Formation

The method developed by Garegg *et al*. [20] to form benzylidene acetals by using benzal bromide under refluxing pyridine for several hours was modified by Oscarson *et al*. [8]. Compound **13** was treated with benzal bromide and *N*-(methylpolystyrene)-4-(methylamino)pyridine (PS-DMAP)

Table 8: Esterification of 43 with dodecanoic acid (3 eq.) at 110°C [18].

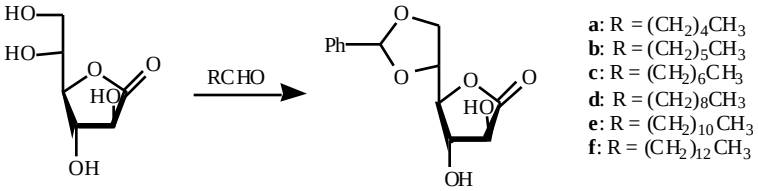
Mode of sample preparation[a]	Time (h)	Power range (W)	Global Yield (%)	45 : 44
A	3	150-60	41	36 : 5
A[b]	3	150-90	39	37 : 2
A	13	150-60	83	80 : 3
B	13	150-60	92	88 : 4
B	13	Oil bath	78	75 : 3
C	13	120-60	32	30 : 2

[a]Mode A: Addition of the acid solution after the desiccation under vacuum. Mode B: Addition of the acid solution at the beginning of the reaction. Mode C: Samples were dried in the microwave reactor at 95 °C during 30 min. [b]Reaction conducted with recovered enzyme.



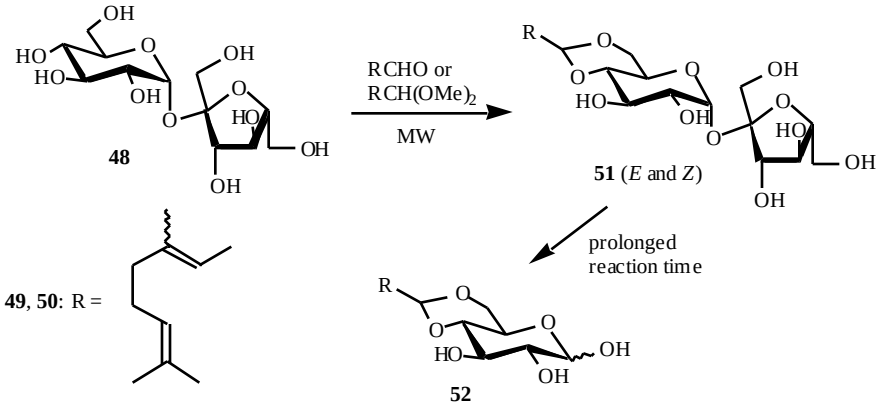
13 **31**

Scheme 14.



46 **47a-f**

Scheme 15.



48 **51** (*E* and *Z*) **52**

Scheme 16.

in acetonitrile to form the 4,6-*O*-benzylidene derivative **31** in 83% yield after 5 min at 170°C (Scheme 14).

Following their interest in products with liquid crystalline and surfactant properties Cisba *et al*. [21] synthetized some amphiphilic derivatives of L-galactono-1,4-lactone **46**, a by-product of the sugar industry available in large quantities [22]. Reactions between **46** and hexyl, heptyl, octyl, decyl, dodecyl, and myristyl aldehydes impregnated on montmorillonite were performed in a focused open-vessel microwave system for 10 min in the absence of solvent (Scheme 15).

The yields obtained (60-66%) were considerably improved with respect to those (22-38%) obtained under heating as well as the proportions of isomers were also more favourable (8:2) than those isolated (6:4) by conventional heating. In the case of dodecyl aldehyde, the authors check the behaviour of montmorillonite K 10 as a catalyst and support with microwave irradiation; the yield was rather higher (89%), but isomer ratio was less favourable (1:1). Compounds **47a-f** could serve as valuable biodegradable surfactants as they are stable under neutral conditions, but susceptible to decomposition under acidic conditions and furthermore they can be transformed into salts derivatives under basic conditions.

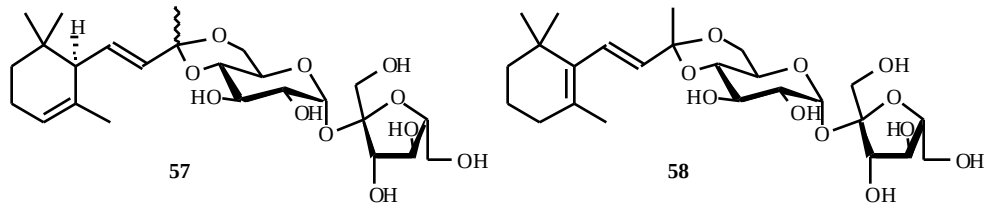
In a research directed to the mono-acetalization of sucrose (**48**) by citral (geranial (**49**) and neral (**50**), widely used as chemical intermediates in the perfume industry [23]), Queneau *et al*. [24] determined the conditions of optimized acidic catalysis in dimethyl formamide which afforded good yields of acetals directly from unprotected **48** in comparison with those in a oil bath. The authors, moreover, investigated the influence of microwave irradiation conducted in a Synthewave S402 apparatus on the reaction outcome (Scheme 16).

In table 9, the yields are given for the reaction of **48** with citral dimethyl acetal (CDMA). A good yield (83%) of sucrose acetals **51** could be obtained under nitrogen at 100 °C provided that the reaction was carefully cooled and neutralized. With prolonged reaction times, cleavage to acetal **52** occurred.

Against the total degradation of both **48** and CDMA in the conditions of the efficient microwave-assisted synthesis

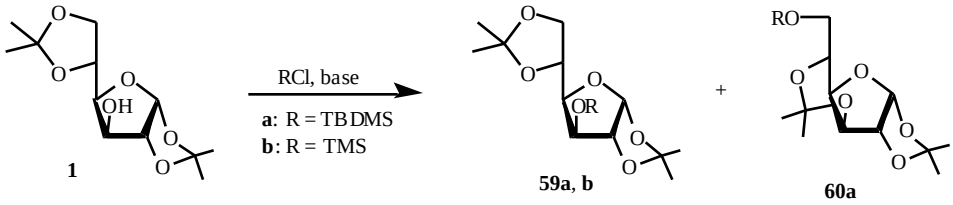
Table 9: Reaction of 48 with CDMA in DMF with pyridinium *p*-toluenesulfonate (PPTS), under classical heating (open or closed system) or microwave irradiation [24].

Time (min)	Classical heating (100 °C)				MW (100 °C)	
	Closed (N_2)		Open		Open	
	51	**52**	**51**	**52**	**51**	**52**
2	83	3	59	13	42	17
5	67	11	34	19	33	21
10	63	18	16	26	30	26
30	19	28	11	24	32	18



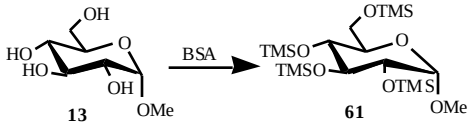
57 **58**

Fig. (1). Structure of **57** and **58**.



1 **59a, b** **60a**

Scheme 17.



13 **61**

Scheme 18.

of L-galactonolactone long chain acetals [21], the irradiation for 2 minutes at 300 W of **48** supported on silica gel as the only acid, with CDMA and very little amount of dimethyl formamide, afforded a 7% yield of **51** (16% after 5 mm at 60 W). In dimethyl formamide solution, no improvement of the reaction could be observed except a slower cleavage to compound **52**. This observation is consistent with a more homogeneous temperature of the system without hot points, confirming the limitation of typical microwave effects for reactions conducted in highly polar solvents [25].

Applying the reaction conditions optimized for the citral to dimethyl acetal **55** and **56** of α- (**53**) and β-ionone (**54**), respectively, the *trans*-esterification of **48** gave the corresponding acetals **57** (66%) and **58** (76%) (Fig. **1**), which were peracetylated for the characterization purpose. Acetal **57** was obtained as a 1:1 mixture of epimers at the cyclohexenyl junction.

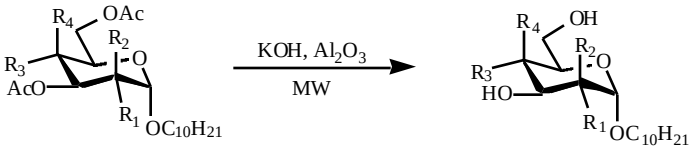
3.3 Silylation

The introduction of *tert*-butyldimethylsilyl groups was conducted by Oscarson [8] by means of *tert*-butyldimethylsilyl chloride in the presence of pyridine or *N*-(methylpolystyrene)-4-(methylamino)pyridine (PS-DMAP) by using a Smith synthesizer (Scheme 17), while *N*,*O*-*bis*-(trimethylsilyl)-acetamide (BSA), a reagent which does not require any additional base, was used for trimethyl silylation (Scheme 18). Once more, short reaction times and high yields were observed. Additionally, silylation with sterically hindered silyl reagents is the most applicable field for microwave heating resulting in reaction rate enhancements of up to around 700 times as compared to conventional methods. Here, too, acetal migration was observed in compound **1**, and the use of a solid supported base did not prevent this side reaction (Table 10).

Table 10: *tert*-Butyldimethylsilyl and trimethyl silylation of compounds 1 and 13 in the presence of imidazole, PS-DMAP or BSA as bases [8].

Product	Reagent	Base	Temp. (°C)	Time (min)	Yield (%)	Ratio 1:2[a]
59a + **60a**	Bu^tMe_2SiCl	Imidazole	200	10	94	3:1
59a + **60a**	Bu^tMe_2SiCl	PS-DMAP	180	15	83	3:1
59b	BSA	---	190	5	93	
61	BSA	---	180	10	70	

[a] Determined by NMR



62, **64**, **66**, **68** **63**, **65**, **67, 69**

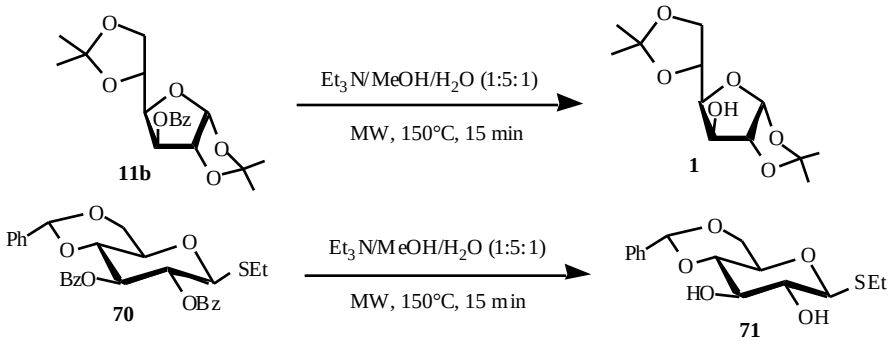
Compd/product	R_1	R_2	R_3	R_4
63/63	OAc/OH	H	OAc/OH	H
64/65	OAc/OH	H	H	OAc/OH
66/67	H	OAc/OH	OAc/OH	H
68/69	NHTroc	H	OAc/OH	H

Scheme 18.

Table 11: Saponification of 62 into 63 in 2 min at 100 °C [11].

Activation method	Amount of materials [g (mmol)]		Total amount (g)	Yield of 63 (%)
	62	KOH/Alumina		
MW, S402	1.09 (2.24)	2.91 (11.2)	4	96
Δ, oil bath	1.09	2.91	4	<2
MW, S1000	54.5 (112)	145.5 (560)	200	85

[a]Yields in isolated product (α-anomer)



Scheme 20.

With compound **13**, the trimethylsilylation was total (Table 10).

Khalafi-Nezhad *et al*. [26] applied the silylation of 5'-hydroxyl function of uridine by using imidazole and triisopropylsilyl chloride (TIPSCl) in a microwave oven at 200 W for 60 sec obtaining a 80% yield of silylated product. For comparison, the literature method [27] for this protection in dimethylformamide gave a 76% yield after 24 hours.

4. DEPROTECTION

For deprotection studies, mild condition methods have been chosen to see if the extended reaction times often connected with the methods, which use conventional heating, could be shortened by the use of microwave heating. Some solid supported reagents were also tested.

4.1 Deacylation

4.1.1 Deacetylation

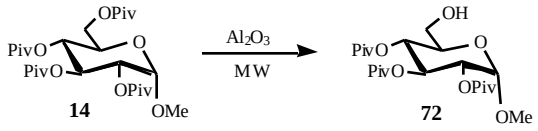
While no reaction was observed by microwave irradiation of adsorbed decyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside **62** on alumina (Varma's conditions) [28], the saponification of the protected glucoside **62** to decyl glucoside **63** was carried out by Limousin *et al*. [10] with a small excess of potassium hydroxide impregnated on alumina in dry conditions (Scheme 19). The same procedures were applied to acetates **64**, **66** and **68** of decyl D-galactoside **65**, D-mannoside **67**, and 2-deoxy-2-(2,2,2-trichloroethoxy-carbonylamino)-D-glucoside 69.

In these reactions, the effect of microwave irradiation is highly decisive because with classical heating no reaction occurred after 2 min at 100°C, whereas the yield was nearly quantitative under microwave.

By estension of the saponification of **62** by a factor of 50, scale up led to satisfactory results under the same conditions using the Synthewave 1000 equipment (85% yield within 2 min) [11] (Table 11).

4.1.2 Debenzoylation

Oscarson *et al*. [8] followed the methods described by Tsuzuki *et al*. [29] and Mori *et al*. [30] with the variation of microwave heating. Compounds **11b** and ethyl 2,3-di-*O*-benzoy1-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (**70**) were heated at 150°C for 15 min in a mixture of triethylamine/methanol/water (1:5:1) to give debenzoylated compounds **1** and **71** in 71% and 78% yield, respectively (Scheme 20).

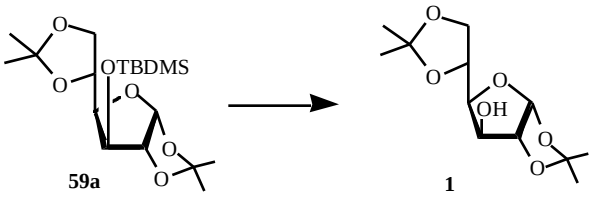


Scheme 21.

Table 12: Deprotection of pivaloyl ester 14 into 72 Silica (Florisil) inorganic oxides [31].

Method[a]	Time (min)	Yield (%)
A	6	89[b]
B	30	91[c]
C	3000	---[d]
B	30	---[d]

[a]Methods: A, Sanyo Microwave, 850 W. B, Proline Microwave, 800 W. C, Oil bath. [b]Products extracted with dichloromethane. [c]Products obtained by soxhlet extraction with ethyl acetate. [d] No deprotection was observed.



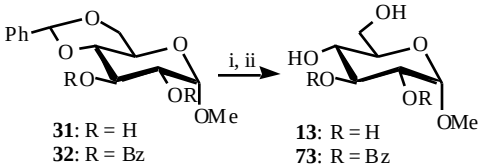
Scheme 22.

4.1.3 Depivaloylation

In a effort to devise a mild, high yielding deprotection strategy for hindered esters Ley and Mynett [31] investigated the possibility of microwave-assisted hydrolysis on neutral alumina of a series of pivaloyl protected alcohols among which also a glycosic system by using a Sanyo EM850 oven or a Proline M2525. The authors show that the deprotection of the six position takes places selectively cleanly and efficiently without group migration or isomerization of the anomeric centre (Scheme 21, Table 12). Deprotection using an alternative heating source (oil bath at 75°C) could not be achieved.

4.2 Desilylation

There are a number of methods for deprotection of silyl groups under both acidic and basic conditions [32]. For basic conditions, Oscarson *et al*. [8] treated **59a** with tetrabutylammonium bromide and potassium fluoride for 2 min at 180°C to give the desilylated compound **1** in 61% yield. For slightly acidic conditions, they used montmorillonite K 10 Clay in methanol/water (1:1) (Scheme 22). Compound **59a** and its desilylated derivative **1** were also treated with K 10 Clay in methanol/water at 150°C for 4 min and 3 min, respectively, to give **3** in high yields (85% and 91%, respectively). This latter can be compared to the original conditions (75°C for 72 h, 77% yield) for deprotection of derivative **1** to **3** [33].



Scheme 23.

4.3 Deacetalation

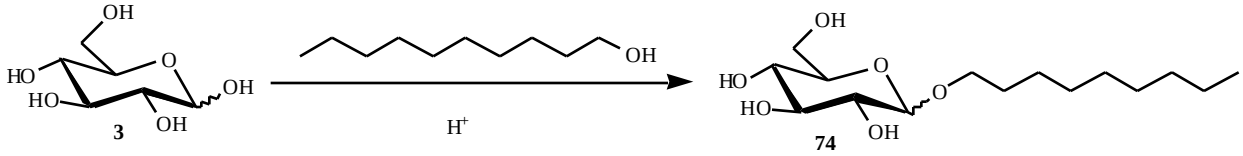
Oscarson *et al*. [8] described the hydrolysis of compound **31** by treatment with K 10 Clay in methanol/water for 2 min at 150°C with a 89% yield. Moreover, since polymer supported reagents worked out well for acylation reactions, they treated **31** with polymer supported PPTS [poly(4-vinylpyridinium-*p*-toluensulfonate) in ethanol/water at 150°C for 2 min to obtain **13** in 94% yield (Scheme 23).

5. ALKYLATION/GLYCOSIDATION

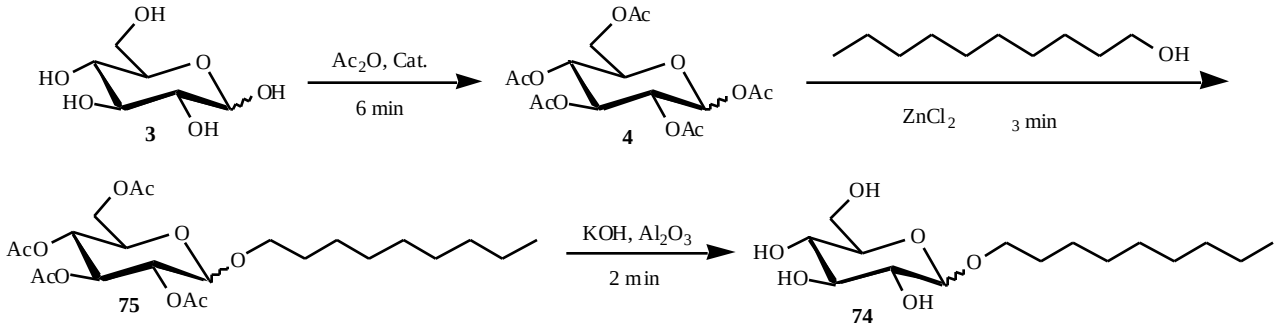
The interest in alkyl- or aryl-glycosides is connected to their physical properties, as liquid crystals and as non toxic and biodegradable surfactans [34, 35]. In particular, alkyl glycosides with long-chain alkyl groups, derived from natural raw materials [36], are used for the production of tenside formulations because of their technological degradability [37]. Moreover, they play an important role as chemical intermediates in the biotechnology [38].

Alkylation of **3** into **74** was carried out by Clèophax *et al*. [10] in an acid catalyzed reaction with a slight excess of 1-decanol (Scheme 24).

The maximum yield of 15% was observed after 10 min of microwave irradiation at a power of 200 to 20 watt and a final temperature of 150°C with 0.5 equiv of *p*-toluenesulfonic acid and absorption of the reagents on Hyflo Super Cel, which, among all solid supports tested (Hyflo Super Cel, Celite, Alumina, Zeolites, Montmorillonites, ion-



Scheme 24.



Scheme 25.

Table 13: Catalyzed alkylation of 4 in the presence of 1-decanol (1.5 eq) with or without supports [10].

Catalyst[a]	Power (W)	Time (min)	Final T (°C)	Total yield (%)	Ratio α/β
TsOH: 0.1 equiv	60-20	5	136	7	5/2
$SnCl_2$: 1 equiv	60-20	4	156	31	24/7
$ZnCl_2$/Silica gel (1 g/5g)	100-20	11	100	30	16/14
$ZnCl_2$/Silica gel (1 g/5g)	100-20	3.5	135	33	24/9
Clayzic[b]	150-20	11	115	20	16/4
$ZnCl_2$/sand (1 g/5g)	60-20	8.5	125	58	30/28
$ZnCl_2$ + sand (1 g/7g)	60-20	8	118	68	53/15
$ZnCl_2$ +HSC[c]	150-20	9	116	74	64/9
$ZnCl_2$ + HSC[d]	150-20	15	115	35	15/20
$ZnCl_2$: 1 equiv	60-20	3	113	74	64/9
$ZnCl_2$: 1 equiv	Oil Bath	10 300	113 113	0 25[e]	21/4

[a]$ZnCl_2$/support = $ZnCl_2$ adsorbed on solid support - $ZnCl_2$ + support = $ZnCl_2$ dispersed with solid support with 1 equiv $ZnCl_2$/sugar in both cases. [b]Clayzic is $ZnCl_2$ adsorbed on montmorillonite K10. [c]1-Decanol adsorbed on Hyflo Super Cel in ratio 1/8; $ZnCl_2$ = 1 equiv. [d]1-Decanol and sugar adsorbed on Hyflo Super Cel in ratio 1/8 and 1/5, respectively; $ZnCl_2$ = 1 equiv. [e]With 9% of *N*-(tetra-*O*-acetyl-α-D-glucopyranolsyl)pyridinium chloride.

Table 14: Zinc dichloride-catalyzed glycosylation of 1-decanol with 4 at 110°C [11].

Heating mode	Time (min)	Amount of material (g)			Total amount (g)	Yield of 74 (%)[a]
		4	1-decanol	$ZnCl_2$		
MW, S402	3	1.95	1.19	0.68	3.82	74[b]
Δ, oil bath	3	1.95	1.19	0.68	3.82	0[c]
MW, S1000	4	97.5	59.4	34.1	191	72[d]

[a]Yields in isolated product. [b]Yields of anomers (%): α/β = 64/10. [c]After 5 h, yield is only 25%. [d]Yields of anomers (%): α/β = 62/10.

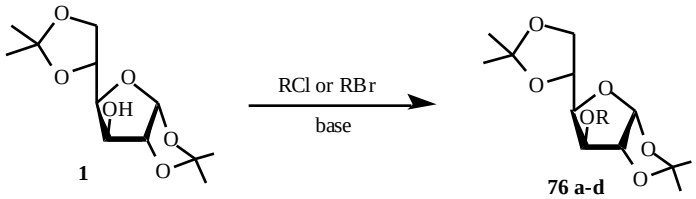
exchange resins and Florosil) gave significant yields. The limitation in yield is mainly due to glucoside decomposition in the presence of acids (sulphuric or *p*-toluensulfonic acid, alone or in the presence of a variety of solid supports). The results obtained were quite noteworthy in regard to reaction time and low excess of reagents when compared with results from the classical Fischer synthesis [34, 39] and enzyme-catalyzed glycosylations [40], but the method was not totally satisfactory.

Alternatively, a microwave assisted three-step procedure of glycosidation of **3** into **74**, which was extended to other sugars such as **5**, **7**, and **9** with high yields, was carried out. This procedure uses the peracetylation of the sugar, Lewis acid-catalyzed reaction with the alcohol and then the deacylation (Scheme 25).

The reaction of **4** with 1-decanol was attempted in the presence of several Lewis acids ($ZnSO_4$, $Zn(OTf)_2$, MgF_2, $FeCl_3$, $CoCl_2$, $CuCl_2$ $CeCl_3$, $MgCl_2$, $LiPF_6$, TsOH, $ZnCl_2$, $ZnBr_2$, $SnCl_2$), but only zinc chloride was the catalyst of choice for this reaction [10]. The results obtained under similar conditions by classical heating or microwave activation are compared in the Table 13.

Scale-up of this three-step procedure was found fairly interesting by Loupy *et al*. [11], who obtained yields similar to those obtained under very close conditions from the glycosylation of decanol with peracetyl derivatives of **4** and **5** at 110°C by using Synthewave 402 and 1000 (Table 14). An important non-purely thermal effect is involved when one considers the 72-74% yields compared to those obtained in the absence of reaction under classical heating.

Oscarson *et al*. [8] carried out different microwave-assisted alkylations on **1** in a Smith synthesizer (Scheme 26), by using a ratio of 1:2, with a strong base in very short reaction times and excellent yields (Table 15). Also with a weak base an acceptable yield of alkylated product was obtained in about 20 minutes. Most interesting is that the



Scheme 26. R: **a** = All; **b** = Bn; **c** = 4-Me-Bn; **d** = 2-NO_2-Bn

Table 15: Protection of 1 with RCl or Br in the presence of a base [8].

Product	Reagent	Base	Temp.(°C)	Time/Yield (min/%)
76a	AllBr	NaH	190	1/88
76b	BnC1	NaH	190	1/95
76b	BnBr	NaH	180	1/96
76b	BnC1	KOH	150	2/98
76b	BnBr	Ag_2O	190	20/68
76c	*p*-CH_3BnBr	KOH	160	5/90
76d	*o*-NO_2BnBr	NaH	180	2/94

Table 16: Reaction of sugars 3, 5, 7 or sugar derivatives with alcohol in a microwave batch reactor (catalyst: HCl or AcCl) [41].

Sugar	Alcohol	Temp. (°C)	Time (min)	Power (W)	Yield (%)	Ratio α:β
D-glucose	Methanol	Reflux	60	500/300	100	100:0
	Methanol	140	20	500	100	100:0
	Ethanol	140	30	750	100[a]	
	Butanol	reflux	40	750	90[a]	
	Butanol	Reflux	60	750	100	95:5[b]
	Octanol	120	20	500	10[c]	
	Octanol	120	20	500	95[a]	
D-mannose	Methanol	Reflux	35	500	100	100:0
	Ethanol	Reflux	40	750	100[a]	
D-galactose	Methanol	Reflux	35	500	100	100:0
	Ethanol	Reflux	40	750	100[a]	
Butyl D-glucose	Decanol	120	30	500	85[a]	
Starch	Methanol	140	20	500	60	100:0
	Methanol	140	20	500	100	100:0

[a]Mixture of anomers; [b]Three-fold amount of educts; [c]90% of D-glucose is degraded.

Table 17: Reaction of 3 or its derivatives with alcohol in a microwave flow reactor (System: ETHOS, Catalyst:AcCl, 0:5%) [41].

Sugar	Alcohol	Reaction conditions	Residence time (min)	Yield (%)	Anomeric ratio α:β
3	Methanol	140°C, 16 bar	10	100	95:5
3	Methanol	140°C, 12 bar	4	100	10:90
3	Octanol	120°C, 12 bar	5	95	[a]
77	Octanol	120°C, 12 bar	5	100	[a]
77	Octanol	110°C, 15 bar	12	100	[b]
77	Decanol	110°C, 12 bar	5	100	[a]
78	Octanol	120°C, 12 bar	5	100	[a]

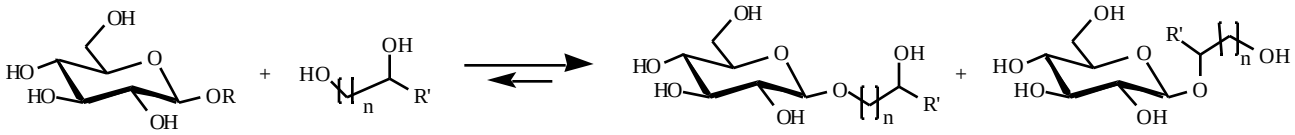
[a]Mixture of anomers; [b]The octyl α-D-glucopyranoside is produced only.

short reaction time permits the use of a strong base even with base-labile starting materials.

By means of an ETHOS MR oven, Nuchter *et al*. [41] accomplished a scaling-up of microwave-assisted Fischer glycosidations to the Kg-scale with an improvement in economic efficiency.

In batch reactions carbohydrates were converted in 50-g scale with 3-30-fold molar amount of alcohol in the presence of a catalytic amount of acid. The results of the reactions of **3** and its derivatives such as butyl D-glucose (**77**) and starch, in addition to **5** and **7** with different alcohols are summarized in Table 16. Furanosides are not stable under reaction conditions.

In further experiments, the feasibility of the Fischer glycosidation was tested in the microwave flow system with **3**, **77** and ethyl D-glucose (**78**). The premixed educts were pumped through the reactor under variation of residence time, pressure, temperature and microwave energy. The results of these tests are given in Table 17.



3: R = H;
81: R = Ph;
85: R = 4-O-Glu.

79: R' = Ph, n = 6;
82: R' = Me, n = 1;
82: R' = Me, n = 1.

80: R' = H, n = 6;
83: R' = Me, n = 1;
86: R' = Me, n = 1.

84: R' = Me, n = 1;
87: R' = Me, n = 1.

Scheme 27.

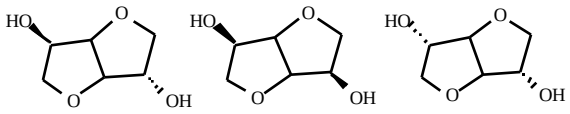
Table 18: Glicosidase catalyzed *trans*-glycosidation of donors 3, 81, and 85 under microwave irradiation (MW) and classical heating conditions (Δ) [42].

Donor	Acceptor (mmol)	Time (h)	Temp. (°C)	Mode	Global Yield (%)	Relative Yields (%)			Hydrolysis (%)
						80	**83**	**84**	
3[a]	**79** (2)	1	80	MW	16	16			
3[a]	**79** (2)	6	80	Δ	17	17			
81[b]	**82** (10)	2	110	MW	97		77	20	0
81[c]	**82** (2)	2	110	MW	77		62	15	0
81[c]	**82** (2)	0.5	110	MW	67		49	11	7
81[c]	**82** (2)	0.5	110	Δ	47		31	18	8
81[c]	**82** (2)	1	95	MW	81		57	16	8
81[c, e]	**82** (2)	1	95	MW	55		38	9	8
81[c, e]	**82** (2)	2	95	Δ	62		40	9	13
81[c, f]	**82** (2)	1	95	Δ	100		19	5	76
81[c]	**82** (2)	2	80	MW	52		36	6	10
81[c, e]	**82** (2)	2	80	MW	40		28	8	4
81[c]	**82** (2)	2	80	Δ	17		12	3	2
85[d]	**82** (2)	3	100	MW	95		63	15	17

[a]Support: Type C Al_2O_3; [b]No Support; [c]Support: Neutral Al_2O_3; [d]Support: Eupergit; [e]Biocatalyist (cell/support) reused twice; [f]Reaction performed in a closed system.

Enzymatic methods have become commonly used in carbohydrate syntheses, among which glycohydrolase mediated reactions allow stereo- and regio-selective synthesis of glycosides by *trans*-glycosidation or reversed hydrolysis. The major drawback of this reaction is the hydrolysis of the donor and/or the product. As a consequence, yields do not exceed 40%. Likewise, reversed hydrolysis, which is an equilibrium controlled reaction, also gives poor yields. According to their work on enzyme mediated reactions using microwave activation instead of classical heating, in many cases of which kinetics, selectivities and yields were found improved, Gelo-Pujic *et al*. [42] performed some *trans*-glycosidations in a Synthewave 402 monomode reactor using almond-β-glucosidase, β-glucosidase present in crude homogenates of *Sulfolobus solfataricus* and *Pyrococcus furiosus* glucosidase. The synthesis by reversed hydrolysis was performed with glucose **3** and hexane-1,6-diol **79**, while *trans*-glycosidation was studied with phenyl β-D-glucoside **81** and cellobiose **85** as donors and propane-1,2-diol **82** as acceptor (Scheme 27). The reactions were performed in an open system, except one case, where a closed system was used. The results are given in Table 18.

The advantage of microwave irradiation when compared to classical heating is evident. In particular, the trans-glycosidation results in complete conversion within 2-3 h, while hydrolysis is lowered to 10% and the excess of acceptor to only 2 equiv. The optimal conditions for enzymatic reactivity and stability under microwave are 95°C with water activity a_w 0.80 and using an open system.



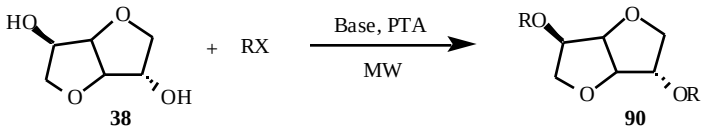
38 **88** **89**

Fig. (2). Structure of compounds **38** and **89**.

Loupy *el al*. [43] studied the alkylation of isosorbide (**38**), isomannide (**88**), and isoiodide (**89**) (Fig. **2**), three chiral stereoisomer dianhydrohexitols which are obtained from sugar industry by double dehydration of starch [44], in order to be used as starting monomers in polymerization reactions with the intent to access to some biodegradable chiral macromolecules with complexing properties.

The authors first examined dialkylation of isosorbide **38** involving *n*-octyl bromide under microwave irradiation with control of several significant parameters (Scheme 28, Table 19) including different medium (using solvent-free conditions, a non-polar and a polar solvent), bases and phase transfer agents.

The best set of conditions were extrapolated to a series of various alkylating agents. In the optimal cases, in order to check the possible specific (non-purely thermal) microwave



Scheme 28.

Table 19: Reaction of 38 with R-X = *n*-$C_8H_{17}Br$ under microwave irradiation in the presence of a base and PTA (molar ratio = 1:3:3:0.1) [43].

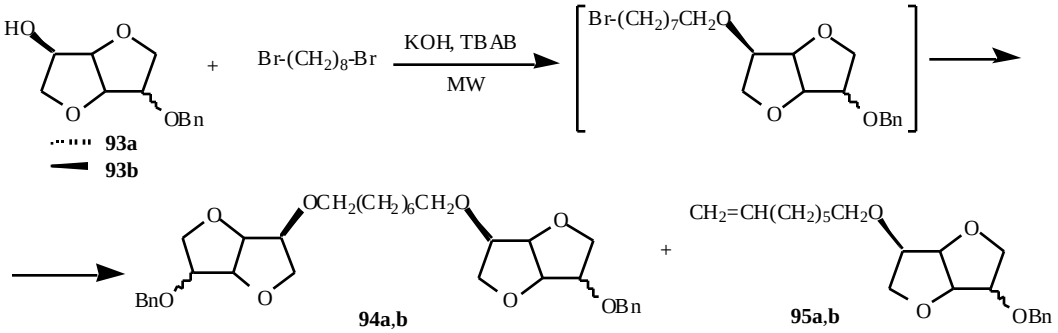
Base	PTA	Solvent	Time (min)	Temp. (°C)	Yield[a] of 90 (%)
KOH	Aliquat 336	---	10	200	14
KOH	Aliquat 336	DMF	10	150	20
KOH	Aliquat 336	Xylene	10	140	40
KOH	Aliquat 336	Xylene	60	140	90 (80)
KOH	TBAB[b]	Xylene	5	140	96 (86)
KOH	Crown-18,6	Xylene	5	140	5
K_2CO_3	TBAB[b]	Xylene	5	140	1
$KOBu^t$	TBAB[b]	Xylene	5	140	25

[a]Gc yield using an internal standard (dioctyl phthalate); yields in isolated products are indicated in brackets; [b]tetra-*n*-butylammonium bromide.

Table 20: Reaction of 38 with several R-X using KOH and TBAB (relative amount 1:3:3:0.1) in xylene [43].

R-X	Time (min)	Temp. (°C)	Yield[a] of 90 (%)	
			MW	Δ
n-$C_8H_{17}Br$	5	140	96 (90)	10
n-$C_8H_{17}Cl$	5	140	32	2
n-$C_8H_{17}Cl$ + NaBr[b]	20	105	85 (80)	40
$C_6H_5CH_2Cl$	5	125	98 (90)	13
3-Cl-$C_6H_4CH_2Cl$	5	125	95 (90)	15
4-$ClC_6H_4CH_2Cl$	5	125	96 (89)	14
3-F-$C_6H_4CH_2Cl$	5	125	95 (90)	15
$CH_3CH_2OCH_2CH_2Br$[c]	30	100	78 (66)	45
$CH_3OCH_2CH_2OCH_2CH_2Cl$ + NaBr[b]	40	100	76 (68)	15

[a]Gc yields using an internal standard; yields in isolated products are given in brackets. [b]1:R-X:NaBr = 1:4:4. [c]1:R-X = 1:4.



Scheme 29.

effects, yields were compared with conventional heating (Δ) under the same conditions (Table 20).

Finally, also the other D-hexitols **88** and **89** were alkylated into the corresponding ethers **91** and **92** under the optimal conditions indicated in Tables 19 and 20.

It appears clearly that: i) excellent yields in diethers were obtained in all cases examined under the optimal conditions determined with *n*-octyl bromide; ii) alkyl chlorides need to be transformed *in situ* under phase transfer catalysis conditions in their bromide equivalents; iii) a very strong specific microwave effect is involved in this reaction as by comparison of microwave and thermal yields; iv) the presence of a rather small amount of an apolar solvent is here of a great benefit as transparent to microwave exposure and allowing a good control in temperature and medium viscosity.

Later, an alkylation of mono-benzylated **93a**,**b** was accomplished by Loupy *et al*. [45] with mono- and di-alkylating agents under conditions of phase transfer catalysis (PTC) using concomitant microwave irradiation and

Table 21: Reaction of 93a with 1,8-dibromooctane under microwave irradiation in the presence of KOH and TBAB (relative amounts 93a:base:R-X = 2:3:1.5) [45].

TBAB (%)	Solvent (0.25 L)	Time (min)	Temp. (°C)	Yields[a] (%)		
				93a	94a	95a
1	*p*-Xylene	5	140	30	47	23
1	*p*-Xylene	30	140	10	70 (67)	20
2	*p*-Xylene	5	140	0	72 (68)	28
5	*p*-Xylene	5	140	2	70 (65)	28
2	Toluene	5	110	5	66 (62)	28
2	Toluene	15	110	0	68 (66)	32

[a]Yields determinedby ^{1}H NMR and given in brackets for isolated products.

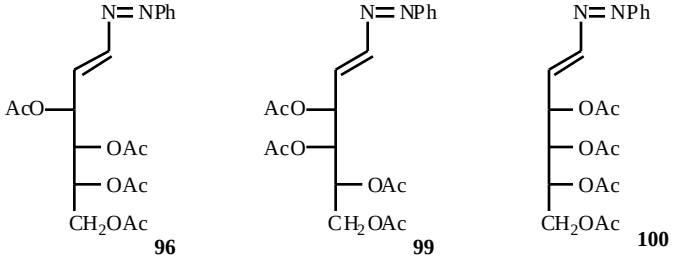
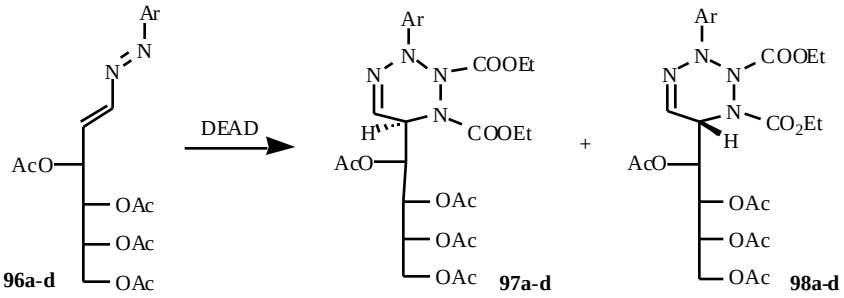


Fig. (3). Structure of 1,2-diazi-1,3butadienes **96**, **99** and **100**.



Ar: **a** = C_6H_5; **b** = 4-ClC_6H_4; **c** = 4-$CH_3C_6H_4$ **d** = 4-$CH_3OC_6H_4$

Scheme 30.

moreover di- and tri-ethylene glycols in the presence of sodium bromide to enhance the possible complexing properties of the target molecules.

In alkylation with 1,8-dibromooctane, besides the expected ethers **94a**,**b**, some amounts of alkene **95a**,**b** were obtained resulting from a dehydrobromination of the common intermediate involved in S_N2-E2 competitive processes (Scheme 29, Table 21).

With the aim to enlarge the scope of the reaction of dialkyl chloride, generally cheaper and easily commercially available when compared to their bromide equivalents, Loupy *et al* [46] has studied also cation and leaving group effects as well as other parameters such as the salt and solvent influence of catalyst under phase transfer catalysis (PTC) conditions. By using concomitant microwave irradiation during di-*n*-octylation of **38** investigations were conducted in order to optimize experimental conditions and to evaluate microwave effects on the polymerization. In the absence of catalyst, no reaction occurred so it was necessary to induce the formation of a strong base. Increasing the amount of catalyst was of course favourable by shifting equilibrium to the right side. Bromide seemed to a better counter ion when compared to chloride. This could be the result of an halogen exchange reaction on *n*-octyl chloride with formation of *n*-octyl bromide as a more efficient electrophile. The addition of several alkaline salts have important and several effects. Furthermore, the extension of the study of alkylation to *n*-octyl tosylate and mesylate showed that the first needed a significantly higher temperature to give a satisfactory yield, while the reaction of the second occurred with higher yields at a lower temperature. In all cases, comparison of reactions under microwave with conventional heating in the same conditions shows clearly a specific (non-thermal) microwave effect.

6. HETEROCYCLES FROM CARBOHYDRATES

6.1 5,6-Dihydro-1,2,3,4-Tetrazenes

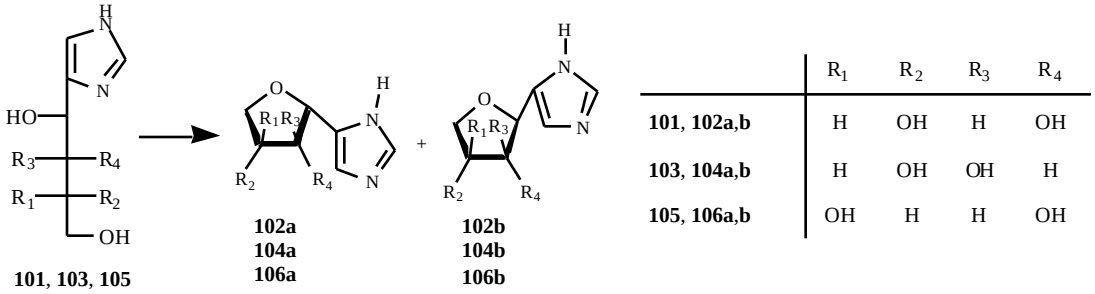
The stereoselective normal electron-demand Diels-Alder reactions of chiral 1,2-diaza-1,3-butadienes, derived from acyclic carbohydrates having different configurations (Fig. **3**), with diethyl azodicarboxylate (DEAD) are impractical at room temperature.

Jimenez *et al*. [47], on the contrary, completed these reactions within a few hours under microwave heating with the same sense and level of stereoselection by using a reactor of focused microwaves operating at a maximum power

Table 22: Normal electron demand aza-Diels-Alder reactions of carbohydrate based 1-aryl-1,2-diaza-1,3-butadienes 96a-d, 99 and 100 with DEAD [47].

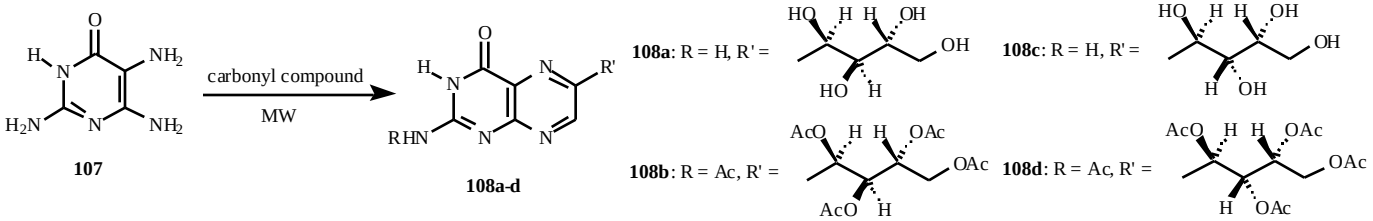
Heterodiene	Yield (%)[a]	Diastereomeric ratio α/β[b]
96a	93	85:15
96b	96	84:16
96c	87	88:12
96d	92	85:15
99	91	66:33
100	80	35:65

[a]Combined yields of (6*R*)- and (6*S*)-diastereomers. [b]Determined by ^{1}H NMR peak integration in $CDCl_3$ solution.

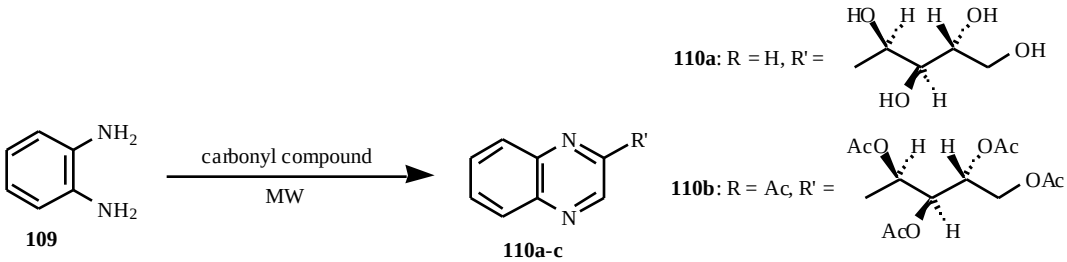


	R_1	R_2	R_3	R_4
101, **102a**,**b**	H	OH	H	OH
103, **104a**,**b**	H	OH	OH	H
105, **106a**,**b**	OH	H	H	OH

Scheme 31.



Scheme 32.



Scheme 33.

output of 300 W. A diastereomeric mixture of (6*S*)- and (6*R*)- configured 1,2,3,6-tetrahydro-1,2,3,4-tetrazines is afforded in good yields (Table 22). Scheme 30 illustrates reactions of **96a**,**d** which give **97a**,**d** and **98a**,**d**. To rationalize the experimental results, theoretical calculations on the reactants, products, and transition structures were performed at semiempirical level, which have been forced to employ because of the complexity of the system. This exploration reveals that the steric course is not critically affected by the nature of substituents, and a better stabilization is due to the electrostatic interaction during the approach of both reactants.

6.2 *C*-Nucleosides

Based on the pyrolysis of the neat hydrochloride salts of imidazolyl tetritols, e.g. **101**, **103** and **105** which leads to the 4-glycofuranosyl-1*H*-imidazoles, e.g., **102**, **104** and **106** and their anomer mixtures, Tschamber *et al*. [48] obtained the same pairs of *C*-nucleosides in one-pot procedures by microwave irradiation with a domestic Whirpool MO 100 oven for 1.7-3 min. Mixtures containing formamidine acetate, a few drops of water, and the appropriate hexose or hexulose, i.e., D-fructose (or D-glucose), D-galactose, and L-sorbose, respectively, gave an overall yield of 19-28% (Scheme 31). Irradiation for longer periods of time led to caramelization. Microwave irradiation clearly brought about sequential double condensation of formamidine with hexoses or hexuloses and acid-catalyzed intramolecular cyclization of the intermediate linear imidazolyl tetritols.

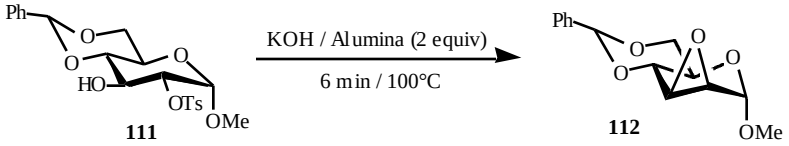
6.3 Pterins

By Isay type condensation of a pyrimidinediamine **107** with aldohexoses, Goswami and Adak [49] achieved the construction of a pyrazine ring to afford pterins **108a-d** with

Table 23: Microwave-assisted Isay condensations of 107 and 109 with various monosaccarides.

Diamine	Monosaccaharide	Product	Yield[a]	
			MW (%)	Lit. methods[b]
107	3	108a	40	30[c]
107	5	108c	38	
109	3	110a	60	
109	5	110c	60	20[d]

[a]Isolated yields; [b]Literature methods give mixtures of both 6 and 7-isomers; [c]Ref. [49]; [d]Ref. [50].

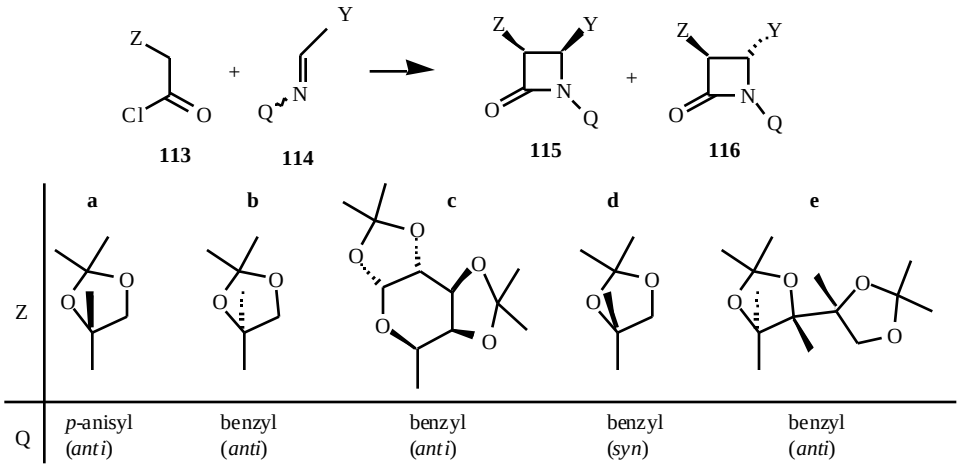


Scheme 34.

Table 24: Epoxidation of 111 into 112 in 6 min at 100°C [11].

Activation method	Amounts of materials (g)		Total amount (g)	Yield of 112[a]
	110	KOH/Al_2O_3		
MW, S402	1	2.1	3.1	99
Δ, oil bath	1	2.1	3.1	25
MW, S1000	20	41.2	61.2	95[b]

[a]Yields in isolated products; [b]Reaction time = 10 min.



Scheme 35.

a sugar substituent (Scheme 32, Table 23) under microwave irradiation (300 W) for 270 sec. Interestingly, the desired isomerically free 6-substituted sugar derivatives were synthesized in moderate to good yields, whereas mixtures of both 6- and 7-isomers (major) are generally obtained using conventional Isay type condensations.

By using benzenediamine **109**, quinoxaline systems **110** were obtained (Scheme 33, Table 23).

6.4 Epoxides

By treatment of the protected 2-*O*-tosyl-α-D-glucopyranoside **111** under microwave irradiation at 100°C for 6 min in the presence of potassium hydroxide/alumina, Clèophax *et al*. [50] obtained epoxide **112** in good yield. Under classical heating (same conditions, oil bath), the required epoxide was obtained in only 25% yield (Scheme 34). Loupy *et al*. [11] repeated the same reaction by using both the Synthewave 402 and Synthewave 1000 equipments and obtained the results indicated in Table 24.

6.5 Azetidinones

During the course of their studies on the synthesis of β-lactams [51], Banikt *et al*. [52] found convenient to conduct several types of synthetic steps under microwave irradiation. Enantiospecific synthesis was developed for α-hydroxy-β-lactams of predictable absolute configuration starting from readily available carbohydrates. Stereospecific approaches and microwave assisted chemical reactions were been

Scheme 36.

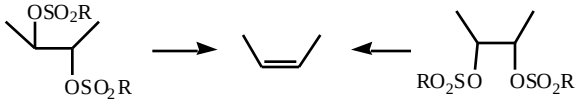
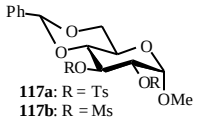
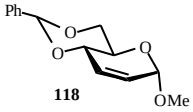
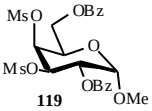
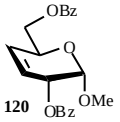
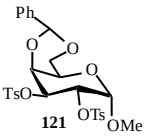
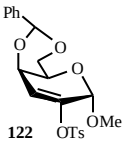
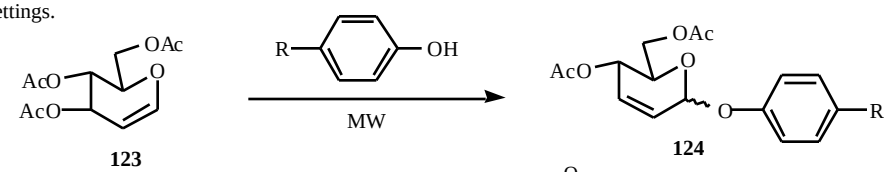


Table 25: Comparative results in representative Tipson-Cohen reactions using classical and microwave procedures [55].

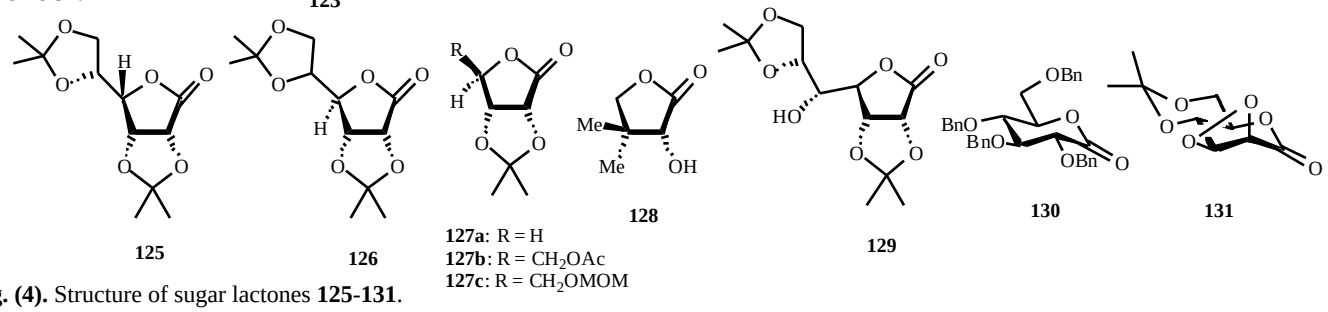
Compound	Methodology	Time (min)	Yield[a] (%)	Product
1	Δ[b] Δ[b] MW[b]	120 240 14	53 40 88	**4**
 **117a**: R = Ts **117b**: R = Ms	Δ[b] Δ[b] MW[b]	120 240 8	42 35 89	 **118**
 **119**	Δ[c] MW[c] MW[e] MW[f]	60[d] 2 4 12	93 90 81 79	 **120**
 **121**	MW[b,g]	--	--	 **122**

[a]Yields are based on isolated products; [b]Ratio substrate:NaI:Zn dust = 1:50:54; [c]Ratio substrate:NaI:Zn dust = 1:18:17; [d]Conventional conditions and results were taken from literature [54a]; [e]Ratio substrate:NaI:Zn dust = 1:9:8.5; [f]Ratio substrate:NaI:Zn dust = 1:4.5:4; [g]This reaction was also made at low, medium and medium-high power settings.

Scheme 37.



123 **124**



125 **126** **127a**: R = H; **127b**: R = CH_2OAc; **127c**: R = CH_2OMOM **128** **129** **130** **131**

Fig. (4). Structure of sugar lactones **125**-**131**.

utilized for the preparation of these 3-hydroxy-2-azetidinones and their conversion to natural or non-natural enantiomeric forms of intermediates for gentosamine, 6-epilincosamine, γ-hydroxythreonine, and polyoxamic acid. Thus they have shown that reaction of acyl chloride **113** and trietylamine with a Schiff base such as **114** gives mostly *cis*-β-lactams **115** at low levels of microwave irradiation, but at higher energy levels, producing higher temperatures, more that 90% of the β-lactam formed may be the *trans*-isomer **116** (Scheme 35). Interestingly with Schiff bases of type **113a-e** the *cis*-β-lactams are formed at all levels of microwave irradiation. On few grams scale, optically active *cis*-β-lactams deriving from **113d**,**e** are obtained in high yield after about 3 min irradiation in a 800 W commercial microwave oven.

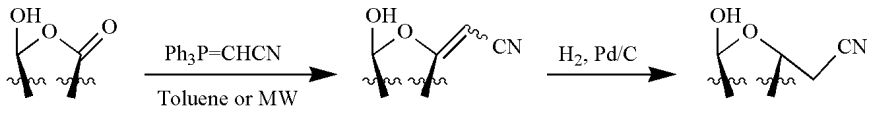
7. UNSATURATED PYRANOSIDES

Among the several literature methods concerning the introduction of a double bond into sugars [53], the classical Tipson-Cohen procedure [54] (substrate, NaI and Zn dust in DMF) provides an excellent alternative which, however, especially when prolonged reaction times are required, affords low yields of unsaturated glycosides because of the decomposition of the reagents (Scheme 36).

Baptistella *et al*. [55] decided to employ microwave irradiation in Tipson-Cohen reactions with gluco- and galacto-di-*O*-mesyl or di-*O*-tosyl derivatives **117a,b**, **119**, and **121** obtaining the results given in Table 25.

From a mechanistic point of view, the microwave-induced Tipson-Cohen reactions seem to be very similar with those conducted by classical heating method.

Balasubramanian *et al*. [56] has applied the micro oven-induced reaction enhancement (MORE) to tri-*O*-acetyl-D-glucal **123** with substituted phenols in the absence of a solvent obtaining the corresponding 2,3-unsaturated *O*-aryl glycosides **124** (Scheme 37) with reaction times reduced of several folds in comparison to those required by thermal conditions.



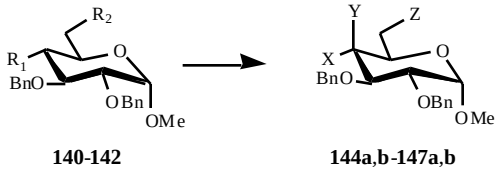
125-131 **132-138**

Scheme 38.

Table 26: Wittig olefination of lactones 125-131 either under microwave irradiation (MW) or in refluxing toluene (Δ) [59].

Starting lactone	Conditions	Time (min)	Product	Yield (%)	*E/Z*[a]
125	Δ	1440	**132**	96	3.5:1
125	MW	4	**132**	98	1.7:1
126	Δ	1440	**133**	76	1.7:1
126	MW	4	**133**	98	1.2:1
127a	Δ	1440	**134a**	83	1:1
127a	MW	4	**134a**	86	1.1:1
127b	Δ	2880	**134b**	69	1:1.8
127b	MW	4	**134b**	85	1:1.8
127c	Δ	4320	**134c**	96	1.1:1
127c	MW	4	**134c**	88	1:1.8
128	Δ	1440	**135**	64	1.9:1
128	MW	4	**135**	96	1:1.2
129	Δ	96	**136**	98	1:1
130	Δ	96	**137**	91	2.8:1
130	MW	6	**137**	90	1.8:1
131	Δ	1440	**138**	86	1.3:1
131	MW	8	**138**	89	1.1:1

[a]Ratio determined from ^{1}H NMR spectrum



140-142 **144a,b-147a,b**

140: R_1 = OBn; R_2 = OH;
141: R_1 = OH; R_2 = OBn;
142: R_1 = OH; R_2 = OAc;

144a: X = OBn; Y = H; Z = Cl;
144b: X = OBn; Y = H; Z = Br;
145a: X = H; Y = Cl; Z = OBn;
145b: X = H; Y = Br, Z = OBn;
146a: X = H; Y = Cl; Z = OAc;
146b: X = H; Y = Br, Z = OAc;
147a: X = OAc; Y = H; Z = Cl;
147b: X = OAc; Y = H, Z = Br;

Scheme 39.

In the search of milder conditions for the olefination of sugar derived lactones, as the resulting *C*-glycosylidenes are of special interest as carbohydrate mimics [57, 58] and for the synthesis of *C*-glycosyl compounds, Chapleur *et al*. [59] turned their attention to the use of microwave activation. They observed a dramatic improvement when going from standard heating to microwave activation, particularly in terms of reaction time. Thus, as shown in Scheme 38, they performed reactions of cyamomethyl triphenyl phosphorane with different sugar lactones (Fig. **4**) obtaining good to excellent yields of the expected olefins which were *E*:*Z* mixtures essentially 1:1 in most cases (Table 26).

Given the versatility of the cyano group as an amide, ester and aldehyde group surrogate, the above microwave-assisted olfination, constitutes an efficient and versatile route to new *C*-glycosylidene nitriles, which can be reduced to the corresponding *C*-glycosyl compounds with complete stereocontrol at anomeric centre.

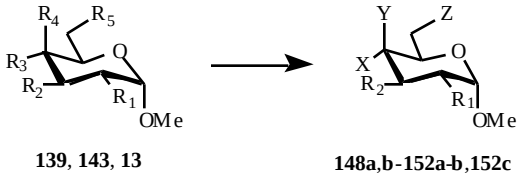
8. HALOGENATION

With the aim at finding a simplification of halogenation conditions at the light of different heating modes (microwave irradiation and oil bath), solvent effects (presence and nature) and added salts, Clèophax *et al*. [60] studied the halogenation of **13** and its 2,3-di-*O*-benzyl- (**139**), 2,3,4-tri-*O*-benzyl- (**140**), 2,3,6,-tri-*O*-benzyl- (**141**), 6-acetyl-2,3-di-*O*-benzyl- (**142**) derivatives, and methyl 2,3-di-*O*-benzyl-α-D-galactopyranoside (**143**) with triphenylphosphine and chlorine or bromine donors. Carbon tetrachloride, hexachloroethane or 1,2-dibromotetrachloroethane were shown to be good halogen donors, while *N*-chloro-, *N*-bromo-succinimide and tetrabromomethane were decomposed almost instantaneously under microwave irradiation. Furthermore, it appeared that in highly concentrated solutions of non polar solvents such as toluene or 1,2-dichloroethane, with, in some cases, addition of potassium chloride, potassium bromide, and/or pyridine, it was possible halogenate primary and secondary alcohol groups in good yields and within short reaction times. Pyridine seems to inhibit extensive decomposition, and allows to raise the reaction temperature; furthermore, contrary to reactions in diluted solution, a dihalogenation are possible. The reactions were observed to be very fast under microwave irradiation (2 to 30 min) as well as by classical

Table 27: Halogenation of monohydroxy compounds 140, 141 and 142 (mmol) [60].

S[a]	M[b]	Reagents (equiv)	Pres. (W)	Temp. (°C)	Time (min)	Solvent[c] (mL)	Salt (equiv)	Product (Yield, %)
140	MW	Ph_3P (2.5)/CCl_4 (5)	150	100	8	B (0.8)	KCl(10)	**144a** (91)
140	Δ	Ph_3P (2.5)/CCl_4 (5)		100	8	B (0.8)	KCl (10)	**144a** (90)
140	MW	Ph_3P (2.5)/$(CCl_2Br)_2$ (2.5)	150	100	7	B (2)	KBr (10)	**144b** (75)
139	Δ	Ph_3P (2.5)/$(CCl_2Br)_2$ (2.5)		100	7	B (2)	KBr (10)	**144b** (65)
141	MW	Ph_3P (2.2)/CCl_4 (5)	200	110	15	B (2)	KCl (10)	**145a** (75)
141	Δ	Ph_3P (2.2)/CCl_4 (5)		110	15	B (2)	KCl (10)	**145a** (85)
141	MW	Ph_3P (3)/$(CCl_2Br)_2$ (2)	200	70	6	B (2)	KBr (5)	**145b** (40)
141	Δ	Ph_3P (3)/$(Cl_2Br)_2$ (2)		70	6	B (2)	KBr (5)	**145b** (16)
142	MW	Ph_3P (2.5)/CCl_4 (5)	100	100	10	B (2)	KCl (5)	**146a** (91) **147a** (4)
142	Δ	Ph_3P (2.5)/CCl_4 (5)		100	10	B (8)	KCl (5)	**146a** (70) **147a** (10)
142	MW	Ph_3P (2.5)/$(CCl_2Br)_2$ (1.5)	200	70	6	A (8)	KBr (5)	**146b** (50) **147b** (13)
142	Δ	Ph_3P (2.5)/$(CCl_2Br)_2$ (1.5)		70	6	A (8)	KBr (5)	**146b** (12) **147b** (29)

[a]S = Substrate. [b]M = Mode: MW = Microwave irradiation; Δ = oil bath heating. [c]Solvents: A, toluene; B, dichloroethane; C, pyridine.



139, **143**, **13** → **148a**,**b**-**152a**-**b**,**152c**

139: $R_1 = R_2 = OBn$; $R_3 = R_5 = OH$, $R_4 = H$
143: $R_1 = R_2 = OBn$; $R_3 = H$; $R_4 = R_5 = OH$
13: $R_1 = R_2 = R_3 = R_5 = OH$; $R_4 = H$

148a: $R_1 = R_2 = OH$; X = H; Y = Cl; Z = Cl
148b: $R_1 = R_2 = OH$; X = H; Y = Br; Z = Br
149a: $R_1 = R_2 = OH$; X = OH; Y = H; Z = Cl
149b: $R_1 = R_2 = OH$; X = OH; Y = H; Z = Br
150a: $R_1 = R_2 = OBn$; X = Z = Cl; Y = H;
150b: $R_1 = R_2 = OBn$; X = Z = Br; Y = H;
151a: $R_1 = R_2 = OBn$; X = H; Y = OH; Z = Cl
151b: $R_1 = R_2 = OBn$; X = H; Y = OH; Z = Br
152a: $R_1 = R_2$ = X = OH; Y = H; Z = Cl
152b: $R_1 = R_2$ = X = OH; Y = H; Z = Br
152c: $R_1 = R_2 = OH$; X = H; Y = Br; Z = Br

Scheme 40.

heating (2 to 45 min) at 80-120 °C. Most often, the yields were better under microwave irradiation and the reaction product distribution was sometimes different from that obtained in classical methods with, in all experiments, the amount of solvent strongly reduced. Thus, for example, the halogenation of monohydroxy compounds **140**-**142** resulted in monohalogenated derivatives **144**-**147** (Scheme 39, Table 27).

Because of the readily accessible 4-hyxdroxyl group, sugar **142** gave 4-chloro derivative **146a** with a low proportion of rearranged 4-*O*-acetyl-6-chloro isomer **147a** in the case of both two methods of heating. On the contrary, applying the microwave irradiation 4-bromo derivative **146a** was the major product, while the rearranged isomer 4-*O*-acetyl-6-bromo derivative **147b** was obtained by classical heating. Such as effect on selectivity is infrequent in the literature, and only described in a very few cases [61]. The results of dichlorination and dibromination of diols **13**, **139** and **143** (Scheme 40) are reported in Table 28.

Scale-up of chlorination of **13**, conducted by Loupy *et al*. [11], with triphenylphosphine and carbon tetrachloride in the presence of pyridine after addition of an excess of potassium chloride, led to improvements in yields as well as by classical heating (Δ, oil bath) and under microwave

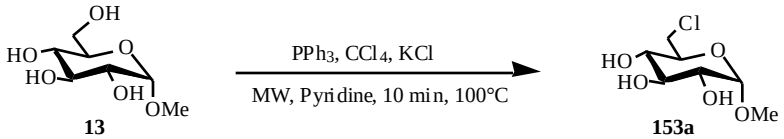
Table 28: Halogenation of polyhydroxy compounds (2 mmol) [60].

S[a]	M[b]	Reagents (equiv)	Pres. (W)	Temp. (°C)	Time (min)	Solvent[c] (mL)	Salt (equiv)	Product (Yield, %)
139	MW	Ph_3P (2.5) CCl_4 (5)	210	110	8	A (0.7)	KCl (20)	**148a** (85) + **149a** (9)
139	Δ	Ph_3P (2.5) CCl_4 (5)		110	8	A (0.7)	KBr (20)	**148a** (30) + **149a** (15)
139	Δ	Ph_3P (2.5) CCl_4 (5)		110	15	A (0.7)	KBr (20)	**148a** (75) + **149a** (6)
139	MW	Ph_3P (1.5) $(CCl_3)_2$ (1)	210	95	15	B (2.6)	KCl (20)	**149a** (69)
139	Δ	Ph_3P (1.5) $(CCl_3)_2$ (1)		95	30	B (2.6)	KCl (20)	**149a** (92)

(Table 28) contd….

139	MW	Ph_3P (3.5) $(CCl_2Br)_2$ (3.5)	80	105	3	B (2.5)		**148b** (53) + **149b** (10)
139	Δ	Ph_3P(2.5) $(CCl_2Br)_2$ (2.5)		100	30	B (2.5)		**148b** (65) + **149b** (2)
139	MW	Ph_3P (2.2) $(CCl_2Br)_2$ (2.1)	210	103	7	A (3) C (1)		**148b** (70) + **149b** (25)
139	Δ	Ph_3P (2.2) $(CCl_2Br)_2$ (2.1)		103	7	A (3) C (1)		**148b** (70) + **149b** (18)
143	MW	Ph_3P (2.5) CCl_4 (5)	210	100	8	A (1)	KBr (20)	**150a** (78) + **151a**(9)
143	Δ	Ph_3P (2.5) CCl_4 (5)		100	8	A (1)	KBr (20)	**150a** (35) + **151a** (24)
143	MW	Ph_3P (1.5) $(CCl_3)_2$ (1.2)	210	100	30	A (2)	KCl (10)	**150a** (1.5) + **151a** (71)
143	Δ	Ph_3P (1.5) $(CCl_3)_2$ (1.2)		100	30	A (2)	KCl (10)	**150a** (62)
143	MW	Ph_3P (2.2) $(CCl_2Br)_2$ (2.1)	210	100	7	A (3) C (1)		**150b** (70) + **151b** (25)
143	Δ	Ph_3P (2.2) $(CCl_2Br)_2$ (2.1)		100	7	A (3) C (1)		**150b** (52) + **151b** (15)
143	MW	Ph_3P (1.5) $(CCl_2Br)_2$(1.45)	210	100	3	B (1) C (1)		**150b** (20) + **151b** (72)
143	Δ	Ph_3P (1.5) $(CCl_2Br)_2$ (1.45)		100	3	B (1) C (1)		**150b** (15) + **151b** (54)
13	MW	Ph_3P (1.5) CCl_4 (4)	210	10	10	C (0.8)	KCl (10)	**152a** (78)
13	Δ	Ph_3P (1.5) CCl_4 (4)		100	10	C (0.8)	KCl (10)	**152a** (68)
13	MW	Ph_3P (3 $(CCl_2Br)_2$ (2.5)	210	100	5	A (0.8) C (1.6)	KBr (10)	**152a** (5) + **152c** (60)
13	Δ	Ph_3P (3) $(CCl_2Br)_2$ (2.5)		100	5	A (0.8) C (1.6)	KBr (10)	**152a** (20) + **152c** (39)
13	MW	Ph_3P (1.5) CCl_4 (4)	210	100	10	C (40)	KCl (10)	**152a** (92)
13	Δ	Ph_3P (1.5) CCl_4 (4)		100	10	C (40)	KCl (10)	**152a** (82)

[a]S = Substrate. [b]M = Mode: MW = Microwave irradiation; Δ = oil bath heating. [c]Solvents: A, toluene; B, dichloroethane; C, pyridine. [d]Experiments on 20 g of **22**.



13 **153a**

Scheme 41.

activation in a Synthewave 402 and Synthewave 1000 equipments (Scheme 41, Table 29). The observed specific microwave effect was rather reduced, with only a 10% difference in yield in favour of the reaction with microwave activation.

9. RADIOPHARMACEUTICAL

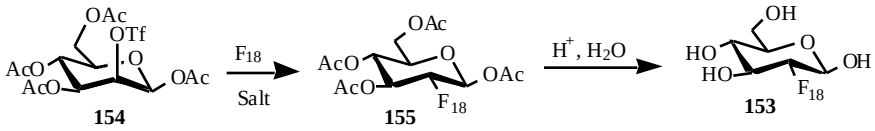
It has always been a challenging task to prepare radiopharmaceuticals labelled with short-lived radionuclesides rapidly and in high yield. The increased rates reported using microwave technology provide a means of decreasing reaction time, and thus increasing the final radiochemical yield of radiopharmaceuticals [62].

A rapid and efficient synthesis of the most widely used radiopharmaceutical of 2-deoxy-2-^{18}F-fluoro-D-glucose (**153**) has been reported by Chirakal *et al*. [63] in which a 33% radiochemical yield was obtained with microwave heating and compared to a 25% yield with conventional heating. Later, the authors [64] investigated by ^{19}F NMR the effect of potassium carbonate, potassium bicarbonate and potassium fluoride on the base-mediated decomposition of 1, 3,4,6-tetra-*O*-acetyl-2-*O*-trifluoro-methanesulphonyl-β-D-

Table 29: Chlorination of 13 in 10 min at 100°C [11].

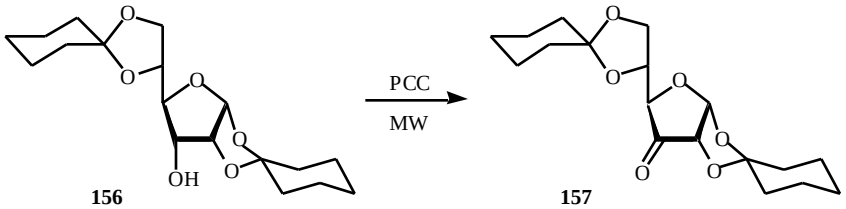
Activation method	Amount of material (mmol)					Yield of 152a (%)[a]
	13	CCl_4	PPh_3	KCl	Pyridine	
MW, S402	2	8	3	20	0.8 mL	78
Δ, oil bath	2	8	3	20	0.8 mL	68
MW, S1000	103	4.12	154.5	1030	40 mL	92
Δ, oil bath	103	4.12	154.5	1030	40 mL	82

[a]Yields in isolated product

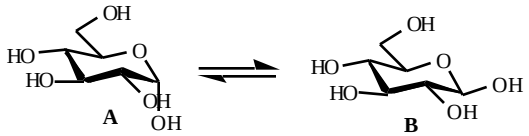


Salt: Tetrabutylammonium bicarbonate
Potassium fluoride
Potassium carbonate
Potassium bicarbonate

Scheme 42.



Scheme 43.



Scheme 44.

mannopyranose (**154**) and they have also shown that the substitution of triflate by [^{18}F]fluoride to give **155** (Scheme 42) is 90% complete in less than a minute when preparation of dry [^{18}F]fluoride and subsequent nucleophilic fluorination is done using a domestic microwave oven. Moreover they showed that by this modified method the average yield of **153** after 30 production runs was very reproducible. Taylor *et al*. [65] improved the radiochemical yield by using tetrabutyl ammonium bicarbonate, as phase transfer reagent, and obtained an average radiochemical yield of 62± 4% in the time of 31 min.

10. Oxidation (BY PYRIDINIUM CHLOROCHROMATE)

In continuation of their ongoing work on development of highly efficient oxidation protocols, Bordoloi and Chakraborty [67] observed that the oxidation of a solution of 1,2:5,6-di-O-cyclohexylidene-α-glucofuranose **156** in dry dichloromethane with pyridinium chlorochromate (PCC) under microwave irradiation can be carried out much more quickly (10 min) than using conventional technique (4 hours under reflux) to the corresponding keton **157** with a 99% yield (Scheme 43). Moreover, besides the drastic reduction of the reaction time, ease of the operation and easy work up procedure, they found that the oxidation can also be performed under solvent-free conditions with moist PCC with the same yield.

11. EFFECT OF MICROWAVE HEATING ON MUTAROTATION, STEREOSPECIFIC C-H BOND ACTIVATION FOR DEUTERIUM AND TRITIUM LABELLING, FLAVOR FORMATION, METHANOLYSIS OF SACCHARIDES, DEGRADATION OF POLYSACCHARIDES

11.1 Mutarotation

The phenomenon of the mutarotation of α-D-glucose (**A**) to β-D-glucose (**B**) has been also studied in a modified commercial microwave oven by Pagnotta *et al*. [67]. By investigating the phenomenon in a range of solvents (ethanol : water, 50:50, 70:30, 90:10, 100% water) at identical temperatures, the authors found a non-thermal microwave effect evidenced both by a more rapid reaction (the ratio of **A** to **B** reaches approximately the value of 1:1 more rapidly by using microwave thermolysis than the conventional heated control) and by a change in relative amounts of **A** and **B** over time (Fig. **4** and **5**). Most interestingly, they found that microwave thermolysis in a particular solvent mixture ($EtOH:H_2O$, 1:1) leads to a change in equilibrium distribution in which a greater proportion of **A** was present (Scheme 44).

11.2 Stereospecific C-H Bond Activation for Deuterium and Tritium Labelling under Microwave Irradiation

Together with the method which uses pre- or continuous ultrasonication to promote the process of exchange reactions between isotopic hydrogen donors and bioorganic glycolconjugates, Cioffi *et al*. [68] used microwave irradiation in a domestic microwave oven to promote these C-H→C-D isotopic exchanges. Isotopic labels, which are

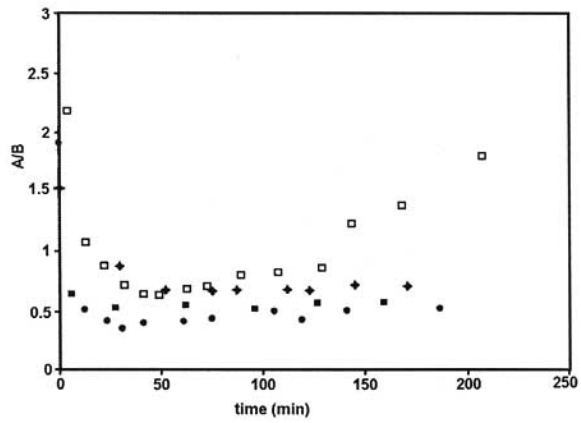
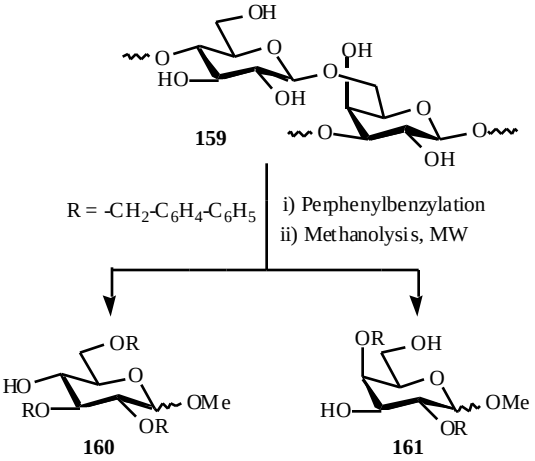


Fig. (5). Ratio of α-D-glucose (**A**) to β-D-glucose (**B**) vs time for microwave heated reactions in (□) 50% ethanol - 50% water, (■) 70% ethanol - 30% water, (➔) 90% ethanol - 10% water, (✹) 100% water; relative amounts of **A** and **B** were determined by measurements of specific rotation.



Scheme 45.

important goals in biochemistry, serve as convenient probes into the molar organization and structural dynamics of cellular membranes, and help to elucidate cellular metabolic and biosynthetic pathways. Simple carbohydrates to oligosaccharides, among other target substrates, have been investigated for deuterium incorporation via stereospecific C-H bond activation, which on the basis of previous studies was realized with Raney nickel alloys, but it was also investigated using transition-metal doped catalysts. This process has proven to be facile, stereospecific, and provides quantitative yields of isotopically labelled substrates.

11.3 Flavour Formation

The flavour formation deriving from the interactions of sugars with amino acids was also investigated under microwave heating. In a study, conducted by Yu *et al*. [69], twenty kinds of amino acids were mixed with 3 or D-xylose (158), individually in propylene glycol or glycerol and were heated in a traditional microwave oven with full power (650 W) for 2 min. The colour, appearance, and aroma of the heated solutions were analyzed. Thus, for example, the appearance of the heated L-tryptophan solutions was the most intense when these amino acids were heated with 3 or 158 in propylene glycol, while those of the heated L-tyrosine solutions were the most intense when this amino acid was heated with the same sugars in glycerol. The heated solutions of L-cysteine, L-methionine, L-proline, L-phenylalanine, L-glutamine, L-leucine, and L-isoleucine had very characteristic and intense flavour sensations.

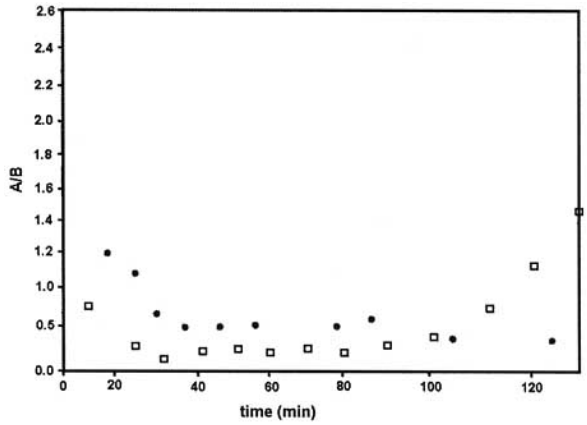


Fig. (6). Ratio of α-D-glucose (**A**) to β-D-glucose (**B**) vs time (min) for conventionally heated (✹) and microwave-heated (□) reactions; relative amounts of **A** and **B** were determined by ^{1}H NMR spectroscopy.

11.4 Methanolysis of Saccharides

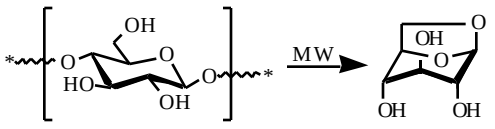
The classical method for structural studies of saccharides is methylation analysis which typically involves overnight reflux in 1N hydrogen chloride/methanol affording metilated derivatives at the anomeric center. Cleavage of the glycosidic linkage in some of the perphenylbenzyl derivatives, however, requires more vigorous conditions, presumably due to hydrophobic shielding of the bulky phenylbenzyl groups. Nakanishi *et al*. [70] found that phenylbenzylsaccharide **159** is cleaved into derivatives **160** and **161** (Scheme 45) within 15 minutes when methanolysis is carried out in an ordinary microwave oven. One very important feature of the microwave-assisted methanolysis is that *the major product is the anomer having the inverted configuration*. Methanolysis of underivatized saccharides followed by per-*p*-bromobenzoylation and HPLC of the product mixture leads to a nanogram scale identification of the sugar moieties and anomeric configurations.

Recently, Nakanishi *et al*. [71] described a technique for the methanolysis of carbohydrates and fatty acids from glycosphingolipids using hydrogen chloride/methanol and a microwave oven. They found that the formation of both methyl glycosides and methyl esters is rapid and completes within two minutes. The results obtained using this technique were compared with those from conventional methanolysis.

11.5 Effect of Microwave Heating on Polysaccharides

11.5.1 Cellulose

Because microwave heating involves a very rapid means of homogenous heat transfer through the substrate, studies



162 **163**

Scheme 46.

have been developed with the aim of narrowing the product distribution and particularly to increase selectivity for specified products. Allen *et al*. [72] reported on the formation of 1,6-anhydro-β-D-glucopyranoside (levoglucosan, **163**) (Scheme 46), useful chiral synthon, upon heating with commercial microwave oven of small cellulose (**162**) samples (< 3 g).

A laboratory study has been done in order to determine what effect high-intensity microwave energy generated by a Gerling-Moore microwave oven has on the thermal degradative pathways of **162**. The authors found that even at low absorption microwave pyrolysis of **162** is a more rapid process and gives increased tar yield at somewhat elevated pressures relative to conventional pyrolysis studies. An explanation consistent with these observations is that with the microwave heating, heat transport limitations are overcome by volume heating of the particle. Heating rate and therefore devolatilization rate are determined by the temperature-dependent property of the material. Owing to volume heating and low external gas temperature, primary volatiles, upon stabilization appear to yield levoglucosan and carbon oxides (Tables 30 and 31).

By large-scale microwave rapid pyrolysis of cellulosic materials, levoglucosan **163** was obtained by Miura *et al*. [73] from a larch log as the main anhydro-sugar in 2.6% yield on the basis of dry wood weight. This yield would be

Table 30: Pyrolysis products from pure 162 [72].

Reaction product	MW[a]	Weight per cent yield, g/g cellulose									
		Δ (°C)[b]	Δ (°C)[c]			Δ (°C)		Δ (°C)[f]		Δ (°C)[i]	
		320	420	520	280	300[d]	300[e]	500[g]	350[h]	500[l]	300[m]
Water	23	9.0	67.8	3.8	15.2						
Carbon Dioxide	4	26.6	17.5	20.2	3.8						
Charred residue	27	20.7	12.8	18.2	30.4	34.2	17.8	8	0	3	21
Tar	43	1.5	10.3	0.06	49.3		58	54	81	60	
Levoglucosan	39	2.8	25.6	0.1		3.57	28.1	20	17	38	34
Furfural	0.9	2.9	28.5	0.08							

[a]Conditions: Cellulose filter pulp pyrolyzed in He at 550 torr for 5 min. Power intensity, 130 W. [b]Conditions: Cellulose filter paper pyrolyzed in a vacuum for 20 min. [c]Conditions: Cotton cellulose pyrolyzed in a vacuum for 11 h. [d]Conditions: Pure cellulose pyrolyzed in N_2 at atmospheric pressure. [e]Conditions: Pure cellulose pyrolyzed in a vacuum. [f]Conditions: Pure cellulose pyrolyzed in N_2 at atmospheric pressure. [g]For 5 min. [h]For 25 min. [i]Conditions: Pure cellulose pyrolyzed in a vacuum. [l]For 5 min. [m]For 180 min.

Table 31: Relative mass concentration of the organic volatiles from microwave pyrolysis of 161 [73].

Compound	Relative mass concentration[a]		Relative retention time (furfural=1.0)
	A (%)	B (%)	
Acetaldehyde	5.6	5.4	0.012
Furan	--	0.3	0.042
<acetone	2.1	0.6	0.060
Propanal	305	5.3	0.077
Methanol	--	trace	0.131
n-Butanal	3.9	2.1	0.143
2,3-Butadione	2.7	7.9	0.196
	--	1.4	0.232
Crotonaldehyde	2.7	2.9	0.286
	--	1.6	0.524
	2.1	1.8	0.560
	--	4.1	0.690
	2.0	4.4	0.839
	--	1.7	0.857
	2.4	0.1	0.923
	--	0.1	0.964
	0.5	1.5	0.976
Furfural	57.0	24.0	1.000

(Table 31) contd….

	0.7	0.2	1.040
2-Furylmethyl ketone	5.2	2.6	1.090
	--	2.3	1.110
	--	1.9	1.120
	--	0.2	1.170
	--	Trace	1.210
5-Methylfurfural	7.6	4.6	1.230
	0.6	0.1	1.270
	--	10.7	1.440
	1.0	0.2	1.510
	0.3	Trace	1.540
	--	2.3	1.810

[a]Percentage in these columns are based on the integrated response of the gas chromatogram. A: Pyrolysis of 2.6 g of pure cellulose with 130 W/cm^2 in helium atmosphere at 550 torr. B: Pyrolysis of 2.6 g of cellulose treated with 0.47% NaOH (by weight) with 130 W/cm^2 in helium atmosphere at 550 torr.

Table 32: Yield of 163 upon microwave irradiation of various (1→4)-D-glucans[a] [74].

Substrate	n[b]	Water content[c] (% w/w)	Density (g/mL)	Yield of 162[d]	
				(mg)	(% w/w)
Cellulose	2,800	6.6	0.41	220	0.94
Starch	14,000	4.2	0.95	398	1.7
Dry starch	14,000	0.0	0.95	382	1.5
Amylopectin	2,000,000	11.0	0.33	226	1.0
Amylose	3,000	13.1	0.73	262	1.2
Maltodextrin	50	9.5	0.46	189	0.84
Maltodextrin 10	10	7.5	0.47	150	0.65
β-Cyclodextrin	7	10.5	0.83	280	1.3

[a]Starch amount: 25 g, irradiation time: 7.5 min. [b]Chain average degree of polimerization. [c]Water content at the start of the reaction (defined by weight loss at 100°C, 3 mm Hg). [d]According to HPLC after work-up.

Table 33: Yield of 3 in the acid hydrolysis of starch in the presence of metal halides under microwave irradiation and with conventional oil-bath heating[a] [78].

Metal halide	Yield of 3 (% w/w)				
	120 s	180 s	200 s	600 s	Δ
[b]	0	0	0	78.37	7.8
LiCl	24.0	105.8	85.1		94.6
NaCl	88.5	96.0	81.1		91.3
KCl	61.9	99.2	60.4		88.5
$MgCl_2$	88.0	96.5	83.4		95.9
$CaCl_2$	59.0	91.1	90.0		76.3
$BaCl_2$	21.7	111.0	70.1		71.4
$FeCl_3$	108.6	45.1			95.0
$AlCl_3$	0.1	25.6	4.4		61.9
NaBr	60.0	92.3	69.3		91.3
KBr	83.9	90.1	82.6		95.6
KI	89.2	77.7	48.8		97.0

[a]Reaction was carried out with 200 mg of soluble starch, 2.00 mL of 0.05% (w/w) hydrochloric acid, and 1 mL of 0.15 mol/L [Cl^-] under 800 W of microwave power irradiation and in an oil-bath at 145°C for 5 h. [b]With 1.00 mL of water to replace the salt solution to maintain the reaction volume. [c]The theoretical yield of D-glucose is 111%.

much higher than that obtainable by conventional pyrolysis in the large-scale reaction. 1,6-Anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose (levoglucosenone) was shown to be produced in one-quarter the amount of **163**. Other anhydro-sugars, e.g. 1,6-anhydro-β-D-mannopyranose (mannosan), 1,6-anhydro-β-D-galactopyranose (galactosan), and 1,4-anhydro-α-D-xylopyranose (xylosan) were also confirmed to be produced as minor components depending on the proportion of the monosaccharide content in the larch. When microwave pyrolysis of used papers and filter papers was performed, the yields of **162** were about 6% and 12%, respectively, suggesting that a higher content of **161** gives a larger amount of **162**.

Table 34: Yield of 3 in the acid hydrolysis of starch in the presence of metal sulfates halide under microwave irradiation[a] [78].

Metal sulfate	Yield of 3 (%)[c]			
	120 s	180 s	240 s	600 s
[b]	0	0	0	78.37
Na_2SO_4	8.0	12.6	9.1	
$MgSO_4$	7.7	7.8	4.4	
$ZnSO_4$	7.0	6.9	4.7	
$Al_2(SO_4)_3$	10.0	66.8	50.9	
$Ce(SO_4)_2$	88.9	88.9	80.7	

[a] Reaction was carried out with 200 mg of soluble starch, 2.00 mL of 0.05% (w/w) hydrochloric acid, and 1 mL of 0.15 mol/L [Cl^-] under 800 W of microwave power irradiation. [b] With 1.00 mL of water to replace the salt solution to maintain the reaction volume. [c] The theoretical yield of D-glucose is 111%.

11.5.2 Starch

The formation of **163** from starch or other 1-4 glucans has been studied by Straathof *et al* [74] by using a household-type microwave oven. An irradiation time of 5 to 15 minutes was required to accomplish complete reaction for 10 to 80 g of starch, respectively. The yield of **163** from different glucans varied from 0.65 to 1,7% (Table 32). HPLC analysis of the reaction mixture showed that **163** was formed together with glucose, fructose, 5-hydroxymethylfurfural, and oligomeric products [75].

No correlation could be found between the reaction efficiency and chemical structure, degree of polymerization or water content, though glucan density may be an important factor. For obtaining a small amount of **163** (*ca*. 1g) the ease of this method outweighs its low yield.

There are also some reports on the hydrolysis of starch in a microwave field [76]. Among these, Yu *et al*. [77] showed that starch (10%) in dilute hydrochloric acid was completely hydrolyzed with 5 min microwave irradiation without formation of coloured by-products. Zuwei *et al*. [78] studied the effect of inorganic salts on the acid hydrolysis of starch and found that these could be coupled with microwave irradiation to accelerate the reaction rate and that different kinds of salts manifest different effects. The yield of **3** obtained reached 111% (equal to the theoretical yield) after the addition of inorganic salts. When compared with conventional heating the reaction rate for the hydrolysis of starch to **3** was accelerated 100 times under heating of a domestic microwave oven. The results (Tables 33 and 34) suggest that the ability of metal halides to promote the hydrolysis of starch is due to the ability of salt to cause superheating of the solution.

12. CONCLUSIONS

Microwave-assisted carbohydrate chemistry is, at the present time, experiencing considerable growth and has the potential to greatly improve the image of carbohydrate chemistry. There are the bases for a growth of this chemistry also in the industrial ambit as it has shown how it is possible to move from small-scale synthesis (grams) to the multigram level (100-300 g). Microwave-heating has actually been shown to be a most useful method to assist manipulation reactions on mono- di- and poly-saccharides. 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 the easy performance and work-up, especially when using solid-supported reagents, make the method most attractive and also suitable for automation. Furthermore, these microwave assisted syntheses could be fairly applied under environmentally benign solvent-free conditions, i.e., according to new rules of so called “green chemistry”.

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