Petasis Olefination in a Continuous-Flow Microwave Reactor: *exo*-Glycals from Sugar Lactones

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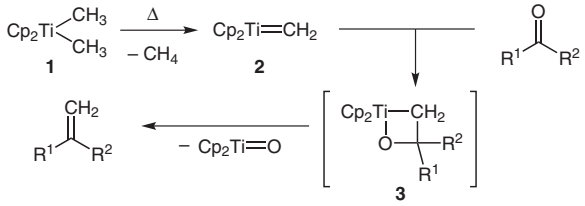
Abstract: An efficient Petasis olefination of sugar lactones under continuous-flow microwave conditions was developed. Their conversion into *exo*-glycals can be steered by adjusting the residence time and the concentration of the solution within the reactor. Applying a continuous-flow procedure, the reaction time can be shortened to less than three minutes, several hundred times shorter compared to values given in the literature for batch procedures. This setup is utilizable for a gram-scale synthesis of enol ethers and *exo*-glycals, in particular, such ones containing potentially (Lewis) acid sensitive acetalic protecting groups.

Key words: Petasis olefination, continuous-flow reactions, *exo*-glycals, sugar lactones, microwave support

Owing to their distinct nucleophilic reactivity, enol ethers and, in particular, *exo*-glycals are considered interesting synthons for further conversion, as for example to spiroketals[1] or *C*-glycosides.[2] Commonly applied olefination reactions, for example, Wittig, Horner, Julia, or Peterson olefination,[3] require basic reaction conditions not applicable to the conversion of carboxylic esters into enol ethers. The Tebbe olefination[4] is useful for the synthesis of enol ethers from esters. However, the required reagent is very sensitive to moisture. In contrast, the Petasis olefination[5] of esters not only provides nonbasic conditions, the reagent dimethyltitanocene (**1**, Scheme 1) dissolved in toluene–THF also is stable towards moisture and air. It can be stored at +4 °C over a longer period without decomposition.[6] Upon heating the molecule eliminates methane and forms the active titan carbenoide species **2**, which can react with the carbonyl compound in a cycloaddition reaction to form the more or less stable titanacycle **3**. After cycloreversion the olefinated product is released.

Under commonly applied batch conditions substrate and reagent are dissolved in toluene–THF and heated in the dark under inert atmosphere at 65–80 °C for several hours to afford a complete conversion.[5] It is assumed that the methane elimination to form the reactive species starts at about 65 °C and is the rate-limiting step.[7]

Consequently, elevating the temperature should strongly enhance the reaction rate, which, however, is limited by the low boiling point of THF of 66 °C under atmospheric pressure. The temperature limitation can be overcome by heating the reaction mixture in a sealed glass tube in a microwave oven accompanied by an increased pressure inside.



Scheme 1 Proposed mechanism of the Petasis olefination

Petasis olefinations accelerated by this means have been reported by Ley et al. for a complex ketone,[8] by Hartley for imino esters,[9] by Gallagher et al. for the olefination of oxalates[10] and, very recently, of sugar lactones.[2]

The latter observation and the limited reaction volume in a microwave glass tube prompted us to perform the reaction under continuous-flow conditions, as previously described for various other reactions.[11]

We now accomplished the first Petasis olefination under continuous-flow conditions combined with microwave irradiation. The experimental setup shown in Figure 1 consists of an HPLC pump for delivering solvents and the reaction mixture, capillaries (PTFE, 3.2 mm OD, 1.6 mm ID) used as both, sample loop (total volume: 6 mL) and flow reactor (total volume: 8.5 mL), a microwave oven for heating the reaction mixture in the reactor followed by a pressure relief valve to ensure the appropriate pressure.

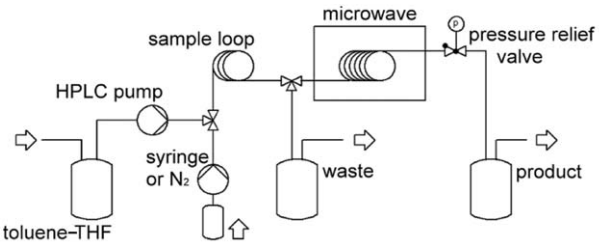


Figure 1 Continuous-flow reactor setup: For the optimization procedure the sample is injected by a syringe into the sample loop outside the microwave oven. For the preparative use, the sample loop is removed, and the reaction mixture is introduced directly by the HPLC pump

With this setup the crucial parameters of increased temperature and pressure as well as an efficient heat transfer to the reaction mixture can be adjusted.

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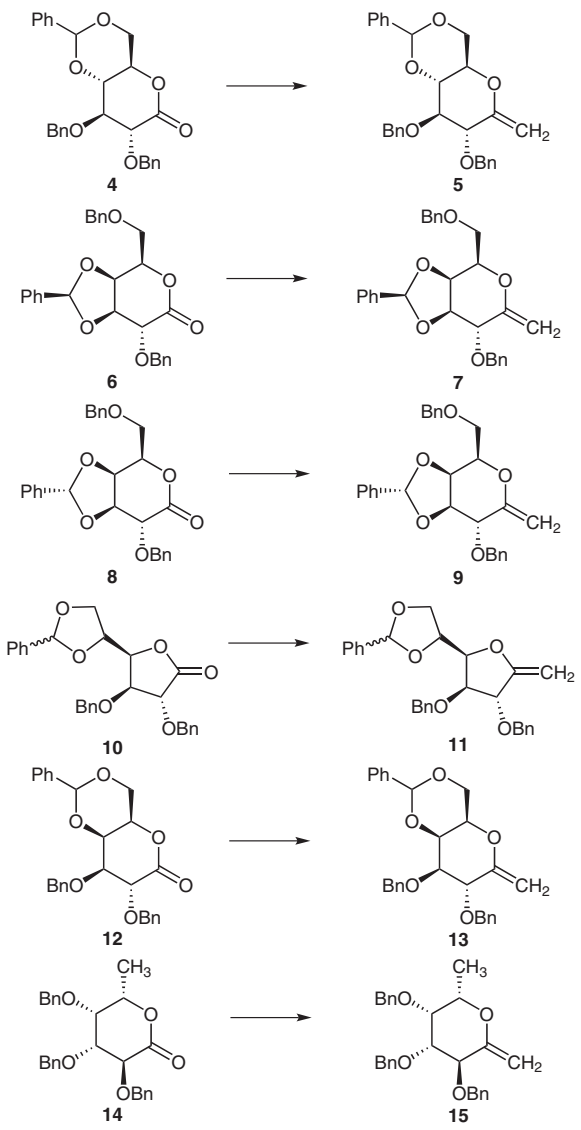


Scheme 2 Conversion of the sugar lactones into *exo*-glycals

For the optimization of the reaction conditions, model experiments with small quantities of the substrates were performed. In order to inject the reaction mixture as a single plug, the sample was not directly introduced by the HPLC pump. Instead, a sample loop – the capillary outside of the reaction zone – was used. This capillary was emptied completely by applying a stream of dry N_2 gas, before the reaction mixture, the solution of lactone and Petasis reagent, was filled in by a syringe.

When running the reaction, the HPLC pump delivers pure solvent (toluene–THF = 1:1) with a constant flow rate, which moves the reaction mixture continuously through the reaction zone. The capillary inside the microwave oven (CEM discover), the actual continuous-flow reactor, is isolated with glass wool in order to minimize thermal losses over the large outer tube surface. Therefore, an exact temperature control directly at the Teflon reactor tubes via an IR sensor is not possible. The reaction is performed with a constant microwave power of 50 W.

The pressure inside the system was adjusted to 8 bar by a pressure relief valve at the outlet. If the back pressure is too low, uncontrolled evaporation of solvent resulting in gas bubbles within the reaction zone would occur.

The increasing gas volume would push the sample solution out of the reactor faster than desired and result in an undefined short residence time and a decreased conversion. On the other hand, too high pressure in addition to increased temperature can possibly lead to a burst of the teflon tubes employed.

As model substrates, six sugar-derived lactones with different protecting-group patterns were chosen (Scheme 2). The olefination of these substances can be monitored by NMR after each run as is illustrated for the galactose-derived substrate **6** in Figure 2.

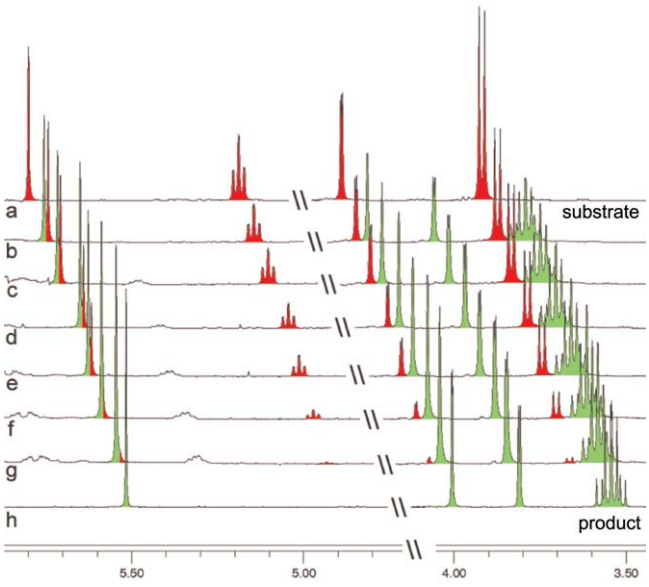


Figure 2 NMR monitoring of the olefination of **6**. a: Substrate; b: 1.5 mL/min; c: 1.0 mL/min; d: 0.75 mL/min; e: 0.5 mL/min; f: 0.35 mL/min; g: 0.25 mL/min; h: product. Decreasing the flow rate substantially increases the amount of product

First experiments showed that especially at low flow rates dilution effects at the interface of the sample plug and the pure solvent occur, even though the sample is initially introduced as a single plug. This resulted in drastic lowering of the reaction rate in the diluted areas and an incomplete conversion with regard to the sample collected at the end of the run. As a consequence, additional plugs of the reagent solution were placed in front and behind the substrate–reagent mixture inside the sample loop, in order to eliminate this effect.

Depending on the flow rate and therewith on the residence time within the reaction zone, the conversion of the substrate **6** into the product **7** changes in a systematic manner (see Figure 2 and Figure 3). For example, at a residence time of 5.67 min (flow rate: 1.5 mL/min) the substrate can still be observed (47% remaining), whereas the conversion can be judged complete after prolongation of the reaction time to 42.5 min (flow rate: 0.2 mL/min).

Under the same conditions, the glucose-derived building block **4** reacted remarkably faster, and complete conversion was already reached after 5.67 min (at 1.5 mL/min, Table 1).

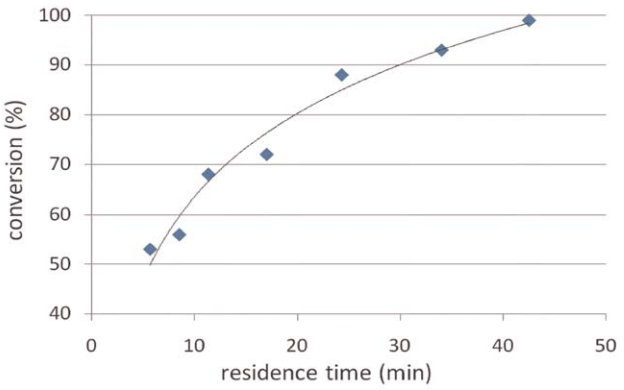


Figure 3 Correlation of residence time inside the microwave zone and the conversion obtained for the olefination of **6** taken from the integration of the corresponding ^{1}H NMR signals of substrate and product shown in Figure 2

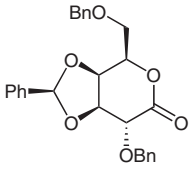
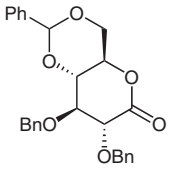
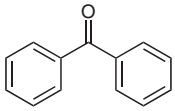
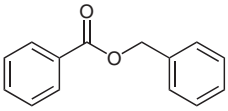
Logically, if the formation of the carbenoide species **2** by α-elimination is complete after a short time in the experiment using the gluconolactone **4**, it should be just the same in the presence of the galactonolactone **6**. However, the reaction rates for the conversion of **4** and **6** to give the corresponding *exo*-glycals differ significantly. This leads to the conclusion, that, in contrast to the batch reaction, the elimination of methane is not the rate-limiting step under the continuous-flow microwave conditions, but the reaction of the carbenoide intermediate **2** with the substrate. This result was confirmed when benzophenone and benzyl benzoate were reacted under the same conditions. Benzophenone reacts slightly faster than the galactonolactone **6**, whereas the ester can only be olefinated to a low extend even at long reaction times (Table 1), although monitoring by NMR showed the complete disappearance of the Petasis reagent.

Assuming that the rate-determining step is a bimolecular reaction, the reaction rate should be strongly dependent on the total concentration of the two reaction partners within the solution. Therefore, a further enhancement should be possible by applying a higher concentration.

Indeed, the increase of the Petasis reagent concentration from 0.18 M to 0.46 M resulted in a remarkably accelerated conversion. For example, up to a flow rate of 3.0 mL/min corresponding to a residence time of only 2.8 min, the two lactones **4** and **6** as well as the diastereomeric mixture of **10** can be olefinated with complete conversion.

After the reaction was complete, the crude product was easily purified by flash chromatography, eluting first the nonpolar impurities and subsequently the pure product. The yields obtained by this method range from about 50% to 74% and are in accordance with the respective yields achieved in analogous batch reactions carried out at maximum 65 °C under microwave irradiation of 200 W and

Table 1 Comparison of the Conversion of Different Substrates Using a 0.18 M Solution of Petasis Reagent in Toluene–THF

Entry	Substrate	Residence time (min)	Conversion (%)
1		5.67	53
2		11.33	68
3		34.00	93
	6		
4		5.67	>99
	4		
5		5.67	77
6		11.33	93
	16		
7		11.33	8
8		34.00	17
	17		

cooling of the reaction tube[12] with an air stream. In both microwave-assisted reactions the reaction times are remarkably shorter than under conventional flask conditions. For example, the fucose derivative **14** is conventionally olefinated at 70 °C within 16 hours with an identical yield of 74%[13] as in the continuous-flow reaction in a residence time of 5.67 min (Table 2).

Table 2 Microwave-Assisted Petasis Olefination under Batch and Flow Conditions Using a 0.46 M Solution of Petasis Reagent in Toluene–THF

Entry	Substrate	Continuous flow		Batch reaction	
		Yield (%)	Time (min)	Yield (%)	Time (min)
1	**4**	65	5.67	67	30
2	**6**	71	5.67	70	30
3	**8**	70	5.67	70	30
4	**10**	50	5.67	51	30
5	**12**	52	5.67	50	30
6	**14**	74	8.5	74	30

An increased flow rate allows for a preparative application of the continuous-flow reaction even on gram scale. It is an important feature of the synthesis under flow conditions that the scale-up of the reaction after optimization with small quantities of the valuable substrate is done by

simply increasing the operation time of the reactor without changes regarding conversion or yield. For example, 2.0 g of the glucose-derived lactone **4** were converted into the corresponding *exo*-glycal **5** at a flow rate of 1.5 mL/min in 30 minutes including conditioning of the flow system.

All obtained olefination products were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as COSY, HSQC, and NOESY experiments if required for complete assignment of the chemical shifts. Additionally, the conformations of the molecules were determined, facilitating the interpretation of the stereochemical outcome of subsequent reactions of the *exo*-glycals, as for example, the hydroboration of the products.[14]

Analysis of the coupling-constant patterns of compound **13** and **15** revealed that both molecules adopt the same conformation as their non-olefinated precursors, namely $^{4}C_{1}$ in the case of the galactose and $^{1}C_{4}$ for the fucose derivative (Figure 4). The latter nearly is a mirror image of **13**.

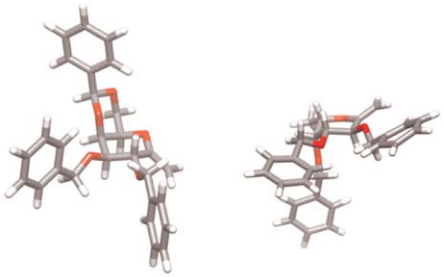


Figure 4 Conformations of compounds **13** (left) and **15** (right)

Probably due to annulation of a second ring formed by the benzylidene acetals in compounds **5**, **7**, and **9** (Figure 5), these molecules all exist in a $B_{2,5}$ boat conformation, bringing the *O*-benzyl group in position 2 into an axial orientation. The *endo* and *exo* orientation of the acetalic phenyl ring derived from the NOESY spectrum and confirmed by X-ray analysis of the *exo* isomer.

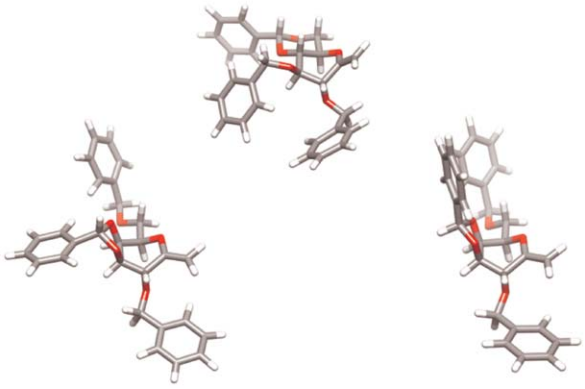


Figure 5 Conformations of compounds **5** (center), **9** (left), and **7** (right)

After HPLC separation of the two isomers of compound **11** (Figure 6), the two were distinguished by the observed NOE contacts. Especially in the case of the *S*-isomer, clear NOE crosspeaks exist for the interaction of the acetal proton with H4 of the furanose ring and of the *ortho* protons of the adjacent phenyl group with H5, which allows an assignment of these groups to the two hemispheres of the acetal ring.

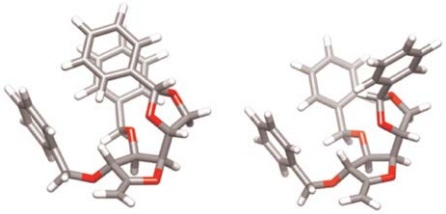


Figure 6 Conformations of the *R*-isomer (left) and *S*-isomer (right) of compounds **11**

In conclusion, the olefination of complex sugar-derived lactones to *exo*-glycals was achieved under continuous-flow conditions. This procedure allowed an optimization of the conversion by regulation of the residence time and the concentration on milligram scale, before the ready scale-up of the reaction to a gram-scale production. It can be concluded from these results that micro reactors are also efficient in preparative microwave-assisted conversions of other sensitive carbonyl substrates under continuous-flow conditions.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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