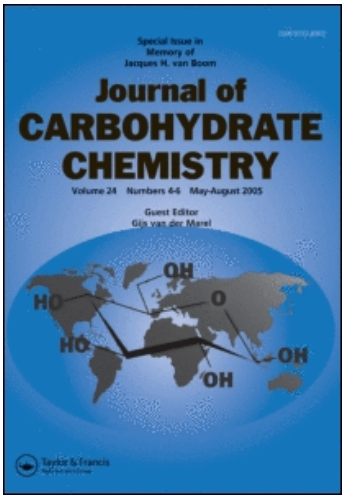

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Application of High-Pressure Technique to Carbohydrates

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To cite this Article Chmielewski, Marek and Jurczak, Janusz(1987) 'Application of High-Pressure Technique to Carbohydrates', Journal of Carbohydrate Chemistry, 6: 1, 1 — 15
To link to this Article: DOI: 10.1080/07328308708058857
URL: http://dx.doi.org/10.1080/07328308708058857

J. CARBOHYDRATE CHEMISTRY, 6(1), 1-15 (1987)

REVIEW ARTICLE

APPLICATION OF HIGH-PRESSURE TECHNIQUE TO CARBOHYDRATES[1]

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I. INTRODUCTION

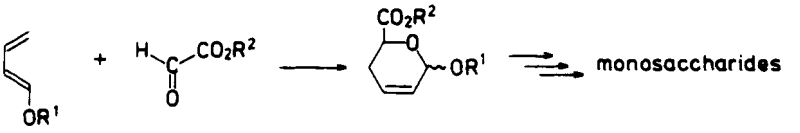
The effect of pressure on the rate and direction of organic reactions in solution has long been known and has been an object of extensive physico-chemical studies.[2] Application of high pres-

sure creates a unique possibility of solving some problems of organic synthesis, which cannot be solved by other, more readily accessible methods. During the past decade this new direction in organic synthesis has greatly developed, and some interesting reviews on this topic have recently been published.[3,4,5] The present paper is not a survey but deals with only two reactions which will illustrate the possibilities and usefulness of high-pressure techniques in carbohydrate chemistry. The first reaction has been a widely used method for construction of the pyranoid ring in total synthesis of carbohydrates or sugar-like compounds.[6,7] The second reaction enables transformation of readily available sugar synthons into desired new sugar species.

II. HIGH-PRESSURE (4+2)CYCLOADDITION OF CARBONYL COMPOUNDS TO 1-METHOXYBUTA-1,3-DIENE

The Diels-Alder reaction of 1-alkoxybuta-1,3-dienes with glyoxylates leads to formation of 2-alkoxy-5,6-dihydro-2H-pyran derivatives in racemic form (Scheme 1). Adducts 1 are convenient substrates for stereoselective total synthesis of many monosaccharides and other natural products.[6] This route has been extensively and thoroughly studied.[6,8] Attempts have been made to obtain adducts 1 in enantiomeric form by cycloaddition of 1-methoxybuta-1,3-diene to optically active esters of glyoxylic acid. However, the enantiomeric purities of the adducts were poor.[8] This can be explained by the

Scheme 1



1

three-bond distance between the stereodifferentiating center and the new chiral center formed. Application of Lewis acid catalysts has some limitations caused by the exceptional sensitivity of 1-methoxybuta-1,3-diene to cationic polymerization. Introduction of a chiral center into the alkoxy group of a diene provides good stereodifferentiation; however, the availability of such dienes is restricted owing to their laborious synthesis.[9]

It could be assumed that a shift of the inductive center to the immediate vicinity of the carbonyl group should enhance asymmetric induction. This is, however, obviously connected with deactivation of heterodienophile, because it leads to "ruling out" of the carbonyl group. This synthesis-related problem can be solved by application of the high-pressure technique.

It is well known that the influence of pressure on organic reactions is essential in the following aspects:

- acceleration of the reaction rate,
- modification of regio- and stereochemistry,
- changes in the reaction equilibrium.

Pressure times volume (PV) has the dimension of energy. Thus the use of pressure constitutes nonthermal means for carrying out reactions. Every reaction is characterized by an activation volume (ΔV^*) defined as the difference between the volume occupied by the transition state and that occupied by reactants ($\Delta V^* = V_{TS} - V_R$). Similarly, each reaction involves a reaction volume (ΔV_{rxn}), representing the difference in volume between products and reactants ($\Delta V_{rxn} = V_P - V_R$). Both values are usually expressed in cm^3/mol.

Pressure can exert an effect on both the reaction rates and equilibria. Pressure influences ΔG^* according to the sign and magnitude of ΔV^*. If $\Delta V^* < 0$, the application of pressure lowers ΔG^* and accelerates the reaction rate. Conversely, if $\Delta V^* > 0$, pressure retards the reaction. The activation volume is a function of pressure, given by the following equation:

$$\Delta V^* = -RT(\partial \ln k / \partial P)_T$$

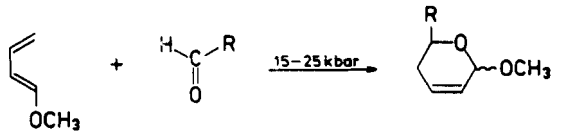
The effect of pressure on the reaction equilibria follows directly from le Chatelier-Brown's principle. Pressure influences ΔG_{rxn} according to the sign and magnitude of ΔV_{rxn}. If $\Delta V_{rxn} < 0$, the application of pressure shifts the equilibrium toward the products. The reaction volume is also a function of pressure:

$$\Delta V_{rxn} = -RT(\partial \ln K/\partial P)_T$$

The 1-25 kbar pressure range (1 kbar=987 atm) is typical for organic synthesis. These pressures can be attained in an earlier reported relatively simple piston-cylinder type apparatus.[10,11]

Organic reactions characterized by a big negative activation volume are substantially accelerated by pressure. Consequently, the reactions can be carried out under mild thermal conditions, this usually preventing adverse side effects. In many instances, the reaction times are shortened and yields are higher. The high-pressure technique is particularly useful in Diels-Alder reactions which cannot be carried out under thermal conditions, since the reactivity of dienophile is too low. Diels-Alder reactions exhibit a particularly big negative activation volume within a range of -30 to -50 cm^3/mol; therefore, significant acceleration of the reaction rate can be expected.

Scheme 2



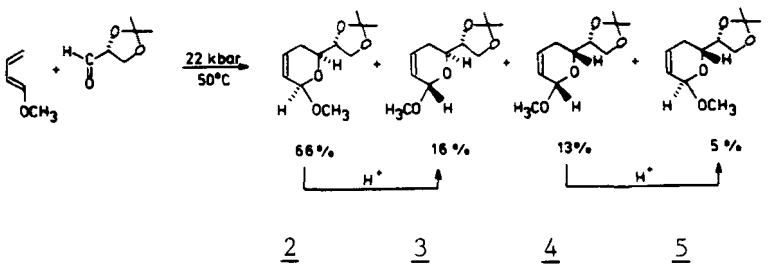
R=alkyl , aryl

Simple alkyl and aryl aldehydes react with 1-methoxybuta-1,3--diene under 15-25 kbar pressure to give the respective adducts in a good yield.[11,12] Very recently we found that the use of $Eu(fod)_3$ as catalyst allows a decrease in the pressure required for successful carrying out of the above cycloadditions.[13] $Eu(fod)_3$ and other

lanthanide complexes have earlier been introduced by Bednarski and Danishefsky[14] as very attractive mild Lewis acid catalysts mediated hetero-Diels-Alder reactions. These reactions open an access to effective asymmetric induction in the construction of the 5,6-dihydro--2H-pyran skeleton.

The first experiments using (R)-menthyl glyoxylate, an activated heterodienophile, showed a noticeable effect of pressure on the direction and magnitude of asymmetric induction.[15] Cycloaddition of 2,3-O-isopropylidene-D-glyceraldehyde, bearing a chiral center located in α-position with respect to the formyl group, to 1-methoxybuta-1,3-diene gives rise to chiral cycloadducts.[16,17] When the reaction is carried out under 22 kbar pressure at 50 °C in diethyl ether as solvent, four diastereomeric adducts are formed: two *cis* diastereomers by *endo* addition (2 and 4) and two *trans* by *exo* addition (3 and 5), in the proportions shown in Scheme 3.

Scheme 3



2 3 4 5

The diastereomeric yield of cycloaddition was found to depend, to some extent, on both the pressure and temperature. The results of cycloaddition may be summarized as follows:[17]

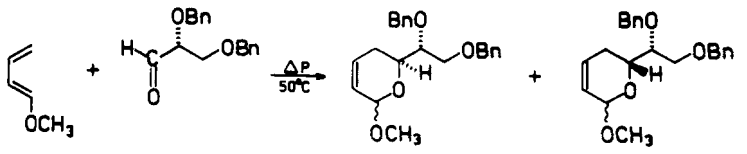
1. The (4+2)cycloaddition yield increases with a rise of pressure and temperature.
2. The ratio of *cis*:*trans* diastereomers resulting from *endo* and *exo* addition, respectively, is consistent with Alder's rule; the *cis* diastereomer content (2+4) increases with a rise of pressure and diminishes with elevation of temperature.
3. Within the investigated pressure and temperature ranges, the

diastereomers of S configuration on C-6 carbon atom (2 and 3) always predominate.

4. The value of asymmetric induction depends on pressure and temperature; a rise of pressure causes an increase in asymmetric induction but with elevation of temperature it decreases.
5. The extent of asymmetric induction depends on the kind of solvent.
6. The degree of asymmetric induction is higher in *endo* addition.

A mixture of diastereomers can be easily separated into two fractions containing diastereomers with S- and R-configuration at the C-6 carbon atom, 2, 3 and 4, 5, respectively. Moreover, acid-catalyzed isomerization at the C-2 carbon atom strongly favors both *trans* isomers (3 and 5). This leads to virtually pure *trans* adducts which can be used for further transformations into desired structures.

Scheme 4



	20 kbar	74 %	26 %
1 % Eu(fod)$_3$	20 kbar	31 %	69 %
"	15 kbar	25 %	75 %
"	7 kbar	51 %	49 %

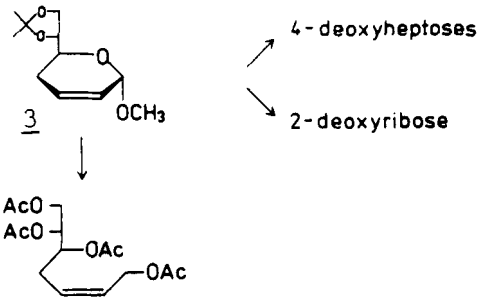
6 7

During further studies of the influence of various factors on asymmetric induction in (4+2)cycloaddition of 1-methoxybuta-1,3-diene and chiral aldehydes we applied 2,3-di-O-benzyl-D-glyceraldehyde as the dienophile (Scheme 4).[18] The reaction carried out in methylene chloride, under 20 kbar, and at 50 °C afforded in 36% yield a mixture of four diastereomers. As before, chromatographic separation afforded two fractions containing *cis-trans* diastereomers with absolute configuration S or R on the chiral center C-6, 6 and 7, respectively. Since the reaction yield was low, we attempted to improve it by application of catalytic amounts of Eu(fod)$_3$ under the

same pressure. Indeed, the reaction yield was much higher (60%), whereas, surprisingly, the direction of induction was opposite. The results shown in Scheme 4 indicate that lowering of pressure from 20 to 15 kbar led to an increase in the content of diastereomers R in the cycloaddition products. Further reduction of pressure (to 7 kbar) drastically lowered the induction degree and changed the direction of asymmetric induction. This phenomenon can be interpreted in terms of an influence of pressure on the form of complexing of the substrate by the catalyst. This leads to different stereochemical pathways of cycloaddition, depending on the pressure applied.[18]

Adducts derived from (4+2)cycloaddition of glyceraldehyde derivatives to 1-methoxybuta-1,3-diene can be utilized for preparation of a variety of interesting sugar compounds.[18] Some applications are shown in Scheme 5.[19,20] For example, hydroxylation of the double bond in 3 led to 4-deoxyheptoses,[19] whereas its ozonolysis followed by hydrolysis gave 2-deoxy-D-ribose.[18] On the other hand, oxidation of the anomeric center in 3 to the hydroperoxide stage and subsequent reduction gave unsaturated heptitol with defined stereochemistry.[20]

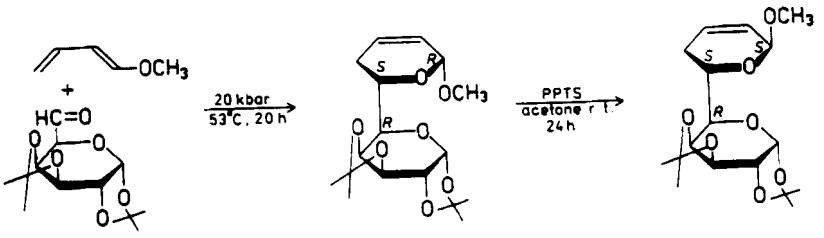
Scheme 5



Application of an aldehyde with steric hindrance exceeding that of glyceraldehyde derivatives in a high-pressure reaction with 1-methoxybuta-1,3-diene should improve the diastereoselectivity. For example, the aldehyde obtained from diisopropylidene-D-

-galactose 8 reacted under 20 kbar pressure at 53 °C with 1-methoxybuta-1,3-diene to afford a cycloadduct 9 with complete stereoselectivity; 9 could be easily isomerized to the *exo* adduct 10 (Scheme 6).[21] This 100% asymmetric induction has never been achieved before in a non-catalyzed Diels-Alder reaction.[22]

Scheme 6



8 9 10

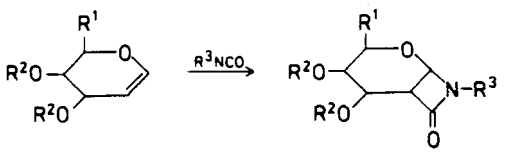
The presented results on (4+2)cycloaddition of 1-methoxybuta--1,3-diene to carbonyl compounds illustrate the kinetic and stereochemical aspects of the high-pressure technique.

The practical aspect of these reactions offering close stereocontrol in the synthesis of selected structures should also be stressed. Moreover, the initial working volume of the high-pressure vessels used (up to 100 cm^3) enables carrying out of the reactions on a preparative scale.

III. (2+2)CYCLOADDITION OF ACTIVE ISOCYANATES TO GLYCALS

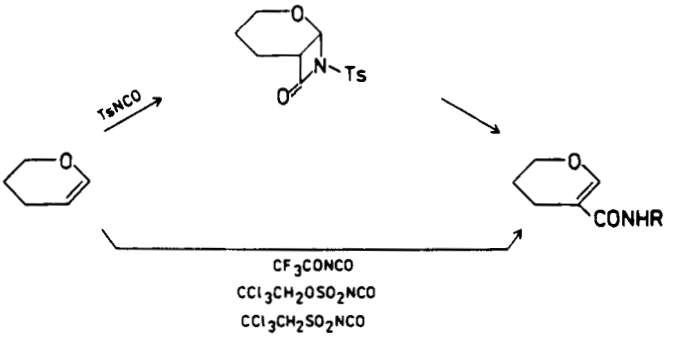
The bicyclic adduct of an isocyanate and a glycal (Scheme 7) represents an interesting structure with potential biological activity, and also a new skeleton suitable for further transformations into known or new compounds.

Scheme 7



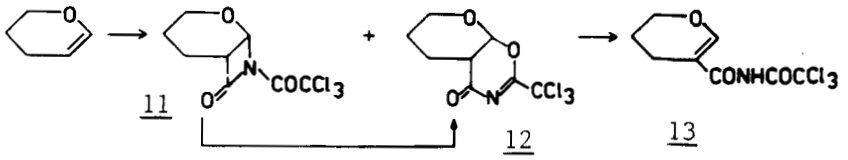
Attempts at adding chlorosulfonyl isocyanate and other active isocyanates to tri-O-acetyl-D-glucal failed, however, to afford the expected β-lactams.[23] Isocyanates acted only as Lewis acids, causing the known dimerization of the sugar material. On the other hand, cycloaddition of tosyl isocyanate to dihydro-2H-pyran at low temperature (~0 °C) and atmospheric pressure has led to formation of bicyclic β-lactams.[24] Elevation of temperature of cycloaddition has caused a rearrangement of the four-membered ring to open-chain amide (Scheme 8). Recently Barrett et al.[25] have found that 2,2,2-trichloroethylsulfonyl, 2,2,2-trichloroethoxysulfonyl, and trifluoroacetyl isocyanate react with dihydro-2H-pyran to give unsaturated amides, no β-lactams being isolated in all three cases (Scheme 8).

Scheme 8



Trichloroacetyl isocyanate has been found to produce with dihydro-2H-pyran the amide 13, *via* intermediate formation of unstable β-lactam 11, and (4+2)adduct 12 (Scheme 9).[26]

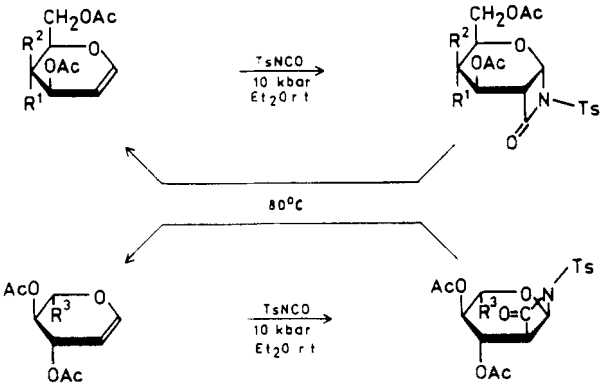
Scheme 9



Both by-products have been only detected in an NMR tube.[26]

Application of 10 kbar pressure enabled (2+2)cycloaddition of tosyl isocyanate to acetylated glycals (Scheme 10).[27] The reaction proceeded with high stereoselectivity to afford a four-membered β--lactam ring which was *anti* with respect to the acetoxy group at C-3. Products crystallized from the post-reaction mixture in nearly pure form. Elevation of temperature of the high-pressure experiments to 50 °C, followed by cooling of the reaction vessel to room temperature before decompression, increased the yield of cycloaddition. All reaction mixtures were, however, contaminated with the respective α,β-unsaturated amides.

Scheme 10

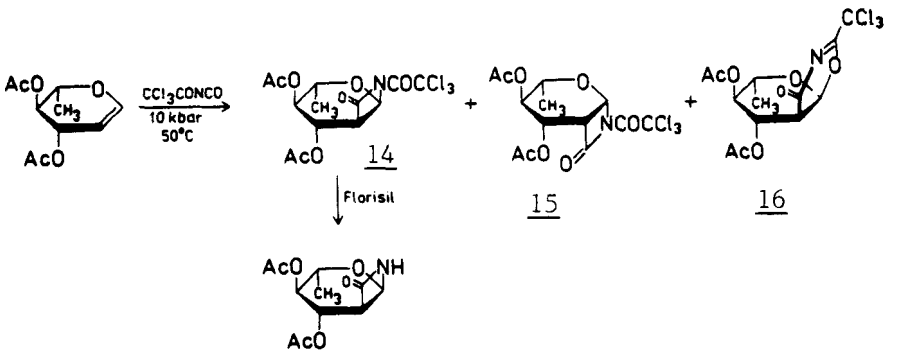


Bicyclic β-lactams obtained by us treated with alcohols or water at room temperature underwent rapid opening of the four-membered ring to give the respective glycosides or hemiacetals. Upon heating or even after standing at room temperature, the adducts exhibited retro-addition to afford the starting glycal. This fact explains why β-lactams could not be obtained from glycals and isocyanates under thermal conditions.

Trichloroacetyl isocyanate is slightly less reactive than tosyl isocyanate. Under 10 kbar pressure the former isocyanate condensed with di-O-acetyl-L-rhamnal yielding the three products 14, 15, and 16 shown in Scheme 11, in a ratio of about 1.4 : 1.0 : 4.0, respectively.[28] The (4+2)cycloadduct 16 crystallized almost quant-

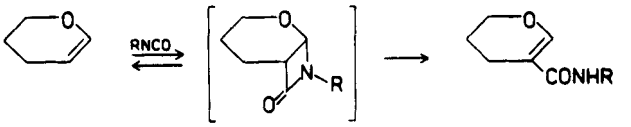
itatively from the reaction mixture. The mixture of cycloadducts 14, 15, and 16, heated in $CDCl_3$, afforded starting rhamnal as the main product.

Scheme 11



When diastereomeric β-lactams obtained after separation of the (4+2)cycloadduct were treated with Florisil, the bicyclic β-lactam with L-*gluco* configuration, unsubstituted at the nitrogen atom, was isolated (Scheme 11).[28]

Scheme 12



R = $COCF_3$, $SO_2OCH_2CCl_3$

Benzoyl isocyanate and ethoxycarbonyl isocyanate did not react with acetylated glycals under 10 kbar pressure.[29] Obviously phenyl isocyanate and methyl isocyanatoacetate were also unreactive even under 15 kbar pressure.[29] On the other hand, trichloroethoxysulfonyl isocyanate or trifluoroacetyl isocyanate favored, under 10 kbar

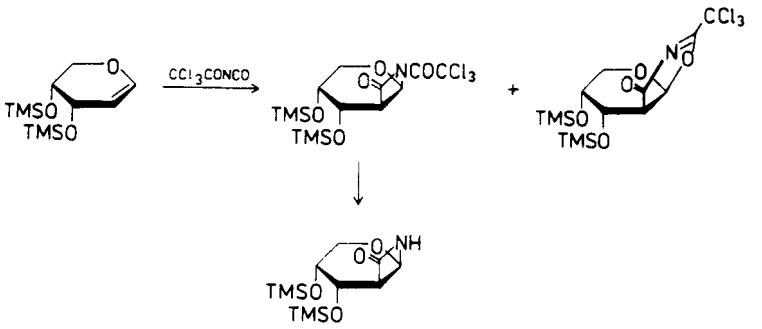
pressure, the formation of α,β-unsaturated amides (Scheme 12). In the case of addition of trichloroethoxysulfonyl isocyanate to tri-O--acetyl-D-glucal, the respective bicyclic β-lactam could be isolated by crystallization only if the reaction time was short (1 h). The product was, however, accompanied by unreacted glucal (about 50% of the initial content).[29]

Our experiments performed under high-pressure conditions clearly point to the reversibility of cycloaddition. High pressure not only accelerates the reaction rate but also allows obtainment of compounds thermodynamically forbidden at normal pressure and room temperature. This thermodynamical aspect of cycloaddition is crucial. In the light of the literature data and our results it can be assumed that the problem of (2+2)cycloaddition of isocyanates to glycals under normal pressure cannot be resolved by enhancement of the reactivity of isocyanate, because the kinetic aspect of the reaction is less important. Moreover, very active isocyanates would eventually shift the reaction toward unsaturated amide. Hence, it is obvious that only modifications of the glycal moiety can help to solve the problem. Bearing in mind these inferences, we turned our attention to glycals having non-polar substituents at the hydroxyl groups. We showed that (2+2)cycloaddition of sulfonyl and trichloroacetyl isocyanate to silylated or benzylated glycals proceeds smoothly under normal pressure at room temperature.[30,31] Three molar equivalents of isocyanate were used. If the isocyanate - glycal ratio was 1 : 1, only 40-60% conversion of the sugar substrate took place, even after prolonged reaction time.

Our results clearly point to the low stability of cycloadducts. It is certainly caused by the electron-withdrawing group attached to the nitrogen atom. Therefore, N-deprotection is necessary prior to isolation or chemical transformation of adducts. So far, attempts at splitting of the sulfonyl substituent without decomposition of the β-lactam ring have been unsuccessful. In the case of the trichloroacetyl group, an addition of benzylamine to the reaction mixture led to removal of N-protection and to formation of stable bicyclic β-lactams (Scheme 13).[30,31] For example, di-O-trimethylsilyl-D-arabinal

added trichloroacetyl isocyanate in acetonitrile solution to give stereospecifically *cis* fused (2+2) and (4+2)cycloadducts. The isocyanate entered exclusively *anti* with respect to the C-3 substituent. Addition of benzylamine, followed by chromatographic separation, afforded the relatively stable, optically pure β-lactams with a unique bicyclic skeleton.

Scheme 13



Owing to the stereospecificity of the reaction, the configuration of glycal is decisive for the configuration at the carbon atom attached to the nitrogen and oxygen atoms. This offers stereocontrol in formation of appropriate configuration at the carbon atom being crucial for the biological activity of β-lactam antibiotics.

IV. CONCLUSION

In summary, the two examples of high-pressure reactions presented illustrate the advantages of this method in organic synthesis. It is shown that pressure can influence both the reaction rates and equilibria. These effects are utilized in organic chemistry not only for studies of reaction mechanisms, but also for carrying out the syntheses of compounds difficult to obtain, if at all, *via* other pathways. Moreover, the influence of pressure on the stereochemical course of reactions is of great importance, particularly in the case

of stereocontrolled syntheses of natural products. Finally, inferences drawn from the high-pressure experiments can help to design reactions under normal pressure.

V. ACKNOWLEDGEMENTS

The authors are grateful to all their collaborators whose names are listed in the references. This work was supported by the Polish Academy of Sciences CPBP-01.13. grant.

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