

High Pressure Approach to the Synthesis of Cryptands and Related Compounds*

JANUSZ JURCZAK,** RYSZARD OSTASZEWSKI,
MAREK PIETRASZKIEWICZ, and PIOTR SALAŃSKI
*Institute of Organic Chemistry and Institute of Physical Chemistry, Polish Academy of Sciences,
ul. Kasprzaka 44/52, 01-224 Warsaw, Poland*

(Received: 2 October 1986; in final form: 27 February 1987)

Abstract. Some fundamentals concerning the high-pressure technique in organic chemistry and recent progress in high-pressure synthesis of cryptands and related compounds are described. A brief discussion is given of several examples illustrating various approaches to high-pressure syntheses of simple and chiral cryptands. Emphasis is placed on double-quaternization reactions carried out under high pressure.

Key words. High-pressure synthesis, cryptands, *N*, *N'*-dimethyldiazacoronands, bisquaternary salt, double quaternization.

1. Introduction

There has been growing interest in synthetic macrocyclic receptors since Pedersen's pioneering work on crown ether synthesis [1]. The introduction of nitrogen into macrocyclic structures as bridge-head atoms created a new branch of host molecules called 'cryptands' – compounds with unique complexing properties. The incorporation of nitrogen pivoting atoms into receptor molecules offers numerous possible structures. Thus, the molecular cavity can be modified in a highly predictable manner, providing molecular architectures for size, shape and chiral recognition.

The most significant contribution in the progress of cryptand synthesis and chemistry is associated with Lehn's research group in Strasbourg. The first report on the synthesis of [2.2.2] cryptand under high-dilution conditions appeared in 1969 [2]. The high-dilution method has been used not only to form simple cryptands, but also in the syntheses of more complex systems. A survey of synthetic methods for cryptands and related compounds has recently been published [3]. One of these methods, developed by Newkome *et al.* [4], consists of double-quaternization of the *N*, *N'*-dimethyl macrocycle with bis(2-iodoethoxy)ethane in boiling acetonitrile to afford the bisquaternary salt of the bicyclic system in *ca.* 40% yield.

The formation of a quaternary ammonium salt from tertiary amine and an alkylating agent (the Menshutkin reaction) is strongly accelerated by pressure [5]. Recently we found that sparteine – a quinolizidine alkaloid – reacts under high pressure with diiodomethane to give the corresponding cyclic bisquaternary salt in quantitative yield [6]. These results inspired further attempts at double-quaternization of

* This review is based on a lecture presented at the Fourth International Symposium on Inclusion Phenomena/Third International Symposium on Cyclodextrins, Lancaster, U.K., 20–25 July 1986.

** Author for correspondence.

N, N'-dimethyldiazacoronands, which led to the formation of the cryptand framework [7].

2. Fundamentals of the High-Pressure Technique Used in Organic Chemistry

It is well known that pressure can exert two influences on organic reactions: (a) acceleration of the reaction rate, and (b) changes in the reaction equilibrium [8].

Pressure times volume (PV) has the dimensions of energy. Thus the use of pressure constitutes a non-thermal means for carrying out reactions. Every reaction is characterized by a volume of activation (ΔV^*) defined as the difference between the volume occupied by the transition state and that occupied by the reactants. Similarly, each reaction involves a volume of reaction (ΔV_{rxn}), representing the difference in volume between products and reactants.

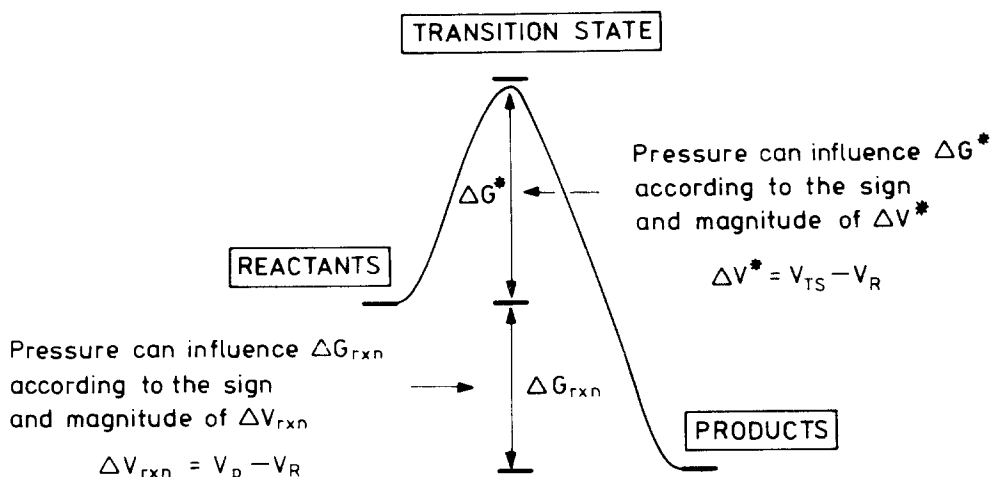


Fig. 1. Energy-reaction coordinate diagram.

Pressure can influence both the reaction rates and equilibria, as shown in Figure 1. 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 influence of pressure on the reaction equilibria follows directly from Le Châtelier–Brown's principle. If $\Delta V_{\text{rxn}} < 0$, the application of pressure shifts the equilibrium towards the products.

High-pressure organic reactions on a preparative scale are mostly carried out in a piston-cylinder type apparatus. In our laboratory, we use a unit of our own design with an initial working volume of about 90 mL, enabling work up to 30 kbar [9]. The main details of the apparatus are shown in Figure 2.

The high-pressure apparatus comprises two external rings (2) surrounding an internal steel conical vessel (1). The cylindrical high-pressure space is closed from below with a steel stopper (3). All electrical connections (manganin manometer, thermocouple, etc.) are led through a conical electrode (6) placed in the stopper. The internal vessel is closed from above by a mobile piston (4) moved by an independent hydraulic force. This piston and the stopper are sealed with resin O-rings and brass rings (5). For reactions performed at higher temperatures, an external heating jacket is used. Flexible Teflon ampoules (7) may be used as reaction vessels [10].

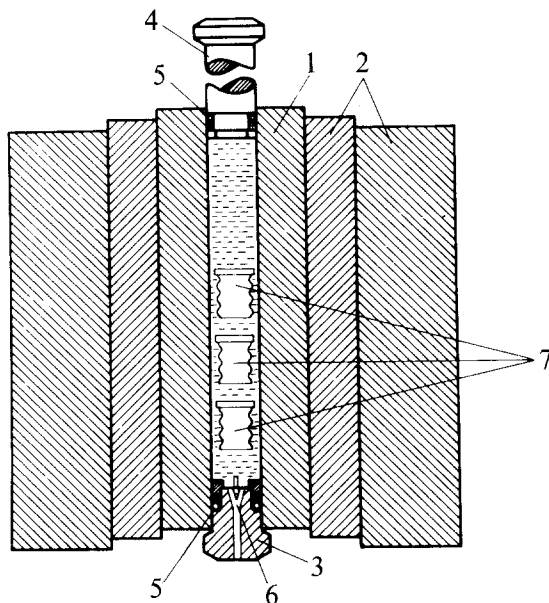
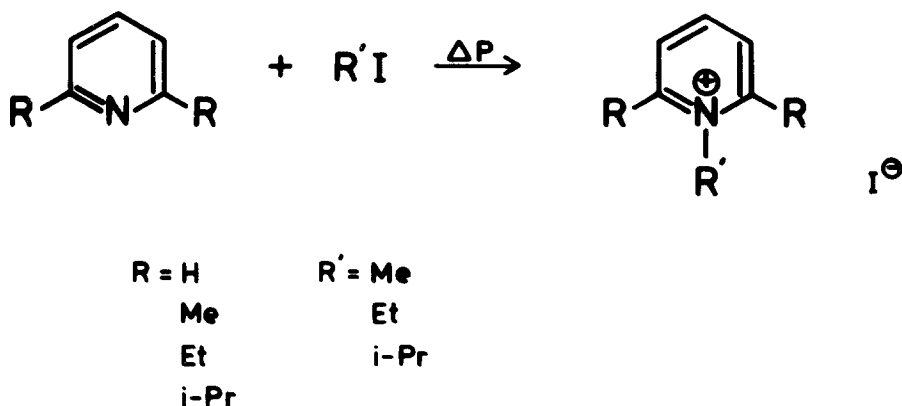


Fig. 2. Direct piston-cylinder high-pressure apparatus.

3. Influence of Pressure on the Menshutkin Reaction

The formation of charged products from neutral substrates usually results in increased solvation. Thus, when the charge develops along the reaction coordinate, ΔV^* is often large and negative. For example, the formation of a quaternary ammonium salt from a tertiary amine and an alkylating agent (the Menshutkin reaction) will have a ΔV^* in the -20 to -50 cm^3/mol range. Such reactions should be dramatically accelerated by the application of a few kbar of pressure. This can be illustrated by the quaternization of substituted pyridines with various alkyl iodides [11] (Scheme 1). The activation volumes for some Menshutkin reactions are compared in Table I.



Scheme 1.

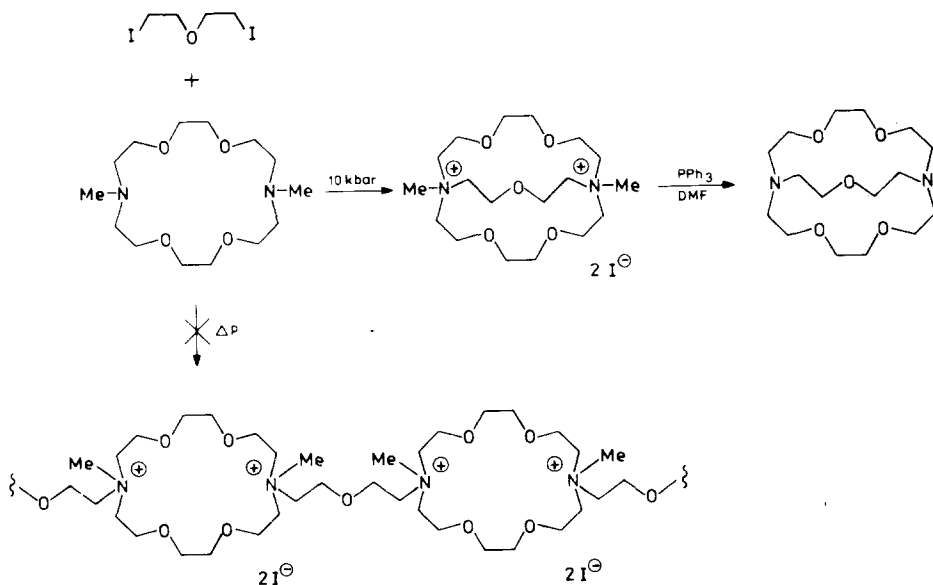
Table I. Activation volumes for some Menshutkin reactions at 25 °C in acetone

Iodide <i>R'</i>	Amine <i>R</i>	ΔV^* (cm ³ /mol)
Me	H	-21.9
	Me	-24.4
	Et	-27.3
	i-Pr	-30.2
Et	H	-23.3
	Me	-23.9
	Et	-28.9
	i-Pr	-35.0
i-Pr	H	-26.5
	Me	-28.2

The results clearly indicate that the volume of activation is more negative for more sterically hindered reactions. This means that the high-pressure approach should be especially effective in cases where highly hindered amines are quaternized.

4. Synthesis of Simple Cryptands via High-Pressure Double-Quaternization

A representative example of the double-quaternization method for the synthesis of simple cryptands [7] is illustrated in Scheme 2. An equimolar mixture of *N,N'*-dimethyldiazacoronand and bis(2-iodoethyl) ether, dissolved in acetone, was exposed to 10 kbar pressure at room temperature for a few hours. During the reaction the bisquaternary salt precipitated quantitatively.



Scheme 2.

An additional experiment was performed using two equivalents of bis(2-iodoethyl) ether under exactly the same conditions; the product was identical with the former one. The conclusion is that under these conditions the transition state leading to the cryptand skeleton is highly favoured over the formation of linear polymers. Finally, [2.2.1] cryptand was obtained by treatment of the bisquaternary salt with triphenylphosphine in boiling dimethylformamide [12].

In order to demonstrate the utility of the high-pressure method, double-quaternization reactions between three other *N, N'*-dimethyldiazacoronands ([12]—N₂O₂, [15]—N₂O₃, and [18]—N₂O₄) [3] and two bridging components (bis(2-iodoethyl) ether and 1,2-bis(2-iodoethoxy)ethane), were studied. All reactions were performed under the same conditions as above. Without exception colourless crystalline solids precipitated in very high yield (81–100%) in the reaction cell, and after a simple work-up, the isolated bisquaternary salts were analytically pure.

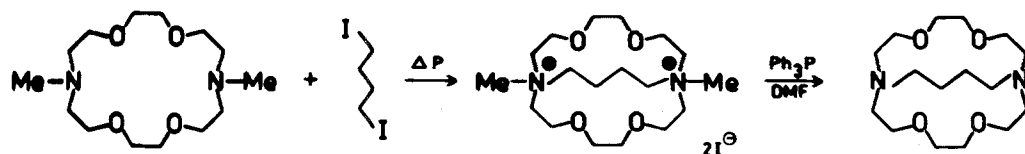
In order to gain more knowledge about the nature of double-quaternization reactions, especially about the role of solvent and leaving group, several additional experiments were carried out [13]. Six different aprotic solvents (toluene, diethyl ether, ethyl acetate, acetone, acetonitrile, and dimethylformamide) were used as a reaction medium. The results indicated that high-pressure double-quaternization was highly accelerated in polar solvents like dimethylformamide or acetonitrile. From the practical point of view, it would be desirable to perform a double-quaternization reaction in dimethylformamide within a short time and to demethylate the resulting compound directly, since dimethylformamide serves as a good solvent.

The influence of the leaving group, present in a bridging component (Br, Cl or OTos, instead of I), was in good agreement with the well known order of reactivity given by I > Br > OTos >> Cl. Evidently, the best bridging components are iodo-compounds; not only will they give the best yields of products, but it was also found that bisquaternary diiodides demethylated easier than the corresponding dibromides, dichlorides or bistosylates.

5. Reactions of *N, N'*-Dimethyldiazacoronands with α, ω -Diiodoalkanes

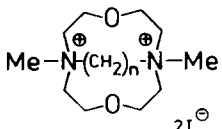
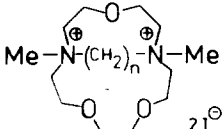
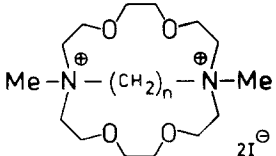
The successful synthesis of simple cryptands stimulated more systematic studies in this field. First, it was interesting to study the influence of the length of the bridging component on the yield obtained for the double-quaternization reaction [14]. The same diazacoronands were selected as above, and several α, ω -diiodoalkanes were used as the bridging components. A typical example is provided in Scheme 3. The yields are presented in Table II.

An important conclusion arises from these results, *viz.* that the yield of the double-quaternization product decreases with increasing length of the α, ω -diiodoalkane.



Scheme 3.

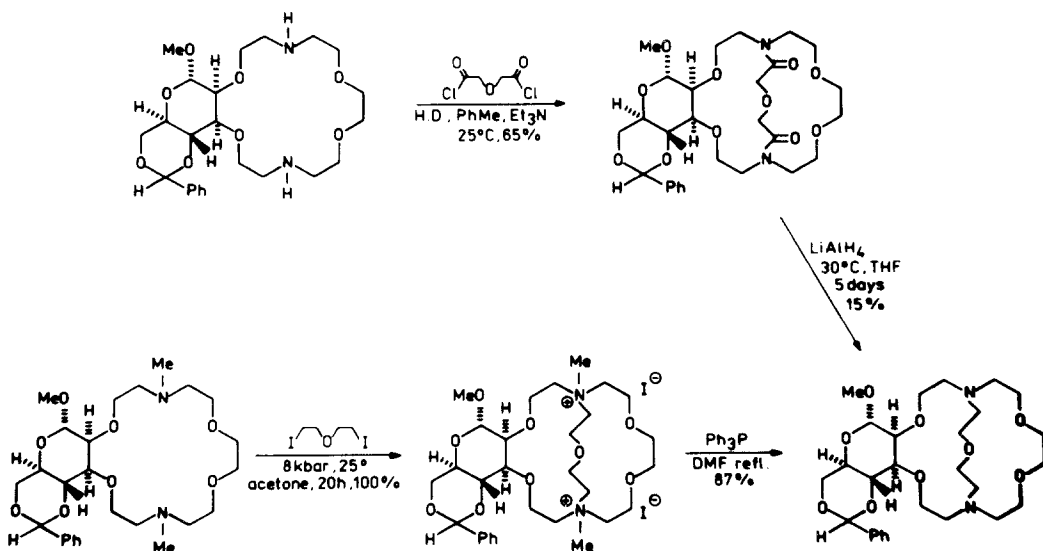
Table II. Yields of bisquaternary salts obtained from *N, N'*-dimethyl diazacoronands and α, ω -diiodoalkanes

					
n	Yield (%)	n	Yield (%)	n	Yield (%)
3	91	3	90	3	100
4	86	4	96	4	97
5	72	5	89	5	76
6	70	6	93	6	63
8	59	8	58	8	58
				10	56

6. Synthesis of Chiral Cryptands Starting from *N, N'*-Dimethyldiazacoronands Incorporating Carbohydrate Units

All chiral crown ethers incorporating one carbohydrate subunit possess two diastereotopic faces of the macrocyclic ring. They are able to form diastereoisomeric complexes with primary alkylammonium cations.

These properties may be followed by the fusion of the cryptand framework and the chiral unit. In our first synthesis of chiral cryptands, *N, N'*-dimethyl diazacoronands incorporating D-manno-, D-gluco-, and D-galacto-pyranosidic subunits [15, 16] served as substrates in the double-quaternization reactions [17–19]. These double-quaternization reactions of four chiral diazacoronands (three of them possessed 4,6-*O*-benzylidene protection of the sugar moiety [17, 18] and the fourth, of D-manno configuration, was blocked by the 4,6-*O*-((*S*)-phenylethylidene) protecting group

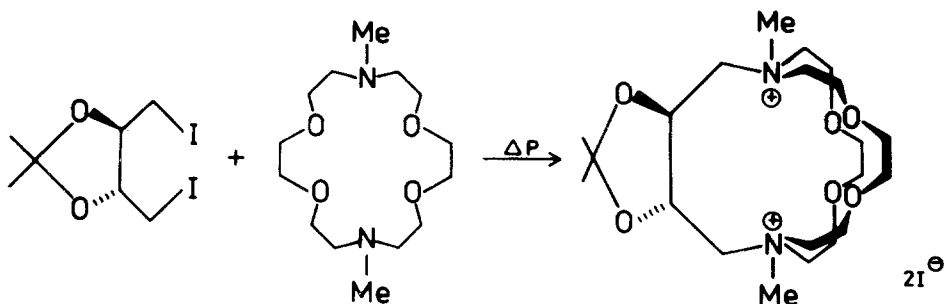


Scheme 4.

[19]) with bis(2-iodoethyl)ether afforded in quantitative yields the corresponding bisquaternary salts as colourless precipitates. Demethylation was followed in the usual manner to give the desired chiral cryptands. The comparison of two approaches – high-pressure double-quaternization and the high-dilution method – to the synthesis of the chiral (2.2.1) cryptand incorporating a D-mannopyranosidic unit is shown in Scheme 4. The high-dilution method afforded the chiral cryptand in only 10% overall yield.

7. Chiral Cryptand Synthesis Starting from Achiral *N, N'*-Dimethyldiazacoronands and Chiral Bridging Units

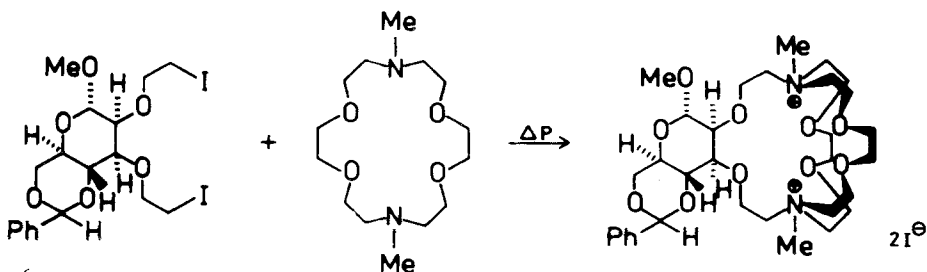
The methodology of obtaining chiral cryptands, presented in the previous Section, requires the use as substrates of chiral *N, N'*-dimethyldiazacoronands whose preparation requires difficult reaction sequences proceeding with a low yield [15, 16]. On these grounds we resolved to change the strategy of chiral cryptands synthesis. According to this new approach, the substrates consist of achiral *N, N'*-dimethyldiazacoronands (easily obtainable by the classical route) and chiral bridging components. An example of the high-pressure synthesis of a chiral cryptand by the proposed method is illustrated in Scheme 5.



Scheme 5.

The double-quaternization reaction of *N, N'*-dimethyl [18]— N_2O_4 with the chiral 1,4-diiodo compound obtained from D-tartaric acid, affords the desired chiral cryptand framework in very good yield [20].

Another example confirming the validity of the strategy adopted involves the synthesis of a chiral cryptand incorporating a carbohydrate moiety with the use of *N, N'*-dimethyl [18]— N_2O_4 and of a properly protected, readily available D-mannopyranose derivative [21] (Scheme 6).

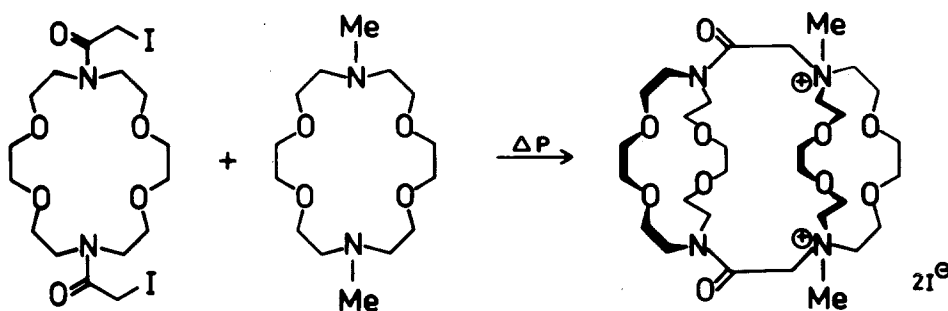


Scheme 6.

Also this high-pressure double-quaternization reaction proceeds with a good yield and high stereoselectivity. Summing up, it can be stated that the new strategy presented adds to the versatility of the high-pressure approach to the synthesis of chiral cryptands, with – moreover – its marked simplification.

8. Concluding Remarks

Undoubtedly, cryptands are a very promising class of macrobicyclic and macropolycyclic receptors. The number of their possible structures is practically unlimited and depends on the researcher's imagination and creativity. Probably the next step in the chemistry of cryptands will, therefore, be the design and synthesis of more elaborate polyfunctionalized macropolycyclic molecules, as well as studies of their properties. High-pressure methods offer exceptional possibilities in the realization of these projects. A convenient high-pressure synthesis of a tricyclic cryptand-related compound is exemplified in Scheme 7 [22].



Scheme 7.

The high-pressure reaction between *N,N'*-dimethyl diazacoronand and the *N,N'*-diiodoamide derivative of [18] $-N_2O_4$ affords the bisquaternary salt in good yield. This can readily be transformed into the desired tricycle.

All the above examples of high pressure application illustrate the great advantages of this new method for cryptand synthesis. The effect of pressure on organic reactions may be utilized for carrying out the syntheses of compounds which are difficult to obtain, if at all, *via* other pathways. Whereas the high-pressure method now has a serious drawback, i.e., the limited availability of equipment, it is to be hoped that this difficulty may be overcome in the near future.

Acknowledgments

Financial support from the Polish Academy of Sciences (Grants CPBP-01.13 and CPBR-3.20) is gratefully acknowledged.

References

1. C. J. Pedersen: *J. Am. Chem. Soc.* **89**, 7017 (1967).
2. B. Dietrich, J. M. Lehn, and J. P. Sauvage: *Tetrahedron Lett.* 2885 (1969).
3. J. Jurczak and M. Pietraszkiewicz: *Top. Curr. Chem.* **130**, 183 (1985).
4. G. R. Newkome, V. K. Majestic, and F. R. Fronczek: *Tetrahedron Lett.* 3039 (1981).

5. K. Matsumoto, A. Sera, and T. Uchida: *Synthesis* **1** (1985).
6. J. Jurczak: unpublished results.
7. M. Pietraszkiewicz, P. Sałański, and J. Jurczak: *Bull. Pol. Acad.: Chem.*, **33**, 433 (1985).
8. J. Jurczak: *Physica* **139 & 140B**, 709 (1986).
9. B. Baranowski: *Ber. Bunsenges. Phys. Chem.* **76**, 714 (1972).
10. J. Jurczak, T. Koźluk, S. Filipek, and C. H. Eugster: *Helv. Chim. Acta* **65**, 1021 (1982).
11. G. Jenner: *Angew. Chem. Int. Ed. Engl.* **14**, 137 (1975).
12. Tse-Lok Ho: *Synth. Commun.* **3**, 99 (1973).
13. M. Pietraszkiewicz, P. Sałański, R. Ostaszewski, and J. Jurczak: *Heterocycles* **24**, 1203 (1986).
14. M. Pietraszkiewicz, P. Sałański, and J. Jurczak: *Heterocycles* **23**, 547 (1985).
15. M. Pietraszkiewicz and J. Jurczak: *J. Chem. Soc., Chem. Commun.* 132 (1983).
16. M. Pietraszkiewicz and J. Jurczak: *Tetrahedron* **40**, 2967 (1984).
17. M. Pietraszkiewicz, P. Sałański, and J. Jurczak: *J. Chem. Soc., Chem. Commun.* 1184 (1983).
18. M. Pietraszkiewicz, P. Sałański, and J. Jurczak: *Tetrahedron* **40**, 2971 (1984).
19. M. Pietraszkiewicz and J. Jurczak: *J. Carbohydr. Chem.* **4**, 429 (1985).
20. J. Jurczak and R. Ostaszewski: unpublished results.
21. J. Jurczak, R. Ostaszewski, M. Pietraszkiewicz, and P. Sałański: unpublished results.
22. J. Jurczak and R. Ostaszewski: unpublished results.