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Organic Synthesis Utilizing Five-membered Heterocycles

Stereoselective Construction of Monosaccharides

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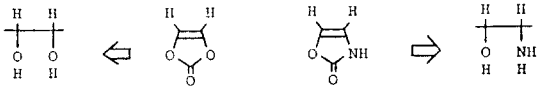
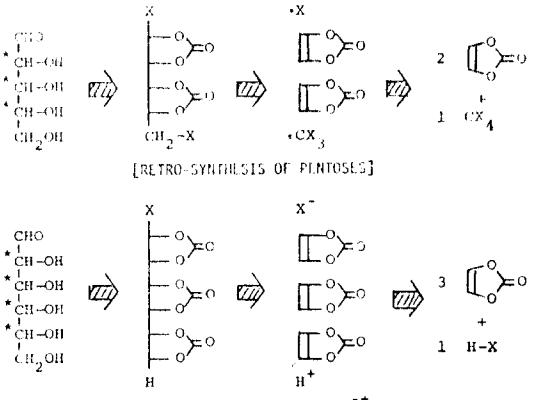
Heterocycles can play an important and critical role as building blocks or activating mediators in the strategy of organic synthesis. This lecture deals with the synthetic utility of five-membered heterocycles such as 1,3-dioxol-2-one (vinylene carbonate) and 2(3H)-oxazolone, which might serve as the versatile building blocks for carbohydrates and amino alcohols including amino sugars. These heterocycles which are of broad utility as "1,2-dihydroxy"



1,3-Dioxol-2-one 2(3H)-Oxazolone

and "1-amino-2-hydroxy" synthons, may be obtainable in an industrial scale starting from ethylene oxide.



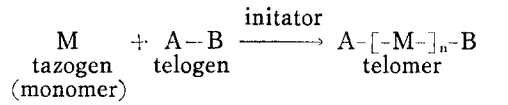
[RETRO-SYNTHESIS OF PENTOSES]

[RETRO-SYNTHESIS OF HEXOSES]*

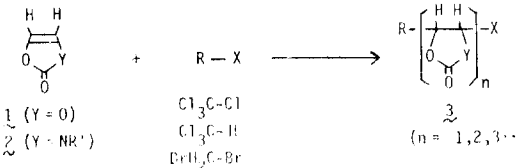
Fig. 1: Retrosynthetic routes to aldo-pentoses and hexoses. (*The ionic telomerization has not been described).

As shown retrosynthetically in Fig. 1, aldosugars might be prepared by cooligomerization of the cyclic carbonate and polyhalomethane. The most suitable procedure for such a conversion would be telomerization reaction, which is recognized well in polymer chemistry.

Oligmerization in the presence of a chain transfer agent to yield a series of low molecular weight products (called telomer) is termed telomerization, which is formally described by



M: tazogen (monomer); A–B: telogen; A-[-M-]$_n$-B: telomer



1 (Y = O)
2 (Y = NR')
Cl_3C-Cl
Cl_3C-H
BrH_2C-Br
3 (n = 1,2,3···)

In principle, it is possible to obtain any average chain length distribution desired simply by adjusting the ratio of taxogen to telogen.

Well stereocontrolled telomerizations of **1** and **2** (as taxogens) have been found to proceed smoothly in the presence of chain transfer agents such as polyhalomethanes under free radical initiation to give versatile polyfuncti onal telomers (**3**), which are not otherwise easily accessible with high stereo and regioselectivity. Such reactions capable of simulta-

neously attaining the stereoselective carbon-carbon bond formation and polyfunctionalization in a single step have great potential as a synthetic methodology for the construction of complex arrays of multiple asymmetric centers. The polyfunctional products thus controlled in a low molecular weight range are useful as synthetic intermediates, particularly for monosaccharides including deoxy and aminosugars. Thus, this methodology would provide the

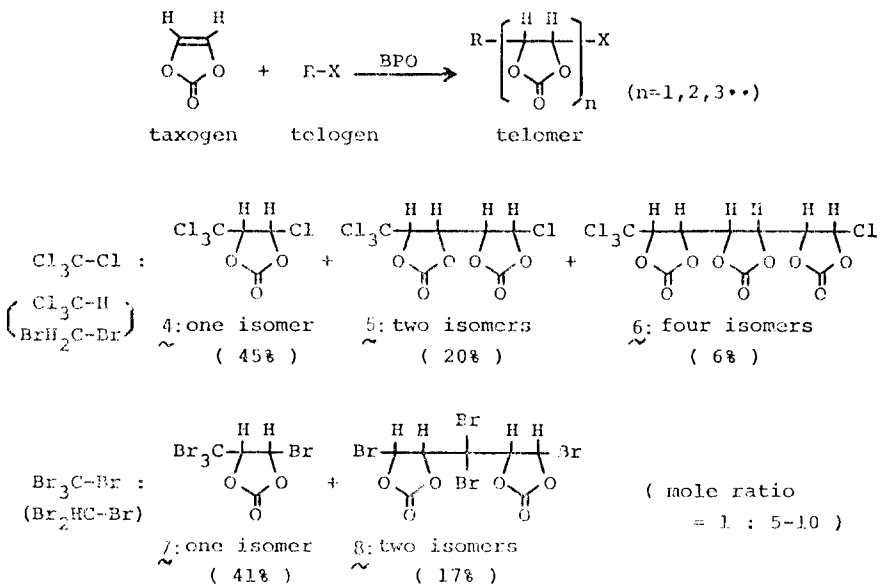


Fig. 2: Telomerization of vinylene carbonate with polyhalomethanes.

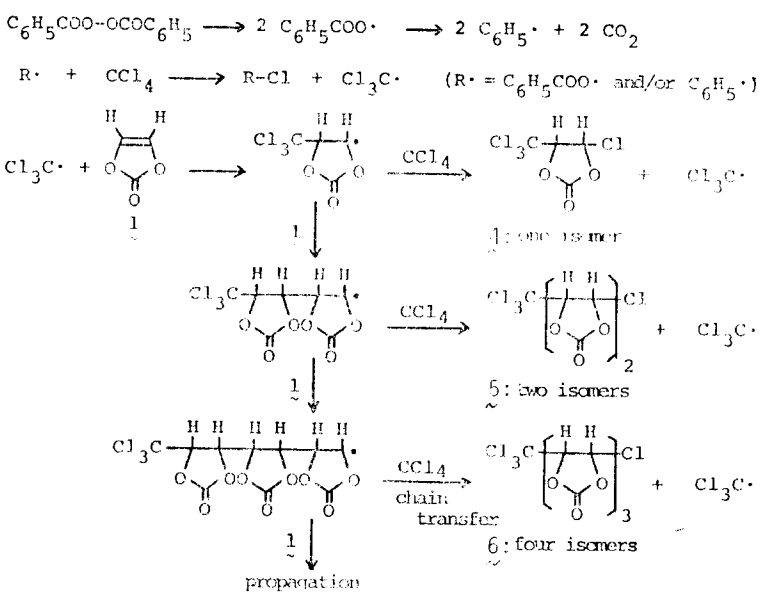


Fig. 3: Reaction pathways of telomerization.

stereoselective synthetic routes from such heterocycles to monosaccharides.

Vinylene Carbonate Telomers

The expected telomers were readily obtained by heating (at 80° C) the mixture of vinylene carbonate (**1**) and polyhalomethanes such as CCl_4, $CHCl_3$ and CH_2Br_2, in the presence of catalytic amounts of radical initiators, benzoyl peroxide (BPO) or azobisisobutyronitrile, for 20-30 hr. In contrast, the reactions using polybromomethanes as a telogen gave the different type products (such as **8**) (Fig. 2). Low telomers thus formed could be cleanly separated into stereohomogeneous telomers by chromatography on silica gel. It should be emphasized here that the telomer formation was highly stereoselective and only one isomer (**4**) as n=1, two isomers (**5a, b**) as n=2 and four isomers (**6a,b,c,d**) as n=3 telomers were selectively obtained. Their yields shown here were those in the taxogen to telogen ratio of 1:10.

Figure 3 shows the reaction pathways for the formation of typical telomers. Thus, the

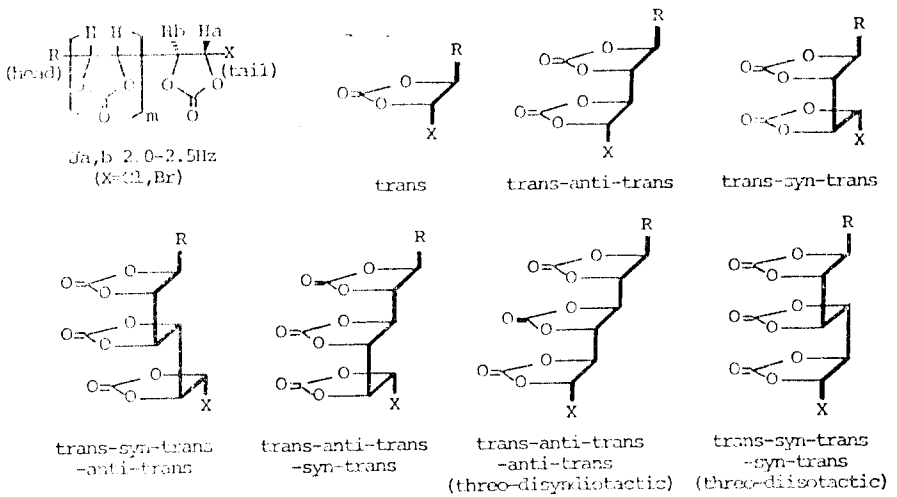


Fig. 4: Stereochemistry of vinylene carbonate lower telomers.

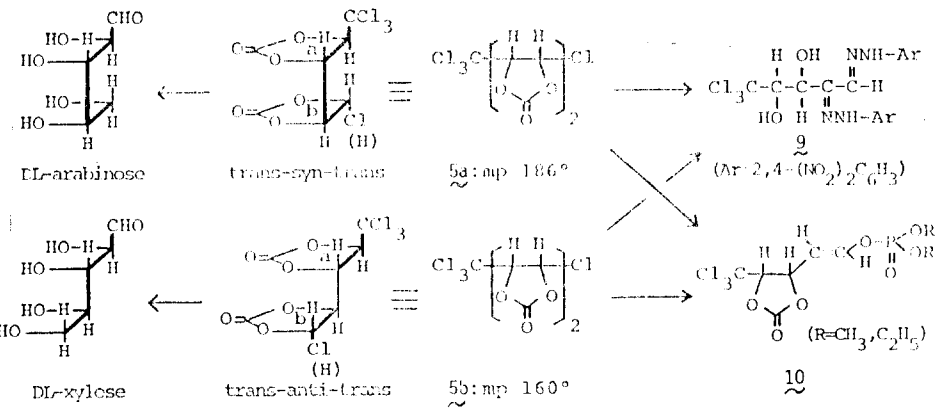


Fig. 5: Stereochemistry of vinylene carbonate telomers ($n=2$).

formation of oligomeric mixture is inevitable in this reaction, though the telomer distribution may be controlled considerably.

Stereochemistry of Telomers

In Figure 4 is shown the stereochemistry of the isolated carbonate telomers. In the proton nmr spectra, all of the low telomers isolated so far have shown small coupling constants (J= ~2.0 Hz) betweem Ha and Hb of the terminal carbonate rings, strongly suggesting trans stereochemistry. Thus, the 1:1 adduct should have-trans geometry as shown. Similar trans structures may be anticipated for the n=2 and n=3 telomers. Conclusive assignment of these stereochemistry has been provided by chemical transformation into the authentic sugars as discussed below.

Two isomeric telomers **5a** and **b,** isolated in nealry equal amounts, gave the identical osazone **9** and enol phosphate **10** on treatment with phenydrazine and trialkyl phosphite, respectively. This means the same configuration at the upper **a** rings. Furthermore, isomers **a** and **b** were converted to arabinose and xylose, respectively, by the ioutes rnvolving the conversion of the trichloromethyl groups to the aldehyde functions. Thus, trans stereochemistry of the n=2 telomers was clearly established.

As to the n=3 telomers, the configurations were determined by chemical conversions to the authentic heptitols and the enol phosphates **11.** Among four isomers **6a,b,c** and **d,** isomers **b**and **c** gave the identical enol phosphate, indicative of the configurational difference only at the terminal ring **c**. And they gave the heptitols which were identical with D-glycero-D-ido-heptitol and meso glycero-ido-heptitol, respectively. These reactions permit the assignment as shown in Fig. 6. Similar treatment of other isomers **a** and **d** supports trans stereochemistry.

Thus, a free-radical telomerization of five-membered heterocycles with polyhalomethanes is greatly anticipated to proceed exclusively in trans-addition mode.

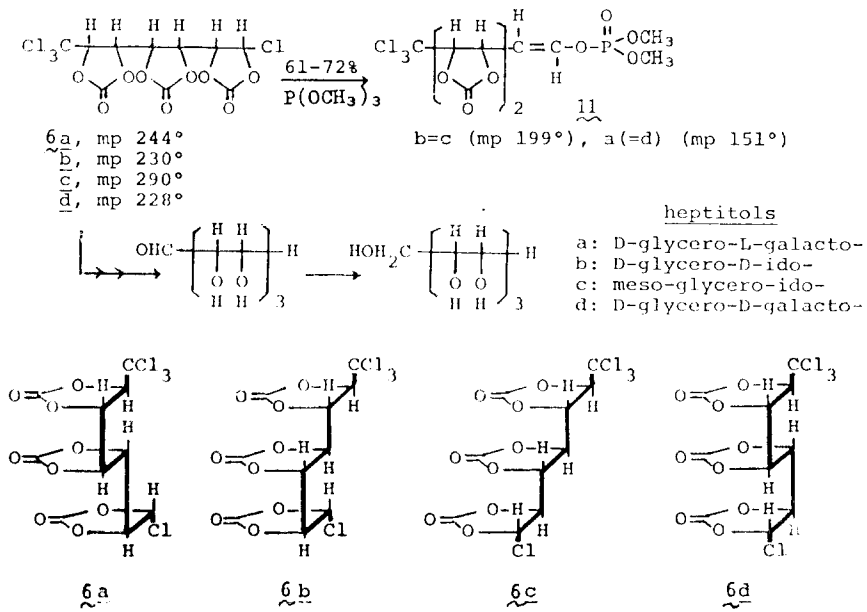


Fig. 6: Configurational assignment of vinylene carbonate telomers (n=3) (**6a, b, c** and **d**).

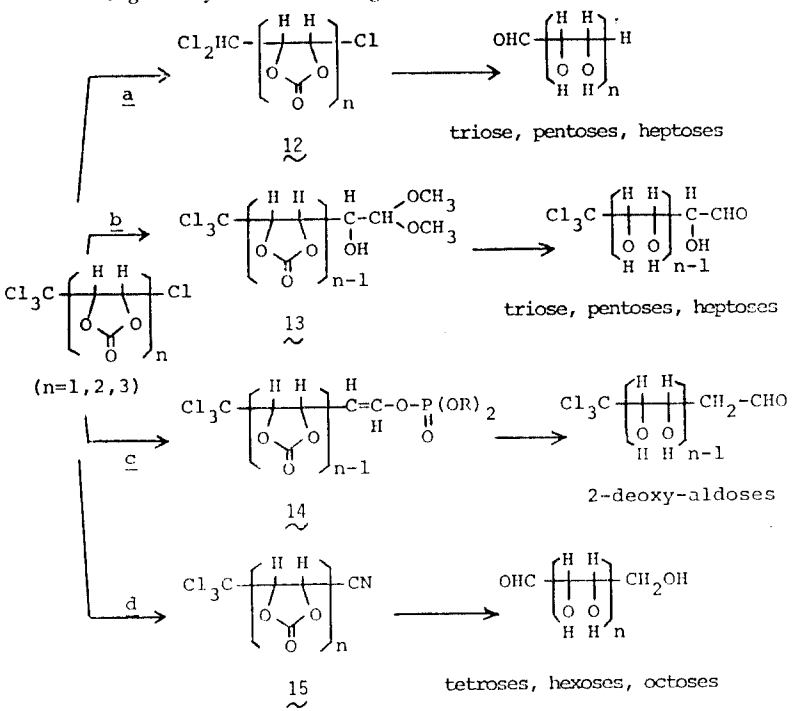


Fig. 7: General routes to aldosugars from vinylene carbonate telomers.

Conversion to Aldoses

Figure 7 shows the general routes to aldosugars from such carbonate telomers. The routes **a** and **b** are convenient for the conversion to the oddnumbered carbon sugars, triose, pentoses and heptoses. Route **a** involves the selective reduction of trichloromethyl groups to the dichloromethyls **12** followed by hydrolysis. The opposite site of the telomers may be easily converted to the aldehyde groups via **13** by hydrolytic route **b**, in which each step proceeds nearly quantitatively. As mentioned above, treatment of the telomers with trialkyl phosphites gives high yields of trans enol phosphates **14**, which can be readily hydrolyzed to 2-deoxy-aldoses. Route **d** involves the introduction of C_1-units as cyanide group into the telomers. This provides a feasible route to the even-numbered carbon sugars.

Two effective methods have been developed for the conversion of trihalomethyl groups to dihalomethyls, which are essential in the route **a** (Fig. 8). Method **A** involves treatment with nickel carbonyl in tetrahydrofuran at room temperature and method **B** involves photolysis by UV-irradiation in tetrahydrofuran. Both reactions presumably involve the initial formation of the radical intermediates followed by abstraction of hydrogen from the solvent. Mildness of the conditions employed permits the conversion of polyfunctional and labile compounds such as vinylene carbonate telomers in good yields. Further reduction to monohalomethyl groups is negligible even on prolonged treatment. Thus. both methods have distinct advantages, but method **B** is superior to method **A** which requires highly toxic agent.

A typical example is given in Fig. 9. Telomers **16a** and **5a** isolated using chloroform and carbon tetrachloride as telogens, were

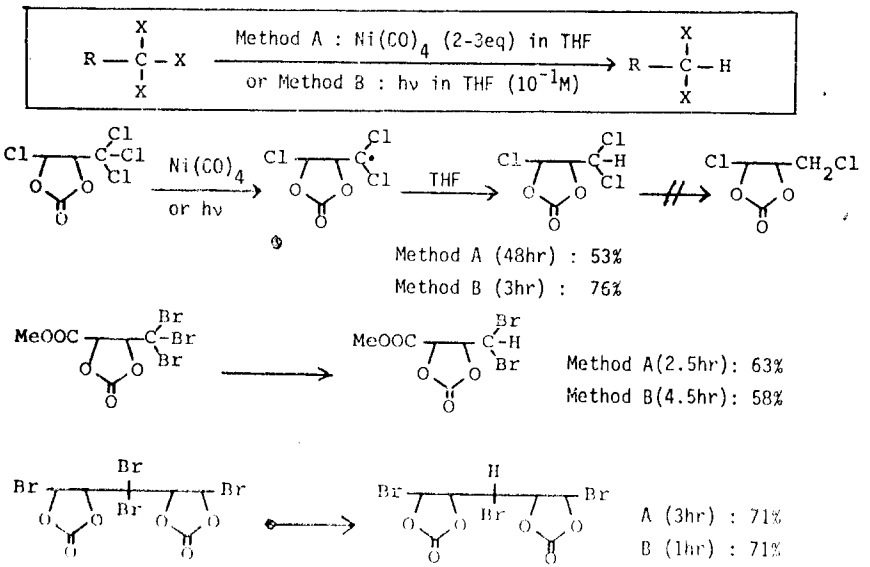


Fig. 8: Reductive conversion to lower halides.

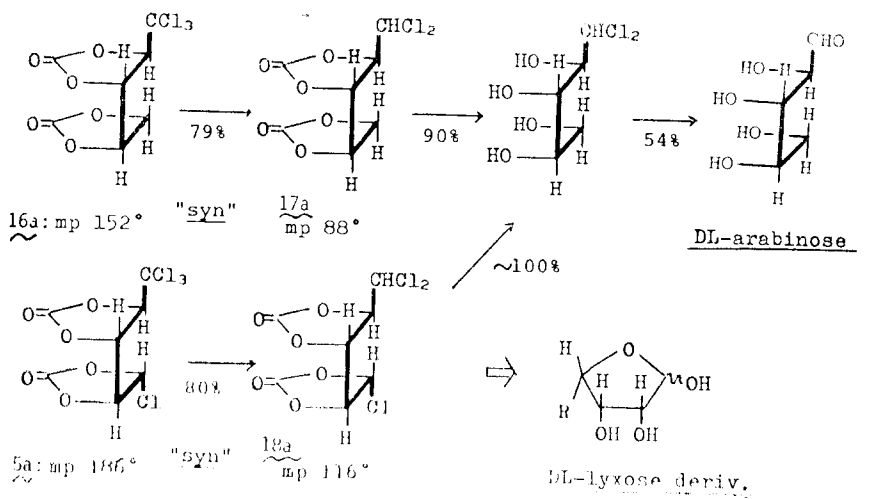


Fig. 9: A typical example performed by route a.

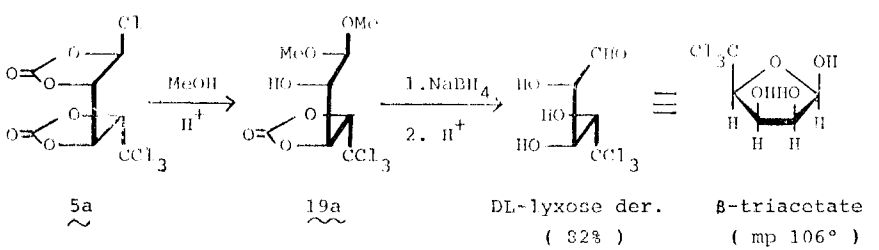


Fig. 10: A typical example performed by synthetic route b.

reductively converted to the dichloromethyl compounds **17a** and **18a**, respecsively, by the above methods. Hydrolysis of the dichloromethyl groups with silver nitrate in water provided a feasible route to DL-arabinose in moderate yield.

Figure 10 gives a typical example performed by synthetic route b. This hydrolytic route involving acetal (**19a**) formation as a key step gave high yield of xylose derivative.

As summarized in Fig. 11, aldopentoses have been stereoselectively synthesized from two

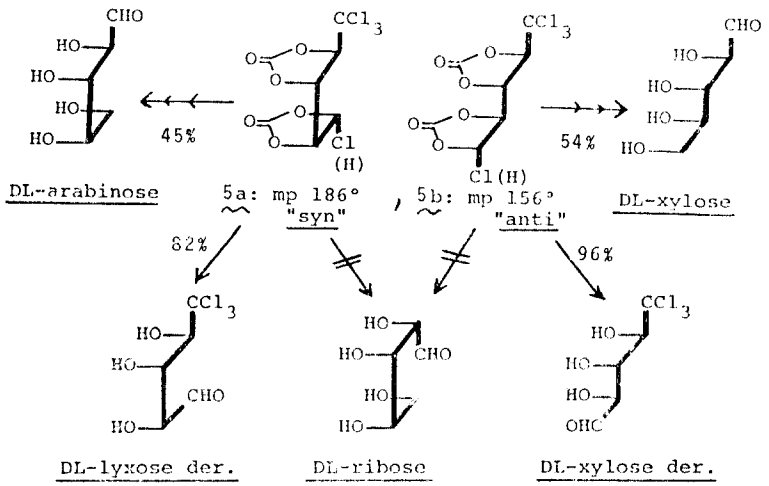


Fig. 11: Conversion of telomers to aldo-pentoses by routes a and b.

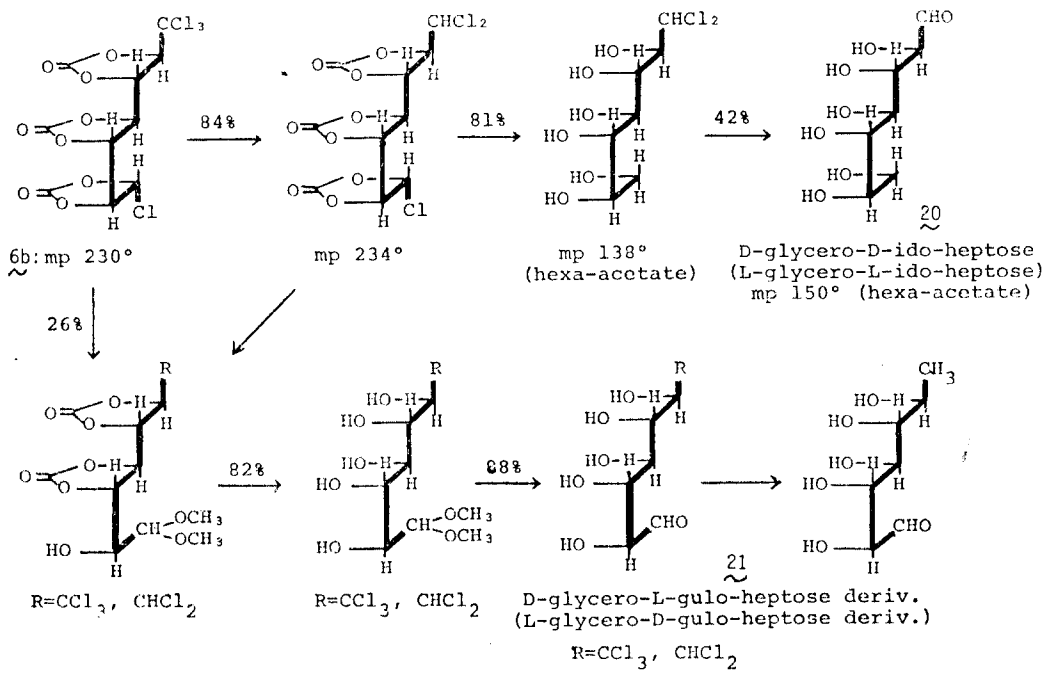


Fig. 12: Preparation of aldo-heptoses.

dimeric ($n=2$) telomers 5a and b, except ribose which has cis or erythro configuration at C_2 and C_3 atoms.

Preparation of two kinds of heptoses (**20** and **21**) from one of the $n=3$ telomers are shown in Fig. 12. The procedures are analogous to the synthesis of pentoses.

Figure 13 shows synthetic route to 2-deoxy-aldoses rom such ftelomers. Reaction of the telomers with phosphites gave high yields of trans enol phosphates **14**, while the formation of type **22** phosphonate was negligible even in the case of bromo compounds (**3**, X=Br). Fluoride ions have been found to be the most effective catalyst for the cleavage of P-O bond to give the aldehyde. Conversion of **5a** to **23**

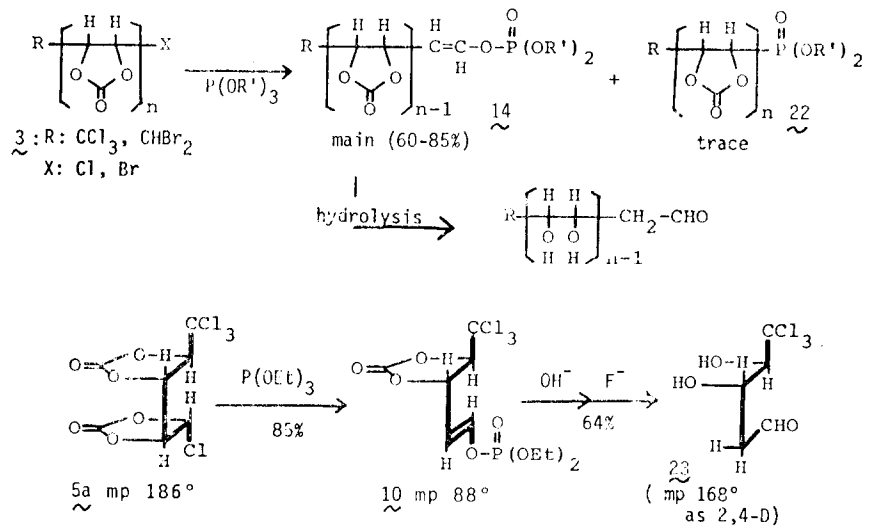


Fig. 13: Route to 2-deoxy-aldoses.

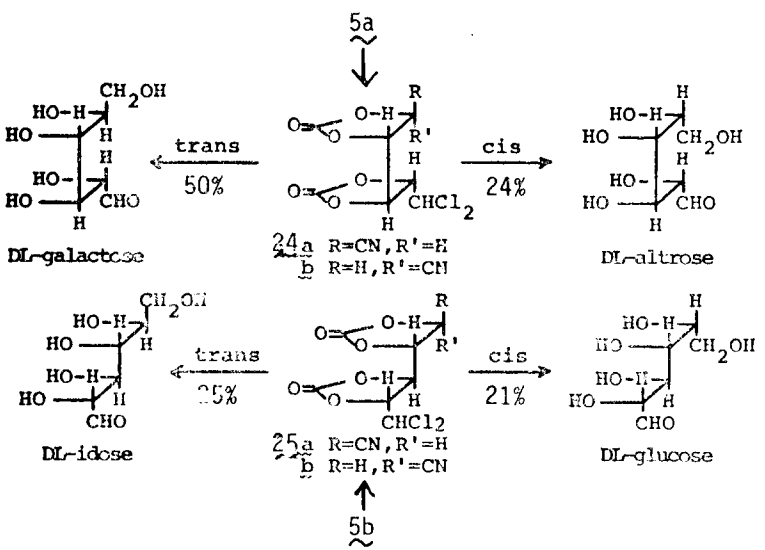


Fig. 14: Conversion to aldo-hexoses.

is given as a typical example.

As indicated in route **d**, smooth displacement of reactive chlorine with cyanide group gave a nearly equal ratio of trans and cis nitriles. This elongation procedure permits the conversion of **5a** and **b** to galactose, altrose, idose and glucose (Fig. 14). Similarly the $n=3$ telomers **6a-d** may be the useful intermediates for octoses.

2-Oxazolone Telomers

Just as the five-membered cyclic carbonate (**1**) mentioned above, 4,5-unsubstituted 2-oxazolone (**2**) has been found to undergo the smooth radical polymerization to give high yield of homopolymer (**26**) with carbon back-bone structure. Therefore, in the presence of carbon tetrachloride, the expected telomers **27** were similarly formed in yields comparable to those of vinylene carbonate telomers. The telomer formation was highly regio and stereoselective and among many possible isomers, only one isomer (**28**) as $n=1$ and two isomers (**29a** and **b**) as $n=2$ telomers were selectively obtained. The latter compounds would be the important

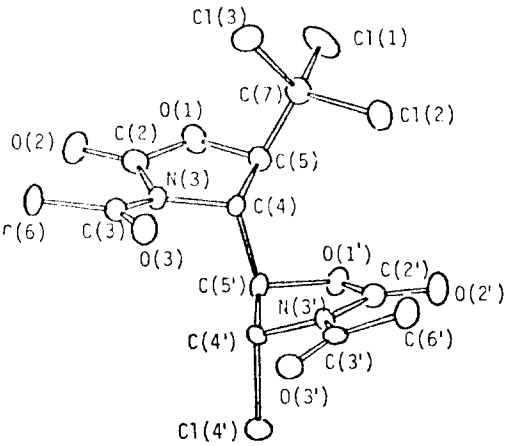


Fig. 16: Computer-generated perspective drawing of the X-ray model of telomer **29a**. Hydrogens are omitted for clarity.

intermediates for the preparation of diamino sugars which occur in nature as a unique component of antibiotics. Stereochemistry of these products was determined by spectral data, particularly ^{13}C-nmr and x-ray analysis. Figure 16 shows a typical example determined by x-ray analysis.

Some applications of the oxazolone telomers are shown in Fig. 17. The 1:1 adduct **28** is useful

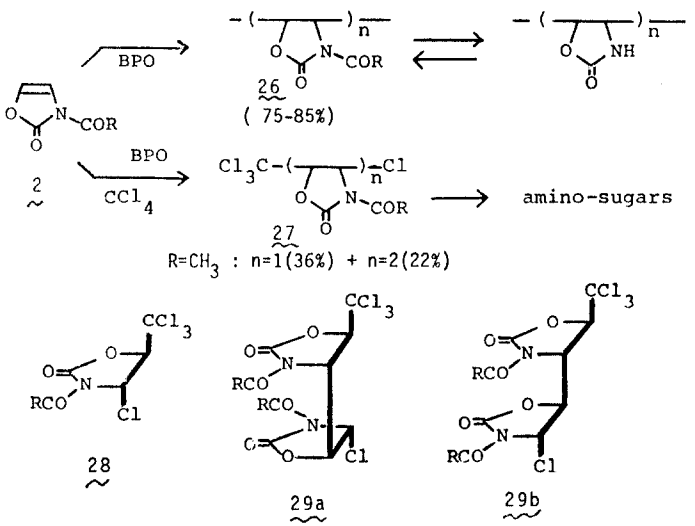


Fig. 15: Telomerization of 3-Acyl-2-oxazolone.

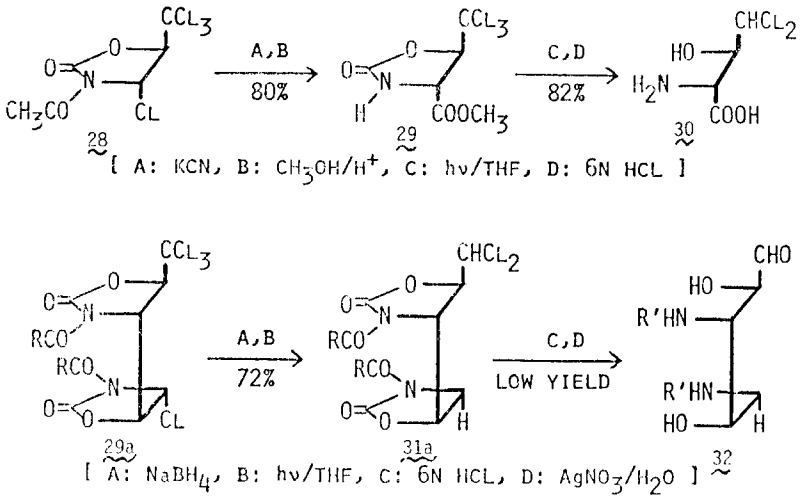


Fig. 17: Conversion of oxazolone telomers to amino-alcohols.

for the preparation of dichloro-α-amino acid (**30**) which is known to inhibit the growth of some kinds of micro-organisms as an armentomycine analogue. Optically active $n=1$ telomer may be obtained by treatment of 3-(N-Boc-L-prolyl-2-oxazolone) with ruthenium complex [$RuCl_2(PPh_3)_3$] in carbon tetrachloride.

An example for amino sugar preparation is shown by the conversion of **29a** to diamin opentose (**32**) of arabino-configuration, though yield is not good.

As seen in several examples presented here, the telomers arising from free radical reactions of 4,5-unsubstituted five-membered heterocycles **1** and **2** serve well as versatile intermediates for stereoselective synthesis of monosaccharides. The biggest merit of telomerization as a simple and useful synthetic tool would be one step preparation of polyfunctional compounds of much synthetic potential.

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