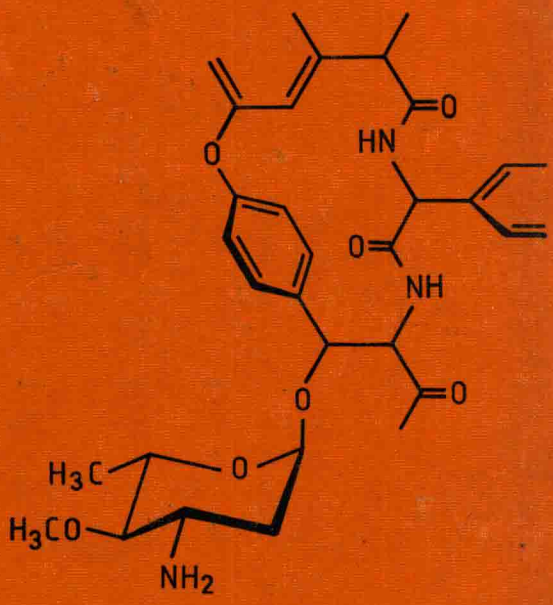
I. F. Pelyvás C. Monneret P. Herczegh

Synthetic Aspects of Aminodeoxy Sugars of Antibiotics



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With 9 Figures, 206 Schemes, and 23 Tables

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To Professor Rezső Bognár

on the occasion of his 75th birthday

Foreword

The synthetic chemistry of carbohydrates has advanced at a scarcely equalled rate in the last 25 years, due to the great interest of biologically active natural products containing sugar moieties. It suffices to note that in the review by J. D. Dutcher appearing in "Advances in Carbohydrate Chemistry" vol. 18, 1963, only the structures of less than ten aminodeoxy sugars were reported. This book deals exclusively with a single class of carbohydrates, namely the aminodeoxy sugars of antibiotics, the most popular of which is probably daunosamine, a compound for which more than 20 different synthetic approaches have been reported in the literature since the publication of its structure in 1964. No compound in the 3-amino-2-deoxy-L-hexose series had been prepared by chemical synthesis when we started our synthetic work in this field in 1972 on the wave of the successful therapeutic applications of adriamycin. The compounds with *xylo* stereochemistry were unknown even in the more easily accessible D-series. The size of this book documents the rapid development of the field. I wish to add that the improvements of chemical methodology reported in the volume outspan the specific field and are of importance in the design of synthetic approaches to other carbohydrate structures. These also include compounds involved in chemical interactions of great biological interest, but hitherto unexplained at the molecular level, such as those related with cell recognition, adhesiveness and differentiation.

It is certainly very appropriate and by no means surprising that the endeavour to write the first comprehensive book discussing the currently available knowledge on the synthesis of aminodeoxy sugars be undertaken by two well-known members of the established Hungarian School of carbohydrate chemistry to whose founder the book is dedicated, and by a knowledgeable French researcher who has contributed greatly to the chemistry of the anthracycline antibiotics in recent times. I agree with the authors that the separate presentation of the different reaction steps occurring in the synthesis represents an original organization of the literature data that will be of considerable help to those planning synthetic schemes in this interesting field. All organic chemists will be grateful to Drs. Pelyvás, Monneret and Herczegh for their outstanding work.

Firenze, April 1988 — Federico Maria Arcamone

Preface

In the therapy of infections caused by resistant bacteria and also in the treatment of certain neoplastic diseases, antibiotics containing aminodeoxy sugar building elements have emerged as major chemotherapeutic agents. Including only mono-amino-mono-, di- and trideoxyhexoses, more than forty representatives have been isolated from various antibiotic substances so far. The elaboration of definitive and preparative syntheses for such rare aminodeoxy sugars have offered great challenges for carbohydrate chemists during the past two decades. In many cases related efforts have brought the introduction of novel, ingenious methodologies that made valuable contributions to research on carbohydrates and another organic compounds.

The present work is aimed at summarizing the applied and potentially useful strategies for the synthesis of the specific aminodeoxy sugars occurring in antibiotics with a particular emphasis on 3-amino-polydeoxyhexoses. It provides hitherto unexplored contexts and offers a general outlook on the syntheses of such compounds. The book is concerned with the methodological construction and systemic layout of molecules of the daunosamine-type unbranched- and branched-chain natural aminodeoxy hexoses, and their synthetic derivatives starting with both carbohydrates and non-sugar precursors. The methodologies employed for the preparation of 2-deoxyhexoses and for the introduction of a nitrogen function into such sugars, and also the strategies for the conversion of aminodeoxy hexoses into their polydeoxy analogs are outlined as are total synthesis approaches. Examples of the utilization of these type of carbohydrates as "chiral templates" for transformations into non-sugar organic substances with potential biological activities follow.

The reader may notice that the reaction sequences employed for the preparation of 3-amino-2,3,6-trideoxyhexoses are in many cases divided into individual reaction steps that are, in turn, discussed — for the previously mentioned methodological reasons — in separate chapters. However, with such a treatment of the subject the reader can get a thorough inside view of the major synthetic methods and can also obtain a basis for comparing the applied and potential strategies. This kind of benefit has not yet been offered by the reviews covering these aminosugars. In this respect the volume can help carbohydrate chemists in designing the synthesis of similar molecules because many of the methods discussed might also be adapted to other fields of carbohydrate research.

To ensure the general clarity of the complete synthetic routes to 3-amino-2,3,6-trideoxyhexoses, cross references are given throughout the volume. Closely related methods are discussed in tabular form whenever possible. Information on more than four-hundred of the functionalized derivatives of these aminohexoses that have so far been prepared are included and collected in the Appendix.

The literature is covered through December, 1987. Because of the huge number of contributions to this research cited, we have concentrated our efforts on presenting the details of methods that offer significantly exploitable results that might help in the work of those engaged in related areas of carbohydrate chemistry.

Debrecen, April, 1988

I. F. Pelyvás
C. Monneret
P. Herczegh

Acknowledgements. The authors are indebted to Professors Rezső Bognár and Ferenc Sztaricskai for encouragement and to Mrs. Erzsébet L. Magyar for the extensive art work. Financial support for certain parts of the authors' related research work and for the preparation of the manuscript was obtained from grants TPB KKFA and OTKA-1728 given by the Hungarian Academy of Sciences.

Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
All	allyl
anhydr.	anhydrous
aq.	aqueous
Bn	benzyl
BOC	*tert*-butyloxycarbonyl
Bu	*n*-butyl
Bu^t	*tert*-butyl
Bz	benzoyl
ca.	circa
CAN	cerium ammonium nitrate
cat.	catalyst, catalytic
Cbz	benzyloxycarbonyl
cc.	concentrated
c-Hex	cyclohexyl
d	day(s)
DAST	diethylaminosulfur trifluoride
DBU	1,5-diazabicyclo-[5,4,0]-undec-5-ene
DCAc	dichloroacetyl
DCC	N,N-dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
DHP	dihydropyran
DIBAL	diisobutylaluminum hydride
diphos-4	1,4-bis-(diphenylphosphino)-butane
DMF	N,N-dimethylformamide
DMP	2,2-dimethoxypropane
DMSO	dimethylsulfoxide
DPPA	diphenyl phosphorazidate
EE	ethoxyethyl
EOC	ethoxycarbonyl
Et	ethyl
eq.	equivalent, equivalents
HMPT	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
Ip	isopropyl
LDA	lithium diisopropylamide

liq.	liquid
L-Selectride	lithium tri-(*sec*-butyl)-borohydride
LTBH	lithium triethylborohydride
Me	methyl
MEM	methoxyethoxymethyl
MOC	methoxycarbonyl
MOM	methoxymethyl
MCPBA	*meta*-chloroperbenzoic acid
Ms	methanesulfonyl
nbd	norbornadiene
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NMO	N-methylmorpholine oxide
PCC	pyridinium chlorochromate
Ph	phenyl
Pht	phthalyl
*p*NBz	*para*-nitrobenzoyl
Prop	*n*-propyl
pyr.	pyridine
Ref.	reference
refl.	reflux
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TCAc	trichloroacetyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic anhydride
TFAc	trifluoroacetyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMNO	trimethylamine oxide
TMS	trimethylsilyl
Tr	trityl
Ts	*para*-toluenesulfonyl

Contents

1. Introduction

During the past decade, research work on the structural elucidation of sugar-containing antibiotics significantly contributed to the development of certain areas of carbohydrate chemistry. The structural and synthetic studies on various rare monosaccharide derivatives (deoxy and aminodeoxy sugars and their branched-chain analogs) isolated from metabolic substances and antibiotics produced by numerous microorganisms necessitated the elaboration of new and more sophisticated investigation techniques. New methods of isolation and structural determination were accompanied by the introduction of new and ingenious synthetic strategies and methodology.

Since the mid 1960s, research on deoxy and aminodeoxy sugars has been steadily urged on and stimulated by approaches focussed on the chemical modification and total synthesis of aminocyclitol antibiotics (1, 2) and the anticancer anthracycline glycoside antibiotics (3–8). Some characteristic representatives of the latter group are shown in Fig. 1.

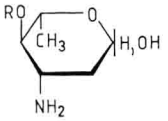
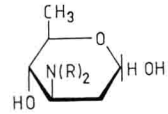
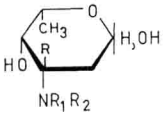
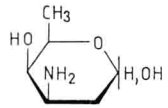
A common structural feature of both class I and class II anthracycline antibiotics **(1–7)** is the 3-amino-2,3,6-trideoxy-L-hexose moiety attached to the substituted naphtacenequinone aglycone at position C-7 through an α-O-glycosidic linkage (8).

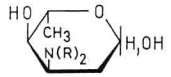
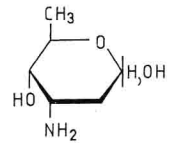
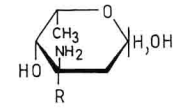
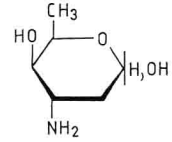
In addition to the anthracycline glycosides, 3-amino-2,3,6-trideoxyhexoses are important structural elements of other types of antibiotic substances as well. Thus, five of the eight stereoisomeric 3-amino-2,3,6-trideoxy-D- and L-hexoses (Table 1) have been found in nature as building blocks of antibiotics.

The first representative of such sugars, rhodosamine (**14**, 3-dimethylamino-2,3,6-trideoxy-L-*lyxo*-hexose) (33), was isolated from the anthracycline-type rhodomycins in 1963. One year later daunosamine **(12)**, obtained from daunomycin, was identified (19) as the N-di-demethyl analog of rhodosamine. During the past twenty years these two aminosugars have been found to be components of a large number of anthracycline antibiotics.

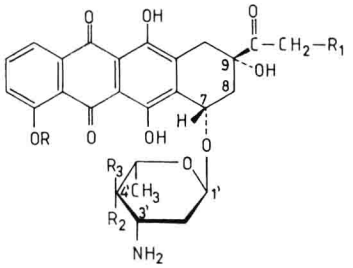
Isolated third in 1966, angolosamine (**11**, 3-dimethylamino-2,3,6-trideoy-D-*arabino*-hexose) (14) was obtained from the macrolide-type angolamycin and later from antibiotics with an aromatic polycyclic C-glycoside (anthra[1,2-b]-pyran) structure (13–17). These latter antibiotics contain N,N-dimethylvancosamine **(16)** as well. Both aminohexoses are attached to the aglycone moieties with C-glycosidic bonds. Either of the enantiomeric forms of angolosamine can also be incorporated in to the molecule of lactoquinomycin (18), and a recent paper reported that the antibiotics benzanthrin A and benzanthrin B (18a) contain L-rhodosamine and L-angolosamine, respectively, as O-glycosidic components and that both variants carry D-angolosamine as the C-glycosidic moiety.

Table 1. Naturally occuring 3-amino-2,3,6-trideoxyhexoses

Sugar		Name	Antibiotic	References
L		8 R = H 9 R = CH_3	L-Acosamine L-Actinosamine	Actinoidin	9–11
Arabino				
D		10 R = H 11 R = CH_3	D-Acosamine Angolosamine	Sporaviridin Angolamycin, Kidamycin Isokidamycin, Hedamycin Pluramycins	12 13–17
		12 $R = R_1 = R_2 = H$	L-Daunosamine	Daunomycin Adriamycin Carminomycin and additional anthracyclines	19–21 22 23 24–31
L		13 $R = R_2 = H$; $R_1 = CH_3$ 14 $R = H$; $R_1 = R_2 = CH_3$	N-Methyldaunosamine Rhodosamine	Antibiotic MA 144 L1 Rhodomycins Aclacinomycins and additional anthracyclines	32 33–35 36, 37 38–46
Lyxo		15 $R = CH_3$; $R_1 = R_2 = H$	Vancosamine	Vancomycin Sporaviridin	47 12
		16 $R = R_1 = R_2 = CH_3$	N,N-Dimethylvancosamine	Kidamycins Hedamycin Pluramycins	15, 16 16 17
D		17 D-Daunosamine	Has not been found in Nature		

L		18 R = H	L-Ristosamine	Ristomycin (Ristocetin) Avoparcins	48–50 51 52–53
		19 R = CH_3	Megosamine	Megalomycins	54, 55
Ribo					
D		20 D-Ristosamine	Has not been found in Nature		
L		21 R = CH_3	3-Epi-vancosamine	Antibiotic A 35512 B	56
Xylo					
D		22 Has not been found in Nature			

Class I anthracycline antibiotics



1 $R = CH_3$; $R_1 = R_3 = H$; $R_2 = OH$ Daunomycin

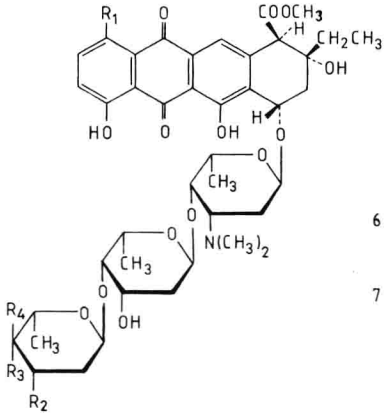
2 $R = CH_3$; $R_1 = R_2 = OH$; $R_3 = H$ Adriamycin

3 $R = R_1 = R_3 = H$; $R_2 = OH$ Carminomycin

4 $R = CH_3$; $R_1 = R_2 = H$ $R_3 = OH$ 4'-Epidaunomycin (synthetic)

5 $R = CH_3$; $R_1 = R_3 = OH$; $R_2 = H$ 4'-Epiadriamycin (synthetic)

Class II anthracycline antibiotics



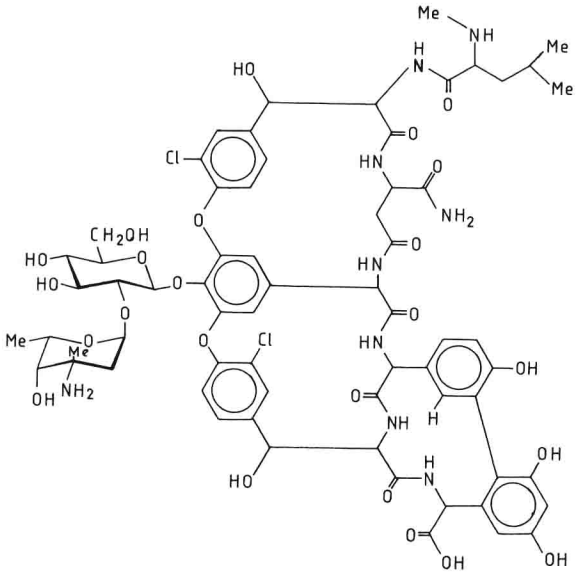
6 $R_1 = R_2 = H$; R_3, $R_4 = O$
Aclacinomycin A

7 $R_1 = R_2 = R_3 = OH$; $R_4 = H$
Marcellomycin

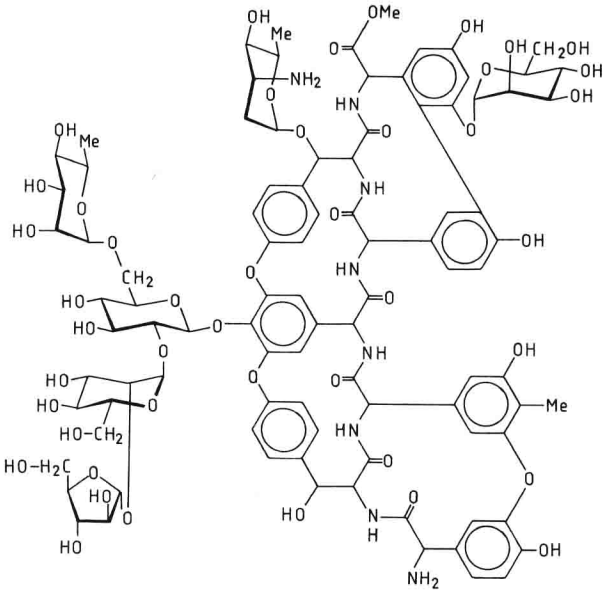
Fig. 1. Characteristic representatives of class I and class II anthracycline glycoside antibiotics

The structure of the aminodeoxy sugar isolated from the macrolide-type megalomycins was identified (57) in 1969 as 3-dimethylamino-2,3,6-trideoxy-D-*arabino*-hexose. However, NMR and X-ray studies performed (54, 55) ten years later proved that the correct structure of this compound (megosamine) is 3-dimethylamino-2,3,6-trideoxy-L-*ribo*-hexopyranose **(19)**.

Vancosamine **(15)**, the 3-C-methyl analog of daunosamine, is present (47) in the molecule of vancomycin (Fig. 2), the first representative of the vancomycin group of antibiotics (58) to be isolated. Structural elucidation (58) of the other members of this family of antibiotics showed that the basic sugar component of each is a 3-amino-2,3,6-trideoxyhexose steroisomer. Thus, ristomycin — identical (49) with ristocetin (51) — contains L-ristosamine (**18**, 3-amino-2,3,6-trideoxy-L-*ribo*-hexose)



Vancomycin



Ristomycin (ristocetin) A

Fig. 2. The structure of antibiotics vancomycin and ristomycin A