Carbohydrate Research, 82 (1980) 283–301

SYNTHESIS OF AMINOCYCLITOLS FROM L-QUINIC ACID*

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(Received October 16th, 1979; accepted for publication in revised form, February 14th, 1980)

ABSTRACT

A variety of 1,3-diamino and 1,4-diaminocyclitols, monoaminocyclitols, and triaminocyclohexanol have been synthesized starting with the chiral ketone intermediate **2**, derived from L-quinic acid. Reduction of **2** with lithium borohydride afforded two epimeric diols (**4** and **5**), both of which were transformed by straightforward but distinctly different chemical procedures into potentially useful aglycons for preparing novel types of bioactive, aminocyclitol glycoside antibiotics. The disposition of the substituents at C-1, C-3, C-4, and C-5 in **19** and **37** is identical with that present in the 2-deoxystreptamine nucleus in the naturally occurring antibiotics.

INTRODUCTION

Until recently, the 1,3-*cis* orientation of amino groups in 2-deoxystreptamine-containing antibiotics was considered to be an essential prerequisite for biological activity. However, the isolation of fortimicin[1], sporaricin[2], minosaminomycin[3], sorbistin[4], and the synthetic[5] bioactive Sch 22591, which differ in their aglycons from the most important first-generation antibiotics, has opened up new dimensions for research on the aminocyclitol antibiotics. Further developments toward total, partial, and mutasynthetic routes require the synthesis of novel aminocyclitols and their derivatives.

Despite intensive research interest in this area, only streptamine, 2-deoxystreptamine (obtained from degradation of natural antibiotics), and 2,5-dideoxystreptamine[6] are readily available. These aminocyclitols undergo bioconversion into new bioactive products by using idiotrophs isolated from antibiotic-producing strains, as first described by Rinehart and co-workers[7] in 1969. However, these substrates are not suitable for total chemical synthesis. 2-Deoxystreptamine and 2,5-dideoxystreptamine are *meso* compounds, and in order to avoid formation of complex diastereoisomeric mixtures on glycosylation, properly protected derivatives must be prepared and resolved into their enantiomerically pure forms[6b].

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*Dedicated to Professor Stephen J. Angyal on the occasion of his retirement.
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A particularly attractive approach for the synthesis of chiral aminocyclitols is the use of such readily available chiral starting materials as carbohydrates or cyclic polyols, and the like. Synthetic studies of this type have been few[8] and have proved extremely difficult and unrewarding for our purposes.

We demonstrate here that L-quinic acid, which constitutes a functionally rich dideoxycyclitol chiral synthon, is a very useful and inexpensive building block for the preparation of an impressive variety of aminocyclitols for mutasynthesis of novel aminoglycoside antibiotics[9], as well as useful non-nitrogenous intermediates for chemical glycosylation procedures[10].

As part of a programme directed toward the mutasynthesis and total chemical synthesis of novel, bioactive, aminocyclitol glycosides having modified cyclitol nuclei, we report here a general route for the preparation of 1,3- and 1,4-diaminocyclitols related to 2-deoxystreptamine and fortamine and their synthetic precursors, together with 5-amino-2,5,6-trideoxystreptamine and monoaminocyclohexane-diols and -triols.

Preparation of 2,6-dideoxystreptamine (**19**), *2,5,6-trideoxystreptamine* (**37**), *and 5-amino-2,5,6-trideoxystreptamine* (**40**)

In the neomycin, paromomycin, ribostamycin, lividomycin, and butirosin antibiotics, the 2-deoxystreptamine aglycon is di-*O*-glycosylated at C-4 and C-5. Consequently, we considered 2,6-dideoxystreptamine (**19**) to be a promising aminocyclitol aglycon.

Although such 4-*O*-substituted 2-deoxystreptamines as neamine, gentamine, and tobramine, fragments of naturally occurring antibiotics, exhibit antibacterial activity, 2-deoxystreptamine itself is not bioactive. These pseudodisaccharides are considered to be antibacterial determinants. Furthermore, apramycin, a new aminocyclitol antibiotic[11], is also a 4-*O*-monosubstituted 2-deoxystreptamine. The biological activity of apramycin, neamine, gentamine, and the like suggests that the substitution of only one position, namely C-4, might lead to bioactive pseudodisaccharides. Therefore, it seemed attractive to prepare 2,5,6-trideoxystreptamine (**37**) and the related 5-amino-2,5,6-trideoxystreptamine (**40**).

Our chosen route to these target aglycon molecules, **19**, **37**, and **40**, consisted of elaborating the readily accessible ketone **2**, which may be transformed into crystalline intermediates and be properly functionalized, either for glycosylation procedures or for conversion into potential mutasynthons.

Synthesis of 2,6-dideoxystreptamine (**19**, *Chart I*). — L(−)-Quinic acid is readily transformed into the cyclohexylidene derivative (**1**) of quinicol[12], which by oxidation with sodium metaperiodate in aqueous solution at pH 5–6 gave the crystalline ketone **2** in quantitative yield (95%). The corresponding oxime **3** was also prepared.

Compound **2**, on treatment with a variety of alkali-metal borohydrides in different alcohols, furnished a mixture of epimeric alcohols **4** and **5**. The best results were obtained when the reduction was conducted in diglyme using 1.5 equiv. of lithium borohydride. The isomer **4** was isolated in 57% yield. From the mother

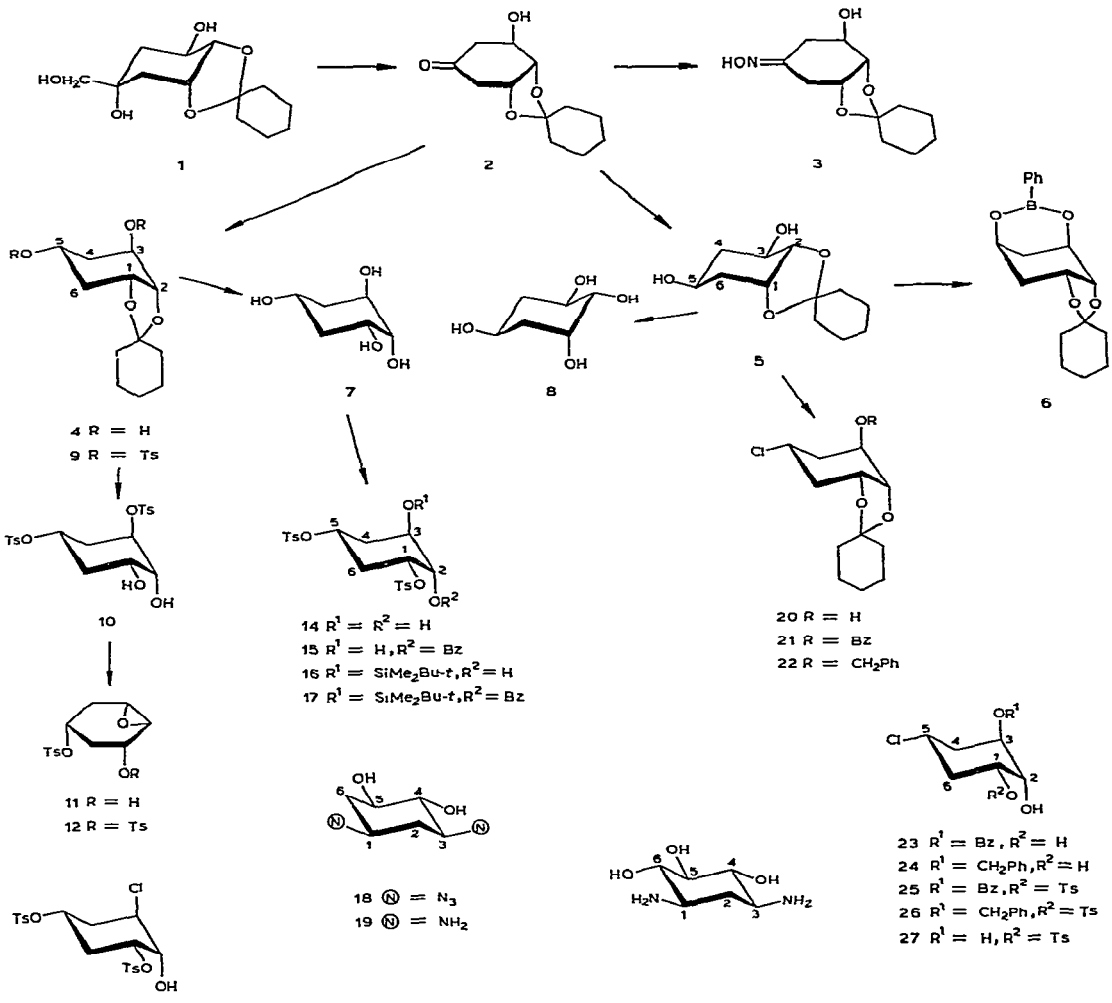


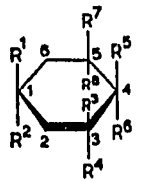
Chart I

liquors, the other isomer (**5**) was obtained *via* its benzeneboronic ester **6**, thus establishing the *cis* relationship between the two 3,5-hydroxyl groups. The structures of compounds **4** and **5** were also confirmed by hydrolysis to the known cyclohexanetetrols[13] **7** and **8**, respectively.

Both epimers **4** and **5** were utilized in synthesis. The diol **4** was first converted into its disulfonate **9**. Acid hydrolysis of **9** afforded the ditosyloxycyclohexanediol **10**, which on treatment with methanolic sodium methoxide yielded the epoxide **11**. Tosylation of the latter by *p*-toluenesulfonyl chloride in pyridine gave the expected ditosyl epoxide **12**, together with the chlorohydrin **13** formed by regiospecific ring-opening of the epoxide by chloride anion. Compound **13** was quantitatively recyclized to the epoxide **12** by treatment with base. Hydrolysis of **12** with 0.75M aqueous sulfuric acid in dimethoxyethane provided the ditosyloxycyclohexanediol **14** (overall yield

TABLE I

^{1}H-N.M.R. DATA[a]



Compound	Substituents								Proton chemical-shifts (δ) in $CDCl_3$								Coupling constants (Hz)									
	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	H-1	H-2a	H-2e	H-3	H-4	H-5	H-6a	H-6e	$J_{1,2a}$	$J_{1,2e}$	$J_{1,6a}$	$J_{1,6e}$	$J_{3,2a}$	$J_{3,2e}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6e}$
15	H	OTs	H	OTs	H	OBz	OH	H	4.9 (sex)			5.02 (sex)	5.05 (q)	4.25 (q)			8.5	4.25	8.5	4.25	8.5	4.5	4.5	4.25	5	4.25
17	H	OTs	H	OTs	H	OBz	OG[b]	H	4.65			4.75	4.8	4.05									5	4.5		
25	H	Cl	H	OTs	H	OH	OBz	H	4.08 (sex)			4.62	3.95 (q)	5.30 (q)			11	5.5	11	5.5	10.5	6	3.5	3.5	3.5	3.5
26	H	Cl	H	OTs	H	OH	OCH_2Ph	H	3.98 (sex)			4.68 (dq)	4.06 (t)	3.75 (q)							11.5	5	2.5	2.5	2.5	2.5
44	N_3	H	H	OBz	OBz	H	OTs	H	3.94 (tt)	1.88	2.42	5.77	5.27 (q)	5.12 (td)	1.88	2.79	14.5	4	14.5	4			3	10	11.5	5
47	N_3	H	H	OH	N_3	H	H	OH	4.1	1.6	2.0	3.5 (td)	3.1 (t)	3.5 (td)	1.6	2.0	2.7		2.7		10	4.5	10	10	10	4.5
48	N_3	H	H	OH	H	OH	N_3	H	3.8	1.6	2.3	4.2	3.5 (q)	3.7	1.5	2.3	12		12		5.5	5.5	4	10	12	
49	N_3	H	H	OBz	N_3	H	H	OH	4.1	1.7	2.5	5.2 (td)	3.5 (t)	3.8 (td)	1.7	2.3	3	3	3	3	10	4.8	10	10	10	4.8
50	N_3	H	H	OBz	H	OH	N_3	H	3.7	1.6	2.4	5.6	3.7	3.7	1.5	2.4	10		10		5	5	5	10	10	
54	OBz	H	H	OH	H	OBz	OBz	H	5.6	2.04	2.46	4.56 (sex)	5.43 (q)	5.8	2.04	2.68	8.5	4.2	8.5	4.2	2.85	0.5	2.85	8.5	8.5	3.75

[a]Observed spacings; multiplicities are indicated in parentheses: d, doublet; q, quartet; sex, sextuplet; t, triplet; dq, doublet of quartets; td, triplet of doublets; tt, triplet of triplets.
[b]G = *tert*-Butyldimethylsilyl.

TABLE II

^{13}C-N.M.R. DATA (see Table I for notation)

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
14[a]	H	OTs	H	OTs	H	OH	OH	H	75.7	32.7	78.2	70.8	67.6	34
15[a]	H	OTs	H	OTs	H	OBz	OH	H	74.8	33.5	74.8	72.3	65.3	34.8
16[a]	H	OTs	H	OTs	H	OH	OG[b]	H	75.1	33	77.8	69.4	69.4	32
19[c,d]	NH_2	H	NH_2	H	H	OH	OH	H	45.9	32.9	51.9	75.5	70.6	36.8
33[a]	H	OTs	H	OTs	H	OH	H	H	77.2	32.3	79.5	65.9	26.1[e]	25.2[e]
37[c,d]	NH_2	H	NH_2	H	H	OH	H	H	48.6	33.3	54.4	70.5	31.1	28.9
38[a]	N_3	H	N_3	H	H	OH	N_3	H	54.5	35	61.6	77.1	61.6	35
39[a]	N_3	H	N_3	H	N_3	H	H	OH	53.7	33.3	56.9	64.1	67.9	30.8
40[a,d]	NH_2	H	NH_2	H	NH_2	H	H	OH	45.9	32.6	52.2	71.5	52.2	32.6
47[a]	N_3	H	H	OH	N_3	H	H	OH	55.6	36.3	68.2	72.9	68.2	36.3
48[a]	N_3	H	H	OH	H	OH	N_3	H	53.4	35.6	68.6	74.5	59.8	34.9
49[a]	N_3	H	H	OBz	N_3	H	H	OH	55.5	33.9	71.2	70.6	67.7	35.8
50[a]	N_3	H	H	OBz	H	OH	N_3	H	53.6	34.2	71.5	73.8	60.0	35.0
62[a]	H	H	H	OTs	H	OH	OCH_2Ph	H	18.4	27.6[e]	77.7	71.8	81.6	26.6[e]
64[c,d]	H	H	NH_2	H	H	OH	OH	H	21.3	29.2	55	76.6	73.8	32.7

[a]Chloroform-*d*. [b]G = *tert*-Butyldimethylsilyl. [c]Acidic salt. [d]D_2O. [e]Assignments for these peak positions may be reversed.

from **2**, 25%). Although **14** could also be obtained by selective tosylation of the cyclohexanetetrol **7**, in 88% yield, the first route for the synthesis of **14** provided a useful variety of versatile intermediates (see later).

The ditosyloxycyclohexanediol **14** is a good precursor of 2,6-dideoxystreptamine. Furthermore, we envisaged that selective protection of the 3-hydroxyl group would afford an ideal intermediate for synthesis of pseudodisaccharides.

To our surprise, benzoylation of **14** with benzoyl chloride in the presence of imidazole gave in high yield (85%) the 2-benzoate **15**, whereas reaction with *tert*-butylchlorodimethylsilane in *N,N*-dimethylformamide in the presence of imidazole furnished the desired 3-silyl ether **16** in 85% yield. The structural assignment of **15** was based on ^{1}H- and ^{13}C-n.m.r. spectroscopy. The ^{1}H-n.m.r. spectrum of **15** exhibited a quartet at δ 4.25 p.p.m. (Table I) which, from its chemical shift, was attributed to the H–C–OH proton. This proton was shown by irradiation to be coupled with the methylene protons. In addition, comparison of the ^{13}C chemical-shifts observed for **15** and **14** (Table II) gives agreement with the shift effect expected for *O*-esterification at C-2 [$\Delta\delta$C-4 +1.5, $\Delta\delta$C-1 −3.4, $\Delta\delta$C-3 −2.3].

The structure of the 3-silyl ether **16** was deduced from the ^{1}H-n.m.r. spectrum of its benzoate **17** (Table I), based on the values of chemical shifts and by irradiation experiments.

As expected, the ditosyloxycyclohexanediol **14** can be transformed smoothly into 2,6-dideoxystreptamine* **19**, by azidolysis in hexamethylphosphoric triamide followed by catalytic hydrogenation of the diazide **18**.

Although the foregoing procedure from the diol **4** provided a good route to **19**, an alternative synthesis was also realized from the diol **5** by regio- and stereo-specific introduction of a chlorine atom at position 5 in **5**. Treatment of the diol **5** with sulfuryl chloride[15] in pyridine and chloroform at −70° afforded the monochlorosubstitution product **20** in 85% yield. Esterification with benzoyl chloride, or etherification with α-bromotoluene in the presence of sodium hydride in *N,N*-dimethylformamide, provided derivatives **21** and **22**, respectively. Acid hydrolysis of **21** and **22** yielded the diols **23** and **24**, which were selectively tosylated to give the crystalline monosulfonates **25** and **26**, respectively. The ^{1}H-n.m.r. spectra of **25** and **26** (Table I) support the proposed structures.

Compounds **25** and **26**, having two leaving-groups at positions 1 and 5 and only one free hydroxyl group at position 2 (as for **16**), were hence of further synthetic utility. Debenzoylation of **25** yielded the chlorotosyloxydiol **27**, which on azidolysis and subsequent catalytic reduction furnished 2,6-dideoxystreptamine **19**.

Both isomeric diols (**4** and **5**) thus provided a good starting point for preparation of the mutasynthon 2,6-dideoxystreptamine (**19**) and several intermediates (**16**, **25**, and **26**) for glycosylation procedures.

Synthesis of 2,5,6-trideoxystreptamine (**37**, *Chart II*). — 2,5,6-Trideoxystreptamine **37** and its precursor **33** were prepared from the key intermediate **2** by the

*Racemic 2,6-dideoxystreptamine and 2,5,6-trideoxystreptamine were recently reported; see ref. 14.

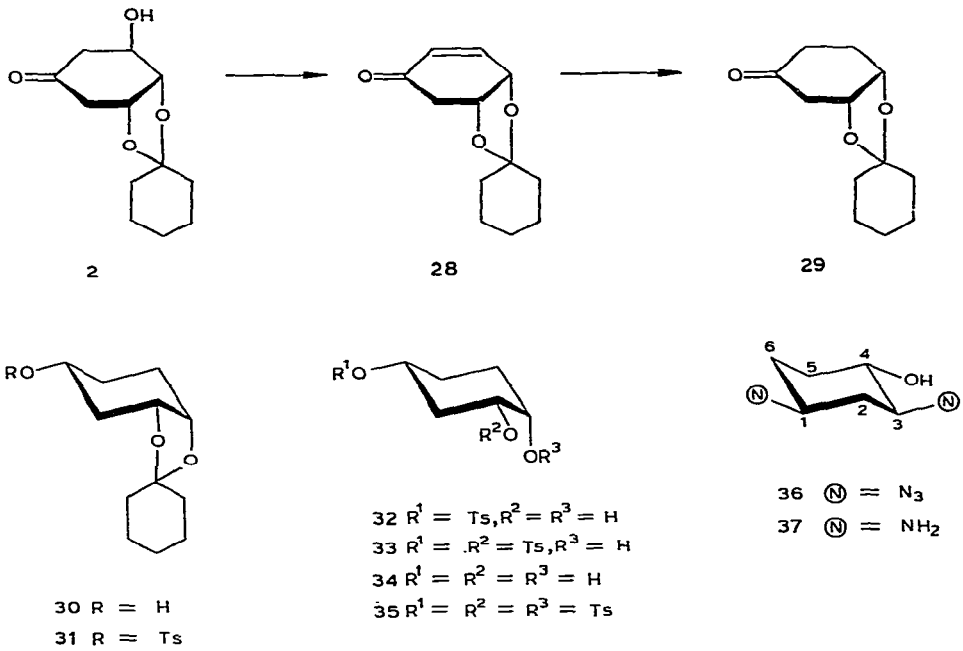


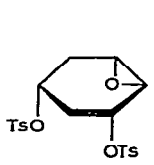
Chart II

following sequence. Treatment of the ketone **2** with *p*-toluenesulfonyl chloride in pyridine for 5 days gave the crystalline α,β-unsaturated ketone **28** in 95% yield. Catalytic hydrogenation of **28** over palladium-on-charcoal (10%) afforded the saturated ketone **29**. Reduction of **29** in diglyme with lithium borohydride furnished exclusively the syrupy alcohol **30**, which was converted into its crystalline sulfonic ester **31**. The acetal group of **31** was hydrolyzed in methanol by using Amberlite IR-120 (H^+) resin, to give the amorphous diol **32**, which was selectively tosylated to produce the target ditosyloxycyclohexanol **33**. Alternatively, **33** was also obtained by acid-catalyzed removal of the acetal group of **30**, followed by selective tosylation of the cyclohexanetriol **34**. The overall yield for the preparation of **33** was 55%, based on **2**. The physical data obtained for **34** and its trisulfonate (**35**) were identical with those reported in the literature for the corresponding racemic compounds[16], except for their optical rotations.

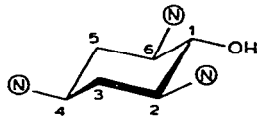
The ditosyloxycyclohexanol **33** is the intermediate of choice for α-glycosylation procedures. Azidolysis of **33** in *N*,*N*-dimethylformamide produced the oily diazide **36**, which was catalytically reduced to 2,5,6-trideoxystreptamine[14] **37**, isolated as its dihydrochloride salt.

Synthesis of 5-amino-2,5,6-trideoxystreptamine (**40**, *Chart III*). — It was of interest to prepare bioactive pseudodisaccharides related to 4-*O*-substituted deoxystreptamine fragments of antibiotics in which the 2-deoxystreptamine aglycon has been replaced by 5-amino-2,5,6-trideoxystreptamine (**40**). We chose, therefore, to in-

vestigate the azidolysis of the ditosyloxy epoxide **12**, readily prepared from the diol **4**, as simultaneous displacement of the tosyloxy groups and opening of the epoxide ring could lead to triazides. Treatment of **12** with sodium azide in *N*,*N*-dimethylformamide yielded two syrupy triazides, **38** and **39**, in the ratio of 1 : 1, whose structures follow from their $[\alpha]_D$ values of 0° for **38** and +70° for **39**, and also from their ^{13}C-n.m.r. spectra (Table II).

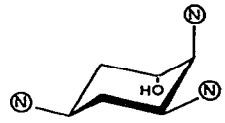


12



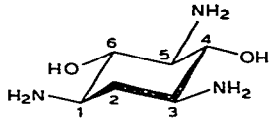
38 Ⓝ = N_3

40 Ⓝ = NH_2



39 Ⓝ = N_3

Chart III



The ^{13}C-n.m.r. spectra of the desired *meso* compound **38** and the chiral azide **39** exhibited four and six signals, respectively.

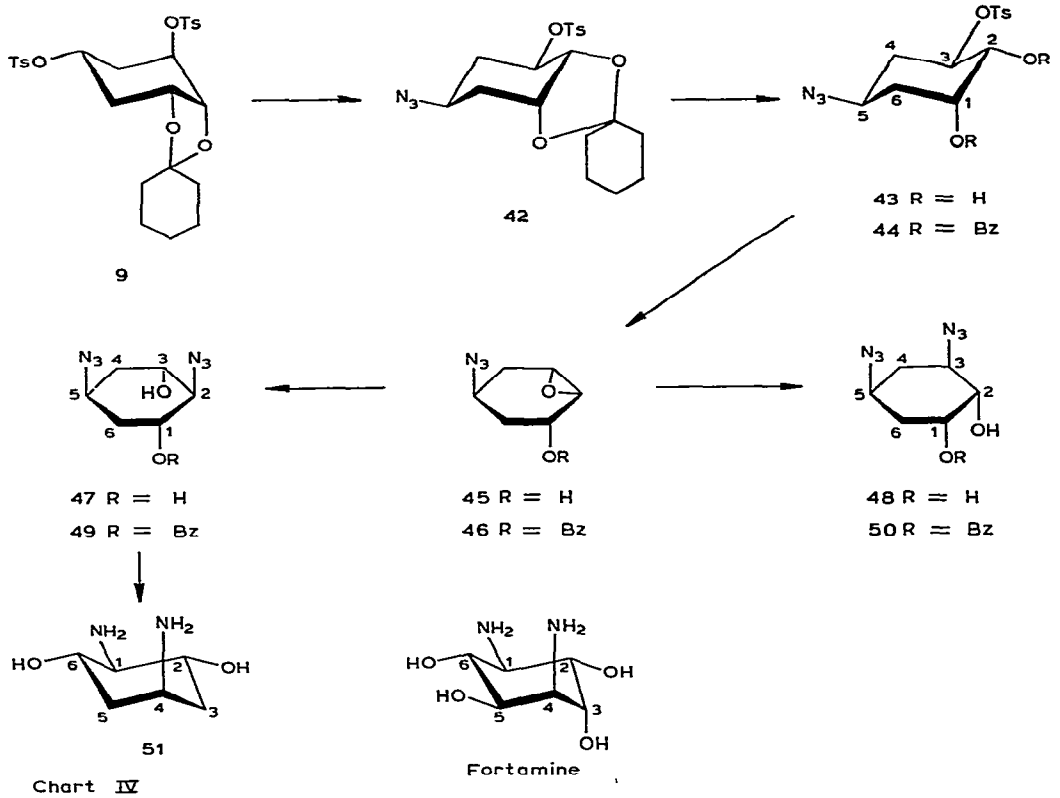
The triazide **38** was hydrogenated over Adams catalyst in methanol to give the potential mutasynthon 5-amino-2,5,6-trideoxystreptamine (**40**).

The microbial transformation of triaminocyclitol **41**, by an idiotroph of *Micromonospora inyoensis*, into a bioactive product has recently been reported[17].

Synthesis of 3,5-dideoxyfortamine (**51**)

The isolation[1] in 1977 of fortimicins containing the hitherto unknown 1,4-diamino-L-*chiro*-inositol aglycon, inspired us to develop the synthesis of the dideoxy analogue (**51**) of fortamine, and its precursors **47** and **49**, for total synthetic and mutasynthetic studies.

The disulfonate **9** provides (Chart IV) a convenient starting material for synthesis of 3,5-dideoxyfortamine, **51**. Treatment of the disulfonate **9** under carefully controlled conditions with sodium azide in *N*,*N*-dimethylformamide led to the monoazide **42** in 80% yield. Acid-catalyzed hydrolysis of **42** furnished the crystalline diol **43**, which was readily transformed into its dibenzoate, **44**. The ^{1}H-n.m.r. data obtained for **44** (Table I) accord with the structure proposed, and confirm that selective displacement of the tosyloxy group occurred at C-5. The diol **43** was converted by treatment with methanolic sodium methoxide into epoxide **45**, which was readily benzoylated to its corresponding benzoate **46**.



Azidolytic ring-opening of the epoxide **45** gave almost exclusively the *meso*-2,5-diazide **47** (80% yield) and a trace of the 3,5-diazide **48**, whereas similar treatment of its benzoate **46** afforded a mixture of 2,5- and 3,5-diazides (**49** and **50**) in the ratio of 2:3, respectively. The former (**49**) is an appropriate chiral intermediate for the preparation of dideoxyfortamine glycosides. Structural assignment of the diazides **49** and **50** was based on ^{1}H- and ^{13}C-n.m.r. data (Tables I and II) and also on chemical correlation. Thus, saponification of **49** and **50** yielded the parent *meso* **47** and chiral **48** diazidocyclohexanediols. Catalytic reduction of the *meso* 2,5-diazide **47** provided the potential mutasynthon 3,5-dideoxyfortamine (**51**).

Preparation of monoaminocyclohexanetriols **53** *and* **57**, *and monoaminocyclohexanediol* **64**

As far as we are aware, only a few monoaminocyclitol antibiotics, such as minosaminomycin[3] and[18] LL-BM 123α, containing *myo*-inosamine-1 and *myo*-inosamine-2, respectively, have been isolated from natural sources.

In addition, Rinehart and Stroshane[19] have suggested that monoaminocyclitols are involved as intermediates in the biosynthesis of 2-deoxystreptamine. Daum and co-workers[20] made the interesting observation that *myo*-inosamine-2 is incorporated

into an antibiotic by the idiotroph of *Micromonospora purpurea*. These results encouraged us to prepare such monoaminocyclitols as **53** and **57**.

It also appeared interesting to prepare, for α-glycosylation, the 1-deamino analogue of 2-deoxystreptamine (**64**) and its precursor **62**, in order to assess the role exerted by the 1-amino group on the biological properties of this class of antibiotics.

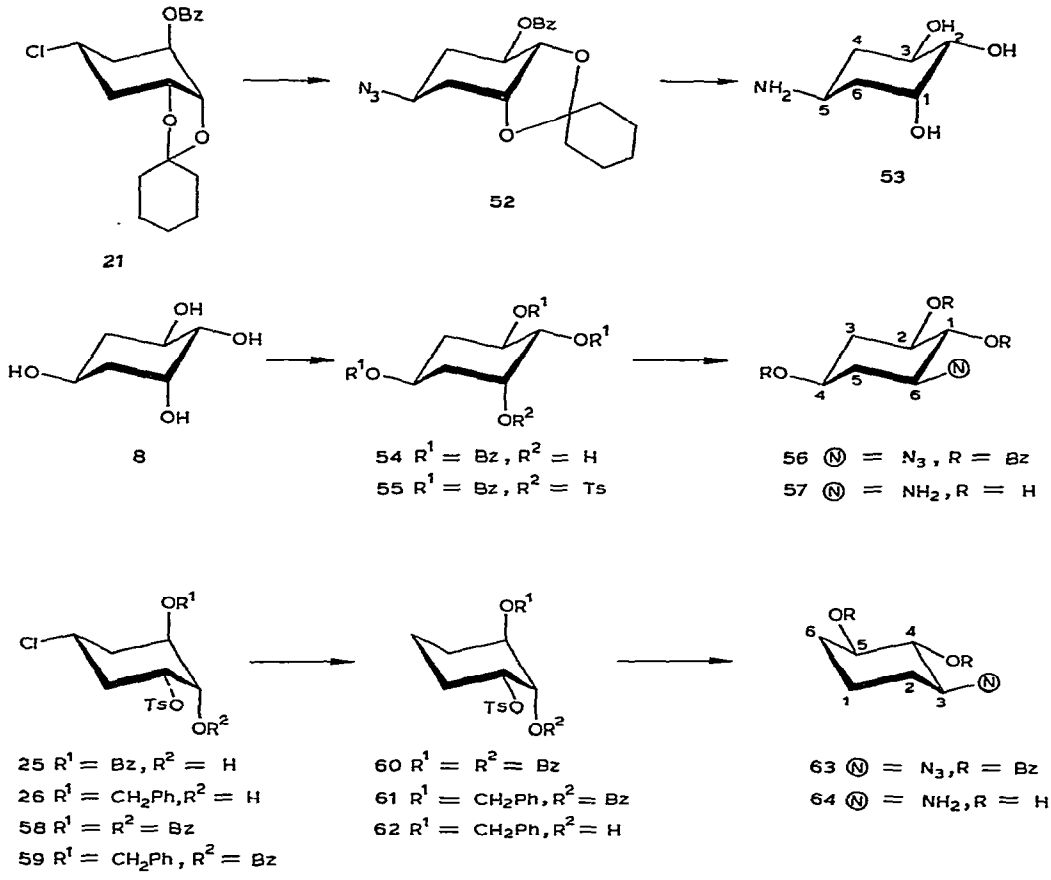


Chart V

It was hoped that the reduction of the oxime **3** might provide a convenient route to monoaminocyclitols. Unfortunately, reduction of **3** by various methods led to an epimeric mixture of two amines whose separation proved extremely tedious.

However, the 5-aminocyclitol **53** was prepared (Chart V) from compound **21**, derived from the diol **5**. Azidolysis of **21** yielded the crystalline azide **52**, which, on stepwise saponification, reduction, and acid hydrolysis of the acetal group, afforded the 5-aminocyclohexanetriol **53**, isolated as its hydrochloride salt.

The synthesis of the 6-aminocyclitol **57** started also from the diol **5** *via* the cyclohexanetetrol **8**. Selective benzoylation of the three equatorial hydroxyl groups

of the tetrol **8** provided, in 60% yield, the tribenzoate **54**, which upon treatment with *p*-toluenesulfonyl chloride yielded the fully esterified cyclohexanetetrol derivative **55**. The ^{1}H-n.m.r. spectrum of **54** was in accord with the structure proposed (Table I). Azidolysis of **55** afforded the azide **56** which, after saponification followed by catalytic reduction, gave the 6-aminocyclohexanetriol **57**.

The elaboration of the 1-deamino-2,6-dideoxystreptamine **64** and its precursor **62** proceeded smoothly from **58** and **59**, prepared by benzoylation of **25** and **26**, respectively. Reductive dechlorination of **58** and **59**, by using tributylstannane[21] in toluene in the presence of α,α'-azobis(isobutyronitrile), afforded in high yield **60** and **61**, respectively.

Saponification of **61** yielded compound **62**, an intermediate required for the α-glycosylation procedure.

Azidolysis of **60**, followed successively by debenzoylation and catalytic reduction, provided the desired 1-deamino-2,6-dideoxystreptamine **64**, isolated as its hydrobromide salt. Racemic **64** has been reported[22].

Several convergent synthetic methods have been explored here for the preparation of novel aminocyclitols from L(—)-quinic acid. The transformation of these aglycons by either mutasynthetic or chemical means is currently under way[23].

EXPERIMENTAL

Nomenclature. — Compounds named as derivatives of deoxystreptamine and fortamine are numbered as in the antibiotic literature. The naming and numbering of all other compounds follows the IUPAC-IUB 1973 Recommendations for Cyclitols[24]. The configurations about chiral centers have been specified by the Sequence Rule[25].

General methods. — Evaporations were performed under diminished pressure below 45°. Optical rotations were measured on a "Quick" Roussel and Jouan polarimeter. Melting points were determined on a Reichert hot-plate and are uncorrected. Silica Gel PF_{254} (Merck) was used for preparative chromatography. ^{1}H-N.m.r. spectra were recorded with a Cameca TSN-250 instrument or with a Varian T60 spectrometer. ^{13}C-N.m.r. spectra were recorded with Bruker WP-60 (15.08 MHz) or HX-90 (22.63 MHz) instruments. Chemical shifts (δ) are reported with reference to tetramethylsilane.

Compounds recorded in Table III were prepared by such standard chemical procedures as benzoylation, *p*-toluenesulfonylation, epoxide formation, and the like.

(*3*R,*4*S,*5*R)-*3,4*-O-*Cyclohexylidene-3,4,5-trihydroxycyclohexanone* (**2**). — To a stirred solution of sodium metaperiodate (40 g) in water (330 mL) cooled in an ice–water bath, (1*R*,2*S*,3*R*,5*R*)-1,2-*O*-cyclohexylidene-5-*C*-(hydroxymethyl)cyclohexane-1,2,3,5-tetrol[12] (**1**, 21 g) was added portionwise. Stirring was then continued for an additional 1.5 h at room temperature and the pH was maintained between 5 and 6 by addition of M sodium hydrogencarbonate.

The mixture was filtered and the solid washed with chloroform. The filtrate

TABLE III

PHYSICAL DATA

Compound	M.p. (degrees)		$[\alpha]_D$ (degrees)	Solvent	Molecular formula	Calc. (%)			Elemental analysis	Found (%)				Ref.
						C	H	N	(B, S, Cl)	C	H	N	(B, S, Cl)	
3	146–148	$CHCl_3$–Hexane	+27	$CHCl_3$	$C_{12}H_{19}NO_4$	59.73	7.94	5.81		59.65	8.06	5.70		
6	102–103	Hexane	+4	$CHCl_3$	$C_{18}H_{23}O_4B$	68.81	7.38		B, 3.44	68.63	7.32		B, 3.02	
7	211–214	EtOH–AcOEt	−6	H_2O	$C_6H_{12}O_4$	48.64	8.16			48.40	8.18			13
8	152–153	EtOH–AcOEt	−57	H_2O	$C_6H_{12}O_4$	48.64	8.16			48.62	8.14			13
9	104–105	EtOH	−22	$CHCl_3$	$C_{20}H_{32}O_8S_2$	58.20	6.01		S, 11.93	58.07	6.06		S, 11.94	
11	142–144	EtOH	+19	$CHCl_3$	$C_{13}H_{10}O_5S$	54.93	5.67		S, 11.26	54.72	5.59		S, 11.26	
23	105–107	Ether–Hexane	+10	$CHCl_3$	$C_{13}H_{15}ClO_4$	57.68	5.59		Cl, 13.10	57.92	5.54		Cl, 13.11	
24			−10	CH_2Cl_2										
27	165–166	AcOEt–Hexane	−31	MeOH	$C_{13}H_{17}ClO_5S$	48.67	5.34		Cl, 11.05; S, 10.00	48.49	5.44		Cl, 10.89; S, 10.13	
34	137–138		+18	EtOH	$C_6H_{12}O_3$	54.54	9.10			54.45	8.97			16
35	158	EtOH	+20	$CHCl_3$	$C_{27}H_{30}O_9S_3$	54.54	5.05		S, 16.16	54.29	5.13		S, 16.20	16
42	76–77	EtOH	−128	$CHCl_3$	$C_{19}H_{25}N_3O_5S$	56.01	6.19	10.31	S, 7.85	56.11	6.27	10.27	S, 7.91	
43	118–119	AcOEt	−9	$CHCl_3$	$C_{13}H_{17}N_3O_5S$	47.71	5.23	12.84	S, 9.78	47.56	5.14	12.65	S, 9.75	
44	131–132	AcOEt	+187	$CHCl_3$	$C_{27}H_{25}O_7N_3S$	60.58	4.71	7.85	S, 5.98	60.58	4.55	7.93	S, 6.10	
46	Syrup		+108	$CHCl_3$	$C_{13}H_{13}N_3O_3$	60.23	5.02	16.22		60.32	5.09	16.01		
52	76–77	EtOH	−56	$CHCl_3$	$C_{19}H_{23}N_3O_4$	63.85	6.49	11.76		63.86	6.51	11.92		
54	103–105	CH_2Cl_2–Hexane	−33	$CHCl_3$	$C_{27}H_{24}O_7$	70.42	5.25			70.10	5.20			
55	193–195	CH_2Cl_2–Hexane	−47	$CHCl_3$	$C_{34}H_{30}O_9S$	66.44	4.92		S, 5.21	66.14	5.01		S, 5.22	
56	171–173	CH_2Cl_2–Hexane	−23	$CHCl_3$	$C_{27}H_{23}N_3O_6$	66.79	4.78	8.66		66.61	4.86	8.76		
58	138–140	EtOH	−56	CH_2Cl_2	$C_{27}H_{25}SClO_7$	61.30	4.76		Cl, 6.70; S, 6.06	61.09	4.71		Cl, 7.08; S, 5.95	
59	130–131	EtOH	−11	CH_2Cl_2	$C_{27}H_{27}ClO_6S$	62.96	5.28		Cl, 6.88; S, 6.22	63.02	5.13		Cl, 7.07; S, 6.41	
60	170	EtOH	−64	CH_2Cl_2	$C_{27}H_{26}O_7S$	65.57	5.29		S, 6.48	65.41	5.41		S, 6.31	

was extracted with ethyl acetate and the extracts dried over sodium sulfate and evaporated to dryness under diminished pressure. The residue was crystallized from ethyl acetate–hexane to give **2** (17.6 g, 95%), m.p. 98°, $[\alpha]_D$ +103° (*c* 1.36, chloroform).

Anal. Calc. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.92; H, 7.85.

Reduction of **2** *with lithium borohydride.* — To a stirred solution of ketone **2** (22 g) in diglyme (140 mL) cooled to 0°, lithium borohydride (2.5 g) was added in portions. After 4 h, the reaction mixture was diluted with ice–water, the pH was adjusted to 7 by addition of dilute acetic acid, and the mixture extracted with dichloromethane. The organic phase was dried (sodium sulfate) and concentrated until crystallization occurred. The mixture was refrigerated overnight and the crystalline product collected by filtration, to give (1*R*,2*S*,3*R*,5*R*)-1,2-*O*-cyclohexylidenecyclohexane-1,2,3,5-tetrol (**4**; 12.7 g, 57%), m.p. 130–131° (from ethyl acetate–petroleum ether, $[\alpha]_D$ +6° (*c* 1.2, methanol).

Anal. Calc. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.02; H, 8.75.

From the mother liquors, (1*R*,2*S*,3*R*,5*S*)-1,2-*O*-cyclohexylidenecyclohexane-1,2,3,5-tetrol (**5**) was isolated by repeated recrystallization from ethyl acetate–petroleum ether (yield 2 g, 10%); m.p. 119–120°, $[\alpha]_D$ −71° (*c* 1.3, methanol).

Anal. Calc. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.03; H, 8.81.

Compound **5** may also be obtained, in better yield, *via* its benzeneboronate **6** (Table III).

p-*Toluenesulfonylation of* (*1*S,*2*R,*3*R,*5*S)-*1,2-anhydro-5-*O-*tosylcyclohexane-1,2,3,5-tetrol* (**11**). — To a solution of the epoxide **11** (4 g) in dry pyridine (20 mL) at 0° was added dropwise a solution of *p*-toluenesulfonyl chloride in pyridine (25 mL). The mixture was kept overnight at 0°, poured into ice–water, and extracted with chloroform. Conventional isolation yielded a mixture of two products, as indicated by t.l.c. (1*S*,2*S*,3*R*,5*R*)-1,2-Anhydro-3,5-di-*O*-tosylcyclohexane-1,2,3,5-tetrol (**12**) was isolated from the crude mixture by crystallization from ethyl acetate (yield 4.3 g, 70%); m.p. 144–145°, $[\alpha]_D$ +34° (*c* 1.93, chloroform).

Anal. Calc. for $C_{20}H_{22}O_7S_2$: C, 54.79; H, 5.06; S, 14.60. Found: C, 54.52; H, 4.94; S, 14.75.

The mother liquors were evaporated to dryness and the residue, on trituration with methanol, provided crystalline (1*R*,2*R*,4*S*,6*R*)-6-chloro-2,4-di-*O*-tosylcyclohexane-1,2,4-triol (**13**), m.p. 114–116°, $[\alpha]_D$ +12° (*c* 1.74, chloroform).

Anal. Calc. for $C_{20}H_{23}ClO_7S_2$: C, 50.57; H, 4.88; Cl, 7.45; S, 13.50. Found: C, 50.78; H, 4.91; Cl, 7.49; S, 13.38.

A second crop of **12** was obtained in quantitative yield on treatment of **13** with methanolic sodium methoxide at room temperature (total yield of **12**: 5.6 g, 90%).

(*1*R,*2*S,*3*R,*5*R)-*1,5-Di-*O-*tosylcyclohexane-1,2,3,5-tetrol* (**14**). — *A. From* **12**. To a solution of **12** (3.2 g) in 1,2-dimethoxyethane (10 mL) was added 0.75M sulfuric acid (50 mL), and the mixture was boiled for 2.5 h under reflux. The solution was cooled to 0°, made neutral with aqueous sodium hydrogencarbonate, and extracted

with ethyl acetate. Removal of the solvent afforded **14** (3.1 g, 90%), which crystallized from chloroform; m.p. 121–123°, $[\alpha]_D$ +10° (*c* 1, methanol).

Anal. Calc. for $C_{20}H_{24}O_8S_2$: C, 52.63; H, 5.30; S, 14.02. Found: C, 52.37; H, 5.46; S, 14.10.

B. From (*1*R,*2*S,*3*R,*5*R)-*cyclohexane-1,2,3,5-tetrol* (**7**). To a stirred solution of cyclohexanetetrol (**7**, 17 g) in dry pyridine (35 mL) at 0° was added dropwise a solution of *p*-toluenesulfonyl chloride (50 g) in dry pyridine (110 mL). The mixture was kept overnight at room temperature and then poured into ice–water. Isolation gave **14** (yield 80%).

(*1*R,*2*S,*3*R,*5*R)-*2*-O-*Benzoyl-1,5-di*-O-*tosylcyclohexane-1,2,3,5-tetrol* (**15**). — To a cooled solution of imidazole (1.49 g) in dry chloroform (15 mL) was added benzoyl chloride (1.25 mL). After 15 min, the mixture was filtered and the filtrate added to a solution of **14** (5 g) in chloroform (15 mL). The solution was boiled under reflux overnight and then poured into ice–water and sodium hydrogencarbonate. Extraction with dichloromethane and standard processing yielded **15**, which crystallized from ethanol (yield 5.34 g, 87%); m.p. 172–174°, $[\alpha]_D$ +6° (*c* 1.63, chloroform).

Anal. Calc. for $C_{27}H_{28}O_9S_2$: C, 57.86; H, 5.04; S, 11.42. Found: C, 57.94; H, 4.89; S, 11.12.

(*1*R,*2*S,*3*R,*5*R)-*3*-O-tert-*Butyldimethylsilyl-1,5-di*-O-*tosylcyclohexane-1,2,3,5-tetrol* (**16**). — To a solution of compound **14** (8 g) in *N*,*N*-dimethylformamide (50 mL) were added *tert*-butylchlorodimethylsilane (6.25 g) and imidazole (5.3 g). The mixture was stirred overnight at room temperature and then processed to give **16** (8.5 g, 85%), which crystallized from dichloromethane–petroleum ether; m.p. 153–154°, $[\alpha]_D$ +21° (*c* 1.2, chloroform).

Anal. Calc. for $C_{26}H_{38}O_8S_2Si$: C, 54.71; H, 6.71; S, 11.23. Found: C, 54.57; H, 6.64; S, 11.02.

(*1*R,*2*R,*3*S,*5*R)-*3,5-Diaminocyclohexane-1,2-diol* (**19**). — *A. From* **14**. A mixture containing sodium azide (3.3 g) and **14** (5.78 g) in hexamethylphosphoric triamide was heated with stirring for 4 h at 80°, poured into ice–water, and the mixture extracted with dichloromethane. Evaporation of the solvent yielded (1*R*,2*R*,3*S*,5*S*)-3,5-diazidocyclohexane-1,2-diol (**18**; 2.2 g, 88%), m.p. 63–63.5° (from chloroform–petroleum ether), $[\alpha]_D$ +2° (*c* 1.05, methanol).

Anal. Calc. for $C_6H_{10}N_6O_2$: C, 36.36; H, 5.09; N, 42.42. Found: C, 36.24; H, 5.05; N, 42.27.

The diazide **18** (300 mg) was dissolved in methanol (5 mL) and hydrogenated overnight over Adams catalyst. After removal of the catalyst, the filtrate was concentrated, acidified with M hydrochloric acid, and kept overnight at 5°. The precipitate was filtered off, giving the colorless, amorphous dihydrochloride salt of **19** (yield 65%); m.p. 230–232°, $[\alpha]_D$ +4° (*c* 1.17, water).

Anal. Calc. for $C_6H_{16}Cl_2N_2O_2$: C, 32.91; H, 7.36; N, 12.79; Cl, 32.38. Found: C, 33.14; H, 7.47; N, 13.09; Cl, 32.58.

B. From (*1*R,*2*S,*3*R,*5*R)-*5-chloro-1*-O-*tosylcyclohexane-1,2,3-triol* (**27**). A mixture containing **27** (456 mg) and sodium azide (260 mg) in *N*,*N*-dimethylforma-

mide (5 mL) was heated for 2 h at 80°. Isolation as already described yielded **18** (yield 70%).

(*1*R,*2*S,*3*R,*5*R)-*5-Chloro-1,2*-O-*cyclohexylidenecyclohexane-1,2,3-triol* (**20**). — To a solution of **5** (10 g) in chloroform (130 mL)–pyridine (40 mL) was added dropwise sulfuryl chloride (14 mL) at −70°. After stirring for 2 h at −40° and conventional processing, the residue obtained was dissolved in methanol (300 mL), and then sodium hydrogencarbonate (15 g) and a methanolic solution (50 mL) of sodium iodide (12 g) were added. The mixture was stirred for 3 h. The precipitate was filtered off and washed with methanol. The combined filtrates were evaporated to dryness and the residue was dissolved in ether. The solution was washed with water, dried (sodium sulfate), and evaporated, yielding **20** (10 g) as a red syrup that was characterized as its crystalline benzoate **21**, m.p. 121–122° (from methanol), $[\alpha]_D$ +32° (*c* 1.48, chloroform).

Anal. Calc. for $C_{19}H_{23}ClO_4$: C, 65.04; H, 6.61; Cl, 10.11. Found: C, 64.98; H, 6.64; Cl, 10.34.

(*1*R,*2*S,*3*R,*5*R)-*3*-O-*Benzyl-5-chloro-1,2*-O-*cyclohexylidenecyclohexane-1,2,3-triol* (**22**). — To a suspension of sodium hydride (4 equiv.) in *N*,*N*-dimethylformamide under nitrogen was added a solution of **20** (2 g) in *N*,*N*-dimethylformamide (20 mL) and, after 30 min, α-bromotoluene (2 equiv.) was added dropwise. The mixture was stirred overnight at room temperature and, after addition of a few drops of methanol, poured into ice–water and extracted with dichloromethane. Evaporation to dryness gave **22** (2.1 g, 80%) as a colorless syrup, $[\alpha]_D$ +12° (*c* 1.16, dichloromethane).

(*1*R,*2*S,*3*R,*5*R)-*3*-O-*Benzoyl-5-chloro-1*-O-*tosylcyclohexane-1,2,3-triol* (**25**). — Selective *p*-toluenesulfonylation of (1*R*,2*R*,3*R*,5*S*)-3-*O*-benzoyl-5-chlorocyclohexane-1,2,3-triol (**23**) was performed as described for the preparation of **14** from **7**. The crude product recrystallized from ethanol to give **25** (yield 76%), m.p. 151–152°, $[\alpha]_D$ −42° (*c* 2.7, chloroform).

Anal. Calc. for $C_{20}H_{21}ClO_6S$: C, 56.53; H, 4.98; Cl, 8.34; S, 7.55. Found: C, 56.70; H, 4.85; Cl, 8.50; S, 7.27.

(*1*R,*2*S,*3*R,*5*R)-*3*-O-*Benzyl-5-chloro-1*-O-*tosylcyclohexane-1,2,3-triol* (**26**). — Selective *p*-toluenesulfonylation of (1*R*,2*R*,3*R*,5*S*)-3-*O*-benzyl-5-cyclorocyclohexane-1,2,3-triol (**24**) as described already for the preparation of **14** from **7** afforded **26** (yield 90%), which crystallized from ether–hexane; m.p. 106–107°, $[\alpha]_D$ −12° (*c* 1, dichloromethane).

Anal. Calc. for $C_{20}H_{23}ClO_5S$: C, 58.46; H, 5.64; Cl, 8.63; S, 7.8. Found: C, 58.49; H, 5.65; Cl, 8.34; S, 8.07.

(*4*S,*5*R)-*4,5*-O-*Cyclohexylidene-4,5-dihydroxy-2-cyclohexenone* (**28**). — To a cooled solution of the ketone **2** (10 g) in pyridine (80 mL) was added portionwise *p*-toluenesulfonyl chloride (16.2 g). The mixture was stirred for 5 days at room temperature. Conventional treatment yielded **28**, isolated as a yellow solid (95%). An analytical sample was obtained by sublimation; m.p. 56–58°, $[\alpha]_D$ +135° (*c* 1, chloroform).

Anal. Calc. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.21; H, 7.73.

(*3*R,*4*S)-*3,4*-O-*Cyclohexylidene-3,4-dihydroxycyclohexanone* (**29**). — The α,β-unsaturated ketone **28** (9 g) was dissolved in ethyl acetate (170 mL) and 10% palladium-on-charcoal (5.5 g) was added to the solution under nitrogen. The mixture was shaken under hydrogen in a Parr apparatus for 72 h. The catalyst was removed by filtration on a bed of Celite and the filtrate was evaporated to dryness to give **29** (7.2 g, 80%) as a pink solid. Further recrystallization from hexane yielded an analytical sample; m.p. 86–87°, $[\alpha]_D$ +136° (*c* 1.4, chloroform).

Anal. Calc. for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.66; H, 8.45.

(*1*S,*2*R,*4*R)-*1,2*-O-*Cyclohexylidenecyclohexane-1,2,4-triol* (**30**). — The ketone **29** was reduced with lithium borohydride as described for the ketone **2**. Compound **30** was obtained in quantitative yield as a syrup and was characterized as its crystalline sulfonic ester **31**; m.p. 88–89° (from methanol), $[\alpha]_D$ +42° (*c* 1.08, chloroform).

Anal. Calc. for $C_{19}H_{26}O_5S$: C, 62.29; H, 7.10; S, 8.74. Found: C, 62.54; H, 7.20; S, 8.99.

(*1*S,*2*R,*4*R)-*2,4-Di*-O-*tosylcyclohexane-1,2,4-triol* (**33**). — (1*S*,2*R*,4*R*)-Cyclohexane-1,2,4-triol (**34**) was selectively *p*-toluenesulfonylated as described for the preparation of **14** from **7**. The crude product crystallized from ethanol to give **33** (yield 80%), m.p. 134°, $[\alpha]_D$ +19° (*c* 1.25, chloroform).

Anal. Calc. for $C_{20}H_{24}O_7S_2$: C, 54.53; H, 5.49; S, 14.56. Found: C, 54.58; H, 5.50; S, 14.28.

(*1*S,*2*S,*4*S)-*2,4-Diaminocyclohexanol* (**37**). — Azidolysis of **33** in *N,N*-dimethylformamide for 1 h at 120° gave (1*S*,2*S*,4*S*)-2,4-diazidocyclohexanol (**36**) as a syrup (yield 80 %), $[\alpha]_D$ +82° (*c* 1, chloroform). Catalytic hydrogenation of **36** over Adams catalyst in methanol, as described for the preparation of **19**, afforded **37**, which was isolated as its dihydrochloride salt (yield 90%), m.p. 305–310° (dec.), $[\alpha]_D$ +17° (*c* 1.15, water).

Anal. Calc. for $C_6H_{16}Cl_2N_2O$: C, 35.48; H, 7.94; Cl, 34.91; N, 13.79. Found: C, 35.32; H, 7.91; Cl, 35.04; N, 13.49.

Azidolysis of (*1*S,*2*S,*3*R,*5*R)-*1,2-anhydro-3,5-di*-O-*tosylcyclohexane-1,2,3,5-tetrol* (**12**). — A suspension of **12** (1 g) and sodium azide (890 mg) in *N,N*-dimethylformamide (30 mL) was treated with stirring for 1 h at 120°. The mixture was poured into ice–water and extracted with dichloromethane. The crude residue was chromatographed on preparative silica gel plates (2:3 ethyl acetate–petroleum ether), giving (1*r*,2*S*,4*r*,6*R*)-2,4,6-triazidocyclohexanol (**38**) (higher R_F, yield 49%) as an unstable syrup, $[\alpha]_D$ 0°, and (1*S*,2*S*,3*S*,5*R*)-2,3,5-triazidocyclohexanol (**39**, yield 37%), $[\alpha]_D$ +70°.

(*1*r,*2*S,*4*r,*6*R)-*2,4,6-triaminocyclohexanol* (**40**). — Catalytic hydrogenation of **38** (600 mg) over Adams catalyst, as described for the preparation of **19**, yielded **40** (350 mg, 90%), which was isolated as its trihydrochloride salt; m.p. 200–205° (dec.), $[\alpha]_D$ 0° (*c* 1.1, water).

Anal. Calc. for $C_6H_{18}Cl_3N_3O$: C, 28.31; H, 7.13; Cl, 41.78; N, 16.51. Found: C, 28.60; H, 7.38; Cl, 41.68; N, 16.65.

Ring-opening of (*1*S,*2*R,*3*R,*5*R)-*1,2-anhydro-5-azidocyclohexane-1,2,3-triol*(**45**).

— A stirred mixture containing the epoxide **45** (1 g), sodium azide (3 g), and ammonium chloride (3 g) in 2-methoxyethanol (30 mL) was boiled under reflux for 30 min, and then poured into ice–water saturated with brine and the product extracted with dichloromethane. The residue obtained was dissolved in hot ethyl acetate, from which the *meso* (1*R*,2*r*,3*S*,5*s*)-2,5-diazidocyclohexane-1,3-diol (**47**, yield 80%) crystallized on cooling; m.p. 115–117°, $[\alpha]_D$ 0° (*c* 1.3, methanol).

Anal. Calc. for $C_6H_{10}N_6O_2$: C, 36.36; H, 5.09; N, 42.41. Found: C, 36.32; H, 5.02; N, 42.37.

From the mother liquors, (1*R*,2*S*,3*R*,5*S*)-*3,5*-diazido-cyclohexane-1,2-diol (**48**) was obtained as a syrup by chromatography on preparative silica gel plates (9:1 chloroform–ethanol) (yield 18%); $[\alpha]_D$ −106° (*c* 0.4, methanol).

Anal. Calc. for $C_6H_{10}N_6O_2$: C, 36.36; H, 5.09; N, 42.41. Found: C, 36.08; H, 5.18; N, 42.68.

(*1*R,*2*r,*3*S,*5*s)-*2,5-Diaminocyclohexane-1,3-diol* (**51**). — To a solution of **47** (400 mg) in ethanol (20 mL) were added 2 mL of 20% ethanolic hydrochloric acid and Adams catalyst (50 mg). The mixture was hydrogenated in a Parr apparatus for 6 h. After filtration through a bed of Celite to remove the catalyst, the filtrate was concentrated under diminished pressure. Dropwise addition of acetone and ether at 0° precipitated the dihydrochloride salt of **51**, which was collected by centrifugation (yield 380 mg, 86%); m.p. 255° (dec.).

Anal. Calc. for $C_6H_{16}Cl_2N_2O_2$: C, 32.91; H, 7.36; Cl, 32.38; N, 12.79. Found: C, 32.54; H, 7.43; Cl, 32.21; N, 12.88.

Ring-opening of (*1*S,*2*S,*3*R,*5*S)-*1,2-anhydro-5-azido-3*-O-*benzoylcyclohexane-1,2,3-triol* (**46**). — To a solution of the epoxide **46** (560 mg) in *N,N*-dimethylformamide (15 mL) were added sodium azide (1.1 g) and ammonium chloride (1.1 g). The mixture was heated for 2.5 h at 120°. After standard treatment as described for **45**, the residue was chromatographed on preparative silica gel plates (1:3 ethyl acetate–hexane). The band having R_F 0.5 was eluted to give (1*R*,2*R*,3*S*,5*S*)-2,5-diazido-1-*O*-benzoylcyclohexane-1,3-diol (**49**, 257 mg), which crystallized from ether–hexane; m.p. 110–111°, $[\alpha]_D$ −69° (*c* 0.83, chloroform).

Anal. Calc. for $C_{13}H_{14}N_6O_3$: C, 51.65; H, 4.68; N, 27.81. Found: C, 51.66; H, 4.69; N, 27.71.

The band having R_F 0.4 gave (1*R*,2*S*,3*R*,5*S*)-3,5-diazido-1-*O*-benzoylcyclohexane-1,2-diol (**50**) as a syrup, $[\alpha]_D$ −68° (*c* 2.2, chloroform).

Anal. Calc. for $C_{13}H_{14}N_6O_3$: C, 51.65; H, 4.63; N, 27.81. Found: C, 51.48; H, 4.58; N, 27.79.

(*1*R,*2*S,*3*R,*5*S)-*5-Aminocyclohexane-1,2,3-triol* (**53**). — (1*R*,2*R*,3*R*,5*R*)-5-Azido-3-*O*-benzoyl-1,2-*O*-cyclohexylidenecyclohexane-1,2,3-triol (**52**) was treated with methanolic sodium methoxide for 2 h, then the mixture was made neutral by using IRC-50 (H^+) resin. The resin was filtered off and the filtrate evaporated to dryness to give a syrup that was dissolved in 10 mL of 7:3 acetic acid–water. The solution was boiled overnight under reflux. The solvents were removed by evaporation, the residue was dissolved in water, and the solution was made neutral with IR-45

(OH^-) resin, with swirling. The resin was filtered off, washed with water, and the filtrate concentrated to give **53**, which was purified by chromatography on IR-120 (H^+) resin. The resin was eluted successively with water and 0.5M hydrochloric acid. The acidic eluates were concentrated and the hydrochloride salt of **53** was precipitated by addition of acetone and recrystallized from acetone (yield 55%); m.p. 220–225° (dec.), $[\alpha]_D$ −47° (*c* 1.27, water).

Anal. Calc. for $C_6H_{14}ClNO_3$: C, 39.24; H, 7.68; Cl, 19.31; N, 7.63. Found: C, 39.30; H, 7.63; Cl, 19.13; N, 7.46.

(*1*R,*2*R,*4*R,*6*S)-*6-Aminocyclohexane-1,2,4-triol* (**57**). — (1*R*,2*R*,4*R*,6*S*)-6-Azido-1,2,4-tri-*O*-benzoylcyclohexane-1,2,4-triol (**56**, 245 mg) was dissolved in methanol (10 mL) and a catalytic amount of sodium was added. After 1 h, the solution was made neutral with IRC-50 (H^+) resin. The resin was filtered off and the filtrate evaporated to dryness. The residue was dissolved in methanol and hydrogenated over Adams catalyst to yield **53** (70 mg), which was isolated as its sulfate; m.p. >260°, $[\alpha]_D$ +3° (*c* 1.6, water).

Anal. Calc. for $C_6H_{13}NO_3 \cdot 0.5\ H_2SO_4 \cdot 0.75\ H_2O$: C, 34.36; H, 7.09; N, 6.68; S, 7.64. Found: C, 34.23; H, 7.34; N, 6.53; S, 7.72.

(*1*R,*2*S,*3*R)-*2*-O-*Benzoyl-3*-O-*benzoyl-1*-O-*tosylcyclohexane-1,2,3-triol* (**61**). — To a solution of (1*R*,2*S*,3*R*,5*R*)-2-*O*-benzoyl-3-*O*-benzyl-5-chloro-1-*O*-tosylcyclohexane-1,2,3-triol (**59**, 3 g) in toluene (40 mL) kept under a stream of nitrogen, was added tributylstannane (2.5 mL) and a catalytic amount of α,α′-azobis(isobutyronitrile). The mixture was treated with stirring for 2.5 h at 80°. The solution was evaporated to dryness to give a white solid that was triturated with petroleum ether several times to remove organotin compounds. Subsequent recrystallization from ethanol afforded **61** (2.75 g, 95%), m.p. 120–121°, $[\alpha]_D$ −25° (*c* 1, dichloromethane).

Anal. Calc. for $C_{27}H_{28}O_6S$: C, 67.48; H, 5.87; S, 6.67. Found: C, 67.29; H, 5.73; S, 6.90.

Compound **61**, treated with methanolic sodium methoxide, afforded **62**, which crystallized from ethyl acetate–hexane; m.p. 99–100°, $[\alpha]_D$ −28° (*c* 1, dichloromethane).

Anal. Calc. for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.42; S, 8.52. Found: C, 63.91; H, 6.47; S, 8.50.

(*1*R,*2*R,*3*S)-*3-Aminocyclohexane-1,2-diol* (**64**). — To a solution of (1*R*,2*S*,3*R*)-2,3-*O*-benzoyl-1-*O*-tosylcyclohexane-1,2,3-triol (**60**, 1.2 g) in *N*,*N*-dimethylformamide (15 mL) was added sodium azide (250 mg), and the mixture was heated for 1 h at 100°. After standard processing, (1*R*,2*R*,3*S*)-3-azido-1,2-di-*O*-benzoylcyclohexane-1,2-diol (**63**; 770 mg, 85%) was obtained as a syrup. Compound **63** was debenzoylated and the product reduced, and the resultant product[22] isolated as its hydrobromide salt (yield 70%), m.p. 166–167°, $[\alpha]_D$ +5° (*c* 1, water).

Anal. Calc. for $C_6H_{14}BrNO_2$: C, 33.98; H, 6.65; Br, 37.68; N, 6.60. Found: C, 34.02; H, 6.69; Br, 37.52; N, 6.57.

ACKNOWLEDGMENTS

The authors thank the Institut National de la Santé et de Recherche Médicale for financial support (INSERM Grant No. 77.4.205.3).

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