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2-Deoxystreptamine: Central Scaffold of Aminoglycoside Antibiotics†

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Contents

1. Introduction

A key structural feature of the aminoglycoside antibiotics is a 1,3-diaminocyclohexanetriol termed streptamine or, in cases where the 2-hydroxy function is deoxygenated as in most aminoglycosides, 2-deoxystreptamine. This central position of 2-deoxystreptamine suggests a crucial role for the biological activity of the aminoglycosides, that form a large class of clinically important antibiotics with a broad antibacterial spectrum and proven efficacy, particularly against Gram-negative bacteria (Table 1).[1] Most of the aminoglycosides are naturally occurring substances and are readily obtained from actinomycetes of either genus *Streptomyces* (labeled "-mycin") or *Micromonospora* (labeled "-micin").[2] The most relevant members of the family are streptomycin, tobramycin, and gentamicin, the latter of which is used in the clinic most frequently due to its low cost and reliable activity. In general, aminoglycosides show a strong synergistic effect upon coadministration with penicillin, a particularly useful combination for treatment of patients with infections of unknown origin. Some semisynthetic derivatives, that is, amikacin, netilmicin, arbekacin, isepamicin, and dibekacin, are also on the market and display particular activity against bacterial strains that have developed resistance against the early aminoglycosides.[3] However, in recent years it has become apparent, after a long era of marginal interest in the research and development of antibacterials, that the battle against pathogenic bacteria is not over. In contrast, resistant strains of bacteria are reported with increasing frequency, with the associated dramatic consequences such as untreatable patients or the temporary closure of hospital intensive cares.[4]

Apart from being versatile antibiotics, recent years have seen a shift of scientific interest in aminoglycosides to a related field of interest that has the potential of much broader application: the regulation of protein production at the RNA-level. Due to the fact that aminoglycosides are rather promiscuous ligands for all sorts of RNA, often in low micromolar concentration, they have earned themselves a strong position in the emerging research field "RNA as a drug target": the perception that RNA plays a central (and active) role in the biochemical pathway required to produce proteins from DNA provides nearly un-

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† In memory of the late Professor Jacques H. van Boom.

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Floris P. J. T. Rutjes was born in Heiloo, The Netherlands, in 1966. He studied chemistry at the University of Amsterdam, where he received his Ph.D. with Prof. Nico Speckamp in 1993. After conducting a postdoctoral study in the group of Prof. K. C. Nicolaou (The Scripps Research Institute, La Jolla, CA), he was appointed assistant professor at the University of Amsterdam in 1995. Four years later he became full professor at the University of Nijmegen. In 2002, he was awarded the Gold Medal of the Royal Netherlands Chemical Society (KNCV), and in 2003, he received the AstraZeneca award for research in organic chemistry. His research interests include the use of biocatalysts and metal-catalysts in organic synthesis and the development of novel synthetic methodology.

tapped opportunities for biological and pharmacological development. For example, RNA is the genetic material of pathogenic viruses such as HIV or hepatitis C. Apart from that, the complex functions of RNA molecules in the control of gene expression in humans provide numerous opportunities to target specific RNA structures for treating a variety of chronic and degenerative conditions.[5,6]

1.1. Mechanism of Action

Aminoglycoside antibiotics bind to the A-site decoding region of the bacterial 16S ribosomal RNA.[7,8] Since the natural role of the ribosome is to provide an environment for protein production, the effect of binding is expressed in mistranslation of mRNA or premature termination of protein synthesis, leading to cell death. In a more general sense, the aminoglycosides are found to have a broad, rather promiscuous preference for binding to A-form nucleic acids.[9] An interesting observation of this phenomenon is the binding of neomycin with HIV RRE, as a competitive inhibitor of the natural protein ligand Rev, resulting in attenuated HIV replication in tissue culture cells.[10−12]

Floris L. van Delft was born in Utrecht, The Netherlands, in 1968. He studied chemistry at the University of Leiden (The Netherlands), where he also performed his Ph.D.-research. After his graduation in 1996 (*cum laude*, under the supervision of the late Prof. J. H. van Boom), he moved to The Scripps Research Institute (La Jolla, CA) for a postdoctoral stay with Prof. K. C. Nicolaou. In 1998, he was appointed assistant professor at the University of Amsterdam. In the year 2000, he moved to the University of Nijmegen and continued in the same position. He received a "Vernieuwingsimpuls" fellowship in that same year and is currently heading a research group focusing on aminoglycoside antibiotics and other carbohydrate-related natural products.

1.2. Toxicity

Despite the apparent advantages, extensive clinical use of the aminoglycoside antibiotics is limited due to the associated toxicities, most notably nephrotoxicity and ototoxicity and to a lesser extent neuromuscular blockade.[2] The exact mechanism of toxicity is unknown although aminoglycosides are known to accumulate in renal cortical cells and are able to damage proximal tubules. Nephrotoxicity is dose-dependent and generally reversible in the majority of patients when the drug is discontinued. Of higher impact is the associated ototoxicity that may lead, depending on the phenotype of a particular patient, to irreversible vestibular and/or cochlear damage.

1.3. Resistance

Another and arguably more alarming drawback of the aminoglycosides (and antibiotics in general) is the global development of microbial resistance. In the case of the aminoglycosides, which are used predominantly against aerobic Gram-negative bacteria, the most common resistance mechanism is structural modification by bacterial enzymes: aminoglycoside phosphotransferases (APH), adenylyltransferases (AAD or ANT), and acetyltransferases (AAC). Typical sites of bacterial modification are exemplified (Figure 1) for kanamycin B, the aminoglycoside most susceptible to resistance.[3,13,14] A second mechanism of resistance is decreased uptake and/or accumulation of the drug in bacteria. Finally, streptomycin is

Table 1. Aminoglycosides in Clinical Use

aminoglycoside	year of introduction	effective against bacterial strain[a]	disease(s) associated with bacteria
streptomycin	1944	*M. tuberculosis*	tuberculosis
		E. histolytica	diarrhea
		C. parvum	diarrhea
		F. tularensis	tularemia
		Y. pestis	plague
neomycin	1949	*Enterobacteriacea* spp.[c] (including *E. coli*, *Klebsiella* spp.,[c] etc.)	several infections, sepsis
		Salmonella spp.[c]	diarrhea
		S. aureus	wound infections, sepsis, toxic shock syndrome
kanamycin	1957	*Enterobacteriaceae* spp.[c]	several infections, sepsis
		P. aeruginosa[b]	outer ear infection, sepsis, long infections
paromomycin	1959	*E. histolytica*	diarrhea
		C. parvum	diarrhea
spectinomycin	1962	*N. gonorrheae*	gonorrhea
		P. aeruginosa[b]	outer ear infection, sepsis, long infections
gentamicin	1963	*P. aeruginosa*[b]	outer ear infection, sepsis, long infections
		Enterobacteriaceae spp.[c]	several infections, sepsis
tobramycin (nebramycin factor 6)	1967	*Enterobacteriaceae* spp.[c]	several infections, sepsis
		P. aeruginosa[b]	outer ear infection, sepsis, long infections
sisomicin[d]	1970	*Enterobacteriaceae* spp.[c]	several infections, sepsis
		P. aeruginosa[b]	outer ear infection, sepsis, long infections
		S. aureus	wound infections, sepsis, toxic shock syndrome
dibekacin	1971		
amikacin[d]	1972	*Enterobacteriaceae* spp.[c]	several infections, sepsis
		P. aeruginosa[b]	outer ear infection, sepsis, long infections
		M. tuberculosis	tuberculosis
		MOTT	opportunistic infections
		N. asteroides	opportunistic infections
netilmicin[d]	1975	*Enterobacteriaceae* spp.[c]	intestinal infections
		P. aeruginosa[b]	outer ear infection, sepsis, long infections
isepamicin[d]	1978		nosocomial pneumonia
arbekacin[d]	1990		

[a] *M. tuberculosis* = *Mycobacterium tuberculosis*; *E. histolytica* = *Entamoeba histolytica*; *C. parvum* = *Cryptosporidium parvum*; *F. tularensis* = *Francisella tularensis*; *Y. pestis* = *Yersinia pestis*; *E. coli* = *Escherichia coli*; *S. aureus* = *Staphylococcus aureus*; *P. aeruginosa* = *Pseudomonas aeruginosa*; *N. gonorrheae* = *Neisseria gonorrheae*; MOTT = mycobacterium other than tuberculosis; *N. asteroids* = *Nocardia asteroids*. [b] Tobramycin and sisomicin show a better activity against *Pseudomonas aeruginosa*. [c] spp. = species. [d] Semisynthetic adducts.

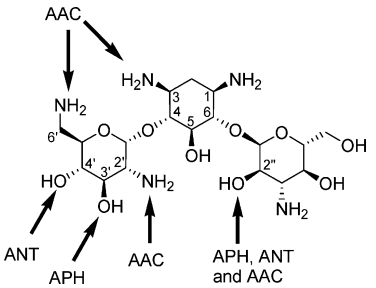


Figure 1. Major aminoglycoside-modifying enzymes acting on kanamycin B.[3]

susceptible to resistance by alteration of the ribosomal binding sites.

1.4. Structural Features

As the name aminoglycoside suggests, members of the aminoglycoside family are predominantly built up by a wide variety of aminosugars (Figure 2). These aminosugars, often of the 6-amino or the 2,6-diamino type, may be further decorated or functionalized, for example, by deoxygenation or *N*- or *C*-methylation, or may contain additional stereocenters, and they are always 1,2-cis glycosidically linked. Some additional rings or rare carbohydrates can also be identified in some aminoglycosides, but of higher significance is a cyclohexitol present in each of the structures of Figure 2. This ring, termed streptamine or 2-deoxystreptamine (2-deoxy-*myo*-inosa-1,3-diamine or *all-trans*-1,3-diamino-4,5,6-trihydroxycyclohexane), as highlighted in Figure 2, provides the central scaffold of any known aminoglycoside. It is an all-trans cyclohexitol, 1,3-substituted by two amino groups. Due to the presence of the plethora of amino functionalities, aminoglycosides are heavily protonated under physiological conditions, thus providing a rationale for the strong affinity for (negatively charged) nucleotides.[15] Apart from the conserved 1,3-diamino functionality, the cyclohexitol contains three (2-deoxystreptamine) or four (streptamine) hydroxyls, that provide the anchoring points for the aminosugars. Based on the substitution pattern of the streptamine ring, the aminoglycosides may be categorized as 4,5- or 4,6-linked. Although the streptamine numbering seems rather odd at first, it is directly derived from its biogenic precursor, *myo*-inositol (Figure 3), and is therefore numbered according to the method proposed by Fletcher *et al*. for inositols.[16] The same numbering is adapted in the case of 2-deoxystreptamine (or 2-deoxy-*myo*-inosa-1,3-diamine), despite the fact that it is not biosynthetically derived from *myo*-inositol (as will be delineated later) but from D-glucose-6-phosphate.

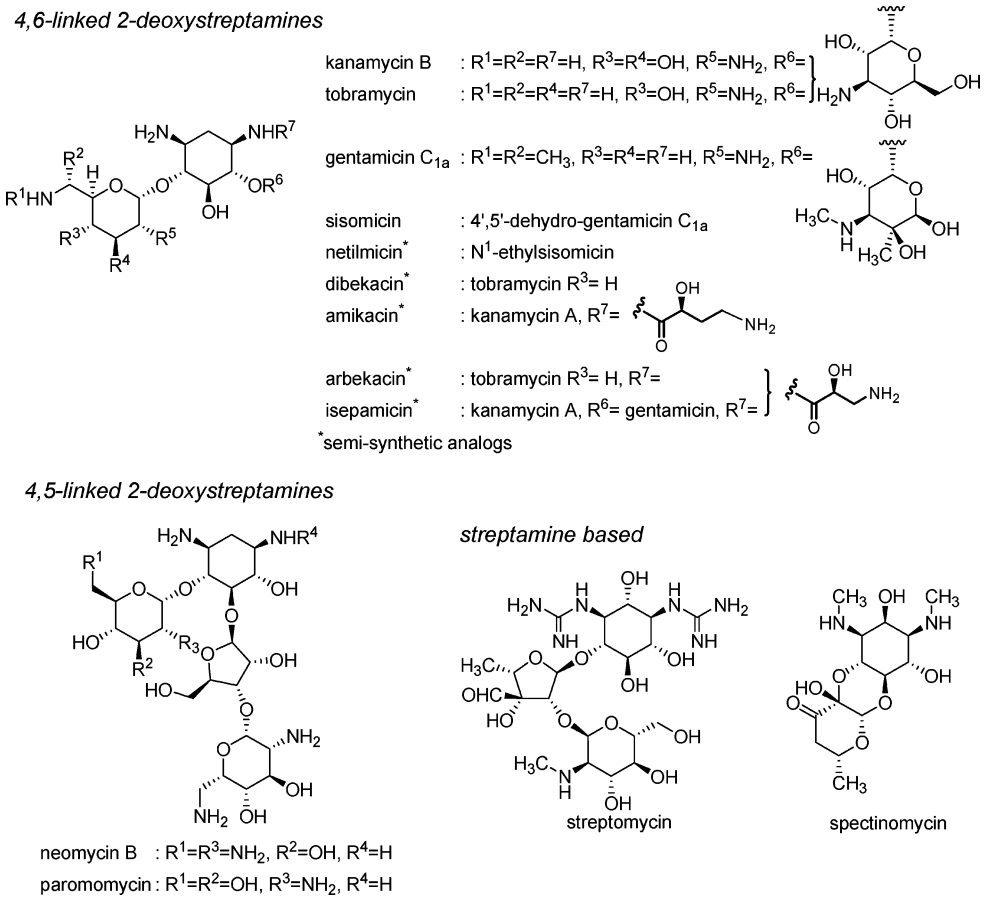


Figure 2.

1.5. Central Scaffold of Aminoglycosides: 2-Deoxystreptamine

The omnipresence and central location of 2-deoxystreptamine in aminoglycoside structures suggests a pivotal role for biological activity, an intuitive assumption that is underlined by recently published X-ray crystal structures of several aminoglycosides complexed to the 30S ribosomal particle[17−20] or an A-site oligonucleotide sequence[21−23] which reveal without exception a similar binding pattern to 2-deoxystreptamine, regardless of its 4,5- or 4,6-substitution.

Recently, X-ray crystal structures have been reported of paromomycin,[17−19] of hygromycin[20] complexed to the 30S ribosomal subunit, and of paromomycin,[21] tobramycin,[22] and geneticin[23] complexed to oligonucleotides containing the minimal bacterial ribosomal A-site.[24] Apart from that, synthetic approaches toward novel aminoglycoside type RNA-ligands have also revealed a crucial role of the 2-deoxystreptamine for biological activity,[25] although some exceptions have been reported as well.[26,27] Convincing evidence of the strong affinity of 2-deoxystreptamine for RNA was most recently provided by the observation that the presence of the bivalent structure of 2-deoxystreptamine alone, that is without aminosugar decoration, already shows low micromolar binding to RNA hairpin loops.[28] An important reason, therefore, to synthesize 2-deoxystreptamine is that by having the core structure in hand it should be possible to develop new and innovative antibiotics or, in a broader sense, RNA-binding molecules. From a chemical perspective, 2-deoxystreptamine poses an interesting synthetic challenge due to the five contiguous stereogenic centers. In this respect, it is not surprising that numerous attempts have been made to obtain this aminocyclitol moiety synthetically, and in this review a comprehensive overview of the synthetic routes that have appeared in the literature will be provided.

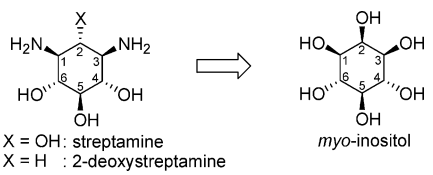


Figure 3.

A summary of the synthetic efforts aimed at (derivatives of) 2-deoxystreptamine (**1**) in terms of retrosynthetic analysis to starting materials, is provided in Figure 4. It is interesting to note that the starting materials vary from simple cycloalkenes to highly oxygenated structures, such as inositols and carbohydrates, and in most cases already contain stereocenters. Keeping in mind that 2-deoxystreptamine is a meso compound, the choice of a starting material from the chiral pool seems rather awkward at first sight, but in this manner a range of useful enantiomerically pure (protected) derivatives could be obtained (marked with an asterisk in Figure 4). A comprehensive overview of the synthetic efforts will be provided in this paper, preceded by a discussion on the biosynthesis of 2-deoxystreptamine (section 2). Next, the organic chemistry efforts will

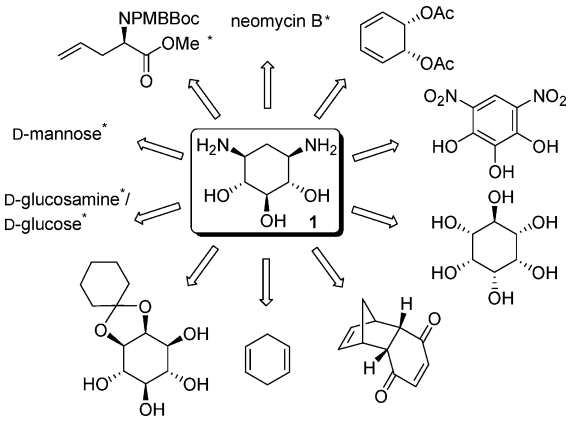


Figure 4.

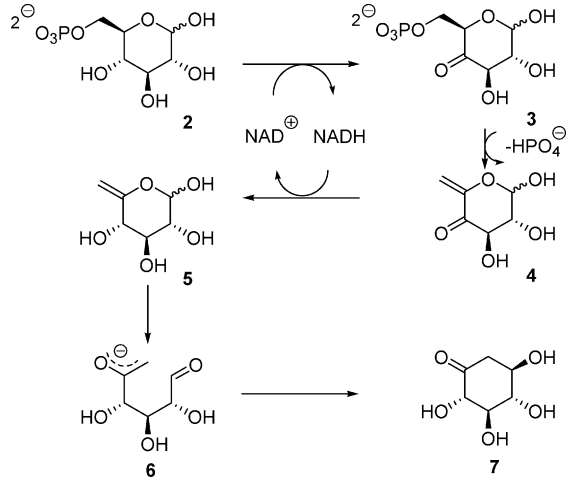
be delineated in sections 3 and 4, in three segments: (a) collection of *meso*-2-deoxystreptamine and hyosamine (methyl-2-deoxystreptamine) by degradation of neomycin (section 3.1) or via synthetic routes (section 3.2); (b) enantiomerically pure *protected* derivatives of *meso*-2-deoxystreptamine, either by enzymatic resolution (section 3.3) or from starting materials from the chiral pool (section 3.4); and (c) synthetic routes leading to regioisomers and dideoxy derivatives (section 4). Syntheses of streptamine have also been reported but are scarcer and are not included in this article.

To date, the most practical method to obtain 2-deoxystreptamine is by a straightforward acidic degradation of neomycin. One may wonder, therefore, "What is the value of fully synthetic procedures that are inevitably more expensive and time-consuming?" The answer to this question lies in the fact that the "naked" compound obtained by hydrolysis of neomycin is as such useless for synthetic purposes. It demands extensive protective group manipulation, but apart from that, since it is a meso compound, it also needs to undergo desymmetrization before incorporation in (enantiopure) aminoglycoside entities can be undertaken. For these reasons only, *de novo* synthesis from individually prepared components can already effectively compete with synthesis from neomycin. Apart from that, total synthesis has the obvious advantage that not only does it allow full flexibility in design and preparation of novel aminoglycoside-type structures but synthetic approaches at the same time open avenues leading to unnatural analogues.

2. Biosynthesis of 2-Deoxystreptamine

Although the biosynthetic pathway leading to 2-deoxystreptamine has not completely been elucidated so far, it is already clear that the biosynthesis outperforms all of the synthetic routes, and it will, therefore, be described first. As stated before, 2-deoxystreptamine is biosynthetically derived from D-glucose-6-phosphate (**2**), which is in surprising contrast with the formation of streptamine from *myo*-inositol.[29−34,42,43] Thus, the first step in the 2-deoxystreptamine synthesis is the conversion of D-glucose-6-phosphate (**2**) into 2-deoxy-D-*scyllo*-inosose (DOI, **7**) under the influence of the enzyme *2*-deoxy-*scyllo*-inosose synthase

Scheme 1

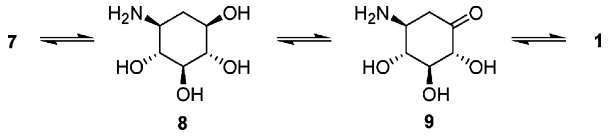


(DOIS, Scheme 1).[35−38] This single enzyme is able to catalyze the full carbocycle-forming process from **2** to **7** in the presence of NAD^+ and Co^{2+} as cofactors. The multistep process includes (i) oxidation at C-4 and elimination of phosphate (**2** → **3** → **4**), (ii) stereoselective reduction at C-4 (**4** → **5**), (iii) deprotonation and ring-opening of the hemi-acetal to an enolate-aldehyde (**5** → **6**), and, finally, (iv) stereoselective intramolecular aldol condensation between C-1 and C-6 (**6** → **7**).

The stereochemistry of the DOIS reaction in ribostamycin-producing *Streptomyces ribosidifidicus* was first elucidated by *in vivo* labeling experiments[39,40] and later confirmed by kinetic isotope effect experiments.[41−43] The purified enzyme DOIS[44] has paved the way for the successful location of the gene (*btr*C) in *Bacillus circulans*. Overexpression of DOIS in *Escherichia coli*[45] afforded insight into the importance of both the C-2 and C-3 hydroxyls in DOIS recognition by hydrogen bonding interactions.[46]

Candidate enzymes for the transamination step (**7** → **8**, Scheme 2) have also been identified by several

Scheme 2

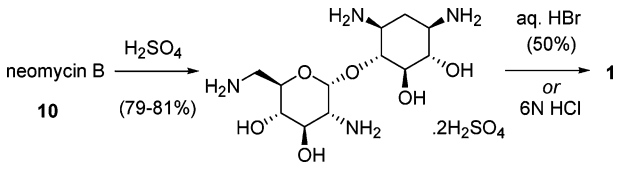


groups.[47−50] However, enzymes responsible for conversion of the remaining pathway have so far not been found. It has been proposed that the remaining pathway involves oxidation of **8** to **9**, probably catalyzed by a *dehydrogenase* and finally a transamination to form **1** (Scheme 2).[48] Further work in this field is still being carried out and may eventually contribute to the production of 2-deoxystreptamine (**1**) by fermentation. At this moment, however, no biochemical production process has been reported.

3. Synthetic Routes toward 2-Deoxystreptamine

In contrast to the lack of a suitable fermentation for the production of 2-deoxystreptamine, a plethora of synthetic routes has been described over the years and will be discussed in the next section. Apart from

Scheme 3



that, a range of analogues of 2-deoxystreptamine has also been synthesized, and these will be covered in section 4.

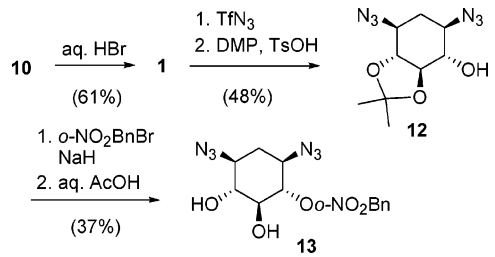
3.1. Degradation of Neomycin

Despite all efforts described later in this review, the simplest method to obtain 2-deoxystreptamine still is by hydrolytic degradation of a natural aminoglycoside. In a strict sense, to obtain 2-deoxystreptamine in this manner is not a synthesis, but since it is such a straightforward way to access 2-deoxystreptamine, it is by far the most popular route applied to date. The usual aminoglycoside of choice for this purpose is neomycin B trisulfate (**10**), since it is readily obtained from *Streptomyces* fermentation[51] and is commercially available for a reasonable price (±0.6 €/mmol). Treatment of neomycin with sulfuric acid gives compound **11** by selective cleavage of a single glycosyl linkage (Scheme 3). This compound, originally termed neomycin A, as it was identified as a constituent of a mixture of three neomycins (A−C)[52] obtained from the bacterial broth, is now better known as neamine.[53]

From neomycin B, two direct procedures to obtain (ammonium salts of) 2-deoxystreptamine (**1**) have been described (Scheme 3), either by reaction of **11** with HBr (50% yield)[54] or by heating **11** in 6 N hydrochloric acid (yield not reported).[55]

In an alternative to these two-step procedures, 2-deoxystreptamine (**1**) can also be directly obtained by complete hydrolysis of neomycin B, as first described by Georgiadis.[56] To separate **1** from the other carbohydrate constituents of neomycin, this route involves the isolation of **1** in a protected form. For example, selective *N*-protection of **1** with an acyl or urethane protective group is possible, but for spectroscopic and solubility reasons, it is most conveniently converted to a bisazide by diazotransfer. The latter transformation, first reported by Alper *et al.*,[57] converts both amines of 2-deoxystreptamine directly to azides by a Cu^{2+}- or Zn^{2+}-catalyzed diazotransfer (Scheme 4). As reported by Swayze *et al.*, [58−60] the

Scheme 4

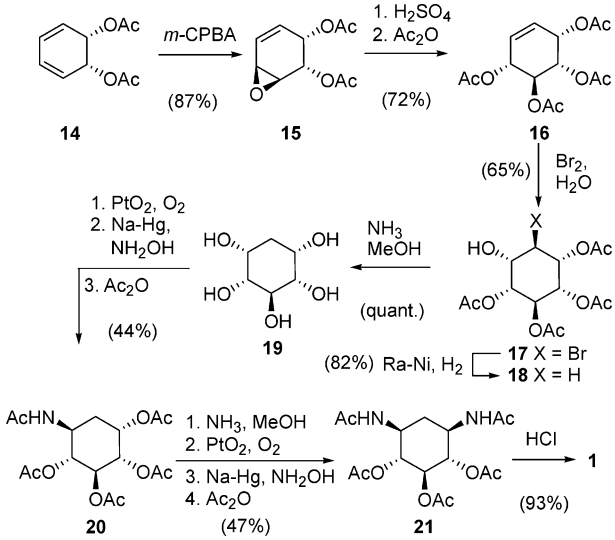


resulting triol can be selectively blocked at O-4 and O-5 with an isopropylidene group to give **12** in racemic form. Finally, protection of the 6-position with a 3-nitrobenzyl group, followed by removal of the isopropylidene group, leads to compound **13** in an overall yield of 11% for the five steps.

3.2. *De Novo* Synthesis of 2-Deoxystreptamine

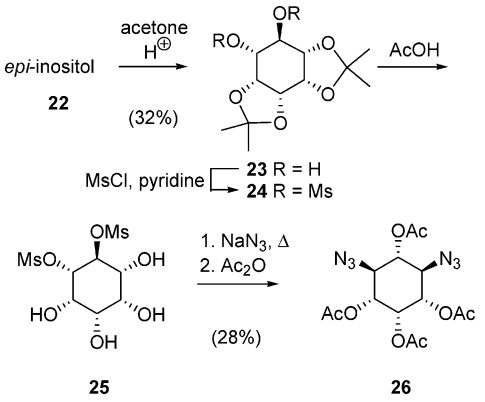
As was already apparent from Figure 4, a large variety of starting materials has been applied for the synthesis of 2-deoxystreptamine. Several of these, such as (amino)sugars and inositols, may be categorized as rather obvious due to the presence of a large number of stereogenic centers with an alcohol and/or amino functionality. A less likely choice of starting material, in the first synthetic route to 2-deoxystreptamine reported in 1964 by Nakajima *et al.*,[61−63] is 1,2-anhydroconduritol-E (**15**, Scheme 5). Compound **15**, itself readily obtained by epoxidation of diacetyl-*cis*-cyclohexadiene-1,2-diol (**14**)[64] was subjected to epoxide hydrolysis followed by acetylation to obtain tetra-*O*-acetylconduritol-F (**16**). Subsequent bromohydrin formation with bromine-water, directed by the pseudoaxial *O*-acetyl functionality, leads regio- and stereoselectively to **17**. Hydrogenolysis of **17** with Raney-nickel W-2 catalyst gives tetra-*O*-acetyl-3-deoxy-*epi*-inositol (**18**) and the fully unprotected 3-deoxy-*epi*-inositol (**19**) after aminolysis. In the next step, regioselective catalytic oxidation of one of the two axial hydroxyls with oxygen in the presence of platinum black afforded the corresponding monoketone, while formation of the corresponding diketone was negligible.[65] Hydroxylamine addition and subjection of the thus obtained oxime to sodium amalgam reduction at pH 6−6.5 gave, after acetylation, the protected amino alcohol **20**. After *O*-deacetylation, reiteration of the oxidation−oxime formation−reduction sequence gave the pentaacetyl-2-deoxystreptamine **21** and finally 2-deoxystreptamine, after deprotection with 4 N HCl and anion exchange, in 13 steps and an overall yield of 6.4% from **14**.

Scheme 5



A few years after the first synthesis, Suami *et al.* reported their efforts in the field of streptamines. Earlier studies on inositol had already provided access to streptamine (*myo*-inosa-1,3-diamine) in a synthetic route commencing with acid-catalyzed ac-

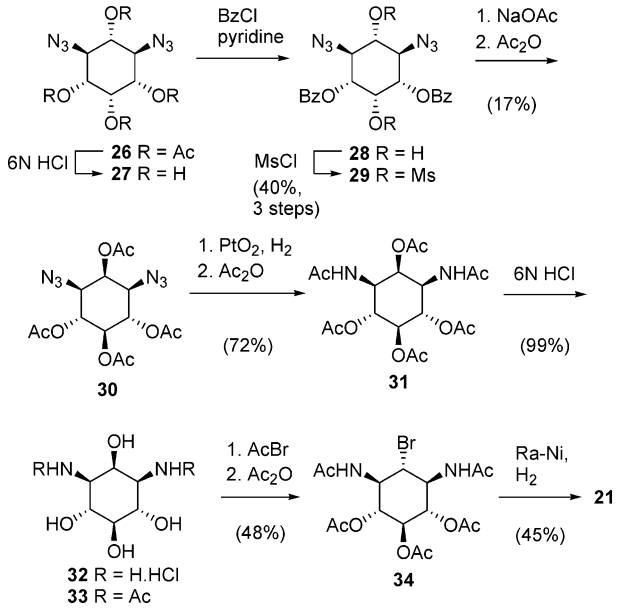
Scheme 6



etonation of *epi*-inositol (**22**, Scheme 6). After a lengthy separation of the three crystalline products that were obtained, regioisomer **23** (other products are not depicted) was reacted with methanesulfonyl chloride in pyridine to give the dimesylate **24**.[66] Isopropylidene removal by heating in acetic acid followed by reaction with sodium azide in aqueous 2-methoxyethanol under reflux for 40 h afforded, after acetylation, 4,6-diazido-4,6-dideoxy-*myo*-inositol tetraacetate (**26**) in a yield of 28% (intermediate yields are not mentioned).[67]

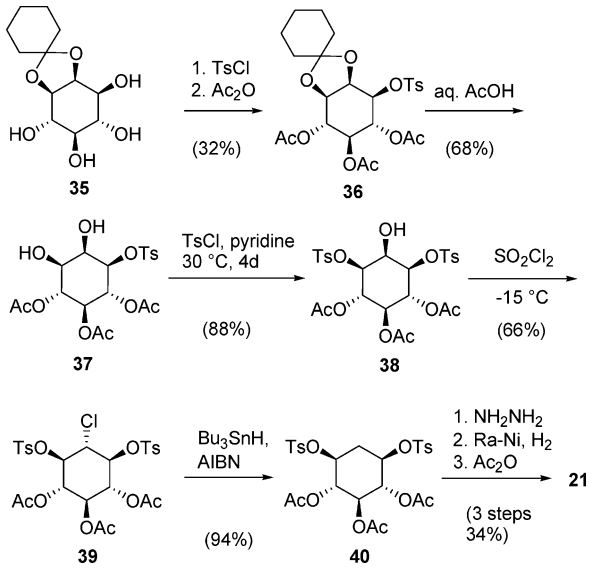
Obviously, *en route* to 2-deoxystreptamine, inositol **26** still requires deoxygenation at C-5 as well as inversion of stereochemistry at C-2. Therefore, the ester functions of **26** were hydrolyzed in refluxing 6 N HCl followed by selective di-*O*-benzoylation at low temperature, to give the 4,6-diazido-1,3-di-*O*-benzoyl-4,6-dideoxy-*myo*-inositol (**28**, Scheme 7).[68] Having

Scheme 7



gained selective access to O-2 and O-5, condensation with methanesulfonyl chloride was followed by displacement of the methanesulfonyloxy groups by acetate ions to give, after reprotection, compound **30** in a yield of 17%. Catalytic hydrogenation and subsequent acetylation to diamide **31**, followed by global hydrolysis, led to *myo*-inosadiamine-1,3-dihydrochloride (**32**).

Scheme 8

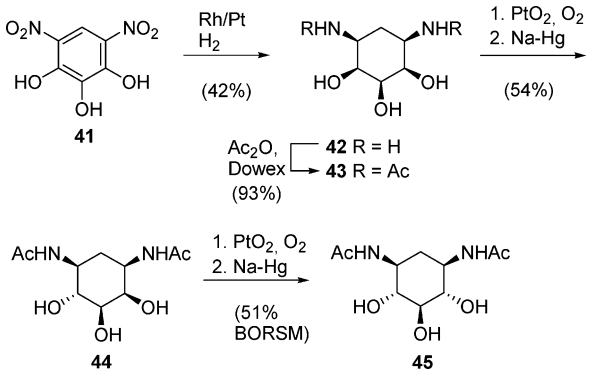


The latter compound (**32**), or the readily accessible di-*N*-acetyl derivative **33**, could be conveniently converted into 2-deoxystreptamine[69,70] in a two-step sequence. Heating with acetyl bromide, followed by acetylation, leads to **34** in 48% yield. Subsequent reductive debromination affords the pentaacetyl aminocyclitol **21**. The overall yield for the 16 steps from **26** was 0.09%.

In a similar synthesis reported by the same research group, 1,2-cyclohexylidene-*myo*-inositol (**35**)[71] was reacted with *p*-toluenesulfonyl chloride to afford, after subsequent acetylation, the monosulfonyl derivative **36** (Scheme 8).[72] Removal of the cyclohexylidene group with refluxing aqueous acetic acid (**36** → **37**),[73] followed by another monotosylation of the equatorial hydroxyl, led to 4,5,6-tri-*O*-acetyl-1,3-di-*O*-tosyl-*myo*-inositol (**38**) and finally chloride **39** upon treatment with sulfuryl chloride in pyridine.[74] Radical dechlorination with tri-*n*-butyltin hydride and α,α′-azobis(isobutyronitrile) was followed by the simultaneous introduction of both amino functionalities with hydrazine, presumably proceeding via intermediate oxiranes. Finally, reduction and acetylation gave the penta-*O*-acetyl-2-deoxystreptamine (**21**), although contaminated by 5-deoxy-2-epistreptamine (not depicted), in 8 steps and an overall yield of 4.0%.

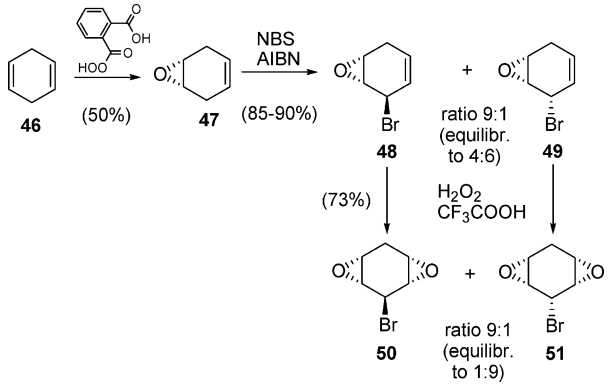
Around the same time (1968), Dijkstra[75] synthesized 2-deoxystreptamine following a completely different approach, starting from the aromatic 4,6-dinitropyrogallol (**41**, Scheme 9). Hydrogenation of **41** over a rhodium−platinum catalyst under carefully controlled pH led to a mixture of diastereoisomeric aminocyclitols. Separation of the products by column chromatography and crystallization gave as the major compound (∼50%) 2-deoxy-1,3-*cis*-inosadiamine (**42**). By selective *N*-protection, catalytic monooxidation, and stereoselective reduction with sodium amalgam in a procedure identical to that applied by Nakajima,[61,64] epimer **44** was obtained. By the same sequence of steps, **44** could be converted to *N*,*N*′-diacetyl-2-deoxystreptamine (**45**) in an overall yield of 11%.

Scheme 9



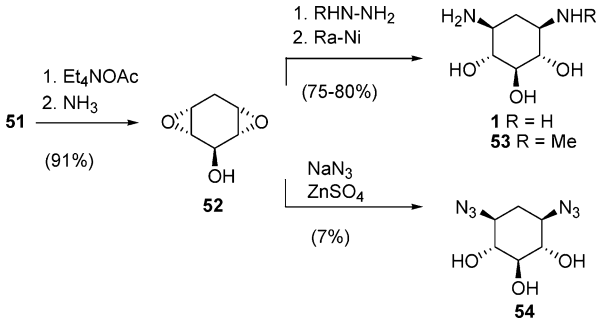
Around a decade later, Prinzbach and coworkers[76−78] reported a synthesis of 2-deoxystreptamine starting by epoxidation of 1,4-cyclohexadiene (**46**, Scheme 10) with monoperphthalic acid (**46** → **47**).[79] Subsequent allylic bromination with *N*-bromosuccinimide in CCl_4 gives a 9:1 mixture of (the rather explosive) compounds *trans*-**48** and *cis*-**49**. Although it was possible to equilibrate the latter mixture to a more desirable ∼4:6 ratio upon the action of tetrabutylammonium bromide in MeCN (or acetone), a more desirable route involved *cis*-diastereoselective epoxidation of the crude mixture of **48** and **49** with trifluoroperacetic acid. It was found that the resulting 9:1 mixture of diepoxides **50** and **51** was also amenable for equilibration under the influence of an ammonium bromide in acetone, to give the mirror 1:9 ratio of **50** to **51**.[80] The desired *all-cis*-diepoxide **51** could thus be obtained in pure form after selective crystallization from the mixture in methanol.

Scheme 10



Having the *cis*-diepoxide **51** in hand, three alternative routes were described to synthesize 2-deoxystreptamine. First, treatment of **51** with tetraethylammonium acetate in acetone led to nucleophilic substitution of the bromide and, after subsequent deacetylation, alcohol **52** (Scheme 11). Application of Suami's hydrazinolysis/hydrogenation procedure as described above gave aminocyclitol **1** in 75−80% yield. The total yield of compound **1** starting from 1,4-cyclohexadiene in 7 steps is approximately 24%. Similarly, subjection of **52** to methylhydrazine led to (±)-hyosamine (**53**), the *N*-methyl derivative of 2-deoxystreptamine, in a yield of approximately 70%. The diazidocyclitol **54** could also be obtained from **52**

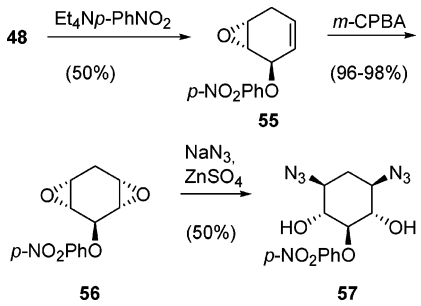
Scheme 11



by reaction with sodium azide, but in this case the overall yield is only 2.1% for the 6 steps.

A third variation on the theme provided by the same research group involves conversion of monoepoxide **48** to the *p*-nitrophenyl ether **55** with tetraethylammonium 4-nitrophenolate (Scheme 12). Subsequent stereoselective epoxidation to diepoxide **56** followed by opening of both epoxides with sodium azide led to a much improved yield of 50% and an overall yield of the protected 2-deoxystreptamine derivative **57** in 5 steps of 6.6%. Final removal of the *p*-nitrophenyl group was not reported.

Scheme 12

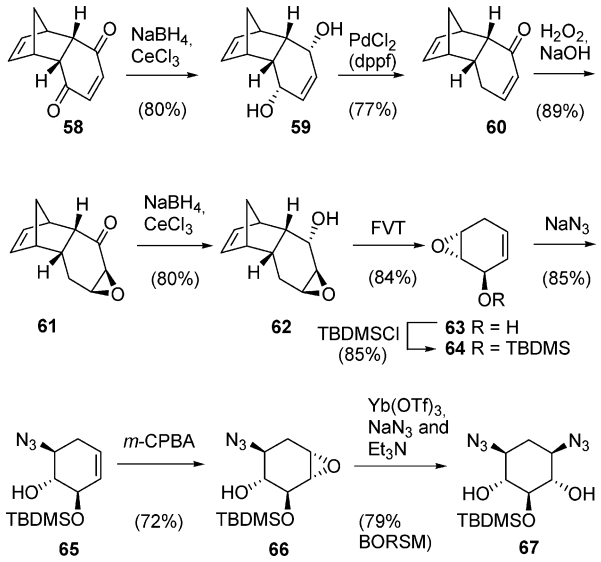


A recent contribution of our group to the field of 2-deoxystreptamine synthesis starts from the Diels−Alder adduct of cyclopentadiene and *p*-benzoquinone (**58**, Scheme 13).[81] Reduction under Luche conditions led to diol **59**, which was converted into enone **60** by a palladium(0)-catalyzed 1,4-hydrogen migration, a procedure reported by Takano *et al.*[82] Nucleophilic epoxidation of **60** to epoxide **61** (83% yield) followed by Luche reduction at −78 °C afforded alcohol **62** in a yield of 80%. Next, retro-Diels−Alder by flash vacuum thermolysis (0.04 mbar, sublimation at 80 °C, thermolysis at 600 °C) resulted in the formation of the epoxy alcohol **63** in a yield of 84%. In the following steps, the hydroxyl was protected with a *tert*-butyldimethylsilyl group and the epoxide was opened with sodium azide to form azido alcohol **65**. Electrophilic double bond epoxidation with *m*-CPBA revealed the *trans*-epoxide **66** stereoselectively (72%, 4:1 diastereoselectivity). Finally, chelation-controlled $Yb(OTf)_3$-catalyzed azidolysis[83] of the oxirane gave the protected diazidocyclitol **67** in an overall yield of 18%.

3.3. Desymmetrization

None of the syntheses of 2-deoxystreptamine discussed above led to enantiopure material. The reason

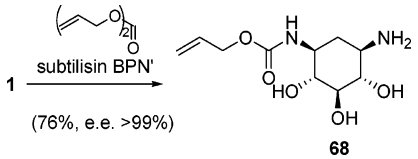
Scheme 13



for this is that, despite its five stereocenters, 2-deoxystreptamine (or any symmetrically protected variant of it) is a meso compound, due to the presence of an internal plane of symmetry (although an unlikely optical rotation of 41.8° was reported once).[56] Obviously, if synthesis of 2-deoxystreptamine itself is the prime goal, molecular symmetry makes life easier. However, if 2-deoxystreptamine is to serve as a scaffold for incorporation in an enantiopure aminoglycoside (analog), a desymmetrized variant is a prerequisite.

A most convenient approach toward an enantiopure derivative of 2-deoxystreptamine, since it is so readily obtained by hydrolysis of neomycin, involves resolution. Nevertheless, the first (enzymatic) resolution of 2-deoxystreptamine was not reported until 1996, by Orsat *et al.*,[84] and involved the conversion of *meso*-2-deoxystreptamine (**1**) into **68** through the combined action of the catalase subtilisin BPN′ and diallyl carbonate in HEPES buffer (Scheme 14).

Scheme 14

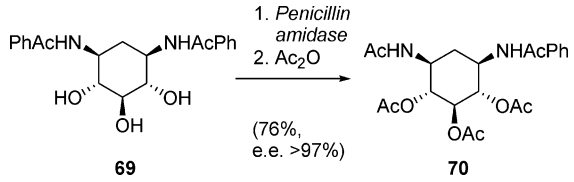


The product (**68**) was obtained (1 week, room temperature) in a yield of 76% and with excellent selectivity (>99% ee).

Nearly at the same time, another example of 2-deoxystreptamine resolution was provided by incubation of a suspension of *N*,*N*′-diphenylacetyl protected 2-deoxystreptamine (**69**) in a 4:1 phosphate buffer:DMF mixture (18 days, 25−35 °C) with *Penicillin amidase* to give, after acetylation, the *N*-acetyl-*N*′-phenylacetyl protected derivative **69** with high enantioselectivity (Scheme 15).[85]

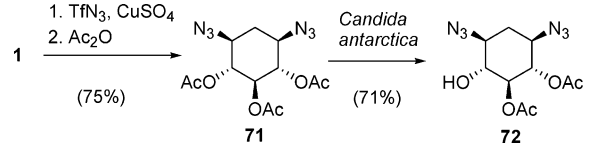
More recently, Wong *et al*. described the desymmetrization of a diazido derivative of 2-deoxystreptamine by either an enzymatic or a chemical approach.[86] Thus, 2-deoxystreptamine was converted

Scheme 15



into the diazido triacetyl derivative (**71**) by a Cu^{2+}-catalyzed diazotransfer with triflyl azide, followed by treatment with acetic anhydride (Scheme 16). Enzy-

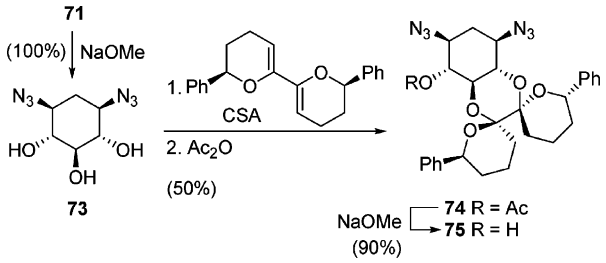
Scheme 16



matic resolution of **71** relied on enantioselective deacetylation using a resin-immobilized lipase Novozym 435 (*Candida antarctica* immobilized, Novo Nordisk), providing **72** in 71% yield (although the ee was not mentioned).

An alternative, chemical desymmetrization approach utilized the chiral dispiroketal protection−desymmetrization protocol of Ley and co-workers.[87] After deacetylation of **71**, the resulting triol **73** was treated with (2*R*,2*R*′)-bis(diphenyl)-6,6′-bis(3,4-dihydro-2*H*-pyran) (PDHP) and catalytic camphorsulfonic acid in refluxing chloroform, followed by acetylation to give **74** as the major isomer in 50% (Scheme 17).

Scheme 17



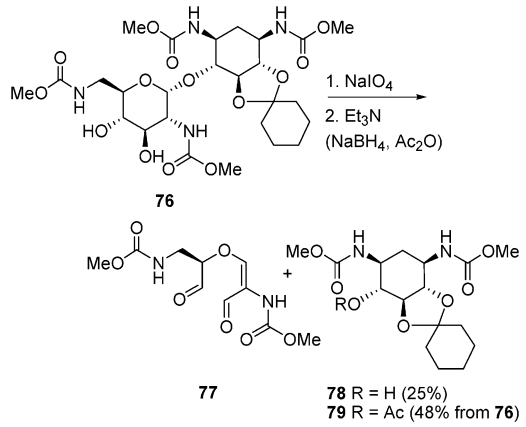
Deacetylation provided **75**, a suitable substrate for selective glycosylation at the 4-position in a dedicated synthesis of aminoglycosides, but **75** was found to be of little value as carbohydrate acceptor due the unreactivity of the (sterically hindered) free hydroxyl.

3.4. Enantiopure 2-Deoxystreptamine (Derivatives) from the Chiral Pool

Apart from strategies employing resolution, a large number of synthetic routes toward enantiopure 2-deoxystreptamine (derivatives) that have appeared in the literature are based on chiral starting materials such as neomycin,[88,91] *N*-acetyl-D-glucosamine,[95] D-mannose,[100] D-glucose,[96] and D-allylglycine.[102]

Canas-Rodriguez[88] reported the first synthesis of an asymmetric (protected) form of 2-deoxystreptamine starting from neamine (**11**). Global *N*-methoxycarbonylation of **11**, followed by regioselective introduction of a cyclohexylidene functionality, led to 5,6-*O*-cyclohexylidene-1,3,2′,6′-tetra-*N*-methoxycarbonyl-D-neamine (**76**, Scheme 18) in an overall yield of

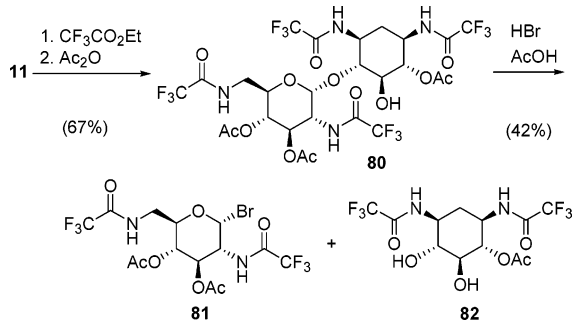
Scheme 18



49%.[88,89] Oxidative cleavage of compound **76** with sodium periodate followed by E2-elimination upon treatment of the resulting dialdehyde with triethylamine gave **78**. For reasons of purification, the crude reaction mixture was subsequently treated with sodium borohydride, after which alcohol **78** could be isolated in 25% yield or, preferably, as the acetate **79**. The overall yields starting from neomycin B are 8.7% and 17% for compounds **78** and **79**, respectively. We have adapted this methodology for the preparation of more conveniently protected *N*-Cbz protected 2-deoxystreptamine (not depicted) and found the procedure works just as well.[90]

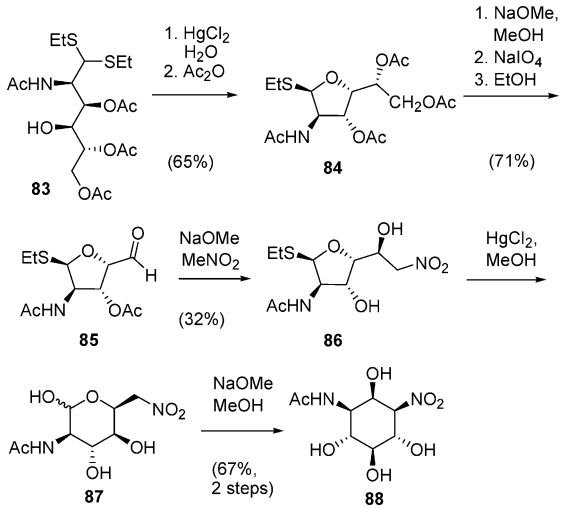
Although not aiming at 2-deoxystreptamine, Tona *et al.*[91] have shown that neamine **11**, after protection of amino functions as trifluoroacetamides, can be selectively monoacetylated at O-6 with acetic anhydride (Scheme 19). The glycosidic bond of the resulting neamine derivative **80** was hydrolyzed with HBr in acetic acid to give the glucosamino bromide (**81**) together with enantiopure protected 2-deoxystreptamine **82** in an overall yield of 28%, starting from neamine.

Scheme 19



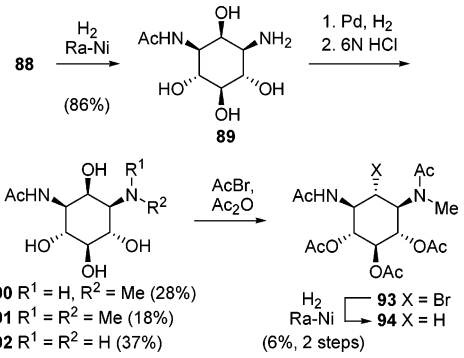
Suami *et al*. showed that (−)-hyosamine could be obtained in a procedure adapted from Wolfrom's streptamine synthesis,[92] starting from d-glucosamine (Scheme 20).[106] Thus, 2-acetamido-2-deoxy-d-glucose (**83**) was treated with mercuric chloride to give, after subsequent acetylation, diastereomerically pure compound **84**. Global *O*-deacetylation with sodium methoxide in methanol followed by oxidative cleavage of the glycol at C-5 and C-6 with sodium periodate gives after crystallization the aldehyde **85**. Henry reaction of the latter with an equimolar amount of nitromethane in the presence of sodium methoxide gave two crystalline condensation products, of which **86** is depicted. The thioethyl group was hydrolyzed with mercuric chloride, after which the crude syrup of nitrosugar **87** was dissolved in absolute methanol and treated with sodium methoxide at 0−5 °C, to give after recrystallization from methanol the pure isomer (1*S*)-1-acetamido-1,3-dideoxy-3-nitro-*myo*-inositol (**88**) in 67% yield. The stereochemistry of **88** was confirmed by hydrogenation and acetyl protection to give the corresponding hexaacetyl-*myo*-inosa-1,3-diamine (not depicted).[107]

Scheme 20



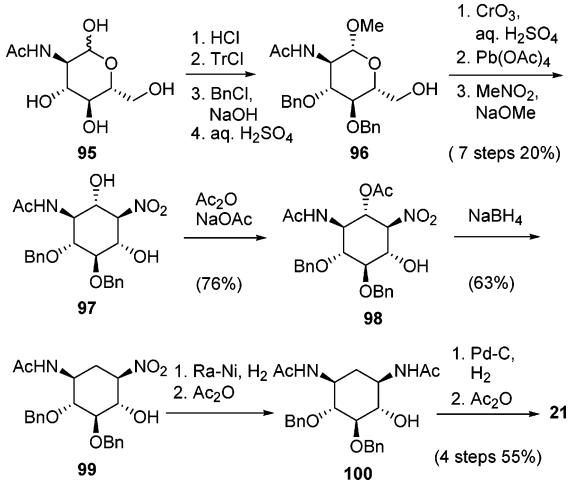
Hydrogenation of compound **88** with Raney-Ni T4 catalyst gave compound **89** (Scheme 21). *N*-Methylation was effected by hydrogenation over palladium on charcoal in aqueous formaldehyde followed by hydrolysis in hydrochloric acid to give three products **90**, **91**, and **92** in respectively 28%, 18%, and 37% yield. Racemic hyosamine was synthesized before from racemic **90,** and the synthesis shown in Scheme 21 followed the reported procedure.[93,94] First, reaction with acetyl bromide and acetic anhydride and then hydrogenation with Raney-Ni T4 catalyst and Amberlite afforded the pentaacetyl derivative of hyosamine **94** in an overall yield of 0.14%.

Scheme 21



Yoshikawa designed a route toward 2-deoxystreptamine centered around nitro-aldol reaction and a one-step elimination−reduction sequence of an acetoxy residue (Scheme 22).[95] To this end, Fisher glycosidation of *N*-acetyl-D-glucosamine (**95**) was

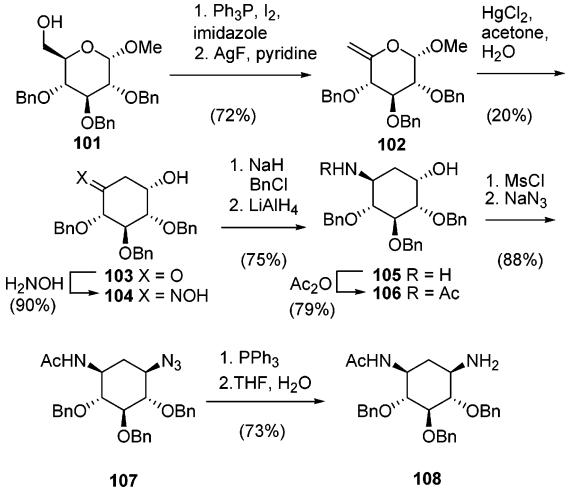
Scheme 22



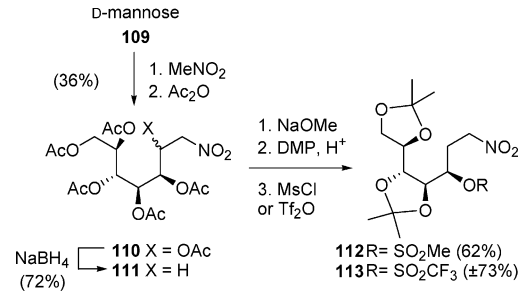
followed by selective liberation of the primary hydroxyl by trityl protection, benzylation, and acidic detritylation to give **96**. Subsequent Jones oxidation with CrO_3 with concomitant hydrolysis at the anomeric center, $Pb(OAc)_4$ cleavage of the masked glycol at O-5, O-6, and Henry reaction of the intermediate dialdehyde with nitromethane gave the all-equatorial **97** with remarkable stereoselectivity. Selective protection of the 1,2-hydroxylamide using $Ac_2O-NaOAc$ in THF was followed by $NaBH_4$-induced elimination of the acetoxy group and reduction leading to nitroaminocyclitol **99**. The overall yield of these 9 steps is 9.6%. The configurational identity of **99** was unambiguously established via reduction of the nitro group, *N*-acetylation, debenzylation, and *O*-acetylation to afford the known 2-deoxystreptamine pentaacetate **21**.

Da Silva *et al*. developed a route toward 2-deoxysteptamine which appears to be inspired by the biosynthetic pathway of 2-deoxystreptamine from D-glucose.[96,97] Oxime **104** was obtained from the α-methyl glycoside **101** via the carbohydrate−inose Ferrier rearrangement (**102** → **103**, Scheme 23).[98,99] Direct reduction of oxime **104** with $LiAlH_4$ was unsuccessful, but benzylation of the oximino group prior to reduction led to a mixture of epimeric amines along with the *O*-benzylhydroxylamine (not depicted)

Scheme 23



Scheme 24

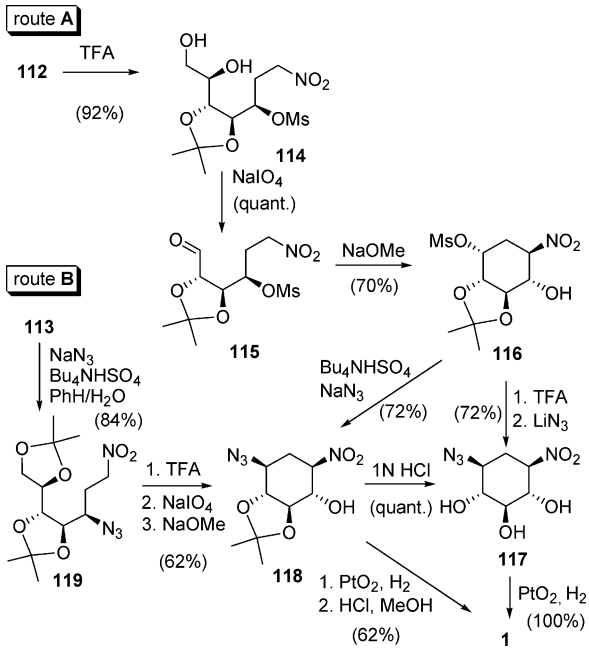


in a 90% combined yield (ratio 1:9:1). Acetylation of the desired *trans*-epimer **106** followed by conversion to the mesylate and reaction with sodium azide led to protected azido 2-deoxystreptamine **107**. Staudinger reaction with triphenylphosphine gave the protected 2-deoxystreptamine derivative (**108**) in an overall yield of 4.9% starting from protected methyl glycoside **101**.

Baer and co-workers[100] developed two (similar) routes toward enantiopure 2-deoxystreptamine analogues, both starting from D-mannose (**109**, Scheme 24). Via a known Henry reaction, D-mannose was first converted into 1-deoxy-1-nitro-D-glycero-D-galacto-heptitol hexaacetate (**110**).[101] Elimination−reduction with sodium borohydride followed by *O*-deacetylation gave the pentanol **111**, which was regioselectively acetonated. Mesylation or triflation afforded the sulfonates **112** and **113** in an overall yield from D-mannose of 20−25%.

Compounds **112** and **113** were the starting materials for two alternative routes. First of all, following route A (Scheme 25), mesylate **112** was selectively

Scheme 25

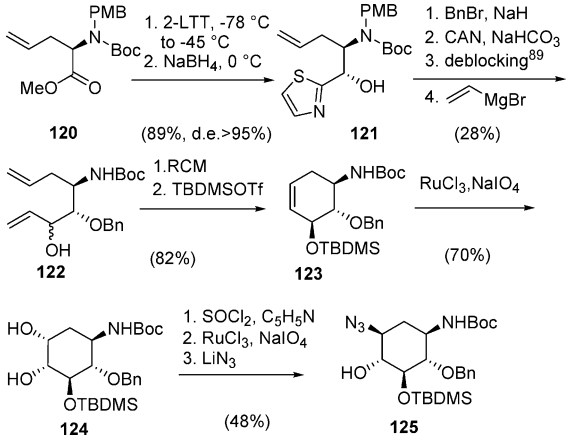


deacetonated at the 6,7-position with trifluoroacetic acid and subsequently cleaved with sodium periodate to afford compound **115**. Nitroaldol cyclization of the sugar effected by sodium methoxide in methanol led to a mixture of epimeric cyclitols that could be separated by chromatography to give predominantly

diastereomer **116** (70% yield). Conversion of **116** into **117** could be executed by two routes, either involving deacetonation with TFA prior to nucleophilic introduction of an azide (72% for 2 steps) or by reaction of **116** with sodium azide under phase transfer catalysis in benzene/water (**116** → **118**) followed by acid hydrolysis (72% yield). Unfortunately, in both cases nucleophilic displacement was accompanied by partial epimerization at the carbinol positions, necessitating tedious chromatographic separation. Final hydrogenolysis of **117** with Adam's catalyst to 2-deoxystreptamine was straightforward. The alternative route B involves the preparation of azido derivative **119** from triflate **113** prior to Henry-aldol cyclization. In similar steps as above, nitro alcohol **118** was obtained, along with its epimer, in 62% overall yield (**118** was isolated by crystallization performed under dynamic epimerization conditions). An alternative route from **118** to **1** was also presented involving hydrogenation to the 4,5-isopropylidene protected 2-deoxystreptamine **118** prior to deacetonation. The total yield for both routes starting from D-mannose is around 13%. It is of interest to note that the enantiopure alcohol **118** is potentially suitable for the preparation of aminoglycoside analogues by *O*-glycosylation.

Most recently, our group contributed a diastereoselective synthetic route to protected enantiopure 2-deoxystreptamine from D-allylglycine (Scheme 26).[102]

Scheme 26



Therefore, a thiazole moiety was introduced onto the *N*-protected methyl ester of D-allylglycine (**120**) by reaction with 2-lithiothiazole (2-LTT). Stereoselective reduction of the resulting ketone with $NaBH_4$ gave the *syn*-*β*-amino alcohol **121** with a de of >95%. After benzylation of the free hydroxyl and removal of the *p*-methoxybenzyl group with CAN, the thiazole ring was subjected to the deblocking[103] protocol to release an aldehyde that was immediately condensed with vinylmagnesium bromide to give **122** as a mixture of diastereoisomers (syn:anti = 4:1). After silica gel separation of diastereomers, ring-closing metathesis followed by protection of the free hydroxyl with a TBDMS group afforded **123**. In the following steps the double bond was dihydroxylated[104] (**123** → **124**), which occurred with exclusive facial selectivity, followed by reaction of diol **124** with thionyl chloride and oxidation to form the cyclic sulfate in 80% yield. Opening of the cyclic sulfate with lithium azide proceeded with exclusive regioselectively to give, after sulfate hydrolysis, the protected 2-deoxystreptamine derivative **125** in enantiomerically pure form in 14 steps and an overall yield of 6.1%.

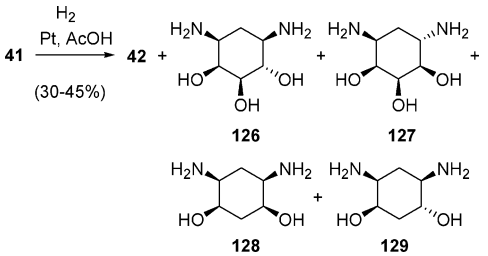
4. Synthesis of Isomeric Deoxystreptamines

It might be expected at first, given the conserved structure (and stereochemistry) of 2-deoxystreptamine in the family of aminoglycosides, that stereo- and regioisomers of 2-deoxystreptamine obtained by synthesis are in advance unlikely to be suitable scaffolds for the generation of aminoglycoside-type analogues with high RNA-affinity. On the other hand, it can never be excluded that minor variations could be of value or possibly even advantageous. The elaborate work on the synthesis of 2-deoxystreptamine as described above has concomitantly generated, intentionally or not, a large number of analogues. Besides that, a plethora of other reports have also appeared in the literature that describe the synthesis of molecules that bear a relationship to 2-deoxystreptamine varying from close to remote. We anticipated it would be of value to include in this review not only the synthesis of 2-deoxystreptamine itself but also the synthesis of stereoisomers *with the same substitution pattern*, as well as regioisomers (4-deoxy- and 5-deoxystreptamine), dideoxystreptamines, and triaminocyclohexanediols *with the same stereochemistry* as 2-deoxystreptamine.

4.1. Stereoisomers of 2-Deoxystreptamine

As was delineated in section 3.2, Dijkstra[75] synthesized 2-deoxystreptamine starting from 4,6-dinitropyrogallol (**41**, Scheme 9). Hydrogenation of **41** over a rhodium−platinum catalyst gave as the major compound (∼50%) 2-deoxy-1,3-*cis*-inosadiamine (**42**). At the same time, Baer also tried to synthesize 2-deoxystreptamine by hydrogenation. It was found that hydrogenation of 4,6-dinitropyrogallol proceeded best with platinum in 50% aqueous acetic acid and at atmospheric pressure (Scheme 27).[105] However,

Scheme 27



apart from compound **42**, two other stereoisomers of 2-deoxystreptamine (**126**, **127**) were also formed, along with two dideoxystreptamines (**128** and **129**). No 2-deoxystreptamine appeared to be produced, as was also demonstrated by Dijkstra.

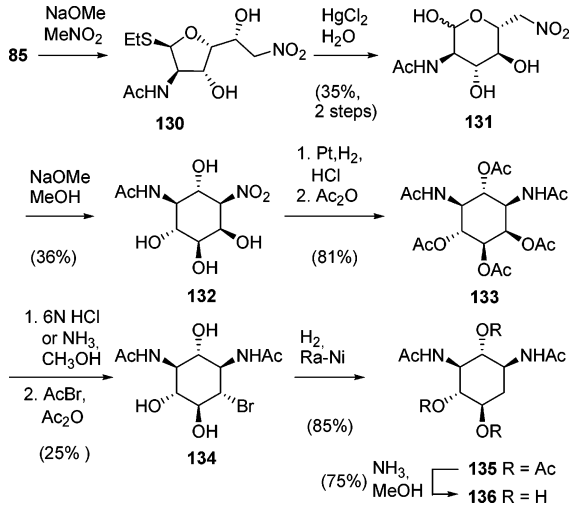
Inadvertently, in a completely different approach, a stereoisomer of 2-deoxystreptamine with all hydroxyls in the *cis*-configuration was obtained as side-product in a route followed by Suami *et al*. aiming at regioisomeric 5-deoxystreptamine and, therefore,

will be discussed in that section (compound **157**, Scheme 32).

4.2. 4-Deoxystreptamine

Derivatives of 4-deoxystreptamine (or 6-deoxystreptamine) were synthesized in a variety of manners. First of all, Suami and co-workers, in a variation of other work discussed above, started from (1*R*)-hexa-*N*,*O*-diacetyl-1,5-diamino-1,5-dideoxy-*myo*-inositol (**133**)[106] which was synthesized in 28% yield from compound **85** (Scheme 20) via (1*R*)-5-acetamido-1,5-dideoxy-1-nitro-*myo*-inositol **132** (Scheme 28).[107]

Scheme 28

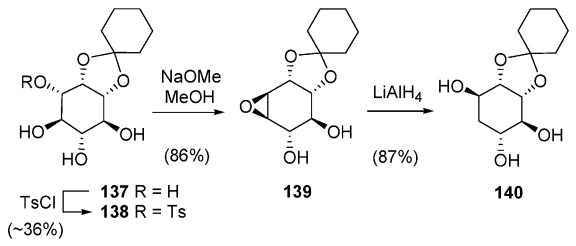


Hydrolysis of compound **133** followed by regio- and stereoselective bromination of the axial alcohol, vicinal and cis- to an amido function, with a mixture of acetylbromide and acetic anhydride gave compound **134**.

Catalytic hydrogenolysis of **134** by a known procedure followed by *O*-deacetylation afforded the pentaacetyl derivative of 4-deoxystreptamine (**135**) and the *N*,*N*′-diacetyl derivative **136**, respectively.

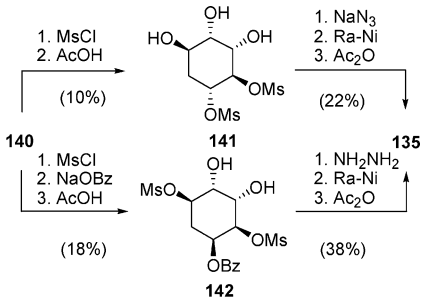
The same 4-deoxystreptamine **135** could also be obtained as a racemate from 1,2-*O*-cyclohexylidene-*myo*-inositol (**137**, Scheme 29),[108] which was converted in a few more steps into the 3,4-*O*-cyclohexylidene-1,3,4/2,5-cyclohexanepentol **140**.

Scheme 29



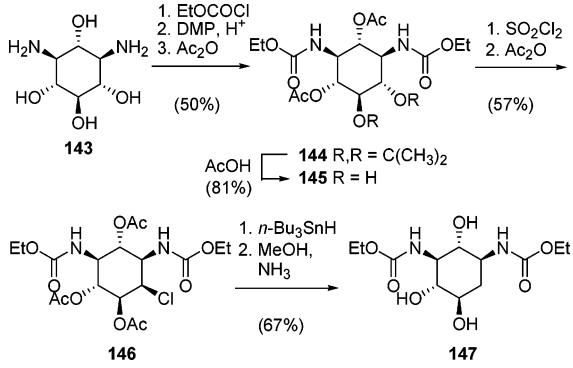
Conversion of **140** to the dimesylate and cyclohexylidene removal gave **141** (Scheme 30).[74] Treatment of **141** with excess sodium azide gave, via an intermediate epoxide, a mixture of diazidocyclohexanetriols, hydrogenation of which with Raney-nickel followed by acetylation gave the protected 4-deoxystreptamine **135** along with tri-*O*-acetyl-(1,2,3)-4,5-diacetamido-1,2,3-cyclohexanetriol (not depicted). Alternatively, the cyclohexanepentol **140** could be converted to the corresponding trimesylate and reacted with sodium benzoate before removal of the cyclohexylidene group to give the corresponding dimesylate **142** (Scheme 30). Hydrazinolysis of **142** in the usual manner, followed by hydrogenation and acetylation, then gave the protected 4-deoxystreptamine **135** as the sole crystalline product.

Scheme 30



Deoxygenation of *N*,*N*′-diethoxycarbonylstreptamine is reported to be suitable for large scale synthesis of racemic 4-deoxystreptamine, although the source of streptamine remains undefined.[74] To this end, ethoxycarbonylation of streptamine (**143**) and isopropylidene introduction gave upon acetylation the protected streptamine **144** (Scheme 31). Deacetonation followed by regioselective chlorination with sulfuryl chloride and acetylation gave rise to the chloro derivative **146**. Finally, radical dechlorination with tri-*n*-butyltin hydride/AIBN followed by deacetylation with methanolic ammonia afforded the *N*,*N*′-diethoxycarbonyl derivative **147**.

Scheme 31

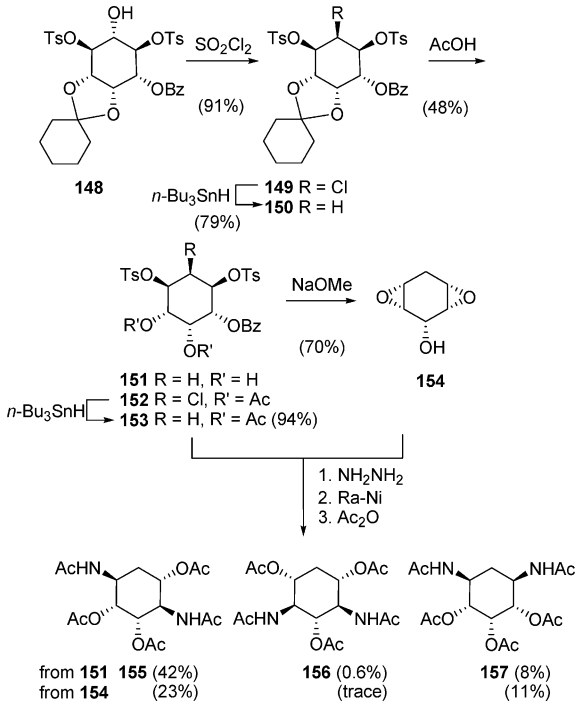


4.3. 5-Deoxystreptamine

Synthesis of the title compound was first attempted by hydrazinolysis of a ditosylate derived from *myo*-inositol (**148**). Also in this route, the electrophilic chlorination/radical dechlorination strategy is applied to give, via chlorodeoxy derivative **149**, the corresponding 2-deoxy-*myo*-inositol **150** (Scheme 32) and diol **151** by *O*-cyclohexylidene removal.[74]

By an alternative sequence of events, the di-*O*-acetyl derivative **153** could also be obtained via **152** by dechlorination in the usual way. Hydrazinolysis of **151** followed by hydrogenation and acetylation gave a mixture of **155**−**157**, in respective yields of 42%, 0.6%, and 8%. Under similar conditions, **153**

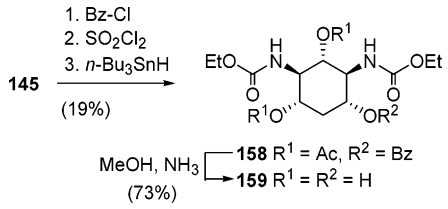
Scheme 32



could also be converted to **156**. To this end, **153** was first reacted with sodium methoxide and the intermediate **154** subjected to hydrazinolysis. After hydrogenation and acetylation, a mixture of **155** and **157** was obtained in respectively 23% and 11% yield, along with a trace of **156**. It is interesting to note that compound **157** is itself a diastereoisomer of 2-deoxystreptamine with three hydroxyls in 1,2-cis conjunction.

Since the 6-hydroxyl group of **145** (from Scheme 31) was found to be preferentially displaced by a chloride ion, selective 6-OH benzoylation was carried out first, the product of which was chlorinated and hydrogenated in the usual manner to give deoxy compound **158** (Scheme 33).[74] De-*O*-acetylation gave the *N*,*N*′-diethoxycarbonyl derivative **159**.

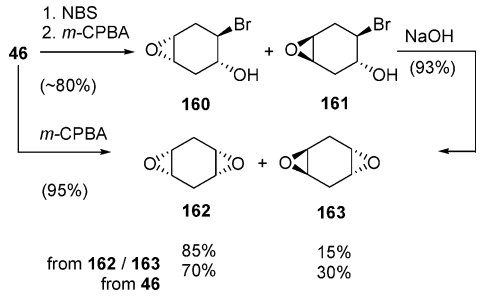
Scheme 33



4.4. Dideoxystreptamines

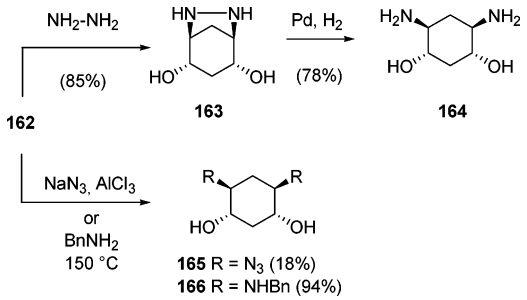
Dideoxystreptamines have been synthesized starting from 1,4-cyclohexadiene in a few different methods.[109−111] Hydrobromination of 1,4-cyclohexadiene with NBS in water produced **160** in 85−88% yield which was epoxidized with *m*-chloroperoxybenzoic acid to give a mixture of epoxybromohydrins **160** and **161** (85:15 at 0 °C). Accordingly, base-induced intramolecular bromide displacement gave predominantly *cis*-bisepoxide **162**, in 85% yield. However, direct bisepoxidation of 1,4-cyclohexadene with *m*-chloroperoxybenzoic acid turned out to be more convenient to synthesize the *cis*-bisepoxide **162**, which led to a mixture of the bisepoxides with, contrary to a previous report,[110] the *cis*-bisepoxide predominating (70%, Scheme 34).

Scheme 34



A few possibilities to open the *cis*-bisepoxide **162** are now available. First of all, hydrazinolysis followed by reduction with palladium or Raney-nickel gave the 2,5-dideoxystreptamine **164** in 78%[111] or 88%[109] yield, respectively (Scheme 35). Alternatively, the epoxide

Scheme 35



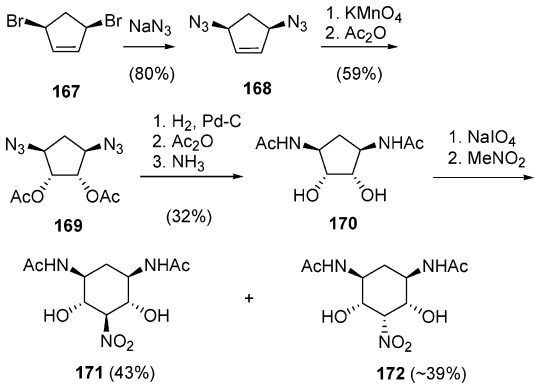
can be opened with sodium azide, but under standard conditions, only the regioisomeric 1,4-diazido-2,5-diol is formed (double *trans*-diaxial opening according to the Fürst−Plattner rule).[112] However, it was found that the use of aluminum azide in THF leads to the desired 1,3-azido isomer **165**, albeit in low yield (18%).[113] Most recently, it was reported that the 1,3-diazido analogue **165** can also be obtained by reaction of compound **164** with triflyl azide (89% yield).[114] It has also been reported that opening of bisepoxide **162** in neat benzylamine proceeds with complete 1,3-regioselectivity to amino alcohol **166**.[115]

4.5. Triaminocyclohexanediol

In contrast to all other isomers of 2-deoxystreptamine, triaminocyclohexanediols differ, as the name indicates, in the number of amino functionalities. A single example of such a structure has been reported by the group of Hasegawa[116] and has been included here because the obtained triaminocyclohexanediol (**171**) has the same symmetry and stereochemistry as 2-deoxystreptamine. In the elegant route, to well-known *cis*-dibromo-1-cyclopentene (**167**) was added sodium azide, which gave after oxidation with $KMnO_4$ and subsequent acetylation the corresponding 3,5-diazido-1,2-diacetyl-cyclopentane-1,2-diol (**169**). Hydrogenation followed by acetylation and selective removal of the *O*-acetyl groups afforded the diacetamidodiol **170**. Oxidation with $NaIO_4$ yielded

the corresponding pentanedial, which was condensed with nitromethane to give a mixture of epimers **171** and **172**. The triaminocyclohexanediol **171** was synthesized in 8 steps and an overall yield of 6.5%.

Scheme 36



5. Conclusion

The field of research on aminoglycoside analogues is rapidly expanding. The search is on for new antibiotics, new anti-HIV entities, or any new RNA-affinity drug that may be derived from a natural aminoglycoside (or bear a close similarity). A quick combined search in Chemical Abstracts on the terms "aminoglycoside" and "synthesis" clearly reveals the increase in interest in the field (Figure 5, with the number for 2004 extrapolated from August 1st). However, apart from the rapid increase in interest in synthesis in the past few years, it is interesting to observe that Figure 5 also shows a reduced interest in aminoglycoside synthesis in the late 1980s and 1990s, which reflects the attenuated interest in antibiotic research in general in that era.

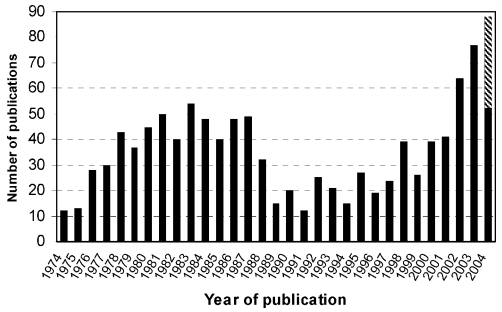


Figure 5. Number of publications on the synthesis of aminoglycosides in the period 1974−2004.

With the recent number of papers in the aminoglycoside field rapidly increasing, the omnipresence of 2-deoxystreptamine in the family indicates the high value of such an aminohexitol as a scaffold for the generation of new molecules with RNA-affinity. To take this into consideration, an efficient route to 2-deoxystreptamine may serve as a practical starting point for the assembly of aminoglycoside-type libraries in the development of novel RNA-ligands. As such, the syntheses discussed in this review are not of sole academic interest, since they lead to a valuable starting material for biological and medicinal purposes.

Table 2. Summary and Scaling of Synthesis of 2-Deoxystreptamine (Analogues)

starting cmpd	cost,[a] €/mmol	no. of steps	overall yield (%)	final cmpd	chirality[b]	suitability[c]
1[d]	20	1	76	**68**	ep	3
		3	53	**72**	ep	4
		6	34	**75**	ep	4
10	0.64	2	40	**1**	meso	1
		2	ng[e]	**1**	meso	1
		5	11	**13**	racemic	3
		1	61	**1**	meso	1
11	230	>2	<25	**78**	ep	4
		>3	<48	**79**	ep	3
		3	28	**82**	ep	4
14	0.3[f]	>14	<6	**1**	meso	1
22	396	16	0.09	**21**	meso	1
35	3	9	4	**21**	meso	1
41	6	6	11	**45**	meso	2
46	120	7	24	**1**	meso	1
		7	24	**53**	racemic	2
		6	2	**54**	meso	2
		5	7	**57**	meso	2
		>9	<18	**70**	ep	3
58	0.005	10	18	**67**	meso	3
83	0.015[g]	>13	<0.14	**94**	ep	3
95	0.1	9	10	**99**	ep	4
101	0.002[h]	>11	<5	**108**	ep	3
109	0.07	8	13	**118**	ep	4
120	6	14	6	**125**	ep	5

[a] Prices are approximate as indicated by ACD and calculated from the largest amount available. [b] ep = enantiopure. [c] Estimated generalized applicability of final compound. [d] 2-Deoxystreptamine dihydrobromide. [e] ng = not given (for all steps). [f] *cis*-3,5-Cyclohexadiene-1,2-diol. [g] D-(+)-Glucosamine hydrochloride. [h] D-Glucose.

It is apparent, however, that the above-described synthetic sequences aiming at 2-deoxystreptamine are characterized by a wide variety of strategies. Apart from that, nearly each route starts from its own unique starting material (with the exception of neomycin) and, more importantly, leads to a unique 2-deoxystreptamine analogue, rather than 2-deoxystreptamine itself, in most of the cases. In a more or less chronological order, the syntheses that led to a (protected form of) 2-deoxystreptamine are summarized in Table 2. The stereo- and regioisomers discussed in Chapter 4 are omitted.

From the table, a few observations can be readily made. First of all, by far the highest overall yield to acquire "naked" 2-deoxystreptamine is by degradation of the relatively cheap and commercially available aminoglycoside neomycin. Although the synthetic elegance of the approach is poor, with 75% of starting material degraded to waste, the ease and straightforwardness of the procedure outperform any of the *de novo* syntheses. Therefore, if plain 2-deoxystreptamine is required, acid hydrolysis of neomycin obviously is the method of choice (apart from direct acquisition of 2-deoxystreptamine).

The syntheses summarized in Table 2 start from a large diversity in starting material, both in structure and in price. However, for cost-effective synthesis of 2-deoxystreptamine, or an analogue thereof, the price of the starting material is only one of the factors to be taken into consideration. Apart from that, the number of synthetic steps, costs of reagents and purification, intermediate yields, and applicability to large scale are only some of the additional factors

that define the value of a synthetic sequence. Because it lies out of our expertise to provide such an estimate, we have only provided the total number of steps and overall yields, which at least partly reflects the simplicity and applicability of a particular route.

The true value of the 2-deoxystreptamine analogues for further application is and cannot be expressed in a number. Obviously, naked′ 2-deoxystreptamine or a symmetrically protected variant thereof can be readily obtained, but the practicality of these meso compounds (or any other analogue) depends entirely on an individual's particular goal. We have attempted to roughly categorize the final products on a scale of 1−5, based on two aspects: (a) is the final product meso or is it an enantiopure analogue (or direct precursor) of 2-deoxystreptamine and (b) what is the level of orthogonal protection of the three hydroxyls and two amino groups? First, application of a meso compound still necessitates resolution, which may not always be obvious or simple and is therefore scaled with a maximum of 3. The second argument is weighed here as well because a higher level of differentiation between functional groups allows maximal convergence in any synthesis requiring selective substitution at a defined position. Ease of heteroatom differentiation at a later stage, the number of steps to do so, and ease of deprotection are also considered. Although we are aware that such an estimate is highly subjective, it does provide some insight into the general applicability of a given final product for practical purposes. Obviously, the true value of the here described final 2-deoxystreptamine derivatives as starting materials for further application depends entirely on an individual's specific demands.

6. List of Abbreviations

Ac	acetyl
ACD	Available Chemicals Directory
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	2,2′-azobis(isobutyronitrile)
aq	aqueous
AAC	aminoglycoside acetyltransferases
AAD	aminoglycoside adenylyltransferases
ANT	aminoglycoside adenylyltransferases
APH	aminoglycoside phosphotransferases
Bn	benzyl
BORSM	based on recovered starting material
*btr*C	gene in *Bacillus circulans*
Bz	benzoyl
°C	degrees Celcius
CAN	ceric ammonium nitrate
CSA	camphorsulfonic acid
CH_2Cl_2	dichloromethane
Cbz	benzyloxycarbonyl
compd	compound
d	days
de	diastereomeric excess
DMAP	4-(dimethylamino)pyridine
DMP	2,2-dimethoxypropane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DOI	2-deoxy-D-*scyllo*-inosose
DOIS	2-deoxy-*scyllo*-inosose synthase
ee	enantiomeric excess
ep	enantiopure
et al.	et alia
Et_2O	diethyl ether
FVT	flash vacuum thermolysis
h	hours
HIV	human immunodeficiency virus
LTT	2-lithiothiazole
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
mRNA	messenger ribonucleic acid
N	normal (equivalents per liter)
NAD	nicotinamide adenine dinucleotide
NADH	reduced NAD
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
Ra-Ni	Raney nickel
RCM	ring-closing metathesis
RRE	Rev response element
rt	room temperature
TBDMS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

7. Acknowledgment

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