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Selective reactions of reactive amino groups in polyamino compounds by metal-chelated or -mediated methods

So Ha Lee and Chan Seong Cheong*

Life Sciences Division, Korea Institute of Science and Technology, #39-1, Hawolkok-dong, Seongbuk-ku, Seoul 136-791, South Korea

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Contents

1. Introduction

Methods for the selective protection of polyamino groups in organic compounds are of great importance in organic synthesis. When a chemical reaction is to be carried out selectively at one reactive site in a compound having multifunctional groups, the other reactive sites must be temporarily blocked and become nonreactive. For compounds having a difference in reactivity between an amino group and a hydroxyl moiety, general protecting groups such as carbamates, or amide and imine derivatives are of value, but they have a more limited use for those compounds having two primary amines, or one primary-one secondary amine, and over two amino groups. The selective reactions of amines have been hampered by difficulties in differentiating between the reactivities of the functional groups.

Overcoming this problem, various methods have been introduced to provide an efficient means of conventional chemical reagents,[1–4] including metal-chelated or -mediated techniques and enzymatic methods.[5–6] We have investigated a number of methods for the selective reactions of polyamine groups and will now review those which are metal-chelated or -mediated, excluding the examples which use metal compounds as a simple base.

2. Selective reactions of polyamino compounds by metal-chelated or -mediated methods

2.1. Selective reactions of polyamines in aminoglycosides

Aminoglycosides[7–14] are potent bactericidal antibiotics that act by creating fissures in the outer membrane of the bacterial cell. They are practically active against aerobic, gram-negative bacteria and act synergistically against certain gram-positive organisms. The first aminoglycoside, streptomycin,[15] was isolated from *Streptomyces griseus* in 1943. Gentamicin, isolated from *Micromonospora purpurea* in 1963, was a breakthrough in the treatment of gram-negative bacillary infections. Other aminoglycosides have subsequently been developed, including sisomicin, netilmicin, isepamicin and arbekacin, and these are all currently available for systemic use worldwide.

The relative reactivity of the amine groups in the aminoglycoside antibiotics is pH dependent. Although the C_6-amino group of sisomicin is more reactive, the C_1-amino group reacts more selectively at low pH. As the pH of the reaction mixture is increased, the selectivity is lost and mixtures are obtained. This method therefore only gives the product in a low yield.

* Corresponding author. Fax: +82-02-958-5189; e-mail: c2496@kist.re.kr

Abbreviations: All, allyl; AZ, 4-Azidomethylenoxybenzyloxycarbonyl; Bn, benzyl; Cbz-NOS, *N*-(Benzyloxycarbonyloxy)succinimide; Cbz (Z), Benzyloxycarbonyl; Cbz-NOP, *N*-(Benzyloxycarbonyloxy)phthalimide; DIBAL-H, Diisobutylaluminum hydride; DME, Dimethoxyethane; NDMBA, *N,N'*-Dimethylbarbituric acid; HSAB, Hard-soft acid base; PMZ-S-DMP, *S*-(*p*-Methoxybenzyloxycarbonyl)-4,6-dimethylpyrimidinethiol; Ses, [2-(Trimethylsilyl)ethyl]sulfonyl; Su; Succinimide; TCEC-NOS, *N*-(2,2,2-Trichloroethoxycarbonyloxy)succinimide.

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In 1978, Nagabhushan et al.[16] and Hanessian et al.[17] simultaneously reported that in polyamino-organic compounds, especially aminoglycosides and carbohydrates, divalent transition metal salt complexes of neighbouring amino-hydroxy group pairs could be formed selectively and transformed a free amino group into selective *N*-derivatives without protection of the amino group under appropriate reaction conditions. Both vicinal and nonvicinal hydroxy-amino group pairs may be formed as reversible complexes with divalent transition metal cations such as copper(II), nickel(II), cobalt(II), cadmium(II) or with their mixtures and the extent to which the cationic complexes are formed is dependent on the type of transition metal, the availability of the pairs for complexing, the stability of the complex, and the protic or aprotic nature of the solvent. The chelation mode is dependent upon the type of aminoglycosides. A typical example of complex formation of sisomicin **1** with the Zn^{2+} ion is shown in Scheme 1. The 1-NH_2 and 2′-OH group or the 3′-$NHCH_3$ and 4′-OH group were chelated with Zn^{2+} ion to lessen the reactivity of these amino groups towards electrophiles and the reactivity of the 3-, 2′- and 6′-NH_2 groups was preserved to give selective *N*-derivatives (Scheme 1).

With an aprotic solvent, the equilibrium favours the formation of a transition metal salt complex of the aminoglycoside, while a protic solvent favours decomplex at ion (Scheme 2).

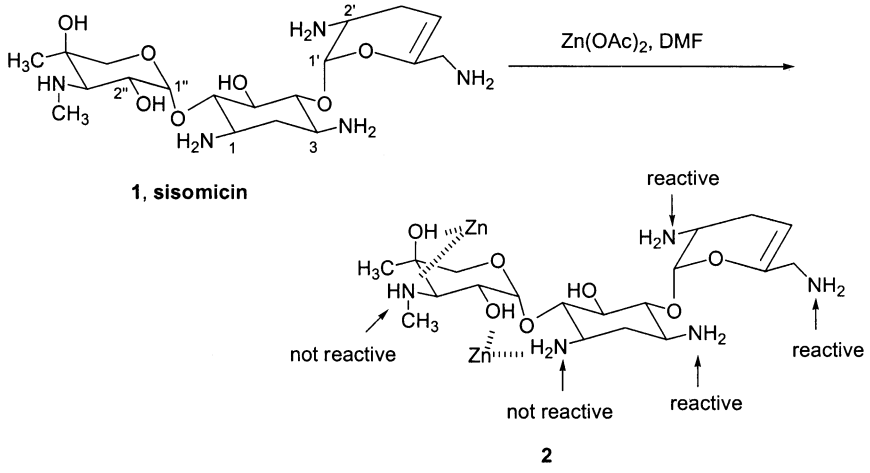
Apramycin **3** was treated with $Ni(OAc)_2$ and *N*-(benzyloxycarbonyloxy)succinimide (Cbz-NOS) to give 2′-*N*-Cbz-apramycin **4** in 82% yield, while at $Cu(OAc)_2$ and $Zn(OAc)_2$, gave 3-*N*-Cbz-apramycin **5** and 1-*N*-Cbz-apramycin **6**, in 87% and 31% yield, respectively (Scheme 3).[18]

Acylation of 6′-*N*-Cbz-nebramine **7** yielded 1,6′-di-*N*-Cbz-nebramine **8** with $Zn(OAc)_2$, 3,6′-di-*N*-Cbz-nebramine **9** with $Cu(OAc)_2$, and 2′,6′-di-*N*-Cbz-nebramine **10** with $Ni(OAc)_2$ (Scheme 4).[18]

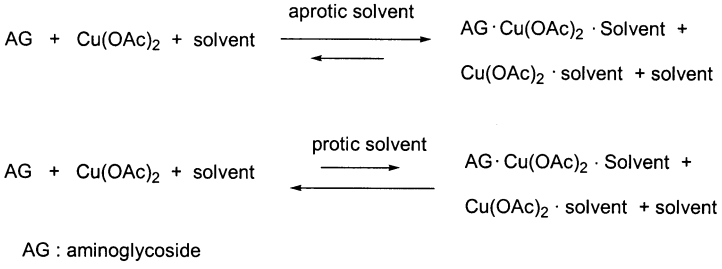
The vicinal and nonvicinal amino-hydroxy group pairs of sisomicin, gentamicin and kanamycin formed reversible complexes with divalent transition metal cations such as copper(II), nickel(II), cobalt(II), cadmium(II) or with their mixtures to selectively furnish the protected aminocyclitols in high yield as shown in Table 1.[16]

According to the reaction solvent and the type of transition metal, selective *N*-acylation of aminoglycosides has largely been made at sites selected for their stereochemical properties as shown in Table 2.[17,19,20,21]

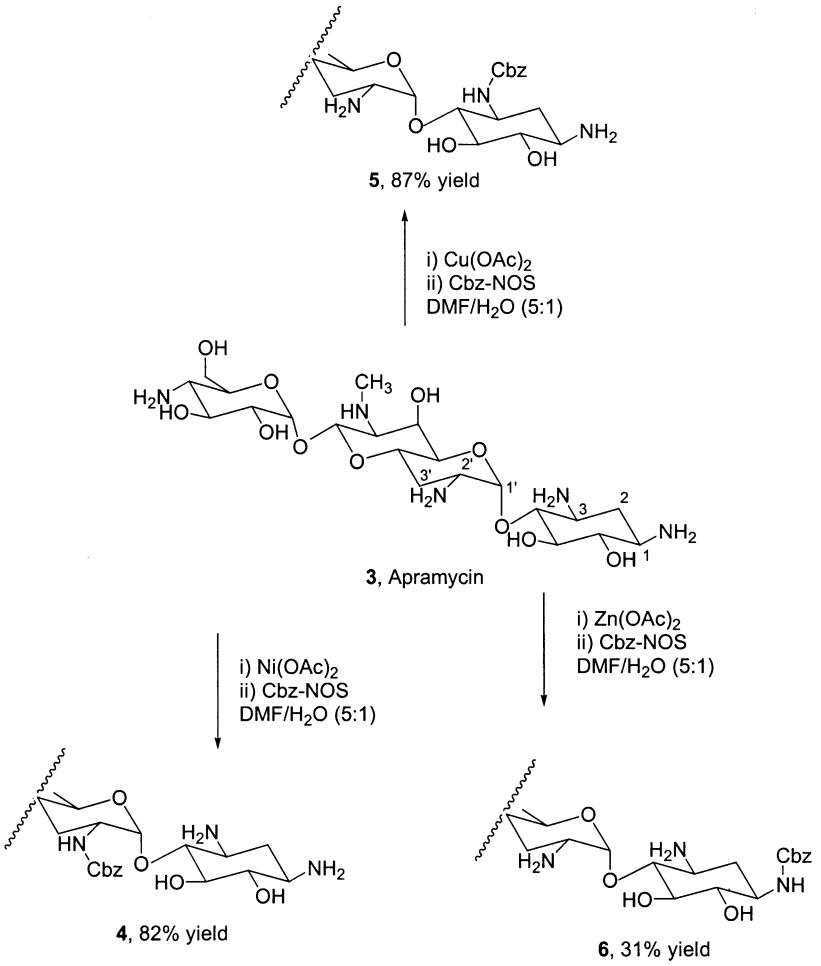
Amino acid derivatives of kanamycin A **11** and netilmicin **15** were obtained by selective functionalization of the amino groups via temporary complexation of the vicinal or non-vicinal amino and hydroxy functions by copper(II) ions (Scheme 5).[22]



Scheme 1.



Scheme 2.



Scheme 3.

2.2. Selective reactions of polyamines in polyazamacrocycles

Metal complexes[23] of some polyazamacrocycles or regioselectively functionalized polyazamacrocycles have found applications as radioimmunotherapeutic agents,[24] in vivo NMR shift reagents, radiopharmaceuticals,[23,24] and luminescence probes.[25] The synthesis of polyazamacrocycles has been extensively reviewed.[26–28] Selectively substituted macrocycles are, however, more complicated to prepare and necessitate several steps. Direct methods,[29–31] pH-controlled selective reactions[32,33] and metal-chelated or -mediated methods have been used in their syntheses. The metal ion plays an important role in directing the steric course of the reaction by a metal template effect.[34]

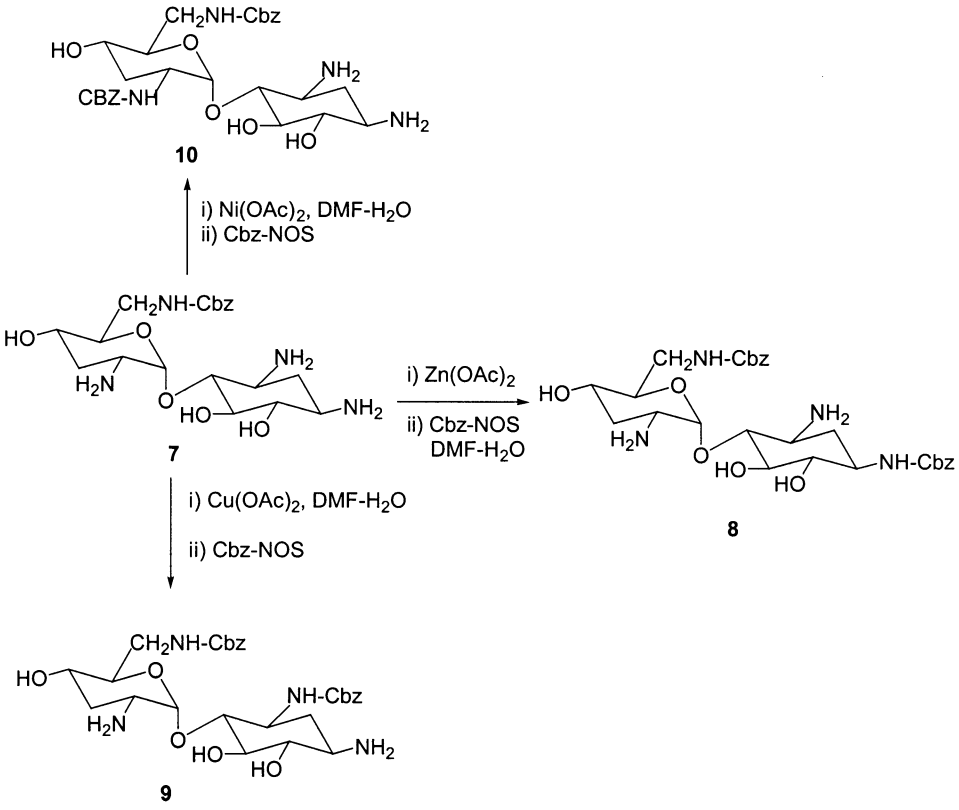
In 1991, Yaouanc et al.[35] reported that prior complexation of the polyazamacrocycle **17** by reaction with chromium hexacarbonyl would give tridentate complexes **18**, allowing one nitrogen atom to be free from coordination for a further selective monoalkylation. These workers additionally described the syntheses of mono *N*-substituted derivatives of cyclam, cyclen and some other tetraazamacrocycles which were achieved by the use of borane compounds (Scheme 6).[36]

The Cu^{2+} complex with the polyazamacrocycle **23**[37] gave a series of pH-dependent equilibria in aqueous solution, in which at a high pH one amino group of the side chain is axially coordinated to the metal ion, while the second NH_2 remains free, and a selective acylation was possible (Scheme 7).

Cyclam **27** was refluxed with a diethylaminotrialkylstannane in dichloromethane to afford the novel macrocyclic compound **28** (Scheme 8)[38] in 77% yield. The trialkyltin derivative was thought to act not only as a base but also as a Lewis acid coordinated at the *N1* and the *N11* atoms.

2.3. Selective reactions of polyamines in other compounds

The well known polyamines such as putrescine, spermidine and spermine[39,40] are widely distributed throughout the plant and animal kingdoms. Besides their presence in the native form as the free aliphatic bases, the common polyamines often°Ccur conjugated with sugars, steroids, phospholipids and peptides, and as substructural units within numerous families of plant alkaloids. Many of these more elaborate structures exhibit a variety of important biological functions such as the stabilization of DNA through electrostatic and hydrogen bonding interactions and cell divisions.[41] Spermidine analogues have diverse biological profiles



Scheme 4.

Table 1. Syntheses of selectively *N*-protected aminoglycosides via transition metals[16]

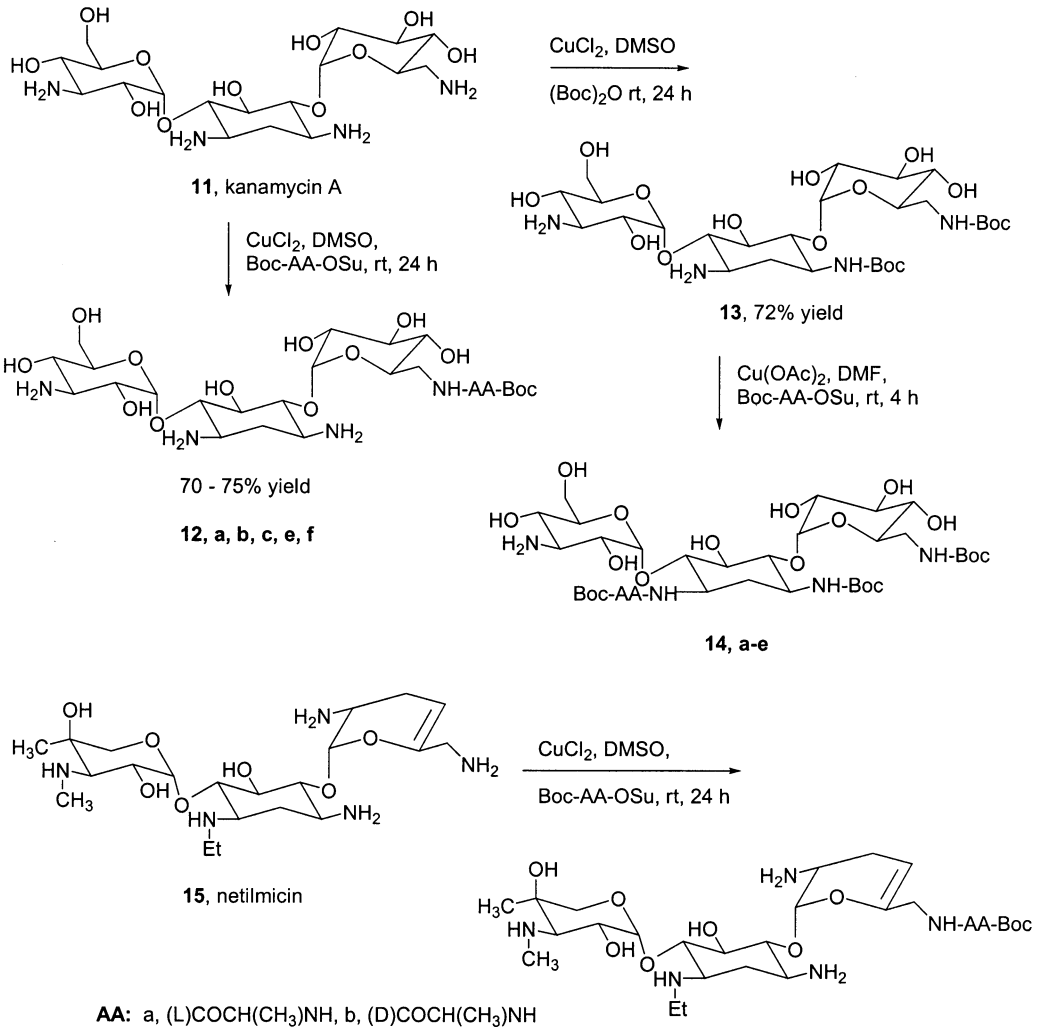
Aminoglycoside —(transition metal, DMSO)→ Aminoglycoside derivative

Entry	Starting compound	Product	Reagent	Yield (%)
1	sisomicin	3,2′,6′-tri-*N*-acetylsisomicin	i)$Co(OAc)_2{\cdot}4H_2O$, Ac_2O, 2 h. ii) H_2S	95
2	sisomicin	3,2′,6′-tri-*N*-TCEC-sisomicin	$Co(OAc)_2{\cdot}4H_2O$, TCEC-NOS	95
3	sisomicin	3,2′,6′-tri-*N*-Cbz-sisomicin	$Cu(OAc)_2{\cdot}H_2O$+$Ni(OAc)_2$, Cbz-NOP	70
4	sisomicin	3,2′,6′-tri-*N*-Cbz-sisomicin	$Co(OAc)_2{\cdot}4H_2O$, Cbz-NOP	95
5	sisomicin	3,2′,6′-tri-*N*-PMZ-sisomicin	$Co(OAc)_2{\cdot}4H_2O$, PMZ-S-DMP	88
6	gentamicin	3,6′-di-*N*-PMZ-gentamicin B	$Co(OAc)_2{\cdot}4H_2O$, PMZ-S-DMP	95
7	gentamicin C_{1a}	3,2′,6′-tri-*N*-Cbz-gentamicin C_{1a}	$Cu(OAc)_2{\cdot}H_2O$+$Ni(OAc)_2$, Cbz-NOP	81
8	gentamicin C_{1a}	3,2′,6′-tri-*N*-Cbz-gentamicin C_{1a}	$Cu(OAc)_2{\cdot}H_2O$+$Ni(OAc)_2$, Cbz-NOP	78
9	gentamicin C_2	3,2′,6′-tri-*N*-Cbz-gentamicin C_2	$Cu(OAc)_2{\cdot}H_2O$+$Ni(OAc)_2$, Cbz-NOP	81
10	gentamicin C_1	3,2′,6′-tri-*N*-Cbz–gentamicin C_1	$Cu(OAc)_2{\cdot}H_2O$+$Ni(OAc)_2$, Cbz-NOP	74

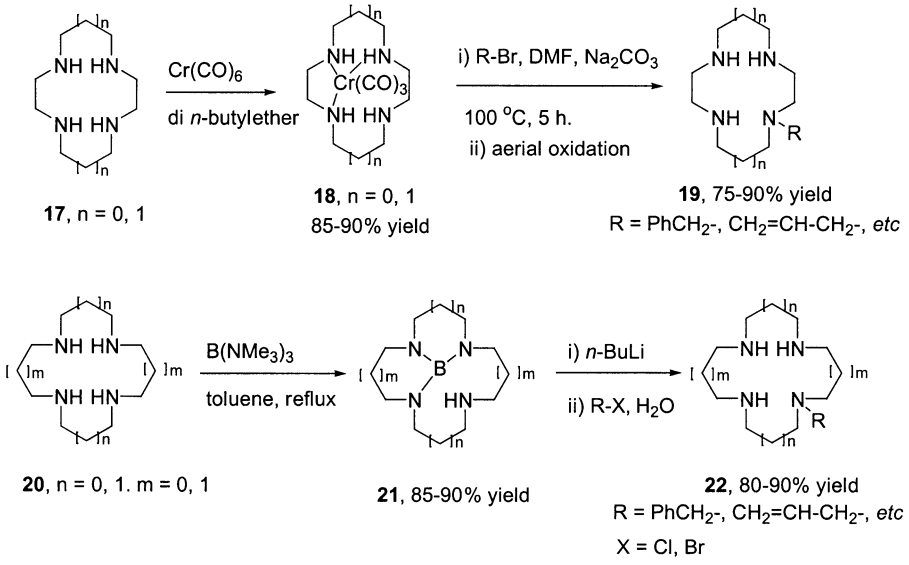
Table 2. Syntheses of selectively *N*-protected aminoglycosides by changing the reaction solvent and the transition metal

Aminoglycoside —(transition metal)→ Aminoglycoside derivative

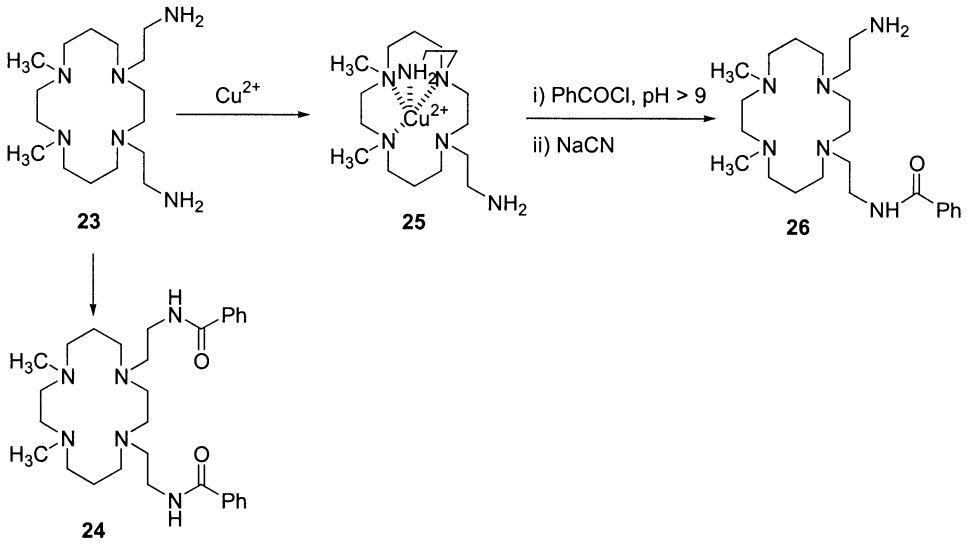
Entry	Starting compound	Product	Reagent	Yield (%)	Ref.
1	kanamycin A	6′-*N*-acetylkanamycin A	$Cu(OAc)_2{\cdot}H_2O$, aq. THF, *p*-nitrophenylacetate	82%	17
2	kanamycin A	6′-*N*-Cbz-kanamycin A	$Cu(OAc)_2{\cdot}H_2O$, aq. THF, *p*-nitrophenylcarbonate	73%	17
3	kanamycin A	1,3,6′-tri-*N*-acetylkanamycin A	$Cu(OAc)_2{\cdot}2H_2O$, aq. $NaHCO_3$-THF, Cbz-NOS	83%	17
4	kanamycin A	1,3,6′-tri-*N*-Cbz-kanamycin A	$Cu(OAc)_2{\cdot}2H_2O$, aq. $NaHCO_3$-THF, Cbz-NOS	84%	17
5	sisomicin	3,2′,6′-tri-*N*-acetylsisomicin	$Cu(OAc)_2{\cdot}2H_2O$, Ac_2O, DMF, 1 h, rt	75%	19
6	sisomicin	3,2′,6′-tri-*N*-acetylsisomicin	$Co(OAc)_2{\cdot}4H_2O$, Ac_2O, DMF, 1 h, rt	87%	19
7	sisomicin	3,2′,6′-tri-*N*-acetylsisomicin	$Co(OAc)_2{\cdot}4H_2O$, Ac_2O, DMSO, 1 h, rt	95%	19
8	kanamycin A	3,2′,6′-tri-*N*-*t*-Boc-kanamycin A	$Co(OAc)_2{\cdot}4H_2O$, Ac_2O, DMSO, 1 h, rt	73%	20
9	dibekacin	3,2′,6′-tri-*N*-Cbz-dibekacin	$Zn(OAc)_2{\cdot}2H_2O$, DMSO, Cbz-NOS, 1 h, rt	85%	21
10	kanamycin A	3,6′-di-*N*-Cbz-kanamycin A	$Zn(OAc)_2{\cdot}2H_2O$, DMSO, Cbz-NOS, 1 h, rt	82%	21



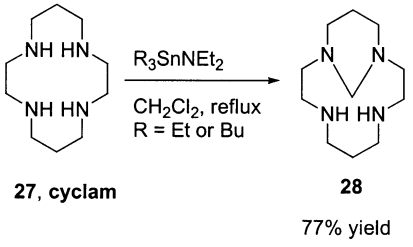
Scheme 5.



Scheme 6.



Scheme 7.

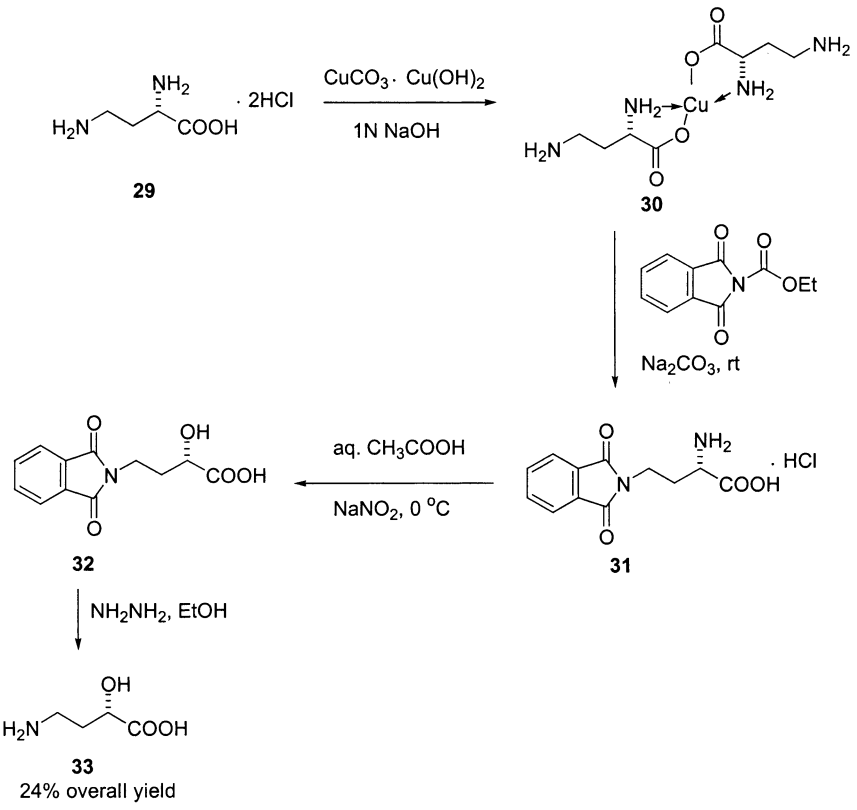


Scheme 8.

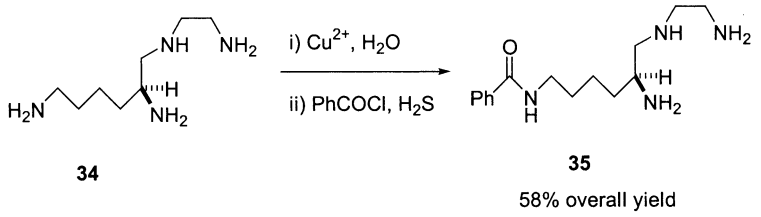
such as antibiotics, and tumor-inhibitory,[42] antihypertensive and anti-ulcer activity.[43]

Several drugs acting as antihypertensive,[44,45] anti-asthmatic agents,[46] calcium antagonist[47] or potent thrombin inhibitors contain a piperazine moiety. In addition to the above-mentioned examples, many polyamino compounds have been found to have pharmaceutical activities.[48,49]

(*S*)-4-Amino-2-hydroxy-*n*-butyric acid (**33**) is not only an



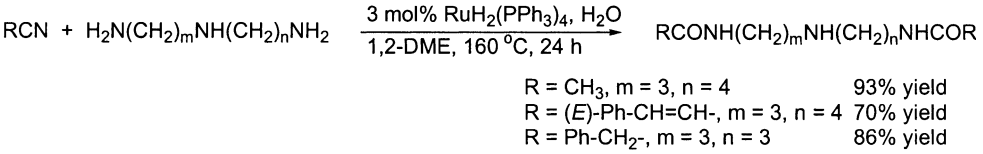
Scheme 9.



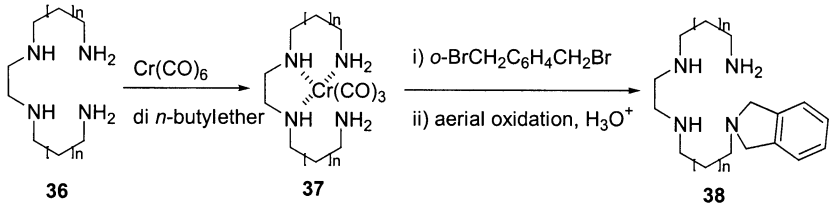
34 **35**

58% overall yield

Scheme 10.

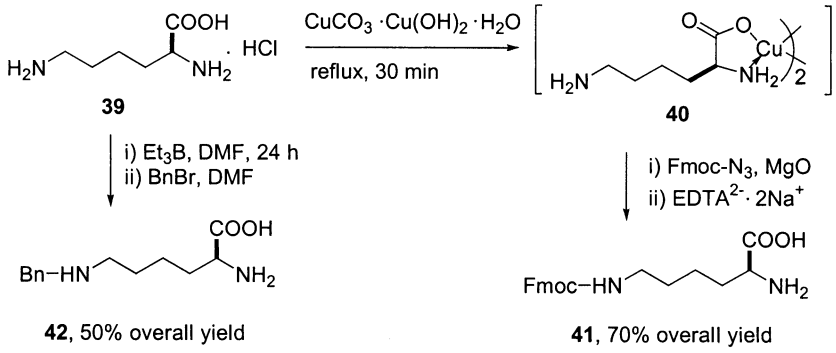


Scheme 11.



36 **37** **38**

Scheme 12.

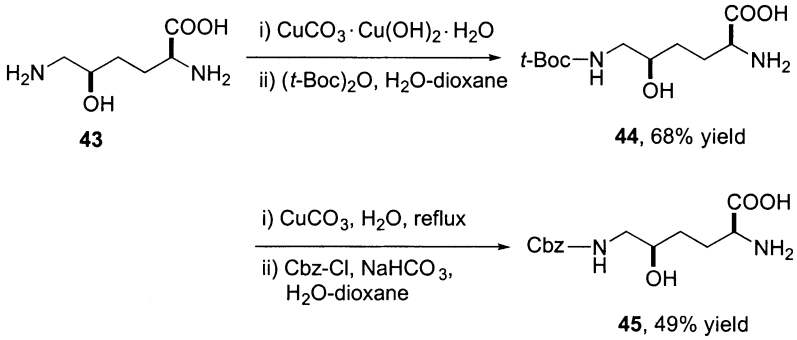


39 **40**

42, 50% overall yield

41, 70% overall yield

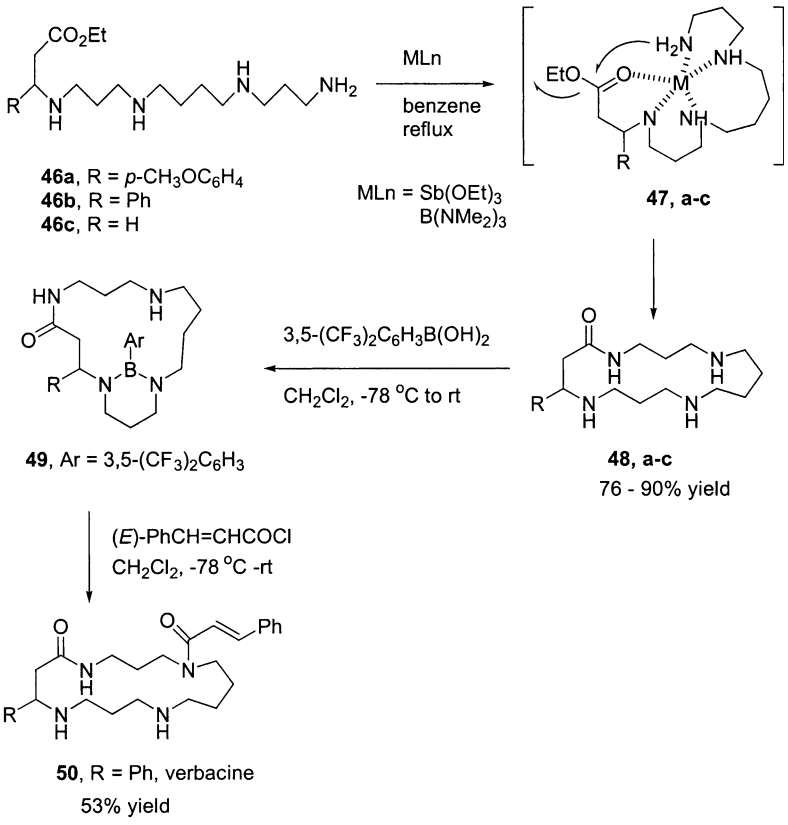
Scheme 13.



43 **44**, 68% yield

45, 49% yield

Scheme 14.



Scheme 15.

amikacin moiety[50] but is also a valuable compound in chemical modification studies of aminosugar antibiotics. (*S*)-2,4-Diaminobutyric acid (**29**) was converted to its copper salt **30** in order to protect the α-amino group by chelate formation and (*S*)-4-amino-2-hydroxybutyric acid (**33**) was synthesized as shown in Scheme 9 in 24% overall yield.[51]

It has been reported that the tetraamine **34** was protected by complexation with copper(II) in aqueous media, thereby permitting selective acylation of the remote primary amino group with benzoyl chloride to give the compound **35** in an overall yield of 58% (Scheme 10).[52]

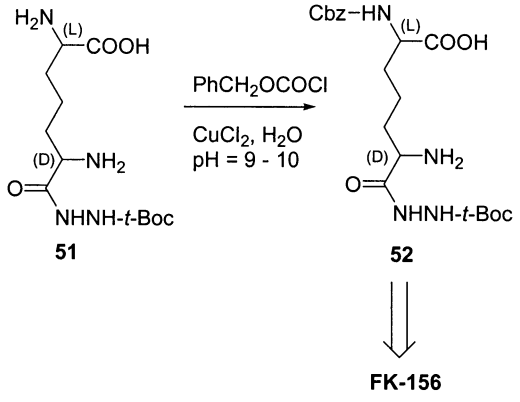
In 1986, Murahashi et al.[53,54] showed that nitrile compounds underwent condensation with spermidine using a ruthenium catalyst to give *N*1,*N*8-bisacetylspermidine and bis(phenylacetyl)spermidine in 93% and 86% yield, respectively, after chromatographic separation (Scheme 11).[53] Maytenine[55] has been prepared using this method by the reaction of *trans*-cinnamonitrile with spermidine in 70% yield.

It was reported that, if tetramines **36** were refluxed under nitrogen with $Cr(CO)_6$ in di-*n*-butyl ether at 142°C, followed by alkylation of the complexes **37** with *m*-dibromoxylenes, the mono-derivatived tetramines **38** were formed (Scheme 12).[35]

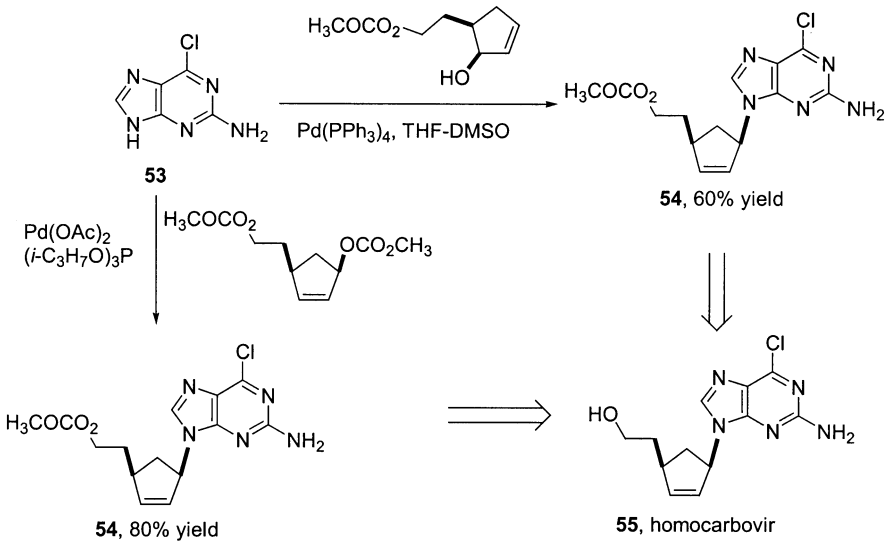
Studies with lysine **39** have shown that selective reaction may be achieved by the formation of a copper(II) complex **40**, which reacted with fluorenylmethoxycarbonyl azide (Fmoc-azide) and underwent decomplexation with ethylenediamine tetraacetic acid disodium salt to give N^{ϵ}-Fmoc-lysine **41**.[56] Lysine also reacted with Et_3B in DMF to form a 5-membered boroxazolidone complex followed by selective formation of N^{ϵ}-benzyl-lysine **42** using benzyl bromide in DMF (Scheme 13).[57]

(5*R*)-Hydroxy-L-lysine **43** was converted to a selectively protected lysine derivative **44** and **45** in 68% and 49% yield, respectively, via the formation of a cupric chelate (Scheme 14).[58]

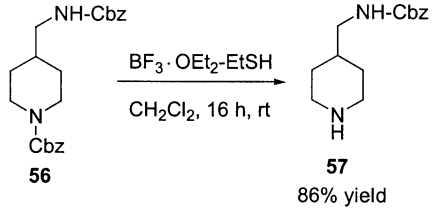
N^{w}-Protected derivatives of α,ω-diamino acids such as lysine, ornithine and 2,4-diaminobutyric acids have been synthesized in high yield using copper complexes, by sequestration of the metal with ethylenediamine tetraacetic acid (EDTA).[59]



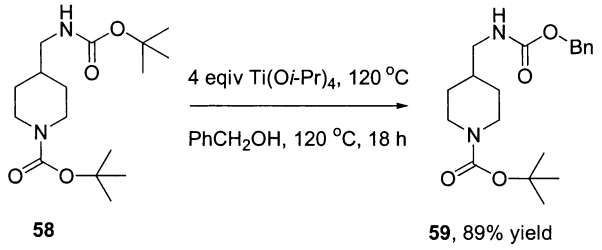
Scheme 16.



Scheme 17.



Scheme 18.

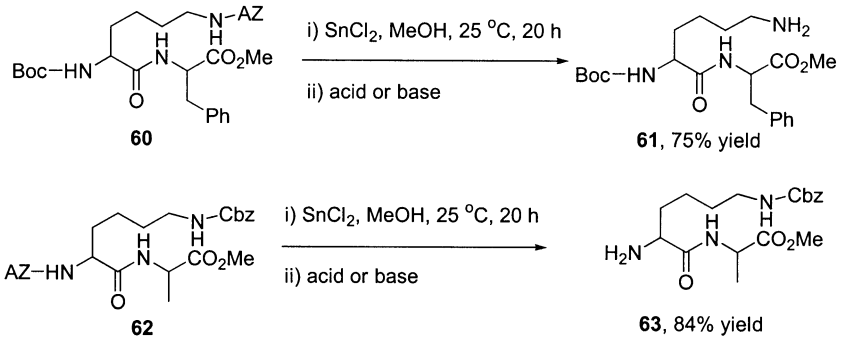


Scheme 19.

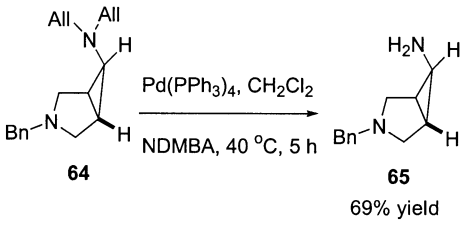
In 1996, Ishihara et al. reported that the tetraamine ester **46** reacted with MLn in benzene to give the lactam **48** via the intermediate complex **47** ascribed to the metal template effect. The spermidine alkaloid **50** was obtained in 53% yield by the addition of cinnamoyl chloride to the borane complex **49** obtained from the reaction of **48c** and [3,5-bis(trifluoromethyl)phenyl)]boronic acid in dichloromethane (Scheme 15).[60]

FK-156, separated from *Streptomyces olivaceogriseus sp. nov.*, was thought to have a unique immuno-stimulating activity. Starting from meso-2,2′-diaminopimelic acid **51**, FK-156 was synthesized using selective carbobenzyloxylation via the chelation of copper by the amino group (Scheme 16).[61] FK-156 analogues have also been synthesized by the copper chelation method.[62,63]

Trost et al.[64] reported in 1988 that adenine reacted selectively with cyclopentadiene monoepoxide in the presence of $Pd(OAc)_2$ and $(i\text{-}C_3H_7O)_3P$ to give the carbocyclic nucleoside in 67% yield. As the Pd-based reactions provided a very short and convenient synthesis of the carbocyclic nucleoside analogues, a considerable amount of research in this field has been in progress to date.[65] Trost's Pd-catalyzed coupling of a purine base **53** with an allylic carbonate gave the purine carbonate adduct **54** in the presence of $Pd(PPh_3)_4$[66] or $Pd(OAc)_2$ and $(i\text{-}C_3H_7O)_3P$[67] in 60% and 80% yield, respectively, and homocarbovir **55** was finally formed after hydrolysis (Scheme 17).



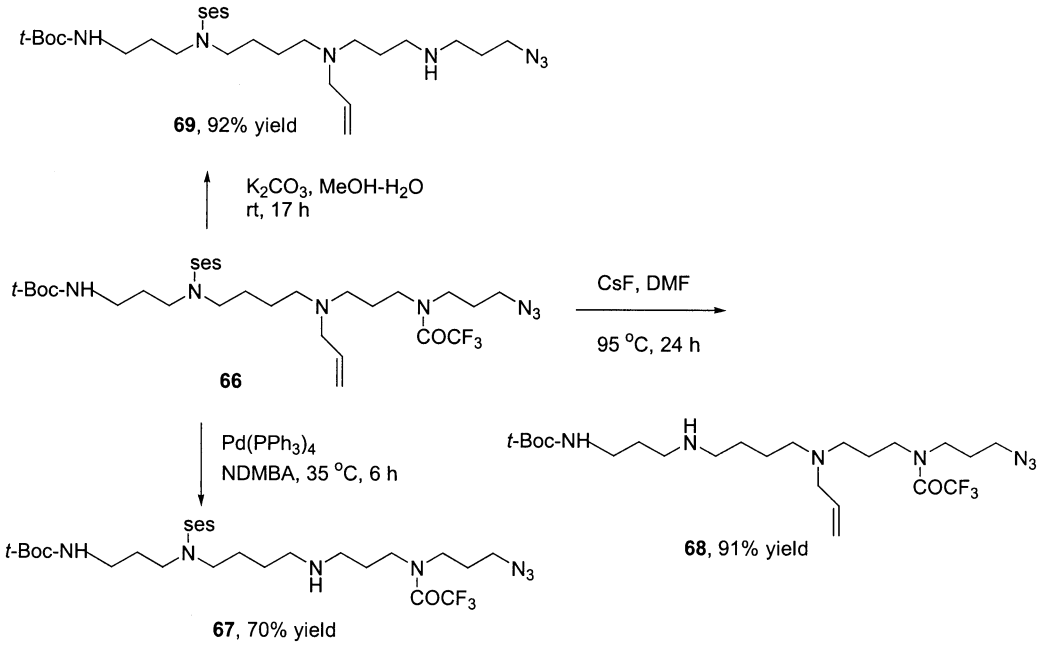
Scheme 20.



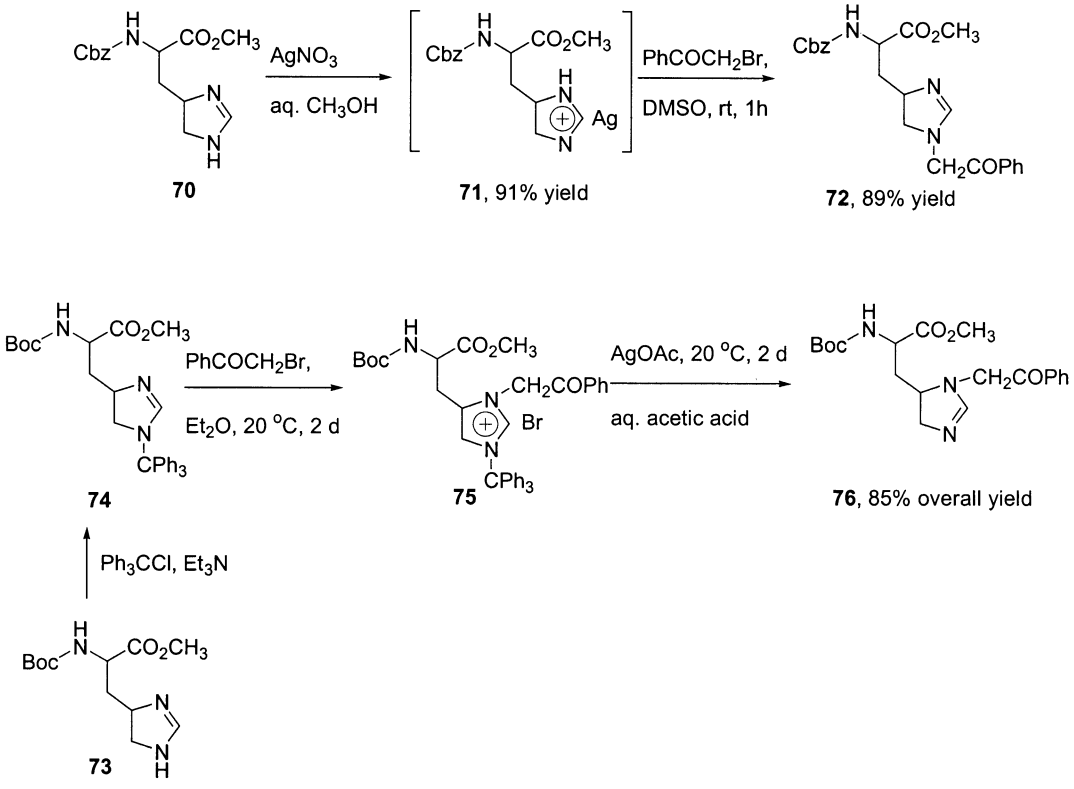
Scheme 21.

Cleavage of the secondary carbamate group was preferred over that of the primary carbamate in the reaction of a diamino compound **56** with $BF_3{\cdot}OEt_2$-EtSH (Scheme 18)[68] and this reaction could be useful in a situation where selectivity between a primary and secondary amine was required.

Treatment of a diamino compound **58** with 4 equiv Ti(O-*i*-Pr)$_4$ in benzyl alcohol resulted in the smooth conversion of the primary rather than the secondary *t*-Boc group by a transesterification reaction (Scheme 19).[69]

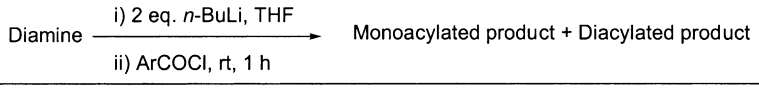


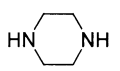
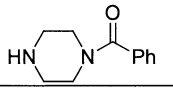
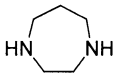
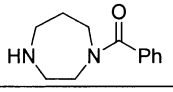
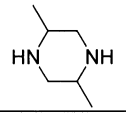
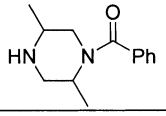
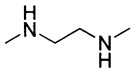
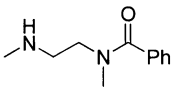
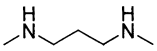
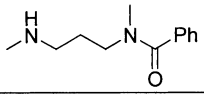
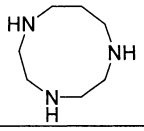
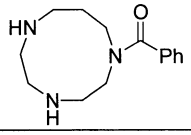
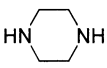
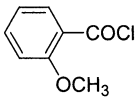
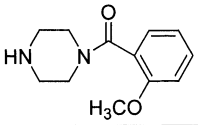
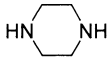
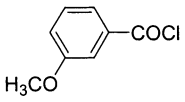
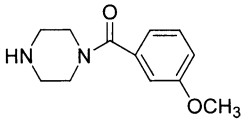
Scheme 22.



Scheme 23.

Table 3. Monoacylation of secondary amines by *n*-BuLi



Entry	Diamine	ArCOCl	Major product	Yield (%)
1		PhCOCl		81
2		PhCOCl		88
3		PhCOCl		74
4		PhCOCl		68
5		PhCOCl		82
6		PhCOCl		81
7				89
8				88

With polyamino compounds **60** having an Fmoc, Cbz, Boc or a 4-azidomethylenoxybenzyl-oxycarbonyl group (AZ), only the AZ group was selectively deprotected by $SnCl_2$ in methanol (Scheme 20).[70] This reaction was carried out in two stages namely reduction of the AZ group by $SnCl_2$ to the 4-hydroxybenzyloxycarbonyl moiety, followed by acid- or base-catalyzed 1,6-elimination and decarboxylation.

As an intermediate to trovafloxacin diastereomer, the protected diamine **64** can selectively be deallylated to monobenzyldiamine **65** in the presence of tetrakis(triphenylphosphine)palladium (Scheme 21).[71]

The polyamino derivative **66** was deallylated to **67** using 1,3-dimethylbarbituric acid (NDMBA) as an allyl group scavenger and $Pd(PPh_3)_4$ as a catalyst, while the reaction of **66** with CsF or K_2CO_3 selectively removed the [2-(trimethylsilyl)ethyl]sulfonyl (ses) or the $COCF_3$ group, respectively, to provide the desired derivatives **68** and **69** in high yield (Scheme 22).[72] The ses group is quite stable under acidic and basic conditions, but can be cleaved in good yield by CsF.

The selective deprotection of polyamino groups in polyamino compounds has been extensively reported.[73–80]

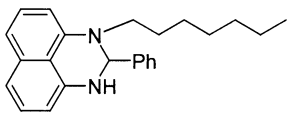
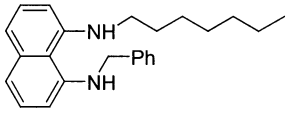
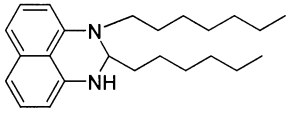
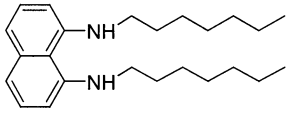
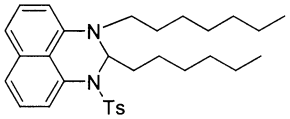
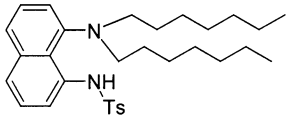
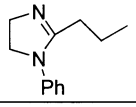
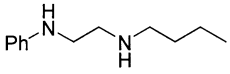
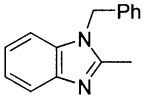
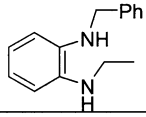
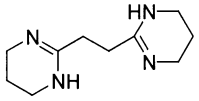
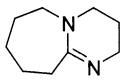
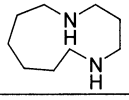
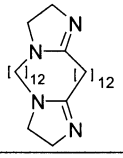
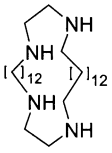
Treatment of the silver salt **71** with phenacyl bromide in dimethylsulfoxide gave only the major product **72** without giving the mixture which was obtained from the reaction of *Nα*-benzyloxycarbonylhistidine methyl ester **70** with phenacyl bromide. The *Nα*-*t*-butyloxycarbonylhistidine methyl ester **73** was processed in three steps to give **76** in 85% yield (Scheme 23).[81]

The reactivity of the diamine in compounds such as piperazine, homopiperazine and acyclic diamines can be altered by making the mono or disalt of the diamine, which should be more reactive towards an acyl chloride than the free diamine, affording the monoacylated product in high yield under kinetic control (Table 3).[82]

Various dihydropyrimidines and cyclic amidines were reduced with diisobutylaluminum hydride (DIBAL-H) to furnish the regiospecifically alkylated polyamines in excellent yield (Table 4).[83] The selective cleavage of

Table 4. Syntheses of polyamines by DIBAL-H

Polyamine —DIBAL-H→ Product

Entry	Polyamine	Product	Reaction conditions	Yield (%)
1			toluene, 2 h, reflux	85
2			*n*-hexane, 30 min, reflux	88
3			*n*-hexane, 30 min, 0 °C to rt	91
4			*n*-hexane, 2 h, rt to reflux	95
5			*n*-hexane, 2 h, 0 °C to rt	97
6		$NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$	i) $[(CH_3)_3Si]_2NH$, cat H_2SO_4. ii) xylene, reflux, 3d	63
7			toluene, 7 h, reflux	96
8			toluene, 2h, reflux	83

dihydropyrimidines by DIBAL-H can be explained by initial chelate formation of diisobutylaluminum amide, followed by the coordination of another nitrogen atom to DIBAL-H, and finally C-N bond cleavage by DIBAL-H. DIBAL-H is an effective reducing agent for the conversion of imines to amino derivatives and the method can be extended to the reductive cleavage of the amidine system by DIBAL-H (entries 4, 5, 6, 7 and 8).

3. Conclusions

Polyamino compounds found in animals, plants and bacteria have recently attracted a great deal of interest because of their potential biological functions as pharmaceuticals and agrochemicals. Their metal complexes have attracted interest for the selective reactions of polyamines, for the treatment of metal intoxication and for the stabilization of metal cations in diagnostic radiopharmaceuticals.

By systematically studying the binding properties of polyamino compounds with a bidentate or multidentate ligand around metal in terms of an empirically-derived HSAB principle[84] or a metal template effect,[34] the metal-chelated or -mediated methods may be considered as a useful tool for the selective modification of polyamino compounds, and as an adjunct to conventional chemical reagents and enzymatic methods.

4. Summary

Organic compounds having several amino groups have received a great deal of attention because of their biological and pharmaceutical properties. Consequently, selective reactions of their amino groups are of great importance for the preparation of additionally useful polyamino compounds. Metal-chelated or -mediated methods can clearly play a useful role in this area.

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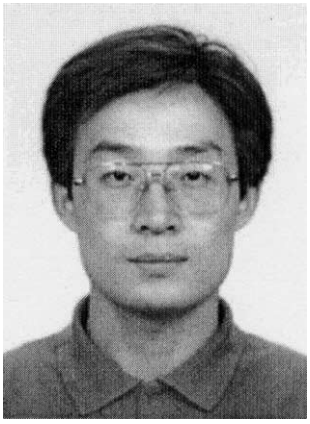
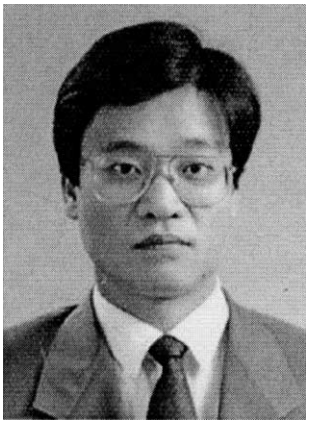
Biographical sketch



So Ha Lee was born in 1962 in Kongju, Korea. He received his PhD from Korea University in 1999 for work on the synthesis of bisoxazine ligands and 3-substituted piperidine ligands, and their enantioselective reactions, supervised by Professor Bong Young Chung. From 1987–1989, he worked at the Korea Institute of Energy and Resources; from 1991 to the present time, he has been based at the Korea Institute of Science and Technology as a researcher. He worked on the synthesis of agrochemicals and pharmaceuticals until 1997. His research interests include the synthesis of the novel drugs utilizing chemical genetics and bioinformatics, the use of enzymes, particularly epoxide hydrolases, for the synthesis of biologically active compounds.



Chan Seong Cheong was born in 1956 in Incheon, Korea. He received his MS and PhD in chemistry under Professor Kwan Su Kim from Yonsei University in 1988 and 1993 and worked on enzymatic reactions with Professor R. J. Kazlauskas at McGill Univeristy, Canada as a Postdoctoral Fellow in 1997. From 1979 to the present time, he has studied process developments for synthesizing various organic chemicals including agrochemicals and pharmaceuticals at the Korea Institute of Science and Technology. His current interests include the application of biocatalysts to organic synthesis for manufacturing commercial chemicals and studies of the relationship between enzymes and substrates.