HETEROCYCLES, Vol. 65, No. 3, 2005, pp. 667 - 695
Received, 1st November, 2004, Accepted, 22nd December, 2004, Published online, 24th December, 2004

NUCLEOSIDE CHEMISTRY IN CROP PROTECTION[1]

Clemens Lamberth

Syngenta AG, Crop Protection Research, Chemistry, Schwarzwaldallee 215,
CH-4002 Basel, Switzerland
Fax: +41 61 323 8529; e-mail: clemens.lamberth@syngenta.com

Abstract - This review aims to give an overview of the significance of nucleosides in crop protection. The main herbicidally, fungicidally and insecticidally active nucleoside classes are presented together with their synthetic issues, mode of action and biological efficacy.

CONTENTS

1 INTRODUCTION

In today's crop protection research, the discovery of new agrochemical compound classes with novel modes of action becomes more and more difficult.[2] In this context herbicidally, fungicidally and insecticidally active natural products are gaining importance as inspiration and starting point for the development of new lead structures.[3] Nucleosides constitute a ubiquitous class of naturally occurring compounds, which is well-known for its significant biological activities.[4] Nucleosides display not only antibacterial, antiviral and antitumor efficacy, but also the efficient control of weeds, insects and fungal diseases is possible with several derivatives out of this class of compounds. This will be demonstrated in this review. The fact, that nucleosides *per se* are chiral compounds emphasizes the significance of chirality in modern crop protection.[5]

2 HERBICIDES

2.1 Hydantocidin and Other Inhibitors of *Adenylosuccinate Synthetase*

The isolation of hydantocidin (**1**) from the fermentation broth of *Streptomyces hygroscopicus* (SANK 63584) provided the first example of a naturally occuring spironucleoside (Figure 1).[6] It exhibits powerful non-selective, post-emergent herbicidal and plant-growth regulatory activity against a broad spectrum of mono- and dicotyledonous annual, biennial and perennial weeds without showing toxicity to microorganisms and animals. Hydantocidin acts as an inhibitor of *adenylosuccinate synthetase* after it has been converted into its active principle **2** by phosphorylation within the plant.[7]

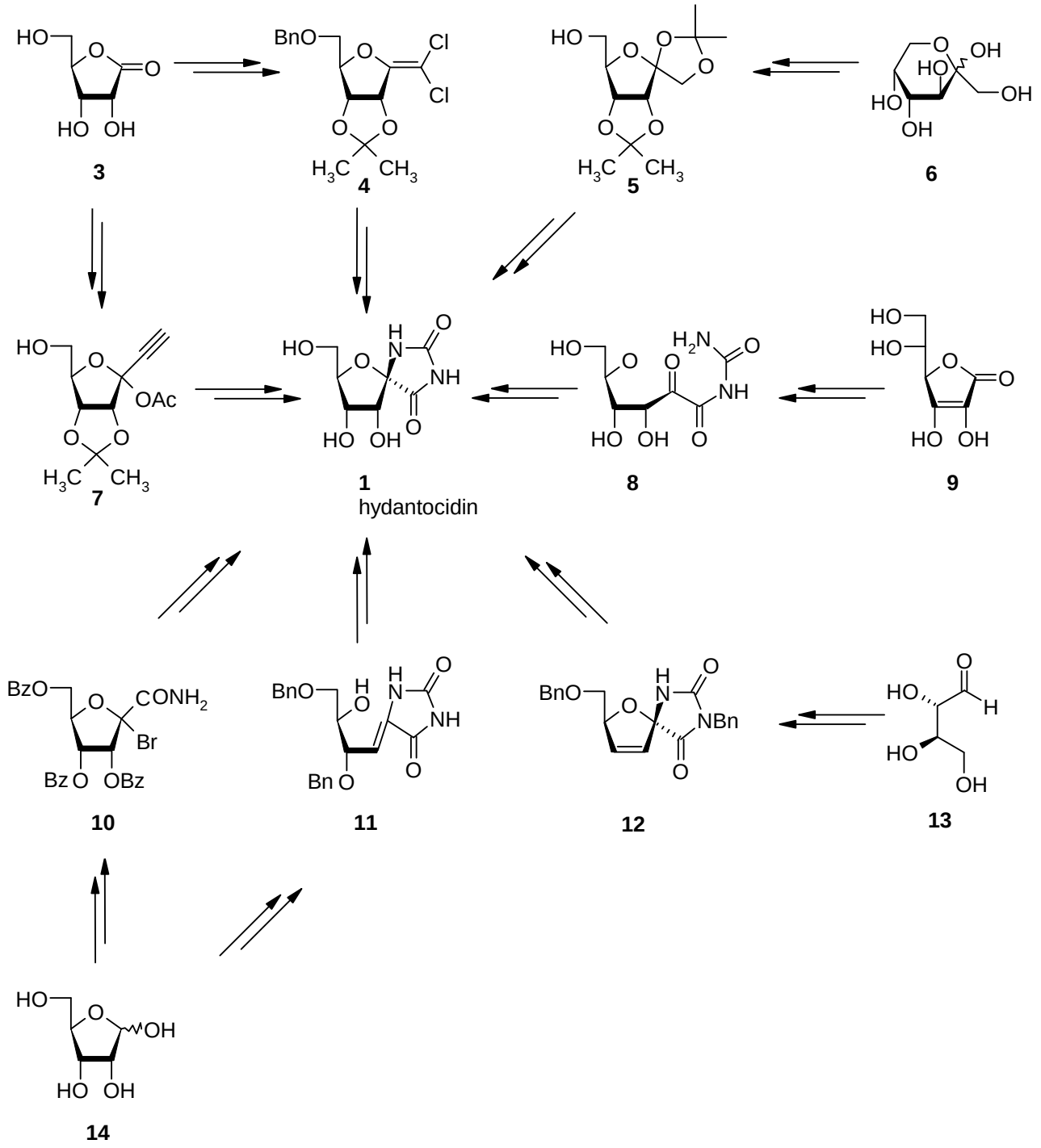
1
hydantocidin

2

Figure 1

Because hydantocidin combines unique structural features with a remarkable biological and ecotoxicological profile, several approaches for the preparation of **1** have been reported recently from such diverse starting materials as ribono-1,4-lactone (**3**),[8,9] D-fructose (**6**),[9-11] D-isoascorbic acid (**9**),[10] D-threose (**13**)[12] and D-ribose (**14**)[13,14] (Scheme 1). Key intermediates of the ribonolactone routes are the interesting dichloro-substituted *exo*-glycal (**4**)[8] and the acetylene-sugar (**7**).[9] A requirement for the application of D-fructose (**6**) as educt for the synthesis of hydantocidin is its transformation into the

psicofuranose derivative (**5**). Ribose can be converted into **1** by Wohl-Ziegler reaction to **10**[13] or *via* the Bucherer-Bergs adduct (**11**).[14] The dihydroxylation of the didehydrospironucleoside (**12**) delivered not only the ribo-configurated natural product (**1**),[12] but also its arabino-, lyxo- and xylo-isomers.[15]



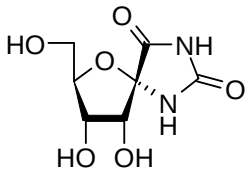
Scheme 1

Structure-activity relationship studies revealed that among all 16 stereoisomers of hydantocidin resulting from its four contigous chiral centers, mainly the naturally occuring **1** is biologically active. Only its 5-*epi*

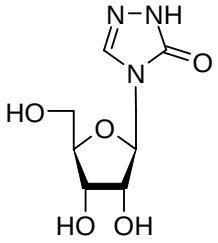
isomer (**15**), to which **1** is converted under acidic conditions because of its higher thermodynamic stability, has also considerable herbicidal activity (Figure 2).[16] Not only the evaluation of the structure-activity profile, but also the search for more easily accesible analogs fostered the synthesis of several hydantocidin derivatives, which are altered either in the ribose or in the hydantoin moieties. Amongst the sugar-modified hydantocidin analogs are its L-configurated enantiomer,[17] and spirohydantoins with deoxy-,[18] carbocyclic,[19] hexofuranoic[20] as well as hexopyranoic sugar units.[21]

On the other hand, the hydantoin part of **1** has been replaced by thiohydantoin,[22] succinimide,[23] imidazolidinone,[24] thiazolidinedione,[25] diketopiperazine[26] and dihydrouracil.[27] It is noteworthy, that none of these synthetic hydantocidin derivatives had a biological potency in the range of the parental natural product.

Also other herbicidal nucleosides act by blocking *adenylosuccinate synthetase*. The triazolone (**16**) was isolated from an *Actinomadura* fermentation broth and exhibits, like hydantocidin, the broad-spectrum activity of a total herbicide (Figure 2).[28]



15
5-*epi*-hydantocidin



16

Figure 2

2.2 Coformycin (17) and Other Inhibitors of *AMP Deaminase*

Coformycin (**17**) was discovered in culture filtrates of *Nocardia interforma* and *Streptomyces kaniharaensis* and found to be active against different grass species like *Sorghum halepense* (johnsongrass), *Echinochloa crus-galli* (barnyardgrass) and *Digitaria adscendens* (crabgrass) (Figure 3).[29,30] Its carbocyclic derivative (**18**), isolated from a *Saccharothrix* species, displayed a potent post-emergent activity against *Polygonium lapathifolium* (pale smartweed), *Chrysanthemum segetum* (corn marigold) and *Avena fatua* (wild oat).[31] Both compounds are strong blockers of *AMP deaminase*. This enzyme catalyses the hydrolytic conversion of adenosine-5'-monophosphate (AMP) into inosine-5'-monophosphate. Inhibition of AMP deaminase leads to the death of the plant by perturbation of the intracellular ATP pool.[32] Other herbicidally active AMP deaminase inhibitors are nebularin (**19**),[33] deaminoformycin (**20**)[34] and the 5'-monophosphates of both the imidazolotriazine nucleoside (**21**)[35] and

the triazolotriazine nucleoside (**22**),[36] which in aqueous solution exists predominantly as the covalent hydrate (**23**).

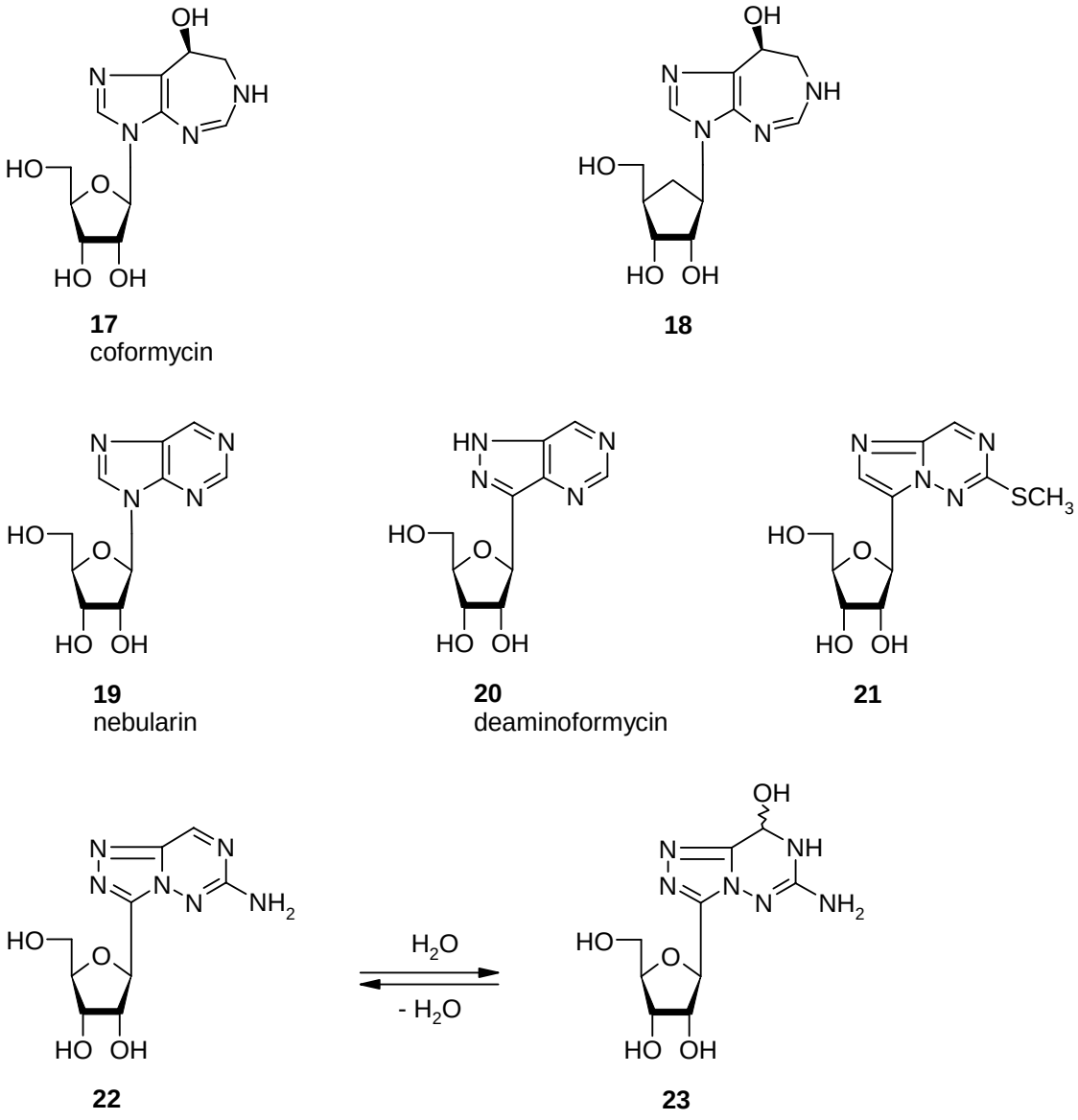
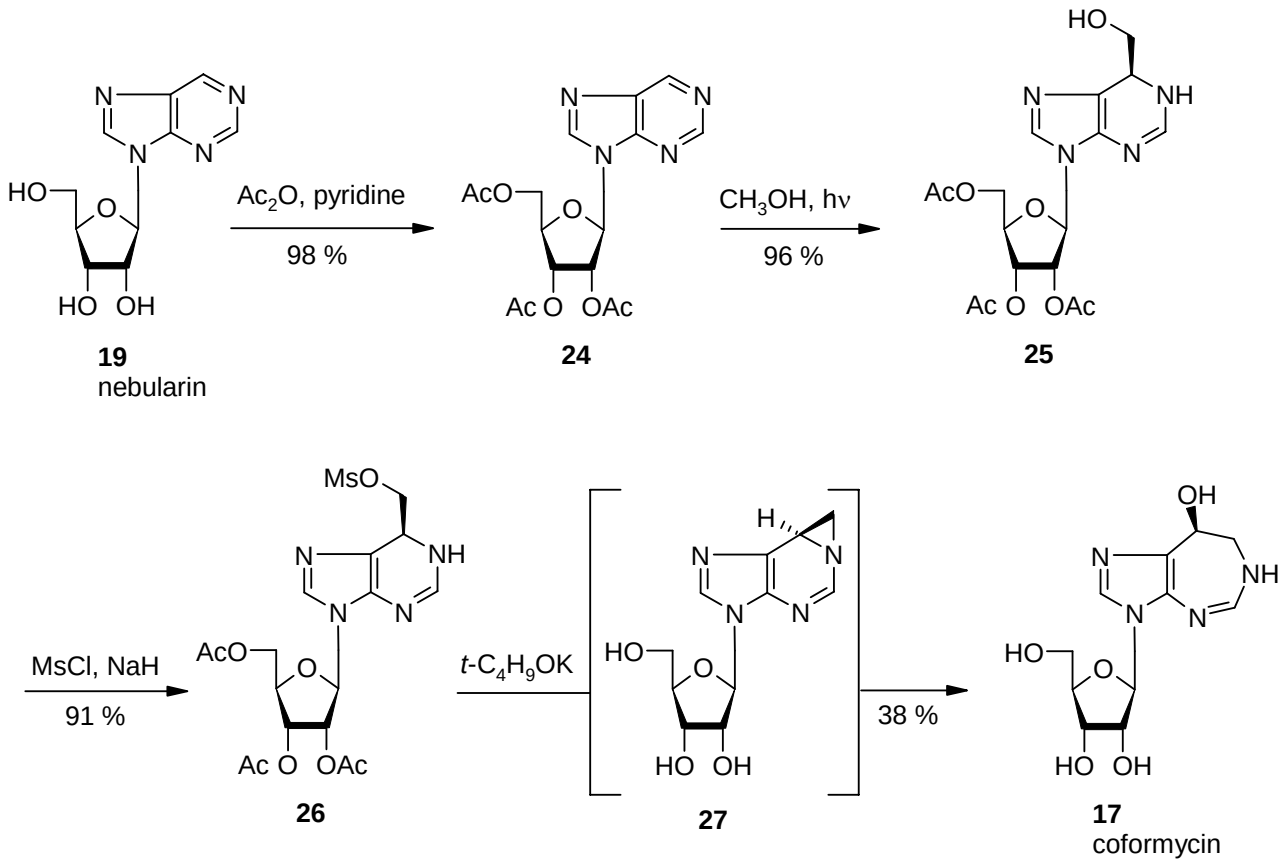


Figure 3

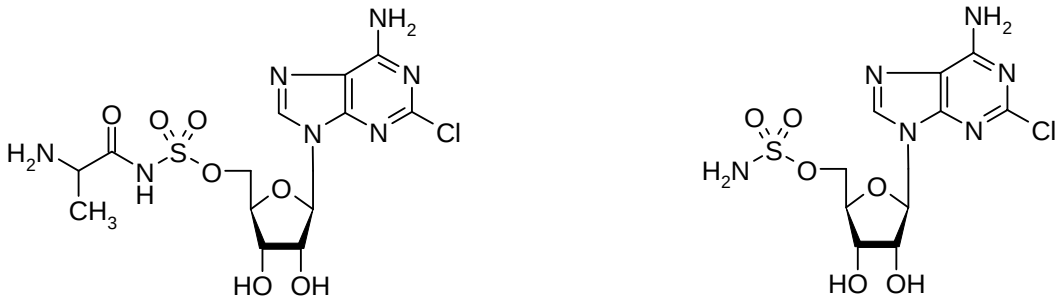
Several syntheses of coformycin (**17**) have been published,[37,38] a concise approach by Ohno *et al*. *via* ring expansion of the naturally occurring nucleoside antibiotic nebularin (**19**) is especially intriguing (Scheme 2).[37] After peracetylation of the starting material (**19**) to **24**, the stereospecific photoaddition of methanol led to the alcohol (**25**). Mesylation of its hydroxy function to **26** was immediately followed by a base-catalyzed ring closure / ring opening sequence, which led through the unstable aziridine intermediate (**27**) under simultaneous cleavage of the protecting groups to the desired natural product (**17**).[37]



Scheme 2

2.3 Ascamycin (28) and Other Inhibitors of *Amino Acyl tRNA Synthetase*

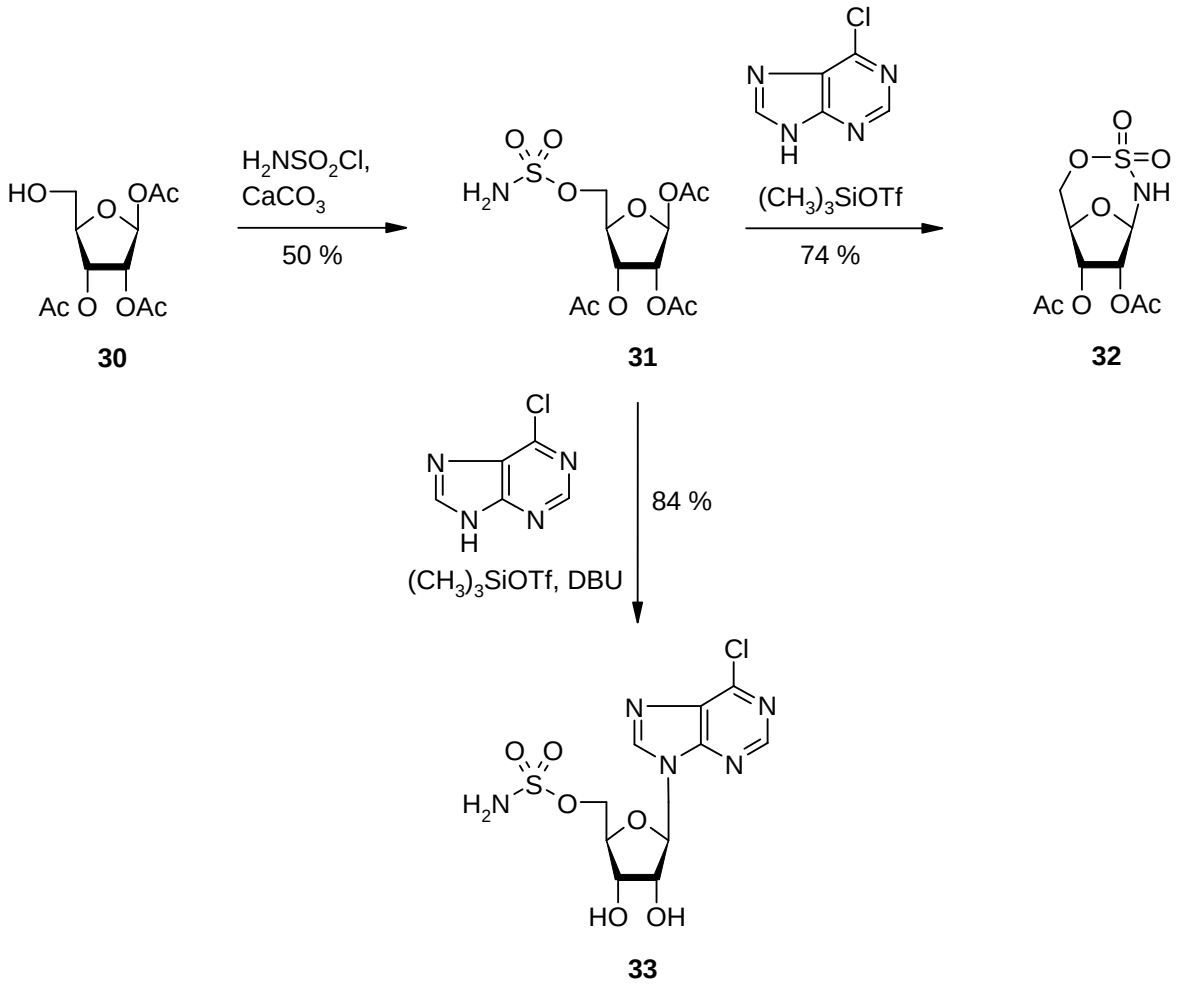
Ascamycin (**28**) and its deacylated derivative dealanylascamycin (AT-265) (**29**) have been both isolated from a *Streptomyces* fermentation broth (Figure 4).[39] Especially **29** displays a remarkable postemergence activity against a wide array of mainly broadleaf weeds. At 100 g/ha, a use rate typical for modern commercial herbicides, it fully controls for instance *Euphorbia helioscopia* (sun spurge), *Abutilon theophrasti* (velvetleaf), *Stellaria media* (chickweed), *Solanum nigrum* (black nightshade) and *Veronica persica* (speedwell).[40] 5'-Sulfamoylnucleosides like **28** or **29** are bioisosteres of the corresponding nucleotides, in which the sulfamoyl mimics the natural phosphate group. They inhibit protein biosynthesis by blocking *amino acyl tRNA synthetases*.[41] Therefore many other amino acid derivatives of **28** were prepared. In addition to alanine, also glycine,[42,43] valine,[42] isoleucine,[42] phenylalanine,[44] proline[44] and several non-proteogenic amino acids[42] were linked to **29**. Also several other derivatives have been made, replacing mainly the amino and the chloro substituents in the purine moiety with hydrogen, alkyl, aryl, alkynyl, hydroxy, alkoxy, alkylthio, bromo, iodo or cyano functions.[43,45] Moreover derivatives with uracil,[45,46] cytosine,[45,46] benzimidazole[45] and benzotriazole[45] nucleobases were made. However, the mammalian cytotoxicity of **29** and its analogues unfortunately precluded a commercial development.



28
ascamycin

29

Figure 4



30 **31** **32** **33**

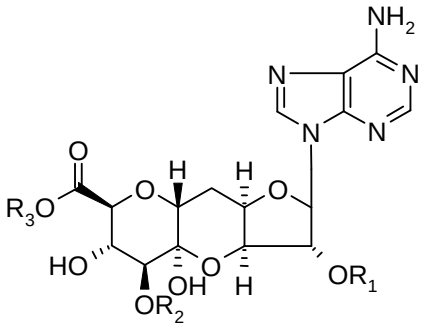
Scheme 3

A concise route to 5'-sulfamoylnucleosides has been worked out recently, which allows high flexibility in the introduction of various heterocyclic base moieties (Scheme 3).[45] The tri-*O*-acetylated β-D-ribose (**30**) is transformed into the 5-*O*-sulfamoyl derivative (**31**). Its attempted coupling with a nucleobase under

standard Vorbrüggen conditions led only to the bicyclic compound (**32**). The crucial modification leading to the desired product (**33**) in high yield was the presence of a tertiary base in the reaction mixture.[45]

2.4 Herbicidins (34 – 39)

The herbicidins (**34** – **39**) are a family of nucleoside antibiotics, which have been isolated from strains of *Streptomyces saganonensis* (Figure 5).[47,48]



34
herbicidin A ($R_1 = CH_3$, $R_2 = CH_3CH{=}CH(CH_2OH)CO$, $R_3 = CH_3$)

35
herbicidin B ($R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$)

36
herbicidin C ($R_1 = H$, $R_2 = H$, $R_3 = CH_3$)

37
herbicidin E ($R_1 = CH_3$, $R_2 = ((CH_3)_2CHCO$, $R_3 = CH_3$)

38
herbicidin F ($R_1 = CH_3$, $R_2 = CH_3CH{=}C(CH_3)CO$, $R_3 = CH_3$)

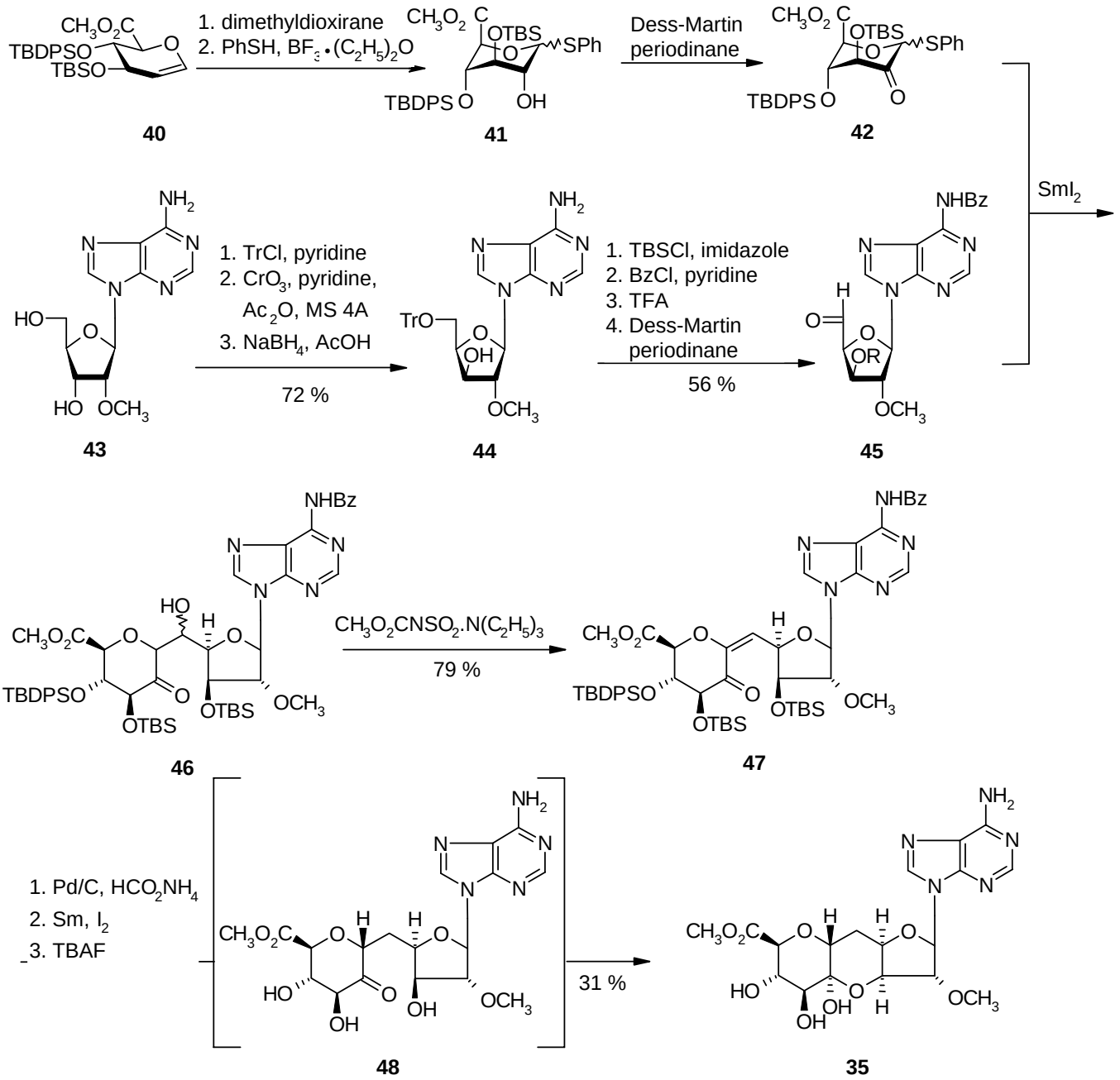
39
herbicidin G ($R_1 = H$, $R_2 = CH_3CH{=}C(CH_3)CO$, $R_3 = H$)

Figure 5

Herbicidins A, B, E, F and G exhibit strong herbicidal activity with selective efficacy against dicotyledonous weeds. Herbicidins A (**34**) and B (**35**) also efficiently inhibit the growth of *Xanthomonas oryzae*, a bacterium responsible for rice leaf blight. The biosynthetic relationship of the herbicidins was studied with blocked mutants by means of a bioconversion method using growing and resting cells.[49] It is proposed that herbicidin G (**39**) is an intermediate in the biosynthesis of all other herbicidins, and that it is converted into herbicidin A (**34**) *via* herbicidin F (**38**). Both herbicidins A and F can be transformed to herbicidin B by pH-dependent non-enzymatic reactions.[49]

Although several approaches to the tricyclic sugar moiety of the herbicidins as well as to analogues and congeners of them have been published by the teams of Gallagher,[50] Sinay,[51] Vogel[52] and Whiting,[53] a total synthesis is so far only described by Matsuda for herbicidin B (**35**) (Scheme 4).[54]

Key intermediate of this total synthesis of herbicidin B was **46**, which could be obtained by a special SmI_2-promoted aldol-type *C*-glycosidation reaction[55] between the phenylthioulose (**42**) and the 1-β-D-xylosyladenine-5'-aldehyde (**45**). The aldehyde (**45**) was readily prepared from 2'-*O*-methyladenosine



Scheme 4

(**43**). The phenylthioulose (**42**) was synthesized from the glycal (**40**), which is derived from D-glucurono-3,6-lactone in four steps. The steric repulsion of the two adjacent bulky silyl protecting groups in the phenylthioulose (**42**) leads by restriction to the rather unusual $^{1}C_{4}$-like conformation stereoselectively to **46**, which can be dehydrated with Burgess reagent to the corresponding enone (**47**) as single isomer in almost 80 % yield. Smooth reduction of the C-C double bond with ammonium formate as hydrogen donor and subsequent removal of the protecting groups led to the unstable intermediate (**48**), which cyclised spontaneously by intramolecular ketalisation to herbicidin B (**35**) (Scheme 4).[54]

2.5 Miscellaneous Herbicidally Active Nucleosides

3-Hydroxyuridine (**49**) was isolated as an alleopathic factor from *Baillonella toxisperma*, a tree found in the tropical rain forest of Cameroon. It exhibited inhibitory effects on the growth of a wide variety of weeds, for instance *Abutilon avicennae* (velvetleaf), *Cassia tora* (sicklepod) and *Pharbitis purpurea* (tall morningglory) (Figure 6).[56] A further carbocyclic nucleoside with herbicidal activity is coaristeromycin

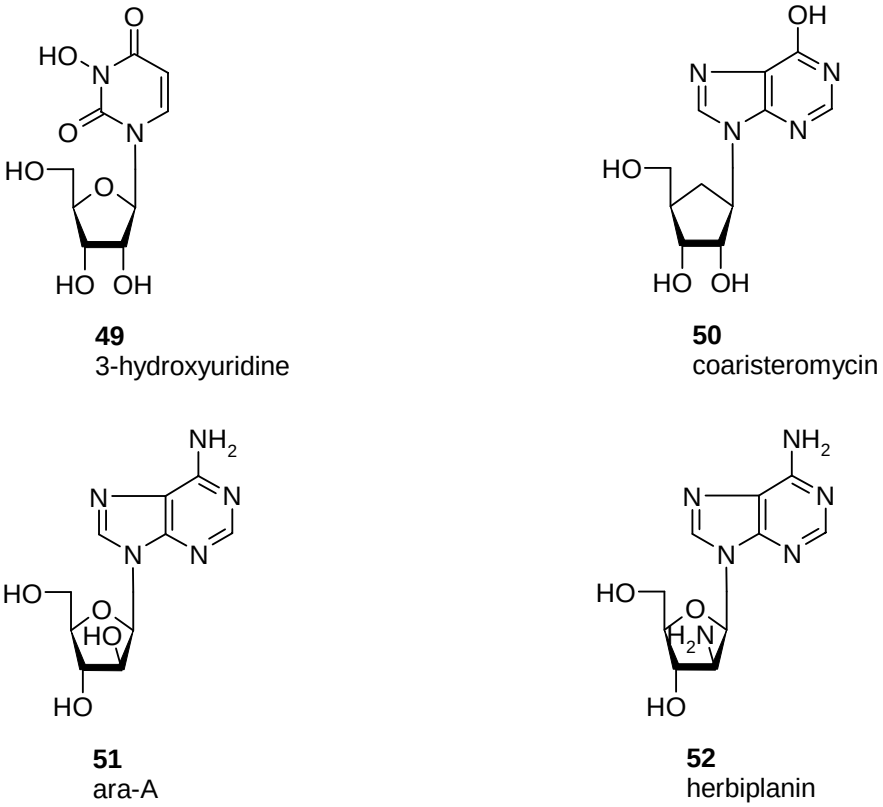


Figure 6

(**50**). It was isolated from a *Streptomyces* species and found to control *Cyperus esculentus* (yellow nutsedge), *Echinochloa crus-galli* (barnyardgrass) and *Sorghum halepense* (johnsongrass).[30,57] 9-β-D-Arabinofuranosyladenine (ara-A) **51**[30,58] and its 2'-amino derivative herbiplanin (**52**)[59] were isolated from

different *Streptomyces* strains (Figure 6). **51** possesses powerful preemergent herbicidal activity against *Echinochloa crus-galli* (barnyardgrass), *Digitaria adscendens* (crabgrass) and *Chenopodium ficifolium* (lambsquarter).[58] **52** is effective for instance against different *Lepidium* (pepperweed) and *Sinapis* (mustard) species.[59]

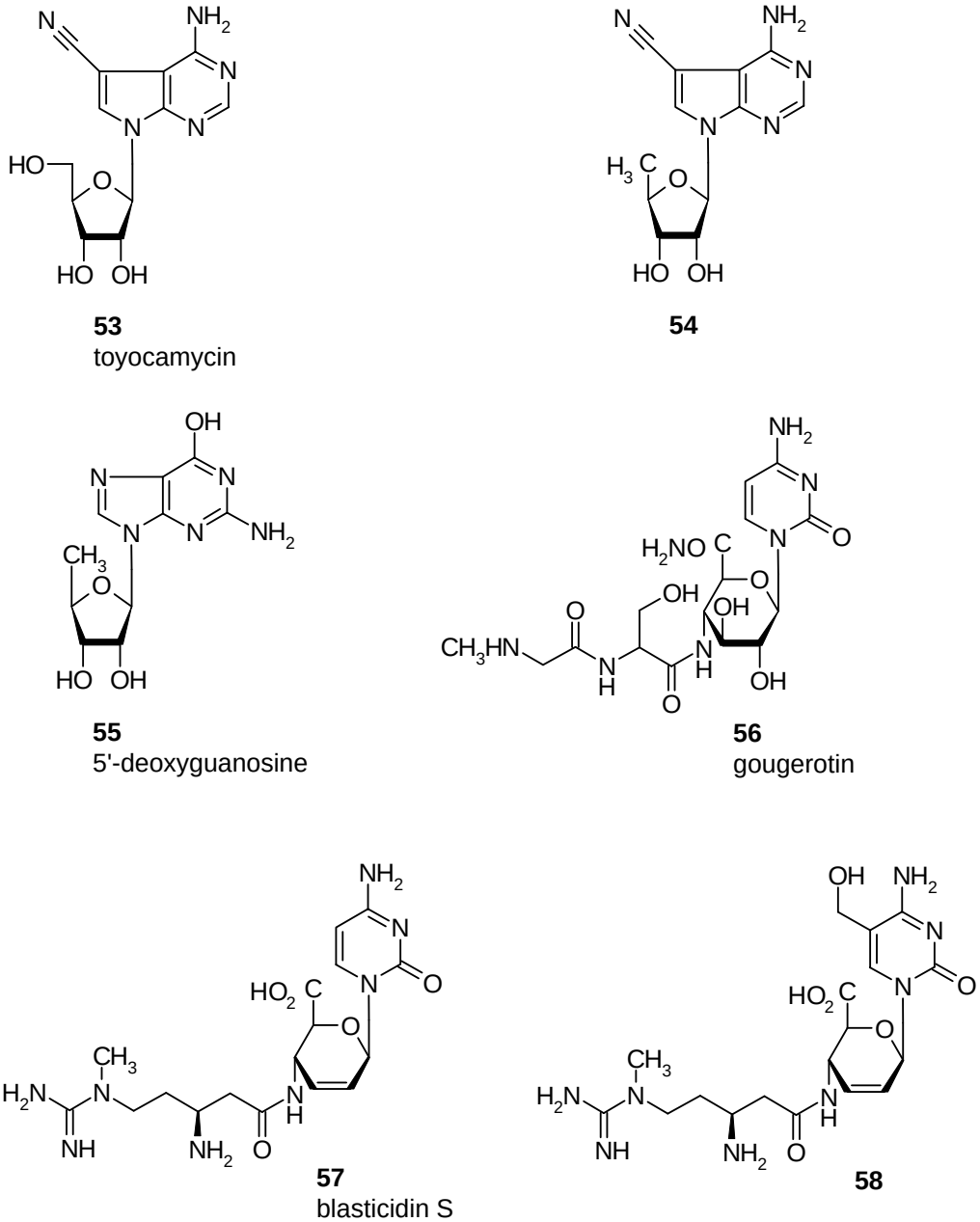


Figure 7

3 FUNGICIDES

3.1 Blasticidin S (57) and Other Inhibitors of Protein Biosynthesis

Blasticidin S (**57**), a metabolite of *Streptomyces griseochromogenes*,[63] was once used commercially on a large scale for the control of *Pyricularia oryzae* (rice blast). It blocks protein biosynthesis in eukaryotic and prokaryotic cells by interference of peptidyl transfer reactions.[64] Detailed biosynthetic studies revealed, that L-α-arginine, D-glucose, cytosine and L-methionine are the primary precursors.[65] Also 5-fluoroblasticidin (**59**) is active against the rice blast disease.[66]

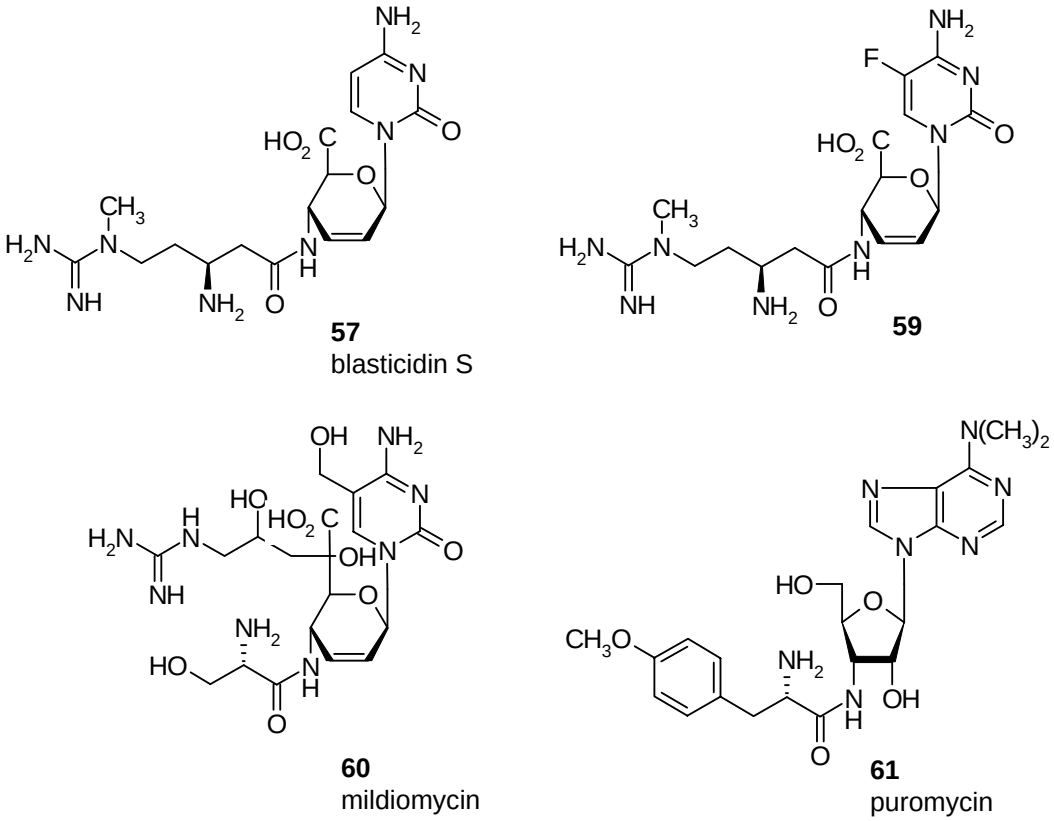
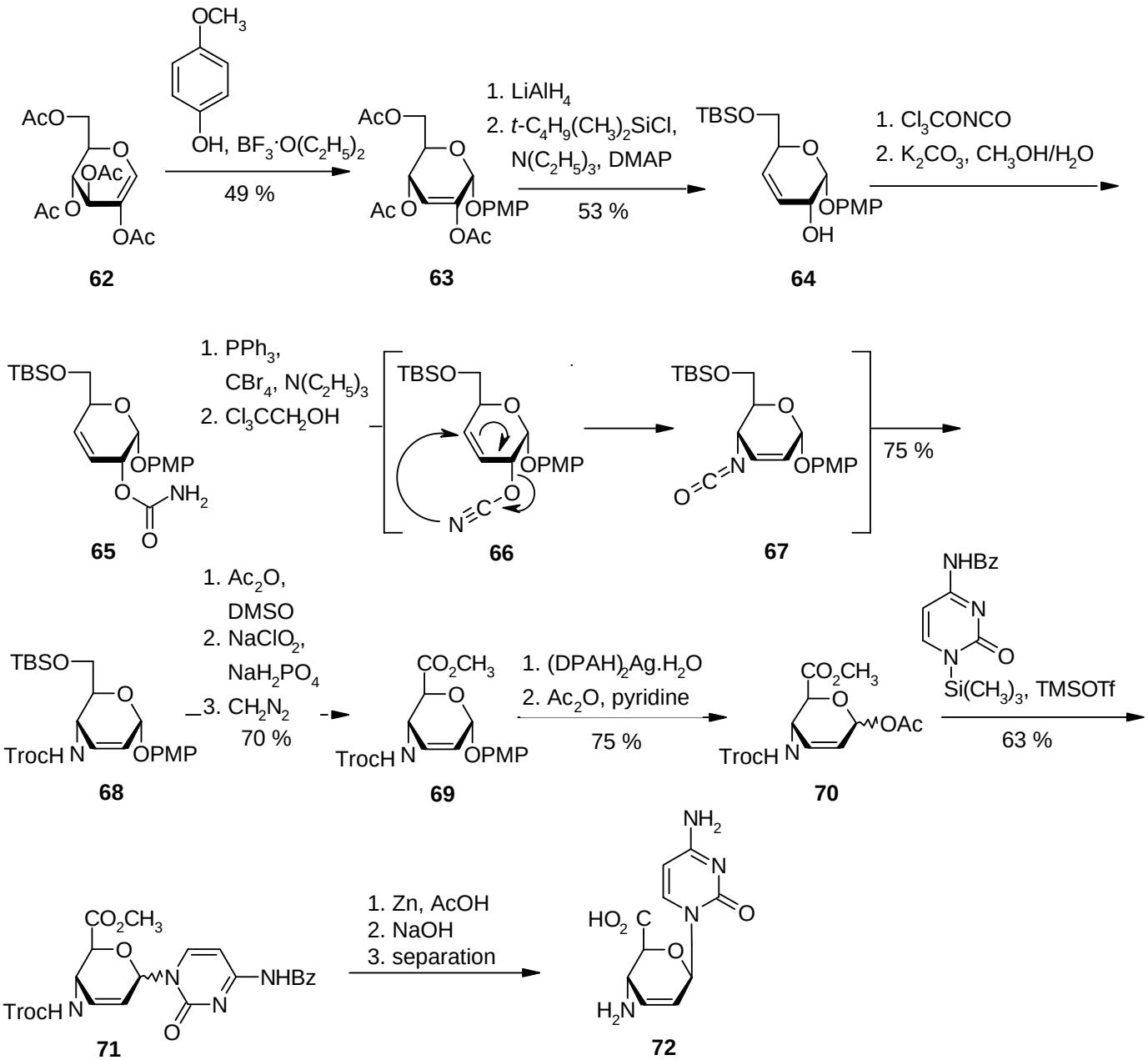


Figure 8

Mildiomycin (**60**) was isolated from *Streptoverticillium rimofaciens*[67] and like blasticidin S inhibits fungal protein biosynthesis.[68] It combines a strong activity against powdery mildew diseases of several different crops with a remarkably low mammalian and fish toxicity.[69] Puromycin (**61**), another protein biosynthesis inhibitor, is effective against various growth stages of *Erysiphe graminis* (powdery mildew) on barley.[70]

Careful acidic amide hydrolysis of blasticidin S (**57**) delivers its principle components *N*-methyl-L-β-arginine (blastidic acid) and the unusual nucleoside cytosinine (**72**), which both possess a β-amino acid functionality. Although a few syntheses of **72** have been described already,[71] an especially interesting route to cytosinine starting from tetra-*O*-acetyl-D-glucal (**62**) was published just recently.[72] The C-C double bond of 2-acetoxy-tri-*O*-acetyl-D-glucal (**62**) could be sequentially moved to the 3,4-position, as

in **6**4, by Ferrier-type glycosylation with *p*-methoxyphenol, followed by treatment with lithium aluminum hydride. The dehydration of the carbamate (**65**) gave the allyl cyanate (**66**), which underwent a unique [3,3]sigmatropic rearrangement to the allyl isocyanate (**67**). Because of its instability, **67** was trapped as the trichloroethoxy carbamate by transformation with 2,2,2-trichloroethanol. After oxidation of the

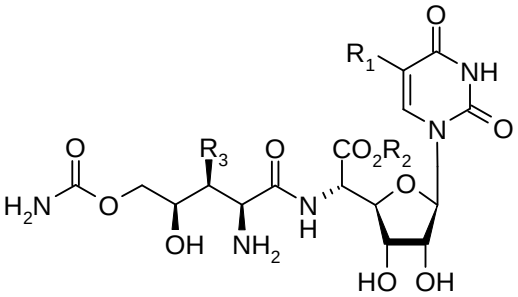


Scheme 5

6-hydroxy group to a carboxylic acid function, Vorbrüggen coupling of the anomeric acetate (**70**) gave a 1:1 mixture of the fully protected cytosinine derivative (**71**). Deprotection and separation of the anomeric epimers led to cytosinine (**72**).[72]

3.2 Polyoxin B (73) and Other Inhibitors of *Chitin Synthetase*

The polyoxins are an important class of peptidyl nucleosides, which were isolated as metabolites of *Streptomyces cacaoi* var. *asoensis* (Figure 9).[73,74] They interfere with fungal cell wall synthesis by specifically blocking *chitin synthetase*, the enzyme which facilitates the polymerisation of *N*-acetylglucosamine (GlcNAc) to chitin through the activated precursor UDP-*N*-acetylglucosamine (UDP-GlcNAc).[75] This linear macromolecule is an essential structural component for growth in most fungi,



73
polyoxin B (R_1 = CH_2OH, R_2 = OH, R_3 = OH)

74
polyoxin D (R_1 = CO_2H, R_2 = OH, R_3 = OH)

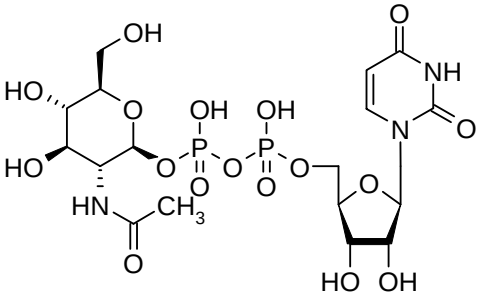
75
polyoxin E (R_1 = CO_2H, R_2 = OH, R_3 = H)

76
polyoxin G (R_1 = CH_2OH, R_2 = OH, R_3 = H)

77
polyoxin J (R_1 = CH_3, R_2 = OH, R_3 = OH)

78
polyoxin L (R_1 = H, R_2 = OH, R_3 = OH)

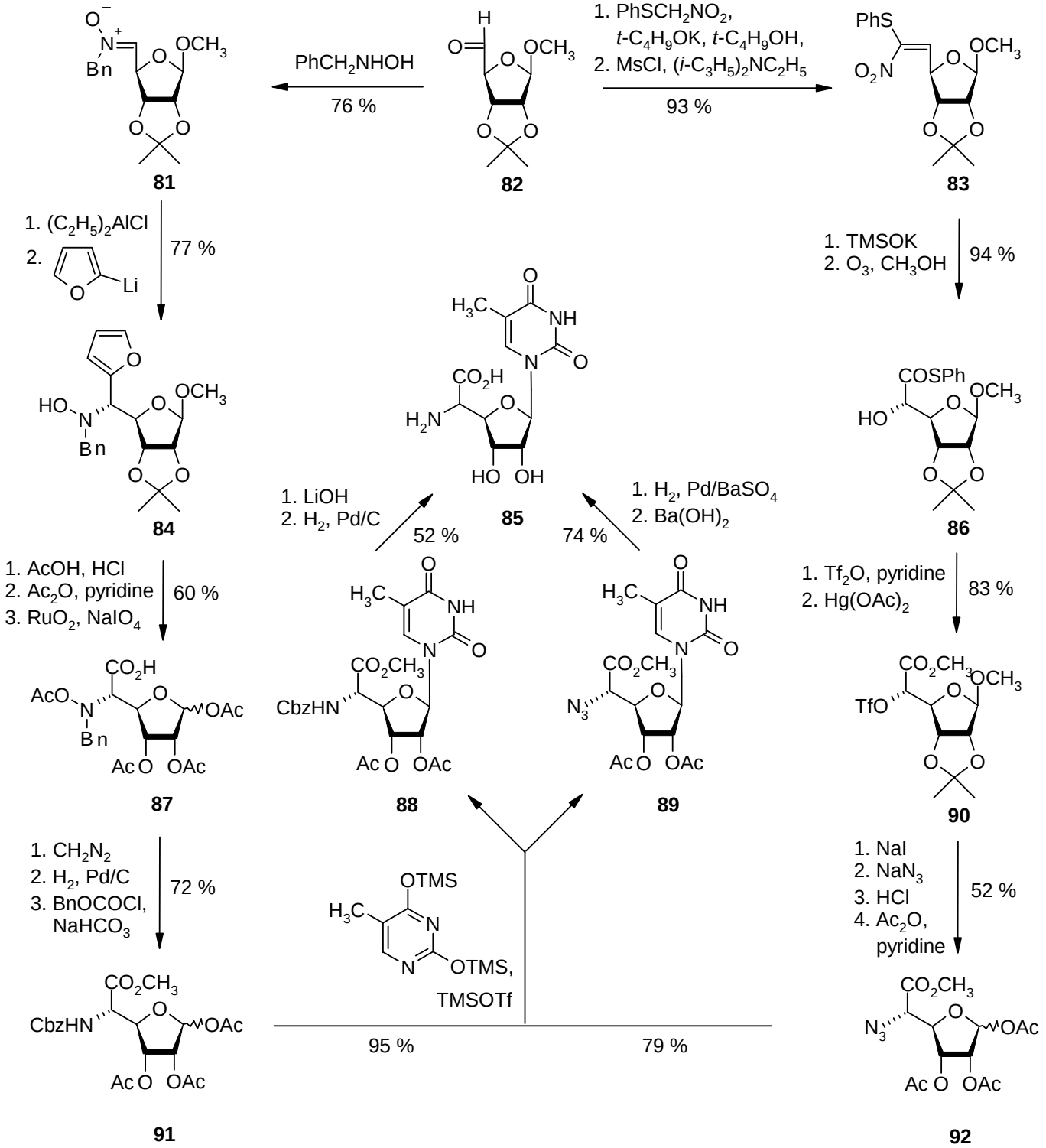
79
polyoxin M (R_1 = H, R_2 = OH, R_3 = H)



80
UDP-GlcNAc

Figure 9

where it is responsible for the shape and rigidity of the cell walls. This competitive inhibition is based on the fact, that the polyoxins are structural analogues of UDP-GlcNAc (**80**), the natural enzyme substrate. Both **73** and **74** are commercially produced via fermentation. Polyoxin B (**73)** found ample application against a number of different fungal pathogens in fruits, vegetables and ornamentals, while polyoxin D



Scheme 6

(**74**) is marketed as Zn salt for the control of *Rhizoctonia solani* (rice sheath blight) and *Alternaria kikuchiana* (pear black spot).[76] Several total syntheses have been described for polyoxins B (**73**),[77] C,[78] D (**74**),[77] J (**77**)[79-81] and L (**78**).[81] Also several unnatural derivatives of the polyoxins have been prepared and screened for biological activity. Modifications have been made in all parts of the molecule, for instance the peptidyl side chain was exchanged by α-amino fatty acids[82] or by tryptophan;[83] polyoxins have been prepared with carbocyclic[84] or 2'-deoxygenated[85] carbohydrate moieties, the nucleobase was altered by introduction of fluorine substituents[86] and by replacement of the original pyrimidine by a purine.[87] With polyoxin N[88] and neopolyoxins A and B,[89] also three members of the polyoxin family have been isolated with five-membered pyrazolinone or imidazolinone nucleobases. The neopolyoxins show especially excellent activity against *Pyricularia oryzae* (rice blast), *Botrytis cinerea* (grey mould) and *Cochliobolus miyabeanus* (brown spot).[89] Further chitin synthetase inhibitors with fungicidal properties are the nikkomycins, which are related to the polyoxin family. They will be discussed in chapter 4.1.

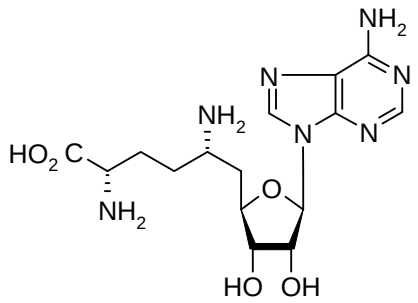
The readily available aldehyde (**82**) was the common starting material in two completely different stereoselective total syntheses of thymine polyoxin C (deoxypolyoxin C, **85**). Dondoni and coworkers[80,90] converted **82** into the *N*-benzylnitrone (**81**) (Scheme 6). The stereoselective addition of 2-lithiofuran to **81** was achieved by complexation of the nitrone with diethylaluminum chloride. The resulting *N*-benzylhydroxylamine was then converted into the glycosyl α-amino ester (**91**) through a sequence of oxidation and protecting group transformations. Vorbrüggen coupling with the silylated nucleobase and deprotection delivered thymine polyoxin C (**85**).[80,90]

A different approach was used by Barrett and Lebold (Scheme 6).[78] The aldehyde (**82**) was condensed with (phenylthio)nitromethane, and the resulting nitro olefin (**83**) was converted into the corresponding nitronate by addition of potassium trimethylsilanoate. Ozonolysis of this nitronate afforded stereoselectively the α-hydroxy thioester (**86**), which could be further elaborated into the α-azido ester (**92**). Vorbrüggen coupling with the same silylated nucleobase used by Dondoni *et al.* followed by deprotection and azide reduction led to the desired product (**85**).[78]

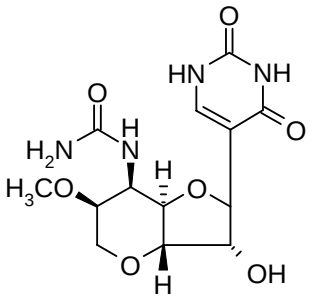
3.3 Miscellaneous Fungicidally Active Nucleosides

Sinefungin (**93**) was isolated from a strain of *Streptomyces griseolus* (NRRL 3739) (Figure 10).[91] This unusual α-amino acid is a competitive inhibitor of different methyltransferases, blocking for instance transmethylation reactions of RNA and proteins.[92] Sinefungin is quite active against foliar diseases like *Erysiphe polygoni* (pea powdery mildew) and *Uromyces phaseoli* (bean rust).[91]

The bicyclic C-nucleoside Malayamycin A (**94**) was isolated from *Streptomyces malaysiensis* (Figure 10).[93] Its total synthesis was recently described by Hanessian and coworkers.[93] Malayamycin displays efficacy against a range of different phytopathogenic fungi, its mode of action is still unknown.



93
sinefungin



94
malayamycin

Figure 10

4 INSECTICIDES

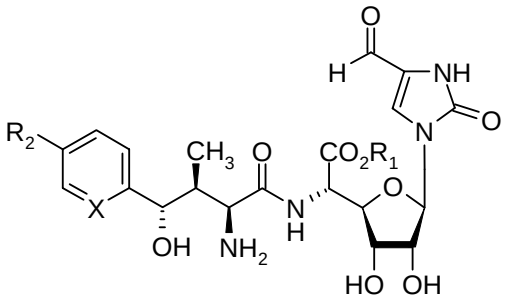
4.1 Nikkomycin X (98) and other inhibitors of Chitin Synthetase

The fact, that chitin, which was discussed already as a structural component of fungal cell walls, forms also the exoskeleton of invertebrates, but does not exist in green plants or vertebrates, makes *chitin synthetase*, the enzyme responsible for the chitin bioproduction, an ideal target for crop protection. As a result, inhibitors of this enzyme, like the above mentioned polyoxins and nikkomycins, exhibit marked activity against phytopathogenic fungi and insects, but are not toxic to bacteria, plants or animals.

In 1970, the first nikkomycin was isolated as metabolite of *Streptomyces tendae*.[94,95] The elucidation of most of the structures was accomplished by the groups of Hagenmaier and König (Figure 11).[96] Their mode of action was confirmed by studies on chitin synthetase isolated from insects.[97] The nikkomycin family consist of several structurally similar derivatives. In contrast to the related polyoxins which bear almost all six-membered uracil-based nucleobases, in the field of nikkomycins also a five-membered formyl-substituted imidazolinone nucleobase is of importance, whose biosynthetic source is L-histidine.[98] Most of the nikkomycins display besides an already mentioned fungicidal activity also potent insecticidal and acaricidal efficacy. A mixture of nikkomycins X (**98**) and Z (**100**) was once taken into consideration for commercial use against *Tetranychus urticae* (two-spotted spider mite).[99] So far total syntheses are only described for nikkomycins B (**95**)[100] and Z (**100**).[101] The combinatorial synthesis of libraries with hundreds of novel nikkomycin analogues was accomplished by a Ugi four component condensation on a solid support.[102]

Nikkomycin C (**103**), one of the two amino acids of nikkomycin Z (**100**), could be recently converted into interesting nikkomycin derivatives (Scheme 7). A 4 : 3 mixture of the cycloadducts (**101**) and (**102**) was obtained in a thermal cascade reaction of nikkomycin C with pyridine-2-carboxaldehyde and *N*-methylmaleimide.[103] After the initial formation of the imine of the amino acid, the decarboxylative formation of an azomethine ylide and a subsequent cycloaddition with a dipolarophile leads to the

diastereomeric **101** and **102**. Both pyrrolidino-pyrrolidindiones result from endo-cycloaddition to either diastereotopic face of the intermediate azomethine ylide.[103]

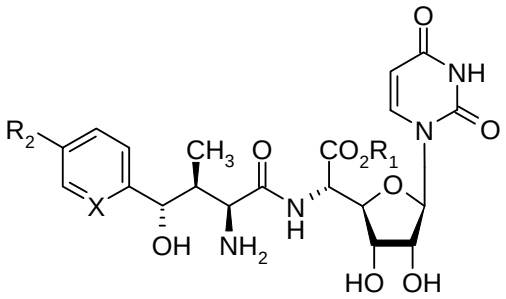


95
nikkomycin B (R_1 = OH, R_2 = OH, X = CH)

96
nikkomycin E (R_1 = OH, R_2 = H, X = N)

97
nikkomycin I (R_1 = $NHCH(CO_2H)CH_2CH_2CO_2H$, R_2 = OH, X = N)

98
nikkomycin X (R_1 = OH, R_2 = OH, X = N)

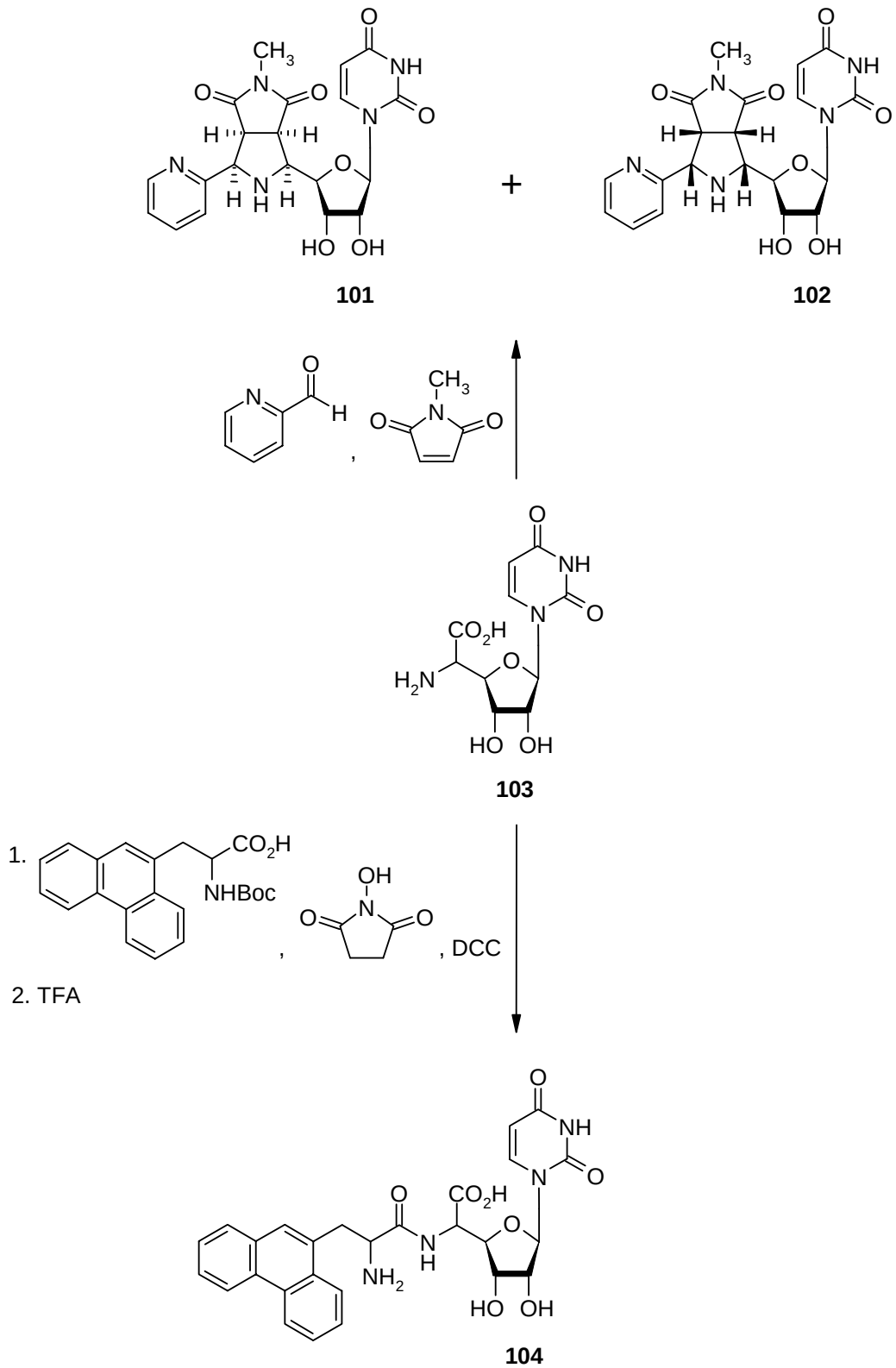


99
nikkomycin J (R_1 = $NHCH(CO_2H)CH_2CH_2CO_2H$, R_2 = OH, X = N)

100
nikkomycin Z (R_1 = OH, R_2 = OH, X = N)

Figure 11

On the other hand, nikkomycin C can be linked to other amino acids by standard peptide coupling methods (Scheme 7). The nikkomycins (and the polyoxins too) enter the fungal or insect cell *via* a dipeptide transport pathway,[104] therefore the replacement of the terminal peptide moiety of nikkomycins by another non-proteogenic amino acid might lead to nikkomycin analogues with even better ability to penetrate the target cell walls. Actually **104**, which bears a lipophilic phenanthrene group at the terminal



Scheme 7

amino acid, possesses with an IC_{50} value of 0.31 (μg/mL) a slightly better *in vitro* chitin synthetase inhibition than nikkomycin Z (**100**, IC_{50}: 0.393 μg/mL).[105]

4.2 Miscellaneous Insecticidally Active Nucleosides

Clitocine (**105**), isolated from the mushroom *Clitocybe inversa*, shows strong insect growth inhibitory activity against *Pectinophora gossipiella* (pink bollworm) (Figure 12).[106] The nucleotide thuringiensin

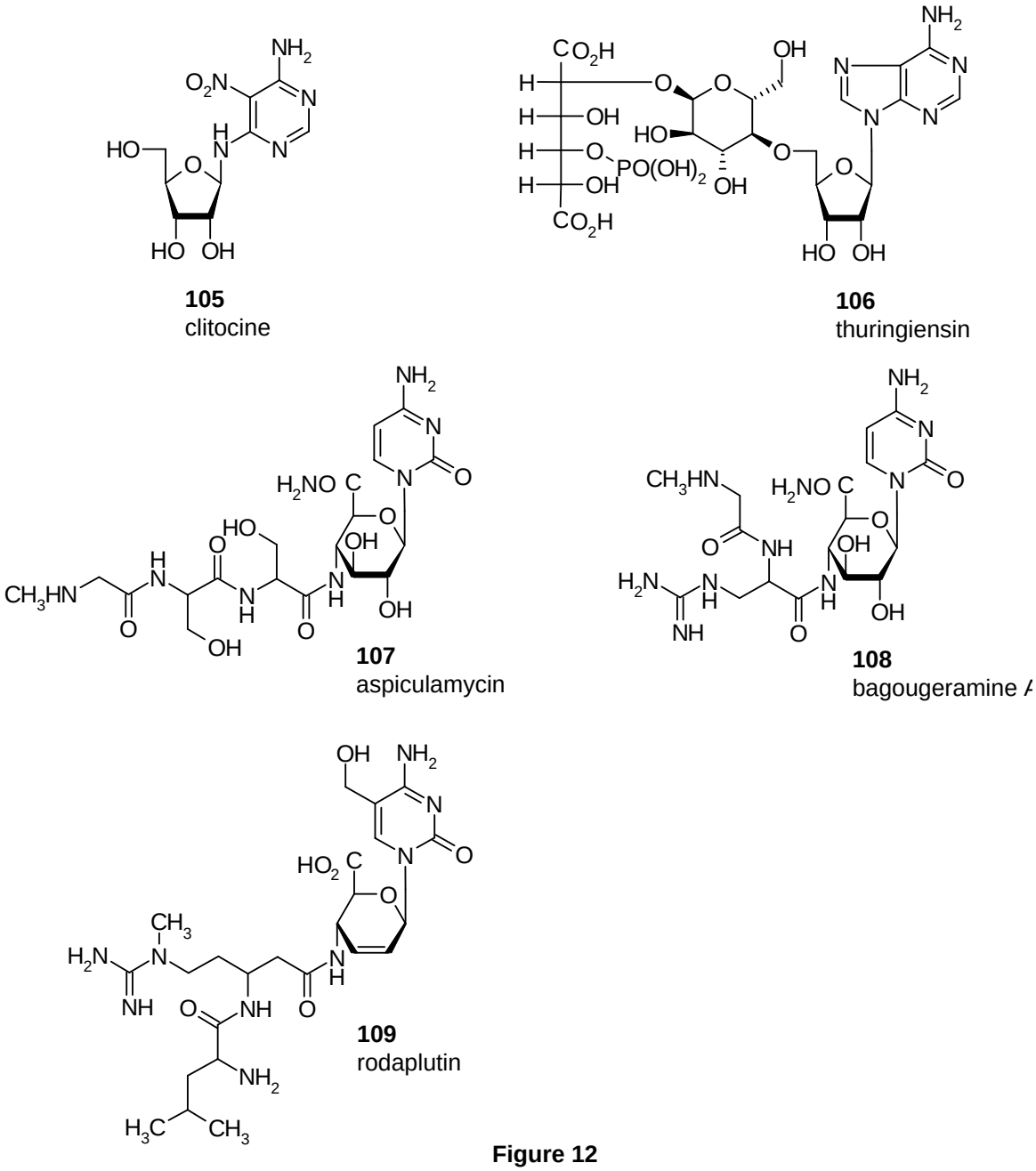


Figure 12

(*beta*-exotoxin, **106**), a metabolite isolated from *Bacillus thuringiensis*, possesses high insecticidal activity.[107,108] At very low use rates of about 50 g / ha, it is very effective against *Leptinotarsa decemlineata* (Colorado potato beetle),[109] *Lygus hesperus* (lygus bug),[110] *Heliotis virescens* (tobacco budworm)[111] and *Panonychus ulmi* (European red mite).[112] The two peptidylnucleosides aspiculamycin (**107**) and bagougeramine A (**108**) bear both cytosine as nucleobase and a gluco-pyranosyl sugar moiety.

Both display excellent acaricidal activty against *Tetranychus urticae* (two-spotted spider mite).[113,114] Aspiculamycin (**107**) was isolated from the fermentation broth of *Streptomyces toyocaensis* var. *aspiculamyceticus*,[113] Bagougeramine A (**108**) is produced by *Bacillus circulans*.[114] Finally, the peptidylnucleoside rodaplutin (**109**) was isolated from *Nocardioides albus* strains and is active against a broad range of insects and mites, for instance *Phaedon cochlearia* (mustard beetle), *Plutella maculipennis* (diamondback moth), *Myzus persicae* (peach-potato aphid), *Dysdercus intermedius* (cotton stainer) and *Tetranychus urticae* (two-spotted spider mite).[115]

5 CONCLUSION

Many nucleosides display significant biological activities in the control of weeds, insects and plant diseases. Their structural diversity is impressive as well as the wide range of different modes of actions involved. Most of these nucleosides were first isolated from nature. This fact emphasizes the importance of natural product chemistry as a relentless supplier of novel lead structures in crop protection research.

ACKNOWLEDGEMENT

The author is very grateful to his nucleoside-experienced Syngenta colleagues Wayne Craig, Kurt Nebel, Tony O'Sullivan and Sebastian Wendeborn for helpful and stimulating discussions.

REFERENCES AND NOTES

1. Part two of a series of reviews about "Chemistry in Crop Protection". For part one see: C. Lamberth, *J. Sulfur Chem.*, 2004, **25**, 39.
2. J. Stetter and F. Lieb, *Angew. Chem.*, 2000, **112**, 1792; *Angew. Chem., Int. Ed.*, 2000, **39**, 1724; *Agrochemical Discovery: Insect, Weed and Fungal Control*, ACS Symposium Series 774, ed. by D. R. Baker and N. K. Umetsu, American Chemical Society, Washington DC, 2001.
3. J. P. Pachlatko, *Chimia*, 1998, **52**, 29; L. Crombie, *Pestic. Sci.*, 1999, 55, 761; G. D. Crouse in *Pesticides: Managing Risks and Optimizing Benefits*, ACS Symposium Series 734, ed. by N. N. Ragsdale and J. N. Seiber, American Chemical Society, Washington DC, 1999, p. 80.
4. For some recent reviews on bioactive nucleosides see: D. M. Huryn and M. Okabe, *Chem. Rev.*, 1992, **92**, 1745; S. Knapp, *Chem. Rev.*, 1995, **95**, 1859; C. Lamberth, *Org. Prep. Proced. Int.*, 1999, **31**, 379; K. W. Pankiewicz, *Carbohydr. Res.*, 2000, **327**, 87; C. Lamberth, *Org. Prep. Proced. Int.*, 2002, **34**, 149.
5. G. M. Ramos Tombo and D. Bellus, *Angew. Chem.*, 1991, **103**, 1219; *Angew. Chem., Int. Ed.*, 1991, **30**, 1193; J. Crosby, *Pestic. Sci.*, 1996, 46, 11; N. Kurihara and J. Miyamoto (Eds.), *Chirality in Agrochemicals*, Wiley, Chichester 1998.

6. M. Nakajima, K. Itoi, Y. Takamatsu, T. Kinoshita, T. Okazaki, K. Kawakubo, M. Shindo, T. Honma, M. Tohjigamori, and T. Haneishi, *J. Antibiot*., 1991, **44**, 293; H. Haruyama, T. Takayama, T. Kinoshita, M. Kondo, M. Nakajima, and T. Haneishi, *J. Chem. Soc., Perkin Trans*. 1, 1991, 1637.
7. R. Fonne-Pfister, P. Chemla, E. Ward, M. Girardet, K. E. Kreuz, R. B. Honzatko, H. J. Fromm, H.-P. Schär, M. G. Grütter, and S. W. Cowan-Jacob, *Proc. Natl. Acad. Sci. U.S.A.*, 1996, **93**, 9431; B. W. Poland, S.-F. Lee, M. V. Subramanian, D. L. Siehl, R. J. Anderson, H. J. Fromm, and R. B. Honzatko, *Biochemistry*, 1996, **35**, 15753; D. R. Heim, C. Cseke, B. C. Gerwick, M. G. Murdoch, and S. B. Green, *Pestic. Biochem. Physiol*., 1995, **53**, 138.
8. M. Shiozaki, *Carbohydr. Res*., 2001, **335**, 147; M. Shiozaki, *Carbohydr. Res*., 2002, **337**, 2077.
9. T. Früh, P. Chemla, J. Ehrler, and S. Farooq, *Pestic. Sci.*, 1996, **46**, 37.
10. N. Nakajima, M. Matsumoto, M. Kirihara, M. Hashimoto, T. Katoh, and S. Terashima, *Tetrahedron*, 1996, **52**, 1177.
11. S. Mio, Y. Kumagawa, and S. Sugai, *Tetrahedron*, 1991, **47**, 2133; M. Matsumoto, M. Kirihara, T. Yoshino, T. Katoh, and S. Terashima, *Tetrahedron Lett*., 1993, **34**, 6289; P. Chemla, *Tetrahedron Lett*., 1993, **34**, 7391.
12. S. Mio, R. Ichinose, K. Goto, S. Sugai, and S. Sato, *Tetrahedron*, 1991, **47**, 2111.
13. P. M. Harrington and M. E. Jung, *Tetrahedron Lett*., 1994, **35**, 5145.
14. H.-P. Fischer, H.-P. Buser, P. Chemla, P. Huxley, W. Lutz, S. Mirza, G. M. Ramos Tombo, G. Van Lommen, and V. Sipido, *Bull. Soc. Chim. Belg*., 1994, **103**, 565.
15. S. Mio, M. Ueda, M. Hamura, J. Kitagawa, and S. Sugai, *Tetrahedron*, 1991, **47**, 2145.
16. A. J. Fairbanks, P. S. Ford, D. J. Watkin, and G. W. J. Fleet, *Tetrahedron Lett*., 1993, **34**, 3327; A. J. Fairbanks and G. W. J. Fleet, *Tetrahedron*, 1995, **51**, 3881; N. Nakajima, M. Kirihara, M. Matsumoto, M. Hashimoto, T. Katoh, and S. Terashima, *Heterocycles*, 1996, **42**, 503.
17. S. Mio, M. Shiraishi, S. Sugai, H. Haruyama, and S. Sato, *Tetrahedron*, 1991, **47**, 2121.
18. S. Mio, H. Sano, M. Shindou, T. Honma, and S. Sugai, *Agric. Biol. Chem*., 1991, **55**, 1105; A. Renard, M. Kotera, and J. Lhomme, *Tetrahedron Lett*., 1998, **39**, 3129, A. Renard, M. Kotera, M.-C. Brochier, and J. Lhomme, *Eur. J. Org. Chem*., 2000, 1831.
19. H. Sano and S. Sugai, *Tetrahedron*, 1995, **51**, 4635; H. Sano and S. Sugai, *Tetrahedron: Asymmetry*, 1995, **6**, 1143.
20. J. W. Burton, J. C. Son, A. J. Fairbanks, S. S. Choi, H. Taylor, D. J. Watkin, B. G. Winchester, and G. W. J. Fleet, *Tetrahedron Lett*., 1993, **34**, 6119; T. W. Brandstetter, Y. Kim, J. C. Son, H. M. Taylor, P. M. de Q. Lilley, D. J. Watkin, L. N. Johnson, N. G. Oikonomakos, and G. W. J. Fleet, *Tetrahedron Lett*., 1995, **36**, 2149; T. W. Brandstetter, C. de la Fuente, Y. Kim, L. N. Johnson, S.

Crook, P. M. de Q. Lilley, D. J. Watkin, K. E. Tsitsanou, S. E. Zographos, E. D. Chrysina, N. G. Oikonomakos, and G. W. J. Fleet, *Tetrahedron*, 1996, **52**, 10721; J. C. Estevez, M. D. Smith, A. L. Lane, S. Crook, D. J. Watkin, G. S. Besra, P. J. Brennan, R. J. Nash, and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 1996, **7**, 387; Y. S. Agasimundin, M. W. Mumper, and R. S. Hosmane, *Bioorg. Med. Chem*., 1998, **6**, 911.

21. C. J. F. Bichard, E. P. Mitchell, M. R. Wormald, K. A. Watson, L. N. Johnson, S. E. Zographos, D. D. Koutra, N. G. Oikonomakos, and G. W. J. Fleet, *Tetrahedron Lett*., 1995, **36**, 2145; T. W. Brandstetter, M. R. Wormald, R. A. Dwek, T. D. Butters, F. M. Platt, K. E. Tsitsanou, S. E. Zographos, N. G. Oikonomakos, and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 1996, **7**, 157; J. C. Estevez, M. D. Smith, M. R. Wormald, G. S. Besra, P. J. Brennan, R. J. Nash, and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 1996, **7**, 391; E. Osz, E. Sos, L. Somsak, L. Szilagyi, and Z. Dinya, *Tetrahedron*, 1997, **53**, 5813.
22. H. Sano, S. Mio, J. Kitagawa, M. Shindou, T. Honma, and S. Sugai, *Tetrahedron*, 1995, **51**, 12563; C. Gasch, B. A. B. Salameh, M. A. Pradera, and J. Fuentes, *Tetrahedron Lett*., 2001, **42**, 8615.
23. H. Sano, S. Mio, N. Tsukaguchi, and S. Sugai, *Tetrahedron*, 1995, **51**, 1387.
24. H. Sano, S. Mio, M. Hamura, J. Kitagawa, M. Shindou, T. Honma, and S. Sugai, *Biosci. Biotech. Biochem*., 1995, **59**, 2247.
25. C. Lamberth and S. Blarer, *Synth. Commun*., 1996, **26**, 75.
26. L. A. Paquette, S. Brand, and C. Behrens, *J. Org. Chem*., 1999, **64**, 2010.
27. H. Sano, S. Mio, J. Kitagawa, and S. Sugai, *Tetrahedron: Asymmetry*, 1994, **5**, 2233.
28. P. R. Schmitzer, P. R. Graupner, E. L. Chapin, S. C. Fields, J. R. Gilbert, J. A. Gray, C. L. Peacock, and B. C. Gerwick, *J. Nat. Prod*., 2000, **63**, 777.
29. T. Sawa, Y. Fukagawa, I. Homma, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1967, **20**, 227; H. Nakamura, G. Koyama, Y. Iitaka, M. Ohno, N. Yagisawa, S. Kondo, K. Maeda, and H. Umezawa, *J. Am. Chem. Soc.*, 1974, **96**, 4327.
30. B. G. Isaac, S. W. Ayer, L. J. Letendre, and R. J. Stonard, *J. Antibiot*., 1991, **44**, 729.
31. B. D. Bush, G. V. Fitchett, D. A. Gates, and D. Langley, *Phytochemistry*, 1993, **32**, 737.
32. J. E. Dancer, R. G. Hughes, and S. D. Lindell, *Plant Physiol*., 1997, **114**, 119.
33. J. M. Milton, M. Konuk, and E. G. Brown, *Mycologist*, 1992, **6**, 44.
34. S. D. Lindell, B. A. Moloney, B. D. Hewitt, C. G. Earnshaw, P. J. Dudfield, and J. E. Dancer, *Bioorg. Med. Chem. Lett*., 1999, **9,** 1985.
35. P. J. Dudfield, V.-D. Le, S. D. Lindell, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2929.

36. G. Bojack, C. G. Earnshaw, R. Klein, S. D. Lindell, C. Lowinski, and R. Preuss, *Org. Lett.*, 2001, **3**, 839.

37. M. Ohno, N. Yagisawa, S. Shibahara, S. Kondo, K. Maeda, and H. Umezawa, *J. Am. Chem. Soc.*, 1974, **96**, 4326.

38. L. D. Hawkins, J. C. Hanvey, F. L. Boyd, D. C. Baker, and H. D. H. Showalter, *Nucleosides Nucleotides*, 1983, **2**, 479; H. J. Thomas, J. M. Riordan, and J. A. Montgomery, *Nucleosides Nucleotides*, 1986, **5**, 431.

39. E. Takahashi and T. Beppu, *J. Antibiot.*, 1982, **35**, 939; K. Isono, M. Uramoto, H. Kusakabe, N. Miyata, T. Koyama, M. Ubakata, S. K. Sethi, and J. A. McCloskey, *J. Antibiot.*, 1984, **37**, 670; K. Isono, M. Uramoto, H. Osada, M. Ubukata, H. Kusakabe, T. Koyama, N. Miyata, S. K. Sethi, and J. A. McCloskey, *Nucl. Acids Res. Symp. Ser.*, 1984, **15**, 65.

40. A. Scacchi, R. Bortolo, G. Cassani, and E. Nielsen, *Pest. Biochem. Physiol.*, 1994, **50**, 149.

41. H. Ueda, Y. Shoku, N. Hayashi, J. Mitsunaga, Y. In, M. Doi, M. Inoue, and T. Ishida, *Biochim. Biophys. Acta*, 1991, **1080**, 126.

42. K. Beautement, E. T. Chrystal, J. Howard, and S. M. Ridley, *Spec. Publ. – Royal Soc. Chem.*, 2000, **257**, 288.

43. J. Castro-Pichel, M. T. Garcia-Lopez, and F. G. De las Heras, *Tetrahedron*, 1987, **43**, 383.

44. M. Ubukata, H. Osada, J. Magae, and K. Isono, *Agric. Biol. Chem.*, 1988, **52**, 1117.

45. H. Kristinsson, K. Nebel, A. C. O'Sullivan, F. Struber, T. Winkler, and Y. Yamaguchi, *Tetrahedron*, 1994, **50**, 6825; H. Kristinsson, K. Nebel, A. C. O'Sullivan, J. P. Pachlatko, and Y. Yamaguchi, 'Synthesis and Chemistry of Agrochemicals, Vol. 4', ACS Symposium Series 584, ed. by D. R. Baker, J. G. Fenyes, and G. S. Basarab, American Chemical Society, Washington DC, 1995, pp. 206 – 219.

46. J. Castro-Pichel, M. T. Garcia-Lopez, F. G. De las Heras, and R. Herranz, *Liebigs Ann. Chem.*, 1988, 737.

47. M. Arai, T. Haneishi, N. Kitahara, R. Enokita, K. Kawakubo, and Y. Kondo, *J. Antibiot.*, 1976, **29**, 863; T. Haneishi, A. Terahara, H. Kayamori, J. Yabe, and M. Arai, *J. Antibiot.*, 1976, **29**, 870; Y. Takiguchi, H. Yoshikawa, A. Terahara, A. Torikata, and M. Terao, *J. Antibiot.*, 1979, **32**, 857; Y. Takiguchi, H. Yoshikawa, A. Terahara, A. Torikata, and M. Terao, *J. Antibiot.*, 1979, **32**, 862.

48. A. Terahara, T. Haneishi, M. Arai, T. Hata, H. Kuwano, and C. Tamura, *J. Antibiot.*, 1982, **35**, 1711.

49. H. Yoshikawa, Y. Takiguchi, and M. Terao, *J. Antibiot.*, 1983, **36**, 30.

50. N. J. Newcombe, M. F. Mahon, K. C. Molloy, D. Alker, and T. Gallagher, *J. Am. Chem. Soc.*, 1993, **115**, 6430; P. J. Cox, A. M. Griffin, N. J. Newcombe, S. Lister, M. V. J. Ramsay, D. Alker,

and T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1443; H. M. Binch and T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 1996, 401; H. M. Binch, A. M. Griffin ,and T. Gallagher, *Pure Appl. Chem.*, 1996, **68**, 589.

51. A. J. Fairbanks, E. Perrin, and P. Sinay, *Synlett*, 1996, 679.
52. F. Emery and P. Vogel, *Tetrahedron Lett.*, 1993, **34**, 4209; F. Emery and P. Vogel, *J. Org. Chem.*, 1995, **60**, 5843.
53. J. R. Bearder, M. L. Dewis, and D. A. Whiting, *Synlett*, 1993, 805; J. R. Bearder, M. L. Dewis, and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1995, 227.
54. S. Shuto, S. Ichikawa, and A. Matsuda, *Nucl. Acids Symp. Ser.*, 1999, **42**, 21; S. Ichikawa, S. Shuto, and A. Matsuda, *J. Am. Chem. Soc.*, 1999, **121**, 10270.
55. S. Ichikawa, S. Shuto, and A. Matsuda, *Tetrahedron Lett.*, 1998, **39**, 4525.
56. H. Ohigashi, M. Kaji, M. Sasaki, and K. Koshimizu, *Phytochemistry*, 1989, **28**, 1365.
57. S. W. Ayer, B. G. Isaac, D. M. Krupa, K. E. Crosby, L. J. Letendre, and R. J. Stonard, *Pestic. Sci*., 1989, **27**, 221.
58. J. Awaya, K. Matsuyama, Y. Iwai, S. Omura, H. Oiwa, Y. Hasegawa, and T. Ikai, *J. Antibiot.*, 1979, **32**, 1050.
59. D. Berg, R. R. Schmidt, K. Ditgens, W. Frommer, W. Gau, J. Kurz, D. Schmidt, C. Wünsche, and D. Schäfer, *Hoppe-Seyler's Z. Physiol. Chem*., 1980, **361**, 219.
60. O. Yamada, Y. Kaise, F. Futatsuya, S. Ishida, K. Ito, H. Yamamoto, and K. Munakata, *Agric. Biol. Chem*., 1972, **36**, 2013.
61. S. Murao and H. Hayashi, *Agric. Biol. Chem*., 1983, **47**, 1135.
62. A. Scacchi, R. Bortolo, G. Cassani, G. Pirali, and E. Nielsen, *J. Plant Growth Regul.*, 1992, **11**, 39.
63. S. Takeuchi, K. Hirayama, K. Ueda, H. Sakai, and H. Yonehara, *J. Antibiot.*, 1958, **11**, 1; N. Otake, S. Takeuchi, T. Endo, and H. Yonehara, *Tetrahedron Lett.*, 1965, 1411; H. Yonehara and N. Otake, *Tetrahedron Lett.*, 1966, 3785; N. Otake, S. Takeuchi, T. Endo, and H. Yonehara, *Agric. Biol. Chem.*, 1966, **30**, 132.
64. H. Yamaguchi and N. Tanaka, *J. Biochem.*, 1965, **60**, 632; H. Yamaguchi, C. Yamamoto, and N. Tanaka, *J. Biochem.*, 1965, **57**, 667.
65. H. Seto, I. Yamaguchi, N. Otake, and H. Yonehara, *Tetrahedron Lett.*, 1966, 3793; H. Seto, I. Yamaguchi, N. Otako, and H. Yonehara, *Agric. Biol. Chem.*, 1968, **32**, 1292; P. C. Prabhakaran, N.-T. Woo, P. S. Yorgey, and S. J. Gould, *J. Am. Chem. Soc.*, 1988, **110**, 5785; J. Guo and S. J. Gould, *Bioorg. Med. Chem. Lett.*, 1991, **1**, 497; S. J. Gould, J. Guo, A. Geitmann, and K. Dejesus, *Can. J. Chem.*, 1994, **72**, 6; Q. Zhang, M. C. Cone, S. J. Gould, and T. M. Zabriskie, *Tetrahedron*, 2000, **56**, 693.

66. A. Kawashima, H. Seto, T. Ishiyama, M. Kato, K. Uchida, and N. Otake, *Agric. Biol. Chem.*, 1987, **51**, 1183.

67. S. Harada and T. Kishi, *J. Antibiot.*, 1978, **31**, 519; S. Harada, E. Mizuta, and T. Kishi, *Tetrahedron*, 1981, **37**, 1317; S. Harada, E. Mizuta, and T. Kishi, *J. Am. Chem. Soc.*, 1978, **100**, 4895.

68. E. Feduchi, M. Cosin, and L. Carrasco, *J. Antibiot.*, 1985, **38**, 415.

69. T. Iwasa, K. Suetomi, and T. Kusuka, *J. Antibiot.*, 1978, **31**, 511.

70. D. W. Hollomon, *Pestic. Biochem. Physiol.*, 1979, **10**, 181.

71. T. Kondo, H. Nakai, and T. Goto, *Tetrahedron Lett.*, 1972, 1881; T. Kondo, H. Nakai, and T. Goto, *Tetrahedron*, 1973, **29**, 1801.

72. Y. Ichikawa, M. Ohbayashi, K. Hirata, R. Nishizawa, and M. Isobe, *Synlett*, 2001, 1763; Y. Ichikawa, K. Hirata, M. Ohbayashi, and M. Isobe, *Chem. Eur. J.*, 2004, **10**, 3241.

73. S. Suzuki, K. Isono, J. Nagatsu, T. Mizutani, Y. Kawashima, and T. Mizuno, *J. Antibiot. Ser. A*, 1965, **18**, 131; K. Isono and S. Suzuki, *Tetrahedron Lett.*, 1968, 1133; K. Isono and S. Suzuki, *Agric. Biol. Chem.*, 1968, **32**, 1193; K. Isono, K. Asahi, and S. Suzuki, *J. Am. Chem. Soc.*, 1969, **91**, 7490.

74. For excellent reviews of the polyoxins see: K. Isono and S. Suzuki, *Heterocycles*, 1979, **13**, 333; D. Zhang and M. J. Miller, *Curr. Pharm. Design*, 1999, **5**, 73.

75. A. Endo and T. Misato, *Biochem. Biophys. Res. Commun.*, 1969, **37**, 718; M. Hori, K. Kakiki, S. Suzuki, and T. Misato, *Agric. Biol. Chem.*, 1971, **35**, 1280; M. Hori, K. Kakiki, and T. Misato, *Agric. Biol. Chem.*, 1974, **38**, 691 and 699.

76. P. A. Worthington, *Nat. Prod. Rep.*, 1988, 5, 47.

77. K. Uchida, K. Kato, K. Yamaguchi, and H. Akita, *Heterocycles*, 2000, **53**, 2253.

78. A. G. M. Barrett and S. A. Lebold, *J. Org. Chem.*, 1990, **55**, 3853.

79. A. K. Gosh and Y. Wang, *J. Org. Chem.*, 1999, **64**, 2789; N. Chida, K. Koizumi, Y. Kitada, C. Yokoyama, and S. Ogawa, *J. Chem. Soc., Chem. Commun.*, 1994, 111; H. Kuzuhara, H. Ohrui, and S. Emoto, *Tetrahedron Lett.*, 1973, 5055.

80. A. Dondoni, F. Junquera, F. L. Merchan, P. Merino, and T. Tejero, *J. Chem. Soc., Chem. Commun.*, 1995, 2127; A. Dondoni, S. Franco, F. Junquera, F. L. Merchan, P. Merino, and T. Tejero, *J. Org. Chem.*, 1997, **62**, 5497.

81. H. Akita, K. Uchida, and K. Kato, *Heterocycles*, 1998, **47**, 157; K. Uchida, K. Kato, and H. Akita, *Synthesis*, 1999, 1678.

82. R. K. Khare, J. M. Becker, and F. R. Naider, *J. Med. Chem.*, 1988, **31**, 650.

83. P. Shenbagamurthi, H. A. Smith, J. M. Becker, A. Steinfeld, and F. Naider, *J. Med. Chem.*, 1983, **26**, 1518.

84. D. Zhang and M. J. Miller, *J. Org. Chem.*, 1998, **63**, 755; V. K. Aggarwal and N. Monteiro, *J. Chem. Soc. Perkin Trans. 1*, 1997, 2531; V. K. Aggarwal, N. Monteiro, G. J. Tarver, and S. D. Lindell, *J. Org. Chem.*, 1996, **61**, 1192.

85. C. Dehoux, E. Fontaine, J.-M. Escudier, M. Baltas, and L. Gorrichon, *Adv. Chitin Sci.*, 1997, **2**, 279; C. Dehoux, E. Fontaine, J.-M. Escudier, M. Baltas, and L. Gorrichon, *J. Org. Chem.*, 1998, **63**, 2601.

86. K. Isono, P. F. Crain, T. J. Odiorne, J. A. McCloskey, and R. J. Suhadolnik, *J. Am. Chem. Soc.*, 1973, **95**, 5788.

87. T. Azuma, K. Isono, P. F. Crain, and J. A. McCloskey, *J. Chem. Soc., Chem. Commun.*, 1977, 159; T. Azuma and K. Isono, *Chem. Pharm. Bull.*, 1977, **25**, 3347.

88. M. Uramoto, J. Uzawa, S. Suzuki, K. Isono, J. G. Liehr, and J. A. McCloskey, *Nucl. Acid Res.*, 1978, **5**, 327; M. Uramoto, M. Matsuoka, J. G. Liehr, J. A. McCloskey, and K. Isono, *Agric. Biol. Chem.*, 1981, **45**, 1901.

89. K. Kobinata, M. Uramoto, M. Nishii, H. Kusakabe, G. Nakamura, and K. Isono, *Agric. Biol. Chem.*, 1980, **44**, 1709; M. Uramoto, K. Kobinata, K. Isono, T. Higashijima, T. Miyazawa, E. E. Jenkins, and J. A. McCloskey, *Tetrahedron Lett.*, 1980, **21**, 3395; M. Uramoto, K. Kobinata, K. Isono, T. Higashijima, T. Miyazawa, E. E. Jenkins, and J. A. McCloskey, *Tetrahedron*, 1982, **38**, 1599.

90. A. Dondoni, F. Junquera, F. L. Merchan, P. Merino, and T. Tejero, *Tetrahedron Lett*., 1994, **35**, 9439.

91. R. L. Hamill and M. M. Hoehn, *J. Antibiot.*, 1973, **26**, 463; R. S. Gordee and T. F. Butler, *J. Antibiot.*, 1973, **26**, 466.

92. M. Vedel, F. Lawrence, M. Robert-Gero, and E. Lederer, *Biochem. Biophys. Res. Commun.*, 1978, **85**, 371; R. T. Borchardt, L. E. Eiden, B. Wu, and C. O. Rutledge, *Biochem. Biophys. Res. Commun.*, 1979, **89**, 919; A. W. Li, R. A. Singer, and G. C. Johnston, *Arch. Biochem. Biophys.*, 1985, **240**, 613.

93. S. Hanessian, S. Marcotte, R. Machaalani, and G. Huang, *Org. Lett.*, 2003, **5**, 4277.

94. U. Dähn, H. Hagenmaier, H. Höhne, W. A. König, G. Wolf, and H. Zähner, *Arch. Microbiol.*, 1976, **107**, 143.

95. For excellent reviews of the nikkomycins see: H. P. Fiedler, T. Schuez, and H. Decker, *Clin. Dermatol*., 1993, **7,** 325; D. Zhang and M. J. Miller, *Curr. Pharm. Design*, 1999, **5**, 73.

96. H. Hagenmaier, A. Keckeisen, H. Zähner, and W. A. König, *Liebigs Ann. Chem.*, 1979, 1494; W. A. König, W. Hass, W. Dehler, H.-P. Fiedler, and H. Zähner, *Liebigs Ann. Chem.*, 1980, 622; H. Hagenmaier, A. Keckeisen, W. Dehler, H.-P. Fiedler, H. Zähner, and W. A. König, *Liebigs Ann. Chem.*, 1981, 1018; W. A. König, H. Hahn, R. Rathmann, W. Hass, A. Keckeisen, H. Hagenmaier, C. Bormann, W. Dehler, R. Kurth, and H. Zähner, *Liebigs Ann. Chem.*, 1986, 407.

97. E. Cohen and J. E. Casida, *Pestic. Biochem. Physiol.*, 1980, **13**, 129; U. Mothes and K.-A. Seitz, *Pestic. Sci.*, 1982, **13**, 426; U. Mothes-Wagner, *Pestic. Sci.*, 1986, **17**, 607.

98. D. R. Evans, R. B. Herbert, S. Baumberg, J. H. Cove, E. A. Southey, A. D. Buss, M. J. Dawson, D. Noble, and B. A. M. Rudd, *Tetrahedron Lett.*, 1995, **36**, 2351.

99. G. Zoebelein and U. Kniehase, *Pflanzenschutz-Nachr. Bayer*, 1985, **38**, 203.

100. A. G. M. Barrett and S. A. Lebold, *J. Org. Chem.*, 1990, **55**, 5818; A. G. M. Barrett and S. A. Lebold, *J. Org. Chem.*, 1991, **56**, 4875; H. Akita, C. Y. Chen, and K. Uchida, *Tetrahedron: Asymmetry*, 1995, **6**, 2131; H. Akita, C. Y. Chen, and K. Kato, *Tetrahedron*, 1998, **54**, 11011.

101. A. K. Saksena, R. G. Lovey, V. M. Girijavallabhan, H. Guzik, and A. K. Ganguly, *Tetrahedron Lett.*, 1993, **34**, 3267.

102. A. Suda, A. Ohta, M. Sudoh, T. Tsukuda, and N. Shimma, *Heterocycles*, 2001, **55**, 1023.

103. H. A. Dondas, C. W. G. Fishwick, R. Grigg, and C. Kilner, *Tetrahedron*, 2004, **60**, 3473.

104. H. Müller, R. Furter, H. Zahner, and D. M. Rast, *Arch. Microbiol.*, 1981, **130**, 195; P. J. McCarthey, D. J. Newman, L. J. Nisbet, and W. D. Kingsbury, *Antimicrobial Agents and Chemotherapy*, 1985, **28**, 494.

105. K. Obi, J. Uda, K. Iwase, O. Sugimoto, H. Ebisu, and A. Matsuda, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1451.

106. I. Kubo, M. Kim, W. F. Wood, and H. Naoki, *Tetrahedron Lett.*, 1986, **27**, 4277; T. Kamikawa, S. Fujie, Y. Yamagiwa, M. Kim, and H. Kawaguchi, *J. Chem. Soc., Chem. Commun.*, 1988, 195.

107. J. Farkas, K. Sebesta, K. Horska, Z. Samek, L. Dolejs, and F. Sorm, *Coll. Czech. Chem. Commun.*, 1969, **34**, 1118; L. Kalvoda, M. Prystas, and F. Sorm, *Coll. Czech. Chem. Commun.*, 1973, **38**, 2529; L. Kalvoda, M. Prystas, and F. Sorm, *Tetrahedron Lett.*, 1973, 1873.

108. For excellent reviews on thuringiensin see: K. Sebesta, *Frontiers in Bioorganic Chemistry and Molecular Biology*, Proc. Int. Symp., ed. by S. N. Ananchenko, Pergamon, Oxford, 1980, pp. 193 – 200; K. Sebesta, J. Farkas, K. Horska, and J. Vankova, *Microbial Control of Pests and Plant Diseases 1970 - 1980*, ed. by H. D. Burges, Academic, London, 1981, pp. 249 – 281.

109. T. E. Anderson, A. E. Hajek, D. W. Roberts, H. K. Preisler, and J. L. Robertson, *J. Econ. Entomol.*, 1989, **82**, 83.

110. L. K. Tanigoshi, D. F. Mayer, J. M. Babcock, and J. D. Lunden, *J. Econ. Entomol.*, 1990, **83**, 2200.

111. D. A. Wolfenbarger, A. A. Guerra, H. T. Dulmage, and R. D. Garcia, *J. Econ. Entomol.*, 1972, **65**, 1245.

112. R. N. Royalty, F. R. Hall, and B. A. Lucius, *Pestic. Sci.*, 1991, **33**, 383.

113. M. Arai, T. Haneishi, R. Enokita, and H. Kayamori, *J. Antibiot.*, 1974, **27**, 329; T. Haneishi, A. Terahara, and M. Arai, *J. Antibiot.*, 1974, **27**, 334; T. Haneishi, M. Arai, N. Kitano, and S. Yamamoto, *J. Antibiot.*, 1974, **27**, 339.

114. A. Takahashi, N. Saito, K. Hotta, Y. Okami, and H. Umezawa, *J. Antibiot.*, 1986, **39**, 1033; A. Takahashi, D. Ikeda, H. Naganawa, Y. Okami, and H. Umezawa, *J. Antibiot.*, 1986, **39**, 1041.

115. H. Dellweg, J. Kurz, W. Pflüger, M. Schedel, G. Vobis, and C. Wünsche, *J. Antibiot.*, 1988, **41**, 1145.