Chapter 3
N-glycosides

N-glycosides are generated when a sugar component is attached to an aglycon, through a nitrogen atom, establishing as a result a C–N–C linkage. Nucleosides are among the most relevant *N*-glycosides since they are essential components of DNA, RNA, cofactors, and a variety of antiviral and antineoplastic drugs.

Usually for nucleosides, a pyrimidine or purine base is linked to the anomeric carbon of a furanoside ring. The nucleosides responsible for the formation of the genetic material DNA and RNA are: adenine, guanine, cytosine, and thymine, the latter replaced with uracil in the case of RNA (Scheme 3.1). Nucleosides can be classified into natural nucleosides such as those involved in the genetic storage of information, naturally modified nucleosides, and synthetic nucleosides.

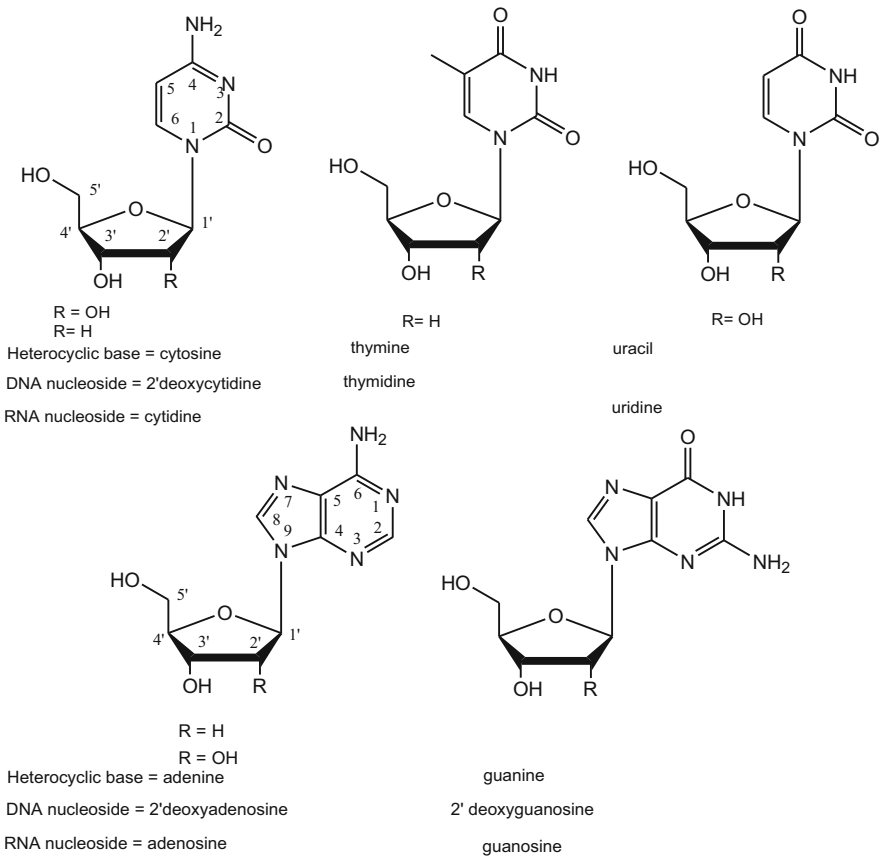
Naturally modified nucleosides include a significant and diverse number of compounds, some of them with slight changes mostly at the base, or major structural modifications done by enzymes. So far most of them have unknown biochemical function [1], nonetheless they have been strongly associated with antiviral, antitumoral, and growth regulation processes (Scheme 3.2).

Representative examples of natural modified nucleosides include queuosine (Q) and Wye base (W) which have been found in the tRNA of some plants and bacteria, and they play an important role in the inhibition of tumor processes. Derived from this relevant biological function the total synthesis of these unique nucleosides has been reported for Q [2–4] and W [5].

Moreover, the synthesis of complex nucleoside antibiotics has been reviewed [6, 7]. The analysis was focused on the challenging synthetic methods for carbohydrate and nucleoside chain elaboration, glycosidation, methods for controlling stereochemistry and for joining subunits. As a result, the total synthesis of polyoxin J [8], sinefungin [9], thuringiensin [10], tunicamycin V [11], nikkomycin B, [12] octosyl acid A [13], hikizimycin [14], and capuramycin [15] was completed (Scheme 3.3).

Important cofactors playing a key rule as biological catalysts required by the enzymes for the optimal performance of biochemical transformations are nucleotides.

M. Brito-Arias, *Synthesis and Characterization of Glycosides*,
DOI 10.1007/978-3-319-32310-7_3

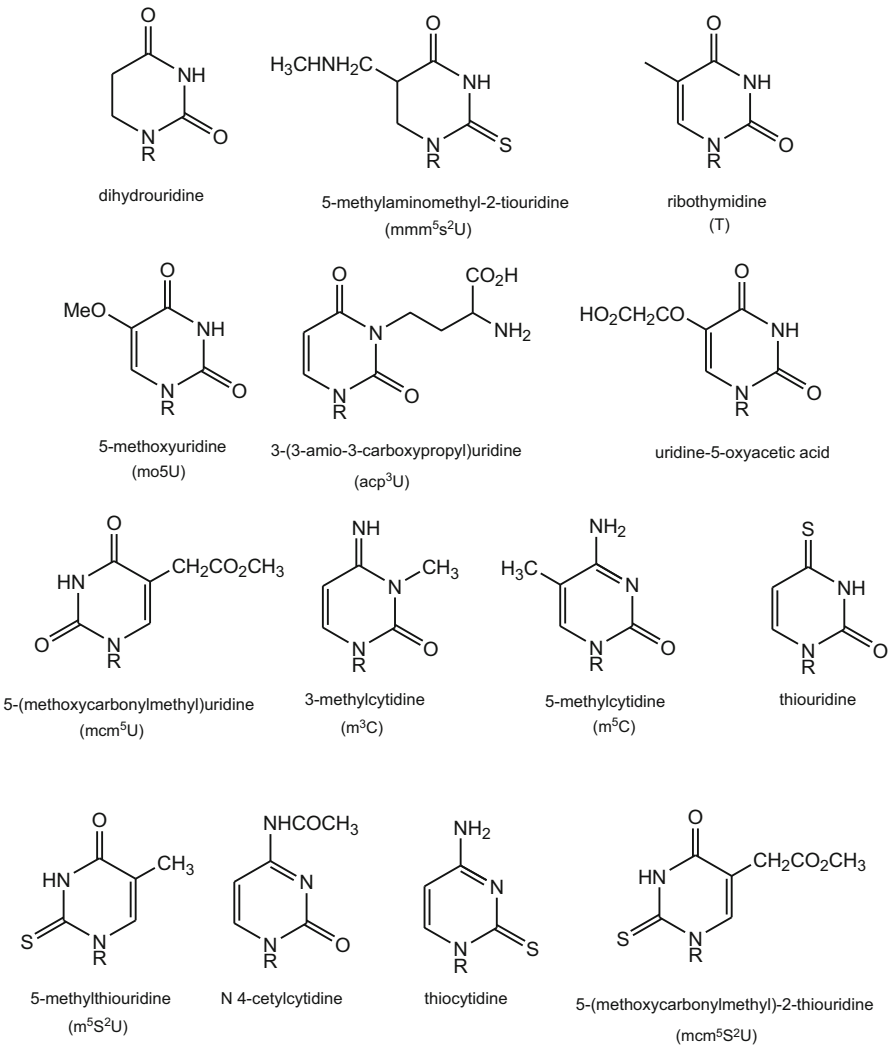


Scheme 3.1 DNA and RNA nucleosides

Such is the case of Adenosine triphosphate ATP and Nicotinic acid adenine dinucleotide NAD that are constituted by an adenosine nucleoside combined with phosphate for the former, and phosphate and nicotinamide for the latter (Scheme 3.4).

3.1 Nucleoside Formation

Considering a disconnection analysis there are two major general routes for nucleoside syntheses [16]. The first is based on the attachment between the aglycon base and the protected sugar activated with a good leaving group at the anomeric position. Under these conditions, the stereoselectivity is conditioned by the protecting group attached at position 2. The second general procedure considers the coupling reaction between a base precursor and the sugar derivative which contains the free amine linked to the anomeric carbon. The ring closure generally takes place after

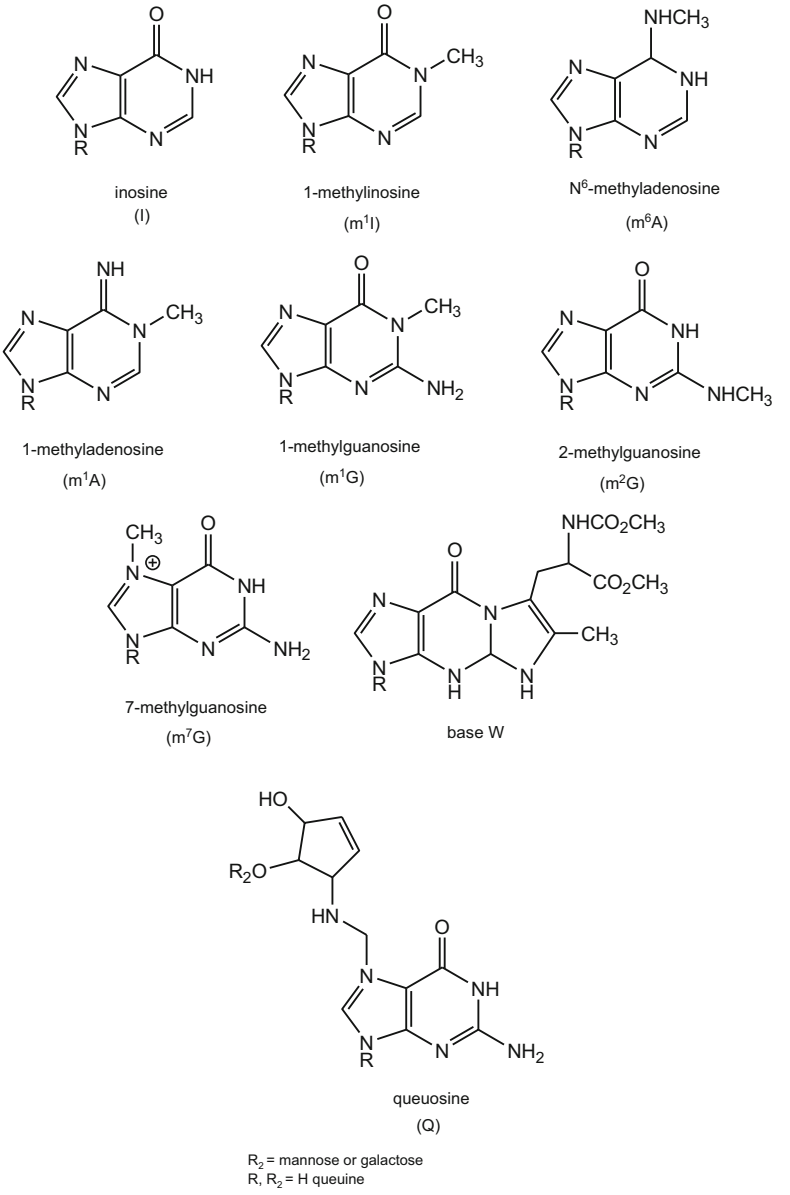


Scheme 3.2 Naturally modified nucleosides

the glycosidation reaction and the configuration is predetermined by the nitrogen attached to the anomeric carbon. The latter approach has been most efficiently used for preparing carbocyclic nucleosides (Scheme 3.5).

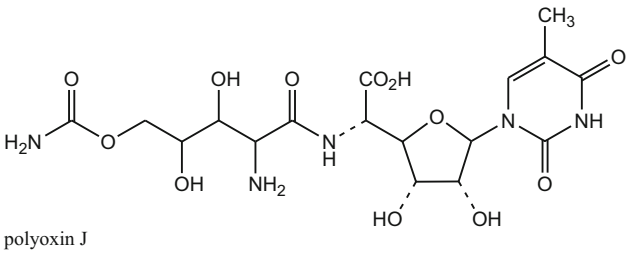
3.2 Protecting Groups

It has been mentioned in the previous chapter that protecting groups are important components for most of the general methodologies designed for establishing glycosidic bonds. Usually the methods for glycoside formation require prior protection of

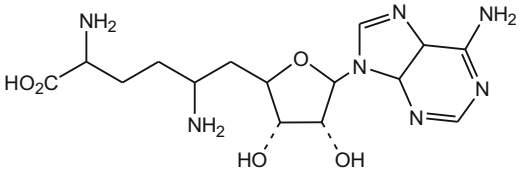


Scheme 3.2 (continued)

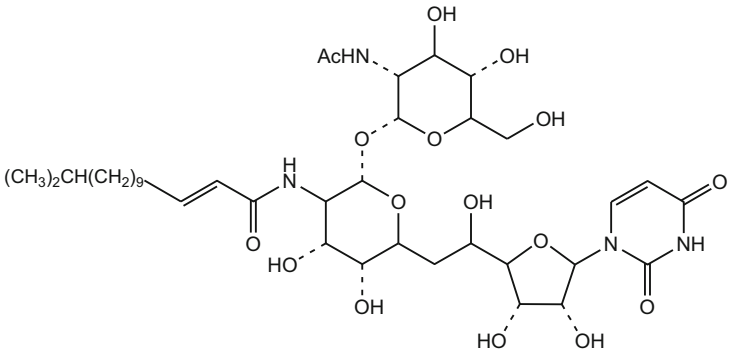
those elements (usually heteroatoms) within the molecule that are needed to remain unaltered. Also important is the fact that the cleavage of the protecting group should be carried out under preferentially mild conditions and in the case of complex nucleosides the installation and removal of the protecting groups for nitrogen, oxygen,



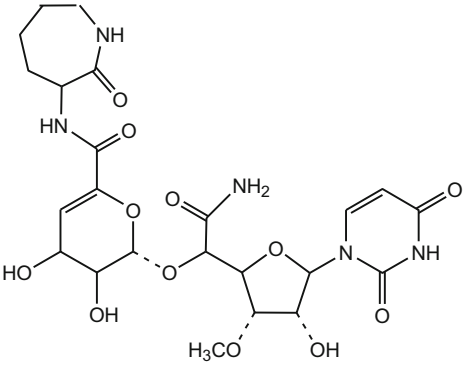
polyoxin J



sinefungin

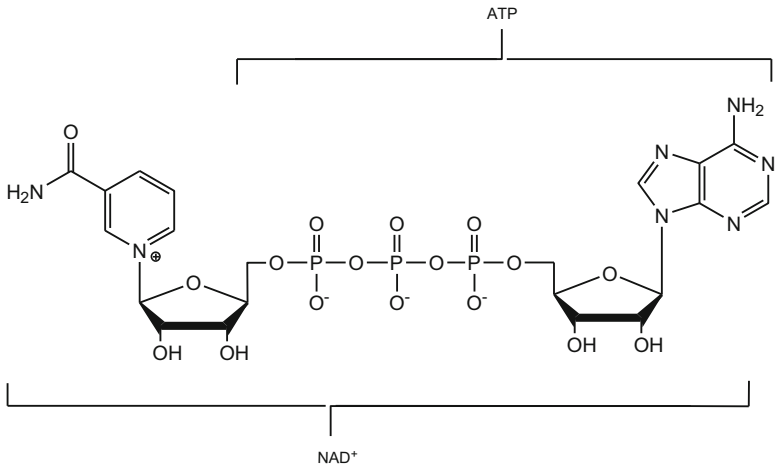


tunicamycin V

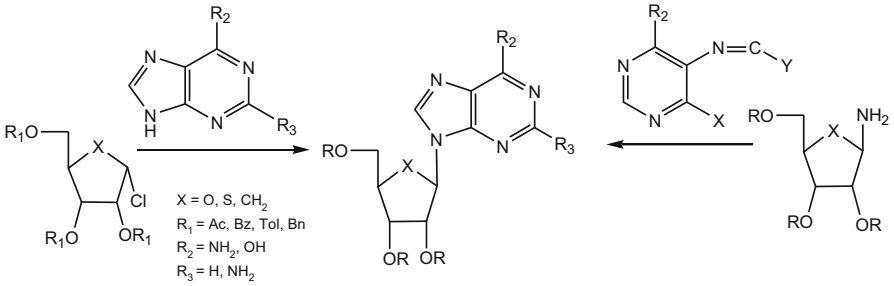


capuramycin

Scheme 3.3 Complex nucleoside antibiotics



Scheme 3.4 Structure of nucleoside cofactors ATP and NAD



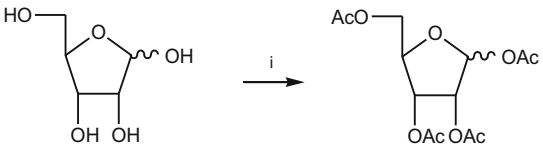
Scheme 3.5 General procedures for *N*-glycoside formation

and sulfur should be accomplished under compatible conditions. The protection and deprotection of nucleosides can be done by chemical or enzymatic means. Some of the most commonly used protecting groups used in the preparation of *O*-glycosides are also useful in the synthesis of nucleosides (Scheme 3.6).

3.2.1 Ribofuranoside Protecting Groups

Enzymes have been found to be interesting alternatives for installing protecting groups on nucleosides. Some of the enzymes used for this purpose are *subtilisin* mutant (8350) [18, 19] and lipases mainly from *Pseudomonas* and *Candida* strains [20, 21]. Representative protections of purine and pyrimidine nucleosides are indicated in Scheme 3.7.

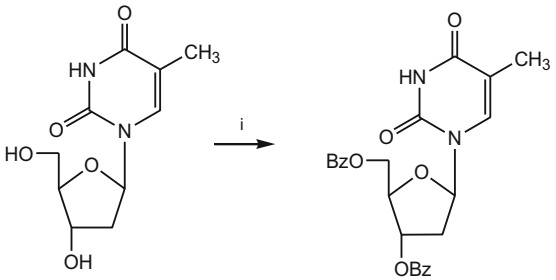
Acetate (CH_3CO-)



i) Ac_2O, CH_2Cl_2, DMAP, r.t.

cleavage: (1) NaOMe, MeOH.
(2) Aqueous NH_3, dioxane.

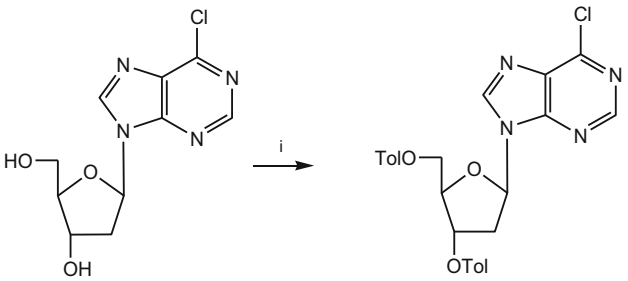
Benzoyl (PhCO-).



i) Bz-Cl, pyridine.

cleavage: (1) R-NH_2, EtOH, 100°C.
(2) EtOH, KOH, reflux, 3h.
(3) NH_3, MeOH

Toluyl (p-MePhCO-)

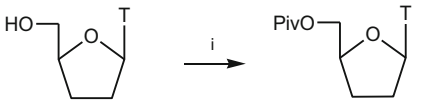


i) Tol-Cl, pyridine.

cleavage: NH_3, MeOH, 100°C, 78%.

Scheme 3.6 Common ribose protecting groups [17]

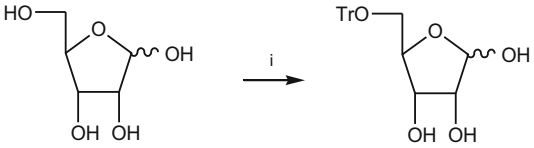
Pivaloyl (Me_3CCOCl)



i) Piv-Cl, pyridine.

cleavage: NaOMe, MeOH.

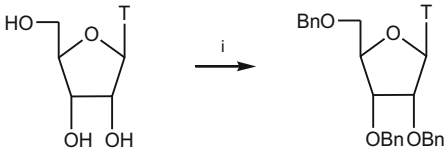
Trityl (Ph_3C-)



i) Tr-Cl, pyridine, r.t.

cleavage: (1) 80%, AcOH, 60ºC.
(2) HCO_2H, Et_2O.

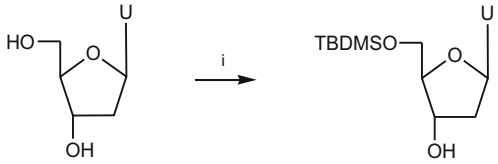
Benzyl ($PhCH_2$-)



i) BnBr, NaH, DMF.

cleavage: $H_2/Pd(OH)_2$, EtOH.

Tertbutyldimethylsilyl ($^tBuMe_2Si$-)

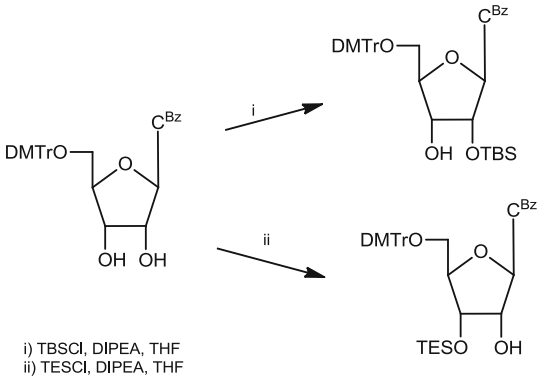


i) TBDMS-Cl, pyridine, r.t.

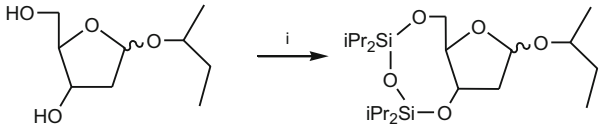
cleavage: (1) tetrabutylammonium fluoride (TBAF).
(2) pTsOH,MeOH,H_2O,7h.

Triethylsilane (TES-), *tert*-butyldimethylsilyl (TBS-)

Scheme 3.6 (continued)



Tetraisopropylsilyl ([(^{i}Pr)$_2$Si]$_2$O-)



i) $Pr_2iSi(Cl)OSi(Cl)Pr_2i$, imidazole, THF, rt, 90 min.

cleavage: Bu_4NF, THF.

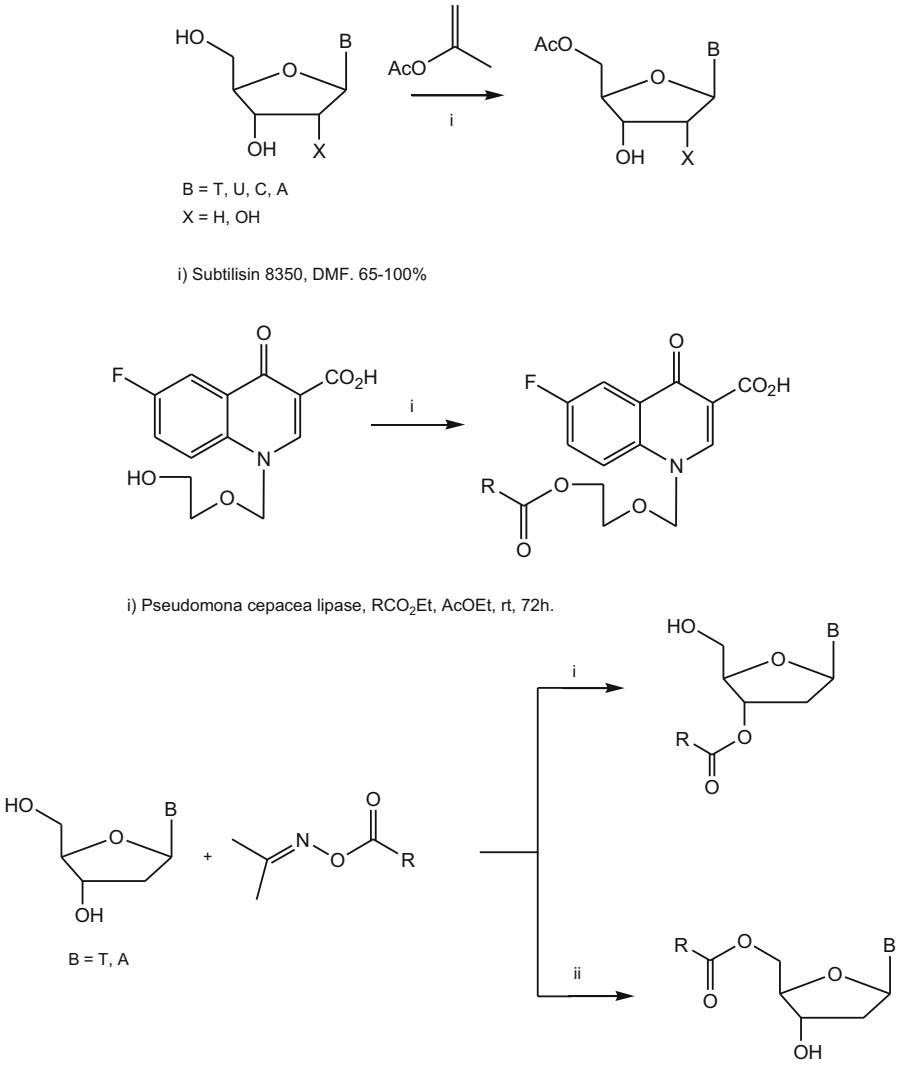
Scheme 3.6 (continued)

By using the appropriate lipase it is possible to achieve regioselective acyl protections on nucleosides. For instance, the enzymatic transesterification reaction of 5′-fluorouridine with n-octanoic anhydride catalyzed with *Candida Antarctica* (CAL), *Pseudomonas* sp. (PS), (KIWI-56), and *Mucor javanicus* (M) lipases was performed, producing 5′-, 3′-, and 2′-acylnucleosides, respectively (Scheme 3.8) [22].

Regioselective removal of certain protecting groups such as acetates attached to the ribosyl moiety of nucleosides might be carried out by enzymes. For instance *subtilisin* strain selectively hydrolyzes the 5′-position of purine and pyrimidine tri-*O*-acylated esters to produce 2′,3′-di-*O*-acylribonucleosides in 40–92 % (Scheme 3.9) [23].

On the other hand, diastereoselective deacetylation of peracetylated 2′-deoxyribofuranosyl thymine was carried out using wheat germ lipase (WGL) and porcine liver esterase (PLE), forming pure β-anomer thymidine in 29 % and 31 %, respectively (Scheme 3.10) [24].

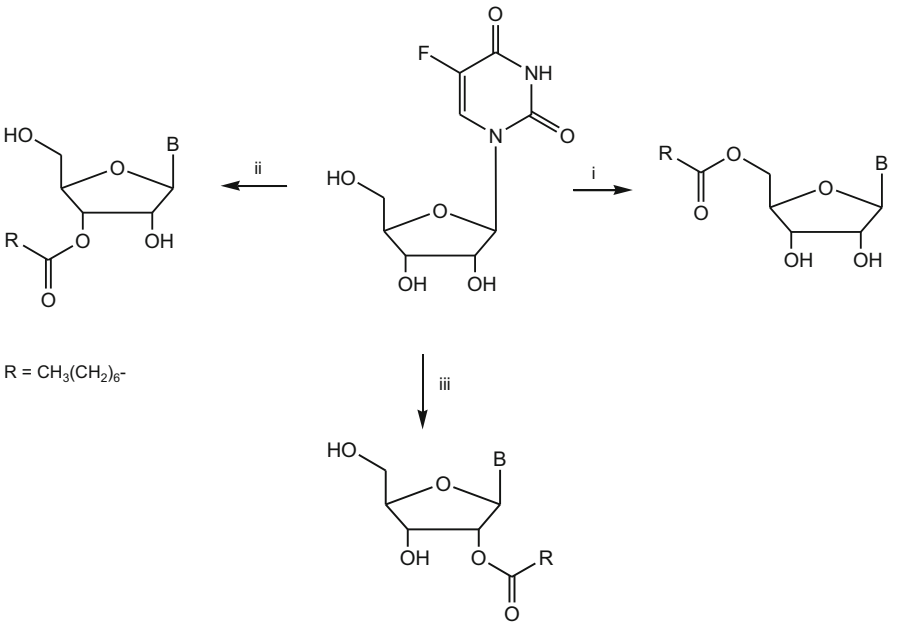
When porcine pancreas lipase (PPL) in phosphate buffer is used for deacetylation of 3′,5′-di-*O*-acetylthymine, the removal of the acetyl group at the 5′- position is achieved, leading to the 3′-*O*-acetylthymidine (Scheme 3.11) [25].



Scheme 3.7 Enzymatic regioselective acylation by oximeacetates and lipases

Other suitable selective protections and deprotections useful for chemical manipulations which might occur at the ribosyl moiety are illustrated in Scheme 3.12.

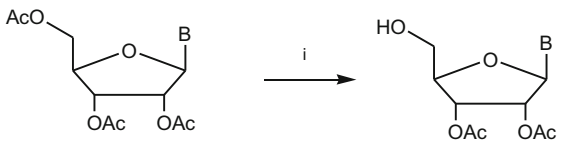
Regioselective protections and deprotections is often a critical step especially for the preparation of complex nucleosides. Some suitable deprotections of complex nucleosides which do not alter the original composition of the structure have been described (Scheme 3.13) [6, 7].



i) Candida antarctica lipase (CAL), 90%. ii) Pseudomona sp.lipase (PS), 92%.
iii) Mucor javanicus lipase (M), 42%.

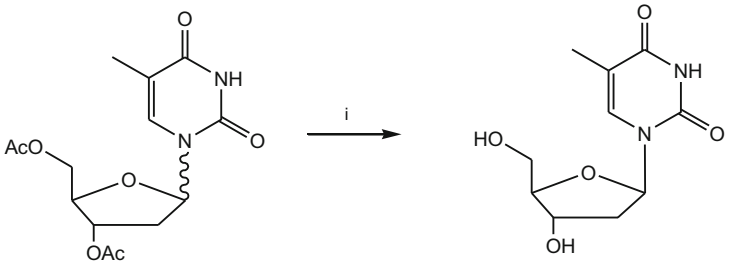
Scheme 3.8 Regioselective acyl protection by lipase

Scheme 3.9 Selective enzymatic 5′-acetyl deprotection



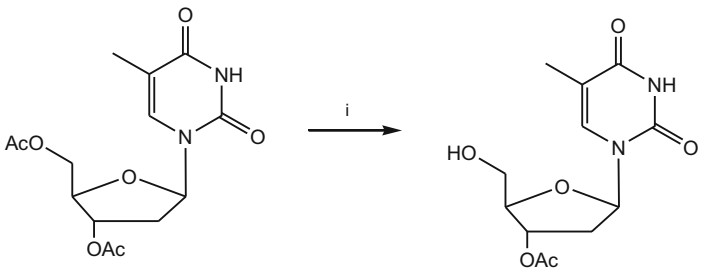
B = U, C, A, G, N-2AcG, H

i = Subtillisin or PPL, organic solvent, phosphate buffer, pH 7.



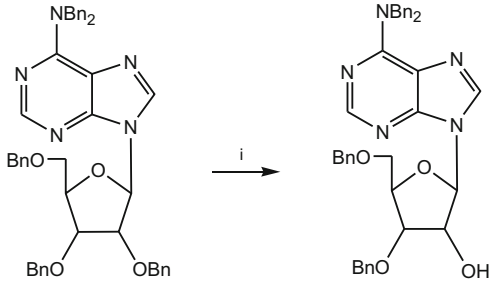
i) WGL, phosphate buffer, 29%. or PLE, phosphate buffer, 31%.

Scheme 3.10 Lipase-catalyzed deacetylation of anomeric nucleoside

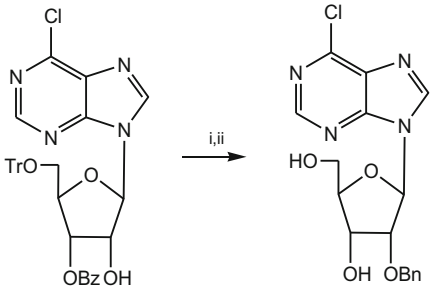


i) PPL, phosphate buffer, 98%.

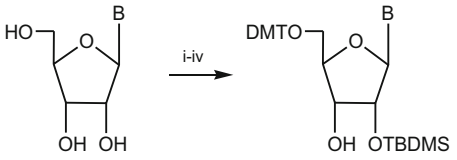
Scheme 3.11 Selective enzymatic 5′-deacetylation of 3′,5′-di-*O*-acetyl thymidine



i) t-BuMgBr, PhH, 80°C, 69%



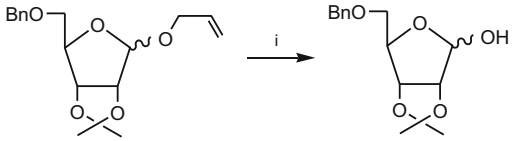
i) BnOH, $Me_2NCON = NCONMe_2$. ii) NH_3/MeOH



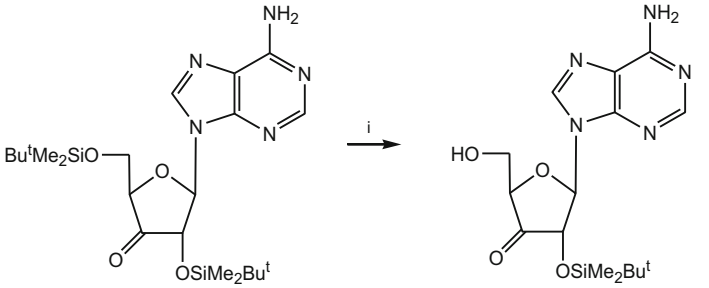
B = G, A, C, U

i) t-$Bu_2Si(OTf)_2$, Im, DMF, 0°C. ii) t-$BuMe_2SiCl$, Im, DMF,60°C, 80-87%. iii) HF-Py, CH_2Cl_2,0°C, 90%
iv) DMT-Cl, Py, 0°C, 90%.

Scheme 3.12 Miscellaneous chemical protection and deprotection [25–29]

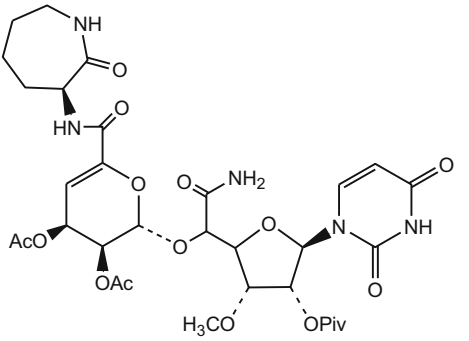


i) DIBAL, $NiCl_2$, Et_2O, 0°C, 55%

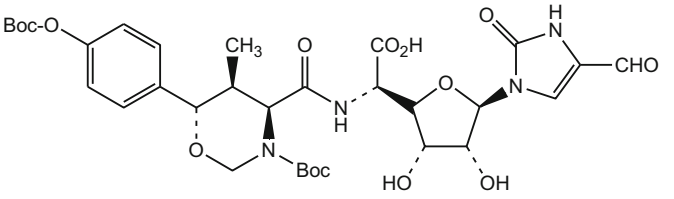


i) CF_3COOH-H_2O (9:1), 0°C, 95%.

Scheme 3.12 (continued)

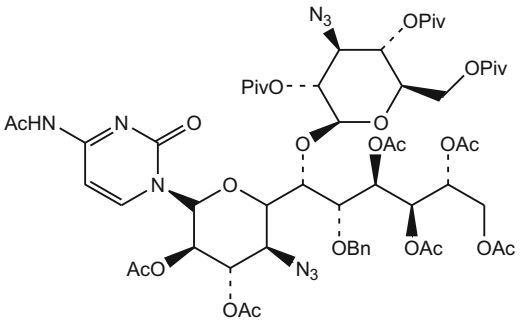


1. NaOH, aqMeOH, 2.5h (cleavesO-Ac and O-Piv)

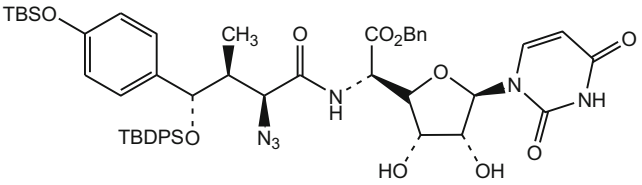


1. TFA, 0°C, 15min. (cleaves O- and N-BOC)
2. H_2O, thenlyophilize (cleaves acetal)

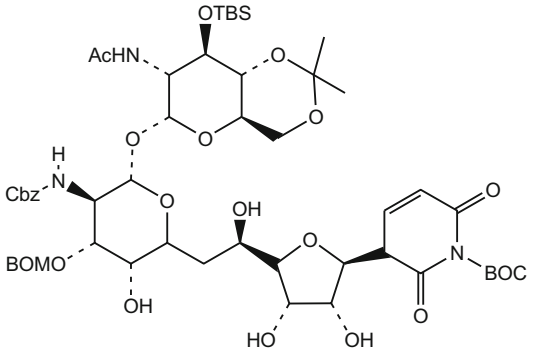
Scheme 3.13 Suitable deprotection of complex nucleosides



1. DDQ, CH_2Cl_2, 58°C, 43h (cleaves O-Bn)
2. n-Bu_4NOH, MeOH, reflux, 2h (cleaves acyls)
3. H_2, Lindlar, H_2O (reduces azide groups)



1. n-Bu_4NF, THF, 30min. (cleaves 2 O-SiR_3)
2. H_2, 10 % Pd-$BaSO_4$, aq. MeOH, 30min. (cleaves benzyl ester and reduces -N_3)



1. 10% HCO_2H, Pd, 1.5h (cleaves O-BOM, N-Cbz)
2. 13% HCO2H, MeOH, 40°C, 5h (cleaves N-BOC, acetonide)
3. HF, MeOH, CH_3CN (cleaves O-TBS)

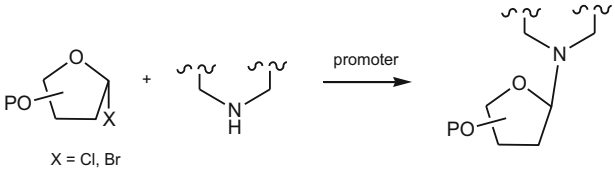
Scheme 3.13 (continued)

3.3 General Methods

- Michael reaction
- Fischer–Helferich reaction
- Davol–Lowy reaction
- Silyl mediated reaction
- Sulfur mediated reaction
- Imidate mediated reaction
- Mitsunobu reaction
- Palladium mediated reaction
- Microbial/enzymatic approach

3.3.1 Michael Reaction

3.3.1.1 General Scheme and Conditions

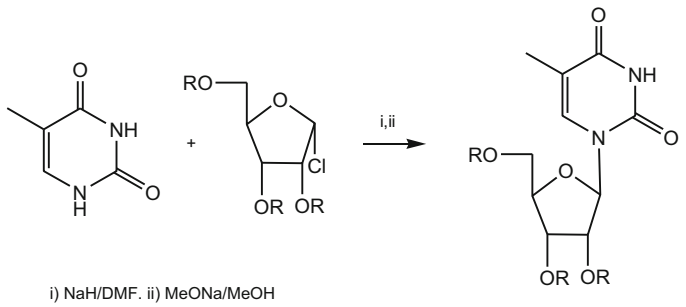


Promoter	Conditions
NaH	DMF
K_2CO_3	DMF
KOH-TBA	CH_2Cl_2

It is a classical procedure for preparing nucleosides, and it can be considered a modified *O*-glycoside approach. In this way, the sugar derivative is an R-*O*-furanosyl halide where R can be acyl, benzoyl, benzyl, tosyl, or silyl, and the halogen is commonly chlorine instead of bromine, since it has proved to be more stable for furanose derivatives than its counterpart. The nitrogen base (purine or pyrimidine) is reacted under basic conditions, usually NaH or K_2CO_3 in DMF (Scheme 3.14).

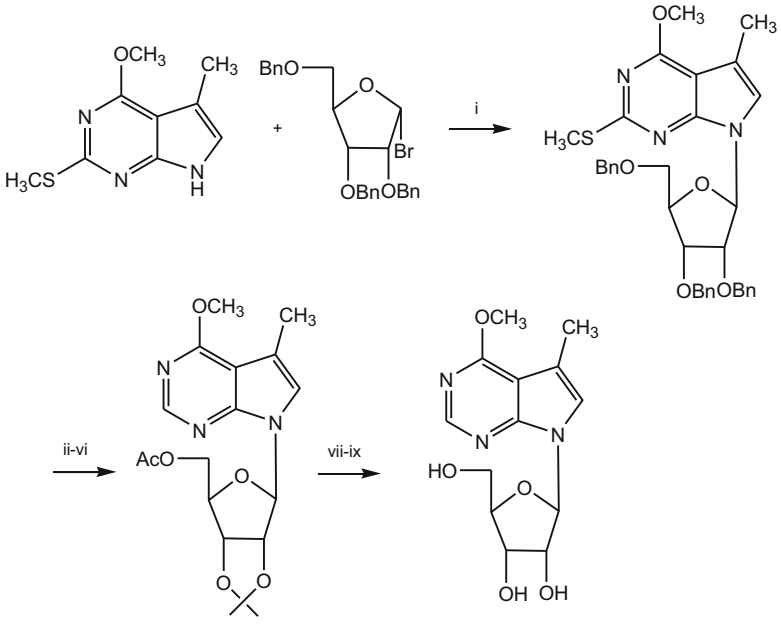
A variety of antibiotics have been prepared according to this method, as in the case of the nucleoside known as methyltubercidine. For achieving this goal, the 7-deazaguanine was used as nitrogen base which was condensed to 2,3,5-tri-*O*-benzylribofuranosyl bromide under NaH/DMF conditions to form a 1:1 anomeric mixture of *N*-glycosides (Scheme 3.15) [30].

More recently Battaharya [31] reported the synthesis of fluoroarabinotubercidine, toyocamicine, and sangivamicine, under the current *N*-glycoside formation procedure. Other deazapurines have been described by Seela et al. [32] involving the condensation between the purine base and protected ribosyl halides under basic conditions.



i) NaH/DMF. ii) MeONa/MeOH

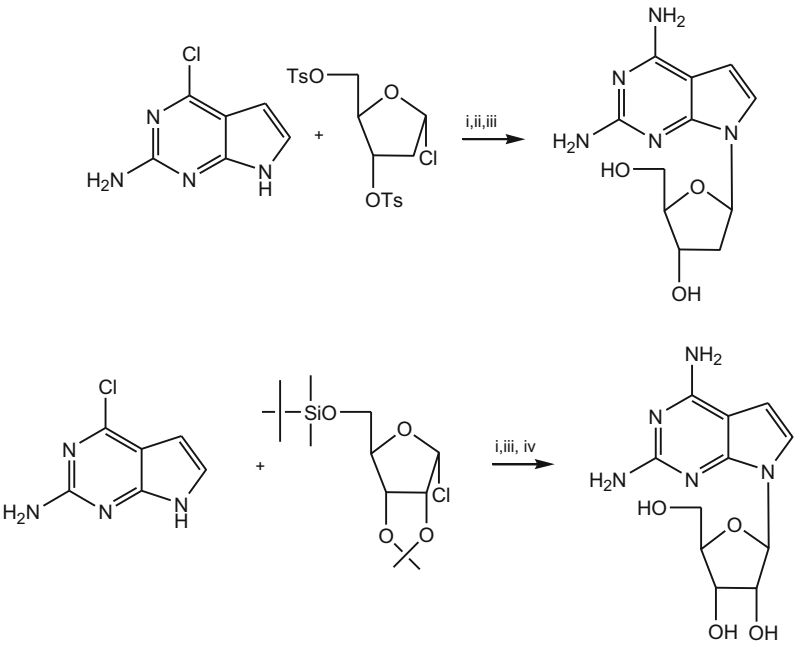
Scheme 3.14 Michael modification



i) NaH/DMF. ii) Ni/EtOH-PhH. iii) HCl/dioxane. iv) H_2,Pd-C. v) a) acetone/p-TsOH. b) Ac_2O/Py. vii) $POCl_3$. viii) NH_3/MeOH. ix) F_3CCOOH/H_2O.

Scheme 3.15 Synthesis of methyltubercidine

According to Seela [33] and Kazimierczuk [34] the stereoselective glycosylation of the sodium salts of halopurines, with 2-deoxy-3,5-di-*O*-*p*-tolouyl-α-D-*erytro*-pentofuranosyl chloride gave β-nucleosides via Walden inversion. This was demonstrated in the preparation of 2-amino 2′-desoxytubercidine and 2-aminotubercidine by condensation of 3,5-di-*O*-(*p*-tolyl)-α-D-pentafuranosylchloride and 5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethyliden)-α-D-ribofuranosylchloride with the halopurine under Michael conditions. Final ammonia treatment provided the target deazanucleoside (Scheme 3.16).



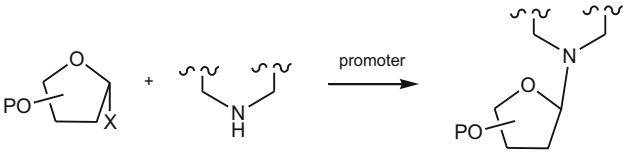
i) KOH, TBA/CH_2Cl_2. ii) MeONa/MeOH. iii) NH_3/MeOH. iv) CF_3COOH/H_2O.

Scheme 3.16 Synthesis of 2-aminotubercidine and 2-amino-2′-deoxytubercidine

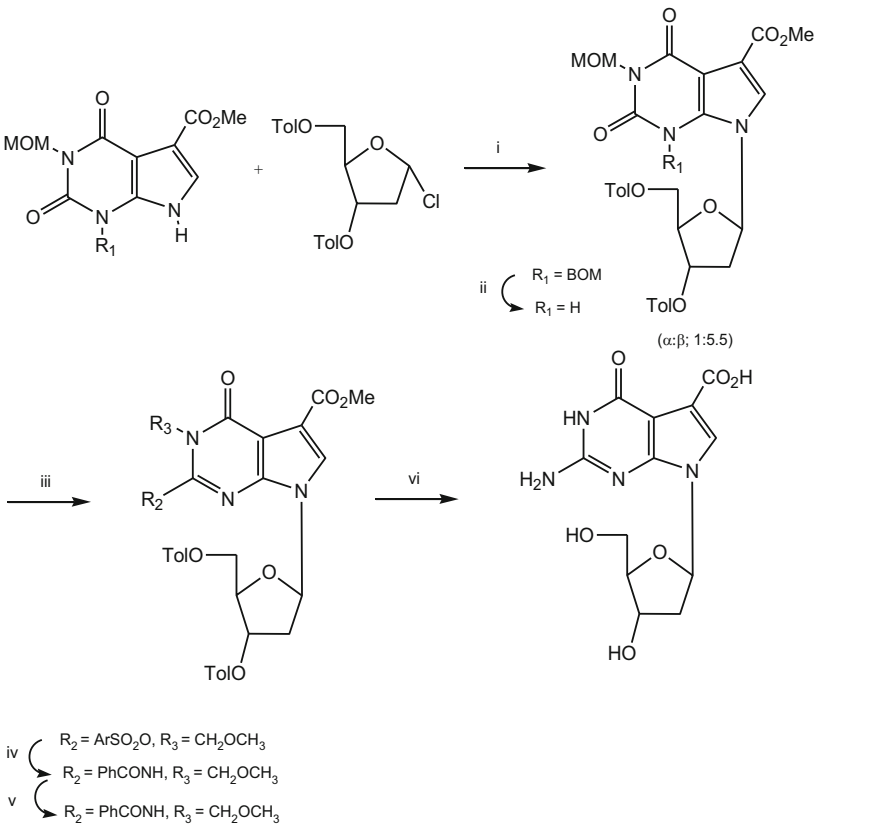
The 7-deazapurine nucleoside cadeguomycin isolated from strain of the actinomycete culture filtrate *Streptomyces hygroscopicus* was also synthesized under this approach. Thus, coupling reaction between protected 7-deazapurine derivative and 1-chloro-2-deoxy-3,5-ditoluyl-α-D-erythro-pentofuranose was effected with preference for the β-isomer. Subsequent transformations provided the target molecule 2′-deoxycadeguomycin (Scheme 3.17) [35].

3.3.2 Fischer–Helferich Reaction

3.3.2.1 General Scheme and Conditions



Promoter	Conditions
Silver salts	xylene



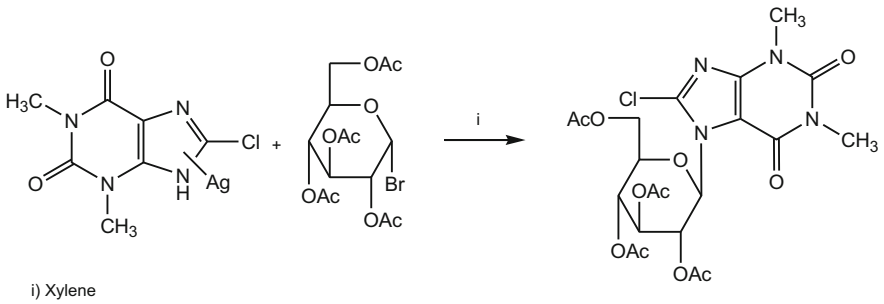
i) NaH,CH_3CN, 25°C.ii)H_2/Ph$(OH)_2$, MeOH,25°C. iii) NaH, THF, TIPBS-Cl. iv) $PhCONH_2$, NaH, THF. v) TFA, $CH_2C\ l_2$.

Scheme 3.17 Synthesis of 7-deazapurine nucleoside 2-deoxycadeguomycin

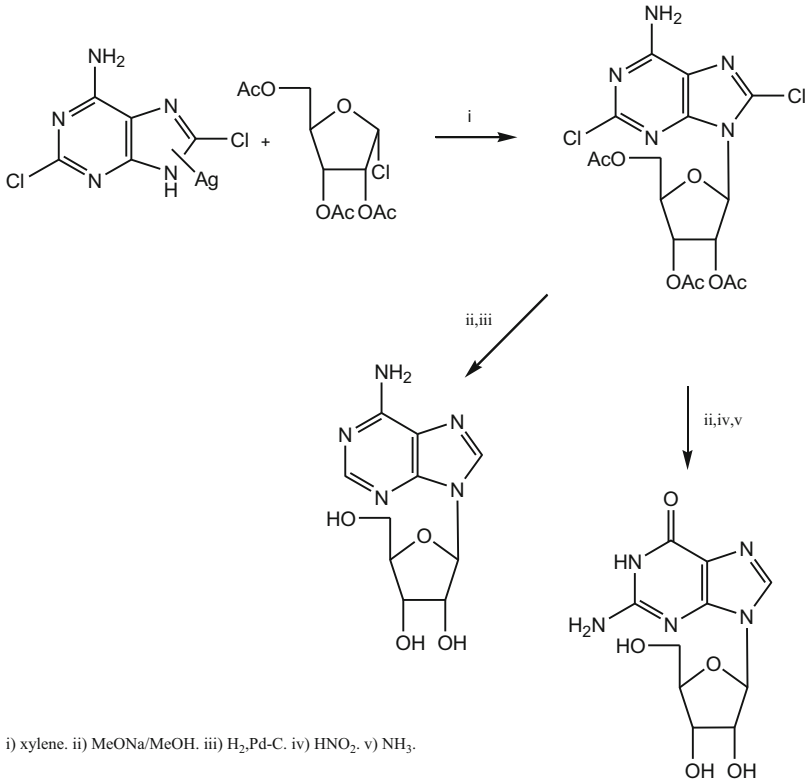
This general procedure consists in the use of an acylfuranoside or acylpyranoside, which is reacted with the silver or mercury salts of a nitrogen base. The original reaction involves the condensation between silver salt of theophylline and aceto-bromoglucose in hot xylene, giving preferentially the N-7 regioisomer (Scheme 3.18).

The feasibility of this method is observed in the synthesis of adenosine and guanosine by condensation of tri-*O*-acetyl-α-D-ribofuranosyl chloride with the silver salt of 2,8-dichloroadenine to generate an intermediate which under the conditions described below can generate either adenosine or guanosine (Scheme 3.19) [36].

The stereochemistry of this reaction can be predicted by applying the "trans rule" proposed by Tipson [37, 38] and extended by Baker. The rule establishes that the condensation between the purine or pyrimidine salt and the acyl-*O*-glycosyl halide will generate a nucleoside with C1-C2 trans configuration regardless of the initial configuration of C1-C2 of the sugar.

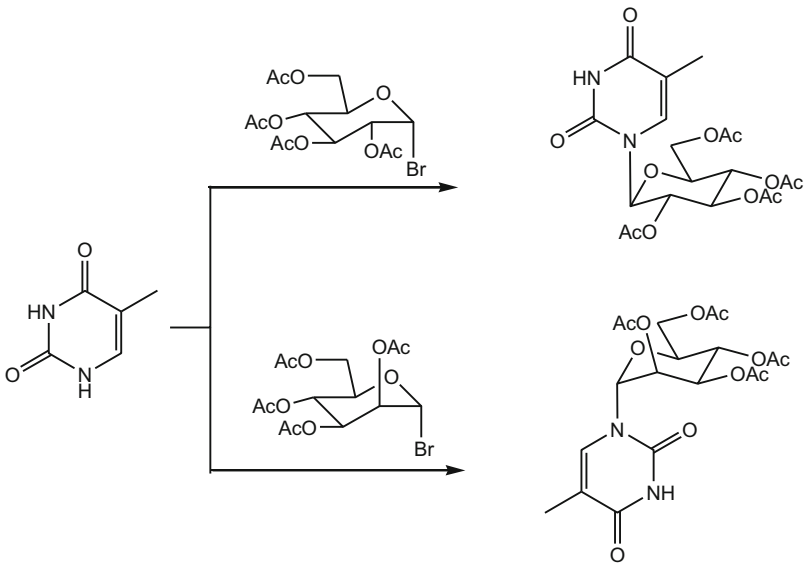


Scheme 3.18 Fischer–Helferich method



Scheme 3.19 Synthesis of adenosine and guanosine

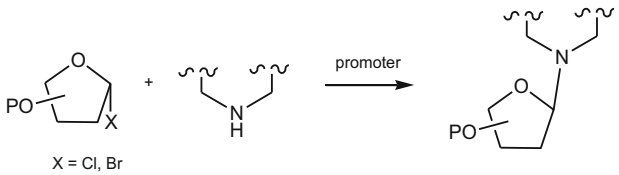
The trans rule is demonstrated in the preparation of thymidine acetoglucopyranose and mannopyranose, where -OH at position 2 for the former is equatorial, and for the latter axial. By following the rule, the coupling reaction generates β- and α-anomers, respectively, both of them having a trans disposition between substituents at positions 1 and 2 (Scheme 3.20).



Scheme 3.20 Tipson's trans rule

3.3.3 The Davol–Lowy Reaction

3.3.3.1 General Scheme and Conditions

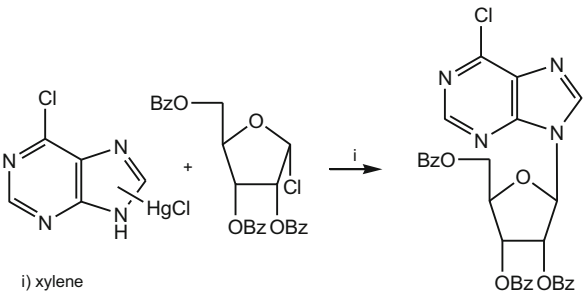


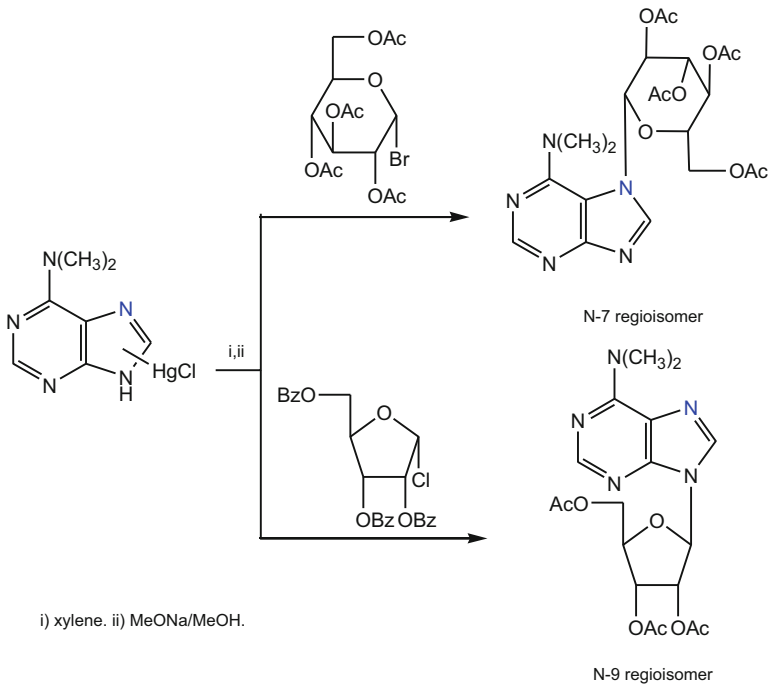
Promoter	Conditions
$Hg(CN)_2$	CH_3NO_2, reflux
$Hg(CN)_2$	Xylene

This method has been also considered a modified Fischer–Helferich procedure and involves the use of mercury chloride instead silver salts. Under these conditions the useful intermediate chloropurine nucleoside has been prepared under mild conditions (Scheme 3.21).

The nature of the glycosyl halide is important for determine the regioselectivity of the glycosidic linkage. If the condensation reaction occurs between purines and acetobromoglucose the N-7 regioisomer is obtained preferentially. On the other

Scheme 3.21
Davol–Lowy method

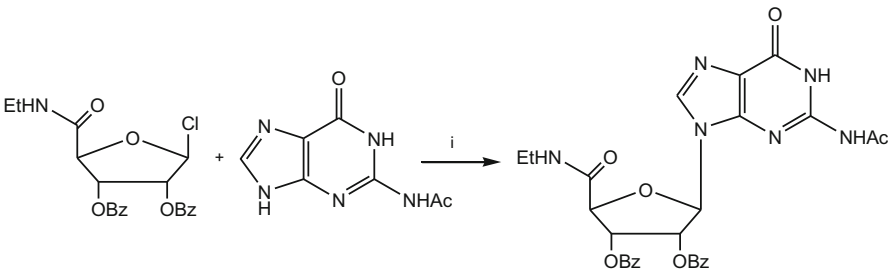




Scheme 3.22 Preparation of N-7 and N-9 regioisomers

hand, if acetoribosyl chloride is condensed with the same purine, the N-9 regioisomer is the major product observed (Scheme 3.22).

Another purine nucleoside prepared under these conditions is shown in Scheme 3.23, consisting in the coupling reaction between protected guanine and protected furanosyl chloride in nitromethane under refluxing conditions produced the corresponding *N*-glycoside in 50 % yield [39].

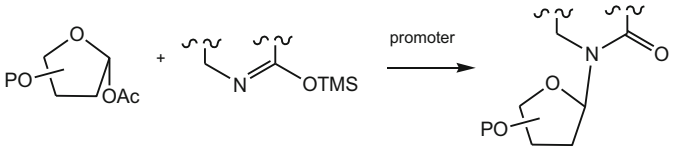


i) $Hg(CN)_2$, CH_3NO_2, reflux, 16 h.

Scheme 3.23 Glycosidation reaction for preparation of guanine derivative

3.3.4 Silyl Coupling Reaction

3.3.4.1 General Scheme and Conditions

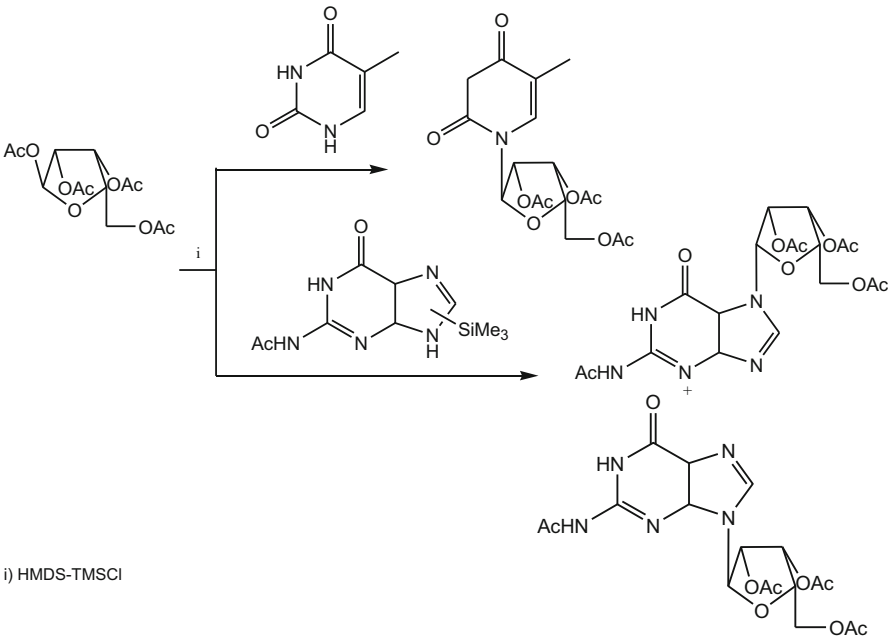


Promoter	Conditions
TMS-OTf	CH_3CN, 0 °C → r.t
TMS-OTf	$PhNO_2$, 127 °C
$SnCl_4$	CH_3CN
HMDS-TMDS	
$(MeSi)_2NAc$	
$CF_3(CF_2)_3SO_3K$/HMDS-TMSCl	
HMDS/$(NH_4)_2SO_4$	

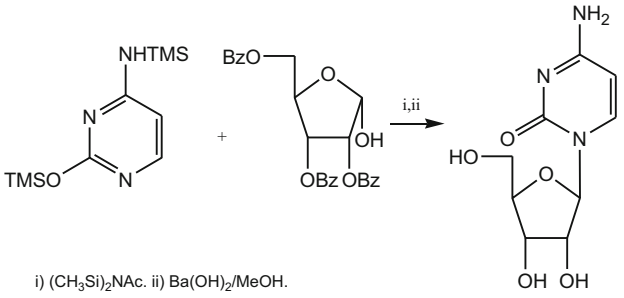
Various types of silyl agents have been tested as either protecting groups and or *N*-glycoside promoters. Among them trimethylsilyl chloride (TMS-Cl), bis(trimethylsilyl) acetamide, trimethylsilyltriflate, and hexamethyldisilazane are representative examples.

De Clercq et al. [40] prepared purine and pyrimidine α-D-lyxofuranosyl nucleosides employing HMDS, TMS, and TMSF as silyl coupling agents. Nucleoside α-D-lyxofuranosyl thymine was prepared by condensation between 1,2,3,5-tetra-*O*-acetyl-α-D-lyxose and thymine in the presence of HMDS-TMSCl mixture (Scheme 3.24).

Likewise cytidine has been synthesized in 95 % through condensation of silyl cytidine obtained from cytosine with bis [trimethylsilyl] acetamide, and sugar derivative 2,3,5-tri-*O*-benzoylribose, as represented in Scheme 3.25.



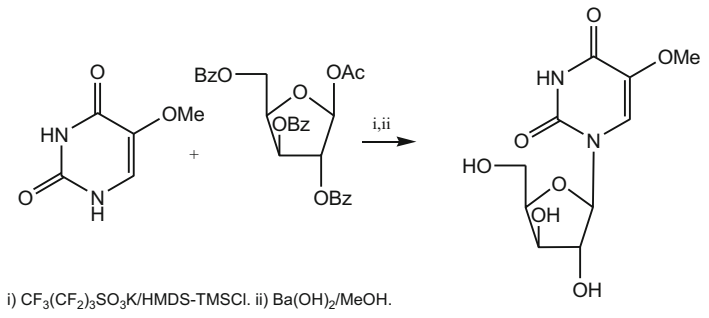
Scheme 3.24 Preparation of α-D-lyxofuranosyl thymine and guanine protected nucleosides



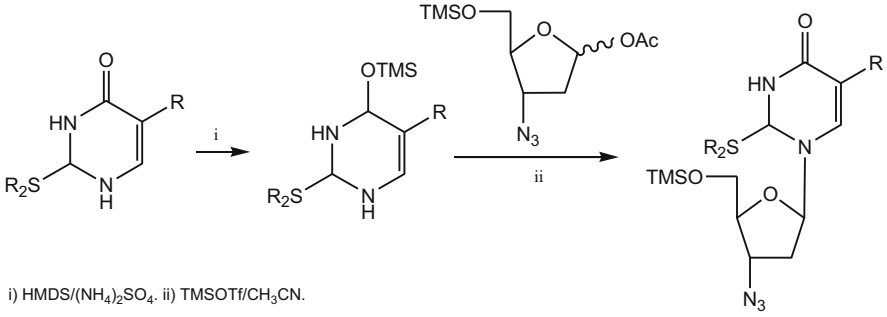
Scheme 3.25 Silyl mediated coupling reaction

Hilbert and Johnson [41] developed a procedure for preparing nucleosides employing a mixture of hexamethyldisilane (HMDS), trimethylsilane chloride and potassium nonaflate. According to this procedure 5-methoxyuridine was prepared by condensing 5-methoxyuracil, with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (Scheme 3.26).

A widespread silyl-based methodology was developed by Vorbrüggen [42, 43] which is based in the use of persilylated purines or pyrimidines, which are condensed with peracylated sugars in the presence of Lewis acid catalysis. Usually silylation of the base is achieved with hexamethyldisilazane (HMDS) or N,O-bis(trimethylsilyl)



Scheme 3.26 Hilbert and Johnson approach



Scheme 3.27 Vörbruggen's synthesis of AZT thioderivatives

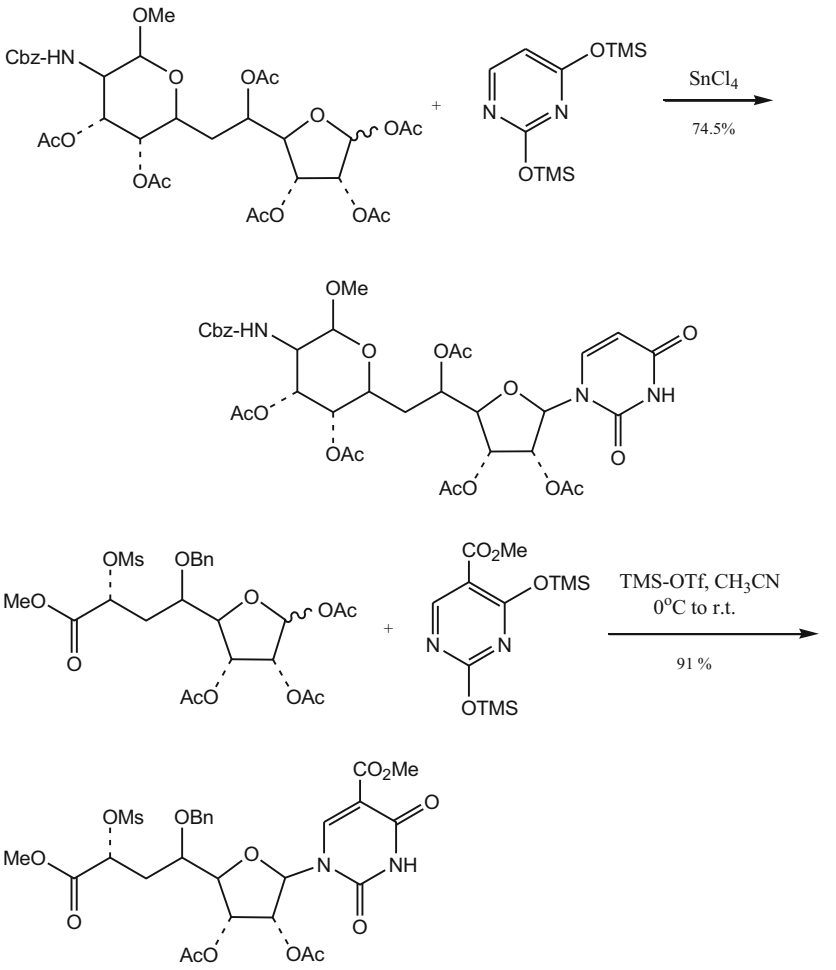
acetamide, the latter less difficult to remove during the workup process. Among the Lewis acids employed as catalysts, trimethylsilyl triflate (TMSOTf) has been the most suitable condensing agent for this reaction.

AZT alkylthioanalogs have been synthesized under the method reported by Vorbrüggen. This condition requires hexamethyldisilane for activation of the anomeric center, and trimethylsilyltriflate as condensing agent (Scheme 3.27).

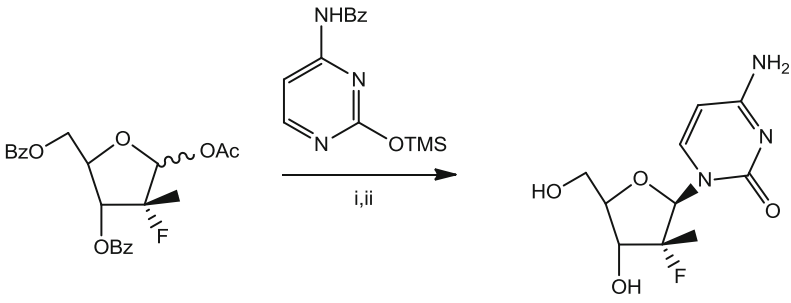
Vörbruggen-type coupling reaction has been method of choice in the *N*-glycoside bond formation of various complex nucleosides such as octosyl acid A, tunicaminyl-uracil, sinefungin, and hikizimycin. Some of the general conditions reported for the accomplishment of the mentioned synthesis are described in Scheme 3.28 [6, 7].

Likewise by following a variant of this protocol Wang et al. were able to prepare 2′-deoxy-2′-fluoro-2′-C-methylcytidine (PSI-6130), a potent and selective inhibitor of HCV NS5B polymerase. Thus, the N-glycosylation step was carried out by coupling reaction between 2′-deoxy-2′-fluoro-2′-methyl ribose acetate and silylated *N*-benzoylcytosine tin(IV) chloride as a catalyst (Scheme 3.29) [44].

The N-glycosylation of protected (triethylsilyl)ethynyl furanoside with 2-fluoroadenine to produce after deprotection and 2-deoxygenation the remarkably

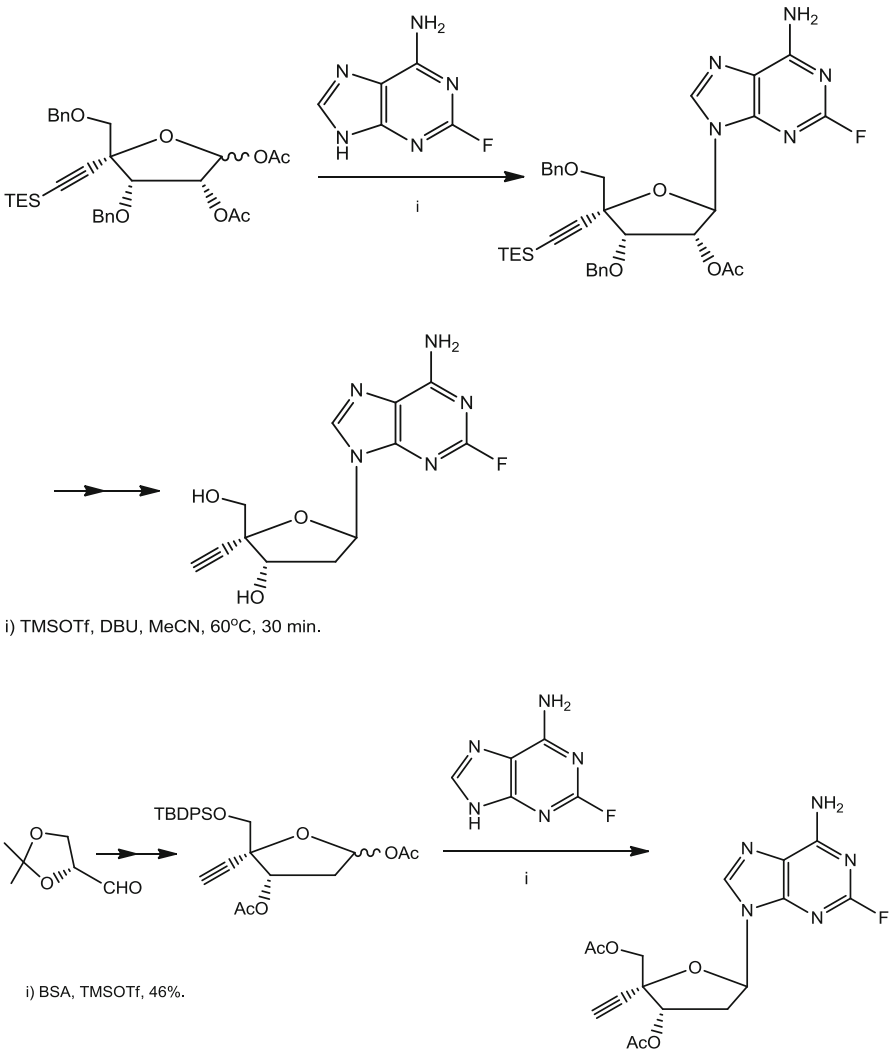


Scheme 3.28 Vörbruggen-type coupling reactions



i) $SnCl_4$, PhCl, 65°C. ii) NH_3, MeOH, rt

Scheme 3.29 Synthesis of antiviral 2′-deoxy-2′-fluoro-2′-C-methylcytidine (PSI-6130)

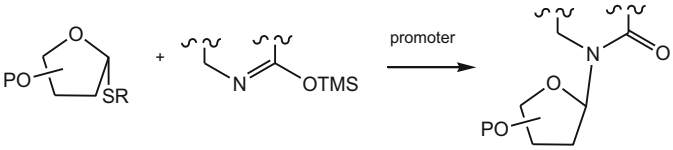


Scheme 3.30 Methods for preparing anti-HIV 4′-Ethynyl-2-fluoro-2′-deoxyadenosine (EfdA)

potent anti-HIV nucleoside 4′-ethynyl-2-fluoro-2′-deoxyadenosine (EfdA) was performed with TMSOTf and DBU in MeCN. Another approach for preparing this modified nucleoside was described by following a 12-step sequence starting from (R)-glyceraldehyde acetonide in 18 % overall yield (Scheme 3.30) [45, 46].

3.3.5 *Sulfur Mediated Reaction*

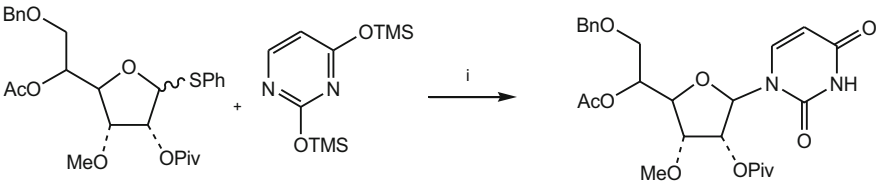
3.3.5.1 General Scheme and Conditions



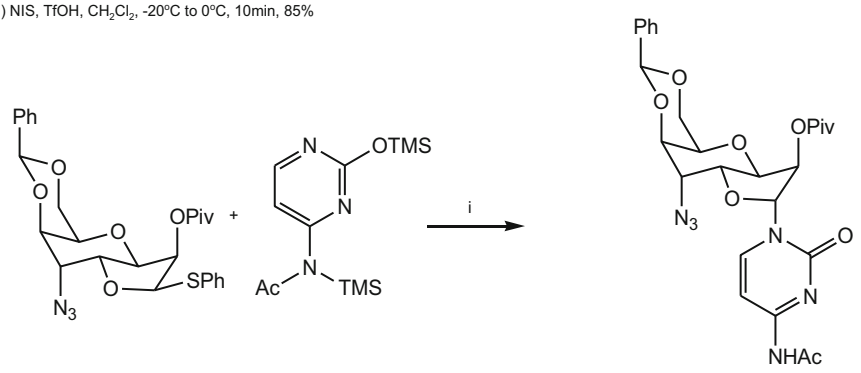
R = Ph, (=O)Ph

Promoter	Conditions
NIS-OTf	CH_2Cl_2
TMS-OTf	DCE r.t.
Br_2	DMF

Derived from their extensive use in the preparation of *O*-glycosides, the sulfur glycosyl donors have become another standard procedure for N-glycosylations. The conditions reported for the coupling reactions involves the sulfur glycosyl donor, the silyl protected heterocycle acceptor and usually *N*-iodosuccinimide, triflic acid as catalyst (Scheme 3.31) [47].



i) NIS, TfOH, CH_2Cl_2, -20°C to 0°C, 10min, 85%



i) NIS, TfOH, CH_2Cl_2, 1h, 95%

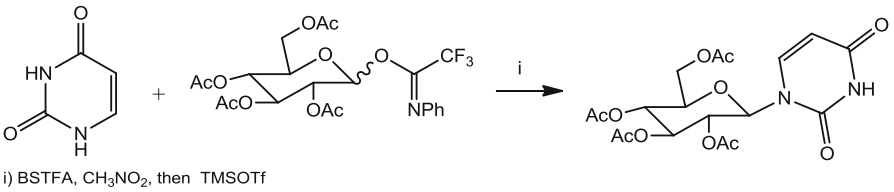
Scheme 3.31 *N*-glycoside formation via sulfur glycosyl donor

3.3.6 *Imidate Mediated Reaction*

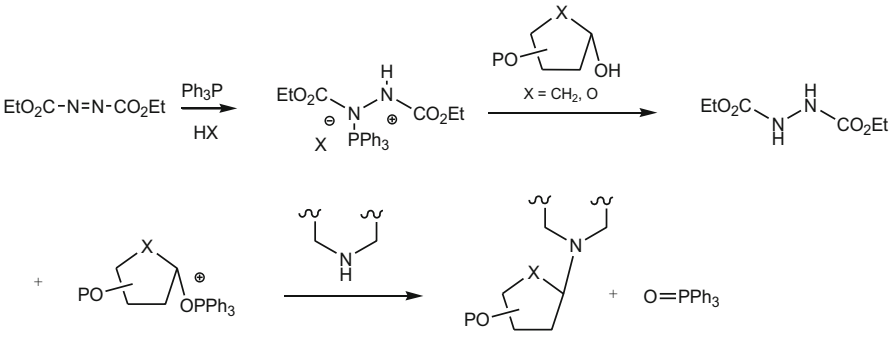
The imidate reaction is by far a method established for preparation of *O*-glycosides; however, some N-glycosylation has been achieved by following this protocol. An interesting novel step is the incorporation of N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) as a silylating reagent when glycosyl trifluoroacetimidates were used as donors, providing the β-nucleoside in 80 % yield (Scheme 3.32) [48].

3.3.7 *Mitsunobu Reaction*

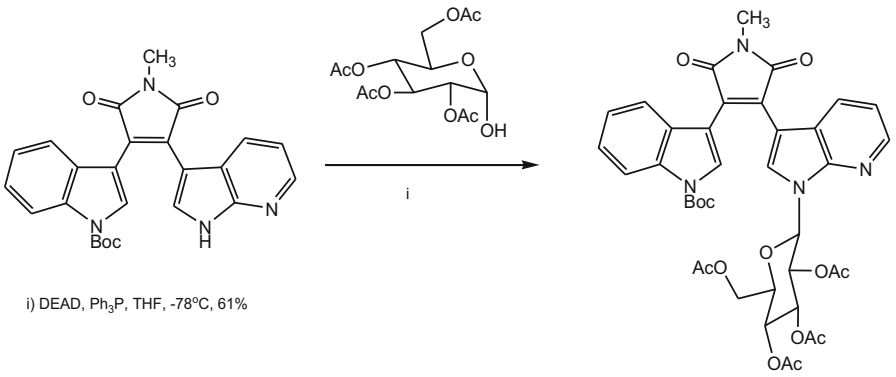
This reaction has been selected as another strategy for preparing N- and carbocyclic nucleosides. The mechanism involves a nucleophilic substitution displacement with inversion of the configuration between species bearing poor leaving groups with nucleophiles. The reaction mechanism involves the initial reaction of triphenylphosphine (Ph_3P) with diethylazodicarboxylate (DEAD) to produce a dipolar intermediate which will react with an alcohol to form an alkoxy phosphonium salt and diimide. Then the nucleophile will displace triphenylphospine oxide to give the substitution product (Scheme 3.33) [49].



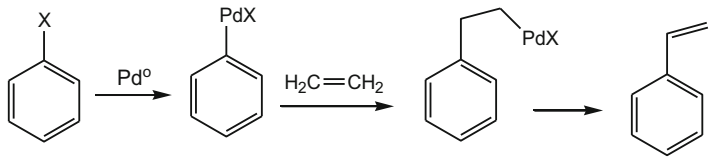
Scheme 3.32 Synthesis o glucopyranosyl pyrimidine from glycosyl trifluoroacetimidates



Scheme 3.33 Mitsunobu reaction for the construction of glycosidic bond



Scheme 3.34 Mitsunobu reaction for preparation of *N*-glycosides



Scheme 3.35 Heck reaction

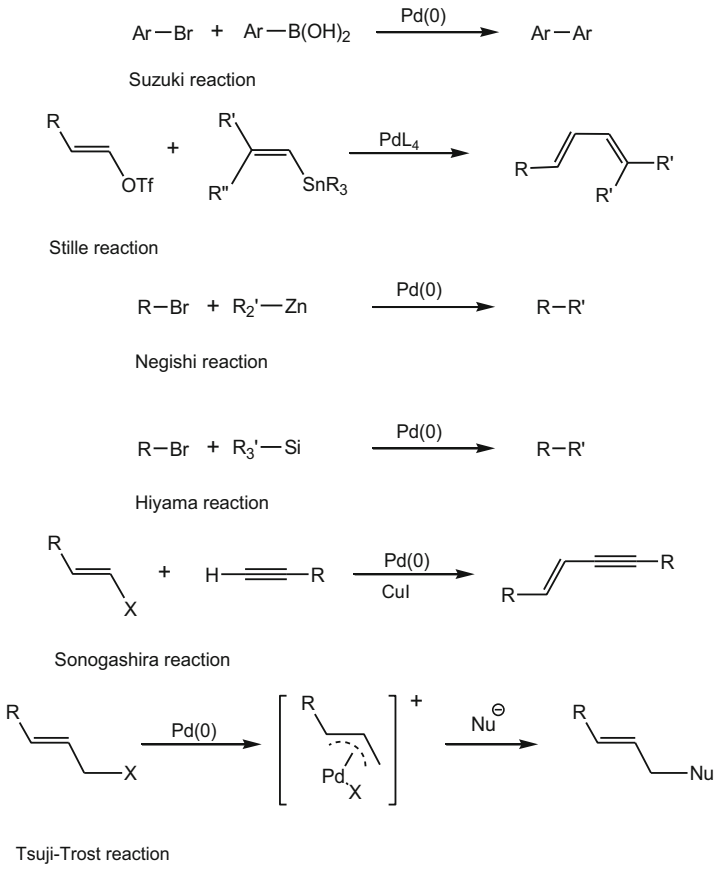
This procedure was used successfully for preparing the *N*-glycoside shown in Scheme 3.34 by reacting 2,3,4,6-tetraacetyl glucose with the heterocyclic base under the Mitsunobu conditions [50].

3.3.8 Palladium Mediated Reaction

Palladium catalysis is a well-established and versatile methodology for the preparation of nucleosides. Also known as the Heck reaction, it was developed initially for C–C bond formation and consists in the coupling of an aryl halide with activated olefin in the presence of palladium (0) as catalyst (Scheme 3.35) [51].

More recently other palladium mediated reaction have been developed with great potential for heterocycle coupling reaction with furanosides, to produce an interesting variety of nucleosides. The group of reactions includes the Suzuki (organoboranes) [52], Stille (organostannanes) [53], Negishi (zincated) [54], Sonogashira (alkyne-CuI) [55], Hiyama (organosilicon) [56], and Tsuji–Trost [57, 58] (Scheme 3.36).

Early reports in the use of Heck-type reactions for the preparation of nucleosides were described by Bergstrom [59–61]. More recently a comprehensive overview about palladium mediated reactions for *N*-glycoside bond formation or modifications at the base or the sugar moieties were described. A general scheme summarizing such possibilities is shown in Scheme 3.37 [62].

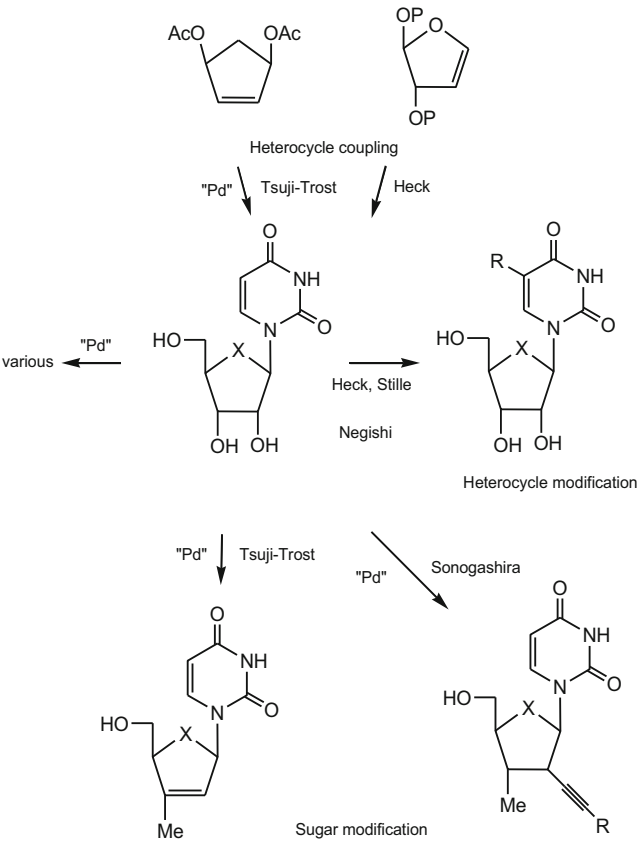


Scheme 3.36 Palladium mediated coupling reactions

Palladium-catalyzed reaction was applied for a N-heterocyclic glycosylation, by using glycal type donors with methyl isatin through a classic Ferrier rearrangement, in the presence of dppb ligand which improved the yield to 50 % (Scheme 3.38) [63].

3.3.9 Ortho-alkynylbenzoates Protocol

This method consist in the coupling reaction between ribofuranosyl ortho-alkynylbenzoate as donor and purines or pyrimidines in the presence of $Ph_3PAuNTf_2$ providing the *N*-glycosides in high β-selectivity. This method can be successfully applied in the preparation of complex nucleosides such as antibiotic A201A, and tunicamycin (Scheme 3.39) [64, 65].

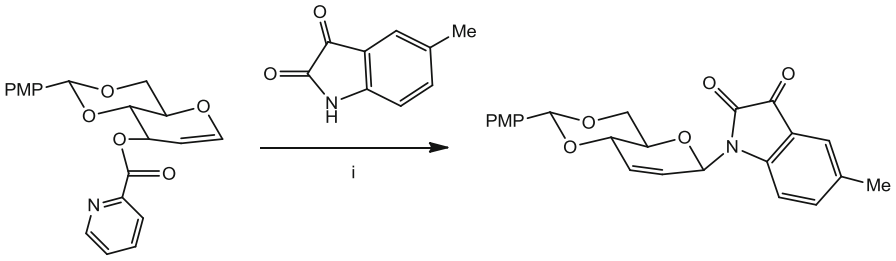


Scheme 3.37 Palladium-assisted modifications

3.3.10 Microbial/Enzymatic Approach

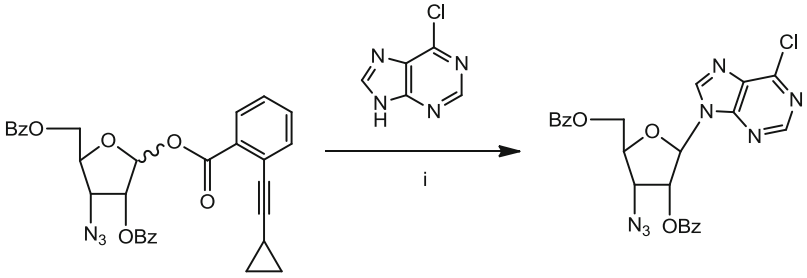
The synthesis of nucleosides by enzymatic methods is another extended possibility, and for this purpose the enzyme nucleoside phosphorylase has been selected as one of the most appropriate one. Usually the conversion proceeds by the reversible formation of a purine or pyrimidine nucleoside and inorganic phosphate from ribose-1-phosphate (R-1-P) and a purine or pyrimidine base. The general approach consists in the reaction of R-1-P as glycosyl donor which is condensed with purine or pyrimidine analogs. Following this method any heterocycle recognized by this enzyme can be glycosylated (Scheme 3.40).

The enzyme synthetase phosphoribosyl pyrophosphate PRPP was used for nucleotide synthesis of UMP. The sequence involves the conversion of ribose-6-phosphate with PRPP synthetase to produce phosphoribosyl pyrophosphate which

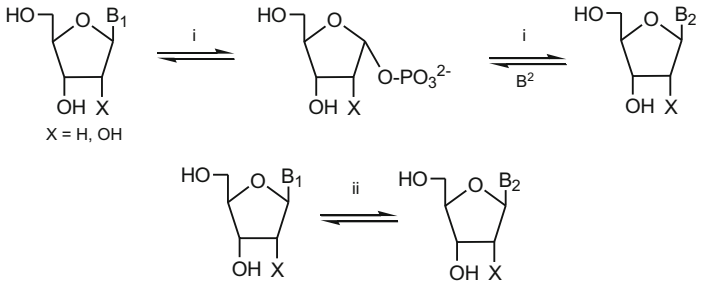


i) $Pd(PPh_3)_4$ DPPB, THF, 70°C

Scheme 3.38 Synthesis of glycosyl isatin through a classic Ferrier rearrangement



Scheme 3.39 Ortho-alkynylbenzoates method catalyzed by gold complex

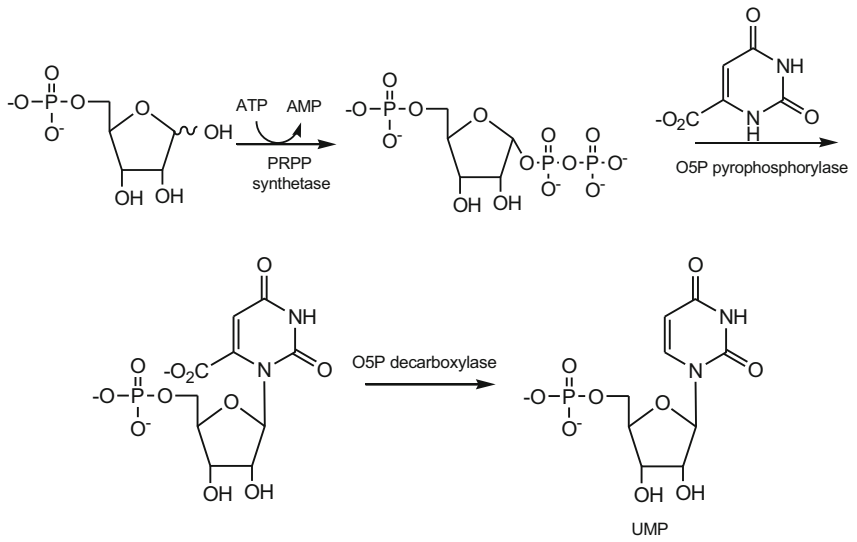


i) nucleoside phosphorilase. ii) trasribosylase.

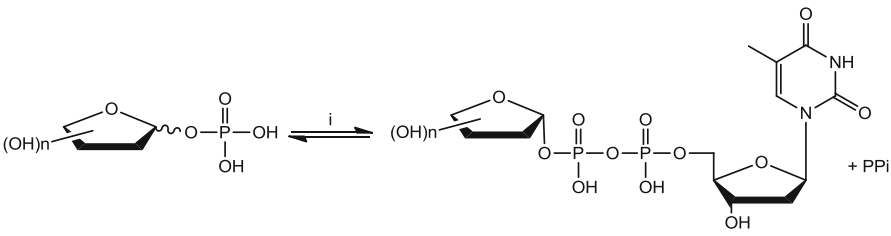
Scheme 3.40 General scheme for enzyme-mediated nucleoside synthesis

was condensed with orotate in the presence of O5P-Pyrophosphorylase to yield the nucleotide intermediate orotidine 5′-phosphate which after decarboxylation produced by the action of O 5P-decarboxylase the nucleotide Uridine monophosphate (Scheme 3.41) [66].

Bacterial α-D-glucopyranosyl-1-phosphate thymidylyltransferase was assayed as a catalyst for the synthesis of furanosyl nucleotides. Thus, five furanosyl-1-phosphates were evaluated as potential substrates for the bacterial thymidylyltransferase to produce only the β-anomer (1,2-*cis*-phosphate) of the sugar nucleotide as confirmed by proton NMR (Scheme 3.42) [67].



Scheme 3.41 Enzyme catalyzed synthesis of nucleotide



i) thymidylyltransferase CPs2L, deoxythymidine 5'-triphosphate, Mg^{2+}

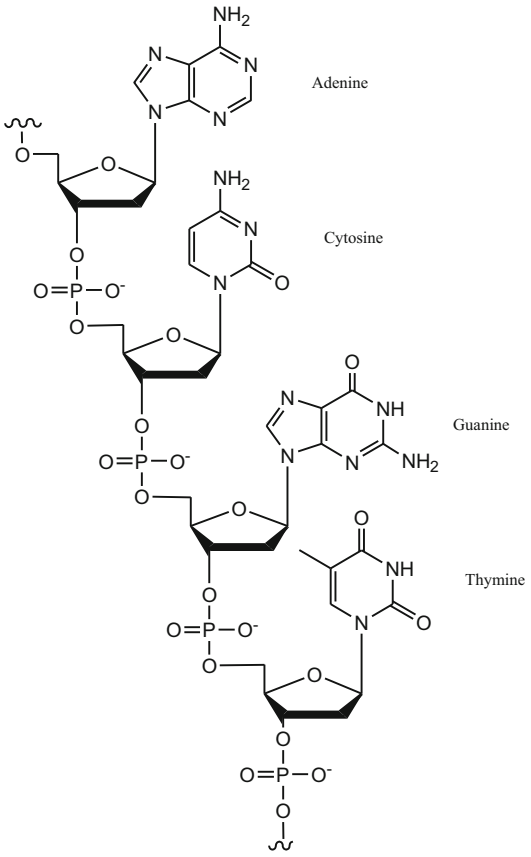
Scheme 3.42 Enzyme catalyzed synthesis of nucleotide by thymidylyltransferase

3.4 Oligonucleotide Synthesis

Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) are very important natural polymers responsible for the processing of the genetic information of all organisms.

The basic repetitive unit known as nucleotide is composed of a nucleotide base, a sugar moiety, and a phosphate. The combinatorial pattern of the four different nucleosides constituted by the heterocyclic bases cytosine, thymine, guanine, and adenine is the base of DNA structure. In RNA strands uracil replace thymine and the furanoside is ribose instead of 2-deoxyribose. The phosphate group is attached at position 3′ of one sugar unit and the 5′ position of the next one forming a 3′–5′ elongation chain (Scheme 3.43).

Scheme 3.43 Fragment of single strand of DNA structure



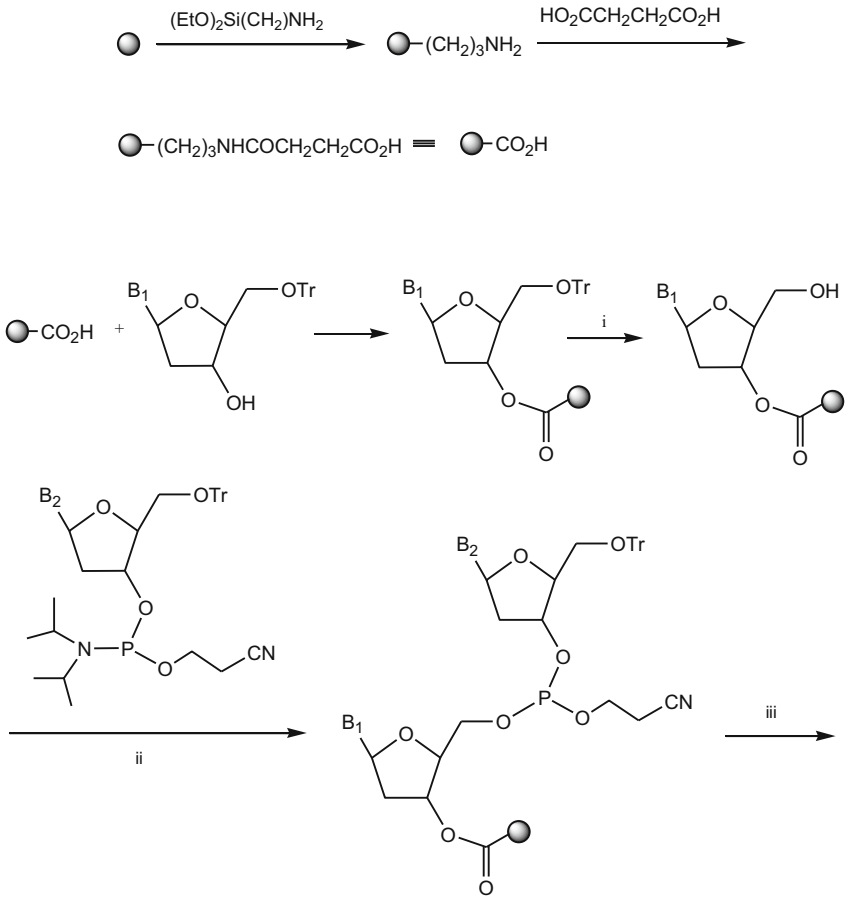
Oligonucleotide synthesis does not involve *N*-glycoside bond formation, but requires the design of nucleoside donors and nucleoside acceptors, following the same principle that applies for glycoside coupling reactions where suitable protecting groups, glycosyl donors and acceptors are required.

Solid phase procedures appear to be of great advantage for the coupling of nucleosides, and unlike for oligosaccharide solid phase chemistry, the attachment positions are always the same (3′ and 5′). The sequence of reactions that occurs in oligonucleotide synthesis starts on the attachment of 3′-OH position of 5′-protected nucleoside to a resin. Next, is deprotection of 5′-OH and subsequent attachment to a nucleoside donor which contains a phosphate precursor which in turn will be converted to phosphate group.

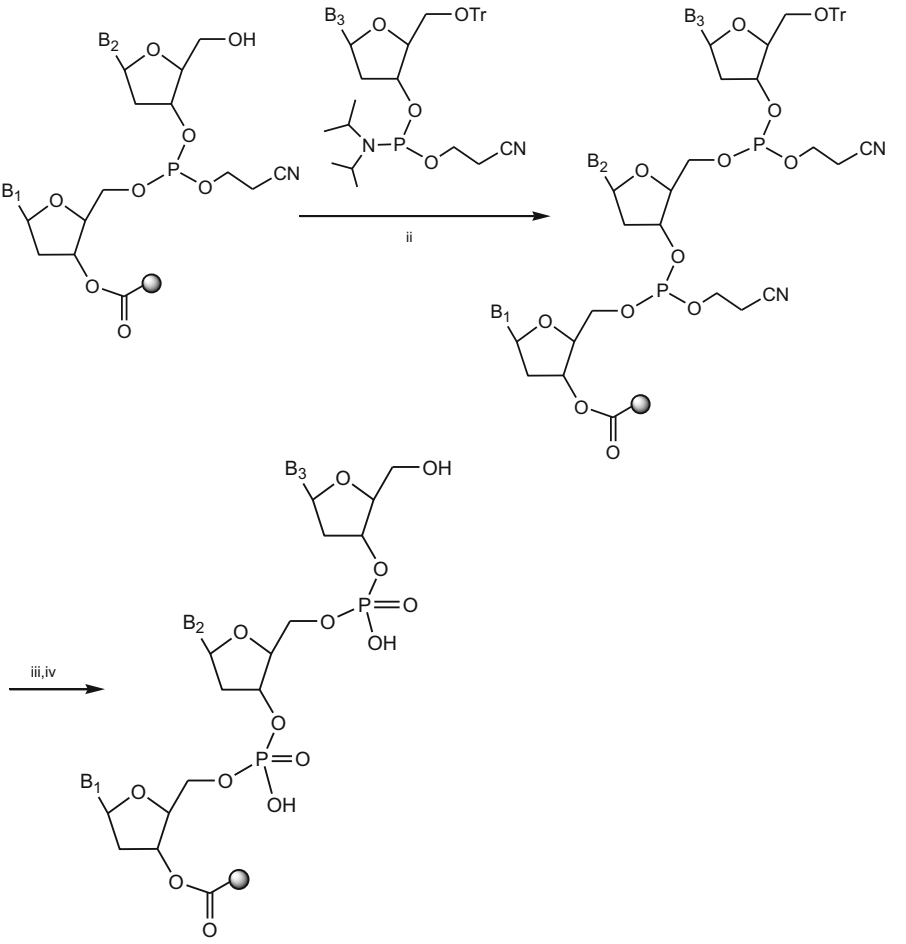
There are mainly two procedures for oligonucleotide synthesis: The phosphoramidite and the phosphonate method [16, 68].

3.4.1 Phosphoramidite Method

This methodology involves the use of the air-sensitive reagent 2-cyanoethyl tetraisopropylphosphorodiamidite $\{[(CH_3)_2CH]_2N\}POCH_2CH_2CN$ or 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite $(iPr)_2NP(Cl)OCH_2CH_2CN$ for activation of nucleoside donor [69]. This intermediate can be obtained by treatment of PCl_3 with 2 eq of diisopropylamine, and 1 eq of cyanoethylethanol. The general phosphoramidite approach, is outlined in Scheme 3.44, and begins with a nucleoside previously protected at the 5′-OH position with 4,4′-dimethoxytrityl group (Tr-), also attached to a silica support. The trityl group is then removed from the 5-OH position and allowed to react with a nucleoside donor protected at position 5-OH with trityl group and activated at position 3′ with 2-cyanoethyl diisopropylphophoroamidite. The coupling reaction being the critical step is catalyzed by tetrazol, and the process



Scheme 3.44 Phosphoramidite oligonucleotide strategy



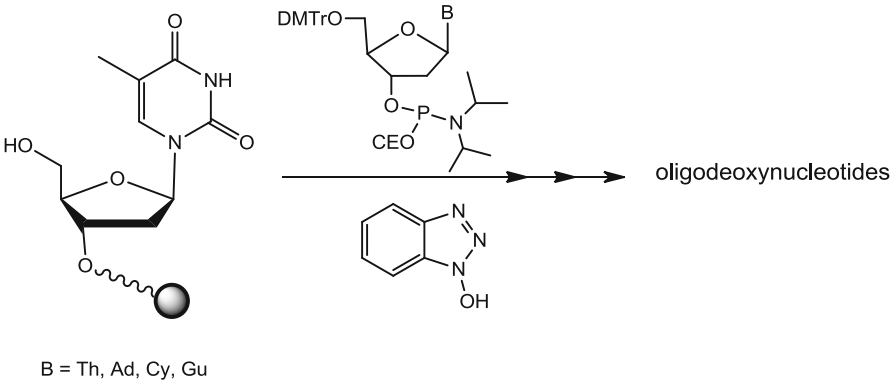
i) Cl_3CCOOH. ii) tetrazol. iii) Cl_3CCOOH. iv) a) I_2/H_2O. b) NH_4OH

Scheme 3.44 (continued)

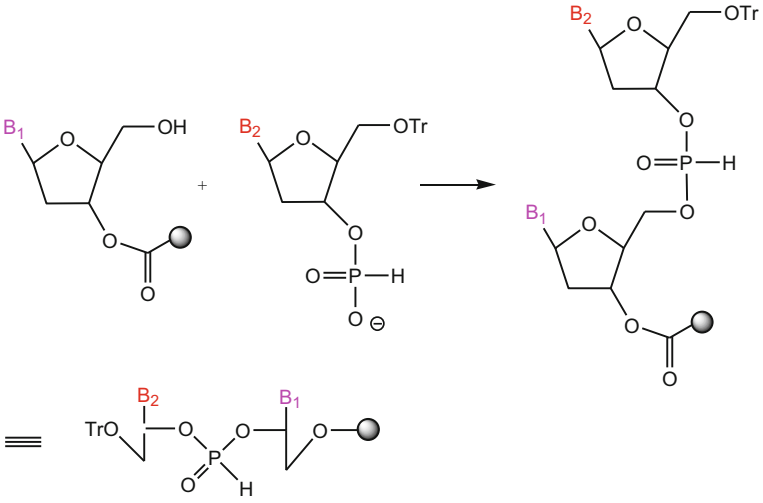
is repeated for the installation of subsequent nucleoside unit. Once the oligonucleotide chain is formed, the phosphoramidite group is transformed to phosphate with I_2-H_2O and released from resin with ammonia.

3.4.2 HOBt Solid Phase Synthesis

This protocol involves the initial attachment of a deoxy nucleoside with a highly cross-linked polystyrene resin and then reacted with a second phosphoramidite nucleoside in the presence of 1-hydroxybenzotriazole (HOBt) as the promoter to the solid-phase



Scheme 3.45 HOBt solid phase synthesis



Scheme 3.46 Phosphonate method

synthesis. Further deprotection with I_2-MeOH, tricholoracetic acid, and ammonia provides the desired oligonucleotides in good yields (Scheme 3.45) [70, 71].

3.4.3 Phosphonate Method

In this method the nucleoside donor is functionalized as a phosphotriester sugar derivative which reacts with nucleoside acceptor at 5-OH position which is available for linkage. An advantage of this method is the possibility of introducing substituents to the phosphate position giving place to the preparation of modified oligonucleotides Scheme 3.46.

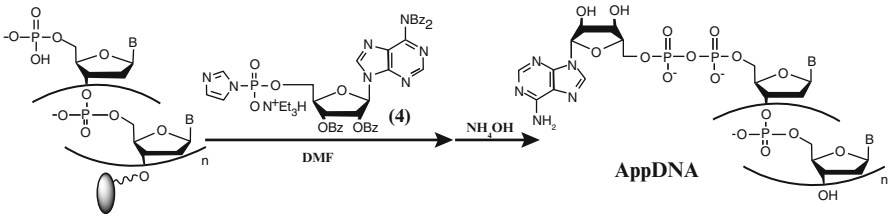
3.4.4 *Phosphorimidazolides Method*

This method propose a coupling reaction between a phosphate nucleoside attached to a resin and adenosine 5′-phosphorimidazolidate, to produce the corresponding protected AppDNA, which if finally debenzoylated with ammonia (Scheme 3.47) [72].

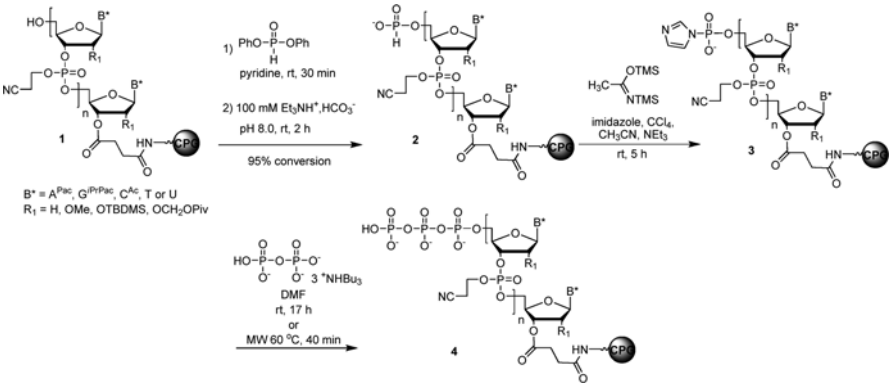
Another example on the applicability of this method is observed in the solid-phase preparation of the solid-phase dinucleotide triphosphate. This report consisted in the treatment of resin bounded phosphoramidite dinucleoside with a solution of diphenyl phosphite in pyridine, followed by hydrolysis, forming the solid-supported Hp-ON. Next the intermediate was oxidized to an activated 5′-phosphoroimidazolidate and subsequently treated with excess of (tri-*n*-butylammonium) pyrophosphate forming solid-phase nucleoside triphosphate (Scheme 3.48) [73].

3.4.5 *Modified Oligonucleotides*

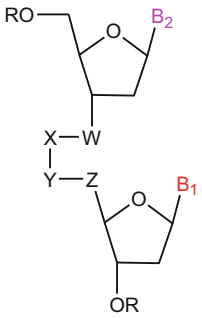
Modified oligonucleotides are another important application of solid phase oligonucleotide synthesis. It is known that natural oligonucleotides used as therapeutic strategy against viral infections as *antisense* for targeting RNA sequences may



Scheme 3.47 Phosphorimidazolides approach



Scheme 3.48 Another example of the phosphorimidazolides approach



W	X	Y	Z
O	-P(O)S-	O	CH_2
O	-P(O)CH_3-	O	CH_2
O	-P(O)NHR-	O	CH_2
O	-P(O)OR-	O	CH_2
NH	-P(O)O-	O	CH_2

Scheme 3.49 Modified oligonucleotides

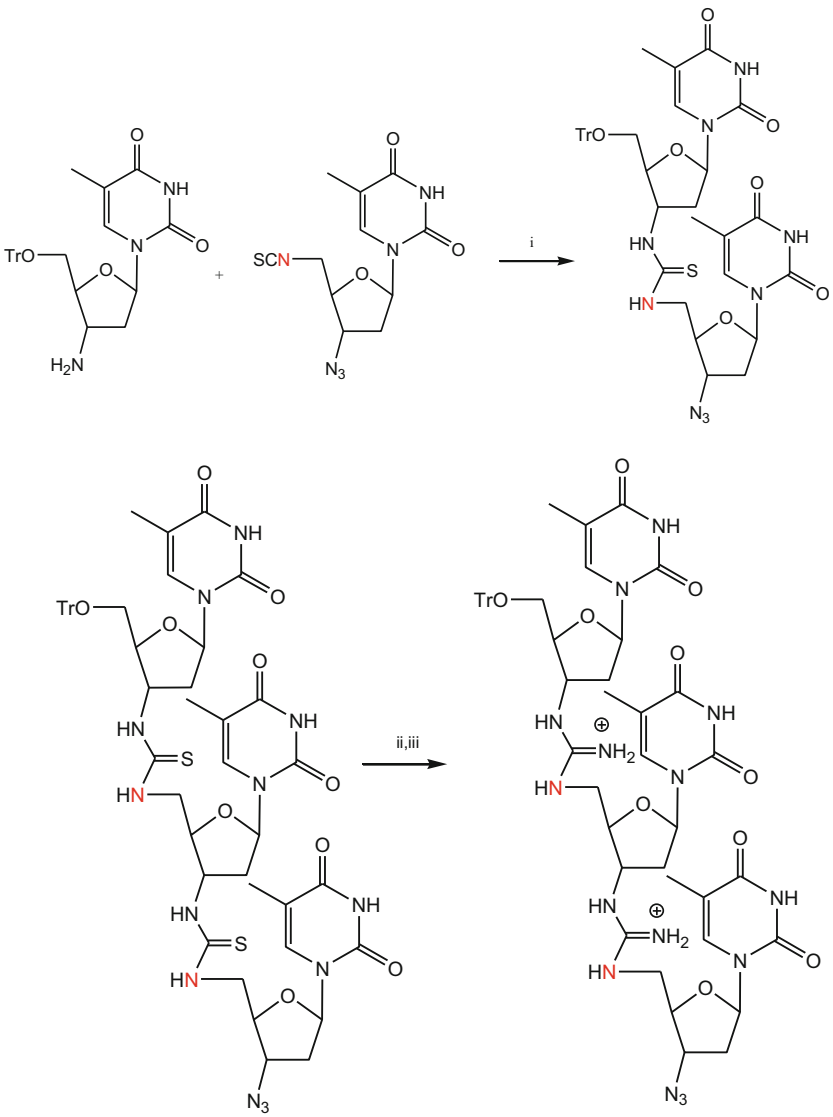
undergo enzymatic hydrolysis by endonucleases. Series of modified oligonucleotides carrying the modification either on the base, sugar or phosphate moiety provides ideally endonuclease resistance as well as high affinity for complementary RNA sequences.

Phosphodiester bond is the primary target for endonuclease breakage; therefore, the effort has been focused mainly on the modification of this segment of the chain. As a result of this, a first generation of modified phosphorous oligonucleotides such as phosphorothioates, methylphosphonates, phosphoramidates, phosphotriesters, and phosphodithioates were synthesized. Although these phosphorous derivatives showed increased resistance to endonuclease activity, the affinity for complementary sequences was decreased [74–76] For instance the synthesis of the antisense oligomer phosphorothioate analog of a 28-nucleotide homo-oligodeoxycytidine (S-dC_{28}) was achieved, and tested as a potent inhibitor of HIV in vitro, showing significant inhibition of reverse transcriptase activity and syncytium formation between HIV-1 producing cells and $CD4^+$ [77].

A second generation proposed the replacement of phosphodiester group by a bioisoster such as amides, urea, and carbamate (Scheme 3.49). In general the observations reveal better enzymatic hydrolysis resistances, but again poor affinity toward RNA complementary sequences.

Alternatively Dempcy et al., [78] reported the synthesis of modified guanidine–thymidine oligonucleotide following the procedure depicted in Scheme 3.50. The reactions involved are the condensation between 3′-amino-5′-*O*-trityl-3′-deoxythymidine and 3′-azido-5′-isothiocyano-3′,5′-deoxythymidine, to generate $5' \rightarrow 3'$ thiourea–nucleoside dimer. Reduction followed by coupling reaction of dimer with the latter nucleoside produced a chain elongation reaction. Guanidine conversion was done with aminoiminosulfonic acid and ammonium hydroxide, forming guanidinium thymidyl pentamer.

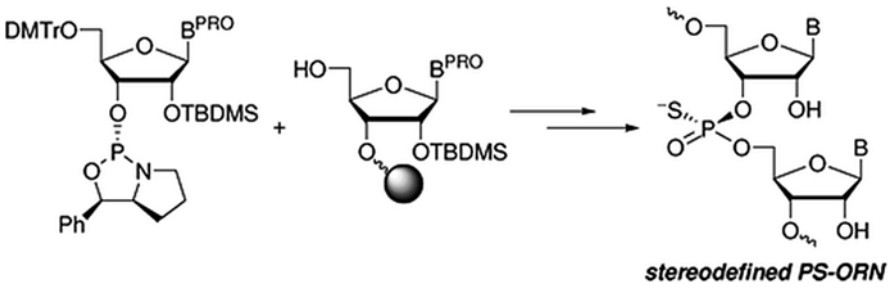
Another type of modified oligonucleosides more recently described correspond to the oligoribonucleoside phosphorothioates (PS-ORNs) which were prepared by using ribonucleoside 3′-*O*-oxazaphospholidine derivatives as monomer unit and submitted to react under activating conditions with protected 5′-OH nucleoside anchored to a highly cross-linked polystyrene (Scheme 3.51) [79].



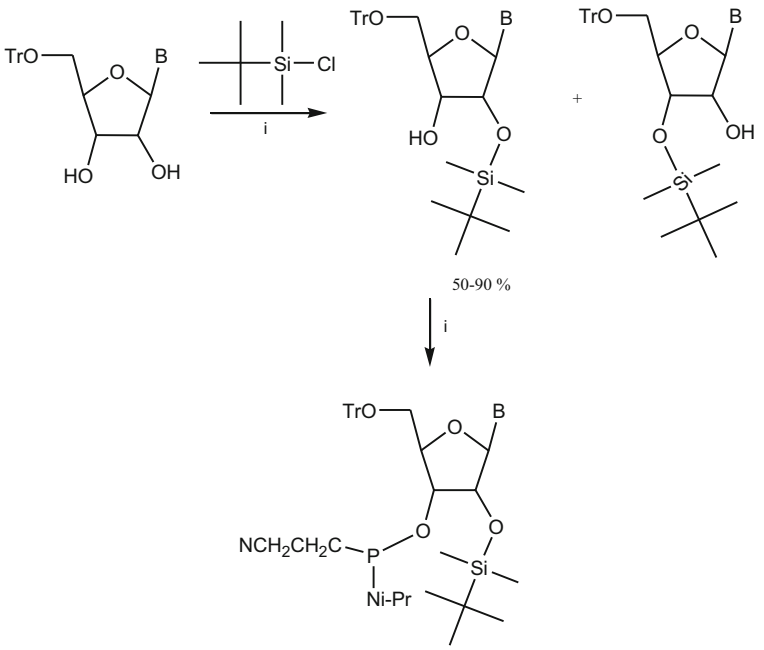
i) DMF. ii) H_2S. iii) 3´-azido-5´-isothiocyano-3´,5´-deoxythymidine. iv) a) TFA.
b) $H_2NC(=NH)SO_2H$. c) NH_4OH.

Scheme 3.50 Preparation of guanidinium oligonucleotides

The unit assemble for oligoribonucleotide synthesis is to some extend similar to deoxyribonucleotides synthesis; however, an additional consideration should be taken into account, which is the suitable protection of position 2-OH of ribose. The use of silyl protecting group, is one of the best choices so far reported, in particular



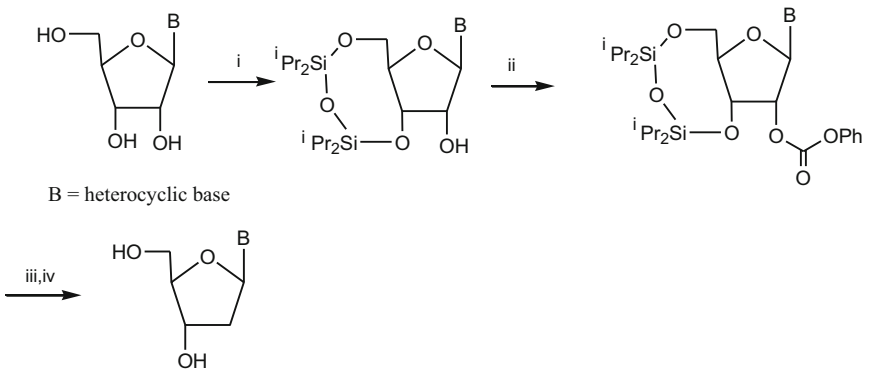
Scheme 3.51 Preparation of oligoribonucleoside phosphorothioates (PS-ORNs)



Scheme 3.52 Ribose protecting groups for oligoribonucleotide synthesis

the hindered *tert*-butyldimethyl silyl (TBDS) group. The protection of tritylribonucleoside produced a mixture of isomers, being the 2-OH silyl derivative generated in between 50 and 90 % yield. Final removal of this protecting group is usually achieved with 1 M tetrabutylammonium fluoride in THF (Scheme 3.52).

Some other choices for 2-OH protection are: tertahydropyran-1-il, 4-methoxytetrahydropyran-4-il and modified ketal of 1-(2-fluorophenyl)-4-methoxypiperidin-4- il (Fpmp); however, it has been found that acid conditions for removal of these protecting groups are not compatible with trityl protecting group.



i) $[(iPr)_2SiCl]_2O$, Py. ii) ClC(S)OPh, DMAP, MeCN. iii) Bu_3SnH, AIBN, $PhCH_3$.
iv) Bu_4NF, THF.

Scheme 3.53 Barton–McCombie procedure for the preparation of 2′ deoxynucleosides

Simultaneous protection of position 3′ and 5′ can be achieved by using the silyl protecting group tetraisopropyldisiloxychloride (TIPS-Cl) in pyridine. This type of protection has been useful in the conversion of adenosine to 2′-deoxyadenosine under the conditions reported by Barton and McCombie [80] (Scheme 3.53).

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