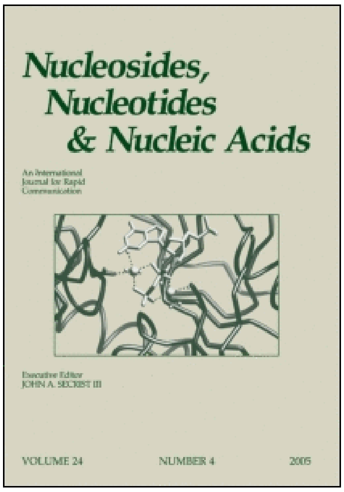


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

D-Arbinose-Based Synthesis of homo-*C*-d4T and homo-*C*-thymidine

Bogdan Doboszewski[a][b]
[a] Departmento de Química, Universidade Federal Rural de Pernambuco, Recife, Pernambuco, Brazil [b] Departamento de Antibióticos, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil

To cite this Article Doboszewski, Bogdan(2009) 'D-Arbinose-Based Synthesis of homo-*C*-d4T and homo-*C*-thymidine', Nucleosides, Nucleotides and Nucleic Acids, 28: 10, 875 — 901
To link to this Article: DOI: 10.1080/15257770903306518
URL: http://dx.doi.org/10.1080/15257770903306518

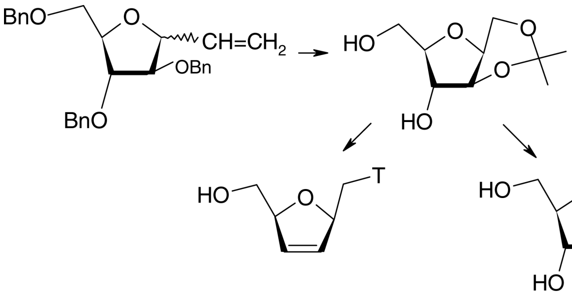
Nucleosides, Nucleotides and Nucleic Acids, 28:875–901, 2009
Copyright © Taylor & Francis Group, LLC
ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770903306518

D-ARBINOSE-BASED SYNTHESIS OF HOMO-*C*-d4T AND HOMO-*C*-THYMIDINE

Bogdan Doboszewski

Departmento de Química, Universidade Federal Rural de Pernambuco, Recife, Pernambuco and Departamento de Antibióticos, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil

□ *2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl halides (chloride, bromide) were reacted with AllMgBr, MeMgBr, and VinMgBr to furnish anomeric mixtures of the* C*-glycosyl products. The factors that influenced the β/α ratio are discussed. The α,β-*C*-vinyl derivative was transformed into 1-deoxy-1-*C*-hydroxymethyl-β- and -α-D-arabinofuranoses (2,5-anhydro-D-glucitol and -mannitol, respectively), separable after isopropylidenation step. 2,5-Anhydro-1,3-*O*-isopropylidene-D-glucitol was converted into 2,5-anhydro-6-*O*-triphenylmethyl-D-*erythro*-hex-3,4-enitol and 2,5-anhydro-4,6-di-*O*-benzoyl-3-deoxy-D-*ribo*-hexitol, which were coupled with N-3-benzoylthymine under the Mitsunobu conditions to furnish two analogs of nucleosides with a -CH_2- insert between sugar moieties and thymine.*



Received 8 August 2008; accepted 18 August 2009.

Prof. Alexander Y. Nazarenko, Chemistry Department, State University of New York, College at Buffalo, USA, is acknowledged for x-ray structure of **4**; Dr. Kent Dailey, Brigham Young University, Provo, UT, USA, for permission to use the x-ray facilities; Prof. Francesco Nicotra, Department of Chemistry, University of Milano-Bicocca, Italy for the NMR data of **27**α; and Prof. Peter G. Goekjian, Department of Chemistry, University Claude Bernard Lyon 1, Villeurbanne, France, for helpful discussion. Financial support from the Brazilian National Research Council is appreciated.

Address correspondence to Bogdan Doboszewski, Departmento de Química, Universidade Federal Rural de Pernambuco 52171-900, Recife, PE, Brazil. E-mail: bdoboszewski@hotmail.com

Keywords D-arabinose, deoxygenation; *C*-glycoside; Grignard reagents; Mitsunobu coupling; *C*-nucleoside; stereoselectivity

INTRODUCTION

Long-lasting synthetic interest in nucleoside analogs is dictated by the hope to obtain compounds capable to interfere with functioning of enzymes, which can manifest as antiviral, anticancer, antibacterial, insecticidal, fungicidal or herbicidal activity. A spread of HIV, hepatitis B, herpes simplex, and other viruses gave strong impulse to this type of work.[1–13] Basically, there are three possibilities to obtain analogs of nucleosides: (1) to change a carbohydrate part; (2) to change a heterocyclic part; or (3) to change a mode of connection between both moieties. Selected examples that illustrate the last possibility are illustrated in Figure 1. Most of the compounds shown are the homo-*C*-nucleosides, which have a -CH_2-linker between a sugar and heterocyclic moieties.[14–27] Some of them, like DADMe-immucillin-H **8** are active at a picomolar range in several biological systems.[21,22] One of the synthetic possibilities to obtain homo-*C*-nucleoside is to prepare appropriately functionalized *C*-glycosyl precursor and to couple it with a heterocyclic moiety. We used this approach to obtain the homo-*C*-analog **3**[16] of the commercial anti-HIV drug d4T, and also homo-*C*- thymidine **4**.[16] This article reports the full experimental details of this work.

The literature about *C*-glycosyl compounds is abundant,[29–39] however obtention of these derivatives in a stereochemically predictable manner is generally difficult. Nevertheless, many diversified methods to obtain β-*C*-arabinofuranosides or α-*C*-arabinofuranosides with predetermined configuration were published:

1. intramolecular substitutions in appropriately functionalized mannoses;[40]
2. reaction of arabinolactone with 2-lithiumthiazole followed by SmI_2 reduction;[41]
3. intramolecular substitution in aldonic acid esters;[42]
4. $BH_3.SMe_2$-$BF_3.Et_2O$ cleavage of inulin or levan;[43]
5. cyclizations of aminoglucitol mediated by anh. HF;[44]
6. thermal ring contractions of 2-*O*-trifluoromethanesulfonates;[45]
7. oxidation of 2-deoxy-2-selenophenyl derivatives with mCPBA followed by ring contraction;[46]
8. ring contraction in 3,4,6-tri-*O*-benzyl-D-glucal in the presence of $Tl(NO_3)_3$;[47]

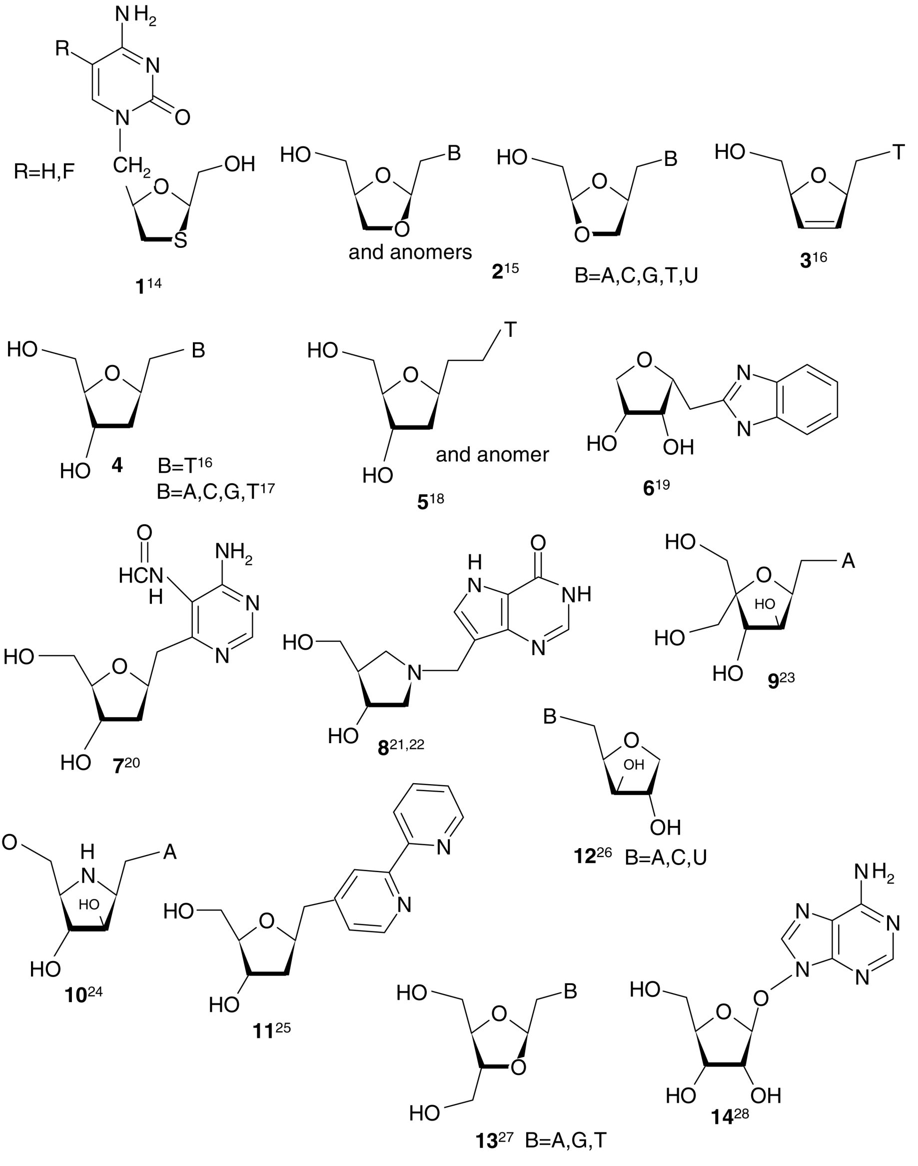


FIGURE 1 Analogs of nucleosides with a different mode of connection between hetercyclic bases and sugar moieties.

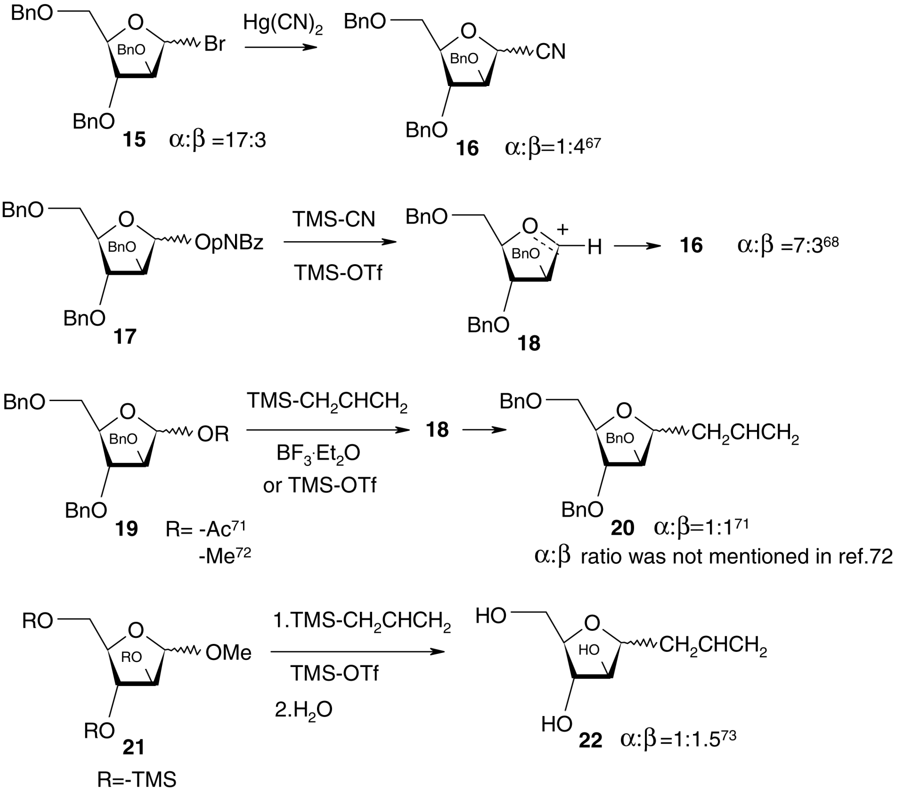
9. cyclization of 2-amino-2-deoxy-D-glucose in the presence of $NaNO_2$-HCl;[48]
10. acid catalyzed dehydration of D-mannitol[49,50] or 1,6-di-*O*-benzoyl-D-mannitol;[51]
11. tris(trimethylsilyl)silane-AIBN reduction of 2-selenophenyl derivatives of D-fructofuranose;[52]
12. intramolecular Friedel-Crafts reaction;[53]

13. reaction of D-arabinose with Meldrum's acid;[54]
14. acid-catalyzed cyclizations of 1-deoxy-1-dimetylphenylsilyl-L-glucitol;[55]
15. opening of cyclic sulfates derived from alditols;[56]
16. $PdCl_2$-CuCl-O_2 mediated cyclizations followed by Et_3SiH-BF_3.Et_2O reductions;[57]
17. stereospecific opening of alditol epoxides[58] or diepoxides;[59]
18. intramolecular aglycon delivery;[60]
19. reactions of bromomagnesium phenolates with 2,3,5-tri-*O*-benzyl-D-arabinofuranose followed by cyclization and *O*→*C* migration;[61]
20. cyclizations of arabinohex-1-enitols;[62–65]
21. BF_3.Et_2O mediated coupling between allyltrimethylsilane and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-arabinofuranose;[66]
22. substitutions with inversion of configuration at the anomeric center in the presence of a nonparticipating group using a cyanide ion;[67]
23. Lewis acid mediated reactions of 1-*O*-p-NO_2-benzoyl-2,3,5-tri-*O*-benzyl-D-arabinofuranose and TMS-CN;[68]
24. rection of 2,3,5-tri-O-benzylarabinofuranosyl chloride and sodium diethylmalonate;[69]
25. photochemical reaction between exocyclic methylene glycal and chlorodiethylmalonate.[70]

The data from Acton et al.[67] is particularly relevant to our project since it demonstrates a possibility to obtain the β-*C*-arabinofuranosides with acceptable selectivity via the inversion of configuration at the anomeric center (Scheme 1). It was clearly demonstrated that the bromides **15** (α:β = 17:3) furnished the cyanides **16** (α:β = 1:4) with inverted α:β ratio. At the same time intermediacy of the oxocarbenium cation **18** (derived from p-nitrobenzoates **17** under the influence of TMS-OTf in this case[68]) should be avoided since it may favor formation of the α-*C*-products.[68] Similar procedures starting from **19** (R = -OAc) furnished *C*-allyl arabinofuranosides **20** with no selectivity at all.[71] The trimethysilylated glycoside **21** furnished **22** with a small selectivity towards the β anomer.[73]

RESULTS AND DISCUSSION

Since we were interested to obtain the analogs of nucleosides which have β configuration, we concentrated attention on the 2,3,5-tri-O-benzyl-α-D-arabinofuranosyl chloride **24** and bromide **25** as substrates. Both **24** and **25** have a nonparticipating group at the C2 atom and good leaving groups at the C1 position. The leaving groups and the H2 atom are *cis*-oriented, so E2 elimination is unfavorable during reactions with basic reagents, whereas elimination via the E1cb mechanism is not probable due to a lack of anion-stabilization capacity of the 2-*O*-Bn group. Consequently, the inversion of

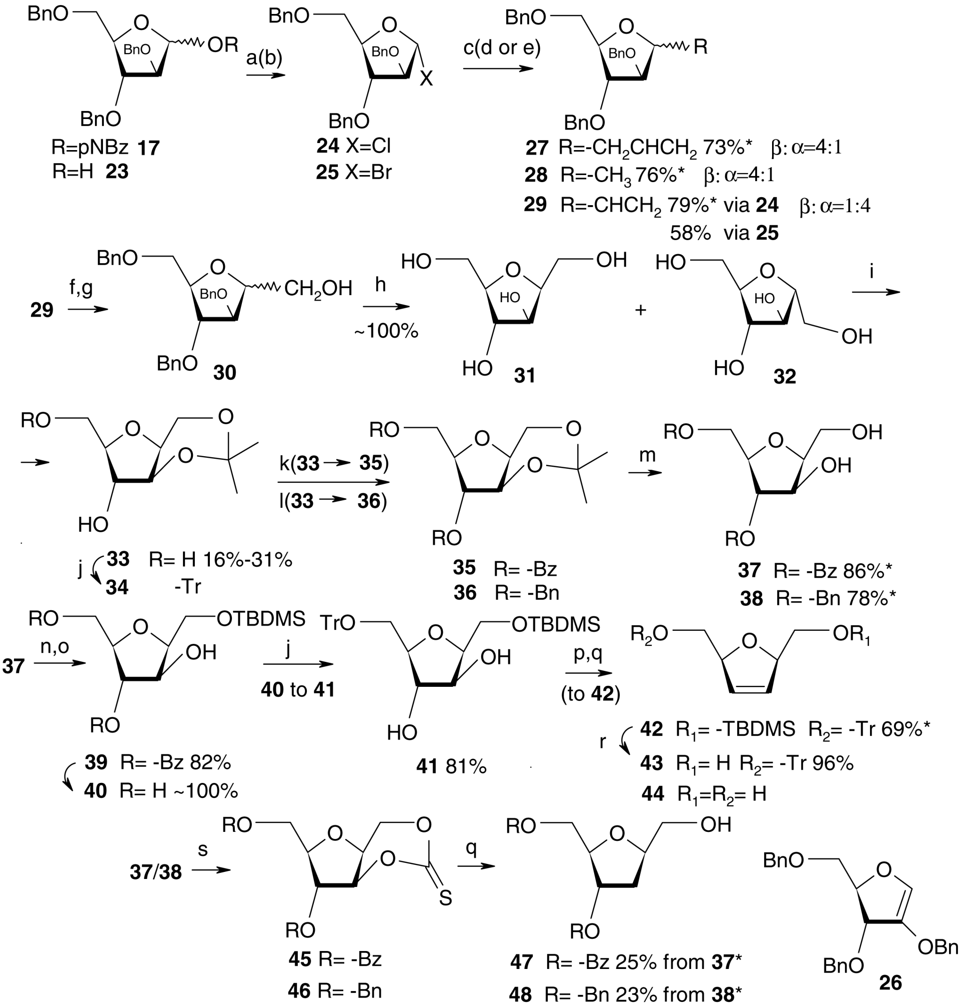


SCHEME 1 Stereoselectivity of formation of the *C*-arabinofuranosides using different conditions.

configuration at C1 should favor formation of the β configured 1,2-cis product with a suppression of elimination, as noticed before in a *manno* series.[74,75] It should be pointed out that a substitution with inversion of configuration at the anomeric center may not imply an S_N2 mechanism even if a group at C2 position has a nonparticipating character. In fact, an S_N1 ion-pair mechanism was suggested for methanolysis on the basis of kinetic data in several arabinofuranosyl chlorides.[76] In one case elimination of HCl was observed during a reaction involving the chloride **24**. Glaudemans et al.[77] isolated glycal **26** during a reaction of **24** with p-nitrophenol in the presence of 4Å molecular sieves. No explanation was offered to rationalize this fact.

Both **24** and **25** were used to obtain *C*-glycosyl intermediates **43** and **47** as shown in Scheme 2.

The chloride **24** was obtained from *p*-nitrobenzoates **17** by the published procedure[78] as an α:β = 95:5 mixture by ^{1}H 200 MHz measurement. Attempts to obtain **24** directly from 2,3,5-tri-O-benzyl-D-arabinofuranose **23** by the method of Perlin et al.[79] (MsCl, *sym*-collidine) were negative and resulted only in black, heterogeneous mixtures, whereas triphosgene and **23**



a.HCl/CH_2Cl_2, O°
b.HBr/CH_2Cl_2, O°
c.AllMgBr, -78° to rt.
d.MeMgBr, -78° to rt
e.VinMgBr, -78° to rt.
f.O_3, -78°
g.$NaBH_4$
h.Pd/C, H_2
i.acetone, H^+
j.TrCl, Py
k.BzCl, Py
l.BnCl, KOH
m.H^+
n.TBDMSCl, imidazole
o.iPr_2NH, MeOH
p.PhOC(S)Cl, Py
q.Bu_3SnH, AIBN
r.Bu_4NF
s.$(imid)_2C{=}S$

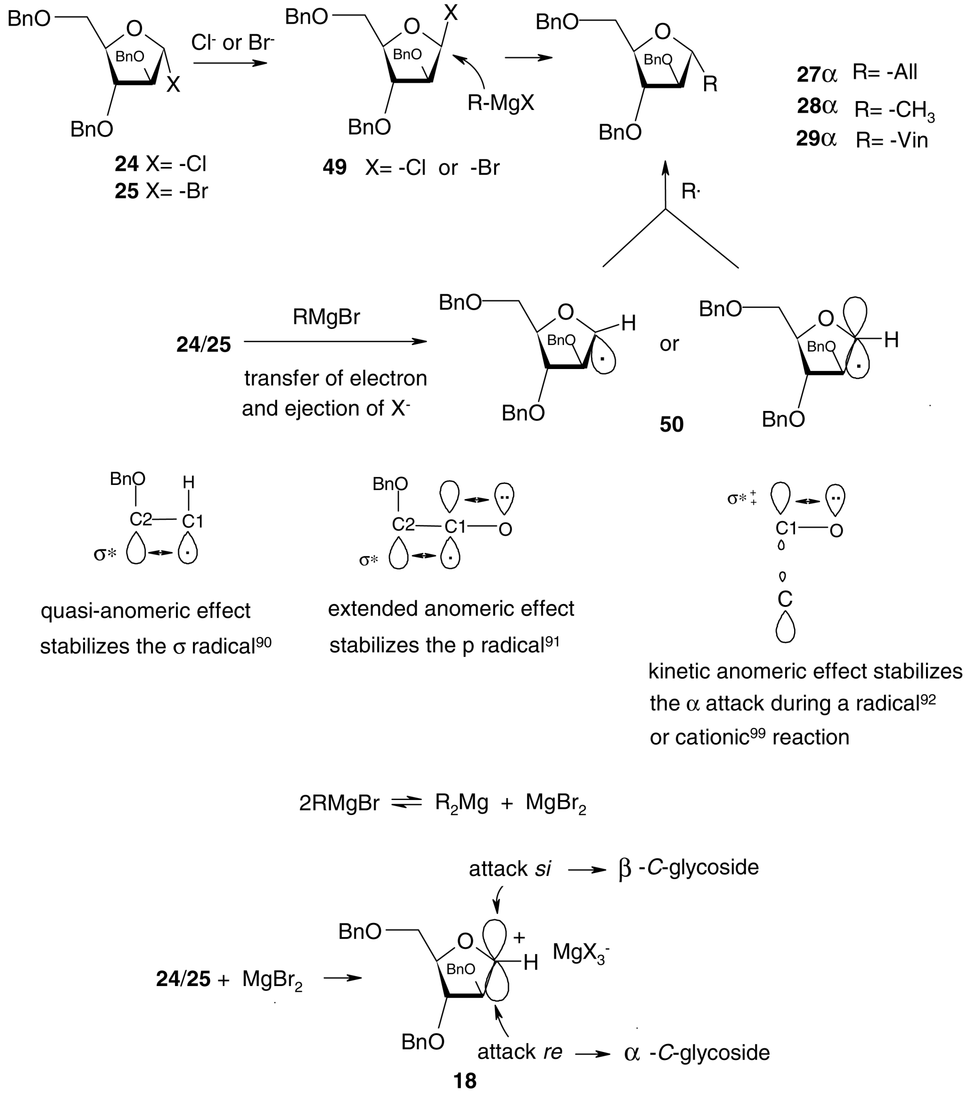
* Yields for two consecutive steps

SCHEME 2 Preparation of the *C*-glycosyl alcohols **43** and **47**.

was published to yield **24** with a higher content of the unwanted β anomer (α:β = 86:14).[80] The bromide **25** was also obtained from **17**,[81] but due to its instability the ^{1}H NMR spectrum was not run. Since obtention of *C*-arabinosyl compounds starting from **24** and Grignard reagents doesn't seem to have been reported, we reacted it with AllMgBr and MeMgBr to test a reaction since the *C*-allyl[71,72] and C-methyl[63] derivatives **27** and **28**, respectively, obtained in different ways are known. Indeed, the chloride **24** furnished inseparable β:α = 4:1mixture **27**, with predominant formation of the β anomer as expected. It was evident from the ^{1}H and ^{13}C spectra of the mixture which show that the minor component matches its signals with those of the pure **27**α whose configuration was established by the NOE measurement.[71] Likewise **24** reacted with MeMgBr and formed β:α = 45:10 mixture **28**, again with predominant formation of the β anomer as established by comparison of its NMR data with those of the known compound.[63] Interestingly, 2,3;5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride and AllMgBr furnished allyl *C*-mannofuranosides in roughly the same β:α = 3.5:1 proportion.[74] The β preference shown here remains in contrast with the results obtained during Lewis acid catalyzed reactions as mentioned above.[71,73] Having confirmed that **24** can furnish the *C*-glycosides with acceptable β selectivity, we treated it with vinylmagnesium bromide with a hope to obtain predominantly the β-*C*-vinyl anomer. Unexpectedly, the proportion of both anomers in **29** was inverted (β:α ≈1:4) by comparison with the chemical shifts of the known derivatives.[64] More reactive bromide **25** and VinMgBr resulted in a higher content of the β anomer as evidenced by the higher yields of the acetonide **33** (see the Experimental section). **29** decomposed substantially even in a refrigerator probably via free-radical polymerization, as evidenced by formation of a long streak on TLC. It should be stressed that the $J_{H1\text{-}H2}$ coupling constants in *C*-arabinofuranosides cannot be used to judge their anomeric configurations[61,82] contrary to the *O*-arabinofurosides.[83,84]

Formation of the β *C*-glycosides in the abovementioned experiments can be interpreted as a result of substitutions with inversion of configuration at the anomeric center. These "β" attacks can be additionally facilitated by complexation of the incipient RMgBr molecules by the C2-*O*-Bn and/or C5-*O*-Bn oxygen atoms. A similar idea was expressed by van Boeckel et al.[85] and Dahlhoff et al.[75] to rationalize formation of the β configured *O*-alkyl mannopyranosides and mannofuranosides, respectively. Thus, formation of a hydrogen bond between attacking alcohol and the C2-O atom[85] or formation of a transient borate-like intermediates during initial stage of reaction of sodium alkoxides and 2,3;5,6-di-*O*-ethylboradienyl-α-D-mannofuranosyl$^{\text{chloride}}$[75] would facilitate a displacement of a leaving group with inversion. Also, Dunkerton et al.[86] noticed that some "β selectivity" during a Ferrier rearrangement could be obtained by chelation of Lewis acid catalyst with a nucleophile and a leaving group at C3 atom in glucal moieties. These possibilities resemble a mechanism of intramolecular aglycon delivery.[87]

Formation of the α-*C*-anomers in turn can be rationalized by three independent mechanisms as illustrated in the Scheme 3. The first possibility is a halide-ion catalysis.[88] The highly reactive β chloride or bromide **49** (a source of Br^{-} can also be MgBr$_2$ resulting from a Schlenk equilibrium[89])



SCHEME 3 Possible mechanisms of formation of the α-*C*-arabinofuransides.

could be formed during X^- attack on the α substrate **24** or **25**, which could then react with inversion of configuration at C1 to furnish the products **27**α, **28**α, or **29**α. Alternatively, a free-radical mechanism can be considered, particularly when AllMgBr was used. A transfer of one electron from a Grignard reagent to **24** or **25** could form the anomeric radical **50** after ejection of the halide anion. If this radical is σ, its configuration should be α due to a favorable interaction with the σ^* orbital of the C2-OBn bond ("quasi anomeric effect"[90]). Recombination of the **50**α and.R should furnish the α product. If the unpaired electron occupies the p orbital, an extended anomeric effect ($n_{\text{endocyclic O}}$-p_{C1}- $\sigma^*_{\text{C2-OBn}}$) would be responsible for its stabilization.[91] Subsequent attack of the R should proceed from the "α side" due to the kinetic anomeric effect.[92] It is clear that, irrespective of the character of the anomeric radical (σ or p), the product should have a configuration α. Similar substitution with retention of configuration via Grignard reagent-induced single electron transfer process was noticed during a synthesis of desoxybiotin.[93] The last mechanism involves interaction of **24** or **25** with $MgBr_2$ which is a Lewis acid. Abstraction of Cl^- or Br^- anion from **24**/**25** would furnish a cation **18**, which could be attacked by nucleophiles from the *re* side at C1 to yield the α product, or from the *si* side to furnish the β product. The *re*/*si* selectivities in similar systems were discussed.[94–99] Schmitt et al.[94] used Felkin-Anh type analysis to rationalize the stereochemistry of the products resulting from reactions of oxocarbenium cations formed from monosubstituted γ-lactols and BF_3 Et_2O, and allylic/propargylic silanes or silyl enol ethers as nucleophiles. Their conclusions were that the substituents at the 3, 4, or 5 positions (a γ-lactol numbering) all favor formation of the *trans* products. The influence of the C4 substituent is particularly efficient. On assumption that these effects are independent of each other one could translate them to the case of the arabinosyl cation **18** and to conclude that the 2-OBn and 4-CH_2OBn groups should favor formation of the α anomers, whereas the 3-OBn group should favor formation of the β anomers. The results of Nicotra[71,73] may suggest that both tendencies cancel each other and this results in no preference towards the α or the β anomer. The analysis of Woerpel[95–98] is based on a combination of three factors: (1) conformation of the reacting oxocarbenium ion which can be influenced by electrostatic interactions with the axially disposed alkoxy substituents; (2) stereoelectronically controlled attack of a nucleophile (allyltrimethylsilane) on the oxocarbenium cations; and (3) steric interactions in the newly formed products. The conclusion derived from this analysis was that the C3-attached (carbohydrate numbering) –OR group influences the reactive conformation in such a way that a 1,3-*syn* product is predominant. Thus, the 2-deoxy-threopentofuranosyl derivatives favor formation of the β-*C*-allyl glycoside, whereas the ribo- or 2-deoxy-erythropentofuranosyl derivatives favor formation of the α-*C* glycosides.[96] The *arabino* case is still different since two flexible reactive conformations are possible: the first one with axial(pseudoaxial) substituents, which favors formation of the α arabinoside, and the second one with equatorial(pseudoequatorial) substituents which favors formation of the β arabinoside.[98] Another issue is a relative population of both conformations and their reactivities.[95] Experimental results suggest that all the factors anihilate each other and result in no selectivity at all.[71,73] Both analyses must be somehow limited, since TMS-OTf catalyzed installation of the –CN group at the anomeric position of **17** via oxocarbenium cation **18** furnished a product **16** with clear preference towards the α anomer (see Scheme 1).[68] Tomura et al.[99] have shown that if a conformation of the ring is secured ($^4C_1$ or $^1C_4$) by judicious choice of the protecting groups, very high degree of α or β selectivity, respectively, can be obtained in xylopyranosyl system during *C*-glycosylation thanks to the kinetic anomeric effect. The same idea was applied to L-arabinofuranose: If a reactive oxocarbenium cation was locked in its $_3E$ conformation (e.g., by formation of the cyclic 3,5-di-*t*-butylsilane) high β selectivities were obtained.[100] This was realized for *O*-arabinofuranosides only. It is interesting to notice that 1-*O*-acetyl 2,3,5-tri-*O*-**benzoyl**arabinofuranose, AllTMS and $BF_3.Et_2O$ furnished α:β = 10:1 proportion of the allyl arabinofuranosides[66] whereas the 1-*O*-acetyl 2,3,4-tri-*O*-benzylarabino**pyranose** and AllTMS/$BF_3.Et_2O$ furnished α:β = 1:2 proportion of the product.[101] The latter case was explained on the conformational ground.

To summarize this part of the project, AllMgBr and MeMgBr reacted with the chloride **24** to furnish **27**/**28** in β:α ≈ 4:1 proportion, whereas VinMgBr and **24** furnished **29** in inverted proportion of the anomers β:α ≈ 1:4. The percentage content of **29**β was higher if more reactive bromide **25** was used. These results can be rationalized in terms of differences of reactivities of the three Grignard reagents, reactivities of the α halides **24**/**25** and reactivities of the in situ formed β halides **49**. Both AllMgBr and MeMgBr (evidently more reactive than VinMgBr) reacted rapidly with the α chloride **24** with the inversion of configuration at the C1 atom to furnish the β products **27**β/**28**β. This was accompanied by little in situ anomerization to form the β halide **49** which was a precursor of **27**α/**28**α (The radical **50** might contribute to formation of **27**α as well.). In the case of evidently less reactive VinMgBr, the contribution of these two pathways was clearly inverted. VinMgBr reacted sluggishly with the α chloride **24**, and slightly more rapidly with the α bromide **25** to yield **29**β. At the same time, it reacted faster with the highly energetic β halides **49** formed in situ, to yield **29**α which was a predominant anomer formed. The same mechanism was used to rationalize formation of the 1-deoxy-2,3;5,6-di-*O*-isopropylidene-1-phenyl-α-D-mannofuranose as the only anomer from the 2,3;5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride and phenylmagnesium bromide.[102] Participation of the cation **18** during formation of **27**, **28,** and **29** was probably small, since its extensive presence would result in roughly equal β:α proportions,[71,73] which is incompatible with the experimental results obtained.

Inseparable mixture **29** was subjected to ozonolytic cleavage[103] at low temperature to avoid overoxidation of the benzyl ethers to benzoates,[104] followed by $NaBH_4$ reduction[105] to furnish again inseparable hydroxymethyl products **30**. These compounds were then de-*O*-benzylated by hydrogenolysis to yield the 1-deoxy-1-*C*-hydroxymethyl-β-D-arabinofuranose **31** (2,5- anhydro-D-glucitol) and 1-deoxy-1-*C*-hydroxymethyl-α-D-arabinofuranose **32** (2,5-anhydro-D-mannitol). The compound **31** is a secondary metabolite of the fungus *Fusarium solani* and exhibits marked phytotoxicity.[106] Separation of **31** from **32** was easily performed after isopropylidenation (acetone, cat. $HClO_4$), since only **31** can react with acetone (→ **33**), whereas **32** remained unchanged. The yields of **33** varied between 16–31% and were higher if the bromide **25** was used. **33** had its structure confirmed by x-ray analysis[107] and it was additionally transformed to the known triphenylmethyl ether **34**.[108] **33** can be alternatively obtained by acid-catalyzed dehydration of mannitol[49,50] or 1,6-di-O-benzoylmannitol.[51] **33** was converted to its di-*O*-benzoate **35** (BzCl, Py) and its di-*O*-benzyl ether **36** using either BnCl- KOH or phase-transfer catalysis (50% aq KOH, Bu_4NHSO_4, BnCl). In the latter case, the reaction mixtures were invariably dark, and the yield were much lower, presumably because of base-induced elimination of benzyloxy moiety[109,110] and subsequent secondary processes. Acid cleavage of the acetonide group in **35**/**36** furnished the diols **37**/**38**. Selective silylation of the primary –OH group in **37** (TBDMSCl, imidazole) furnished **39**, which was debenzoylated (*i*Pr_2NH, MeOH) to give a triol **40**. Selective tritylation of the primary –OH group in this triol furnished a crystalline derivative **41** which was converted to the olefin **42** *via* Bu_3SnH/AIBN reduction of its bis-thiocarbonyl ester.[111,112] Removal of the –TBDMS group (Bu_4NF) furnished the unsaturated alcohol **43**. It should be pointed out that **43** in its deprotected form **44** has a plane of symmetry, therefore both hydroxymethyl groups are enantiotopic. The monoprotected compound **43,** however, is enantimerically pure, because both –CH_2OH groups remained well differentiated during the whole course of the synthesis.

The diol **37** was used in a different way to get another intermediate which has a structure **47**. Thus, selective mono-deoxygenation at the secondary position *via* cyclic thionocarbonate **45** (Bu_3SnH/AIBN) furnished a mixture of products from which the necessary primary alcohol **47** was obtained in ca. 25% yield. This compound was formerly used to obtain (+)-muscarine[113] and 2′-deoxy-showdomycin.[114] Application of the same deoxygenation process to a dibenzylated substrate **38** furnished **48** without improvement of the yield.

The alcohols **43** and **47** were then coupled with the *N*-3-benzoyl-thymine **51**[115] under the Mitsunobu conditions[116] (DEAD, Ph_3P) to furnish **52** and **53**, respectively (Scheme 4). Due to difficulties encountered during isolation of **52** by chromatography (interference with triphenylphosphine oxide), its characterization was skipped, and debenzoylation ($Na^+ {}^-OMe$, MeOH) followed by detritylation (90% AcOH, Δ) was performed. At

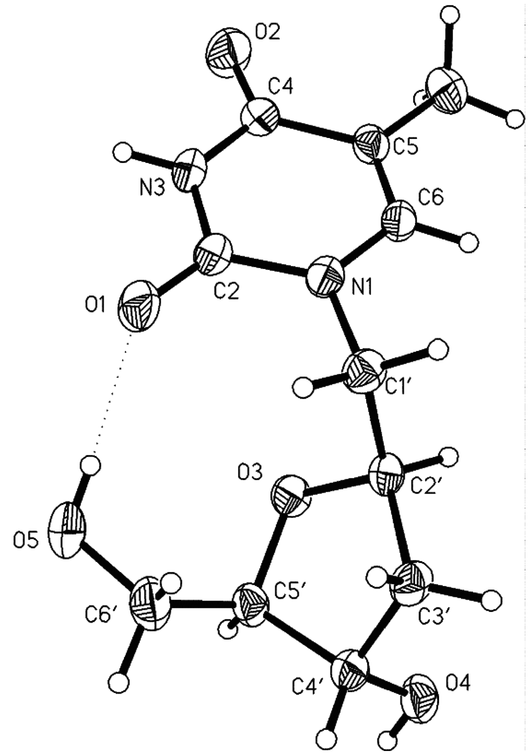
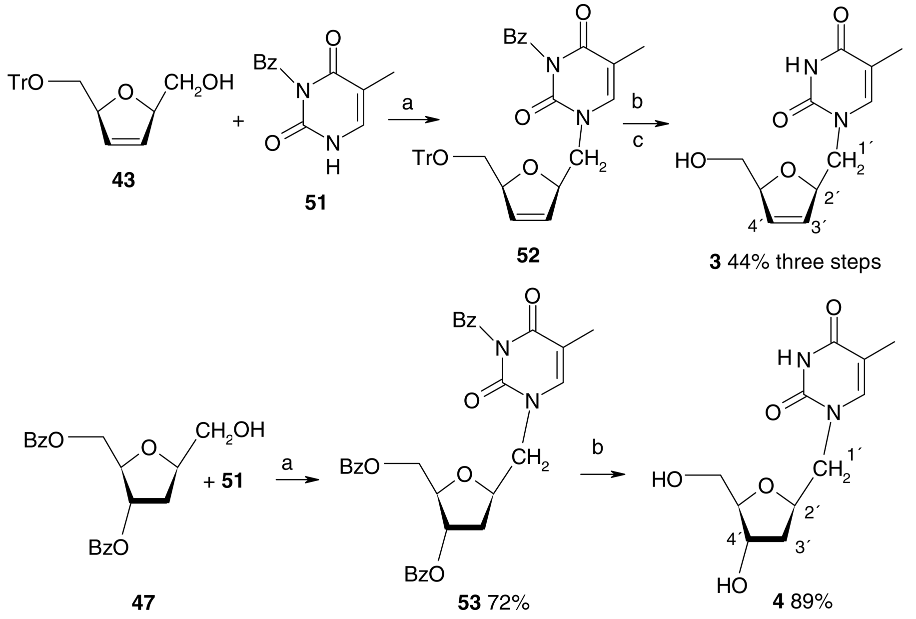


FIGURE 2 ORTEP drawing of the homo-*C*-thymidine **4**.

this stage, a fully deprotected homo-*C*-analog of d4T **3** was isolated in a cumulative yield of 44% for three steps. The compound **53** in turn was isolated in 72% yield after column chromatography, and was subjected to *O*,*N*-debenzoylation (Na^{+} $^{-}$OMe, MeOH) to furnish homo-*C*-thymidine **4**. We wanted to firmly confirm its structure particularly in a context of inverted α/β ratios of **27**/**28** versus **29**. Since **4** is a highly crystalline compound, it was subjected to x-ray analysis. Its ORTEP drawing (shown in the Figure 2) clearly shows a β configuration of this target compound.

In summary, a synthesis of two *C*-analogues of thymidine, **3** and **4**, is described. The procedure is based on a formation of the critical C-N bond between *N*3-benzoylthymine **51** and the carbohydrate alcohols **43** and **47** using the Mitsunobu protocol. Both carbohydrate components were obtained from *C*-vinyl-D-arabinofuranose **29**. The results of further application of this methodology to obtain different types of *C*-nucleoside analogs based on derivatives of **38** and of **48** as well as the results of screening will be published in due course.



SCHEME 4 Coupling of the *C*-glycosyl alcohols **43** and **47** with *N*3-benzoylthymine **51**. a) DEAD, PPh_3; b) NaOMe, HOMe; c) 90%HOAc, 100°.

EXPERIMENTAL

General

Evaporations were performed at ca. 30°C on an evaporator coupled to an oil pump. Vacuums were broken using a balloon filled with dry argon. The solvents were dried by distillation from $LiAlH_4$ (dioxane, THF), P_2O_5 (CH_2Cl_2) or by azeotropic distillation (toluene). "Xylenes" refers to a mixture of isomers. Inert atmospheres during the reactions which employ moisture-sensitive reagents were maintained using an overpressure of argon or nitrogen dried by passage through a "blue silica gel." Dry solvents were transferred using syringes under a blanket of argon or nitrogen. Column chromatography was performed on a silica gel G 70–230 mesh, and TLC chromatography on aluminum plates precoated with silica gel 60 F_{254} (both from Merck Darmstadt, Germany). Ten percent of H_2SO_4 in MeOH was used to char the TLC chromatograms. $MgSO_4$ was used to dry the extracts. The NMR spectra were recorded on Varian or Bruker instruments operating at the indicated frequencies. Exact mass measurements of the samples judged to be at least 98% pure by ^1H NMR were performed on a Jeol SX 102A spectrometer using the FAB mode in NaOAc-thioglycerol matrices or using a chemical ionization (CH_4). Optical rotations were measured on a Perkin-Elmer automatic polarimeter at ca. 24°C.

1-Allyl-3,4,5-tri-*O*-benzyl-1-deoxy-α,β-D-arabinofuranose 27

2,3,5-Tri-*O*-benzyl-D-arabinofuranose **23** was prepared by analogy to its L-enantiomer[117] and converted to the anomeric p-nitrobenzoates **17** and further to the chloride **24** as described.[78] **17** (2.1 g, 3.7 mmol) was added to a cold (ice bath) saturated solution of HCl in CH_2Cl_2 (50 ml). After 1 hour a slow stream of HCl was passed through the resulting heterogeneous mixture during 10 minutes, and incubation was continued for 50 minutes more at ca. 0°C. TLC in hexane-EtOAc 3:1 showed that all **17** reacted. The mixture was rapidly filtered through a sintered glass and collected p-nitrobenzoic acid was washed with toluene. The volatiles were evaporated. More toluene was added and evaporated to expel HCl. **24** prepared in this way was yellowish oil and was ca. 95:5 mixture of α:β anomers (H1 β: 6.18, J_{12} = 4.2 Hz; H1 α: 6.15, s; lit.[80] H1 β: δ 6.21, J_{12} = 4.2 Hz, α: 6.17, s). To this oil was added dry CH_2Cl_2 (100 ml) and a solution was cooled in acetone-dry ice under a blanket of N_2. 1M allylmagnesium bromide in Et_2O (4.5 ml) was added via a syringe and the mixture was left to reach room temperature overnight. Extraction (CH_2Cl_2-aq NH_4Cl), drying, and evaporation of volatiles furnished yellow oil, which was applied on top of a silica gel column. Elution with hexane-EtOAc 10:1 furnished **27** (1.2 g, 73% for two steps) as colorless oil. A proportion of the anomers was β:α = ca. 4:1 by integration of the separated signals in the ^{1}H spectrum. Numbering of the allyl moiety is: -$CH_2{}^3CH^2 = CH_2{}^1$; a glycosyl part is numbered 4, 5, etc. ^{1}H (400 MHz, $CDCl_3$): 7.35–7.18 (H aromatic); major β anomer: 5.80 (ddt, J_{23a} = 7.0 Hz, J_{23b} = 7.0 Hz, J_{21a} = 10.5 Hz, J_{21b} = 17.0 Hz, H 2); 5.10 (d of apparent q, J = 1.3 Hz, J = 1.3 Hz, J = 1.3 Hz, J_{1b2} = 17 Hz, H 1_b); 5.03 (d of irregular signals, J_{1a2} = 10 Hz, H 1_a); 4.57–4.44 (m, 5H) and 4.33 (d, J = 12.1 Hz, 1 H), -CH_2Ph; 4.12–4.06 (unresolved, H 7 superimposed on H 4 of the α anomer); 4.03 (dt, J_{45} = 3.5 Hz, J_{43a} = J_{43b} = 7.5Hz, H 4 superimposed on H 6 of the α anomer); 3.93 (d, J_{67} = 2.6 Hz, H 6); 3.79 (d, J_{54} = 3.5 Hz, H 5); 3.63 (dd, J_{8a7} = 5.6 Hz, J_{8a8b} = 9.8 Hz, H 8_a); 3.51 (dd, J_{8b7} = 7.0 Hz, J_{8b8a} = 9.8 Hz, H 8_b); 2.53–2.45 (m, H 3_a, H 3_b); minor α anomer: 4.23 (dt, J_{76} = 4.0 Hz, J_{78a} = J_{78b} = 6.0 Hz, H 7); 3.86 (dd, J = 3.0 Hz, J = 4.5 Hz, H 5); 3.58 (dd, J_{8a7} = 6.0 Hz, J_{8a8b} = 10.5 Hz, H 8_a); 3.53 (dd, J_{8b7} = 6.0 Hz, J_{8b8a} = 10.5 Hz, H 8_b); 2.40 (apparent dq, J ~1 Hz, J = 7.0 Hz, H 3_a, H 3_b). ^{13}C (100 MHz): 138.06; 137.72; 128.21; 128.17; 128.10; 127.56; 127.50;127.44; 127.35 C aromatic; 73.13; 73.07; 71.60; 71.53; 71.14, -CH_2Ph; major β anomer: 134.69 C2; 116.67 C1; 83.52 C6; 82.67 C5; 82.50 C7; 80.77 C4; 70.45 C8; 33.06 C3; minor α anomer: 134.09 C2; 117.21 C1; 86.72 C5; 85.13 C6; 81.73 C4; 81.40 C7; 70.08 C8; 37.47 C4. Identification of the anomers was performed by comparison with the data of the α anomer kindly provided by Prof. F.Nicotra.

2,3,5-Tri-*O*-benzyl-1-deoxy-1-metyl-α,β-D-arabinofuranose 28

The chloride **24** was freshly prepared from **17** (2.1 g, 3.7 mmol) as described above, solubilized in CH_2Cl_2 (30 ml), cooled in ethanol-dry ice and reacted with 3M MeMgBr in Et_2O (1.5 ml) as described for AllMgBr. Extraction and chromatography in hexane-EtOAc 10:1 furnished **27** (1.2 g, 76%), as colorless oil. Numbering of the protons is: -Me^1; glycosyl part is 2, 3, etc. ^{1}H (400 MHz, $CDCl_3$): 7.37–7.23 (15H, H aromatic), 4.61–4.39 (unresolved, 6 H, -CH_2Ph), 4.24–4.19 (unresolved, α), 4.14 (dq, J_{23} = 3.5 Hz, J_{21} = 6.6 Hz, H 2β), 4.06–4.00 (unresolved, H 5β), 3.89 (dd, J = 3.5 Hz, J$\sim$1Hz), 3.76 (dd, J = 4.0 Hz, J = 1.0 Hz), 3.62 (dd, J_{6a5} = 6.0 Hz, J_{6a6b} = 10.0 Hz, H 6_a β), 3.53 (dd, J_{6b5} = 6.5 Hz, J_{6b6a} = 10.0 Hz, H_6 β), 1.31 (d, J_{12} = 6.3 Hz, CH_3 β), 1.30 (d, $J_{12}$$\sim$7Hz, CH_3 α). ^{13}C (100 MHz):138.16, 138.02, 137.80, 128.34, 128.31, 128.24, 127.73, 127.68, 127.57, 127.47, C aromatic; major β anomer: 84.51, 83.78, 82.34, 77.19, 14.06 -Me; minor α anomer: 81.03, 78.14, 89.24, 85.43, 19.17 -Me; 73.32, 73.25, 71.85, 71.43, 71.28, 70.71, 70.38, -CH_2Ph, and C5. Identification of the signals was based on comparison of the chemical shifts with the known compounds obtained in a different way.[63]

2,3,5-Tri-*O*-benzyl-1-deoxy-1-vinyl-α,β-D-arabinofuranose 29

A. The chloride **24** was freshly prepared form **17** (7.2 g, 12.6 mmol) in CH_2Cl_2 (70 ml) as described above. To the oily **24** was added dry CH_2Cl_2 (150 ml) and the solution was cooled in acetone-dry ice under a blanket of N_2. 1M vinylmagnesium bromide in THF (17 ml) was added via a syringe and the mixture was left to reach room temperature overnight. Extraction (CH_2Cl_2-aq NH_4Cl), drying and evaporation of volatiles furnished yellow oil which was applied on top of a chromatographic column. Elution with hexane-EtOAc 10:1 furnished **29** (4.3 g, 79% for two steps) as colorless oil. A proportion of β:α anomers was ca. 1:4 by integration of the separated signals in the ^{1}H spectrum.

B. HBr was bubbled through a solution of **17** (9.3 g, 16.3 mmol) in CH_2Cl_2 (50 ml) during 5–6 minutes at room temperature. This operation must not be prolonged to avoid splitting of the benzyl ethers by HBr. p-Nitrobenzoic acid started to precipitate immediately. The heterogeneous mixture was rapidly filtered through a sintered glass and the solids were washed with toluene. Evaporation of volatiles and short drying on an oil pump furnished the bromide **25** as oil. CH_2Cl_2 (100 ml) was added and the flask maintained under N_2 was cooled in ethanol-dry ice. 1M VinMgBr in THF (20 ml) was added. The mixture was left to reach room temperature overnight. Work-up as above furnished 4.1 g, 58% of **29**. The content of the β anomer was higher as evidenced by higher yield of the acetonide **33** (see below). **29** should not be stored for more than few days. Its decomposition products form a more polar streak on TLC. The vinyl moiety is numbered $–CH^2 = CH_2{}^1$, whereas the glycosyl part is numbered 3, 4, etc.

^{1}H (400 MHz, $CDCl_3$) : 7.35–7.22 (H aromatic); major anomer α: 5.94 (ddd, $J_{23} = 6.9$ Hz, $J_{21a} = 10.4$ Hz, $J_{21b} = 17.0$ Hz, H 1_b); 5.34 (dt, $J_{21b} = 17.0$ Hz, $J_{1a1b} = J_{1a3} = 1$ Hz, H 1_a); 5.18 (dt, $J_{1a2} = 10.5$ Hz, $J_{1a1b} = J_{1a3} = 1$ Hz, H 1_a); 4.58–4.41 (m, 7H, $-CH_2Ph$, H 3α, H 3β); 4.23 (q, $J_{56} = J_{67a} = J_{67b} = 5.2$ Hz, H 6); 4.09 (t, $J_{54} = J_{56} = 4.0$ Hz, H 5); 3.94 (dd, $J_{45} = 3.6$ Hz, $J_{43} = 5.0$ Hz, H 4); 3.59 (dd, $J_{7a6} = 5.3$ Hz, $J_{7a7b} = 10.2$ Hz, H 7_a); 3.56 (dd, $J_{7a6} = 5.3$ Hz, $J_{7b7a} = 10.3$ Hz, H 7_b); minor anomer β: 6.06 (ddd, $J_{23} = 8.0$ Hz, $J_{21a} = 11.0$ Hz, $J_{21b} = 18.0$ Hz, H 2); 5.38 [d of broad s (half-width ca. 5 Hz), $J = 11$ Hz, H 1_b); 5.27 [d of broad s (half-width ca. 4 Hz), $J = 11$ Hz, H 1_a); 4.12 (dd, $J_{65} = 3.5$ Hz, $J_{67} = 6.2$ Hz, H 6); 3.96 (dd, $J_{54} = 1.0$ Hz, $J_{56} = 4.0$ Hz, H 5); 3.89 (dd, $J_{43} = 4.0$ Hz, $J_{45} = 1.0$ Hz, H 4); 3.65 (dd, $J_{7a6} = 5.0$ Hz, $J_{7a7b} = 10.0$ Hz, H 7_a); a signal of H 7_b is superimposed on the signal of H 7_b of the major anomer. ^{13}C (100 MHz): 137.96; 137.72; 137.59; 128.17; 128.14; 127.55;127.50; 127.38; 127.34 C aromatic; 73.17; 73.11; 71.81; 71.69; 71.45; 71.31 $–CH_2Ph$; major α anomer: 136.52 C2; 116.85 C1; 87.95 C4; 84.73 C5; 83.34 C3; 81.23 C6; 70.13 C7; minor β anomer: 133.48 C2; 118.44 C1; 84.16 C4; 84.06 C5; 82.44 C3; 82.17 C6; 70.36 C7. Identification of the anomers was based on comparison the chemical shifts with the known compounds obtained in a different way.[64]

2,5-Anhydro-1,3-*O*-isopropylidene-D-glucitol 33

29 (3.6 g, 8.4 mmol) in MeOH (60 ml) was cooled in acetone-dry ice, and a stream of O_3 in O_2 was passed through it until the solution remained blue (ca. 30 minutes). TCL (hexane-EtOAc 4:1) at this point showed that **29** (R_f 0.54) reacted and a more polar product was formed (R_f 0.17). $NaBH_4$ (0.3 g, 7.9 mmol) was slowly added[105] and the mixture was allowed to reach room temperature. MeOH was evaporated and the residue was passed through a short bed of silica gel in hexane-EtOAc 2:1 to furnish **30** (3.1 g) as inseparable mixture, which was used in the next step without characterization. This material was solubilized in EtOH (40 ml) and 10% Pd/C (0.2 g) was added. Hydrogenolysis in a Parr apparatus at 30 psi was performed overnight to furnish a mixture of **31**/**32** (R_f 0.1 in CH_2Cl_2-MeOH 5:1). The solids were filtered off using a bed of celite (attention: dry Pd is pyrophoric) and washed with EtOH. Evaporation of the solvent furnished **31**/**32** (1.2 g, quantitative yield) as a glassy material. Acetone (50 ml) was added followed by 2 drops of 70% $HClO_4$ and the mixture was incubated overnight. TLC in $CHCl_3$-MeOH 10:0.5 showed a presence of the acetonide **33** (R_f 0.20) and a spot $R_f \sim 0$ of unreacted **32**, which was not isolated. Neutralization with NH_4OH, evaporation and chromatography in $CHCl_3$-MeOH 10:0.5 furnished **33** (0.24 g, 16%) counting on a mixture of **31**/**32**. If the vinyl derivative **29** obtained starting from the bromide **25** was used in this preparation, a yield of the acetonide **33** was 31% evidently reflecting a higher content of the β vinyl anomer. **33** crystallized spontaneously in a refrigerator. M.p. 94–96°C ($CHCl_3$-MeOH); α_D +21.4°, c 6.1, EtOH; lit.[49] m.p. 95–97°C; α_D +27° (EtOH). ^1H (200 MHz, DMSO—d_6): 5.32 (d, exchangeable, J = 4.2 Hz, 1 H); 4.64 (t, exchangeable, J = 5.7 Hz, 1 H); 4.04 (d, J = 2.8 Hz, 1.5 H); 3.67 (d, J = 3.0 Hz, 0.5 H); 3.83 (d, J = 3.6 Hz, 1 H); 3.80–3.61 (m, 3 H); 3.46 (t, J = 6.1 Hz, 2 H; after D_2O exchange: d, J = 7.0 Hz); 1.34 and 1.21 (two s, 3 H each, 2 Me). ^{13}C (50 MHz): 96.58 $\mathbf{C}(CH_3)_2$; 87.08, 77.43, 76.07, 71.88, 62.39, 60.03, 28.86 and 19.10 $C(\mathbf{C}H_3)_2$.

31 was also converted to 2,5-anhydro-1,3-O-isopropylidene-6-*O*-triphenylmethyl-D-glucitol **34** for a purpose of further characterization. **34**: m.p. 181–182.5°C (cryst. from $CHCl_3$-hexane); lit.[108] m.p. 183.5–184°C.

2,5-Anhydro-4,6-di-*O*-benzoyl-D-glucitol 37

33 (1.1 g, 5.4 mmol) in CH_2Cl_2 (10 ml), pyridine 3 ml and benzoyl chloride (2.3 ml, 20 mmol) was left overnight. Extraction (CH_2Cl_2-aq $NaHCO_3$), drying and evaporation of volatiles furnished a crude dibenzoate (m.p. 90–99°C cryst. from EtOH; lit.[113] m.p. 127–129°C), which was incubated in MeOH (80 ml) and 1% H_2SO_4 (20 ml) at 50–60° during 30 minutes. TLC showed a spot of **37** R_f 0.39 (dichloroethane-EtOH 10:1.2). Most of MeOH was evaporated. Extraction with $CHCl_3$, washing with water, drying, evaporation and chromatography in hexane-EtOAc 1:1 gave **37** (1.7 g, 86%) for two steps. M.p. 102–103°C (hexane-EtOAc); α_D +18.1°, c 2.6, $CHCl_3$; lit.[113] oil, α_D +21°, c 3, $CHCl_3$. ^1H (200 MHz, DMSO—d_6): 8.04–7.95 (4 H) and 7.71–7.45 (6 H, H aromatic); 5.58 (d, J = 4.3 Hz, exchangeable, 3 OH); 5.21 (bs, 1 H, H 4); 4.74 (t, J = 5.4 Hz, 1 OH); 4.47 (apparent dd, J = 2.0 Hz and J = 6.3 Hz, 2 H, H 5,6_a); 4.30–4.26 (unresolved, partially superimposed on the signal of H 6_a, H 3); 4.22 (dd, J = 2.5 Hz, 5.8 Hz, H 6_b); 4.09–4.00 (unresolved, 1 H, H 2; after D_2O exchange: 4.03 apparent dq, J = 3.2 Hz, 4.2 Hz, 4.2 Hz, H 2); 3.77–3.54 (m, 2H, H 1_a, H 1_b; after D_2O exchange: 3.70, dd, J_{1a2} = 5.2 Hz, J_{1a1b} = 11.3 Hz, H 1_a; the signal of 1_b is hidden under the HOD signal). ^{13}C (50 MHz): 165.77; 165.19; 133.86; 133.61; 129.86; 129.73; 129.53; 128.92; 83.04; 81.36; 80.53; 74.09; 65.18; 59.53.

2,5-Anhydro-4,6-di-*O*-benzyl-D-glucitol 38

Acetonide **33** (0.22 g, 1.1 mmol) in 1,2-dichloroethane (5 ml) and benzyl chloride (1.2 ml, 10.8 mmol), Bu_4NHSO_4 (0.055 g), and 50% aq KOH (5 ml) were vigorously stirred at 60°C. After 7 hours the aqueous layer was replaced by the same volume of a fresh 50% solution of KOH. More Bu_4NHSO_4 was added and stirring was continued during 3 hours more at the same temperature. The dark brown mixture was transferred to a separate funnel charged with CH_2Cl_2 and ice cold H_2O, and extraction was performed. The lower organic phase was drained out and the solvents were evaporated. To the resulting mixture containing **36** was added MeOH (6 ml) and 1% aq H_2SO_4 (1 ml). The mixture was heated at 60°C during 1 hour. Neutralization with NH_4OH and evaporation of MeOH furnished dark oil which was purified by chromatography (gradient of EtOAc in hexane: 1:5 to 2:1) gave **38** (0.16 g, 43% for two steps) as a yellowish thick oil. In another run acetonide **33** (0.31 g, 1.5 mmol) in THF (20 ml), BnCl (15 mmol, 1.7 ml), pulverized KOH (0.6 g) and Bu_4HSO_4 (0.06 g) were magnetically stirred under exclusion of moisture during 4 hours at room temperature followed by stirring at ca 50°C during 2 hours. Work-up, hydrolysis (MeOH 15 ml, 1% aq H_2SO_4 3 ml) and chromatography as above furnished **38** (0.40 g 78%); α_D +18.1°, c 2.6, $CHCl_3$. ^1H (200 MHz, DMSO—d_6): 7.35–7.28 (10 H, H aromatic); 4.98 (d, exchangeable, $J_{OH,3} = 4.6$ Hz, 1 H, 3 OH); 4.60 (d, J = 11.8 Hz, -CH_2Ph); 4.57 (t, exchangeable, $J_{OH,1} = 5.1$ Hz, 1 OH); 4.52 (d, J = 12.0 Hz, -CH_2Ph); 4.51 (s, -CH_2Ph); 4.12 (t, $J_{32} = 4.1$ Hz, $J_{3,OH} = 4.1$ Hz, 1H, H 3); 3.93 (apparent dd, $J_{23} = 2.8$ Hz, J = 6.0 Hz, H 2); 3.90–3.80 (m, H 5); 3.77–3.71 (m, 2 H, H6_a, 6_b); 3.69–3.47 (m, H 1_a, H 1_b); 3.54 (d, $J_{45} = 5.8$ Hz, superimposed on the signal of H 1_a and H 1_b, H 4). The signals which were changed after D_2O exchange: 4.57 (d, J = 11.8 Hz, 1H, -CH_2Ph); 4.49 (d, J = 12.0 Hz, 1 H, -CH_2Ph); 4.48 (s, 2 H, -CH_2Ph); 4.10 (d, $J_{32} = 3.8$ Hz, 1 H, H 3); 3.90 (apparent dd, $J_{23} = 2.8$ Hz, $J_{21a} = 6.0$ Hz, downfield part of the signal of H 2); 3.85–3.80 (m, 1 H, H 5); 3.76–3.70 (superimposed on the signal of HOD, H 6_a, H 6_b); 3.64 (dd, $J_{1a\,2} = 5.2$ Hz, $J_{1a1b} = 11.4$ Hz, 1 H, H 1_a); 3.51 (d, $J_{45} = 5.4$ Hz, 1 H, H 4); 3.51 (dd, $J_{1b2} = 6.0$ Hz, $J_{1b1a} = 11.4$ Hz, 1 H, H 1_b). ^{13}C (50 MHz): 138.38; 138.28; 127.68; 127.65; 127.62, 127.59; 127.54; 87.05; 82.45; 81.81; 74.52; 72.30; 70.94; 70.50; 59.55. Exact mass (CI): calc. for $C_{20}H_{24}O_5 + H^+ = 345.1702$; found: 345.1705.

2,5-Anhydro-4,6-di-*O*-benzoyl-1-O-*t*-butyldimethylsilyl-D-glucitol 39

To a solution of the diol **37** (0.38 g, 1.0 mmol) and imidazole (0.18 g, 2.6 mmol) in THF (10 ml), was added *t*-butyldimethylsilylchloride (0.36 g, 1.3 mmol). Next day extraction was performed (CH_2Cl_2-H_2O). The organic phase was dried and evaporated. The residue was purified by chromatography in hexane-EtOAc 5:1 to furnish **39** (0.41 g, 82%) as a syrup; α_D +13.2°, c 0.6, $CHCl_3$.^1H (200 MHz, DMSO—d_6): 8.03–7.95 and 7.72–7.45 (H aromatic, 10 H); 5.64 (d, exchangeable, $J_{OH,3} = 4.2$ Hz, 1 H, OH); 5.22 (t, $J_{43} = J_{45} = 1.7$ Hz, 1 H, H 4); 4.52–4.43 (m, 2 H, H 6_a, H 6_b); 4.31–4.22 (m, 2 H, H 3, H 5); 4.08 (dt, $J_{21a} = J_{23} = 4.1$ Hz, $J_{21b} = 6.1$ Hz, 1 H, H 2); 3.88 (dd, $J_{1a2} = 4.5$ Hz, $J_{1a1b} = 10.8$ Hz, 1 H, H 1_a); 3.75 (dd, $J_{1b2} = 6.4$ Hz, $J_{1b1a} = 10.8$ Hz, 1 H, H 1_b); 0.83 (s, 9 H, *t*Bu); ~ 0 (s, 6 H, 2 Me). ^{13}C: 165.71; 165.19; 133.56, 129.74; 129.57; 128.95; 82.65; 81.14; 80.48; 73.95; 65.19; 62.00; 26.03;

18.28; −5.06; −5.15. Exact mass (CI): cal for $C_{26}H_{34}O_7Si + H^+ = 487.2156$; found: 487.2152.

2,5-Anhydro-1-*O*-*t*-butyldimethylsilyl-6-*O*-triphenylmethyl-D-glucitol 41

Debenzoylation of **39** (0.41 g, 1.1 mmol) in MeOH (7 ml) and $(i\text{Pr})_2NH$ (0.6 ml, 8.2 mmol) was performed overnight. Evaporation of volatiles and chromatography in $CHCl_3$-MeOH (gradient, 10:0.5–10:0.8) furnished the triol **40** (0.23 g, quantitative yield), which was subjected to tritylation without further characterization. Thus, the whole amount of **40** (0.23 g, 0.83 mmol) in pyridine (5 ml) was treated with TrCl (0.46 g, 1.6 mmol) overnight. Few drops of H_2O were added to hydrolyze the excess of TrCl. 30 minutes. later an extraction was performed (CH_2Cl_2-H_2O). The organic phase was co-evaporated with xylenes to furnish a glassy material. Chromatography in hexane-EtOAc 3:1 furnished **41** (0.35 g, 81%); m.p. 125–127°C (hexane-EtOAc), α_D +27.7°, c 1.6, $CHCl_3$. ^1H (200 MHz,. $CDCl_3$): 7.51–7.22 (15 H, H aromatic); 4.17–3.99 (m, 4 H); 3.93 (q, $J_{21a} = J_{21b} = J_{23} = 4.4$ Hz, 1 H, H 2), [after irradiation of the protons H_{1a1b} at 3.39 ppm: d, $J_{23} = 3.9$ Hz]; 3.80 (d, J = 7.3, 1 H); 3.46 (dd, $J_{1a2} = 4.8$ Hz, $J_{1a1b} = 9.8$ Hz, 1 H, H 1_a); 3.34 (dd, $J_{1b2} = 4.6$ Hz, $J_{1a1b} = 9.8$ Hz, 1 H, H 1_b); 2.33 (d, J = 3.3 Hz, two OH); 0.92 (s, 9 H, *t*Bu); 0.13 and 0.09 (two s, 6 H, 2 CH_3). ^{13}C (50 MHz): 143.55; 128.75; 127.88; 127.15; 87.38; 83.29; 80.21; 80.04; 79.08; 77.65; 77.03; 76.38; 64.76; 62.52; 25.86; 18.21; −5.36. Exact mass (CI): cal. for: $C_{31}H_{40}O_5Si + H^+ = 521.2723$; found: 521.2728.

2,5-Anhydro-1-*O*-*t*-butyldimethylsilyly-6-*O*-triphenylmethyl-D-*erythro*-hex-3,4-enitol 42

Diol **41** (0.40 g, 0.77 mmol) in CH_2Cl_2 (10 ml), pyridine (0.5 ml) and cat. quantity of DMAP was reacted with phenyl chlorothionoformate (0.32 ml, 2.3 mmol) overnight. Extraction (CH_2Cl_2-H_2O) of the resulting dark green solution followed by evaporation of the organic phase and co-evaporation with xylenes to expel any residual pyridine furnished green glassy material which was used for the next step without further purification. To this material solubilized in toluene (10 ml) and under reflux was added dropwise a solution of Bu_3SnH (0.43 ml, 1.6 mmol) and AIBN (0.04 g, 0.24 mmol) in toluene (10 ml) during 15 minutes. After a total of 2 hours TLC showed a presence of a new product, which was isolated after evaporation of the solvent and chromatography in hexane-EtOAc 20:1 to yield syrupy **42** (0.26 g, 69% for two steps). α_D −8.1°, c 1.9, $CHCl_3$. ^1H (500 MHz, DMSO—d_6): 7.39–7.22 (H aromatic, 15 H); 5.909 (apparent q of broadened signals, J ~6.6 Hz, 2 H, H 3, H 4); 4.87 and 4.75 (pair of unresolved signals, 1 H each, H 2, H 4); 3.621 (dd, J = 5.5 Hz, 11.0 Hz, 1 H); 3.547 (dd, J =

5.0 Hz, 10.5 Hz, 1 H); 3.040 (dd, J = 5.5 Hz, 9.5 Hz, 1 H); 2.945 (dd, J = 4.0 Hz, 9.5 Hz, 1 H); 0.770 (s, 9H, *t*Bu); −0.060 and −0.086 (two s, 6 H, 2 Me). ^{13}C (50 MHz, $CDCl_3$): 144.60; 130.09; 129.73; 129.31; 129.14; 128.25; 127.43; 121.43; 87.68; 86.94; 86.33; 67.88; 67.38; 26.47; 18.89; −4.76. Exact mass (CI): calc.for: $C_{31}H_{38}O_3Si + H^+$: 487.2668; found: 487.2651.

2,5-Anhydro-6-*O*-triphenylmethyl-D-*erythro*-hex-3,4-enitol 43

Compound **42** (0.23 g, 0.48 mmol) in THF (5 ml) was treated with 1M Bu_4NF in THF (0.6 ml) during 3 hours at 0°C. The solvent was evaporated. Chromatography of the residue in hexane-EtOAc 2:1 furnished **43** (0.17 g, 96%) as a syrup; α_D −48.2°, c 1.6, $CHCl_3$. ^{1}H (200 MHz, DMSO—d_6): 7.42–7.22 (15 H, H aromatic); 5.96 and 5.90 (two apparent d, J~5 Hz, 1 H each, H 3, H 4); 4.86 (bs, 1 H); 4.73 (unresolved, superimposed on the signal of –OH) [after D_2O exchange: bs]; 4.69 (t, exchangeable, J = 5.5 Hz, -OH); 3.52–3.28 (m, superimposed on the signal of residual H_2O, H 1_a, H1_b) [after D_2O exchange: 3.42 (dd, J_{1a2} = 5.9 Hz, J_{1a1b} = 10.8 Hz); 3.31 (dd, J_{1b2} = 5.5 Hz, J_{1b1a} = 10.8 Hz)]; 3.06–2.90 (m, 2 H, H 6_a, H 6_b). ^{13}C (75 MHz, acetone d_6): 145.67; 130.64; 130.20; 129.21; 128.45; 89.00; 87.87; 86.93; 68.75; 67.04. Exact mass: molecular ion was not present using FAB or CI ionization mode.

2,5-Anhydro-1′-(thymin-1-yl)-D-*erythro*-hex-3,4-enitol 3

To a solution of the alcohol **43** (0.28 g, 0.75 mmol), $(Ph)_3P$ (0.59 g, 2.3 mmol) and *N*-3-benzoylthymine[115] **51** (0.52 g, 2.3 mmol) in dioxane (10 ml) under argon, was injected DEAD (0.36 ml, 2.3 mmol). After an overnight reaction at room temperature the volatiles were evaporated and the residue was passed through a bed of silica gel in hexane-EtOAc 1:1 to furnish **52** contaminated with $(Ph)_3PO$. This mixture was solubilized in MeOH (30 ml) and a piece of Na was added. After 3 hours de-*N*-benzoylation was completed. A small chip of dry ice was added and MeOH was evaporated. The residue was passed through a bed of silica (CH_2Cl_2-MeOH 20:1.5). After evaporation of the solvents the residue was solubilized in 90% AcOH (12 ml) and maintained at 100°C during 2 hours. Evaporation of AcOH and chromatography in CH_2Cl_2-MeOH 10:1 furnished **3** (0.079 g, 44% for three steps) as foam. ^{1}H (500 MHz, DMSO—d_6): 11.226 (s, 1 H, H 3); 7.401(q, J = 1 Hz, 1 H, H 6); 5.923 and 5.923(two d of quintettes, J = 1.0 Hz, 6.4 Hz, 2 H, H 3′,H 4′); 4.895 (unresolved, 1 H); 4.745 (t, J = 5.7 Hz, OH); 4.676 (unresolved,1 H); 3.807 (dd, J = 2.9 Hz, 14.2 Hz, 1 H); 3.711 (dd, J = 6.4 Hz, 14.3 Hz, 1 H); 3.343 (bs superimposed on residual H_2O); 1.733 (d, J = 1 Hz, CH_3). ^{13}C (75 MHz, MeOH-d_6): 166.956; 153.733; 144.639; 130.850; 129.326; 110.530; 89.184; 86.307; 65.647; 52.840; 12.254. Exact mass (FAB): calc. for $C_{11}H_{14}N_2O_4 + Na^+$: 161.0851; found: 161.0847.

2,5-Anhydro-4,6-di-*O*-benzoyl-3-deoxy-D-*ribo*-hexitol 47

Diol **37** (1.5 g, 3.9 mmol) in THF (20 ml) was treated with 1,1′-thiocarbonyldiimidazole (90% pure, 0.85 g, 4.3 mmol) overnight. The resulting thionocarbonate **45** was much less polar than the diol **37** (TLC in hexane-EtOAc 1:1). The solvent was evaporated. The residue was solubilized in CH_2Cl_2 and washed twice with H_2O. The organic phase was dried and evaporated. The resulting yellow syrup was dissolved in toluene (20 ml). This solution was purged with argon and warmed to gentle reflux. A solution of Bu_3SnH (3.1 ml, 11.7 mmol) and AIBN (0.16 g, 1.0 mmol) in toluene (10 ml) was added dropwise during 15 minutes. Reflux was maintained during a total of 2 hours. Some reversion to the diol **37** took place. Evaporation of the solvent followed by a chromatography in hexane-EtOAc 7:3 furnished **47** (0.36 g, 25% for two steps). α_D +17.9° c 1.4 $CHCl_3$; m.p. 72–75°C) cryst. from hexane-EtOAc); lit.[114] m.p. 69–71°. ^1H (200 MHz, DMSO—d_6): 8.01–7.98 and 7.97–7.47 (10 H, H aromatic); 5.45 (apparent quintet. J = 2.3 Hz, 1 H, H 4) [after irradiation of H 3_a/H 3_b at 2.13 ppm: d, J = 2.1 Hz]; 4.81 (t, exchangeable, J = 5.7 Hz, 1 H, 1-OH); 4.41 (apparent d, J = 4.7 Hz, 2 H, H 6_a, H 6_b); 4.34 (dd, J = 2.4 Hz, J = 4.0 Hz, 1 H, H 5); 4.30–4.19 (m, 1 H, H2) [after irradiation of H 3_a/ H 3_b at 2.13 ppm: t, $J_{21a} = J_{21b}$ = 4.3 Hz]; 3.60–3.41 (m, 2 H, H 1_a, H 1_b) [after D_2O exchange: 3.53 (dd, J_{1a2} = 4.0 Hz, J_{1a1b} = 11.7 Hz, 1 H, H 1_a); 3.44(dd, J_{1b2} = 4.8 Hz, J_{1b1a} = 11.7 Hz, 1 H, H 1_b)]; 2.51–2.11 (m, 2 H, H 3_a, H 3_b). ^{13}C (50 MHz): 165.75; 165.54; 133.67; 129.67; 129.43; 128.91; 81.67; 79.99; 77.01; 64.99; 63.07; 34.19.

2,5-Anhydro-4,6-di-*O*-benzyl-3-deoxy-D-*ribo*-hexitol 48

Diol **38** (0.73 g, 2.1 mmol) in DMF (15 ml) was treated with 1,1′-thiocarbonyldiimidazole (90% pure, 0.56 g, 2.5 mmol) overnight. TLC (hexane-EtOAc 5:3) showed that **46** was much less polar than **38**. Partition between CH_2Cl_2 and H_2O was performed and organic layer was dried and evaporated to furnish yellow syrup. This material was solubilized in toluene (10 ml) and treated with a solution of BuSnH (1.7 ml, 6.3 mmol) and AIBN (0.13 g, 0.8 mmol) in toluene (10 ml) as described above for **45**. The reaction was continued for a total of 2 hours. TLC showed that a small amount of unreacted **46** was still present and that some reversion to the diol **38** took place. The product **48** was slightly less polar than a diol **38**. The solvent was evaporated. Chromatography of the residue in hexane-EtOAc 2:1 furnished **48** (0.16 g, 23%) as thick colorless oil. α_D +35.0°, c 1.6, $CHCl_3$. ^1H (200 MHz, DMSO—d_6): 7.35–7.26 (10 H, H aromatic); 4.63 (t, exchangeable. J = 5.6 Hz, 1 H, 1-OH); 4.48 (apparent d, J = 3.7 Hz, 4 H, -CH_2Ph); 4.11–3.95 (m, 2 H); 3.50–3.34 (m, 5 H); 1.96 (ddd, J = 1.7 Hz, 5.7 Hz, 12.5 Hz, 1 H, H 3_a); 1.74 (ddd, J = 5.6 Hz, 9.8 Hz, 13.2 Hz, 1 H, H 3_b). ^{13}C (50 MHz): 138.59; 128.39; 127.57; 82.91; 80.82; 79.51; 72.51; 71.13;

70.20; 34.01. Exact mass (CI): calc. for $C_{20}H_{24}O_4 + H^+$ = 329.1753, found: 329.1745.

2,5-Anhydro-4,6-di-*O*-benzoyl-1-(*N*-3-benzoylthymin-1-yl)-3-deoxy-D-*ribo*-hexitol 53

Alcohol **47** (0.10 g, 0.28 mmol), $(Ph)_3P$ (0.15 g, 0.56 mmol) and *N*-3-benzoylthymine **51**[115] (0.13 g, 0.56 mmol) were solubilized in CH_3CN (20 ml), whereupon DEAD (0.09 ml, 0.56 mmol) was injected. The mixture was maintained overnight under argon. The solvent was evaporated and the residue was applied on a top of a silica gel column. Elution with CH_2Cl_2-MeOH 20:03 furnished **53** (0.11 g, 72%) as a foam. ^1H (200 MHz, DMSO—d_6): 8.04–7.50 (H aromatic, 6, 16 H); 5.52 (d, J = 5.5 Hz, 1 H, H 4′); 4.70–4.60 (unresolved, 4 H); 4.09 (dd, $J_{6'a\,5'}$ = 2.8 Hz, $J_{6'a6'b}$ = 14.2 Hz, 1 H, H $6'_a$); 3.89 (dd, $J_{6'b5'}$ = 6.6 Hz, $J_{6'b\,6'a}$ = 14.4 Hz, 1 H, H $6'_b$); 2.30 (dd, J = 5.1 Hz, $J_{3'a3'b}$ = 13.6 Hz, 1 H, H $3'_a$); 2.15–2.00 (m, 1 H, H $3'_b$); 1.72 (s, 3 H, CH_3). Irradiation of the 4.70–4.60 signal at 4.50 ppm gave the following modified signals: 4.08 (d, J = 14.8 Hz); 3.88 (d, J = 13.9 Hz); 2.29 (d, J = 14.3 Hz); 2.07 (dd, J = 5.3 Hz, 13.7 Hz). ^{13}C (50 MHz): 169.68; 165.60; 165.34; 162.75; 149.67; 142.93; 135.43; 133.59; 133.53;131.18; 130.28; 129.49; 129.39; 129.16; 128.84; 128.76; 108.19; 81.88; 76.76; 76.55; 64.71; 50.29; 34.78; 11.73. Exact mass (FAB): calc for $C_{32}H_{28}N_2O_8 + H^+$ = 569.1924; found: 569.1908.

2,5-Anhydro-3-deoxy-1-(thymin-1-yl)-D-*ribo*-hexitol 4

To a solution of the compound **53** (0.15 g, 0.26 mmol) in MeOH (20 ml) was added a piece of Na. 6 hours later TLC (CH_2CL_2-MeOH 5:1) showed a more polar **4**. Neutralization with a small chip of dry ice, evaporation of the solvent, and chromatography in CH_2Cl_2-MeOH 10:1.5 furnished **4** (0.060g, 89%); m.p. 175–178°C (MeOH-EtOAc); lit.[17] m.p. 170°C (MeOH-CH_2Cl_2). ^1H (500 MHz, MeOH-d_4): 7.423 (q, J = 1 Hz, 1 H, H 6); 4.3473 (dddd, J = 3.1 Hz, 6.4 Hz, 6.4 Hz, 9.8 Hz, 1 H, H 2′); 4.213 (ddd, J = 2.9 Hz, 2.9 Hz, 5.9 Hz, 1 H, H 4′); 3.973 (dd, J = 2.9 Hz, 14.2 Hz, 1 H, H $1'_a$); 3.799 (dt, J = 2.9 Hz, 4.4 Hz, 4.9 Hz, 1 H, H 5′); 3.736 (dd, J = 7.3 Hz, 14.2 Hz, 1 H, H $1'_b$); 3.569 (dd, J = 6.0 Hz, 12.3 Hz, 1 H, H $6'_a$); 3.509 (dd, J = 5.4 Hz, 12.2 Hz, 1 H, H $6'_b$); 1.937 (ddd, J = 2.4 Hz, 5.9 Hz, 13.2 Hz, 1 H, H $3'_a$); 1.861 (d, J = 1 Hz, CH_3); 1.792 (ddd, J = 6.1 Hz, 9.4 Hz, 13.2 Hz, 1 H, H $3'_b$). ^{13}C (125 MHz): 166.964; 153.320; 144. 295; 110.640; 89.027; 78.048; 73.684; 63.754; 52.508; 38.918; 12.256. Exact mass (FAB): cal. for $C_{11}H_{16}N_2O_5 + Na^+$ = 279.0957; found: 279.0920.

REFERENCES

1. Muhanji, C.I.; Hunter, R. Current developments in the synthesis and biological activity of anti-HIV double-drug inhibitors. *Curr. Med. Chem.* **2007**, 14(11), 1207–1220.
2. Sturmer, M.; Staszewski, S.; Doerr, H.W. Quadruple nucleoside therapy with zidovudine, lamivudine, abacavir and temofovir in the treatment of HIV. *Antiv. Ther.* **2007**, 12(5), 695–703.
3. Golankiewicz, B.; Ostrowski, T. Tricyclic nucleoside analogues as antiherpes agents. *Antiv. Res.* **2006**, 71(2–3), 134–140.
4. Mamidyala, S.K.; Firestine, S.M. Advances in herpes simplex virus antiviral therapies. *Expert Opin. Therap. Pat.* **2006**, 16(11), 1463–1480.
5. Mathe, C.; Gosselin, G. L-Nucleoside enantiomers as antiviral drugs: A mini-review. *Antiv. Res.* **2006**, 71(2–3), 276–281.
6. Robak, T.; Lech-Maranda, E.; Korycka, A.; Robak, E. Purine nucleoside analogs as immunosuppressive and antineoplastic agents: Mechanism of action and clinical activity. *Curr. Med. Chem.* **2006**, 13(26), 3165–3189.
7. Zhou, X.X.; Litter, E. Nucleoside analogs as anti-HBV agents. *Curr. Top. Med. Chem.* **2006**, 6(9), 851–865.
8. Uckun, F.M.; D'Cruz, O.J. Therateutic innovations against HIV. *Expert Opin. Therap. Pat.* **2006**, 16(3), 265–293.
9. De Clercq, E.; Holý, A. Acyclic nucleoside phosphonates: a key class of antiviral drugs. *Nat. Rev. Drug Discov.* **2005**, 4(11), 928–940.
10. Anastasi, C.; Quelever, G.; Burlet, S.; Garino, C.; Souard, F.; Kraus, J.L. New antiviral nucleoside prodrugs await application. *Curr. Med. Chem.* **2003**, 10(18), 1825–1843.
11. Lamberth, C. Nucleoside chemistry in crop protection. *Heterocycles* **2005**, 65(3), 667–695.
12. Lamberth, C. Nucleosides with a carbon bridge between sugar and nucleobase: the chemistry of 1′-homonucleosides and reversed nucleosides. A review. *Org. Prep. Proc. Int.* **2002**, 34(2), 149–167.
13. Pankiewicz, K. Fluorinated nucleosides. *Carbohydr. Res.* **2000**, 327(1–2), 87.
14. Khan, N.; Bastola, K.G. Diastereoselective synthesis of L-(+)-homolamivudine. *Tetrahedron Lett.* **1999**, 40(51), 8989–8992.
15. Efimtseva, E.V.; Mikhailov, S.N.; Victorova, L.S.; Rosovskaya, T.A.; Beabealashvilli, R.S. Synthesis of dioxolane analogues of dideoxynucleosides and their substrate properties in DNA synthesis reactions. *Nucleosides Nucleotides* **1995**, 14(3–5), 727–729.
16. Doboszewski, B. Synthesis of homo-C-D4T and homo-C-thymidine. *Nucleosides Nucleotides* **1997**, 16(7–9), 1049–1052.
17. Hossain, N.; Blaton, N.; Peeters, O.; Rozenski, J.; Herdewijn, P.A. Synthesis of homo-C-nucleosides, a series of C1′ branched-chain nucleosides. *Tetrahedron* **1996**, 52(15), 5563–5578.
18. Boal, J.H.; Wilk, A.; Seremin, C.L.; Gray, G.N.; Phillips, L.R.; Beaucage, S.L. Synthesis of (2-deoxy-α- and -β-D-erhythro-pentofuranosyl(thymin-1-yl)alkanes and their incorporation into oligodeoxynucleotides. Effects of nucleobase-sugar linker flexibility on the formation of DNA-DNA and DNA-RNA hybrids. *J. Org. Chem.* **1996**, 61(24), 8617–8626.
19. Serrano, J.A.; Jiménez, M.; Román, E. Preparation of new nucleoside analogues from 3,6-anhydrosugars. *J. Carbohydr. Chem.* **1997**, 16(7), 1051–1059.
20. Haraguchi, K.; Delaney, M.O.; Wiederholt, C.J.; Sambandan, A.; Hantosi, Z.; Greenberg, M.M. Synthesis and characterization of oligodeoxynucleotides containing formamidopyrimidine lesions and nonhydrolyzable analogues. *J. Am. Chem. Soc.* **2002**, 124(13), 3263–3269.
21. Evans, G.B.; Furneaux, R.H.; Lewandowicz, A.; Schramm, V.L.; Tyler, P.C. Synthesis of second generation transition state analogues of human purine nucleoside phosphorylase. *J. Med. Chem.* **2003**, 46(24), 5271–5276.
22. Clinch, K.; Evans, G.B.; Fleet, G.W.J.; Furneaux, R.H.; Johnson, S.W.; Lenz, K.H.; Mee, S.P.H.; Rands, P.R.; Schramm, V.L.; Taylor Ryngia, E.A.; Tyler, P.C. Synthesis and bio-activities of the L-enantiomers of the potent transition state analogue inhibitors of purine nucleoside phosphorylases. *Org. Biomol. Chem.* **2006**, 4(6), 1131–1139.
23. Liu, K.K.-C.; Wong, C.-H. A new strategy for the synthesis of nucleoside analogues based on enzyme-catalyzed aldol reactions. *J. Org. Chem.* **1992**, 55(18), 4789–4791.

24. Wong, C.-H.; Provencher, L.; Porco Jr. J.A.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D.H. Synthesis and evaluation of homoaza sugars as glycosidase inhibitors. *J. Org. Chem.* **1995**, 60(6), 1492–1501.
25. Weizman, H.; Tor, Y. 2,2′-Bypiridine ligandoside: a novel building block for modifying DNA with intra-duplex metal complexes. *J. Am. Chem. Soc.* **2001**, 123(14), 3375–3376.
26. Sidorova, N.S.; Ioannisian, E.M.; Kolomeytzeva, V.V.; Ustjuzhanin, G.E. Nucleoside analogs based on xylitol anhydrides. *Nucl.Acids Res. Symp. Ser.* **1981**, 9, 119–122.
27. Mikhailov, S.N.; Efimtseva, E.V.; Meshkov, S.V.; Kern, E.R. Nucleotide analogues on the basis of 4(R), 5(R)-dihydroxymethyl-2-methyl-1,3-dioxolane. *Nucleosides Nucleotides* **1994**, 13(1–3), 615–623.
28. Grochowski, E.; Stepowska, H. The synthesis of "C-O-N" analogues of nucleosides via the Mitsunobu reaction. *Synthesis* **1988**,(10), 795–797.
29. Ischikawa, E.; Kato, K. Sugar-modified nucleosides in past 10 years, a review. *Curr. Med. Chem.* **2001**, 8(4), 385–423.
30. Wellington, K.W.; Benner, S.A. A review: synthesis of aryl-*C*-glycosides via the Heck coupling reaction. *Nucleosides Nucleotides Nucleic Acids* **2006**, 25(12), 1309–1333.
31. Yuan, X.J.; Linhardt, R.J. Recent advances in the synthesis of *C*-oligosaccharides. *Curr. Top. Med. Chem.* **2005**, 5(14), 1393–1430.
32. Zou, W. *C*-Glycosides and aza-*C*-glycosides as potential glycosidase and glycotransferas inhibitors. *Curr. Top. Med. Chem.* **2005**, 5(14), 1363–1391.
33. Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *C*-Glycosidation technology with free radical reactions. *Synlett* **1998**, 700–716.
34. Jiménez-Barbero, J.; Espinosa, J.F.; Asensio, J.L.; Cañada, F.J.; Poveda, A. The conformation of *C*-glycosyl compounds. *Adv. Carbohydr. Chem. Biochem.* **2001**, 56, 235–284.
35. Liu, L.; McKee, M.; Postema, M.H.D. Synthesis of *C*-saccharides and higher congeners. *Curr. Org. Chem.* **2001**, 5(12), 1133–1167.
36. Nicotra, F. Synthesis of *C*-glycosides of biological interest. *Top. Curr. Chem.* **1997**, 187, 55–83.
37. Beau, J.-M.; Gallagher, T. Nucleophilic *C*-glycosyl donors for *C*-glycoside synthesis. *Top. Curr. Chem.* **1997**, 187, 1–54.
38. Postema, M.H.D. *C-Glycoside Synthesis.* CRC Press, Boca Raton, FL, 1995.
39. Levy, D.E.; Tang, C. *The Chemistry of C-Glycosides.* Pergamon, Oxford, UK, 1995.
40. Ramana, C.V.; Narute, S.D.; Gonnade, R.G.; Patil, R.S. Stereoselective synthesis of β- C-allyl and β-propargyl-D-arabinofuranosides. *Synthesis* **2008**, 1783–1787.
41. Dondoni, A.; Marra, A. A new synthetic approach to mycobacterial cell wall α-(1 $\rightarrow$5)-D-arabinofuranosyl C-oligosaccharides. *Tetrahedron Lett.* **2003**, 44, 4067–4071.
42. Long, D.D.; Smith, M.D.; Martin, A.; Wheatley, J.R.;. Watkin, D.G.; Müller, M.; Fleet, G.W.J. Complex tetrahydrofurans from carbohydrate lactones: THF amino acids as building blocks for unnatural biopolymers. *J.Chem.Soc. Perkin Trans. I* **2002**, 1982–1998.
43. Oh, I.H.; Gray, G.R. Reductive cleavage of glycosides with borane complexes in the presence of boron trifluoride etherate. *Carbohydr. Res.* **1995**, 278(2), 329–338.
44. Norrild, J.C.; Pedersen, C.; Defaye, J. An efficient and highly stereospecific method for synthesizing aminosubstituted tetrahydrofuranes from 1-amino-1-deoxy-alditols. XVII International Carbohydrate Symposium, Ottawa, Canada, July 17–22, 1994, poster B1.73.
45. Charette, A.B.; Côté, B. Asymmetric cyclopropanation of allylic ethers: cleavage and regeneration of the chiral auxiliary. *J. Org. Chem.* **1993**, 58(4), 933–936.
46. Kaye, A.; Reese, C.B. Glycal ethers as starting materials in *C*-nucleosides synthesis. *Nucleosides Nucleotides* **1988**, 7(5–6), 609–612.
47. Kaye, A.; Neidle, S.; Reese, C.B. Reaction between glycal benzyl ethers and thallium (III) nitrate. Synthesis of showdomycin analogues. *Tetrahedron Lett.* **1988**, 29(15), 1841–1844.
48. Lei, Z.; Min, J.M.; Zhang, L.H. Synthesis of 3-deoxy-3-nucleobase-2,5-anhydro-D-mannitol: a novel class of hydroxymethyl-branched isonucleosides. *Tetrahedron: Asymmetry* **2000**, 11(14), 2899–2906.
49. Hartman, L.A. 2,5-Anhydro-D-glucitol. *Chem. Abstr.* **1970**, 72, 79420e.
50. Hartman, L.A. Separation of hexitans (anhydrohexitols). *Chem. Abstr.* **1970**, 72, 101059t.
51. Koerner, Jr. T.A.W.; Younathan, E.S.; Ashur, A.-L.E.; Voll, R.L. The fructose 6-phosphate site of phosphofructokinase.I.Tautomeric and anomeric specificity. *J. Biol. Chem.* **1974**, 249(18), 5749–5754.

52. Bouali, A.; Descotes, G.; Ewing, D.F.; Grouiller, A.; Lefkidou, J.; Lespinasse, A.-D.; Mackenzie, G. Dramatization of 1,3,4,6-tetra-*O*-benzyl-α-D-fructofuranose at the anomeric site: *O*-alkylation, *O*-acylation, *O*-arylation, amination and selenylation. *J. Carbohydr. Chem.* **1992**, 11(2), 159–169.
53. Martin, O.R. The unexpected intramolecular *C*-arylation of 2-*O*-benzylated cyclic sugar derivatives: a useful 1,2-cis-*C*-glycosylation reaction. *Tetrahedron Lett.* **1985**, 26(17), 2055–2058.
54. Kröll, P.; Wernicke, A.; Kovács, J.; Lützen, A. Comprehensive reinvestigation of the reaction of D-aldoses with Meldrum's acid yielding mainly chain extended 3,6-anhydro-2-deoxy-aldono-1,4-lactones. *J. Carbohydr. Chem.* **2000**, 19(8), 1019–1047.
55. van Delft, F.L.; Valentijn, A.R.P.M.; van der Marel, G.A.; van Boom, J.H. Preparation of 2,5-anhydro hexitols (Part I). Silicon-directed stereocontrolled cyclization. *J. Carbohydr. Chem.* **1999**, 18(2), 165–190.
56. van Delft, F.L.; Valentijn, A.R.P.; van der Marel, G.A.; van Boom, J.H. Preparation of 2,5-anhydro hexitols (Part II). Intramolecular nucleophilic substitution of cyclic sulfates. *J. Carbohydr. Chem.* **1999**, 18(2), 191–207.
57. Sharma, G.V.M.; Chander, A.S.; Krishnudu, K.; Krishna, P.R. A simple and efficient $PdCl_2$ mediated conversion of g,d-olefinic alcohols into C-glycosides. *Tetrahedron Lett.* **1997**, 38(52), 9051–9054.
58. Hiranuma, S.; Shimizu, T.; Nakata, T.; Kajimoto, T.; Wong, C.-H. Synthesis and inhibition analysis of five-membered homoazasugars from D-arabinofuranose via an S_N2 reaction of the chloromethylsulfonate. *Tetrahedron Lett.* **1995**, 36(45), 8247–8250.
59. Kuszmann, J.; Dvortsák Synthesis of 6-amino-2,5-anhydro-6-deoxy- and –1,6-dideoxy-D-glucitol and some derivatives thereof. *Carbohydr. Res.* **1983**, 123(2), 209–229.
60. Stork, G.; Suh, H.S.; Kim, G. The temporary silicon connection method in the control of regio- and stereochemistry. Applications to radical-mediated reactions. The stereospecific synthesis of *C*-glycosides. *J. Am. Chem. Soc.* **1991**, 113(18), 7054–7056.
61. Cornia, M.; Casiraghi, G.; Zetta, L. The diastereoselective arylation of arabinofuranose derivatives using bromomagnesium phenolates: synthesis of β-D- and α-L-arabinofuranosyl phenols. *Tetrahedron* **1990**, 46(8), 3071–3076.
62. Maryanoff, B.E.; Northey, S.O.; Inners, R.R.; Campbell, A.S.; Reitz, A.B. Synthesis of C-arabinofuranosyl compounds. Phosphate and carboxylate isosters of D-arabinose 1,5-bis-phosphate. *Carbohydr. Res.* **1987**, 171, 259–278.
63. Freeman, F.; Robarge, K.D. Stereoselectivity in the electrophile-mediated cyclization of 2,3,5-tri-*O*-benzyl-1,2-dideoxy-D-*arabino*-hex-1-enitol. A stereocontrolled synthesis of 1-amino-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-glucitol. *Carbohydr. Res.* **1987**, 171(1), 1–11.
64. Martin, O.R.; Yang, F.; Xie, F. Spontaneous cyclization of triflates derived from δ-benzyloxy alcohols: efficient and general synthesis of *C*-vinyl furanosides. *Tetrahedron Lett.* **1995**, 36(1), 47–50.
65. Persky, R.; Albeck, A. Synthesis of selectively labeled D-fructose and D-fructose phosphate analogues locked in the cyclic furanose form. *J. Org. Chem.* **2000**, 65(18), 5632–5638.
66. Chang, G.X.; Lowary, T.L. An olefin cross metathesis approach to *C*-disaccharide analogs of the α-D-arabinofuranosyl-(1→5)-α-D-arabinofuranoside motif found in the mycobacterial cell wall. *Tetrahedron Lett.* **2006**, 47(27), 4561–4564.
67. Acton, E.M.; Fujiwara, A.N.; Goodman, L.; Henry, D.W. Synthetic *C*-nucleosides: 3-(α- and β-D-arabinofuranosyl)pyrazol[4,3-*d*]pyrimidine-5,7-diones. *Carbohydr. Res.* **1974**, 33(1), 135–151.
68. Jiang, C.; Baur, R.H.; Dechter, J.J.; Baker, D.C. Synthesis and stereochemical assignments for 2-(α- and β-D-arabinofuranosyl)thiazole-4-carboxamides. *Nucleosides Nucleotides* **1984**, 3(2), 123–146.
69. Pernet, A.G.; Ogawa, T.; Hanessian, S. Synthese, assignation anomerique et epimerization des *C*-pentofuranosyle manonates. *Tetrahedron Lett.* **1975**, 37, 3547–3550.
70. Cipolla, L.; Liguori, L.; Nicotra, F.; Torri, G.; Vismara, E. Glycomimetics via a new glycoexoenitols-malonyl radical C-C bond formation. *J. Chem. Soc. Chem. Commun.* **1996**, 1253–1254.
71. Peri, F.; Bassetti, R.; Caneva, E.; de Gioia, L.; La Ferla, B.; Presta, M.; Tanghetti, E.; Nicotra, F. Arabinose-derived bicyclic amino acids: synthesis, conformational analysis and construction of an $\alpha_v\beta_3$-selective RGD peptide. *J. Chem. Soc. Perkin Trans I* **2002**, 638–644.
72. O'Leary, D.J.; Kishi, Y. Preferred conformation of *C*-glycosides. 13. A comparison of the conformational behavior of several *C*-, *N*-, and *O*-furanosides. *J. Org. Chem.* **1994**, 59(22), 6629–6636.
73. Peri, F.; Airoldi, C.; Colombo, S.; Mari, S.; Jiménez-Barbero, J.; Martegani, E.; Nicotra, F. Sugar-derived Ras inhibitors: group epitope mapping by NMR spectroscopy and biological evaluation. *Eur. J. Org. Chem.* **2006**, 3707–3720.

74. Doboszewski, B. Easy synthesis of 1-allyl-1-deoxy-β- and α-D-lyxofuranoses. *J. Carbohydr. Chem.* **2002**, 21(1–2), 79–88.
75. Dahlhoff, W.V.; Köster, R. Some new *O*-ethylboron-assisted carbohydrate transformations. *Heterocycles* **1982**, 18, 421–449.
76. Glaudemans, C.P.J.; Fletcher, Jr. H.G. The methanolysis of some D-arabinofuranosyl halides having a nonparticipating group at carbon 2. *J. Am. Chem. Soc.* **1965**, 87(11), 2456–2461.
77. Zissis, E.; Glaudemans, C.P.J. Anomers of para-nitrophenyl 2,3,5-tri-O-benzyl-D-arabinofuranoside. *Carbohydr. Res.* **1976**, 50(2), 292–295.
78. Glaudemans, C.P.J.; Fletcher, Jr. H.G. Synthesis with partially benzylated sugars. III. A simple pathway to a "cis nucleoside," 9-β-D-arabinofuranosyladenine (spongoadenosine). *J. Org. Chem.* **1963**, 28(11), 3004–3006.
79. Leroux, J.; Perlin, A.S. Synthesis of glycosyl halides and glycosides via 1-*O*-sulfonyl derivatives. *Carbohydr. Res.* **1978**, 67(1), 163–178.
80. Cicchillo, R.M.; Norris, P. A convenient synthesis of glycosyl chlorides from sugar hemiacetals using triphosgene as the chlorine source. *Carbohydr. Res.* **2000**, 328(3), 431–434.
81. Seela, F.; Winkeler, H.-D. 2-Amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyridin-4(3*H*)-one. Synthesis of *ara*-7-deazaguanosine via phase-transfer glycosylation. *J. Org. Chem.* **1982**, 47(2), 226–230.
82. Cornia, M.; Casiraghi, G.; Zetta, L. *C*-Heteroarylation of sugars by indolylbromomagnesium salts. Synthesis of 3-(alditol-1-yl)indols and their cyclization to indole *C*-nucleosides analogs. *J. Org. Chem.* **1991**, 56(18), 5466–5468.
83. Mizutani, K.; Kasai, R.; Nakamura, M.; Tanaka, O.; Matsuura, H. N.M.R. spectral study of α- and β-*L*-arabinofuranosides. *Carbohydr. Res.* **1989**, 185(1), 27–38.
84. Stevens, J.D.; Fletcher, Jr. H.G. The proton magnetic resonance spectra of pentofuranose derivatives. *J. Org. Chem.* **1968**, 33(5), 1799–1805.
85. van Boeckel, C.A.A.; Beetz, T.; van Aelst, S.F. Substituent effects on carbohydrate coupling reactions promoted by insoluble silver salts. *Tetrahedron* **1984**, 40(30), 4097–4107.
86. Dunkerton, L.V.; Adair, N.K.; Euske, J.M.; Brady, K.T. Regioselective synthesis of substituted 1-thiohex-2-enopyranosides. *J. Org. Chem.* **1988**, 53(4), 845–850.
87. Cumpstey, I. Intramolecular aglycon delivery. *Carbohydr. Res.* **2008**, 343, 15553–1573.
88. Jensen, K.J. *O*-Glycosylation under neutral or basic conditions. *J. Chem. Soc. Perkin Trans.*, **2002**1, 2219–2233.
89. March, J. Carbocations, carbanions, free-radicals, carbenes and nitrenes. In: *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure.* John Wiley & Sons, New York, 4th ed. 1992, chap. 5, pp. 165–204.
90. Praly, J.-P. Structure of anomeric glycosyl radicals and their transformations under reductive conditions. *Adv. Carbohydr. Chem. Biochem.* **2001**, 56, 65–151.
91. Crich, D.; Beckwith, A.L.J.; Chen, C.; Yao, Q.; Davidson, I.G.F.; Longmore, R.W.; de Parrodi, C.A.; Quintero-Cortes, L.; Sandoval-Ramirez, J. Origin of the "β-oxygen effect" in the Barton deoxygenation reaction. *J.Am. Chem. Soc.* **1995**, 117(34), 8757–8768.
92. Abe, H.; Shuto, S.; Matsuda, A. Highly α- and β-selective radical *C*-glycosylations using a controlling anomeric effact based on the conformational restriction strategy. A study on the conformation-anomeric effect-stereoselectivity relationship in anomeric radical reactions. *J. Am. Chem. Soc.* **2001**, 123(48), 11870–11882.
93. Bates, H.A.; Rosenblum, S.B. Nucleophilic displacements on an α-chloro thioether by organocuprates: a novel synthesis of desoxybiotin. *J. Org. Chem.* **1986**, 51(18), 3447–3451.
94. Schmitt, A.; Reissig, H.-U. On the stereoselectivity of γ-lactol substitutions with allyl- and propargylsilane-synthesis of disubstituted tetrahydrofuran derivatives. *Eur. J. Org. Chem.* **2000**, 3893–3901.
95. Smith, D.M.; Tran, M.B.; Woerpel, K.A. Nucleophilic additions to fused bicyclic five-membered ring oxocarbenium ions: evidence for preferential attack on the inside face. *J. Am. Chem. Soc.* **2003**, 125(46), 14149–14152.
96. Larsen, C.H.; Ridgway, B.H.; Shaw, J.T.; Woerpel, K.A. A stereoelectronic model to explain the highly stereoselective reactions of nucleophiles with five-membered-ring oxocarbenium ions. *J. Am. Chem. Soc.* **1999**, 121(51), 12208–12209.
97. Smith, D.M.; Woerpel, K.A. Electrostatic interactions in cations and their importance in biology and chemistry. *Org. Biomol. Chem.* **2006**, 4(7), 1195–1201.

98. Larsen, C.H.; Ridgway, B.H.; Shaw, J.T.; Smith, D.M.; Woerpel, K.A. Stereoselective *C*-glycosylation reactions of ribose derivatives: electronic effects of five-membered ring oxocarbenium cation. *J. Am. Chem. Soc.* **2005**, 127(31), 10879–10884.
99. Tamura, S.; Abe, H.; Matsuda, A.; Shuto, S. Control of α/β stereoselectity in Lewis acid promoted *C*-glycosylations using a controlling anomeric effect based on the conformational restriction strategy. *Angew. Chem. Int. Ed.* **2003**, 42(9), 1021–1023.
100. Zhu, X.; Kawatkar, S.; Rao, Y.; Boons, G.-J. Practical approach for the stereoselective introduction of β-arabinofuranosides. *J. Am. Chem. Soc.* **2006**, 128(36), 11948–11957.
101. Lucero, C.G.; Woerpel, K.A. Stereoselective *C*-glycosylation reactions of pyranoses: the conformational preference and reactions of the mannosyl cation. *J. Org. Chem.* **2006**, 71(7), 2641–2647.
102. Shing, T.K.M.; Gillhouley, J.G. Enantiospecific synthesis of (+)-altholactone and its three stereoisomers. *Tetrahedron* **1994**, 50(29), 8685–8698.
103. Van Orrnum, S.G.; Champeau, R.M.; Pariza, R. Ozonolysis applications in drug synthesis. *Chem. Rev.* **2006**, 106(7), 2990–3001.
104. Angibeaud, P.; Defaye, J.; Gadelle, A.; Utille, J.-P. Mild deprotection of benzyl ether protective groups with ozone. *Synthesis* **1985**, 1123–1125.
105. Clark, R.D.; Heathcock, C.H. Ozonization of silyloxyalkanes. *Tetrahedron Lett.* **1974**, 23, 2027–2030.
106. Tanaka, T.; Hatano, K.; Watanabe, M.; Abbas, H.K. Isolation, purification and identification of 2,5-anhydro-D-glucitol as a phytotoxin from *Fusarium solani*. *J. Nat. Toxins* **1996**, 5(3), 317–329.
107. Doboszewski, B.; Nazarenko, A.Y. 1′-Deoxy-1′-hydroxymethyl-1,2′-*O*-isopropylidene-β-D-arabinofuranose. *Acta Cryst. E*, **2003**, 59(Part 2), 158–160.
108. Koerner, Jr. T.A.W.; Voll, R.J.; Younathan, E.S. Isolation of 2,5-anhydro-1,3-isopropylidene-6-*O*-trityl-D-glucitol and conformations of its 4-*O*-substituted and deprotected, acylated derivatives. *Carbohydr. Res.* **1977**, 59(2), 403–416.
109. Dondoni, A.; Marra, A.; Mizuna, M.; Giovannini, P.P. Linear total synthetic routes to β-D-*C*-(1,6)-linked oligoglucoses and oligogalactoses up to pentaoses by iterative Wittig olefination assembly. *J. Org. Chem.* **2002**, 67(12), 4186–4199.
110. Cipolla, L.; La Ferla, B.; Panza, L.; Nicotra, F. Direct synthesis of the isosteric phosphono analogues of α-L-rhamnose 1-phosphate and β-L-fucose 1-phosphate. *J. Carbohydr. Chem.* **1998**, 17(7), 1003–1013.
111. Barrett, A.G.M.; Barton, D.H.R.; Bielski, R. Reactions of relevance to the chemistry of aminoglycoside antibiotics. Part 11. Preparation of olefins from vicinal diols. *J. Chem. Soc. Perkin Trans. I,* **1979**, 2378–2381.
112. Chu, C.K.; Bhadti, V.S.; Doboszewski, B.; Gu, Z.P.; Kosugi, Y.; Pullaiah, K.C.; Van Roey, P. General synthesis of 2′,3′-dideoxynucleosides and 2′,3′-didehydro-2′,3′-dideoxynucleosides. *J. Org. Chem.* **1989**, 54(9), 2217–2225.
113. Mubarak, A.M.; Brown, D.M. A stereospecific synthesis of (+)-muscarine. *J. Chem. Soc. Perkin Trans. I* **1982**, 809–813.
114. Mubarak, A.M.; Brown, D.M. A synthesis of 2′-deoxy-showdomycin. *Tetrahedron Lett.* **1981**, 22(7), 683–684.
115. Cruickshank, K.A.; Jiricny, J.; Reese, C.B. The benzoylation of uracil and thymine. *Tetrahedron Lett.* **1984**, 25(6), 681–684.
116. Mitsunobu, O. The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural-products. *Synthesis* **1981**, 1–28.
117. Finch, P.; Iskander, G.M.; Siriwardena, A.H. Convenient synthesis of 2,3,5-tri-*O*-benzyl-arabinofuranose and 2,3,5-tri-*O*-benzyl-ribofuranose *via* their allyl glycosides. *Carbohydr. Res.* **1991**, 210, 319–325.