AWP Bioorganik

Abschnitt Kohlenhydrate

Prof. Dr. Torsten Linker

AWP Bioorganik (Bereich Linker) Gliederung

1. Kohlenhydrate

1.1 Einführung: Konzepte, Literatur, historische Einordnung

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- 1.7.4 Radikalische Additionen an Glycale

AWP Bioorganik (Bereich Linker)
Weiterführende Literatur

Bioorganik

Bioorganic Chemistry, Wiley-VCH 1999.

Biotransformations in Organic Chemistry, Springer 1997.

Enzyme in der Organischen Synthese, Spektrum 1997.

Kohlenhydrate

Essentials of Carbohydr. Chem. and Biochem., Wiley-VCH 2007.

Kohlenhydrate, Chemie und Biologie, Thieme 1996.

Carbohydrate Building Blocks, Wiley 1996.

The Chemistry of C-Glycosides, Pergamon 1995.

Protective Groups in Organic Synthesis, Wiley 2007.

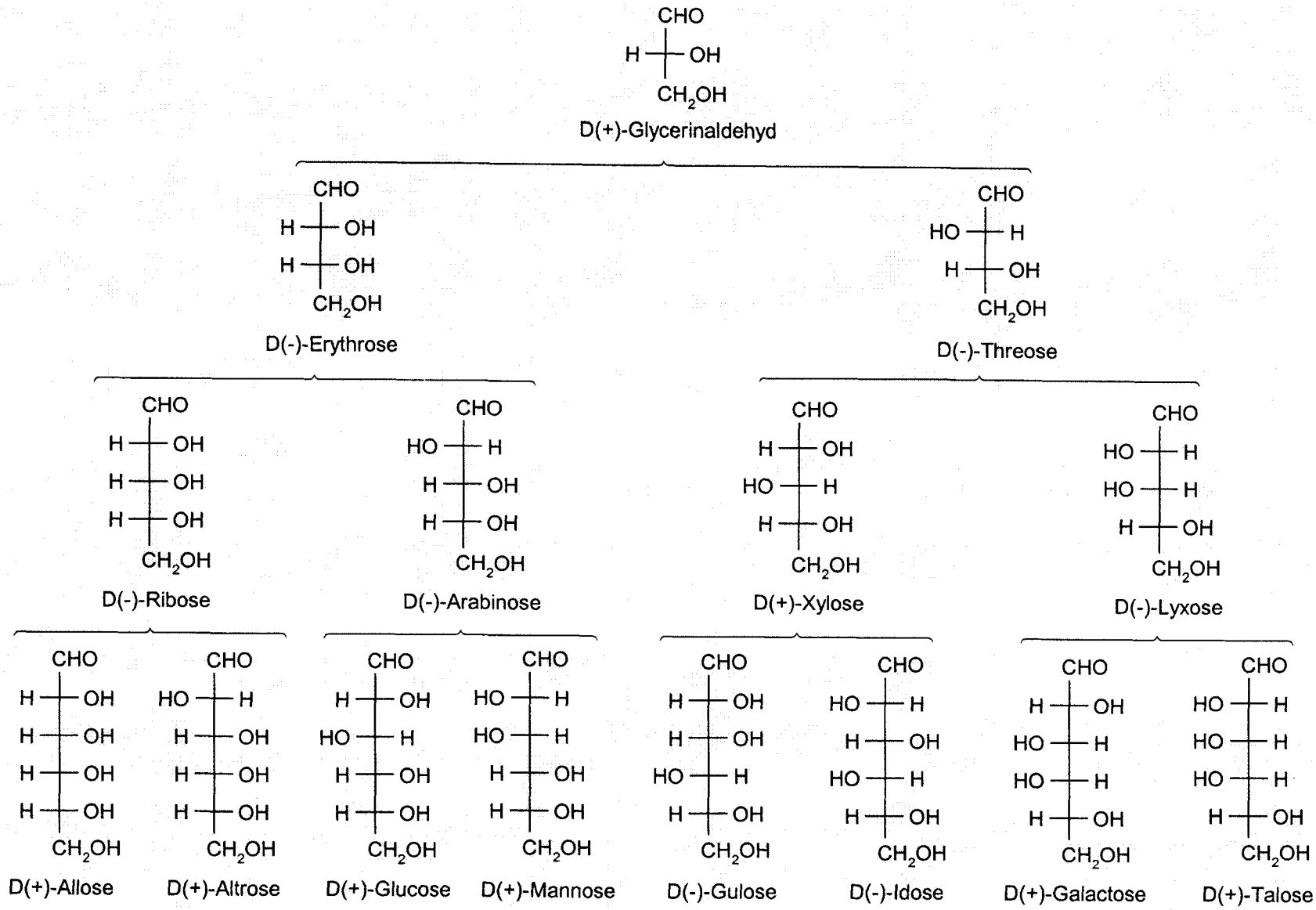
Radikalreaktionen

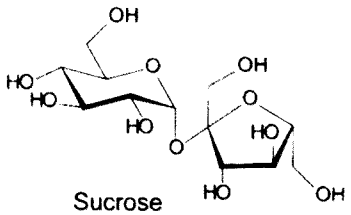
Radikale und Radikalionen in der Organischen Synthese, Wiley 1998.

Radicals in Organic Synthesis, Pergamon 1986.

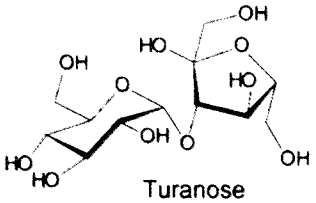
Stereochemistry of Radical Reactions, Wiley-VCH 1996.

Die Familie der D-Aldosen

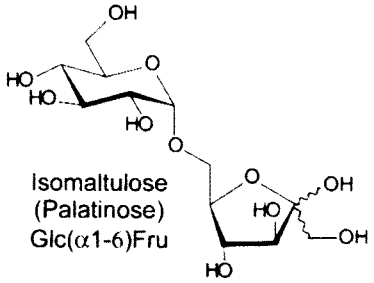




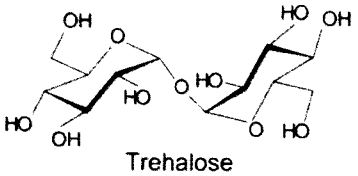
Sucrose
Glc(α1-β2)Fru



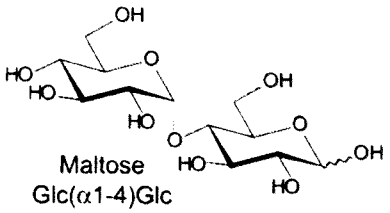
Turanose
Glc(α1-3)Fru



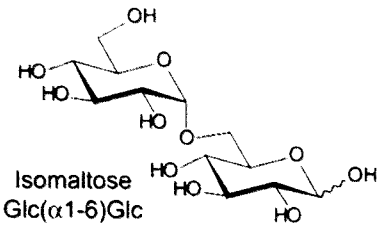
Isomaltulose
(Palatinose)
Glc(α1-6)Fru



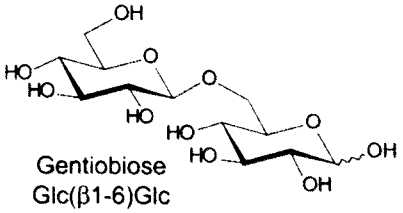
Trehalose
Glc(α1-α1)Glc



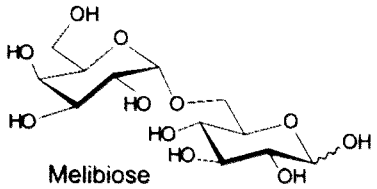
Maltose
Glc(α1-4)Glc



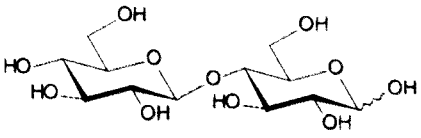
Isomaltose
Glc(α1-6)Glc



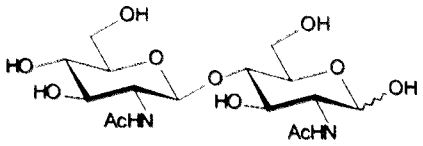
Gentiobiose
Glc(β1-6)Glc



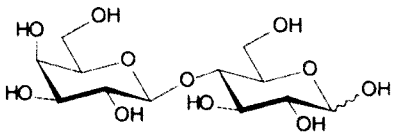
Melibiose
Gal(α1-6)Glc



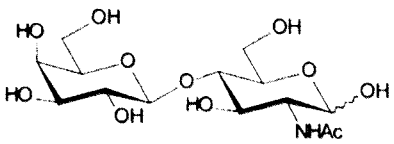
Cellobiose
Glc(β1-4)Glc



Chitobiose
GlcNHAc(ß 1-4) GlcNHAc

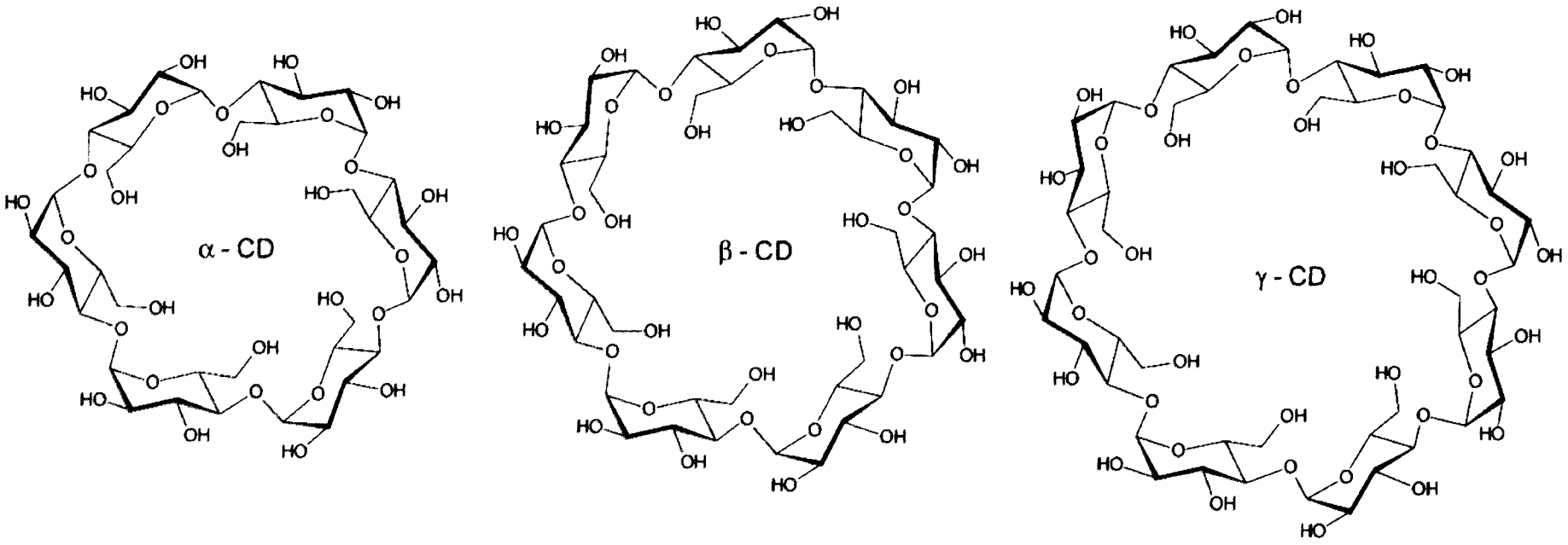


Lactose
Gal(β1-4)Glc

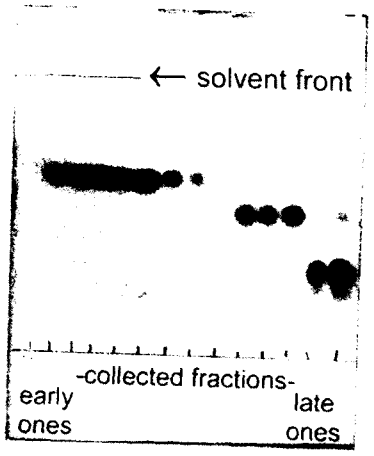


N-Acetyllactosamine
Gal(β1-4)GlcNAc

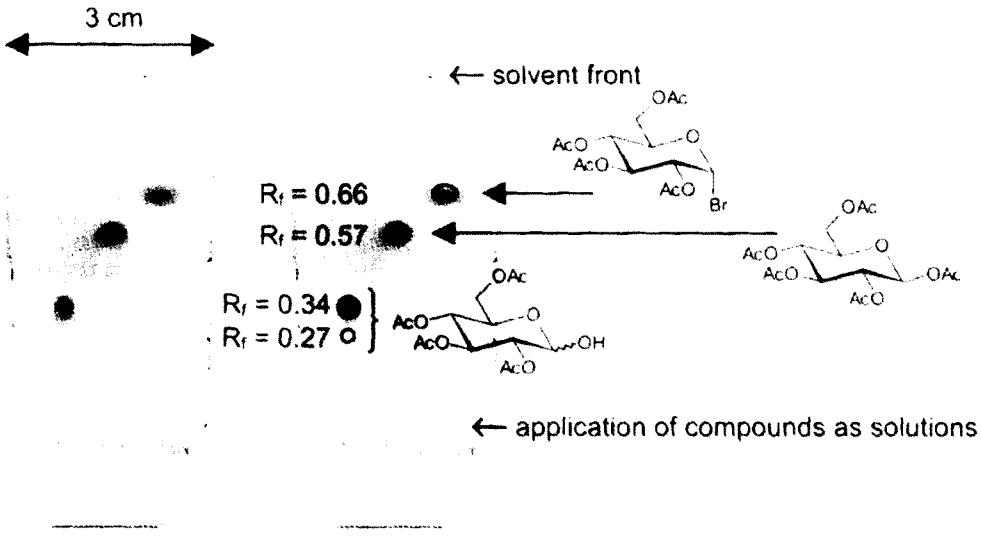
Structures and trivial names of the most common disaccharides.



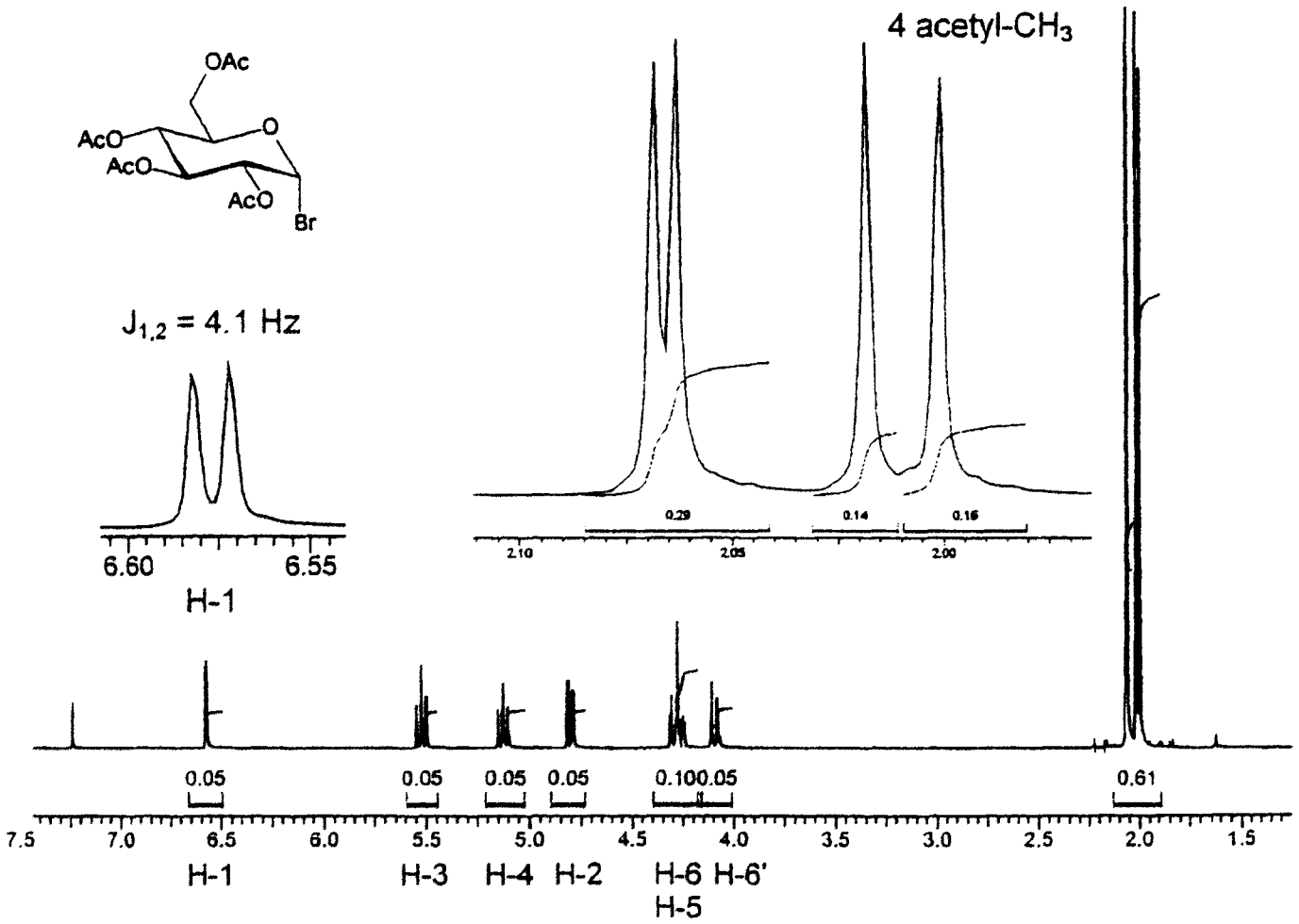
Structures of α–, β–, and γ–cyclodextrin.



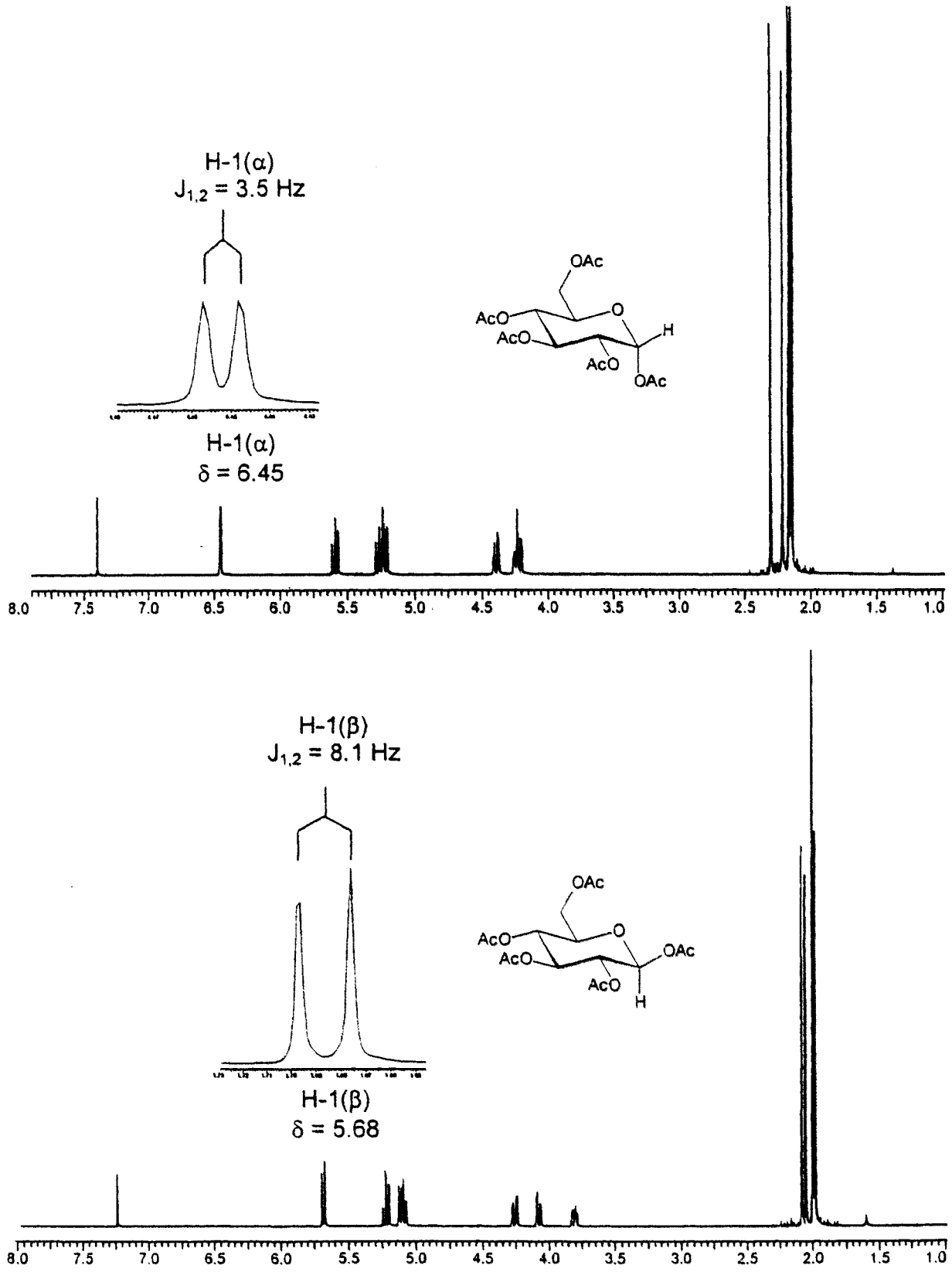
An example of TLC, used to check the result of purification by column chromatography on silica gel. Visualization of the spots was achieved by 10% ethanolic H_2SO_4 and heating. Three carbohydrate derivatives were separated. The compound with the highest R_f value elutes first, the one with the smallest R_f value is the last to be collected. To improve the performance of column chromatography, solvent gradients may be used, in which the polarity of the eluant is slowly increased.



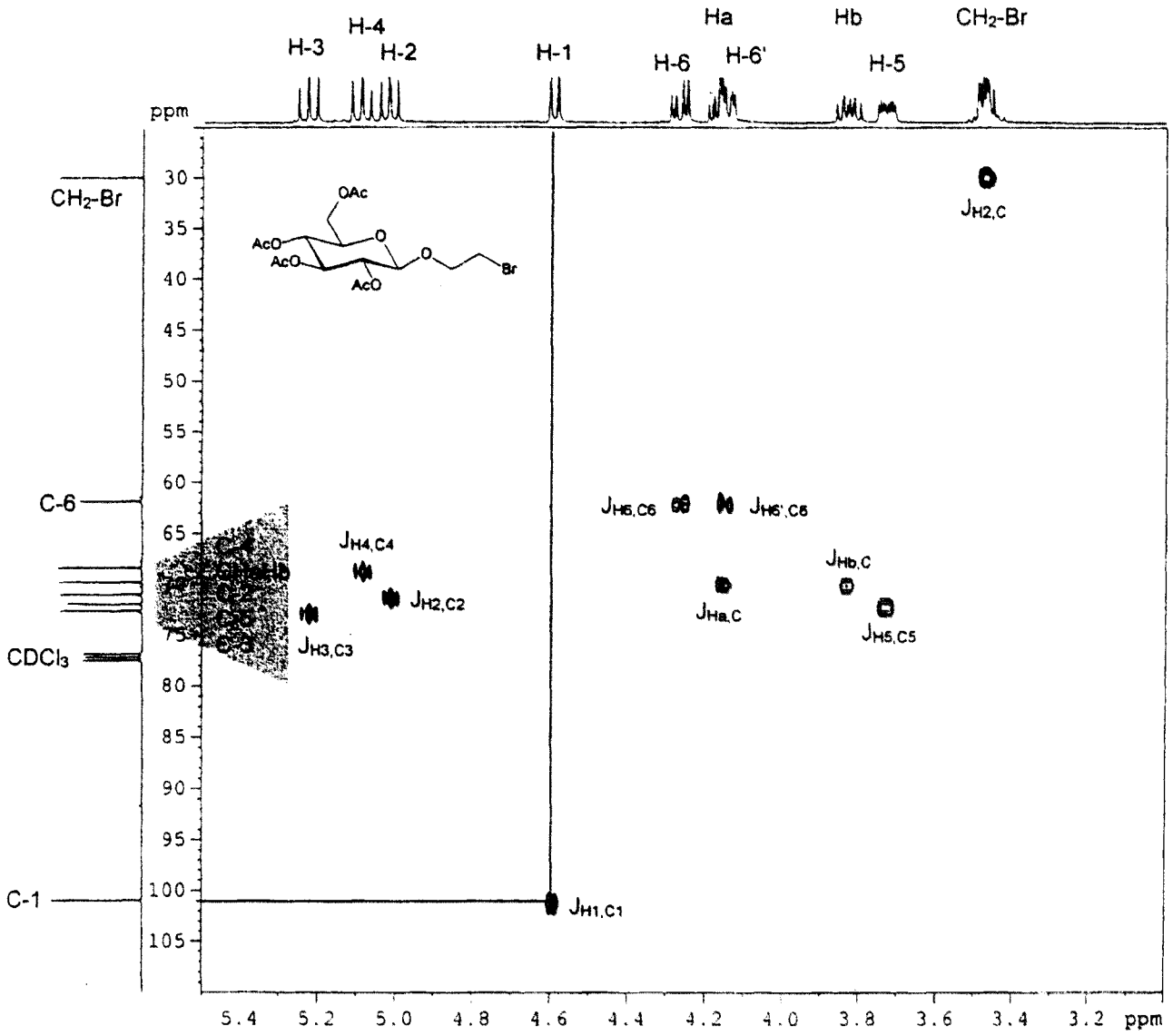
An example of TLC in which the reducing sugar, 2,3,4,6–tetra–O–acetyl–glucose, the corresponding pentaacetate and 2,3,4,6–tetra–O–acetyl–α–D–glucopyranosyl bromide have been distinguished. The TLC plate is labelled on the copy given on the right, indicating R_f values and structures for every spot. In the case of the 1–OH–free glucose derivative a small amount of the second anomer can be seen as shadow below the main spot. This TLC has been performed on silica gel, with ethyl acetate–toluene (1:1) as the mobile phase. Detection of the compounds was achieved by dipping the plate into 10% ethanolic H_2SO_4 followed by heating.



^{1}H NMR spectrum of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide, recorded in $CDCl_3$ at 400 MHz. The doublet for H-1 and the singlets for the acetyl groups are expanded.

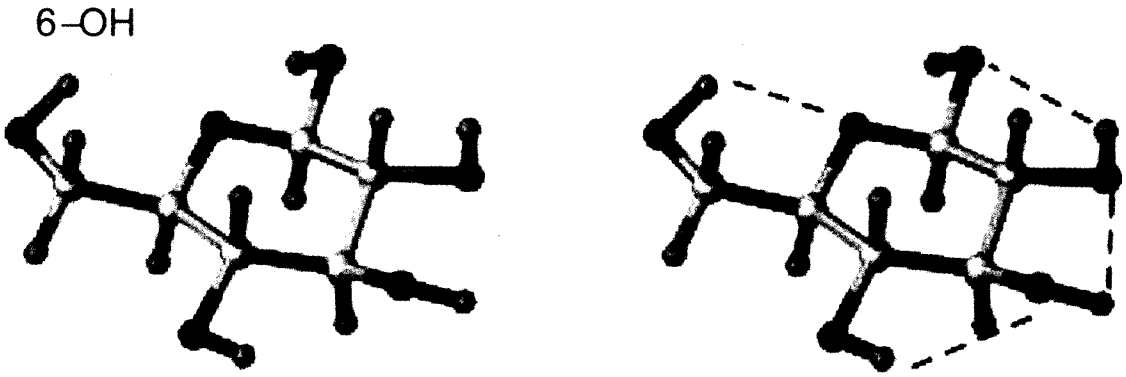


^{1}H NMR (400 MHz, $CDCl_3$) spectra of α– and β–penta–O–acetyl–glucose. The doublet for H-1 is expanded in each case and its chemical shift and coupling constant $^3J_{1,2}$ are indicated.

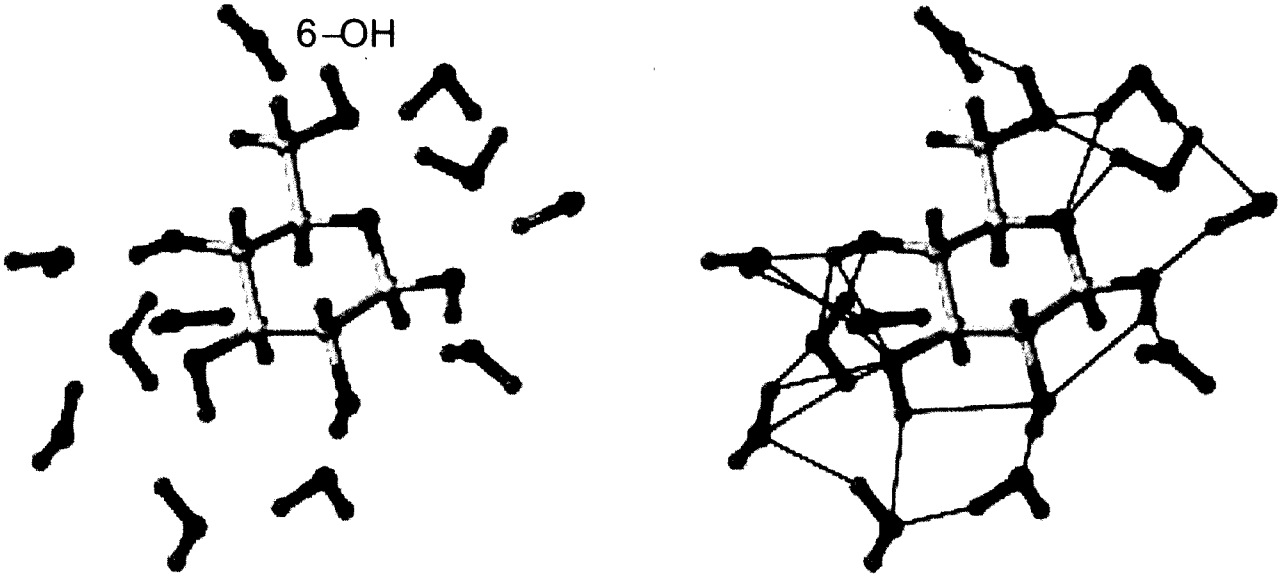


^{1}H–^{13}C–COSY of (2–bromoethyl) 2,3,4,6–tetra–O–acetyl–β–D–glucoside. All multiplets recorded in the ^{1}H spectrum of the compound can be cross–peak–correlated to the carbon atoms to which these hydrogens are attached. This is indicated for the H–1–C–1 correlation. This method facilitates the exact assignment of all ^{13}C peaks.

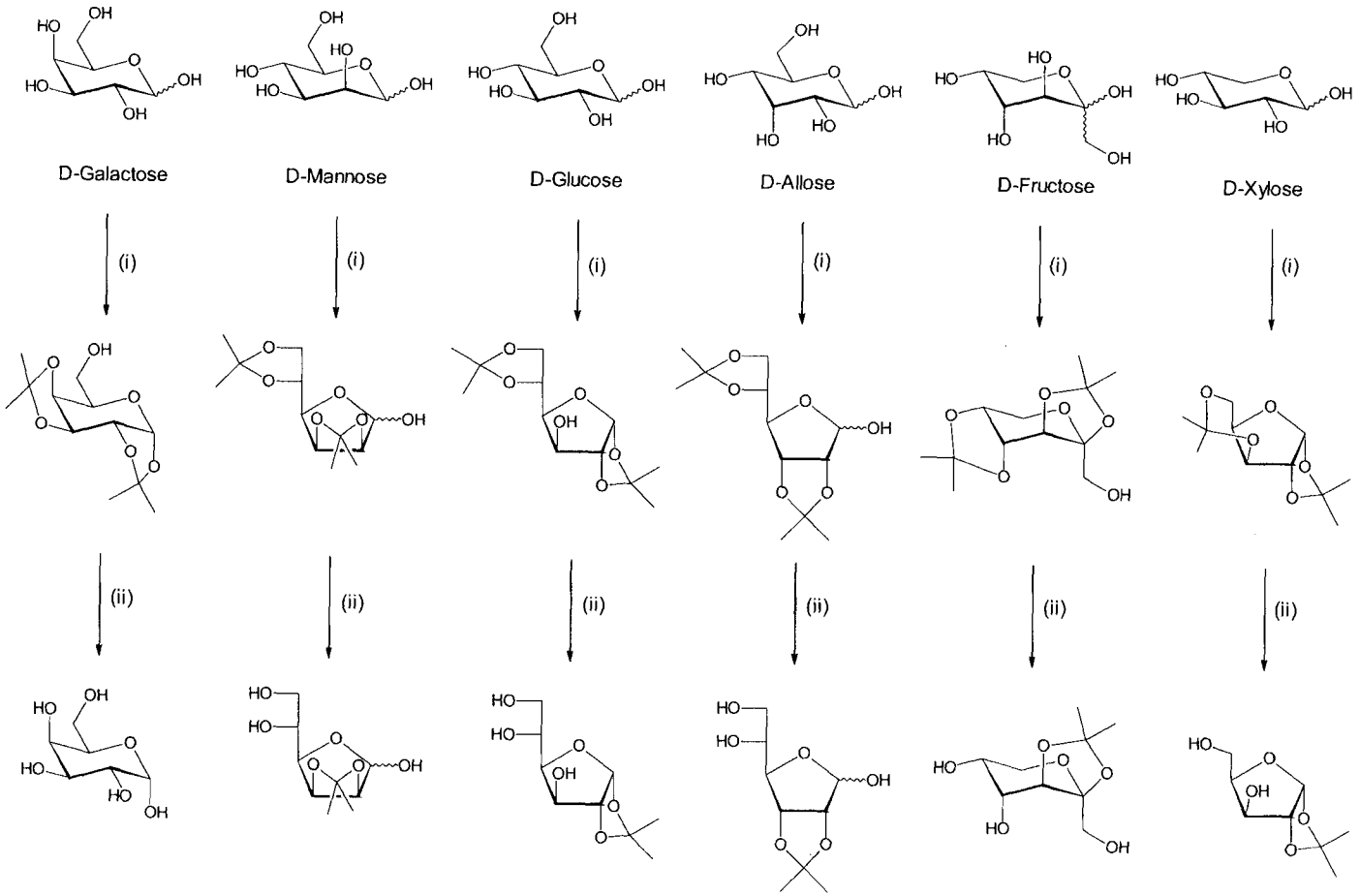
Conformation of glucose in vacuo:



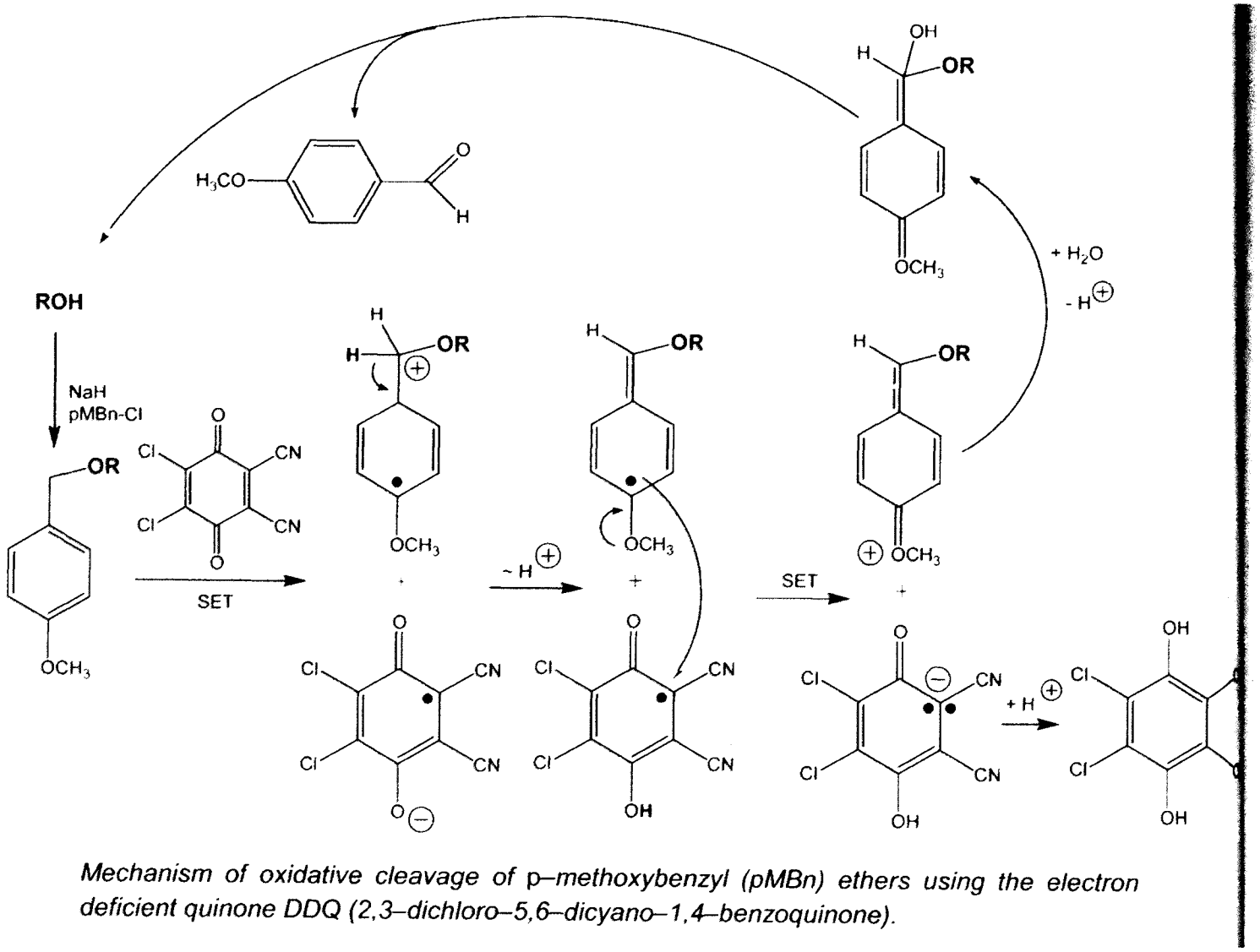
Conformation of glucose in water:



The structure of D-glucopyranose as obtained in vacuo in comparison with the structure of the same molecule dissolved in water as calculated by molecular dynamic simulations. The 6–OH group, e.g., points towards the endocyclic ring oxygen in vacuo, expressing an intramolecular hydrogen bridge, whereas this 6–hydroxyl group is saturated with surrounding water molecules, once the monosaccharide is modeled in aqueous solution.

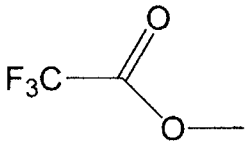
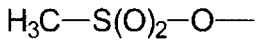
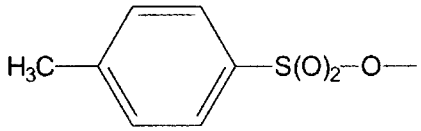
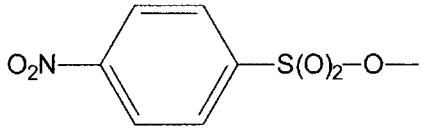
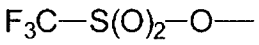


Several free monosaccharides can be converted by isopropylidenation ((i): H^+, acetone) to useful building blocks which possess a single unprotected OH group, in a one step–reaction. The less stable isopropylidene group in each of the obtained diisopropylidene derivatives can be selectively cleaved to produce the respective sugars with 3 free hydroxyl groups ((ii): diluted HOAc). Complete cleavage of all isopropylidene rings is often affectad with conc. TFA.



Mechanism of oxidative cleavage of p–methoxybenzyl (pMBn) ethers using the electron deficient quinone DDQ (2,3–dichloro–5,6–dicyano–1,4–benzoquinone).

Table 4–1. Leaving groups regularly used in substitution reactions with carbohydrate derivatives.

	Leaving group	**Name**
Lower reactivity	Cl–	Chloro-
		Trifluoroacetyl-
	Br–	Bromo-
	I–	Iodo-
		Mesyl-
		Tosyl-
Higher reactivity		*p*–Nitrophenylsulfonyl-
Significantly **more reactive** than all others		Triflyl-

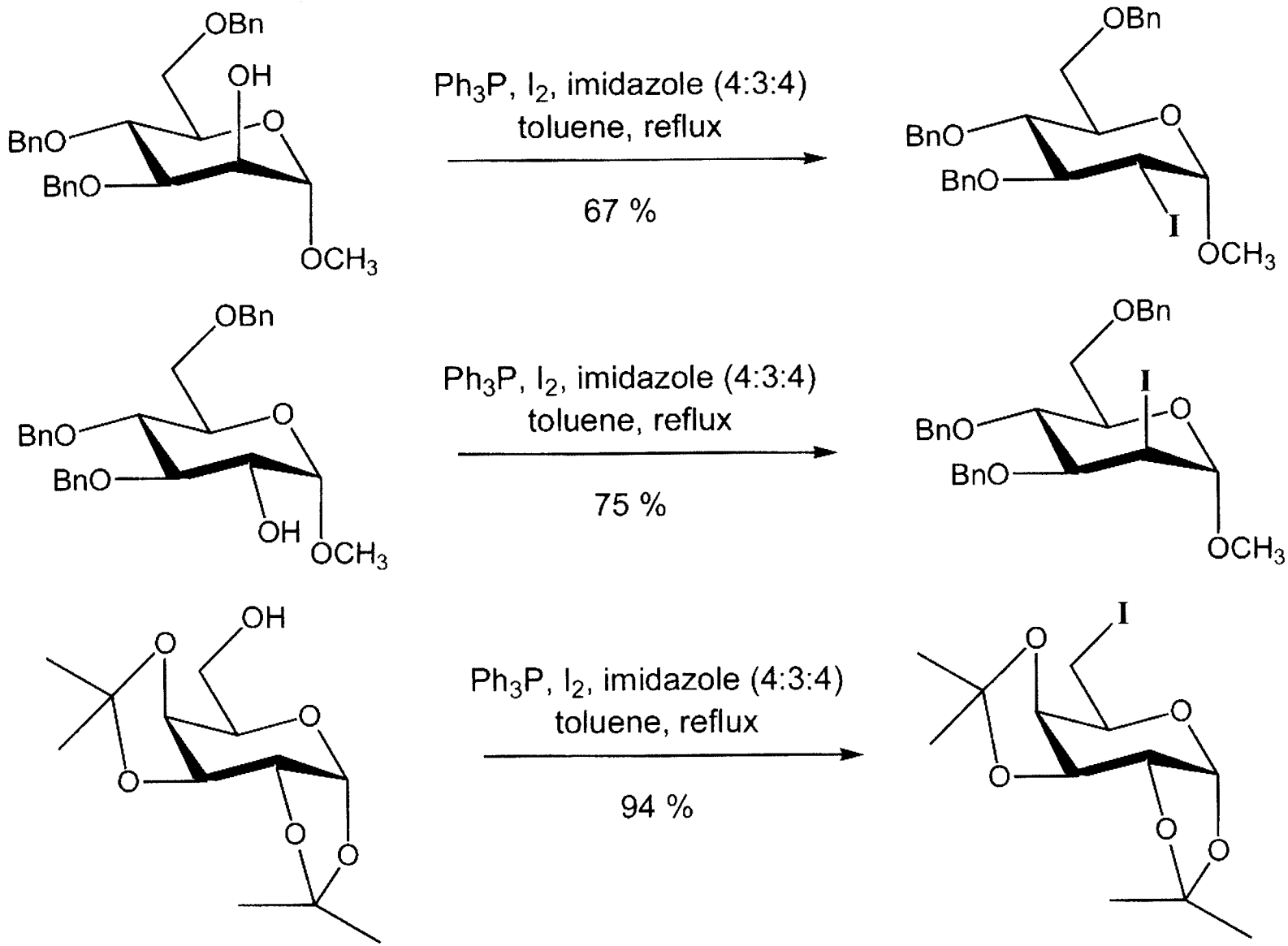
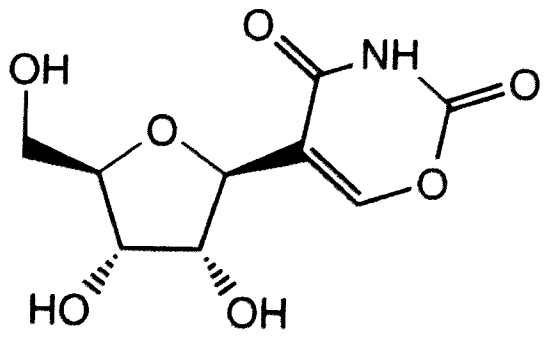
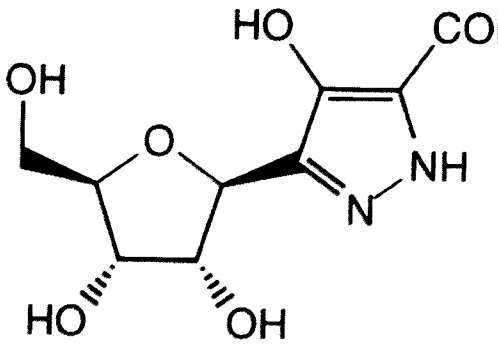

OBn
OH
O
BnO
BnO
OCH3
Ph3P, I2, imidazole (4:3:4)
toluene, reflux
67 %
OBn
BnO
BnO
I
OCH3
OBn
O
BnO
BnO
OH
OCH3
Ph3P, I2, imidazole (4:3:4)
toluene, reflux
75 %
OBn
I
O
BnO
BnO
OCH3
OH
O
O
O
O
O
Ph3P, I2, imidazole (4:3:4)
toluene, reflux
94 %
I
O
O
O
O
O

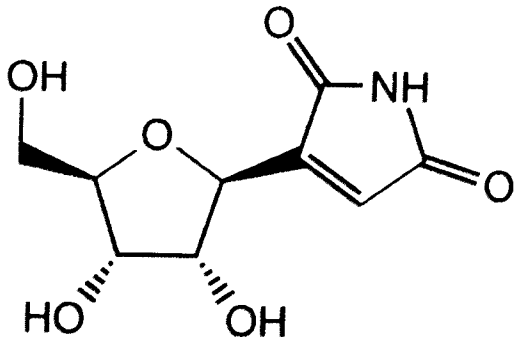
Figure 1.3.6 Naturally Occurring *C*-Nucleosides



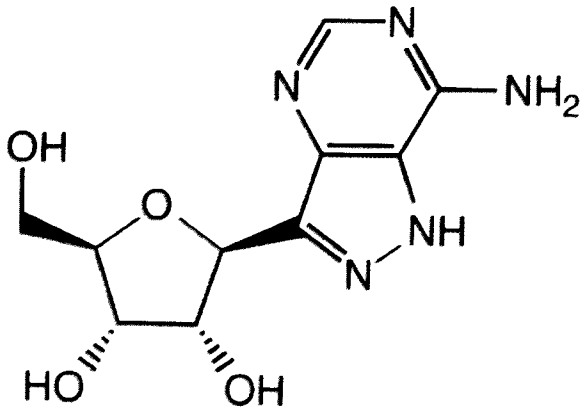
Oxazinomycin, **19**



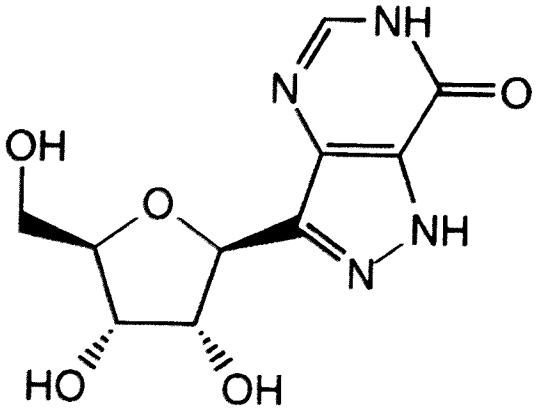
Pyrazofurin, **20**



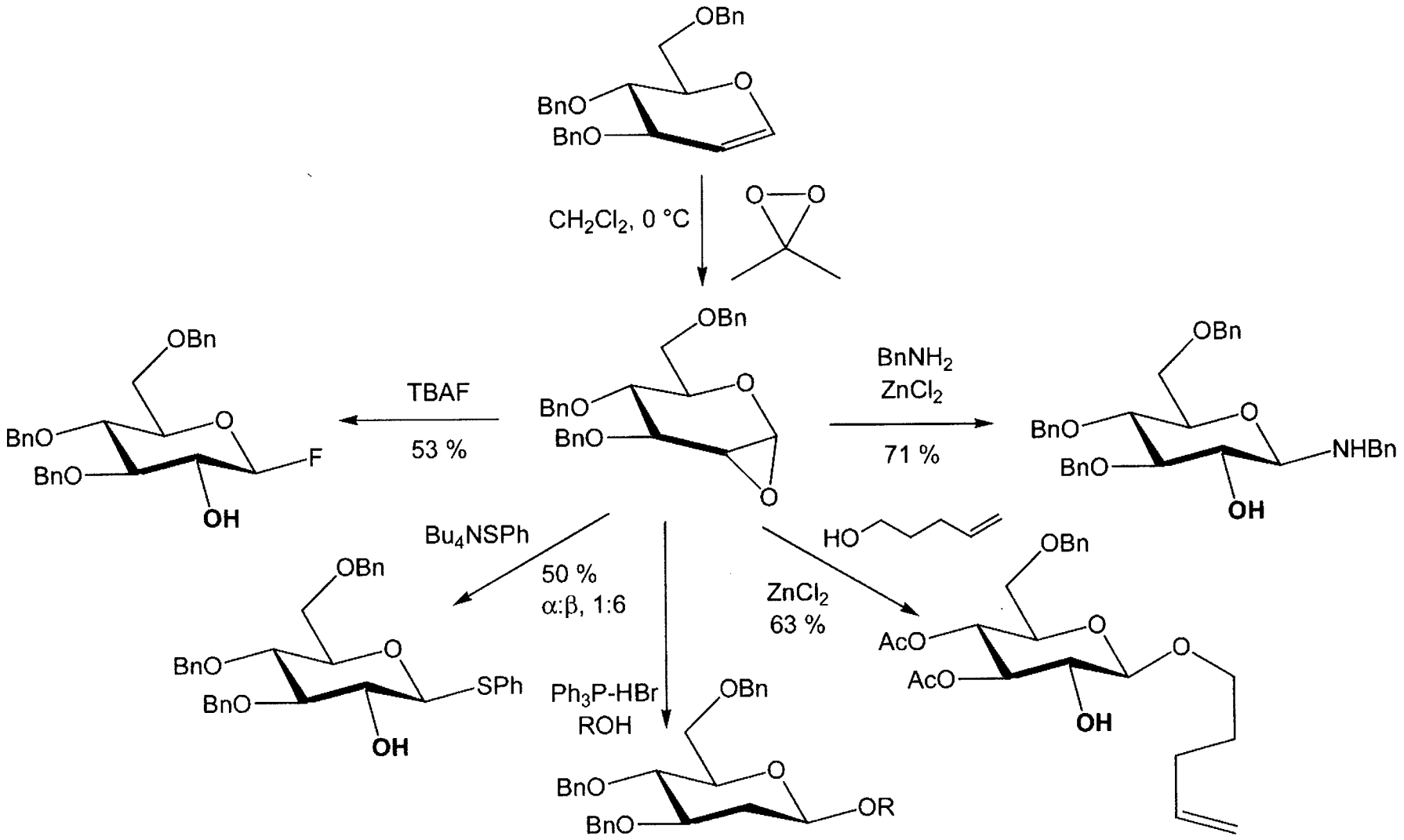
Showdomycin, **21**



Formycin, **22**



Formycin B, **23**


OBn
BnO
BnO
O
CH_2Cl_2, 0 °C
TBAF
53 %
F
OH
$BnNH_2$
$ZnCl_2$
71 %
NHBn
Bu_4NSPh
50 %
α:β, 1:6
SPh
Ph_3P-HBr
ROH
OR
HO
$ZnCl_2$
63 %
AcO

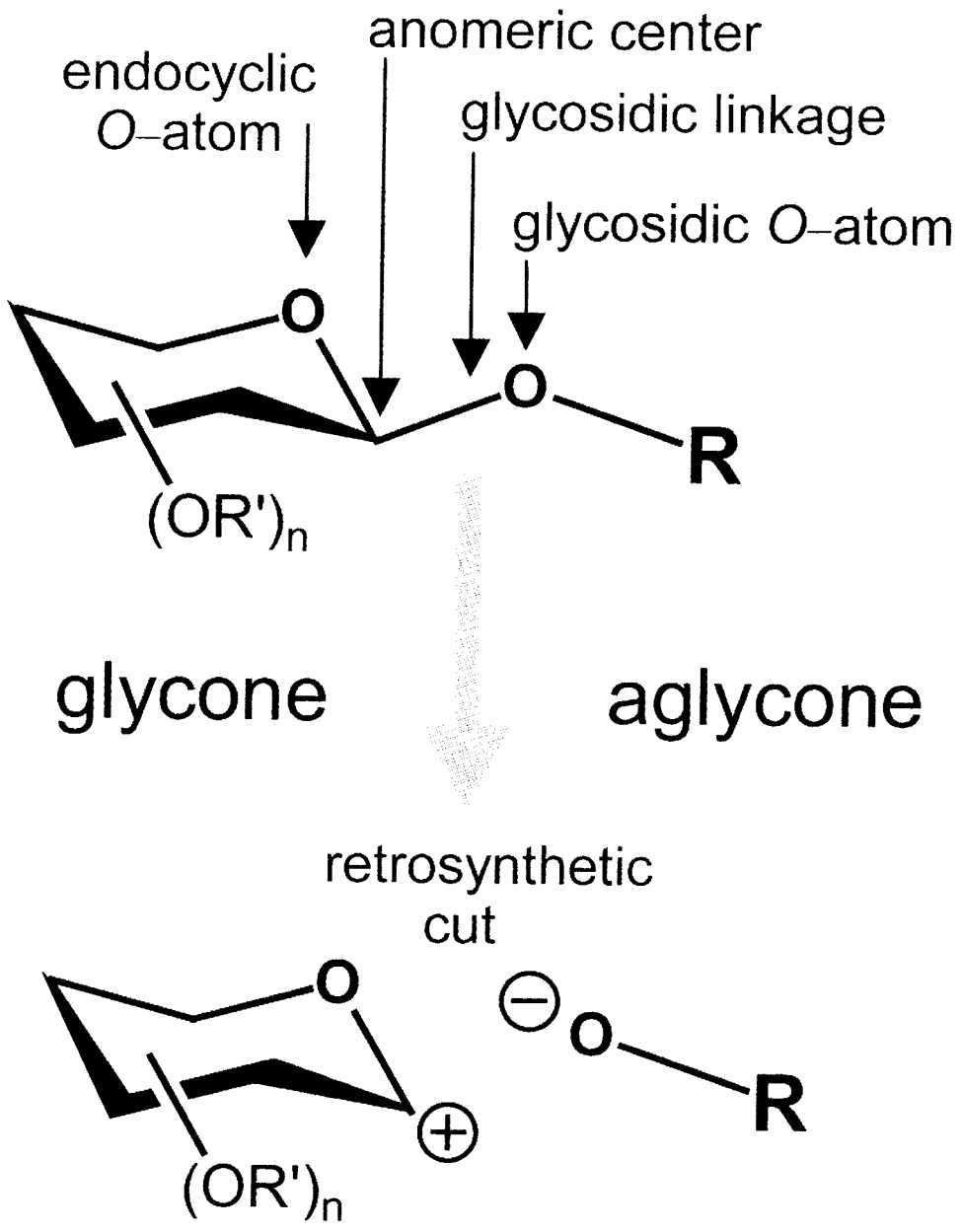
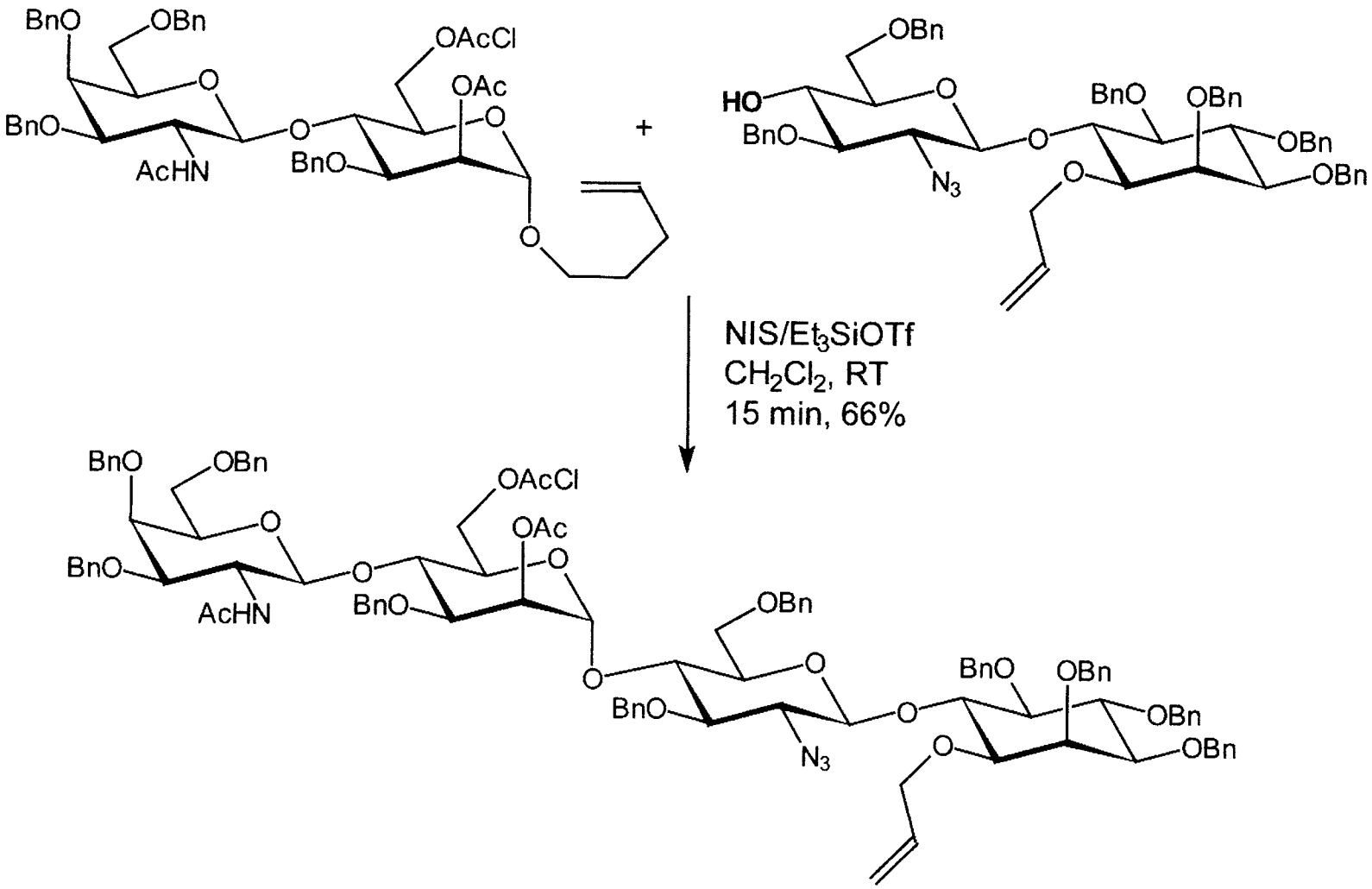
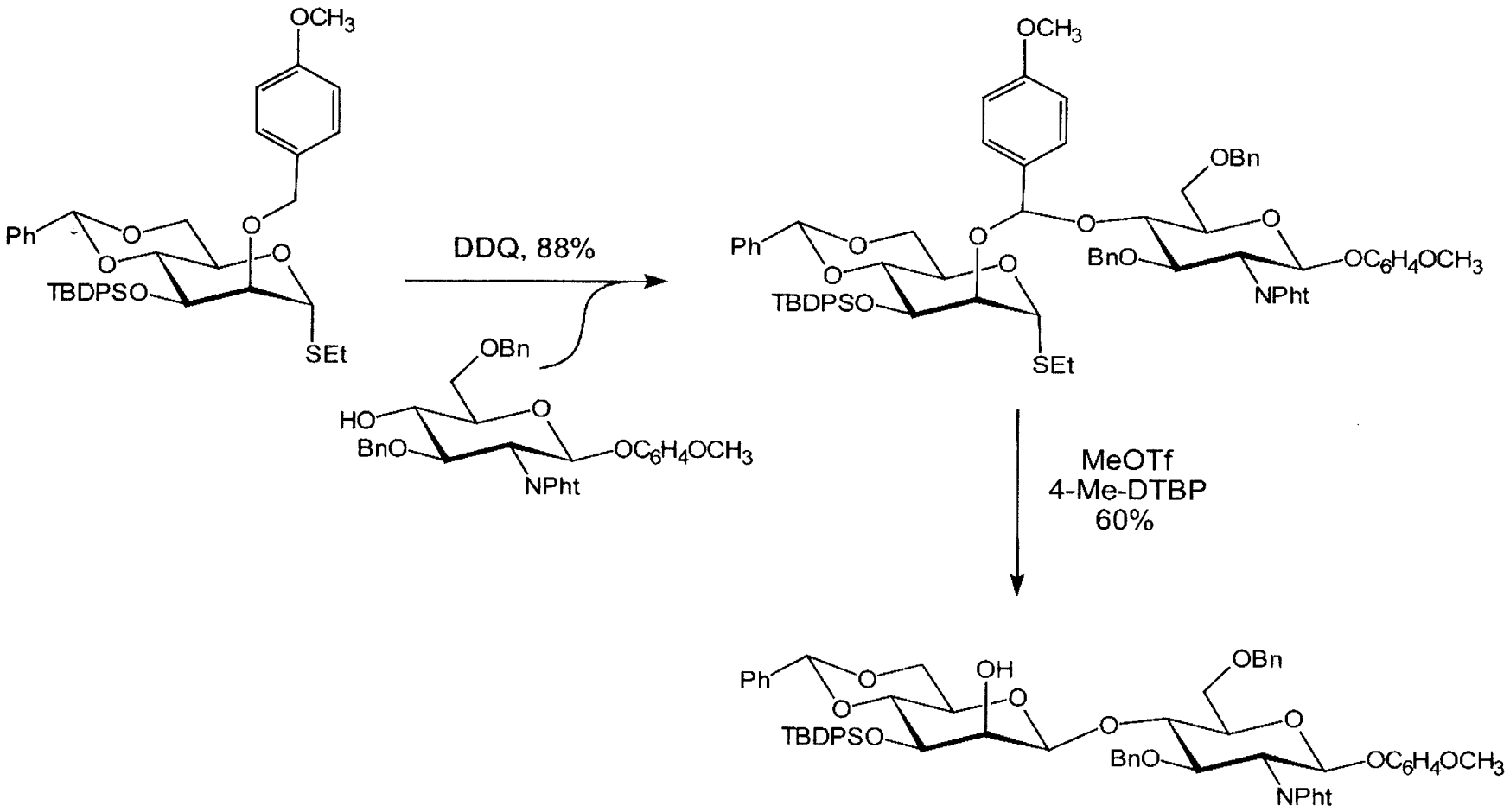
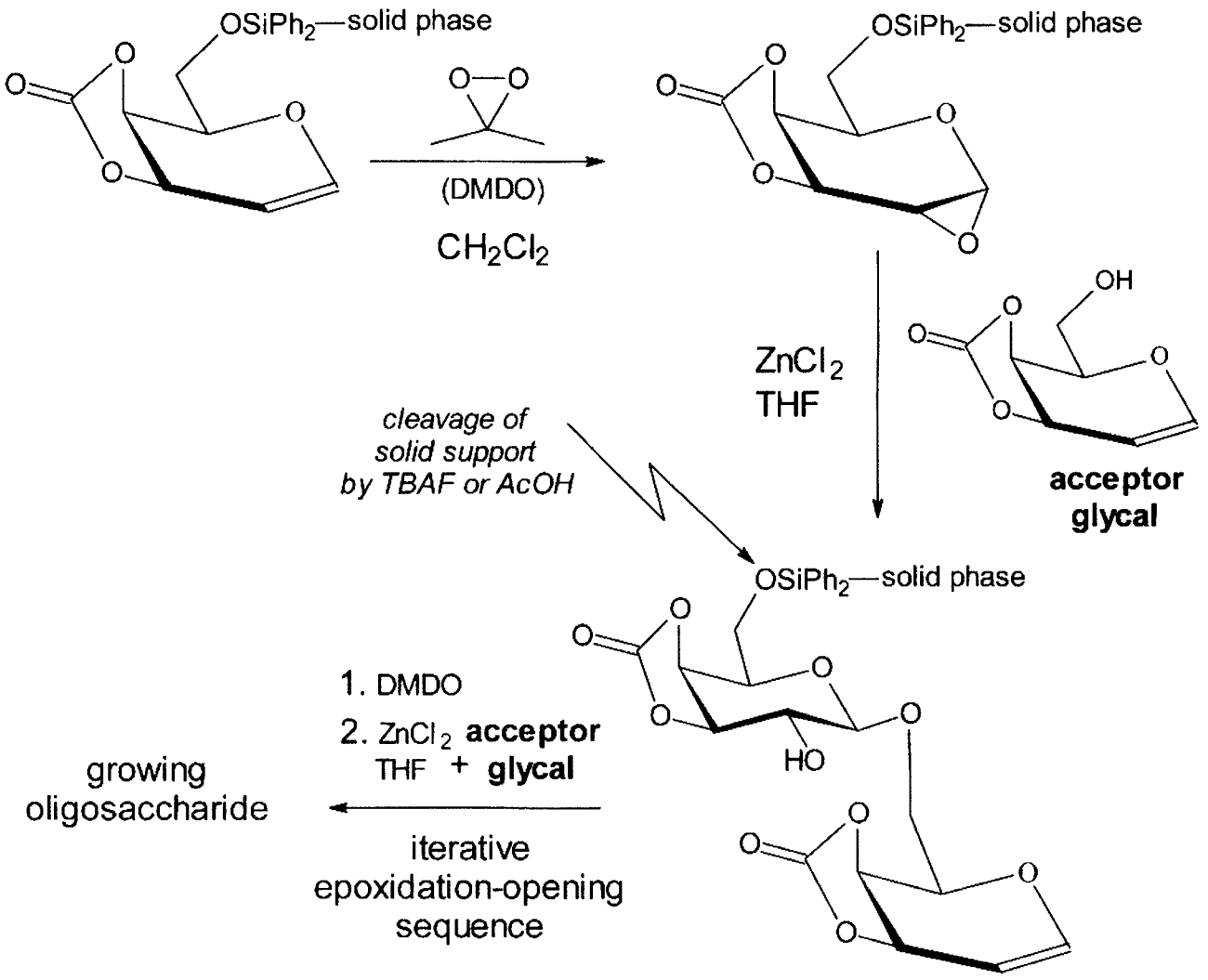

anomeric center
endocyclic
O–atom
glycosidic linkage
glycosidic O–atom
O
O
R
(OR')n
glycone
aglycone
retrosynthetic
cut
O
O
R
(OR')n

Table 5–1. The most common leaving groups in glycosyl donors and a selection of typically employed activators.

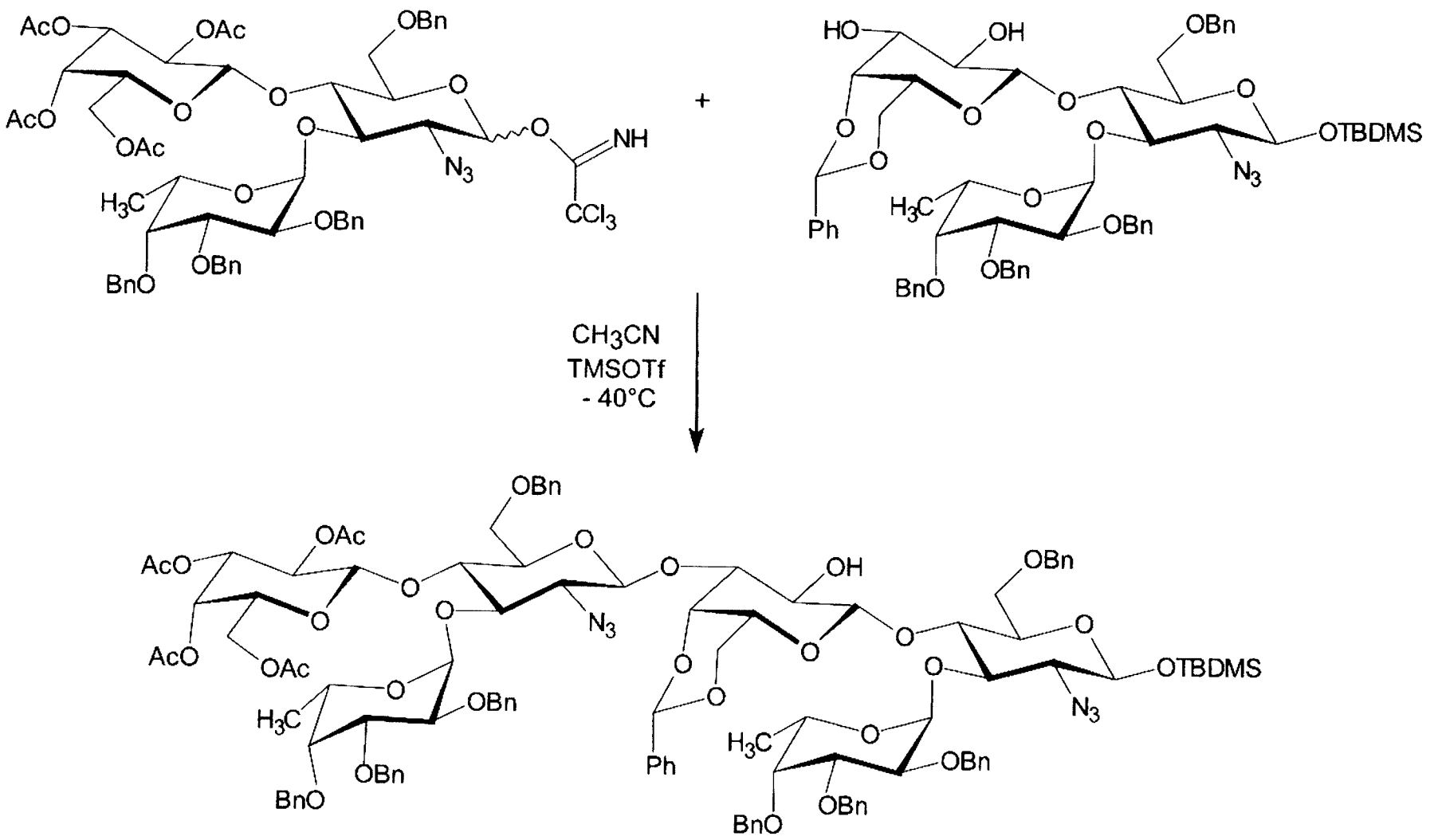
Leaving group	Activator	Comments
LG = OAc	$BF_3{\cdot}Et_2O$, $SnCl_4$, TMSOTf	Not for complex oligosaccharides
LG = Br	$AgCO_4$, AgOTf, $Hg(CN)_2$	Most commonly used donor
LG = Cl	AgOTf, $Hg(CN)_2$, $HgBr_2$	More stable than glycosyl bromide
LG = F	$SnCl_2$–AgOTf	Can be combined with thioglycosides
LG = $OC(NH)CCl_3$	$BF_3{\cdot}Et_2O$, TMSOTf	Mild reaction conditions, widely used
LG = SR	TfOH–NIS, DMTST, IDCP	Can also serve as an acceptor in the absence of thiophilic reagents
LG = $O(CH_2)_3CH{=}CH_2$	NIS–TESOTf, $I(col)_2ClO_4$	Can also serve as an acceptor in the absence of bromine


BnO
OBn
OAcCl
OAc
BnO
AcHN
BnO
O
+
OBn
HO
BnO
N3
BnO
OBn
OBn
OBn
NIS/Et3SiOTf
CH2Cl2, RT
15 min, 66%


OCH3
Ph
O
TBDPSO
SEt
DDQ, 88%
OBn
HO
BnO
NPht
OC6H4OCH3
MeOTf
4-Me-DTBP
60%
OH


OSiPh2—solid phase
(DMDO)
CH2Cl2
OSiPh2—solid phase
ZnCl2
THF
OH
acceptor
glycal
cleavage of
solid support
by TBAF or AcOH
OSiPh2—solid phase
HO
1. DMDO
2. ZnCl2 acceptor
THF + glycal
growing
oligosaccharide
iterative
epoxidation-opening
sequence

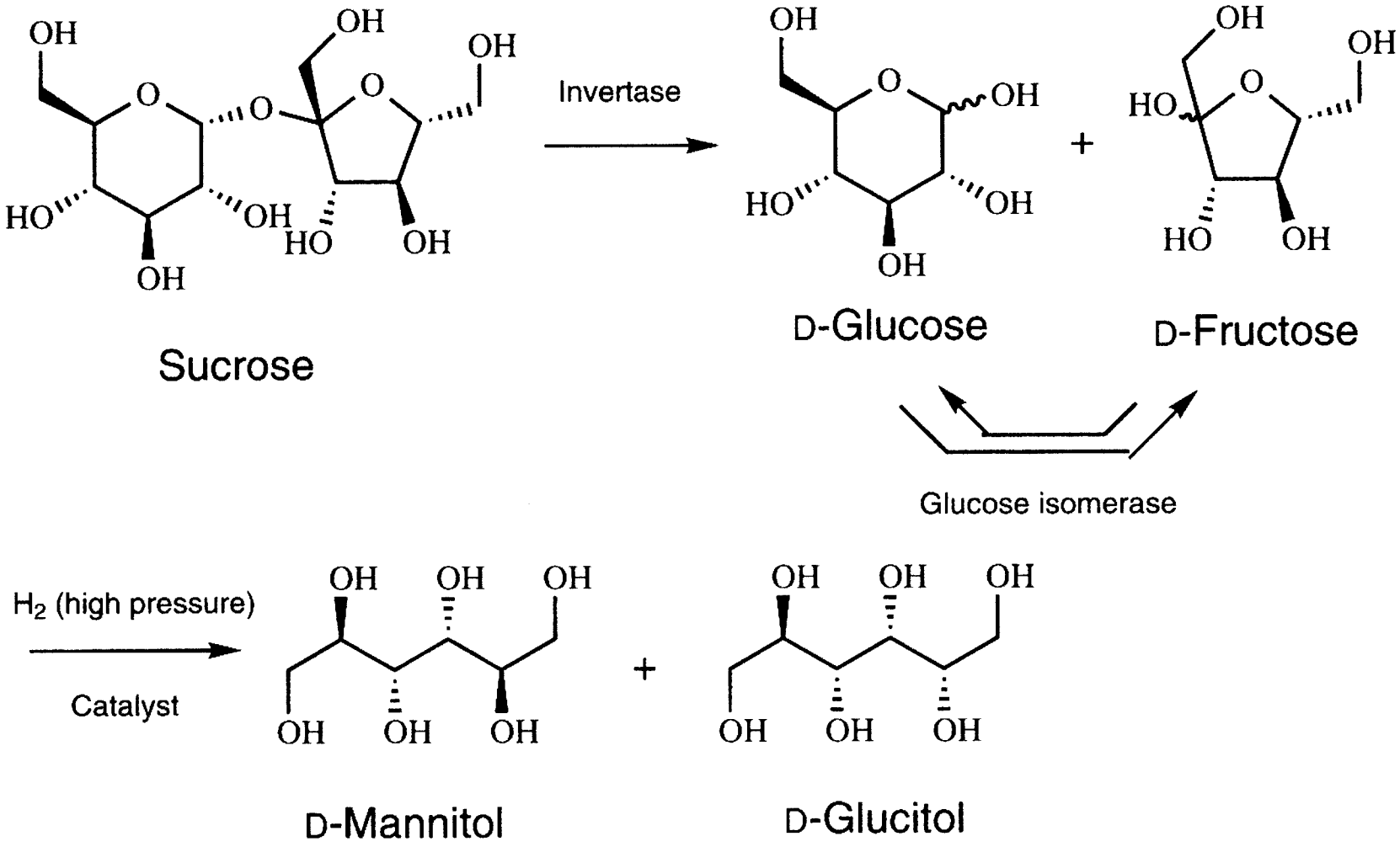
Folie 20



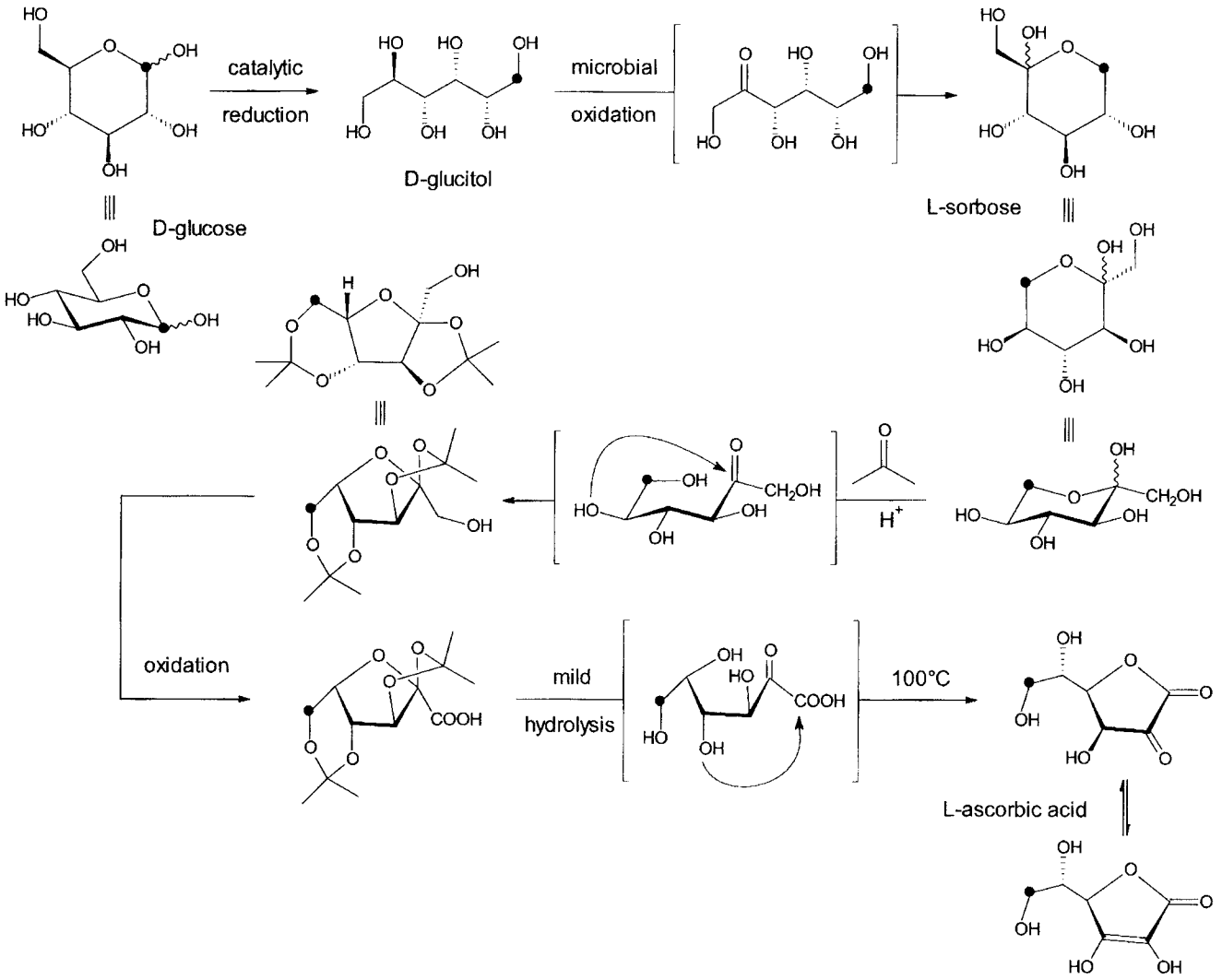
AcO
OAc
OBn
AcO
OAc
O
O
O
O
O
NH
N3
H3C
O
OBn
CCl3
BnO
OBn
+
HO
OH
OBn
O
O
O
O
O
OTBDMS
N3
Ph
H3C
O
OBn
BnO
OBn
CH3CN
TMSOTf
- 40°C
OBn
OAc
AcO
O
O
O
O
OH
OBn
N3
AcO
OAc
O
O
O
O
O
OTBDMS
N3
H3C
OBn
Ph
H3C
O
OBn
BnO
OBn
BnO
OBn

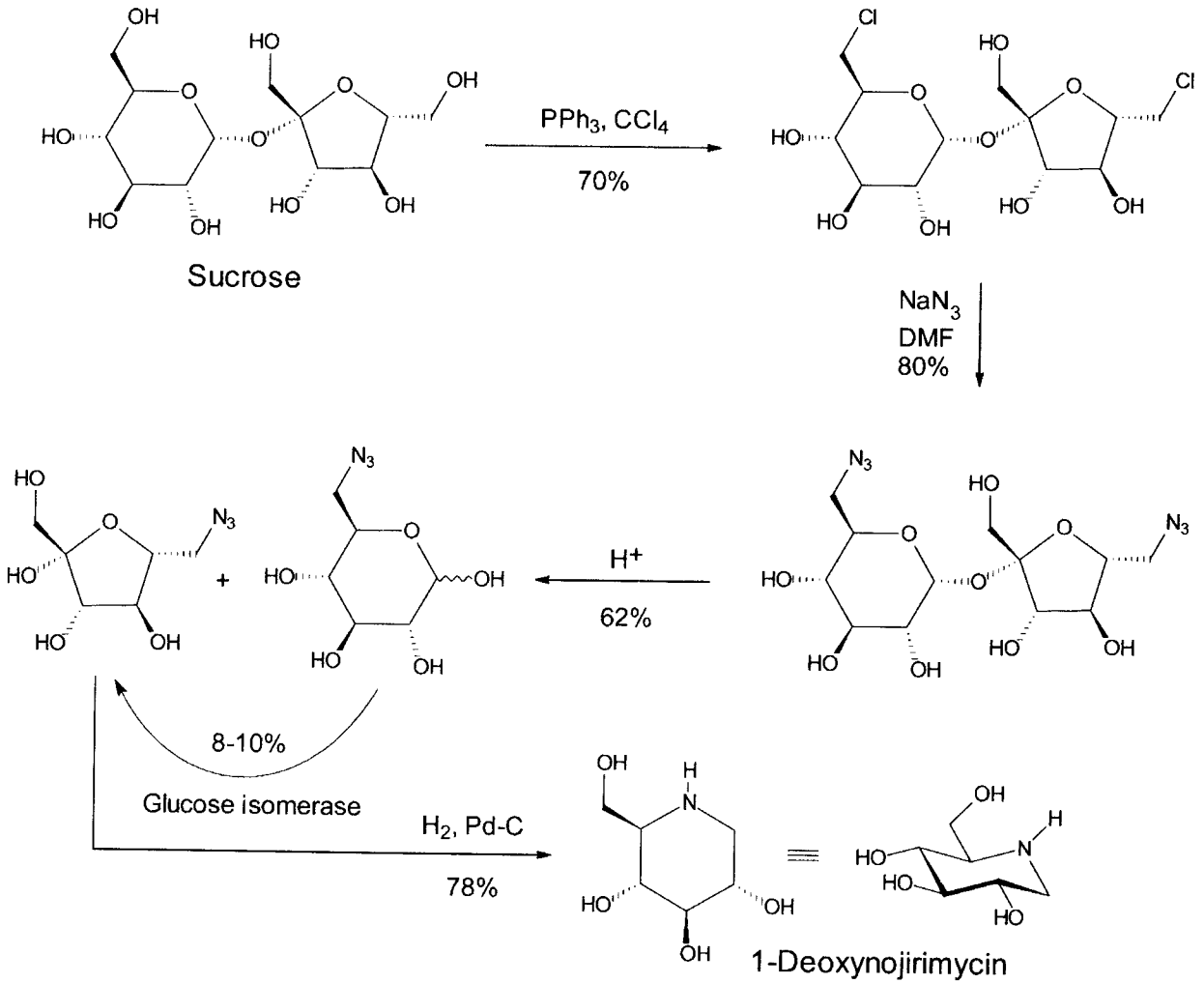
Table 1.1 Approximate prices of carbohydrate derivatives (1995)

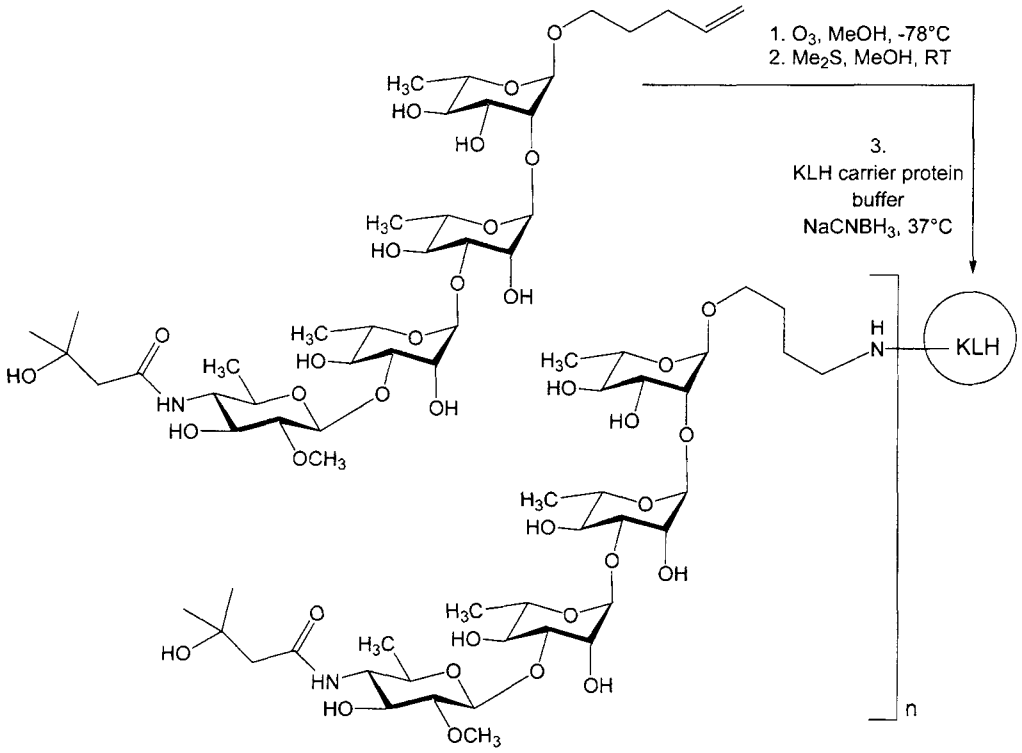
Compound	Price ($/100 g)	Source
Sucrose (**1.23**)	0.5	Sugar cane
D-Glucose (**1.01**)	0.5	Starch
D-Fructose (**1.09**)	1.0	Glucose
D-Gluconic acid (**1.12**)	1.0	Glucose
D-Glucitol (sorbitol) (**1.19**)	1.0	Glucose
Lactose (**1.24**)	1.5	Milk (whey)
D-Mannitol (**1.20**)	2.0	Fructose
Methyl α-glucopyranoside (**1.11**)	4.0	Glucose
Maltose (**1.25**)	4.0	Starch
D-Isoascorbic acid (**1.16**)	4.0	Glucose
D-Glucono-1,5-lactone (**1.12**)	5.0	Glucose
D-Galactose (**1.02**)	6.0	Lactose
L-Sorbose (**1.10**)	7.0	Glucose
D-*Glycero*-D-*gulo*-heptonic acid (**1.13**)	7.0	Glucose
D-Glucosamine (**1.18**)	10	Sea shells
D-Xylose (**1.07**)	10	Wood
Dianhydroglucitol (**1.21**)	12	Glucose
D-Glucurono-3,6-lactone (**1.14**)	13	Glucose
L-Ascorbic acid (**1.15**)	14	Glucose
L-Arabinose (**1.05**)	33	Plant gum
D-Arabinose (**1.04**)	33	Glucose
Diisopropylideneketogulonic acid (**1.22**)	40	Glucose
D-Ribose (**1.06**)	44	Yeast
D-Mannose (**1.03**)	46	Ivory nut
D-Glucaric acid (**1.17**)	57	Glucose
L-Rhamnose (**1.08**)	125	Oak bark



Scheme 1.2 Industrial production of D-mannitol


catalytic
reduction
D-glucitol
microbial
oxidation
L-sorbose
D-glucose
oxidation
mild
hydrolysis
100°C
L-ascorbic acid


Sucrose
PPh3, CCl4
70%
NaN3
DMF
80%
H+
62%
8-10%
Glucose isomerase
H2, Pd-C
78%
1-Deoxynojirimycin

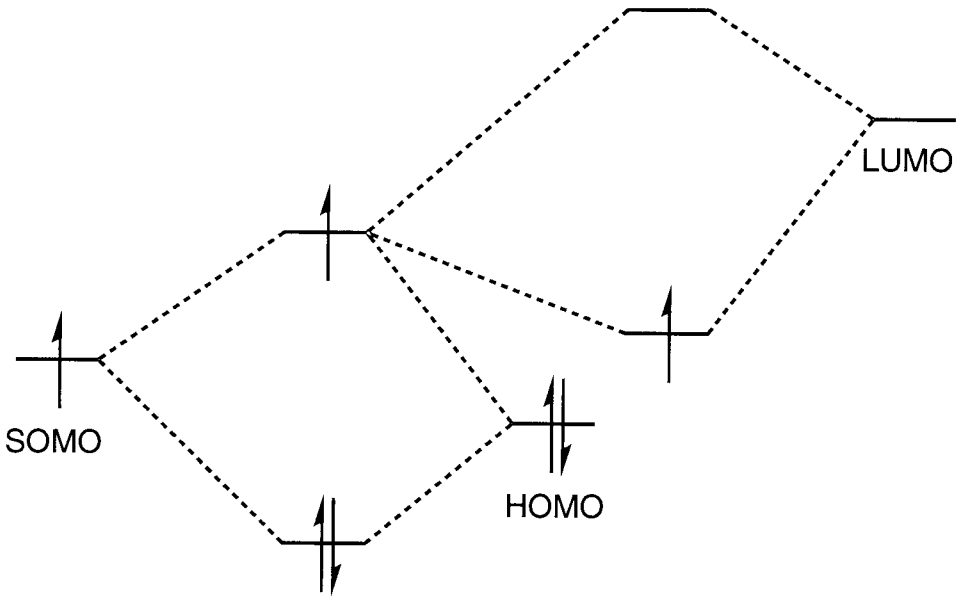


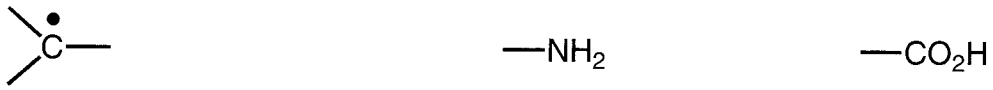
Synthesis of a KHL–conjugated tetrasaccharide which is specific for anthrax and can be used for its detection.[57]

Ausgewählte R-H-Bindungsdissoziationsenergien (BDE) und Stabilisierungsenergien (E_S(•R)) in kcal/mol

R-H	BDE	E_S(•R)
H_3C–H	105	0
H_3CH_2C–H	101	4
$(H_3C)_2HC$–H	99	6
$(H_3C)_3C$–H	95	10
	86	19
PhH_2C–H	85	20
Ph_3C–H	77	28
	73	32
$(Me_3Si)_3Si$–H	79	26
Bu_3Sn–H	74	31 (!)
F–H	136	- 31 (!)
Cl–H	103	2
Br–H	88	17
I–H	71	34
HO–H	119	- 14 (!)
H_3CO–H	104	1
PhO–H	87	18
Ph–H	111	- 6 (!)
HO_2CH_2C–H	97	8
H_2NH_2C–H	95	10
$HO_2C(H_2N)HC$–H	76	29 (!)

Captodative Stabilisierung eines Radikalzentrums





	H_3C-H	H_2NH_2C-H	HO_2CH_2C-H	$HO_2C(H_2N)HC$-H
BDE (kcal/mol)	105	95	97	76

Ausgewählte Bindungsdissoziationsenergien (BDE)

Bindung	BDE (kcal/mol)
HO–H	119
RO–H	95 - 105
R–H	70 - 110
Me–SH	88
$(Me_3Si)_3Si–H$	79
$Bu_3Sn–H$	74
Et–Br	69
Me–SPh	68
$R_2B–R$	65-85
Cl–Cl	58
$Et_3Sn–Et$	57
Et–I	53
$Me_3Pb–Me$	49
Br–Br	46
EtHg–Et	43
$Me_3CO–OCMe_3$	37
$PhCO_2–OCMe_3$	34
$Me_2C(CN)–N=N–CMe_2CN$ (AIBN)	32
$Me_3CO–O_2C–CO_2–OCMe_3$	26
$R–Co^{III}(dmgH)_2py$	20-35

Ausgewählte Bindungsdissoziationsenergien (BDE)

Bindung	BDE (kcal/mol)
HO–H	119
RO–H	95 - 105
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Me_3Pb–Me	49
Br–Br	46
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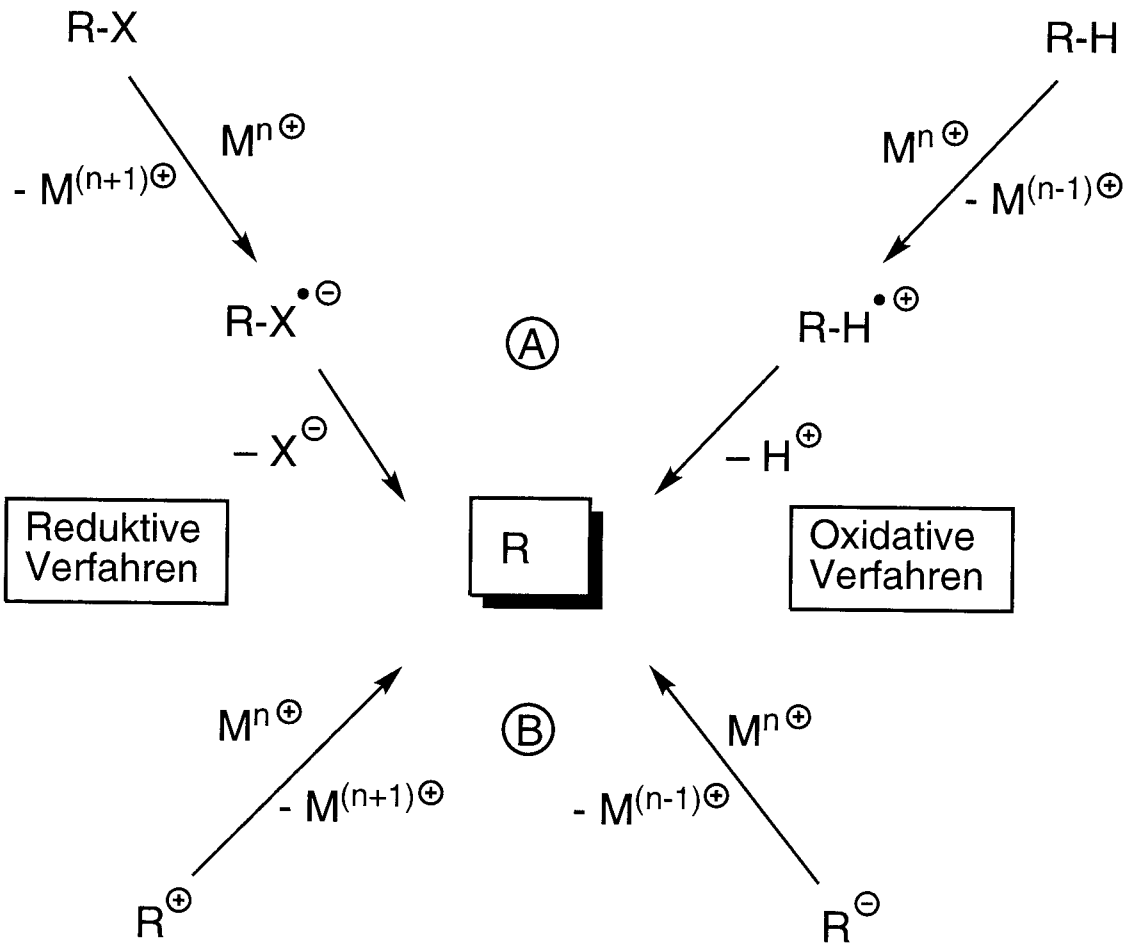
$PhCO_2$–$OCMe_3$	34
$Me_2C(CN)$–N=N–CMe_2CN (AIBN)	32
Me_3CO–O_2C–CO_2–$OCMe_3$	26
R–$Co^{III}(dmgH)_2py$	20-35

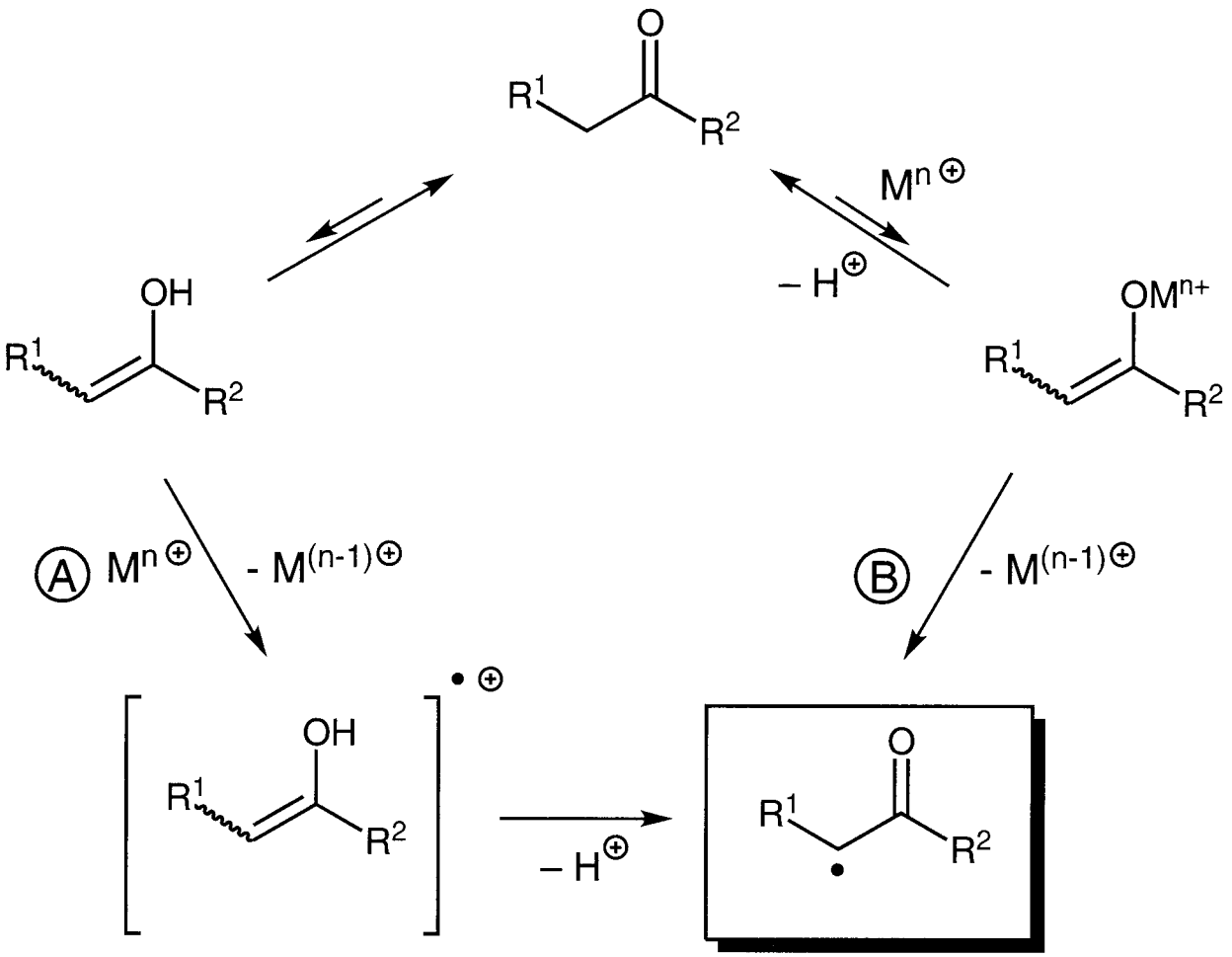
Übergangsmetall-induzierte Radikalreaktionen

(*Chem. Rev.* **1994**, *94*, 519-564; *Tetrahedron* **1995**, *51*, 7579-7653.)



Oxidative Erzeugung von Radikalen

(*Org. React.* **1996**, *49*, 427-675; *J. Organomet. Chem.* **2002**, *661*, 158-167.)

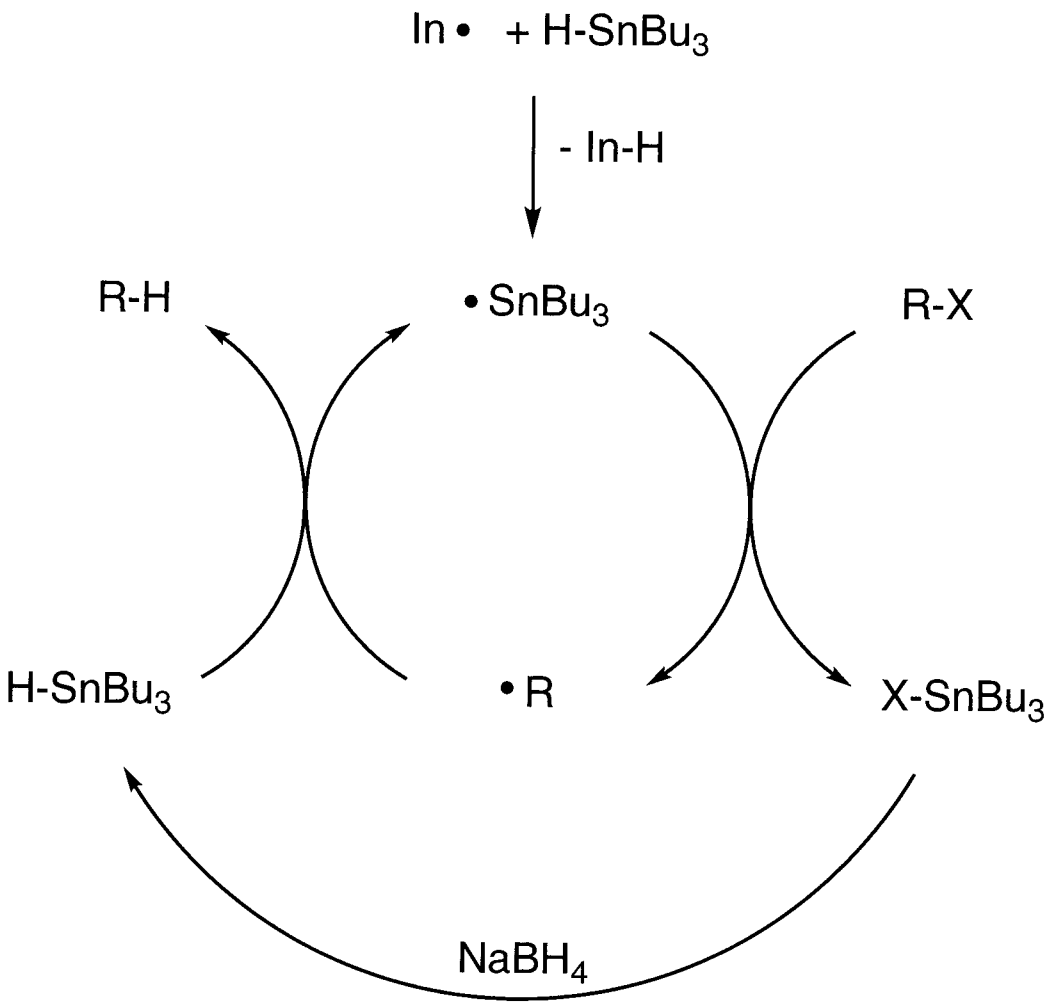


R^1 = alkyl, aryl, COR, CO_2R, CN, NO_2
R^2 = alkyl, aryl, OH, OR

Ⓐ outer sphere electron transfer

Ⓑ inner sphere electron transfer (ligand transfer)

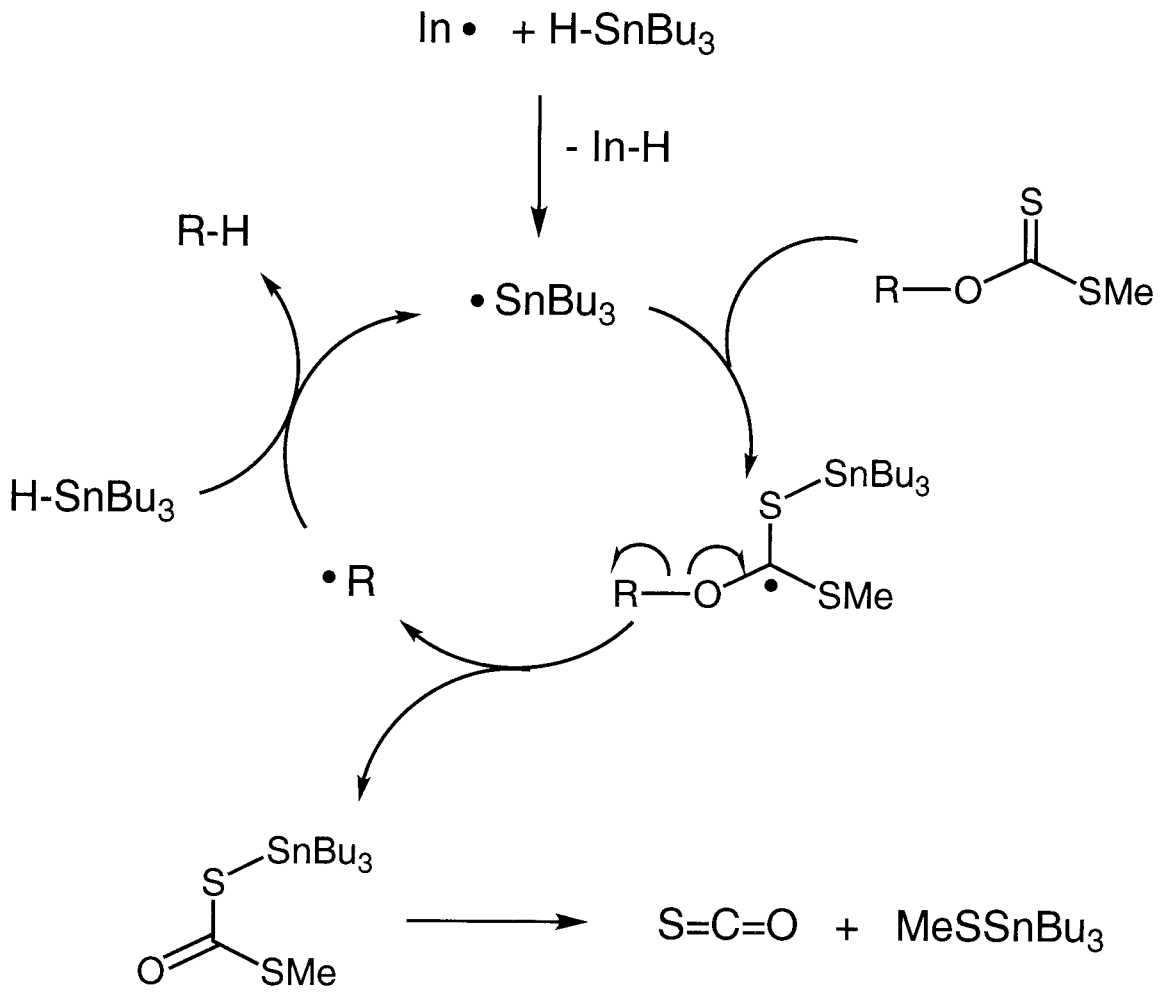
Radikalische Reduktionen mit Tri-*n*-butylstannan



X = I, Br, SePh, Cl, SPh

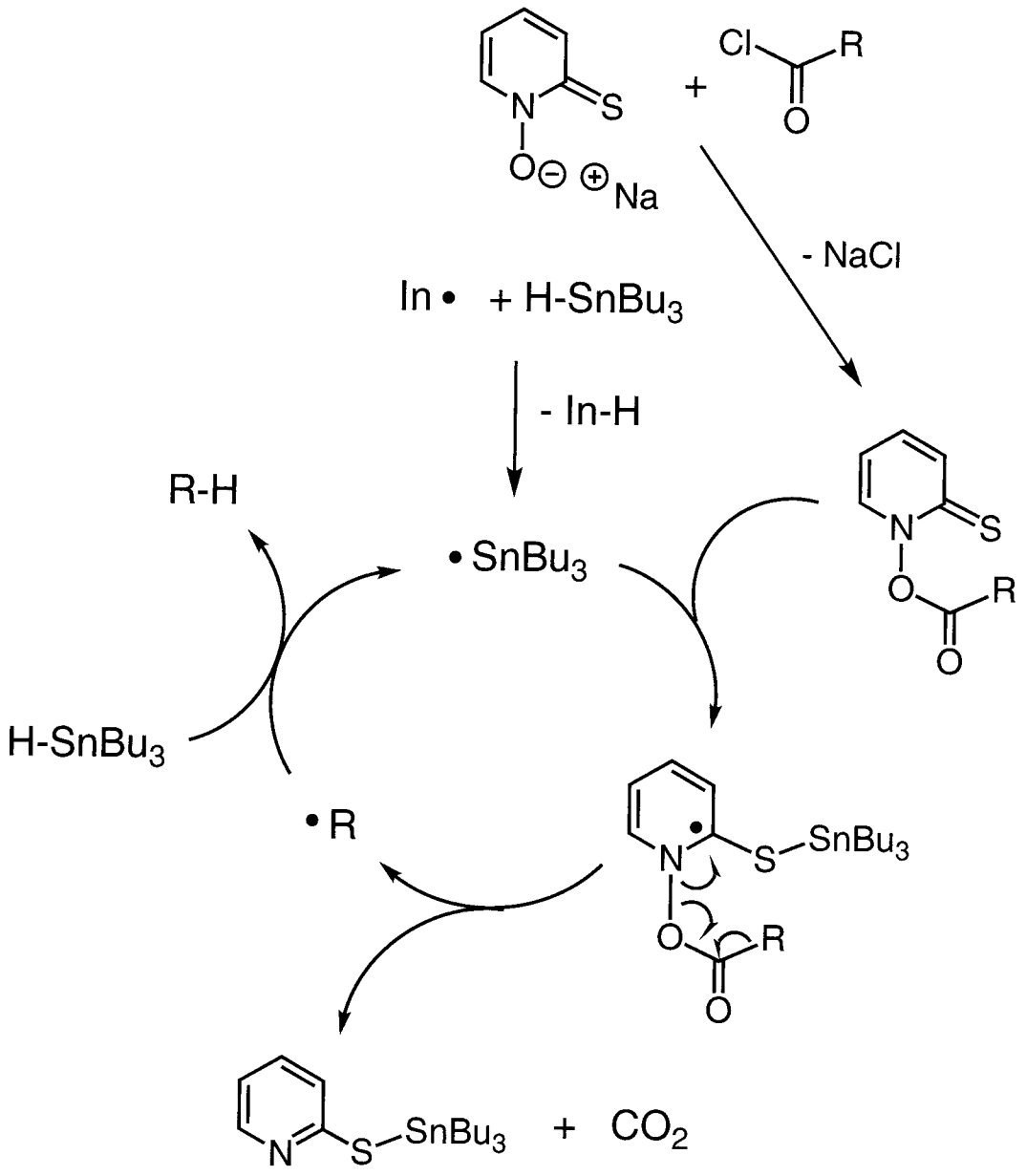
Mechanismus der Barton-McCombie-Reaktion

(*Chem. Rev.* **1989**, *89*, 1413-1432.)

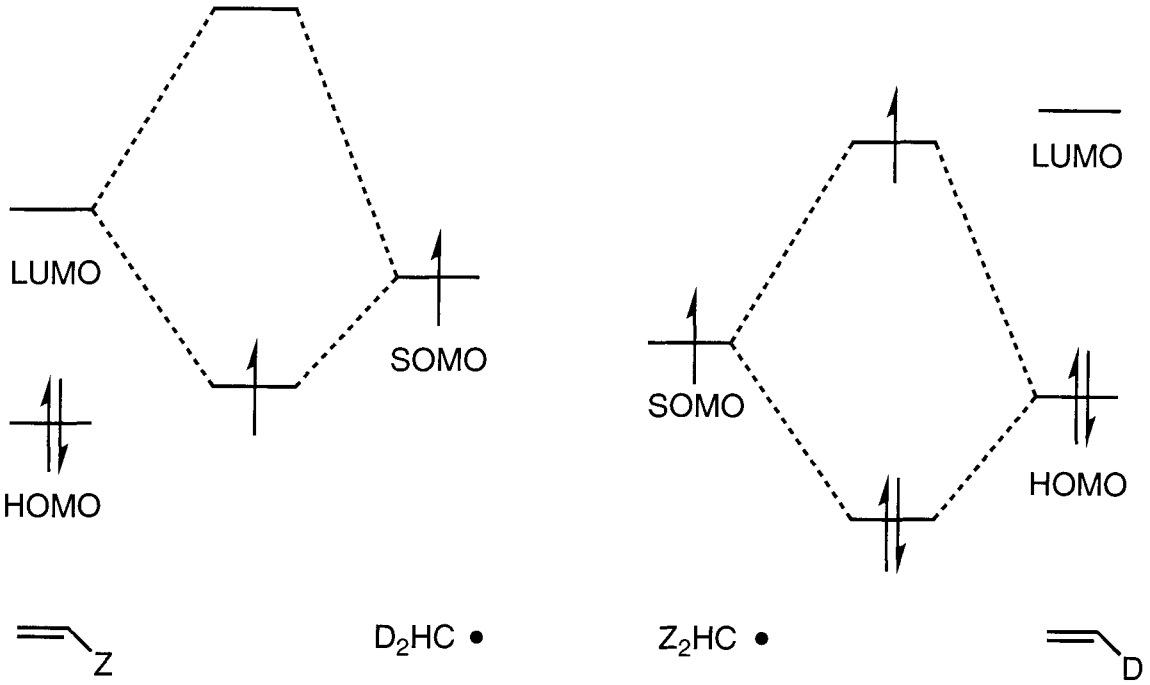


Mechanismus der Barton-Reaktion

(*Tetrahedron* **1985**, *41*, 3901-3924.)

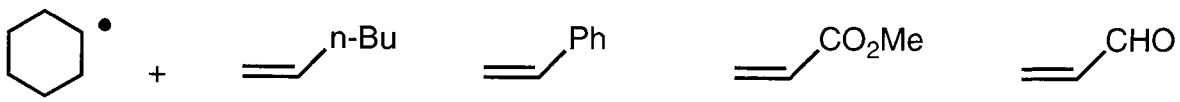


Orbitalbild intermolekularer Additionen an Alkene



Z = Elektronenakzeptor
D = Elektronendonor

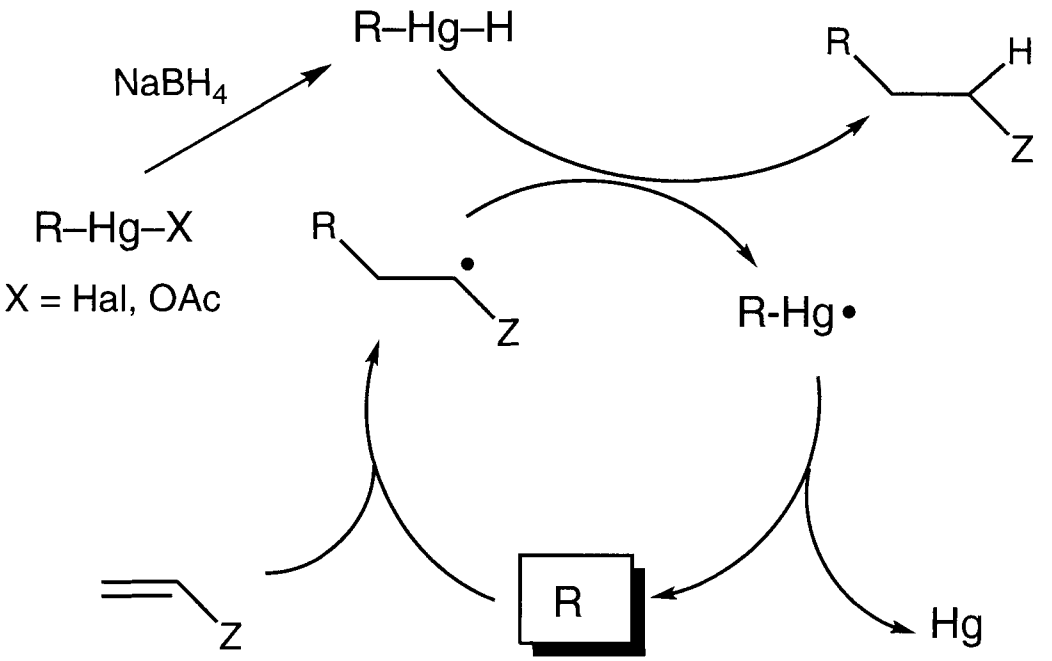
Relative Geschwindigkeiten der Additionen an Alkene



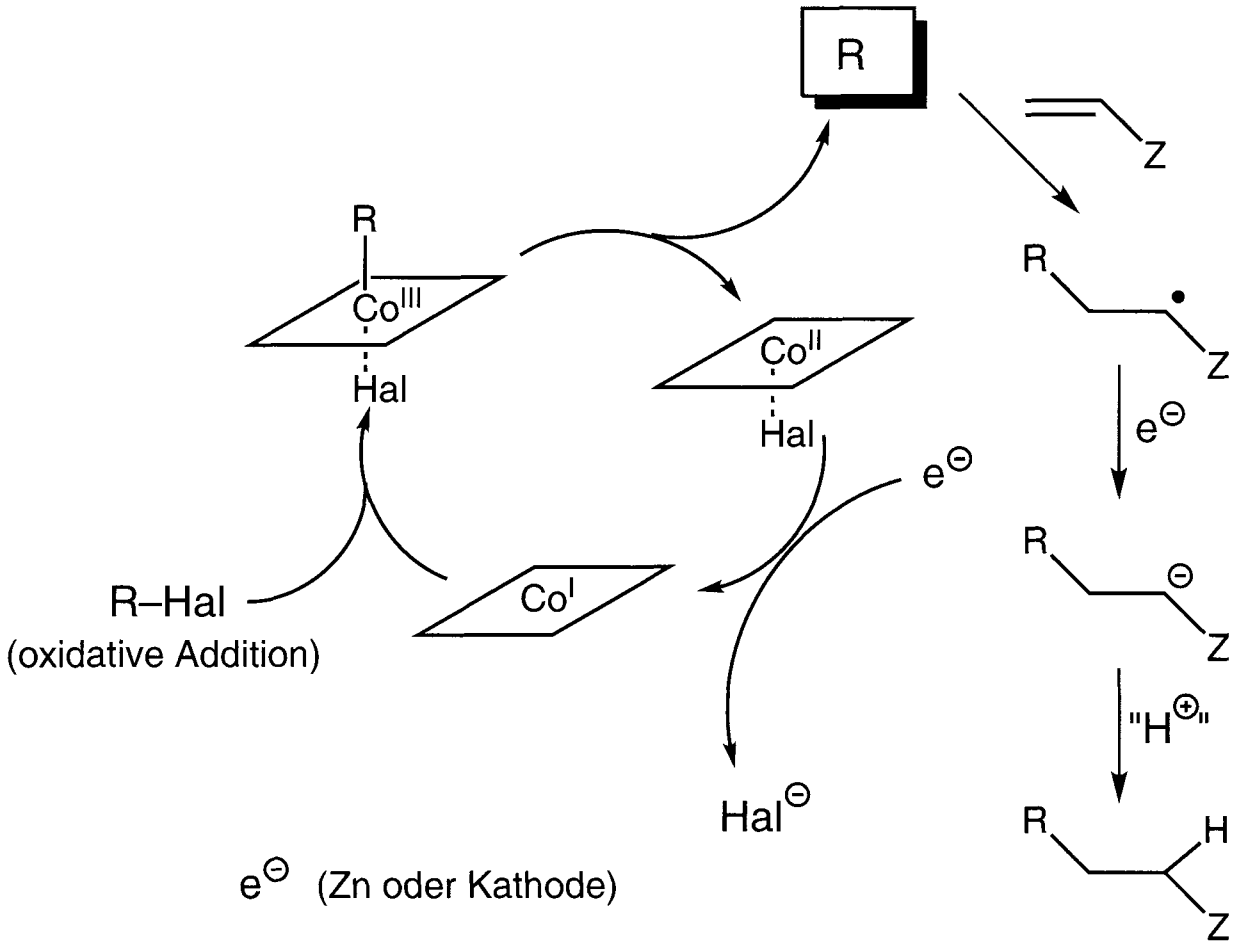
k_{rel} = 1.0 84 3000 8500

k_{rel} = 1.0 3.5 23

Die "Quecksilber-Methode"

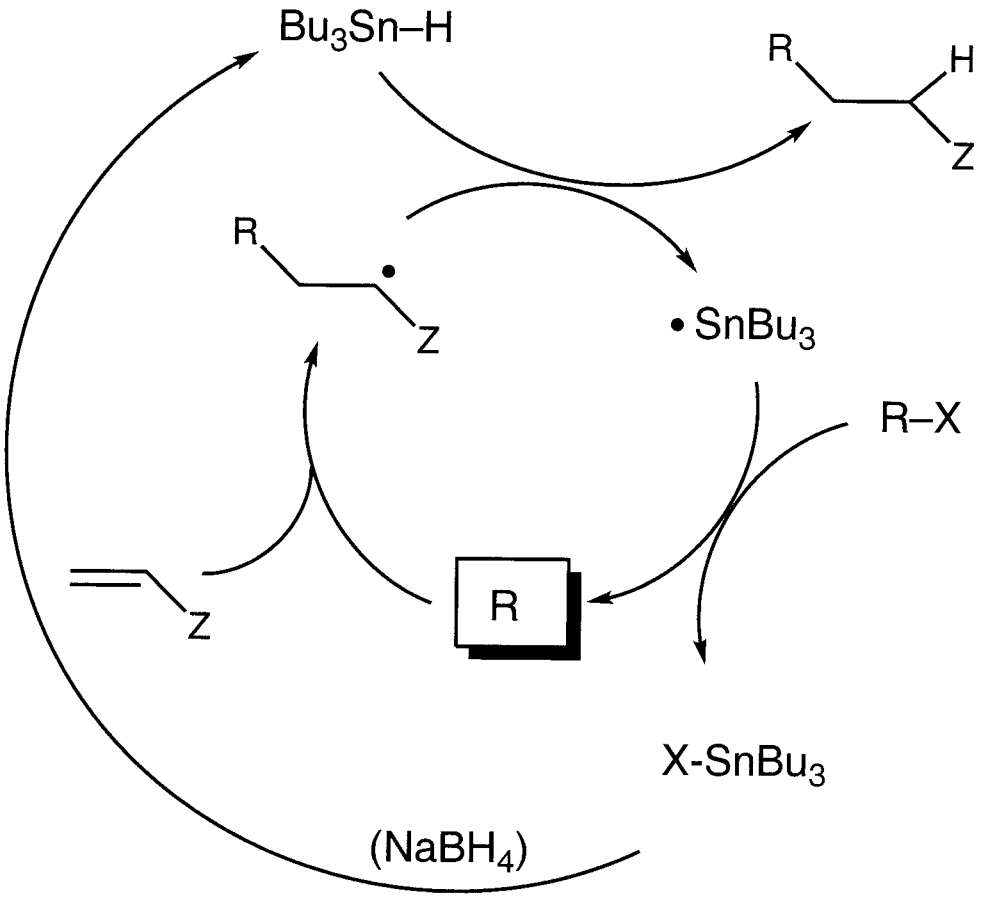


Die "Cobalt-Methode"



Die "Zinnhydrid-Methode" (Giese-Reaktion)

(*Angew. Chem.* **1985**, *97*, 555-567; *Chem. Rev.* **1991**, *91*, 1237-1286.)



X = I, Br, SePh, Cl, SPh

$(Me_3Si)_3Si–H$ als ungiftiger Ersatz für $Bu_3Sn–H$

(*Acc. Chem. Res.* **1992**, *25*, 188-194.)