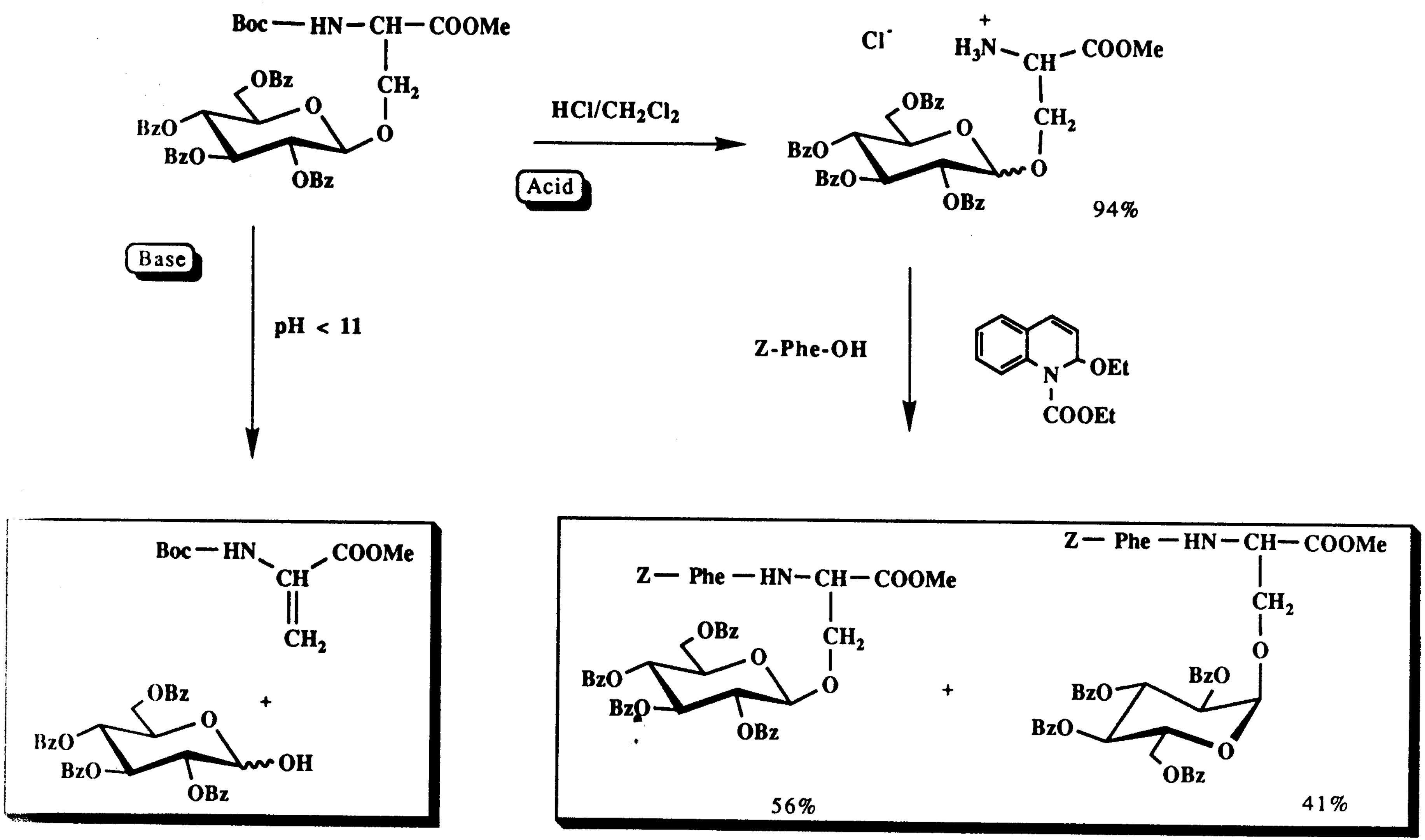
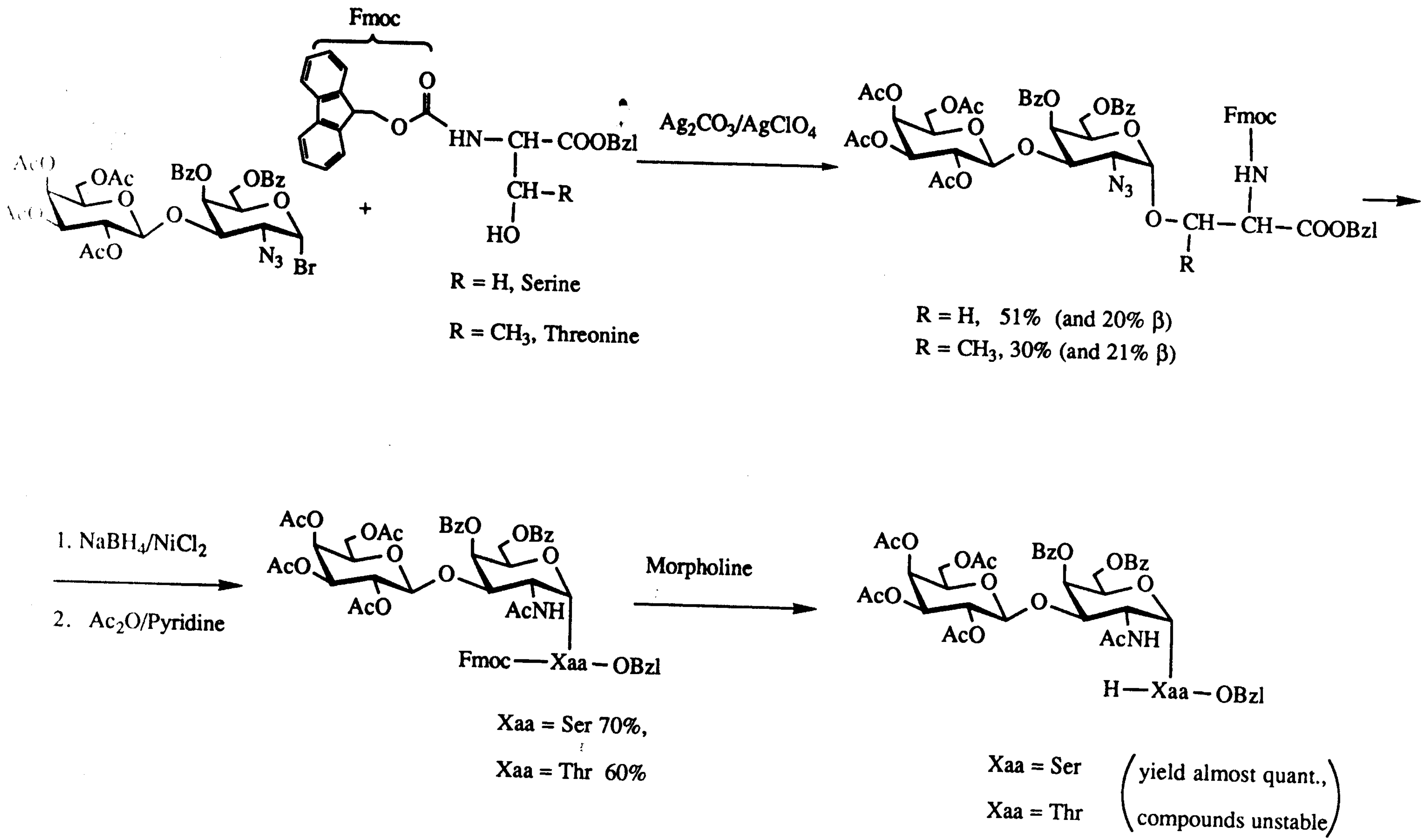
Problems of the Synthesis of Glycopeptides - The Lability of the Glycoside Linkages



Michael Buchholz 1981

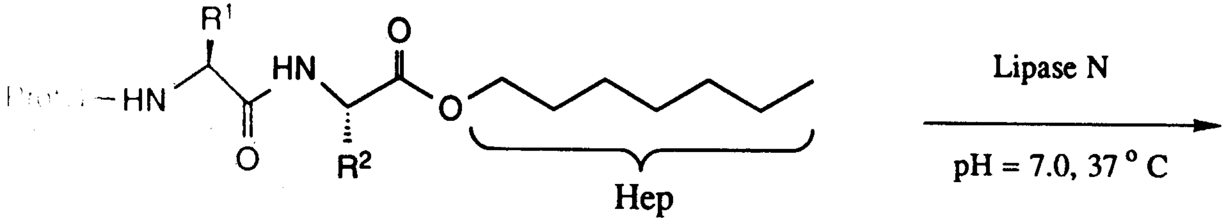
Synthesis of T Antigen -Serine- and -Threonine Derivatives (Tumor Associated O-Glycoprotein Structures)

Using the Fmoc-/Benzyl Ester Technique (P. Schultheiss-Reimann, H. Kunz, Angew. Chem. 1983)



Stefan Birnbach 1985

Enzymatic Removal of the Heptyl Ester Catalyzed by Lipase as a Mild Method of Carboxy Deprotection

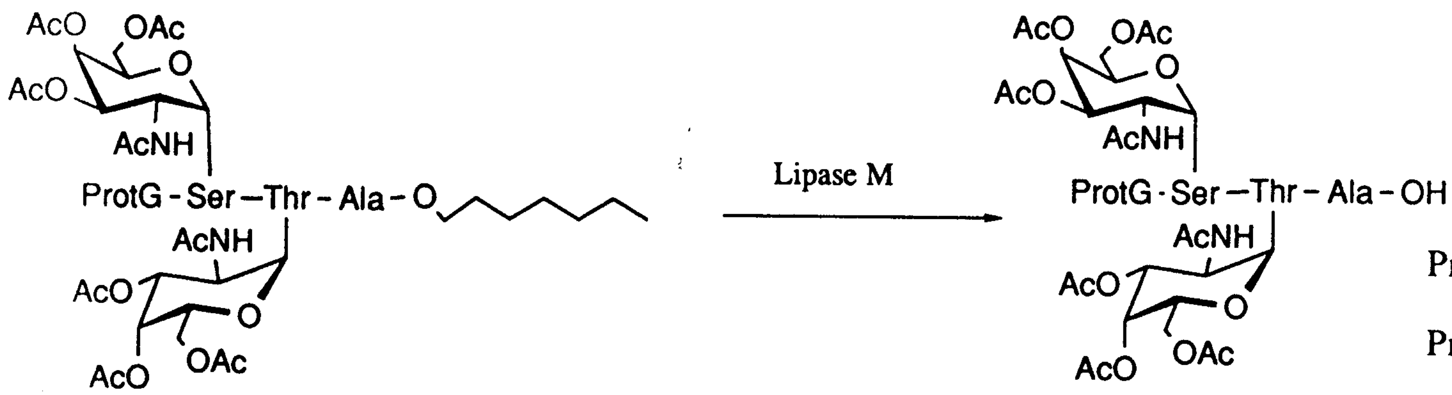


PG_N-Xaa_1-Xaa_2-OH

Boc-Val-Ala-OH	96%
Boc-Val-Leu-OH	50%
Boc-Val-Phe-OH	--
Aloc-Met-Gly-OH	90%
Z-Phe-Ser-OH	63%
Boc-Thr-Pro-OH	--

Herbert Waldmann et al., Liebigs Ann. *1991*, 165

Application of Lipase-catalyzed Cleavage of Heptyl Esters to Glycopeptide Synthesis

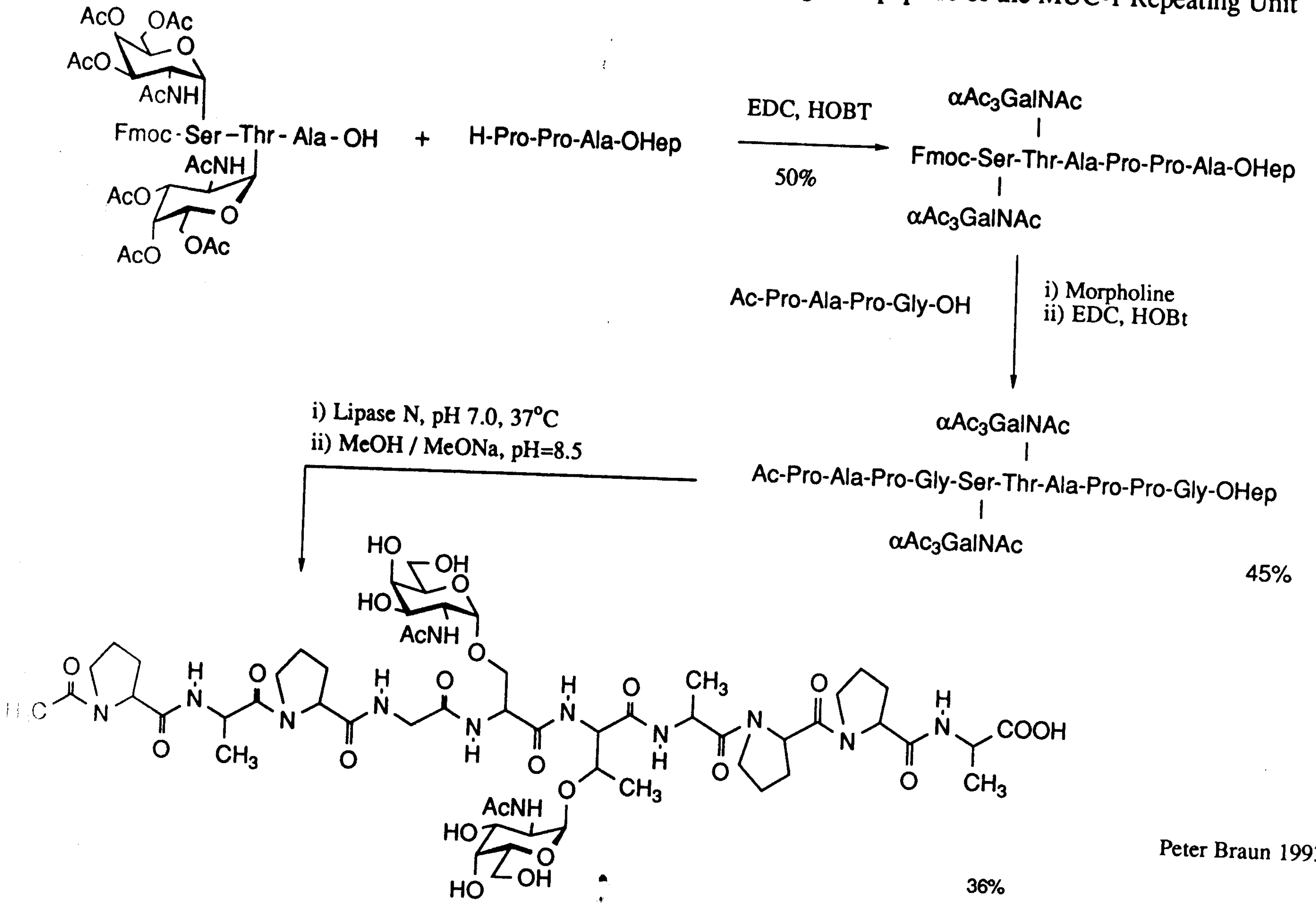


ProtG = Z 76%

ProtG = Fmoc 31%

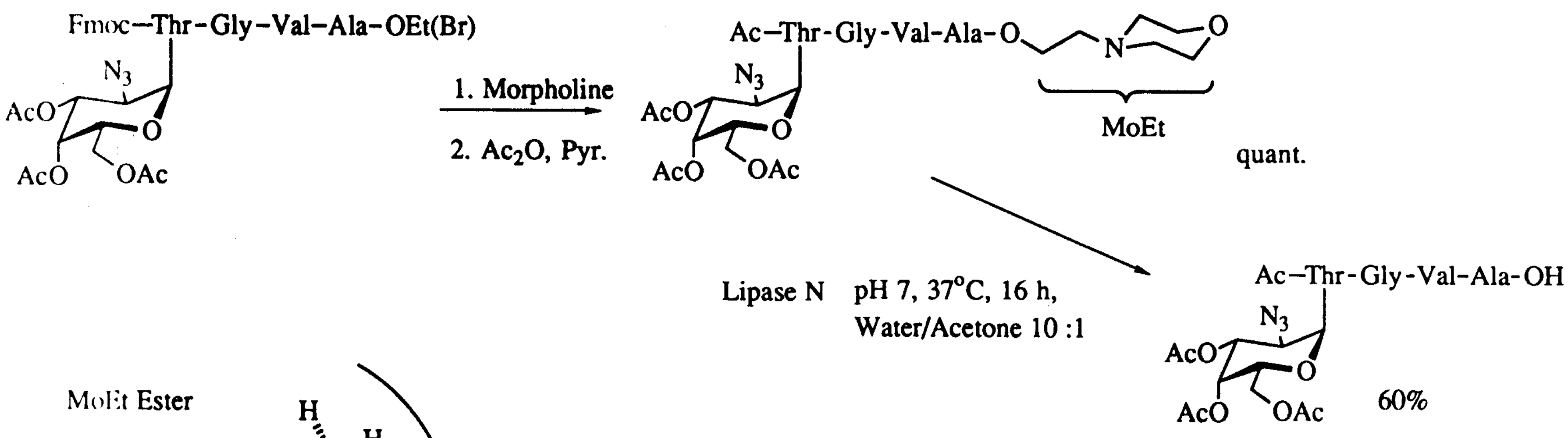
Peter Braun 1993

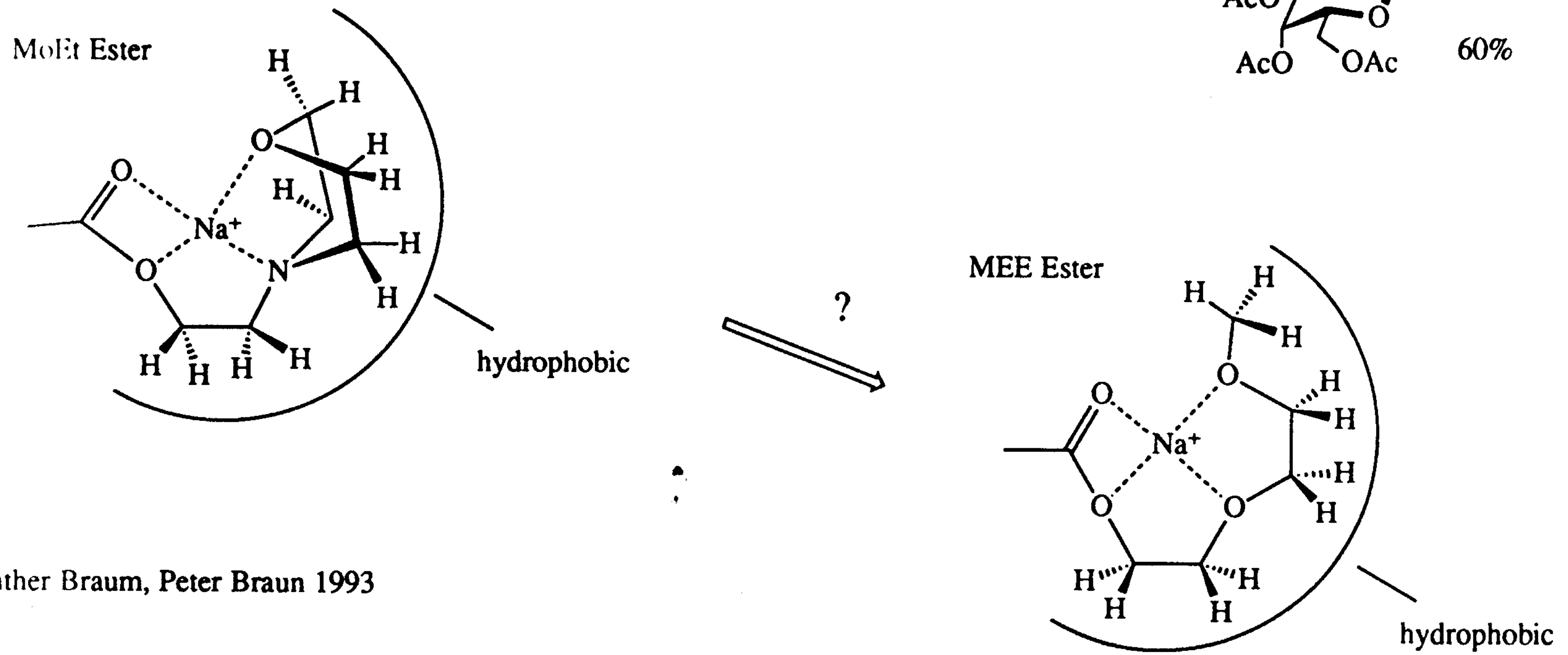
The Heptyl Ester in the Synthesis of a T_N Antigen Bearing Decapeptide of the MUC-1 Repeating Unit



Peter Braun 1993

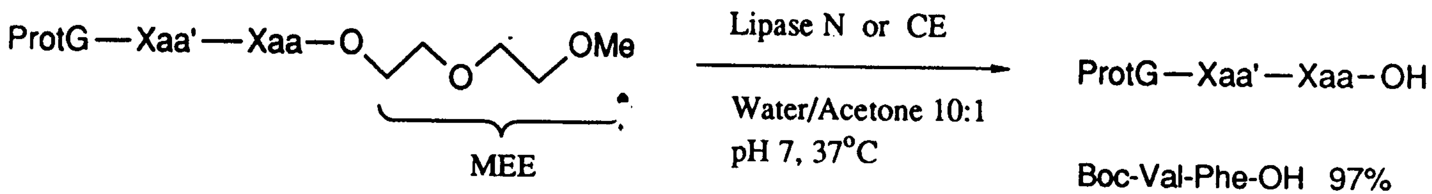
Morpholino-ethyl Esters - Polar Esters which are Surprisingly Cleavable by Lipases





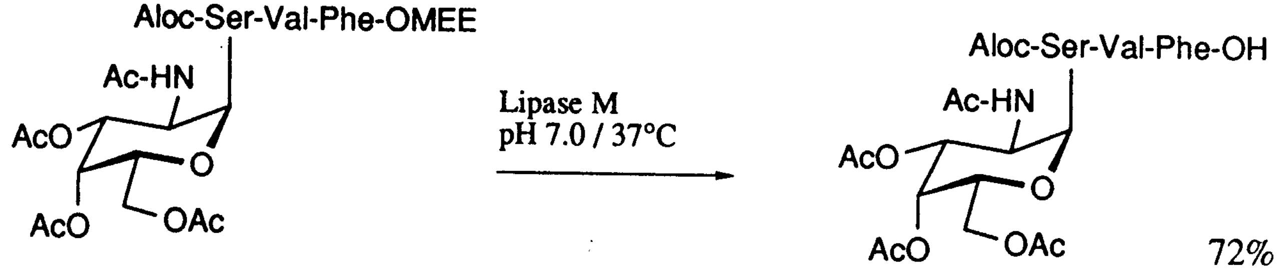
Günther Braum, Peter Braun 1993

Lipase-catalyzed Hydrolysis of Oligoethylene Glycol Esters in Peptide and Glycopeptide Synthesis



Boc-Val-Phe-OH 97%
Boc-Ser-Phe-OH 94%
Tcoc-Ala-Ser-OH 92%

Lipase CE
Z-Ala-Pro-OH 31%

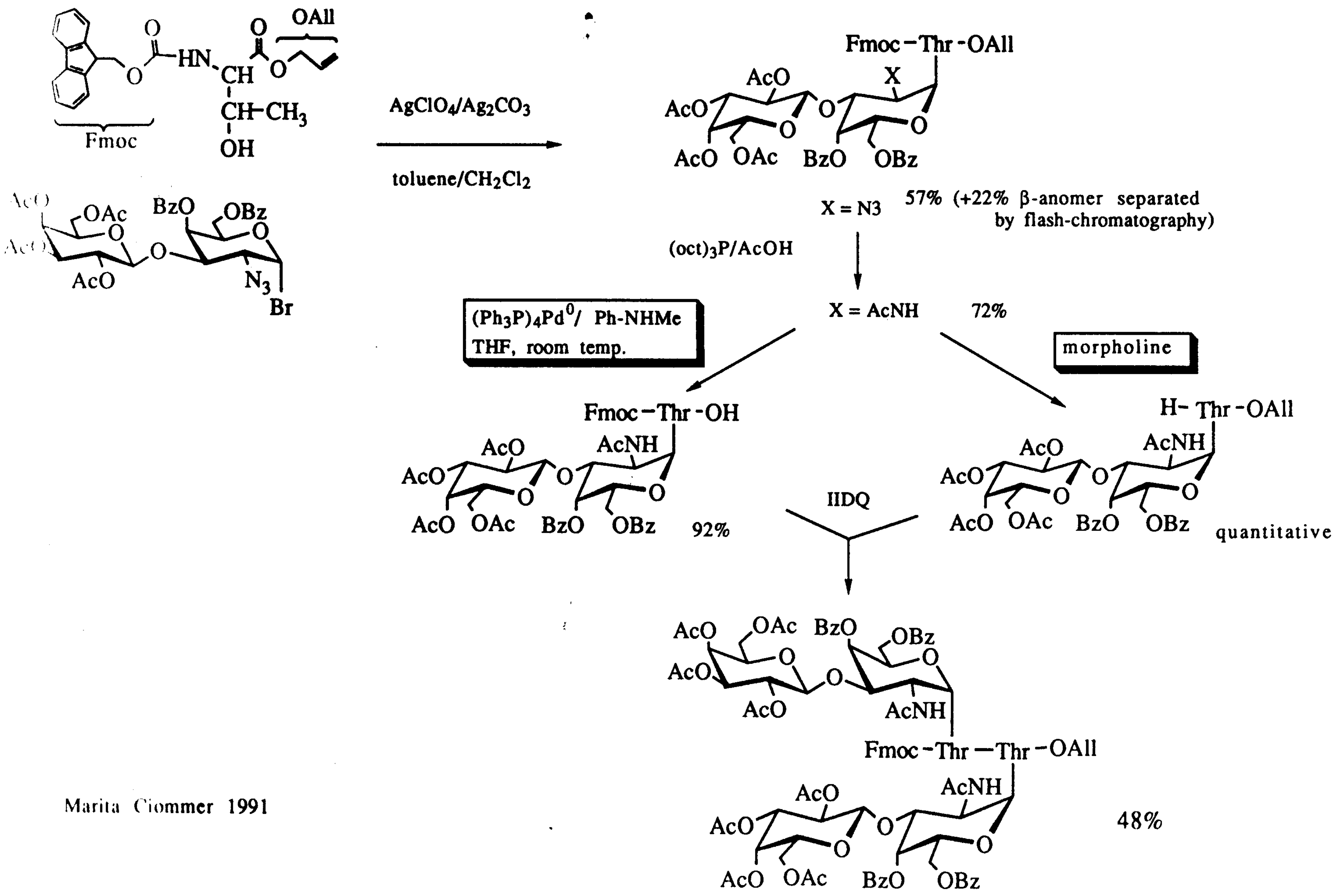


Fmoc-Phe-Ala—Val—OPEG $\xrightarrow[\text{pH 7.0 / 37°C}]{\text{Lipase N}}$ Fmoc-Phe-Ala—Val—OH 77%

PEG Polyethylene Glycol

Peter Braun, Danuta Kowalczyk 1994

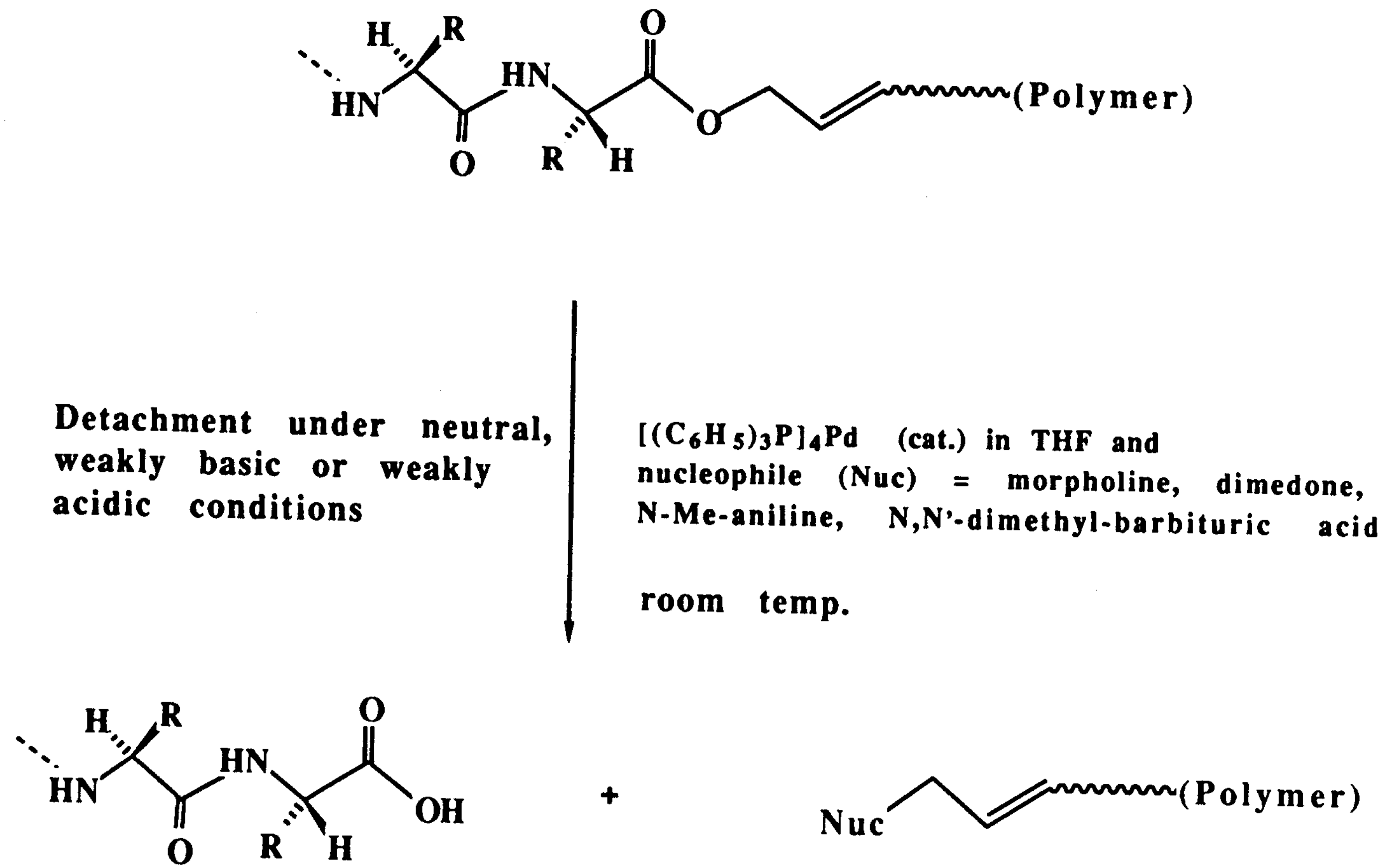
T Antigen Glycopeptides Using the Fmoc/OAll Technique



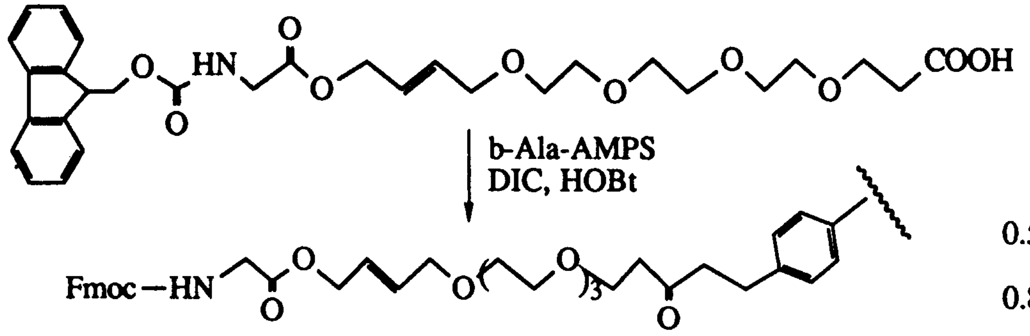
Marita Ciommer 1991

Principle of Solid-Phase-Peptide-Synthesis Using Allylic Anchoring Groups

H. Kunz, B.Dombo, Ger.Pat.Appl. 1987



Synthesis of Mucin Glycopeptides on Hydroxycrotonyl-12-oxy-trioxa-lauroylaminomethyl (HYCRON) Resin

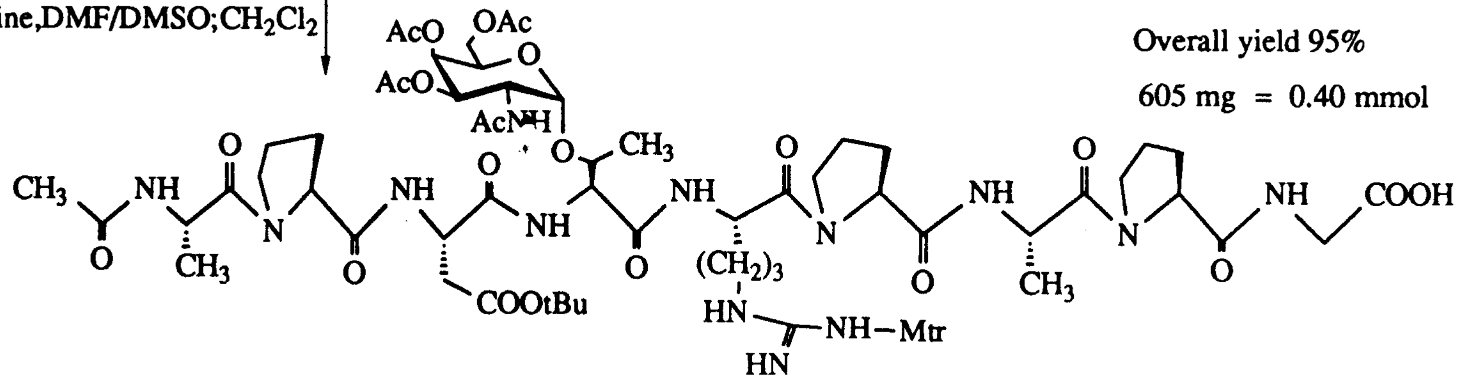


0.5 mmol Gly/ g Resin

0.85 Resin ≈ 0.42 mmol Gly

- DMF/Morpholine 1:1; 3eq Boc-Pro-OH, DIC, HOBt, DMF; Ac_2O/Pyridine
- CH_2Cl_2/TFA; Hünig Base; 4 eq Fmoc-Ala-OH, DIC,HOBt, DMF; Ac_2O
- DMF/Morpholine 1:1; 3eq Fmoc-Pro-OH, DIC, HOBt, DMF; Ac_2O/Pyridine
- DMF/Morpholine 1:1; 3eq FmocArg(Mtr)-OH, DIC, HOBt, DMF; Ac_2O/Pyridine
- DMF/Morpholine 1:1; 3eq Fmoc-Thr(Ac_3GalNAc)-OH, TBTU, HOBt, N-MeMorpholine, DMF; Ac_2O/Pyridine
- DMF/Morpholine 1:1; 3eq Fmoc-Asp(tBu)-OH, TBTU, HOBt, N-MeMorpholine, DMF; Ac_2O/Pyridine
- DMF/Morpholine 1:1; 2 x 3eq Fmoc-Pro-OH, DIC, HOBt, DMF; Ac_2O/Pyridine
- DMF/Morpholine 1:1; 2 x 3eq Fmoc-Ala-OH, DIC, HOBt, DMF; Ac_2O/Pyridine
- DMF/Morpholine 1:1; Ac_2O/Pyridine

$[Ph_3P]_4Pd(0)$,Morpholine,DMF/DMSO;CH_2Cl_2

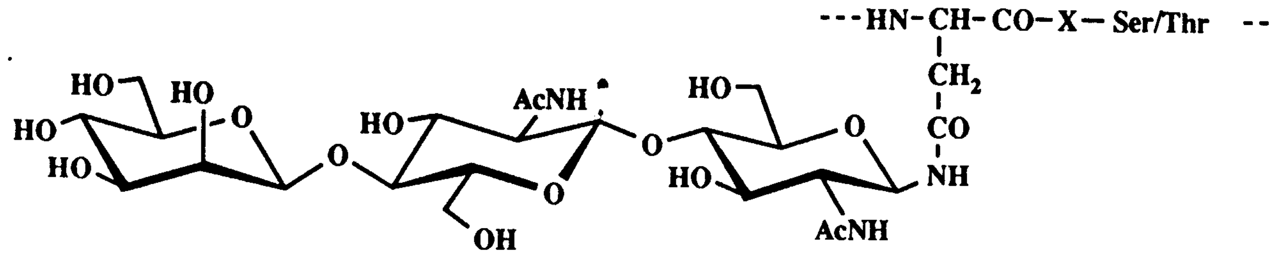


Overall yield 95%

605 mg = 0.40 mmol

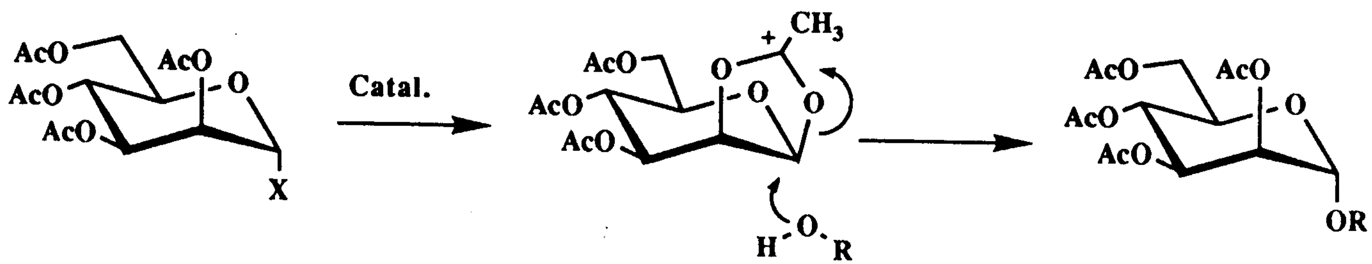
Oliver Seitz 1994

Core Trisaccharide Asparagine Linkage of N-Glycoproteins

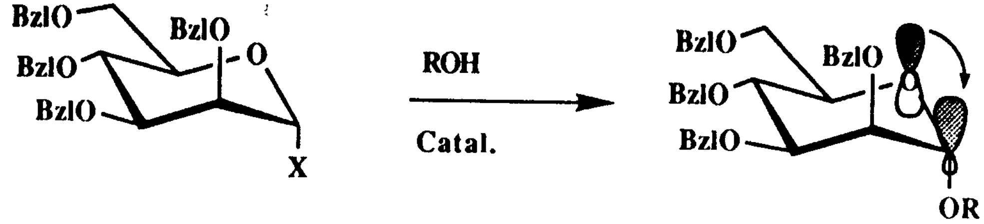


Problems of the β-Mannoside Synthesis:

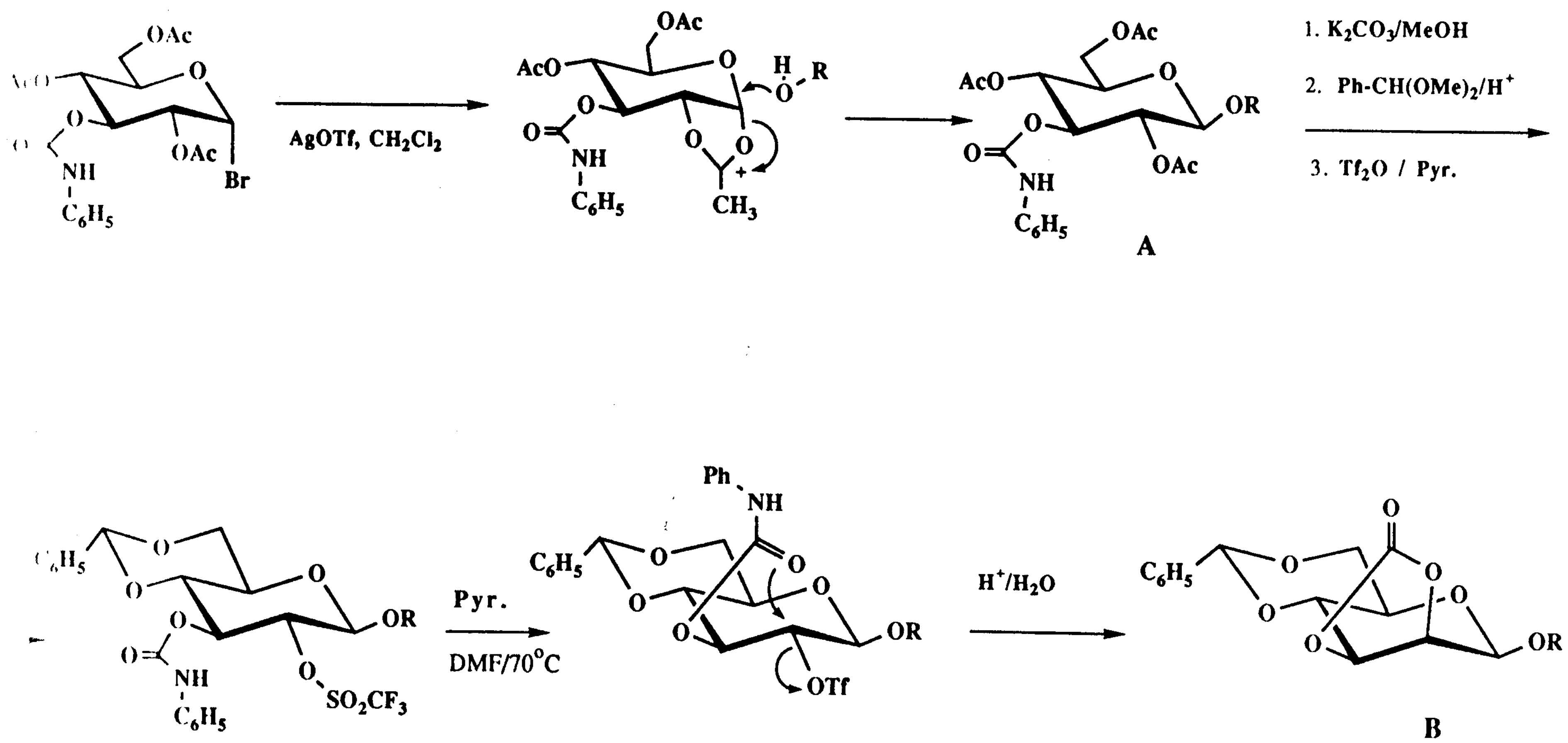
a) neighboring group participation prefers α-mannoside formation



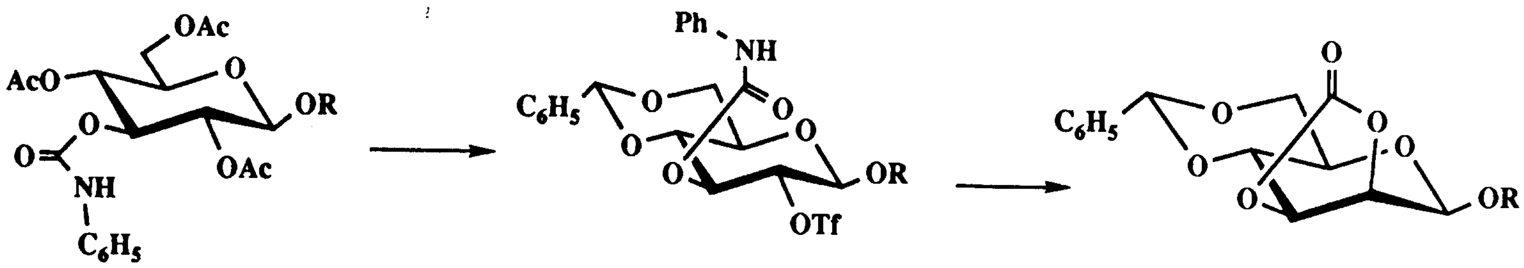
b) thermodynamic control (anomeric effect) also prefers α-mannoside formation

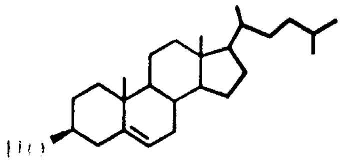
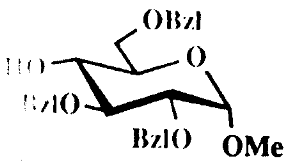
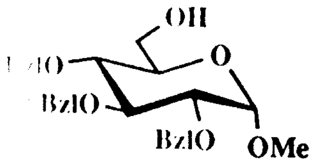
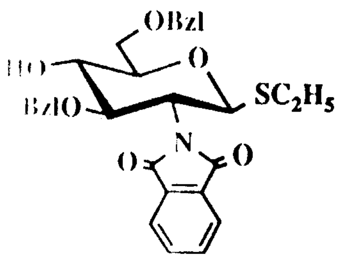


New Strategy for the Synthesis of β-Mannosides



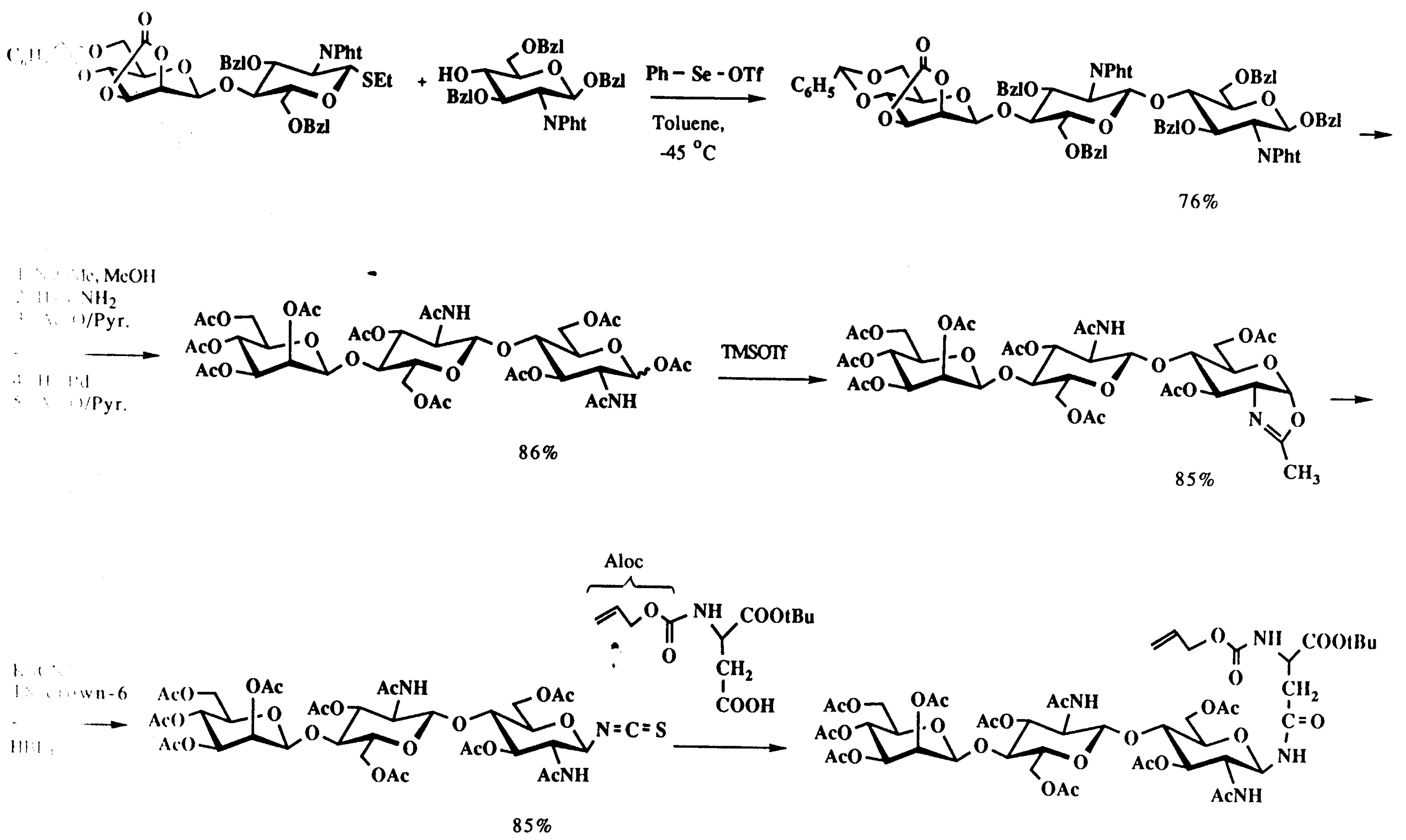
Synthesis of β-Mannosides via Inversion of Configuration at C-2 of β-Glucosides



R-OH			
	65%		65%
	67%		68%
	69%		66%
	>97%	(The only one transformation optimized so far)	96 %

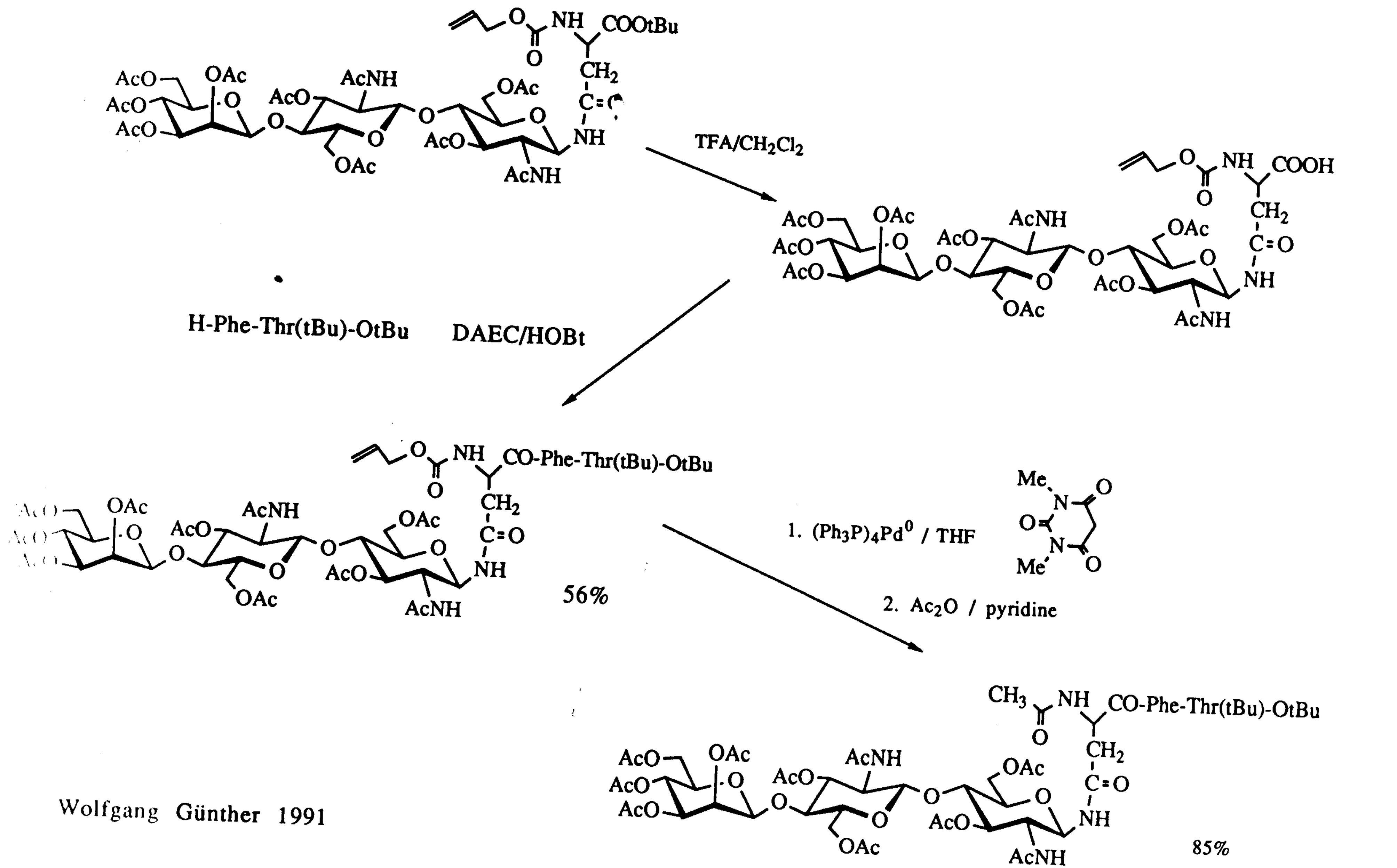
Wolfgang Günther 1989

Construction of the Core Region Trisaccharide Asparagine Conjugate of N-Glycoproteins



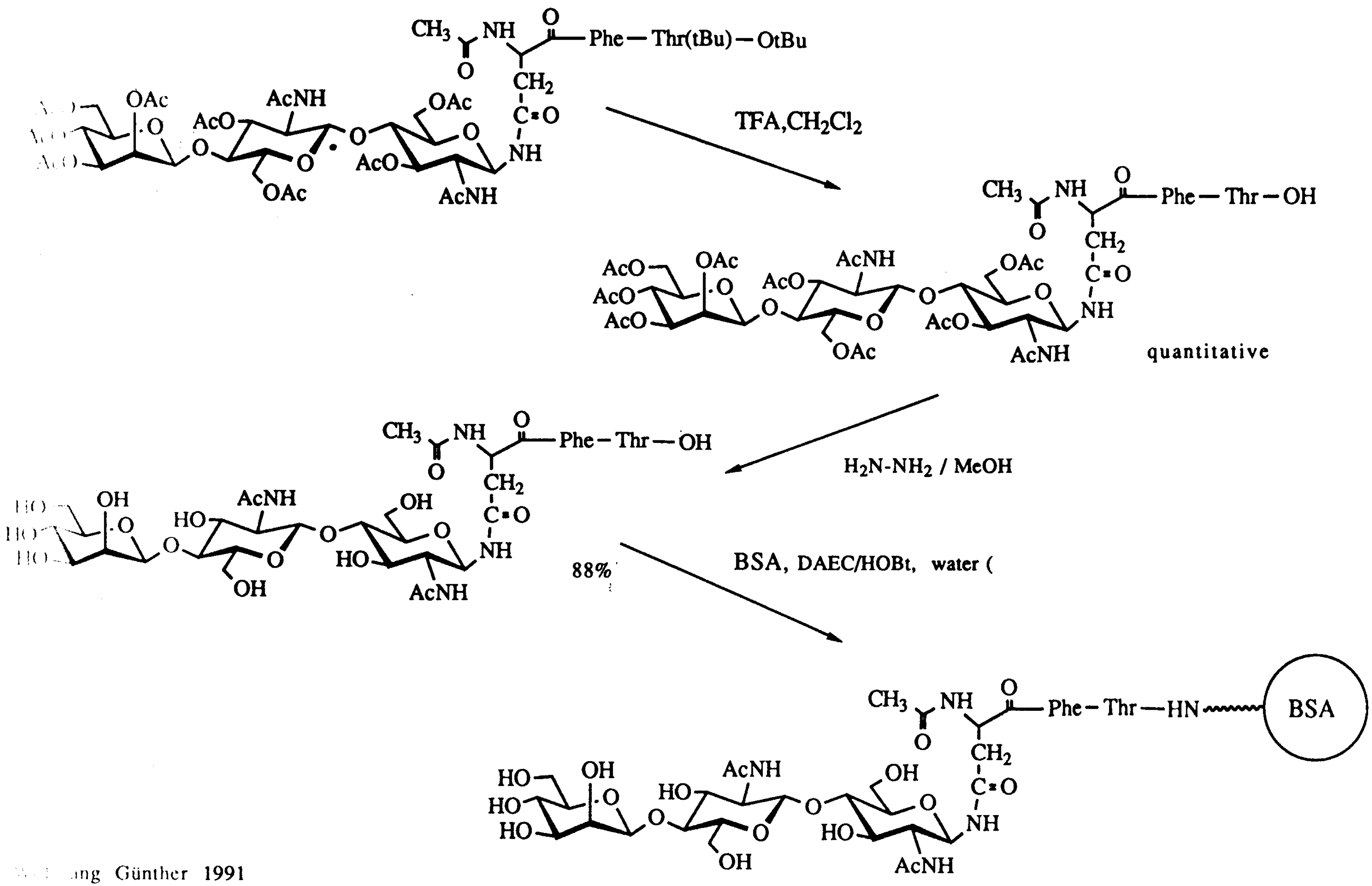
Wolfgang Günther 1990

Selective Deblocking of β-Mannosyl Chitobiosyl Asparagine Glycopeptides via Aloc/OtBu Methodology



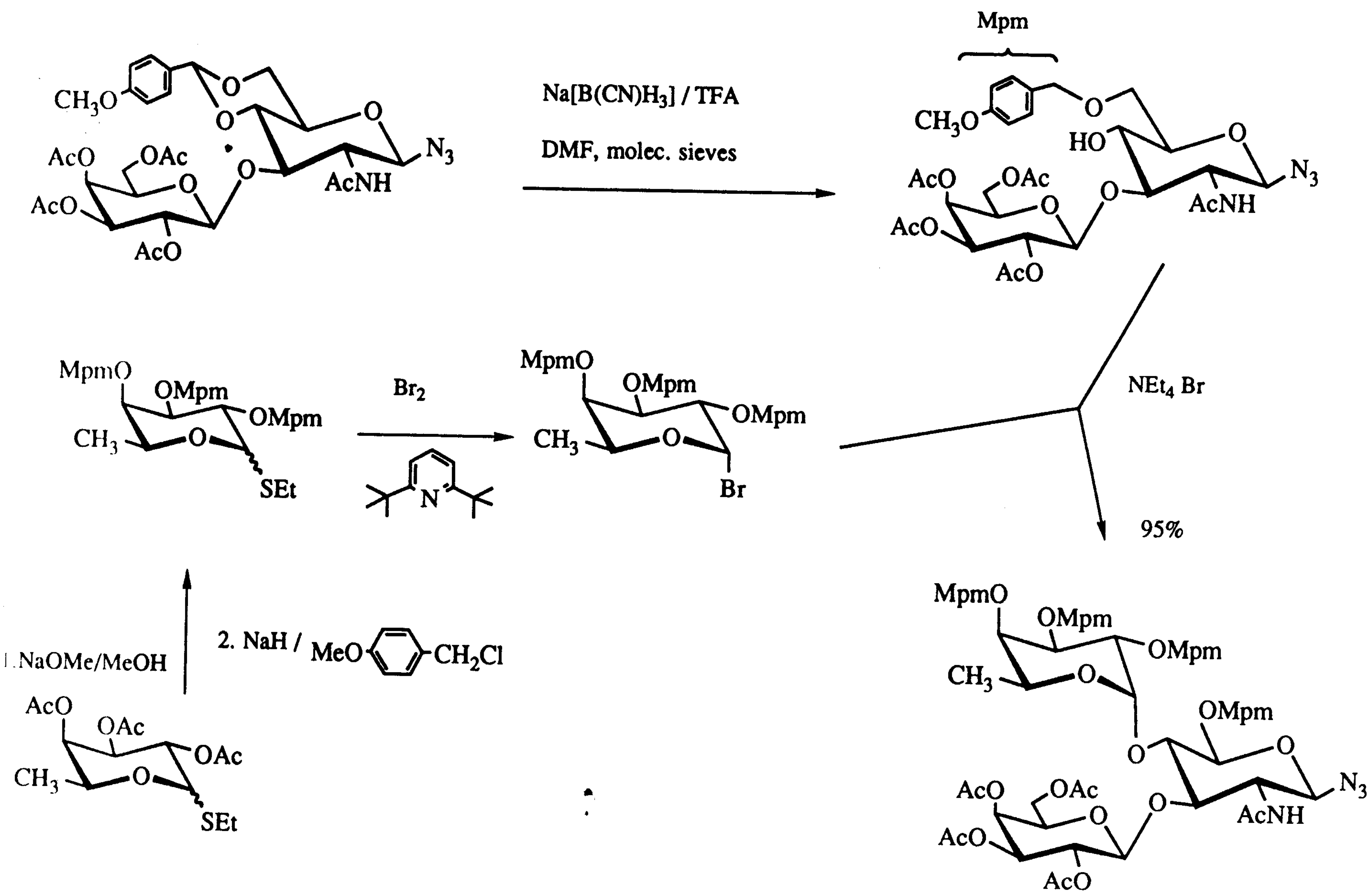
Wolfgang Günther 1991

Synthetic Glycoprotein with β-Mannosyl Chitobiose Core Region Structure

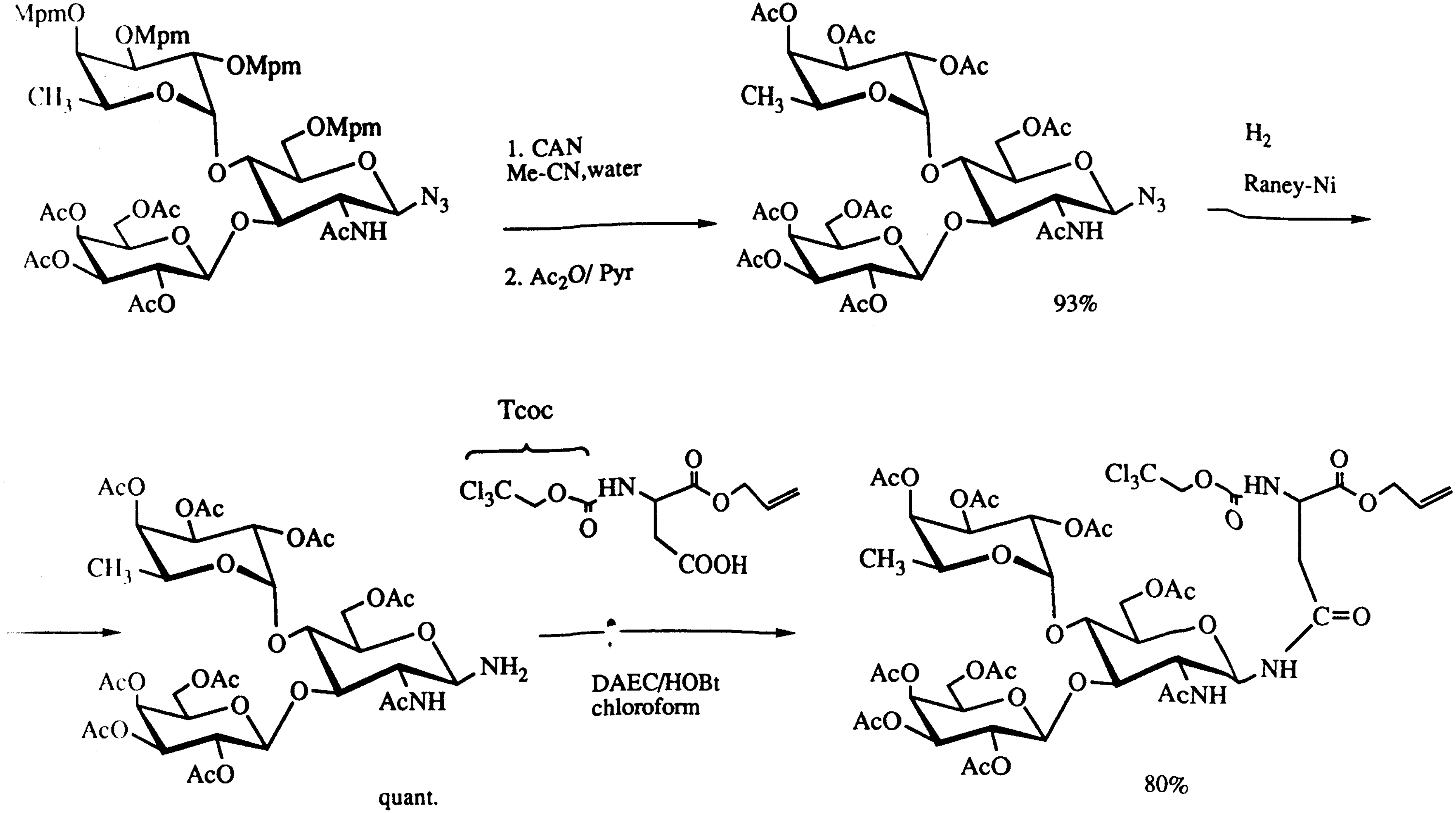


ang Günther 1991

Synthesis of Fucosyl Lactosamine Derivatives - Lewis Antigen Structures

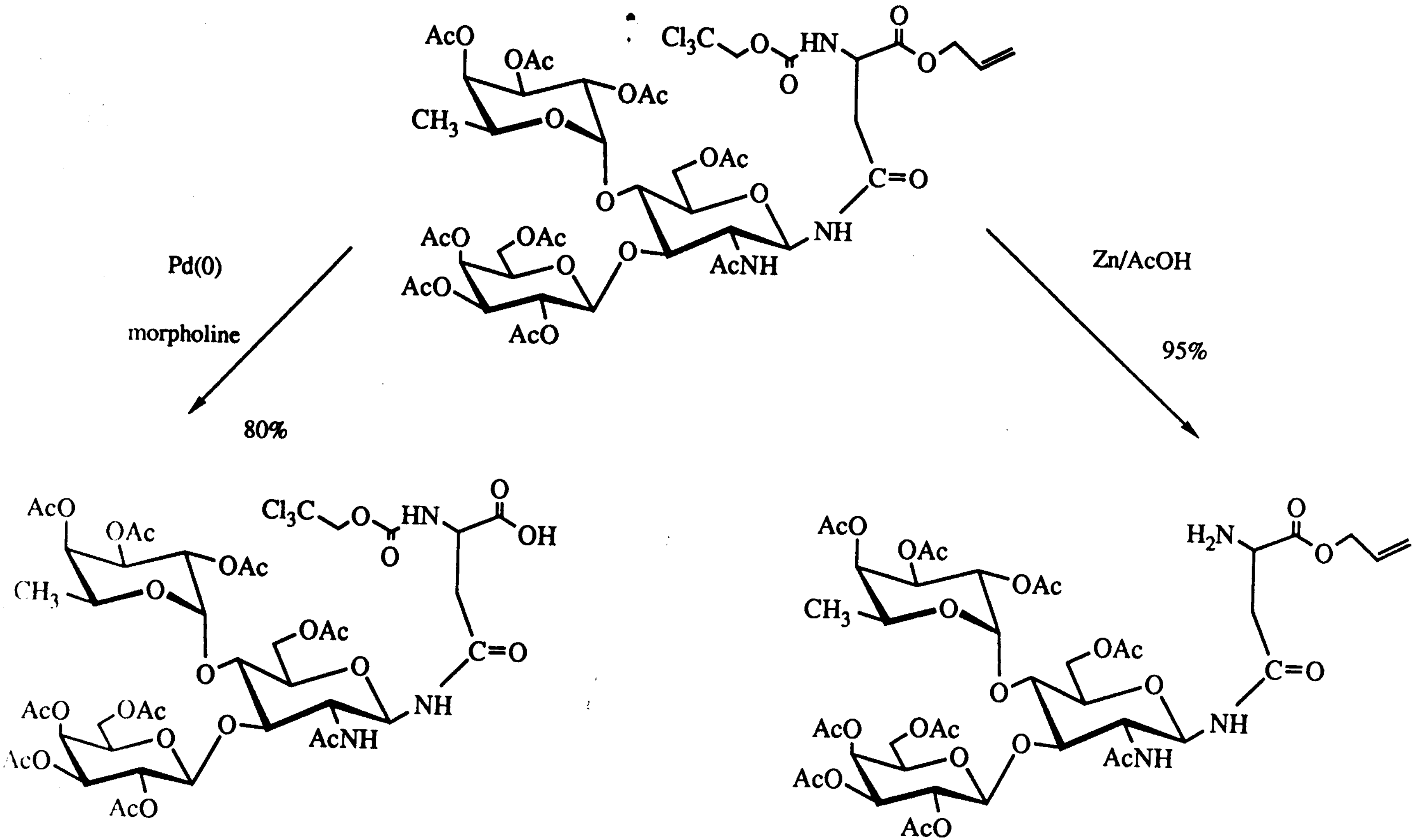


Synthesis of Fucosyl Lactosamine Conjugates with Asparagine



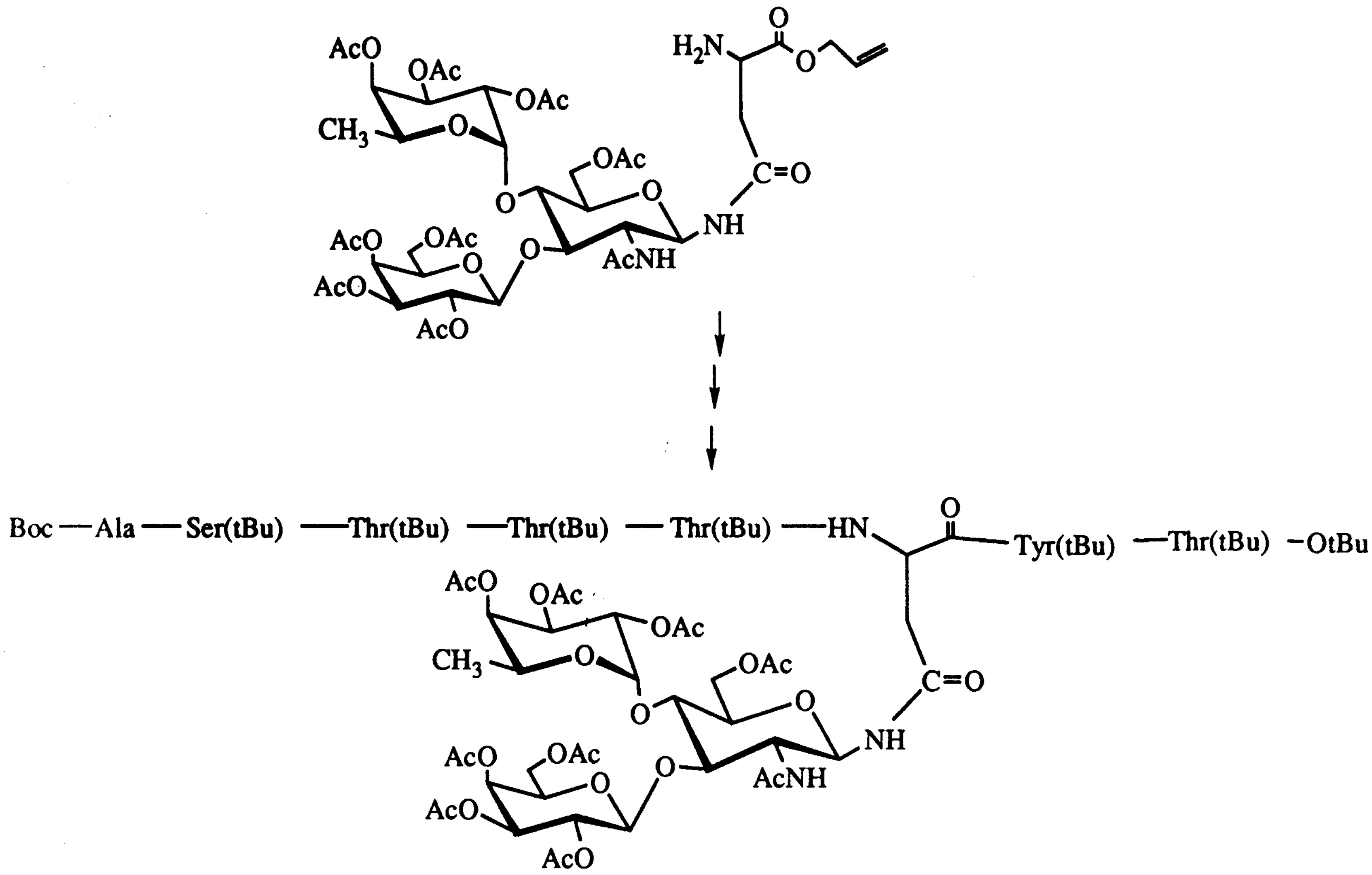
Joachim März 1991

Selective Deprotection of Fucosyl Lactosamine Asparagine Conjugates via Teoc/OAll Technique



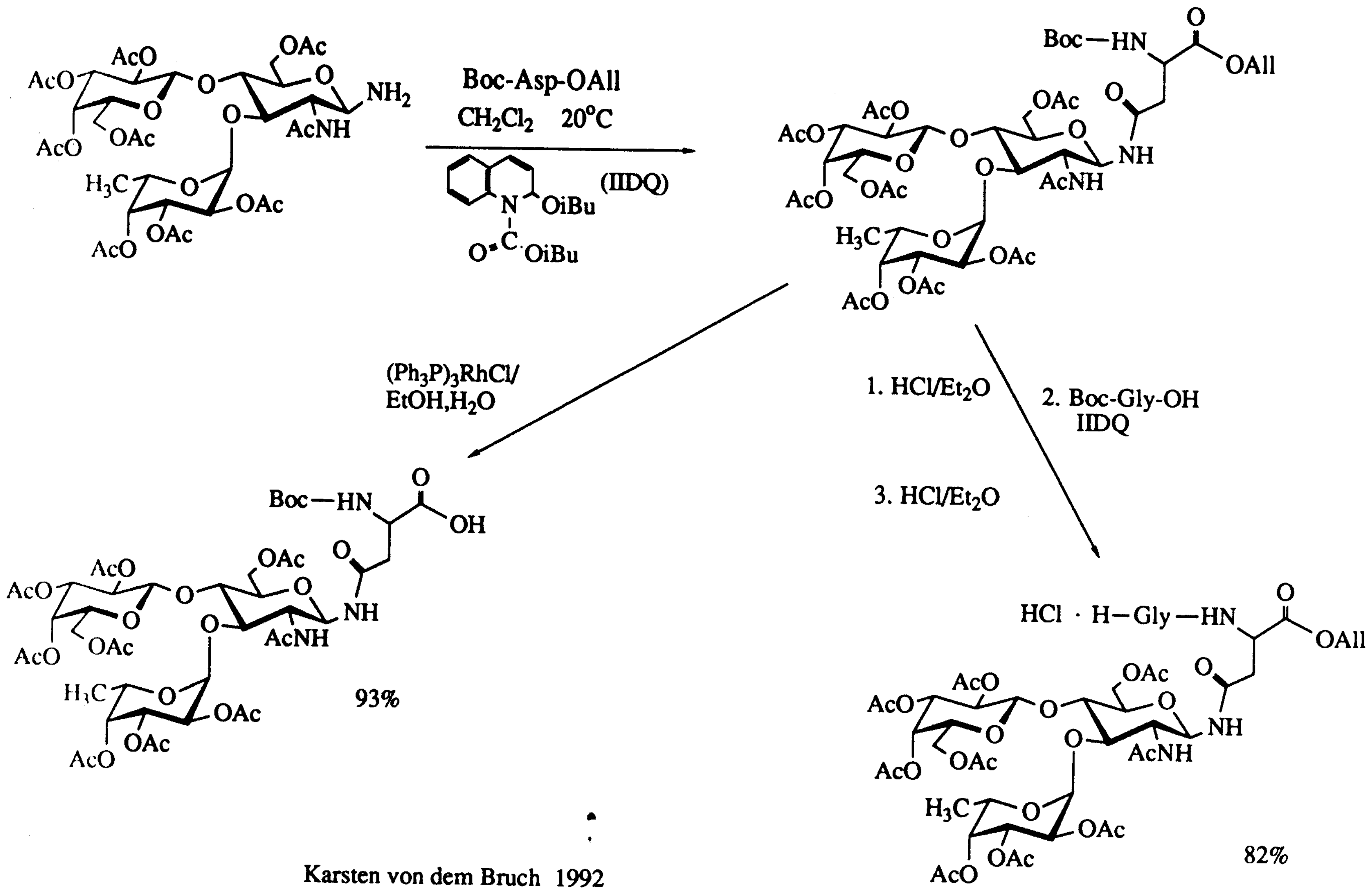
Joachim März 1991

Glycopeptide of Peptide T with Lewis[b] Antigen Side Chain



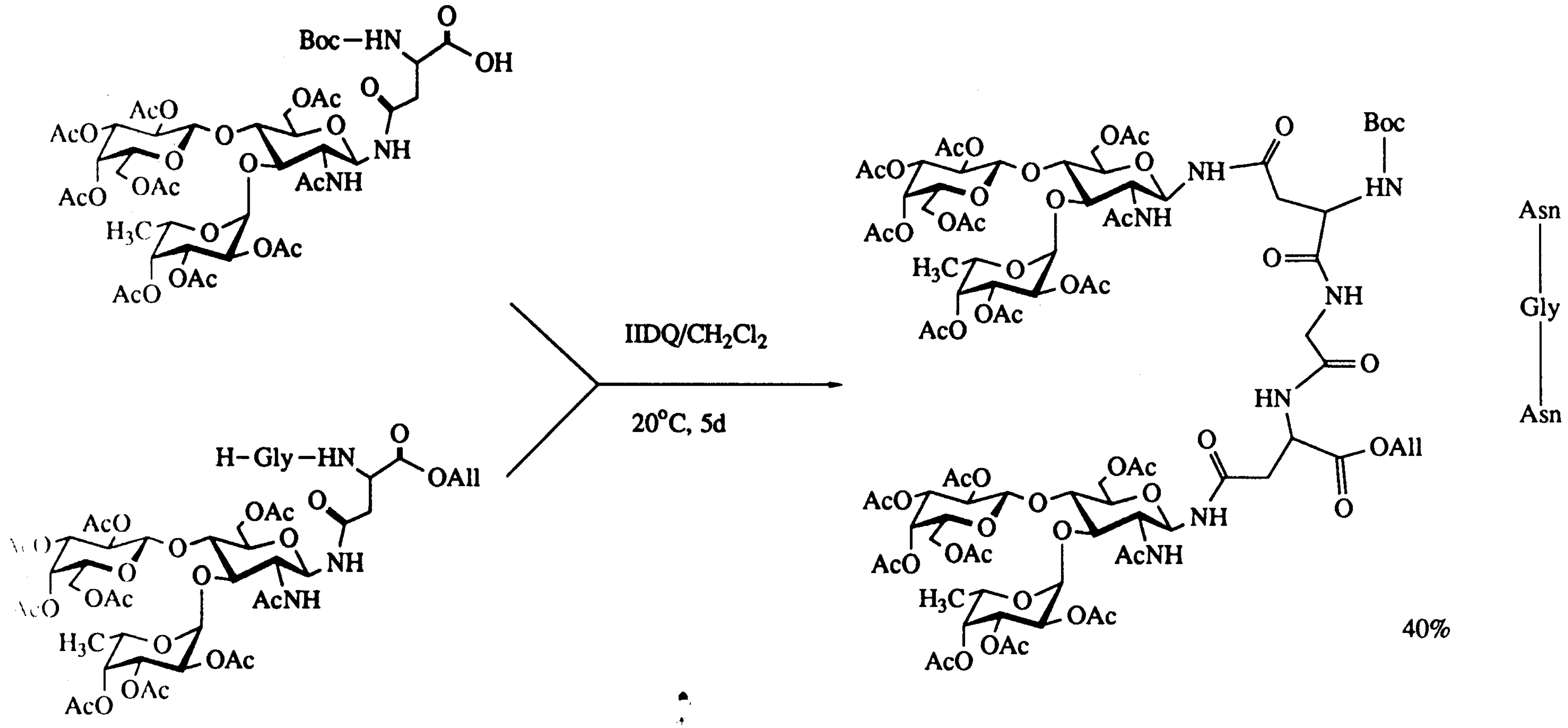
Joachim März 1991

Synthesis and Selective Deblocking of Le^x Asparagine Conjugates



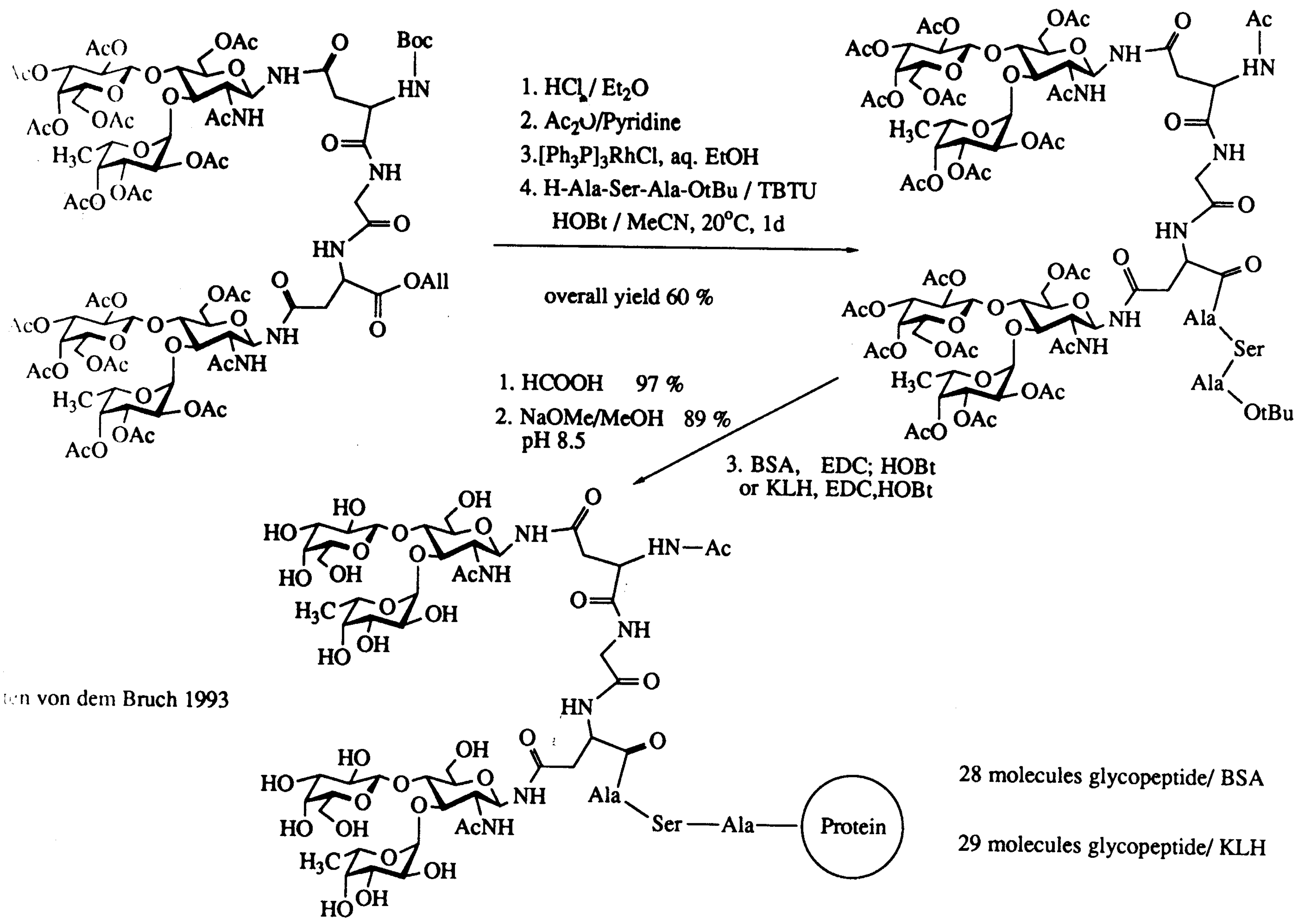
Karsten von dem Bruch 1992

Glycopeptides with Simulated Biantennary Le^x Antigen Structure



Karsten von dem Bruch 1992

Le^x Antigen Glycopeptides - Deprotection and Construction of Protein Conjugates - Synthetic Antigens

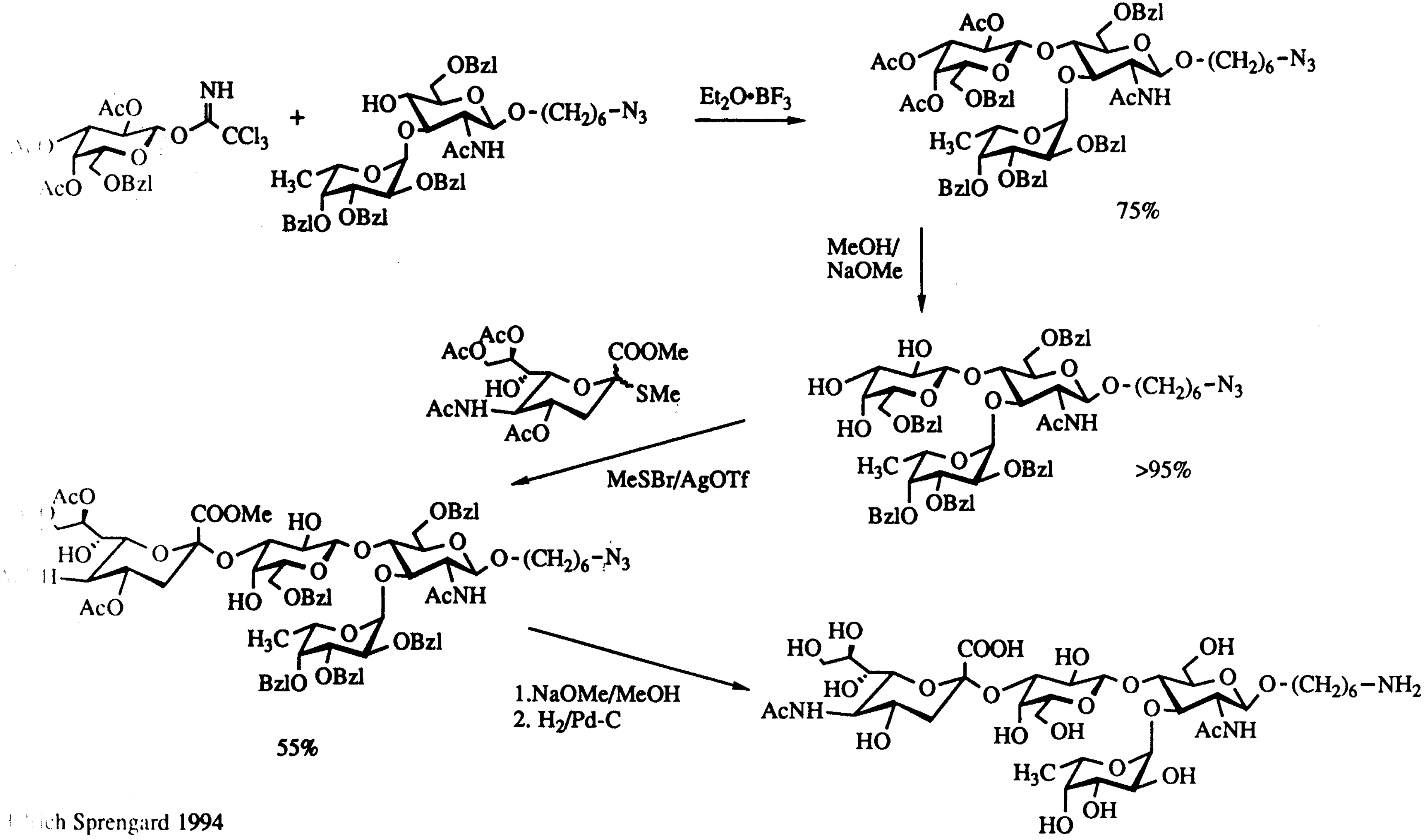


28 molecules glycopeptide/ BSA

29 molecules glycopeptide/ KLH

Ka[illegible]ten von dem Bruch 1993

Synthesis of a Sialyl-Le^x Saccharide Ligand



ich Sprengard 1994

W. Stahl, Dr. G. Kretzschmar, HOECHST AG