

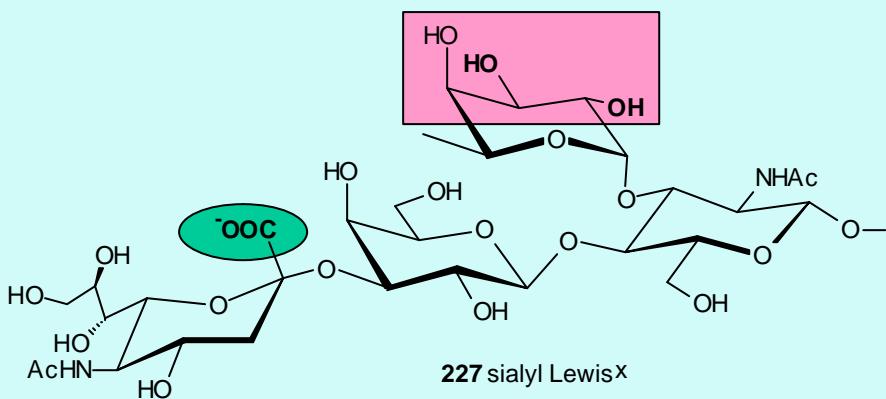


ISCHIA ADVANCED SCHOOL OF ORGANIC CHEMISTRY
September 21-26, 2002

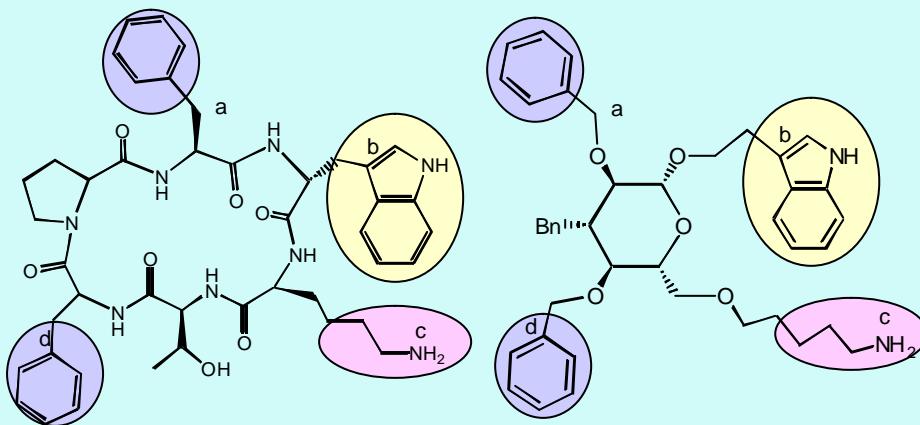
GLYCIDIC SCAFFOLDS FOR THE PRODUCTION OF BIOACTIVE COMPOUNDS

Francesco Nicotra
Università degli Studi di Milano-Bicocca
Dipartimento di Biotecnologie e Bioscienze

SUGARS ARE NATURAL SCAFFOLDS



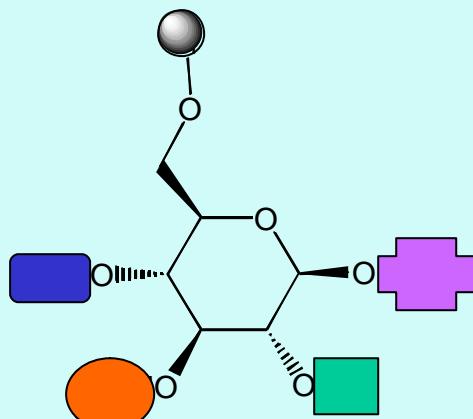
Correctly orienting “pharmacophores” in space

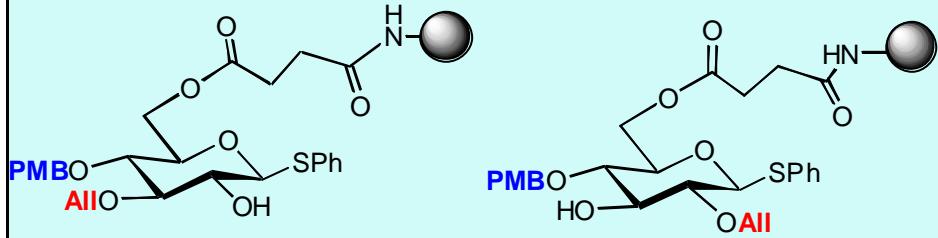


L-363,301 potent somatostatin agonist

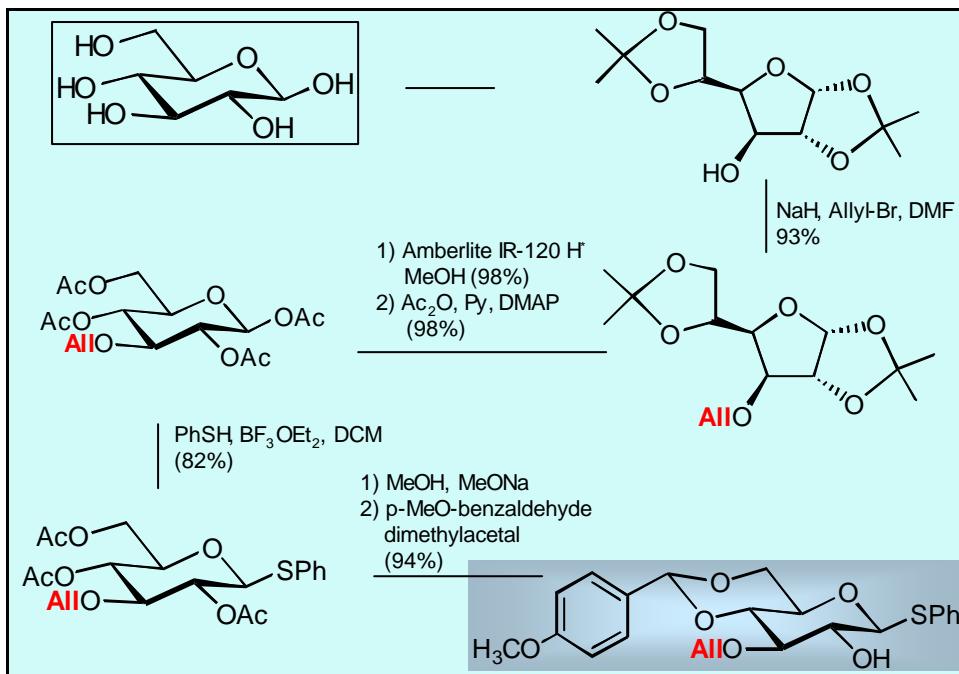
Hirschmann, R.; Nicolau, K. C et al. *J. Am. Chem. Soc.*, **1993**, 115, 12550

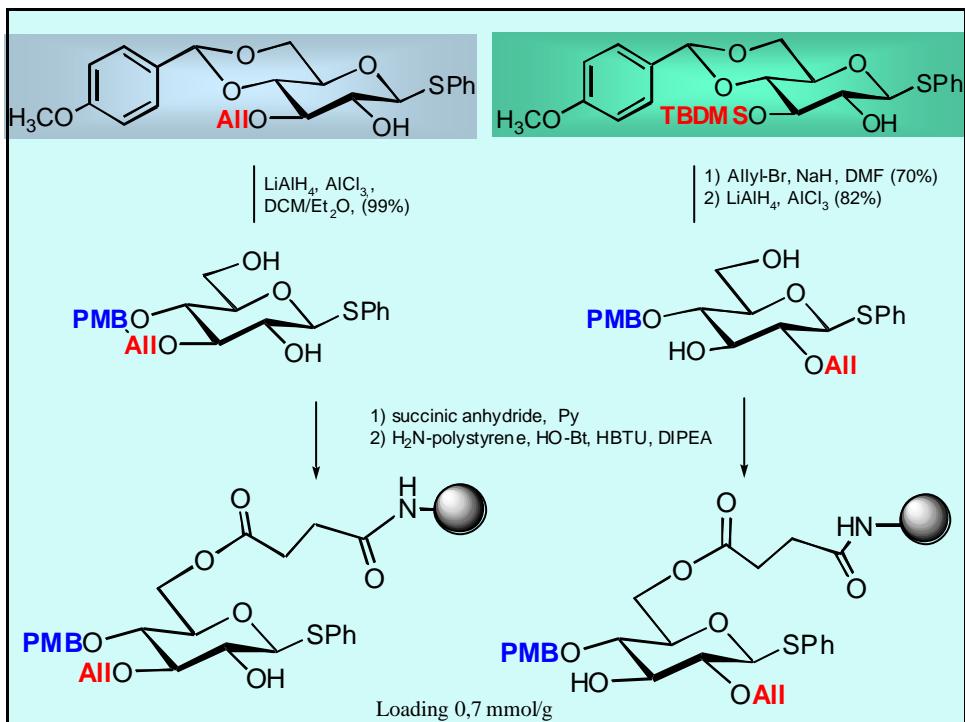
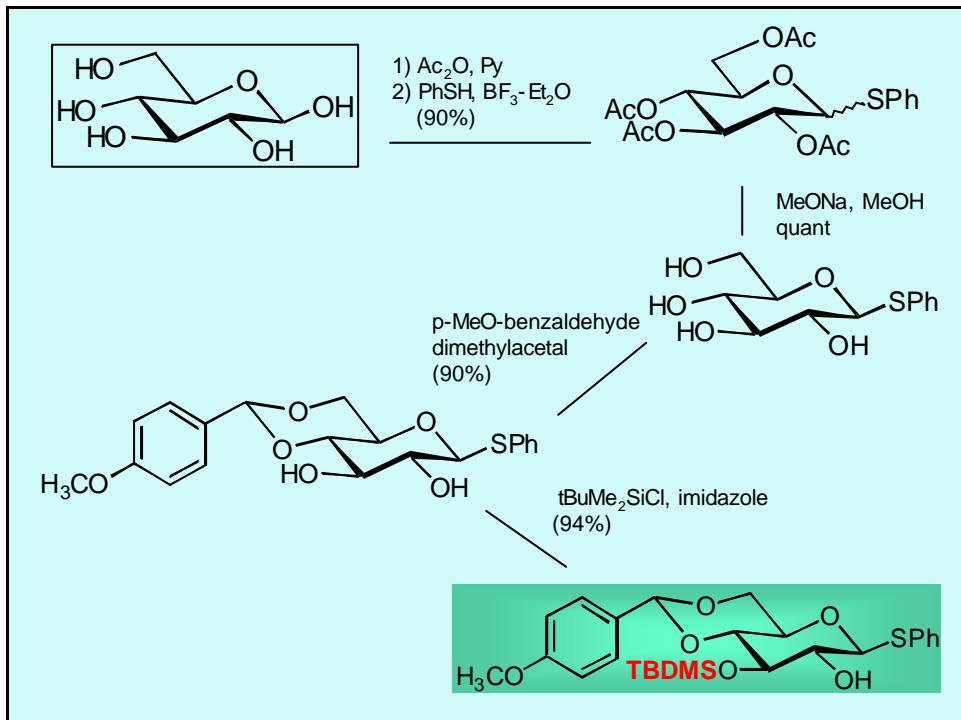
GLYCIDIC SCAFFOLDS & Combinatorial Approach

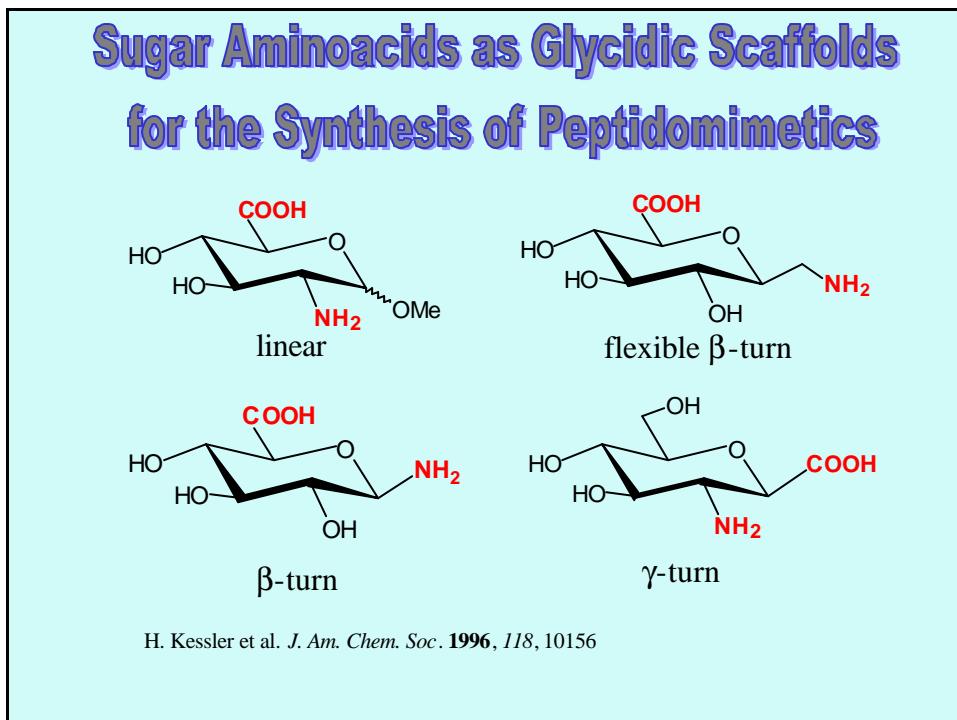
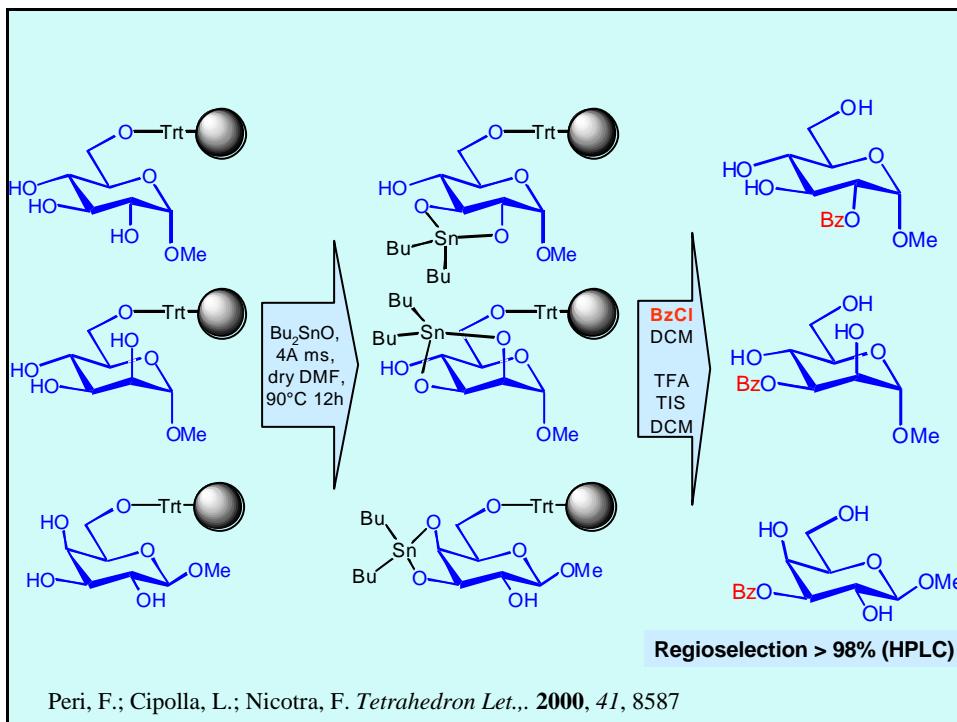


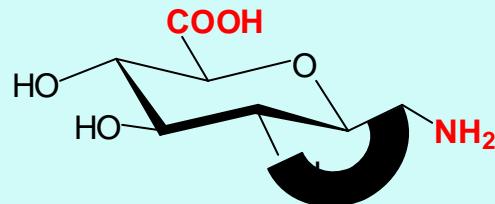


Francesco Peri, unpublished



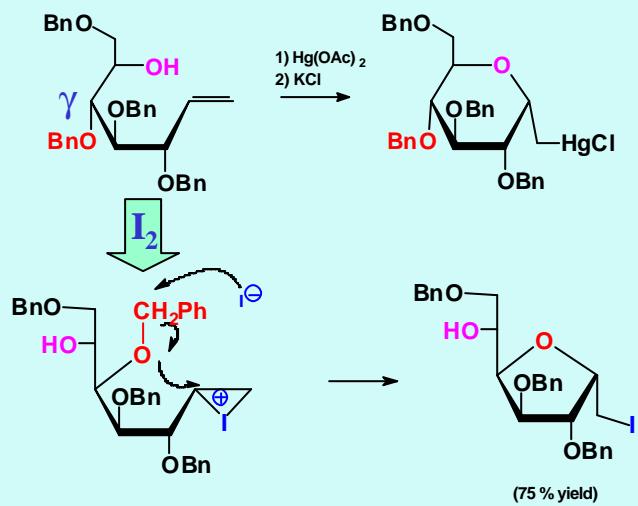




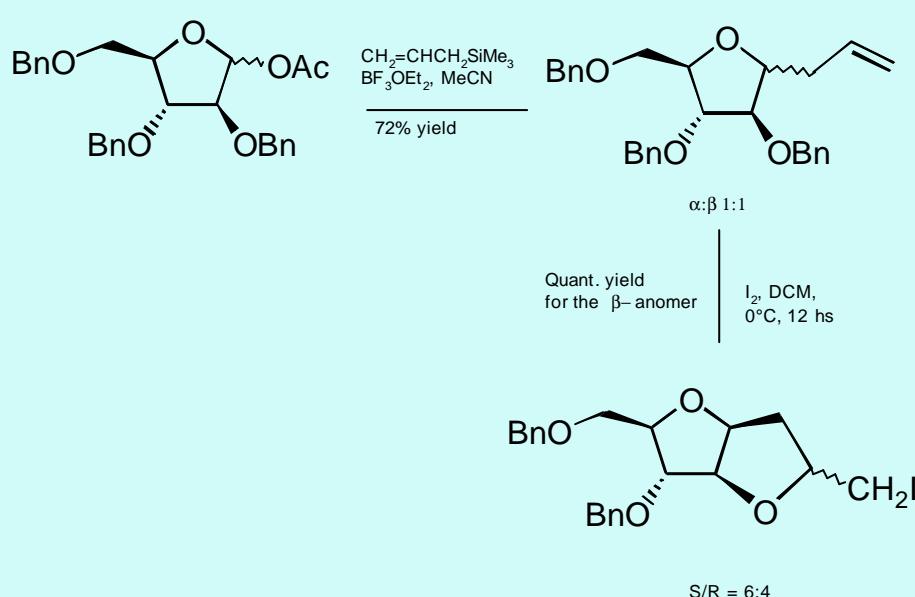
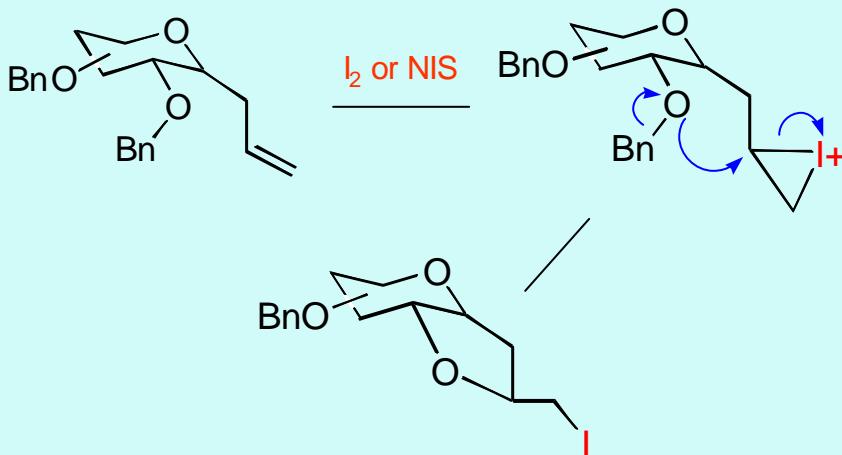


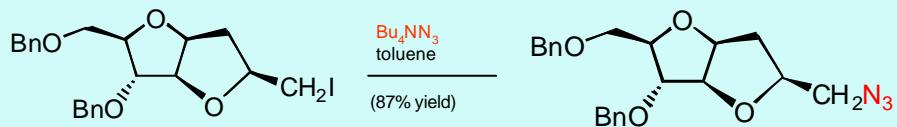
A second cycle
constrains the conformation
and makes the scaffold ORIGINAL!

How to create a second cycle?

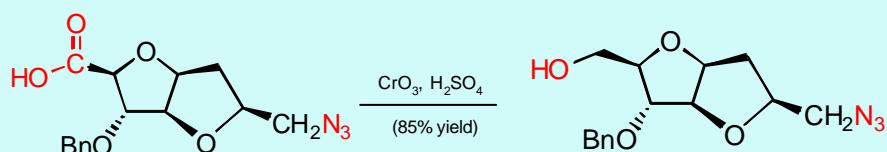


How to create a second cycle?

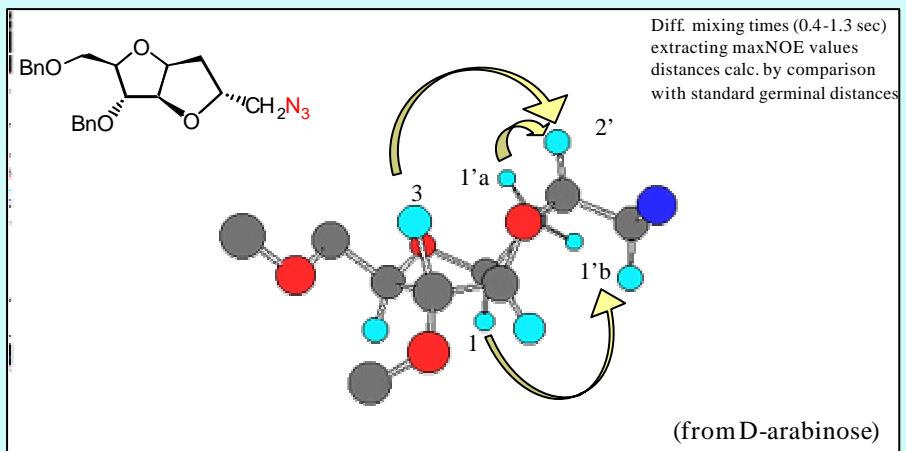




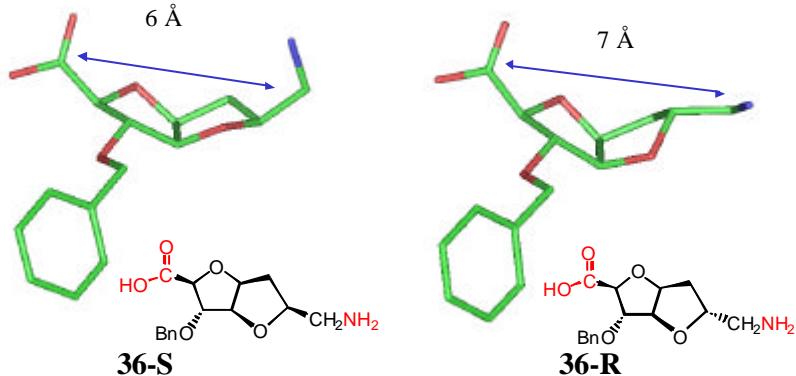
1) Ac_2O , CF_3COOH
 2) MeONa , MeOH
 (75% yield)



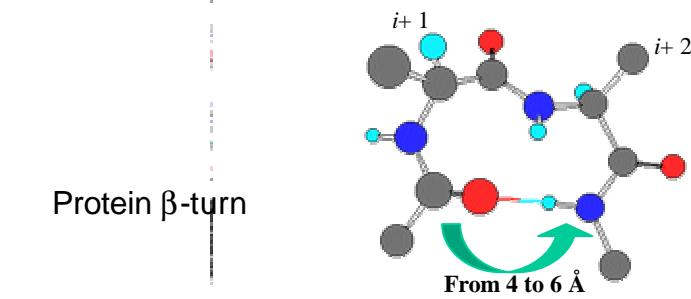
NOE's in compound 30-R (determination of the C-2' absolute configuration)



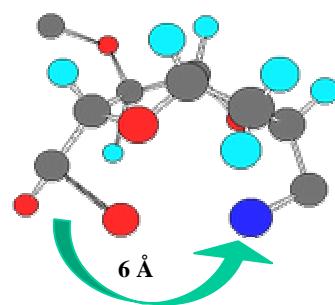
Minimized structures of **36-S** and **36-R**
from D-arabinose



MM+ force field optimised with short MD runs (10 ps)

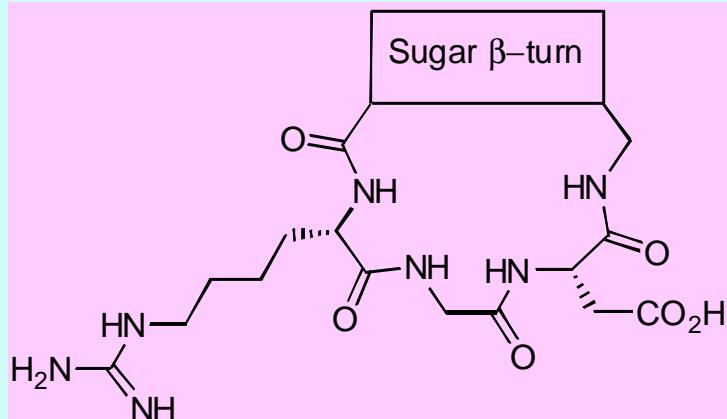


Bicyclic glyco-aminoacid
from D-arabinose



RGD rigid loop

derived from conformationally constrained
aminoacidic glycomimetic



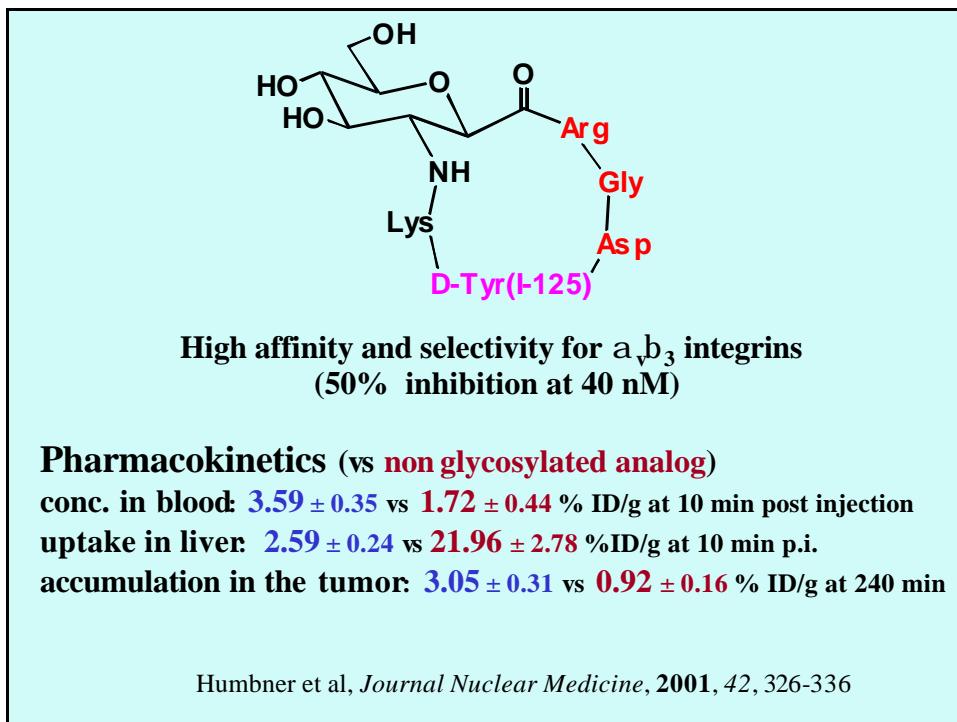
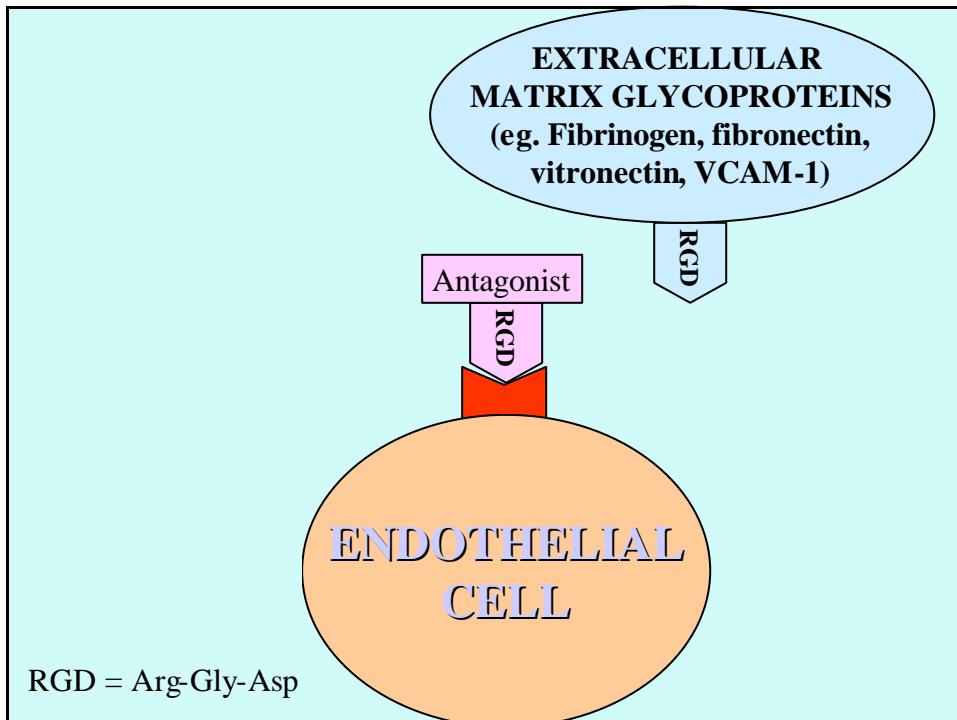
EXTRACELLULAR
MATRIX GLYCOPROTEINS
(eg. Fibrinogen, fibronectin,
vitronectin, VCAM-1)

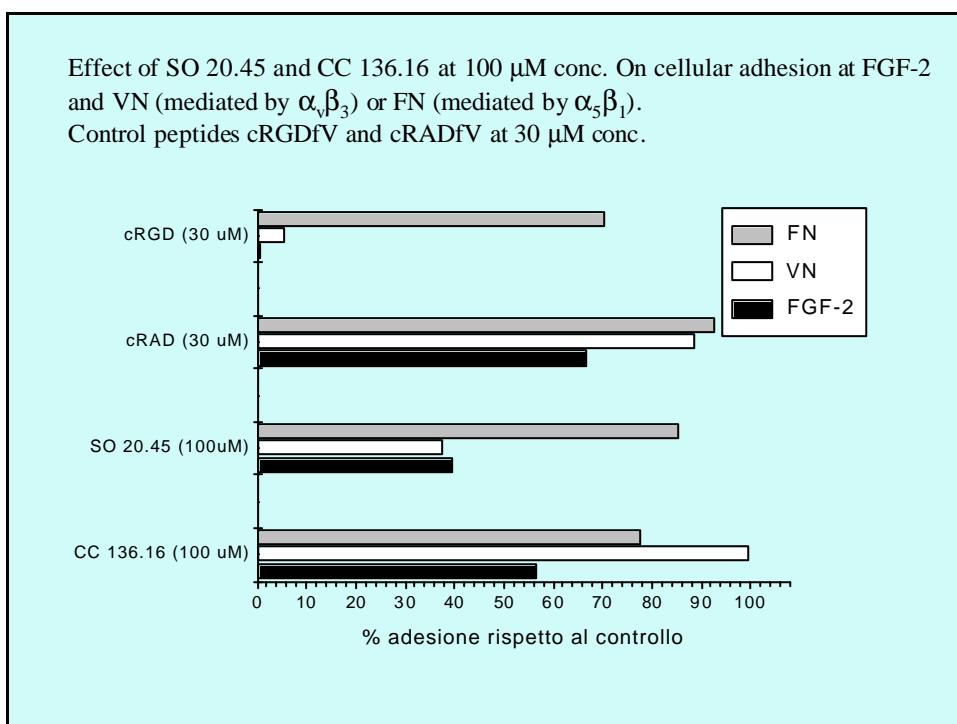
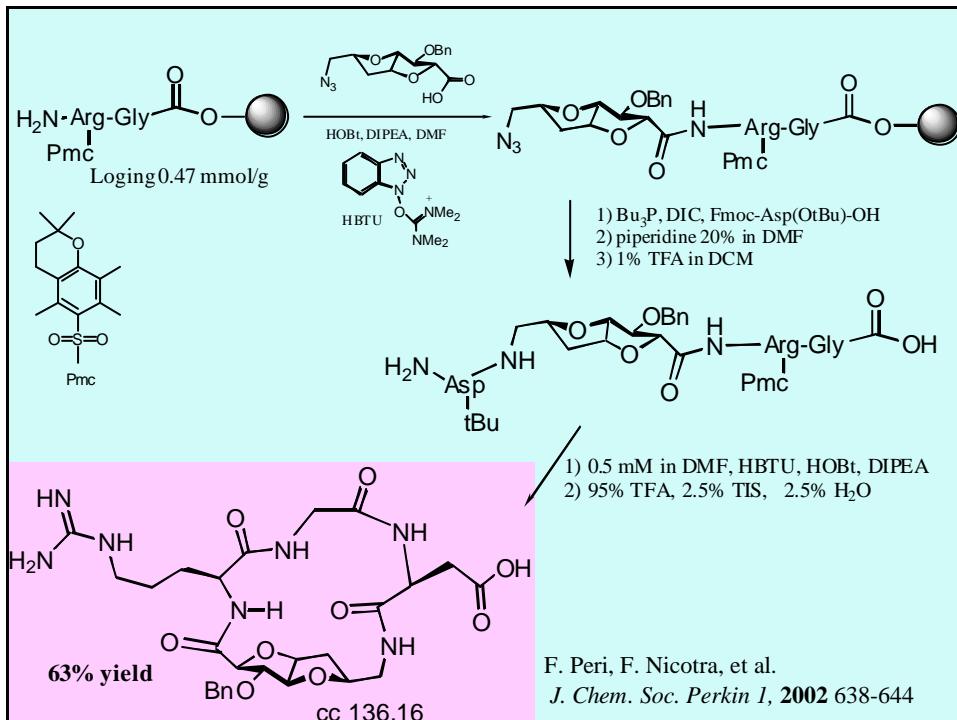
RGD

INTEGRIN ($\alpha_v\beta_3$ or $\alpha_{IIb}\beta_3$)

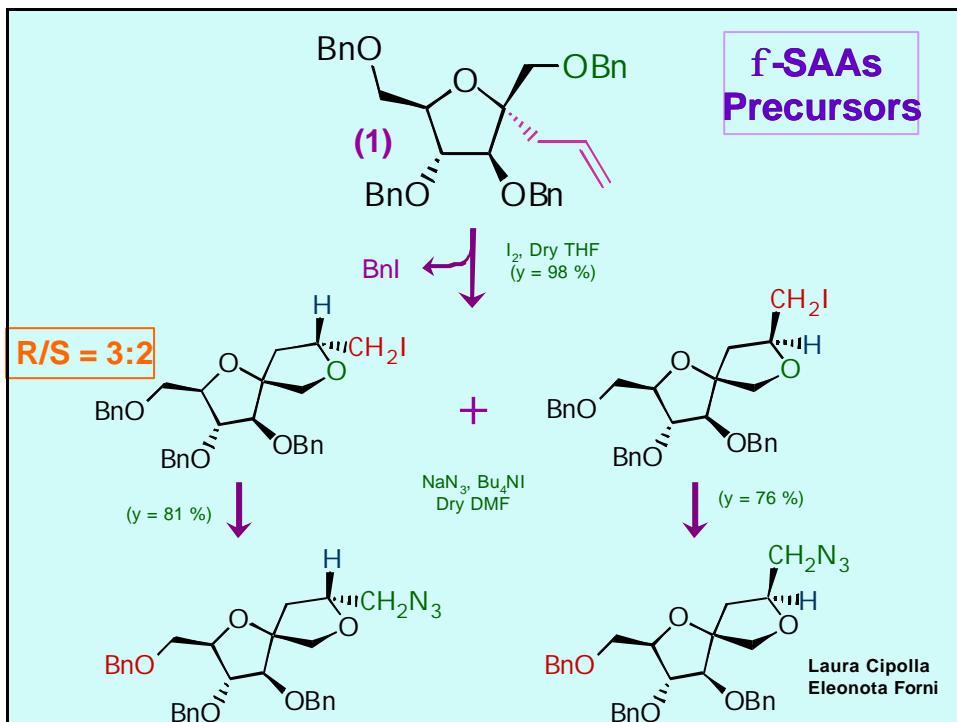
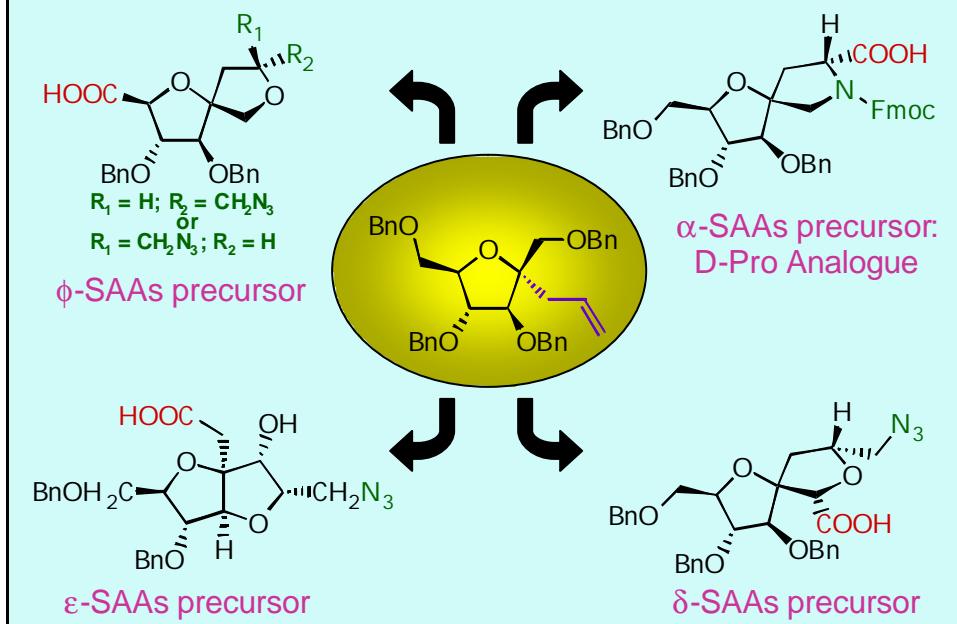
ENDOTHELIAL
CELL

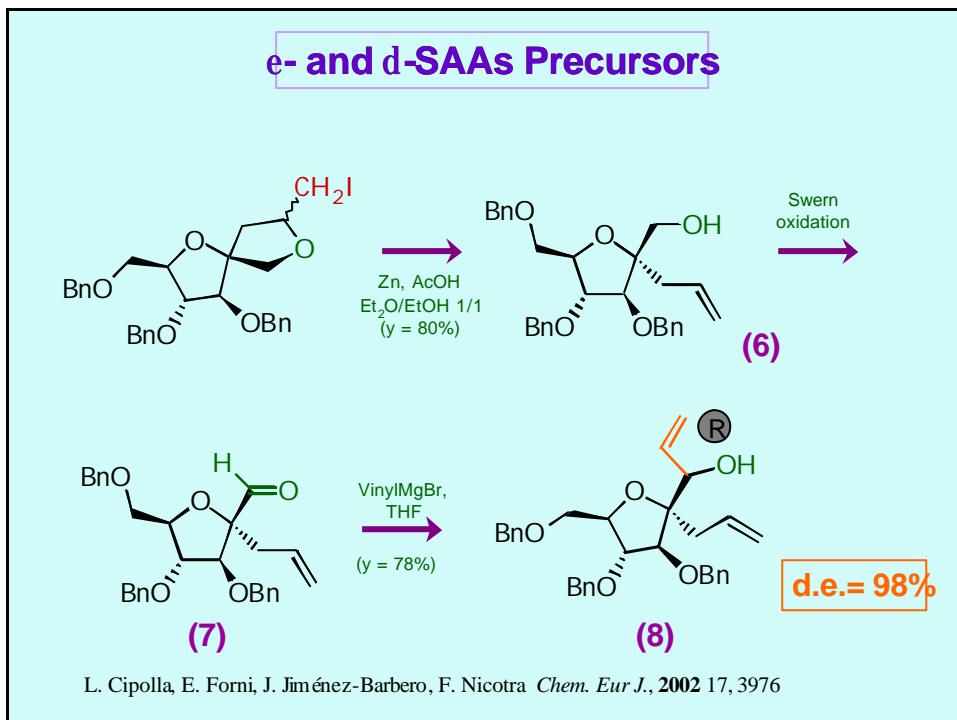
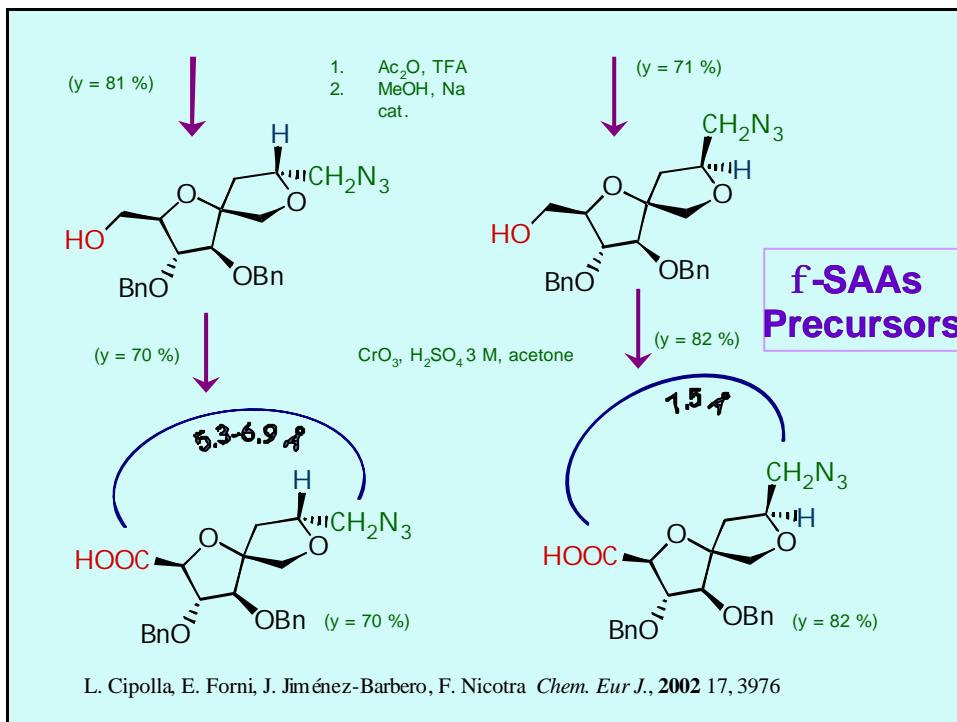
RGD = Arg-Gly-Asp



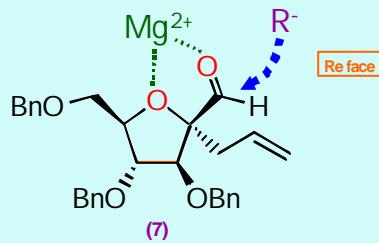


Sugar-aminoacids (SAAs) from fructose

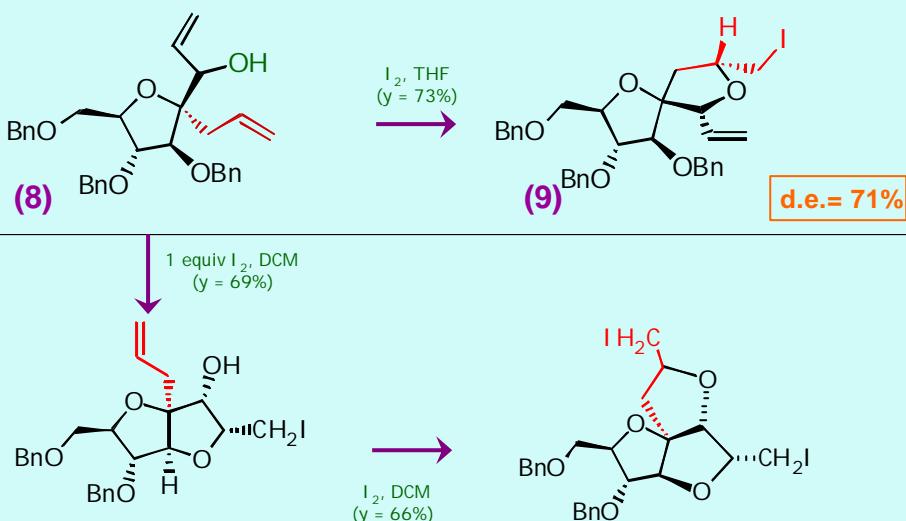




Stereoselection in the Grignard reaction

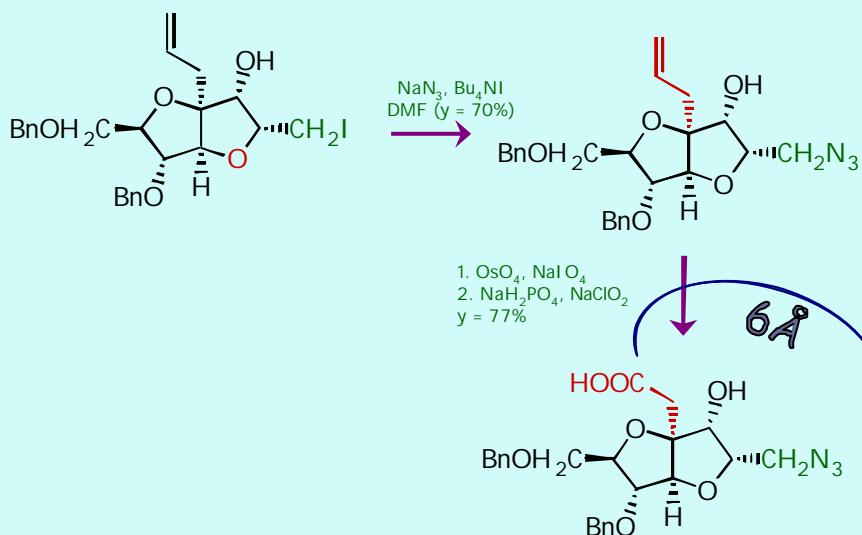


d-SAAs Precursors



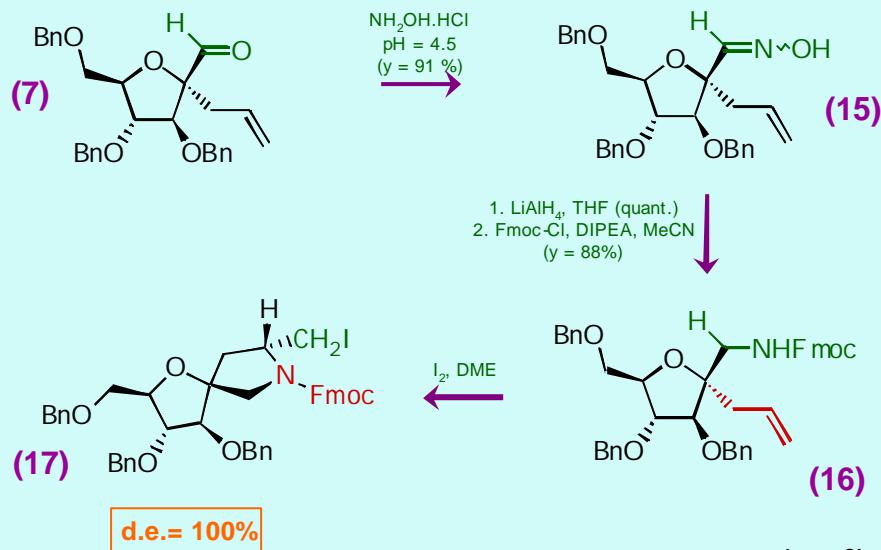
L. Cipolla, E. Forni, J. Jiménez-Barbero, F. Nicotra. *Chem. Eur. J.*, 2002 17, 3976

e-SAAs Precursors



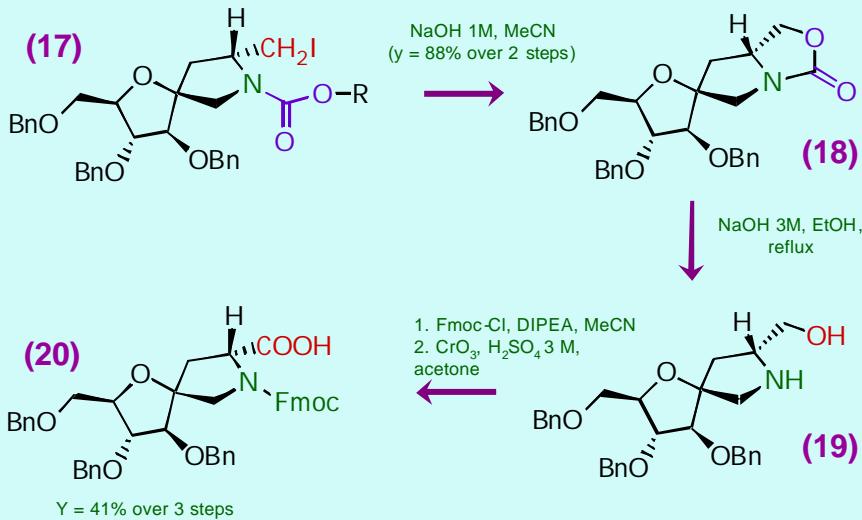
L. Cipolla, E. Forni, J. Jiménez-Barbero, F. Nicotra *Chem. Eur J.*, **2002** 17, 3976

a-SAAs Precursors¹

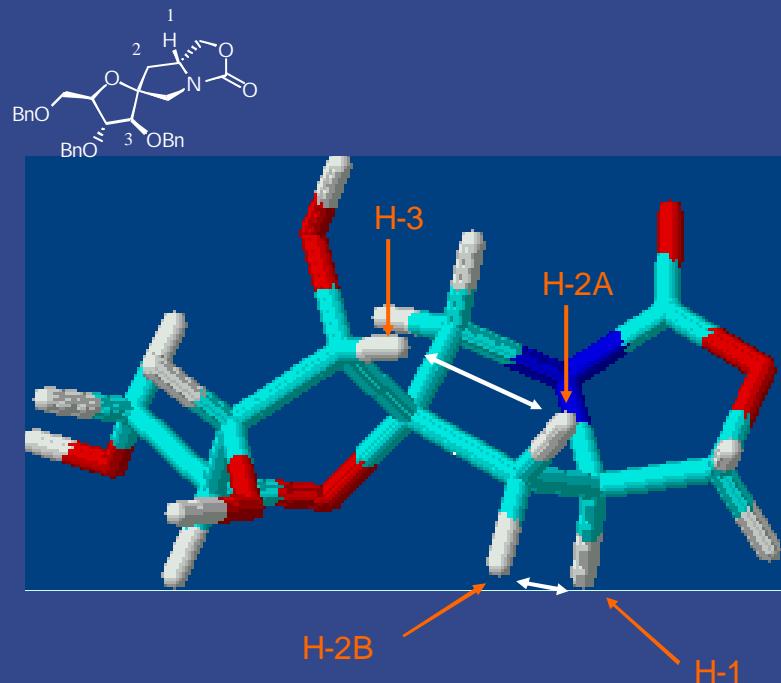


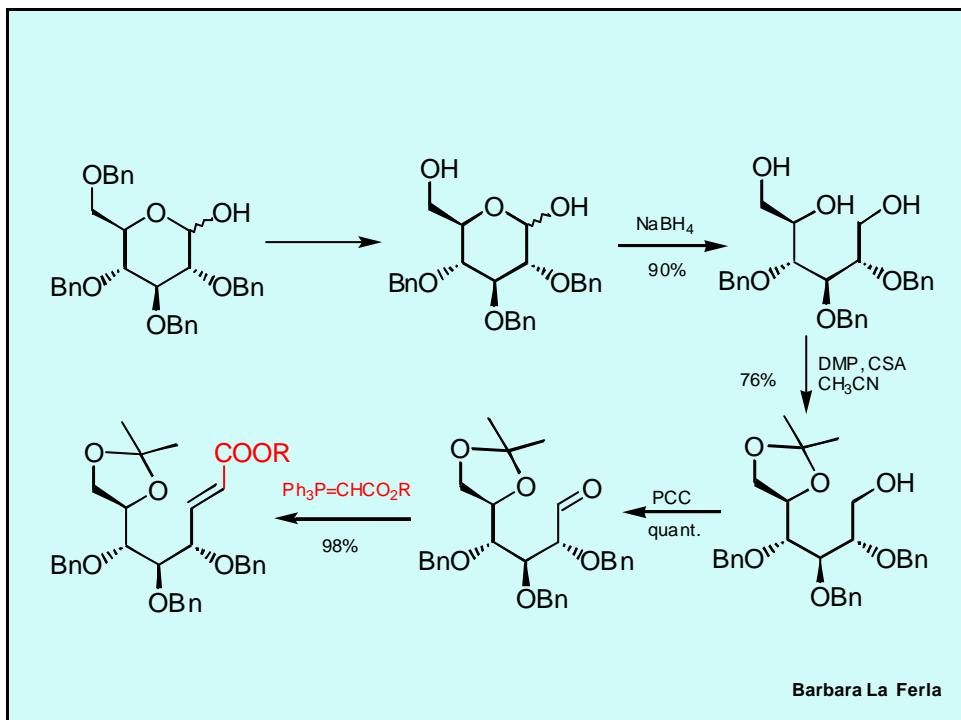
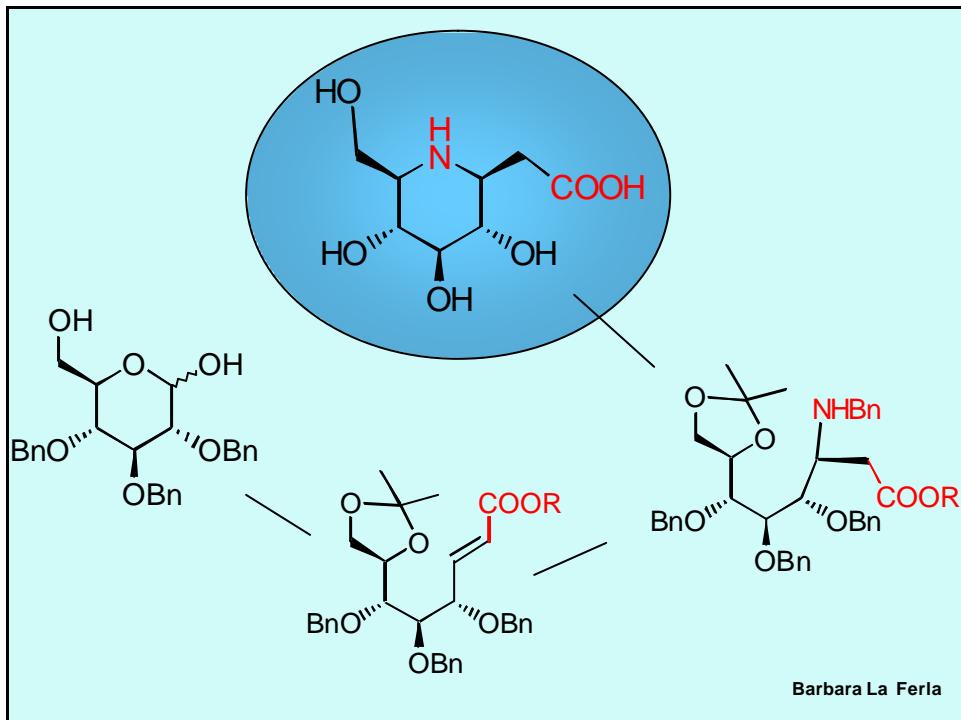
Laura Cipolla
Eleonora Forni

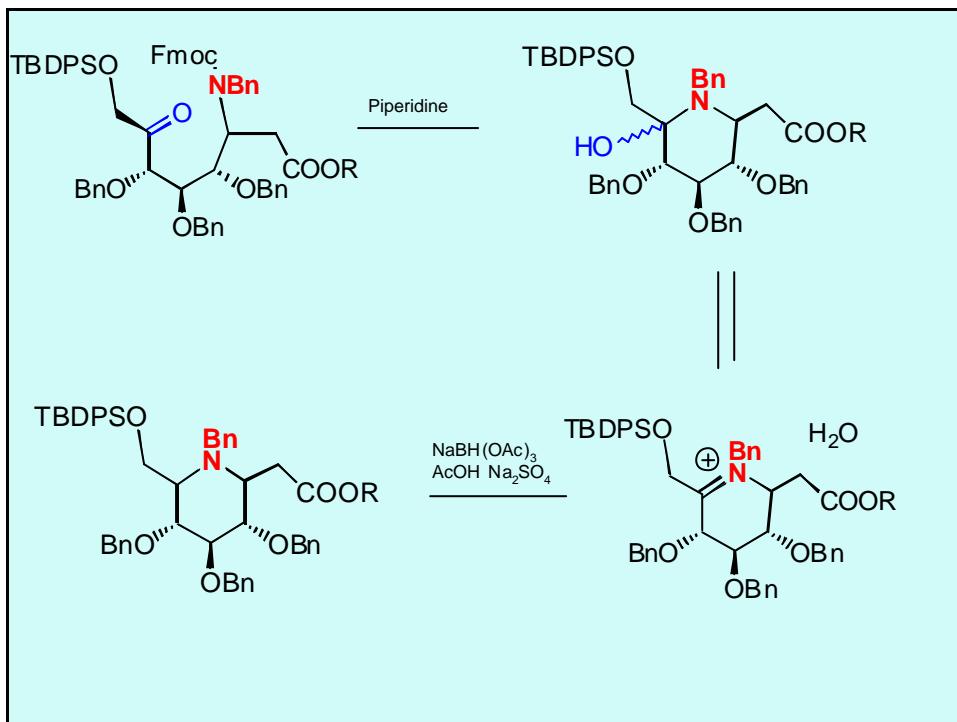
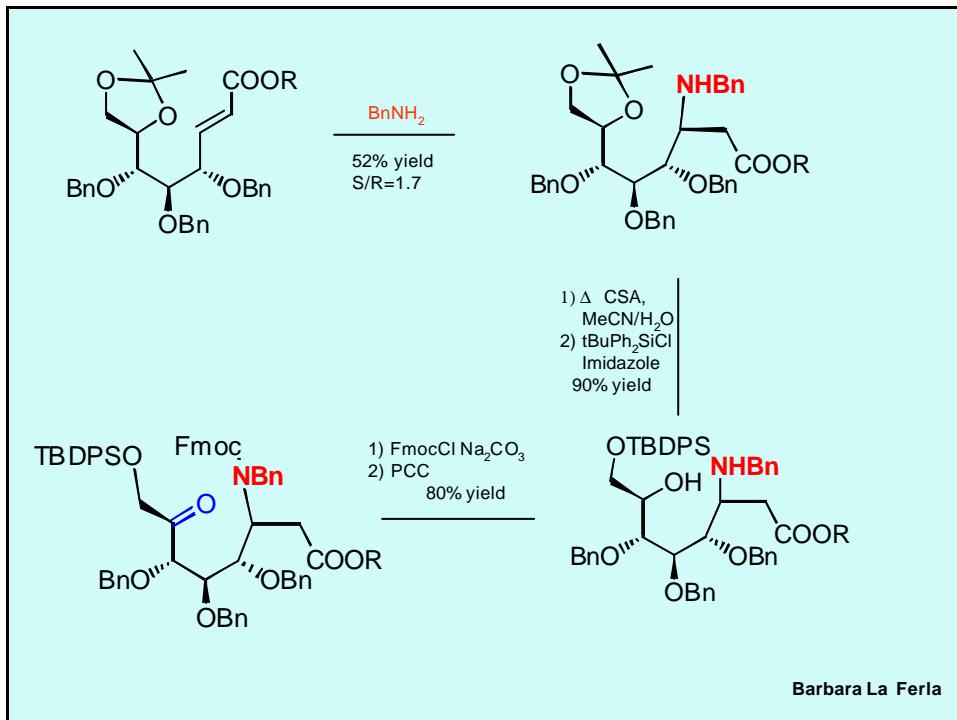
α -SAAs Precursors

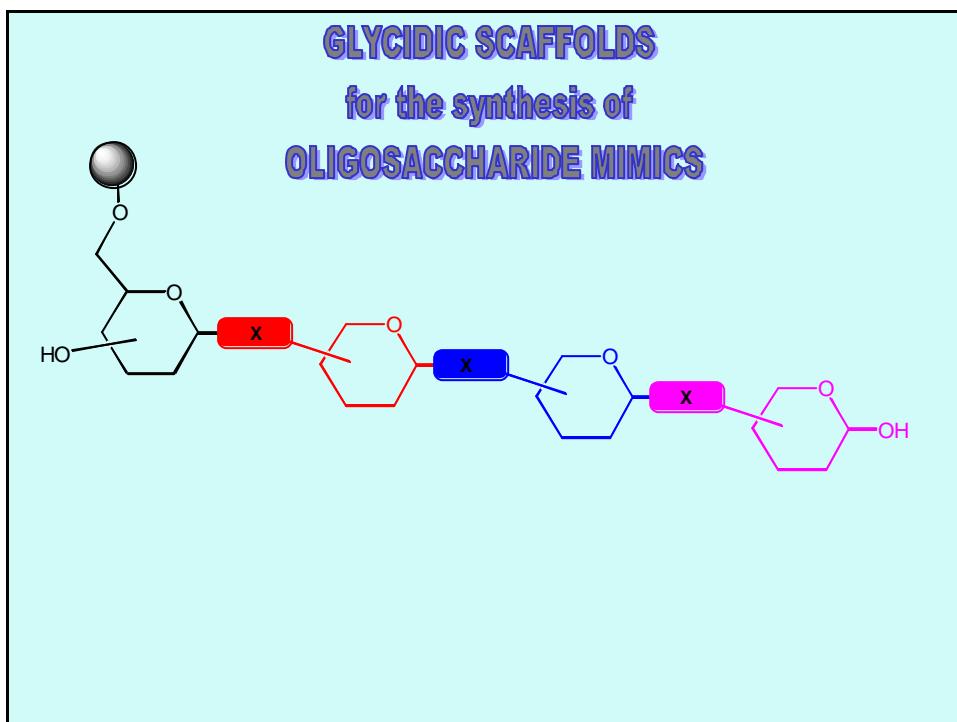
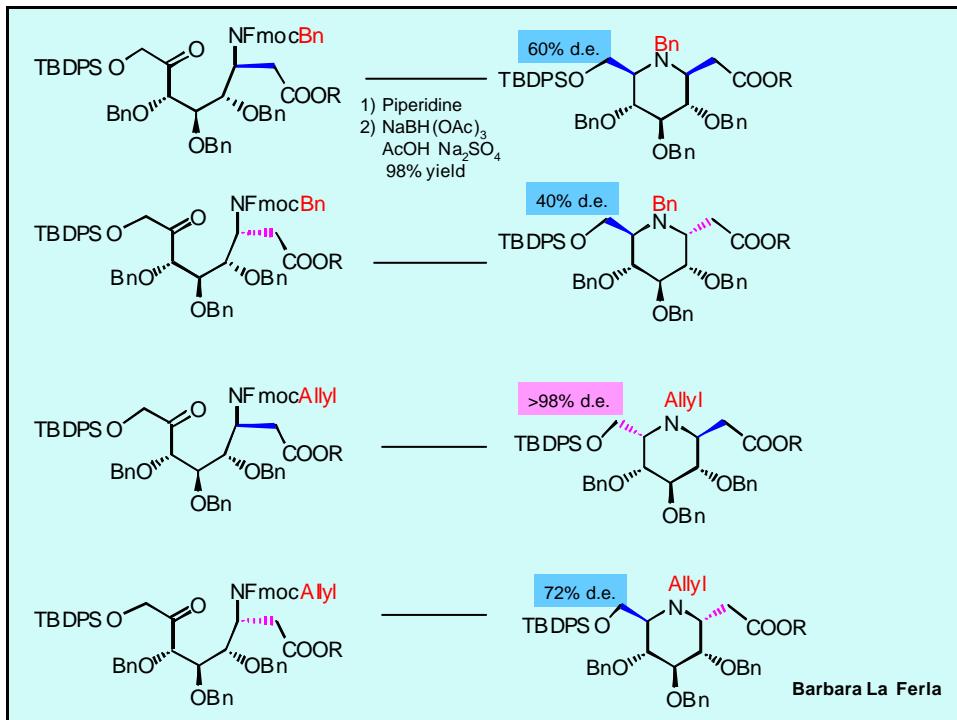


Laura Cipolla
Eleonora Forni







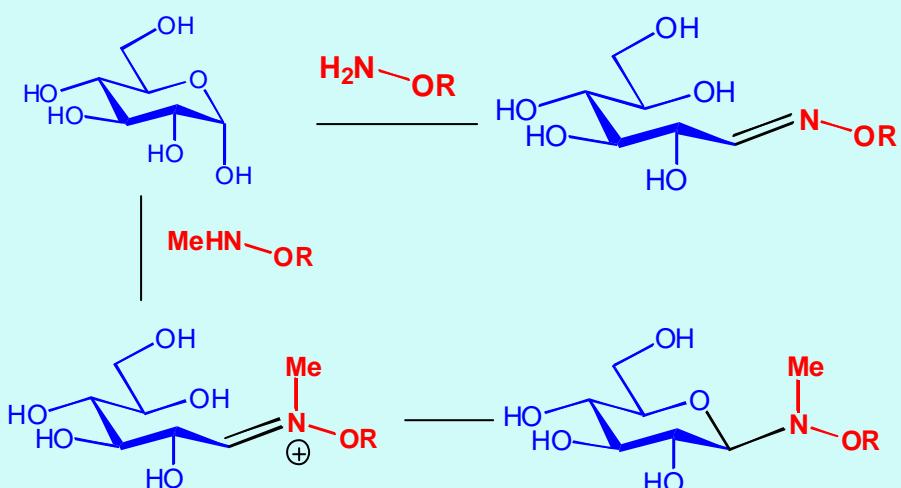


-X-

Metabolic stability

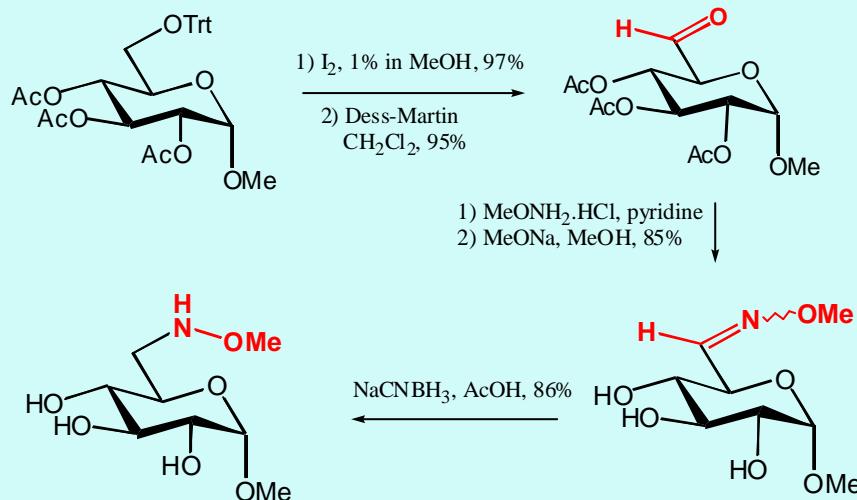
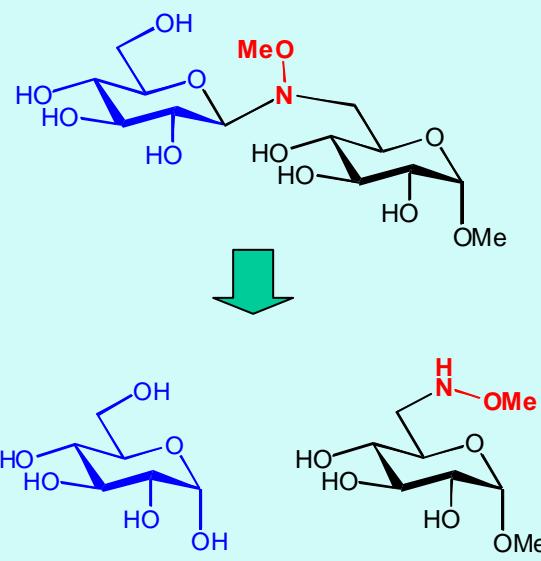
Easy and stereoselective assembly

no protection-deprotection steps
solid phase synthesis

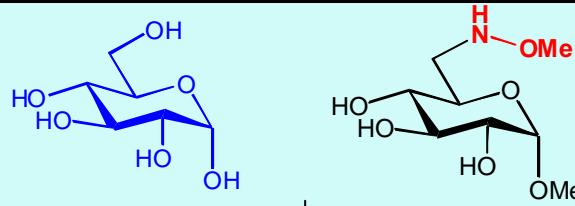


Peri, Doumy, Mutter 1998

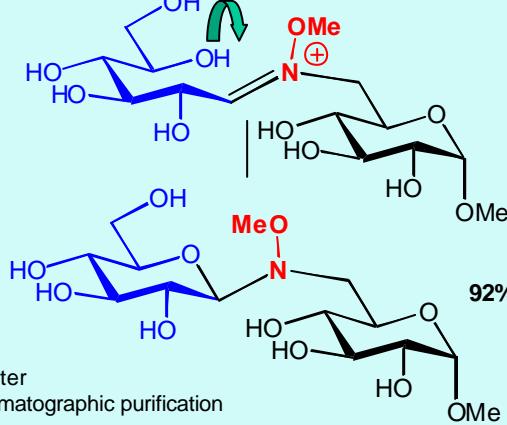
Our idea



Francesco Peri
Alexander Deutman



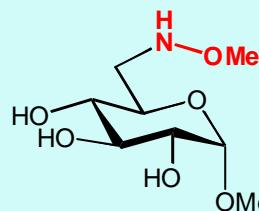
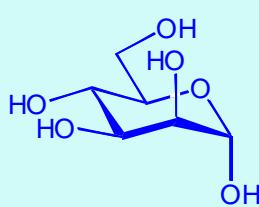
In aqueous AcOH/AcONa buffer (pH = 4.5)
or in 1:1 (v/v) H₂O/AcOH
or in 1:2 AcOH/DMF



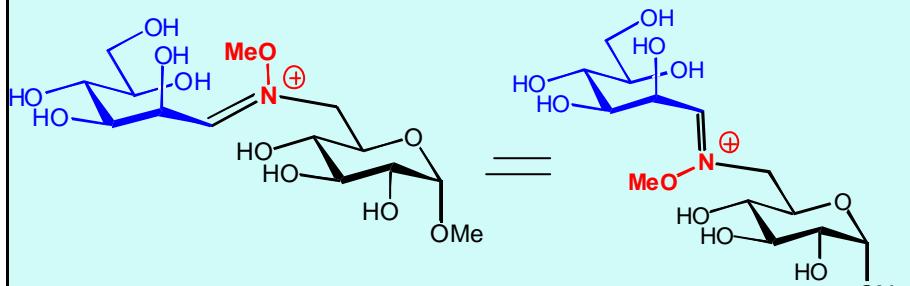
92% yield, only b

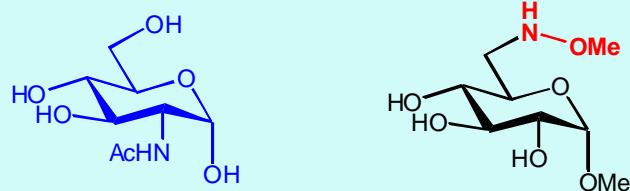
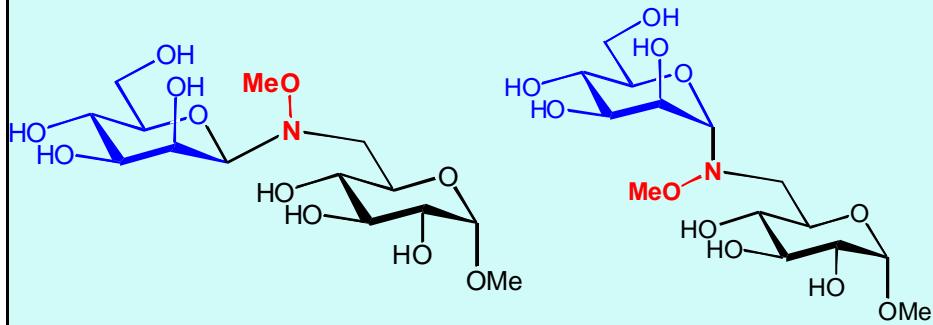
Yields determined after
acetylation and chromatographic purification

Francesco Peri
Alexander Deutman

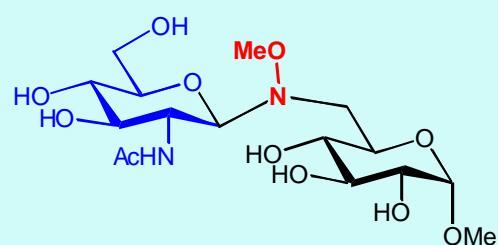


In aqueous AcOH/AcONa buffer (pH = 4.5)
or in 1:1 (v/v) H₂O/AcOH
or in 1:2 AcOH/DMF



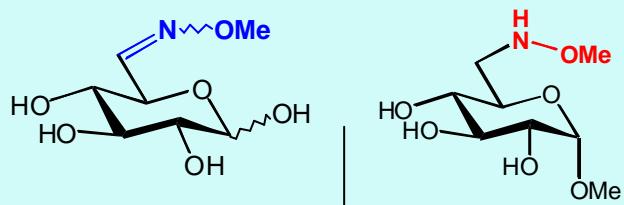


In aqueous AcOH/AcONa buffer (pH = 4.5)
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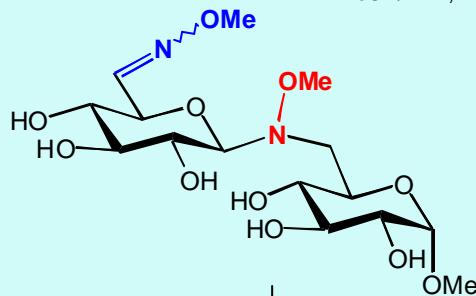


82% yield, only b

iteration

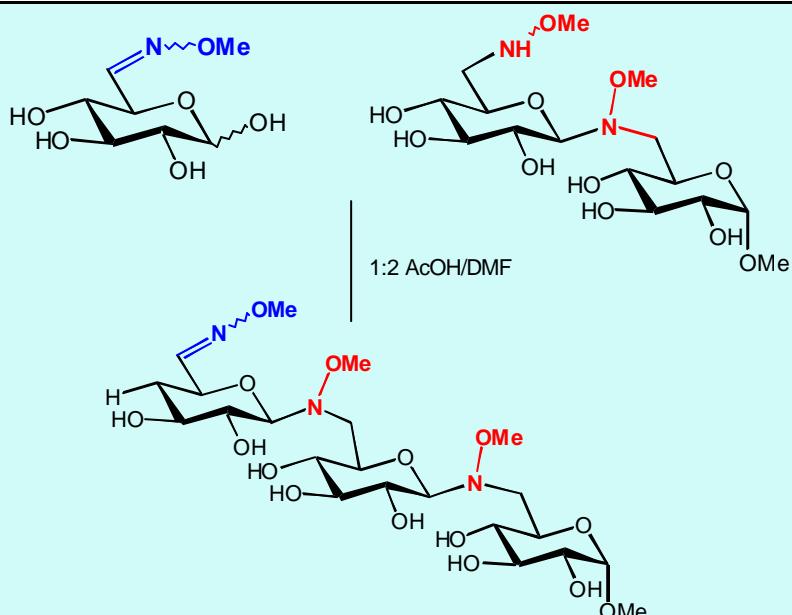


1:2 AcOH/DMF, 75%



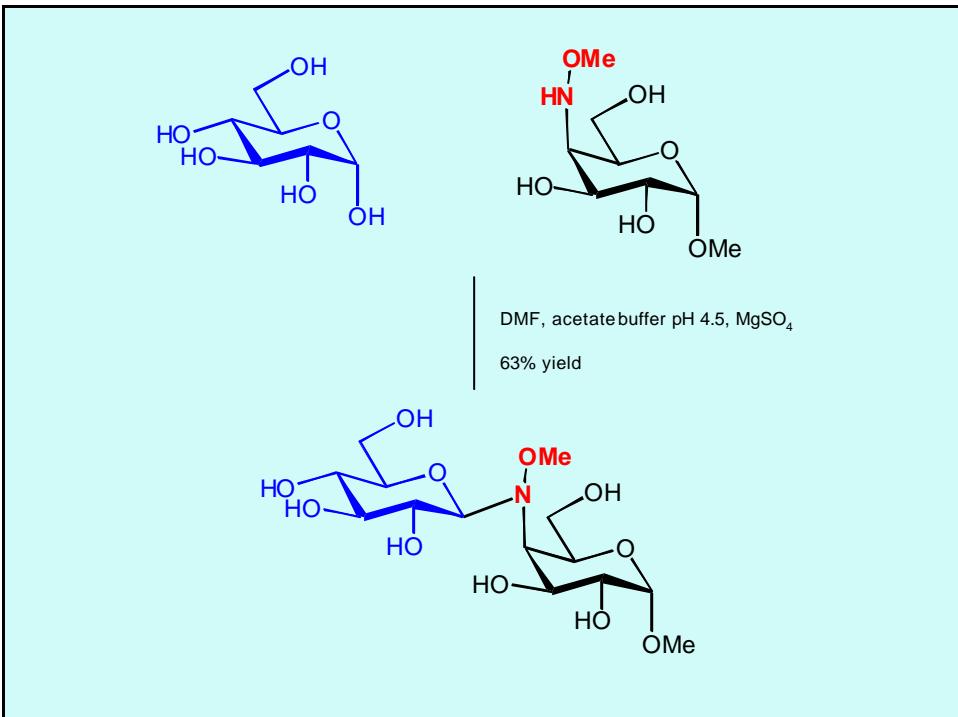
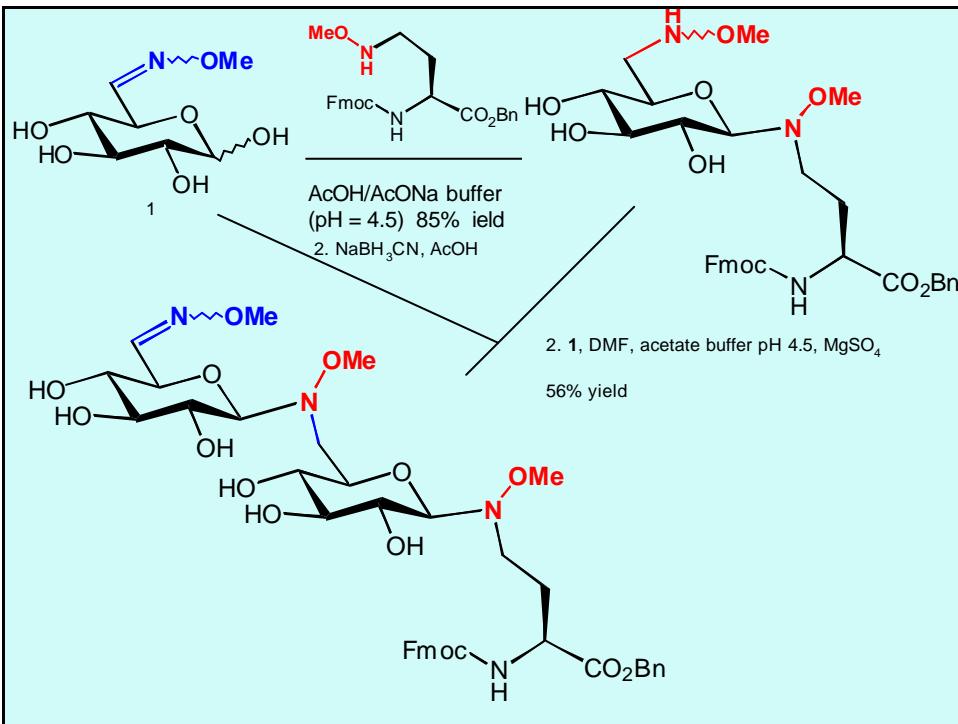
NaCNBH₃, AcOH, 85%

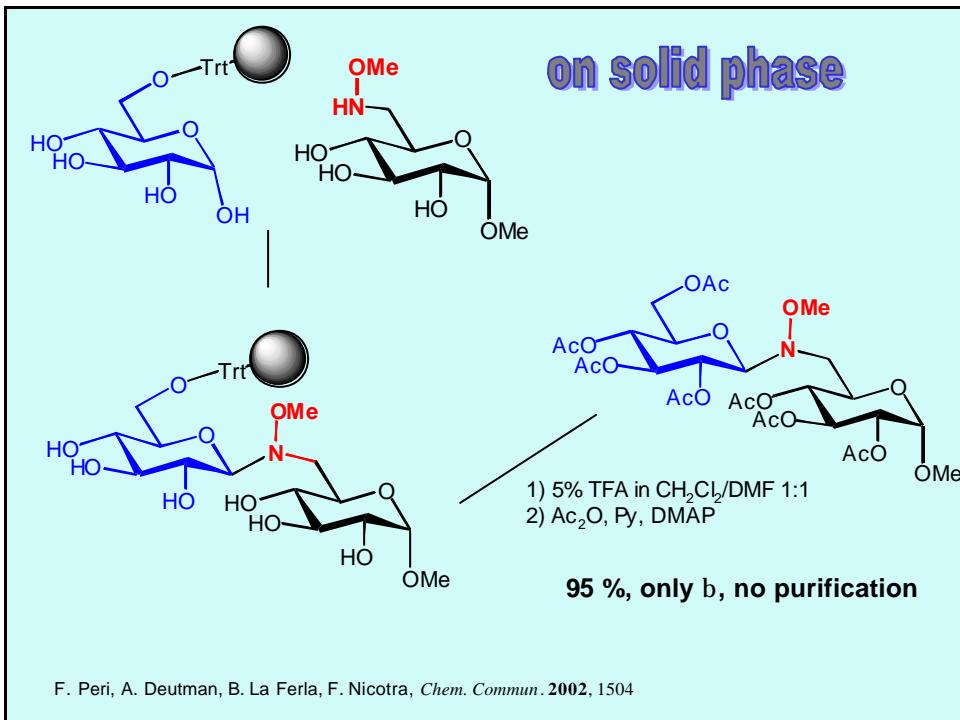
Francesco Peri
Alexander Deutman



1:2 AcOH/DMF

60% yield only b, b (after acetylation and chromatographic purification)





Financial support
Pharmacia, Nerviano
GlaxoWellcome, Verona
Novuspharma, Bresso
MURST

