FURAN, OXYGEN, NITROGEN, AND SULPHUR SILOXYDIENES: THEIR VERSATILITY ILLUSTRATED BY STEREOSELECTIVE SYNTHESES OF DENSELY FUNCTIONALIZED HOMOCHIRAL COMPOUNDS

GIOVANNI CASIRAGHI, GLORIA RASSU, and FRANCA ZANARDI

UNIVERSITY OF PARMA
PHARMACEUTICAL DEPARTMENT

NATIONAL RESEARCH COUNCIL AND
UNIVERSITY OF SASSARI,
DEPARTMENT OF CHEMISTRY

Synthesis

Lucia Battistini
Pietro Spanu
Luigi Pinna

Crystallography

Giovanna Fava Gasparri
Marisa Ferrari Belicchi
Giorgio Pelosi

NMR
Mara Cornia

HPLC
Enrico Gaetani

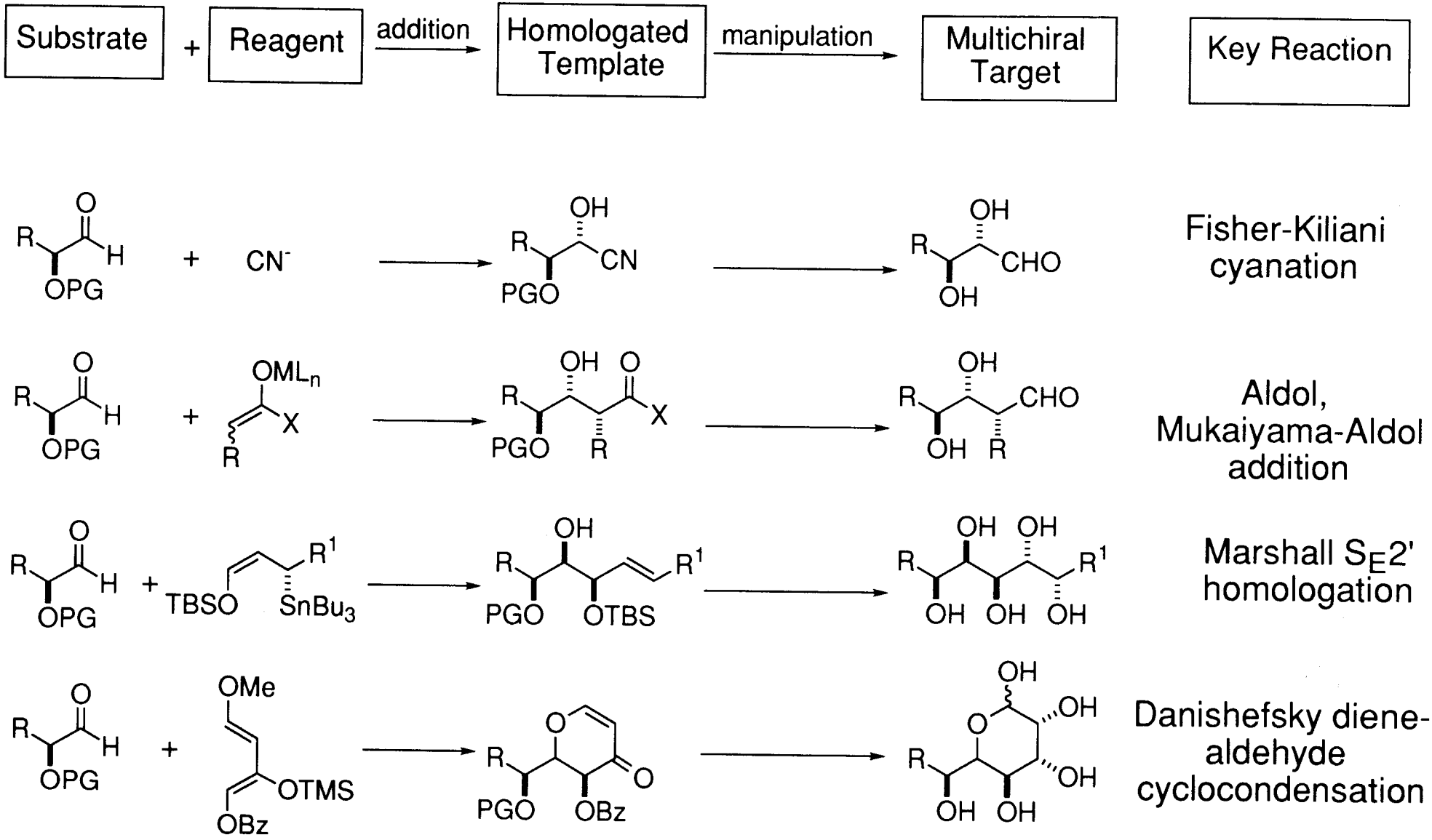
IDEAL SYNTHETIC ROUTES: CRITERIA AND REQUIREMENTS

FLEXIBILITY, SELECTIVITY, AND ERGONOMICS ARE PIVOTAL CONCERNS IN ORGANIC SYNTHESIS, ESPECIALLY WHERE PREPARATION OF FUNCTIONAL MOLECULES IS INVOLVED. IDEALLY, FOR THE EFFECTS OF SHAPE AND STEREOCHEMISTRY ON THE FUNCTIONAL PROFILE TO BE EVALUATED, SYNTHETIC APPROACHES TO A GIVEN FAMILY OF MOLECULES WITH FUNCTIONS SHOULD BE AMENABLE TO IMPLEMENTATION OF MAXIMAL STEREOCHEMICAL VARIATIONS AND PATTERN OF SUBSTITUTIONS IN THE SERIES. FURTHERMORE, TO MINIMIZE THE SYNTHETIC EFFORT, USEFUL SCHEMES SHOULD EXPLOIT PARALLEL AND REPETITIVE EXECUTION OF UNIFIED PROTOCOLS OF A LIMITED NUMBER OF OPTIMIZED TRANSFORMATIONS AND EMPLOY READILY AVAILABLE SYNTHETIC PRECURSORS AND CHEMICALS.

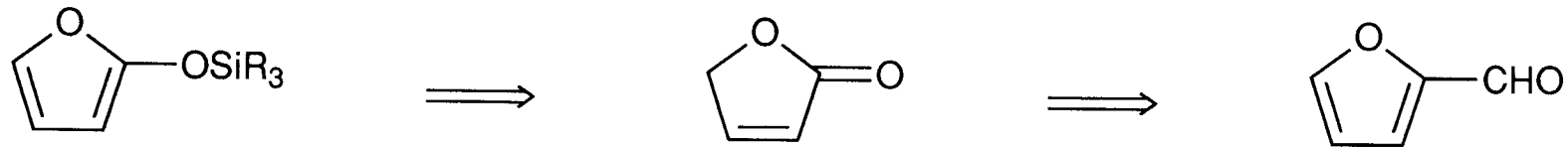
IDEAL SYNTHETIC ROUTES: CRITERIA AND REQUIREMENTS

IN ADDITION, AN IDEAL CHEMICALLY UNIFORMED PROTOCOL SHOULD BE AMENABLE TO INTERDEPENDENT EXECUTIONS OF DIFFERENT SYNTHETIC OPTIONS, E.G.: (1) LINEAR SYNTHESIS FOR SELECTIVE ACCESS TO A GIVEN INDIVIDUAL COMPOUND; (2) PARALLEL SYNTHESIS FOR SELECTIVE ACCESS TO SMALL COLLECTIONS OF INDIVIDUAL COMPOUNDS; AND (3) COMBINATORIAL SYNTHESIS FOR RAPID ASSEMBLY OF COLLECTIONS OF MANY COMPOUNDS TOWARD EASY DISCOVERY OF NEW OR BETTER FUNCTIONS.

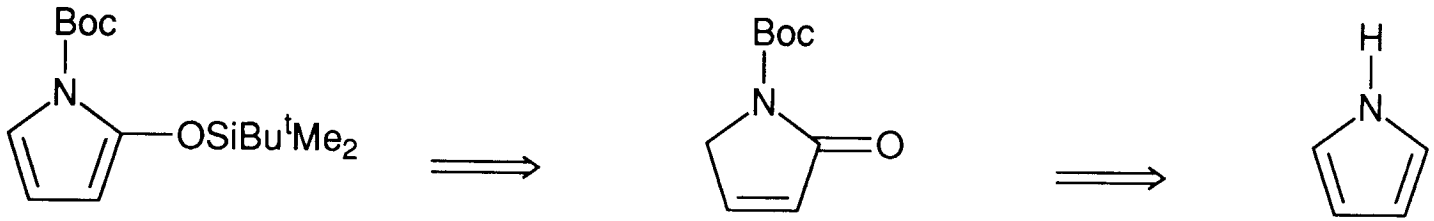
HOMOLOGATIVE C-C BOND-FORMING TECHNIQUES USING THE CHIRON APPROACH: IMPROVING VERSATILITY



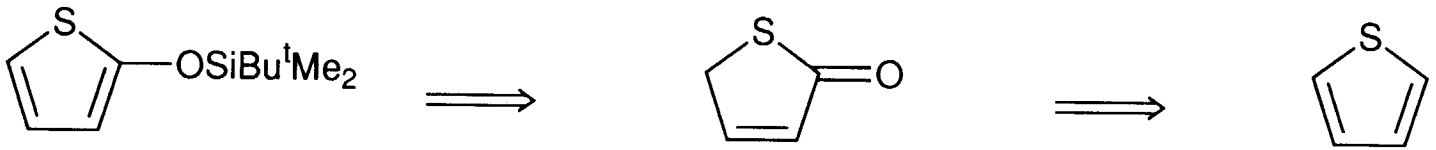
FURAN-, PYRROLE-, AND THIOPHENE-BASED SILOXYDIENES: AN IDEAL HOMOLOGATIVE REAGENT TRIAD



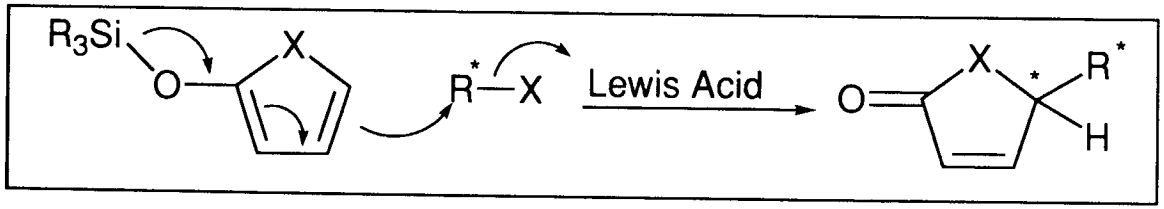
TMSOF: $R_3 = Me_3$
TBSOF: $R_3 = Bu^tMe_2$



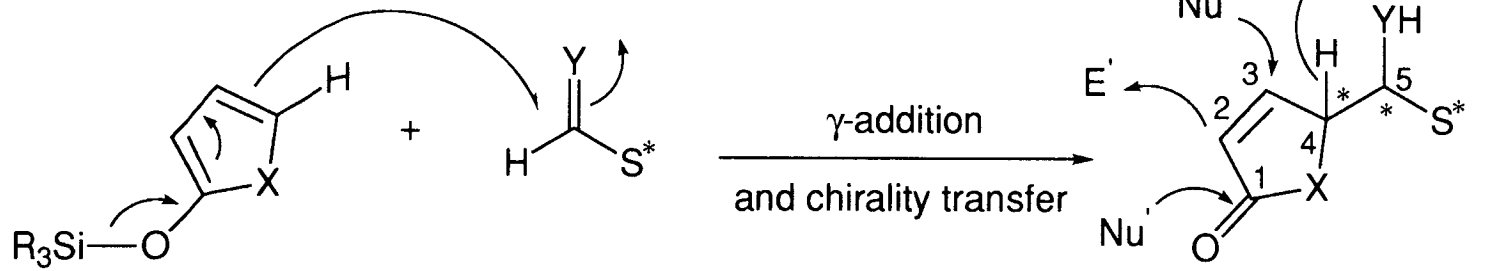
TBSOP



TBSOT



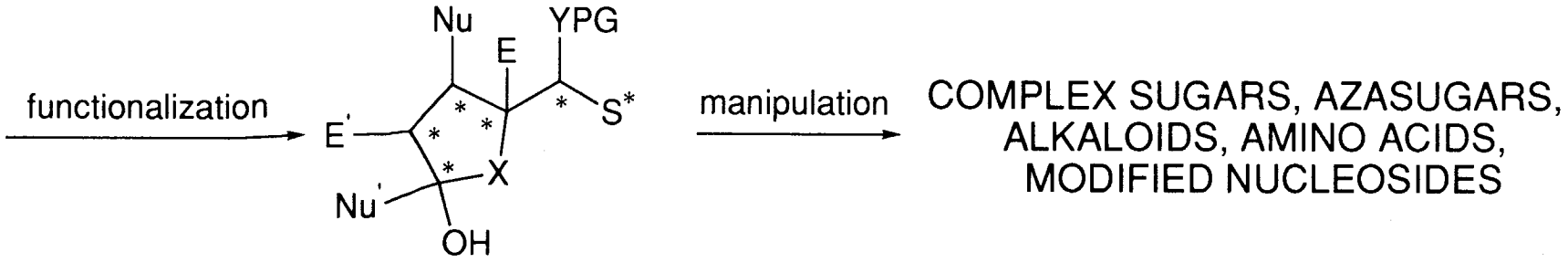
THE SILOXYDIENE ROUTE TO DENSELY FUNCTIONALIZED COMPOUNDS: DESIGN



TMSOF : X = O; R_3 = Me_3
TBSOF : X = O; R_3 = Bu^tMe_2
TBSOP : X = NBoc; R_3 = Bu^tMe_2
TBSOT : X = S; R_3 = Bu^tMe_2

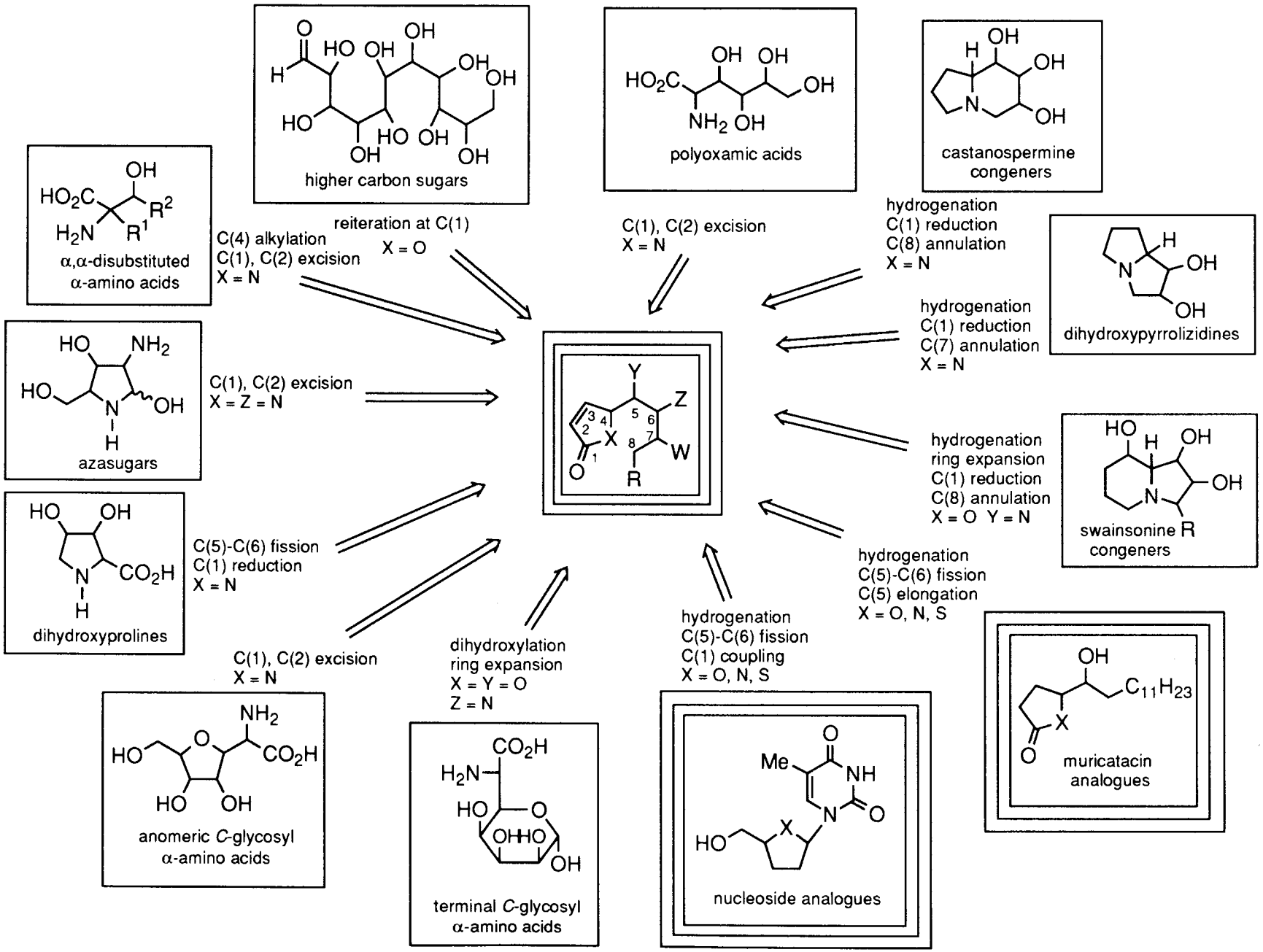
C_n CHIRON

C_{n+4} ADDUCT

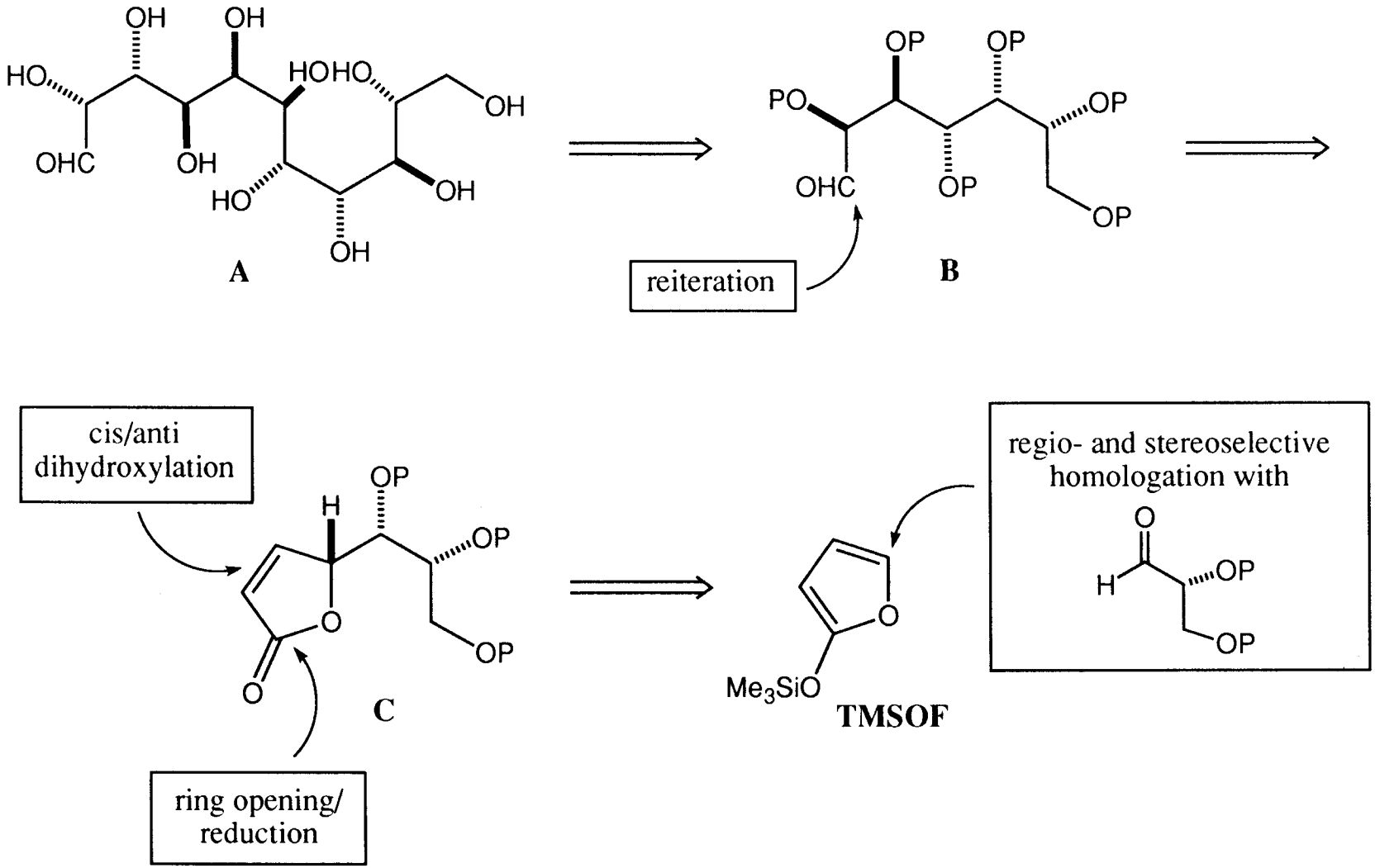


VERSATILITY : X = O, N, S; Y = O, N; Nu, Nu' = H, C, O, N, S nucleophiles; E, E' = C, O, N electrophiles

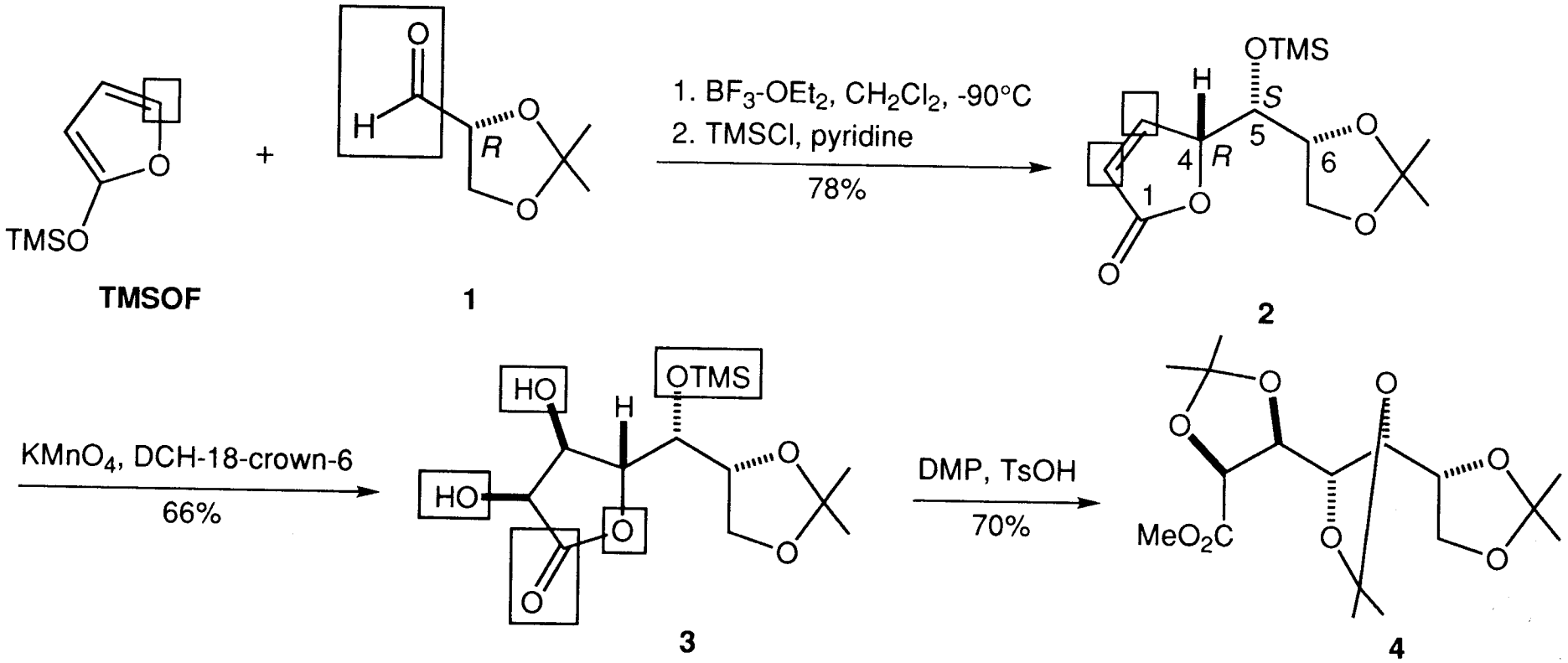
THE SILOXYDIENE ROUTE: IMPLEMENTATION MANEUVERS



ASCENT OF THE ALDOSE SERIES BY FOUR CARBON ATOMS:
D-*glycero*-D-*talo*-L-*talo*-UNDECOSE

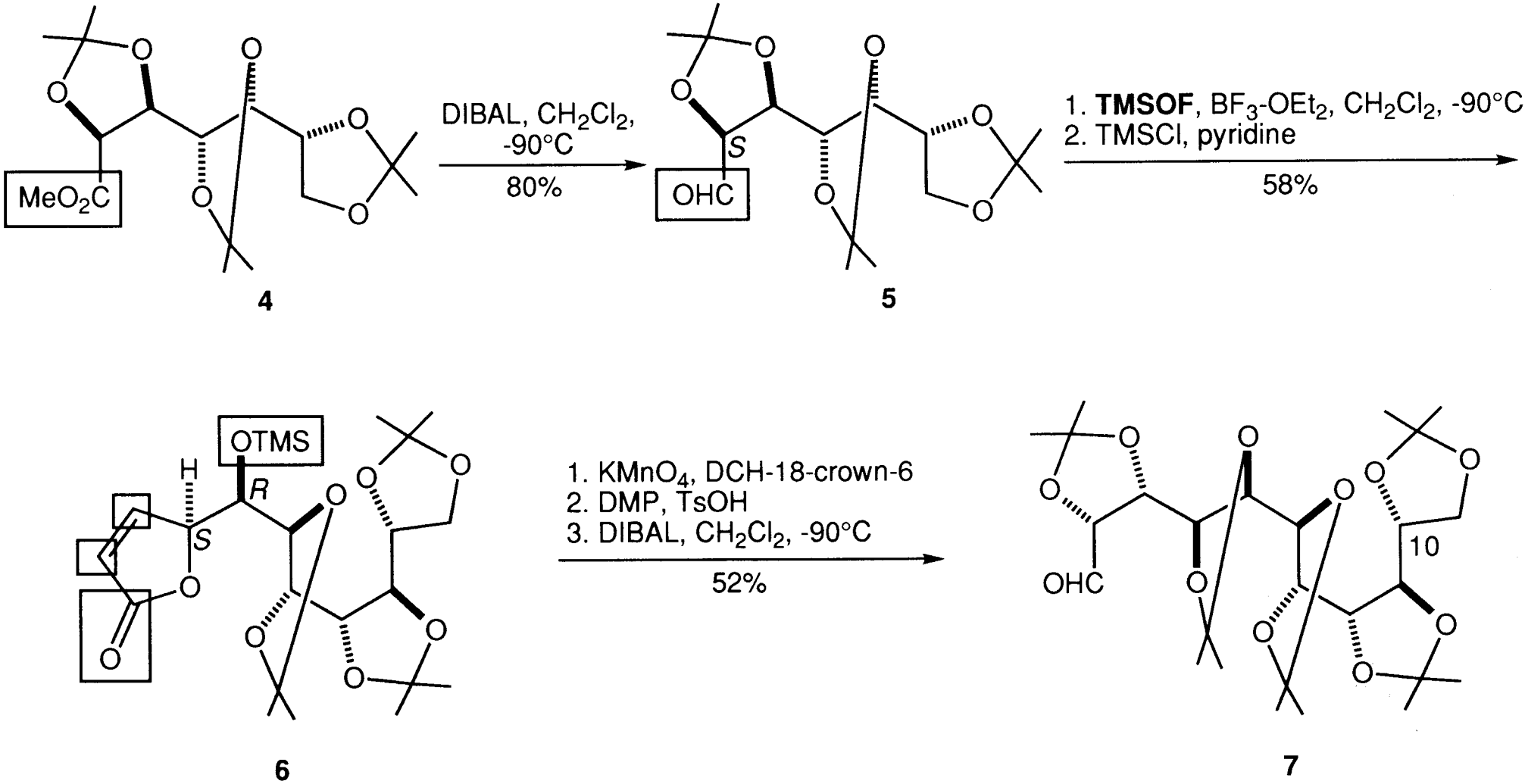


TOTAL SYNTHESIS OF D-*glycero*-D-*talo*-L-*talo*-UNDECOSE PENTAACETONIDE (I)



G. CASIRAGHI et al. *J. Org. Chem.* **1991**, *56*, 2136-2139

TOTAL SYNTHESIS OF D-*glycero*-D-*talo*-L-*talo*-UNDECOSE PENTAACETONIDE (II)

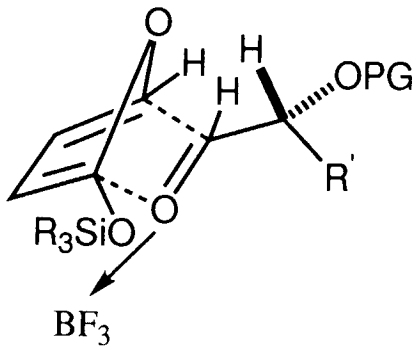


4 **5**

6 **7**

G. CASIRAGHI et al. *J. Org. Chem.* **1991**, *56*, 2136-2139

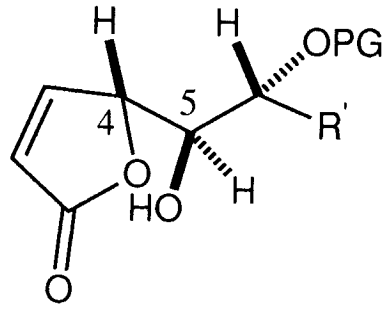
TRANSITION STATE MODELS FOR THE MUKAIYAMA-ALDOL-REACTION BETWEEN TMSOF AND α-CHIRAL α-ALKOXYALDEHYDES



TS1 (Diels-Alder/Felkin)

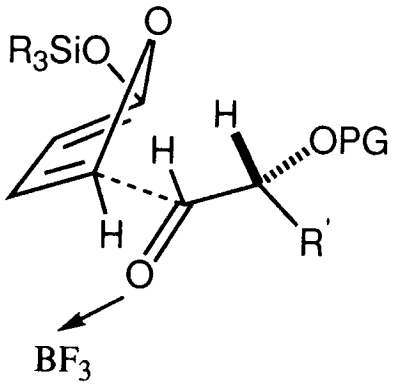
si-si face approach

favored



(4*R*,5*S*)

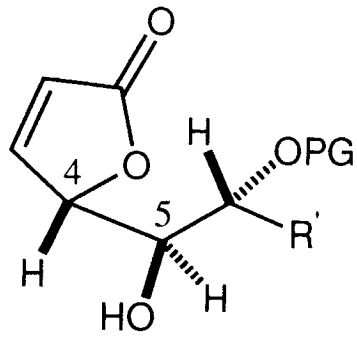
Base-promoted C-4 epimerization



TS2 (Open-chain/Felkin)

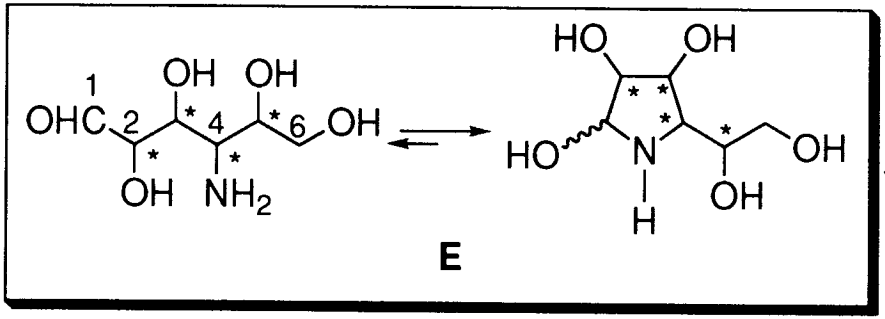
re-si face approach

disfavored

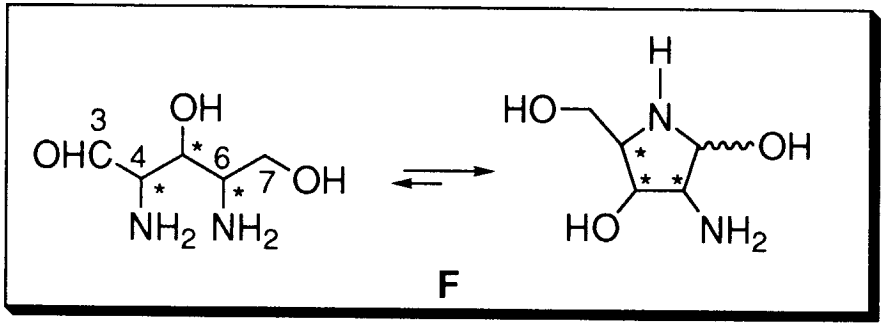


(4*S*,5*S*)

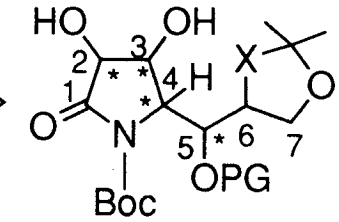
DIVERGENT SYNTHESIS OF HYDROXYLATED PYRROLIDINE DERIVATIVES



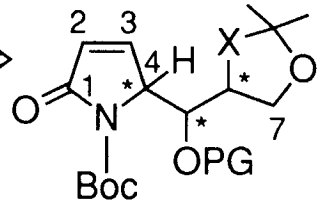
X = O



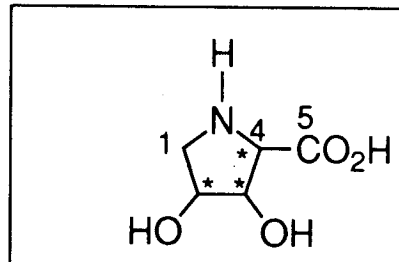
X = N



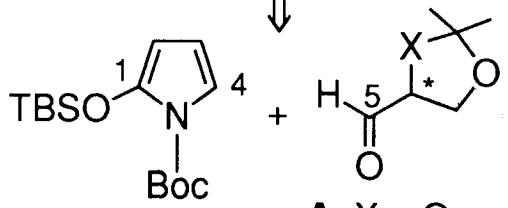
D



C



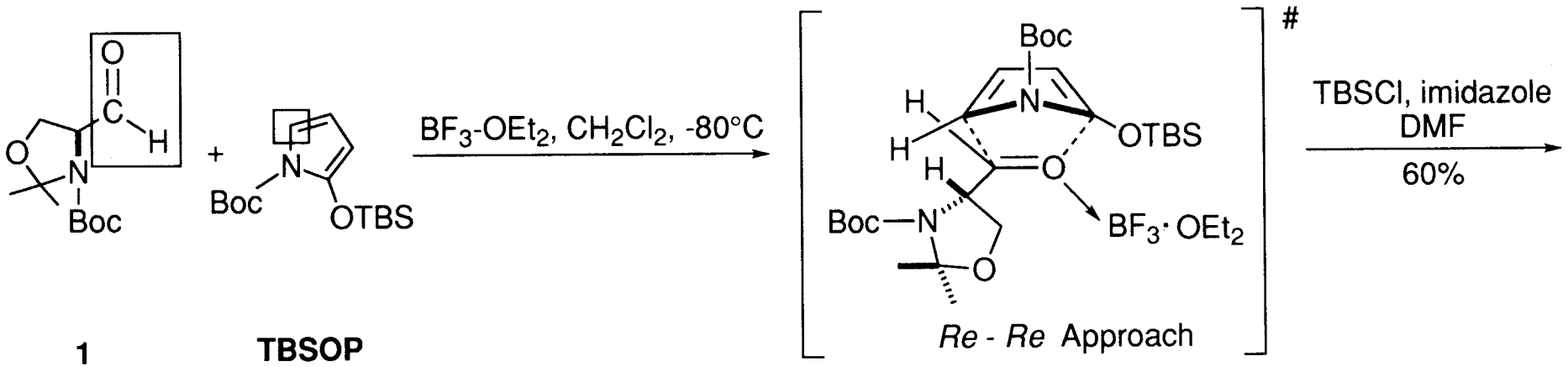
X = O

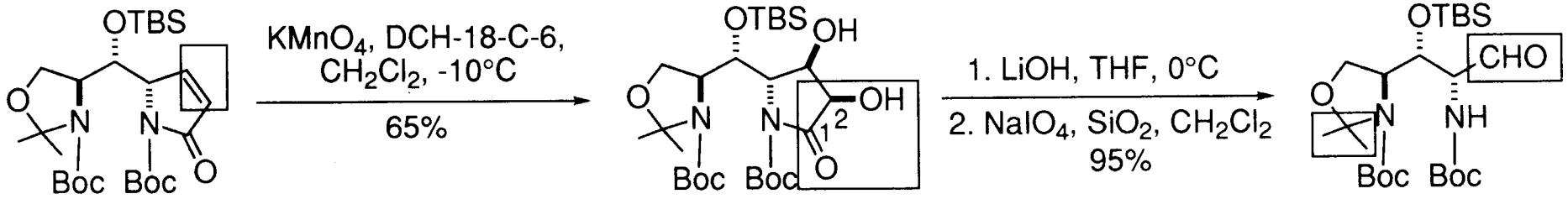


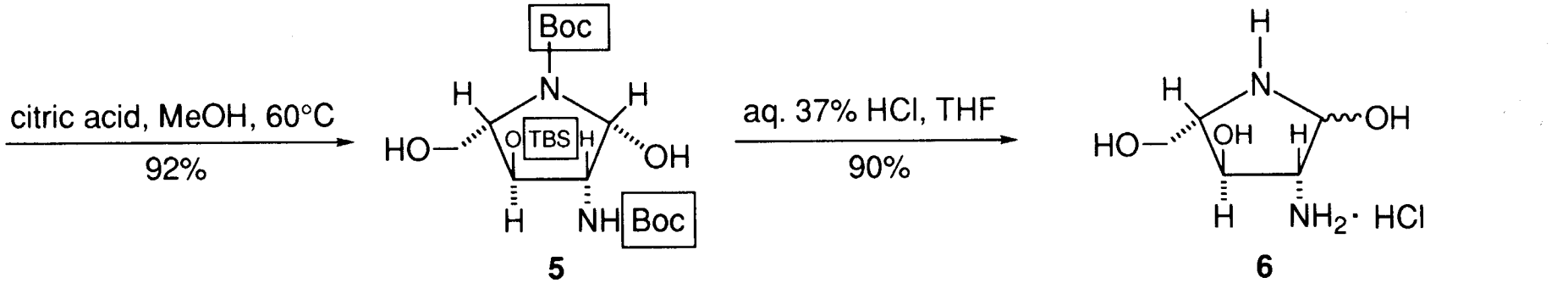
TBSOP

A: X = O
B: X = NBoc

TOTAL SYNTHESIS OF 2,4-DIAMINO-2,4-DIDEOXY-L-ARABINOSE

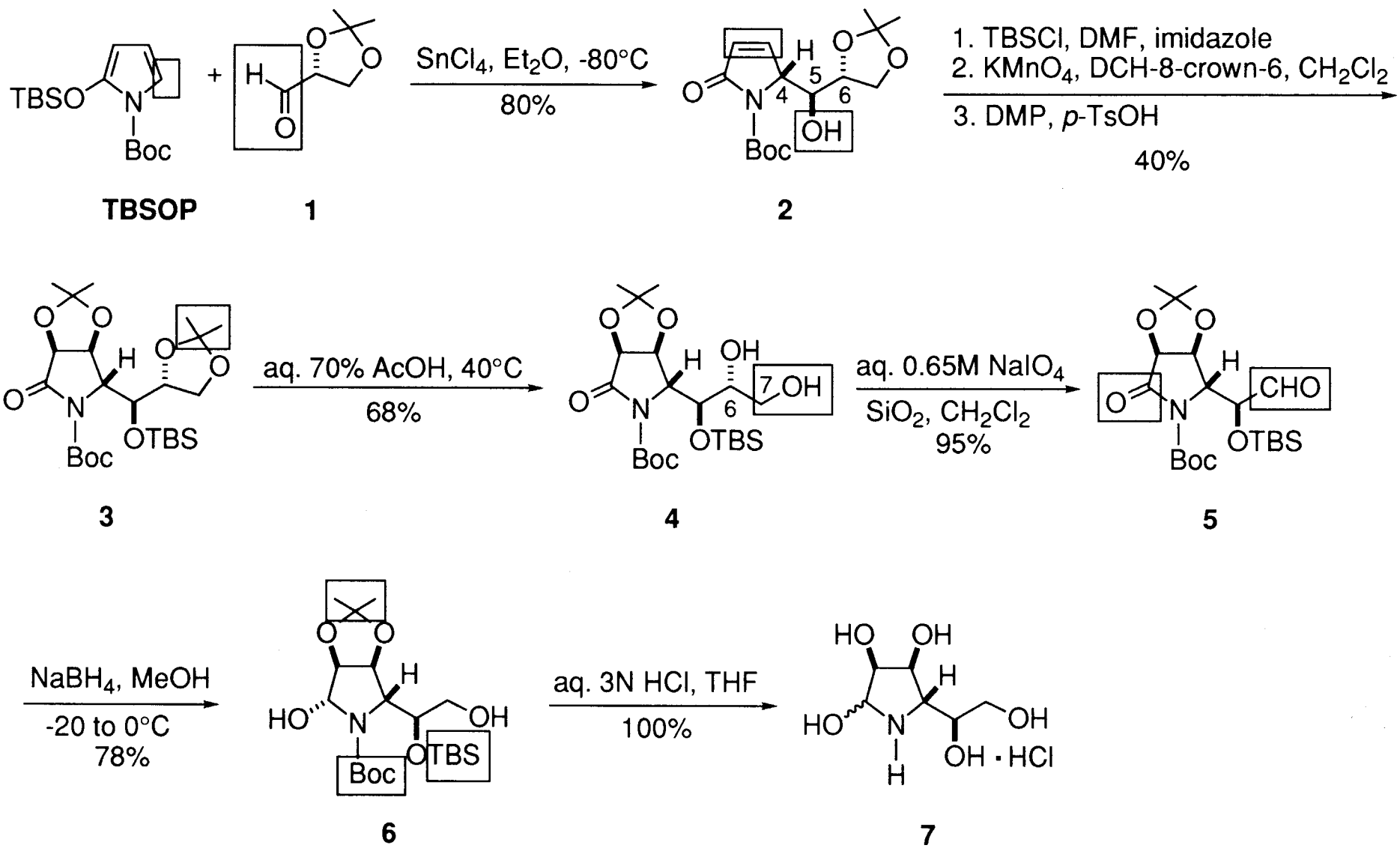






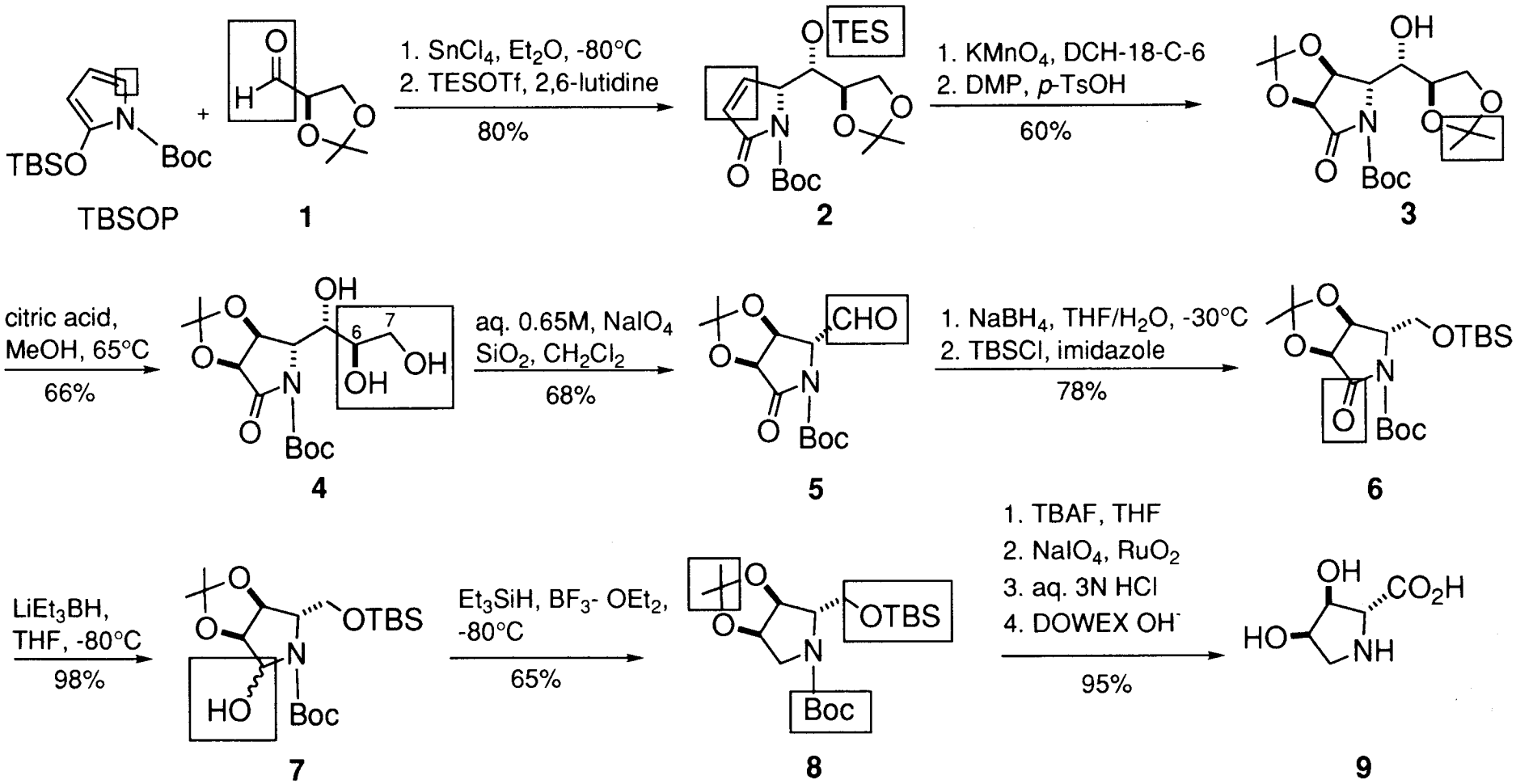
P. SORO et al. *J. Org. Chem.* **1996,** *61*, 5172-5174

SYNTHESIS OF 4-AMINO-4-DEOXY-D-TALOSE



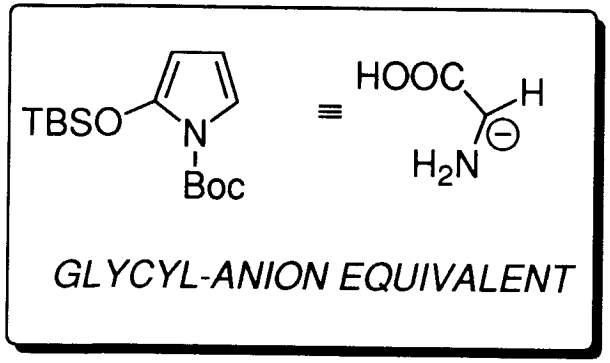
P. SPANU et al. *Tetrahedron* **1996**, *52*, 4829-4838

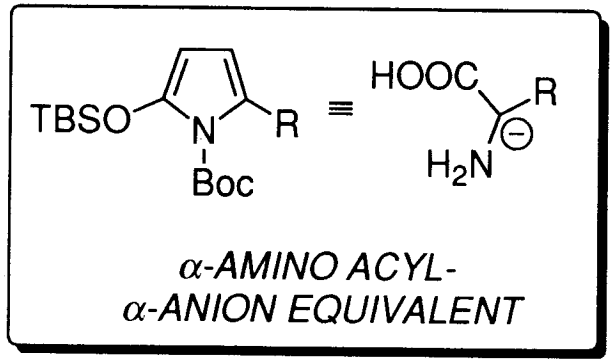
TOTAL SYNTHESIS OF *TRANS*-2,3-*CIS*-3,4-DIHYDROXY-D-PROLINE

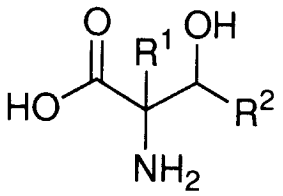


F. ZANARDI et al. *Tetrahedron Asymmetry* **1996**, *7*, 1167-1180

PROJECTED SYNTHESIS OF HYDROXYLATED α-AMINO ACIDS

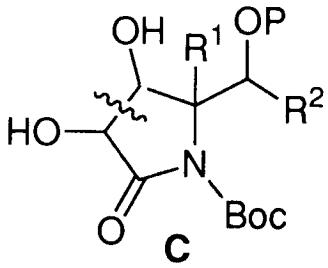






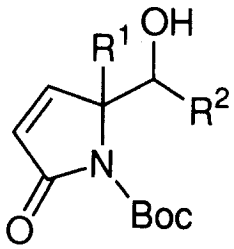
D

C(2)-C(3) fission ⟹



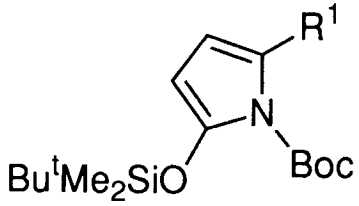
C

dihydroxylation ⟹



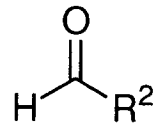
B

homologation ⟹



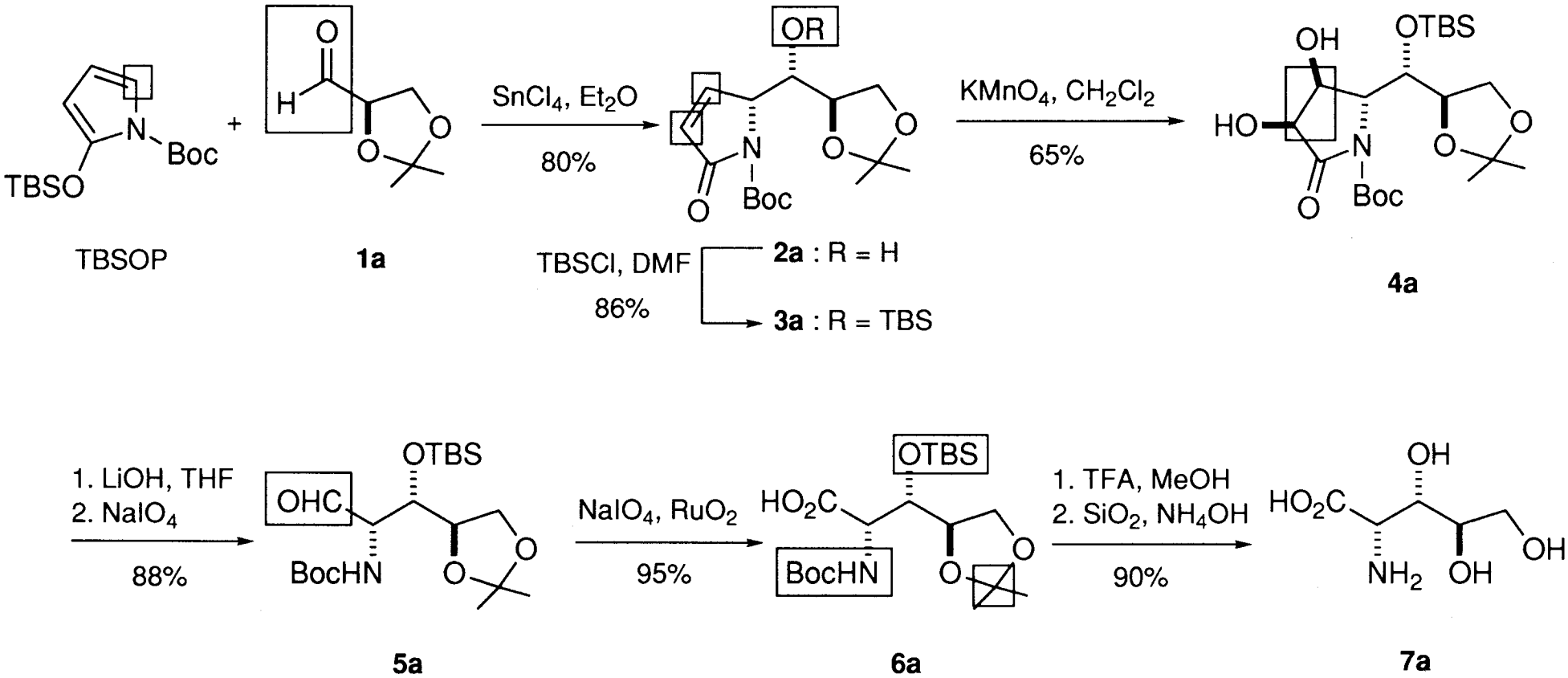
TBSOP

\+



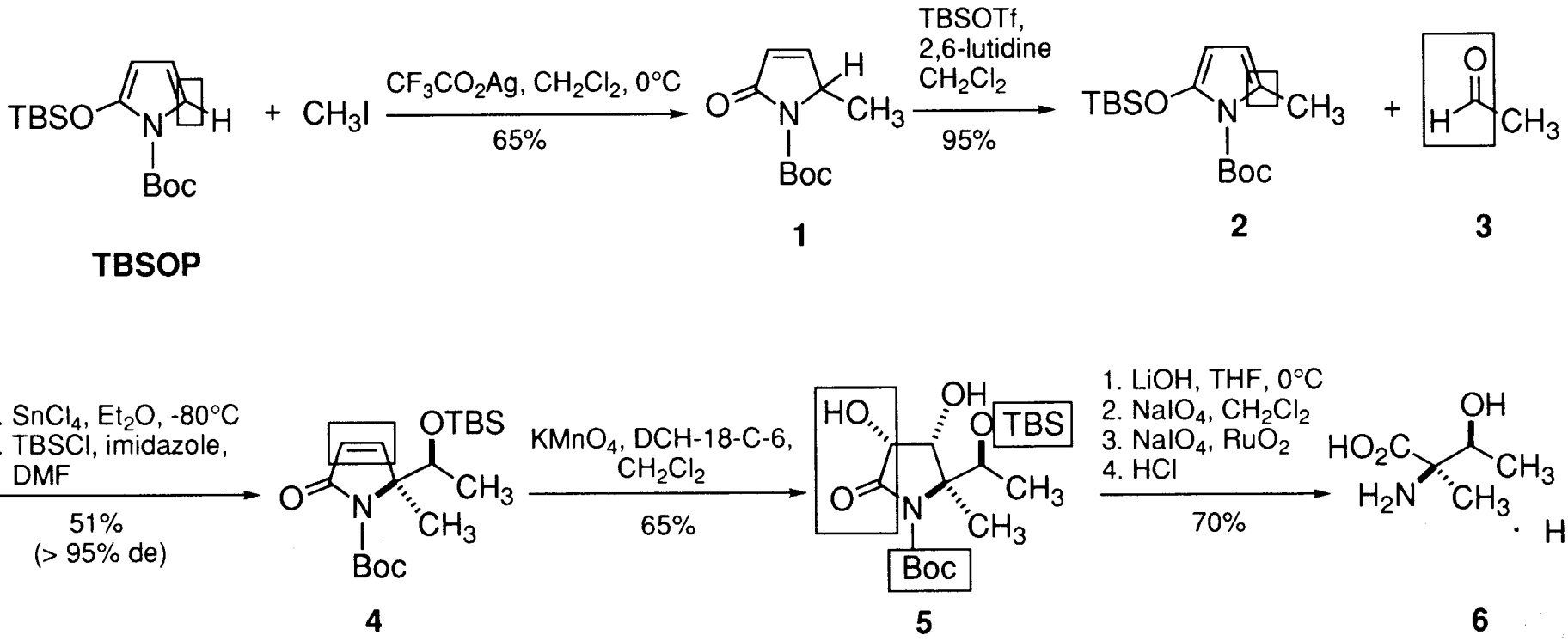
A

OPTIMIZED SYNTHETIC PROTOCOL TO 4-*epi*-POLYOXAMIC ACID



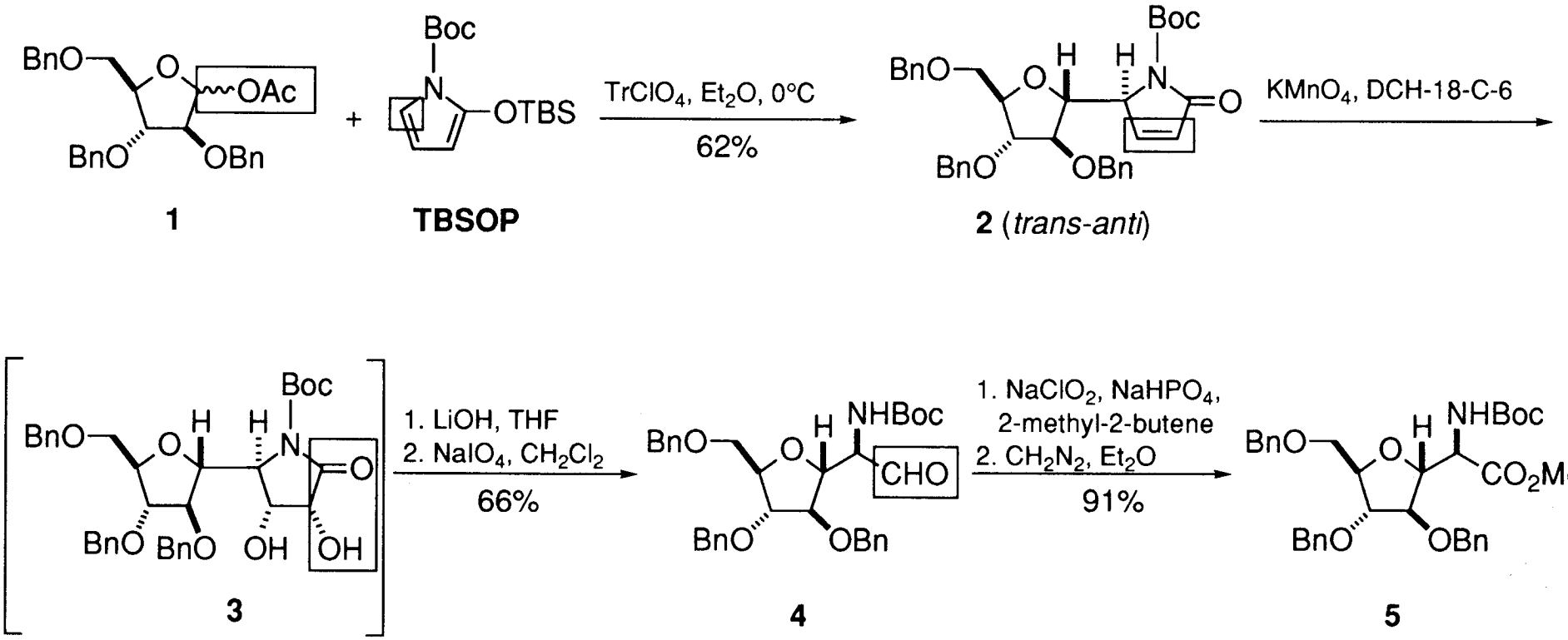
G. RASSU et al. *J. Chem. Soc. Perkin Trans. I* **1994**, 2431-2437

TOWARDS α-ALKYL-β-HYDROXY-α-AMINO ACIDS: TOTAL SYNTHESIS OF (±)-α-METHYLTHREONINE BY SEQUENTIAL γ,γ-FUNCTIONALIZATION



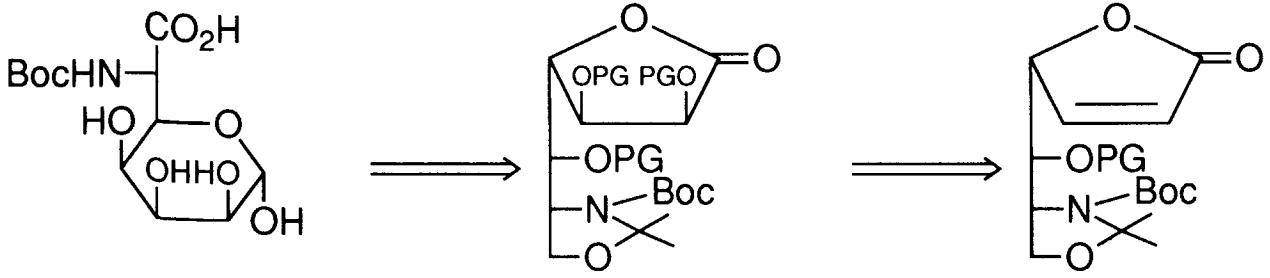
F. ZANARDI et al. *J. Chem. Soc. Perkin Trans. I* **1995**, 2471-2475

DIASTEREOSELECTIVE SYNTHESIS OF α-*C*-ARABINOFURANOSYL GLYCINE: AN "*ANOMERIC*" *C*-CLYCOSYL-α-AMINO ACID

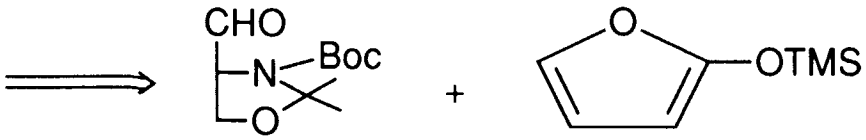


G. RASSU et al. *Tetrahedron Asymmetry* **1995**, *6*, 371-374

"TERMINAL" C-GLYCOSYL-α-AMINO ACIDS: RETROSYNTHETIC ANALYSIS

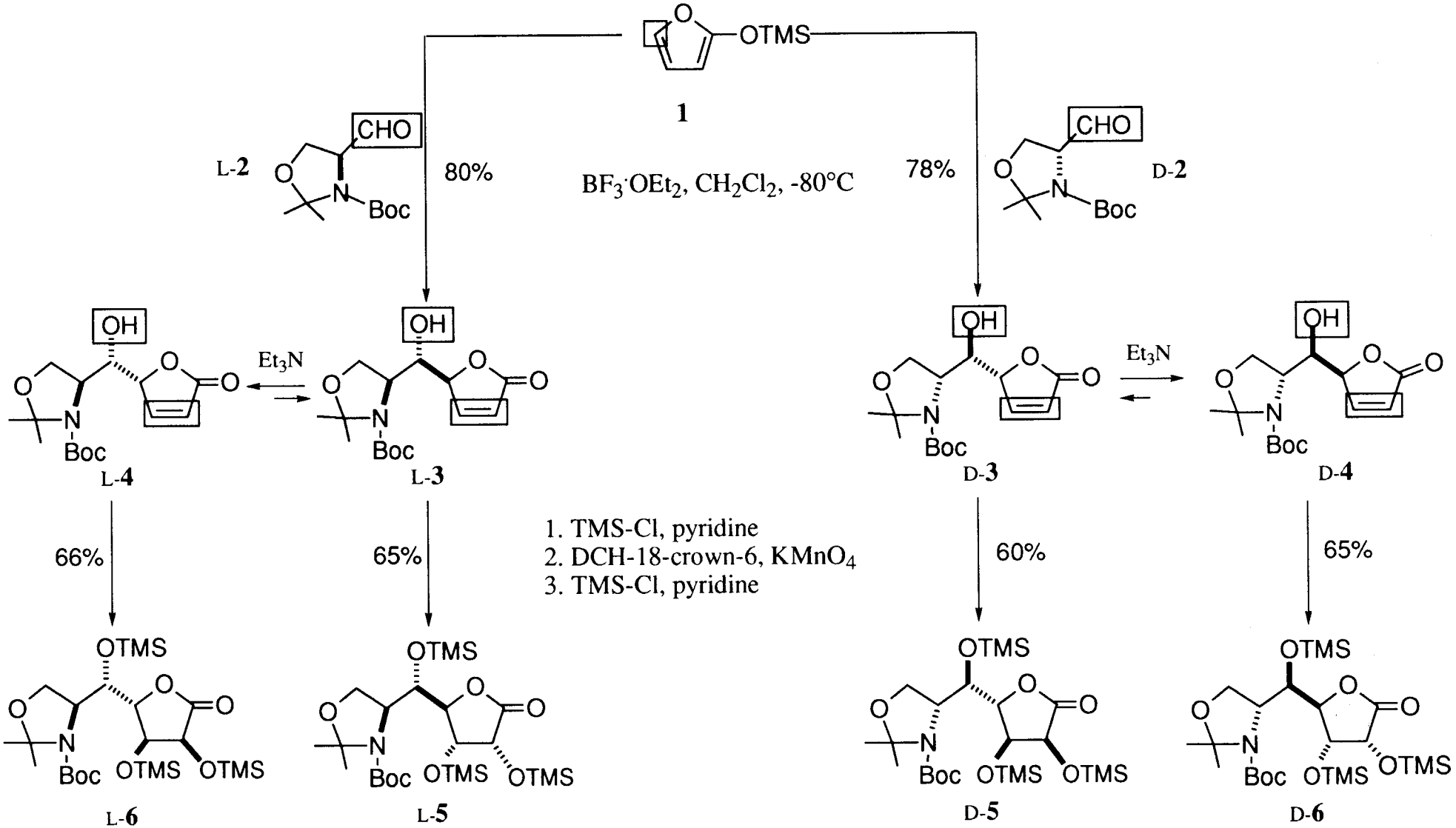


A **B** **C**



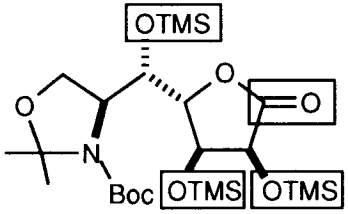
D **TMSOF**

SYNTHESIS OF 6-DEOXY-6-AMINOHEPTOPYRANURONIC ACIDS (I)

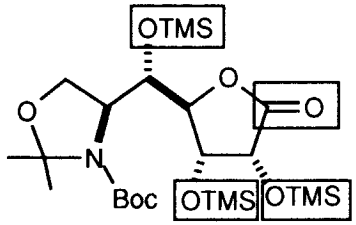


G. CASIRAGHI et al. *J. Org. Chem.* **1991**, *56*, 6523-6527

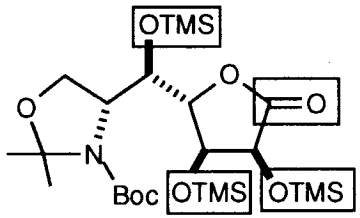
SYNTHESIS OF 6-DEOXY-6-AMINOHEPTOPYRANURONIC ACIDS (II)



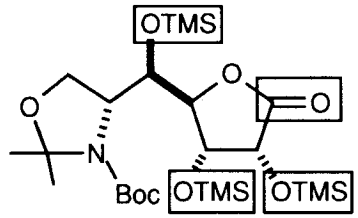
L-**6**



L-**5**



D-**5**



D-**6**

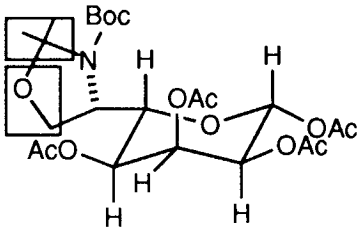
81%

78%

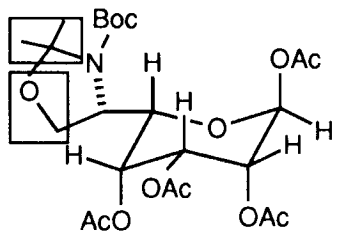
1. DIBALH, CH_2Cl_2, -80°C
2. MeOH, citric acid
3. Ac_2O, pyridine, DMAP

80%

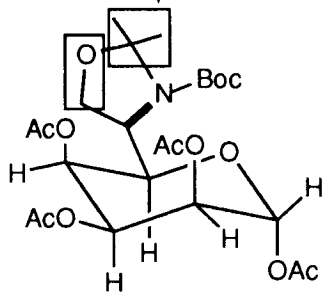
75%



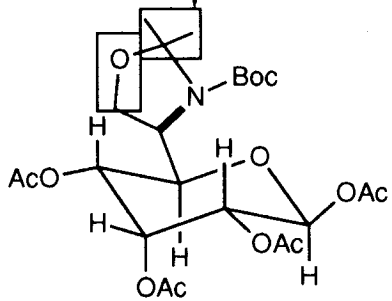
L-**8**



L-**7**



D-**7**



D-**8**

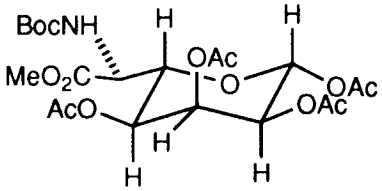
88%

81%

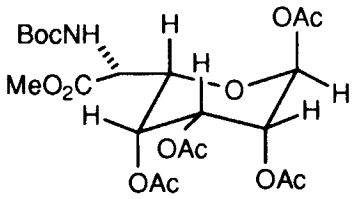
1. 70% aq. AcOH, 60°C
2. $NaIO_4$, cat. $RuO_2.H_2O$
3. CH_2N_2, Et_2O

84%

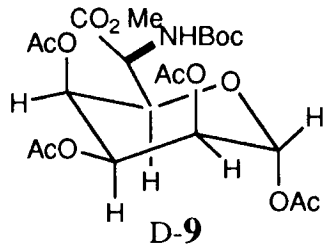
80%



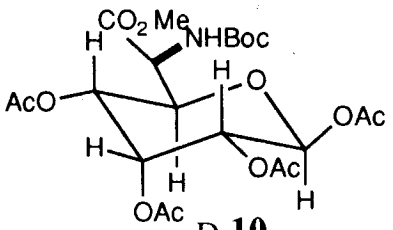
L-**10**



L-**9**



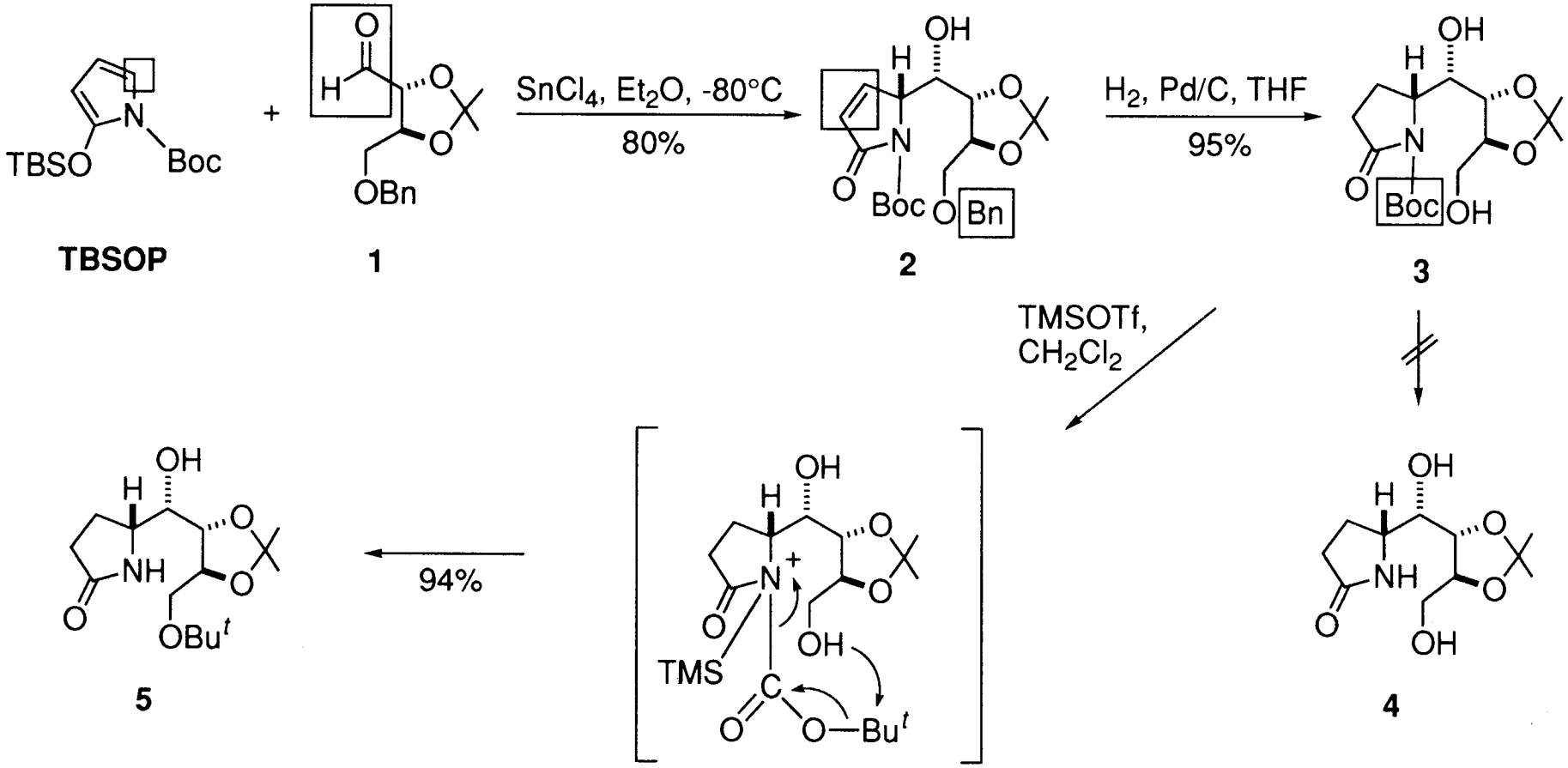
D-**9**



D-**10**

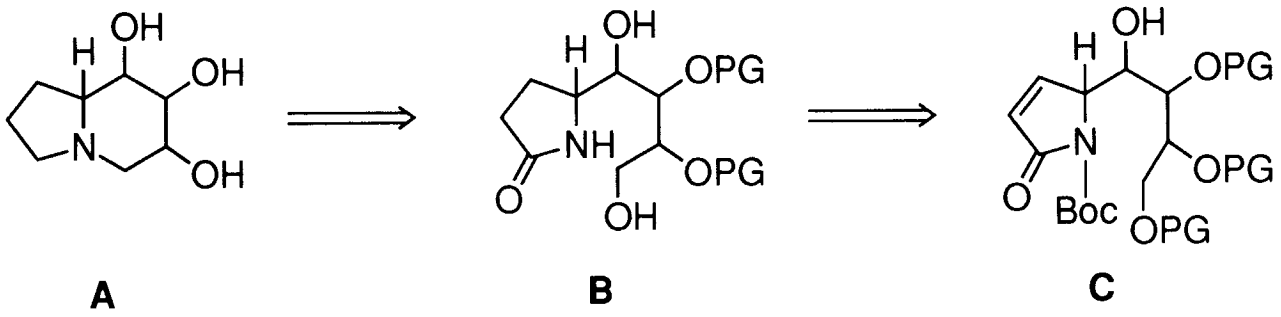
G. CASIRAGHI et al. *J. Org. Chem.* **1991**, *56*, 6523-6527

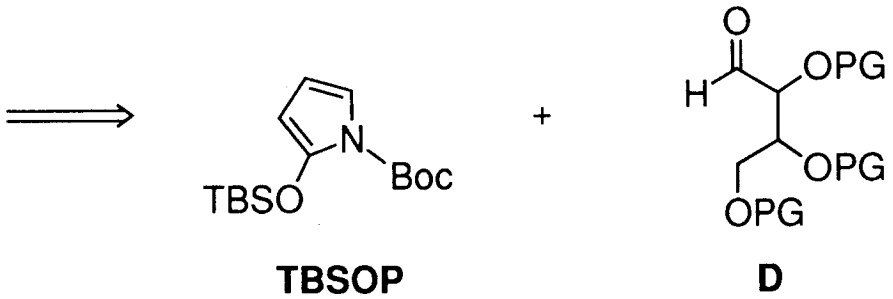
TOTAL SYNTHESIS OF 1-DEOXY-8-*epi*-CASTANOSPERMINE (I)



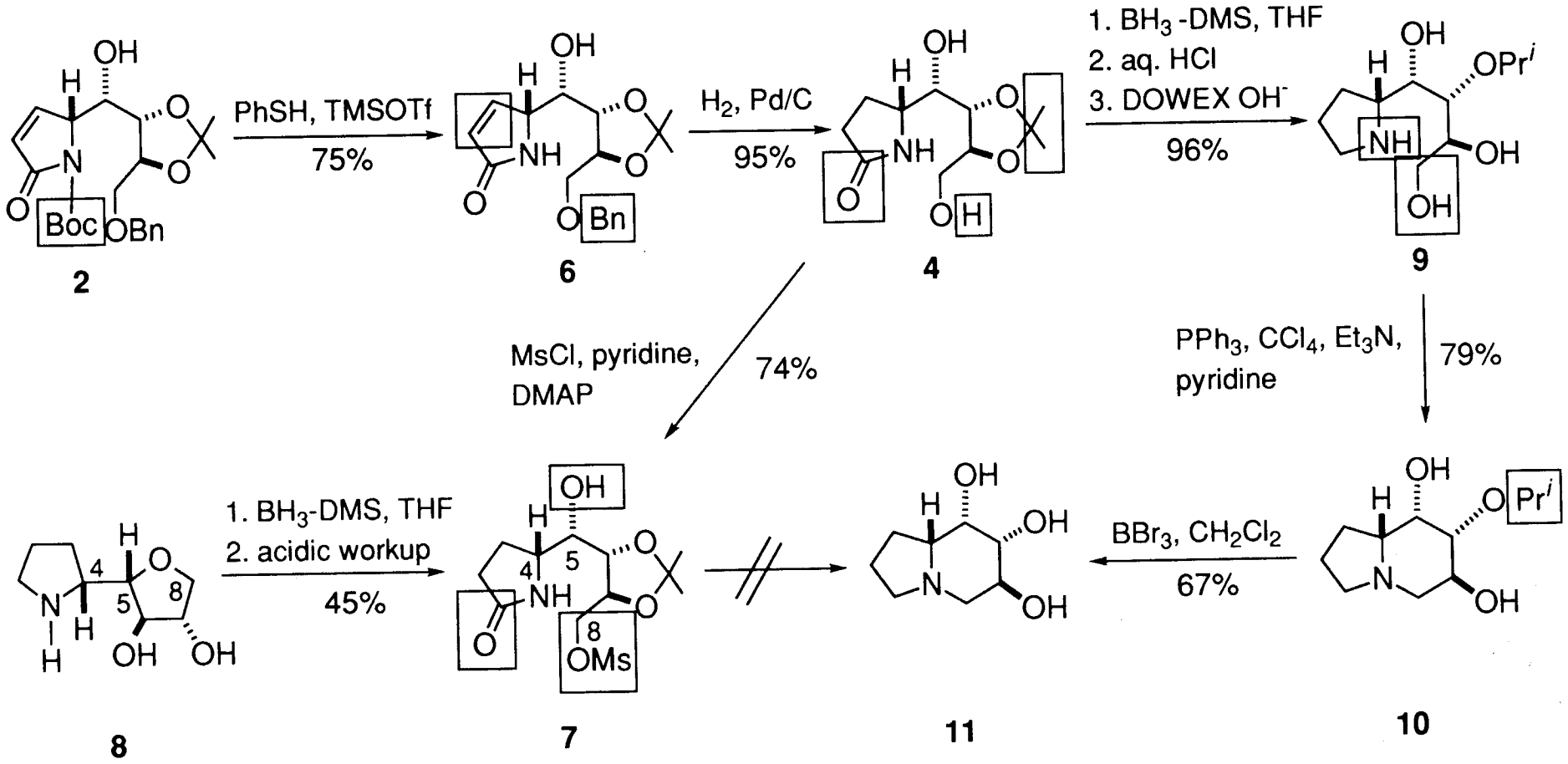
G. CASIRAGHI et al. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2991-2997

PROJECTED ROUTE TO 1-DEOXY-CASTANOSPERMINE CONGENERS



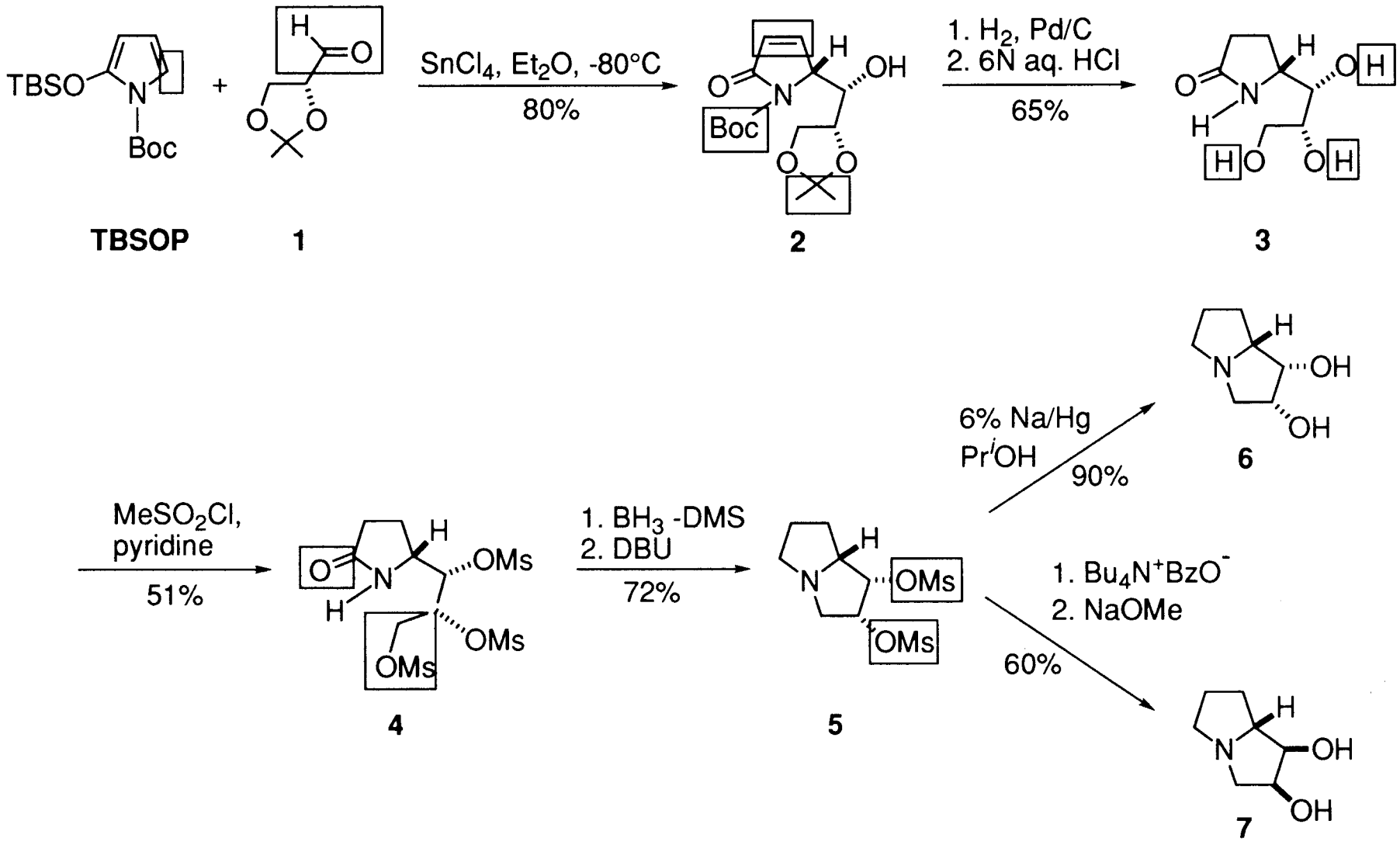


TOTAL SYNTHESIS OF 1-DEOXY-8-*epi*-CASTANOSPERMINE (II)



G. CASIRAGHI et al. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2991-2997

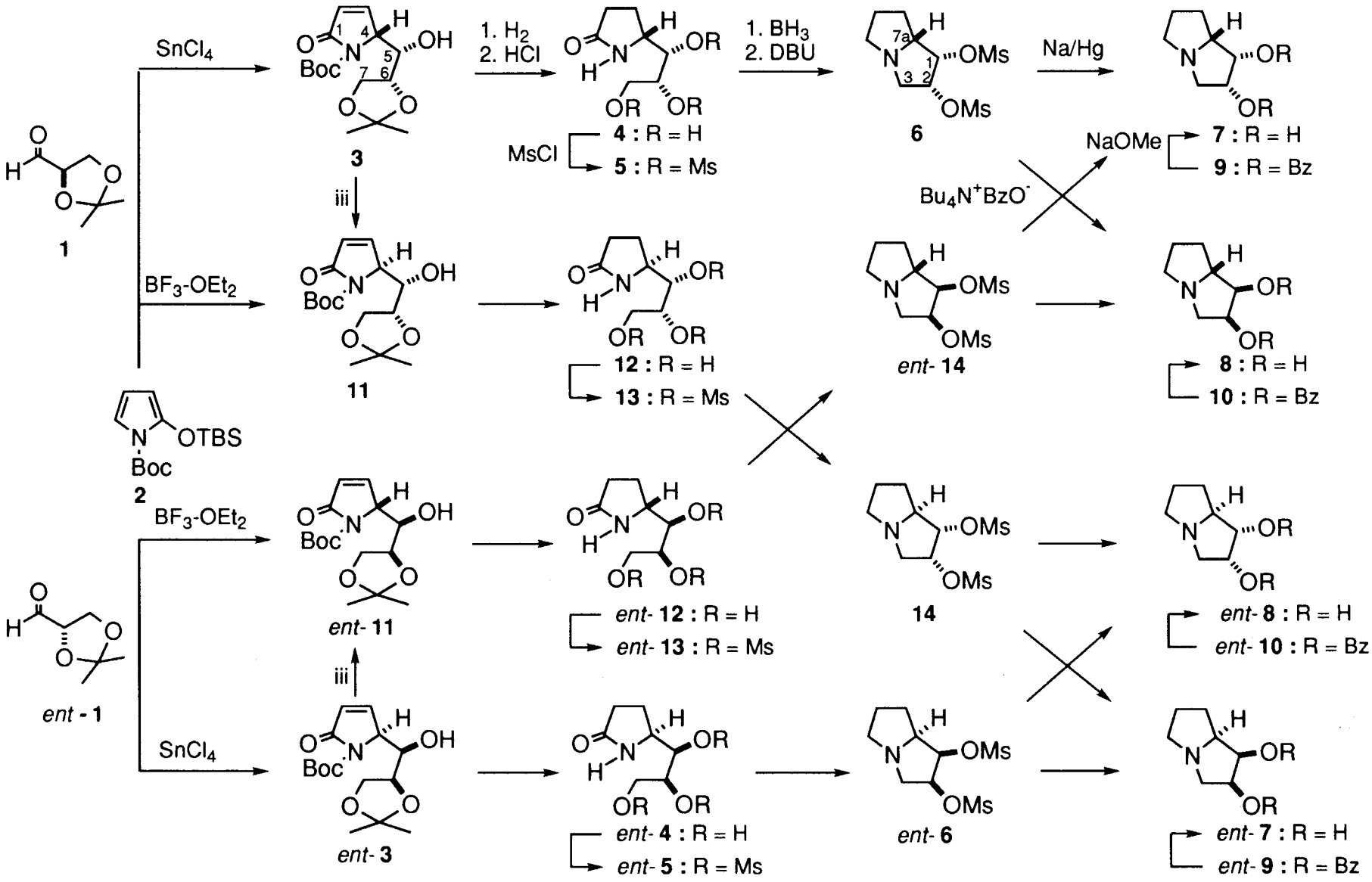
DIVERGENT SYNTHESIS OF *cis*-1,2-DIHYDROXYPYRROLIZIDINE DERIVATIVES



TBSOP **1** **2** **3** **4** **5** **6** **7**

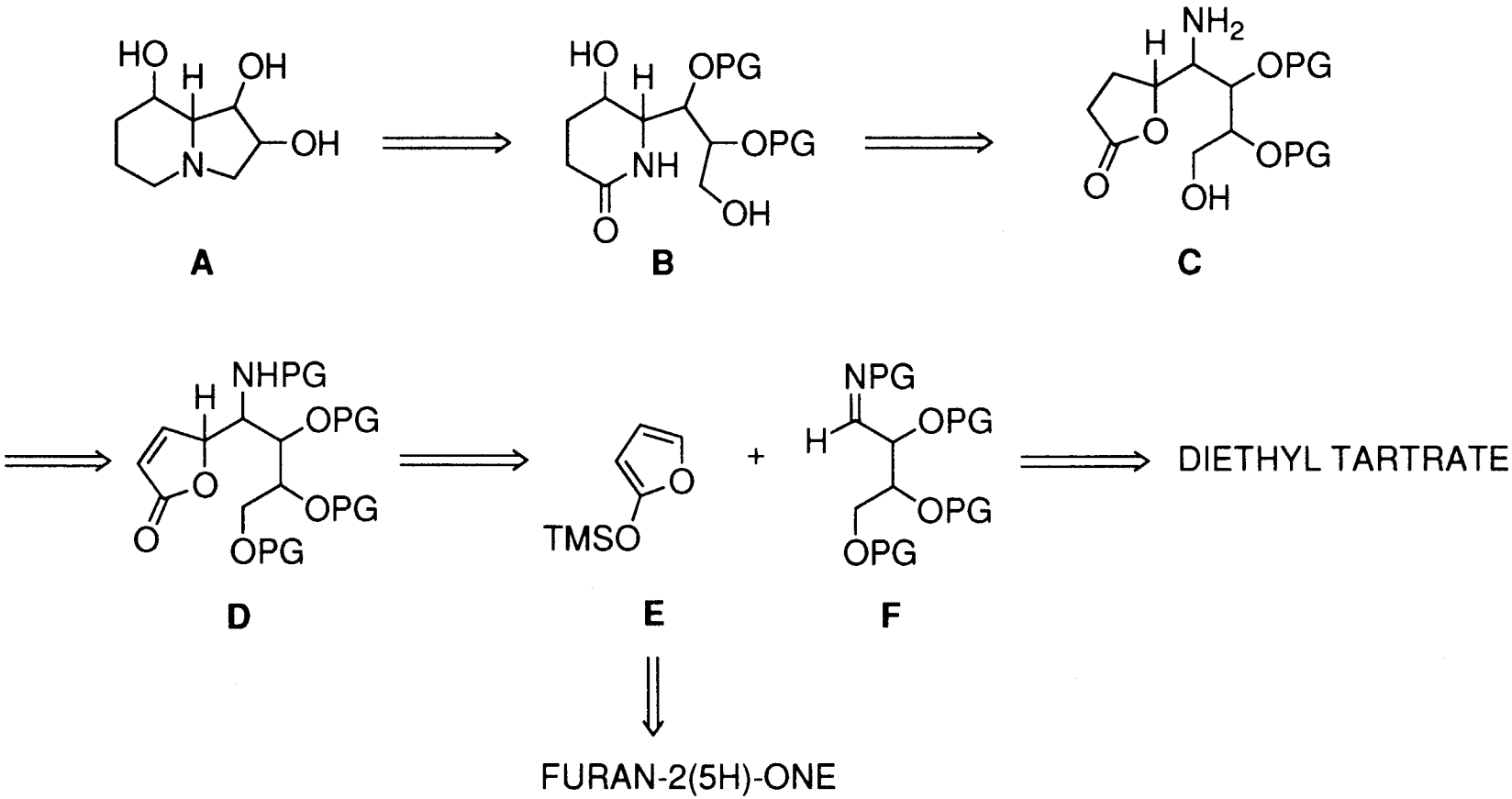
G. CASIRAGHI et al. *J. Org. Chem.* **1994**, 59, *2906-2909*

TOTAL SYNTHESIS OF ALL FOUR ISOMERS OF *cis*-1,2-DIHYDROXYPYRROLIZIDINE

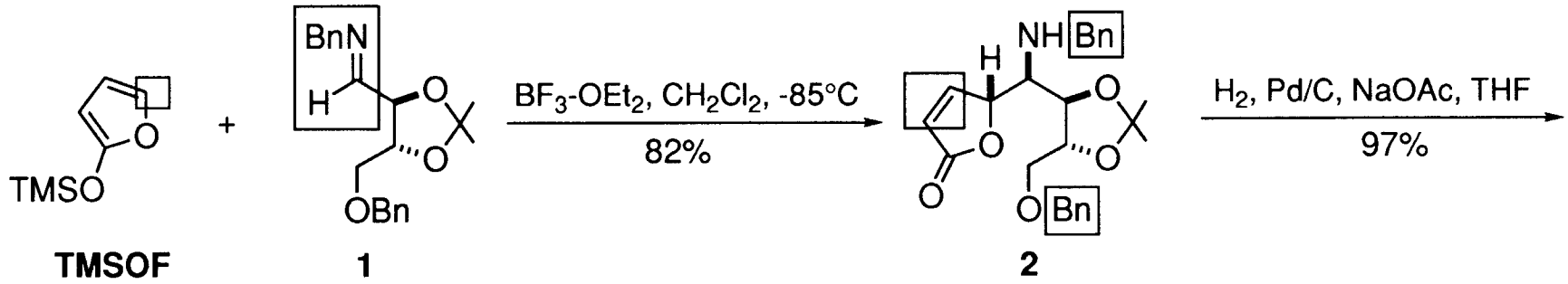


G. CASIRAGHI et al. *J. Org. Chem.* **1994**, *59*, 2906-2909

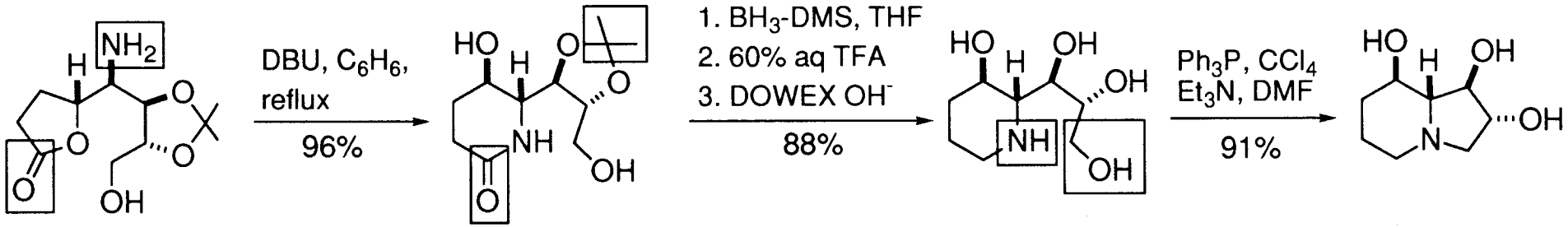
PROJECTED SYNTHESIS OF SWAINSONINE CONGENERS



TOTAL SYNTHESIS OF (-)-1-*epi*-SWAINSONINE



TMSOF **1** **2**

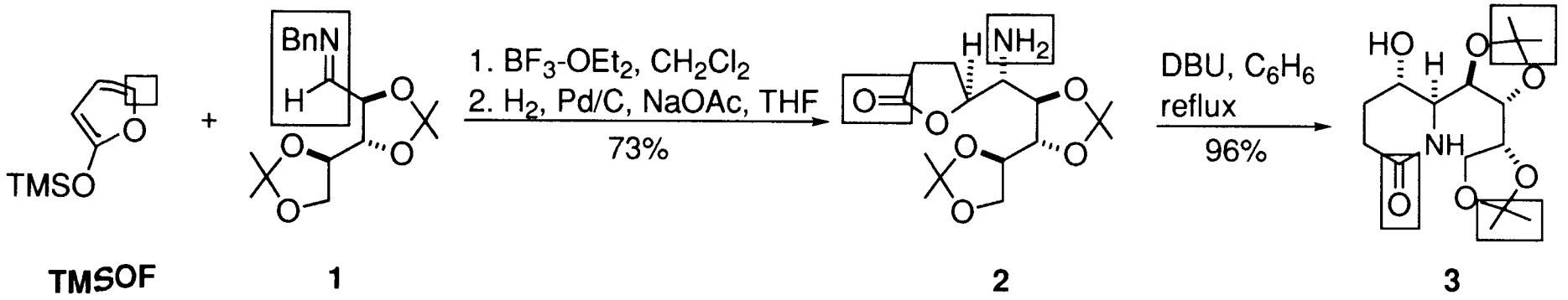


3 **4** **5** **6**

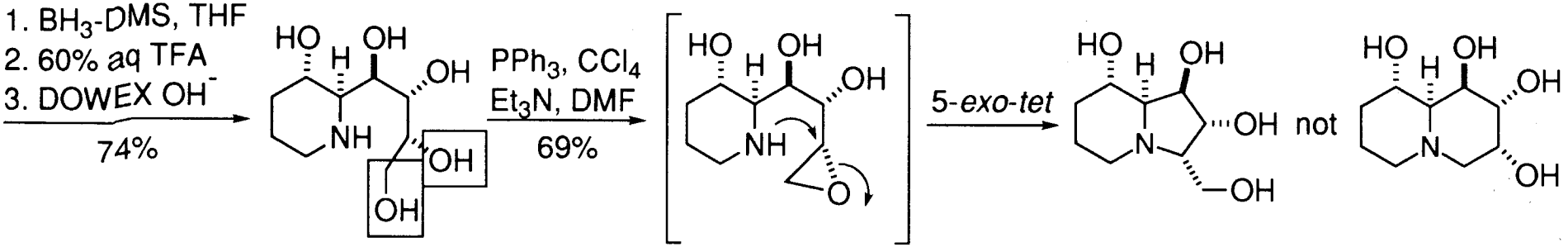
G. CASIRAGHI et al. *J. Org. Chem.* **1993**, *58*, 3397-3400

ATTEMPTED ENTRY TO HYDROXYLATED QUINOLIZIDINES: SYNTHESIS OF A RING-EXPANDED ALEXINE DERIVATIVE

... one can certainly plan research, but not the results.



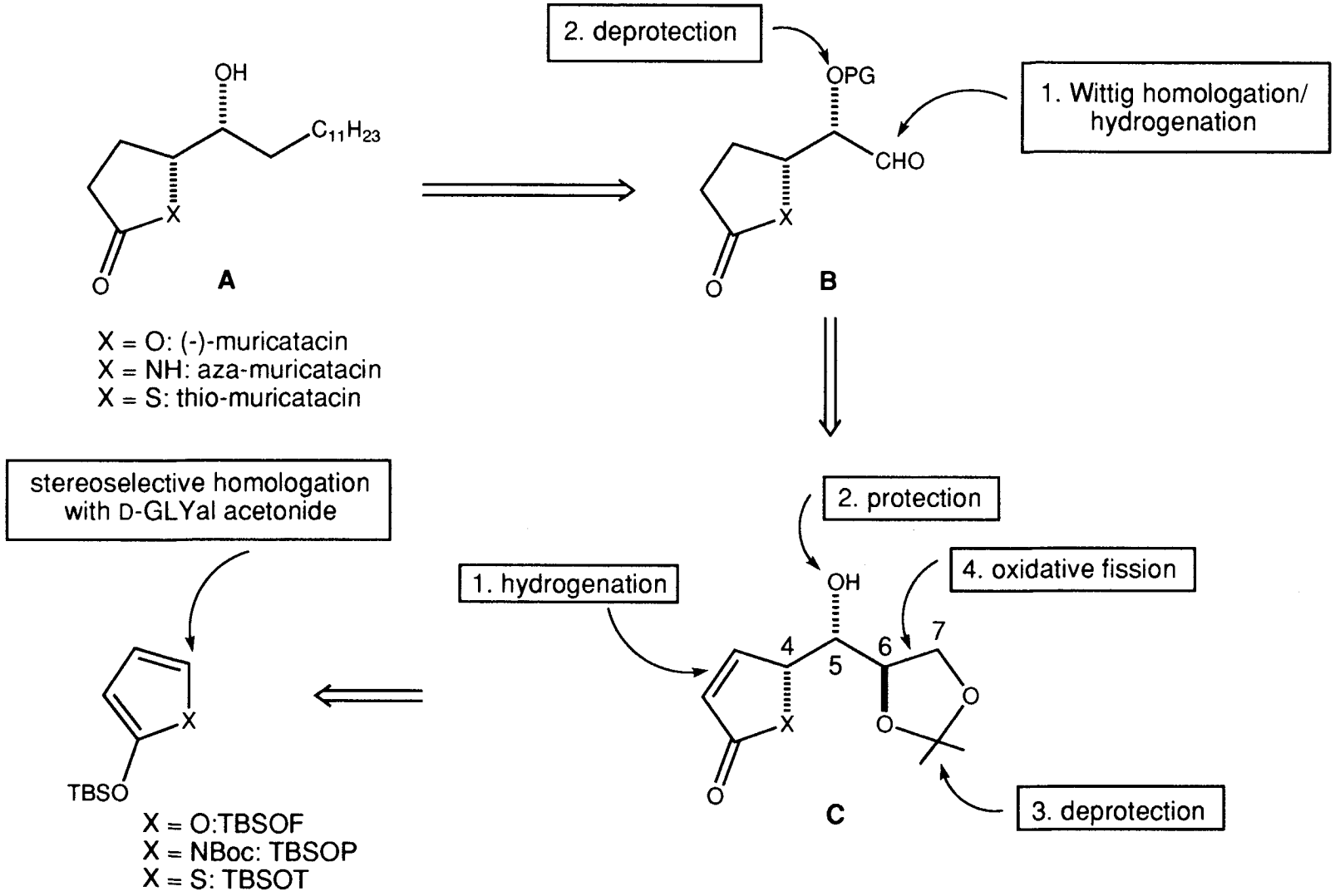
TMSOF **1** **2** **3**



4 **5** **6** **7**

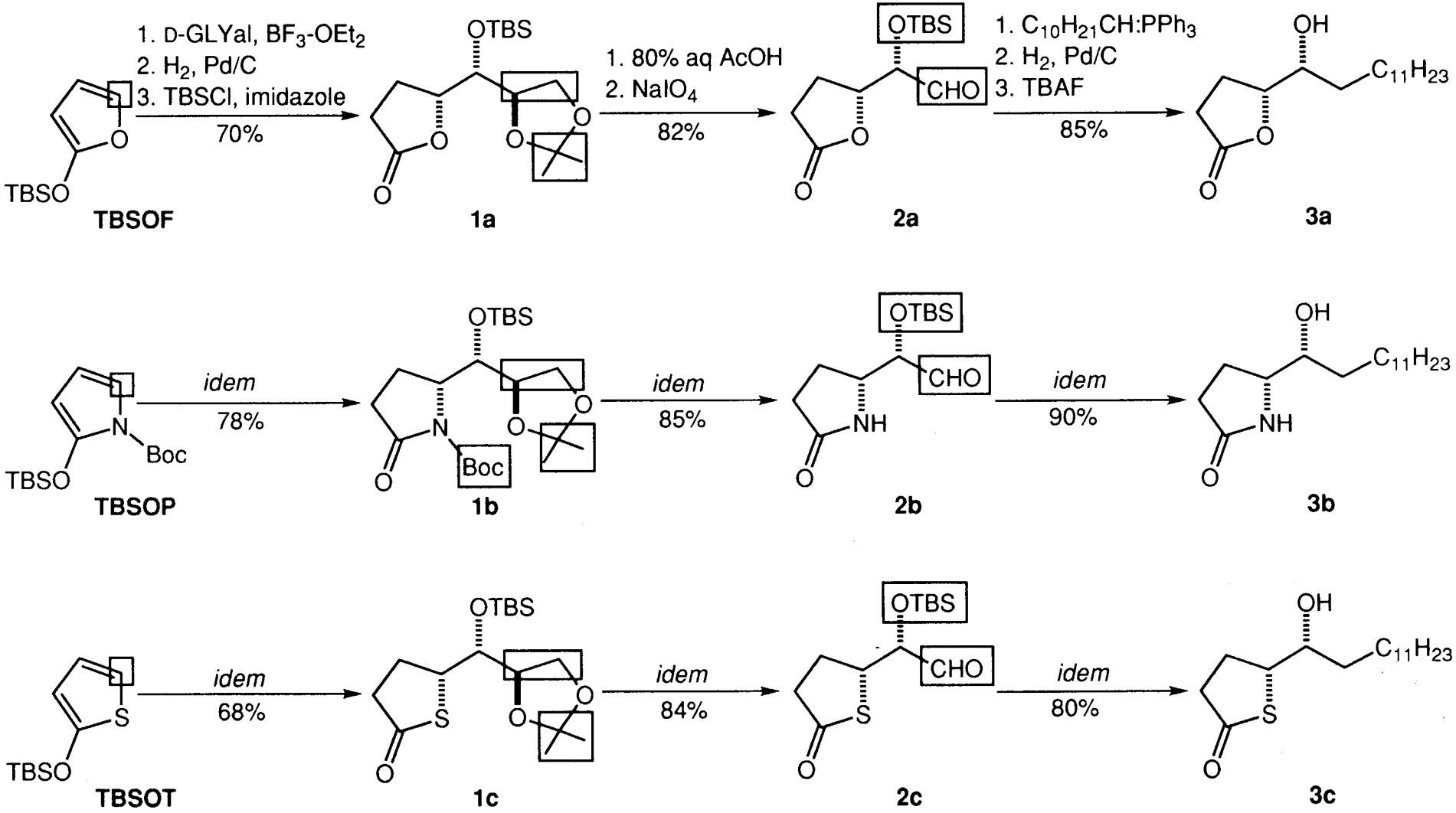
G. CASIRAGHI et al., unpublished results

UNIFORMED PLAN TO (-)-(4*R*,5*R*)-MURICATACIN AND ITS NITROGEN AND SULPHUR MIMICS



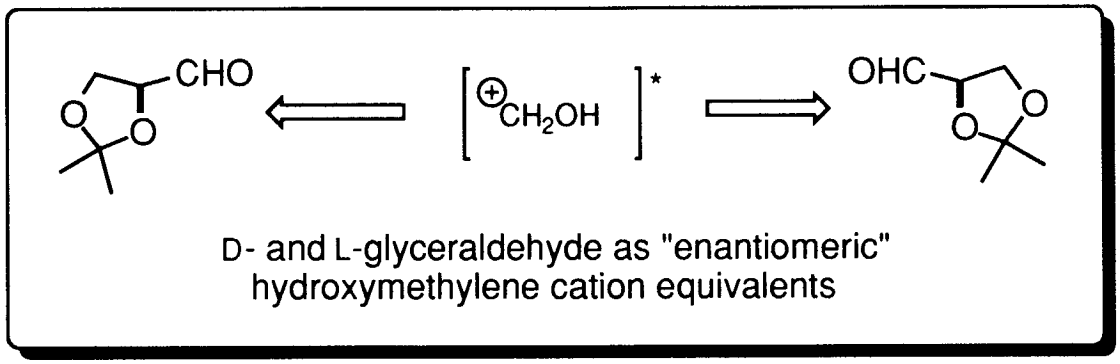
ENANTIOSELECTIVE, PARALLEL SYNTHESES OF MURICATACIN MIMICS

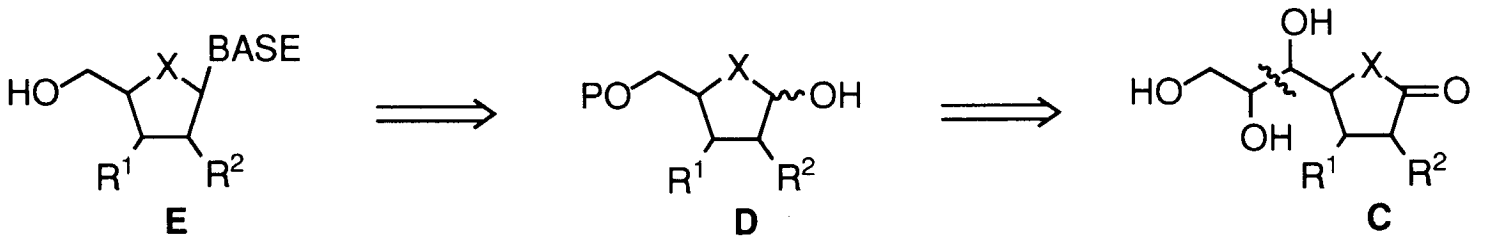
(enantiomeric relatives from L-GLYal)



G. RASSU et al., unpublished results

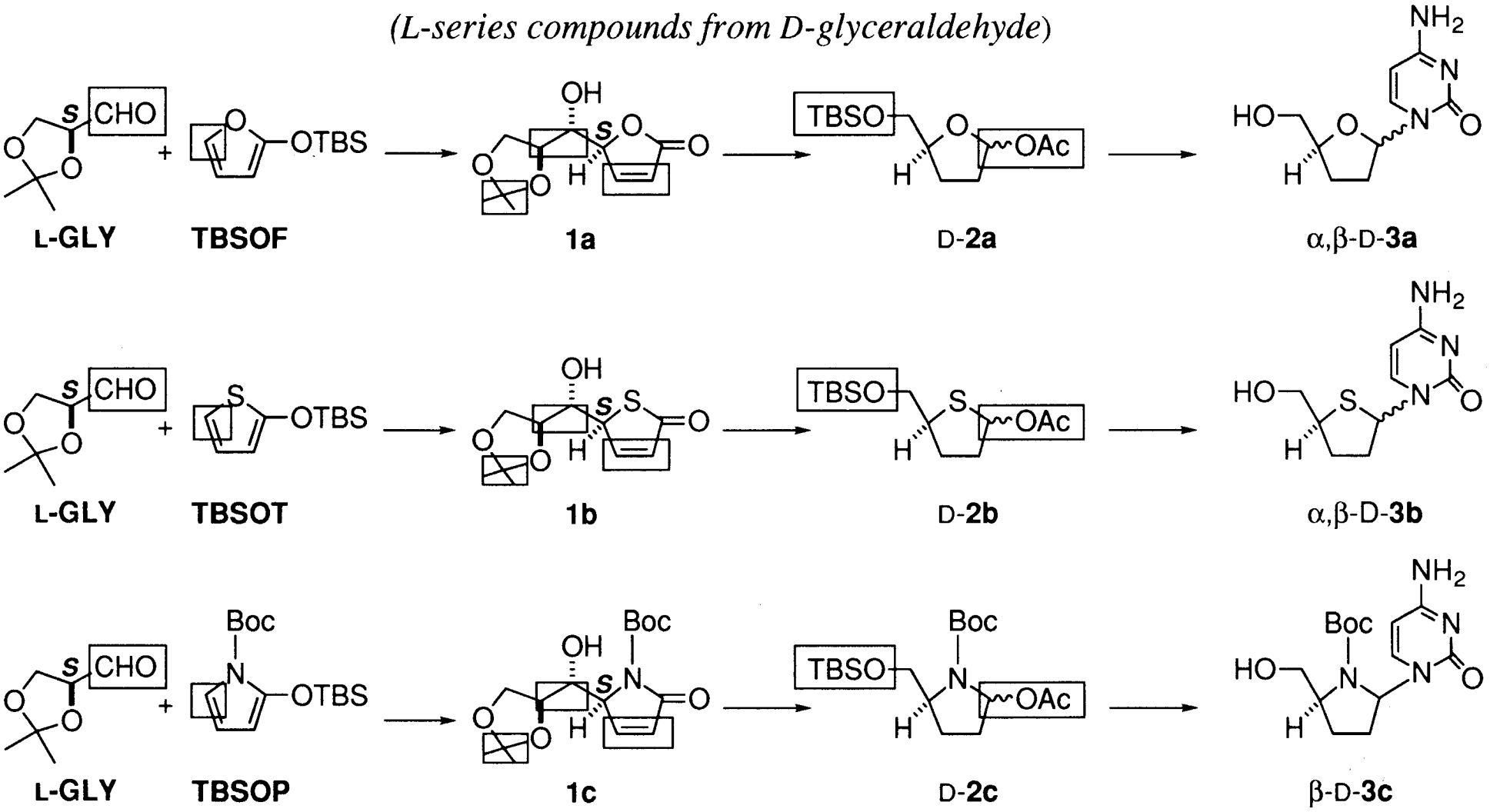
UNIFIED SYNTHESIS OF NUCLEOSIDES AND NUCLEOSIDE MIMETICS





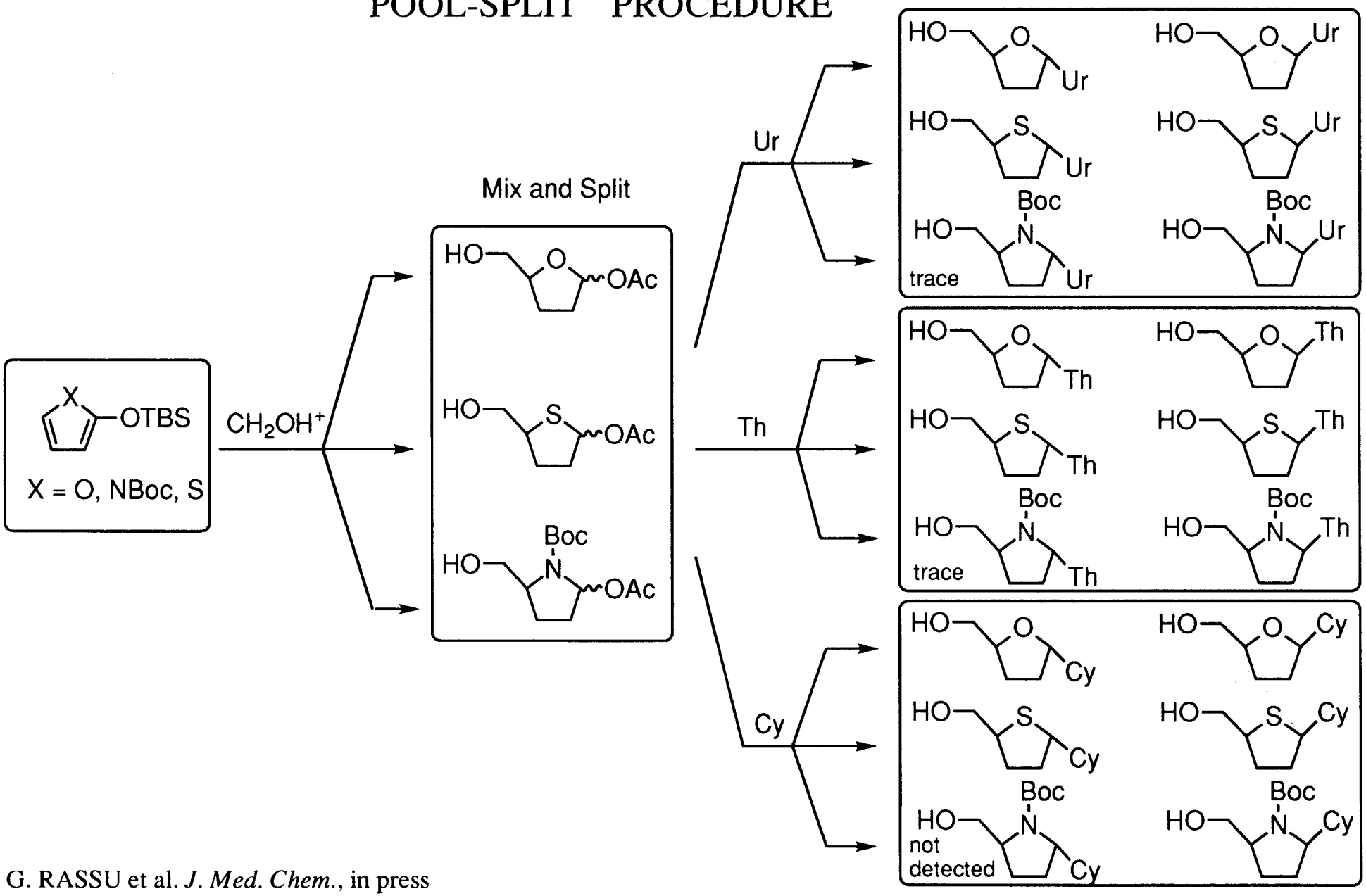
PARALLEL SYNTHESES OF CYTIDINE NUCLEOSIDES OF THE D-SERIES

(L-series compounds from D-glyceraldehyde)



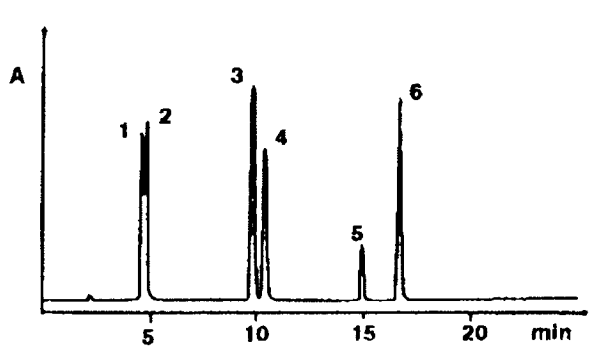
G. RASSU et al. *J. Med. Chem.*, in press

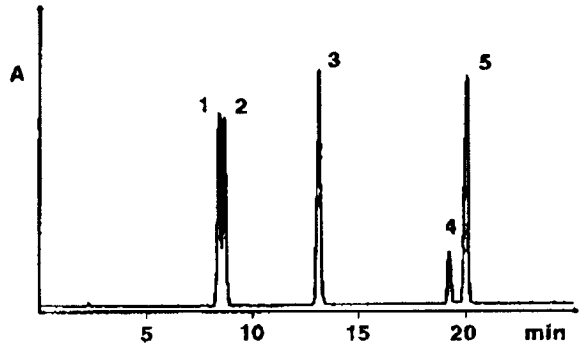
ASSEMBLY OF A SMALL NUCLEOSIDE COLLECTION BY IN-SOLUTION "POOL-SPLIT" PROCEDURE

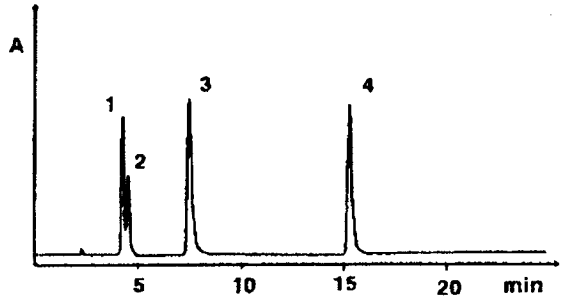


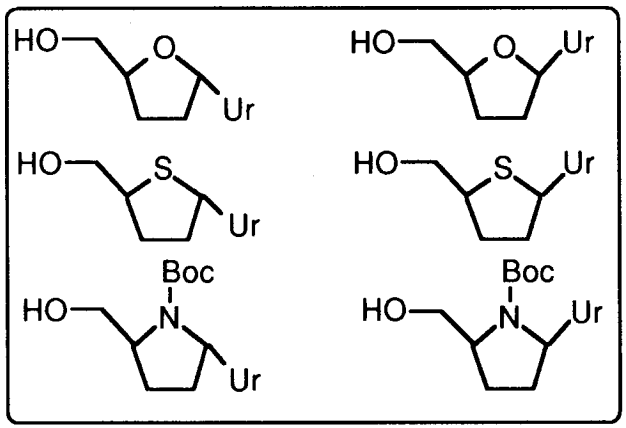
G. RASSU et al. *J. Med. Chem.*, in press

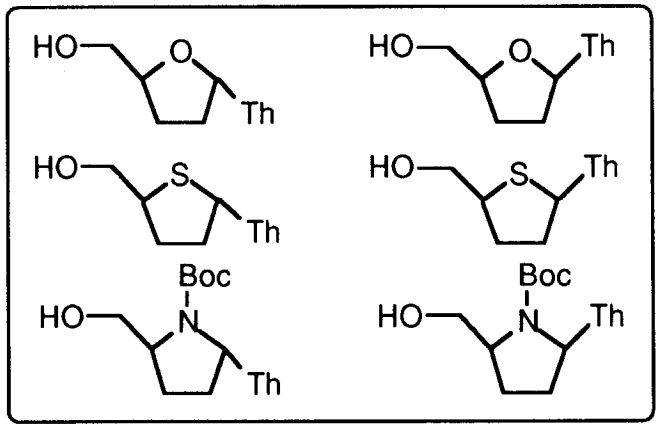
HPLC ANALYSES OF URIDINE, THYMIDINE, AND CYTIDINE SUBLIBRARIES

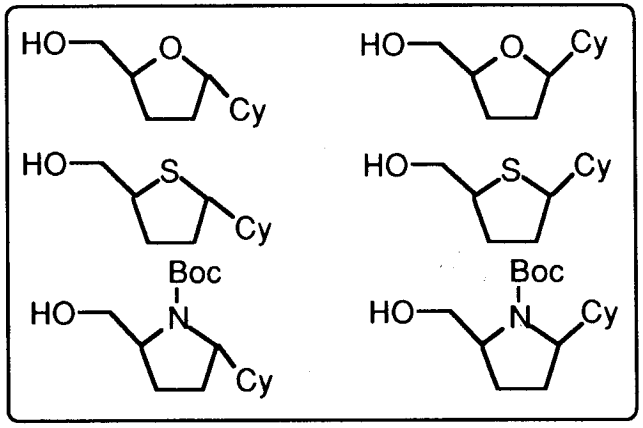












G. RASSU et al. *J. Med. Chem.*, in press

THE SILOXYDIENE ROUTE: ACHIEVEMENTS