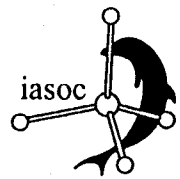


ISCHIA ADVANCED SCHOOL OF ORGANIC CHEMISTRY

New Challenges of Organic Synthesis in the 21st Century

Catalysis, a Key Technology for the Pharmaceutical Industry Past and Future

Walter Cabri

September 23-28

PROCESS RESEARCH AND DEVELOPMENT

1. INDUSTRIAL SYNTHESIS DESIGN
   - LOW COST
   - LOW ENVIRONMENTAL IMPACT
   - "ATOM ECONOMY"
   - FLEXIBLE

2. PATENT PROTECTION

3. MATERIAL SUPPLY

4. REGISTRATION SUPPORT

PROCESS RESEARCH AND DEVELOPMENT

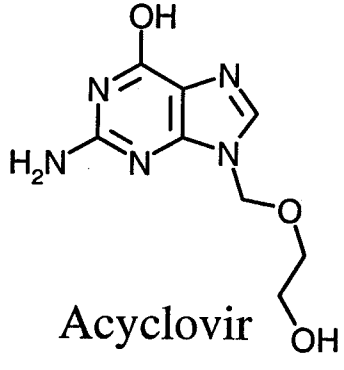
MULTIDISCIPLINARY APPROACH

- CHEMISTRY
- BIOLOGY
- BIOCHEMISTRY
- ENGENEERING

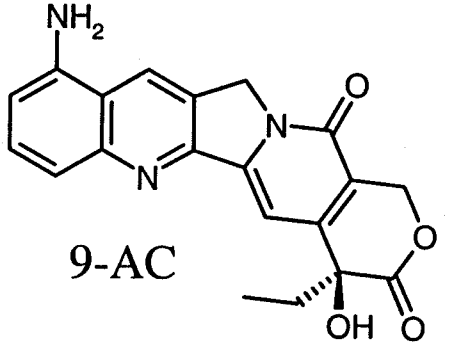
INDUSTRIAL ATOM ECONOMY CONCEPT

Industrially the simple consideration that all the materials (starting materials, solvents, water, gas, charcoal and filter aid, etc.) you put in a vessel come out as product or waste, has a dramatic impact on the"atom economy" concept.

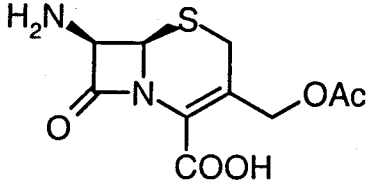
Atom incorporation, selectivity are important, but also to maximise concentrations, to recycle solvents or reagents, to minimise waste, have a determinant direct impact on productivity and cost.



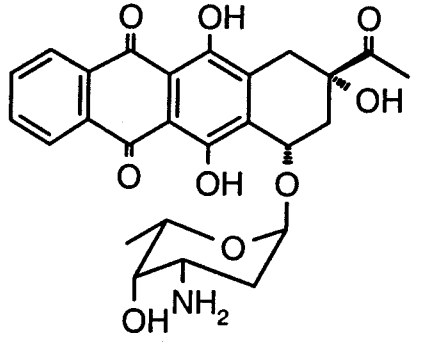
Acyclovir



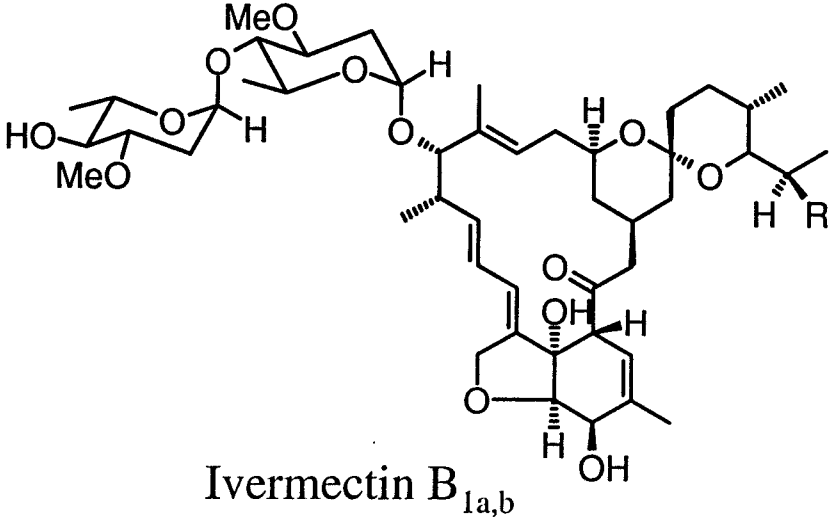
9-AC



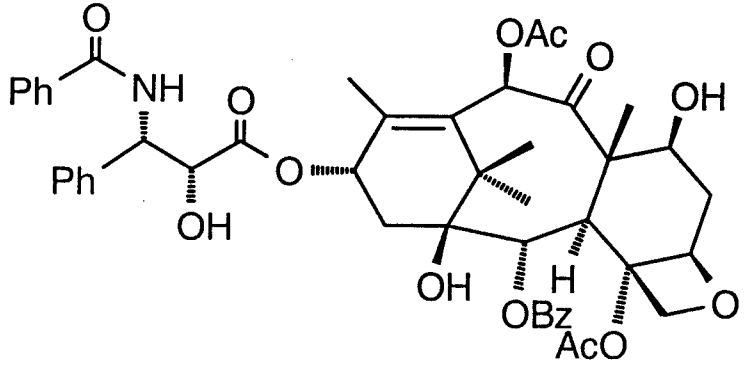
7-ACA



Idarubicin

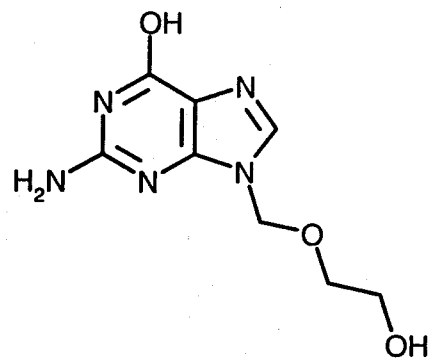


Ivermectin $B_{1a,b}$



Paclitaxel

ACYCLOVIR



Company	Glaxo-Wellcome
CAS	59277-89-3
MW	225.21
Class	Acyclic nucleotide
Source	Synthetic
Therapeutic Area	Antiviral, Treatment of Herpes viruses
Discovery	1974 by Howard J. Shaeffer
TTM	8 years
Formulation	capsules, tablets, suspension, ointment.
Registered Trademark	Zovirax, Zyclir, Acyclo
Turnover	1996:1.3 BUSD; 2000: 0.6 BUSD

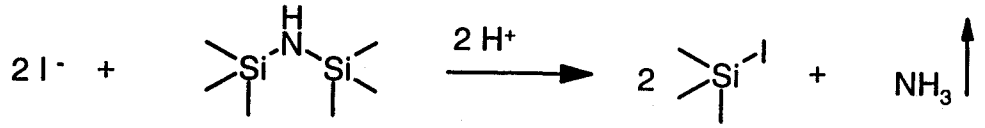
CONSIDERATIONS

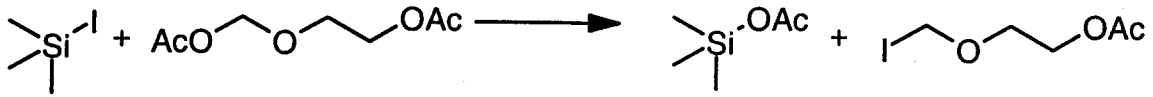
1. All the reported catalysts for HMDS silylation gave poor results in the presence of an organic solvent. Only $(NH_4)_2SO_4$ gave decent silylation time for guanine in toluene or xylene, >24h.
2. (Cl)$BrCH_2OCH_2CH_2OAc$ are toxic.

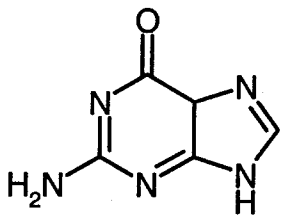
TARGETS

1. Develop a patent free route.
2. Avoid the use of stoichiometric quantities of expensive HMDS.
3. The non toxic side chain synton $AcOCH_2OCH_2CH_2OAc$ must be activated by a Lewis acid.

ACTIVATION OF HMDS AND THE SIDE CHAIN ACETATE



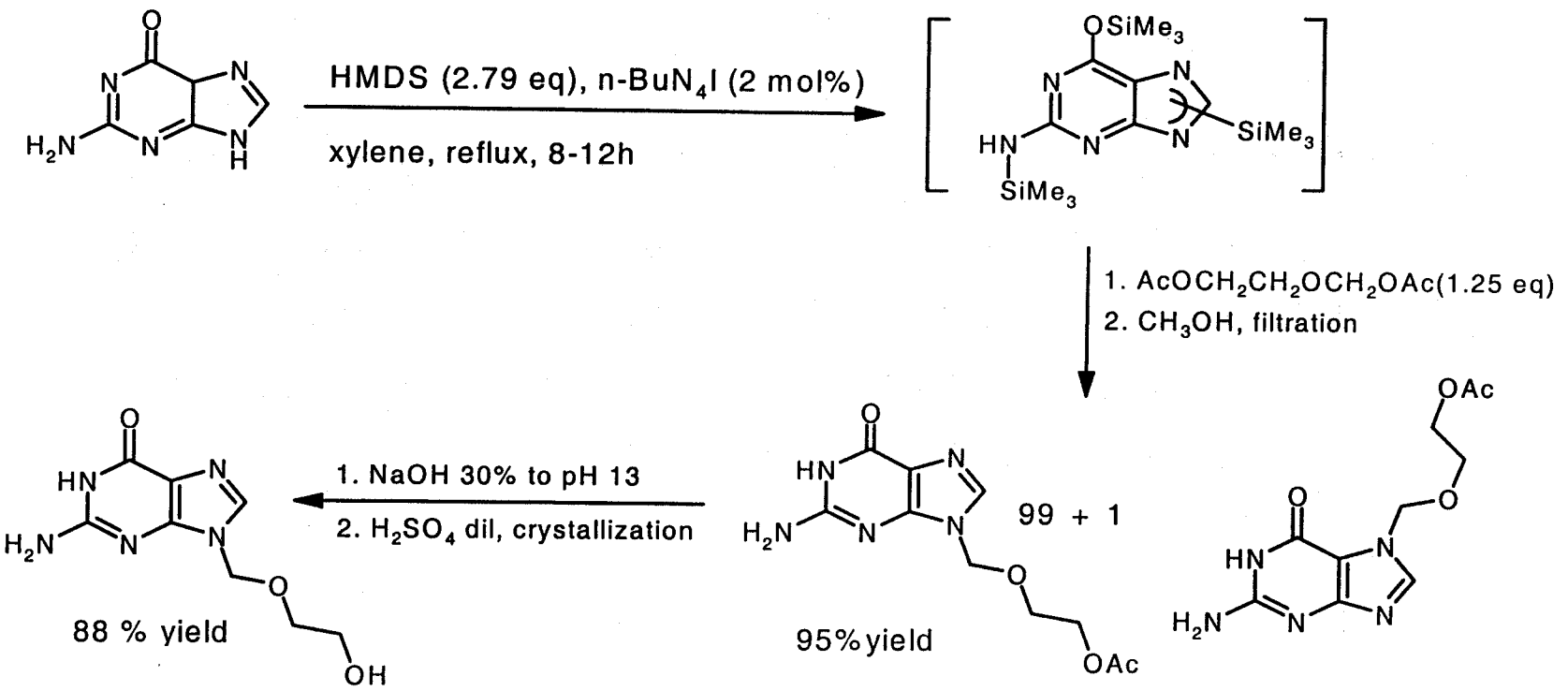




In addition, a phase transfer catalyst can improove the solubility of guanine in organic solvent increasing the reaction rate.

Possible solution of the problem a tetraalkylammonium iodide

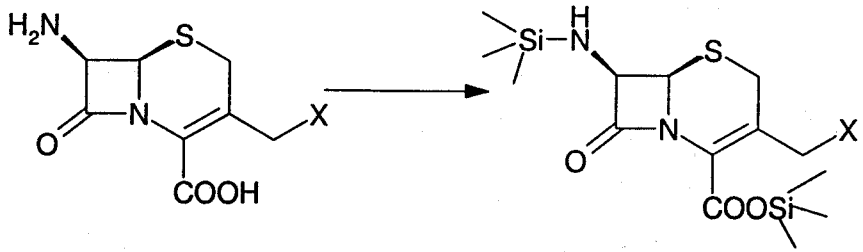
HMDS / nBuNI cat

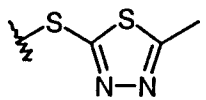


INDUSTRIAL SILYLATION

Silyl groups are widely use in β-lactams and nucleotides chemistry. In these cases the target is not only to protect carboxylic acid or amino groups but also to solubilised the material in a low polar solvent, such as CH_2Cl_2, toluene, xilene to carry out further manipulation of the molecule.

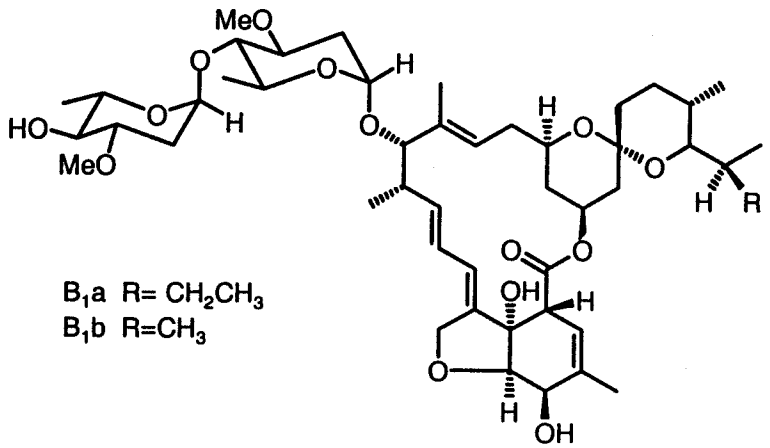
HMDS / nBuNI cat



Entry	X	Substrate	Catalyst	T, h
1	H	7-ADCA	Saccharine	4.5
2	H	7-ADCA	nBu_4NI	2
3	H	7-ADCA	nBu_4NBr	No reaction
4	OAc	7-ACA	nBu_4NI	2
5		3-TD	nBu_4NI	2

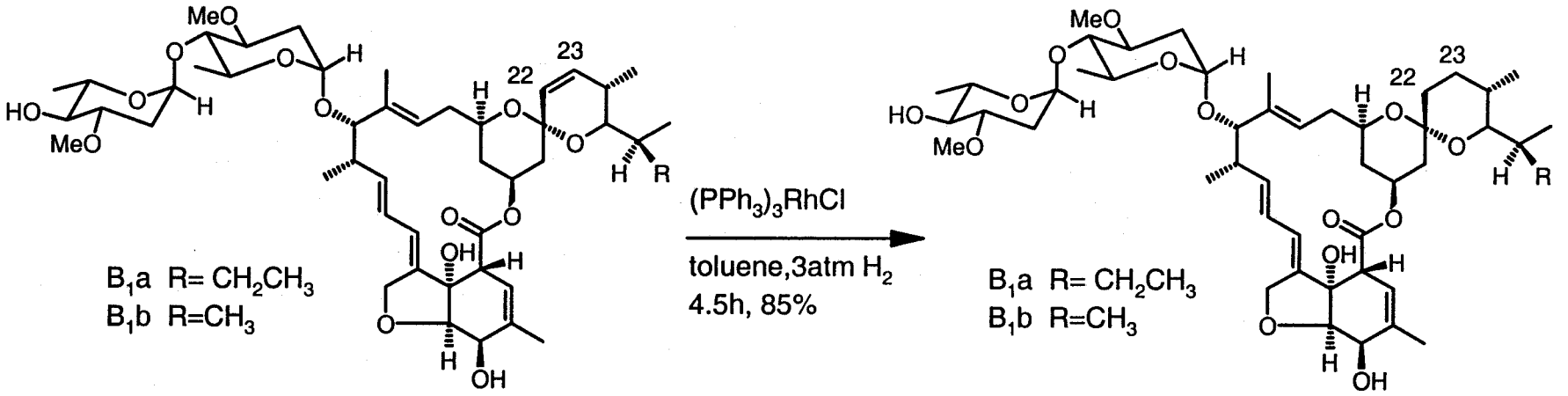
a. All reactions were carried out using a weight of substrate/volume of dichloromethane 1/10 ratio, till a clear solution appeared (100% and 85-90% silylation at COOH and NH_2 respectively by H^1 NMR), using 2% of the catalyst at reflux.

IVERMECTIN $B_{1a,b}$



Company	Merck & Co.
CAS	70288-86-7
MW	872.21-875.10
Class	Macrocyclic lacton disaccharides
Source	Semisynthetic
Therapeutic Area	human and animal health anthelmintic,anti-arthropod
Discovery	1978
TTM	5 years
Formulation	injectable, tablets
Registered Trademark	Mectizan, Stromectol, Ivomec

A SIMPLE HYDROGENATION



Avermectin $B_{1a,b}$

Ivermectin $B_{1a,b}$ >80/20

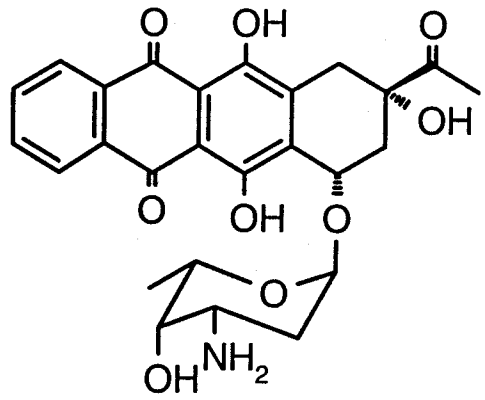
Two main problems:

1. Hydrogenation selectivity (1.5-3% of 3,4-22,23-tetrahydroIvermectin).
2. To remove the Rhodium metal (limit <3-4ppm), Merck researchers defined a method based on treatment of the toluene solution with thiourea (US4413118).

$[Rh(COD)Cl]_2$ + ligand + H_2

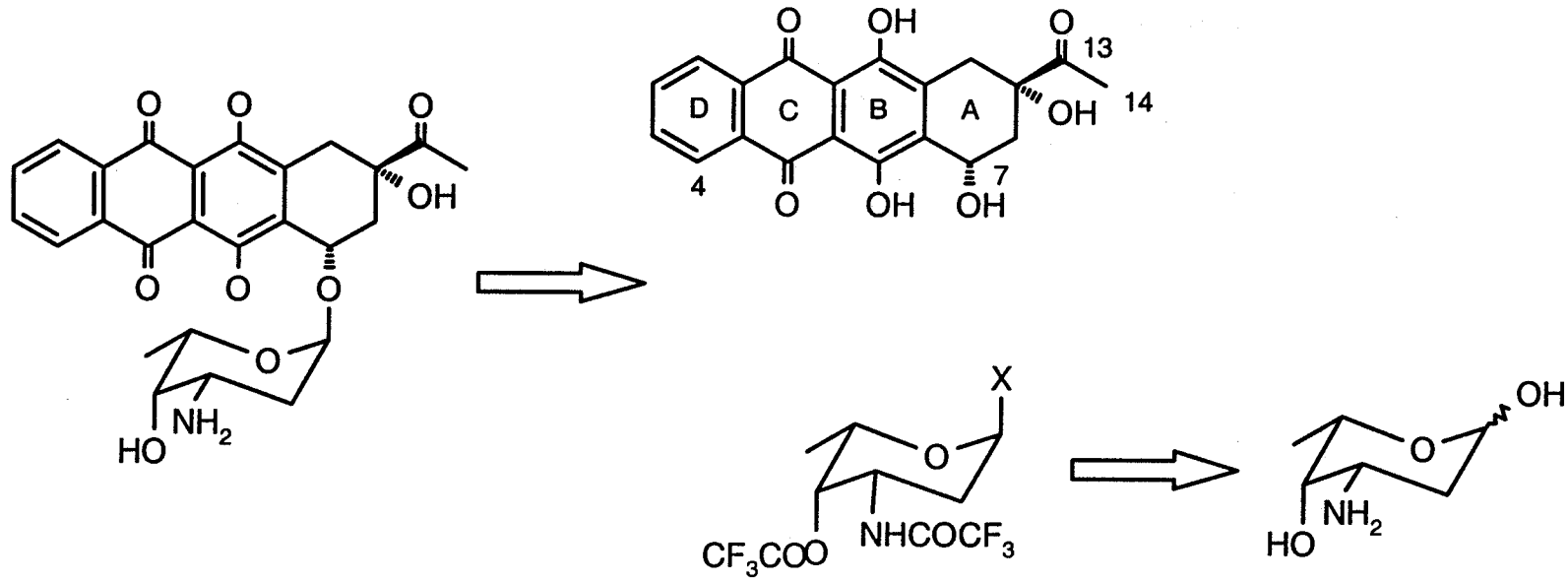
LIGAND	**SOLVENT**	**T** °C	**t** h	**YIELD** %
PPh_3	IPA	50	6	98
PPh_3	toluene	65	6	95
$P(PhSO_3H)_3$	IPA	50	7	40
no ligand	IPA	50	7	50
$P(PhSO_3H)_3$	Toluene/H_2O	65	7	70
$P(PhSO_3H)_3$	Toluene/H_2O/nBu_4NBr	65	7	>98

IDARUBICIN

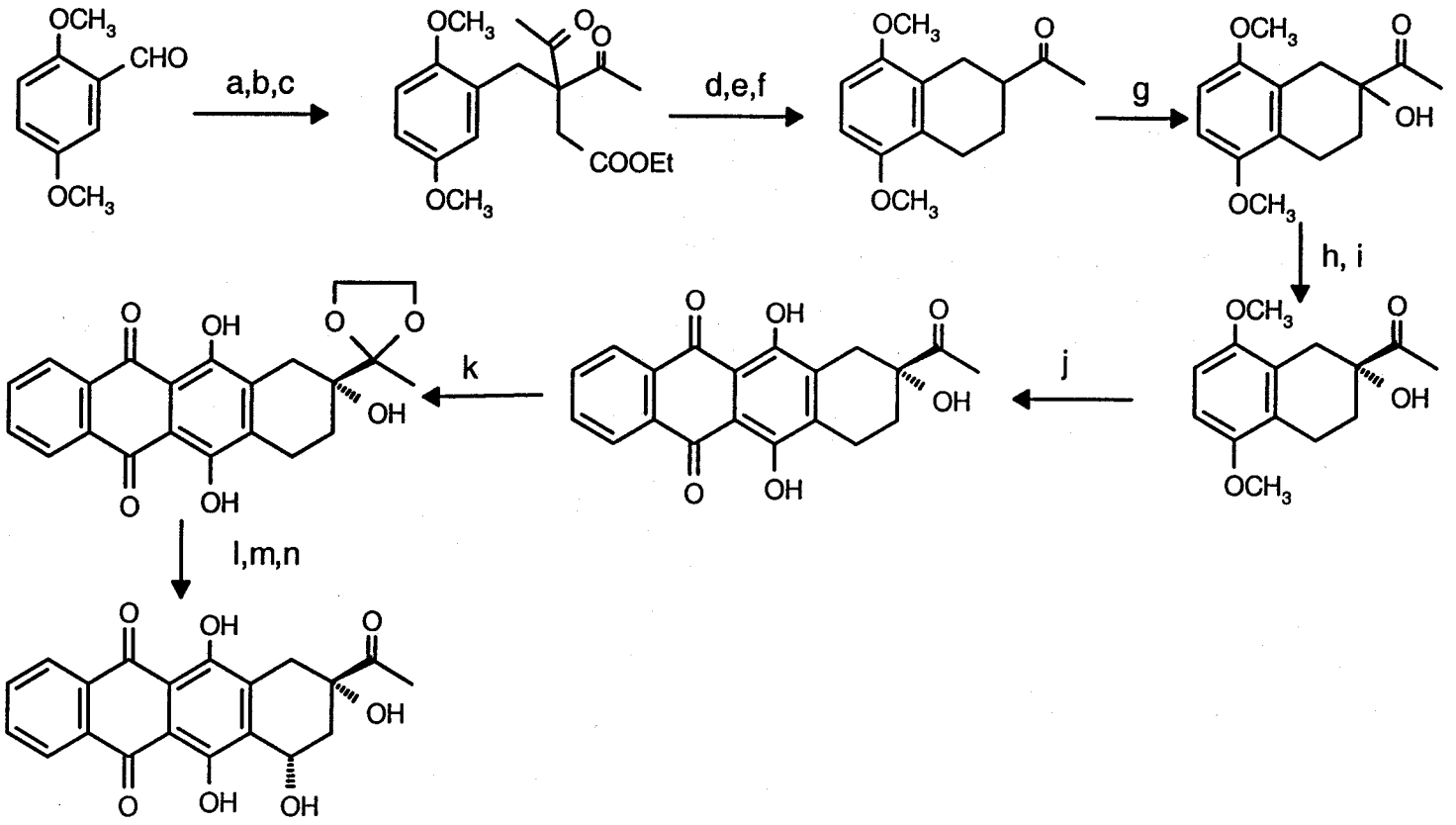


Company	Pharmacia Corporation
CAS	57852-57-0 as hydrochloride
MW	534
Class	Anthracycline Antibiotics
Biosynthetic Class	Poliketides
Source	Synthetic or Semisynthetic
Therapeutic Area	Anticancer
Discovery	1973
TTM	16 years
Formulation	Sterile Injectable
Registered Trademark	Zavedos,Idamycin,Daunoblastina,(IMI 30).

IDARUBICIN RETROSYNTHESIS

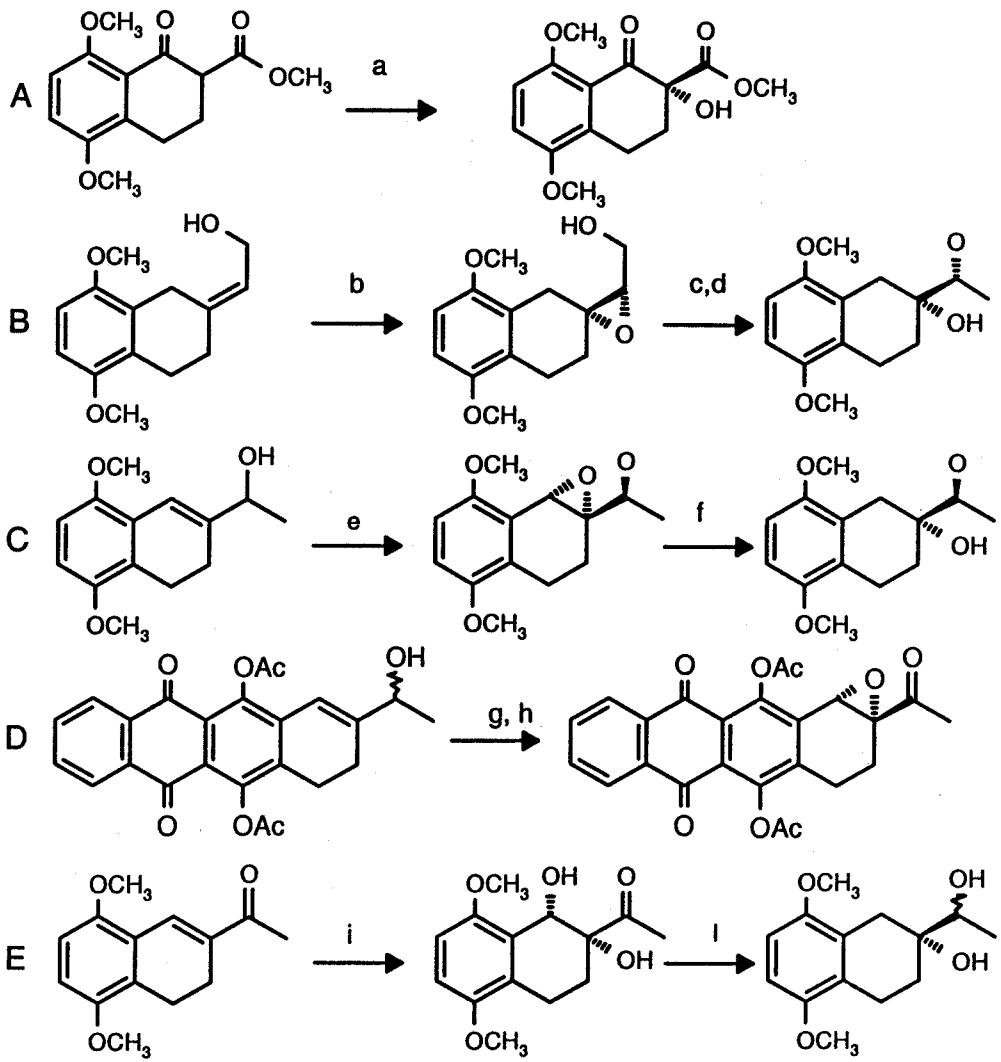


FARMITALIA CARLO ERBA FIRST SYNTHESIS



a. $CH_3COCH_2COCH_3$, Py,AcOH ; b. Pd/C H_2 ; c. NaH, $BrCH_2CO_2Et$; d. OH^- ; e. HF ; f. Pd/C H_2 ; g. t-BuOK, O_2, $P(OEt)_3$, THF; h. (-)$PhCH(CH_3)NH_2$; i. H^+,H_2O; j.Phthalic anhydride, $AlCl_3$/NaCl, 140°C ; k. $(CH_2OH)_2$, H^+ ; l. Br_2/AIBN ; m. OH^- ; n. CF_3COOH.

Other approaches to the aglycon



Davis : asymmetric hydroxylation

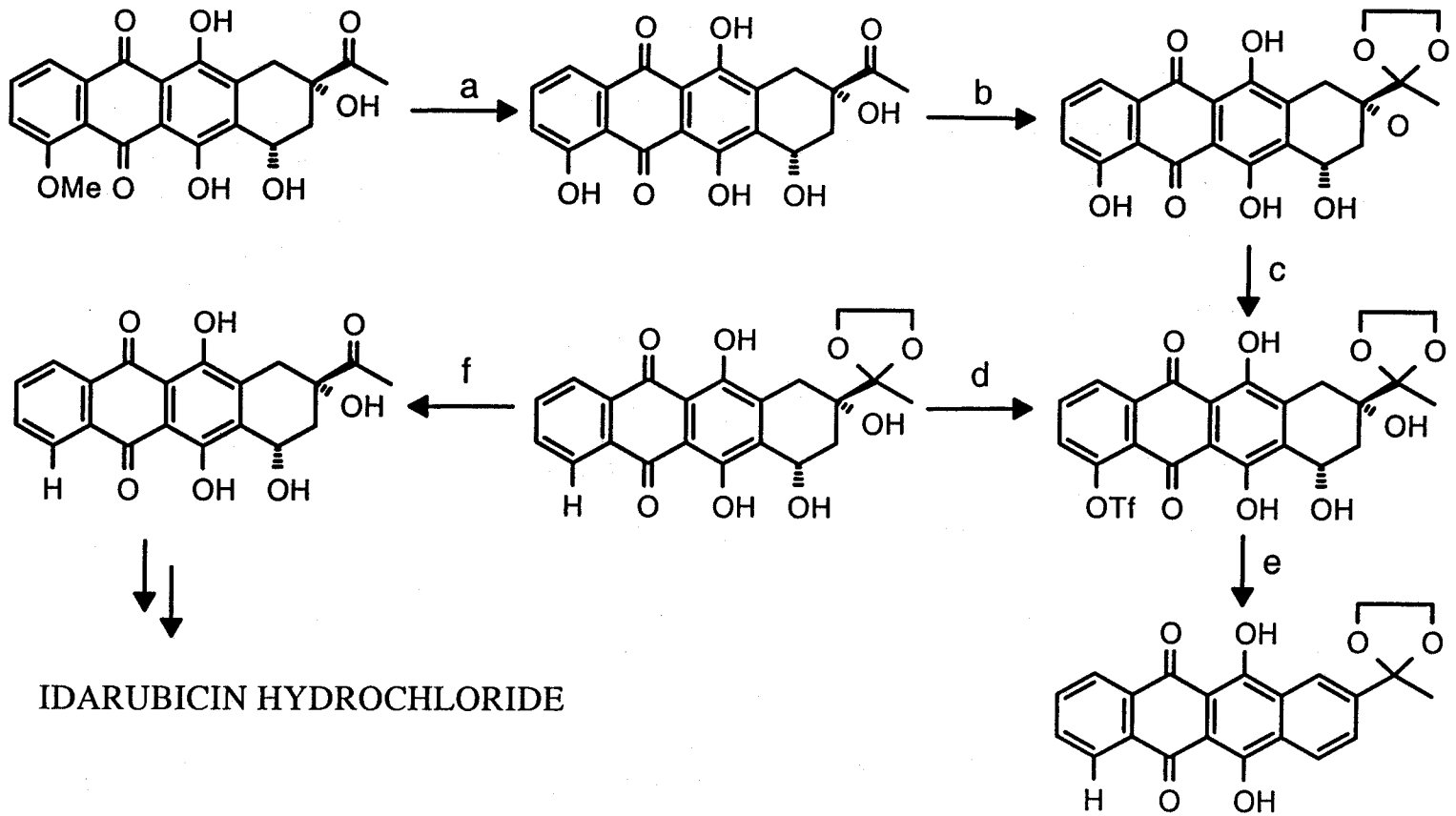
Shibasaki Sharpless epoxidation

Rao Sharpless epoxidation

Cava Sharpless epoxidation

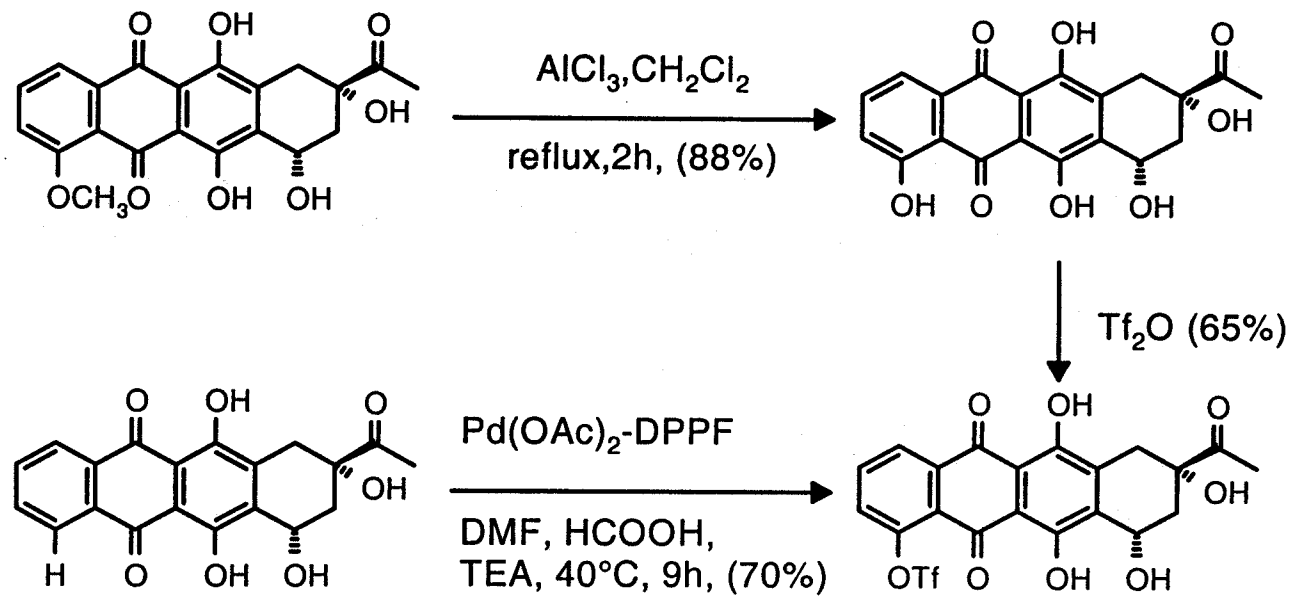
Tomioka stereoselective dihydroxylation

INDUSTRIAL SYNTHESIS

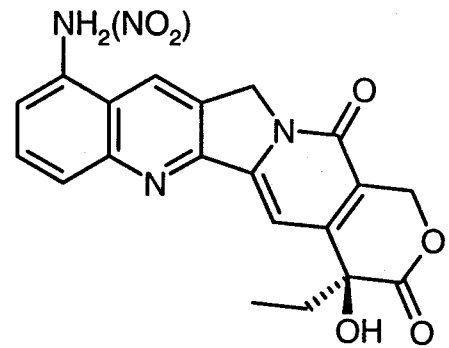


a. $AlCl_3$, CH_2Cl_2, reflux, 2h, (88%). b. $(CH_2OH)_2$, PTSA, benzene, 2h, (90%) ; c. Tf_20, DIPEA, 4-DMAP, Py, 0°C, (≈70%) ; d. $Pd(OAc)_2$-DPPF, DMF, HCOOH, TEA, 40°C, 7h, (82%) ; e. $Pd(OAc)_2$-PPh_3, DMF, HCOOH, TEA, 80°C, 12h. f. CF_3COOH, 0°C, 0.3h (90%).

FINAL SYNTHESIS

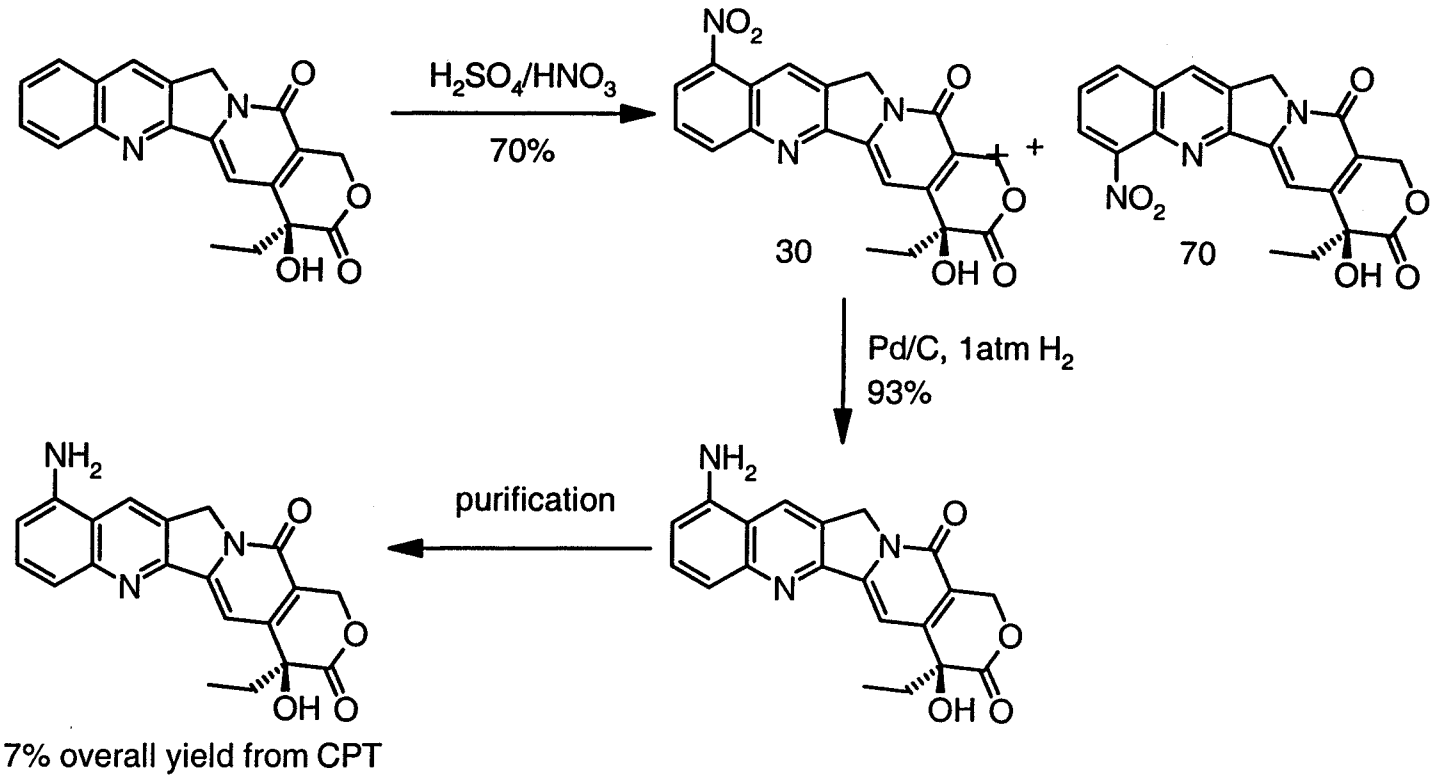


9-SUBSTITUTED CAMPTOTHECIN



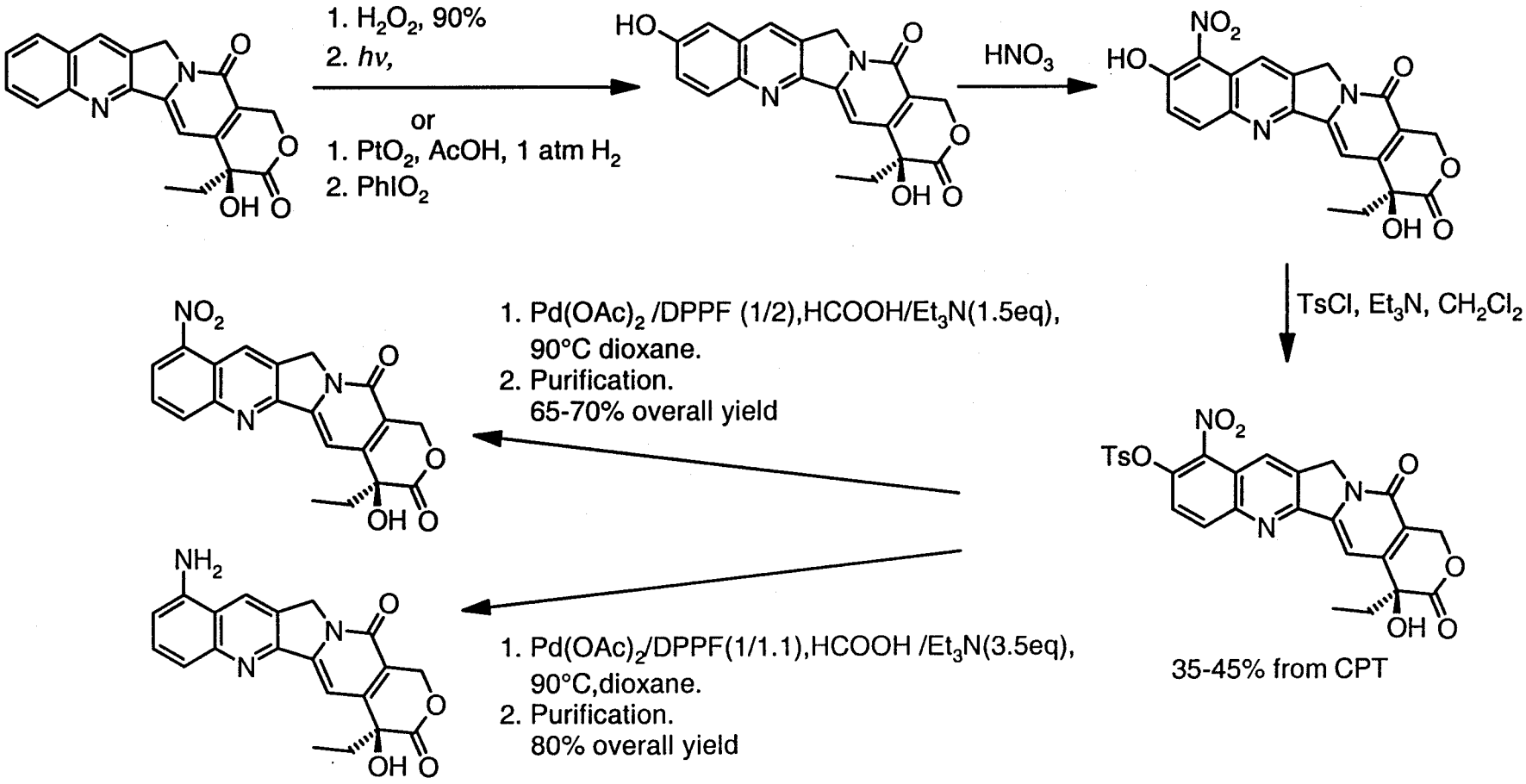
Company	9-AC: IDEC; 9-NO_2-C : Supergen/Abbott
CAS	91421-43-1 (91421-42-0)
MW	363.38 (393.36)
Class	Camptothecin
Source	Semisynthetic
Therapeutic Area	Anticancer
Discovery	1982
TTM	under development
Formulation	Sterile Injectable (oral)
Registered Trademark	for 9-NO_2-C Rubitecan

DIRECT NITRATION

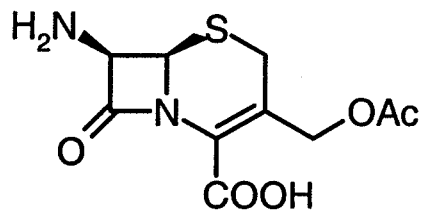


Dramatic impact of low selectivity and purification steps

ALTERNATIVE SYNTHESIS



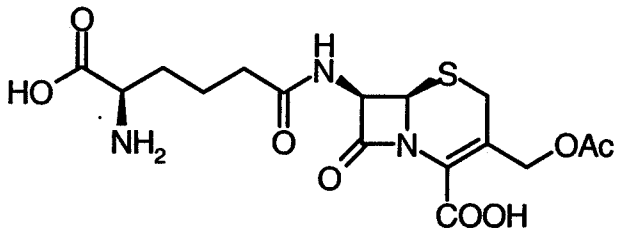
7ACA



Company	Antibioticos, Biochemie, ACS Dobfar etc.
CAS	33069-62-4
MW	272.28
Biosynthetic Class	β-lactams
Source	Semisynthesis, Morin 1962 (Eli Lilly)
Therapeutic Area	Intermediate for cephalosporins production

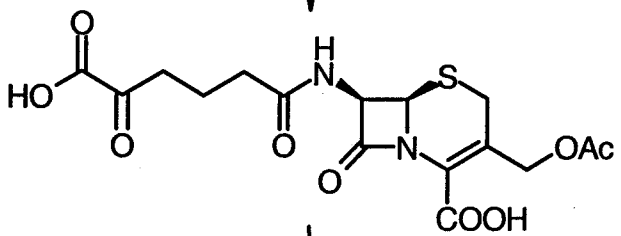
CEPHALOSPORIN C → 7ACA

ENZYMATIC ROUTE

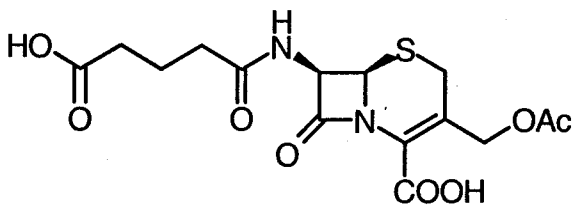


Cephalosporin C filtrated broth

DAO / water / O_2

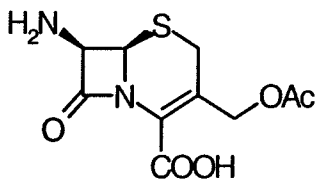


$-CO_2$

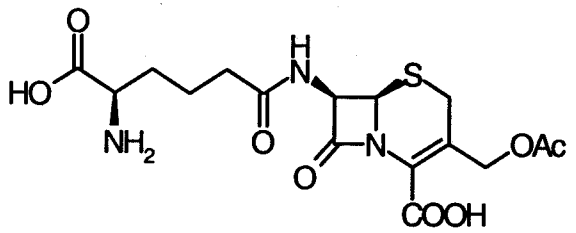


GA

water

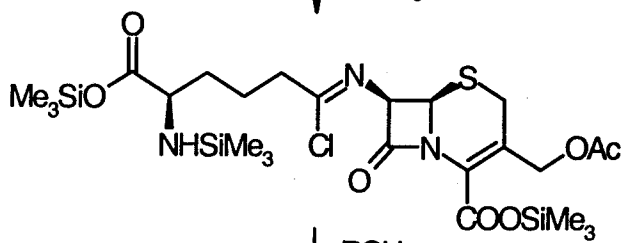


CHEMICAL ROUTE

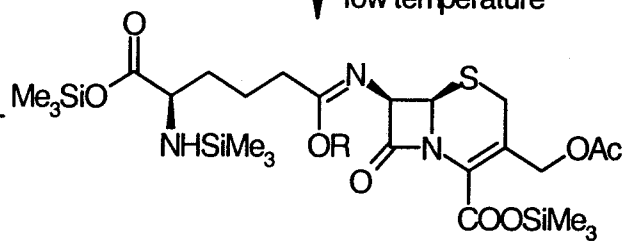


Cephalosporin C dry powder

1. TMCS/DMA/CH_2Cl_2
2. PCl_5 low temperature



ROH
low temperature



water