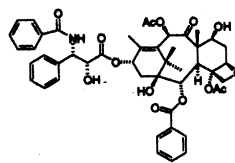


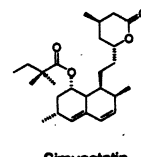
**DESIGNED MODIFICATION OF THE
CARBON-CARBON CONNECTIVITY OF A
COMPLEX NATURAL PRODUCT.
THE LESSON OF TAXOL**

Giovanni Appendino
DISCAFF

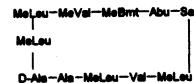
Università del Piemonte Orientale
Novara, Italy



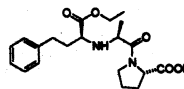
Paclitaxel



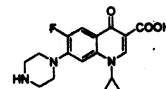
Simvastatin



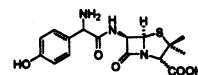
Cyclosporin



Enalapril



Cyprofloracin



Amoxicillin

HTS

Problems

Too few (ca. 180,000)

Difficult to obtain

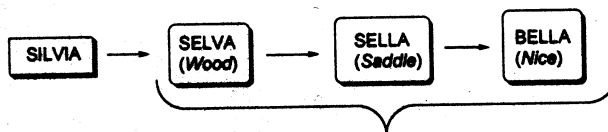
NATURAL PRODUCTS POOL

Amplification

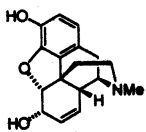
MOLECULAR BIOLOGY

*Derivata patris naturam verba
sequuntur*

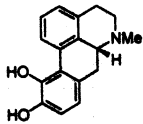
(A. gramm.)



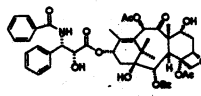
A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, U, V, W, X, Y, Z



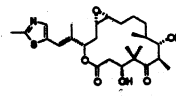
Morphine
(Opioid Receptors)



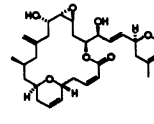
Apomorphine
(Dopamine Receptors)



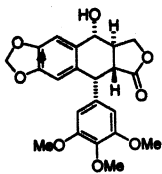
TAXOL



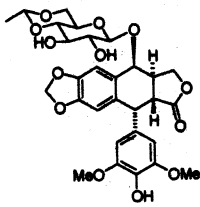
EPOTHILONE A



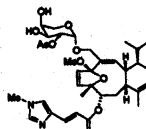
LAURIALIDE



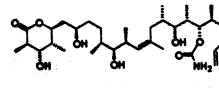
Podophyllotoxin
(Tubulin)



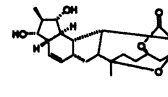
Etoposide
(Topo-2)



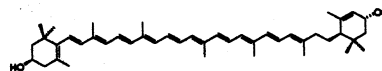
ELEUTEROBIN



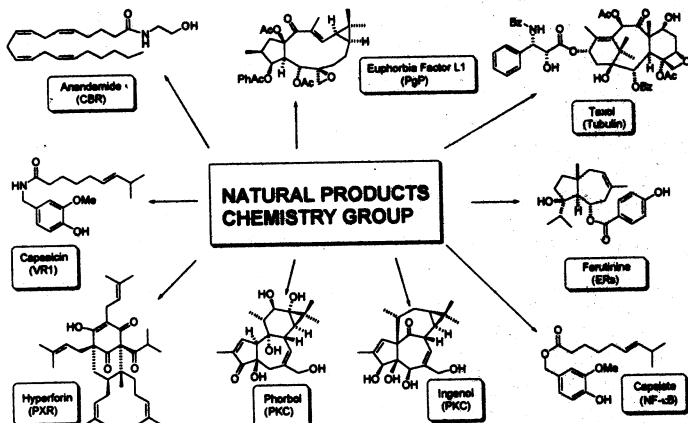
DISCODERMOLIDE



WU 62559



LUTEIN

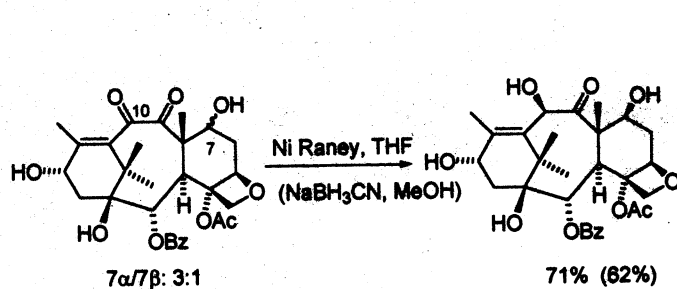
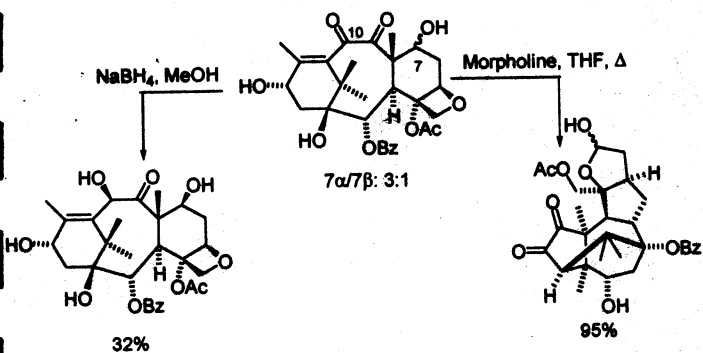
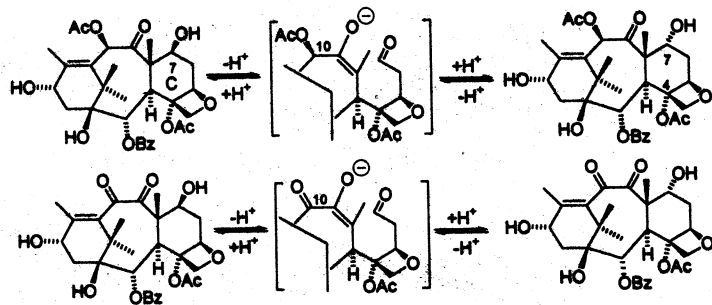
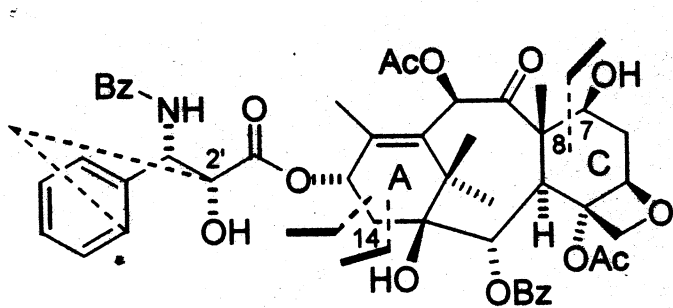


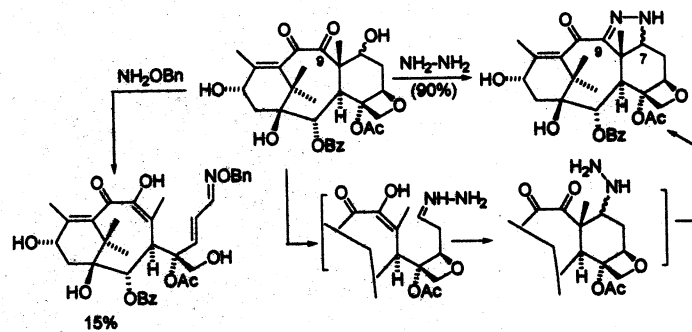
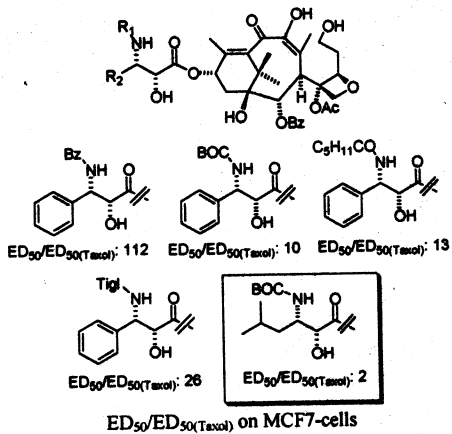
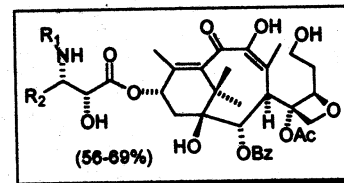
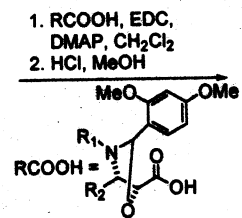
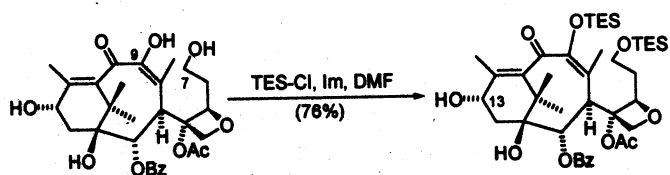
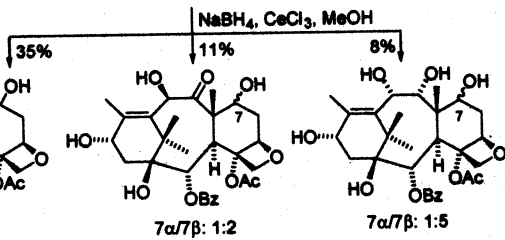
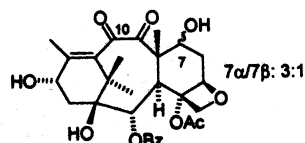
"Taxol is like aspirin. We are finding more use for it other than what was originally intended"

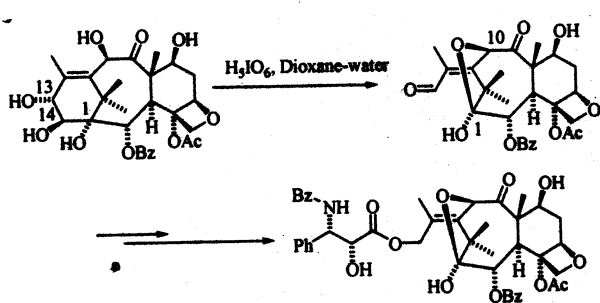
L. Machan, 23rd SCVIR Meeting, 1998

NON-ONCOLOGICAL POTENTIAL APPLICATIONS OF TAXOL

- Alzheimer's Disease
- Multiple Sclerosis
- Restenosis
- Arthritis
- Polycystic Disease
- Psoriasis
- Malaria
- Kidney

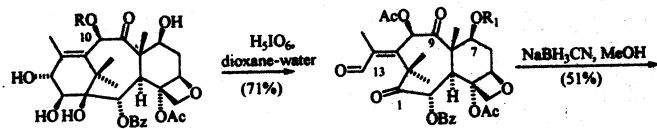
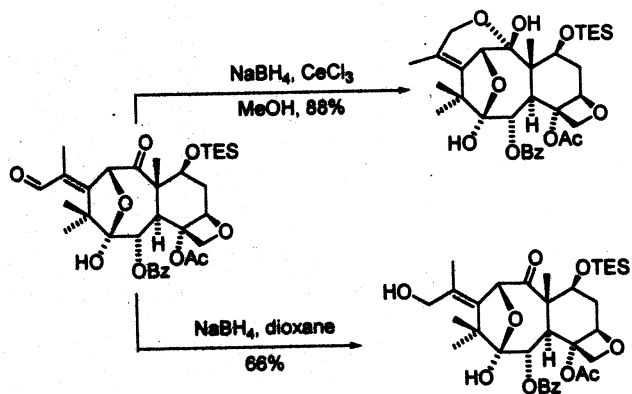






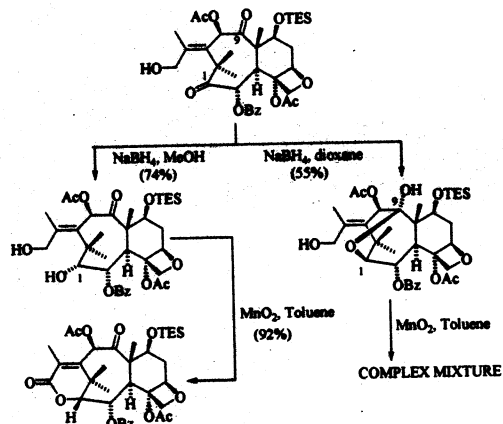
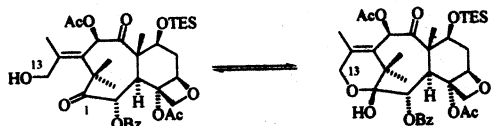
ED₅₀/ED_{50(Taxol)} = 46

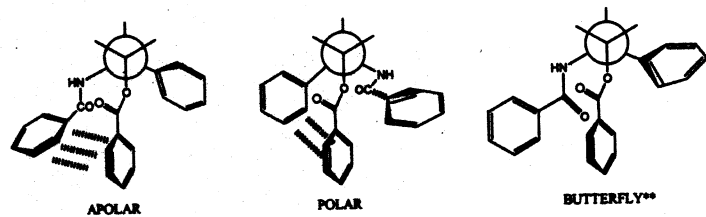
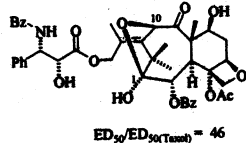
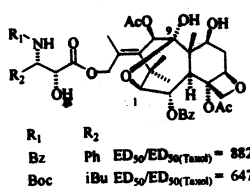
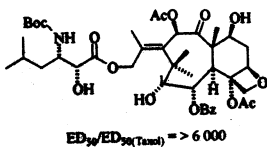
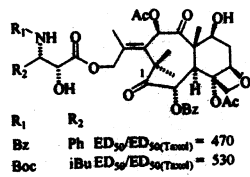
Ojima, I.; Fenoglio, I.; Park, Y.H.; Sun, C.-M.; Appendino, G.; Pera, P.; Bernacki, R. *J. Org. Chem.* 1994, 59, 515-517.



R
 H } Ac_2O , THF, CeCl_3 (90%)
 Ac

R
 H } TES-Cl, im.
 TES } DMF, 82%

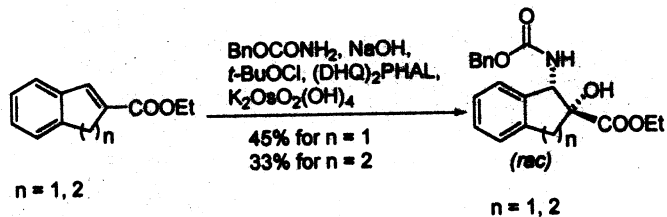
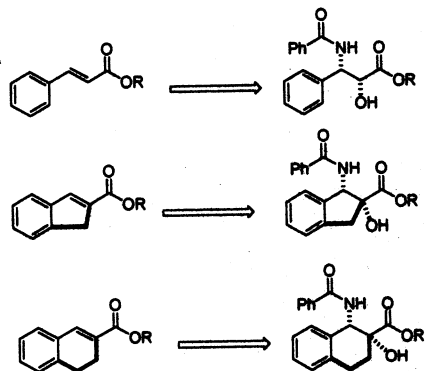


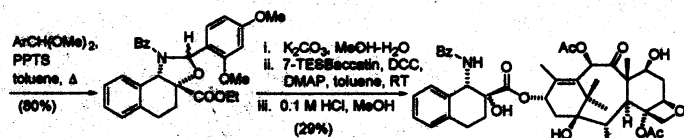
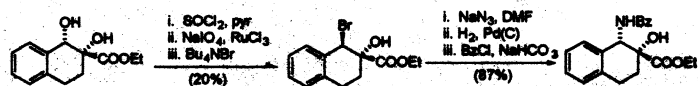
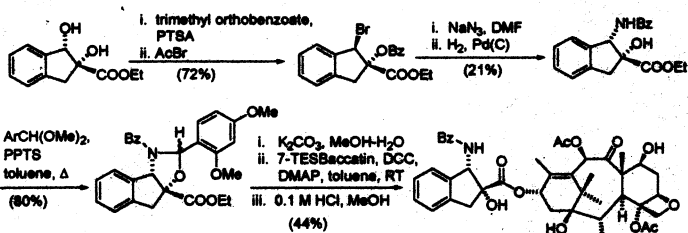
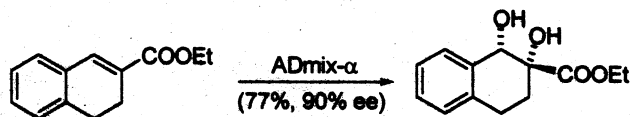
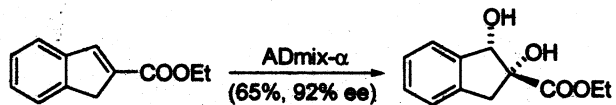
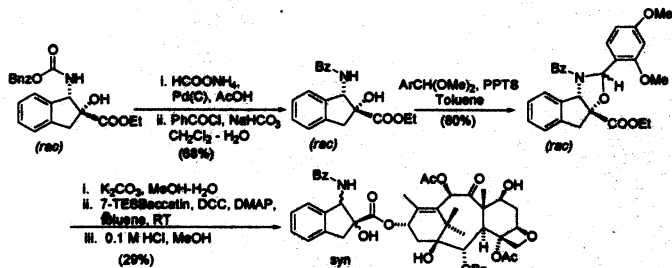


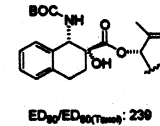
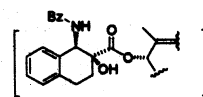
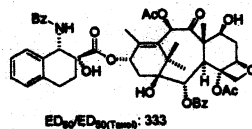
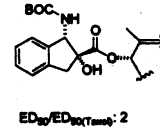
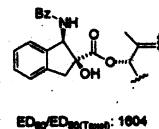
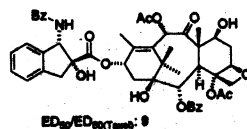
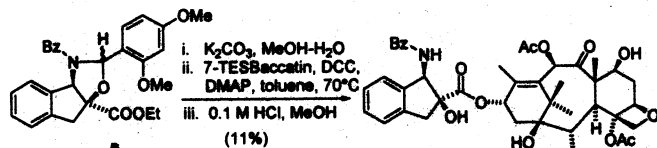
- Definite S/A relationships exist in A-secotaxoids
- Opening of ring A can be compensated by specific modifications on ring B

****Milanesio, M.; Ugliengo, P.; Viterbo, D.; Appendino, G. *J. Med. Chem.* 1999, 42, 291-299.**

**** Snyder, J. P.; Nettles, J. H.; Cornett, B.; Downing, K. H.; Nogales, E. *Proc. Natl. Acad. Sci. USA* 2001, 98, 5312-5316.**







CONCLUSIONS

- THE STRUCTURE-ACTIVITY RELATIONSHIPS OF TAXOIDS ARE COMPLEX, AND DIFFERENT FOR COMPOUNDS WITH DIFFERENT SIDE CHAINS.
- C-SECOTAXOIDS WITH NORSTATIN SIDE CHAINS ARE A NEW CLASS OF ANTICANCER AGENTS WHOSE *IN VIVO* PROFILE SUBSTANTIALLY DEVIATES FROM THAT OF TAXOL.
- IN A-SECOTAXOIDS, THE 1,10-OXIDO BRIDGE CAN COMPENSATE FOR THE OPENING OF RING A.
- TETHERING EXPERIMENTS SUGGEST THAT THE T-CONFORMATION OF TAXOL IS THE MOST SUITABLE TO BIND TUBULIN.

Luciano Barboni, Katia Lambertucci: Constrained analogues

Emanuela Belloro: A- and C- Seco analogues

Giorgio Bettoni, Alain Noncovich: C-seco analogues

Prof. Bruno Danieli (Università di Milano): Side chain chemistry

Dr. Jasmin Jakupovic (Analyticon, Potsdam): NMR spectroscopy

INDENA[§]

[§] Money is like a sixth sense, without which you cannot make a complete use of the other five