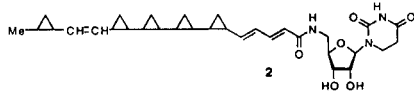
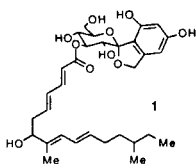


A. G. M. Barrett, W. W. Doubleday, K. Kasdorf, M. Pena,
G. J. Tustin, and J. A. Willardsen

Imperial College of Science, Technology and Medicine,
South Kensington, London SW7 2AY, U.K.

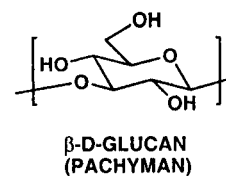
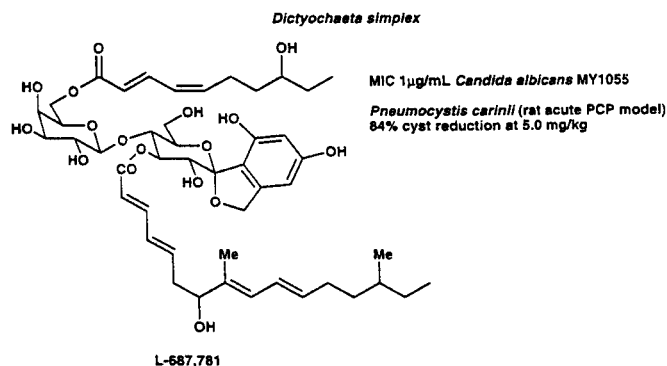
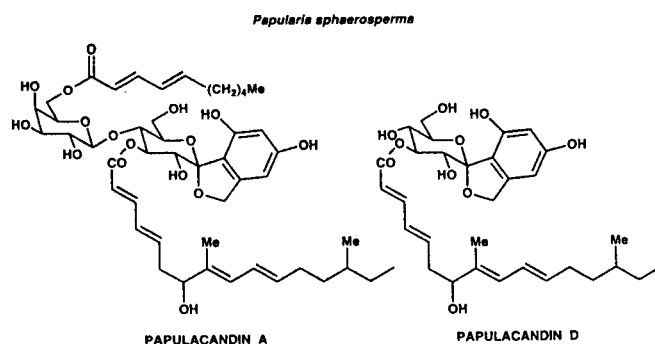
J. Heterocyclic Chem., **33**, 1545 (1996).

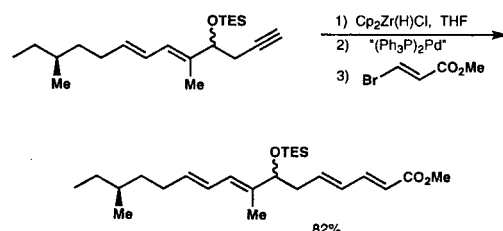
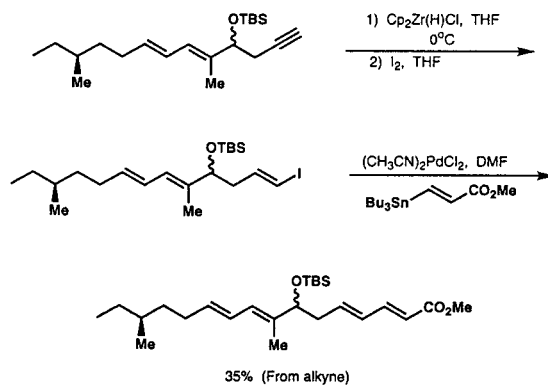
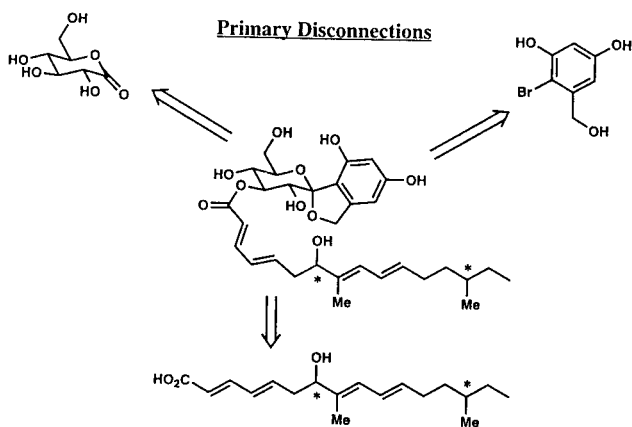
There is very considerable alarm amongst the medical profession regarding fungal disease. Dermatophyte infections such as tinea pedis and candidiasis, although rarely fatal, are common and widespread throughout the world. There are other fungal diseases that are far darker in reputation and significance. Pathogens such as *Candida albicans*, *Cryptococcus neoformans*, *Pneumocystis carinii* and *Aspergillus fumigatus* are the cause of considerable morbidity and mortality in immuno-compromised patients. Populations at risk from these opportunistic fungal infections include AIDS patients, recipients of cancer chemotherapy and persons with genetically impaired immune function. The majority of AIDS patients die from fungal pneumonia induced by *Pneumocystis carinii*. Invasive pulmonary aspergillosis is the scourge of patients to cancer chemotherapeutic regimes. Indeed a significant proportion of patients with this disease are diagnosed only *post-mortem*!! Current therapies for the treatment of serious systemic fungal infections are deficient. The gold standard amphotericin is acutely toxic and there are resistance problems with azole fungistatic agents. There is a need for novel therapies for serious fungal disease and for the management of the legions of topical fungal infections.



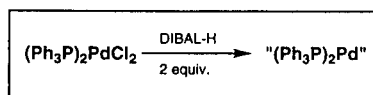
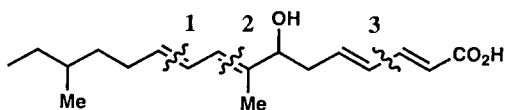
Recent studies on the total synthesis of two naturally occurring antifungal agents will be described. The papulacandins, a group of spiroketal antifungal agents produced by *Papularia sphaerosperma* and *Dictyochaeta simplex*, show potent *in vitro* activities against *Candida albicans* and *Pneumocystis carinii* etc. Studies on the full stereochemical assignment and total synthesis of papulacandin D (1) will be outlined. Secondly, degradation and model multiple cyclopropanation reactions will be used to assign the full structure of FR-900848 (2). In 1990, Fujisawa scientists reported the isolation of this structurally remarkable natural product from the fermentation broth of *Streptoverticillium fervens* HP-891. It shows excellent activities against filamentous fungi including *Aspergillus niger*, *Mucor rouxianus*, *Aureobasidium pullulans*, and various *Trichophyton* sp. etc. As such the structure repre-

sents a unique template for the design of novel fungicidal agents. Stereocontrol in the synthesis of monocyclopropanes, dicyclopropanes and tetracyclopropanes and approaches to completion of the total synthesis will be presented. Both these studies are relevant to the discovery of superior antifungal agents.

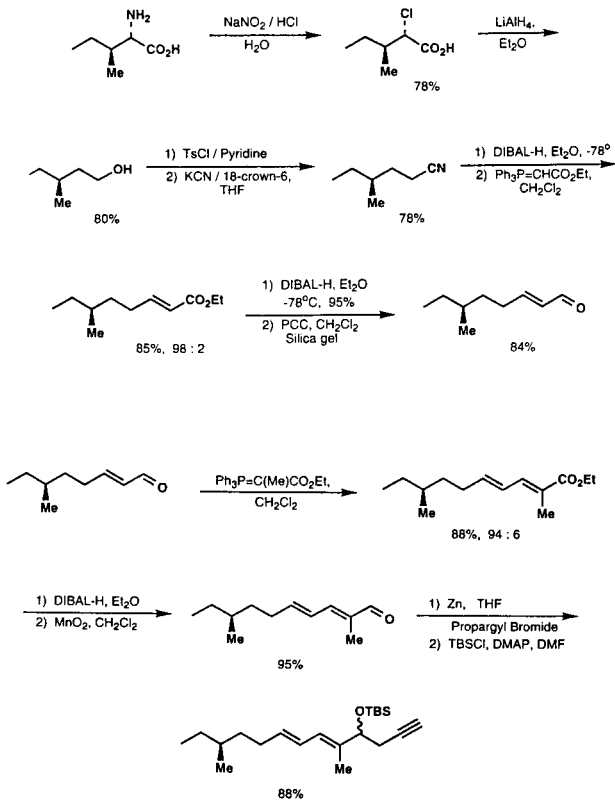




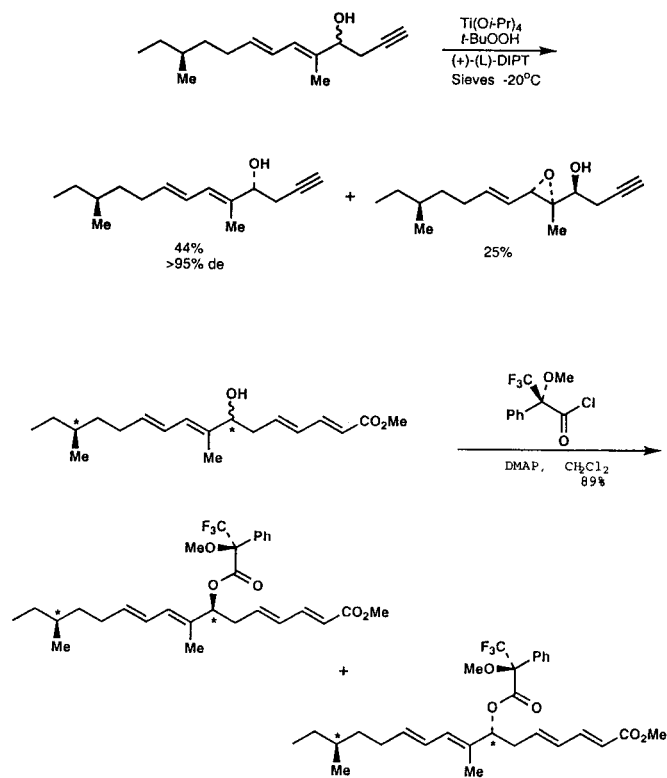
Side Chain Disconnections



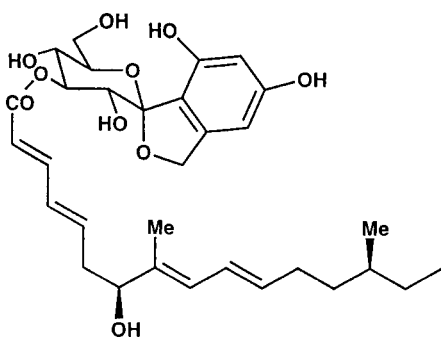
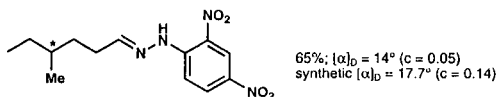
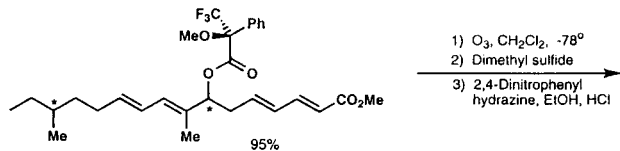
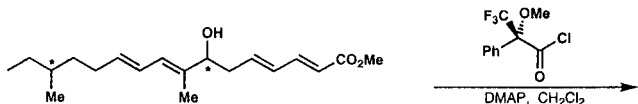
Side Chain Synthesis



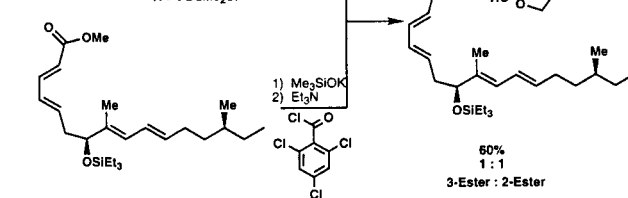
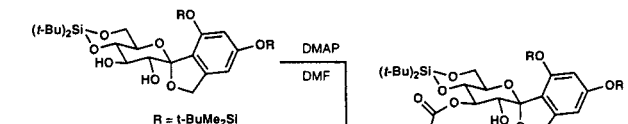
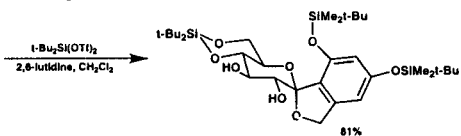
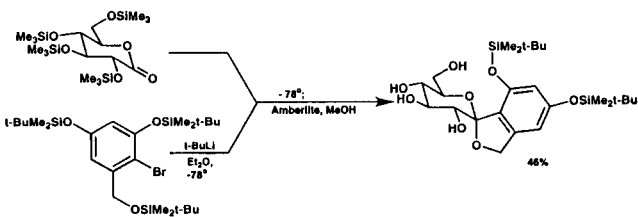
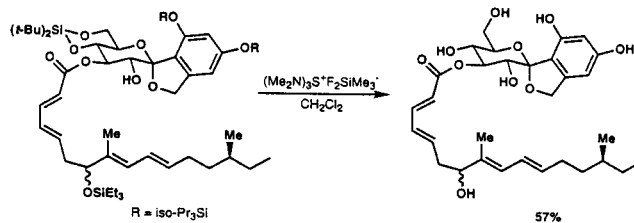
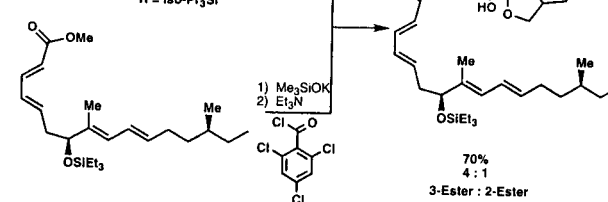
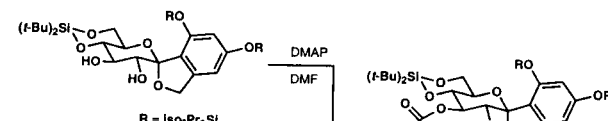
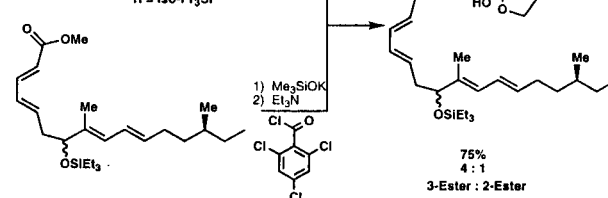
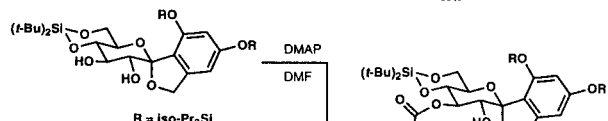
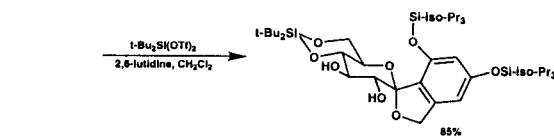
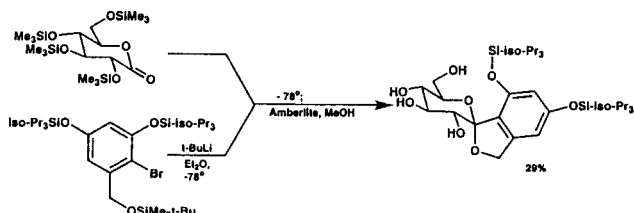
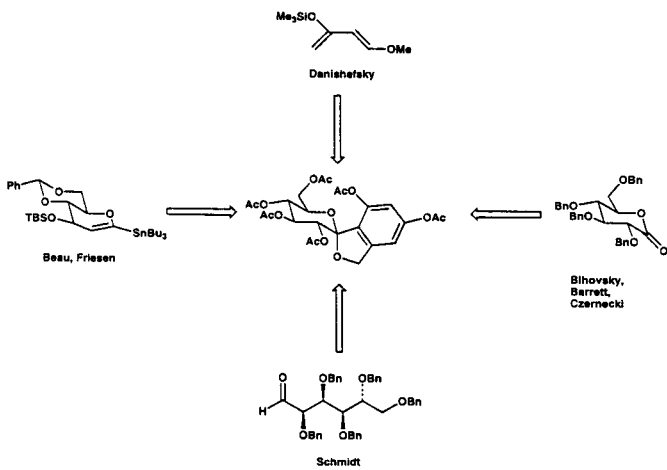
Defining the Stereochemistry at C-7

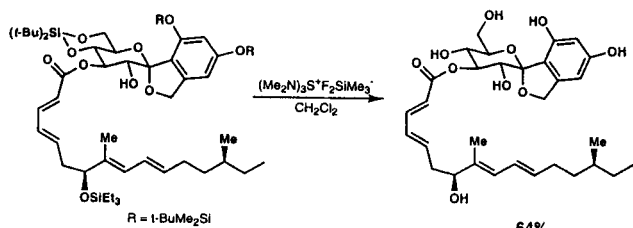
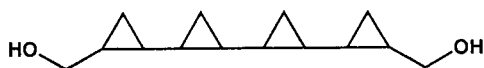
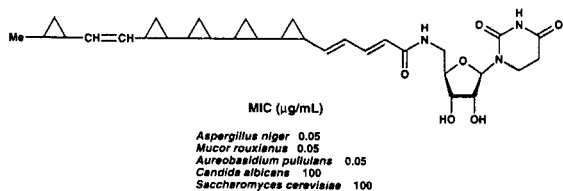
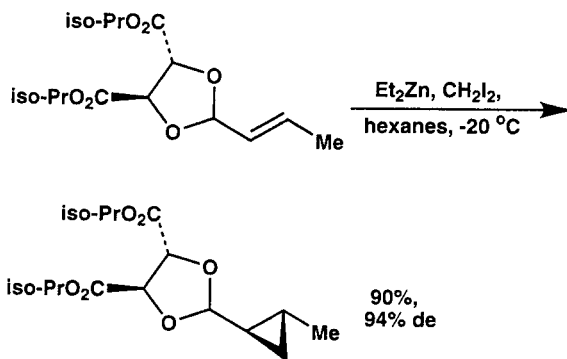
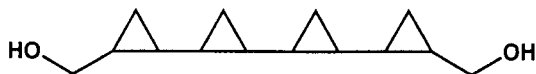
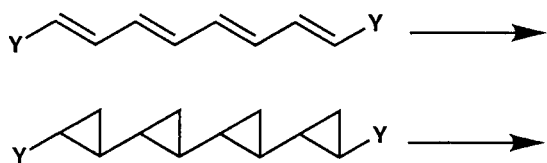
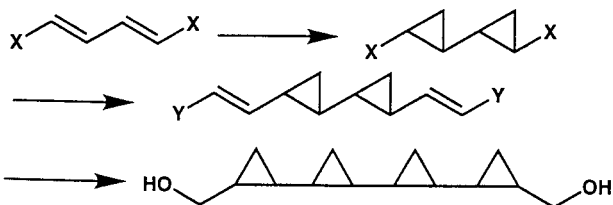
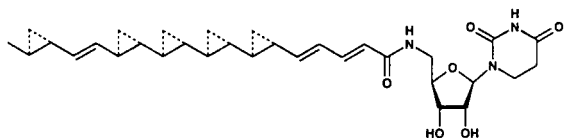
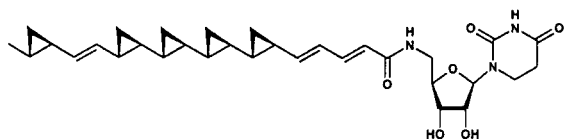
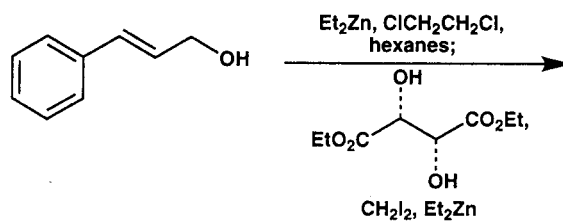
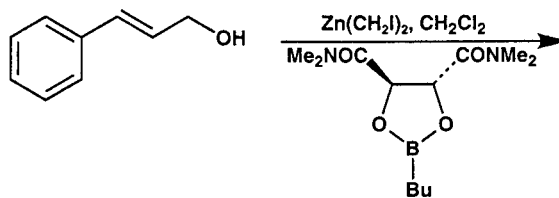
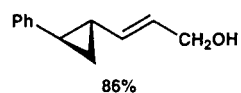
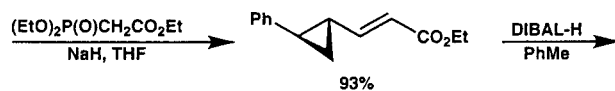
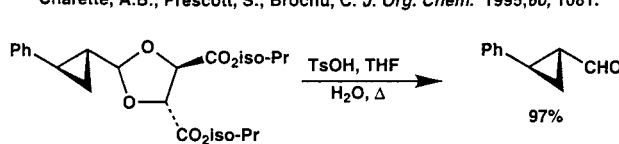


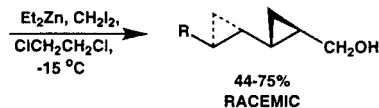
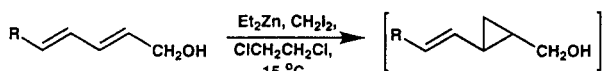
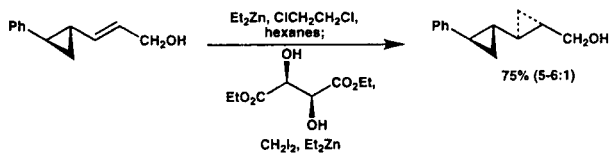
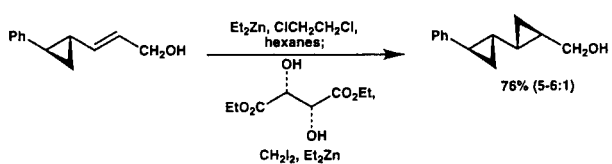
Degradation Studies



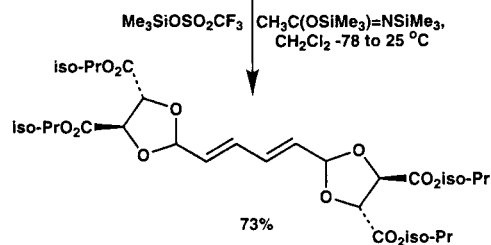
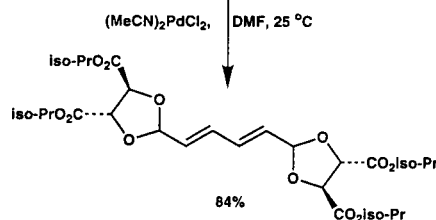
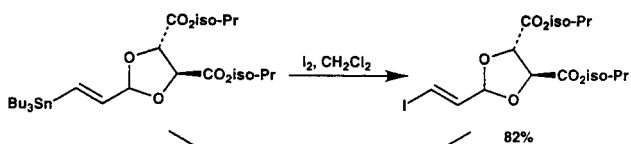
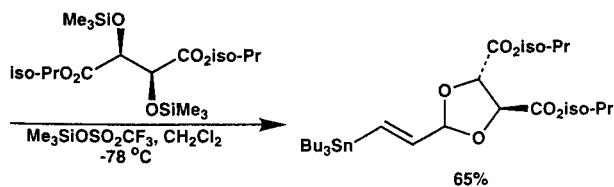
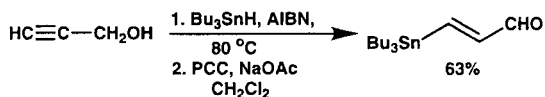
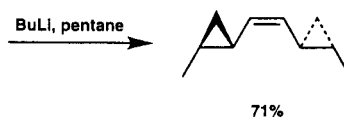
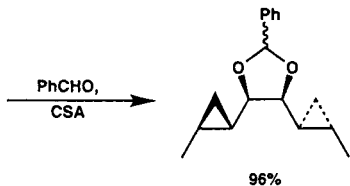
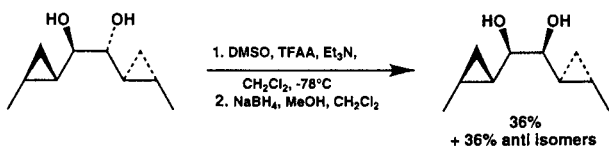
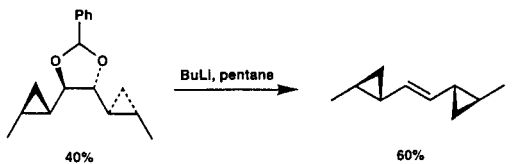
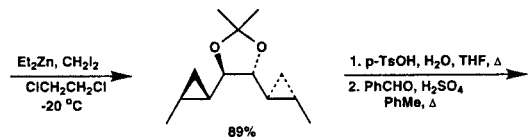
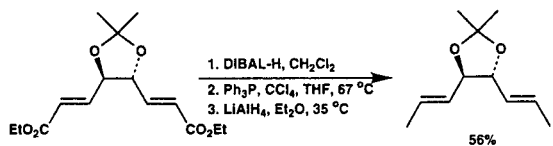
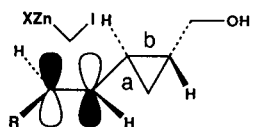
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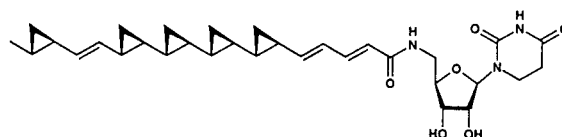
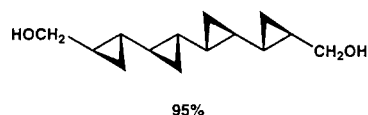
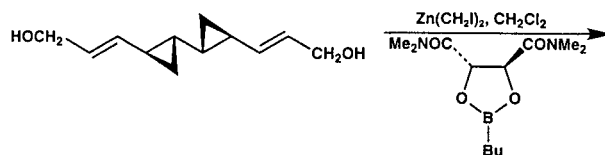
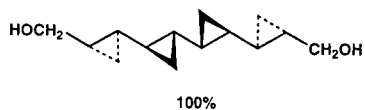
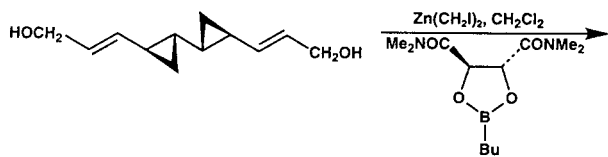
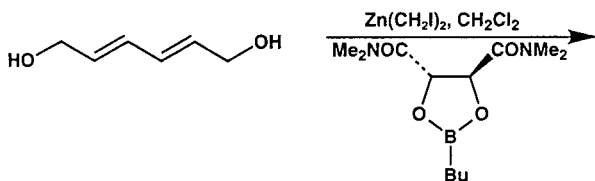
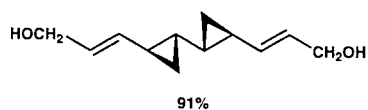
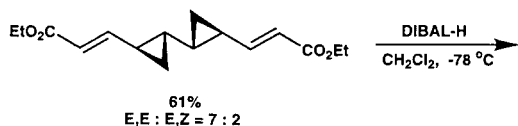
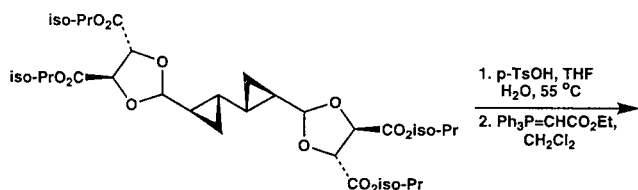
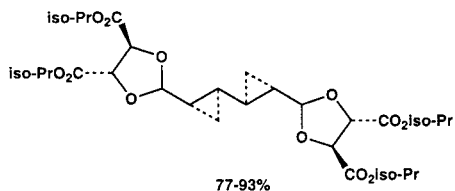
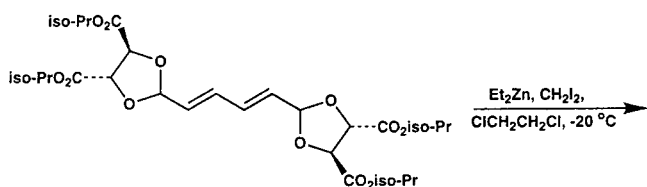


FR-900848 *Streptovorticillium fervens*DIOL IS C_2 SYMMETRICArai, I.; Mori, A.; Yamamoto, H.
J. Am. Chem. Soc. 1985, 107, 8254.Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* 1992, 61.Charette, A.B.; Juteau, H. *J. Am. Chem. Soc.* 1994, 116, 2651.Charette, A.B.; Prescott, S.; Brochu, C. *J. Org. Chem.* 1995, 60, 1081.



R Me, Ph, *iso*Pr, Cyclohexyl, ¹BuPh₂SiOCH₂
 ds 4:1, 6:1, 5:1, 7:1, >95:5





FR 900,848

PAPULACANDINS

WENDEL DOUBLEDAY
GARY TUSTIN
KRISTA KASDORF

ADAM WILLARSEN
MIKE PENA

Engineer:ing and Physical Sciences Research Council

National Institutes of Health
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Glaxo Group Research Ltd

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SmithKline Beechams
Zeneca Corporate Research and Technology