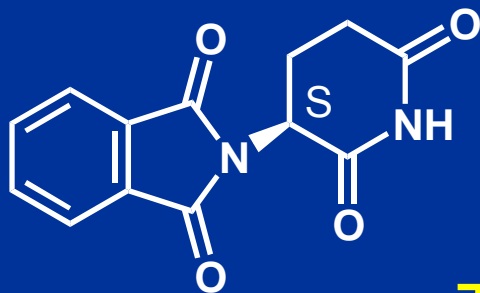
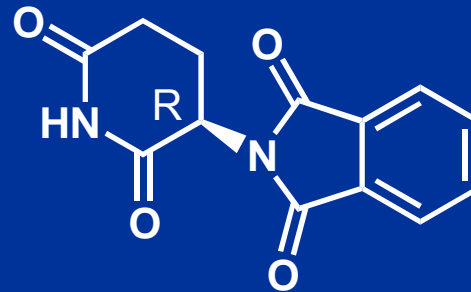


Chirality Transfer in Asymmetric Synthesis: Total Synthesis of Biologically Important Natural Products

**Vinod K. Singh
Department of Chemistry
Indian Institute of Technology
Kanpur – 208016
India**



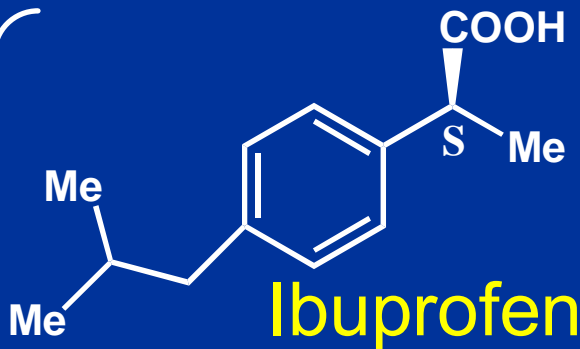
Teratogen



Thalidomide

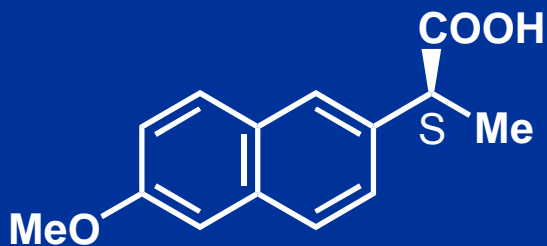
Sedative

Anti-inflammatory and Analgesic

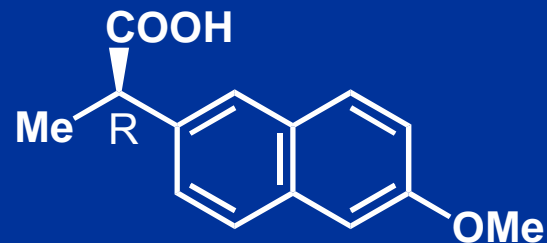


Ibuprofen

(±)-Ibuprofen can be used as body converts inactive *R*-enantiomer into *S*-one, but it takes time. For example, *S*-isomer reaches therapeutic conc. in Body in 12 min whereas racemic one takes 30 min.



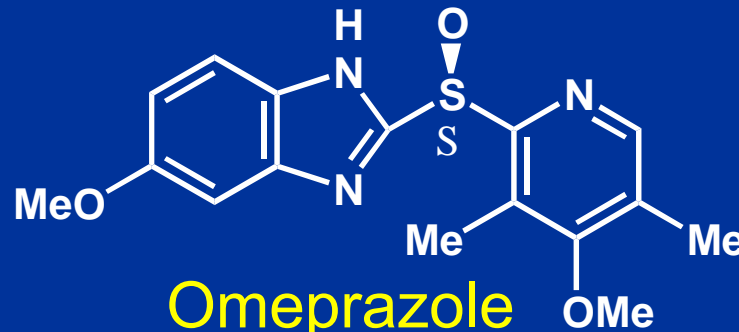
Naproxen



Undesirable side effects

Racemic Switching

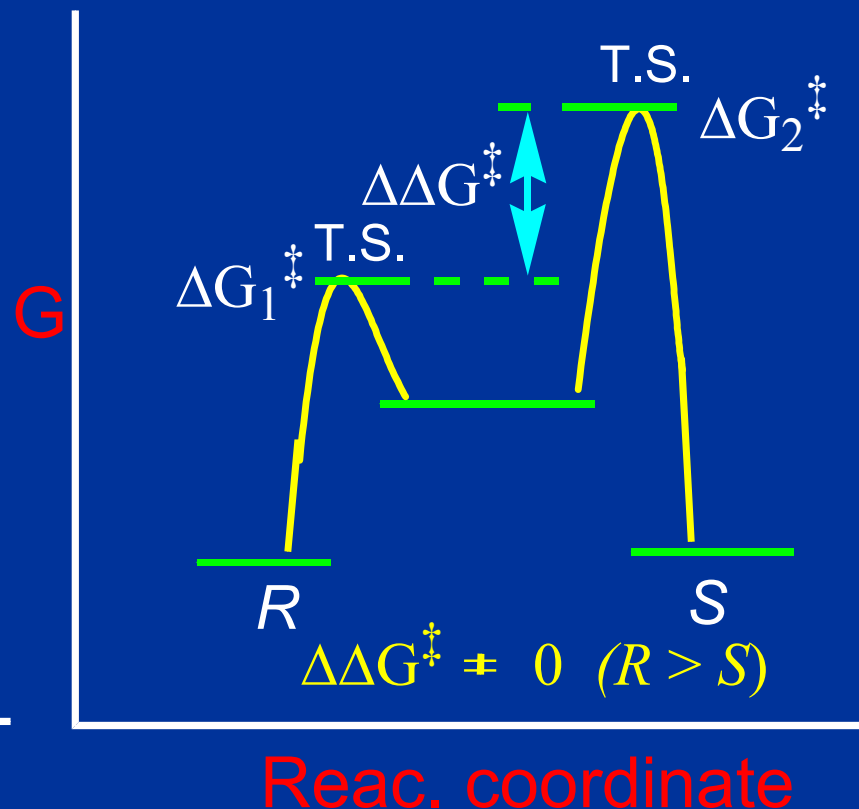
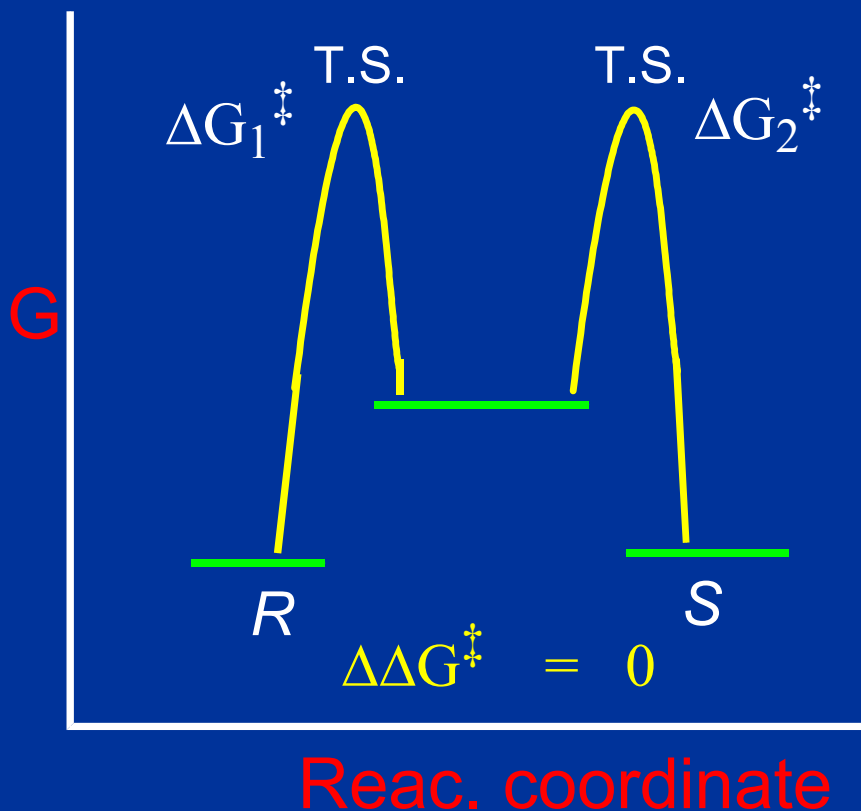
(Use of Chirality to extend patent protection)



Omeprazole
Antiulcer drug
(AstraZeneca)

It was marketed in U.S. as a racemic drug in 1995. The patent ran out in 2002. Since pharmacological property property lies in (S)-enantiomer, the company has patented now (S)-enantiomer.

Principle of Stereoselectivity



Ways to do Asymmetric Synthesis

1. Asymmetric Induction

- a. Internal Auxiliary
- b. External Auxiliary

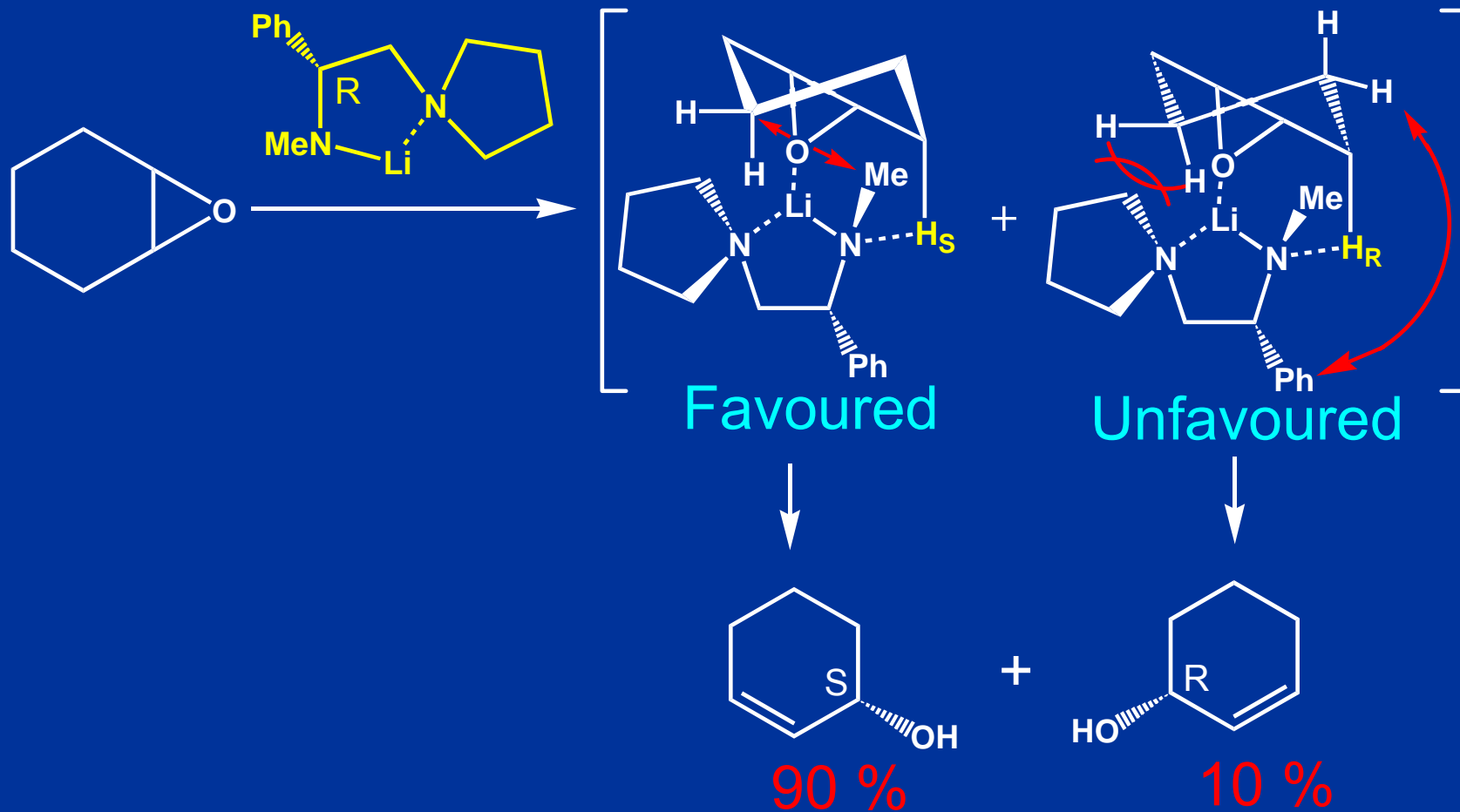
2. Chiron Approach

3. Resolution

- a. Enzymatic
- b. Non-enzymatic

Asymmetric Induction through External Auxiliary

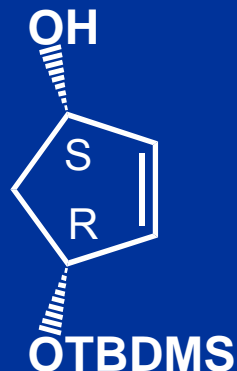
Enantioselective Deprotonation of Epoxides



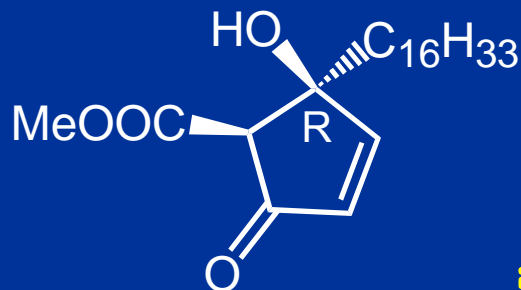
Bhuniya, D.; DattaGupta, A.; Singh, V. K.
J. Org. Chem. **1996**, *61*, 6108.

From our lab

Application in Synthesis

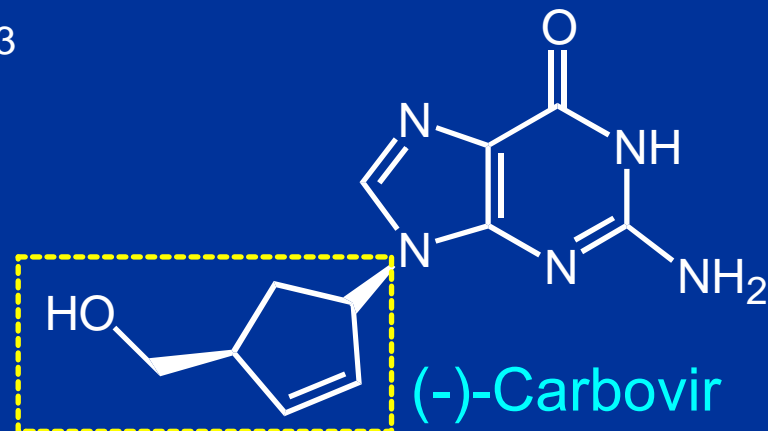


97% ee



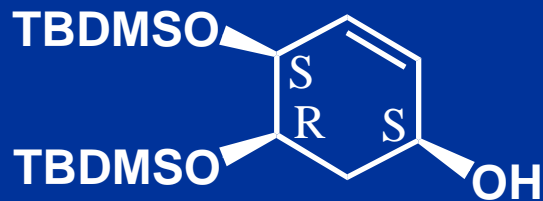
(-)-Utenone A

Anti-leukemic (isolated
from marine sponge)

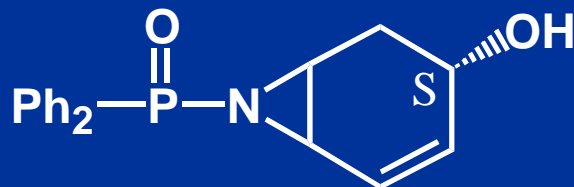


(-)-Carbovir

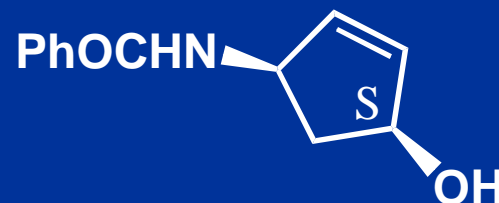
Anti-HIV agent



92% ee



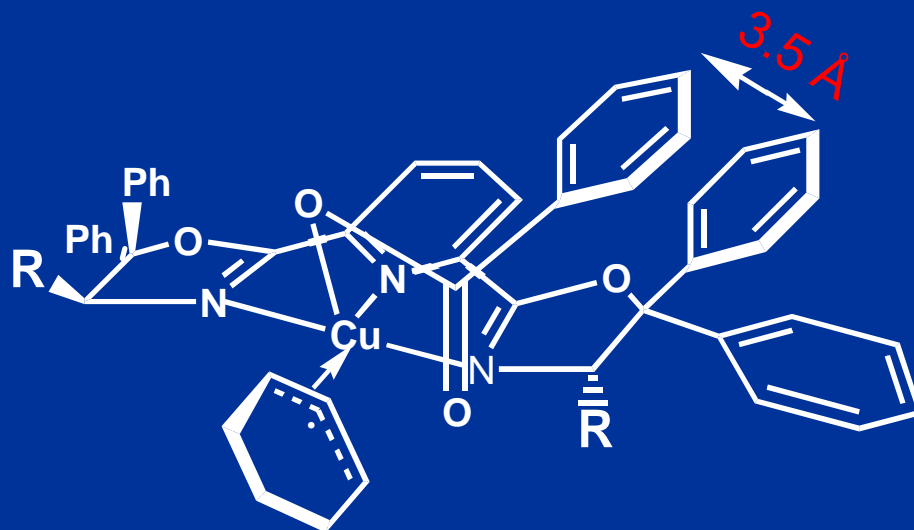
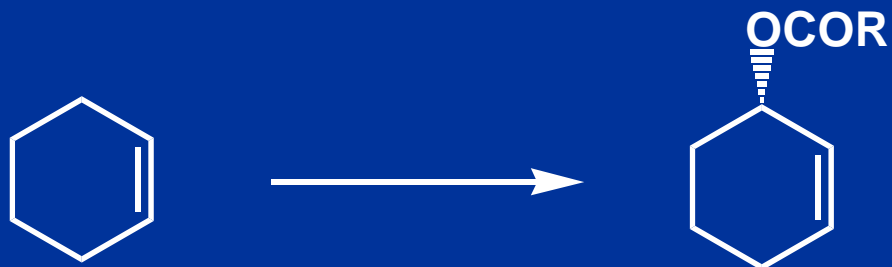
58% ee



60% ee

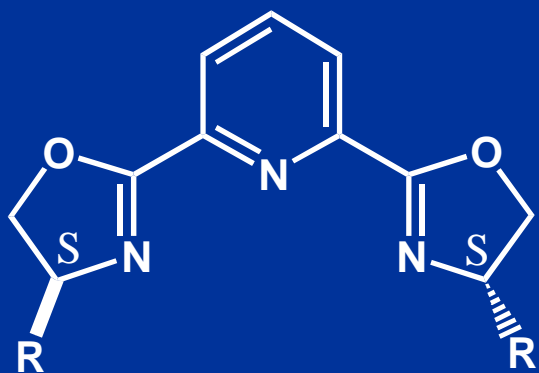
O'Brien *et al.* *Tetrahedron Lett.* **1999**, 40, 8427; **1998**,
39, 8175; **1996**, 37, 8057.

Enantioselective Allylic Oxidation of Olefins



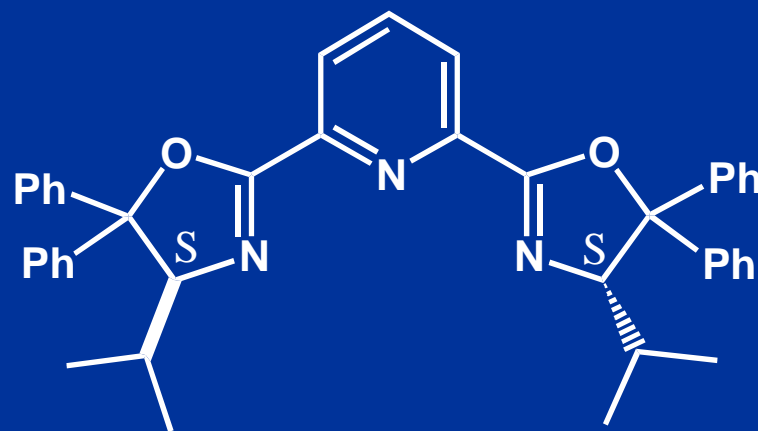
Favourable T. S. Assembly

Pyridine bis(oxazoline) Ligands in Asymmetric Synthesis



Nishiyama introduced in asymm., hydrosilylation (1989), and later used in asymmetric cyclopropanation (1994) and other reactions.

Evans used in asymmetric Diels-Alder (1995) and aldol Reactions (1996).



DattaGupta, A.; Bhuniya, D.; Singh, V. K. *Tetrahedron* 1994, 50, 13725 (asymmetric cyclopropanation reaction).

Reagents:

5 Mole % L* - Cu(OTf)₂, PhNHNH₂,
PhCO₃t-Bu, 4 Å MS, Acetone, rt



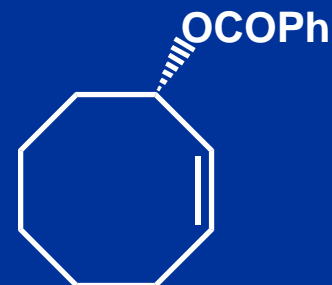
60% ee



86% ee



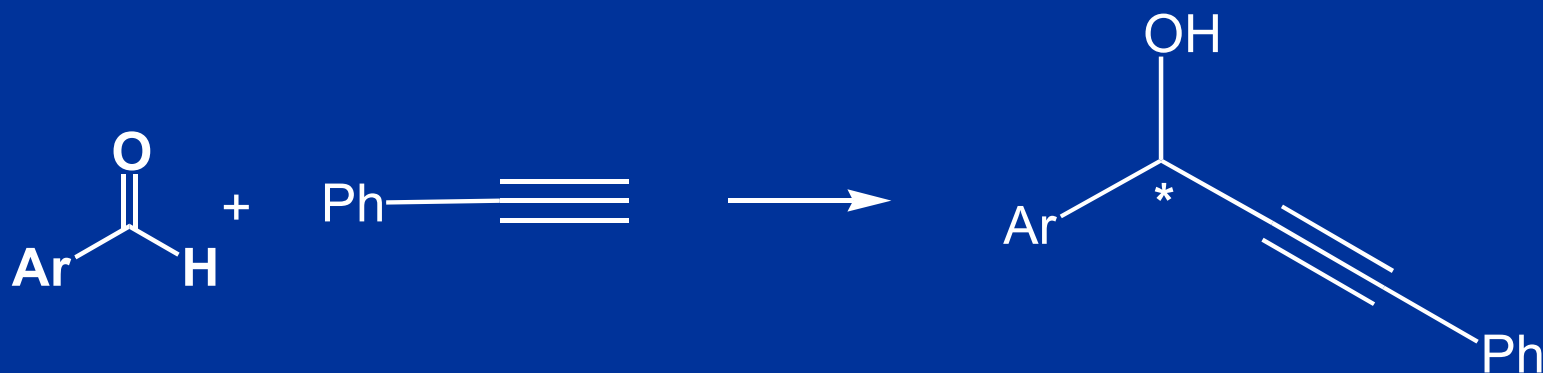
81% ee

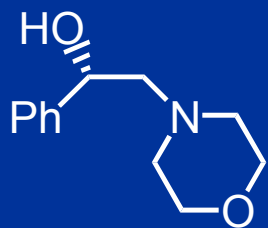
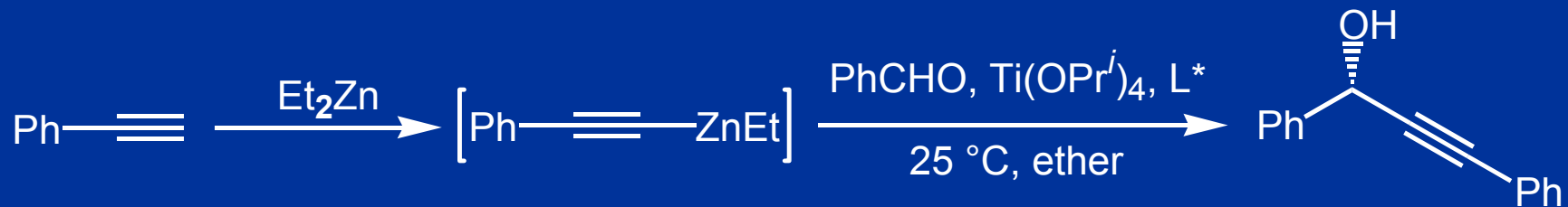


82% ee

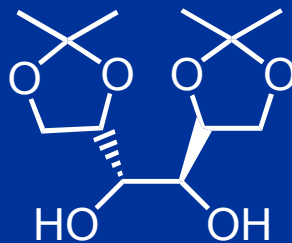
Sekar, G.; DattaGupta, A.; Singh, V. K.
J. Org. Chem. **1998**, 63, 2961.

Enantioselective Propargylation Reaction

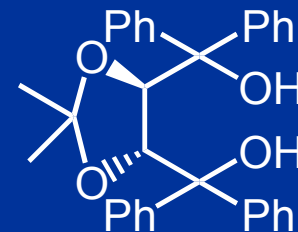




Et₂Zn, Ti(OPrⁱ)₄: 10% ee

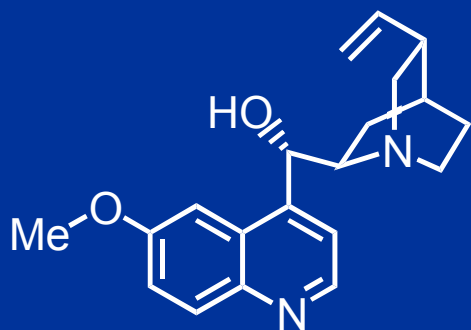


Et₂Zn, Ti(OPrⁱ)₄: 10% ee



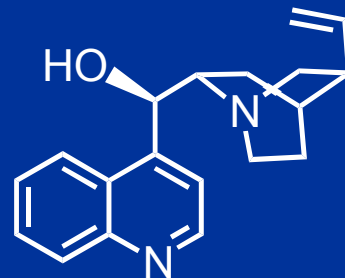
Et₂Zn, Ti(OPrⁱ)₄: 60% ee

Et₂Zn: 4% ee



Et₂Zn, Ti(OPrⁱ)₄: 45% ee

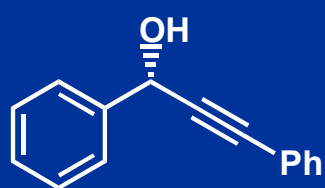
Et₂Zn: 24% ee



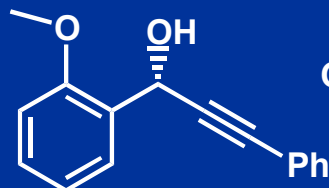
Et₂Zn, Ti(OPrⁱ)₄: 77 % ee

Et₂Zn: 14% ee

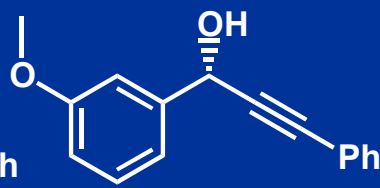
Enantioselective Phenylacetylene Addition to Aldehydes in the presence of Cinchonidine and $\text{Ti}(\text{OPr}^i)_4$



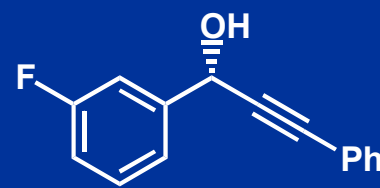
79% ee



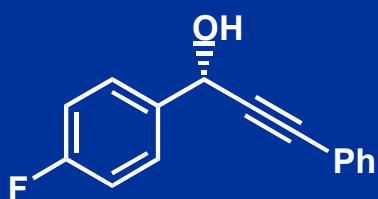
74% ee



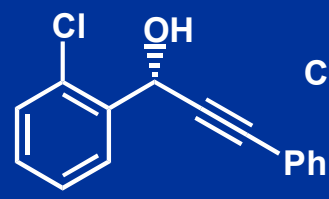
61% ee



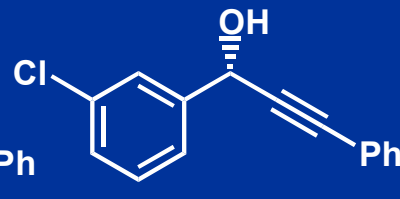
85% ee



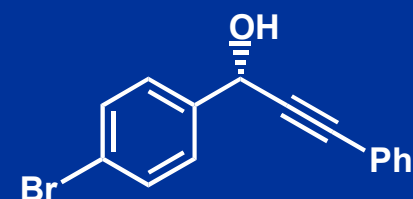
79% ee



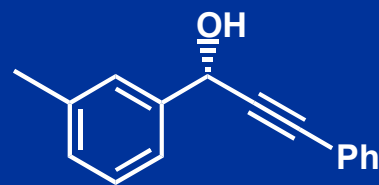
76% ee



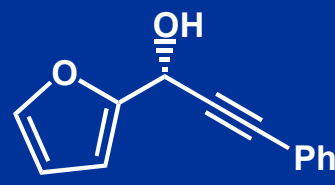
85% ee



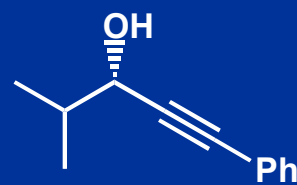
62% ee



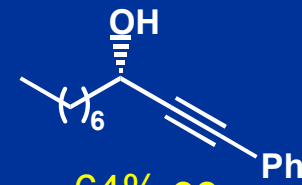
79% ee



86% ee



79% ee



64% ee

Kamble, R.M.; Singh, V. K. *Tetrahedron Lett.* **2003**, 44, 5347

Chiron Approach in Asymmetric Synthesis



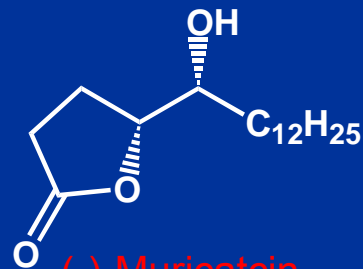
(-)-Lentiginosine

J. Org. Chem., 2002, 67, 4630



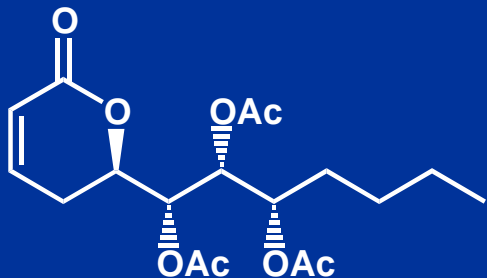
(-)-Acaterin

TL, 2002, 43, 5393



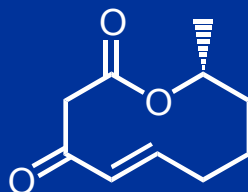
(-)-Muricatoin

TL, 2002, 43, 2773



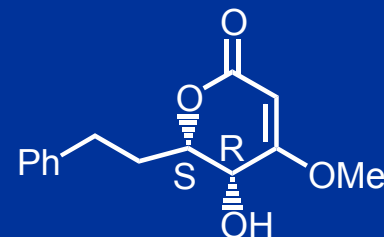
(+)-Boronolide

J. Org. Chem., 2003, 68, 4039

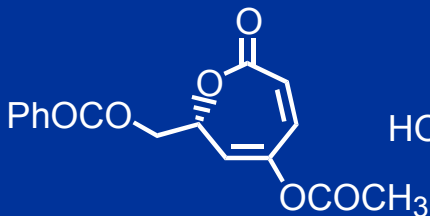


(+)-Diplodialide A

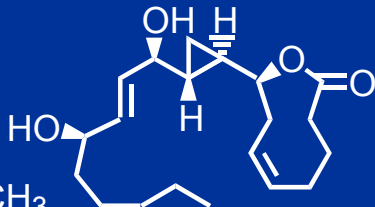
J. Org. Chem., 2003, 68, 3356.



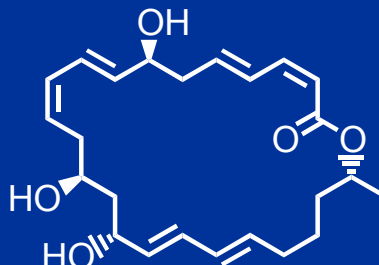
(+)-Dihydrokawain-5-ol
(just completed)



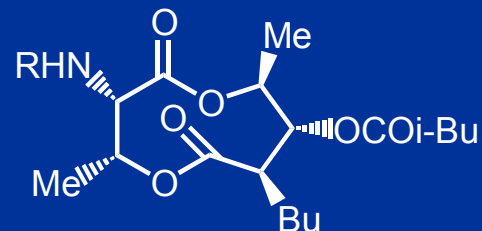
(-)-Klaivanolide
(in progress)



(+)-Halicholactone
(in progress)



(-)-Macrolactin A
(in progress)

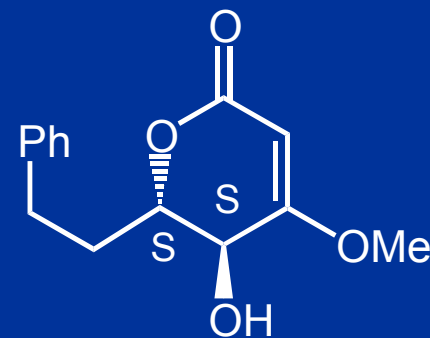
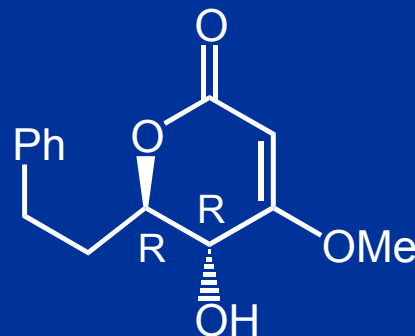
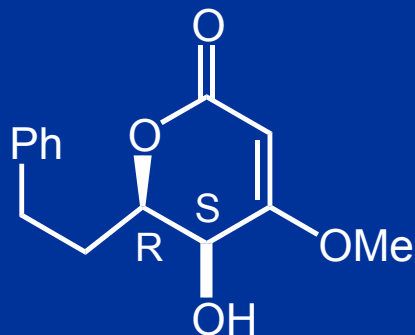


Actinomycin A3
(in progress)

Dihydrokawainol



Natural

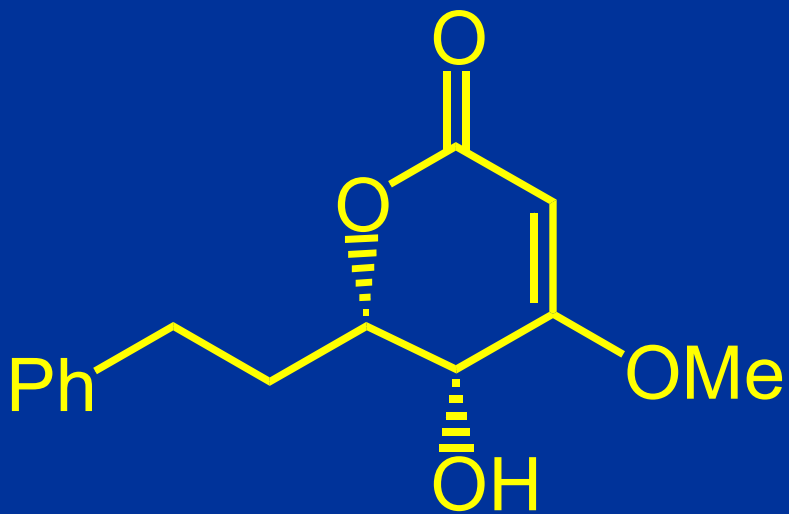


Isolation: From tropical plant *Piper mythisticum*

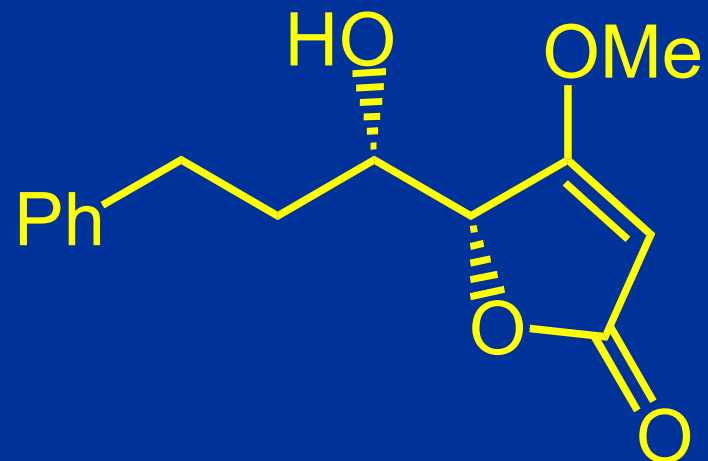
Biol. activity: Anxiolytic, sedative and analgesic

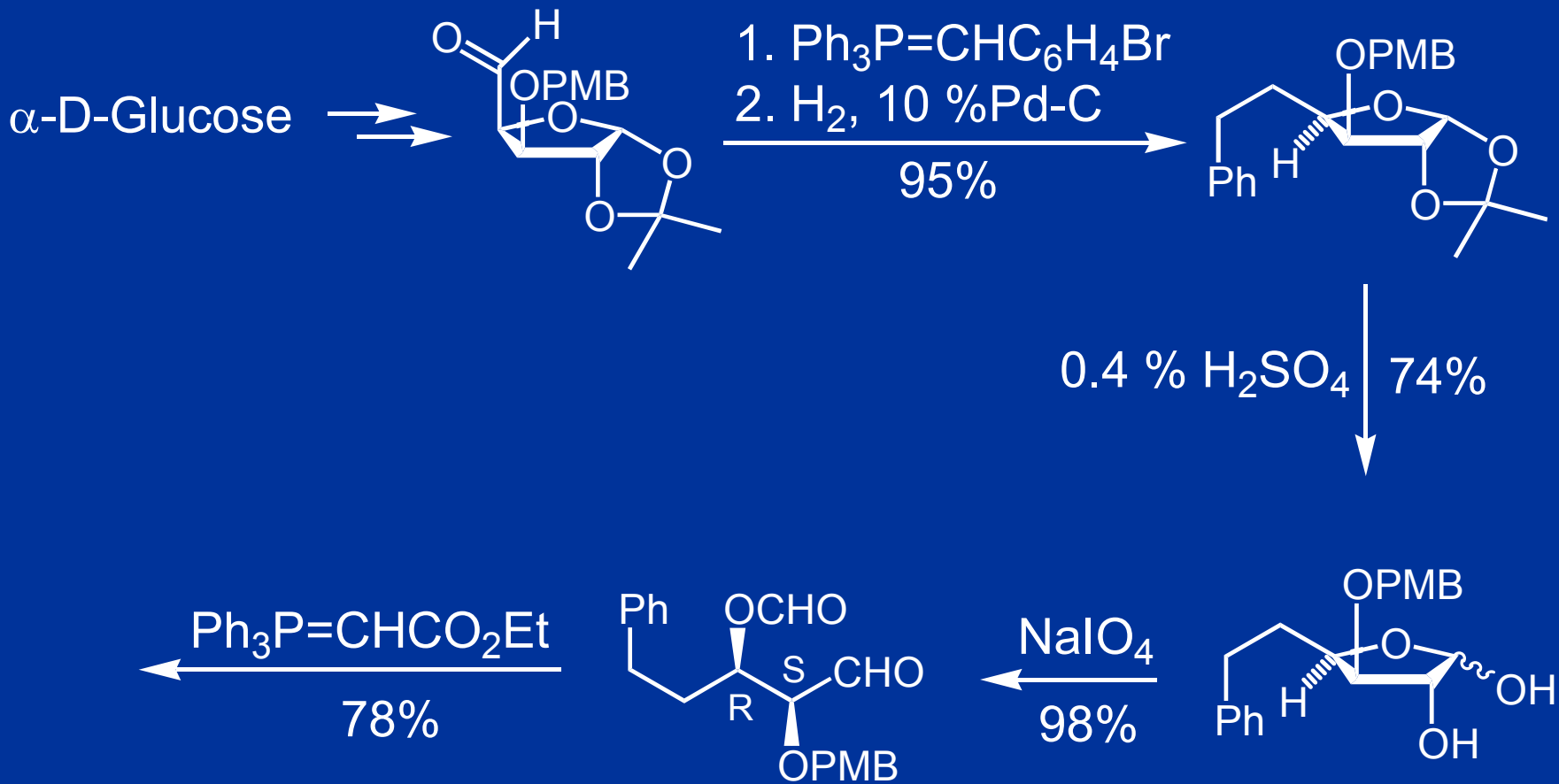
Synthesis:

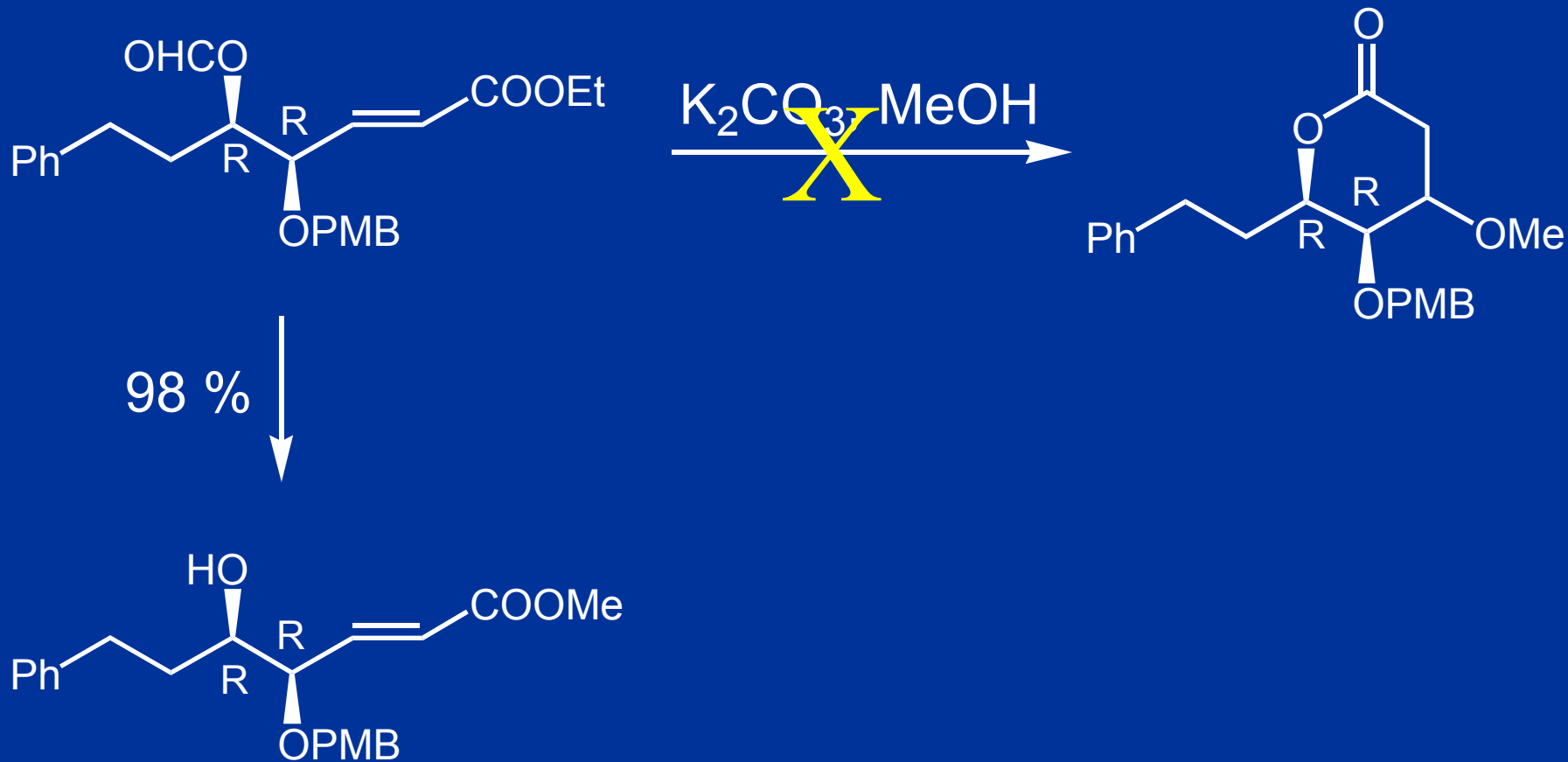
1. Friesen et al. *J. Org. Chem.* **1996**, *61*, 9103 (racemic)
2. Arai et al. *J. Org. Chem.* **2000**, *65*, 258 (chiral).

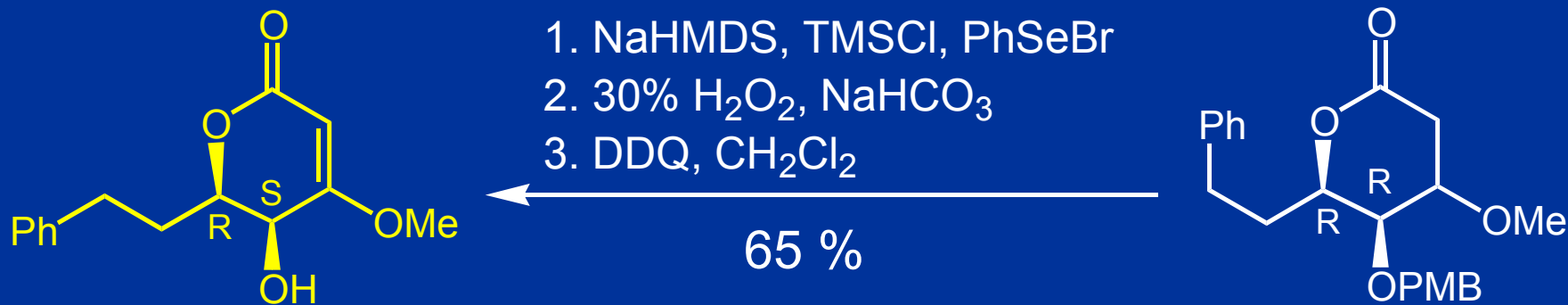
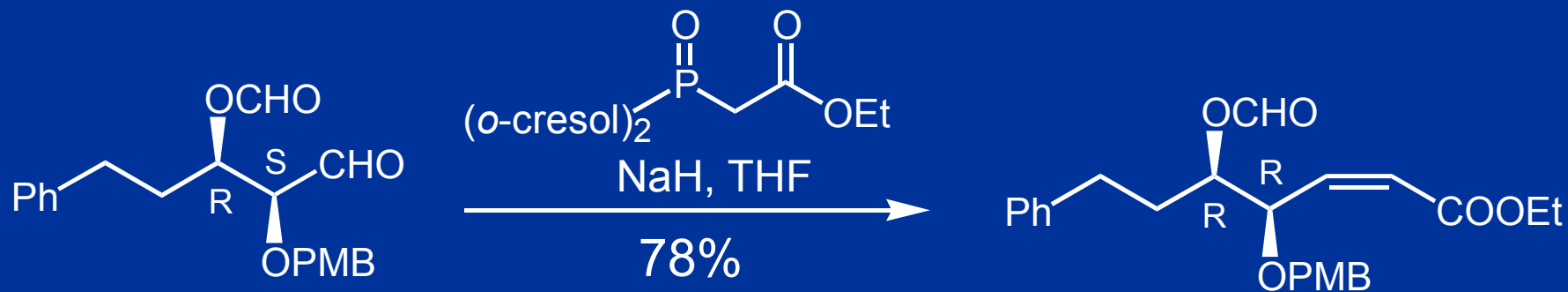


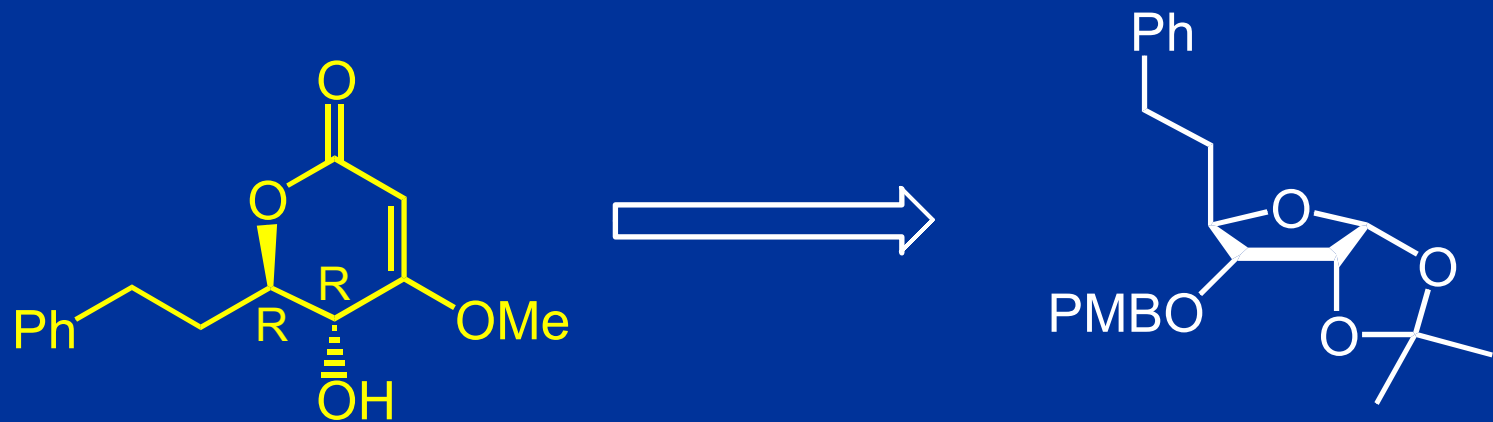
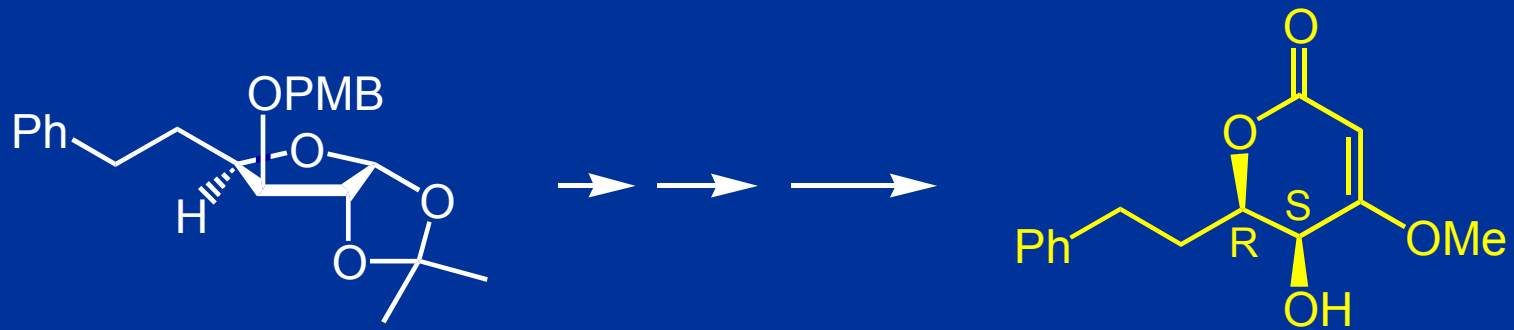
Dihydrokawainol

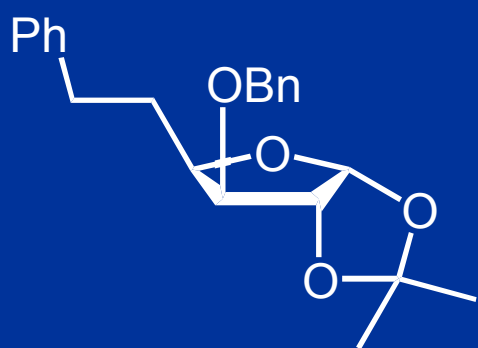






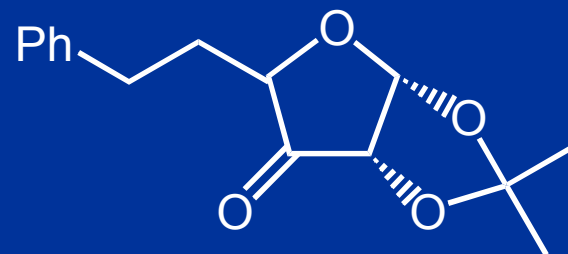






1. H₂, Pd(OH)₂ / C
2. Swern oxid.

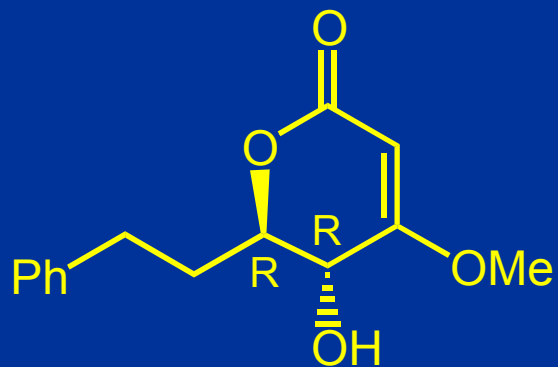
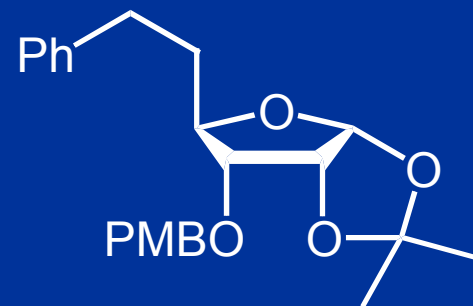
92%

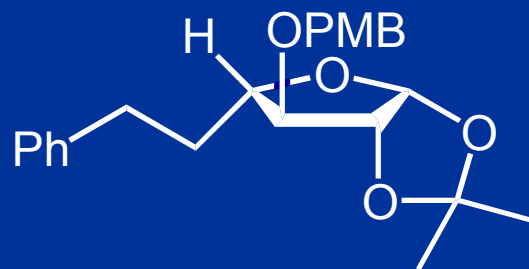
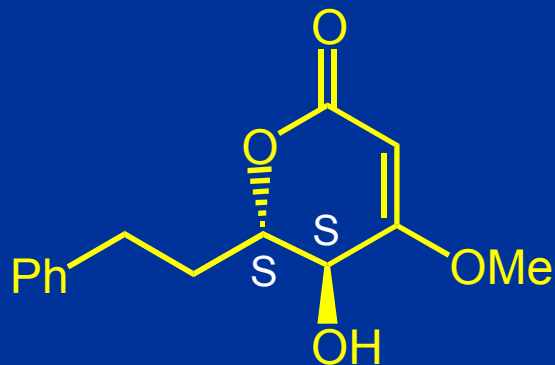
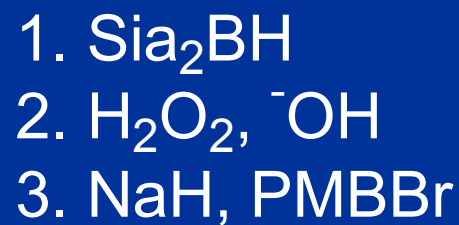
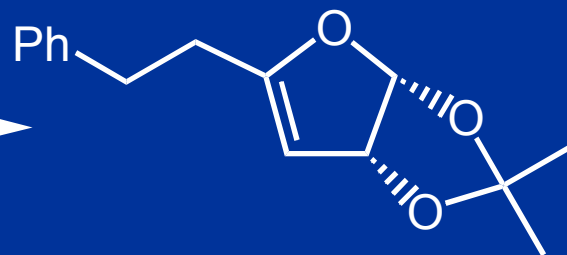
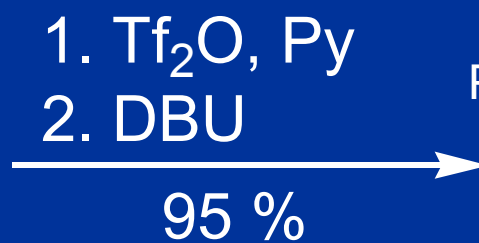
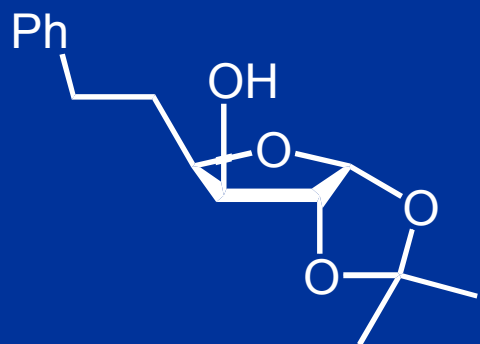


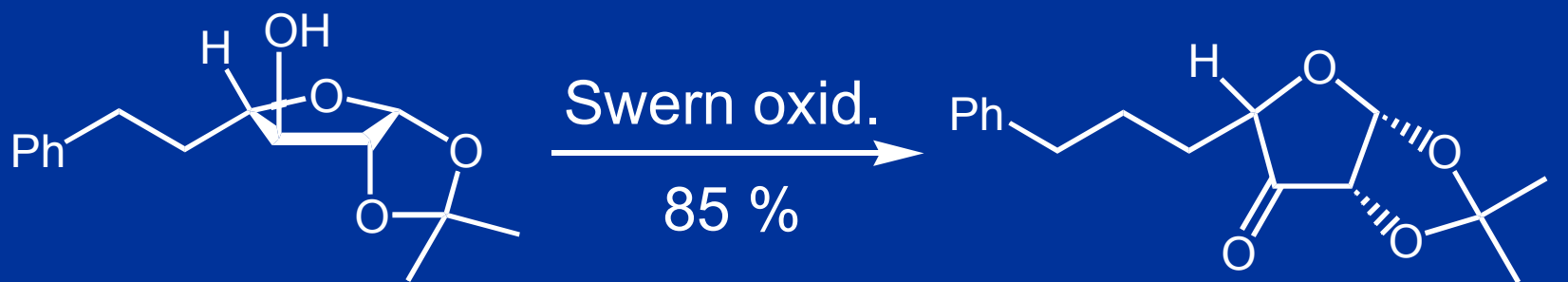
1. NaBH₄

2. NaH, PMBBr

96 %



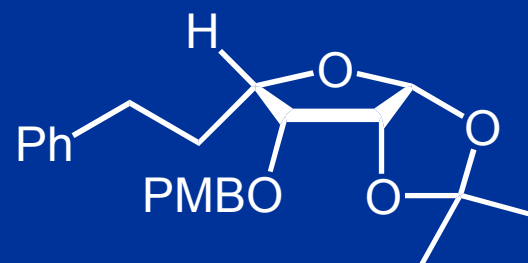




1. NaBH₄
2. NaH, PMBBBr 96 %



Natural
(Dihydrokawainol)



ACKNOWLEDGEMENT

1. Debnath Bhuniya
2. ArpitaDatta Gupta
3. G. Sekar
4. P. Saravanan
5. M. Chandrasekhar
6. R. Vijaya Anand
7. Kusum L. Chandra
8. Rajesh M. Kamble
9. Ravi P. Singh

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CSIR