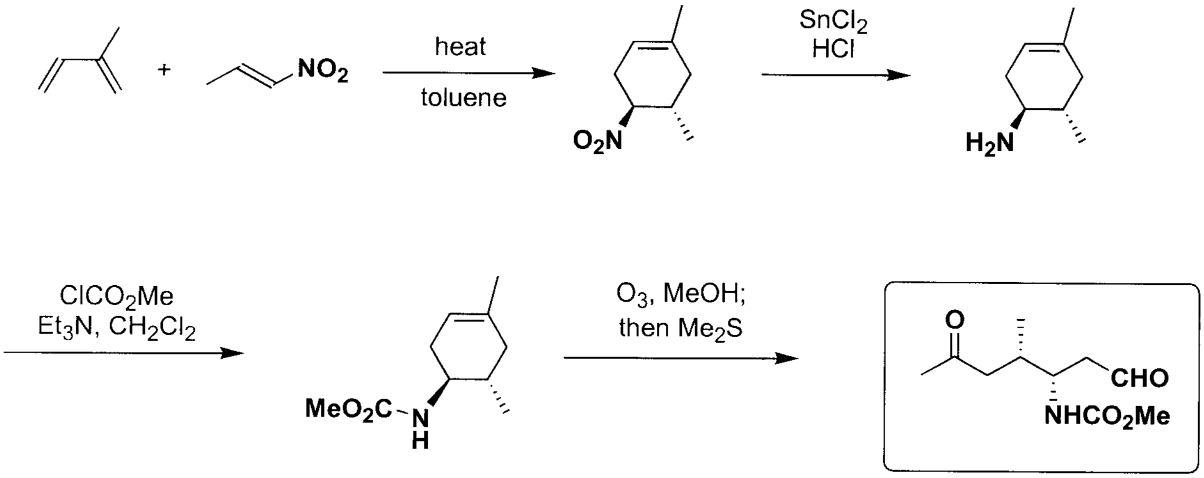
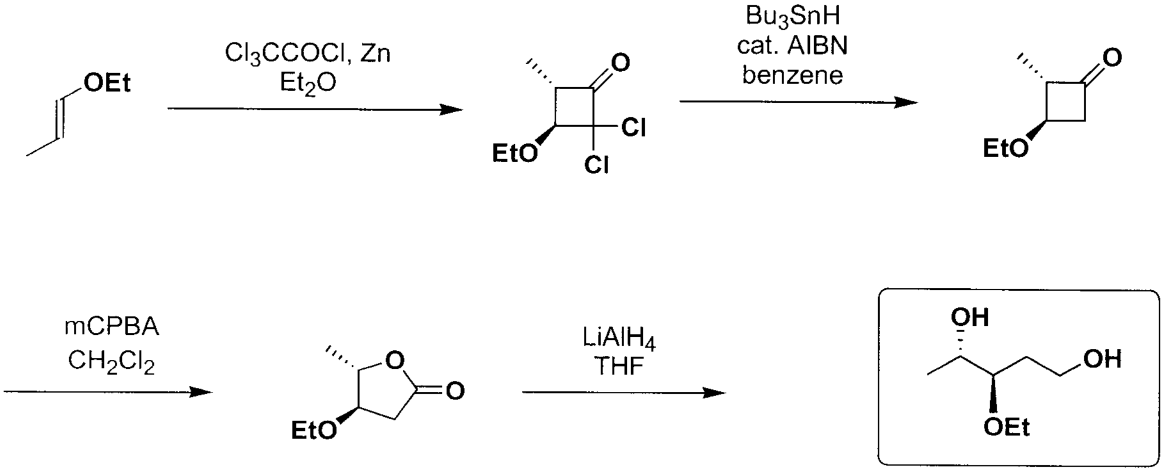
Massachusetts Institute of Technology
Organic Chemistry 5.512

Problem Set 2 Solutions
Strategies for Synthesis of Acyclic Molecules Based on Desymmetrization, Chirality Transfer, the "Chiron Approach", and Ring Template Strategies

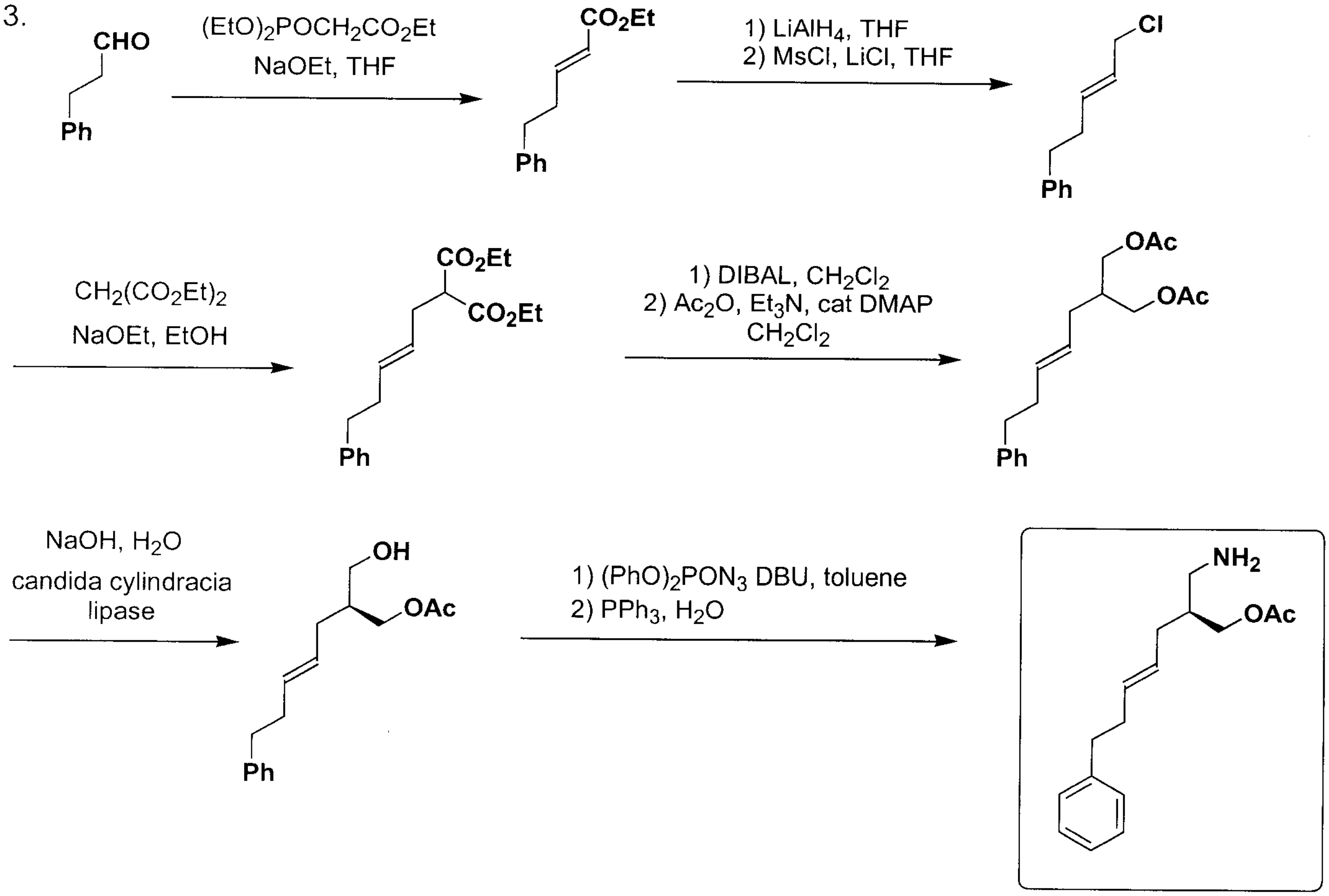
1.



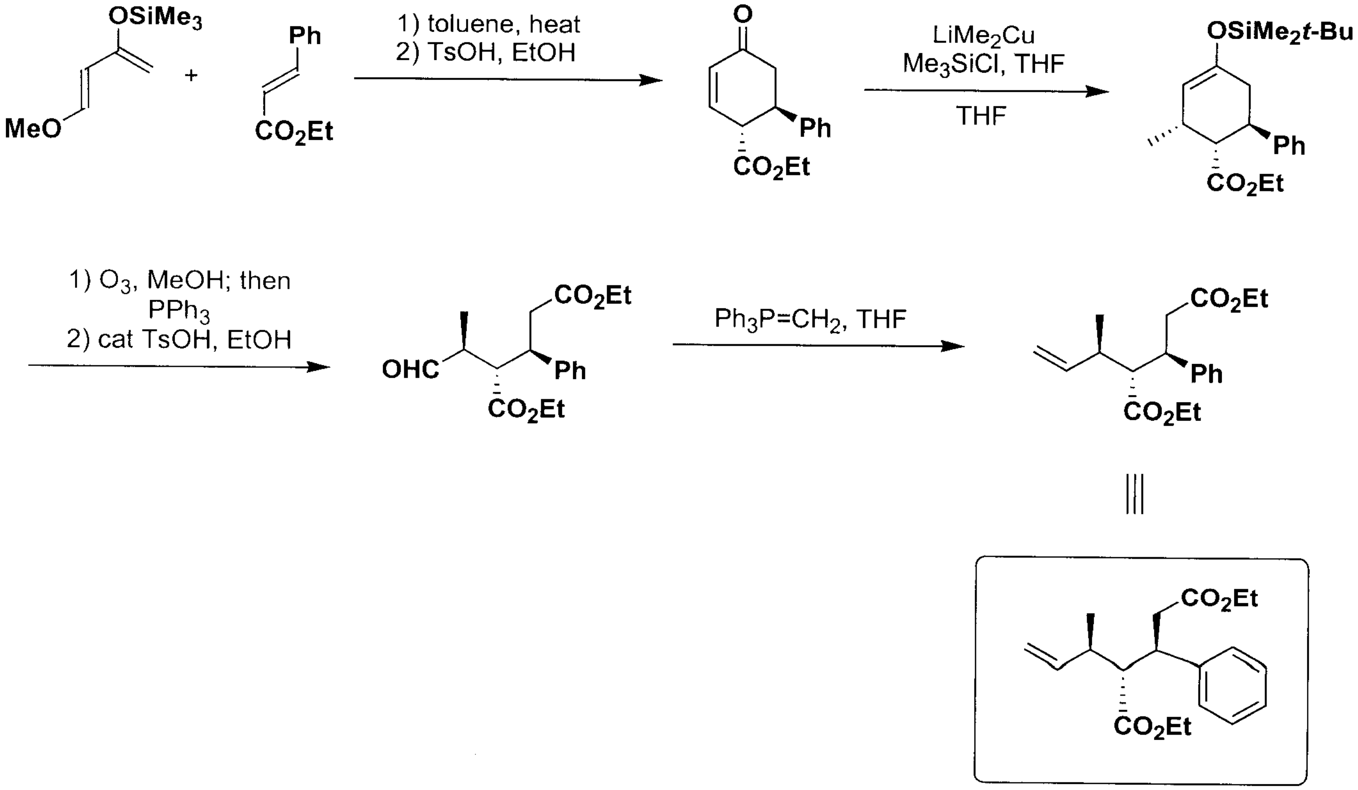
2.



3.


CHO
Ph
(EtO)2POCH2CO2Et
NaOEt, THF
CO2Et
Ph
1) LiAlH4, THF
2) MsCl, LiCl, THF
Cl
Ph
CH2(CO2Et)2
NaOEt, EtOH
CO2Et
CO2Et
Ph
1) DIBAL, CH2Cl2
2) Ac2O, Et3N, cat DMAP
CH2Cl2
OAc
OAc
Ph
NaOH, H2O
candida cylindracia
lipase
OH
OAc
Ph
1) (PhO)2PON3 DBU, toluene
2) PPh3, H2O
NH2
OAc

4.


OSiMe3
MeO
+
Ph
CO2Et
1) toluene, heat
2) TsOH, EtOH
O
Ph
CO2Et
LiMe2Cu
Me3SiCl, THF
THF
OSiMe2t-Bu
Ph
CO2Et
1) O3, MeOH; then
PPh3
2) cat TsOH, EtOH
CO2Et
OHC
Ph
CO2Et
Ph3P=CH2, THF
CO2Et
Ph
CO2Et
|||
CO2Et
CO2Et

II. The creation of a mixture of products favoring one enantiomer over another from a racemic mixture in the absence of chiral reactants is impossible. In the case of the "asymmetric synthesis" of santonin from 2-methyl-2-formylcyclohexanone, the optical rotation is likely due to the presence of impurities in the sample.

Nature, 1944 (153) [redacted] 317

Reported Asymmetric Synthesis of Santonin

Some time ago[1] Paranjape, Phalnikar, Bhide and Nargund reported a synthesis of santonin from optically inactive materials: they now[2] claim that their product was active, being almost entirely the natural (*l*-) isomer. They state that the activity originated in the methylation of a 2-formyl*cyclo*hexanone derivative, and that the crude methylation product from 2-formyl*cyclo*hexanone (I) itself had the large specific rotation of − 26·2° in chloroform. Although they did not isolate 2-methyl-2-formyl*cyclo*hexanone (II), they claim that an optically active derivative was prepared in a state of purity.

Such an asymmetric synthesis from inactive materials violates no fundamental law and might theoretically be expected to occur once in about $(10^{10})^{20}$ trials.

Nevertheless, Paranjape *et al.* claim to have achieved the asymmetric synthesis repeatedly. As we were interested in the products for another reason, it seemed worth while to repeat one of these experiments.

Sen and Mondal[3] prepared (II), though not in a pure condition, and established its structure by hydrolysis to 2-methyl*cyclo*hexanone. We find that (II) may readily be purified by fractionation at low pressure, forming a colourless oil of camphoraceous odour, b.p. 47°/0·05 mm., n_D^{18} 1·4683 (Found: C, 68·2, 68·4; H, 8·6, 8·4. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6 per cent); the hydrolysis to methyl*cyclo*hexanone was confirmed. Neither the crude methylation product from (I) nor pure (II) showed any optical activity whatsoever.

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[1] *Current Science*, 12, 150 (1943).
[2] Nature, 153, 141 (1944).
[3] *J. Ind. Chem. Soc.*, 5, 609 (1928).