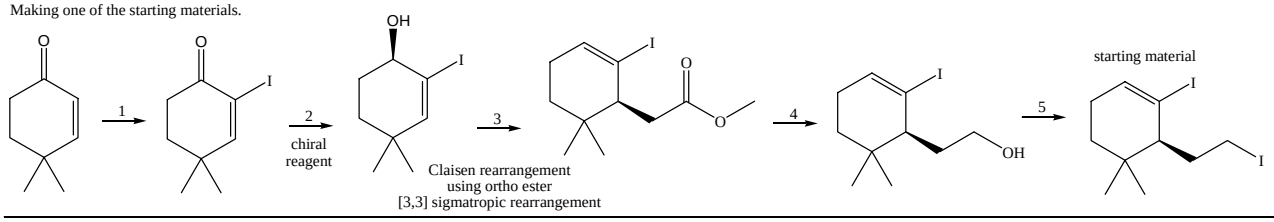
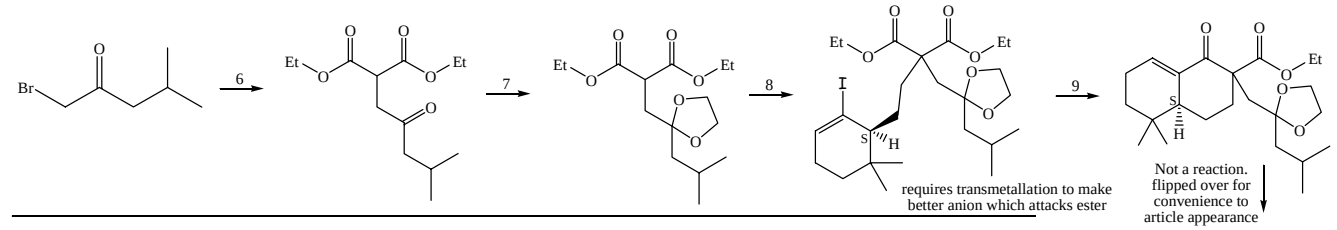
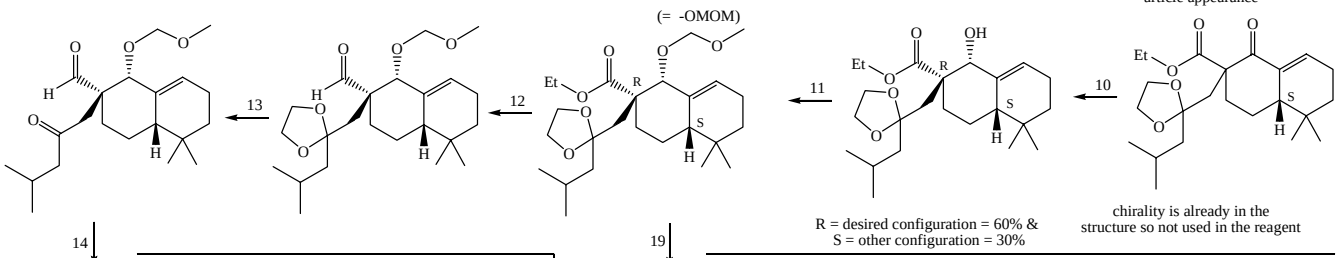
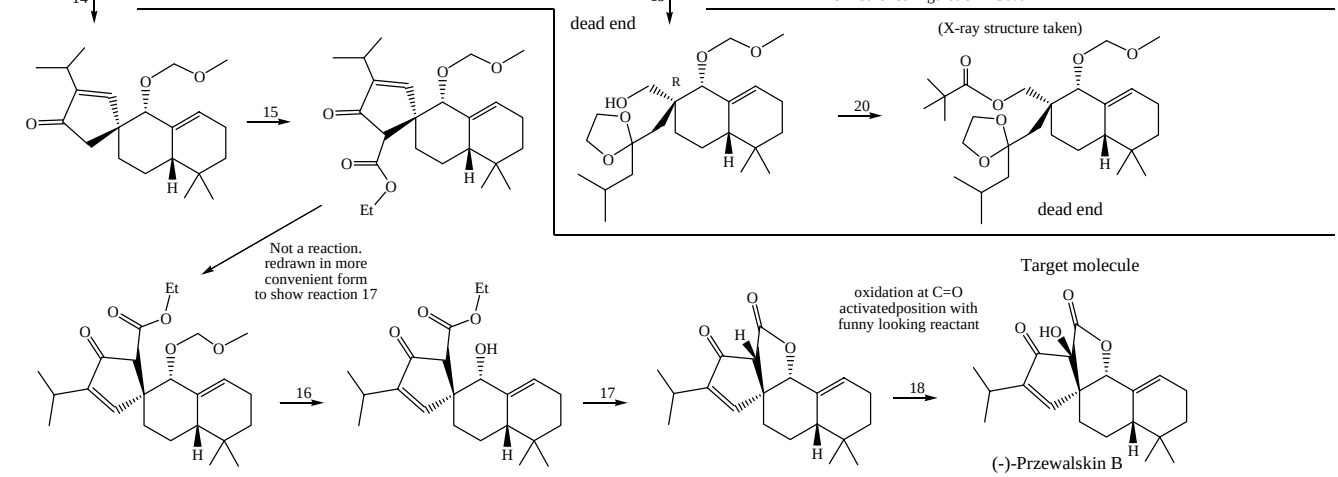
Match the step number in the synthesis with the letter of the reagents listed just below.

Making one of the starting materials.

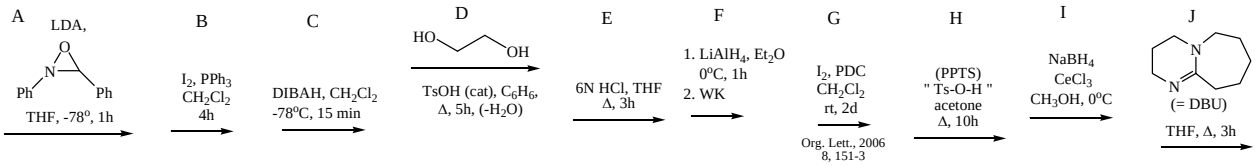


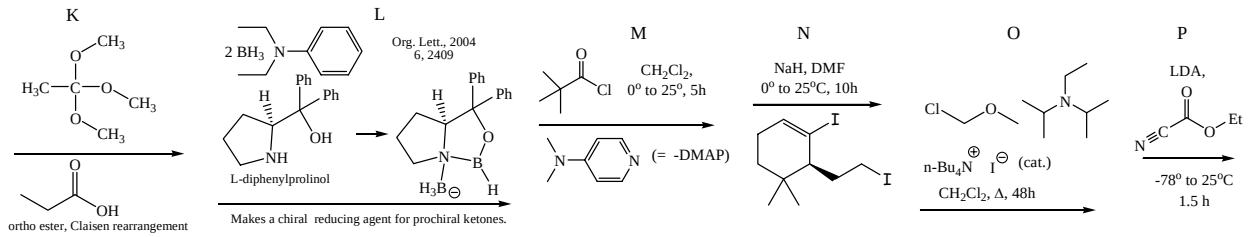



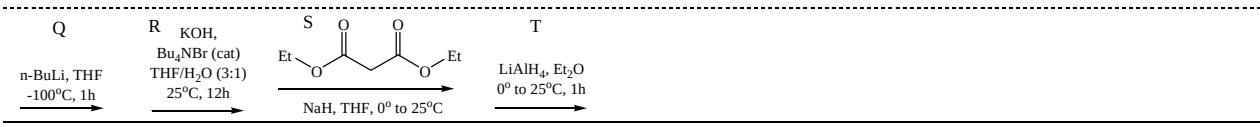




Reagents used in the above 20 steps.

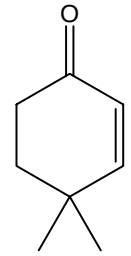


Synthesis of (-)-Przewalskin B (with comments)

Making one of the starting materials.



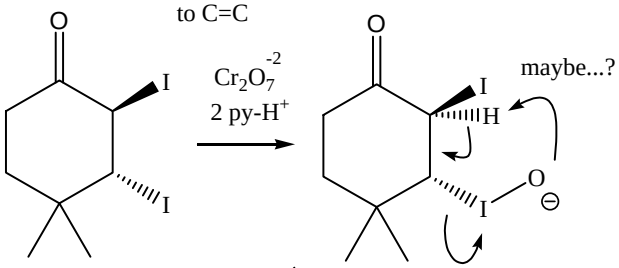
PDC is assumed to be pyridinium dichromate (looking back 2 papers only lists "PDC"). It might be expected that $I_2$ adds to the double bond (anti) and PDC might oxidize the more distant I leading to an elimination reaction of hypoiodous acid (but it's just a guess).

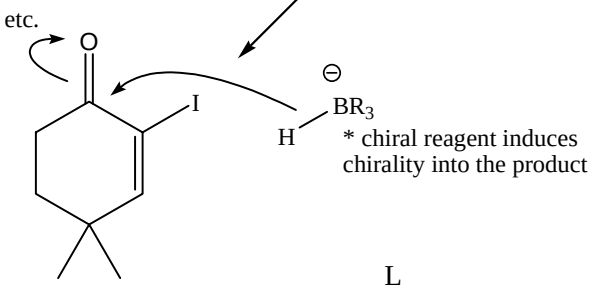
step 1 ↓ G

$I_2$, PDC
$CH_2Cl_2$
rt, 2d

Org. Lett., 2006
8, 151-3

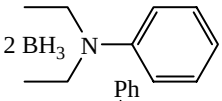
$I_2$, addition to C=C



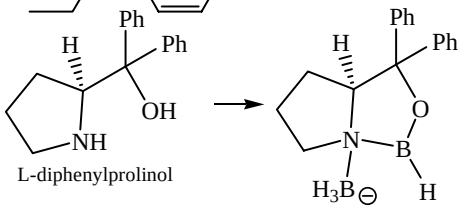

* chiral reagent induces chirality into the product

L



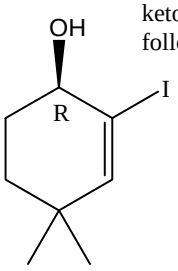

Org. Lett., 2004
6, 2409

step 2 ↓



L-diphenylprolinol

Makes a chiral reducing agent for prochiral ketones. Think of $NaBH_4$ for a mechanism, followed by workup.



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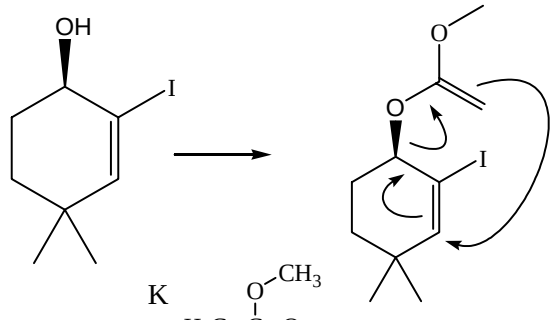
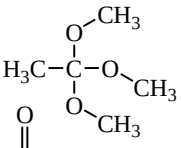
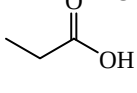


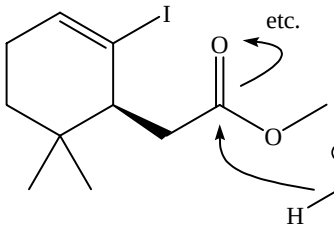
K



step 3 ↓



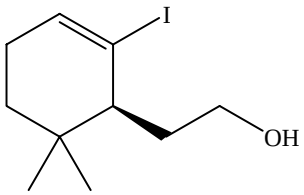
ortho ester forms,
Claisen rearrangement
[3,3] sigmatropic rearrangement




A typical LAH reduction, followed by workup. Needs LAH because esters are less reactive.

step 4 ↓ T

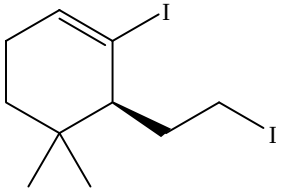
$LiAlH_4$, $Et_2O$
$0^o$ to $25^oC$, 1h



B

step 5 ↓

$I_2$, $PPh_3$
$CH_2Cl_2$
4h

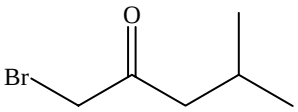


$S_N2$ by "P" on $I_2$ forms P-I bond, followed by $S_N2$ by "O" on "P", forms "P-O-C" bond, followed by $S_N2$ on "C" by "$I^{\ominus}$ ", forms C-I bond.

This molecule is used in the synthesis.

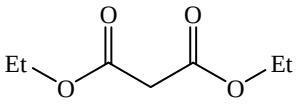
Continue at top of next column.

starting material

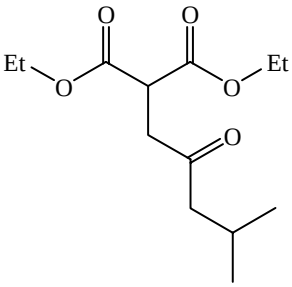


Make the sstabillized enolate using malonic ester, which does an $S_N2$ to displace the very reactive "$C_\alpha$-Br".

step 6 ↓ S

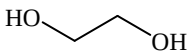


NaH, THF, 0° to 25°C

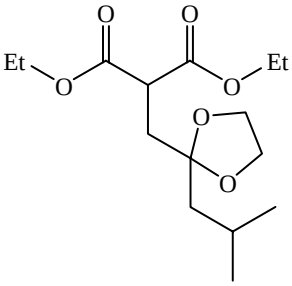


Typical protection of ketone (more reactive than esters).

step 7 ↓ D

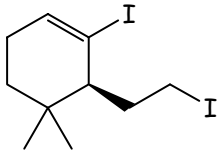


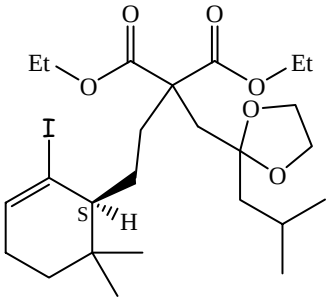
TsOH (cat), $C_6H_6$, Δ, 5h, (-$H_2O$)



Repeat of step 6 with a different electrophile (made in preliminary steps 1-5).

step 8 ↓ N NaH, DMF 0° to 25°C, 10h



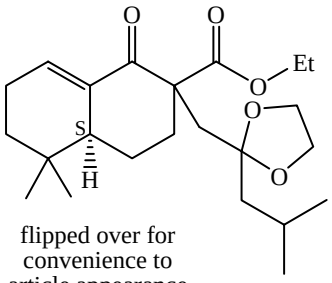


Transmetallation makes a more "$sp^2$" carbanion instead of $sp^3$ carbanion of n-butyl lithium at "I" carbon, which attacks the ester in an acyl substitution reaction to form the bicyclic ketone.

step 9 ↓ Q n-BuLi, THF -100°C, 1h

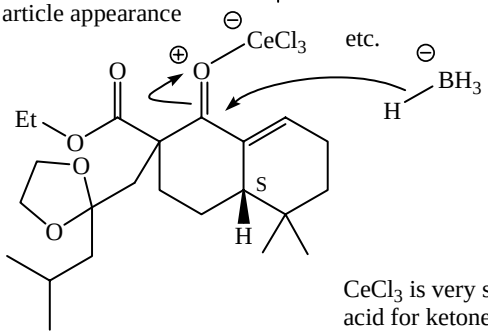
very low temperature keeps everything under control

Continue at top of next column.



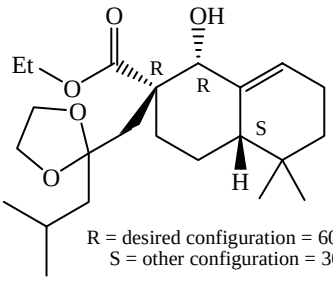
flipped over for convenience to article appearance

not a reaction, structure is redrawn similar to paper.



$CeCl_3$ is very specific Lewis acid for ketone, which is reduced by $BH_4^\ominus$ with chiral approach because of chiriality already in the molecule. 2. Workup

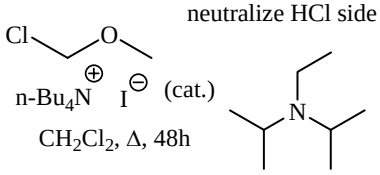
step 10 ↓ I $NaBH_4$, $CeCl_3$, $CH_3OH$, 0°C



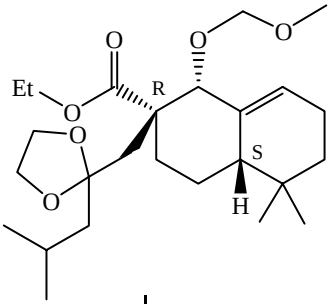
R = desired configuration = 60% &
S = other configuration = 30%

$S_N2$ or $S_N1$ on chloroether. 3° amine acts as base to neutralize HCl side product.

step 11 ↓



$CH_2Cl_2$, Δ, 48h

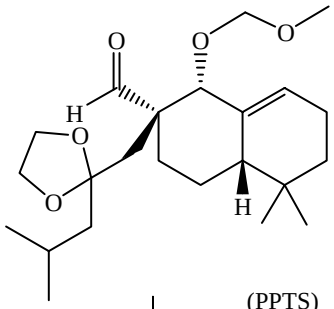


(Referred to as -OMOM protecting group for alcohol).

Typical DIBAH reduction of ester to aldehyde at low temperature, then workup.

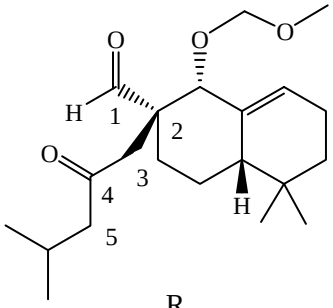
step 12 ↓ C DIBAH, $CH_2Cl_2$ -78°C, 15 min

Continue at top of next column.



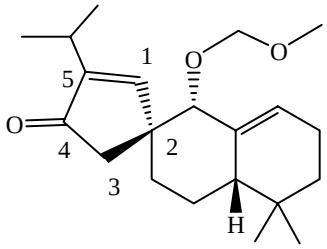
Typical deprotection of ketone using acid and wet acetone.

step 13 — H — (PPTS) " Ts-O-H " acetone/water Δ, 10h

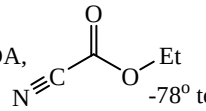


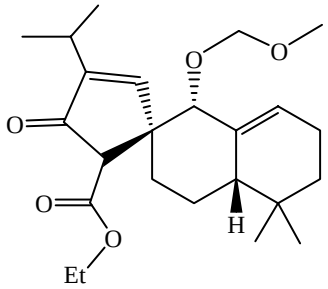
Common "aldol" condensation using ketone enolate attacking aldehyde,then loss of water to form α,β-unsaturated C=O.

step 14 — R — KOH, $Bu_4NBr$ (cat) $THF/H_2O$ (3:1) 25°C, 12h



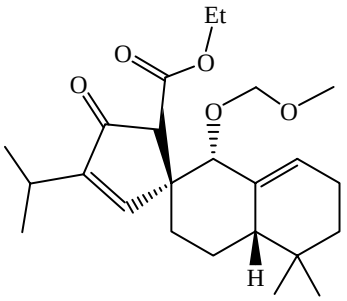
Make enolate at ketone, then acyl substitution with "CN" as the leaving group to make diactivated C=O group.

step 15 — P — LDA,  -78° to 25°C 1.5 h



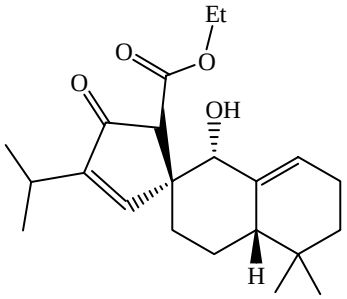
redrawn at top of next column with cyclic ketone in more convenient form to show reaction J.

Continue at top of next column.

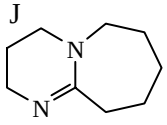


Deprotection of alcohol using aqueous alcohol.

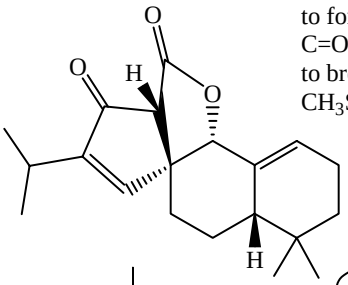
step 16 — E — 6N HCl, THF Δ, 3h

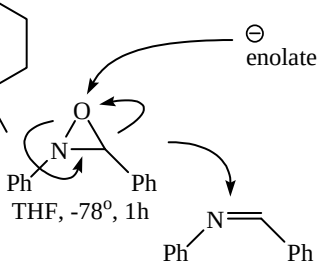


DBU base makes low concentration of alkoxide which attacks ester in acyl substitution reaction to make lactone (cyclic ester).

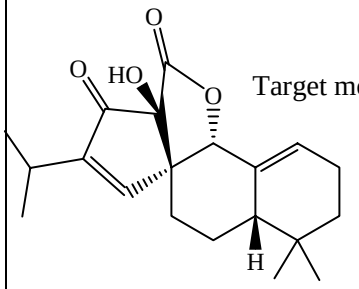
step 17 — J —  (= DBU) THF, Δ, 3h

Make enolate at di-C=O which attacks "O" of 3 atom heterocycle to form alcohol (after workup) at C=O $C_\alpha$ position. Some similarity to breakdown of ozonide using $CH_3SCH_3$.





step 18 — A — LDA, THF, -78°, 1h

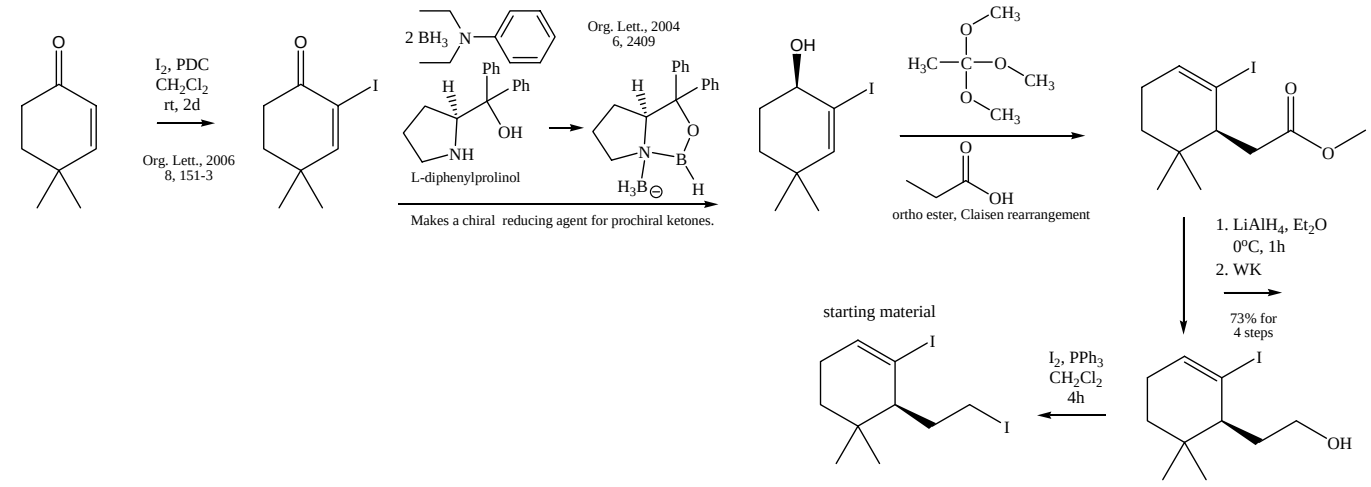


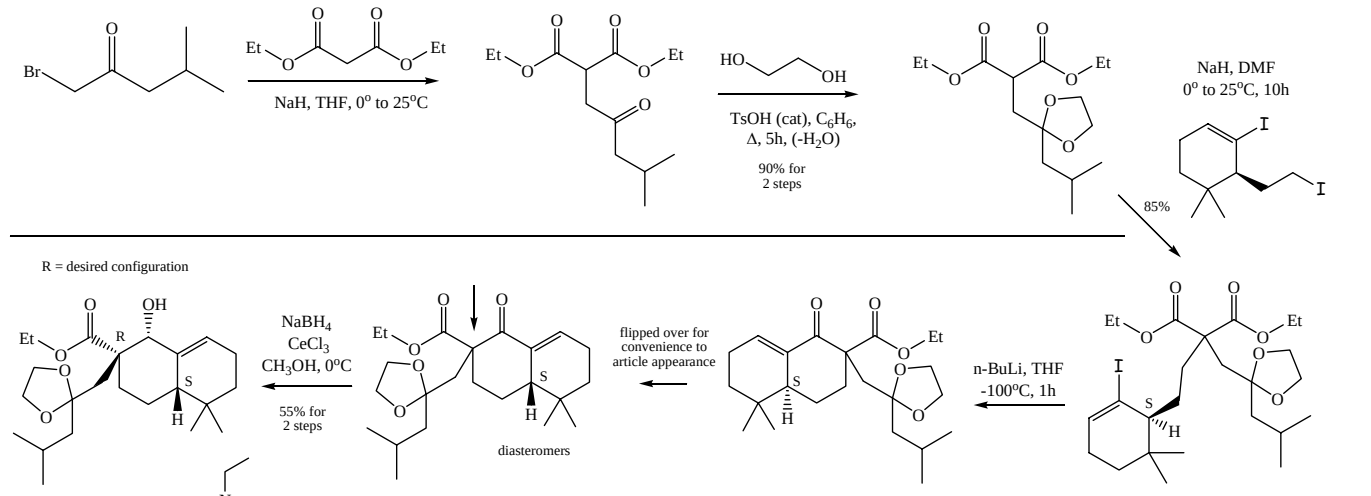
Target molecule

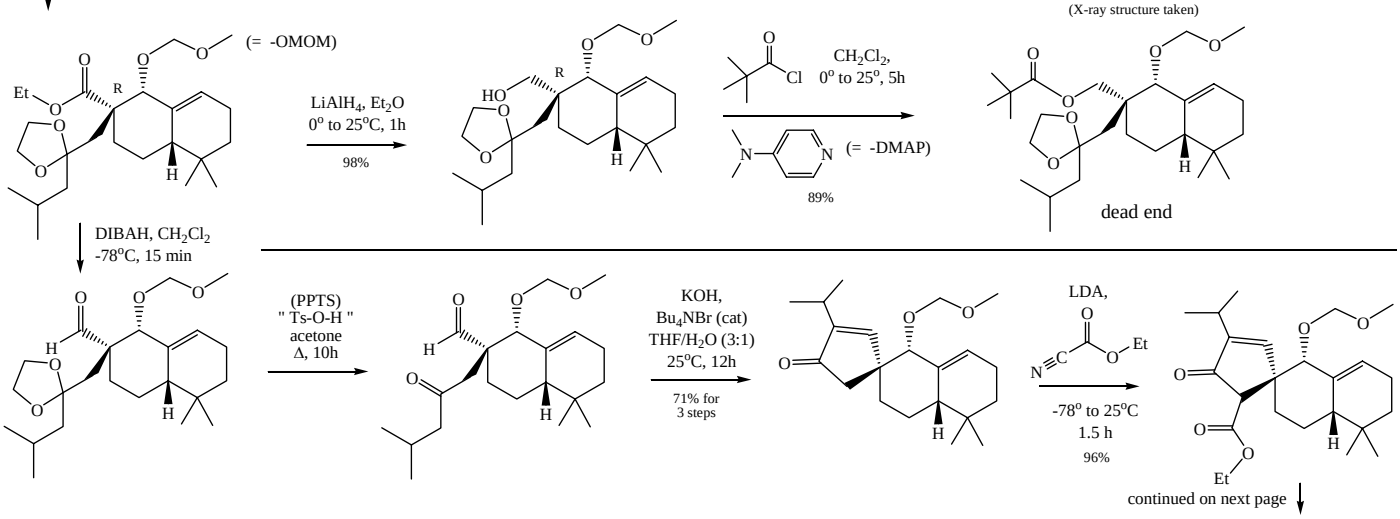
(-)-Przewalskin B

Org. Lett., vol. 13, pp 173-5, 2011
J. Zheng, et. al.

Sequence of reactions listed in paper.

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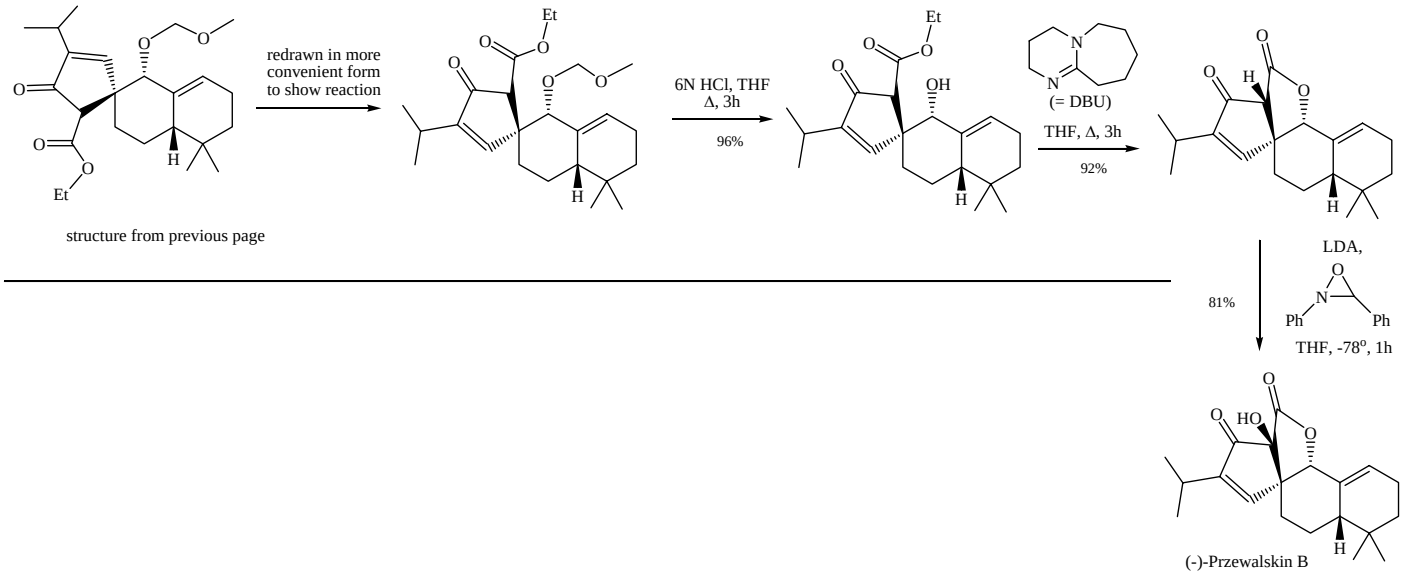


structure from previous page