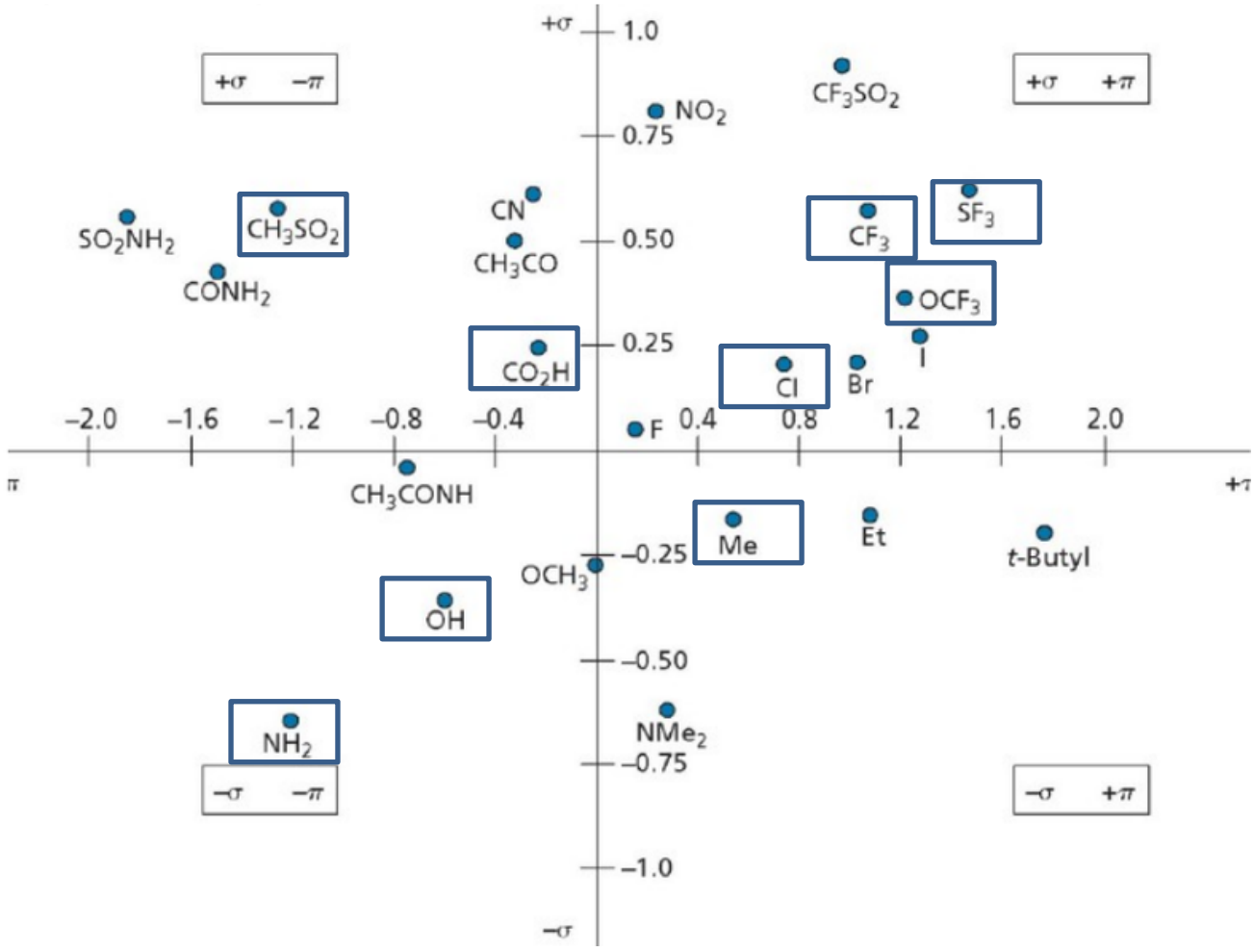
Answers **WOSYPROSS - September 21, 2019**

Problem 1.

Craig Plots is a plot of two substituent parameters (e.g. plotting the sigma constants of the *Hammett equation* versus *hydrophobicity*) used in rational drug design. Complete this diagram by writing all the listed groups in the appropriate boxes:

CF_3, Cl, COOH, OH, CH_3SO_2, OCF_3, NH_2, CH_3, SF_5



Note: *σ (electron effect) constants versus π (hydrophobicity) values for aromatic substituents*

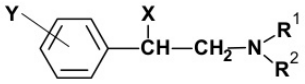
The Craig plot tell us:

- The substituents which have similar σ values (Ethyl, Br, CF3) are interchangeable if σ is the principle factor
- The substituents which have similar π (*hydrophobicity*) values (COOH, Cl, Br, I)

Examples:

1) Hansch equation for the adrenergic blocking activity for beta-haloarylamines:

Log (1/C) = 1.22 π – 1.59 σ + 7.89



Analysis of the equation:

Activity increases when the substituent has a positive (π) value (hydrophobic) and a negative (σ) value (electron donating)

(Craig, P.N (1980) In "Burger´s Medicinal chemistry" (M. E. Wolff, ed.), 4th ed,, Part I, p.343, Wiley, New York)

Problem 2.

The isostere concept was formulated by Irving Langmuir in 1919. The octet theory of valence indicates that if compounds having the same number of atoms have also the same total number of electrons, the electrons may arrange themselves in the same manner. In this case the compounds or groups of atoms are said to be isosteric. Such compounds should show remarkable similarity in physical properties, that is, in those properties which do not involve a separation of the atoms in the molecule.

Place the following anions/cations/gases into 9 groups of Isosteres:

N_2, H^-, Na^+, Mg^{2+},CO, MnO_4^-, NH_4^+, CN^-, Ne, Na^+, Al^{3+}, He^+, SeO_4^{2-}, Cu^{2-}, Cl^-, S^{2-}, K^+, O^{2-}, Li^+, Ar, K^+, N_2O, Zn^{2+}, N_3^-, CNO^-, CH_4, Ne

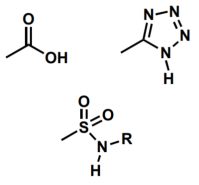
Groups of Isosteres as Identified by Langmuir

groups	isosteres
1	H^-, He, Li^+
2	O^{2-}, F^-, Ne, Na^+, Mg^{2+}, Al^{3+}
3	S^{2-}, Cl^-, Ar, K^+, Ca^{2+}
4	Cu^{2-}, Zn^{2+}
8	N_2, CO, CN^-
9	CH_4, NH_4^+
10	CO_2, N_2O, N_3^-, CNO^-
20	MnO_4^-, CrO_4^{2-}
21	SeO_4^{2-}, AsO_4^{3-}

J. Am. Chem. Soc. 1919, 41, 1543

Problem 3

Draw 2 examples of Carboxylic Acid Isosteres?



Carboxylic Acid Isosteres

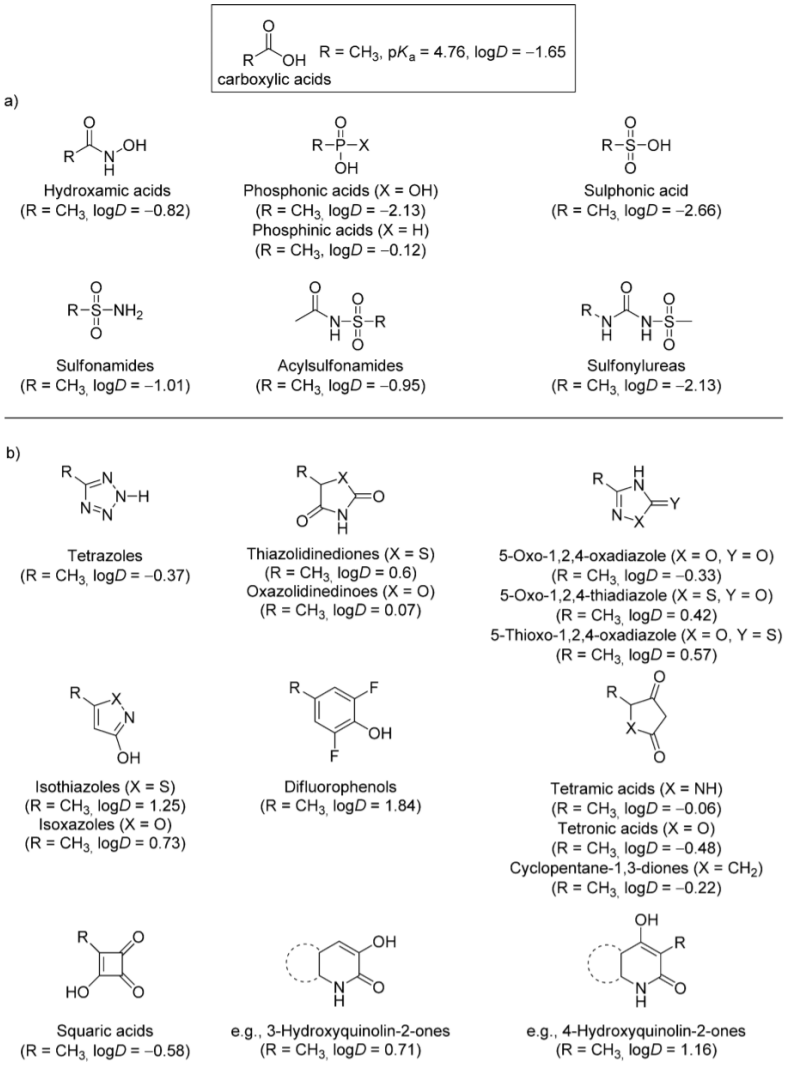


Figure 1. Representative examples of a) acyclic and b) cyclic carboxylic acid bioisosteres and their corresponding predicted log *D* values as determined using Pipeline Pilot version 8.0 (Accelrys, Inc., San Diego, USA).

Carboxylic Acid (Bio)Isosteres in Drug Design, Carlo Ballatore, Donna M. Huryn, Amos B. Smith III. *ChemMedChem*. **2013**, 8, 385 – 395.

Problem 4.

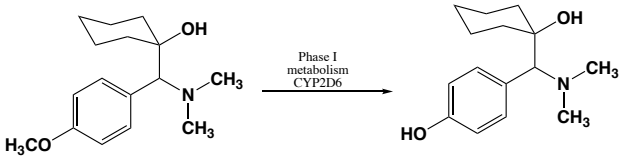
Place the following groups into the groups of bioisosteres:

CF_2H, D, CF_3, OH, F, Cl, SH, H, CH_3

- **CF2H, OH, SH**
- **CF3, Cl, CH3**
- **H, D, F**

Problem 5.

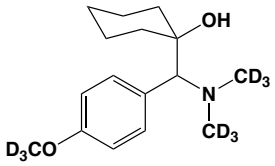
Venlafaxine (**1**) is an approved and marketed antidepressant. Venlafaxine **2** is metabolized primarily by phase I oxidation of the *O*-methyl group off the benzene ring. This demethylation is performed by CYP2D6. The activity of CYP2D6 can vary significantly across different patient populations. Because of this metabolic variability, the Cp-time (plasma concentration (Cp) against time) profile for venlafaxine can also vary from one patient to another. Inconsistent Cp values have been implied to be associated with some of the side effects of venlafaxine.



1
Venlafaxine
(Effexor)
antidepressant

2
O-desmethyl
Venlafaxine

In order to make venlafaxine more predictable, researchers made numerous bioisosteric replacements to the drug. All the hydrogens on the methyl groups - nine hydrogens in all - were replaced with deuterium atoms (D). The resulting compound (**3**) is shown below.



3
nonadeuterovenlafaxine

Compound 3 has completed phase I trials and reportedly shows a more consistent Cp-time profile than venlafaxine. Please explain why?

Deuterium, because

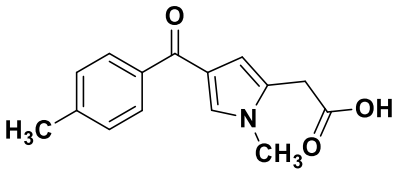
It is identical in size and electronic character to hydrogen, should have no effect on the reversible binding of the molecule to its protein target.

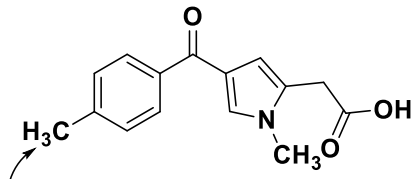
It has a higher mass than hydrogen, can differ in how it participates in chemical reactions.

The deuterium-carbon bond vibrates at a lower frequency than the hydrogen-carbon bond. With the lower frequency comes lower reactivity - potentially a slower rate of metabolism by the population-dependent CYP2D6

Problem 6.

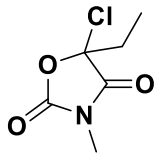
a) The following drug has a relatively short elimination t½. *Draw the structure of an analogue of this structure that will possess a longer duration of action.*

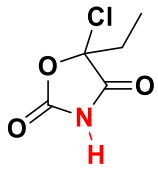




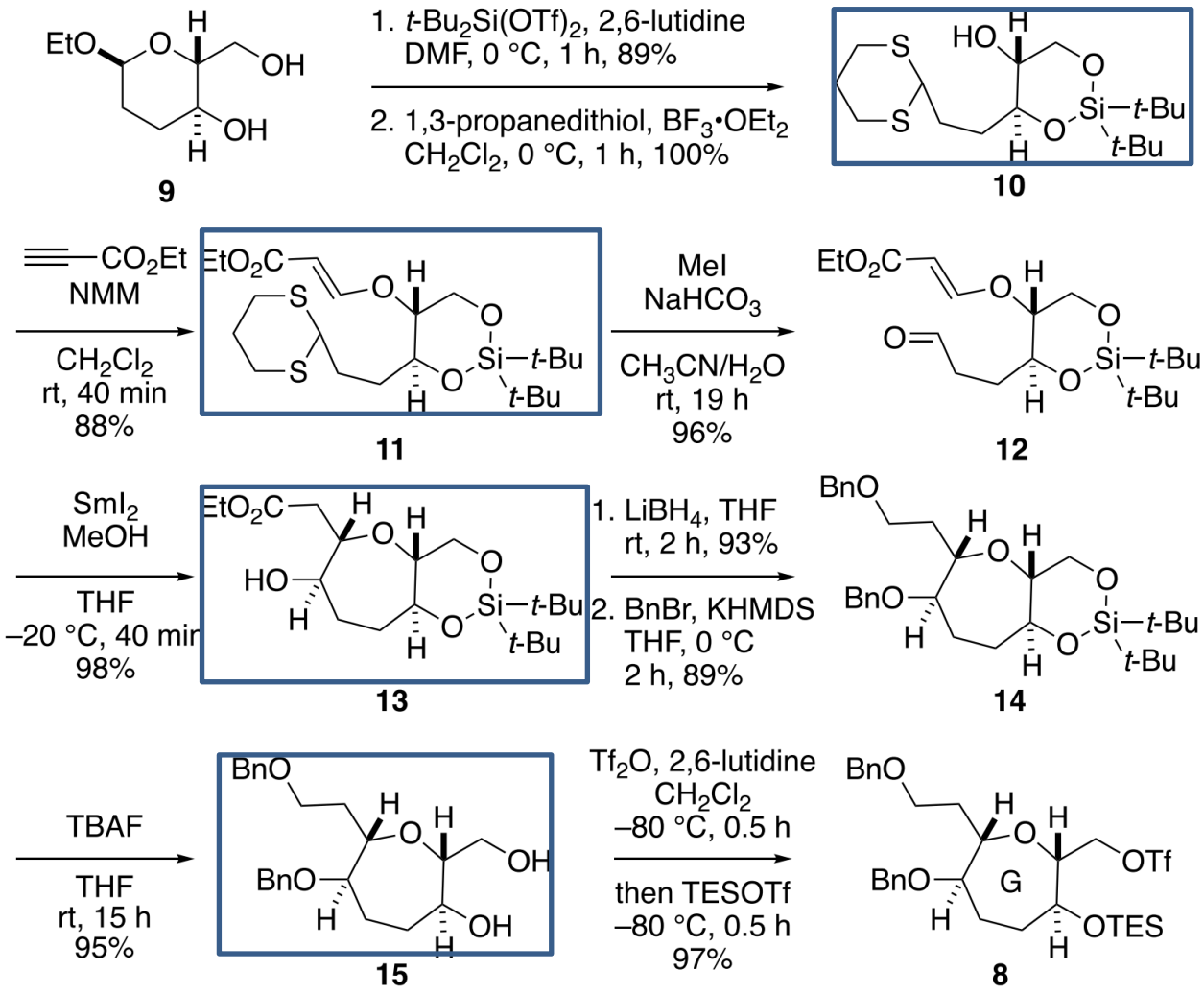
Rapidly oxidized to inactive COOH metabolite. Replace with more stable Cl

b) *Draw the structure of a metabolite of following drug that will bind to plasma proteins*.





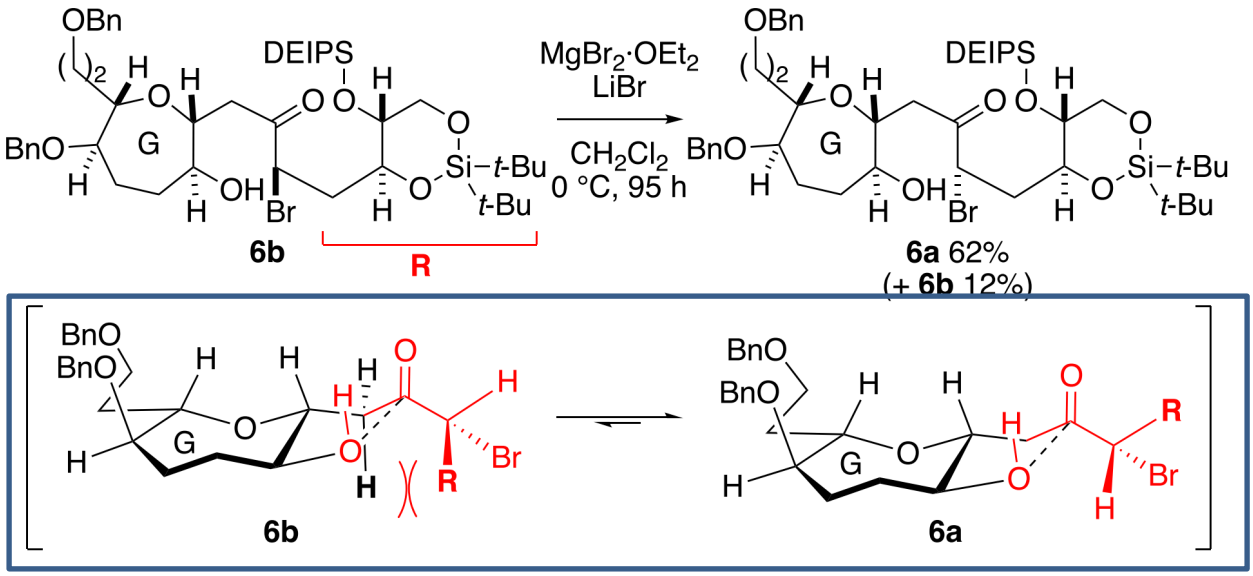
Problem 7.



Elizabeth H. Kelley, Timothy F. Jamison. *Org. Lett.* ***2019****, ASAP***,** https://doi.org/10.1021/acs.orglett.9b03015

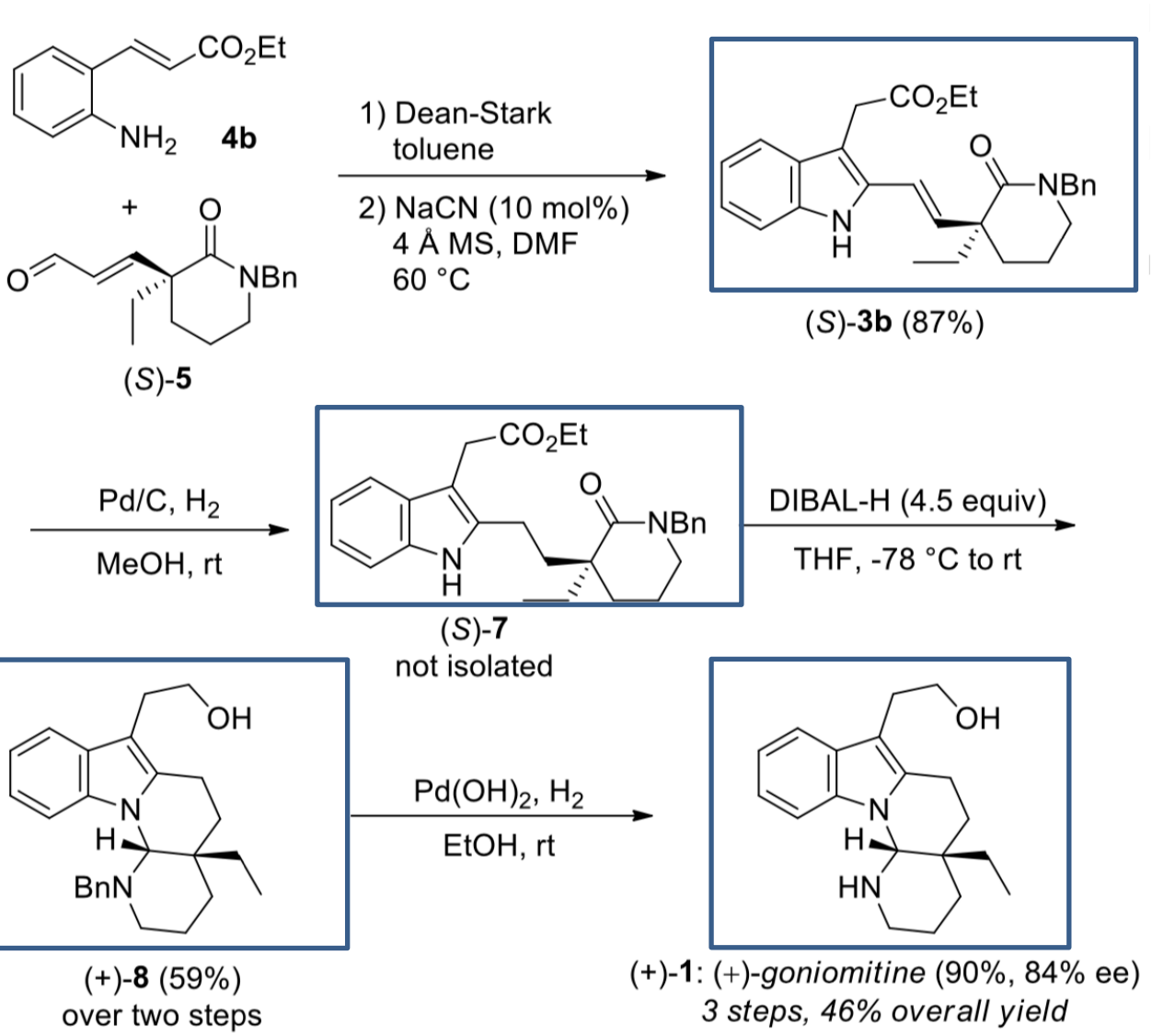
Problem 8.

*Draw mechanism for the isomerization from **6b** to **6a***



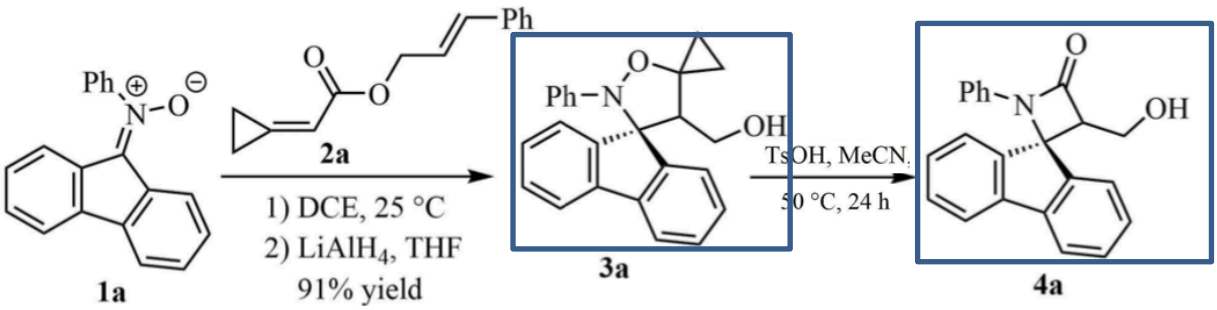
Org. Lett. ASAP, https://doi.org/10.1021/acs.orglett.9b03015

Problem 9.

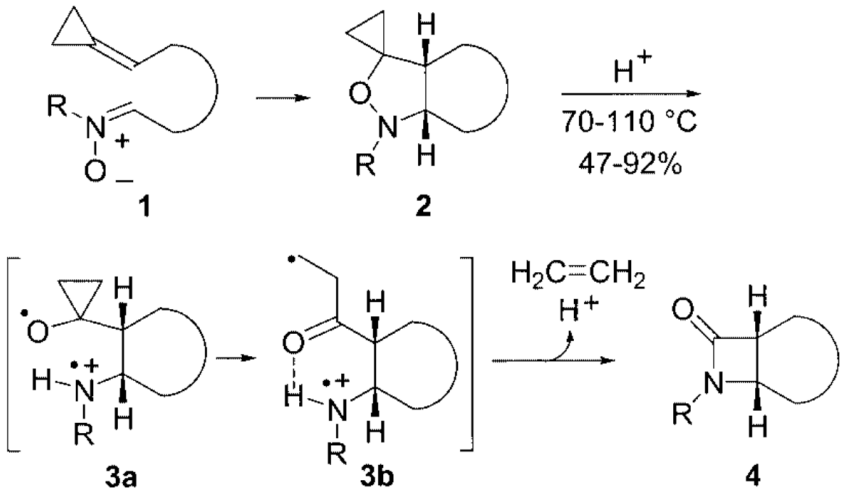


Total Syntheses of *rac*- and (+)-Goniomitine. *Adv. Synth. Catal.* **2019,** ASAP, 10.1002/adsc.201900801

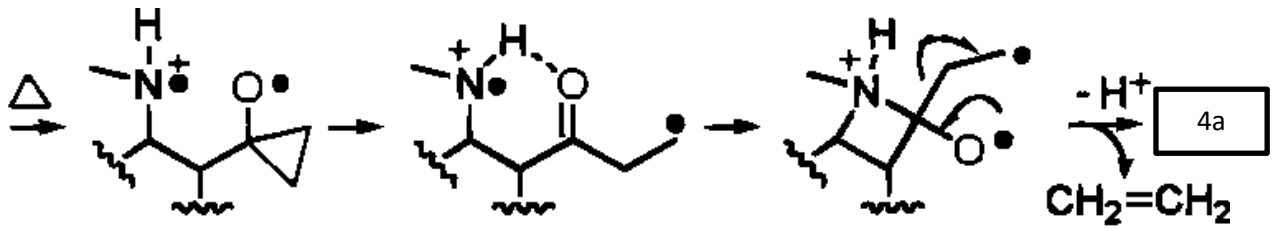
Problem 10.



Adv. Synth. Catal. **2019**, *361*, 1 – 10



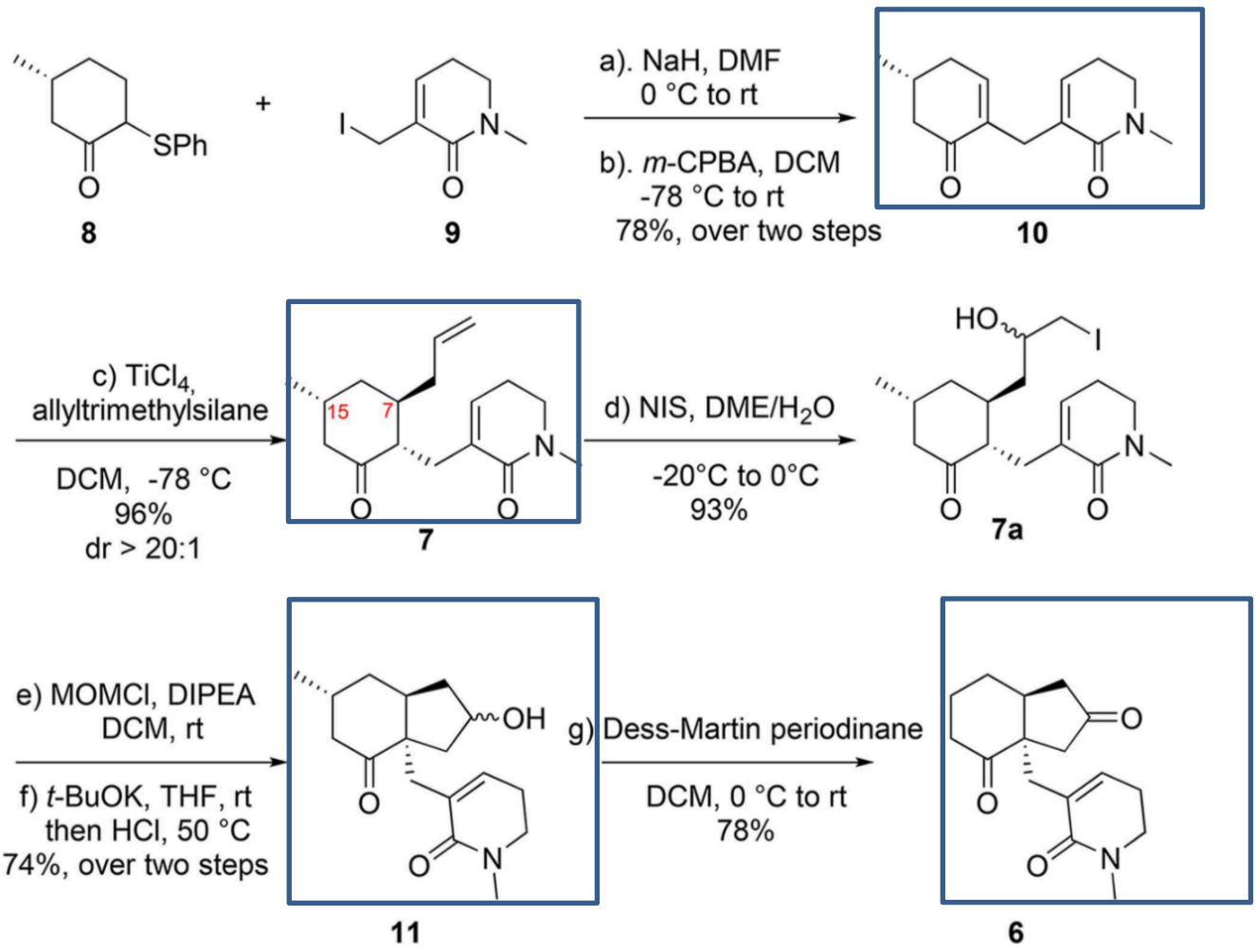
or



J. Am. Chem. Soc. **2000**, *122*, 8075.

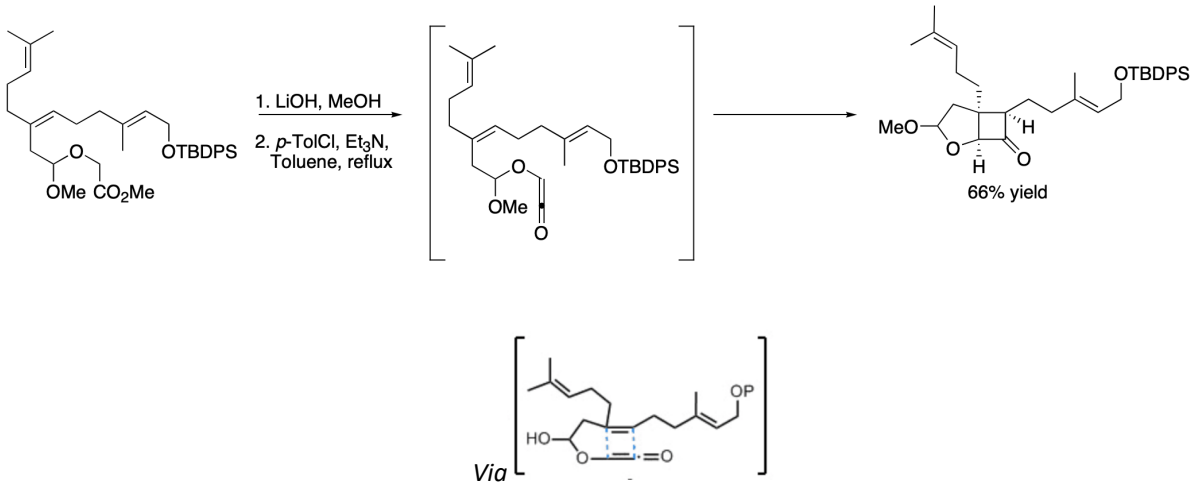
Eur. J. Org. Chem. **2004**, 2205-2213

Problem 11.


SPh
O
8
+
I
N
O
9
a). NaH, DMF
0 °C to rt
b). m-CPBA, DCM
-78 °C to rt
78%, over two steps
N
O
O
10
c) TiCl4,
allyltrimethylsilane
DCM, -78 °C
96%
dr > 20:1
15
7
7
d) NIS, DME/H2O
-20°C to 0°C
93%
HO
I
7a
e) MOMCl, DIPEA
DCM, rt
f) t-BuOK, THF, rt
then HCl, 50 °C
74%, over two steps
OH
11
g) Dess-Martin periodinane
DCM, 0 °C to rt
78%
6

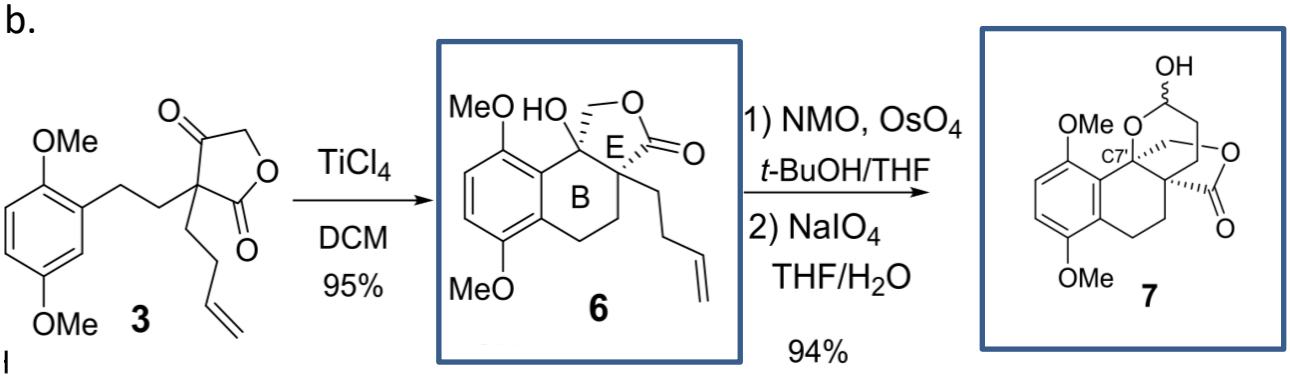
Problem 12.

a.



C. S. Mushti, J.-H. Kim, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 14050-14052.

b.



Org. Lett. **2019**, 21, 6761−6764