Literature Report 2012-09-02

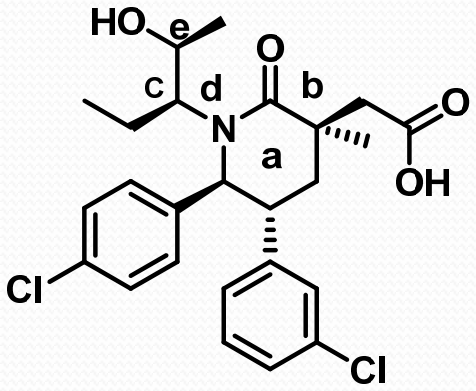
Duan, Y. Checker: Chen, M.-W.

An Expeditious Synthesis of the MDM2–p53 Inhibitor AM-8553

Lucas, B. S. *et al*

J. Am. Chem. Soc. **2012**, *134*, 12855−12860

Key issues from the first generation synthesis of AM-8553



1 (AM-8553)

a) Racemic synthesis of core

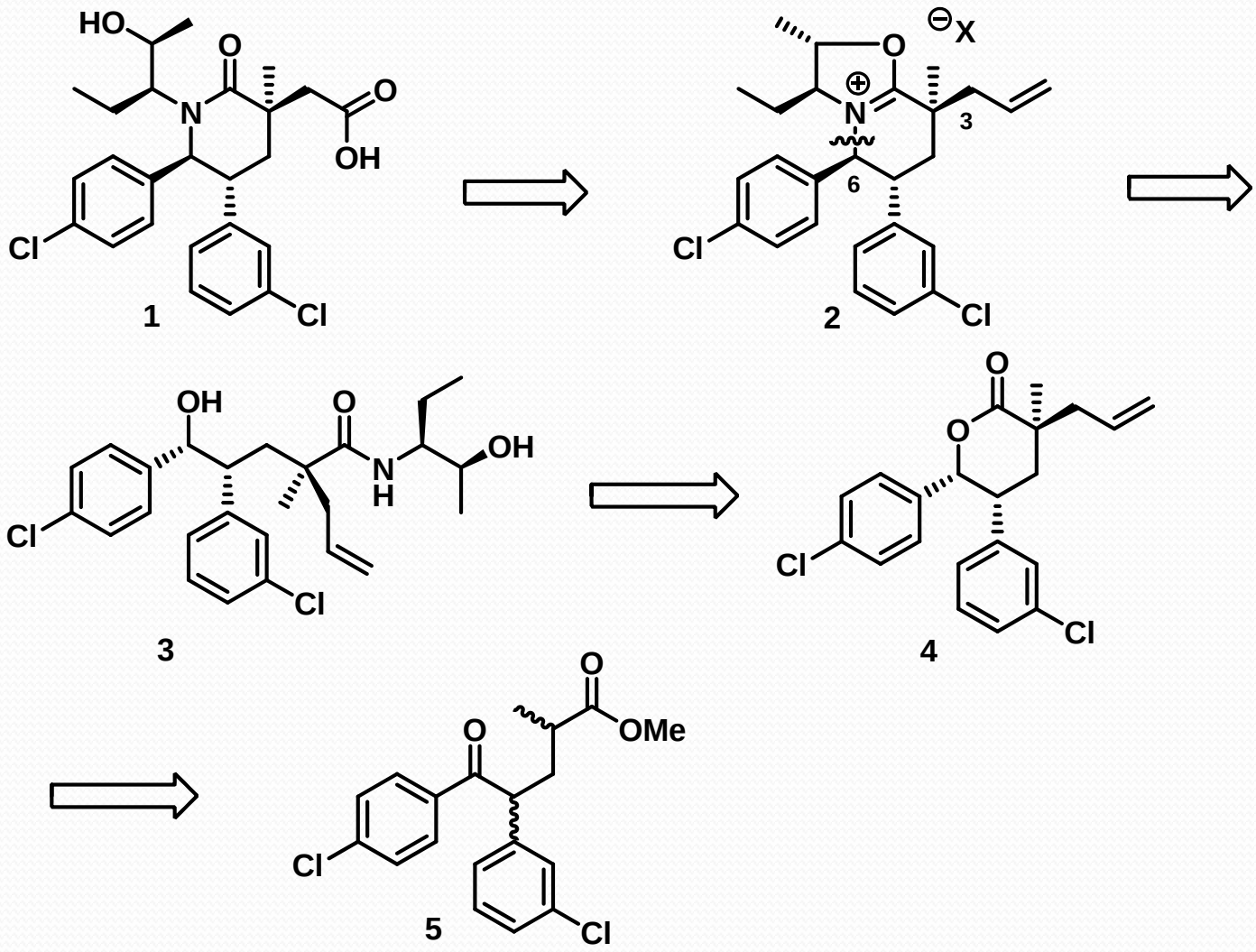
b) 3.9:1 dr

c) 1:1 dr

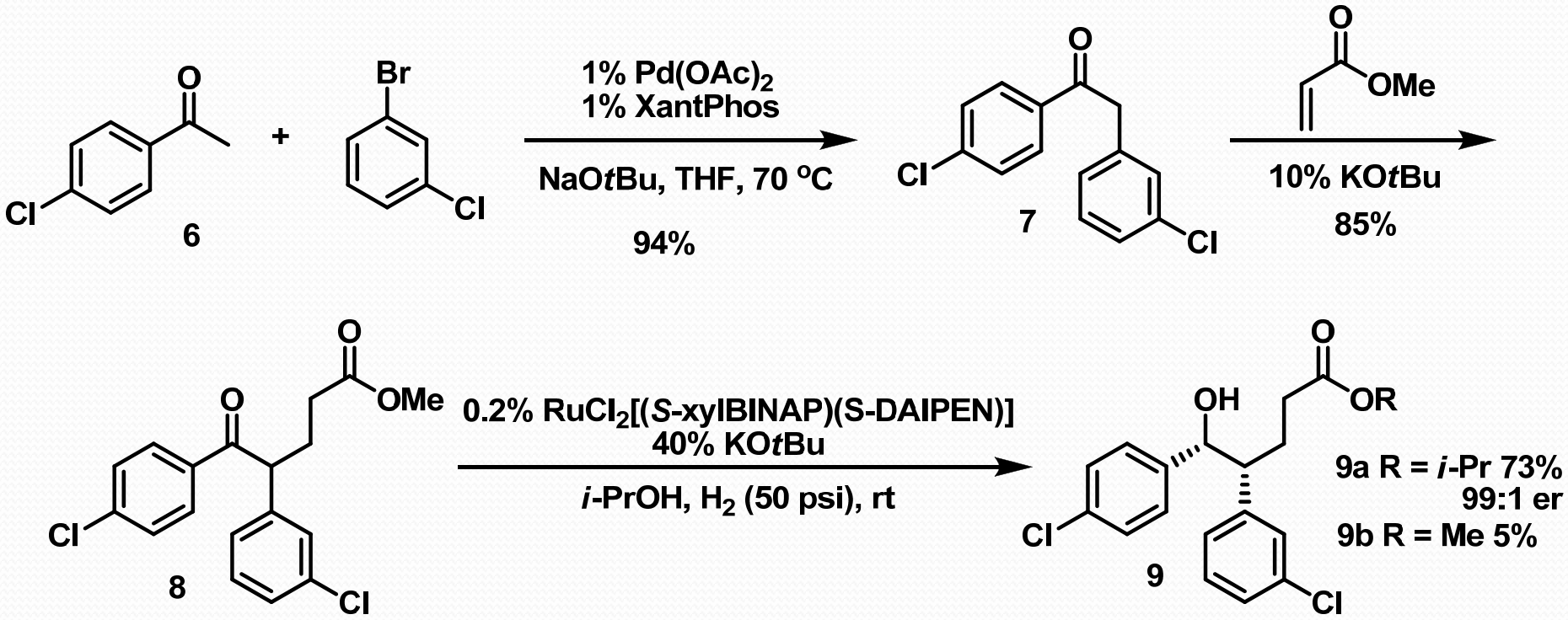
d) Difficult bond formation

e) Ambiguous stereochemistry

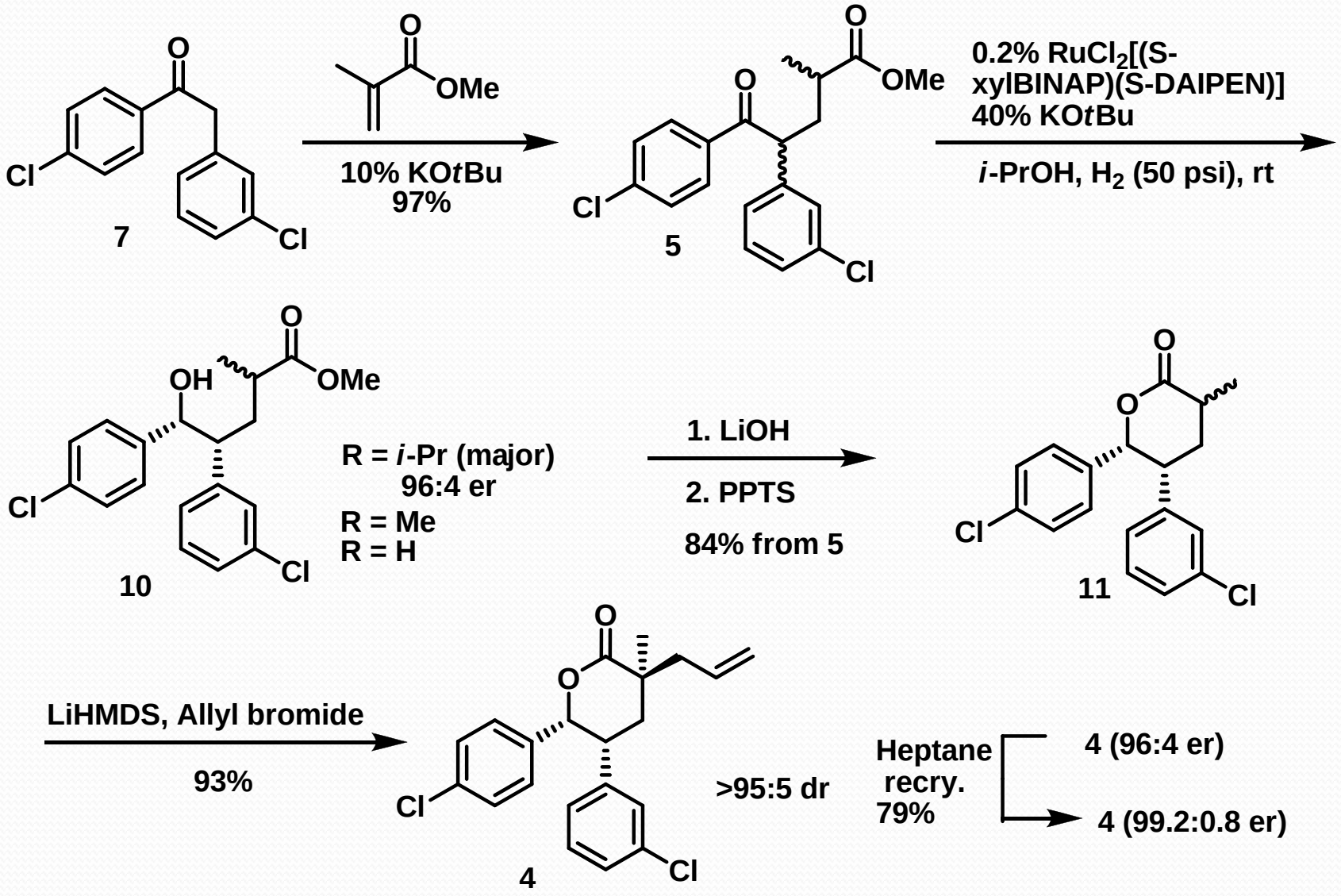
Retrosynthesis of AM-8553 (1)



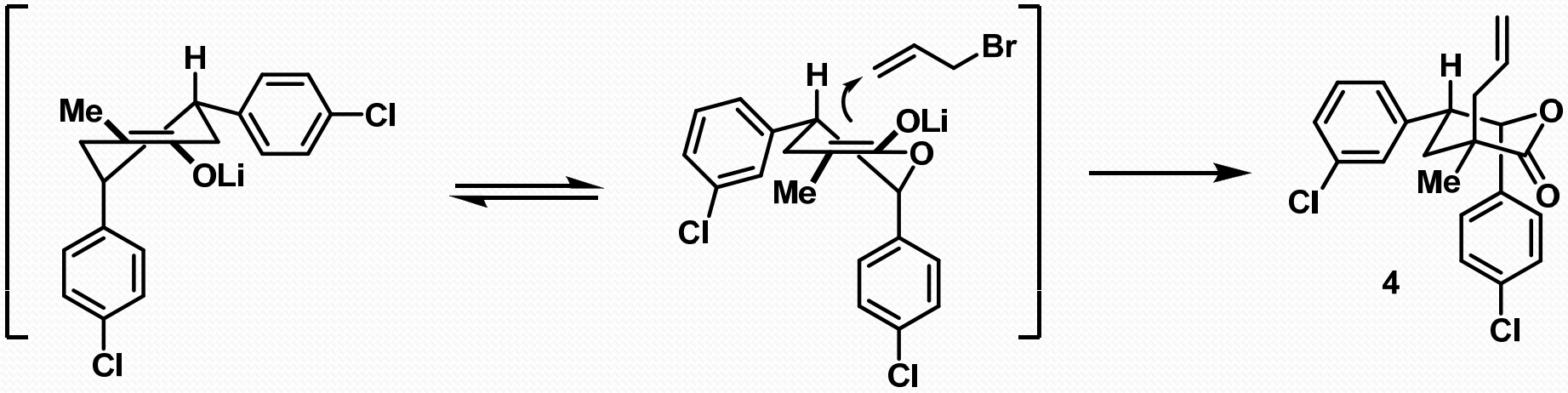
Initial Exploration of the Dynamic Kinetic Resolution



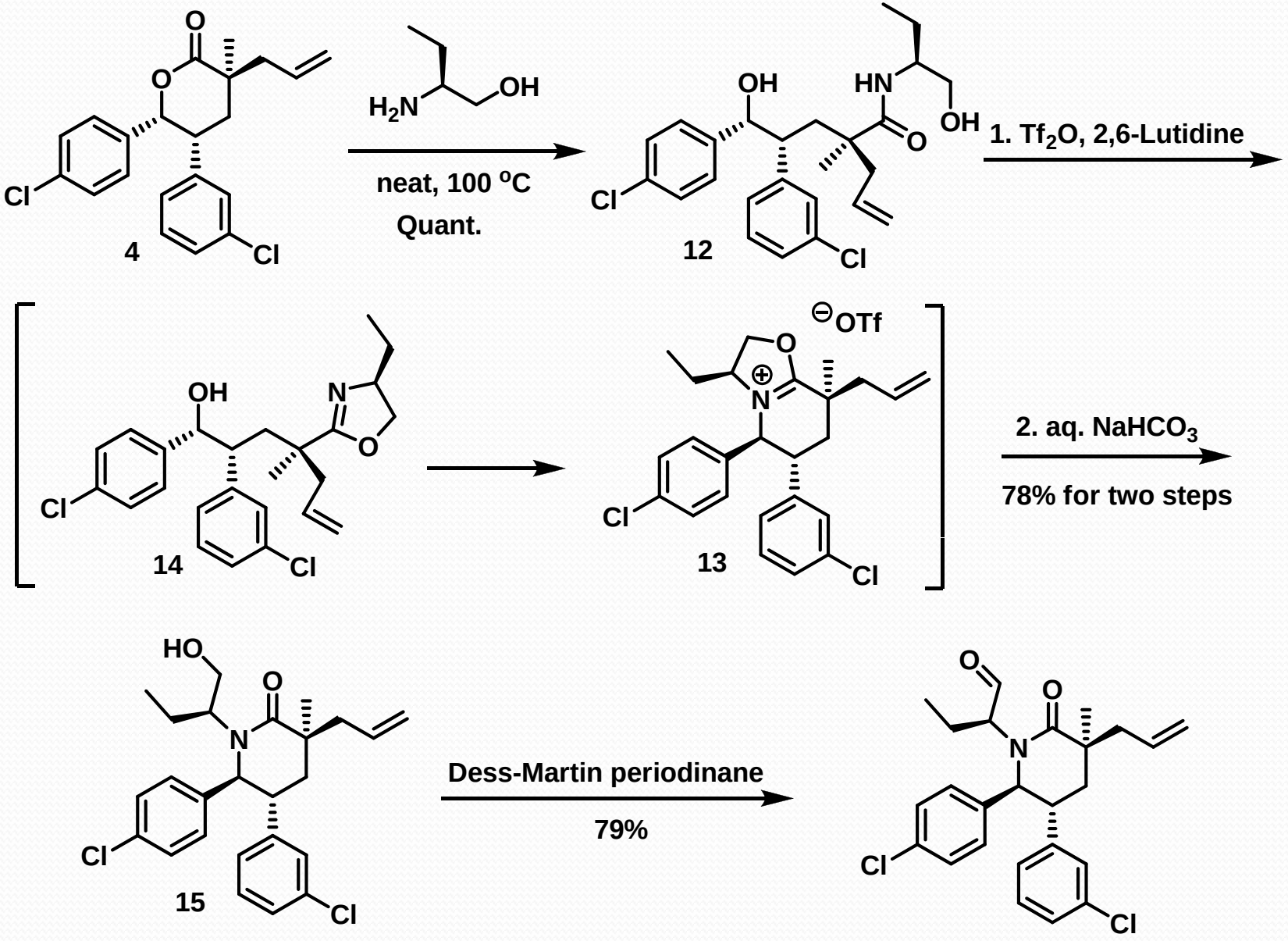
Synthesis of Lactone 4

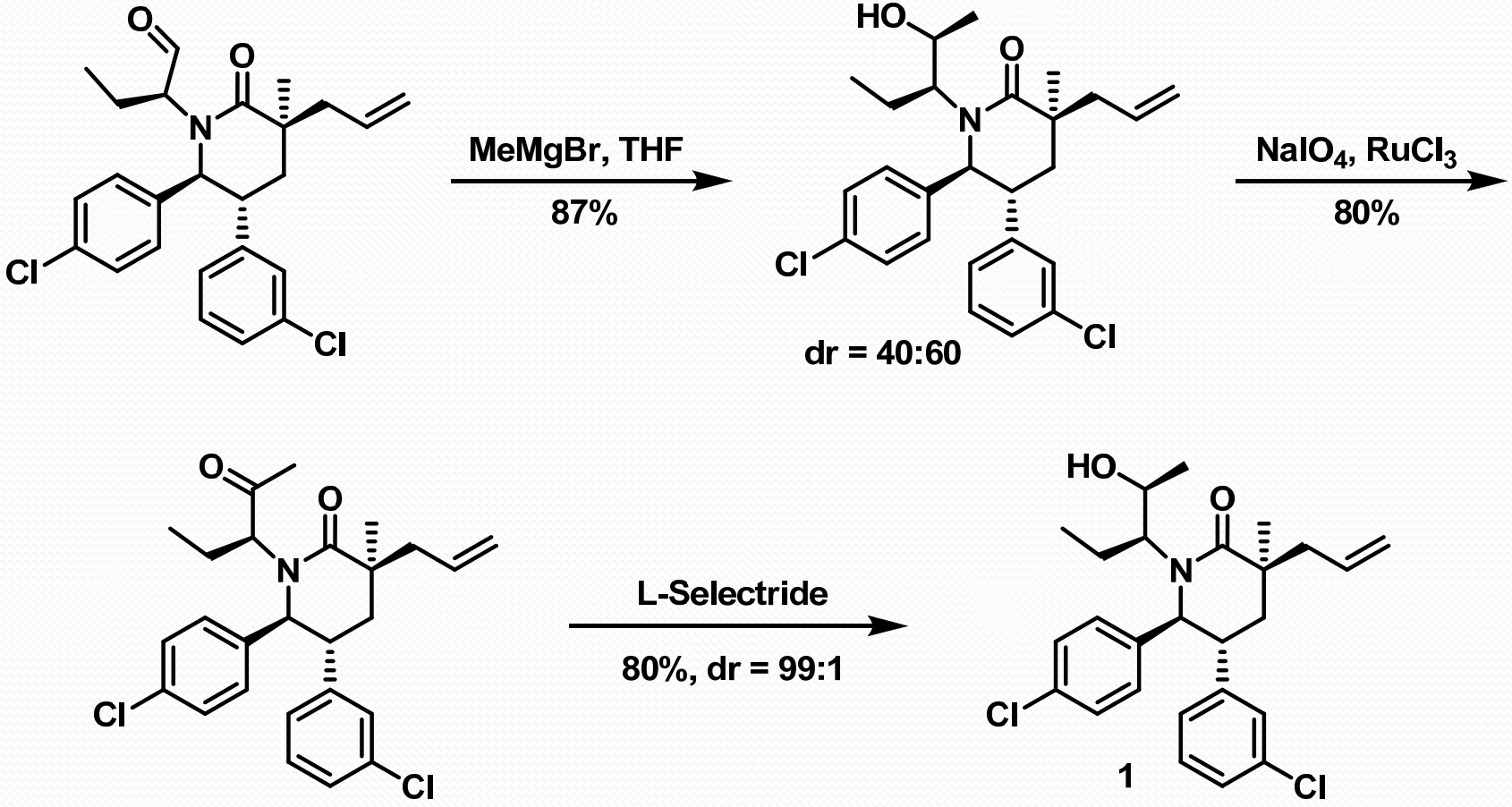


Diastereoselective allylation of 11



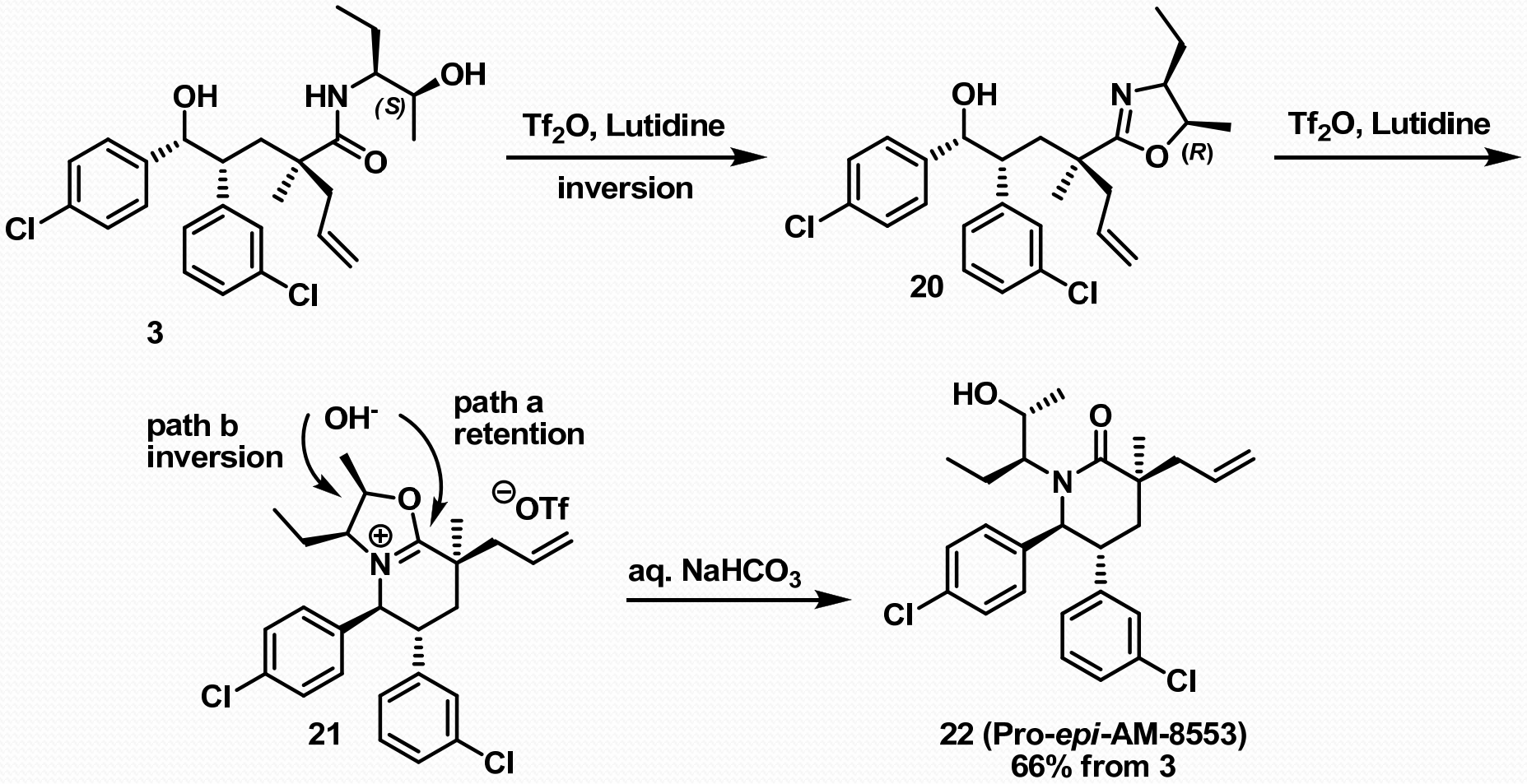
Oxazoline-Assisted Cyclization and Formal Synthesis of 1

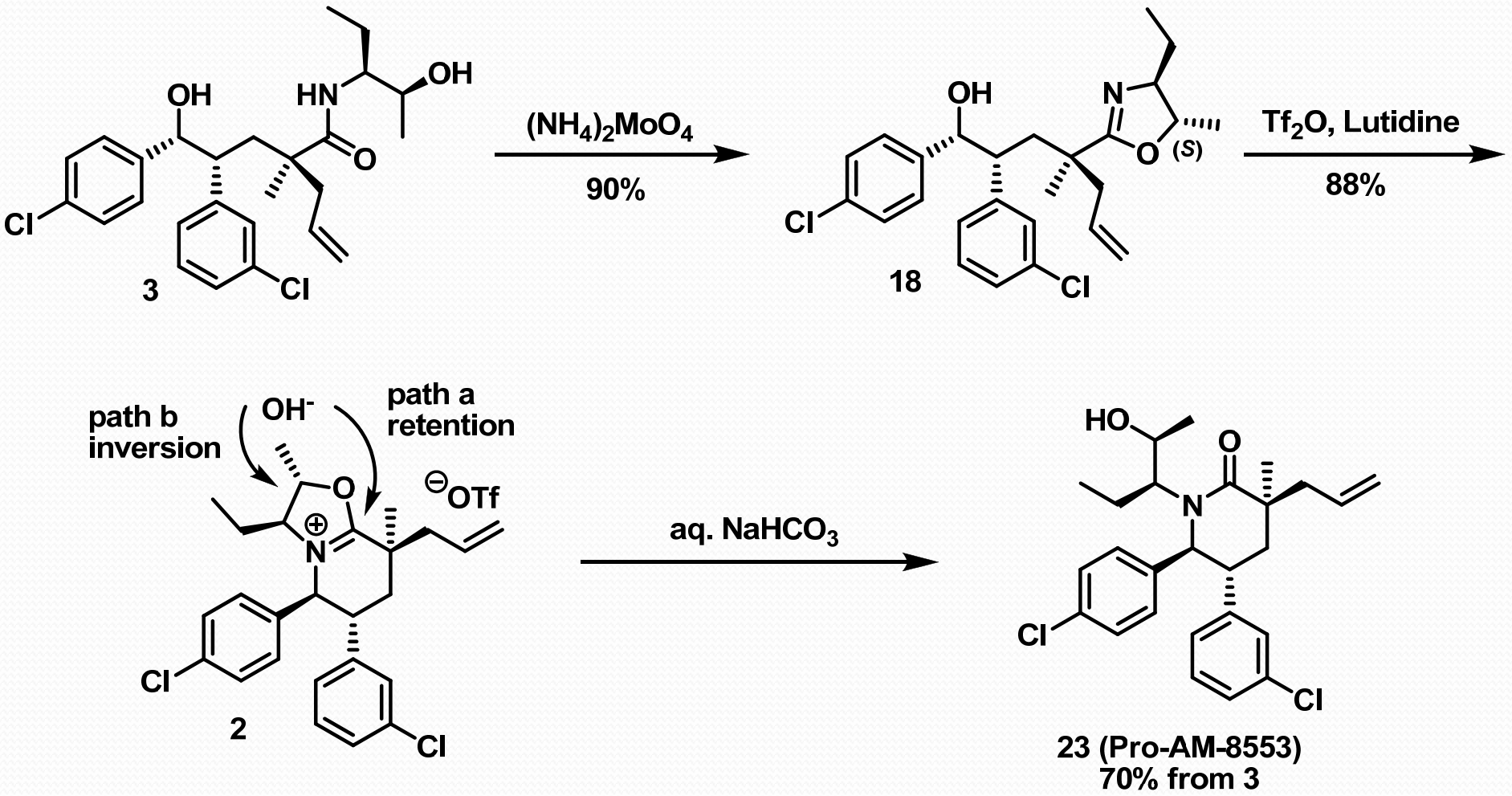




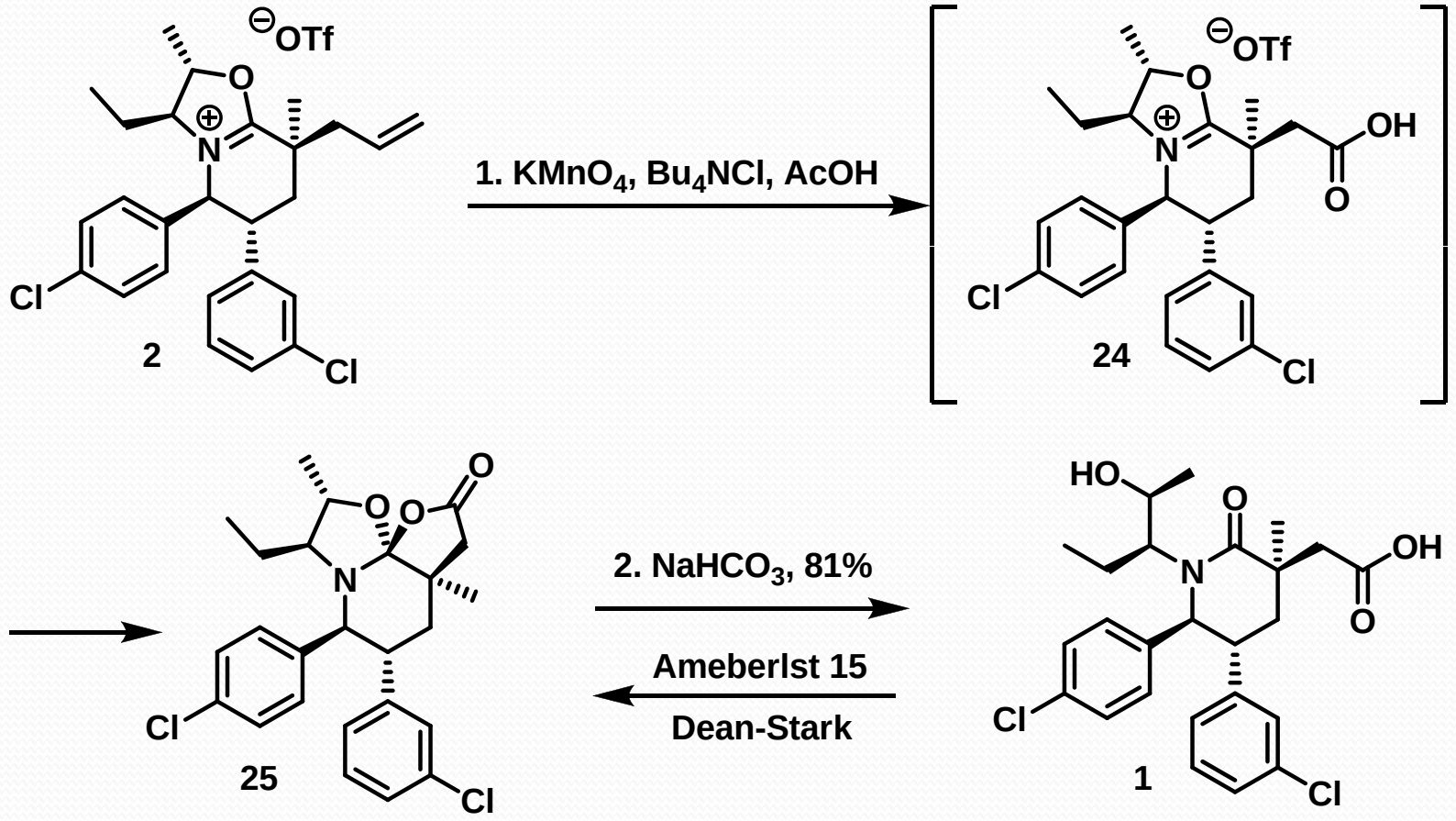
J. Med. Chem. **2012**, *55*, 4936−4954

Oxazoline-Assisted Cyclization Utilizing 2 Hydroxyl Amino Alcohols

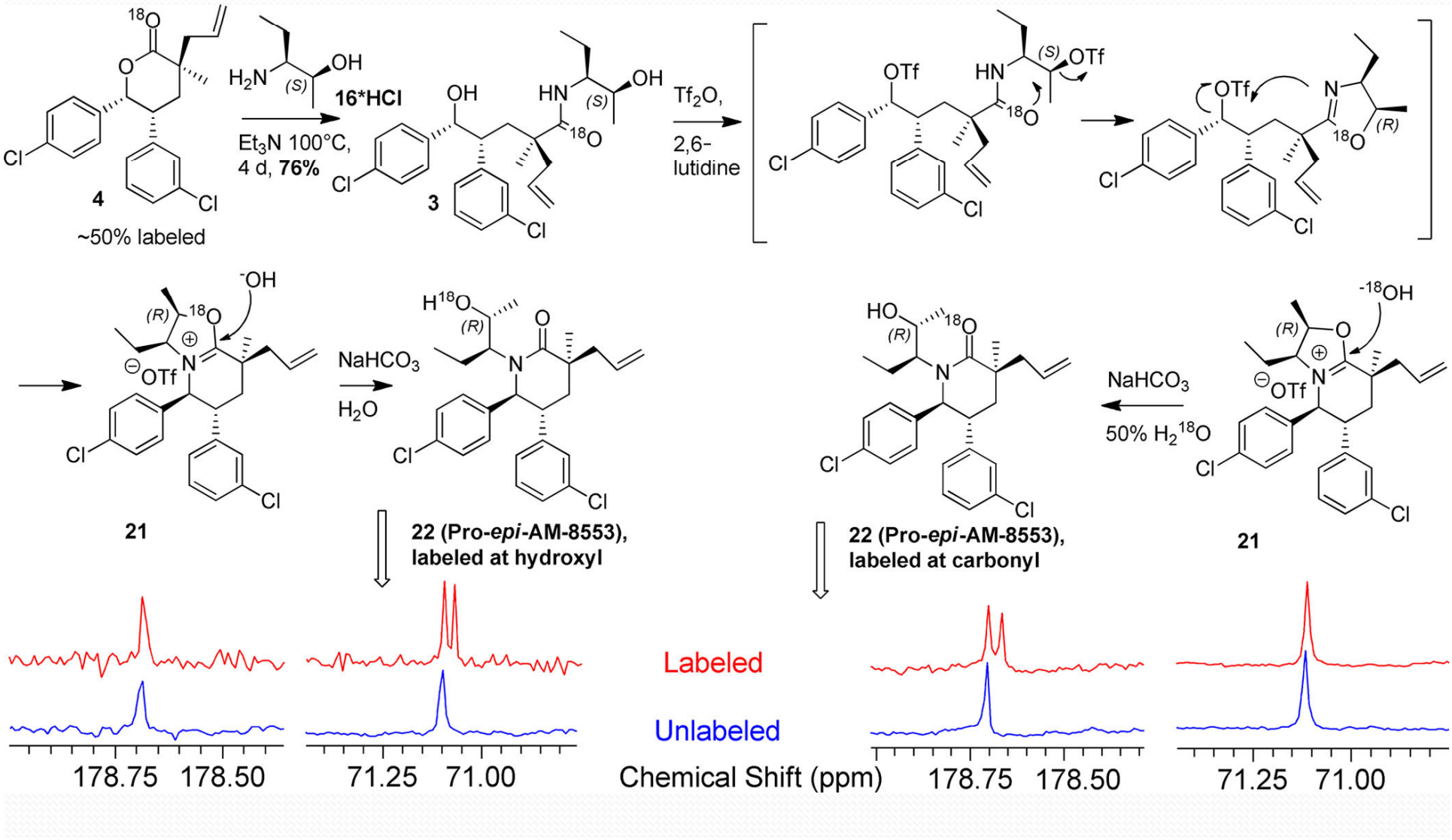



OH
HN
OH
O
Cl
Cl
3
$(NH_4)_2MoO_4$
90%
OH
N
O
(S)
Cl
Cl
18
Tf_2O, Lutidine
88%
path b
inversion
OH^-
path a
retention
O
$^{\ominus}OTf$
N
Cl
Cl
2
aq. $NaHCO_3$
HO
O
N
Cl
Cl
23 (Pro-AM-8553)
70% from 3

Bicyclic Iminium Ether 2 As a Hydroxyl Protecting Group and the Synthesis of 1



^{18}O-Labeling Studies To Determine Stereochemical Outcome of the Iminium Ether Formation and hydrolysis



- Over the past decade, there has been considerable interest in the discovery of molecules that disrupt the protein−protein interaction between p53 and MDM2 as a potential treatment for human cancer. In the presence of cellular stress, the tumor suppressor protein p53 is known to play a pivotal role in controlling cell cycle arrest, DNA repair, senescence, and apoptosis. The MDM2 protein is transcriptionally activated by p53 and, once expressed, serves as a master regulator of p53 by controlling its activity and degradation. Molecules which bind to MDM2 and neutralize the MDM2−p53 protein−protein interaction can disrupt the autoregulatory feedback loop between the two proteins, leading to increased p53 concentration and, eventually, tumor growth inhibition and apoptosis in cancer cells containing wild-type p53.

The densely functionalized and stereochemically rich piperidinone AM-8553 necessitated the development of a highyielding synthetic approach to evaluate this iologically intriguing molecule. An enantio- and diastereo-selective DKR was used to set the relative and absolute stereochemistry of the aryl groups of a δ-lactone, which in turn was used to effect the highly diastereoselective installation of the quaternary center at C3. The lactone was opened to an intermediate amide that underwent a facile double-cyclization to afford a key bicyclic iminium ether that, when hydrolyzed, led to the desired lactam core with all five stereogenic centers correctly set. An understanding of the mechanism of iminium ether formation and hydrolysis was used to elucidate the stereochemistry of the side chain of AM-8553. The iminium ether was also shown to be a competent alcohol protecting group that was stable to oxidative conditions to complete an 11-step synthetic route to AM-8553 in 35.6% overall yield. We expect to describe the large-scale application of this iminium ether lactam synthesis in due course.