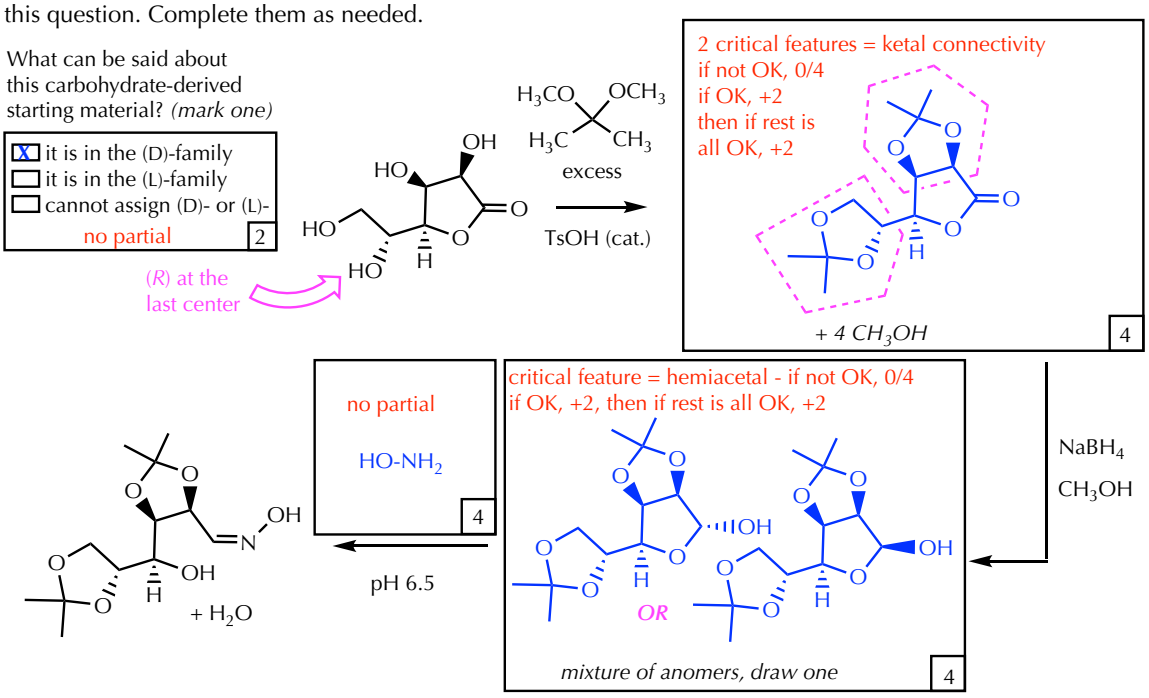
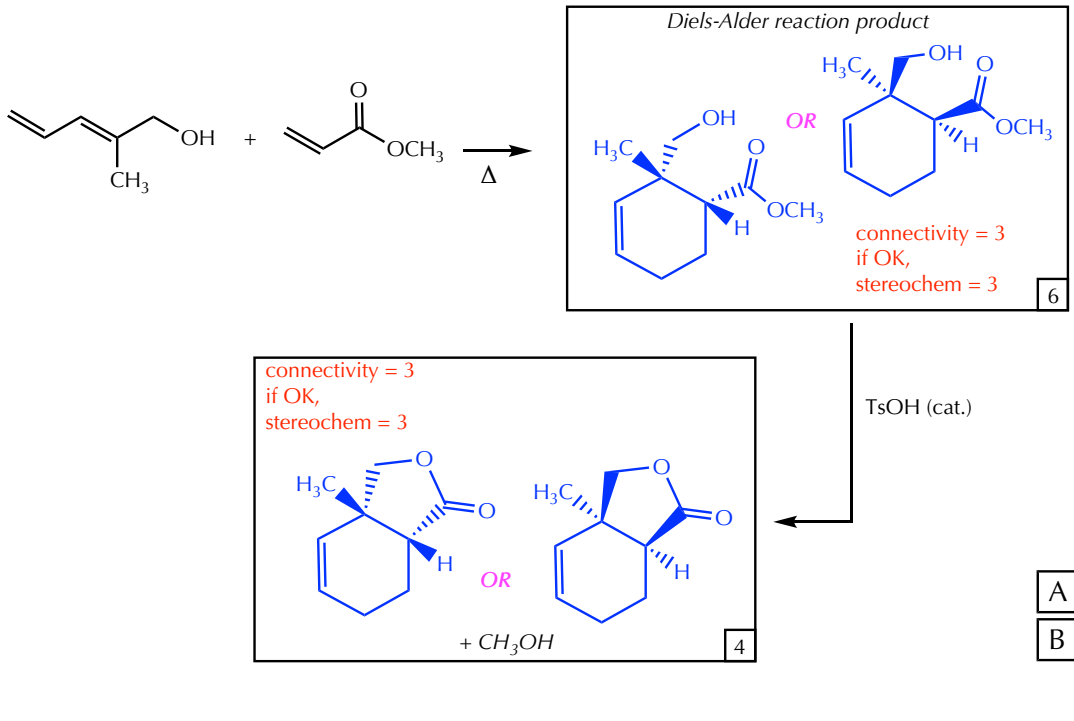
Question I (24 points) Name: _____

A. The following example is drawn from a β-amino acid synthesis that uses a carbohydrate derivative as the starting material (*Org. Process Res. Dev.* **2012**, *16*, 687). A few steps from a reported synthesis are included in this question. Complete them as needed.



B. This transformation starts with a Diels-Alder cycloaddition. The product of the cycloaddition reaction has two functional groups in proximity that then combine in an intramolecular reaction, releasing methanol. (*J. Org. Chem.* **2015**, *80*, 2037). In each case, draw one of the enantiomers of the major product, according to the expected regio- and stereochemical predictions.



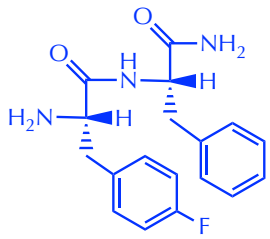
A		/14
B		/10
		/24

Question II (23 points) Name: _____

Complete the following reaction schemes. Be sure to number different experimental steps if needed.

(a) frakefamide, an analgesic (*Org. Process Res. Dev.* **2002**, *6*, 788), contains D and L amino acids

nucleophilic partner:
an uncharged dipeptide derivative



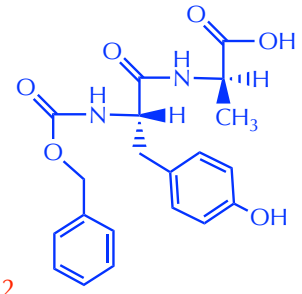
connectivity = 2
stereochem = 2

-2 once if the answers are switched

4

+

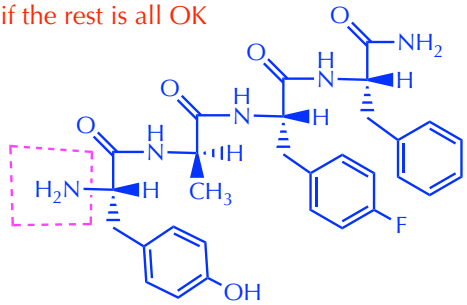
electrophilic partner
an uncharged dipeptide derivative



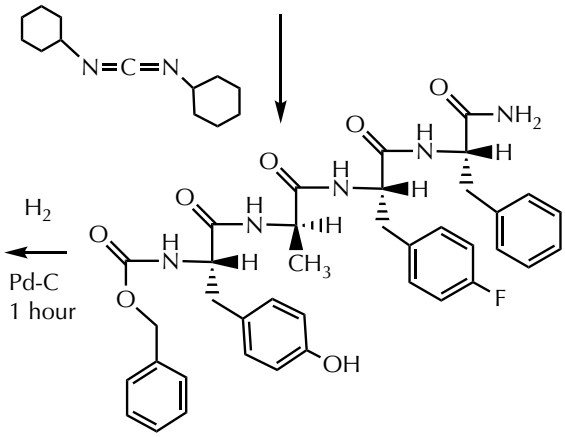
connectivity = 2
stereochem = 2

4

critical feature: the free amine
if not OK, 0/4
if OK, +2, then
+2 if the rest is all OK

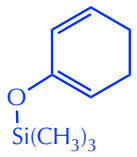


4



(b) an intermediate needed in kilogram quantities for a new drug (*Org. Process Res. Dev.* **2011**, *15*, 1420)

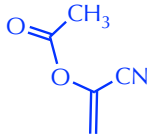
no partial
answers can be switched



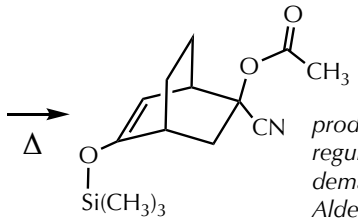
4

+

no partial
answers can be switched

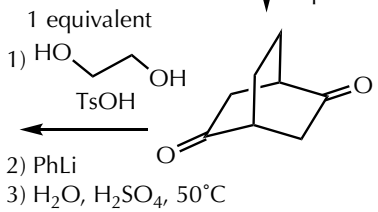


4



product from a regular electron demand Diels-Alder reaction

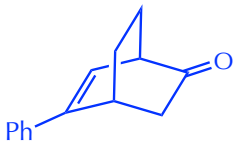
a few steps



$C_{14}H_{14}O$

of note: the third step causes three separate transformations

no partial



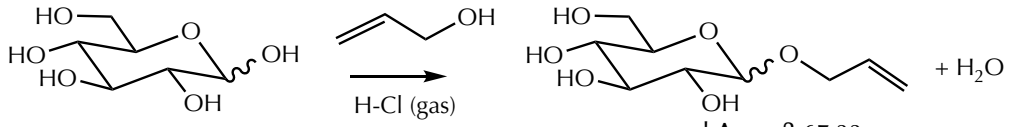
3

a		/12
b		/11
		/23

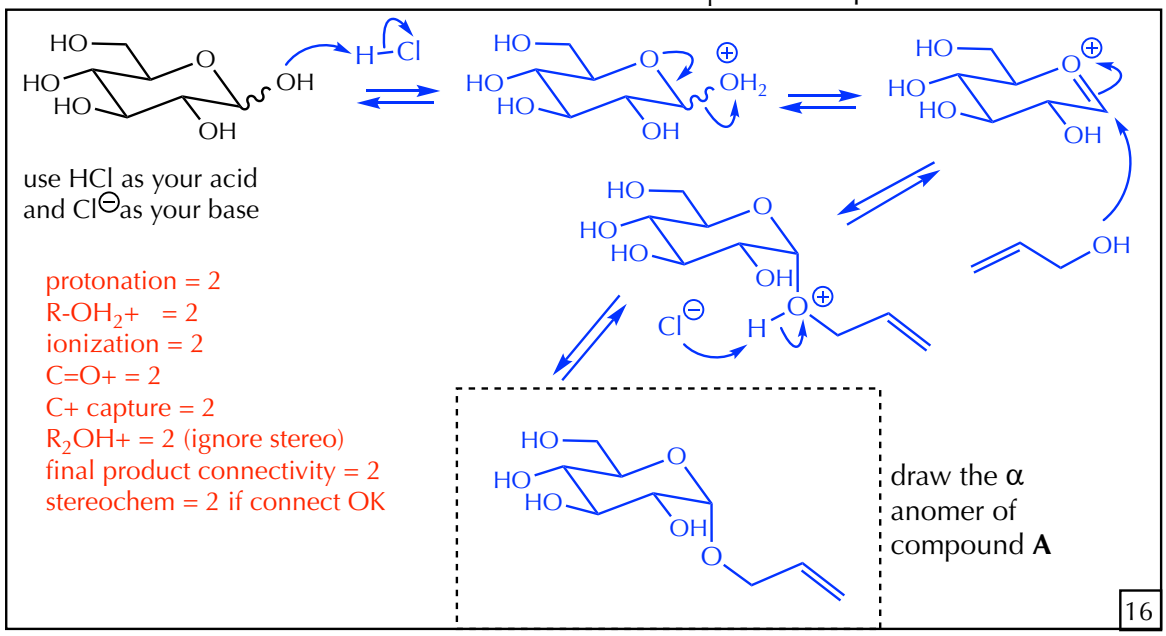
Question III (28 points) Name: _____

Etoposide is an important drug in the treatment of leukemia, testicular cancer, and small cell lung cancer (*Org. Process Res. Dev.* **2000**, *4*, 34).

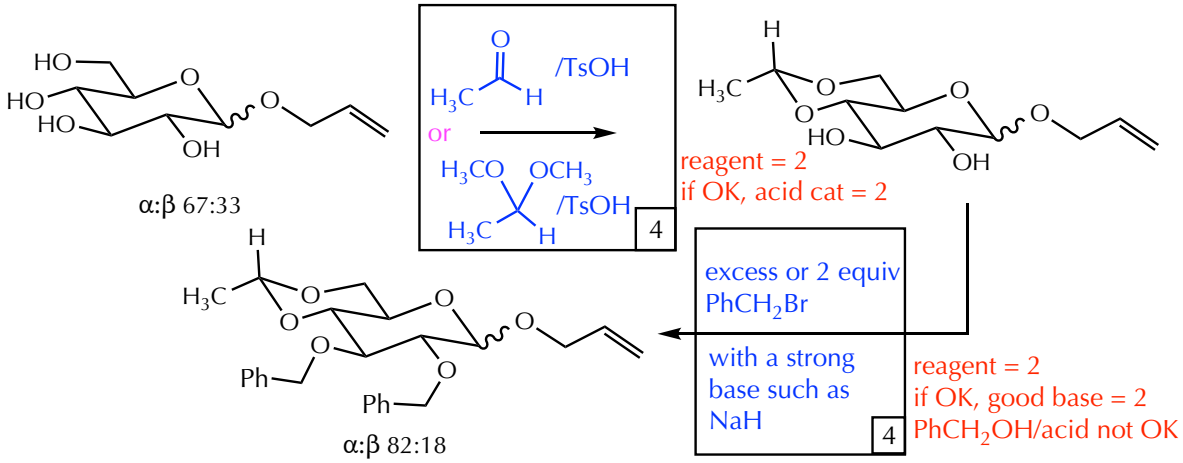
(a) Provide the complete, stepwise mechanism for the acid catalyzed formation of the α anomer of compound **A**, which was prepared on a 10g scale as an 67:33 mixture of α:β anomers.



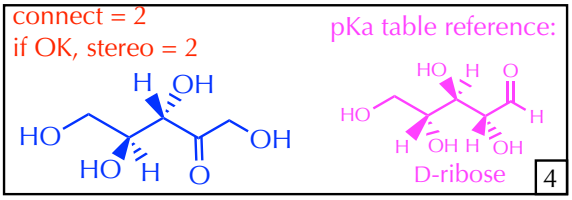
compound **A** α:β 67:33



(b) Provide the reagents needed to carry out the next two transformations.



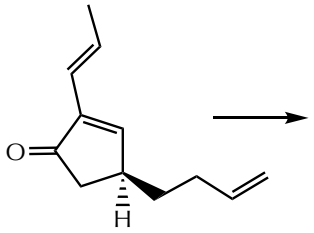
(c) Ribulose is the ketose derived from ribose. Draw L-ribulose using line/dash/wedge notation.



a			/16
b			/08
c			/04
			/28

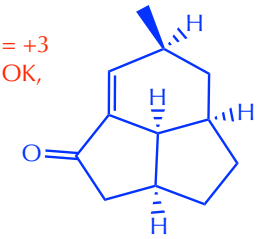
Question IV (25 points) Name: _____

A. Only a few Diels-Alder reactions have been found in nature. One example is an intramolecular reaction that was discovered in the biosynthesis of a fungal metabolite (*Angew. Chem., Int. Ed.* **2002**, *41*, 2158). Draw one of the enantiomers of the major product. Some important notes to guide your drawing are included.



connectivity = 3
if not OK, 0/9
if OK, then the
3 [3.3.0] Hs cis = +3
and if those are OK,
then methyl
stereo = +3

*draw the planar (line/dash/wedge) picture, **not** 3D bridged*



9

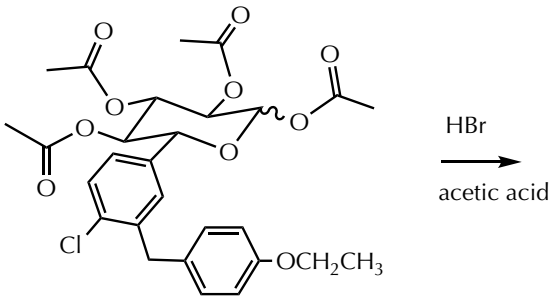
Notes:

a tricyclic structure with two 5-membered rings and one 6-membered ring

the bridgehead hydrogen atoms where bridges connect are all mutually cis

the reaction is stereospecific

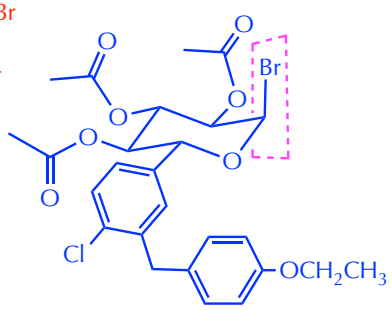
B. Inhibitors of sodium-dependent glucose cotransporters (SGLT) are used to treat diabetes mellitus by inhibiting reabsorption of glucose in the kidneys. Complete the following steps from sotagliflozin, which is a drug candidate whose action is SGLT inhibition (*Org. Process Res. Dev.* **2020**, *24*, 2689).



stereochemical outcome consistent with anomeric effect

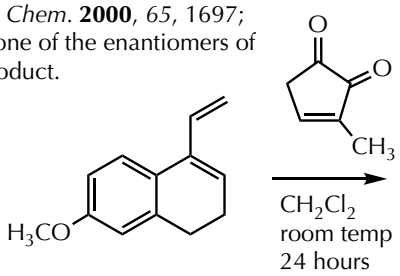
critical feature
= anomeric Br
in axial
if not OK 0/4
if OK, then
+2 for rest

if equatorial
or mixed
Br AND all
else OK, 2/4



4

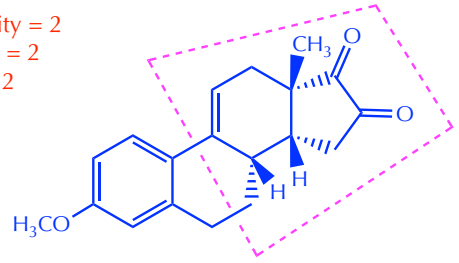
C. *J. Org. Chem.* **2000**, *65*, 1697; draw one of the enantiomers of the product.



high regioselectivity, stereoselectivity, and stereospecificity

critical connectivity = 2
if OK, then stereo = 2
if OK, then rest = 2

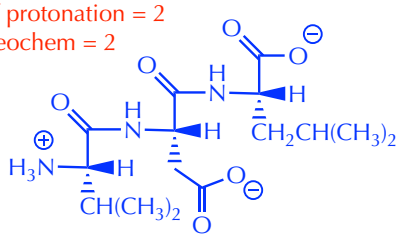
can be the
enantiomer



6

D. The tripeptide Val-Asp-Leu is potential inhibitor of some specific enzymes that degrade proteins, and could be used to treat diseases that affect immune responses (*J. Med Chem.* **2004**, *47*, 1587). Draw the major form of Val-Asp-Leu when in solution of pH = 8.

basic Val-Asp-Leu connectivity,
ignoring state of protonation = 2
if OK, then state of protonation = 2
if all OK, then stereochem = 2



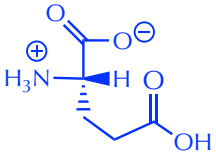
6

A		/09
B		/04
C		/06
D		/06
		/25

Question V (20 points) Name: _____

Provide the missing information in the following synthesis of a tetrapeptide. No abbreviations.

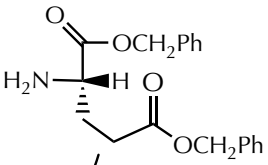
an amino acid at its isoelectric point

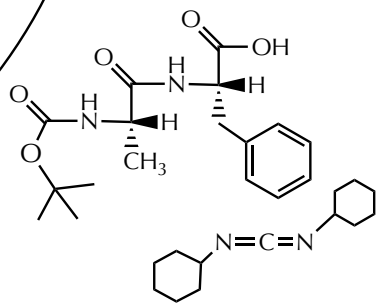


basic Asp structure = 2
if OK, correct protonation = 2 [4]

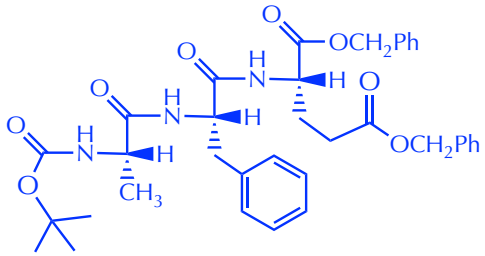
excess or 2 equiv
$PhCH_2OH$/
acid cat.
[2]

followed by a pH adjustment





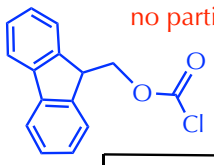
no partial



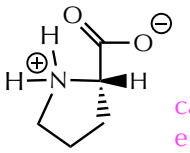
[3]

preparation of the reagent used in step (2), includes a pH adjustment

no partial



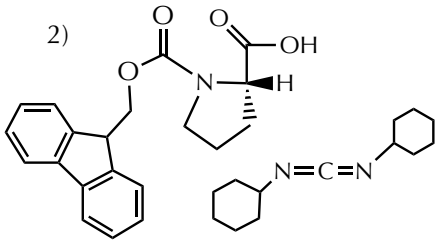
base (optional) [2]



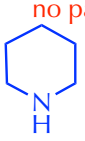
can be either order

1) no partial
CF_3CO_2H
[3]

2)



3) no partial

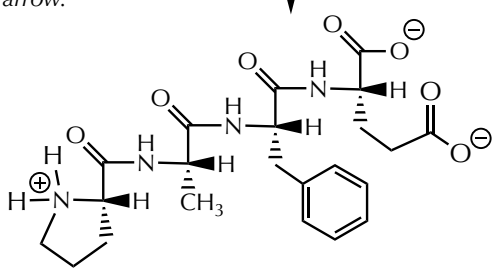


[3]

4) no partial
H_2 / Pd-C
[3]

followed by a pH adjustment

Provide the structures of the reactants needed for steps 1, 3, and 4 of this transformation in the boxes above the arrow.



/20