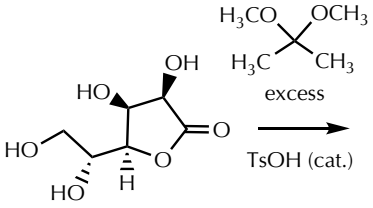
**Question I (24 points)** Name: _____

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.

What can be said about this carbohydrate-derived starting material? *(mark one)*

- ☐ it is in the (D)-family
- ☐ it is in the (L)-family
- ☐ cannot assign (D)- or (L)-

2







excess

TsOH (cat.)

+ 4 $CH_3OH$ 4

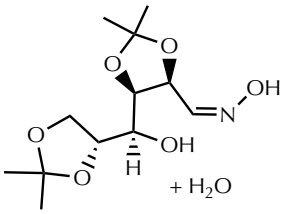
$NaBH_4$

$CH_3OH$

mixture of anomers, draw one 4

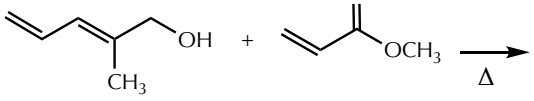
pH 6.5

4




+ $H_2O$

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.




Δ

*Diels-Alder reaction product* 6

TsOH (cat.)

+ $CH_3OH$ 4

| | | |
|---|---|---|
| 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

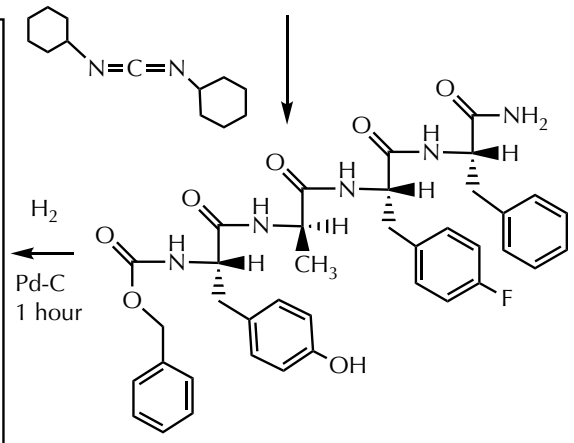
*nucleophilic partner:*
*an uncharged dipeptide derivative*

4

+

*electrophilic partner*
*an uncharged dipeptide derivative*

4



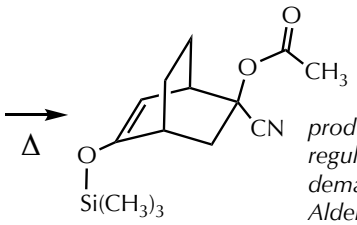

4

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

4

+

4




*product from a regular electron demand Diels-Alder reaction*

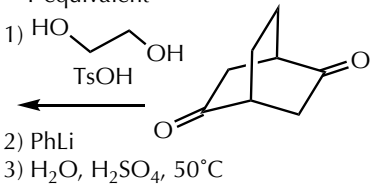
a few steps

$C_{14}H_{14}O$

of note: the third step causes three separate transformations

3

1 equivalent

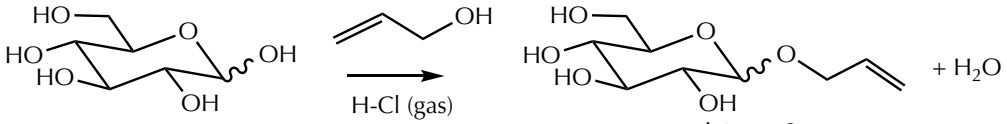



| | | |
|---|---|---|
| a | | /12 |
| b | | /11 |
| | | /23 |

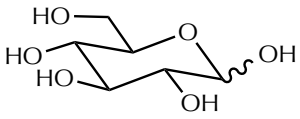
**Question III (28 points)** Name: _____

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

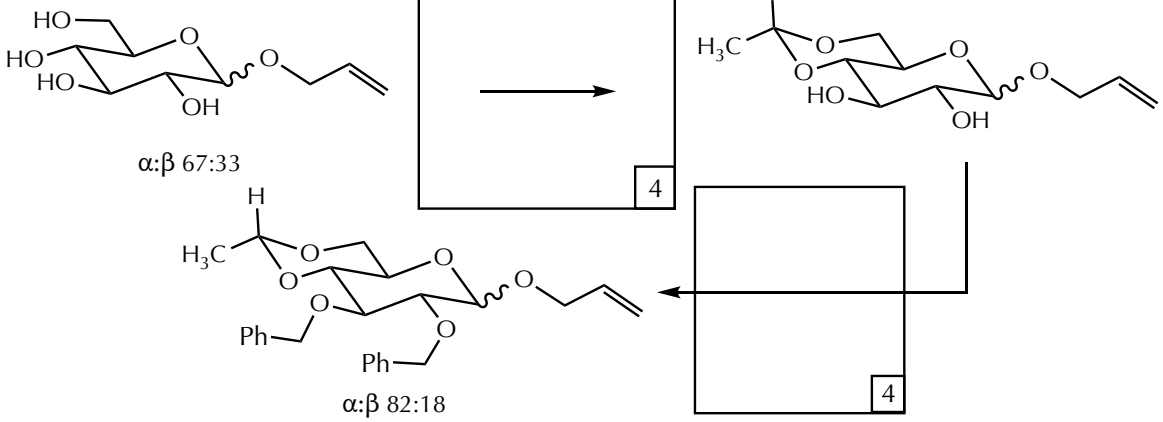



use HCl as your acid
and $Cl^{\ominus}$ as your base

draw the α anomer of compound **A**

16

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



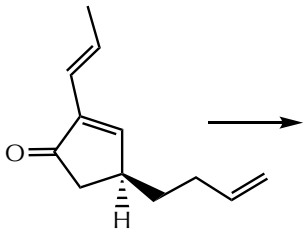

(c) Ribulose is the ketose derived from ribose. Draw L-ribulose using line/dash/wedge notation.

4

| | | |
|---|---|---|
| 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.




*draw the planar (line/dash/wedge) picture, **not** 3D bridged* 9

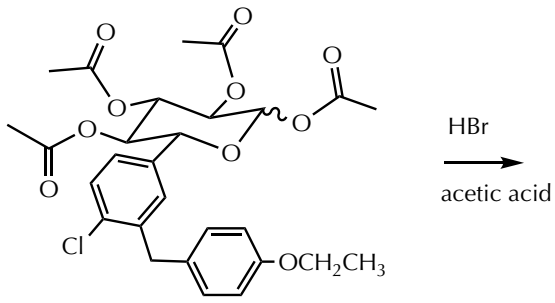
*Notes:*

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

*the bridgehead hydrogen atoms where bridges connect are all mutually cis*

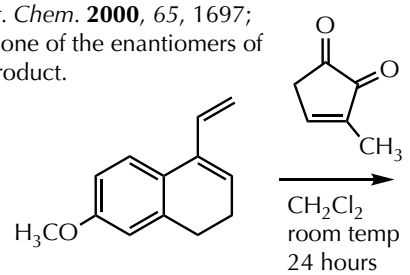
*the reaction is stereospecific*

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* 4

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




*high regioselectivity, stereoselectivity, and stereospecificity* 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.

6

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

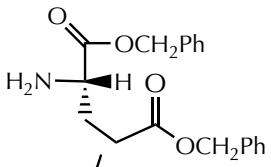
**Question V (20 points)** Name: _____

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

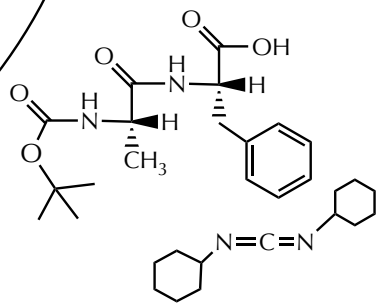
*an amino acid at its isoelectric point* [4]

[2]

*followed by a pH adjustment*

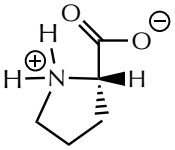


[3]



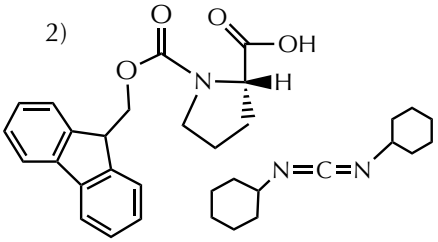
*preparation of the reagent used in step (2), includes a pH adjustment*

[2]



1) [3]

2)

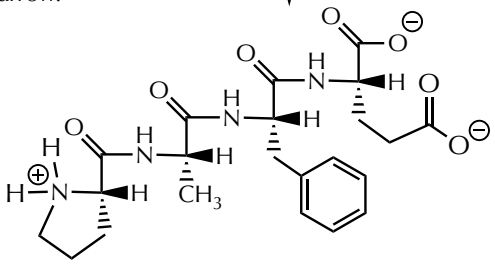


3) [3]

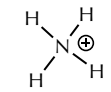
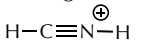
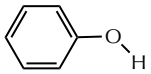
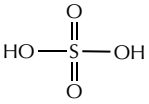
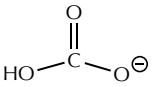
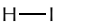
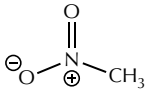
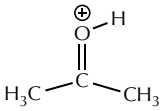
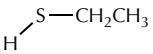
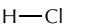
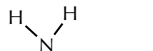
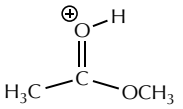
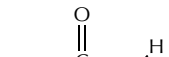
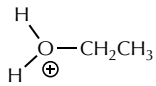
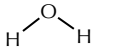
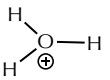
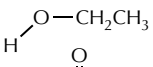
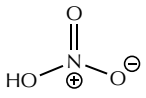
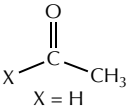
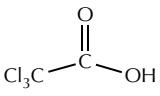
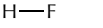
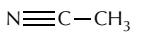
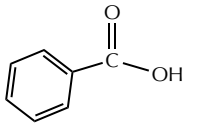
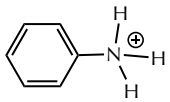
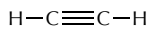
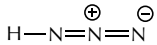
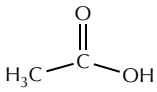
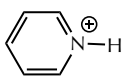
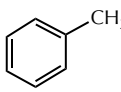
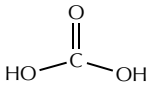
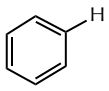
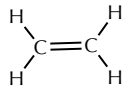
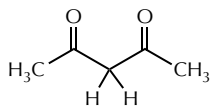
4) [3]

*followed by a pH adjustment*

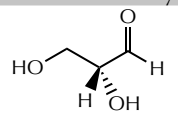
*Provide the structures of the reactants needed for steps 1, 3, and 4 of this transformation in the boxes above the arrow.*

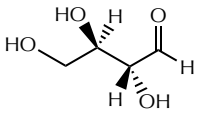


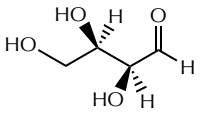
/20

| ACID | $pK_a$ | ACID | $pK_a$ |
|---|---|---|---|
| (strongest acid) | |  | 9.4 |
|  | -12 |  | 10.0 |
|  | -9 |  | 10.2 |
|  | -9 |  | 10.2 |
|  | -7.2 |  | 10.5 |
|  | -7 |  | 10.6 |
|  | -4.6 |  | 15.0 |
|  | -2.4 |  | 15.7 |
|  | -1.7 |  | 17 |
|  | -1.3 |  | X = H 17<br>X = $CH_3$ 19<br>X = $OCH_3$ 22<br>X = $N(CH_3)_2$ 28 |
|  | 0.64 | | |
|  | 3.2 |  | 25 |
|  | 4.2 |  | 25 |
|  | 4.6 |  | 26 |
|  | 4.7 |  | 35 |
|  | 4.8 |  | 36 |
|  | 5.2 |  | 41 |
|  | 6.5 |  | 43 |
|  | 9.1 |  | 44 |
|  | 9.2 | $CH_4$ | 49 |

## common carbohydrates


D-(+)-glyceraldehyde


D-erythrose


D-threose


D-ribose


β-D-ribofuranose


D-glucose


β-D-glucopyranose

## common amino acids


L-proline


≈ ammonium

pK$_a$ values for amino acids

| | *acid* | *ammonium* | *sidechain* |
|---|---|---|---|
| Ala: alanine | 2.35 | 9.87 | |
| Arg: arginine | 2.01 | 9.04 | 12.48 |
| Asn: asparagine | 2.02 | 8.80 | |
| Asp: aspartic acid | 2.10 | 9.82 | 3.86 |
| Cys: cysteine | 2.05 | 10.25 | 8.00 |
| Glu: glutamic acid | 2.10 | 9.47 | 4.07 |
| Gln: glutamine | 2.17 | 9.13 | |
| Gly: glycine | 2.35 | 9.78 | |
| His: histidine | 1.77 | 9.18 | 6.10 |
| Ile: isoleucine | 2.32 | 9.76 | |
| Leu: leucine | 2.33 | 9.74 | |
| Lys: lysine | 2.18 | 8.95 | 10.53 |
| Met: methionine | 2.28 | 9.21 | |
| Phe: phenylalanine | 2.58 | 9.24 | |
| Pro: proline | 2.00 | 10.60 | |
| Ser: serine | 2.21 | 9.15 | |
| Thr: threonine | 2.09 | 9.10 | |
| Trp: tryptophan | 2.38 | 9.39 | |
| Tyr: tyrosine | 2.20 | 9.11 | 10.07 |
| Val: valine | 2.29 | 9.72 | |

alanine: R = $CH_3$
arginine:

asparagine: R = $CH_2CONH_2$
aspartic acid: R = $CH_2CO_2H$
cysteine: R = $CH_2SH$
glutamic acid: R = $CH_2CH_2CO_2H$
glutamine: R = $CH_2CH_2CONH_2$
glycine = R = H
histidine: R =

isoleucine: R = $CH(CH_3)CH_2CH_3$ (S)
leucine: R = $CH_2CH(CH_3)_2$
lysine: R = $CH_2CH_2CH_2CH_2NH_3$
methionine: R = $CH_2CH_2SCH_3$
phenylalanine: R = $CH_2Ph$
serine: R = $CH_2OH$
threonine: R = $CH(OH)CH_3$ (R)
tryptophan: R =

tyrosine: R = $CH_2(C_6H_4)$-OH (para)
valine: R = $CH(CH_3)_2$

## common reagents


DBU
diazabicycloundecane


DBN
diazabicyclononane

$[(CH_3)_2CH]_2NLi$ LDA lithium diisopropylamide
$[(CH_3)_3Si]_2NLi$ LiHMDS lithium hexamethyldisilazide
$R\text{-}SO_2Cl$: R = $CH_3$ (MsCl) methanesulfonyl chloride "mesyl / mesylate"
R = $CF_3$ (TfCl) trifluromethanesulfonyl chloride "trifyl / triflate"
R = p-$CH_3(C_6H_4)$ (TsCl) para-toluenesulfonyl chloride "tosyl / tosylate"
$(CH_3CH_2)_3N$ TEA triethylamine
p-$CH_3(C_6H_4)SO_2OH$ TsOH para-toluenesulfonic acid
$PhCH_2OH$ BnOH benzyl alcohol
$CH_3CH_2OH$ EtOH ethanol
$CH_3OH$ MeOH methanol
$(CH_3)_2CHOH$ iPrOH or $Pr^iOH$ isopropyl alcohol
$(CH_3)_3COH$ tBuOH or $Bu^tOH$ tert-butyl alcohol
$CH_3CH_2CH_2CH_2Li$ BuLi butyllithium
$(CH_3)_2CuLi$ $Me_2CuLi$ lithium dimethylcuprate