Molecules Of Life

06-2015

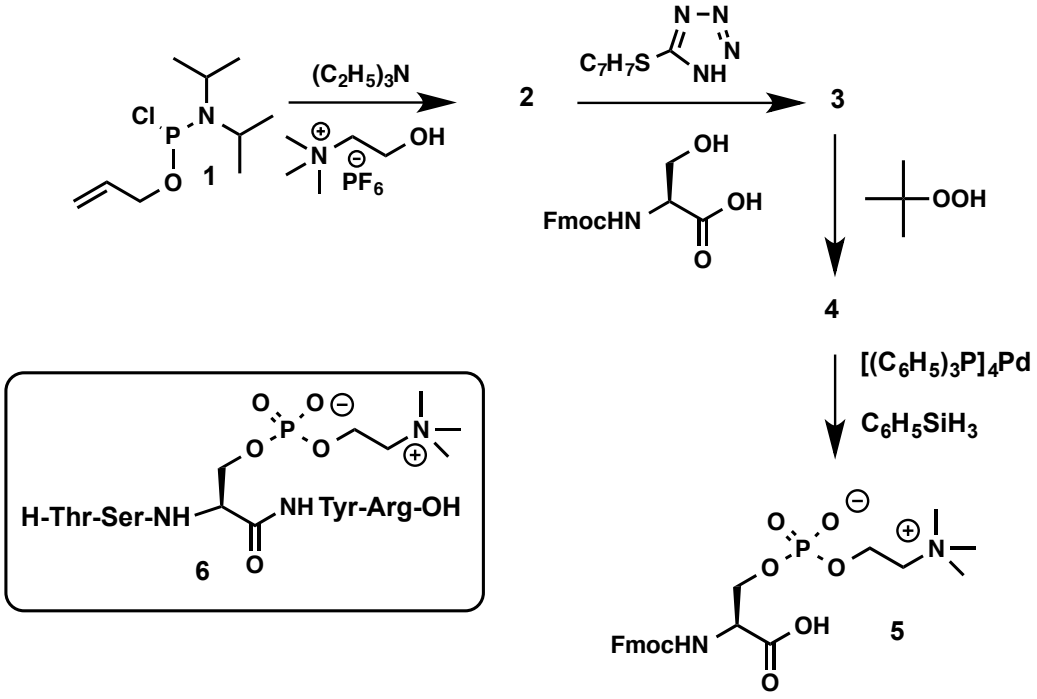
time: 3 hours

Each answer sheet must be provided with your name and student number

Each answer must be provided with the number of the corresponding question

(The maximum points for every question is indicated)

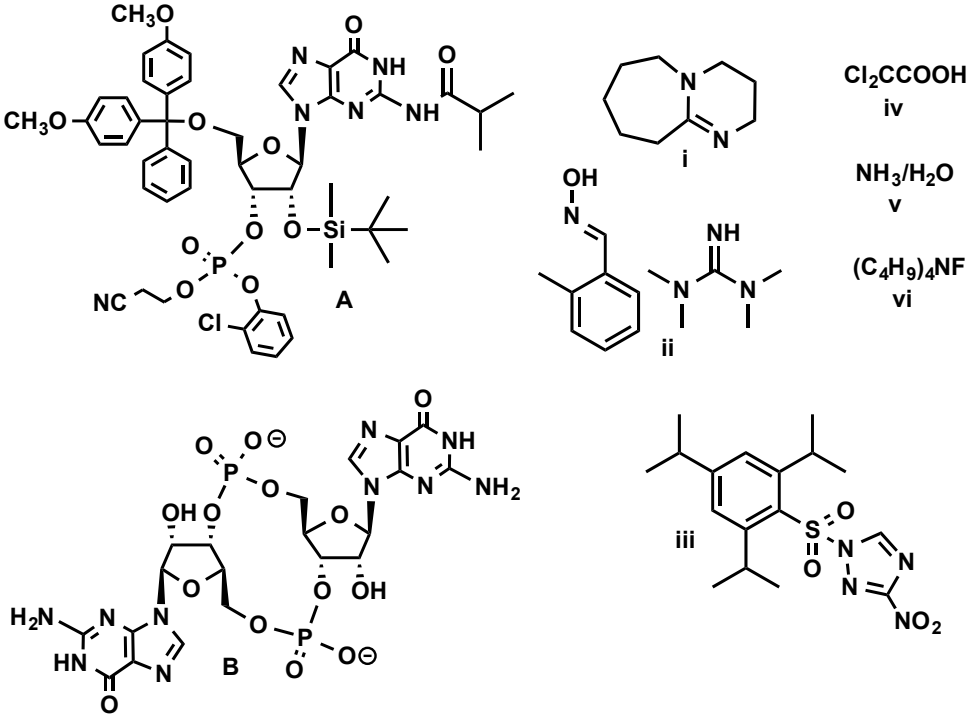
Question 1. *(30 points)*
Phosphocholination of host cell proteins is a post-translational modification important for bacterial pathogenesis. The scheme below shows the synthesis of phosphocholinated serine building block **5**, suitable for solid phase peptide synthesis.



a) Give a synthesis to phosphoramidite **1**, using PCl_3 as starting compound.
b) Draw the structure of compound **2**. Which stereoisomers are formed?
c) Draw the structure of compound **3**. Specify the role of 5-(benzylthio)-1H-tetrazole. Which stereoisomers are formed?
d) Draw the structure of compound **4**. Give an alternative reagent for the oxidation of **3** to **4**.
e) Explain why phosphodiester **5** is more suitable in peptide synthesis than a phosphotriester building block.
f) Building block **5** was used to prepare peptide **6** using solid-phase chemistry. Draw the structures of the other amino acid building blocks necessary to synthesize **6**.

Question 2. *(16 points)*

3’,5’-Cyclic diguanylic acid **B** is a bacterial signaling molecule that plays a role in the regulation of various processes such as biofilm formation.



a) Give a synthetic route to 3’,5’-Cyclic diguanylic acid **B** using protected building block **A** and the reagents (i)-(vi).
b) Give a synthetic route to building block **A** using guanosine as starting compound.

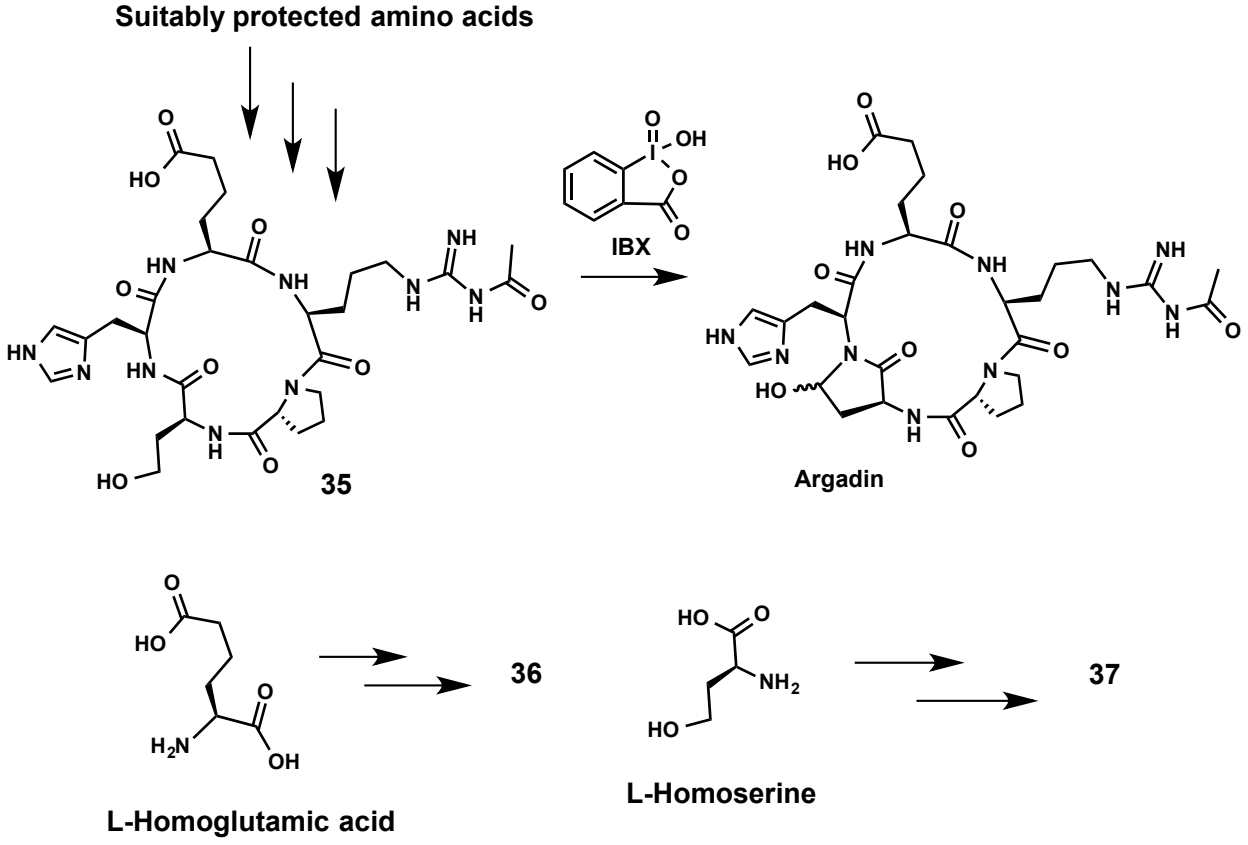
Question 3 (24 points)

Cyclic peptide named Argadin, a naturally occurring potent chitinase inhibitor, was prepared from cyclic precursor **35**.

a) Suggest a synthesis of compound **35** from suitably protected amino acid building blocks. Draw the protected derivatives of all necessary amino acids, show the synthetic scheme towards **35** including the coupling and deprotection conditions.

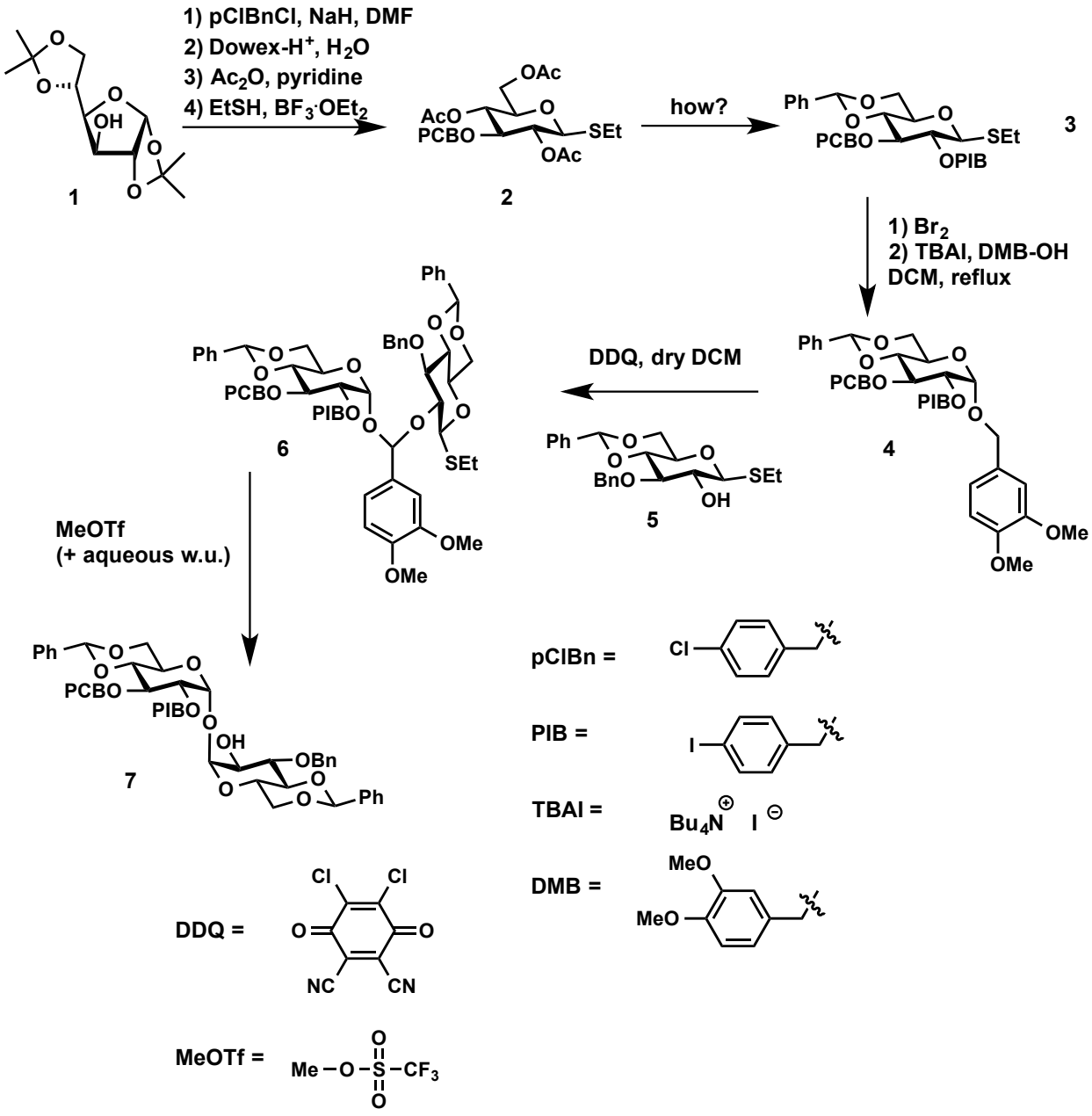
b) Provide a synthetic scheme, reagents and conditions for the preparation of protected L-homoglutamic acid (**36**) and L-homoserine (**37**) building blocks suitable for Argadin synthesis. Use unprotected amino acids as starting material as suggested in the scheme below.

c) Provide a mechanism for the oxidative conversion of **35** into Argadin by IBX treatment.



Question 4. (30points)

Trehalose is an α,α-1,1-linked disaccharide. Below a synthesis of an orthogonally protected version of this disaccharide (**7**) is depicted (The substituted benzyl ethers are used in the synthesis for an orthogonal deprotection at the end. Their chemistry is similar to that of normal benzyl groups).



a) Provide de structures of the intermediates formed in reactions 1-4 that were used to transform **1** into **2** and give (brief) reaction mechanisms to explain your answer.

b) How can you transform thioglycoside **2** into fully protected thioglycoside **3**?

c) Which of the two thioglycosides, **2** or **3**, is more reactive in a glycosylation reaction activated by NIS and TfOH? Explain your answer.

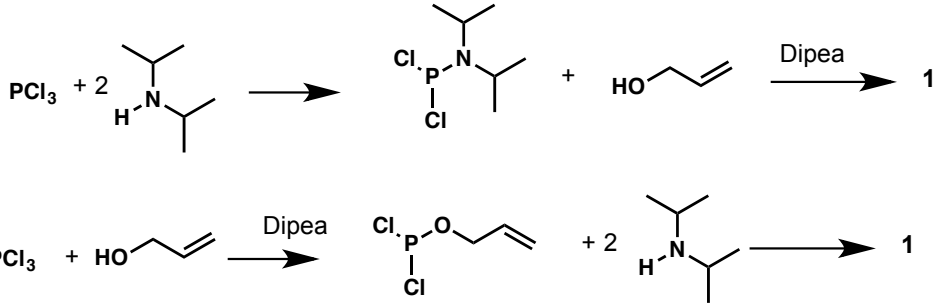
d) Next, thioglycoside **3** is transformed into α-linked dimethoxybenzyl glycoside **4**. Provide a mechanism for this transformation and account for the observed stereoselectivity.

e) Then building blocks **4** and **5** are united using DDQ in dry DCM to give disaccharide **6**. Provide a mechanism for the formation of **6**.

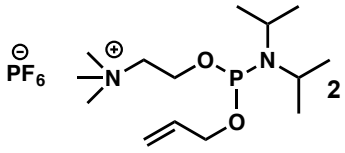
f) Finally MeOTf (a "soft", but reactive electrophile) is used to construct the trehalose linkage. Provide a mechanism for the formation of **7** from **6**.

question 1

a)

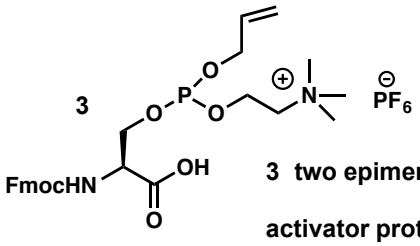


b)



two enantiomers

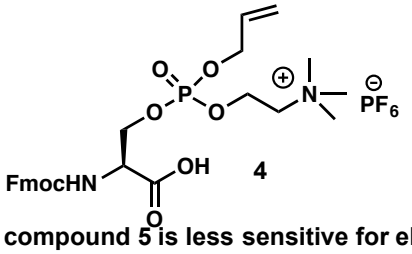
c)



3 two epimers

activator protonates the amine in amidite 2 and creates a leaving group (proposed mechanism)

d)

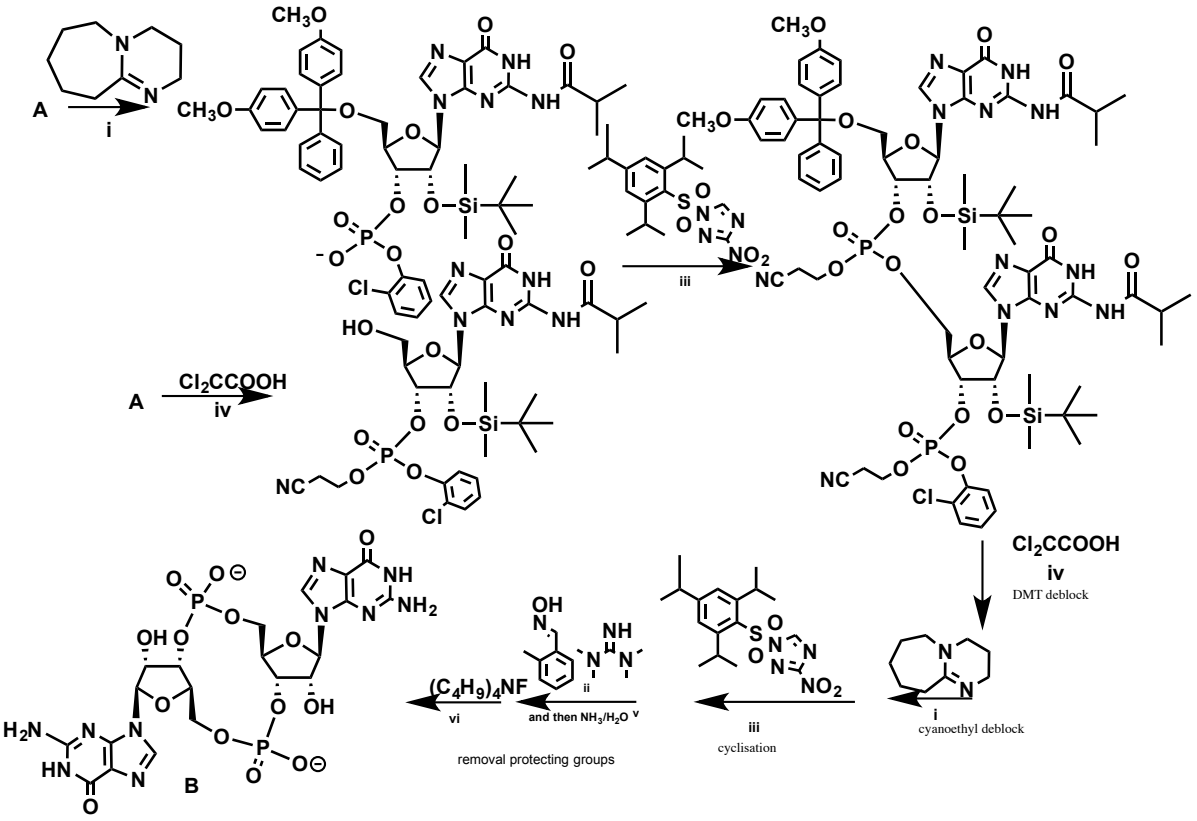


reagent that doesnot harm the double bond of the allyl camphorsulfonyloxaziridine

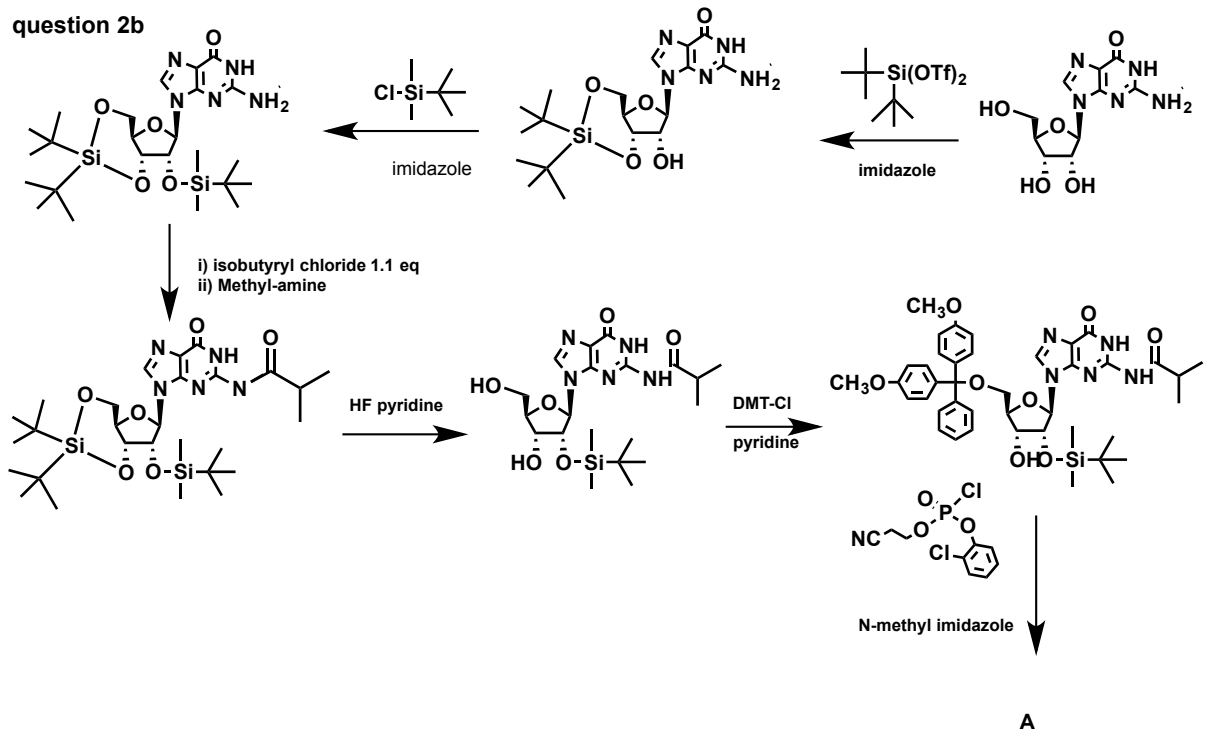
e) **compound 5 is less sensitive for elimination of serine to dehydroalanine**

f)

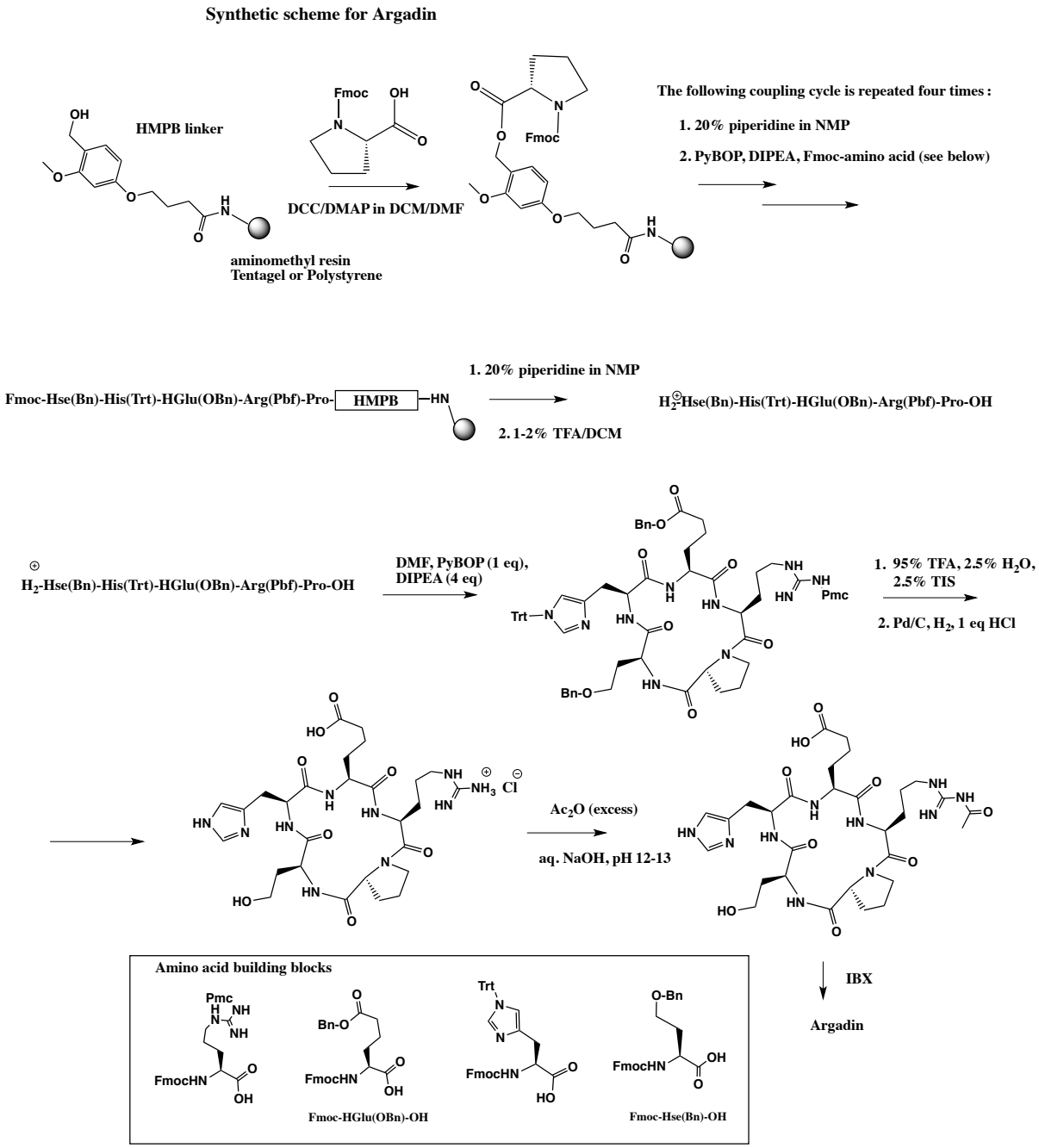
question 2a



question 2b

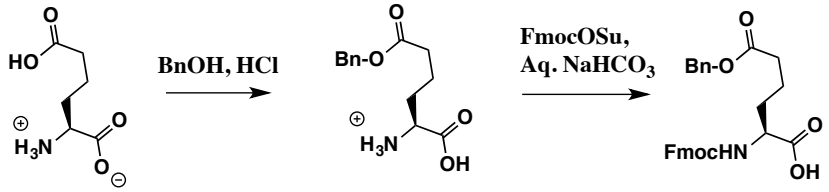


Question 3
a)

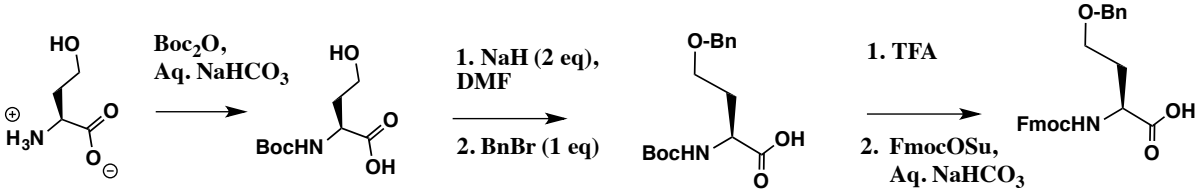

Synthetic scheme for Argadin
HMPB linker
DCC/DMAP in DCM/DMF
aminomethyl resin
Tentagel or Polystyrene
The following coupling cycle is repeated four times :
1. 20% piperidine in NMP
2. PyBOP, DIPEA, Fmoc-amino acid (see below)
Fmoc-Hse(Bn)-His(Trt)-HGlu(OBn)-Arg(Pbf)-Pro-
HMPB
1. 20% piperidine in NMP
2. 1-2% TFA/DCM
H2-Hse(Bn)-His(Trt)-HGlu(OBn)-Arg(Pbf)-Pro-OH
H2-Hse(Bn)-His(Trt)-HGlu(OBn)-Arg(Pbf)-Pro-OH
DMF, PyBOP (1 eq),
DIPEA (4 eq)
1. 95% TFA, 2.5% H2O,
2.5% TIS
2. Pd/C, H2, 1 eq HCl
Ac2O (excess)
aq. NaOH, pH 12-13
IBX
Argadin
Amino acid building blocks
Fmoc-HGlu(OBn)-OH
Fmoc-Hse(Bn)-OH

b)

Synthesis of Fmoc-HGlu(OBn)-OH

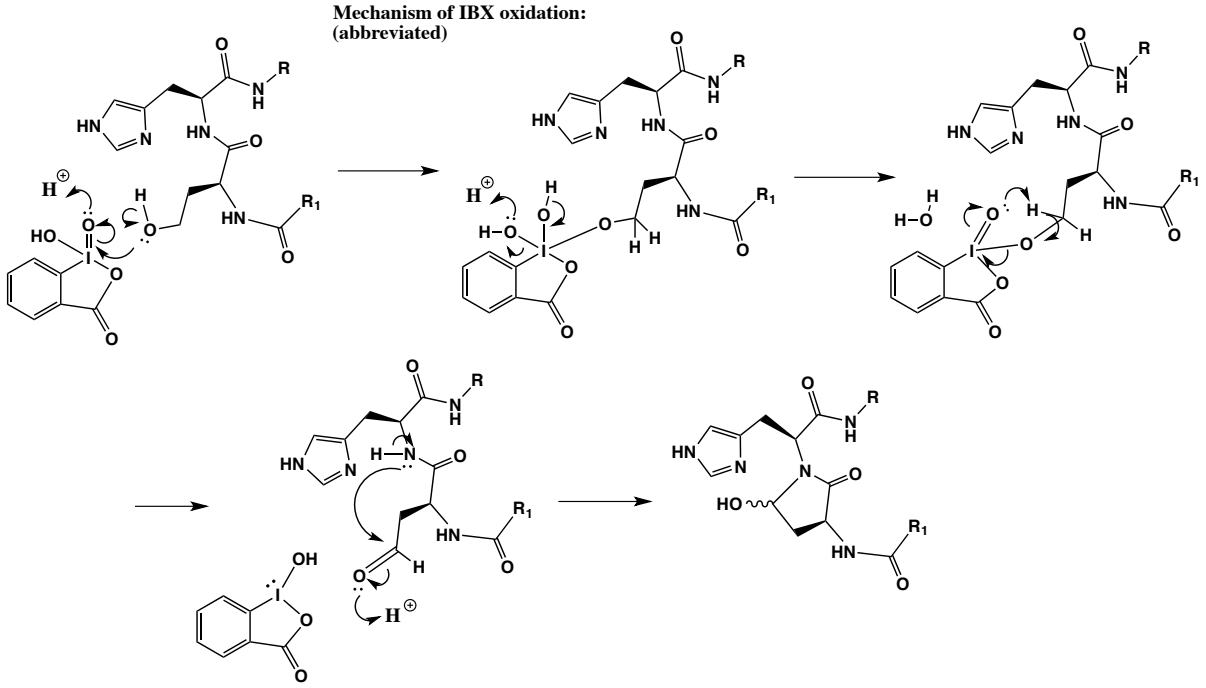


Synthesis of Fmoc-HSer(Bn)-OH

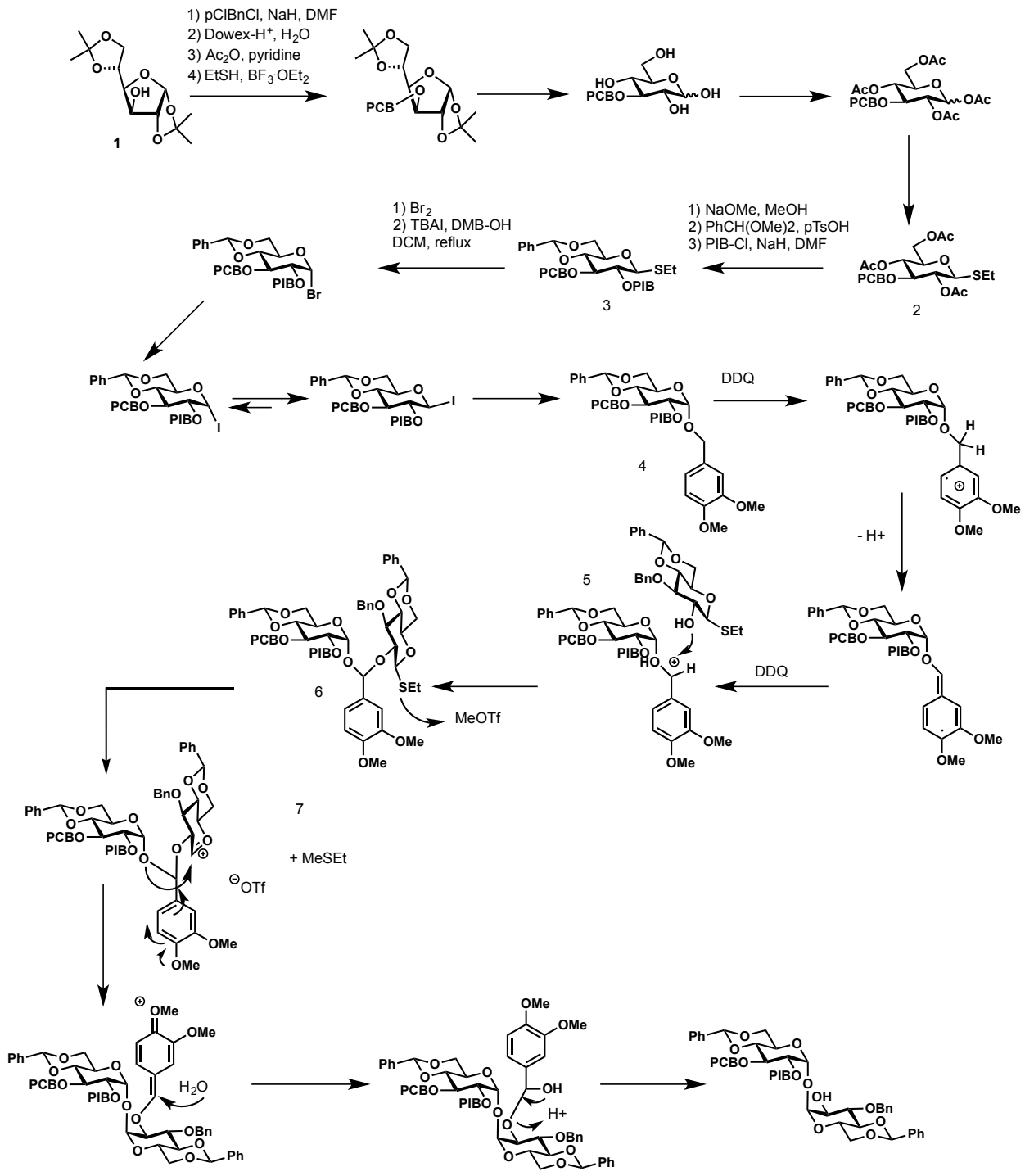


c)

Mechanism of IBX oxidation:
(abbreviated)



Question 4



A) See Figure above.

B) See Figure above.

C) **3** is more reactive because **2** carries 3 electron withdrawing protecting groups "disarming" this thioglycoside.

D) First the thioglycoside is transformed into the anomeric bromide (activation of the thiol function with Br2, expulsion

of Br-Set, attack of Br^-). Next TBAI transfroms the bromide into the mixture of anomeric iodides. Although the alpha-Iodide is the major species in solution, the beta-iodide is most reactive and this species reacts with the primary nucleophile (this is a reactive nucleophile!) to selectively give the alpha-product. See Figure above.

E) See Figure above.

F) See Figure above.