T9. Cyclodextrin Chemistry

7%									
9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	∑
2	6	8	3	2	4	6	18	4	53

Cyclodextrins (CD) are a family of cyclic oligosaccharides, consisting of glucose subunits joined by α-1,4-glycosidic bonds. The three most common cyclodextrins (α-, β-, γ-cyclodextrin) contain 6, 7, and 8 α-D-glucopyranoside units, respectively.

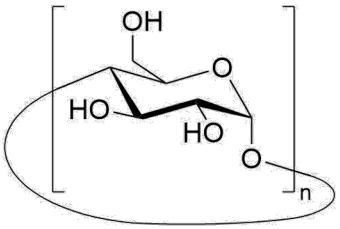
9.1 **Calculate** the molar mass of β-CD. **Assume** M_w(glucose) = 180.16 g mol^{-1}. 2.0 pt

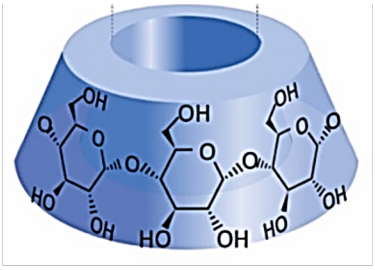
SOLUTION:

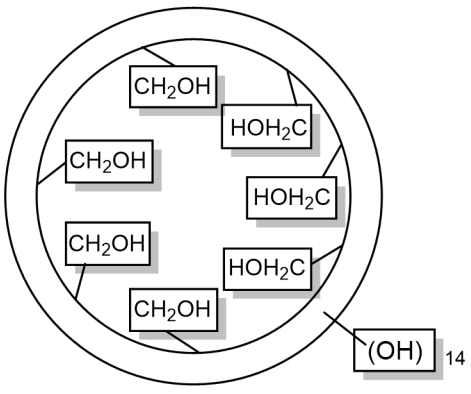
$$M_w(\beta - Cyclodextrin) = 180.16 \cdot 7 – 18.016 \cdot 7 = 1135.01 \text{g/mol}$$

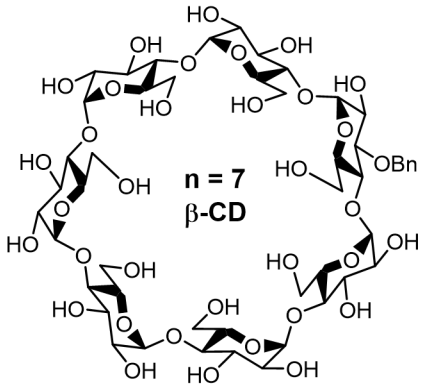
Mw: β-CD = 1135.01 g/mol

2 points

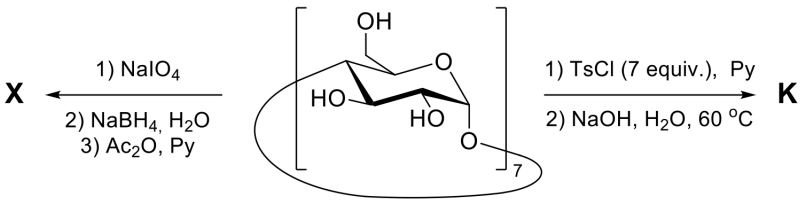


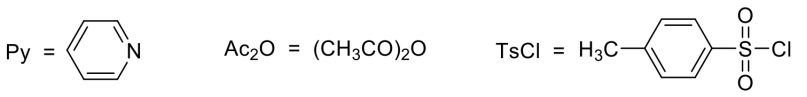






CDs combine macrocyclic properties with glucose chemistry, which was demonstrated in the synthesis of **X**. Primary and secondary hydroxy groups show different reactivity due to being a part of CDs. Stoddart *et al.* synthesised compound **K**, where only one OH group remained free per glucopyranoside unit.



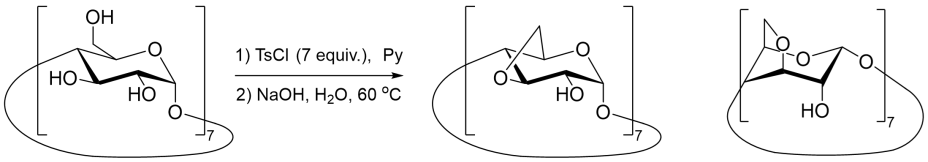


equiv.= equivalent

9.2 **Tick** the favorable chair conformation and **draw** the structure of **K** by completing the CD template. **Show** stereochemistry unambiguously. 6.0 pt

SOLUTION:

Since in this reaction we observe the formation of new ring on glucopyranose unit, the bridging atoms should be at axial positions. Therefore, the second conformation will be favoured.



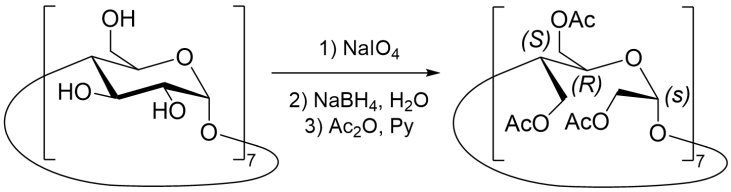
K

6 points for correct structure, -2 points for incorrect conformation, -1 point for each incorrect substituent/stereocentre, 0 if no new ring is formed.

9.3 **Determine** the ring size, *rs*, of macrocycle **X**. **Give** the number of stereocentres, *sc*, in **X.** 8.0 pt

SOLUTION:

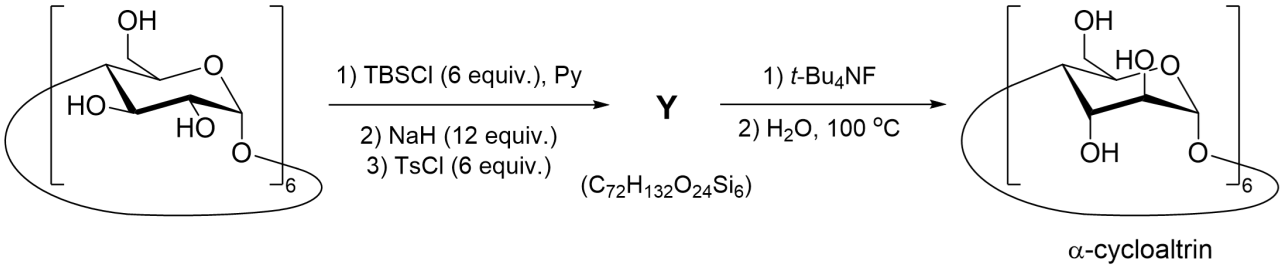
Cleavage of the diol results in reduction of the number of asymmetric atoms in the glucopyranose unit down to three, one of which (the acetal) is pseudo-chiral. Overall, the macrocycle becomes achiral since it consists of *meso*-butanetetrol/glycolaldehyde acetal units. The number of atoms in the macrocyclic ring for each repeat unit is five.



rs: 35 *sc:* 21

rs – 4 points; sc – 4 points; 4 points if sc = 14; 2 points if sc = 3 or 2;

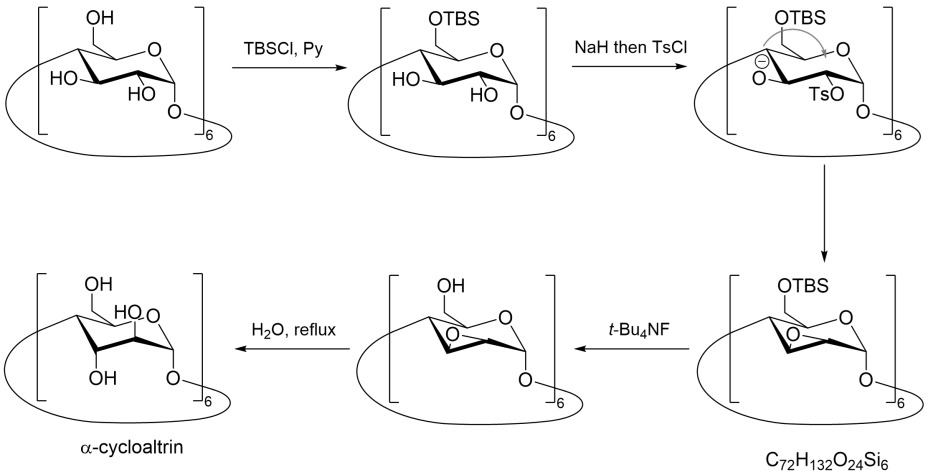
α-Cycloaltrin, a synthetic analogue of α-CD, was synthesised as follows.



α-cycloaltrin

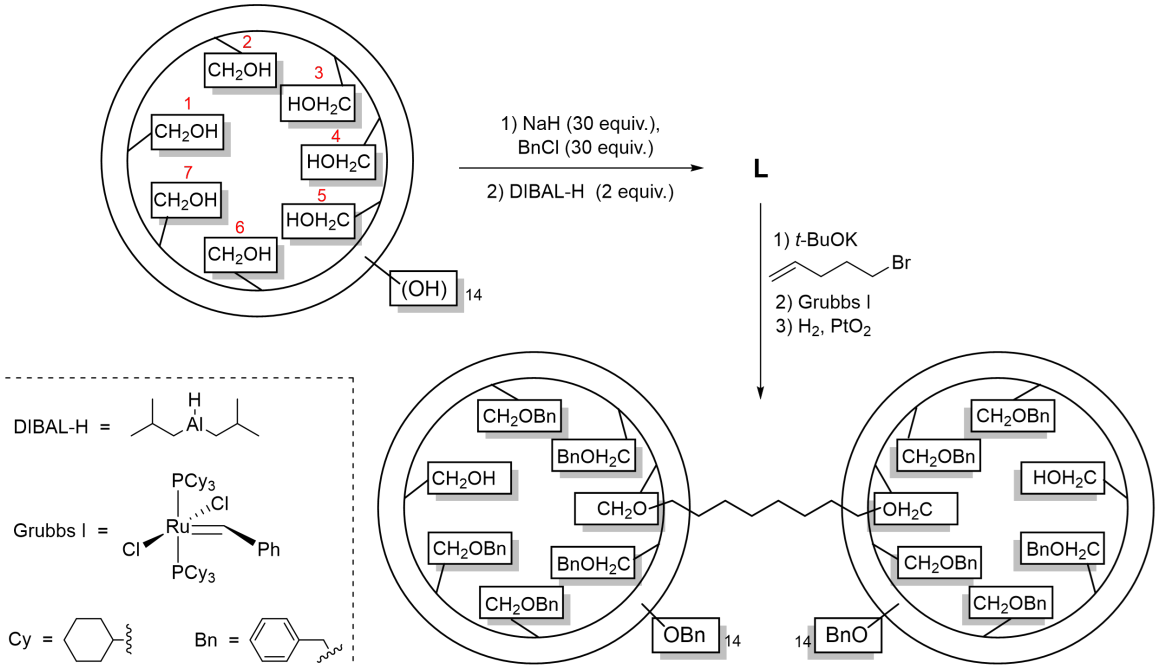
9.4 **Draw** the structure of **Y** with stereochemistry by completing the CD template. 3.0 pt

SOLUTION:



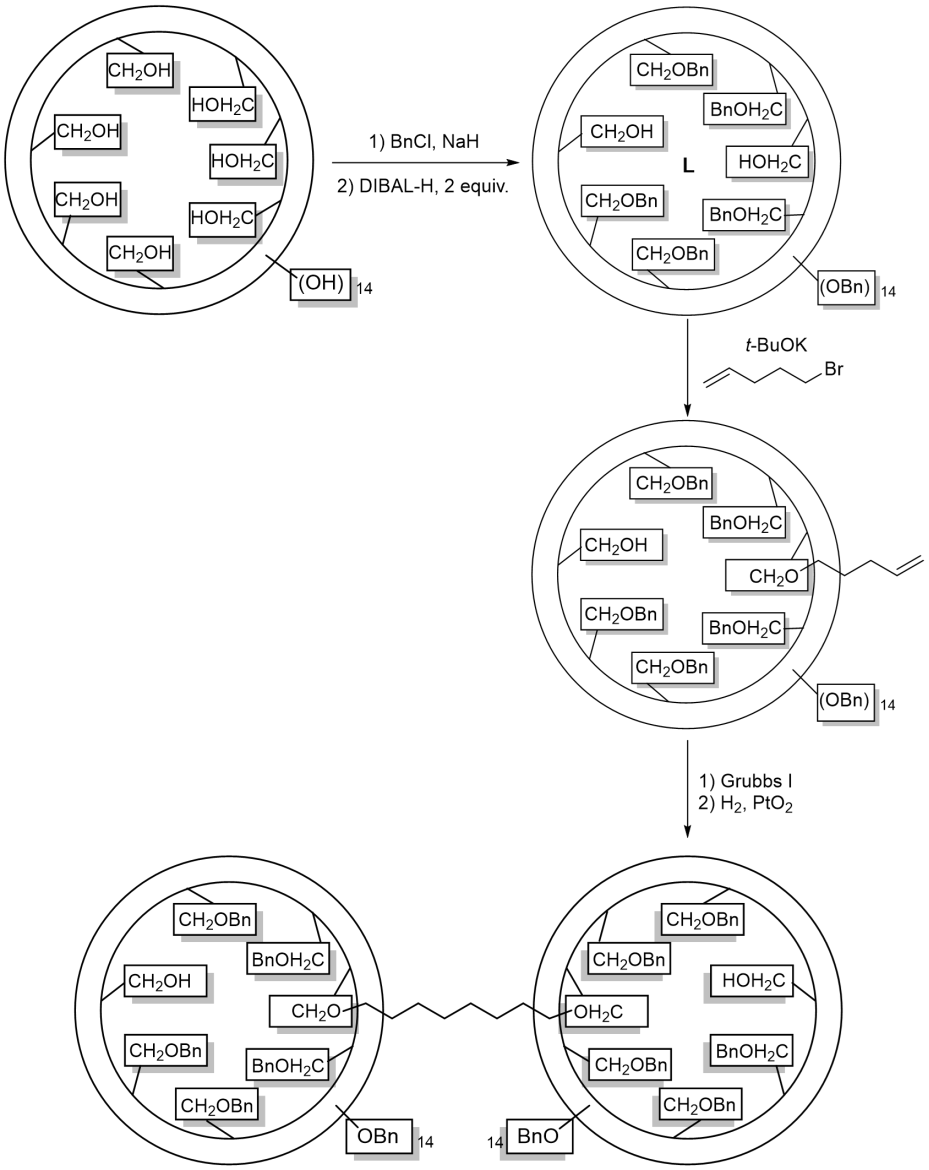
Correct structure 3 points. Epoxide with opposite configuration is also accepted; -1 point for any missing or incorrect substituent.

In 2000, Sinay *et al.* demonstrated that a single protic group (NH and OH) at unit 1 directs the **next** reductive debenzylation of a primary OH group to unit 4 in the macrocyclic ring (or to unit 3 if the unit 4 position is not available). This allowed the synthesis of the following β-CD dimer as a mixture of constitutional linkage isomers.



9.5 **Draw** the structure of **L** on the β-CD template. **Fill in** all the boxes. 2.0 pt

SOLUTION:

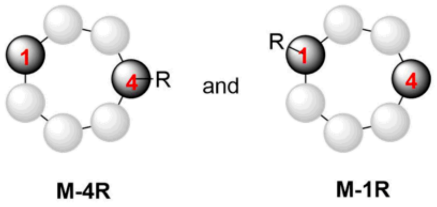


Correct structure 2 points.
-1 p for each incorrect substituent
0 p if 2 or more incorrect substituents

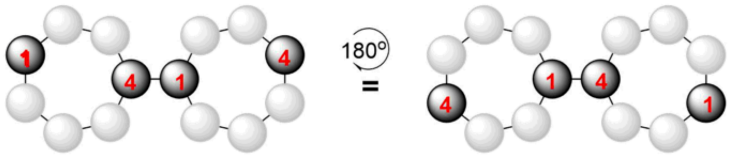
9.6 **Determine** the number of isomers of the β-CD dimer that can form during the synthesis by *Sinay et. al.* 4.0 pt

SOLUTION:

Due to β-CD consisting of seven units and being chiral, two regioisomers are formed in the alkylation reaction (**M-4R, M-1R)**. Therefore, the dimer would have **three** isomers with following connections: 4-4, 1-1, 1-4. (Note 4-1 = 1-4)

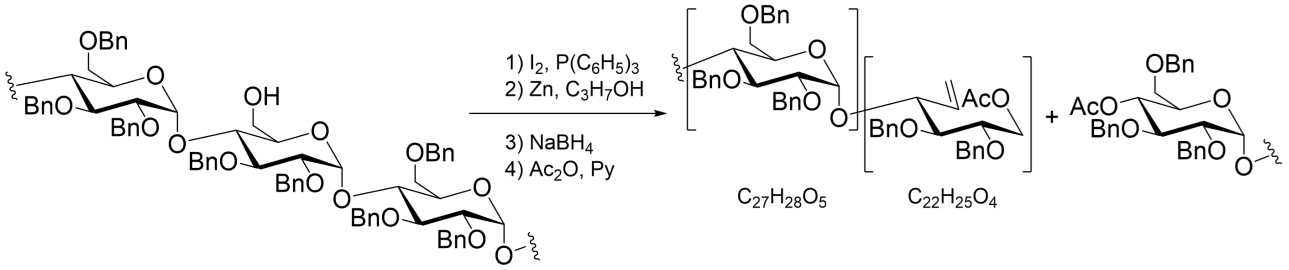


M-4R M-1R



Correct number of isomers 4 points.

To confirm the positions of debenzylation, **L** was subjected to the "hexo-5-enose degradation" reaction, as shown below. The products were then analysed by mass spectrometry.



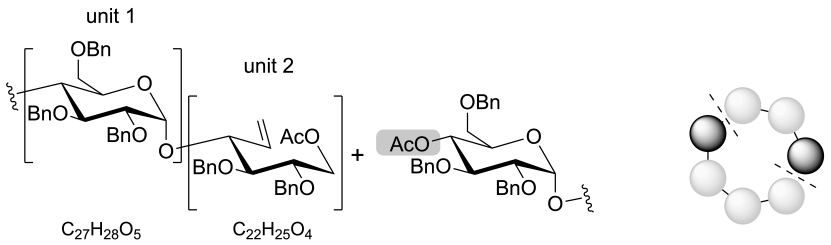
9.7 **Calculate** the m/z value for the two $[M+Na]^+$ peaks that were observed for the degradation products from **L**. **Use** integer values of atomic mass. 6.0 pt

SOLUTION:

Since we know the chemical formula for the units, we can calculate molecular weights of the two products. Each product should have one unit 2 (black sphere) and 2-3 unit 1s (white sphere). Additionally, we should add C2H3O2, which corresponds to the mass of the OAc group. Therefore:

M_1 : $2C_{27}H_{28}O_5 + C_{22}H_{25}O_4 + C_2H_3O_2 = C_{78}H_{84}O_{16}$ $[M_1 + Na]^+ = 1299$

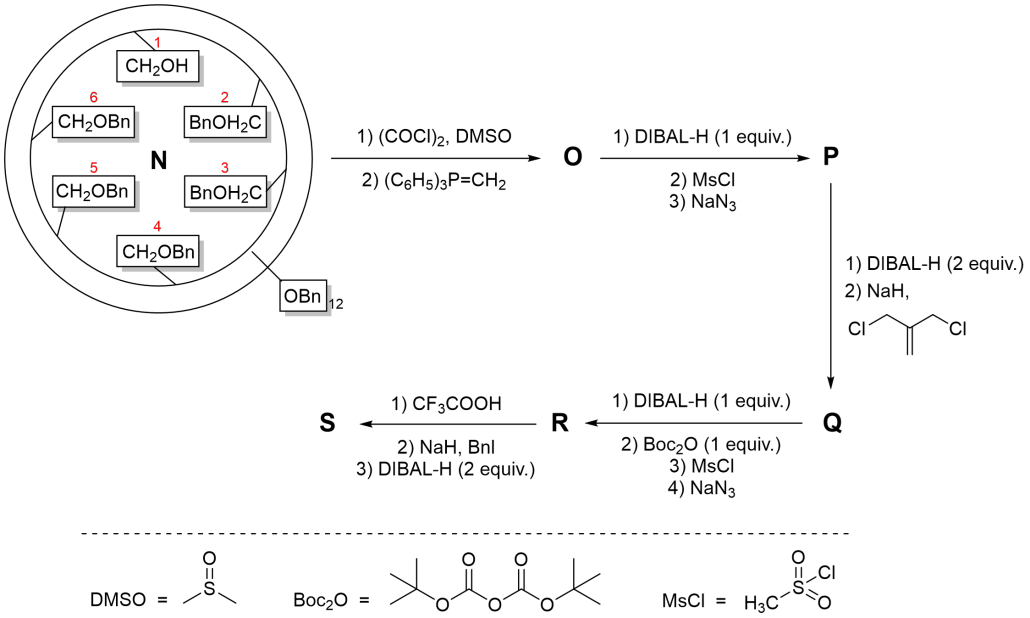
M_2 : $3C_{27}H_{28}O_5 + C_{22}H_{25}O_4 + C_2H_3O_2 = C_{105}H_{112}O_{21}$ $[M_2 + Na]^+ = 1731$



$[M_1 + Na]^+$ = 1299 $[M_2 + Na]^+$ = 1731

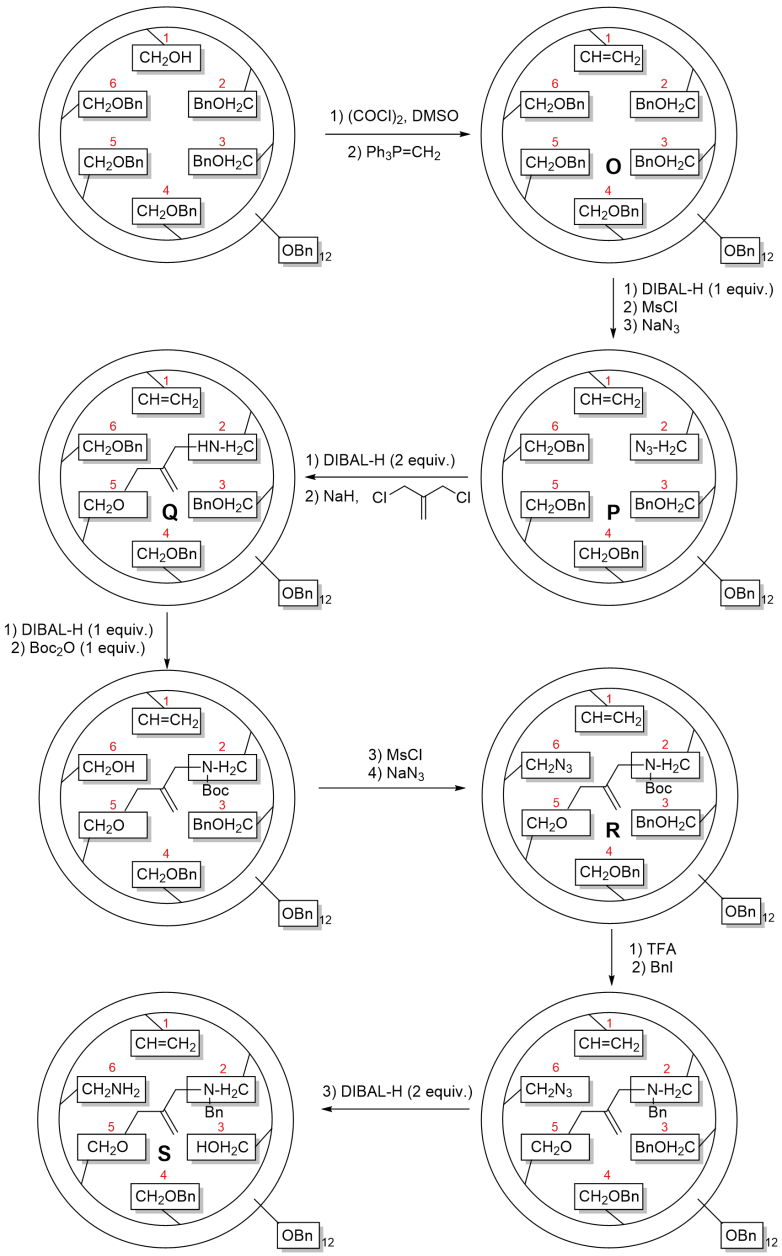
Each correct answer 3 points, total – 6 points
m/z without Na^+ 1p each
m/z without $C_2H_2O_2$ 1p each

Later, Sollogoub *et al.* applied the ability of alkenes to direct the debenzylation to the "*ortho*"-glucopyranose unit for the synthesis of hexadifferentiated α-CD **S**:


1
CH2OH
2
BnOH2C
3
BnOH2C
4
CH2OBn
5
CH2OBn
6
CH2OBn
N
OBn
12
1) (COCl)2, DMSO
2) (C6H5)3P=CH2
O
1) DIBAL-H (1 equiv.)
2) MsCl
3) NaN3
P
1) DIBAL-H (2 equiv.)
2) NaH,
Cl
Cl
Q
1) DIBAL-H (1 equiv.)
2) Boc2O (1 equiv.)
3) MsCl
4) NaN3
R
1) CF3COOH
2) NaH, BnI
3) DIBAL-H (2 equiv.)
S
DMSO =
Boc2O =
MsCl =
H3C
Cl

9.8 **Draw** the structures of **O-S** on the α-CD templates. **Fill in** all the boxes. You may draw structures outside the boxes if appropriate. **Assume** 1,2-unit modification happens **clockwise**, while 1,3-unit modification happens **counterclockwise**. Protic groups have stronger directing effects than alkenes. 18.0 pt

SOLUTION:

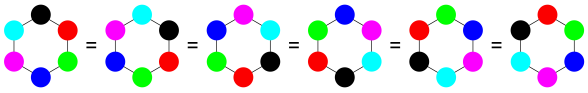


O - 2 points, **P-S** - 4 points, total 18 points. -1 point for incorrect or missing substituents for each structure. Mistakes carried over will be ignored if following structures fit the functional group direction logic.

9.9 **Determine** the number of all possible arrangements of the functional groups on a hexadifferentiated α-CD (**assume** only the CH_2OH groups have been modified). 4.0 pt

SOLUTION:

If we have 6 linear positions for 6 coloured balls, the total number of arrangements will be 6! = 720. But in α-CD, positions are in a circle, which makes all arrangements below equal. The correct answer 6!/6 = 120.



Correct answer 4 points; if the answer 720 or 60– 2 points, if answer 320 - 1 point. All other answers - 0.