ACS Group Meeting – Problem Session Jan/Feb 2010

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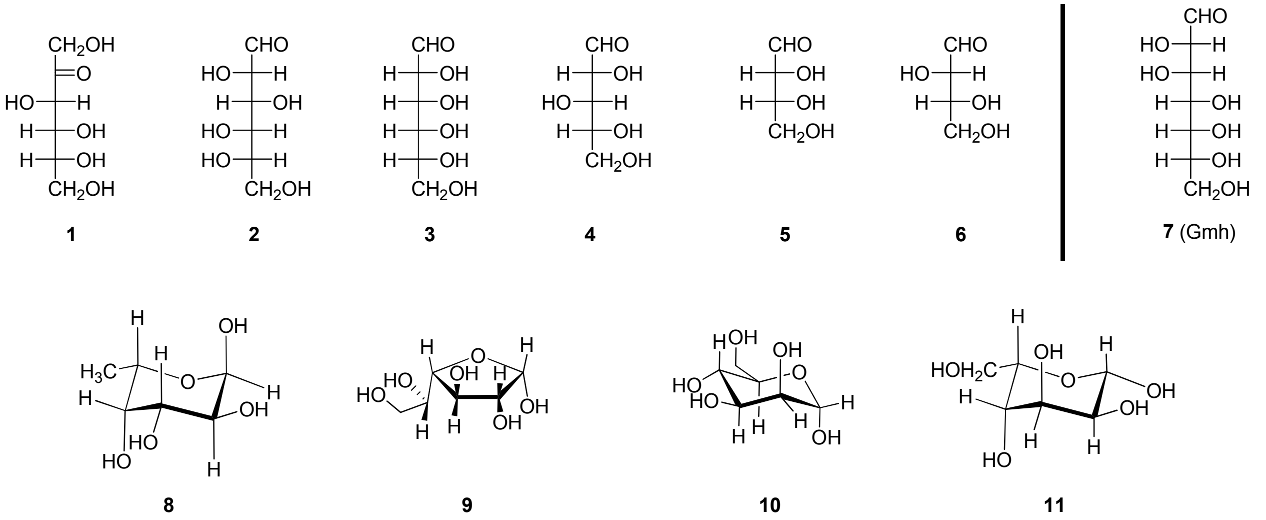
Part-1: Carbohydrates – Basics

Questions for Discussion:

(1) Identify which of the following monosaccharides **1-6** are L-Glucose, D-Allose, D-Xylose, D-Fructose, D-Threose and D-Erythrose (Scheme 1)?

Scheme 1:



(2) How will you represent D-glucose in its furanose and pyranose cyclic forms (use Haworth or staggered or chair representations)?

(3) Draw the α-anomer of the disaccharide Gmh(α1→4)Glc and identify the reducing end.
[Gmh = D-glycero-D-mannoheptose **6** and Glc = D-glucose]

(4) How will you synthesise α-methyl D-glycero-D-manno-heptoside (2,3,4,6)-tetraacetate from D-glycero-D-manno-heptose **7**?

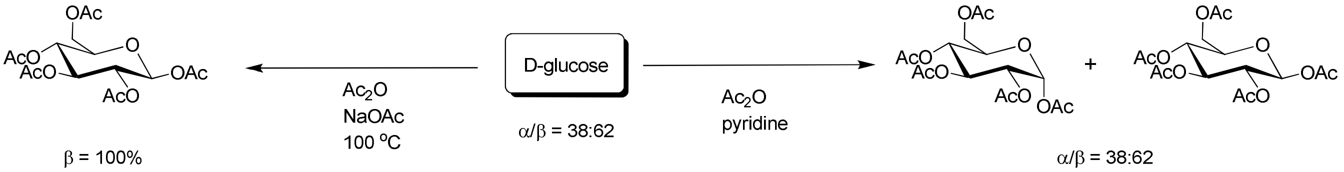
(5) Draw the sugars **8-11** in Fischer projection and identify whether they are D-sugar or L-sugar (Scheme 1)?

(6) $[\alpha]_D$ values (at 20 ^{o}C) of pure α-D-Galactopyranose and β-D-Galactopyranose are +150.7^{o} and +52.8^{o} respectively in H_2O. If either anomer is dissolved in water and allowed to reach equilibrium, the solution exhibits specific rotation of +80.2^{o}, what would be the ratio of its α and β anomers? Please draw the structure of both of these anomers.

(7) When D-glucose is dissolved in water, it exists as a mixture of α and β anomers in the ratio 38:62 (@ ~20 ^{o}C). Why is the β-anomer predominantly observed?

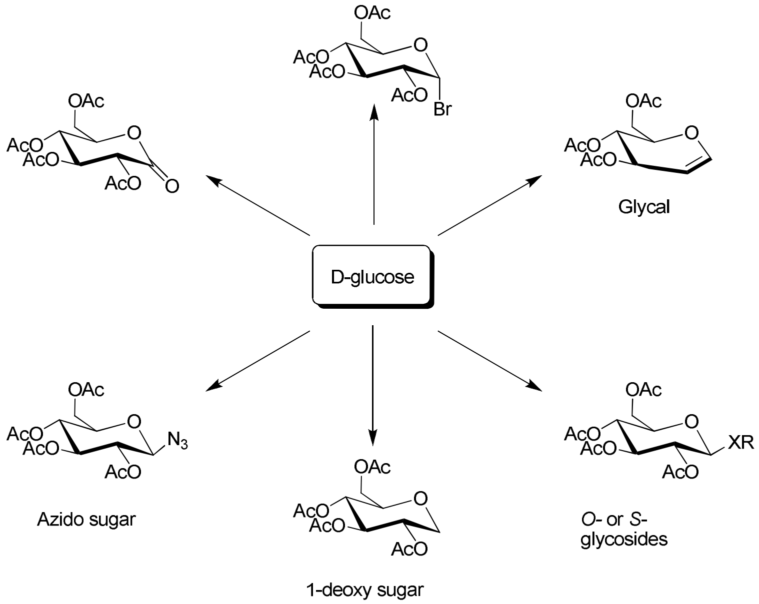
(8) How will you rationalise the following observation (Scheme 2):

Scheme 2:



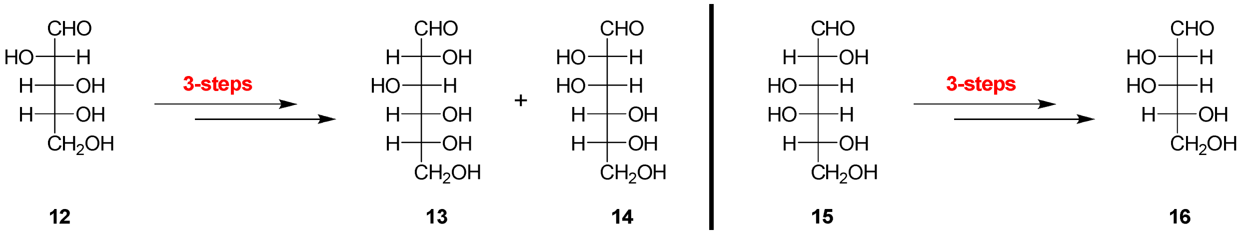
(9) Suggest suitable steps for the following transformations from D-glucose (Scheme 3):

Scheme 3:



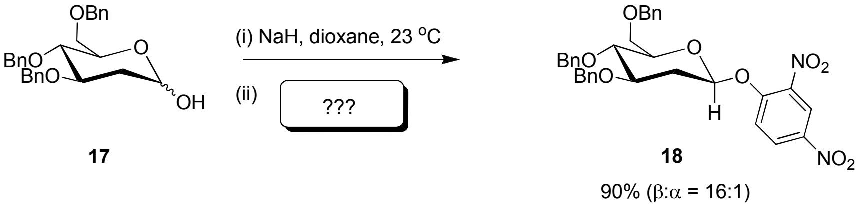
(10) Convert D-Arabinose **12** to a mixture of D-Glucose **13** and D-Mannose **14** in three steps (chain lengthening process) and D-Galactose **15** to D-Lyxose **16** in three steps (chain degradation) (Scheme 4)?

Scheme 4:



(11) In a recent publication, Shair and co-workers reported a stereoselective alkylation and arylation of 2-deoxy sugars. What electrophile did they use for O-arylation of the sugar **17** (Scheme 5)? Explain why this process is stereoselective? Suggest a suitable synthesis of the sugar **17**?

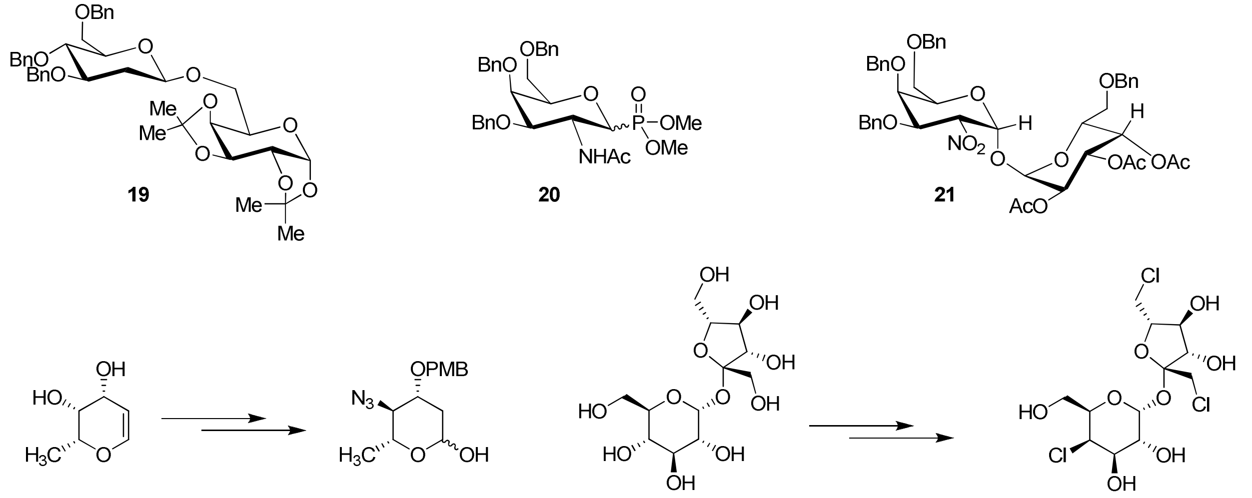
Scheme 5:



Part-2: Carbohydrates – Synthesis

(12) Suggest a suitable synthetic route to the following sugar derivatives **19-21, 23 and 25** (Scheme 6). You may propose the synthesis for **19**-**21** from any commercially available and simple starting material(s).

Scheme 6:



19 **20** **21**

22 **23** **24**, Sucrose

25, Sucralose - S
zero-calorie sugar substitute
(artificial sweetener)
~600 times sweet as sucrose **24**

Total synthesis of (–)-Littoralisone 39 and (–)-Brasoside 37

In 2001, littoralisone **39**, an uniquely complex member of the iridoid class, was isolated from *Verbena littoralis*, a plant that has been widely used in South America as a traditional folk medicine for the treatment of diarrhoea, tonsillitis and typhoid fever.[1-3] This complex natural product, believed to be biochemically derived from brasoside **37**, was shown to be an active agent for increased NGF-induced neurite outgrowth in PC12D cells.[3] Littoralisone **39** is the first novel iridolactone to be reported on the iridoid compounds possessing an unprecedented heptacyclic skeleton bearing a four-, five-, six- and nine-membered rings consisting of glucose unit that posed a variety of challenges for its total synthesis.[1,3] In 2005, MacMillan and co-workers published an elegant and first total synthesis brasoside **37** and littoralisone **39** employing proline catalysed enantioselective aldol additions and C-O bond formation reactions (Scheme 7).

(13) Predict the product **27** formed from the D-proline catalysed dimerisation of benzyloxyacetaldehyde **26**. Account for the correct stereochemistry of the product **27**.

(14) What reagents will you use in steps (3)-(5) to make TMS-ether β-anomer **29** from trisbenzyl-2-cinnamoyl glucose **28**?

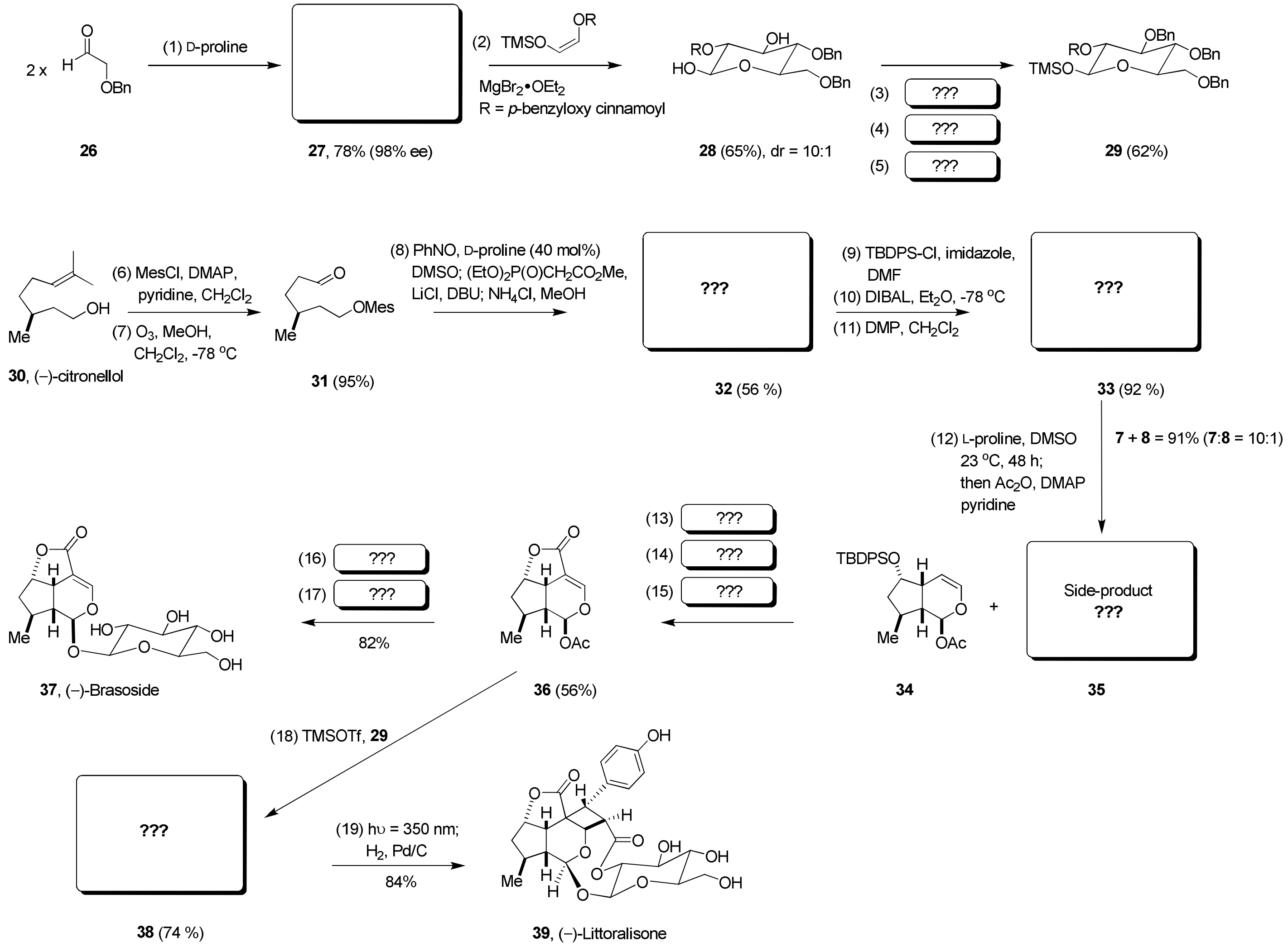
(15) Following steps (8)-(12), predict the structure of the products **32** and **33** and the side product **35**.

(16) What protocols will you use in steps (13)-(15) to obtain the tricyclic iridolactone **36** from the iridoid **34**?

(17) How will you obtain (–)-brasoside **37**, from the tricyclic lactone **36** [steps (16) and (17)]?

(18) Predict the structure of the intermediate **38** and explain the mechanism for the formation of (–)-littoralisone **39** upon irradiation of the intermediate **38** with UV light (hυ = 350 nm)?

Scheme 7: Total Synthesis of (–)-Littoralisone 39 and (–)-Brasoside 37



References:

(1) Li, Y. –S.; Matsunaga, K.; Ishibashi, M.; Ohizumi, Y. *J. Org. Chem.* **2001**, *66*, 2165 [DOI: 10.1021/jo001460d]

(2) Tietze, L. –F. *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 828 [DOI: 10.1002/anie.198308281]

(3) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696–3697 [DOI: 10.1021/ja050064f]

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