CHEMISTRY 4000

Topic #4: Building Block Oriented Synthesis

Spring 2022

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When to Choose a Building Block Approach

- While all retrosynthetic analyses must end with identification of starting materials that are readily available (commercially available or readily prepared from commercially available compounds), occasionally the structure of the synthetic target will immediately suggest what those starting materials should be.

- A building block oriented approach to retrosynthesis usually arises in one of a few circumstances:
  - The target contains repeating units that are recognizably derived from readily available materials
  - The target contains a number of double bonds whose configuration can be mapped to one or more readily available material(s)
  - The target contains a number of chirality centers whose configuration can be mapped to one or more readily available material(s)

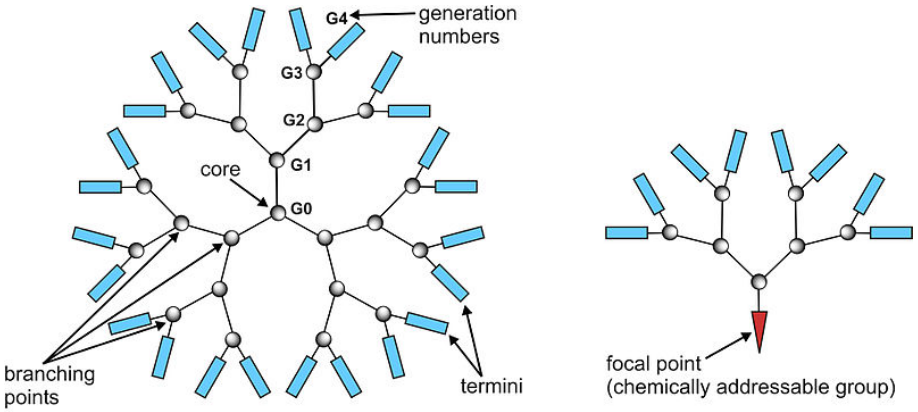
Oligomers, Polymers and Dendrimers

- Clearly, if the target is (or contains) a short sequence of monosaccharides, amino acids or nucleotides, a building block approach to synthesis will be appropriate. In fact, there are "carbohydrate synthesizers", "peptide synthesizers" and PCR machines that will do much of the work for you. The only thing you would need to provide would be the appropriate monomers (and the understanding of the relevant biochemistry to choose the right target in the first place!).

- In fairness, if an unnatural monosaccharide, amino acid or nucleotide is desired as one of the monomers, its synthesis can be a substantial challenge in-and-of itself. It is likely that you might also take a building block oriented approach to its retrosynthesis, attempting to identify an appropriate starting material from the natural monosaccharides, amino acids or nucleotides.

Oligomers, Polymers and Dendrimers

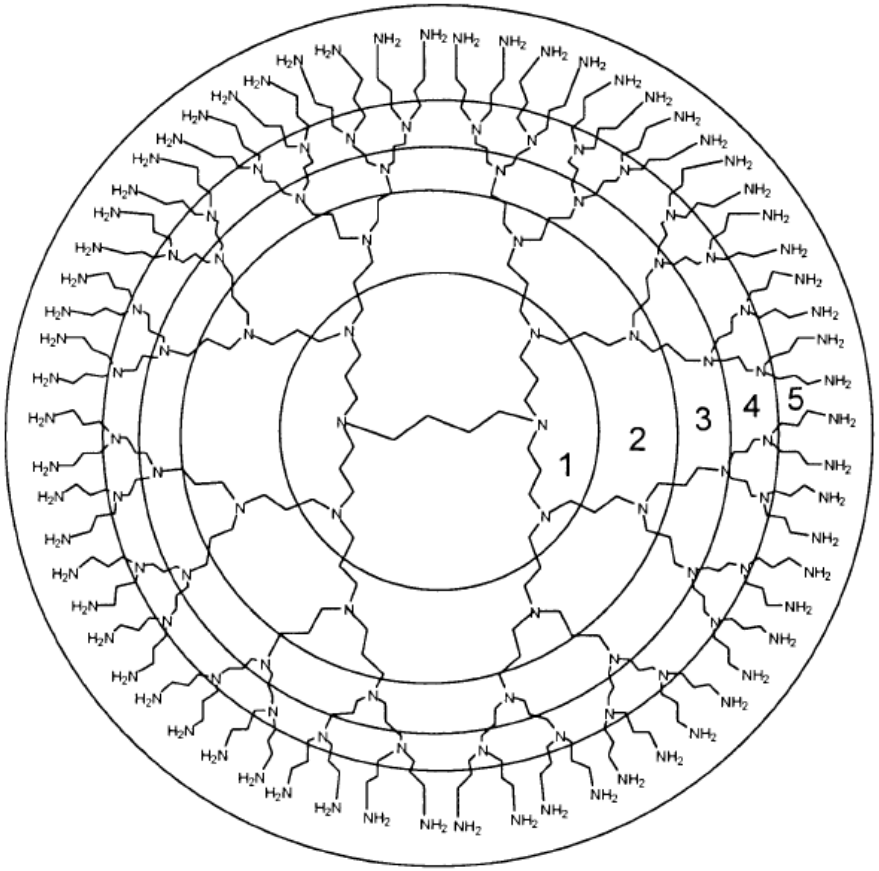
- Similar logic holds true for any other oligomer or polymer.
- A particularly interesting class of molecule that has started to show medicinal relevance is the dendrimer. Where a polymer is usually a long chain of subunits (which are sometimes cross-linked to provide three-dimensional structure), a dendrimer consists of concentric rings of subunits – with each ring having more subunits than the last. The name comes from the Greek word for tree ("dendron").
- A cartoon schematic of a dendimer is shown below:

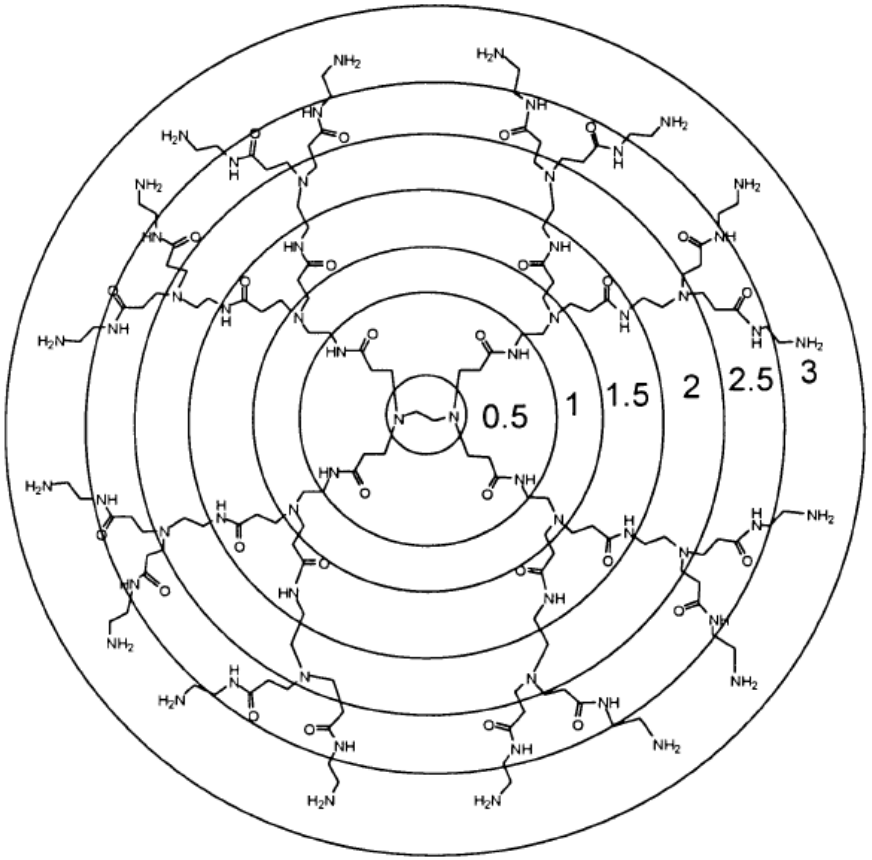


DENDRIMER DENDRON

Oligomers, Polymers and Dendrimers

- Examples of commercially available dendrimers are shown below: *The circles are not part of the structures.*

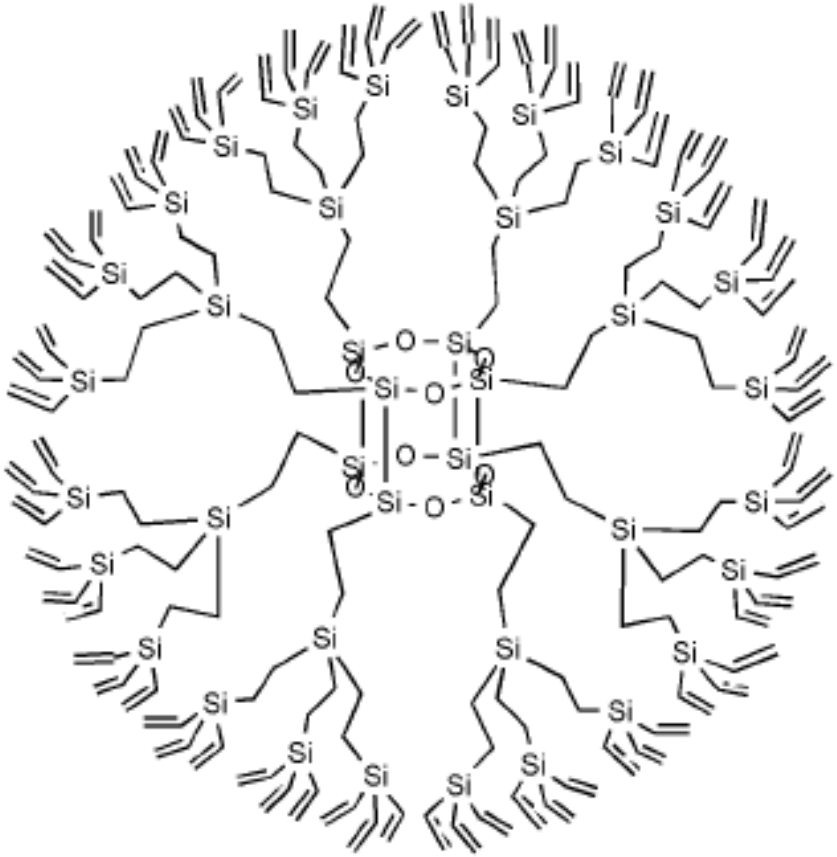


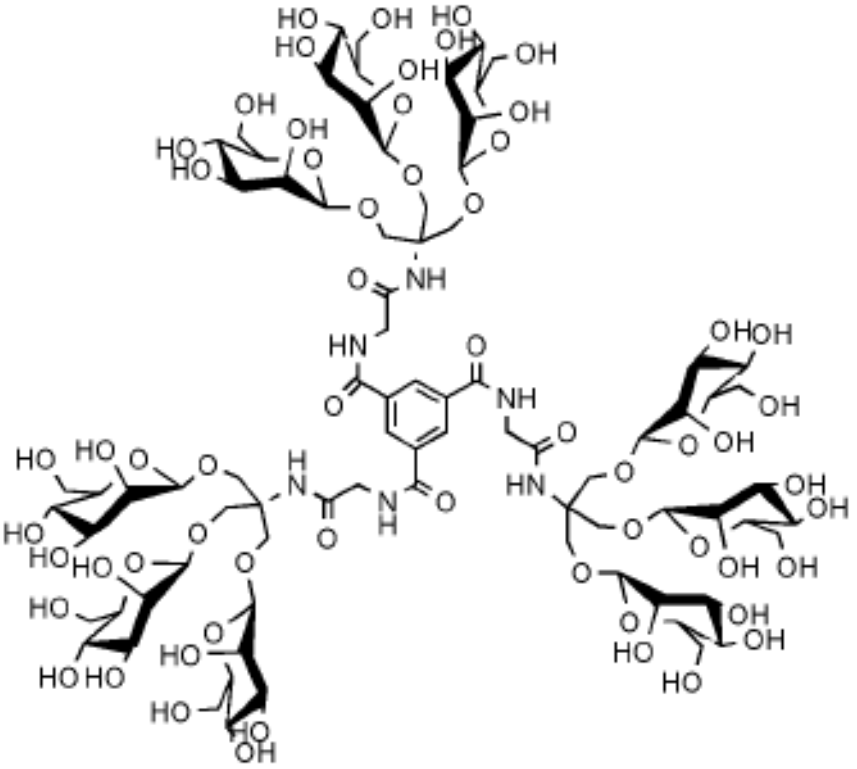


Images from U. Boas and P.M.H. Heegaard Chemical Society Reviews (2004) **33** , 43-63

Oligomers, Polymers and Dendrimers

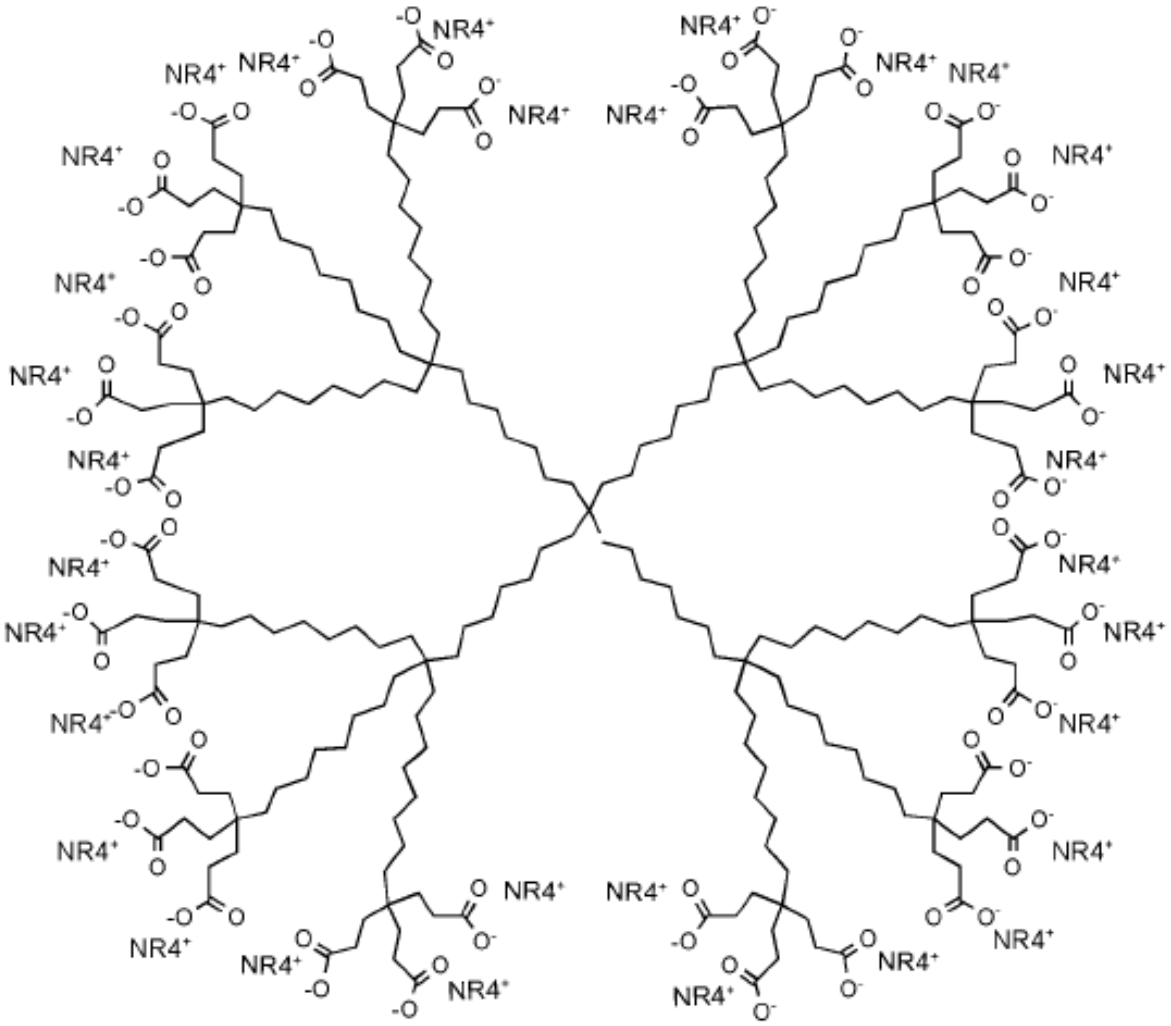
- The core rings and outer rings do not necessarily have to contain the same groups:





Images from U. Boas and P.M.H. Heegaard Chemical Society Reviews (2004) **33** , 43-63

Oligomers, Polymers and Dendrimers



Images from U. Boas and P.M.H. Heegaard Chemical Society Reviews (2004) **33** , 43-63

Oligomers, Polymers and Dendrimers

- Dendrimers are appealing because they are synthesized in layers so that a sample of dendrimer will contain only one kind of molecule (as opposed to polymers which are almost always mixtures containing molecules with a range of molar masses).

- Research suggests that dendimers may be useful in drug delivery in a few different ways:
  - Attach the drug to the outside of the dendrimer using a linkage that can be broken metabolically
  - "Attach" the drug to the outside of the dendrimer via ionic attractions such that it will be released within the body (due to pH changes, etc.)
  - Encapsulate the drug within the sphere that is the dendrimer (like encapsulating it within a micelle). This is particularly attractive for hydrophobic drugs which can be difficult to get into the highly aqueous body.

Oligomers, Polymers and Dendrimers

- The figure below shows the structure of a dendrimer being tested for activity in a gel intended to reduce HIV infection. Can you find the building blocks?

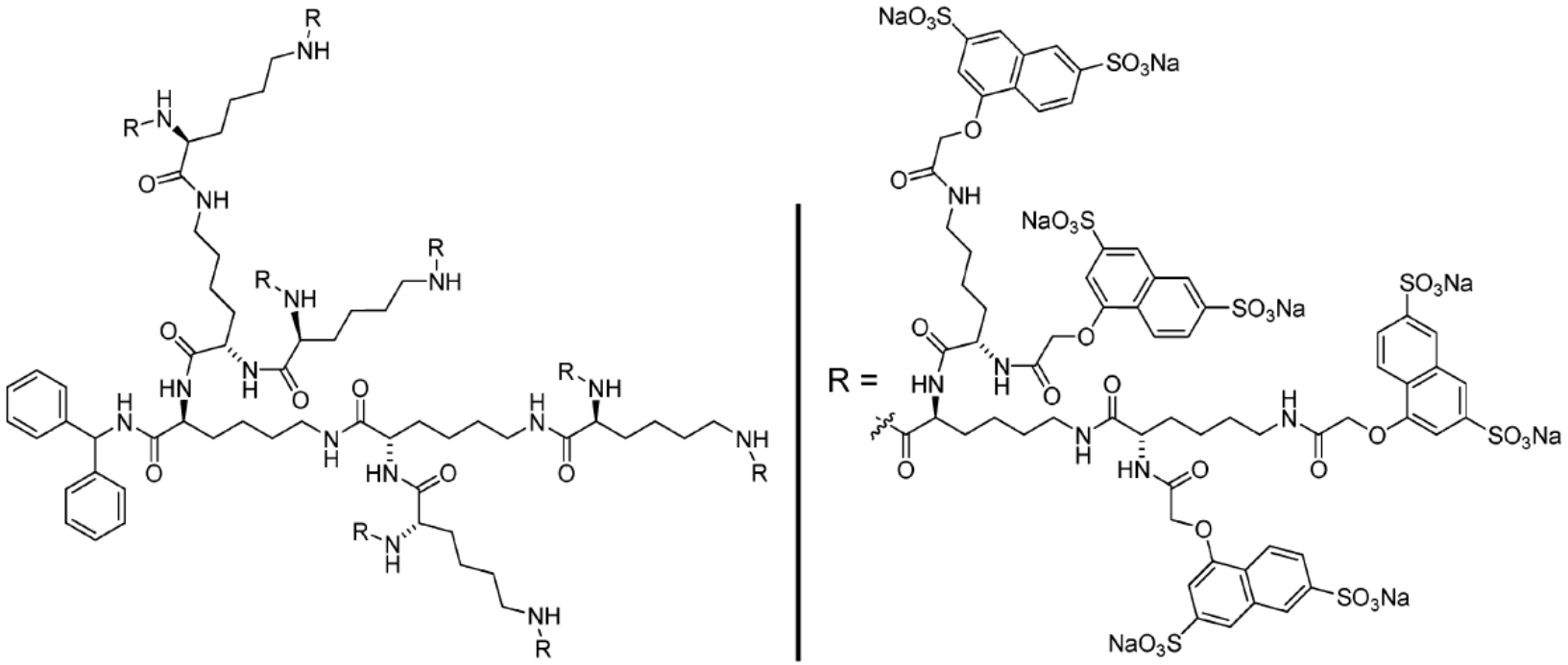
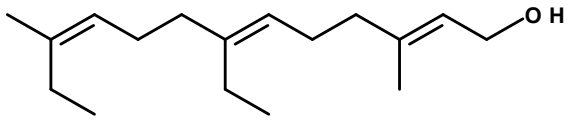


Figure 6. Chemical structure of SPL7013, the dendrimer antiviral in VivaGel.

T.D. McCarthy *et al.* Molecular Pharmaceutics (2005) **2** , 312-318

Building Blocks to Control E/Z Configuration

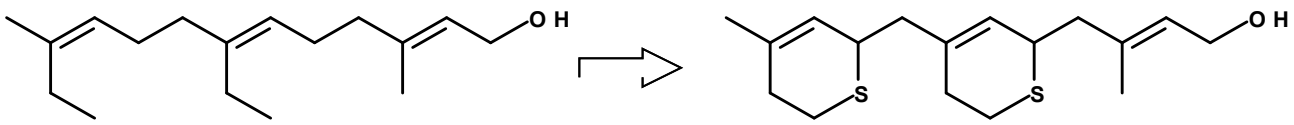
- Hoffmann introduces Chapter 4 with a synthetic approach to a hormone from produced in juvenile moths (*Cecropia sp.*):



- The greatest challenge in synthesis of this hormone is obtaining the correct configuration at each of the three double bonds. Since each double bond could be *E* or *Z*, this is one of 2^3=8 stereoisomers!
- Using building blocks in which the configuration of each double bond has already been set addresses this challenge in a straightforward way. The building blocks chosen were also intended to prevent double bond migration and/or inversion of configuration.
- What sorts of reactions could potentially lead to migration of a C=C double bond and/or inversion of configuration?

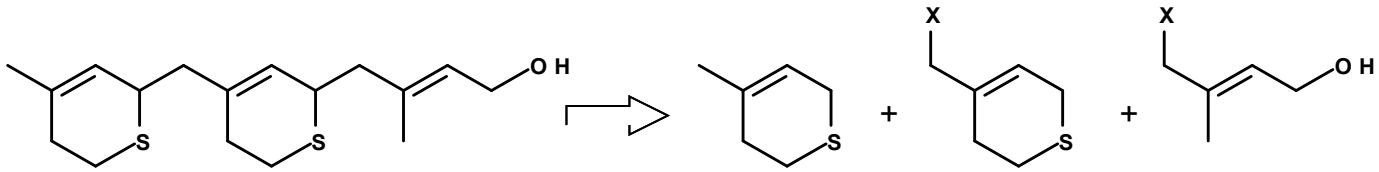
Building Blocks to Control E/Z Configuration

- The synthetic approach used rings to "lock" the *E/Z* configurations:



The authors knew that it was possible to remove the sulfur atoms via reductive desulfurization *(see sidenote)*.

- The next retrosynthetic step broke the molecule into building blocks:



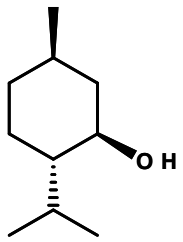
Building Blocks to Control E/Z Configuration

- Since the first two building blocks were very similar, they could be prepared from the same starting material (which the authors knew to be available):

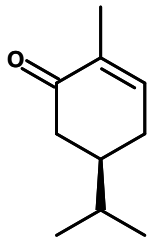
- What reactions would you use for the mini-synthesis on the left?

Building Blocks to Control R/S Configuration

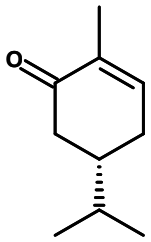
- The term "chiral pool" is used to refer to all of the chiral molecules which are readily available as starting materials for syntheses:
  - Amino acids (naturally occurring enantiomer)
  - Sugars (naturally occurring enantiomers)
  - Other chiral natural products such as menthol, camphor, carvone, limonene, pinene, cholesterol, etc.



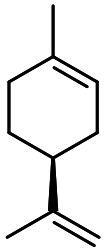
menthol



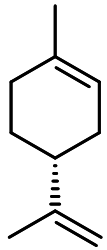
(-)-carvone



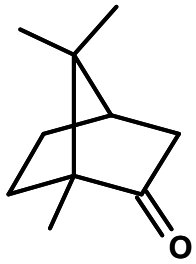
(+)-carvone



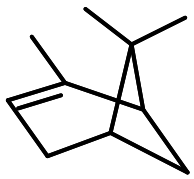
(-)-limonene



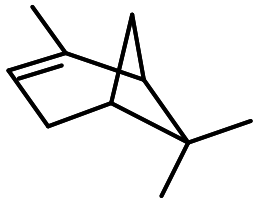
(+)-limonene



camphor



α-pinene



β-pinene

Building Blocks to Control R/S Configuration

- When chemists first attempted to synthesize enantiomerically pure products, they relied heavily on the chiral pool.

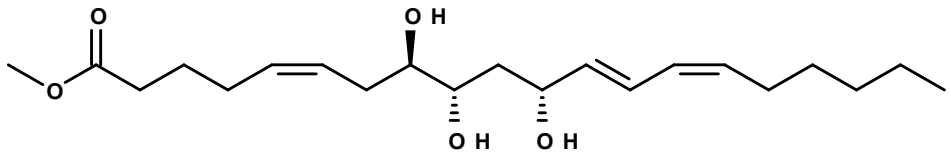
- Today, many enantioselective reactions have been developed so it is possible to make a wide variety of enantiomerically pure products from achiral materials.

- Nonetheless, if nature has already set up a series of chirality centers (and if the starting material is relatively affordable), there is no reason we shouldn't take advantage of that – particularly if the chirality centers are contiguous or if one or more of them are quaternary carbon atoms.

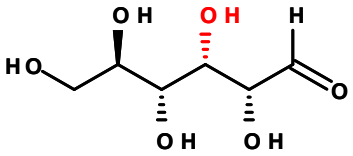
I don't expect you to memorize the chiral pool. If you need the structure of a sugar, amino acid or one of the molecules on the previous page, you'll be given it. Of course, you might be given other structures too, so you need to learn how to recognize which molecules could be useful…

Building Blocks to Control R/S Configuration

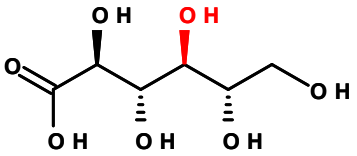
- For example, when the compound below was synthesized, the sequence of chirality centers with –OH groups was noted.



- Sugars are well-known as naturally occurring substances containing series of chirality centers with –OH groups. One approach would therefore be to identify a sugar containing –OH groups with the appropriate configuration at each of those chirality centers. Two possibilities are shown below. D-glucose is much more widely available than L-gulonic acid and was therefore chosen. *The –OH groups in red would have to be removed as part of the synthesis.*



D-glucose



L-gulonic acid

Sidenote – Reductive Desulfurization

- Sulfur can be very useful in an auxiliary functional group.
- This is partly because sulfur-containing groups can be either electron donating or electron withdrawing, depending on the oxidation state of sulfur and it is easy to oxidize the sulfur to take advantage of both types of reactivity:

Sidenote – Reductive Desulfurization

- This is partly because sulfur-containing groups are easily removed.
  - In the chapter 3 notes, we saw two methods for cleavage of an arylsulfonyl group – one giving an alkane and one giving an alkene. Both involved reducing agents and radical mechanisms:
  - In the synthesis of the juvenile moth hormone, we also saw that it is possible to excise a sulfur atom from a disulfide, replacing the C-S bonds with C-H bonds. This also involves a reducing agent and radical mechanism.

Sidenote – Reductive Desulfurization

- Common reducing agents for reductive desulfurization include:
  - Alkali metal dissolved in amine (Na in NH_3, Li in ethanamine, etc.)
  - Raney nickel (an alloy of nickel and aluminium that has been treated with NaOH; see Sorrell, pp. 374-375)

- These reagents both serve as sources of $H^{\cdot}$ (proton + electron).
  - Na in NH_3

  - Raney nickel

Sidenote – Reductive Desulfurization

- The exact mechanism for reductive desulfurization is not known; however, it is generally accepted to be a radical mechanism and likely proceeds something like:

Sidenote – Reductive Desulfurization

- Both C-S bonds are cleaved in reductive desulfurization.
  - In some cases, both carbon atoms will still be in your desired product:

  - In other cases, you may cleave an -SR group from your product (possibly not caring that your other two products are H_2S and RH):

Sidenote – Reductive Desulfurization

- This makes for a handy way to get rid of a carbonyl group, allowing for them to be used as auxiliary functional groups…