Ruben Martinez

Creativity From The Chiral Pool: Sugar Edition

Baran Group Meeting
06/30/14

Disclaimer

This group meeting is in no way meant to be comprehensive. There is an enormous body of literature featuring sugar starting materials in total synthesis of which this group meeting is only a sample. Any comparison made between syntheses are for educational and discussion purposes only.

Resources

The following books and reviews are excellent resources and were very helpful in the preparation of this group meeting.

Total Synthesis of Natural Products: The "Chiron Approach"
Stephen Hanessian ISBN-10: 0080307159

Design and Strategy in Organic Synthesis
Stephen Hanessian ISBN-10: 3527319646

Organic Synthesis with Carbohydrates
Geert-Jan Boons ISBN-10: 1850759138

			World production [a] (metric t/year)	Price [b] (€/kg)
Sugars	Sucrose		130.000.000	0.30
	D-Glucose		5.000.000	0.60
	Lactose		295.000	0.60
	D-Fructose		60.000	1.00
	Isomaltulose		50.000	2.00
	Maltose		3.000	3.00
	D-Xylose		25.000	4.50
	L-Sorbose		60.000	7.50
Sugar Alcohols	D-Sorbitol		650.000	1.80
	D-Xylitol		30.000	5.00
	D-Mannitol		30.000	8.00
Sugar-derived Acids	D-Gluconic	aci	60.000	1.40
	L-Lactic	aci	> 100.000	1.75
	Citric	aci	500.000	2.50
	L-Tartaric acid		35.000	6.00
Amino Acids	L-Lysine		40.000	5.50
	L-Glutamic acid		500.000	7.00

Natural Abundance

Carbohydrates are the single most abundant class of organic compounds associated with living matter.

ACS Symposium Series 841 **2003**, 47.

Is sugar derived chirality right for me?

- End differentiated oxidation state
- Stereochemical diversity
- Carbon chain length varying between 3-7 carbons
- Strong conformational bias
- Ability to introduce other heteroatoms (N, S, X) with inversion or retention of configuration
- Ability to branch using a C nucleophile
- Excellent conformational bias and stereoelectronic effects maximize predictive outcomes based on models

Why don't we see more syntheses based on chiral sugars?

- Overfunctionaliztion with hydroxyl groups that have similar or identical reactivity
- Number of chiral centers present on starting carbohydrate often excessive for the synthetic chemist
- Lack of suitible functional groups (olefin, carbonyl) to which modern organic techniques can be applied
- Outcome of chemical transformations are unique to each sugar based on individual stereochemistry
- Development of outstanding asymmetric methodology

Full exploitation of sugar starting materials

- Retention of the carbon-chain of the sugar
- Reaction sequence should be simple, high yielding with no chromatography. Focus on generating crystaline products.
- Avoid protecting groups or use simple, easy to remove PGs
- Cost.

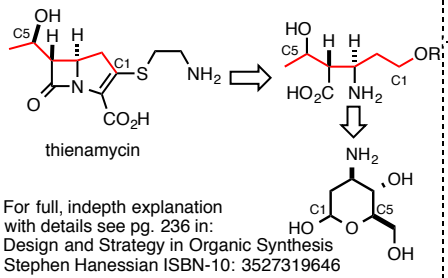
On practicality: reality vs. raw concept

There are a huge variety of chiral carbohydrates available in principle. However, the pool shrinks immensely when practical and operational considerations are applied leaving a relatively small number of realistic chiral sugar starting materials.

Tracking Treasure Down: Hanessian's "Rule of Five"

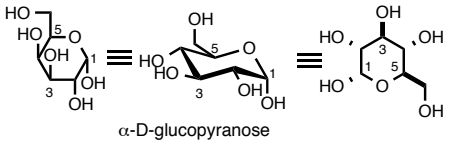
1) Select an sp, sp^2, or sp^3-hybridized carbon atom in target structure
2) Move five bonds away and look for a heteroatom regardless of functionality in between. These two internal reference points correspond to the anomeric C-1 and the C-5 oxygen atoms in the hexapyranose structure
3) Look at only that carbon chain and try to imagine a suitible chiral sugar SM.

An Example:



For full, indepth explanation with details see pg. 236 in:
Design and Strategy in Organic Synthesis
Stephen Hanessian ISBN-10: 3527319646

Different Representations

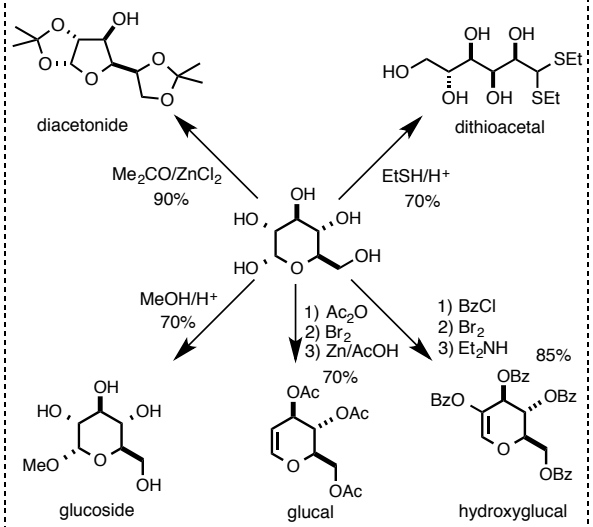


Molecular Target Categories

The target structure can be broken down into three categories based on how easily it can be traced back to the chiral carbohydrate pool.

Typical Reaction Channels

Working from a feedstock carbohydrate is difficult, time consuming and wasteful. Entry into any reaction channel toward an enantiopure building block is mostly limited to chemistry dating back over 100 years in the carbohydrate literature. The initial stage always involves the fixation of the sugar in the respective tautomeric form.



Cat. 1: Apparent Carbohydrates

Usually a lightly modified carbohydrate appended to a structure via glycosidation. Very easy to spot.

Cat 2: Partially hidden carbohydrates

One or two chiral centers may have been removed. Still contains carb. oxidation pattern. Identification likely requires squinting.

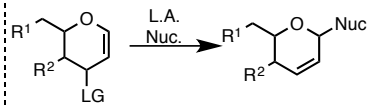
Cat. 3: Totally Hidden Carbohydrates

Identification of carb. SM unlikely. Usually based around application of in-house methodology.

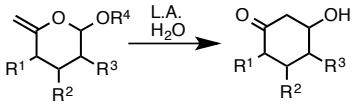
*These are my simplified definitions based on Hanessians own in depth definitions, examples and analysis.

Important Reactions to Keep In Mind

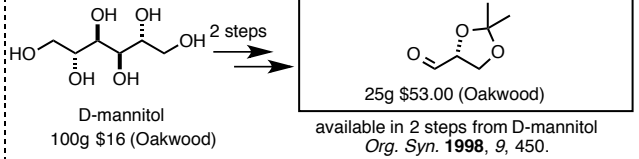
Type I Ferrier reaction



Type II Ferrier rearrangement



Arguably the Most Useful Sugar Based "Chiron" for Modern Total Synthesis



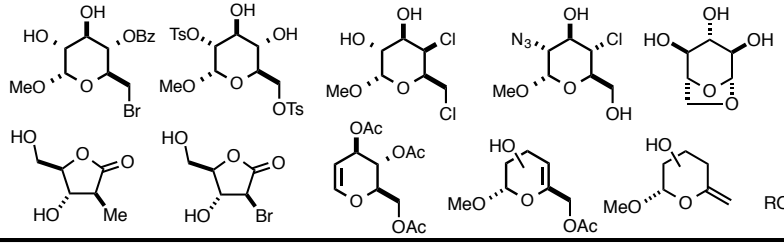
D-mannitol
100g $16 (Oakwood)

available in 2 steps from D-mannitol
Org. Syn. **1998**, *9*, 450.

For every one unit of D-mannitol subjected to protection/oxidative cleavage two desired aldehydes are formed. The resulting aldehyde is higly prone to polymerization and hydrolysis. Long term storage is not recommended

For (*S*)-derivative see:
Org. Syn. **1995**, *72*, 1.
Synlett **2001**, *10*, 1565.

Some Easily Accessible/Commercial/Useful Sugar Based Chirons



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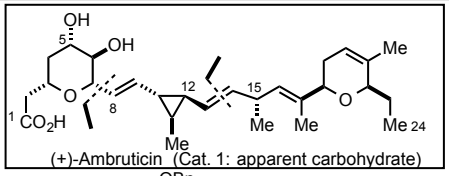
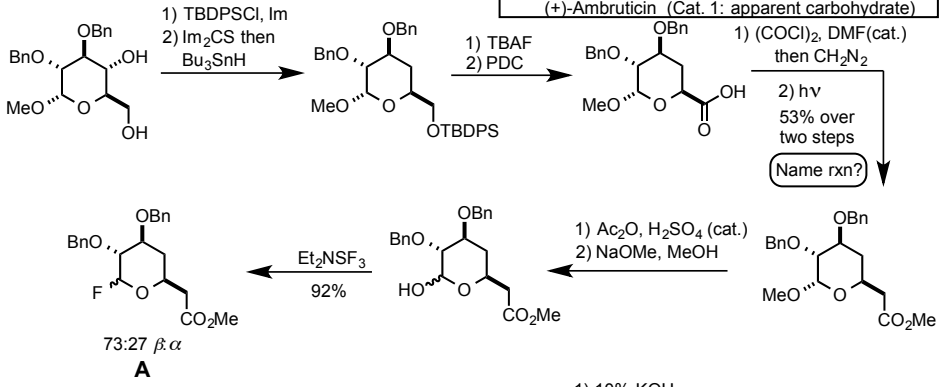
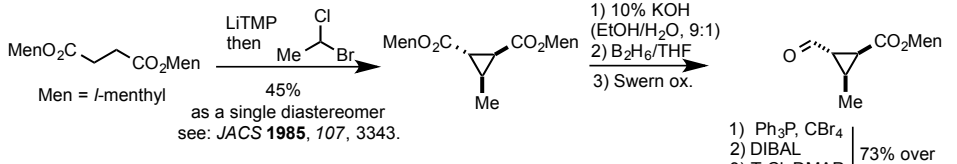
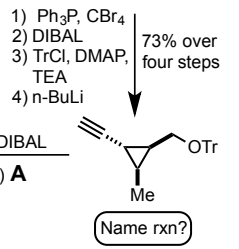
Total Synthesis of (+)-Ambruticin
Kende's chiral sugar approach

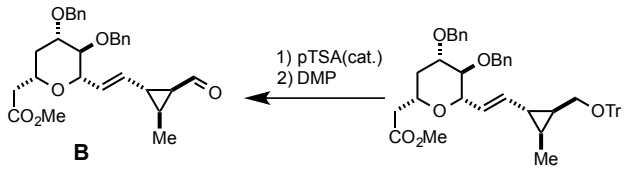
Kende, A. *J. Am. Chem. Soc.* **1990**, *112*, 9645.

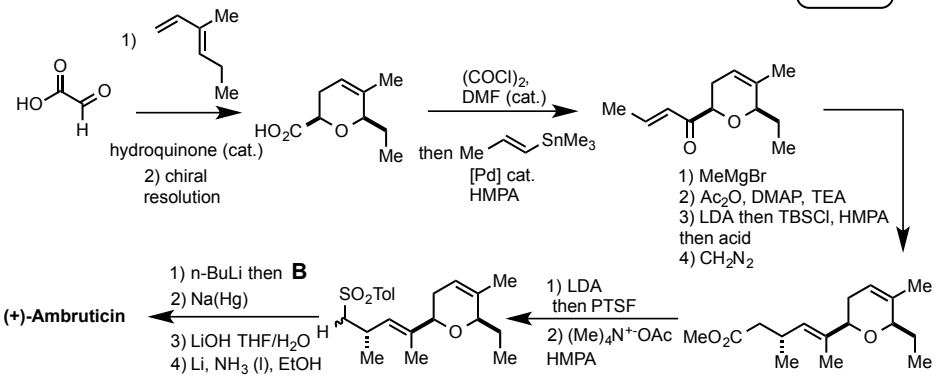






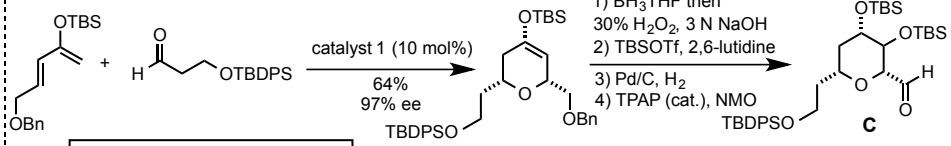


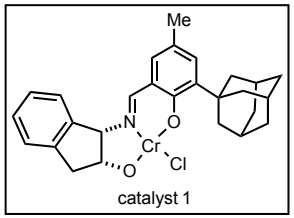


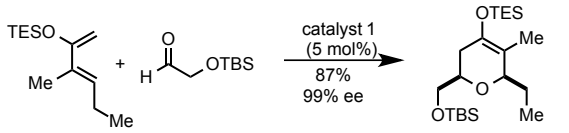


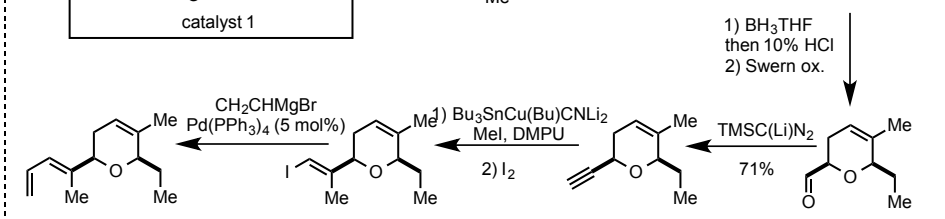
Total Synthesis of (+)-Ambruticin
Jacobsen's asymmetric catalysis approach

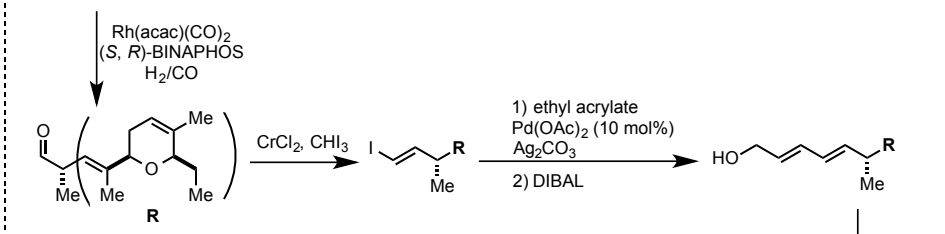
Jacobsen *J. Am. Chem. Soc.* **2001**, *123*, 10772.

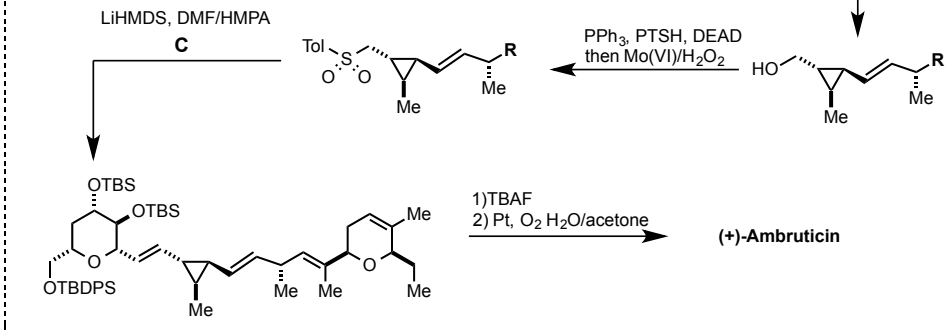












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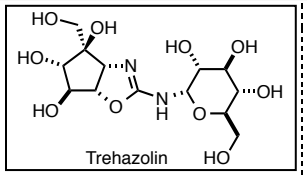
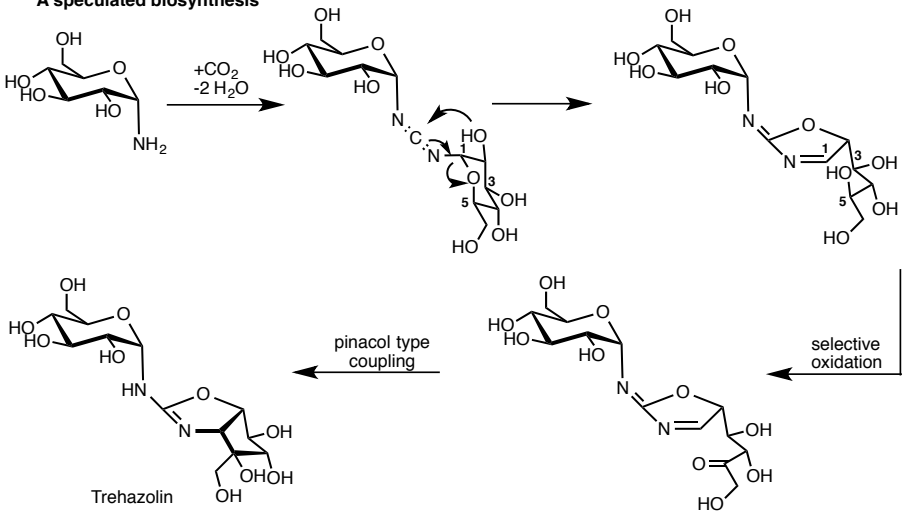
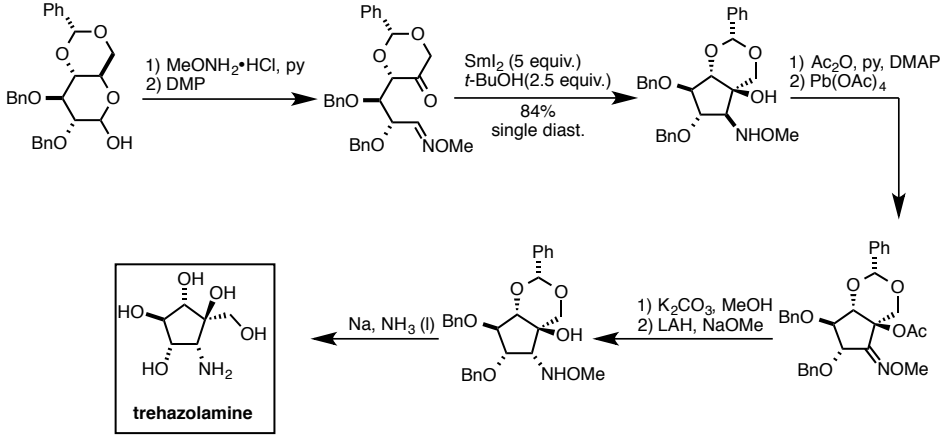
Synthesis of Trehazolin from D-Glucose: following a plausible biosynthesis
Giese, B. *J. Org. Chem.* **1998**, *63*, 5877.
Trehazolin from trehazolamine is known in the literature see *J. Org. Chem.* **1994**, *59*, 813.

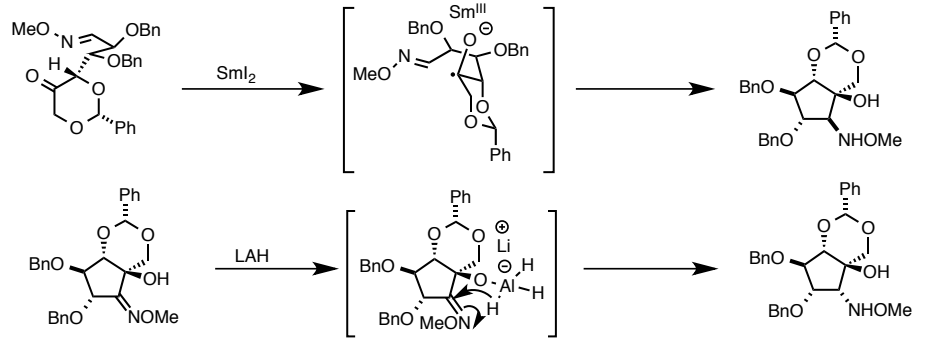


A speculated biosynthesis

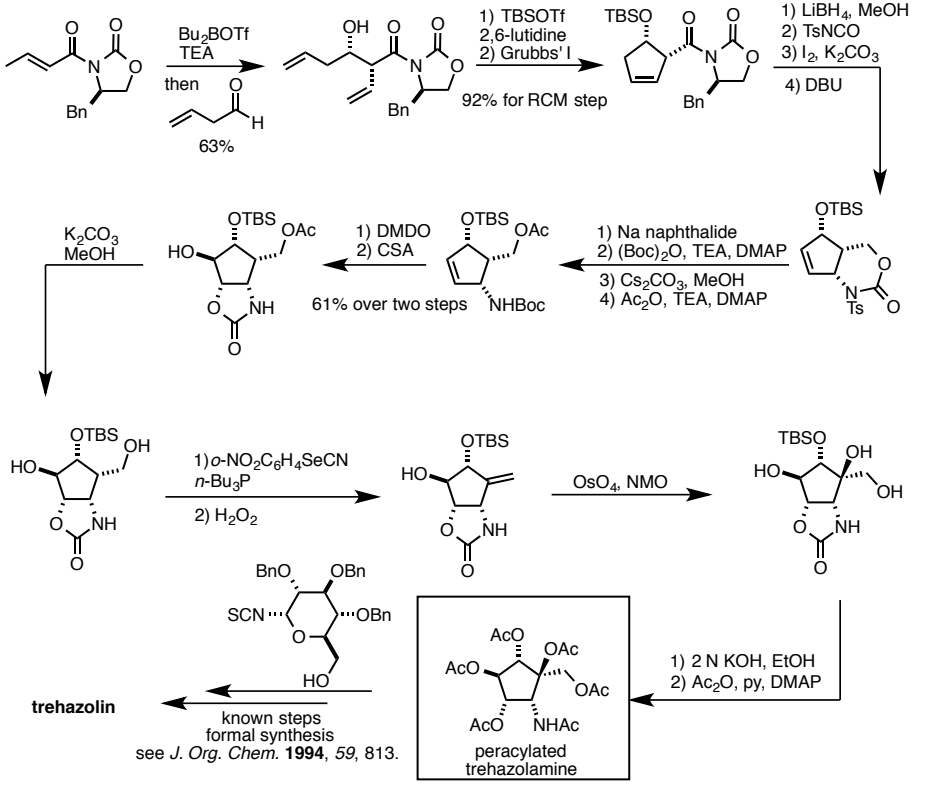


Giese's reductive cyclization approach





The Crimmins' Synthesis of Trehazolin: The chiral auxiliary and RCM approach
J. Org. Chem. **2001**, *66*, 4012.



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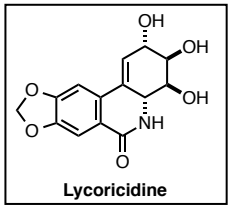
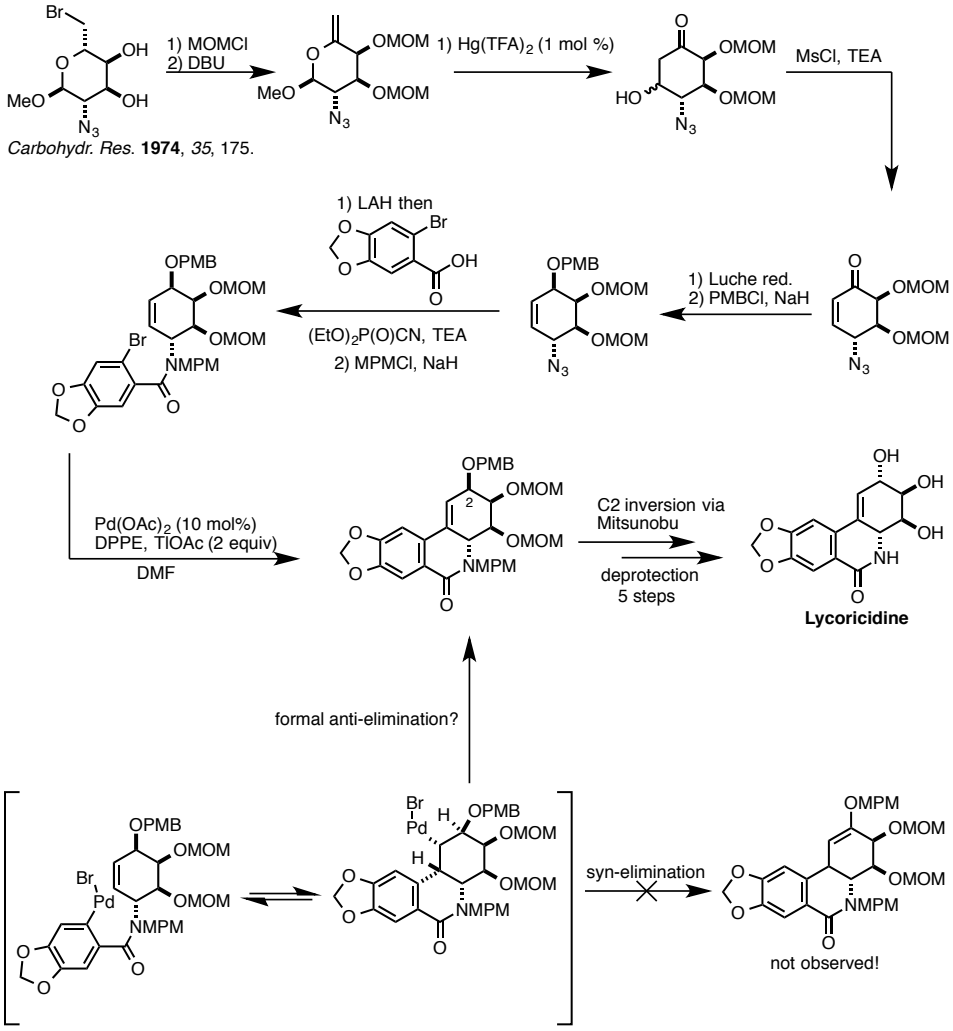
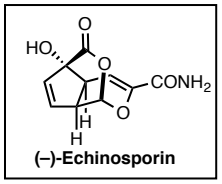
Total Synthesis of (+)-Lycoricidine from D-Glucose
Ogawa, S. *J. Org. Chem.* **1993**, *58*, 4441.

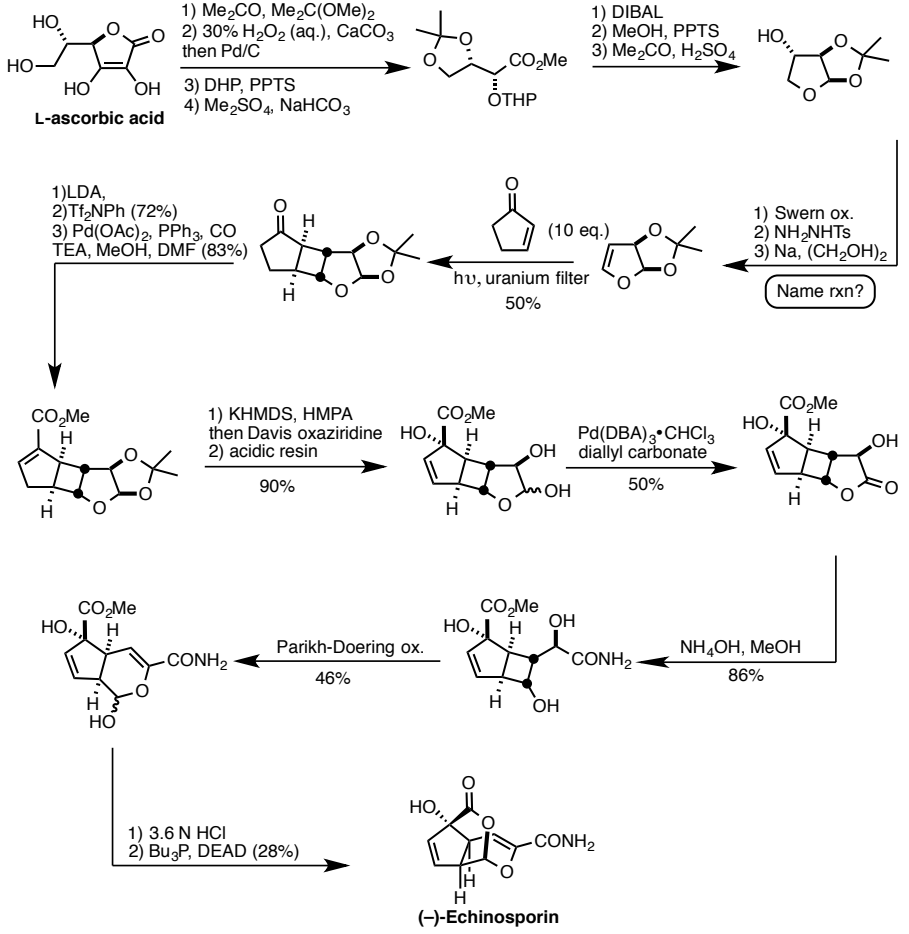




Carbohydr. Res. **1974**, *35*, 175.

Total Synthesis of Echinosporin
Smith III, A. *J. Am. Chem. Soc.* **1989**, *111*, 8039.





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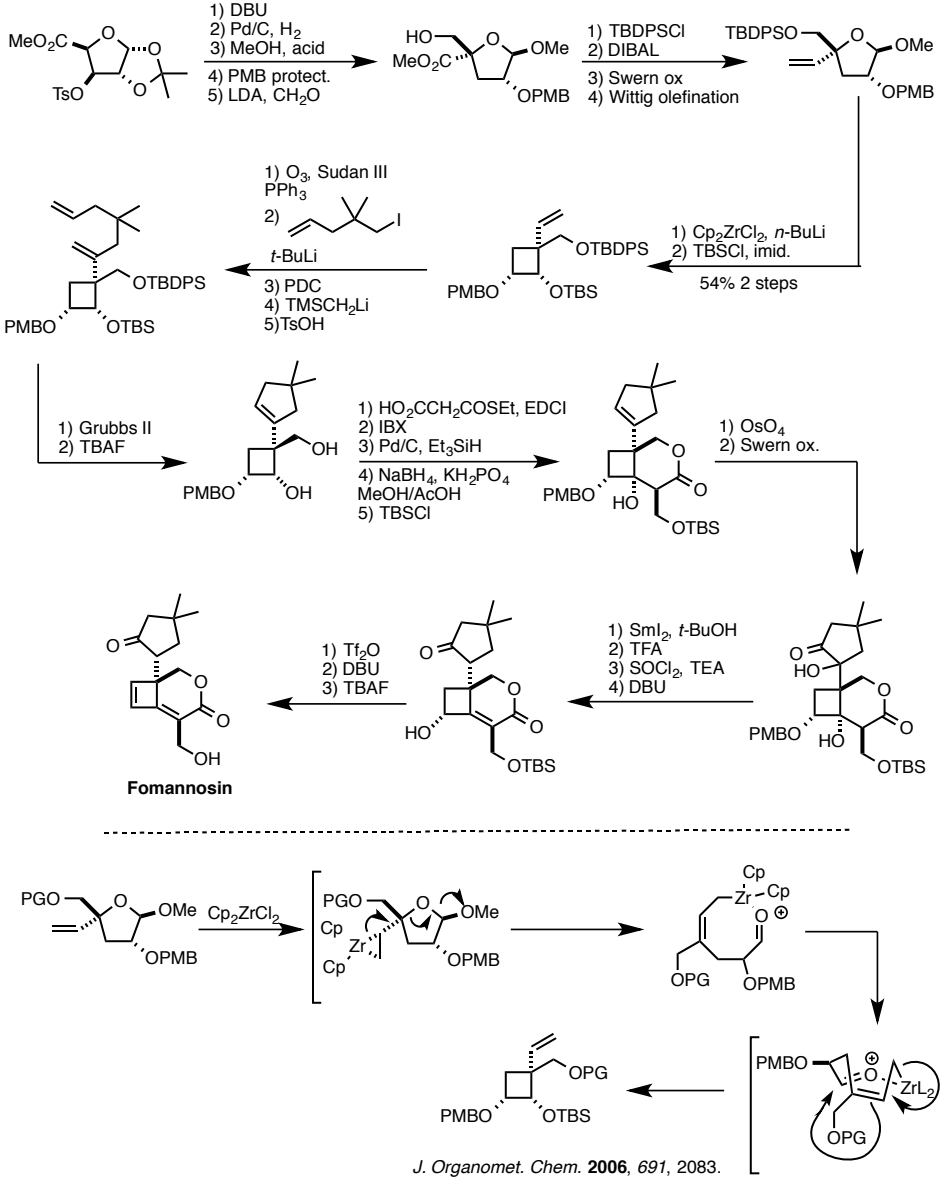
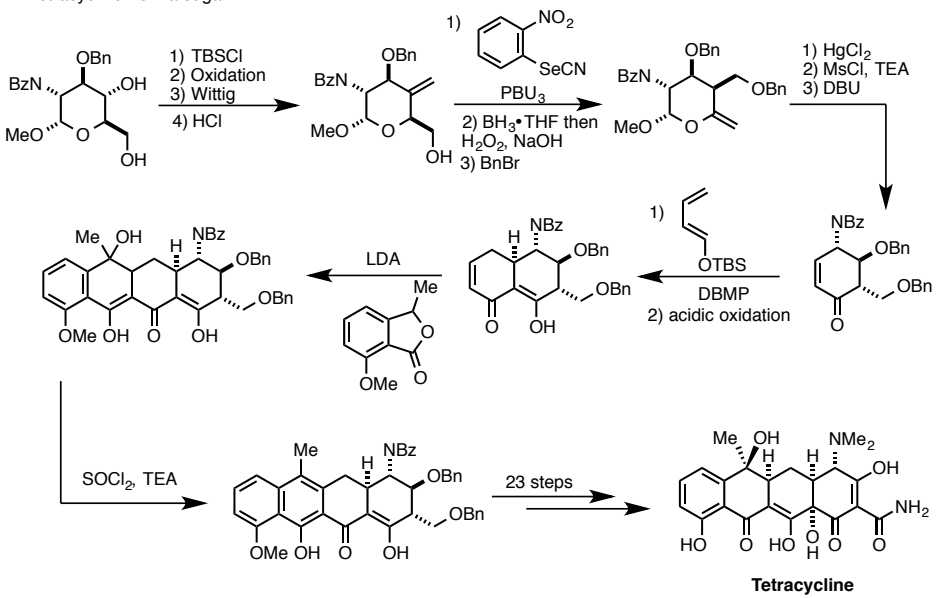
Total Synthesis of Fomannosin
Paquette, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 7817.



J. Organomet. Chem. **2006**, *691*, 2083.

Total Synthesis of (–)-Tetracycline
Tatsuta, K. *Chem. Lett.* **2000**, 647.

Tetracycline from a sugar?



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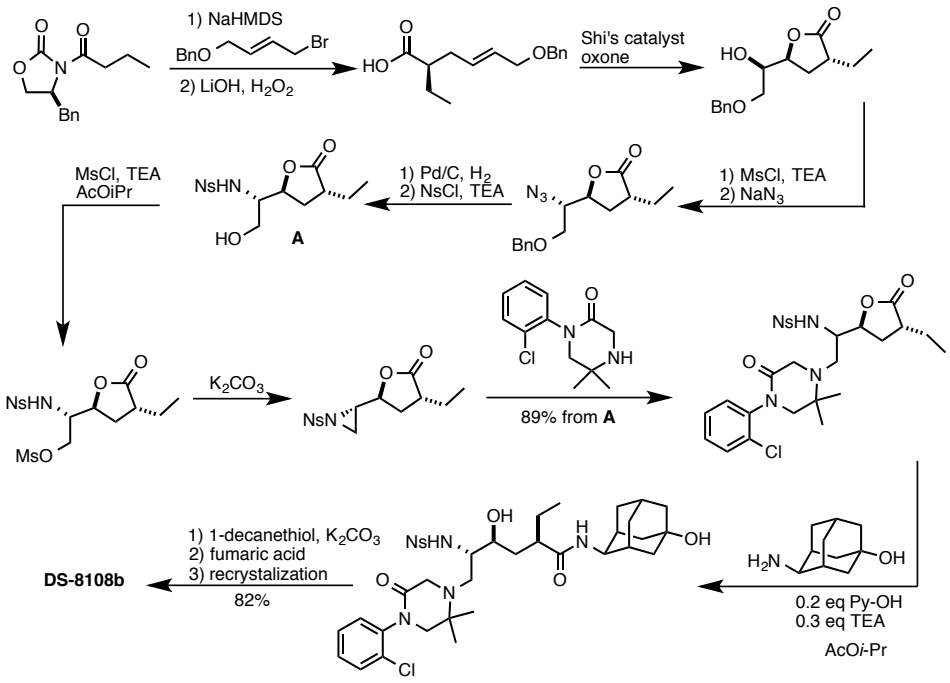
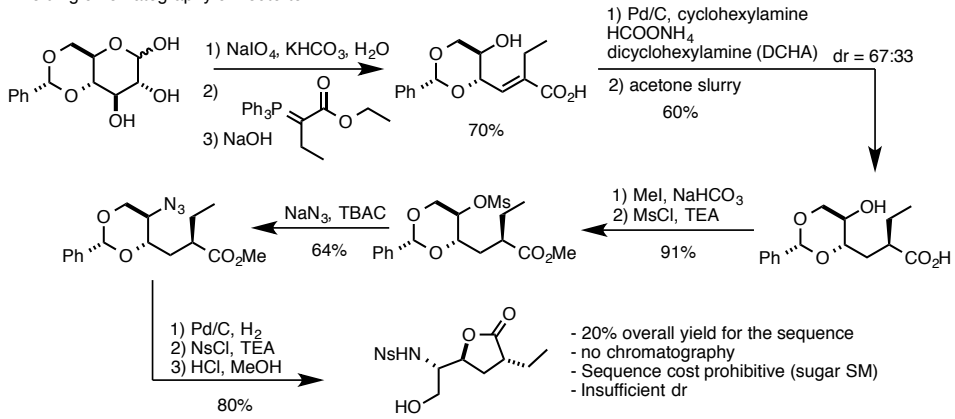
Synthesis of DS-8108b: from chiral aux to sugar and back
Daiichi Sankyo Co. *Org. Process Res. Dev.* **2013**, *17*, 1430.

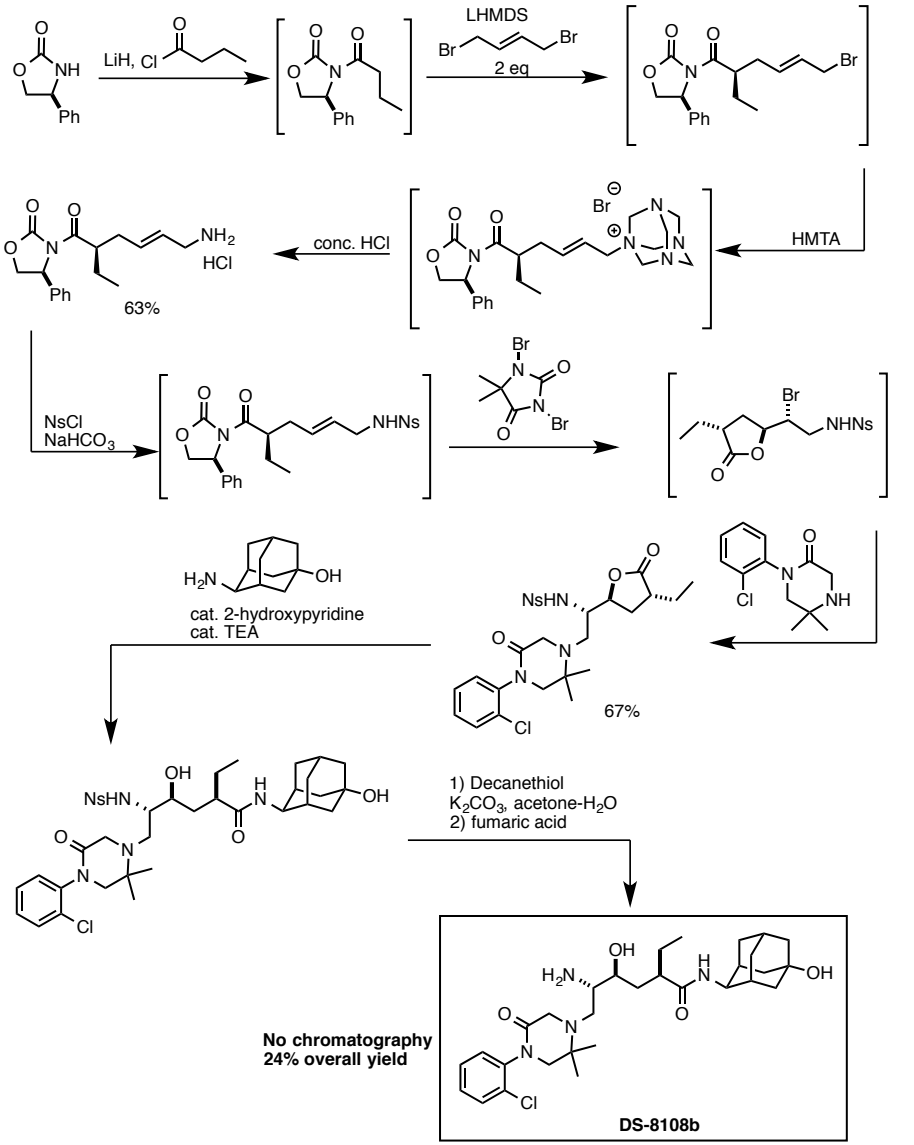
Early-stage synthesis



So where does the sugar come in?
Avoiding chromatography en route to **A**



DS-8108b continued
Sugars: just a bridesmaid, back to the chiral auxiliary
Can your sugar do this?



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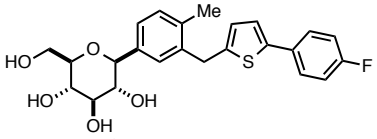
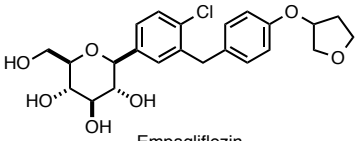
Sugars: What are they good for?

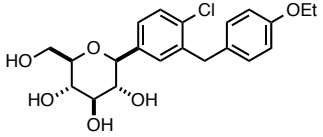
SGLT2 inhibitors. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of drugs for the treatment of type 2 diabetes. Type 2 diabetes affects 23 million Americans making this area particularly interesting for the development of novel treatments.



Canagliflozin
FDA approved



Empagliflozin
limited European approval



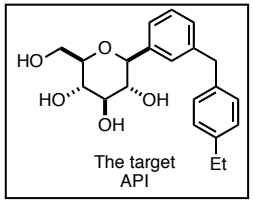
Dapagliflozin
limited European approval

SGLT2 inhibitors, how do they work?

The SGLT family includes the Na/glucose co-transporter SGLT1, which is mainly expressed in the GI tract and is responsible for glucose absorption from the food intake. SGLT2 is mainly expressed in the kidneys. SGLT2 is responsible for ~90% of glucose reabsorption in humans. SGLT2 inhibitors work by blocking the reabsorption of glucose in the kidneys. This prevents the build up of glucose in the blood and allows for excess glucose to be eliminated via urination. One of the most common side effects is genital infection.

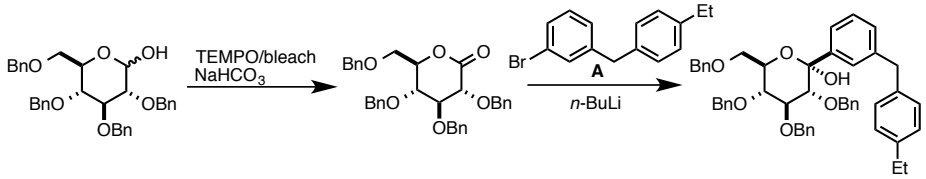
For an indepth discussion see: *Current Pharmaceutical Design* **2014**, *20*, 3647.

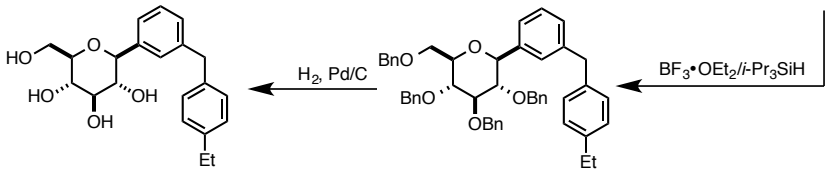
Development of a large scale synthesis of an SGLT-2 inhibitor
Bristol-Myers Squibb *OPRD* **2012**, *16*, 577.



The target API

First-generation synthesis





Process R & D synthetic route: a tale of two protecting groups