2 Jun 2010

- Discussion of aldolase paper
- Problems 1-5 on measuring enantiomeric purity

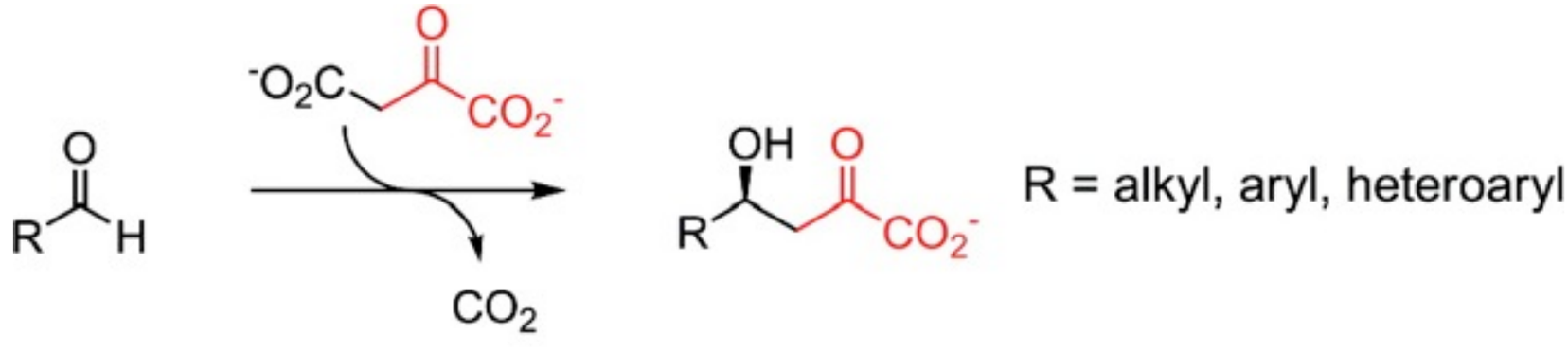
Gillingham et al. (2010) Chemoenzymatic synthesis of differentially protected 3-deoxysugars, *Nat. Chem.*, **2**, 102-105.

- *Da Hye:* Describe the reaction catalyzed by macrophonate synthase; what is its purpose in biosynthesis.
- *Eunok:* MPS initially gained attention because the enolate addition to the pyrone appeared to involve a rare example of a Diels-Alder reaction catalyzed by an enzyme. Explain the importance of this issue and what the current thinking is.
- *Taeho:* Why are 3-deoxy sugars important? What is the Cornforth synthesis and why is it not a good solution?
- *Hoe-suk:* MPS also catalyzes the simple aldol addition of pyruvate enolate to different aldehydes. Describe this reaction. How is this an example of a promiscuous catalytic reaction? What are the common mechanistic steps in both reactions?
- *Joon-ho:* In previous work, Hilvert and coworkers reported the reaction in Figure 1. Explain this reaction including what matched and mismatched mean.
- *Il-Hyang:* Explain how the compounds made in figure 1 can be converted to 3-deoxy sugars (see Figure 2). Also explain the other reactions in Figure 2. Be able to draw an arrow-pushing mechanism for these reactions.
- *Ahram:* Explain this statement: Diisopropylidene-protected sugars work efficiently in both the L- and D-sugar series (see, for example, 10a and 10b in Table 1). In contrast to 8, where the mismatched substrate enantiomer gave only a 4:1 diastereomeric ratio (see 8b to 9b in Fig. 1), the homologated sugar 10 led to the formation of products 16a, 16b and 16c in high diastereoselectivity irrespective of the aldehyde configuration.
- *Yun-Hee:* Explain the authors' rationalization for why MPS favors formation of the S configuration in the aldol addition (Figure 3).

Homework

- Study for final exam next week

The importance of macrophomate synthase



Advantage

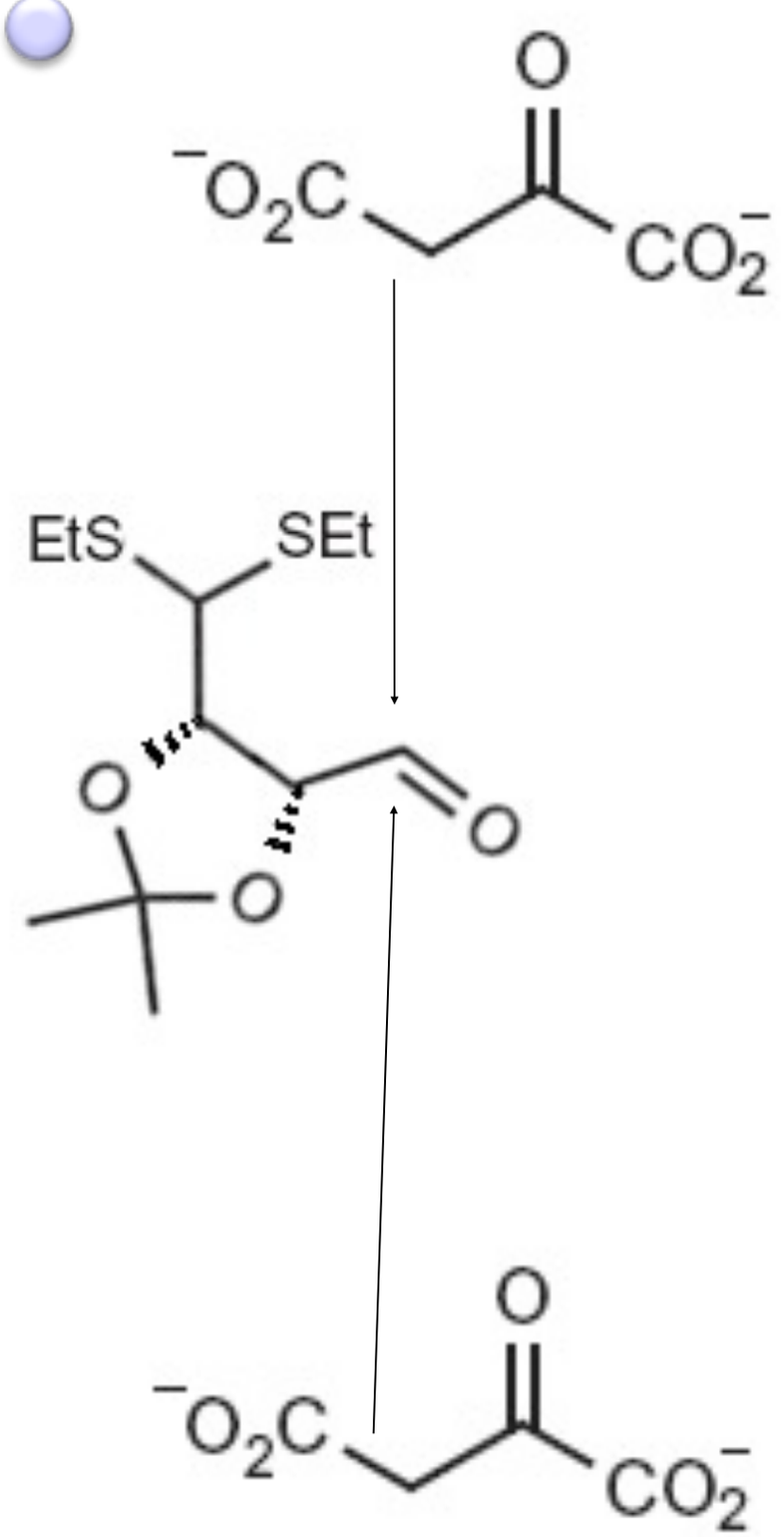
1. Use Various aldehydes as substrate

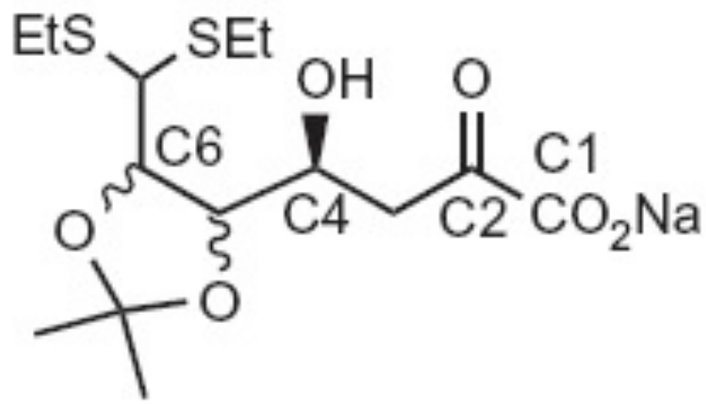
2. Remarkable tolerance to substrate size and shape

3. Glyceraldehyde derivatives can enhance MPS diastereoselectivities

= > MPS might provide a mild and practical route to various 3-deoxysugars

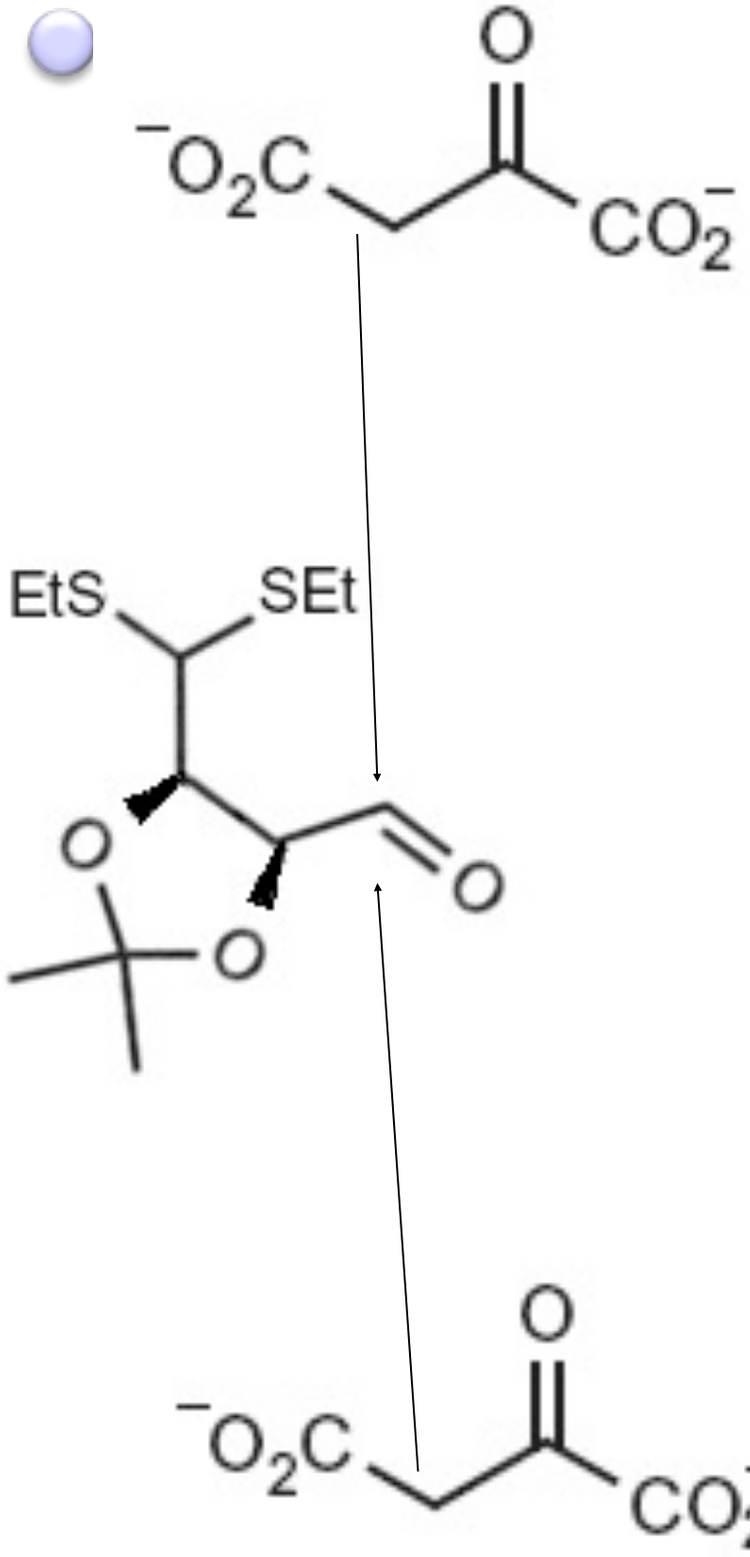
J. Am. Chem. Soc. **2008,** 130, 7798-7799.

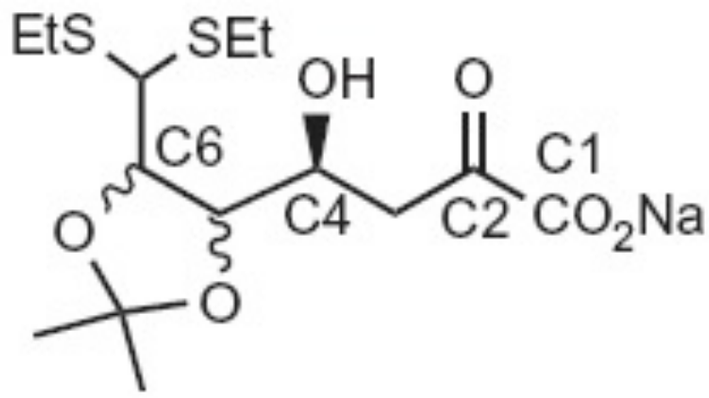




9a, >19:1 d.r., 77 % yield, (4*S*,5*S*,6*S*)

Matched!



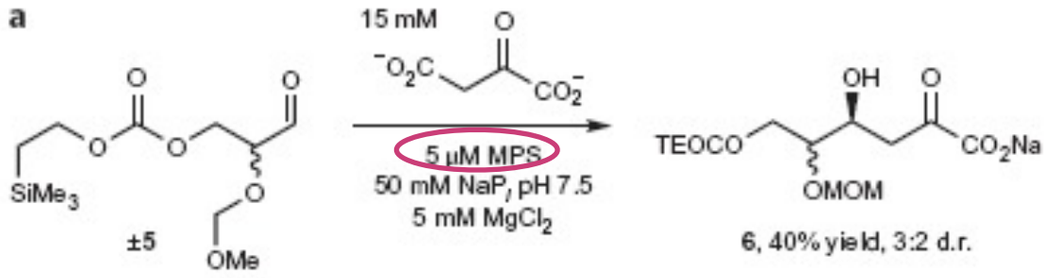


9b 4:1 d.r. 75 % yield, (4*S*,5*R*,6*R*)

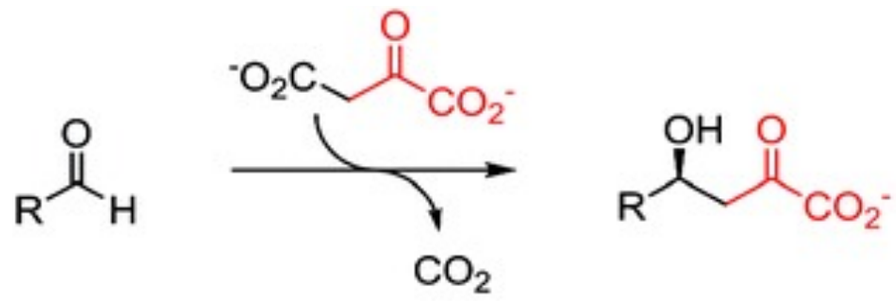
Mismatched!

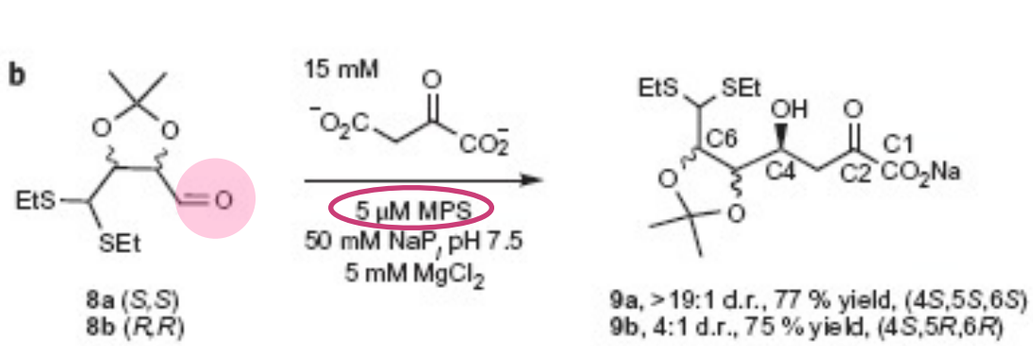
• Explain how the compounds made in Figure 1 can be converted to 3-deoxy sugars (see Figure 2)
• Also explain the other reactions in Figure 2

MPS-catalysed synthesis of representative 3-deoxysugars

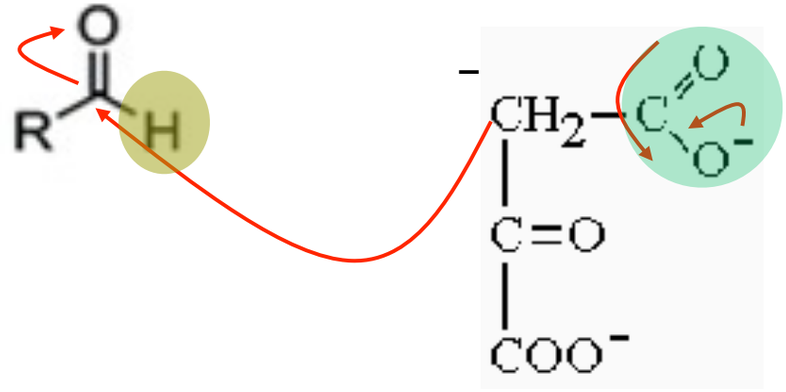


Triose aldehyde is readily converted to the differentially Protected 3-deoxysugar derivate





Both enantiomers of thioacetal tetrose are accepted as substrate by MPS

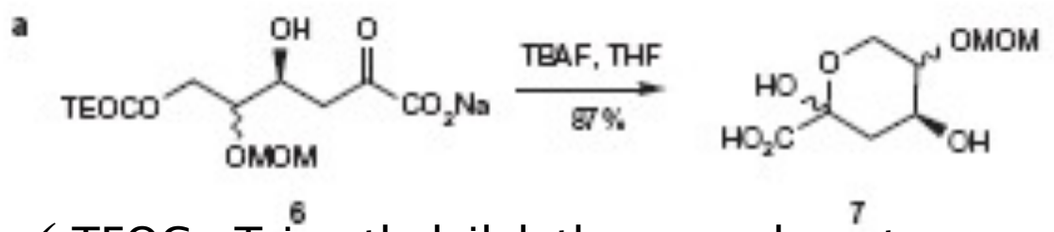


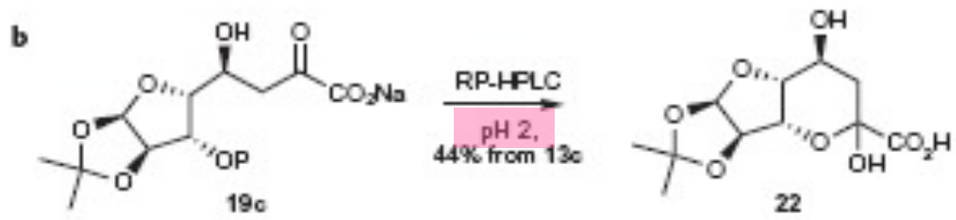
<Native reaction mechanism of MPS>

"The putative Diels-Alderase Macrophomate Synthase is an Efficient Aldolase", JACS, 2008, 130, 7798-7799

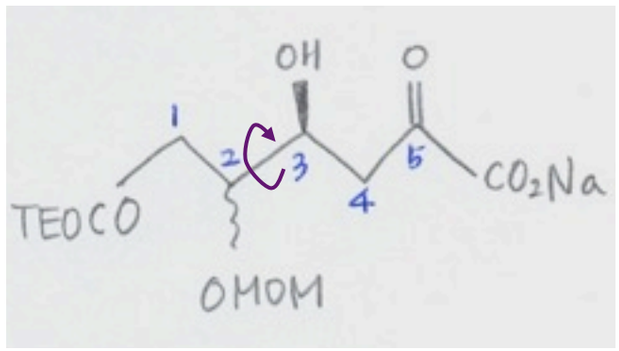
• Explain how the compounds made in Figure 1 can be converted to 3-deoxy sugars (see Figure 2)
• Also explain the other reactions in Figure 2

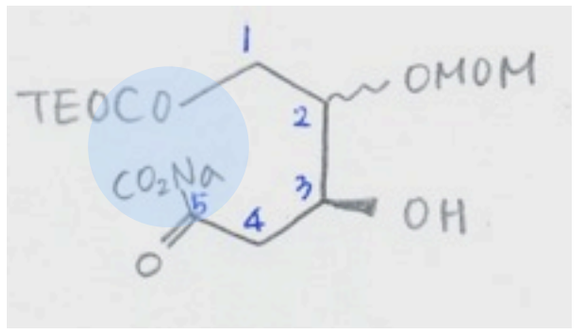
Selective deprotection of 3-deoxysugar derivatives provides strategic control of ring-closure

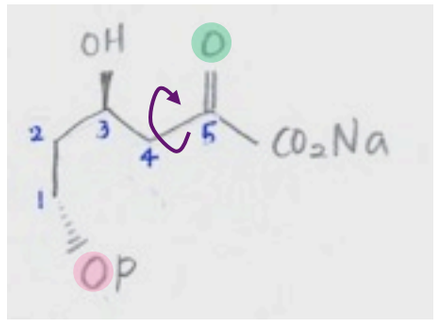


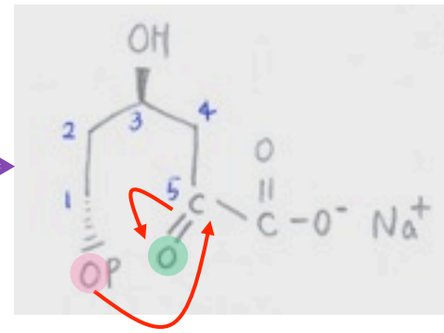


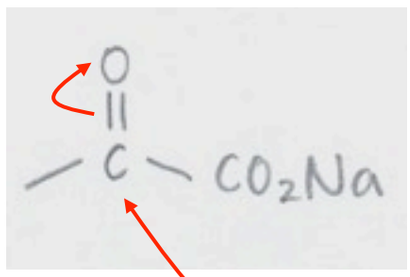
✓ TEOC : Trimethylsilylethoxy-carbonate → protecting group
✓ Cleavage the TEOC group is cleaved by TBAF in THF

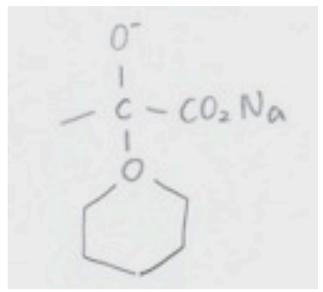


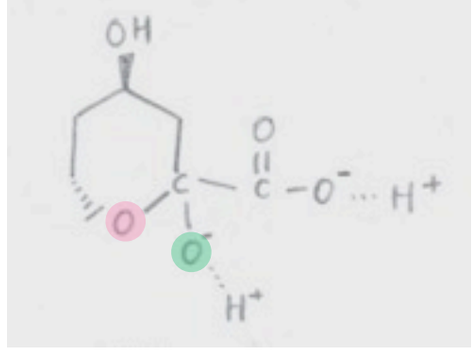


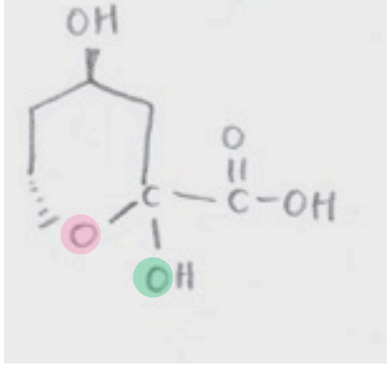












• Explain how the compounds made in Figure 1 can be converted to 3-deoxy sugars (see Figure 2)
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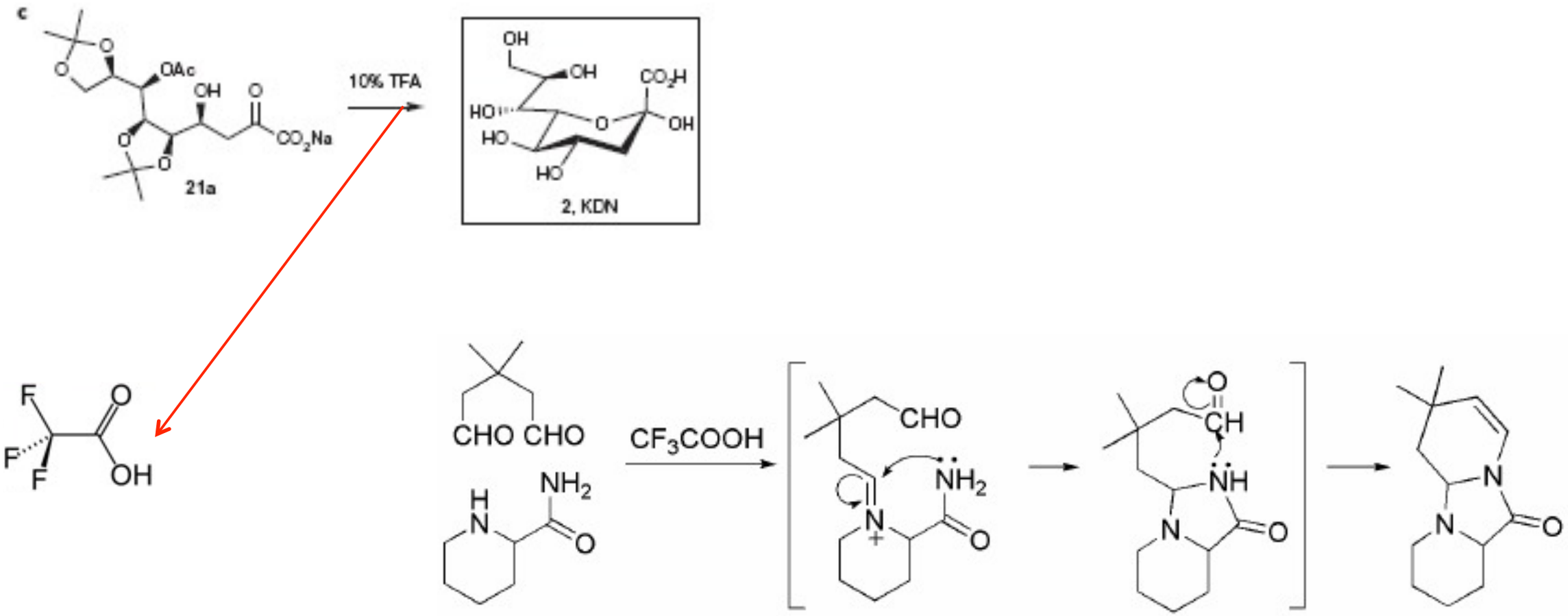
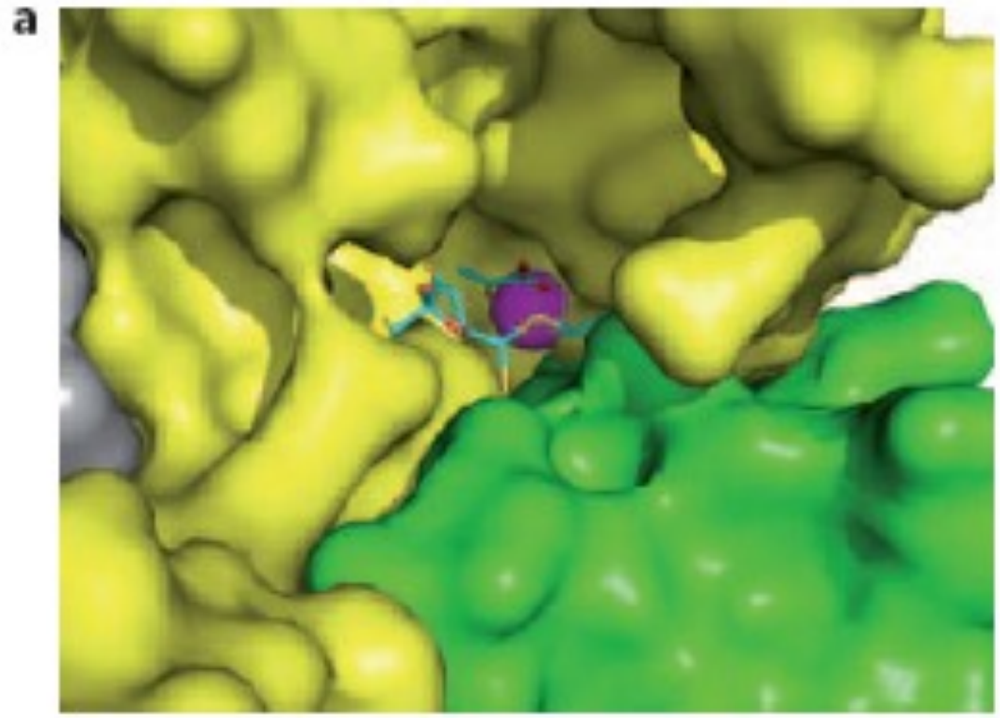
Selective deprotection of 3-deoxysugar derivatives provides strategic control of ring-closure



✓Ring closure reaction by TFA (CF_3COOH)



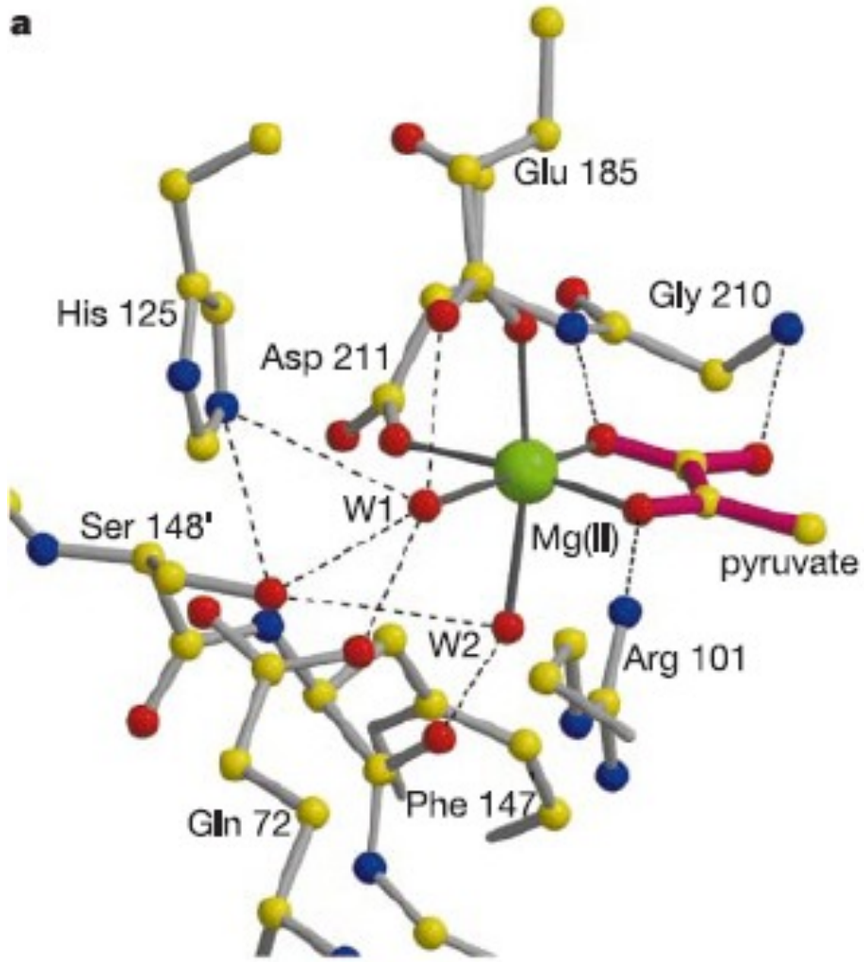
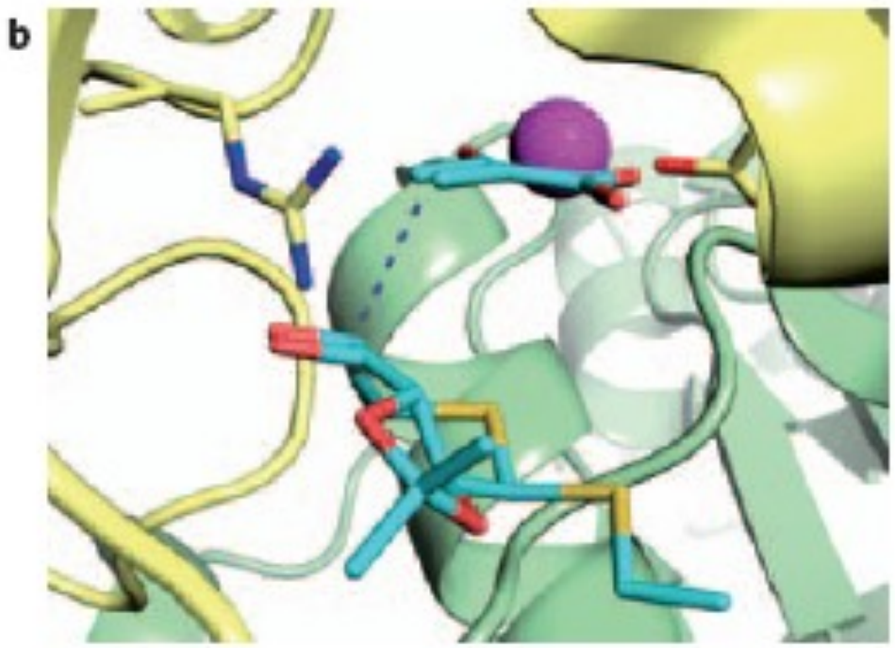


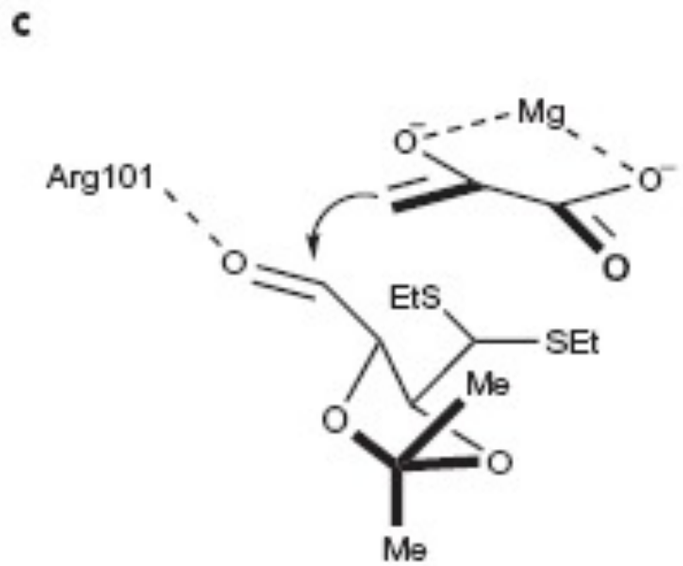
Figure 3. Structural basis for MPS promiscuity.
a, View into the MPS active site with the S,S-thioaldehyde substrate docked proximal to the magnesium-bound pyruvate enolate

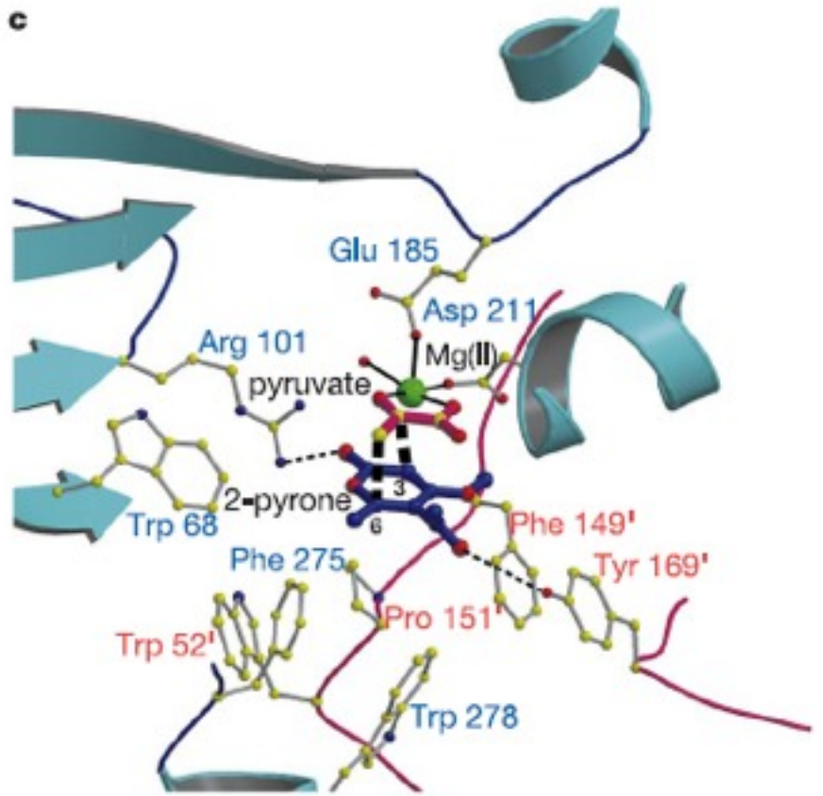
(substrate carbons are shown in teal, magnesium in magenta).

→ Active site formed at the interface of 2 subunits.
→ Wide entrance lead to deeply binding pocket.
→ Broad substrate tolerance

✓ Mg^{2+} is located in an octahedral coordination
✓ stabilized by interaction between the carbonyl oxygen of pyruvate and side-chains of Arg 101.
→ pyruvate is tightly placed at this position
→ pyruvate binding site provide the second substrate (aldehyde) binding site.
→ This space is hydrophobic and large enough to accommodate aldehyde and to allow necessary conformational change owing to the Diels–Alder reaction.







The dimensions of the binding pocket adjacent to the magnesium-bound pyruvate the preferred orientation of the aldehyde substrate.

✓ Placement of the bulky alkyl substituent in the entry chamber allows the carbonyl group to penetrate deeply into the active site and contact Arg101

→ Can orient and activate it for attack by the nearby enolate.
→ Modelled antiperiplanar arrangement of the substrates
→ Formation of the S-configured alcohol
→ Aldehyde should be aligned antiperiplanar to the enolate → open transition state in aldol rxn
→ Preference for reaction → S stereochemistry

c, Stick representation of the interactions illustrated in b.

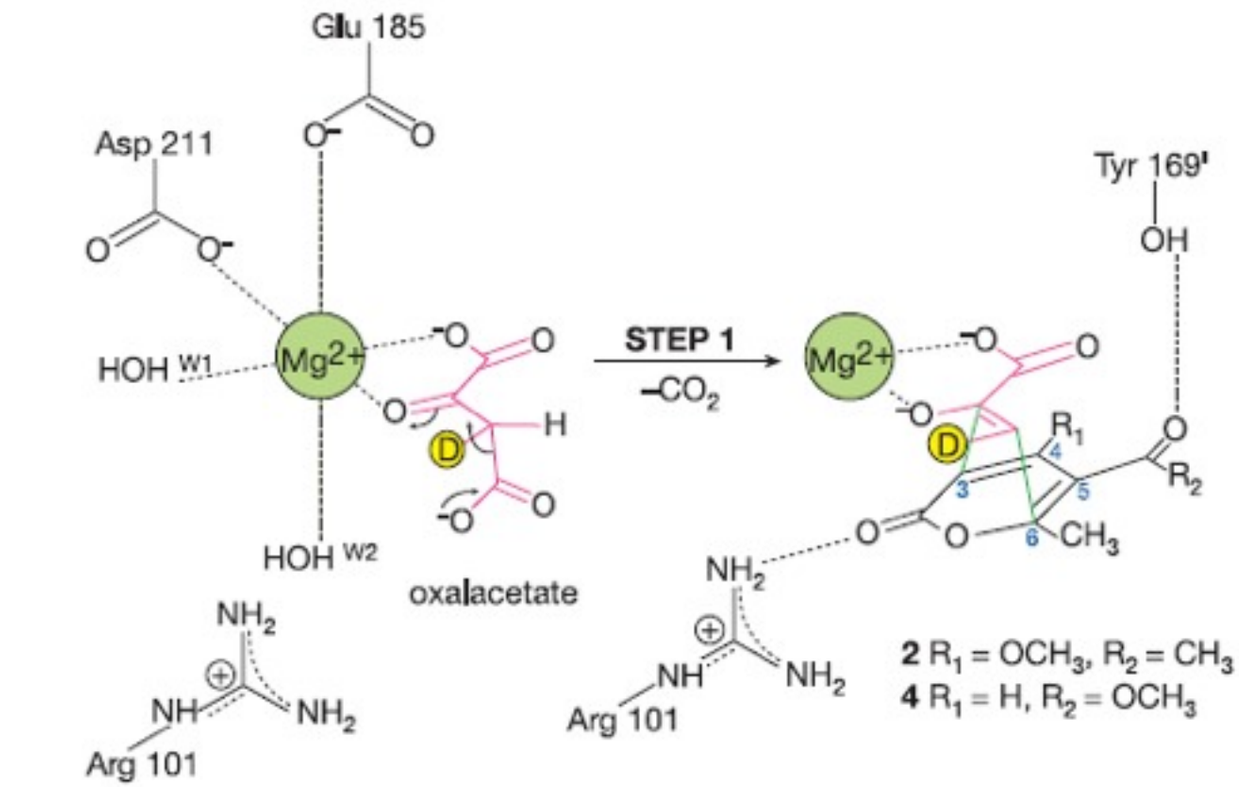


Figure 1. Details of individual reaction steps with macrophomate synthase.
Step 1 is decarboxylation of oxalacetate.
Step 2 are Diels–Alder reactions of the enolate and 2-pyrones 2 and 4 to form higher energy adducts 3 and 5, respectively.
Step 3 is degradation of 3 in which abstraction of hydrogen triggers C–O bond cleavage followed by decarboxylation and elimination of hydroxy group. The steric energies (SE) of each ompound were determined by molecular mechanics calculations using the MM2 force field.