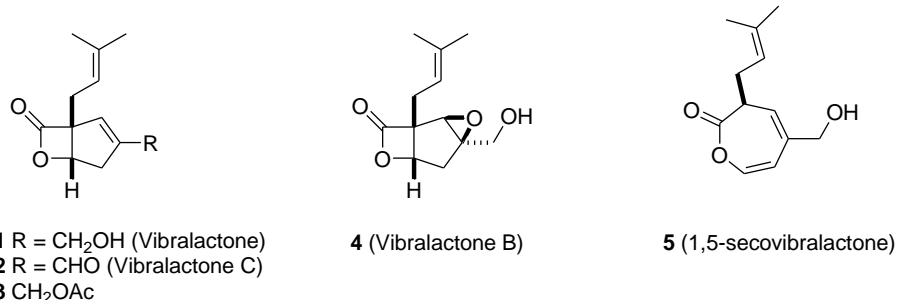


## Problem Questions – Natural product B

### Synthesis of (±)- and (-)-Vibralactone and Vibralactone C.

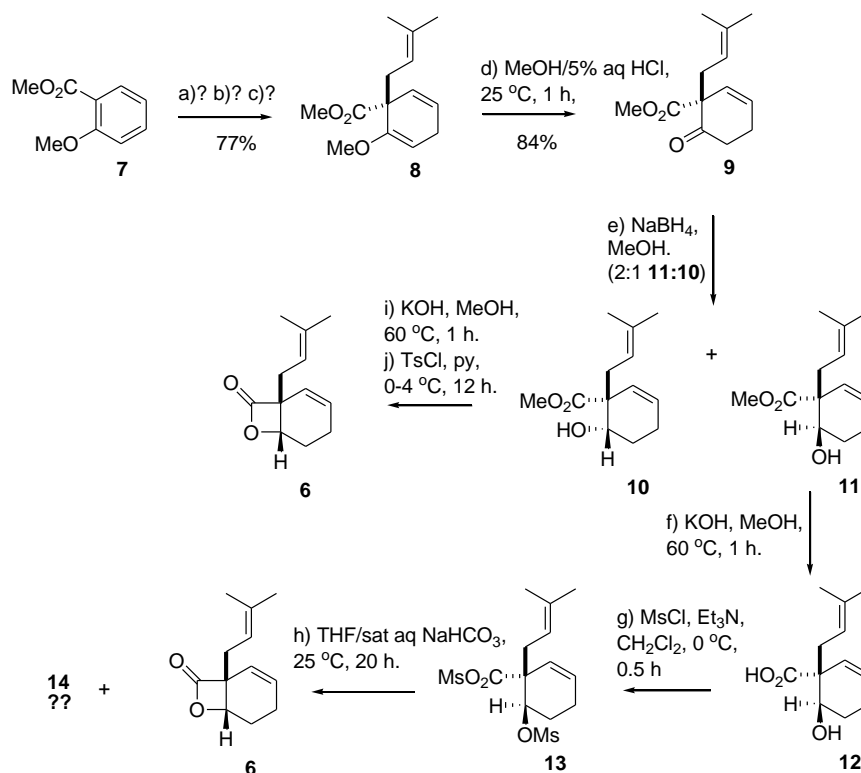
Vibralactone (**1**) (Figure 1), a unusual fused  $\beta$ -lactone, was recently isolated from the culture broth of the fungus *Boreostereum vibrans* by Lui and co-workers.(ref) Lui has also isolated four minor congeners of vibralactone, vibralactone B (**2**), vibralactone C (**3**), vibralactone acetate (**4**) and 1,5-secovibralactone (**5**). (ref) Vibralactone inhibits pancreatic lipase with an  $IC_{50}$  of  $0.4 \mu\text{g/mL}$ . Pancreatic lipase inhibitors are used for the treatment obesity. Snider completed the synthesis of (±)-vibralactone in 10 steps with a 9% overall yield, followed by an 11 step synthesis of (-)-vibralactone in 4.8%.



**Figure 1:** Structures of vibralactone (**1**), vibralactone B (**2**), vibralactone C (**3**), vibralactone acetate (**4**) and 1,5-secovibralactone (**5**).

**Question 1)** Suggest disconnections for vibralactone (**1**) and 1,5-secovibralactone (**5**).

### Scheme 1: Synthesis of model $\beta$ -lactone **6**.

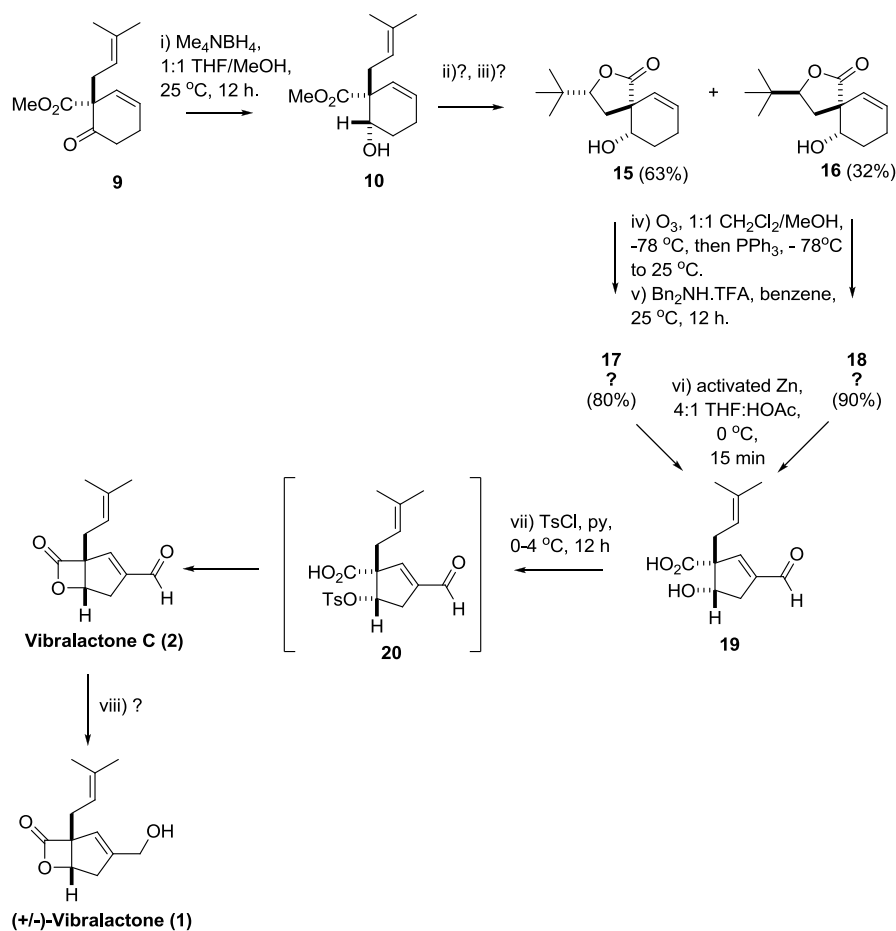


### Questions for Scheme 1:

- 1) Cyclohexadiene **8** was synthesised in 77% from methyl 2-methoxybenzoate (**7**). Suggest reagents and conditions for this reaction.
- 2) The reduction of **7** with NaBH<sub>4</sub> in MeOH gave a poor selectivity (2:1) in favour of *trans*-hydroxy ester **11**. Can you suggest reagents and conditions for step e) with increased selectivity for forming **11**? (NB the best result obtained was a 7.5:1 mixture of *trans*-hydroxy ester **11** and *cis*-hydroxy ester **10**).
- 3) How would you differentiate between hydroxy esters **10** and **11** with IR and NMR spectra.
- 4) After hydrolysis with NaHCO<sub>3</sub> in THF an intramolecular S<sub>N</sub>2 reaction occurs forming the desired lactone **6**. However the major product of the reaction was compound **14**, the product of an undesired side reaction. Give the mechanism of this side reaction and therefore the structure of **14**. What name is given to this reaction?

Due to problems discovered using *trans*-hydroxy ester **11** the synthesis of (±)-vibrallactone was taken forward using *cis*-hydroxy ester **10**.

### Scheme 2: Synthesis of (±)-vibrallactone C and (±)-vibrallactone.



### Questions for Scheme 2:

- 1) Suggest conditions for steps ii) and iii) to give isomers **15** and **16**? (NB: two steps one pot!)
- 2) Given the conditions for iv) and v) give the structures of isomers **17** and **18**.
- 3) Suggest conditions for step viii) taking into consideration the sensitive  $\beta$ -lactone moiety.

Finally the synthesis of (-)-vibralactone required an asymmetric Birch reductive alkylation. Can you suggest substrates that will give that will allow for this asymmetric Birch reduction?