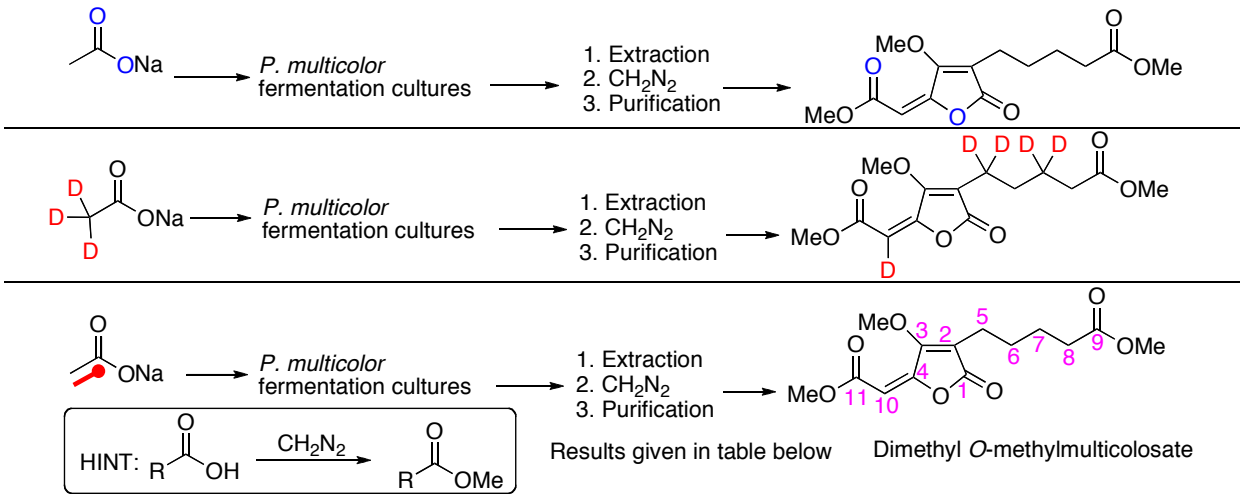
CHEM 7450 / 4580
Natural Products Chemistry and Biosynthesis
Dr. John L. Sorensen
Assignment #2 (Feb 10th 2021)
Due Date: **5:00 pm Thursday Feb 17th 2022**

Question #1: (20 Marks)

Answers can be done by hand or by ChemDraw

The polyketide multicolosic acid is produced in fermentation cultures of a strain of the fungus *Penicillum multicolor.* The results of biosynthetic experiments are summarized below and suggest that an initial polyketide synthase product is further transformed in a series of post-PKS reactions.

Extraction of the fermentation liquor of *P. multicolor* results in a crude extract that is treated with diazomethane to methylate carboxylic acid groups to simplify purification. Three separate feeding experiments with the labeled acetates shown below.

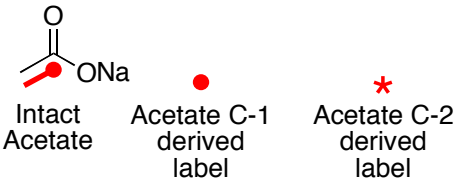


The incorporation pattern for [1,2-^{13}C] sodium acetate was determined by ^{13}C NMR spectroscopy and these results are summarized in a table below. The chemical shift and multiplicity (as determined in the natural abundance spectra) of each carbon signal is given in the second column. In the third column is given the coupling observed in dimethyl *O*–multicolosic acid when the doubly labeled acetate is fed to the culture.

(See Over for Table)

Carbon	δ (^{13}C ppm) (multiplicity)	*J* ^{13}C – ^{13}C (Hz)	[1-^{13}C] acetate incorporation	[2-^{13}C] acetate incorporation
1	160.7 (s)			+
2	109.3 (s)	45	+	
3	168.1 (s)			+
4	150.9 (s)	90	+	
5	23.1 (t)	45		+
6	29.2 (t)	35	+	
7	24.5 (t)	35		+
8	33.4 (t)	55	+	
9	172.9 (s)	55		+
10	101.0 (d)	90		+
11	163.7 (s)		+	
CH_3O- (C-11 *O*–methyl)	52.0 (q)			
CH_3O- (C-9 *O*–methyl)	51.4 (q)			
CH_3O- (C-3 *O*–methyl)	59.5 (q)			

i) (**5 marks**) Re-draw the structure of dimethyl *O*–methylmulticolosic and indicate, based on your analysis of the NMR data above, the pattern of intact acetate incorporation.



Use the labeling convention below to indicate acetate units that are incorporated intact, and (or) labels that result from isolated acetate derived carbons that result from the cleavage of an acetate C–C bond.

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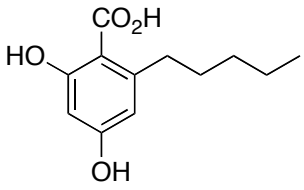
ii) (**5 marks**) Shown at right is 6-pentylresorcylic acid, the proposed product of the polyketide synthase enzyme responsible for multicolosic acid biosynthesis. Re-draw the structure and indicate the pattern of acetate incorporation from [1,2-^{13}C] sodium acetate that would be consistent with the results in the table and the polyketide origin of this molecule.



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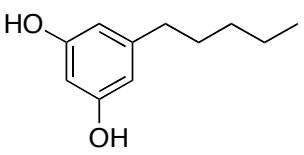
iii) (**10 marks**) Propose a detailed mechanism for the biosynthesis of dimethyl *O*–methylmulticolosic that is consistent with the data provided above. Ensure that the pathway that you propose takes into account not only the double labeling experiment but also the positioning of the oxygen and deuterium atoms derived from acetate. Provide a *brief* rational for the significant steps in your pathway.



(HINT: The compound at right is not an intermediate in the pathway)