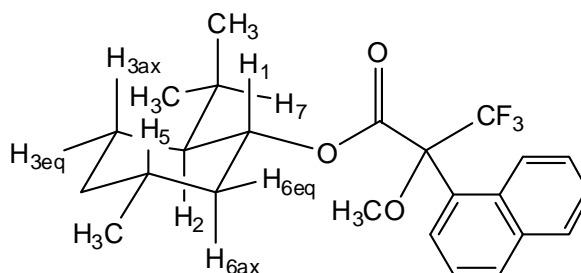


## Exam 2 Answer Key

Exam 2 Mean: 50  
Exam 2 Median: 50  
Exam 2 St. Dev.: 17

1. Problem 1 asks us to focus on diastereomer **A**, so we're going to ignore diastereomer **B** for right now. As always, a primary challenge in this problem is figuring out where to start. Right off the bat, the proton in this structure that is least like all the others is  $H_1$ , which should be all by itself in the  $\delta = 3.5\text{-}4.5$  ppm range. Sure enough,



there is a triplet of doublets (so, three coupling constants total) at  $\delta = 4.77$  ppm which must be  $H_1$ . (There is also a 3H-intensity singlet at  $\delta = 3.35$  ppm, which must be the  $-\text{OCH}_3$  group. Easy to assign, but unfortunately not coupled to anything, so not terribly useful to us right now.) The HMQC spectrum, which shows  $^1J(\text{CH})$  correlations, tells us right away that  $C_1$  is at  $\delta = 77$  ppm.

In the structure above,  $H_1$  has three vicinal neighbors:  $H_2$ ,  $H_{6\text{eq}}$ , and  $H_{6\text{ax}}$ . Not only is that confirmed by the multiplicity of the peak, it is also confirmed by the appearance of three crosspeaks in the COSY spectrum, at  $\delta = 1.75$ ,  $1.28$ , and  $0.54$  ppm. But which of these is which? If all we had were 1D NMR spectra, we might try to figure this out with coupling constants, but things here are clearly too complicated and overlapped for that. Instead, we can use our 2D HMQC to figure out which two of these three resonances are attached to the same carbon. It looks like the  $^1\text{H}$  resonance at  $\delta = 0.54$  ppm is associated not only with a carbon at  $\delta = 40$  ppm, but also with a second proton at  $\delta = 1.75$  ppm. So these two resonances must be  $H_{6\text{eq}}$  and  $H_{6\text{ax}}$ , with  $C_6$  at  $40$  ppm. Pretsch tells us that equatorial protons are downfield of axial ones, so  $\delta(H_{6\text{ax}}) = 0.54$  ppm and  $\delta(H_{6\text{eq}}) = 1.75$  ppm. By elimination, the crosspeak at  $\delta = 1.28$  must belong to  $H_2$ , and the HMQC tells us that  $C_2$  is at  $\delta = 47$  ppm.

At this point things get a little confusing.  $H_2$  should be coupled to a lot more different protons ( $H_7$ ,  $H_{3\text{ax}}$ , and  $H_{3\text{eq}}$ ), but it only shows one crosspeak other than the one we already assigned to  $J(H_1, H_2)$ .  $H_{6\text{eq}}$  overlaps with another resonance (according to integrations), so we might ought to not interpret it yet. And  $H_{6\text{ax}}$  looks like it only couples to  $H_{6\text{eq}}$ . So it looks like we can't move on any of these yet.

One other set of resonances that stands out is the methyl group doublets. There are three of them, corresponding to the three methyl groups, but which is which? It looks as though doublets #1 and #3 share a crosspeak with something at  $\delta = 1.75$  ppm; we already assigned this ppm value to  $H_{6eq}$ , but the integration says there is another proton there. The only proton that's vicinal to two methyl groups would be  $H_7$ , so I would assign that same region--or maybe a tiny bit downfield of it, maybe  $\delta = 1.78$  ppm--to  $H_7$ . HMQC shows a  $^1H$ - $^{13}C$  crosspeak to this peak at  $\delta = 25$  ppm, which corresponds to  $C_7$ . The three methyl groups can also now be assigned; the two coupled to  $H_7$  are  $C_8$  and  $C_9$ , and the other one is  $C_{10}$ .

So what do we have now?

proton	$\delta$ (ppm)
$H_{[1]}$	4.77
$H_{[2]}$	1.28
$H_{[3eq]}$	
$H_{[3ax]}$	
$H_{[5]}$	
$H_{[6eq]}$	1.75
$H_{[6ax]}$	0.54
$H_{[7]}$	1.78
$-C(H_{[8]})_3$	0.79
$-C(H_{[9]})_3$	0.68
$-C(H_{[10]})_3$	0.77
$-OCH_3$	3.35

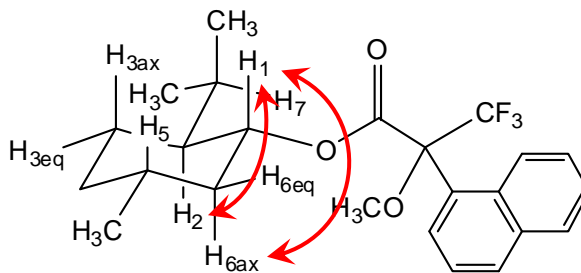
carbon	$\delta$ (ppm)
$C_{[1]}$	77
$C_{[2]}$	47
$C_{[3]}$	
$C_{[4]}$	
$C_{[5]}$	
$C_{[6]}$	40
$C_{[7]}$	25
$C_{[8]}$	21
$C_{[9]}$	16
$C_{[10]}$	22

That's almost the entire chart! We can make out H<sub>5</sub> ( $\delta = 1.40$ ) from the COSY via its crosspeak with the C<sub>10</sub> methyl group. Looking at the HMQC, however, there is no crosspeak lined up with H<sub>5</sub> at  $\delta = 1.39$ . Grrr.... Looking more closely at the HMQC, however, it looks like there is one (alkyl region) <sup>13</sup>C peak on the left that shows no crosspeaks, even though our molecule has no alkyl carbons without attached protons. My guess is that this <sup>13</sup>C resonance (at  $\delta = 31$  ppm) is C<sub>5</sub>.

The very last assignments of H<sub>3eq</sub>, H<sub>3ax</sub>, C<sub>3</sub> and C<sub>4</sub> were difficult. There aren't definitive crosspeaks in the COSY to guide us, and there is some peak overlap that makes multiplet analysis impossible. HMQC tells us which pairs of peaks (H<sub>3eq</sub>/H<sub>3ax</sub>, H<sub>4eq</sub>/H<sub>4ax</sub>) are matched, but it doesn't tell us which is which. As it turns out, the HMBC comes to the rescue here, by telling us that the C<sub>10</sub> methyl H's are coupled (via <sup>3</sup>J) to the <sup>13</sup>C resonance for C<sub>4</sub> at  $\delta = 34$  ppm. This leaves  $\delta = 23$  for C<sub>3</sub>, and sets the two H<sub>3</sub> protons. Completing our chart,

proton	$\delta$ (ppm)	carbon	$\delta$ (ppm)
H <sub>[1]</sub>	4.77	C <sub>[1]</sub>	77
H <sub>[2]</sub>	1.28	C <sub>[2]</sub>	47
H <sub>[3eq]</sub>	1.62	C <sub>[3]</sub>	23
H <sub>[3ax]</sub>	0.96	C <sub>[4]</sub>	34
H <sub>[5]</sub>	1.39	C <sub>[5]</sub>	31
H <sub>[6eq]</sub>	1.75	C <sub>[6]</sub>	40
H <sub>[6ax]</sub>	0.54	C <sub>[7]</sub>	25
H <sub>[7]</sub>	1.78	C <sub>[8]</sub>	21
-C(H <sub>[8]</sub> ) <sub>3</sub>	0.79	C <sub>[9]</sub>	16
-C(H <sub>[9]</sub> ) <sub>3</sub>	0.68	C <sub>[10]</sub>	22
-C(H <sub>[10]</sub> ) <sub>3</sub>	0.77		
-OCH <sub>3</sub>	3.35		

2.  $^1\text{H}$ - $^1\text{H}$  COSY correlations: The crosspeaks relate  $\text{H}_1$  to  $\text{H}_2$  and  $\text{H}_{6\text{ax}}$ . I'm assuming these are much more intense than the  $\text{H}_1$ - $\text{H}_{6\text{eq}}$  crosspeak because of the  $180^\circ$  dihedral angles, which maximizes  $^3J$ .



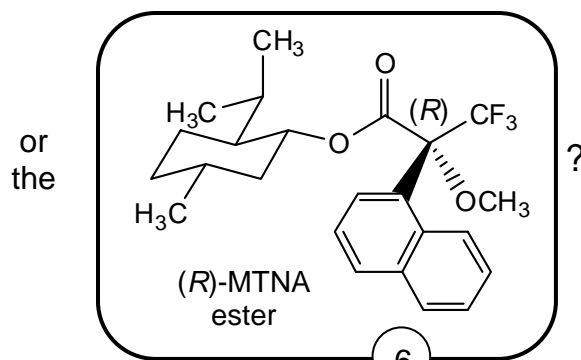
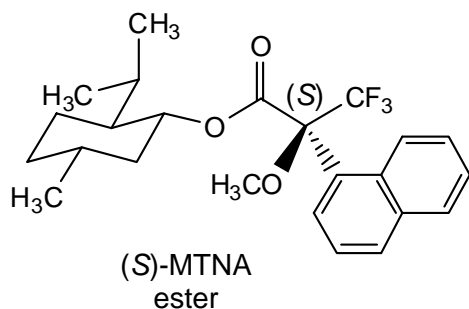
③ points for each arrow.

3. HMQC and HMBC are techniques for detecting heteronuclear ( $^{13}\text{C}$ - $^1\text{H}$ ) correlations. The HMBC spectrum lacks some  $^{13}\text{C}$ - $^1\text{H}$  correlations that are observed in the HMQC spectrum; two such cases are indicated by grey rectangles on the HMBC. Why are there no peaks at these locations?

The HMBC method suppresses  $^1J(\text{CH})$  correlations, which is what these crosspeaks would be. So we don't see them.

⑥ points for stating that HMBC suppresses one-bond or  $^1J$  couplings/correlations.  
*No partial credit.*

4. Based on the attached spectra, is diastereomer **A** the



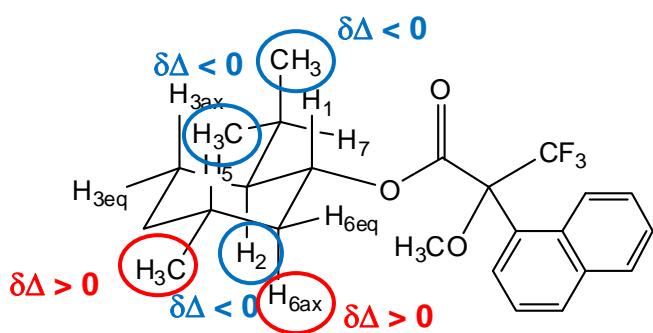
⑥ points for circling correct answer.

We can assume that Enver's MTNA ester works the same as Mosher's MTPA ester, in that protons that are on the same side of the molecule as the naphthoyl group are shifted *upfield* (because they sit above the aromatic ring currents), and protons that are on the same side as the methoxy group are shifted downfield by the electronegative oxygen. You were not given enough information to assign the  $^1\text{H}$  spectrum of diastereomer **B**, so it was difficult to compare that spectrum to that of diastereomer **A**. But there are a few of things that stand out when comparing the two spectra:

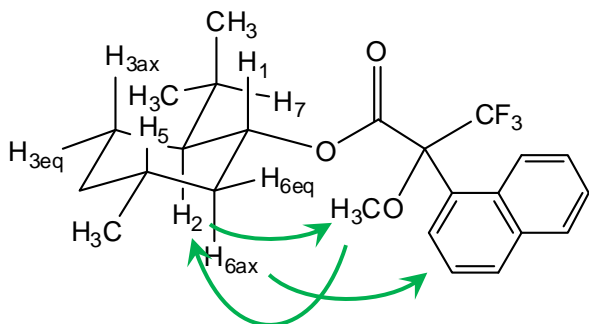
- None of the peaks in the 2.5-8 ppm expansion are informative.
- Going from diastereomer **A** to **B**, two methyl groups shift upfield, and one shifts downfield. That can only happen if the isopropyl group is next to the electron-withdrawing methoxy group in diastereomer **A**, and if the methyl group at C<sub>5</sub> is adjacent to the naphthoyl group.
- Though it is hard to track multiplets between the two spectra, I think that the triplet of triplets for H<sub>2</sub> at 1.27 ppm in diastereomer **A** moves to  $\delta = 0.98$  ppm in diastereomer **B**. That would again be consistent with the methoxy group being in back in diastereomer **A**, next to C<sub>2</sub>.
- You *might* make the argument that H<sub>6ax</sub>, which is at  $\delta = 0.53$  in the  $^1\text{H}$  NMR of diastereomer **A**, must move downfield in diastereomer **B** because there are no other multiplets upfield of it. I don't know that this is true--there is something in the baseline at  $\delta = 0.29$ --but we accepted it.

I think these are the only protons that can be assigned  $\delta\Delta$  signs with any certainty. I've shown five possible answers here, but of course you only needed to draw two.

- 3 points for each combination of correct circle and  $\delta\Delta$  assignment, x2 (6 points total this part).



5. One main criterion of a good NOE experiment is that there has to be an isolated peak that can be selectively irradiated, without accidentally exciting other resonances. Some peaks in the  $^1\text{H}$  NMR of enantiomer **A** overlap, so we need to avoid those. We can also avoid protons that are far away from the MTNA chiral center. I think  $\text{H}_2$  (1.27 ppm) and  $\text{H}_{6\text{ax}}$  (0.54 ppm) would be excellent choices because they are relatively clear of other peaks, and they are close to the methoxy and naphthyl groups in question. The  $-\text{OCH}_3$  group is also all alone, so it would be easy to irradiate as well.



⑤ points for each arrow; two of these three arrows only.

If arrows are incorrect, but consistent with your choice in problem 4—in other words, if your destinations are opposite mine—full credit for this problem.