DEVELOPMENT OF SYNERGISTIC NMR AND MOLECULAR MECHANICS STRATEGIES FOR DETERMINING NATURAL PRODUCT STEREOCHEMISTRY

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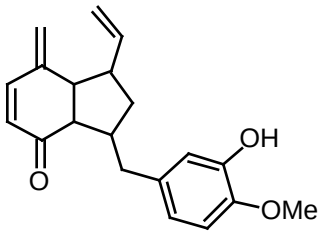
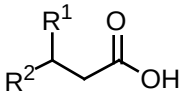
Techniques that exploit straightforward aspects of NMR spectroscopy combined with conformational analysis are being developed in our laboratory. These studies are often driven by a need for new methods for determination of stereochemistry in various natural products. Both coupling constant-based and chemical shift-based NMR methods are interpretted with the help of a thorough analysis of families of conformations identified by appropriate molecular mechanics treatments. This often results in solutions to structure assignment problems that are not addressable by multi-dimensional NMR approaches.

Selected examples of this strategy, such as those outlined below, will be described:

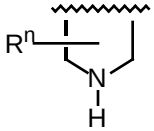
- a study of the relative configuration of two, isomeric, 4-methylene-2-cyclohex-enones of constitution **1**, isolated from *Ottelia alismoides* found in the delta region of the Nile River.

1 

- a general method for the assignment of absolute configuration of β-chiral carboxylic acids (**2**).

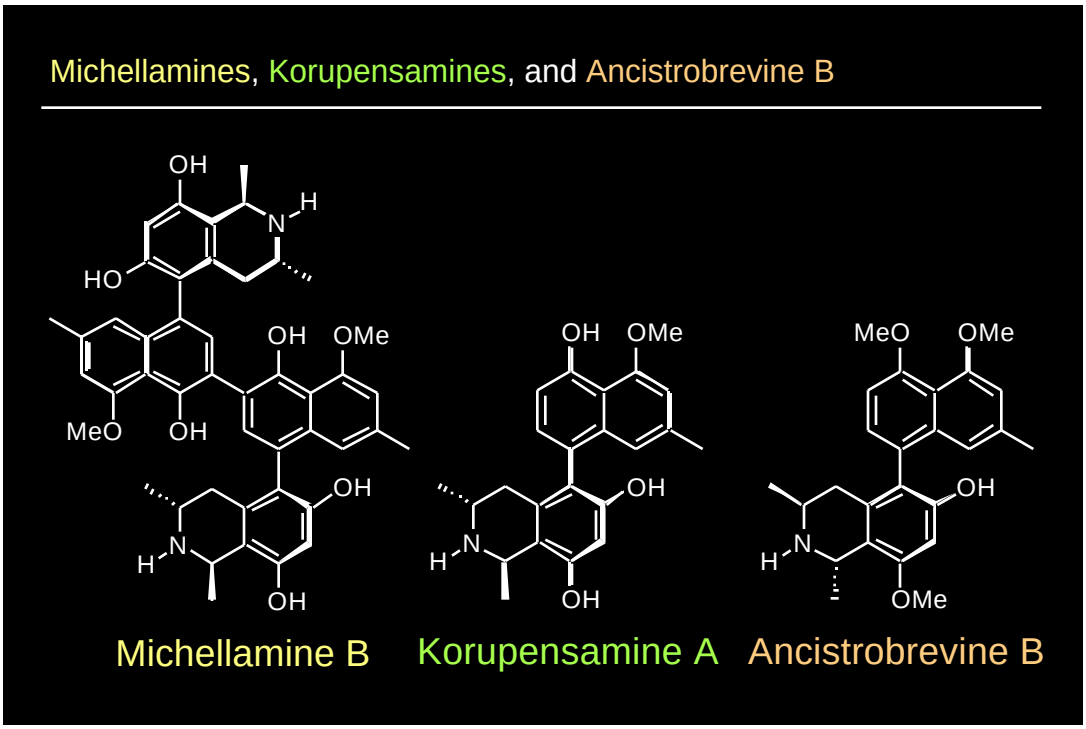
2 

- a general method for the determination of absolute configuration of substituted, cyclic amines (cf., **3**).

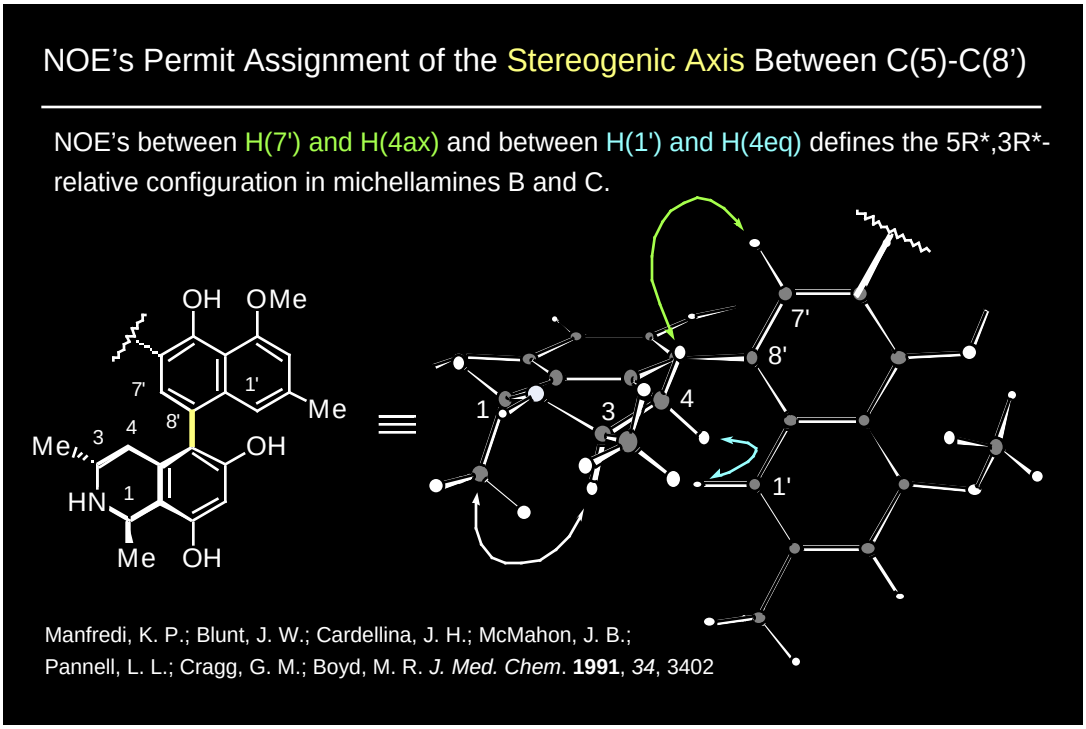
3 

The slides used in this lecture are reproduced below. Three topics were presented in reverse order to their appearance n the abstract. Topic **3** (slides number 1-17) has been the subject of previous publications[1] from our laboratory. Topic **2** (slides number 18-31) includes some previously published work[2] as well as some that is described in a submitted manuscript.[3] Topic **3** (slides number 32-35) is described in another submitted manuscript.[4]

Slide #1



Slide #2



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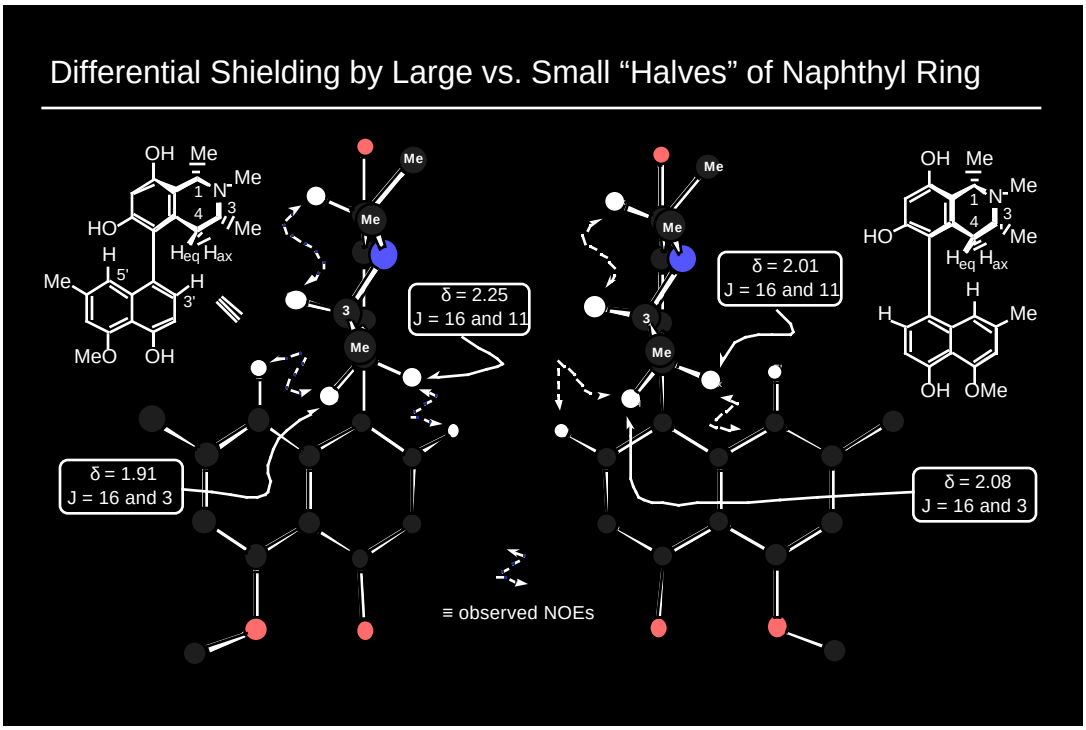

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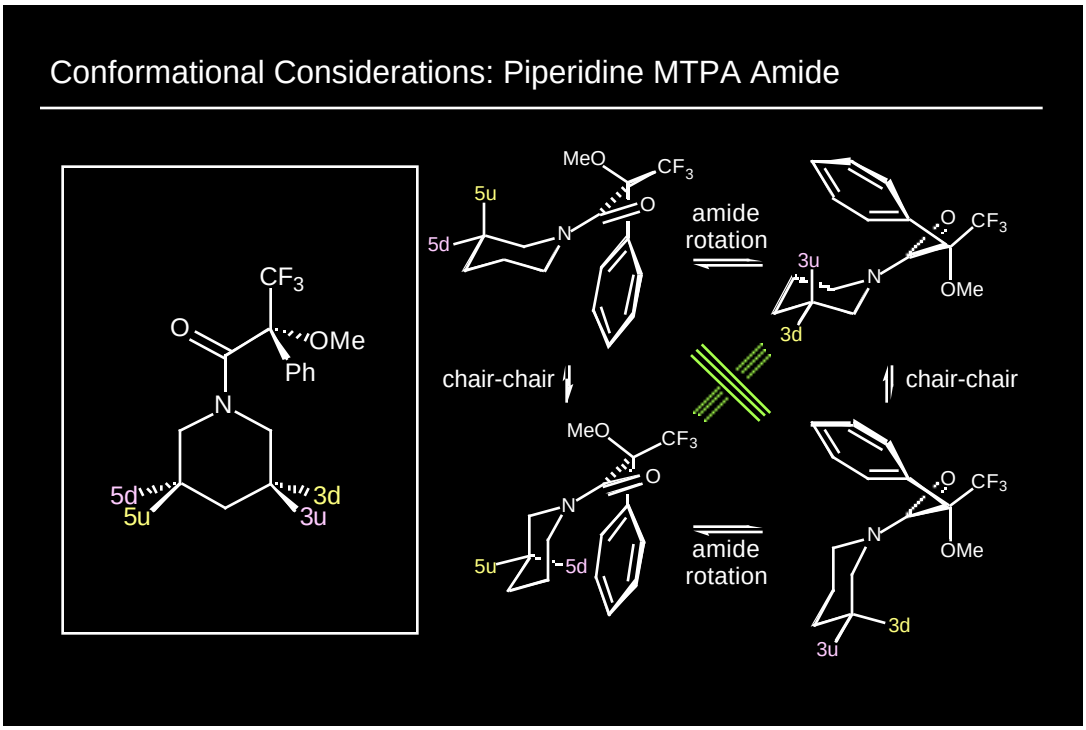
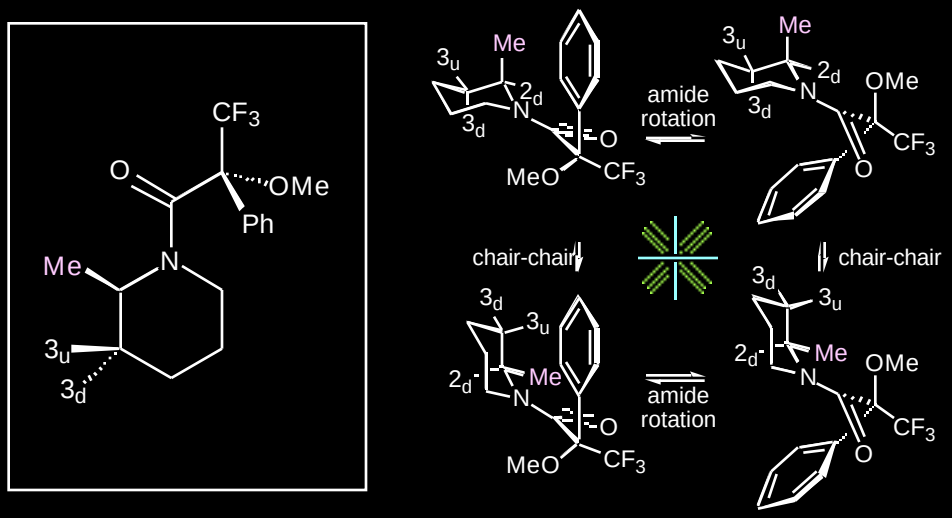


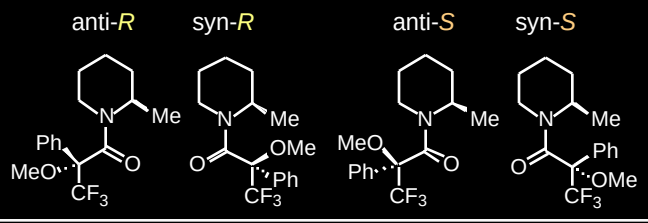
Slide #5

Conformational Considerations: (*R*)-2-Methylpiperidine MTPA Amide



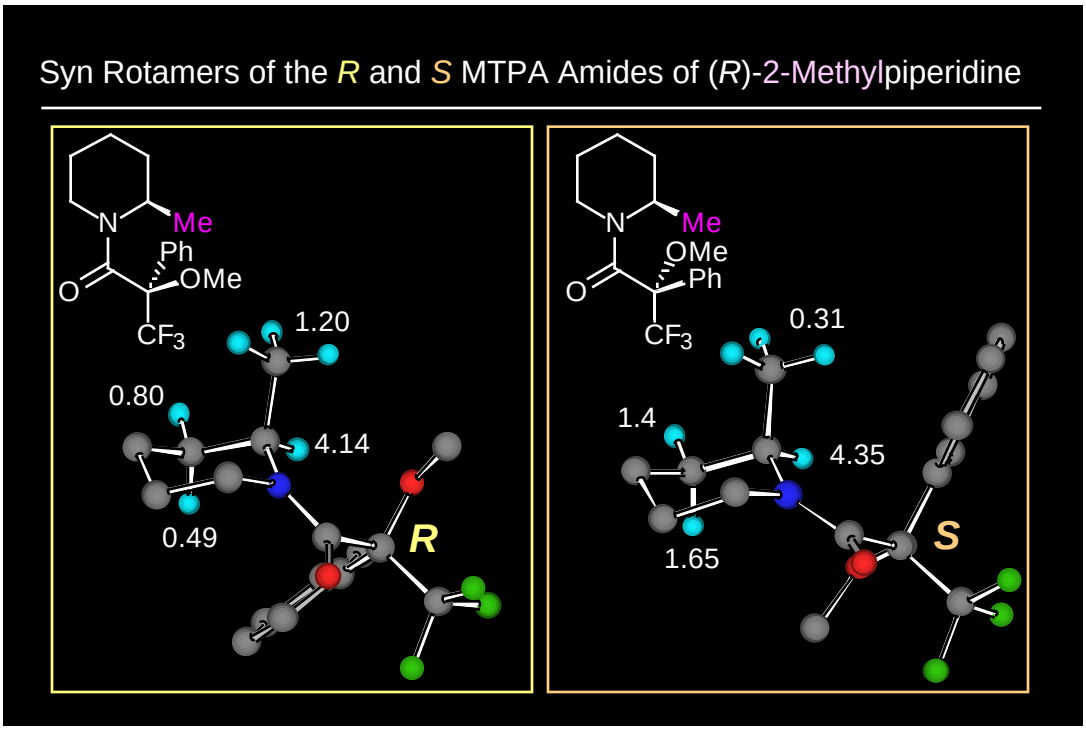
Slide #6

Chemical Shifts (in ppm) and Δδ Values for the Individual Rotamers of *R*- and *S*-MTPA Amides of (*R*)-2-Methylpiperidine



H	anti-*R*	syn-*R*	anti-*S*	syn-*S*	Δδ = δ_S-δ_R (anti)	Δδ = δ_S-δ_R (syn)
2	**4.93**	**4.14**	**5.06**	**4.35**	**0.13**	**0.21**
3a	**1.65**	**0.49**	**1.5**	**1.65**	**-0.15**	**1.16**
3e	**1.6**	**0.80**	**1.6**	**1.4**	**0**	**0.6**
4a	**1.5**	**1.5**	**1.5**	**1.57**	**0**	**0.07**
4e	**a**	**a**	**1.3**	**a**	**a**	**a**
5a	**1.35**	**1.35**	**0.32**	**1.4**	**-1.03**	**0.05**
5e	**1.5**	**1.6**	**1.00**	**1.72**	**-0.5**	**0.12**
6a	**2.17**	**2.76**	**2.92**	**2.68**	**0.75**	**-0.08**
6e	**3.70**	**4.58**	**3.74**	**4.57**	**0.04**	**-0.01**
Me	**1.14**	**1.20**	**1.21**	**0.31**	**0.07**	**-0.89**

Slide #7



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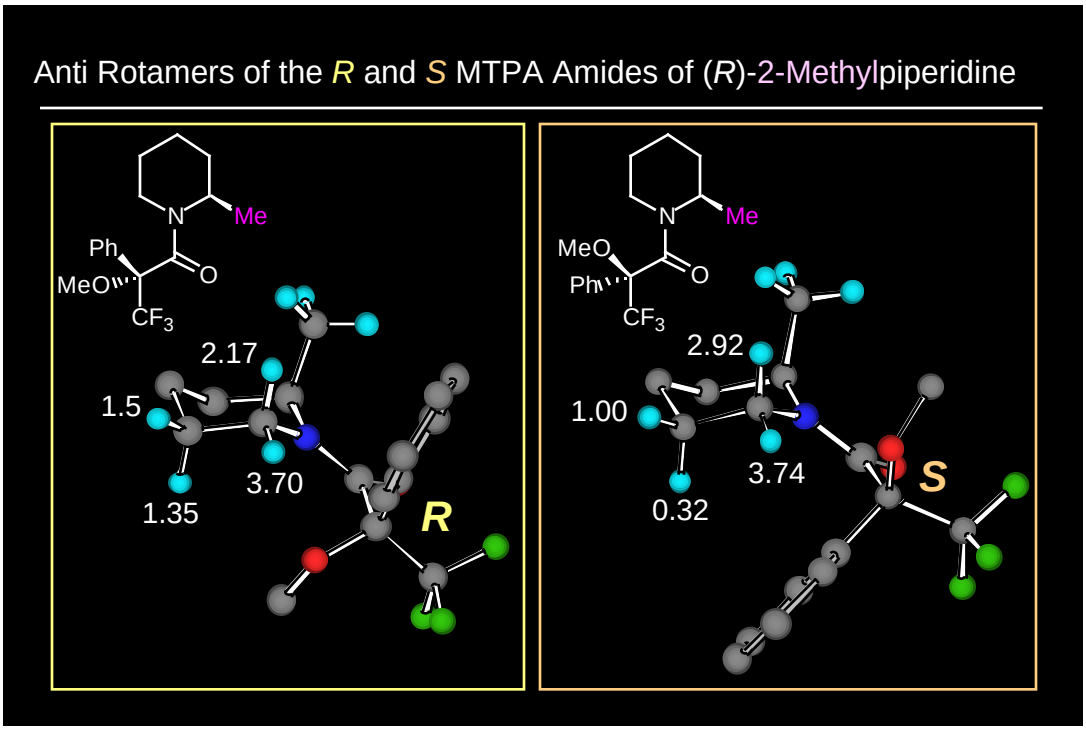

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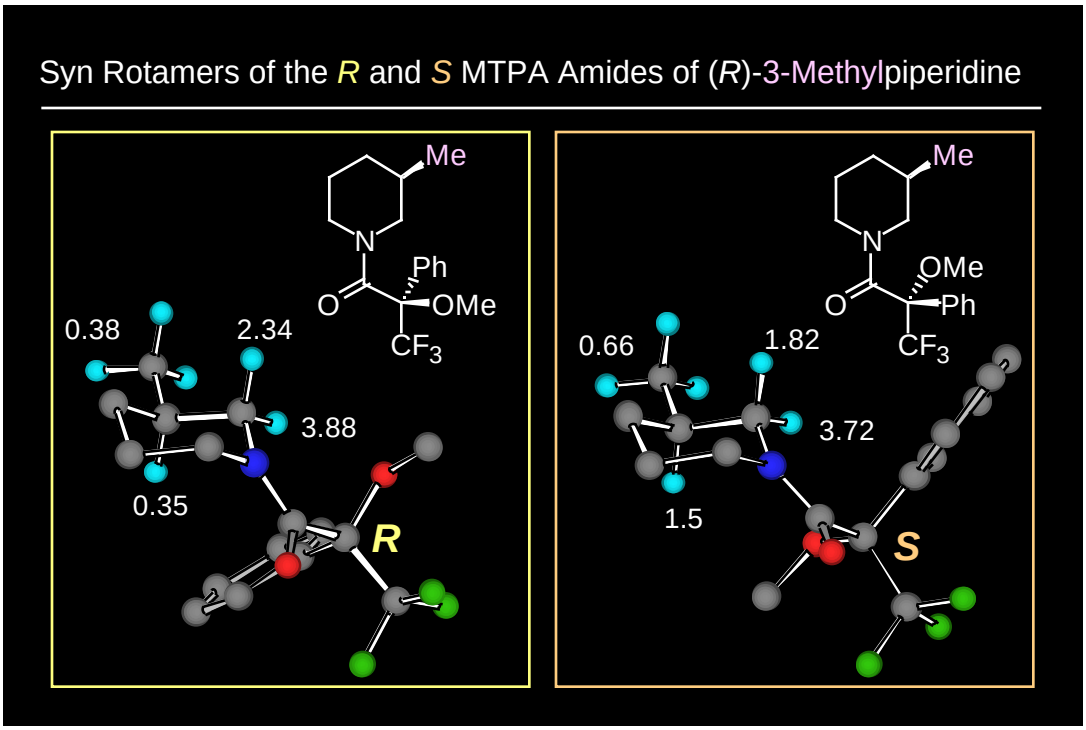

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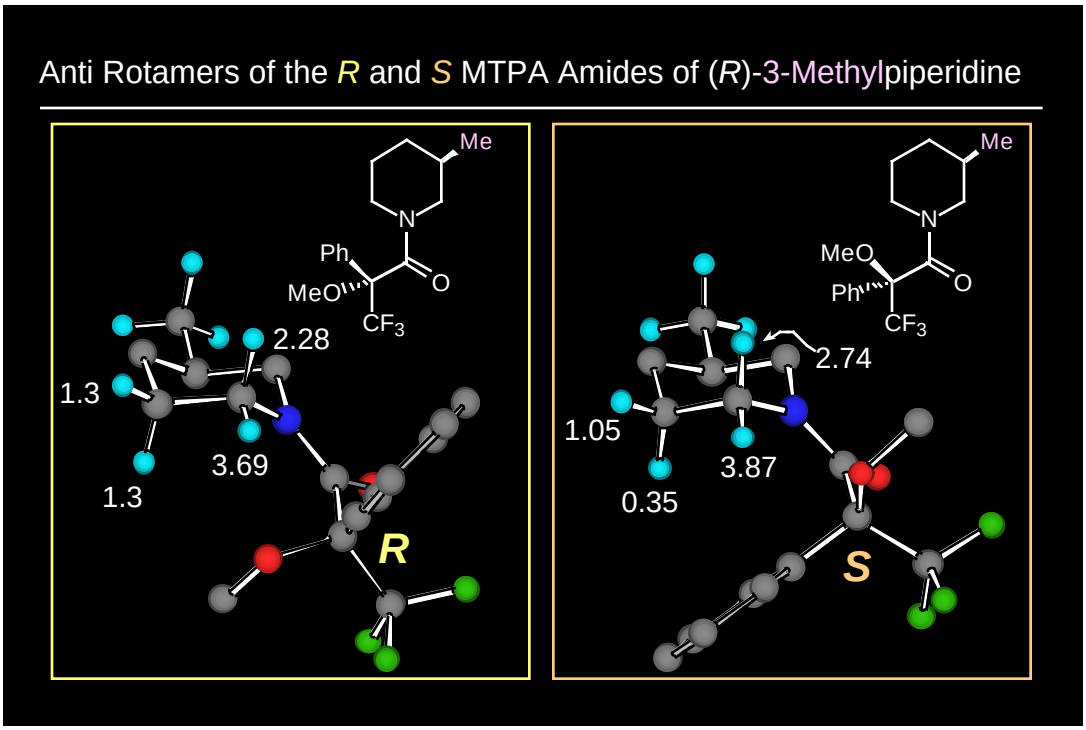

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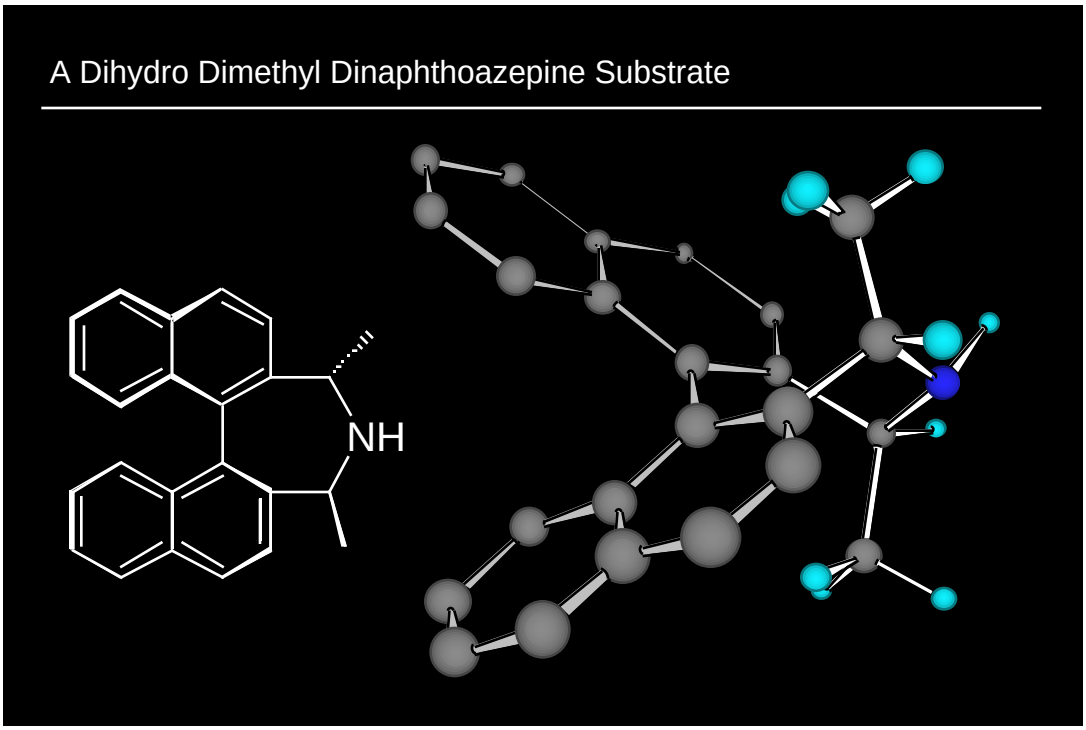

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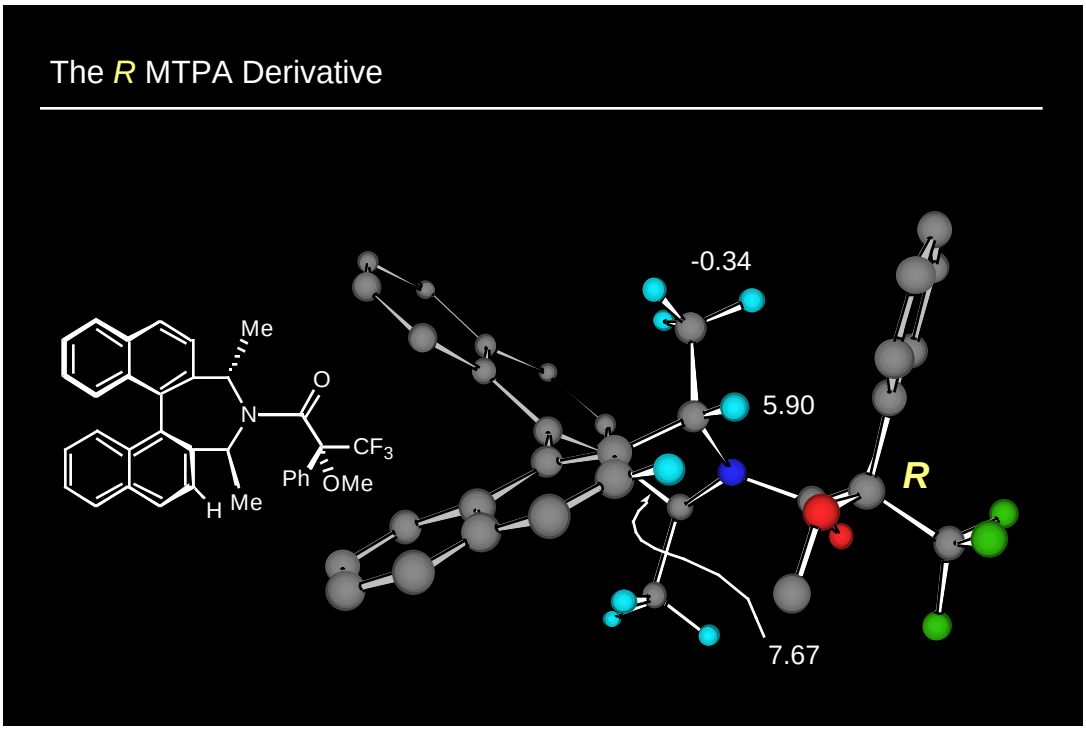

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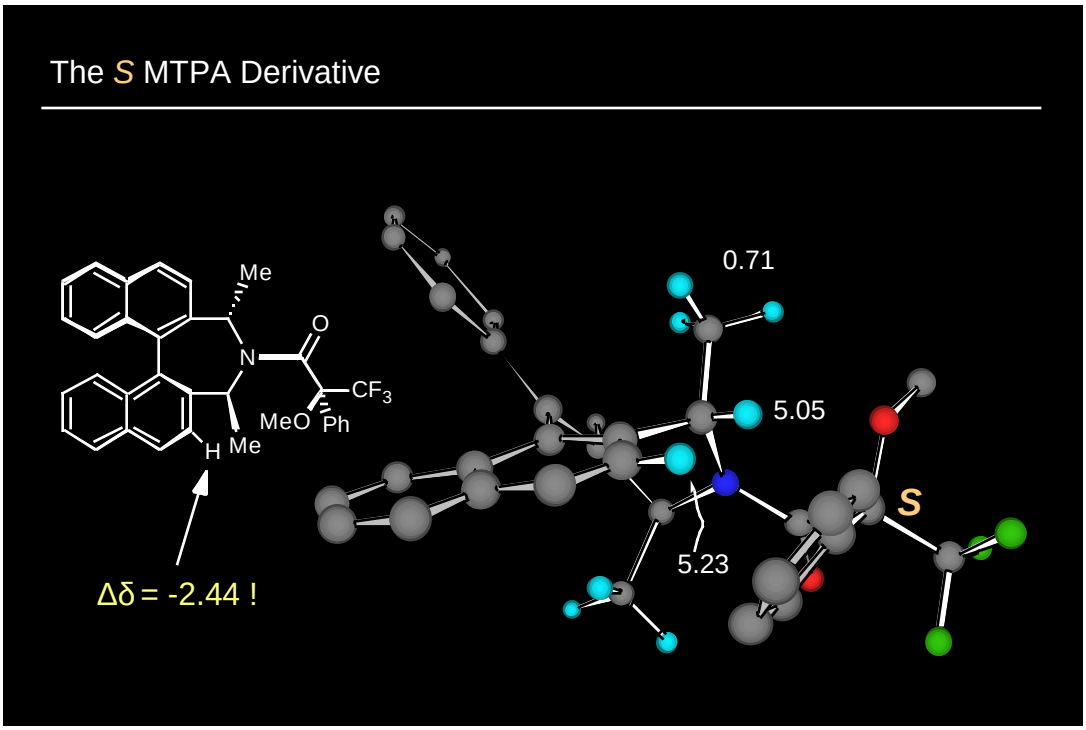

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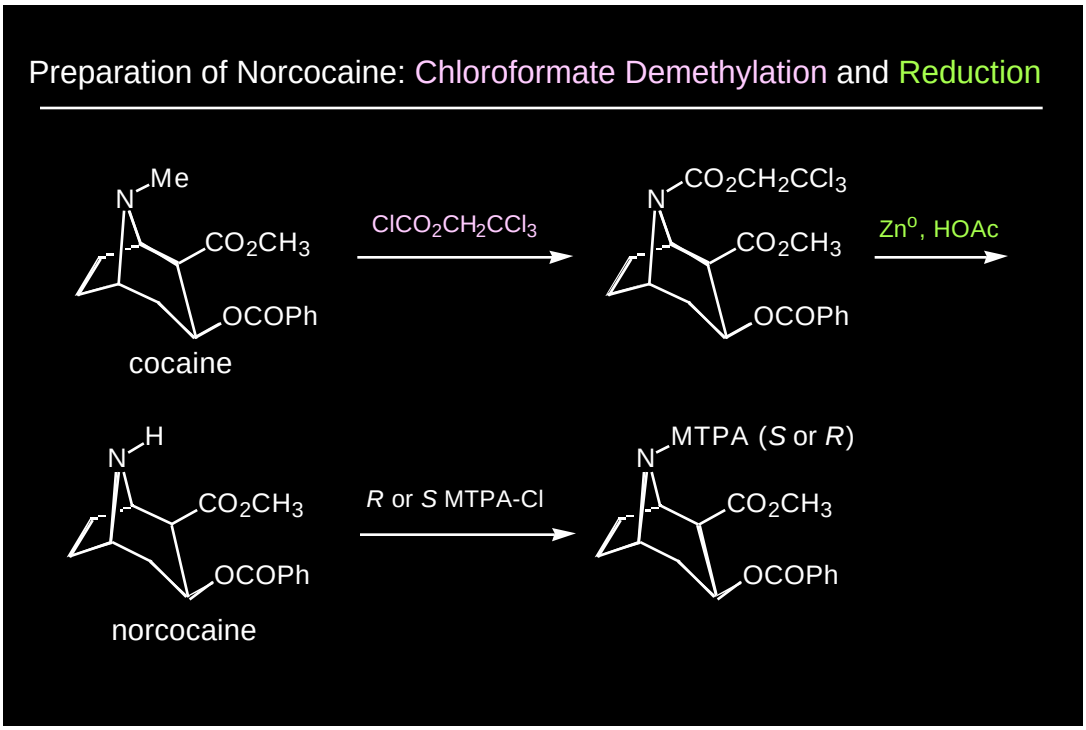

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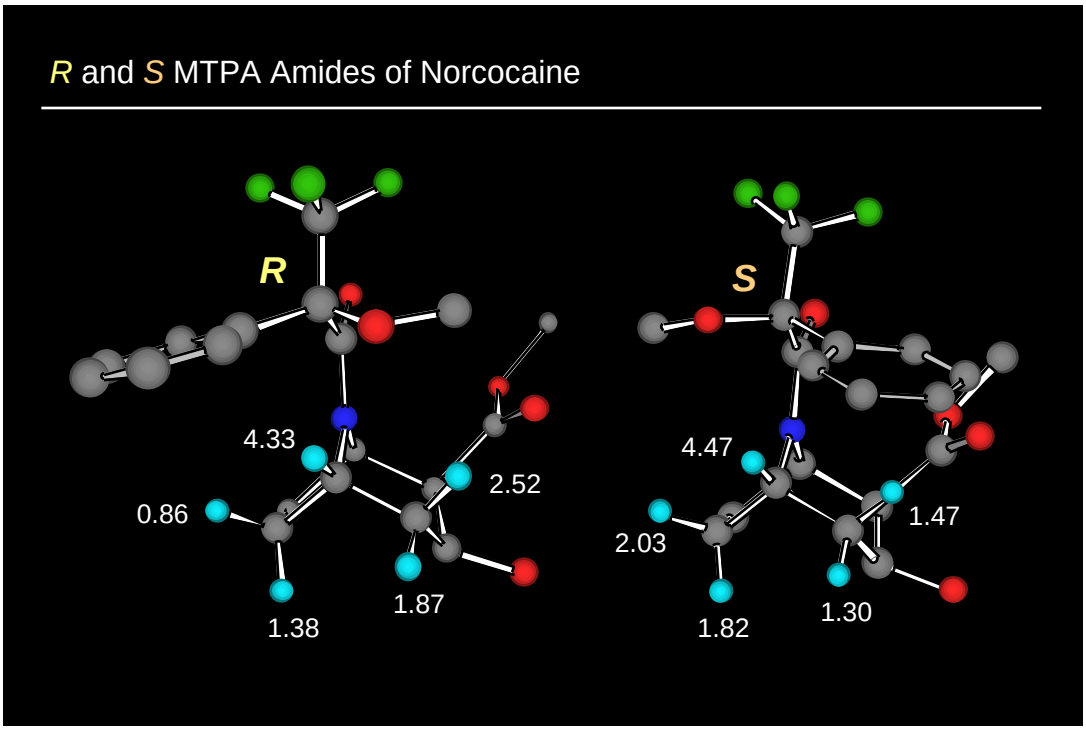

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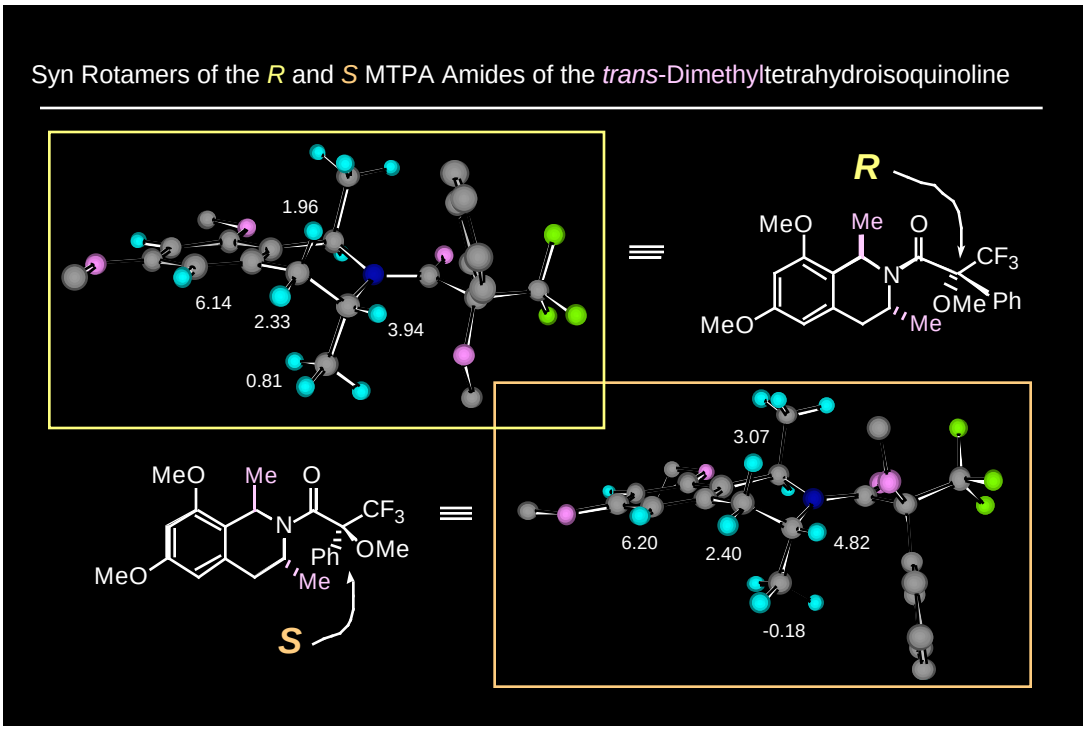

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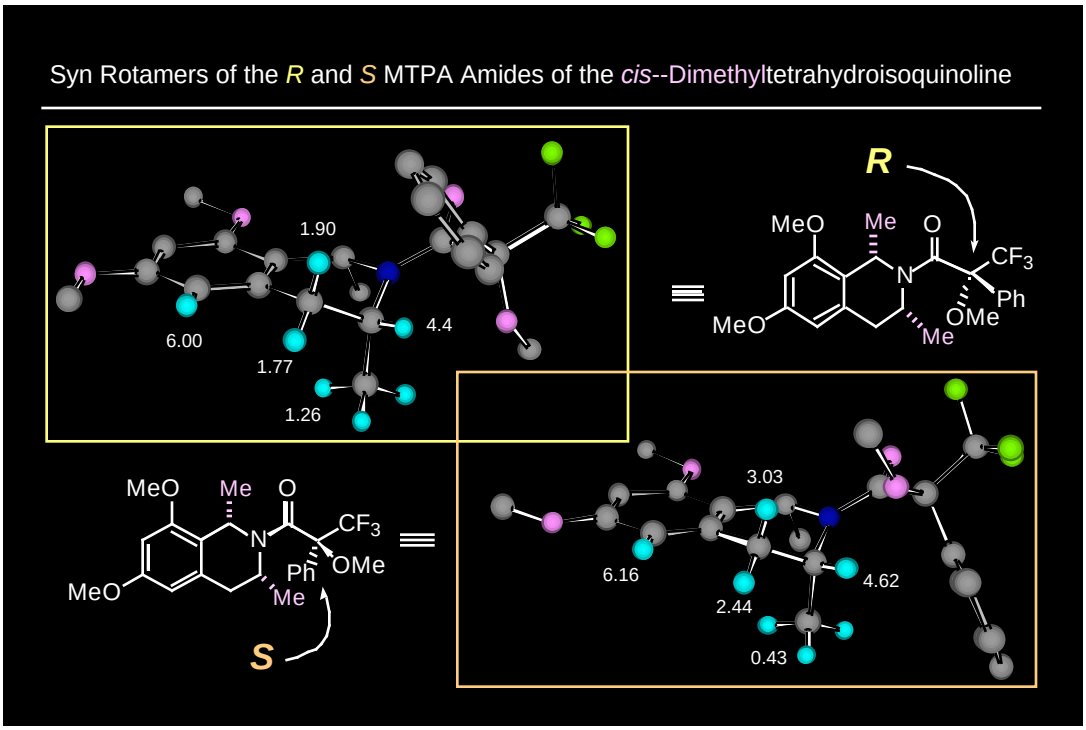

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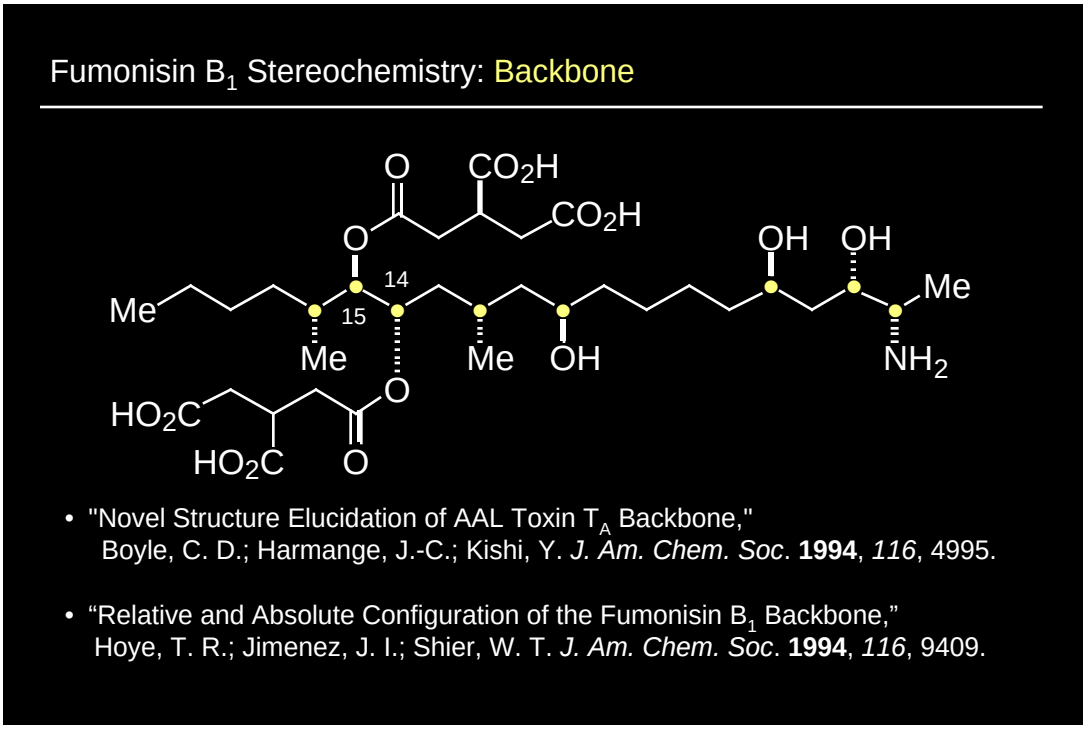


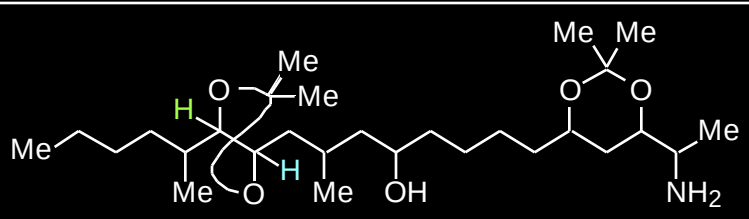
- "Novel Structure Elucidation of AAL Toxin T_A Backbone,"
  Boyle, C. D.; Harmange, J.-C.; Kishi, Y. *J. Am. Chem. Soc*. **1994**, *116*, 4995.

- "Relative and Absolute Configuration of the Fumonisin B_1 Backbone,"
  Hoye, T. R.; Jimenez, J. I.; Shier, W. T. *J. Am. Chem. Soc*. **1994**, *116*, 9409.

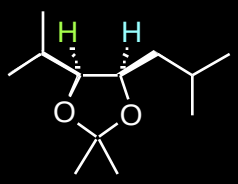
Slide #19

J in bis-Acetonide **1** Modeled by MM2 Analysis of Truncated **2** and **3**

$J_{14\,/\,15}$ = 5.0 Hz

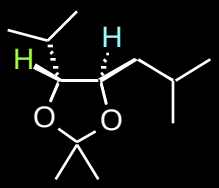


1



J calc = 4.7 Hz

2



J calc = 8.9 Hz

3

Slide #20

Methodology for Calculating J Value for Each Diastereomer

1. Monte Carlo conformation search with MM2 as implemented in MacroModel.
2. Identify all conformations lying within 3 kcal mol^{-1} of the golbal minimum.
3. Determine the J value between the relevant protons in each of these conformers.
4. Calculate (Excel) the weighted average J across the Boltzmann distribution of conformers:

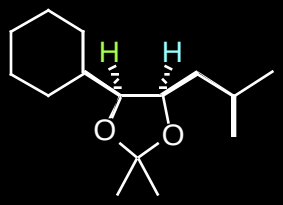
$$\Delta G^\circ = -RT\ln K$$

$$K = \exp\left(\frac{-\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R}\right)$$

$$J_{calc} = \sum_i \frac{\exp\left(\frac{-E_i}{RT}\right)}{\sum_i \exp\left(\frac{-E_i}{RT}\right)} J_i$$

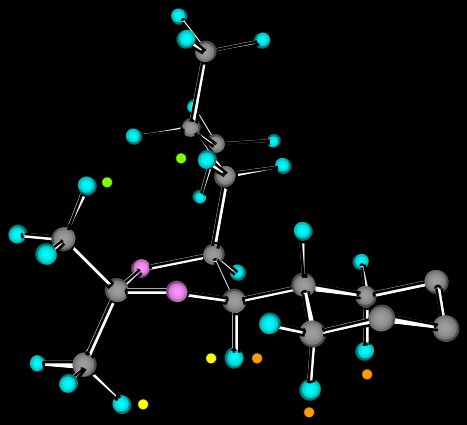
Slide #21

Experimental Verification of Methodology: cis-Acetonide



J exp = 5.2 Hz

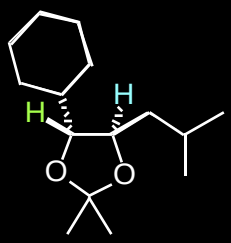
J calc = 4.8 Hz



Global Minimum Geometry (~35%)
supported by NOESY

Slide #22

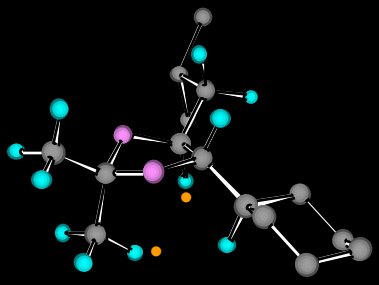
Experimental Verification of Methodology: trans-Acetonide

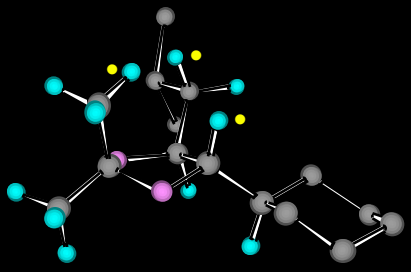


J exp = 7.9 Hz

J calc = 8.8 Hz

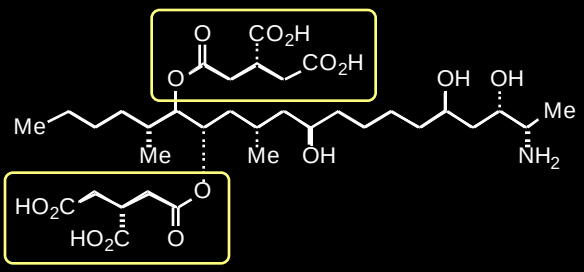
Two Lowest Energy Conformers
(~15% each)
also supported by NOESY





Slide #23

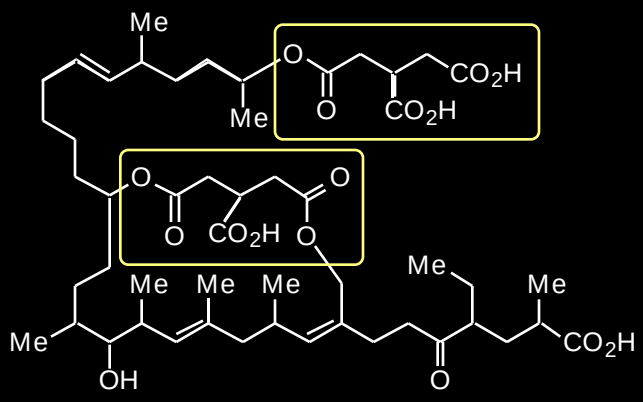
Fumonisin B_1 Stereochemistry: Sidechain Propane Tricarboxylic Acid



- "Complete Structures of the Sphingosine Analog Mycotoxins, Fumonisin B_1 and AAL Toxin T_A: Absolute Configuration of the Side Chains,"
  Shier, W. T.; Abbas, H. K.; Badria, F. A. *Tetrahedron Lett*. **1995**, *36*, 1571.
- "Absolute Configuration at the Tricarballylic Acid Moieties of Fumonisin B_2,"
  Boyle, C. D.; Kishi, Y. *Tetrahedron Lett*. **1995**, *36*, 4579.
- "Absolute Configuration at the Tricarballylic Acid Moieties of Fumonisin B_1 and AAL Toxin T_A,"
  Boyle, C. D.; Kishi, Y. *Tetrahedron Lett*. **1995**, *36*, 5695.

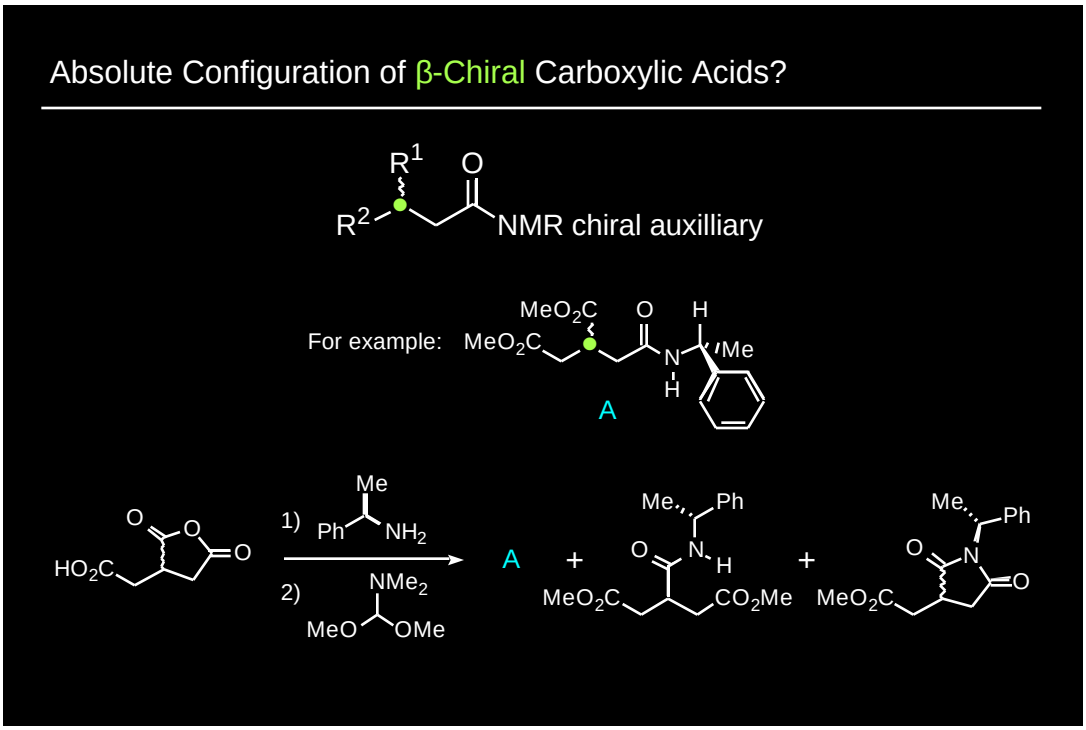
Slide #24

Actinoplanic Acid A: Another (bis) Propane Tricarboxylic Acid Derivative



"Actinoplanic Acid A: A Macrocyclic Polycarboxylic Acid Which Is a Potent Inhibitor of Ras Farnesyl-Protein Transferase," Singh, S. B.; Liesch, J. M.; Lingham, R. B.; Goetz, M. A.; Gibbs, J. B. *J. Am. Chem. Soc*. **1994**, *116*, 11606.

Slide #25



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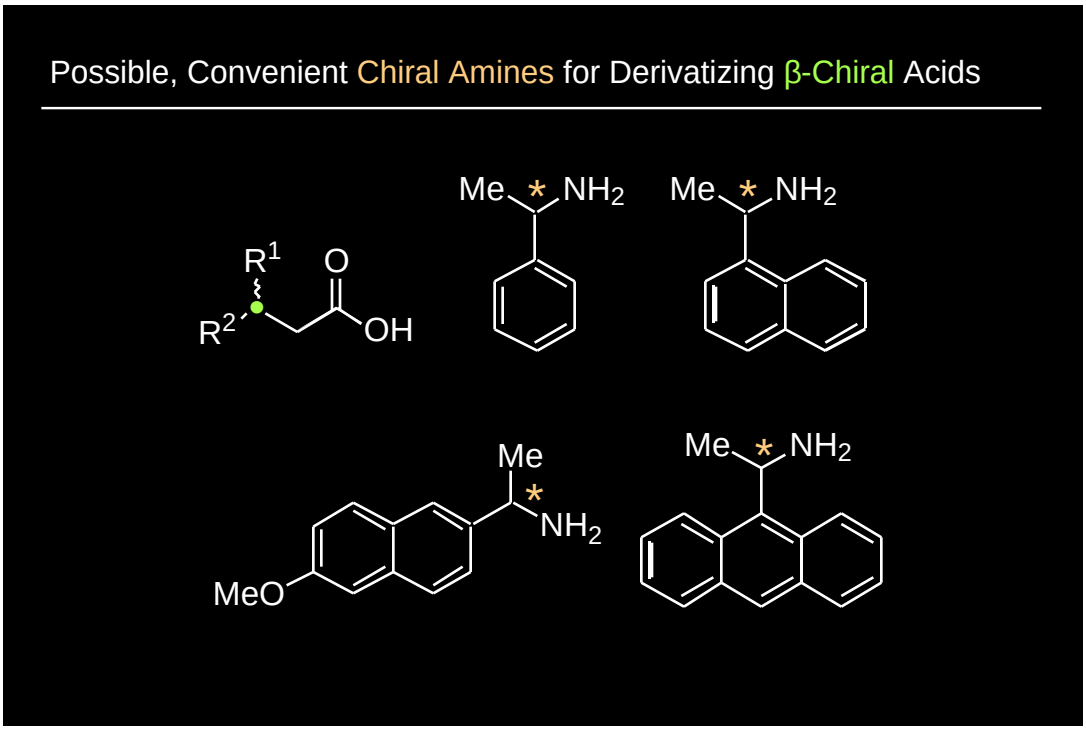

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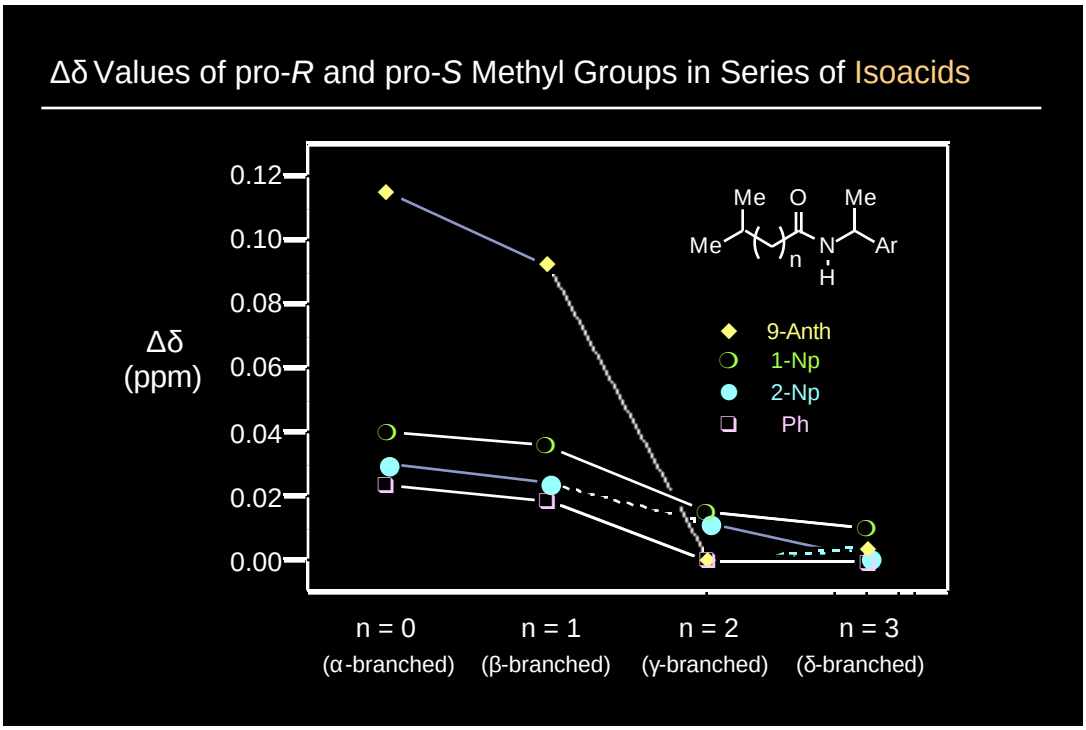

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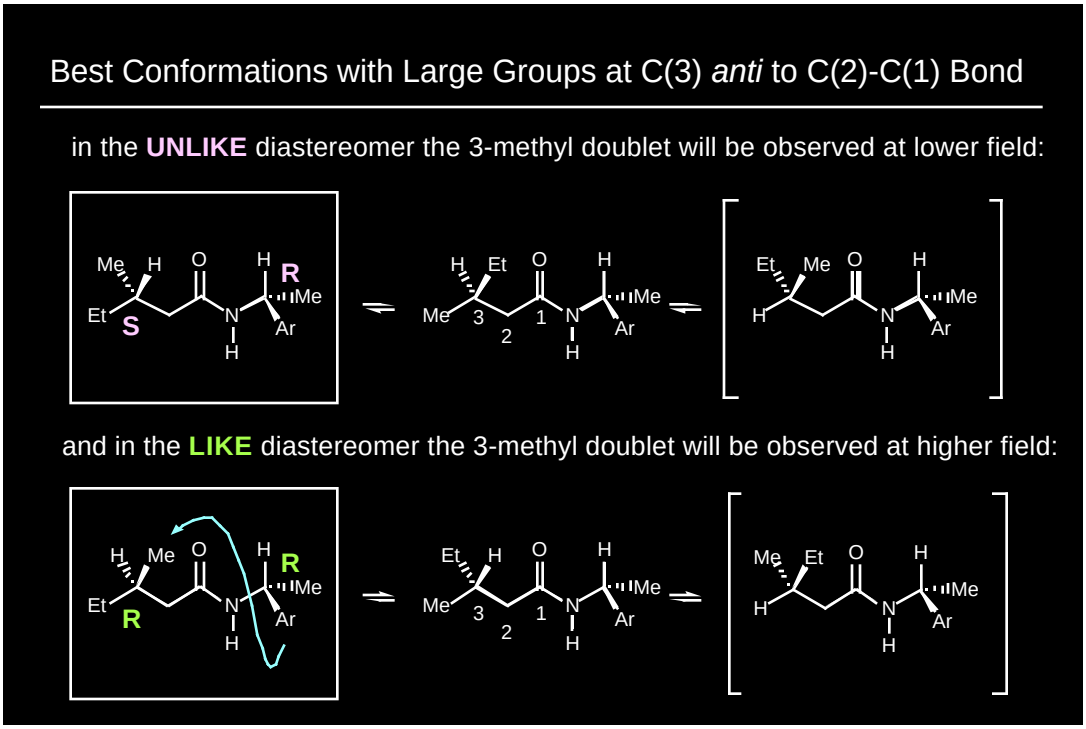

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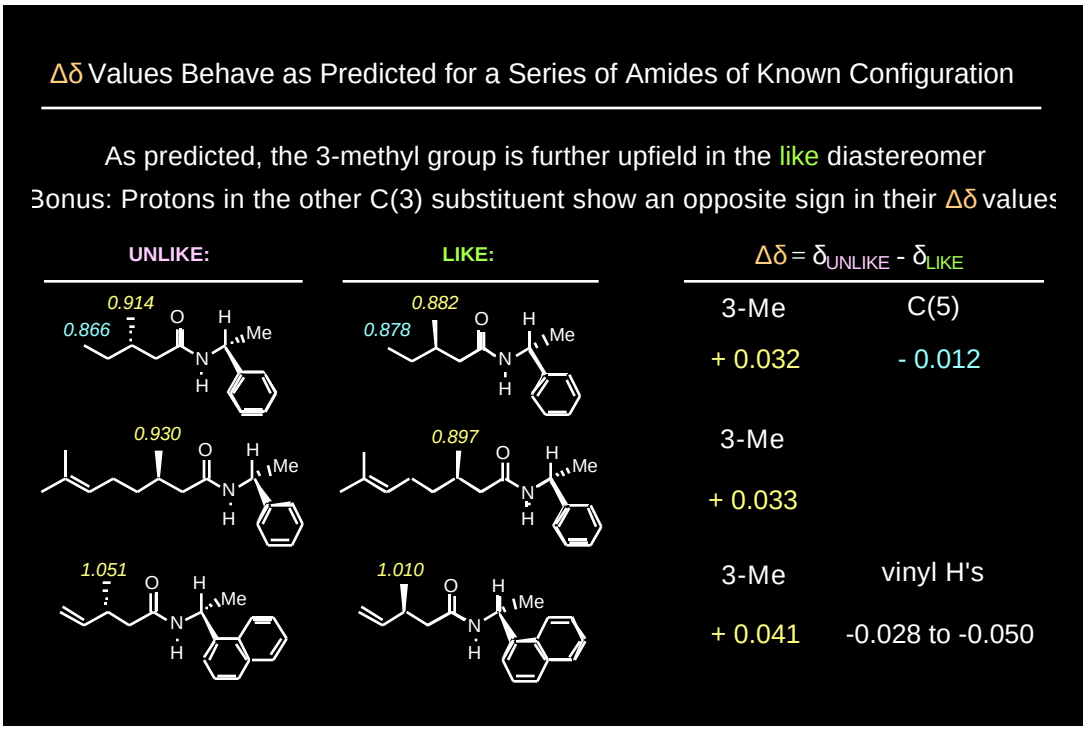
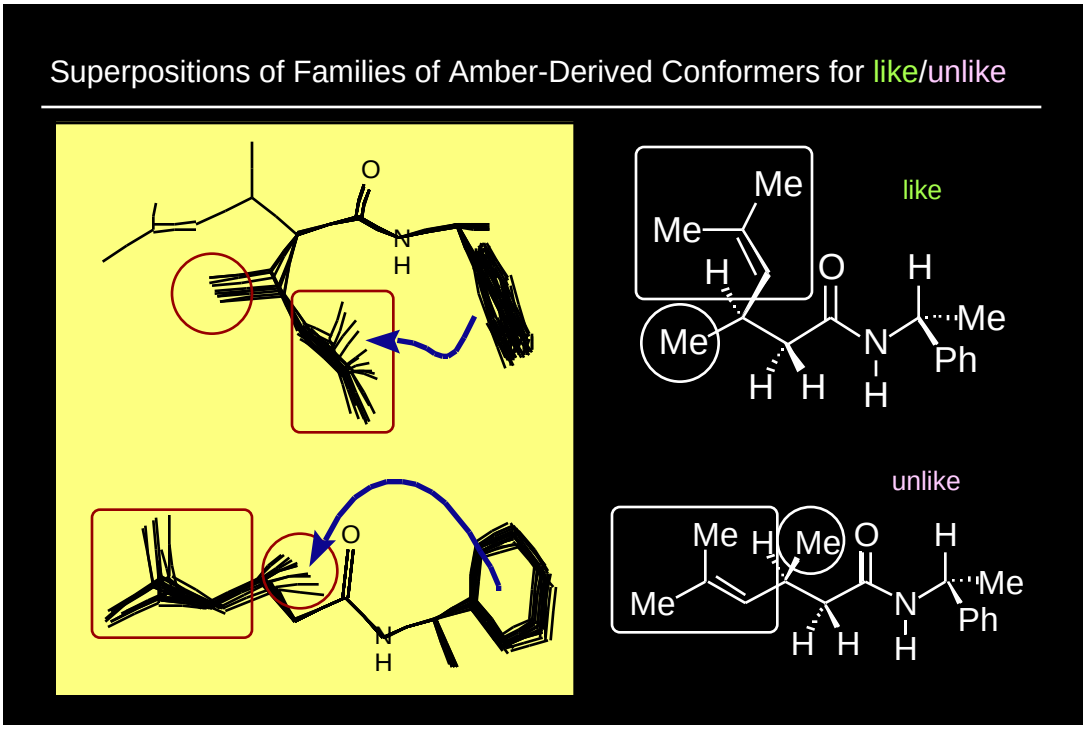


Slide #30



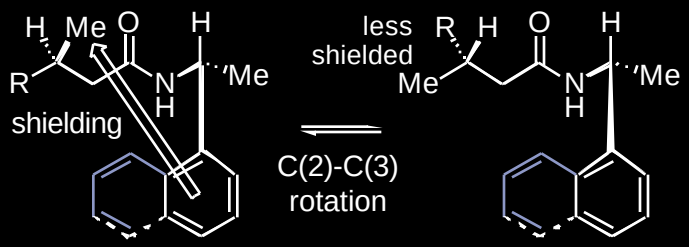
Slide #31

To Apply Method to Determination of Configuration of β-Chiral Acids:

• identify the resonance of the β-Me group as well as distinguishable ^{1}H NMR resonances for protons unique to the other substituent (R) at C(3) in the diastereomeric pair of arylethylamides.

• deduce the C(3)-configurtion by comparing the sign of Δδ for one or more of these resonances with those expected on the basis of the conformational analysis.

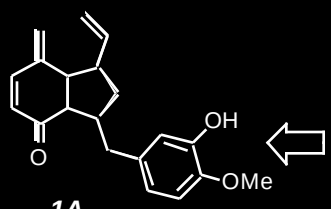
Complementarity exists; that is, the Δδs of resonances within R and those of the methyl resonance will be of opposite sign. This approach to determining the configuration of a remote stereogenic center represents a general strategy that can be adapted to other substructures.



Slide #32

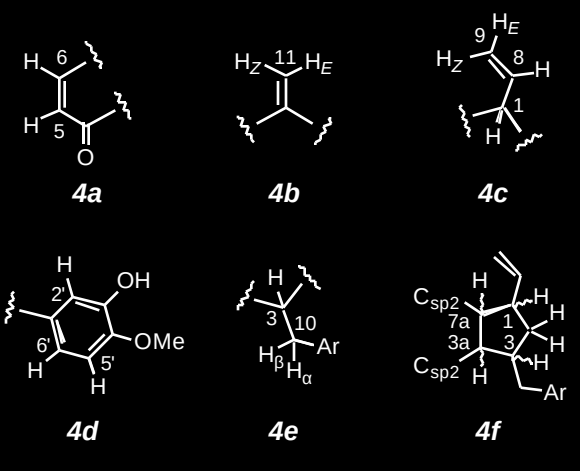
Two New Antitumor Agents

two isomers from *Ottelia alismoides*



1A
1B

potent tumor cytotoxins GI_{50}'s (and some TGI's) less than 1 nM

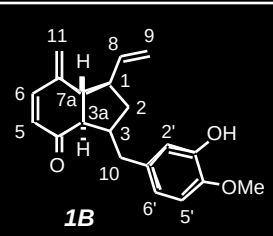


4a ***4b*** ***4c***

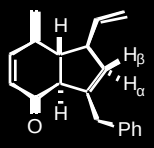
4d ***4e*** ***4f***

Slide #33

Compare Observed J's with Calculated J's for all Possible Diastereomers



1B



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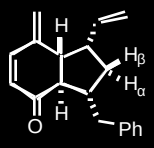

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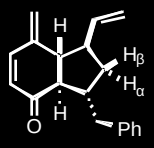


9

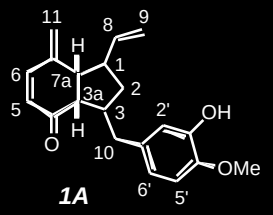
10

	observed vicinal J's	calculated vicinal J's	calculated vicinal J's	calculated vicinal J's	calculated vicinal J's
$J_{1,2a}$ etc.	9.9 etc.	7.5 etc.	1.4 etc.	9.0 etc.	9.7 etc.
		$\%J_{diff}$ = 47%	$\%J_{diff}$ = 27%	$\%J_{diff}$ = 9%	$\%J_{diff}$ = 48%

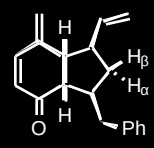
$$\%J_{diff} = \frac{\sum_{\text{vic J's}} \frac{|J_{obs} - J_{calc}|}{J_{obs}}}{\#\text{ of } J_{obs}} \times 100\%$$

Slide #34

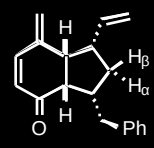
For the *cis*-Fused Isomer, $\%J_{diff}$ is Unable to Distinguish ***11*** from ***12***



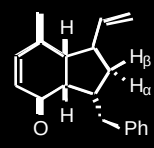
1A



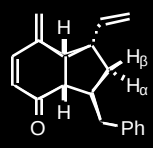
11



12



13

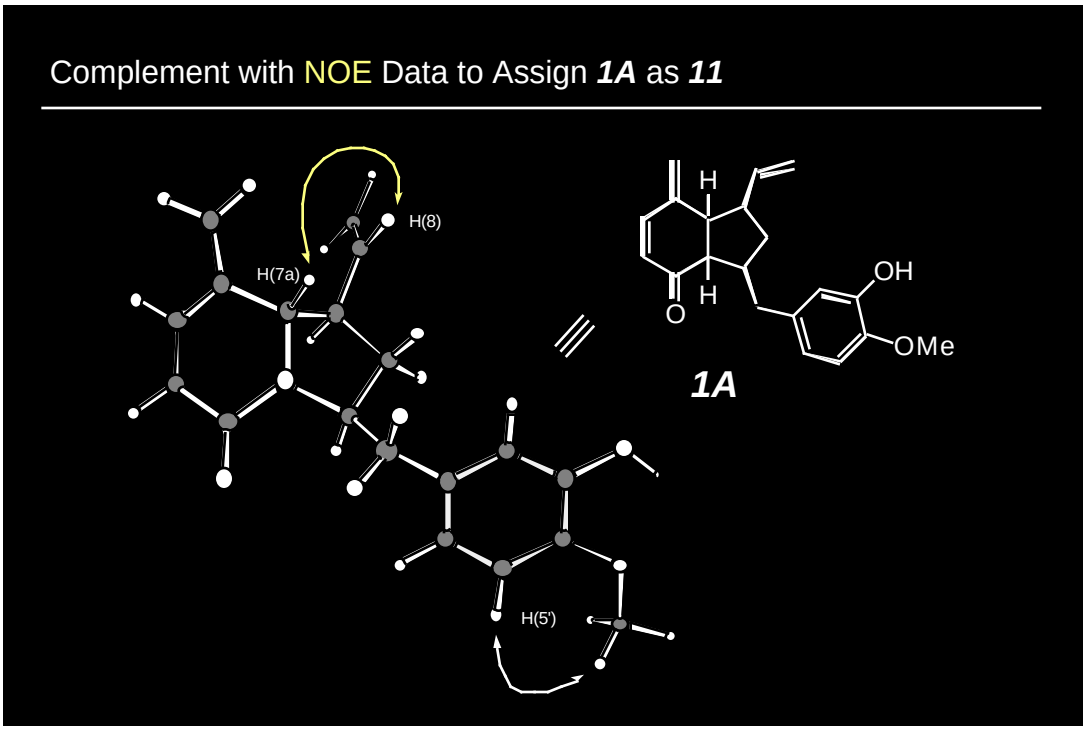


14

	observed vicinal J's	calculated vicinal J's	calculated vicinal J's	calculated vicinal J's	calculated vicinal J's
$J_{1,2a}$ etc.	6.4 etc.	4.9 etc.	10.3 etc.	6.0 etc.	1.6 etc.
		$\%J_{diff}$ = 13%	$\%J_{diff}$ = 14%	$\%J_{diff}$ = 26%	$\%J_{diff}$ = 24%

cannot distinguish on basis of coupling data

Slide #35



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