Department of Chemistry
Cumulative Examinations

January 14, 2017

You may choose to answer any exam from any area covered in the examination booklet. Each exam may contain multiple parts. You may answer more than one exam but each exam is scored separately and is treated as an individual examination result. Thus, answering parts of two exams with a score of 50% would not yield a 100% grade for this cumulative exam. Instead you would receive 50% on each examination attempted.

This booklet contains five examinations.

1) Analytical Cumulative Examination, Pages 1-3
2) Biochemistry Cumulative Examination, Pages 4-5
3) Inorganic Cumulative Examination, Pages 6-8
4) Organic Cumulative Examination, Pages 9-15
5) Physical Cumulative Examination, Pages 16-18

On your examination booklet:

1) Print your student ID number.
2) Print the Exam Booklet number.
3) Print the question number you are answering.
4) Print the Exam Date.

Do not write your name anywhere on the examination booklet. Each exam will be scored anonymously. If you attempt more than one exam, you must use a separate examination booklet for each examination.

When you complete the examination, return the examination and your answer booklet to the proctor. Exam results will be posted on bulletin board #2B on the north side of the hall near BRWN 2124.
1. Carbon monoxide is a criterion pollutant regulated by the US-EPA. The National Ambient Air Quality Standards (NAAQS) for CO measured over an 8-hour period is set at 9 parts per million parts of air. At 298K and 101.3 kPa of pressure, $R = 8.314 \text{ (L kPa)/(mol K)}$, what is the number density of CO in molecules/cm$^3$ (15 pts)?

2. An electrochemical-type CO sensor, found in household CO detectors, are amperometric fuel cells with two electrodes: A working (sensing) electrode, a counter electrode, and an ion conductor in between them. When CO comes in contact with the working electrode, oxidation of CO will occur on it through chemical reaction with water molecules in the air. A reaction with oxygen in the air will occur on the counter electrode. The overall redox reaction is $\text{CO} + \frac{1}{2} \text{O}_2 \rightarrow \text{CO}_2$

   a. What is the change in the oxidation state of C during the reaction (5 pts)?
   b. Write the two balanced electrochemical $\frac{1}{2}$ cell reactions (15 pts)
   c. Calculate the standard electrode potential for the cell (10 pts).
   d. Calculate the standard $\Delta G_{\text{cell}}$ (5 pts)
   e. Is the reaction spontaneous (5 pts)?

3. Ozone is a criterion pollutant. Its concentration is measured by absorption 254 nanometer wavelength light produced by a Hg lamp.

   a. What is the name of element whose symbol is Hg?
   b. Assuming that 254 nm light is breaking a bond in O$_3$ after absorption, what must the minimum O$_3$ bond energy be in kJ/mol?
   c. Write out Beers-Lambert law, define the terms.
   d. If the ratio of detected light intensity to initial intensity is 0.99975 in an absorption cell 10 cm long, given the absorption cross section in figure 1 (define the value you use), what is the [O$_3$]? 
   e. What is this in ppbv (parts per billion by volume) assuming that the O$_3$ is in air at 298K, 101.3 kPa (see problem 1 for shortcut)
4. In the stratosphere $\text{O}_3$ is formed via the Chapman mechanism. In this mechanism the photon concentrations ($h\nu$) are incorporated into the rate constants ($k$'s)

\[
\text{O}_2 + h\nu \rightarrow 2 \text{O} \quad k_1 \ (\text{s}^{-1}) \quad (1) \\
\dot{\text{O}} + \text{O}_2 + \text{M} \rightarrow \text{O}_3 + \text{M} \quad k_2 \ (\text{cm}^6 \text{molecule}^{-2} \text{s}^{-1}) \quad (2) \\
\text{O}_3 + h\nu \rightarrow \text{O} + \text{O}_2 \quad k_3 \ (\text{s}^{-1}) \quad (3) \\
\text{O} + \text{O}_3 \rightarrow 2 \text{O}_2 \quad k_4 \ (\text{cm}^3 \text{molecules}^{-1} \text{s}^{-1}) \quad (4)
\]

a. Write a rate law for $d\text{O}/dt$ and $d\text{O}_3/dt$.
b. Assuming $d\text{O}/dt$ is in steady state, solve for $[\text{O}]$
c. Assuming $d\text{O}_3/dt$ in steady state, solve for $[\text{O}_3]$
d. Assuming $k_3/k_4[\text{O}] \gg 1$, simplify c. (hint divide through by $k_4[\text{O}]$)
e. Use b-d to yield a $d\text{O}_3/dt$ that only depends on $[\text{O}_2], [\text{O}_3], [\text{M}]$ and the rate constants.

5. NOx ($\text{NO} + \text{NO}_2$) are criterion pollutants, emitted during fossil fuel combustion. They are detected and quantified photometrically in a “NOx Box” that utilizes the fact that $\text{O}_3 + \text{NO} \rightarrow \text{NO}_2 + \text{O}_2$ is a chemiluminescent reaction.

a. Explain how chemiluminescence differs from fluorescence and phosphorescence.
b. Is the reaction endothermic or exothermic? Justify.
c. Draw a simple energy diagram (diatomic potential wells) that convey the chemiluminescence mechanism.
d. What type of detector is likely used in this instrument?
e. What type of electromagnetic radiation is likely being emitted (IR, UV, Vis, Microwave, etc) and the corresponding molecular energy transition (vibration, rotation, electronic, nuclear spin, etc.)
f. Define what a molecular radical is. Draw the electron dot structures for NO and NO$_2$ and use them to identify whether these two compounds are radicals.

6. SO$_2$ is a US-EPA criterion pollutant. An older, manual technique to determine the SO$_2$ concentrations was to dissolve SO$_2$ (an acidic gas) from a known volume of air in a hydrogen peroxide solution, forming sulfuric acid, which was then titrated using a sodium hydroxide solution.

a. Write out the equation for the full equilibrium for the acidic gas SO$_2$ reacting with water (no peroxide present). What is the common name of the acid and the two anions.
b. Determine the oxidation state of S for each step of the equilibrium
c. What role is H$_2$O$_2$ playing in the reaction (oxidant, reductant, base, acid, disproportionation). You must justify your answer.
d. In order to accurately titrate the sulfuric acid solution, you must have an accurate sodium hydroxide solution. Discuss the challenges of making a NaOH solution of a known molarity and storing it (in particular any exposure to air).
7. Lead is a US-EPA criterion pollutant because in the dark ages (1970's) it was a gasoline additive that improved engine efficiency. Unfortunately, it is toxic. A tried and true analytical method for lead analysis is AAS. Recently ICP-OES has gained popularity.
   a. What do the AAS and ICP-OES acronyms stand for?
   b. Briefly explain how each works in principle (chemical physics).
   c. Briefly explain the practical steps required to do quantitative analysis on these instruments.
   d. Like many metals, samples are usually prepared in a nitric acid solution. Why is this done?

\[
\begin{align*}
\text{CO}_2 + 2 \text{H}^+ + 2 \text{e}^- & \rightarrow \text{HCOOH} & E_0 &= -0.61 \text{ V} \\
\text{CO}_2 + 2 \text{H}^+ + 2 \text{e}^- & \rightarrow \text{CO} + \text{H}_2\text{O} & E_0 &= -0.53 \text{ V} \\
\text{CO}_2 + 4 \text{H}^+ + 4 \text{e}^- & \rightarrow \text{HCHO} + \text{H}_2\text{O} & E_0 &= -0.48 \text{ V} \\
\text{CO}_2 + 6 \text{H}^+ + 6 \text{e}^- & \rightarrow \text{CH}_3\text{OH} + \text{H}_2\text{O} & E_0 &= -0.38 \text{ V}
\end{align*}
\]

\[h = 6.626 \times 10^{-34} \, J \cdot \text{s} \quad \text{for} \quad \text{CO}_2 + 8 \text{H}^+ + 8 \text{e}^- \rightarrow \text{CH}_4 + 2 \text{H}_2\text{O} \quad E_0 = -0.24 \text{ V}\]
(1) Some proteins are coupled to the plasma membrane through hydrocarbon chain-containing membrane anchors. Provide the names and draw the structures of three types of such membrane anchors and provide their localization within the plasma membrane. (21 points)

(2) The modern view of the plasma membrane is that of a complex, supramolecular system, in which lipids and membrane proteins are organized in small, dynamic patches. One type of those membrane patches is called lipid raft.

(a) What can you say about the abundance of unsaturated phospholipids, glycosphingolipids, and cholesterol in lipid rafts? (9 points)

(b) A key feature of lipid rafts is their ability to regulate the distribution of membrane proteins in the plasma membrane. In contrast to many transmembrane proteins, lipid-anchored proteins in the exoplasmic leaflet of the plasma membrane often have a higher affinity for lipid rafts. Provide the name of this type of raft-associated lipid-anchored protein and explain why those lipid-anchored proteins show a different affinity for raft domains than most transmembrane proteins. (5 points)

(c) The physicochemical nature of raft-mediated protein sequestration processes can be demonstrated in model membranes containing raft-mimicking lipid mixtures. What physicochemical differences of coexisting raft and non-raft regions cause the sequestration of membrane proteins? How do these physicochemical differences impact the sequestration of lipid-anchored proteins versus transmembrane proteins? (10 points)

(d) Binding of native ligands may alter the sequestration of membrane proteins in the presence of lipid rafts. Describe two different molecular mechanisms through which the ligand binding process may influence raft affinity. (10 points)

(3) A hallmark of the plasma membrane is the rotational and lateral diffusion of membrane proteins in the fluid lipid bilayer.
(a) Which of the two diffusion processes is faster? *(3 points)*

(b) How does the size of membrane proteins influence their mobility in the lipid bilayer? Compare the cases of lateral and rotational diffusion. *(12 points)*

(c) Fluorescence recovery after photobleaching (FRAP) represents one frequently used method for the analysis of membrane protein lateral mobility in cell and model membranes. Describe the principle of the method and show one typical FRAP curve. What information can be obtained from a FRAP curve? *(10 points)*

(4) High-speed single molecule tracking experiments demonstrated that membrane proteins diffuse within small membrane compartments before they hop to the next compartment. This process is known as hop diffusion. Explain the underlying mechanism that leads to the observed membrane compartmentalization? *(10 points)*

(5) Imagine, you want to monitor the complex formation between two different laterally mobile membrane proteins in a lipid bilayer. How would you set up such an experimental assay using a single molecule-sensitive fluorescence imaging system, which is equipped with two separate fluorescence channels? *(10 points)*
Inorganic Cume (Jan. 2017)

Olefin Oligomerization Catalysis

The Dinca group recently published several studies on catalytic ethylene dimerization using the metal organic framework (MOF) Ni-MFU-4I. The catalytic units are structurally analogous to previously reported single-site Ni catalysts but produce 1-butene with higher selectivity.


1. The MOF active site and homogeneous catalyst are shown below. (10 points)

![Diagram of MOF and homogeneous catalyst]

a. Determine the point group, total electron count, and Ni oxidation state for the homogeneous complex $\text{Tp}^{\text{Mes}}\text{NiCl}$.

b. Sketch a d-orbital splitting diagram for $\text{Tp}^{\text{Mes}}\text{NiCl}$.

2. The Ni-MFU-4I catalyst, as with many olefin polymerization catalysts, requires activation by an alkyl aluminum reagent such as methylaluminoxane $(\text{Al(CH}_3)_3\text{O}_3)_n$. Propose a mechanism for the activation of the MOF catalyst using $\text{Al(Et)}_3$. You may abbreviate the MOF active site as shown below in all future problems. (10 points)

![Diagram of Ni-MOF active site]
3. Two possible mechanisms are typically proposed for ethylene dimerization to form 1-butene, involving either sequential addition of monomers (Cossee-Arlman) or metallocycle formation. Sketch these two mechanisms. For each intermediate in the catalytic cycle, give the total electron count and oxidation state of Ni. (40 points)

4. A classical mechanistic experiment in ethylene oligomerization involves cofeeding a 1:1 mixture of C₂H₄ and C₂D₄. (10 points)
   a. For the two mechanisms proposed above, assuming no off-cycle reactions, what product distributions would you expect to see? List all possible products in the metallocycle mechanism.
   b. Can you distinguish between the two mechanisms proposed using this experiment?

5. The authors proposed that the Ni-MOF catalyst proceeds through a Cossee-Arlman mechanism. Other catalysts that proceed via the same mechanism such as (bpy)NiBr₂ produce a distribution of molecular weights for the resulting polyethylene oligomers. Based on the relative rates of steps in the catalytic cycle, explain why the Ni-MOF selectively produces 1-butene. (10 points)

6. It has been shown that the molecular catalyst (bpy)NiBr₂ proceeds through a Cossee-Arlman mechanism and produces a distribution of polyethylene oligomers while (PPh₃)₂Ni(cod) proceeds through a metallocycle mechanism and produces primarily 1-butene and small amounts of cyclobutane. (20 points)
   bpy = bipyridine, cod = cyclooctadiene
   a. For (PPh₃)₂Ni(cod), determine its point group and sketch a d-orbital splitting diagram.
   b. Explain why the two catalysts proceed through different mechanisms.

A Communication reporting the total syntheses of Aflavazole and 14-Hydroxyaflavinine by Ang Li was the most read paper in JACS during the month of Dec. 2016.

**Answer any 5 of the 6 Following Questions.**

1. a) The synthesis commences with the preparation of 19. Propose a mechanism using the arrow-pushing convention for the conversion of 20 into 19. (**NOTE: you may abbreviate the chiral ligand as L, and you do not need to account for the absolute stereochemistry). *(15 pts)*

   ![Reaction Scheme](image)

   b) What is the purpose of the TMS group, and why do the authors not use methyl vinyl ketone in the annulation? *(5 pts)*

2. a) The authors employ a Cu-catalyzed reaction to install a stereogenic BPin substituent. Provide a plausible catalytic cycle for the reaction. A complete answer should include a clear indication of the ligands bound to Cu and the Cu oxidation state of each intermediate. (**NOTE: you may abbreviate the structure of the substrate in your mechanism as cyclohexenone). *(15 pts)*

   ![Reaction Scheme](image)

   b) Provide a carefully-rendered three-dimensional representation of 18, and rationalize the observed relative stereochemistry of the newly formed -BPin group. *(5 pts)*
3. The authors employ a Pd-catalyzed reaction to effect a one-carbon homologation and install a methyl ester (30). Provide a plausible catalytic cycle for the reaction. A complete answer should include a clear indication of the ligands bound to Pd and the Pd oxidation state of each intermediate. (**NOTE: you may abbreviate the structure of the substrate in your mechanism). (20 pts)

4. Propose a mechanism using the arrow-pushing convention for the conversion of 12 into 11. (**NOTE: you may abbreviate the structure of the substrate in your mechanism). (20 pts)

5. a) A Julia-type olefination reaction is used to build a triene intermediate (10). Propose a mechanism using the arrow-pushing convention for the conversion of 34 into 10. (**NOTE: you may abbreviate the structure of the substrate in your mechanism). (15 pts)

b) Why might the authors have elected to use a Julia olefination rather than a Wittig olefination? (5 pts)
6. A related natural product, hydroxyeujindole A, is thought to be biosynthetically derived from anominine. Provide a biosynthetic proposal for the conversion of anominine into hydroxyeujindole A. (**NOTE: you do not need to provide any enzymes, use generic oxidants/reductants or acids/bases as needed). (20 pts)
Total Syntheses of Aflavazole and 14-Hydroxyaflavinine

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Supporting Information

ABSTRACT: The first total syntheses of aflavazole (6) and 14-hydroxyaflavinine (8), two sterically congested indole diterpenoids, were accomplished. All3-promoted alkyne Prins cyclization was exploited to construct their key structural motifs. An electrocyclization–aromatization sequence assembled the pentasubstituted arene of 6, and a Stille–Migita coupling furnished the tetrasubstituted olefin of 8. The benzylic and allylic C–O bonds were reductively cleaved at the late stage of the syntheses, respectively.

Indole diterpenoids are intriguing targets to synthetic chemists. In 1989, Cloer et al. isolated anominine (1, Figure 1), an unusual indole diterpenoid possessing a congested decalin scaffold, from Aspergillus. A class of more complex congeners were also discovered (e.g., 2–8), some of which exhibited promising biological properties. Danishefsky et al. reported a beautiful synthesis of racemic 12-demethyl aflavinine (7). Recently, the groups of Bonjoch and Garg accomplished elegant asymmetric syntheses of 1 and 2, respectively, and our endeavors toward indole terpenoid synthesis resulted in the syntheses of 1–3. Aflavazole (6) and 14-hydroxyaflavinine (8) featuring the multisubstituted arene and olefin motifs, respectively, pose considerable synthetic challenges; introduction of the C14 hydroxyl adjacent to the vicinal quaternary carbons adds extra difficulty. Herein, we describe the first and asymmetric total syntheses of 6 and 8.

The structural relationship between 3 and 4 inspired us to develop a reversed bioinspired strategy for the syntheses of 6 and 8 (Figure 2). Biogenetically, 3 may arise from 4 via oxidative etherification. Conversely, we envisioned 9 as an immediate precursor of 6; reductive cleavage of the benzyl ether could afford the natural product. Our experience with electrocyclization and Prins10,11 reactions suggested an opportunity for an expedient route to the heptacyclic scaffold of 9. Triene 10 was considered to

Figure 1. Selected members of the anominine family.

Figure 2. Retrosynthetic analysis of 6 and 8.

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be a suitable substrate for electrocyclization—aromatization.12 Disassembly of 10 led to iodide 11; Pd-catalyzed cross-coupling with iodide 11 would install the indole moiety to the latter. The bridged ring system of 11 could be constructed through Prins cyclization of alkyne 12.22 23 Overman and co-workers elegantly showcased the power of alkyn Prins cyclization in their syntheses of pemiproitoxin alkaloids two decades ago.11b–d However, this reaction has long been underestimated in natural product synthesis since then.11c,14 Alkyne Prins reaction is indeed of significant advantage from the following aspects: (1) the strong driving force to form congested and strained ring systems, (2) the well-defined geometry of multidente substituted olefin products, and (3) versatile transformations of the haloalkene products by transition-metal catalysis. Similarly, 8 was traced back to 13 via the intermediacy of 14, although the bulky isopropyl posed a challenge to Prins cyclization and cross-coupling. In these syntheses, we preferred alkyn iodides to bromides/chlorides because of their superior reactivity in Pd catalysis. Ketones 15 and 16 would serve as precursors of 12 and 13, respectively.14 Disconnection of the C10–C11 bonds of these ketones revealed alkyl iodide 17 as a common substrate for Nozaki–Hiyama reactions. We planned to incorporate the C14 hydroxyl into a substrate such as enone 18, which was further simplified as 19.15b Sequential conjugate addition and Robinson annulation starting from readily available 20, 21, and Me₂Al were expected to deliver this known compound more efficiently.

The synthesis commenced with the construction of tricycle 18 (Scheme 1). Asymmetric 1,4-addition of CuTC, (R,S,S)-22, Me₂Al to 20 established the C16 stereochemistry,4 upon in situ activation with MeI and HMPT, the enolate attacked Stork–Ganem reagent22 21 to give the α-silyl ketone. Treatment with NaOMe afforded 19 in 49% overall yield with 95% ee. This two-step protocol was superior to our previous one involving Stork–Jung vinylsilane16 for the diastereoselectivity at C15 (>30:1 vs 3:8:1). 19 underwent a known three-step sequence to reach iodide 23,5b which was converted to bis-enone 24 via silyl enol ether formation and IBX oxidation.17 Luche cyclization (Zn, Cul) followed by epimerization at C22b provided 18 smoothly.

We then prepared the common intermediate 17 from 18 (Scheme 1). Functionalization at C14 was effected by boron conjugate addition (CuCl, 25, NaOtBu, B(OPh)₃).18 However, X-ray crystallographic analysis of the resultant borone 26 revealed an undesired configuration of C14 (Scheme 1). Triflation of this ketone followed by oxidative cleavage of the C–B bond afforded alcohol 27, which may find direct use in the synthesis of naturally occurring 5,3d Sequential DMP oxidation and Dibal-H reduction inverted the C14 stereochemistry. The resultant alcohol 28 was silylated with 29 and subjected to Pd-catalyzed methoxycarbonylation to generate ester 30. Reduction and iodination (Ph₃P, I₂, imidazole) furnished alyl iodide 17.

We moved forward to the synthesis of Prins substrate 12 (Scheme 2). Nozaki–Hiyama reaction of 17 with acetaldheyde furnished alcohol 31 as a single detectable diastereomer. Hydrogenation of the exocyclic olefin (NaBH₄, NiCl₂) proceeded with excellent facial selectivity to give 32, the structure of which was confirmed by X-ray crystallographic analysis of its distylated derivative (Scheme 2). TPAP oxidation furnished ketone 15, which was converted into terminal alkyn 12 through triflation and TBAP-mediated elimination19 and destylation.

Investigations of the Prins cyclization of 12 are summarized in Table 1. The combination of Bu₄NI and CSA 10b,11d–e proved ineffectively to activate the acetate at 22 °C (entry 1) but decomposed the substrate at elevated temperature. Treatment with TMSCl5b resulted in a complex mixture with a small amount of the desired product 11 (entry 2). In contrast to the commonly used Prins promoters FeCl₃ and Fe(CO)₅, FeCl₃ is unstable due to a self-redox reaction. Thus, we move recourse to the combination of Fe(acac)₃ and TMSCI,11b and 11 was obtained in 43% yield (entry 3). Although SnCl₄ and SnBr₄ worked generally well in alkyn cyclization,12–14 SnI₂ was ineffective in this case (entry 4). Exposure to TiI₄ 13m–n and AlCl₃ in CH₂Cl₂ gave 11 in 32% and 51% yields (entries 5 and 6, respectively). Replacing CH₂Cl₂ with toluene improved the yield of the AlCl₃-mediated cyclization to 68% (entry 7). GaCl₃ was less efficient in this transformation (entry 8). Unfortunately, we could not identify the byproducts of these reactions. The discovery of AlCl₃ as a powerful promoter for the Prins reaction may enable further applications of this transformation in synthesis.

The final stage of the synthesis of 6 is depicted in Scheme 2. Stille–Migita coupling of 11 with 33 gave compound 34, which underwent Julia–Kocienski olefination to reach triene 10. 6x Electrocyclization of the triene occurred at 90 °C, and subsequent DDQ oxidation6e furnished arane 36 in 82% overall yield. Reductive cleavage of the benzylic ether (TiCl₄, Et₃SiH) followed by desulfonation with Mg, afforded 6. Its structure was verified by X-ray crystallographic analysis (Scheme 2).
Scheme 2. Completion of the Synthesis of 6

Table 1. Iodo-Prins Cyclization of 12

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>11 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu₄NI (5 equiv), CSA (2 equiv), MeCN, 22 °C</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>TMSI (5 equiv), toluene, −10 °C</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Fe(acac)₃ (20 mol %), TMSI (3 equiv), Mel, 22 °C</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>Sn₄ (6 equiv), CH₂Cl₂, 22 °C</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>TiCl₄ (6 equiv), CH₂Cl₂, −40 °C</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>AlCl₃ (6 equiv), CH₂Cl₂, −78 °C</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>AlCl₃ (6 equiv), toluene, −78 °C</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>GaCl₃ (6 equiv), toluene, −40 °C</td>
<td>42</td>
</tr>
</tbody>
</table>

We further studied the more challenging Prins reaction for the synthesis of 8 (Scheme 3). The common intermediate 17 was subjected to a similar sequence (vide supra) to give internal alkyne 13 via the intermediary of 37 and 16. The cyclization (AlCl₃, toluene, −78 °C) proceeded smoothly to give a pair of regioisomers; the desired product 14 was isolated in 58% yield, along with its five-membered ring counterpart 38 (19% yield). Treatment of 13 with InCl₃ altered the ratio of 14 and 38 (34% and 30% yields, respectively). 14 underwent sequential cross-coupling (with stannane 39), C–O bond cleavage, and desulphonation to reach 8. The structures of 38 and 8 were confirmed by X-ray crystallographic analysis (Scheme 3), respectively. The spectra and physical properties of synthetic 6 and 8 were identical to those reported for the natural products. Notably, the alkenyl triflates derived from ketones 15 and 16 performed poorly in Pd-catalyzed cross-coupling due to the rapid elimination to form the corresponding alkenes, respectively, which hampered the potential application of the alkene Prins cyclization strategy developed in our epoxidejindole A synthesis to the syntheses of 6 and 8.

In summary, we accomplished the first total syntheses of aflazavole (6) and 14-hydroxyaflavoline (8), featuring a reversed bioinspired strategy and AlCl₃-mediated alkyne Prins reactions. The chemistry developed may and further use in the construction of sterically congested ring systems and facilitate the biological and biosynthetic studies of the indole diterpenoids.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10880.

Experimental procedures; compound characterization (PDF)

Crystallographic data (CIF, CIF, CIF, CIF, CIF)
The paper is dedicated to Prof. Larry Overman. We thank Prof. Jim Gloer for providing the authentic NMR spectra of 6 and 8 and CD spectrum of 6 and remeasuring the optical rotation of 6, and Xiaoli Bao and Lingling Li from the Instrumental Analysis Center of Shanghai Jiao Tong University for X-ray crystallographic analysis. Financial support was provided by Ministry of Science & Technology (2013CB836900), National Natural Science Foundation of China (21525209, 21290180, 21621002), Chinese Academy of Sciences (XDB20020000), and Shanghai Science and Technology Commission (15JC1400400).

**Acknowledgments**


**References**


Consider the 1,3,5-hexatriene molecule, which has six structural isomers, the two lowest energy of which are shown below.

\[ \text{ttt-1,3,5-hexatriene} \quad \text{tct-1,3,5-hexatriene} \]

1. **Molecular shape and symmetry (20 pts = 5 pts each)**
   
   a. Identify the symmetry elements each isomer possesses and their point group symmetry.
   
   b. Sketch the structure of one of the other hexatriene isomers not shown above, and identify its point group symmetry.
   
   c. Identify the reaction coordinate for isomerization between the ttt and tct isomers, and sketch a potential energy curve along this reaction coordinate.
   
   d. Estimate the barrier height you would anticipate for this isomerization, and how you arrived at that estimate.

2. **Vibrations (25 pts = 5 pts each)**
   
   a. How many vibrational degrees of freedom does the molecule possess?
   
   b. What are the symmetries of the two vibrations shown below?
   
   c. Identify whether each of these two vibrations will be infrared and/or Raman active, defending your answer in each case.
   
   d. The harmonic vibrational frequency calculated for the vibration on the left at a certain level of theory is 889.06 cm\(^{-1}\). Make an estimate for the vibrational frequency of the vibration on the right, and state your reasoning.
   
   e. Without doing the calculation, state how you would compute the vibrational zero-point energy for the molecule, if you were given the full set of harmonic vibrational frequencies.
3. Rotations (12 pts = 6 pts each)
Non-linear polyatomic molecules have three rotational degrees of freedom, corresponding to rotation about three unique inertial axes, labeled the ‘a’, ‘b’, and ‘c’ inertial axes, which are perpendicular to one another. The moment of inertia for molecular rotation about the ‘a’ axis is defined as: \( I_a = \sum_i m_i R_i^2 \) where the sum is over the atoms ‘i’ and \( R_i \) is the closest distance of the \( i^{th} \) atom from the ‘a’ inertial axis. The three rotational constants \( A, B, \) and \( C \) are inversely related to the moments of inertia; that is,
\[
A = \frac{\hbar}{8\pi^2 I_a}
\]

a. Without doing any calculations, draw on the figure the approximate positions of the ‘a’, ‘b’, and ‘c’ inertial axes, recalling that by definition, \( I_a < I_b < I_c \).

b. The inertial defect is defined as: \( \Delta = I_b - I_a - I_c \). According to the calculations, \( \text{t} \text{t} \text{h} \text{e} \text{x} \text{t} \text{r} \text{i} \text{e} \text{n} \text{i} \text{e} \) has \( A = 26.273 \) GHz, \( B = 1.3307 \) GHz, and \( C = 1.2666 \) GHz. Calculate the inertial defect, reporting your answer in \( \text{amu} \cdot \text{Å}^2 \), and comment on its size relative to the masses and bond lengths involved. Hint: The deviation from zero of the inertial defect is used to check how nearly planar a molecule is.

4. Electronic states (42 pts = 6 pts each)
Consider the six \( \pi \) electrons of 1,3,5-hexatriene as moving in a one-dimensional particle-in-a-box with one end of the box at \( x=0 \) and the other at \( x=L \), for which the wave functions are
\[
\psi_n(x) = A_n \sin\left(\frac{n\pi x}{L}\right)
\]
where \( n=1,2,3 \ldots \), and energy levels
\[
E_n = \frac{n^2 \hbar^2}{8mL^2}
\]

a. Estimate the length of the box, making reasonable estimates for the bond lengths involved.

b. Calculate the energies in eV for \( n=1-6 \). These are your estimates for the molecular orbitals in this simple model.

c. Construct an energy-level diagram that presents these energy levels, and put the electrons into the molecular orbitals to predict the ground state electronic configuration. This lowest singlet state is called the \( S_0 \) state.

d. Construct a second energy level diagram that shows the expected electronic configuration for the first excited singlet state of the molecule, \( S_1 \).

e. Use the particle-in-a-box model to predict the \( \Delta E \) for this lowest energy transition, the \( S_0 \rightarrow S_1 \) transition, and turn this \( \Delta E \) into a wavelength for the transition.

f. Compare your result to the known wavelength for the \( S_0-S_1 \) transition in \( \text{t} \text{t} \text{h} \text{e} \text{x} \text{i} \text{e} \text{n} \text{i} \text{e} \) of 251 nm, and comment on the accuracy of your simple model.

g. Draw the qualitative shape of the first six molecular orbitals by drawing the set of \( p \)-orbitals associated with each, and including the signs of the lobes of the \( p \)-orbitals from which the molecular orbitals are constructed.

5. Gift (1 pt): True or False:
Purdue’s Loeb Playhouse received that name because the donor who funded its construction was a chemistry major who loved to draw the lobes of orbitals.
\( h = 6.626 \times 10^{-34} \text{ J s} \)

1 amu = \( 1.66 \times 10^{-27} \text{ kg} \)

1 GHz = \( 10^9 \text{ Hz} \)

1 eV = \( 1.6 \times 10^{-19} \text{ J} \)

\[
\begin{array}{c|cccc|c|c|c|c}
C_{2h} & E & C_2 & i & \sigma_h & R_z & x^2, y^2, z^2, xy \\% \\
\hline
A_g & 1 & 1 & 1 & 1 & 1 & z, yz \\
B_g & 1 & -1 & 1 & -1 & 1 & xz, yz \\
A_u & 1 & 1 & 1 & 1 & 1 & x, y \\
B_u & 1 & -1 & 1 & 1 & 1 & x, y \\
\end{array}
\]

\( 1 \text{ J} = 1 \text{ kg m}^2 \text{s}^{-2} \)

\[
\begin{array}{c|ccccccc|c|c|c|c|c}
D_{2h} & E & C_2(z) & C_2(y) & C_2(x) & i & \sigma(xy) & \sigma(xz) & \sigma(yz) & x^2, y^2, z^2, xy \\
\hline
A_g & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & z, yz \\
B_{1g} & 1 & 1 & -1 & -1 & 1 & 1 & 1 & -1 & 1 & z, yz \\
B_{2g} & 1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & 1 & z \\
B_{3g} & 1 & -1 & 1 & -1 & 1 & 1 & -1 & 1 & 1 & z \\
A_u & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & x \\
B_{1u} & 1 & 1 & -1 & -1 & 1 & 1 & 1 & 1 & 1 & y \\
B_{2u} & 1 & -1 & 1 & -1 & 1 & 1 & 1 & 1 & 1 & x \\
B_{3u} & 1 & -1 & 1 & -1 & 1 & 1 & 1 & 1 & 1 & x \\
\end{array}
\]

\[
\begin{array}{c|cccc|c|c|c|c|c}
C_{2v} & E & C_2 & \sigma_c(xz) & \sigma_c'(yz) & x^2, y^2, z^2 \\
\hline
A_1 & 1 & 1 & 1 & 1 & 1 & z \\
A_2 & 1 & 1 & -1 & -1 & 1 & xy \\
B_1 & 1 & -1 & 1 & -1 & 1 & x, R_z \\
B_2 & 1 & -1 & 1 & -1 & 1 & y, R_x \\
\end{array}
\]

\[
\begin{array}{c|cccc|c|c|c|c|c|c}
D_{2d} & E & 2S_4 & C_2 & 2C_2' & 2\sigma_d & x^2 + y^2, z^2 \\
\hline
A_1 & 1 & 1 & 1 & 1 & 1 & z, yz \\
A_2 & 1 & 1 & -1 & -1 & 1 & xy \\
B_1 & 1 & -1 & 1 & -1 & 1 & (x, y); (R_x, R_y) \\
B_2 & 1 & -1 & 1 & -1 & 1 & (x, y); (R_x, R_y) \\
E & 2 & 0 & -2 & 0 & 0 & (R_x, R_y) \\
\end{array}
\]

\[
\begin{array}{c|c|c|c|c|c|c}
C_s & E & \sigma_h & x^2, y^2, z^2, xy \\
\hline
A' & 1 & 1 & x, y, R_z \\
A'' & 1 & -1 & z, R_x, R_y \\
\end{array}
\]

18
## Periodic Classification of the Elements

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### Lanthanides

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| 59 Pr | 140.97 |
| 60 Nd | 144.24 |
| 61 Pm | 147.00 |
| 62 Sm | 150.35 |
| 63 Eu | 151.96 |
| 64 Gd | 157.25 |
| 65 Tb | 158.924 |
| 66 Dy | 162.50 |
| 67 Ho | 164.930 |
| 68 Er | 167.26 |
| 69 Tm | 168.934 |
| 70 Yb | 173.04 |
| 71 Lu | 174.97 |

### Actinides

| 90 Th | 232.038 |
| 91 Pa | 238.03 |
| 92 U | 238.03 |
| 93 Np | 237.03 |
| 94 Pu | 242.03 |
| 95 Am | 243.03 |
| 96 Cm | 247.03 |
| 97 Bk | 247.03 |
| 98 Cf | 249.03 |
| 99 Es | 254.03 |
| 100 Fm | 253.03 |
| 101 Md | 256.03 |
| 102 No | 256.03 |
| 103 Lw | 257.03 |

(Numbers in parentheses are the mass numbers of the most stable isotopes.)