

**Organic Chemistry
Cumulative Exam Answers
September 11, 1998**

[Denmark, S. E.; Herbert, B. *J. Am. Chem. Soc.* **1998**, *120*, 7357.]

GENERAL INSTRUCTIONS: Feel free to use partial structures in writing mechanisms and structures.

NOTE: The high-point questions are II.C (12 points) and IV.E (20 points)

I. (10 points) **Introduction**

- A. Three stereoisomers of a particular class of necine alkaloids (those with a hydroxymethyl group at C₃) are shown; how many additional stereoisomers of this structural type are possible? Justify your answer.
- B. Note that the name under the third compound is shown in quotation marks and that reference 2(b) says "reported synthesis." What is the reason for these unusual features?
- C. This synthetic strategy is described as a "tandem [4+2]/[3+2] cycloaddition of nitroalkenes." What is meant by "cycloaddition"? What is meant by "tandem"?

II. (30 points) **Scheme 1**

- A. The discussion refers to a "suitably configured nucleofugal group LG" in structure **2**. What does "nucleofugal" mean? Give a simple example of a well-known reaction that involves a nucleofugal group.
- B. The discussion of the strategy stipulates "an exo selective intermolecular [3+2] cycloaddition of nitronate **4** with a Z-configured dipolarophile (**3**) from the face of the nitronate opposite the C(4) substituent." Let's explore the many terms in this passage:
 - 1. What is meant by "[3+2] cycloaddition"?
 - 2. Why is **3** called a "dipolarophile"?
 - 3. Had the stereochemistry been endo (instead of exo), what feature(s) of product **2** would be different?
 - 4. Had the dipolarophile been *E* (rather than *Z*), what feature(s) of product **2** would be different?
 - 5. Had the addition been on the same face (rather than the opposite face) as the C(4) substituent, what feature(s) of product **2** would be different?
- C. As mentioned in the text, nitronate (+)-**4** was made according to a previously published procedure: a [4+2] cycloaddition of a nitroalkene (ref. 4). Based on your knowledge of the Diels-Alder reaction, what were the structures (including stereochemistry, if needed) of the reactants (the nitro alkene and its partner) for this [4+2] cycloaddition?

III. (10 points) **Scheme 2**

- A. Compound **8** was selected as having the features discussed for the idealized **3**. What is the structure of TDSOCH₂CHO (shown beneath the first arrow in the synthesis)?
- B. *Syn* reduction of the triple bond in **6** was accomplished by hydroboration/protonolysis. Show the structure of the initially formed hydroboration product from (c-C₆H₁₁)BH + **6** and give a mechanistic explanation for why the protonolysis (which does not occur with strong acids like H-Cl) proceeds smoothly with HOAc.

IV. (50 points) **Scheme 3**

- A. Reaction of **4** with **8** is reported to produce "a 26/1 ratio of diastereomers" in which **9** is the principal component. What is the structure of what the authors suspect is the minor component? Is it a diastereomer of **9**?
- B. Why is **9** described as a "nitroso acetal." Be specific.
- C. If the carbonyl group is going to be reduced to an alcohol (**9** → **10**), why was alcohol **7** oxidized to ketone **8** in the first place?
- D. What is the purpose of the reaction step **10** → **11**? Would the synthesis have worked had this step been omitted?
- E. A *remarkable* transformation occurs when **11** is treated with H₂/Ra-Ni. In order to understand the formation of **12**, follow the sequence of steps, written in parentheses at the end of the middle paragraph below **Scheme 3**, and show the structures of the intermediates following each of these steps. Also, show how the stereochemistry built into the numerous stereo centers of **11** is transformed into the stereochemistry of product **12** as rotation occurs about bonds and as chemical reactions occur.
- F. **12** was subjected to Tamao-Fleming oxidation. Which of the reagents shown in the scheme is the oxidizing agent? What is the purpose of the H₂/Pd-C step?
- G. Much to the authors' surprise, their synthetic material did not have the physical properties (Table 1) reported for (+)-7-epiaustraline isolated from natural sources. The resolution to the discrepancy appears to be this: (1) the synthetic material does have structure **1** and is 7-epiaustraline; (2) the physical data for the natural product were interpreted incorrectly; (3) the material synthesized by Pearson and Hines (Ref. 2b) is, in fact, (+)-australine (the middle structure following the introduction). Had Denmark and Herbert known that (+)-7-epiaustraline was not a natural product and had they decided to direct their synthesis to (+)-australine, instead, could their synthetic scheme have easily been modified to produce this alternative stereochemistry? Be precise in your answer to this question.

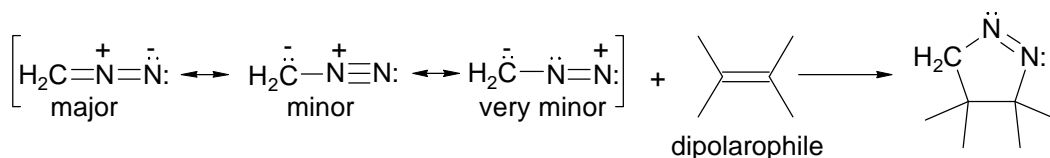
I. (10 points)

- A. There are 5 stereocenters leading to $2^5 = 32$ possible stereoisomers; 29 are not shown.
- B. As one learns from reading the paper to its conclusion, the physical data on the natural product (ref. 2a) were misinterpreted in terms of structure **1**; and the earlier synthesis (ref. 2b) was actually of (+)-australine. For more detail, see the JACS communication by White, *et al.* (directly following Denmark's paper), especially, footnote 14.
- C. Cycloaddition (a word coined by Woodward and Hoffmann) is a type of pericyclic reaction in

which two conjugated δ -systems react to form two σ -bonds and to produce a ring compound. (This is only an approximate definition; for example, vinylcyclopropane can *act* as a 4δ -electron diene even though it has only one C=C.) Tandem is being used in many synthetic procedures to describe a sequence of two events that, together, lead to a desired result. (A dictionary definition of tandem is: "a group of two or more arranged one behind the other or used or acting in conjunction" whatever that may mean!)

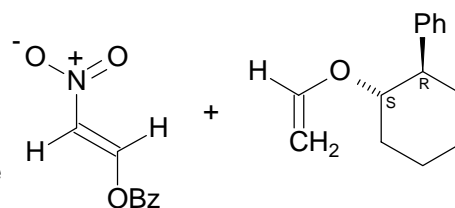
II. (30 points)

- A. A nucleofuge is a leaving group that carries away the bonding electron pair that held it to (usually) a carbon. Thus in an E2 or S_N2 reaction, good leaving groups (i.e., nucleofugal groups) are things like Cl, OTs, etc.
- B. 1. This terminology represents a change from the original orbital symmetry definitions published by Woodward and Hoffmann. In their definition, an $[m+n]$ cycloaddition described the reaction between an m -electron and an n -electron component. Thus, the Diels-Alder reaction, the 1,3-dipolar addition (see below), and the addition of pentadienyl cation to ethene were all described as $[4+2]$ cycloadditions. In recent years, the meaning has changed such that $[m+n]$ refer to the number of atoms in each component that are involved in the reaction. Thus, the Diels-Alder is still described as $[4+2]$ but the 1,3-dipolar addition is $[3+2]$ and the pentadienyl cation + ethene is $[5+2]$.
2. "[3+2] cycloadditions" were originally known as "1,3-dipolar additions" because they involve the cycloaddition of a 1,3-dipole to another partner called a "1,3-dipolarophile" or, simply, dipolarophile. The 1,3-dipole is a compound like nitronate **4** (in this article) or like diazomethane (see below) in which even though the major contributing structure(s) may not have charges in a 1,3-relationship, a (very) minor structure does.



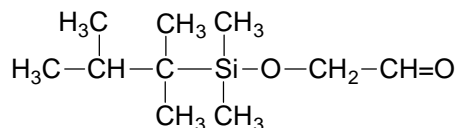
3. The substituents at C_2 and C_3 of **2** would have been down.
4. The substituents at C_2 and C_3 would have been trans to one another; either C_2 's substituent would be pointing up and C_3 's down or vice versa.
5. The H at C_{3a} would have been down (not up). Depending on exo/endo, the substituents at C_2 and C_3 could be either both up or both down.

- C. The nitroalkene happened to have *E* stereochemistry (as shown here) although the *Z* stereoisomer would have been suitable. According to this formulation, the "diene" (the 4δ component) consists of a C=C bond conjugated with an N=O bond. The dienophile in this pseudo Diels-Alder reaction is the enantiomerically pure (1*S*,2*R*)-2-phenylcyclohexyl vinyl ether.

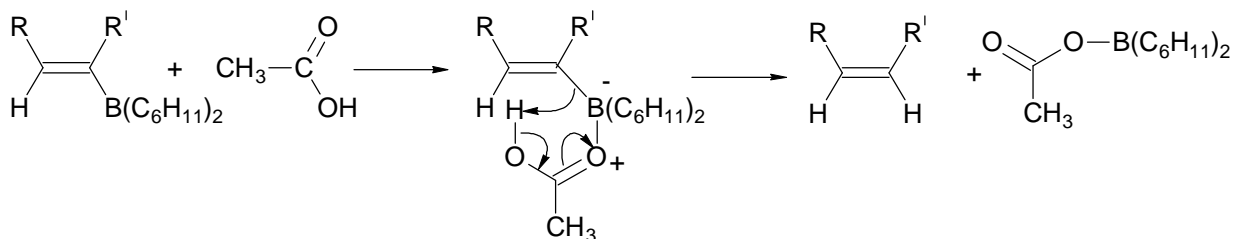


III. (10 points)

- A. As named in the text (p. 7357, right column, line 8) it is the structure to the right in which "thexyl" is an abbreviation for "tert-hexyl" which is, itself, an incorrect name for the $(\text{CH}_3)_2\text{CH}-\text{C}(\text{CH}_3)_2-$ group.

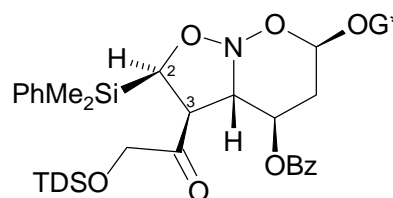


- B. Hydroboration could have produced either of two regioisomers by *syn* addition of H and B across the triple bond. Protonolysis, then, occurs via the 6-centered transition state attainable with a carboxylic acid but not with H-Cl.

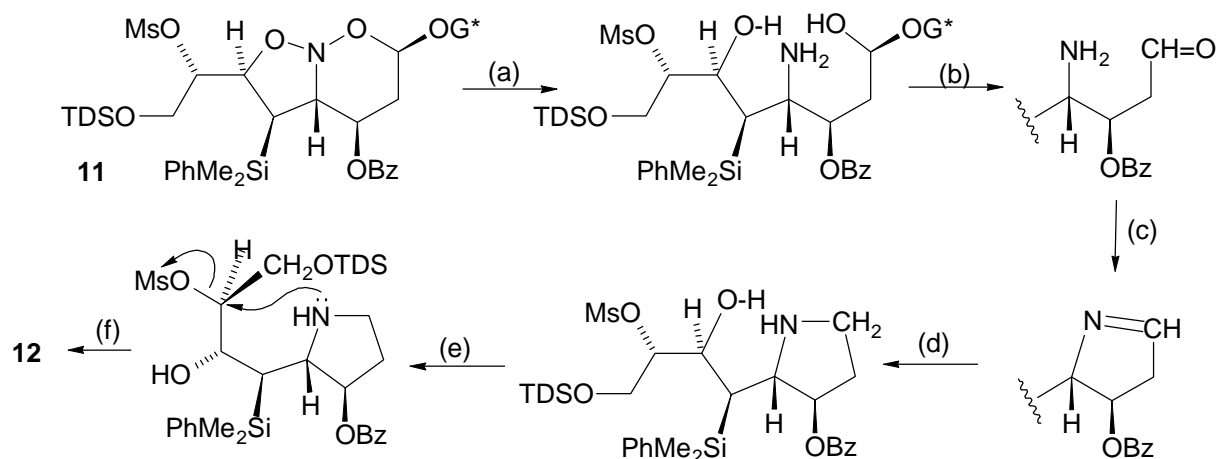


IV. (50 points)

- A. According to footnote 10, the minor isomer is probably a regioisomer (not a stereoisomer) of **9** in which the 2 δ component has turned, end for end; as an *exo* product, the substituents at C₂ and C₃ have a *cis* relationship and are pointing up; presumably attack has still occurred opposite to the OBz group.



- B. A hemiacetal is the product obtained by adding RO to the carbon and H to the oxygen of an aldehyde or ketone; an acetal is obtained when the resulting OH is replaced by OR so that one has $\text{R}_2\text{C}(\text{OR})_2$ from a ketone or $\text{RCH}(\text{OR})_2$ from an aldehyde. If, instead of having a carbonyl compound, one has a nitroso compound $\text{R}-\text{N}=\text{O}$, then its acetal would have the general structure $\text{R}-\text{N}(\text{OR})_2$ (as is found in **9**).
- C. Many cycloadditions occur best when there is a strong electron-withdrawing group (e.g., a carbonyl) attached to one component. This is true for the dienophile in a Diels-Alder reaction and for the dipolarophile **8** in this article.
- D. This step, conversion of an alcohol into a mesylate, produces the "nucleofugal group" discussed in Part IIA. If it weren't done, then the $\text{S}_{\text{N}}2$ reaction in the next step (see Part IIIE) could not occur.
- E. As suggested in the article, hydrogenolysis occurs (a) at both N-O bonds. Loss of $\text{H}-\text{OG}^*$ produces (b) an aldehyde which can react (c) with the amine \rightarrow an imine which is reduced (d) by H_2 . Rotation about C-C bonds (e) puts the C-OMs in position to be attacked (f) by nitrogen in $\text{S}_{\text{N}}2$ fashion with inversion. Product **12** results.



F. The oxidizing agent, shown above the arrow and mentioned in the text, is peroxyacetic acid. As for H₂/Pd-C, this was to reduce the N-oxide that had been formed (see the sentence just above Ref. 12).

G. No, I don't think that it would work. Australine differs from 7-epiaustraline in the stereochemistry at only one carbon, C₇. Recall that OBz at C₄ in compound **4** directed the dipolarophile to the opposite side. In australine, however, with the H at the ring juncture up, the C₇ OH group and C₁ are both pointing down. As an alternative, perhaps the synthesis could be accomplished by making epiaustraline (as in this article) and finding a way to epimerize the C₇-OH. There are many methods available for epimerizing 2° alcohols, but how to do it selectively at C₇ alone is not obvious. (In fact, were it easy Denmark and Herbert certainly would have done it before publishing this paper.)