CHEMISTRY HONOURS SUPPLEMENTARY EXAMINATION: JUNE 2019

MODULE: CEM 8X01 (CEM 0017)- REACTION MECHANISMS AND THEORETICAL ASPECTS

EXAMINERS: Prof. H. Holzapfel and Dr E.M. Mmutlane

MODERATOR: Dr A.L.Rousseau (University of the Witwatersrand)

INSTRUCTIONS

(i) **This examination is out of a Total of 100 Marks and you have 3 Hours (180 Minutes) to complete it. No extra time will be allowed for any reason.**

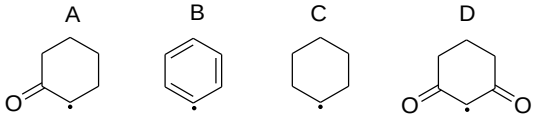
(ii) **The Exam comprises 4 Sections. PLEASE ANSWER EACH SECTION IN A SEPARATE BOOK.**

(iii) **The use of cell phones and other electronic devices is forbidden and they must be switched off.**

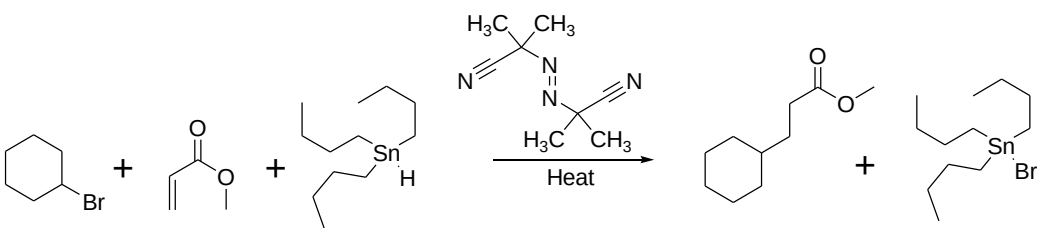
SECTION A: RADICAL REACTIONS (20 MARKS)

QUESTION 1 **[10]**

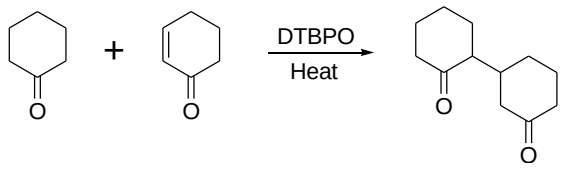
1.1 List the following C-radicals in order of increasing reactivity. Please give an explanation for your answer. (2)



1.2 Explain why the concentration of tributyltin hydride is of critical importance in the following reaction: (3)

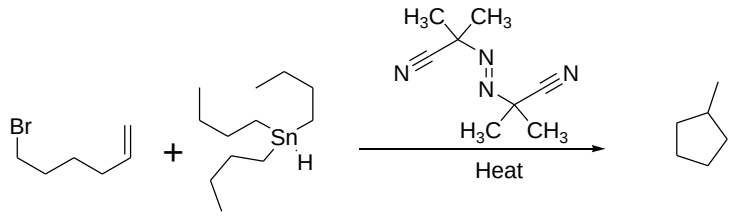


1.3 Explain why the following reaction is not expected to provide the depicted product in good yield. (3)

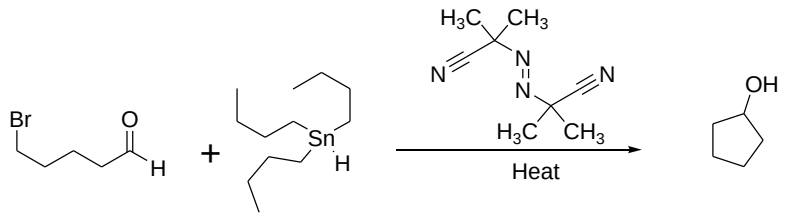


1.4 Explain why REACTION A proceeds successfully whilst REACTION B fails. (2)

REACTION A



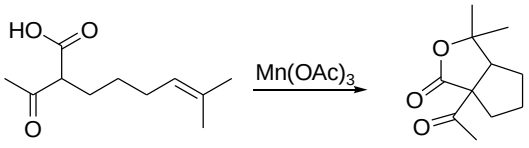
REACTION B



QUESTION 2 **[10]**

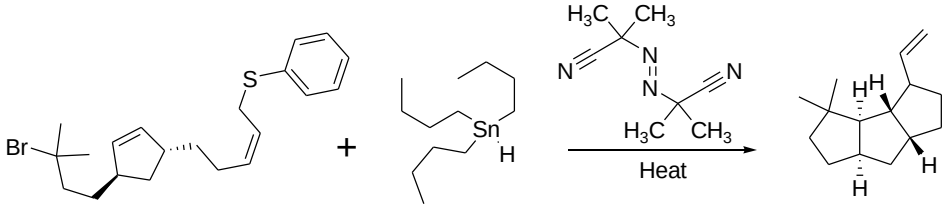
2.1 Give reaction mechanisms for the following transformations. Show all steps, including radical initiation as well as all intermediates.

(i)



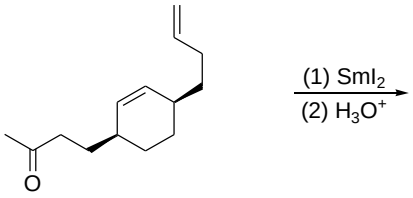
(3)

(ii)



(3)

2.2 Give the structure of the main product of the following reaction and provide a detailed reaction mechanism that accounts for your product. (4)

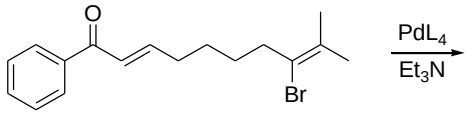


SECTION B: TRANSITION METAL CATALYSIS (30 MARKS)

QUESTION 1 **(14)**

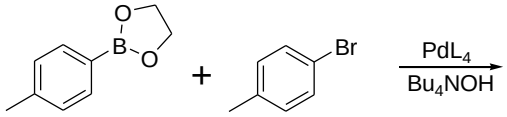
1.1 Give the products of the following reactions and answer the associated questions. For each question, **L = PPh_3**.

(i)



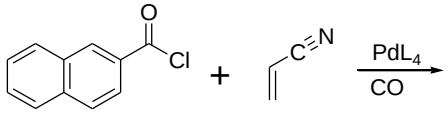
What is the role of Et_3N in the reaction? (2)

(ii)



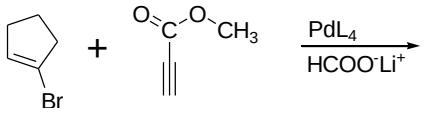
What is the role of Bu_4NOH in the reaction? (2)

(iii)



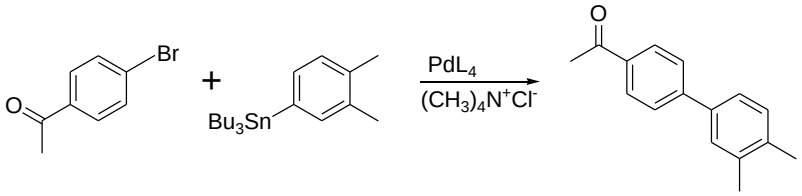
What is the role of carbon monoxide in the reaction? (2)

(iv)



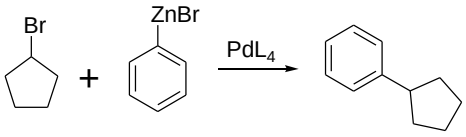
What is the role of lithium formate in this reaction? (2)

1.2 **(i)** Provide a detailed mechanism of the reaction shown below. Name each step of your mechanism according to the reaction type. **L = PPh_3**. (4)

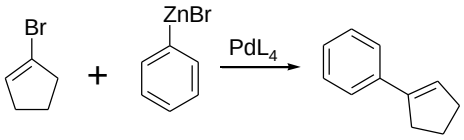


(ii) Explain why REACTION A below would typically not be successful whilst REACTION B would proceed smoothly. **L = PPh_3**. (2)

REACTION A



REACTION B

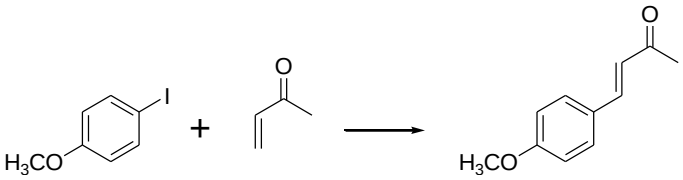


QUESTION 2 **(16)**

2.1 **(a)** Give the structure of a Rh complex used in the hydroformylation of alkenes. Show the major steps in the catalytic cycle corresponding to the Rh-catalyzed hydroformylation of ethene. (3)

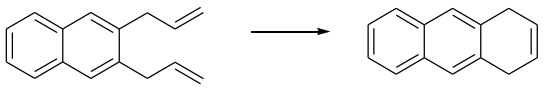
(b) Explain why the overall rate of the reaction above is proportional to the hydrogen pressure but rather insensitive to the CO pressure. (1)

2.2 Suggest a catalyst for the reaction below and explain why the reaction is stereospecific in terms of the reaction mechanism. (4)

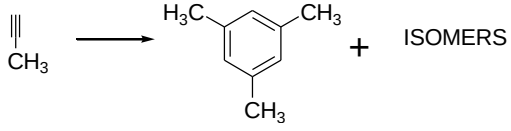


2.3 Suggest a catalyst and propose a mechanism for each of the reactions below. (2×4 = 8)

(a)



(b) 3 x



ISOMERS

SECTION C: FRONTIER MOLECULAR ORBITAL THEORY (23 MARKS)

Zoanthamine alkaloids, some heptacyclic marine natural products isolated from colonial zoanthids of the genus *Zoanthus* sp., have unprecedented structures of formidable complexity. (+)-Zoanthamine(1) was the first zoanthamine alkaloid isolated by Rao et al. in 1984 (Figure1). This marine alkaloid exhibited potent inhibitory activity against phorbol myristate acetate (PMA)-induced inflammation of the mouse ear.

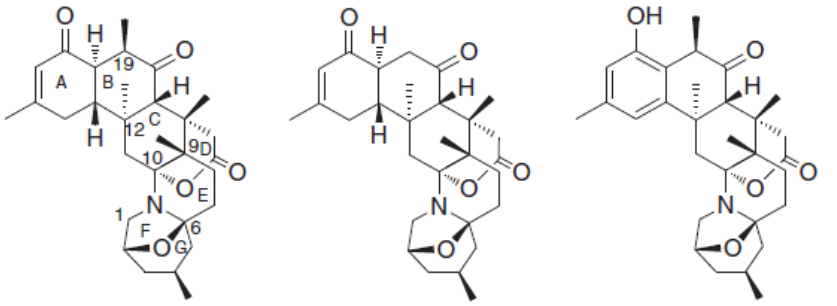
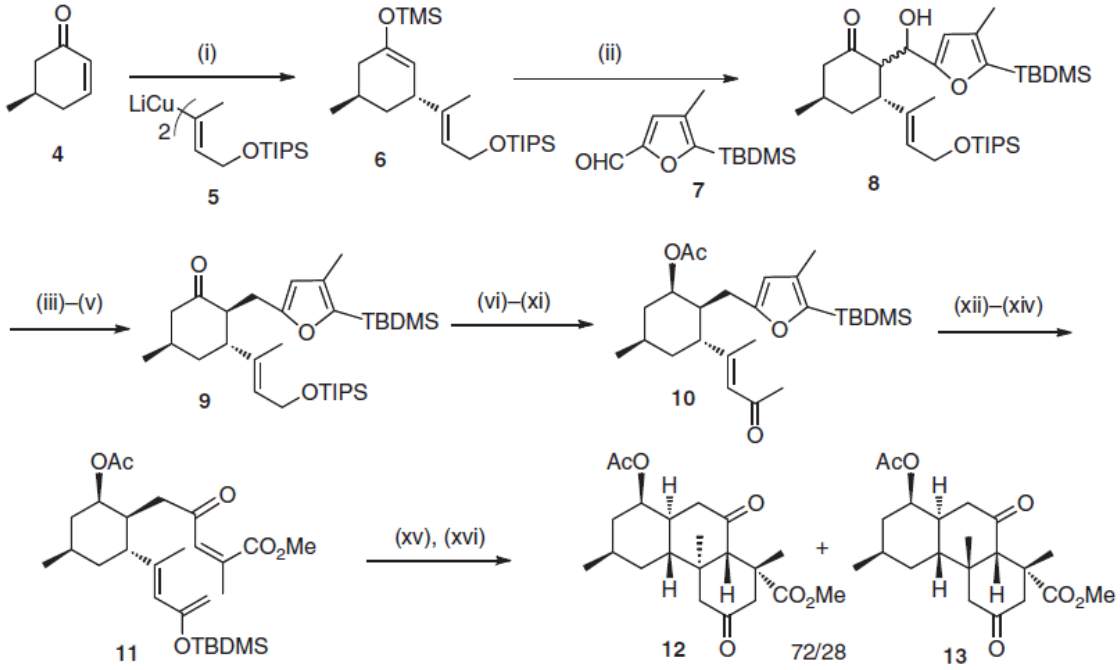


Figure 1 Representatives of the zoanthamine alkaloids.

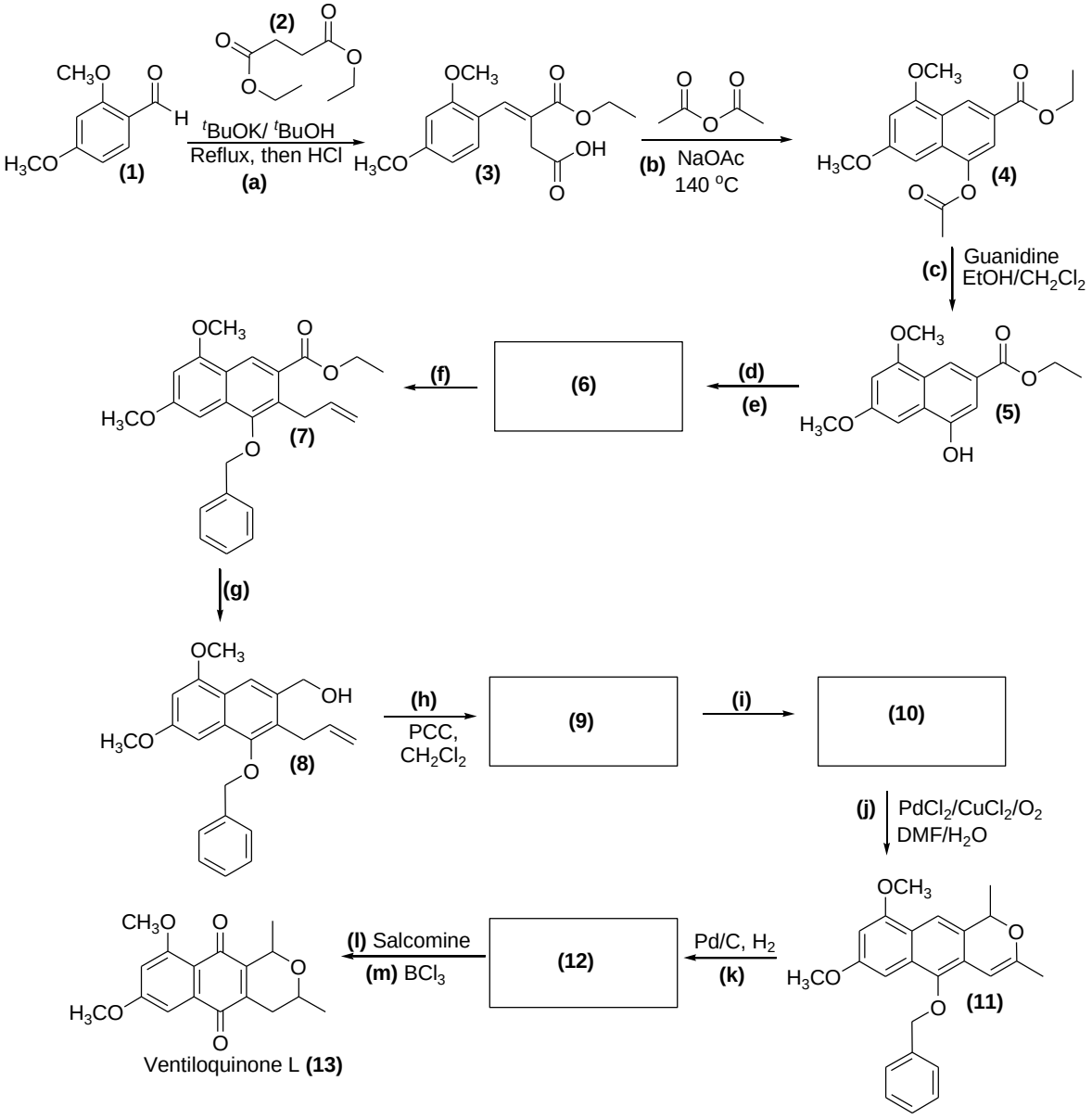
The total synthesis of Norzoanthamine **2** by Miyashita and co-workers is summarized in the Scheme below. The Intra-Molecular Diels-Alder (IMDA) reaction of **11** proceeded successfully at 240 °C (heating in 1,2,4-trichlorobenzene) for 1 h. After desilylation of the resulting adducts (TBDMS-enol ethers), the IMDA products were isolated as a 72/28 diastereomeric mixture in a combined yield of 98%. The expected exo-adduct **12** was the major isomer, which was isolated in pure form by recrystallization in 51% yield. The tricyclic intermediate **12** was successfully transformed to **2**, **1**, and finally **3** in a few additional steps.



Using Frontier Molecular Orbitals, show how product **12** is formed from **11**, explaining the regiochemistry/substitution pattern, as well as the stereochemistry about the newly created stereogenic centers.

SECTION D: RETROSYNTHETIC ANALYSIS (27 MARKS)

The following is the synthesis of ventiloquinone L, as reported by de Koning and co-workers in 2004 (*Org. Biomol. Chem.* **2004**, *2*, 2461-2470). Carefully study it and answer the questions that follow.



QUESTION 1

Steps **(a)** and **(b)**, in the transformation of compound **(1)** to **(4)**, are called Stobbe condensation. Give a (possible) reaction mechanism for step **(a)** and for step **(b)**. (8)

QUESTION 2

A rather obscure method was used for the ester hydrolysis in step **(c)**, instead of using HCl or NaOH. Why do you think this was the case? (2)

QUESTION 3

Transformation of compound **(5)** to **(6)** was done as follows: **(d)** Allyl bromide, K_2CO_3, Acetone, reflux, 16 h, 99%; **(e)** DMF, 170 °C, 12 h, 75%. Compound (6) showed a broad peak at 3400 cm^{-1} in its IR spectrum and its ^{1}H-NMR spectrum showed 1 aromatic proton less than that of compound **(5)**, but with 5 additional non-aromatic hydrogens. On the basis of this information, propose the structure of compound **(6)**. (2)

QUESTION 4

Give the reagents and reaction conditions for step **(f)**. Mechanistically, what type of reaction does this step entail? (2)

QUESTION 5

Give the reagents and reaction conditions for step **(g)**. (1)

QUESTION 6

Propose a structure for compound **(9)**. Its High Resolution Mass Spectrum gave M^+ 362.1519, its IR spectrum showed a strong peak at 1700 cm^{-1} and two weak bands at 2800 and at 2700 cm^{-1} and its ^{1}H-NMR spectrum showed a non D_2O exchangeable singlet at 10.17 ppm for 1 proton. (2)

QUESTION 7

Step **(i)** entailed treating compound **(9)** with methylmagnesium iodide at 0 °C in anhydrous diethyl ether. Propose the structure for the product, compound **(10)**, which had a broad peak at 3502 cm^{-1} and its High Resolution Mass Spectrum gave M^+ 378.1831. (2)

QUESTION 8

Propose a structure for compound **(12)**, the product of step **(k)**. Its High Resolution Mass Spectrum gave M^+ 288.1363. The ^{1}H-NMR data for its non-aromatic protons is as follows:

4.95 (1H, q, *J* 6.2), 3.94 (3H, s), 3.90 (3H, s), 3.90–3.81 (1H, m), 2.95 (1H, dd, *J* 16.3 and 3.0), 2.61 (1H, dd, *J* 16.3 and 11.1), 1.65 (3H, d, *J* 6.2) and 1.35 (3H, d, *J* 6.2). (2)

QUESTION 9

Looking at the outcome of step **(k)**, why do you think a benzyl protecting group was chosen in step **(f)**? Please explain in details. (4)

THE END

TOTAL **100 MARKS**