Supplemental Information for

The Green Chemistry Initiative's Contributions to Education at the University of Toronto and Beyond

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CTFP Assignment by Dr. Nadine Borduas

2014-15 Chemistry Teaching Fellows Program (CTFP) Report

Ph.D. student: Nadine Borduas
Chemistry Faculty Liaison: Dr. Andrew P. Dicks
Course: CHM 343H: Organic Synthesis Techniques (enrollment: 40 students) taught by Dr. Nick Morra
Project: Take-home assignment worth 15% of final course grade

Brief summary of project

Through the CTFP award, I developed a green chemistry assignment for the Organic Synthesis Techniques course CHM 343H. The goal of this assignment is to introduce students to green solvent and green reagent guides published by the pharmaceutical industry. They learn how to read and use the guides in the lecture devoted to the introduction of the assignment. The assignment then requires the students to apply green chemistry principles to the analysis of a previously published synthesis of one of three relevant molecules in the fields of pharmaceutical, agricultural and fragrance industries. The assignment was introduced in the course to replace the mid-term and so was worth 15% of the final grade. The CTFP award was specifically dedicated to revamping the assignment based on student feedback from last year, to giving a one hour lecture on green solvent and reagent guides, to holding office hours during and after the assignment as well as to mark the assignment.

CHM 343H Spring 2015: "Future Leaders in Green Chemistry" Assignment

Due date and time: Monday March 16th – in class (digital copy to be submitted to Turnitin before this)

Worth: 15% of final CHM 343H course grade. Penalty for late submission: 10% per day of lateness

TA: Nadine Borduas, nadine.borduas@mail.utoronto.ca, LM 321

Office hours: Wednesday March 11 from 11am-12 pm in LM 321

Thursday March 12 from 11am-12 pm in LM 321 or by appointment

Assignment context:

Green chemistry is now an intrinsic part of chemical research and process in industry, academia and government. A sustainable future cannot be attained without sustainable chemistry. While we strive as chemists to produce drugs, flavouring agents, pesticides and fragrances to improve the lives of individuals, it cannot be to the detriment of the environment and society in general.

Assignment learning objectives:

This assignment is designed to promote the critical analysis of **ONE** of three such compounds, and to apply the Twelve Principles of Green Chemistry and green chemistry metrics that have been discussed in both the lecture and laboratory components of CHM 343H. The overarching goal is to train a future generation of chemists (i.e. you!) to intuitively think about using greener reagents and solvents for more sustainable research. To this end, you will directly consult with recently-reported commercial solvent and reagent selection guides for greener chemistry, in order to make decisions regarding alternative synthetic pathways.

Assignment reference material:

Solvent selection guides:

Alfonsi, K., Colberg, J., Dunn, P. J., Fevig, T., Jennings, S., Johnson, T. A., Kleine, H. P., Knight, C., Nagy, M. A., Perry, D. A., Stefaniak, M., *Green Chem.* **2008**, *10*, 31-36.

Henderson, R. K., Jimenez-Gonzalez, C., Constable, D. J. C., Alston, S. R., Inglis, G. G. A., Fisher, G., Sherwood, J., Binks, S. P., Curzons, A. D. *Green Chem.* **2011**,*13*, 854-862.

Prat, D., Pardigon, O., Flemming, H.-W., Letestu, S., Ducandas, V., Isnard, P., Guntrum, E., Senac, T., Ruisseau, S., Cruciani, P., Hosek, P., *Org. Process Res. Dev*., **2013**, *17*, 1517-1525.

Reagent guide:
Adams, J. P., Alder, C. M., Andrews, I., Bullion, A. M., Campbell-Crawford, M., Darcy, M. G., Hayler, J. D., Henderson, R. K., Oare, C. A., Pendrak, I., Redman, A. M., Shuster, L. E., Sneddon, H. F., Walker, M. D., *Green Chem.* **2013**, *15*, 1542-1549.

Assignment Outline: (50 marks)

Must be typed: Times New Roman, 12 point font: no longer than 5 pages in total.

PART 1: Introduction (6 marks)

Provide a brief introduction to your assigned molecule and include when the molecule was discovered/isolated, pivotal syntheses of the molecule, interesting/important biological activity, commercial history, etc. Include proper ACS style referencing as adopted in all laboratory reports.

PART 2: Green Solvent Analysis (12 marks)

Consider the solvents used in all stages of the reactions shown in the synthetic scheme of your assigned molecule: the reaction itself, workup and purification. Amongst these, choose **SIX different solvents** to discuss that require replacements, based on the criteria listed below. You may present your answer in table format or bullet point form.

1) Specify which step(s) the solvent is used and at what stage (reaction/workup/purification).

2) **Using the Sanofi solvent selection guide**, describe the issues associated with the solvent.

3) Suggest an appropriate alternative solvent; **again using the Sanofi solvent guide** (the GSK solvent guide may also be helpful here).

4) Justify your choice of alternative solvent by comparing the greenness of the original and suggested replacement. State the most appropriate Green Chemistry Principle in your analysis of each of the six solvents. **NOTE:** Throughout your analysis of the six solvents you must use at least three different Green Chemistry Principles.

PART 3: Green Reagent Analysis (20 marks)

You may present your answer in table format or bullet point form.

1) Based on the boxed steps in the synthetic scheme provided for your assigned molecule, identify FOUR reagents "with some/major issues" listed in **the GSK green reagent selection guide.**

2) Discuss what their respective issues are, **using the GSK guide as a reference.**

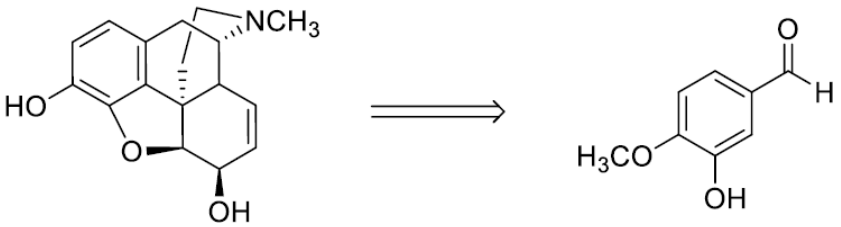
3) Based on your analysis, propose an alternative reagent for the same transformation while taking into consideration chemoselectivity and stereocontrol.

4) Find a procedure in the literature that uses your proposed alternative reagent on a similar substrate. Making sure that you reference appropriately, attach the experimental procedure to your report and include a scheme of the reactants and products of the reported transformation.

PART 4: Green Chemistry Discussion Question (12 marks)

Answer the questions related to your assigned molecule. Use ChemDraw for your schemes and mechanisms as appropriate.

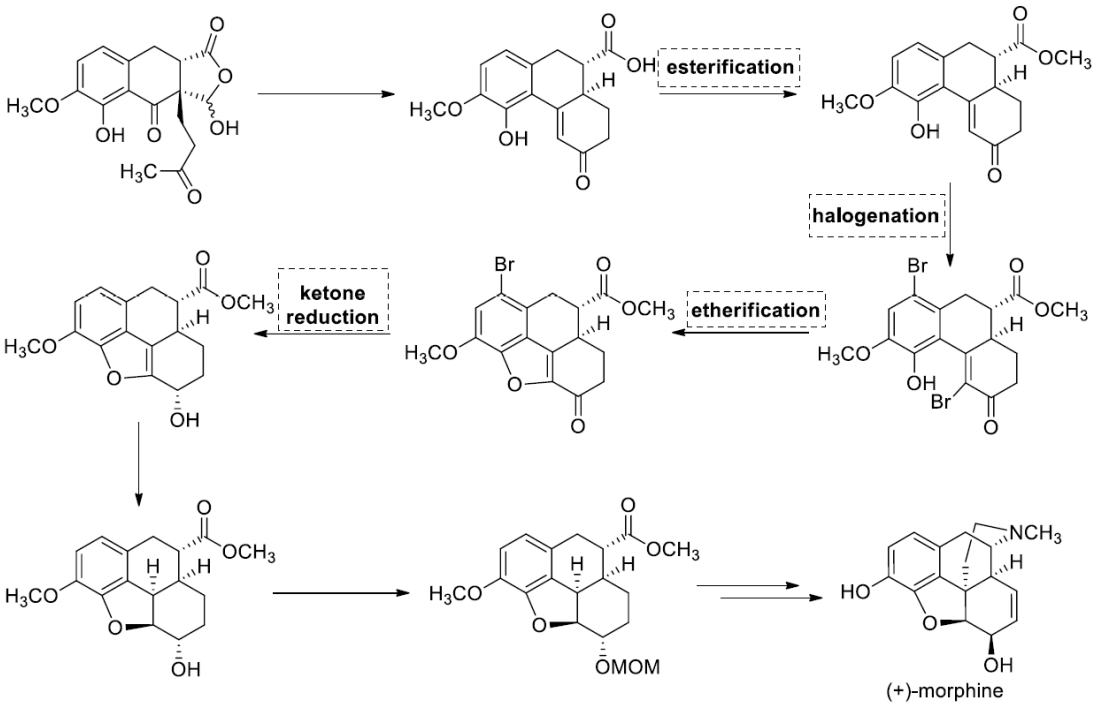
1. From the pharmaceutical industry: morphine



(+)-morphine isovanillin

Reference: *J. Org. Chem.* **1997**

Relevant synthetic scheme for morphine



PART 4: Green metric question for the synthesis of morphine

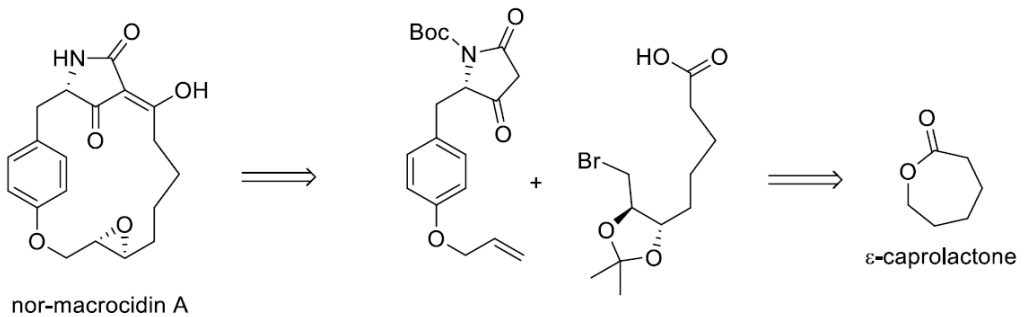
The synthesis of morphine from the given reference involves a Robinson annulation.

1) Identify this step and draw its scheme with reagents and auxiliaries using ChemDraw.

2) Propose a mechanism with curly arrows and draw it using ChemDraw.

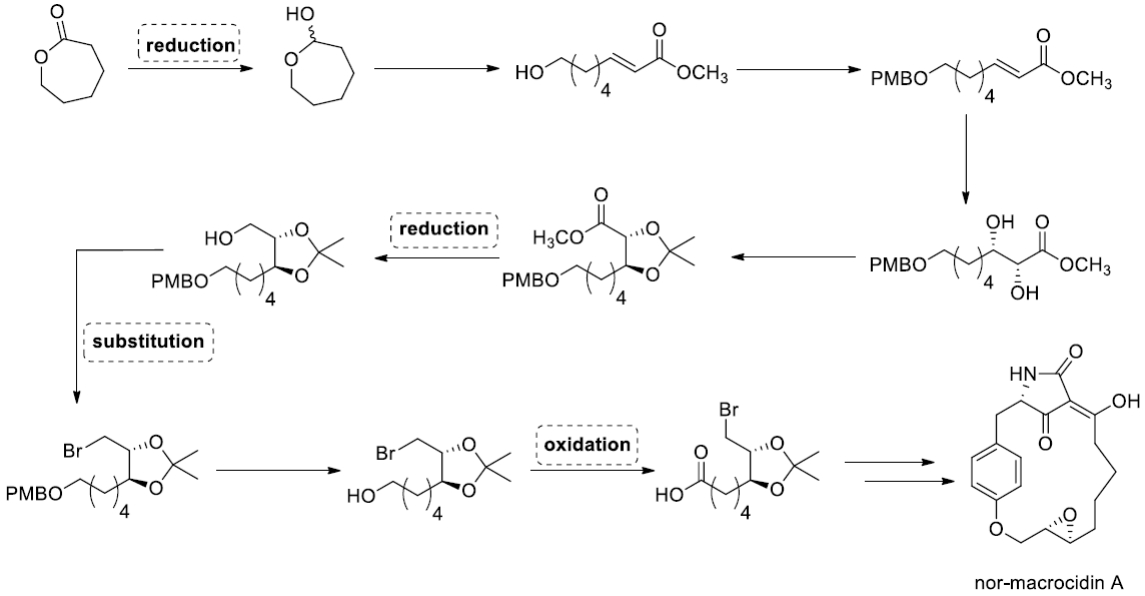
3) Calculate the atom economy of this reaction and comment on your obtained value.

2. From the agricultural industry: nor-macrocidin A



Reference: *J. Org. Chem.* **2010**

Relevant synthetic scheme for nor-macrocidin A



PART 4: Green metric question for the synthesis of nor-macrocidin A

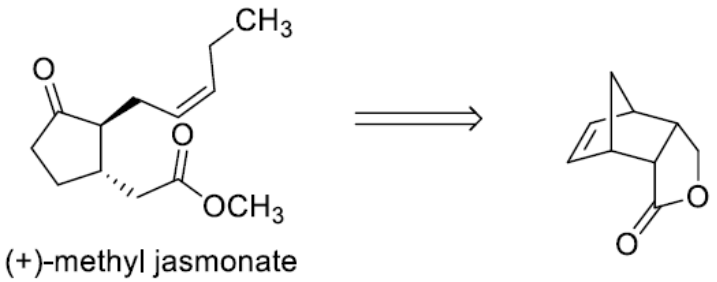
The key step in the synthesis of nor-macrocidin A is the macrocyclization step via a Williamson etherification.

1) Identify this step and draw its scheme with reagents and auxiliaries using ChemDraw.

2) What is the role of Pd in this reaction? As part of your answer, propose the structure of the Pd-intermediate and draw it in ChemDraw.

3) Calculate the reaction mass efficiency of this reaction based on this paper. Comment on the obtained value.

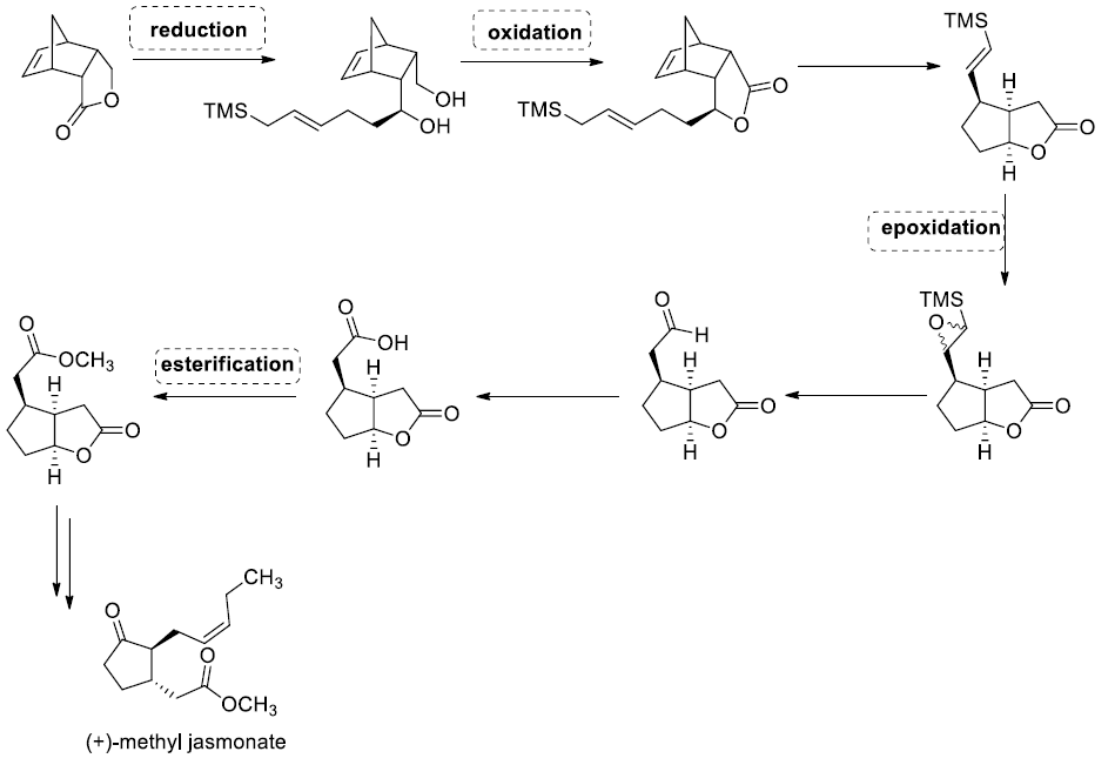
3. From the fragrance industry: Methyl jasmonate (a common substance used in perfumery):



(+)-methyl jasmonate

Reference: *Org. Lett.* **2004**

Relevant synthetic scheme for methyl jasmonate:



PART 4: Green metric question related to the synthesis of methyl jasmonate

Identify the key step in the synthesis of methyl jasmonate (hint: it's in the title!).

1) Identify this step and draw its scheme with reagents and auxiliaries using ChemDraw.

2) Propose a mechanism and draw it in ChemDraw.

3) Calculate the atom economy of this reaction and comment on your obtained value.

CTFP Assignment by Dr. Ian Mallov

Report for 2015-16 Chemistry Teaching Fellows Program (CTFP)

PhD student: Ian Mallov
Chemistry Faculty Liaison: Dr. Andrew P. Dicks
Course: CHM 343H: Organic Synthesis Techniques (enrollment: ~ 40 students)
Type of proposal: Take-home assignment worth 15% of final course grade

Motivation for this Assignment

As environmental resources become scarcer with increasing population and development, it is becoming paramount that chemists' education includes considerations of their roles within the broader context of sustainability. Recently, members of the University of Toronto Department of Chemistry have taken significant leadership in green chemical education. In a third-year organic synthesis course (CHM 343H), a major assignment was implemented over a two-year period by Dr. Nadine Borduas in conjunction with instructors Dr. Andrew Dicks and Dr. Nick Morra. This assignment was an extension of the principles already taught in the laboratory portion of the course, but allowed the students the time to undertake a broader and deeper consideration of the environmental impacts of chemical synthesis. Students in the class were assigned one of three molecules (morphine, nor-macrocidin-A, and methyl jasmonate) and asked to critically evaluate literature syntheses of their assigned molecule, answering a number of questions related to green chemistry principles, solvents, metrics, etc. applied to these syntheses.

Based on student feedback received from the survey conducted for the previous incarnations of the assignment, as well as verbal feedback from both Dr. Borduas and Dr. Dicks, I undertook a number of modifications to the assignment structure. I had three principal objectives to add to the goals of the previous assignment. These objectives were 1) to get students to design a synthetic route to a non-literature molecule (a plausible derivative of a reported organic molecule) from a limited list of reagents; 2) to design the assignment such that it was less time-consuming for both the students to undertake and the CTFP student (myself) to mark; 3) to introduce the concept of a

Life Cycle Assessment to get students to take broad consideration of the origin, use and disposal of reagents involved in a molecular synthesis.

Three major objectives outlined in the previous assignment which I wished to maintain included 1) introducing to students how to use green solvent and reagent selection guides (in this case, the Sanofi Solvent Guide[1] and GlaxoSmithKline Reagent Guide[2]) and getting them to use and refer to these guides when answering their assignment questions; 2) critically analyzing literature syntheses of organic compounds; 3) applying green chemistry principles and metrics to analyze synthetic steps and individual reagents.

[1] Sanofi, *Org. Process Res. Dev*. **2013**, *17*, 1517–1525

[2]*Green Chem*., **2013**, *15*, 1542–1549

[3] F. Gosselin *et. al*., *Org. Process Res. Dev*.**2015**, *19*, 416-26

Summary of the Assignment

After I assembled an initial draft of a new assignment in October 2015, several iterations followed based on feedback I received from Dr. Andrew Dicks, the supervisor for this CTFP and instructor of the laboratory portion of CHM 343H, and Professor Sophie Rousseaux, who taught the lecture portion of the course.

We decided to assign a single, fictional target molecule to all students. This target molecule was to be a derivative of a molecule reported in the literature. The objective in giving students a synthetic target that was not from the literature was to preclude their ability to copy a synthetic route straight from journal reports. However, we chose to make this fictional target molecule simply a derivative of a recently-reported literature compound reported by a commercial company, to ensure that students' designed syntheses would incorporate well-established steps as well as to maintain the aspect of getting students to design a commercially-relevant target.

I chose to design a target molecule which was a derivative of a side chain of GDC-0980, an oncogene inhibitor reported by Genentech, Inc. in 2015[3] and presented by Genentech's Callie Bryan at the American Chemical Society's Summer School on Green Chemistry and Sustainable

Energy in Golden, CO, in 2015. The students were given a list of reagents, but not solvents, and in Part 1 of the assignment instructed to 1) present a retrosynthetic analysis of the target (5 marks) and 2) design a synthesis using these reagents as the major organic building blocks of the final product, giving appropriate solvents, conditions, and reasonable yields based on literature precedents of similar steps (15 marks), and including references for their literature references. From these reagents, one step in the synthesis must form a C_{aryl}-N bond. Students were instructed to present two different methods to form this C_{aryl}-N bond: via a nucleophilic aromatic substitution and a Buchwald-Hartwig coupling.

The target molecule and list of reagents are presented below:

Target Molecule:

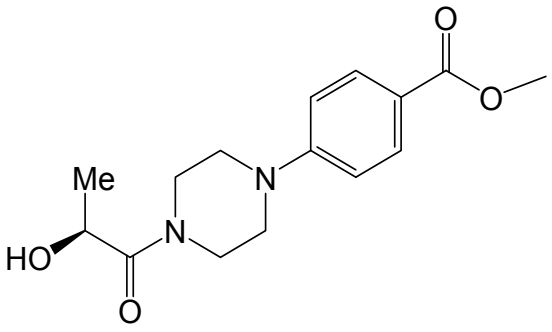
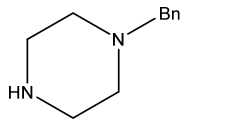
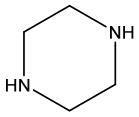
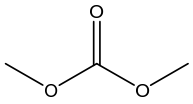
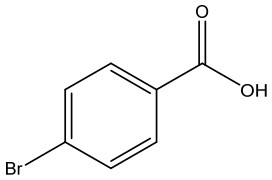


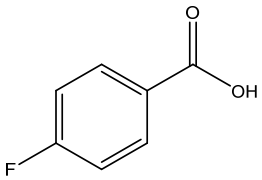
Table of Reagents

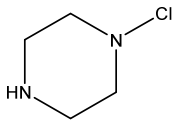


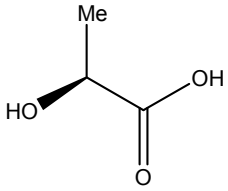


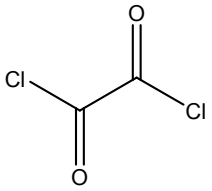


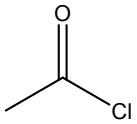


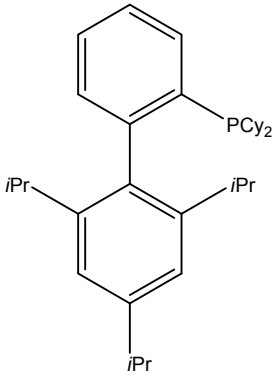




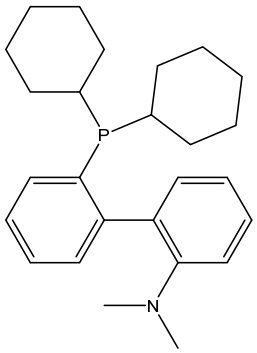




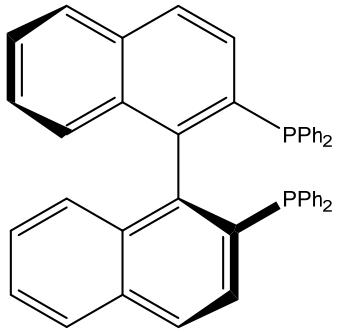




"XPHOS"



"DavePhos"



BINAP

BASES	Other reagents
K_2CO_3	MeI
KO*t*Bu	MeOTf
NaOMe	HCl
$CsCO_3$	$Pd_2(dba)_3$
Na_2CO_3	$Pd(PPh_3)_4$
Et_3N	$Pd(OAc)_2$
	$PdCl_2$
	Pd/C

In Part 2 of the assignment, worth 55 marks and assigned after they had turned in Part 1, students were given a model synthetic route to the target and assigned four questions for discussion on different green chemistry-related aspects of this synthesis.

As Dr. Borduas had done previously, I took one fifty-minute class lecture period to introduce the assignment. I introduced the solvent and reagent guides, the concept and examples of Life Cycle Assessment, and presented the form of the assignment. Students were then given one week to complete Part 1 (their designed synthesis); two days after they handed in their designed syntheses, the model synthesis and assigned questions were posted on the class Blackboard portal, and students had twelve days to complete this Part 2.

Future Leaders in Green Chemistry Assignment

Synthesis Design + Retrosynthetic Analysis: Due Mon. March 7th 4:00 pm in class (10% penalty per day late, and will NOT be accepted past Wednesday, March 9th 4:00 pm)

Analysis Questions: Due Monday March 21st 4:00 pm in class (10% penalty per day late)

In this assignment, you are given a target molecule for which you will design TWO possible syntheses. A list of reagents and starting materials is provided. Please choose at least the major organic building blocks of your target molecule from this list of reagents. While it is possible to design multiple synthetic pathways from this list of reagents, you are also free to use other reagents in your reaction steps. Solvents are not included in this list - you can choose any suitable solvents. Your goal is to design the TWO greenest syntheses possible within the guidelines, and to answer the questions regarding your designed synthesis.

Please note: you will hand in a short retrosynthetic analysis, and your 2 proposed synthetic pathways, on **Monday, March 7th**. On Wednesday, March 9th, you will be provided with a model synthesis of this target compound. It is from this model synthesis that you will base the answers to the questions in the second part of this assignment, **due Monday, March 21st**.

You will have the GSK Reagent Selection Guide and Sanofi Solvent Selection Guide to help guide you in your decisions. It is recommended that you use Scifinder and/or Reaxys to find literature precedents for the synthetic steps you will need to propose. Though your target molecule is similar to several reported in the literature, the exact target compound has not been reported, therefore you will not find reactions using your exact reagents for every step. However, finding literature sources which report the same type of bond-forming reaction using similar reagents for each step will provide you with an idea of which solvents and reaction conditions to use, which major by-products are likely, and what yields you can expect. Textbooks, journal papers, and patents are all acceptable sources.

The synthetic target molecule is a modification of one of the side chains of GDC-980, the active pharmaceutical ingredient in an enzyme inhibitor reported by San Francisco-based Genentech Inc. in *Organic Process Research and Development* in 2015 (see **Bibliography** for the paper reference). GDC-0980 (below) is an active pharmaceutical ingredient (API) developed as an

inhibitor of PI3K kinases. Lipid kinases (enzymes) of the PI3K family can activate oncogenes, which are genes that, if mutated or expressed at high levels, can transform normal cells into tumour cells.

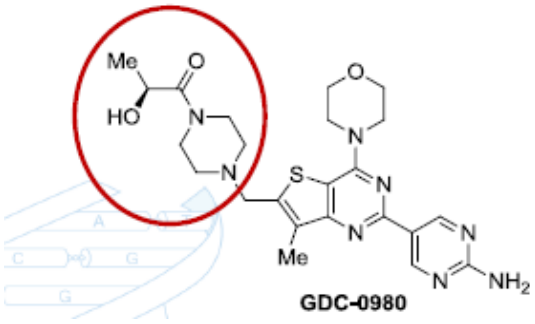


Figure 1 P13K/m TOR inhibitor GDC-980

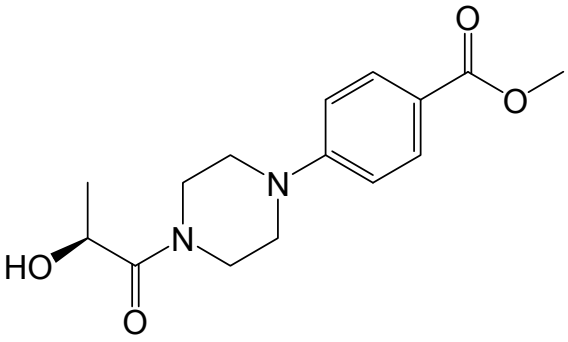


Figure 2 Your target molecule

Report Outline (75 marks total):

Part 1: Synthesis (20 marks): DUE MONDAY, MARCH 7th in class at 4 pm

To synthesize your target, you will need to form a C_{aryl}-N bond in one of your synthetic steps. For this process, show two separate methods: both a method you learned in CHM 247H or CHM 249H or another previous organic chemistry course, as well as one using transition metal catalysis. You may have to use literature resources to familiarize yourself with the transition metal-catalyzed method (though you will be introduced to the topic in this class!). Overall, we are looking for the "greenest" synthesis (make sure that you consider functional group compatibility when planning!). You will compare these two routes below.

Retrosynthetic Analysis (5 marks)

Staring with your target compound, using ChemDraw, show a retrosynthetic analysis leading back to starting materials provided in your list of available reagents. Use a dotted line to show which bonds are being broken. You do not need to show reagents or reaction conditions.

Full Reaction Scheme (15 marks)

Use ChemDraw to show a detailed reaction scheme that shows each step of your proposed greenest synthesis, including all reagents and solvents used, by-products generated, and reasonable reaction conditions (e.g. stoichiometry and temperature) based on literature precedents. You do not need to show any reaction mechanisms (no curved arrows). You also do not need to show how you would work-up and isolate the products of your steps.

Don't forget to include references in the ACS format.

Part 2: Analysis (55 marks): DUE MONDAY, MARCH 21st in class at 4:00 pm

Please answer the questions below, in a maximum of five pages, **based on the model synthesis presented to you on Wednesday, March 9th**. For question 4, please also prepare a table, as detailed below. Late assignments will be penalized 10% for each day late.

1) Compare and contrast the two C-N bond-forming methods with respect to **3 of the 12 principles** of green chemistry discussed in class (choose the 3 that you feel are most relevant to this step). Take into account all aspects of the experimental procedure – including likely work-up and purification methods reported in the literature, even though this is not included in the model reaction scheme. When addressing the greenness of the reagents used, refer to the reagent selection guide, as well as other chemical literature, SDS sheets, etc. **(15 marks)**

2) For one step of your synthesis (NOT the C-N bond-forming step), discuss the greenness of the solvent used. Briefly justify your choice, and discuss an alternative solvent that would have been appropriate for this step but worse from a green chemistry perspective. Why would this alternative solvent be less green? Use the solvent selection guide for help. (**5 marks**)

3) Often the active pharmaceutical ingredient (API) is a single stereoisomer of a compound. Your target molecule is the S enantiomer, though you can assume you are beginning with the

enantiopure starting material and don't have to worry about stereochemistry in your synthesis. Generally, do you think it is "greener" to separate enantiomers earlier or later in a multi-step synthesis? Why? In the case of the amide shown below, where only one enantiomer is desired for the next synthesis step, what could you do with the undesired enantiomer to get more of the desired product? For full marks, show reagents and conditions for your suggested process. (**15 marks**)

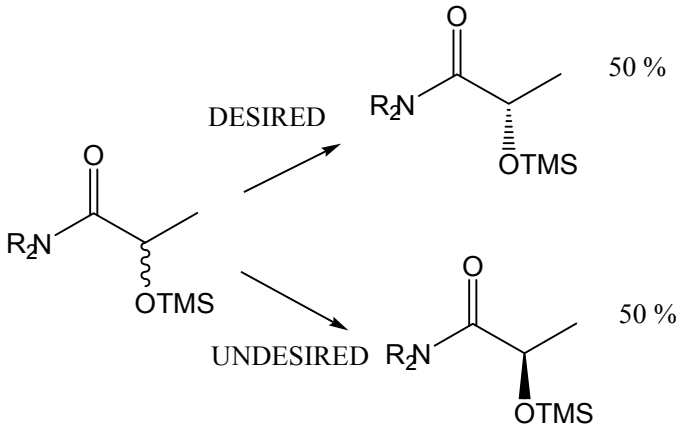


Figure 3 Stereoisomers of the API

4) In the model synthesis provided to you, the benzoic acid is converted to the methyl ester using what is generally considered the greenest methylating agent of those presented in the reagents list. Choose another methylating agent from the reagents list. Compare these two methylating agents by doing a mini Life Cycle Assessment (LCA). Do this by preparing a table comparing categories a-e for the two reagents:

a) original natural feedstock (petroleum products? Crops or biological sources?)

b) oral LD50 (please report rat oral LD 50 in mg/kg)

c) inhalation LC50 (please report rat LC 50 in mg/kg, and the time in hours over which it was measured)

d) vapour pressure (please convert to units of kPa if not already reported in kPa)

e) structures of likely degradation products of both reagents.

Please indicate the sources of each piece data. To do this, you may include a citation (superscript number) with each piece of data and include the source in your bibliography.

Finally, state and explain why either the reagent in the model synthesis is greener, or your chosen alternative is greener. Name one additional factor that you think is important to take into consideration for a LCA, and explain why it is important. (**20 marks total for entire question**)

Answer the questions to the best of your ability using the information found in the paper as well as other literature sources. For questions that require you to find a reference: provide the **reference** in proper ACS formatting in your bibliography **(*do not* attach the paper!)**

For questions that require you to find an experimental procedure in the literature: provide a copy of the **ONE PAGE** that contains the experimental procedure that you are using to answer the question **(*do not* attach the entire supporting information section!)** Please indicate the full reference in ACS format at the top of the page if this information is not already included in your print out.

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