Synthetic efforts towards the natural products brocazine F and G

by

Chathurangani Wasundara Hulangamuwa

B.S., University of Colombo, 2014

AN ABSTRACT OF A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

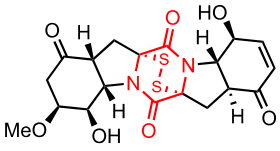
Department of Chemistry
College of Arts and Sciences

KANSAS STATE UNIVERSITY
Manhattan, Kansas

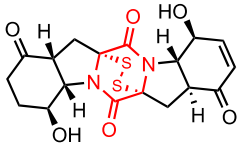
2020

Abstract

The brocazines are a family of natural products bearing a disulfide diketopiperazine core that was isolated by Meng *et al* in 2014 and 2016 from an endophytic fungus derived from the marine mangrove plant *Avicennia marina* named *Penicillium brocae* MA-231. Seven different brocazines (A-G) and three different spirobrocazines were isolated, and of those brocazine F showed the strongest activity against prostate cancer cell line DU145 (IC_{50} of 1.7 μM) and lung cancer cell line NCI-H460 (IC_{50} of 0.89 μM). Brocazine G showed strong activity against ovarian carcinoma cell line A2780 (IC_{50} of 0.664 μM), Ovarian endometrioid adenocarcinoma A2780 CisR cells (IC50 of 0.661 μM) as well as possessing strong and selective activity against human pathogen *Staphylococcus aureus* (MIC of 0.25 μg/mL). Given the potent cytotoxicity of brocazine F and G and their intriguing polycyclic core structure, our laboratory devised a total synthesis route to access this family. By focusing on these compounds, we envision the construction of a screening library yielding a new series of small molecules; which can be accessed through the intermediates of the total synthesis route employed for the construction of brocazine F and G. Each intermediate will serve as the starting material for a unique set of small molecules, structurally different from the original natural product, but potentially having unique and potent biological activity. Therefore, the goal of this dissertation is to establish a reliable and reproducible route to access the brocazine family of diketopiperazine (DKP) natural products, from which the intermediates can be amendable for chemical derivatization for complex screening library construction.



Brocazine A



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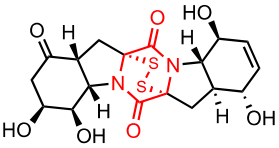

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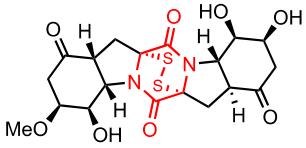

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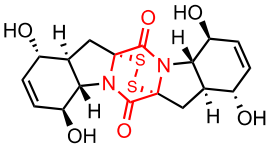

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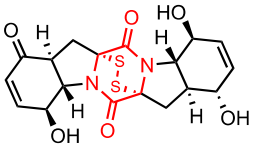

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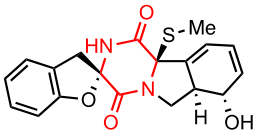

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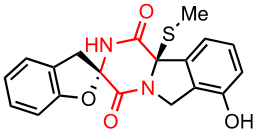

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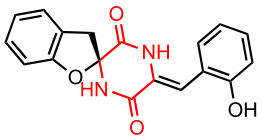

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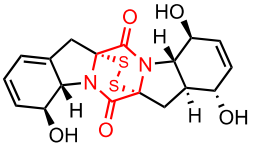

Brocazine G

Synthetic efforts towards the natural products brocazine F and G

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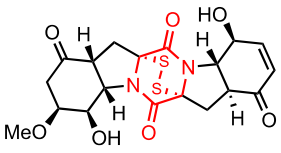
Approved by:

Major Professor
Dr. Ryan Rafferty

Abstract

The brocazines are a family of natural products bearing a disulfide diketopiperazine core that was isolated by Meng *et al* in 2014 and 2016 from an endophytic fungus derived from the marine mangrove plant *Avicennia marina* named *Penicillium brocae* MA-231. Seven different brocazines (A-G) and three different spirobrocazines were isolated, and of those brocazine F showed the strongest activity against prostate cancer cell line DU145 (IC_{50} of 1.7 μM) and lung cancer cell line NCI-H460 (IC_{50} of 0.89 μM). Brocazine G showed strong activity against ovarian carcinoma cell line A2780 (IC_{50} of 0.664 μM), Ovarian endometrioid adenocarcinoma A2780 CisR cells (IC50 of 0.661 μM) as well as possessing strong and selective activity against human pathogen *Staphylococcus aureus* (MIC of 0.25 μg/mL). Given the potent cytotoxicity of brocazine F and G and their intriguing polycyclic core structure, our laboratory devised a total synthesis route to access this family. By focusing on these compounds, we envision the construction of a screening library yielding a new series of small molecules; which can be accessed through the intermediates of the total synthesis route employed for the construction of brocazine F and G. Each intermediate will serve as the starting material for a unique set of small molecules, structurally different from the original natural product, but potentially having unique and potent biological activity. Therefore, the goal of this dissertation is to establish a reliable and reproducible route to access the brocazine family of diketopiperazine (DKP) natural products, from which the intermediates can be amendable for chemical derivatization for complex screening library construction.



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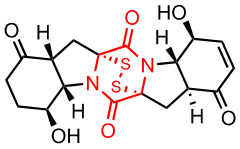

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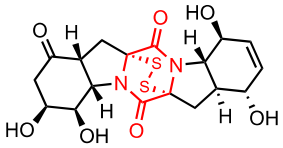

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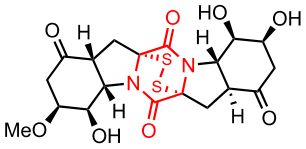

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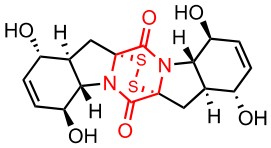

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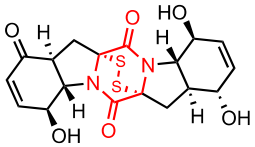

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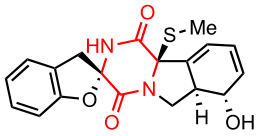
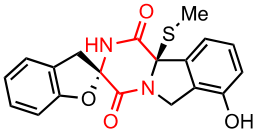


Spirobrocazine A



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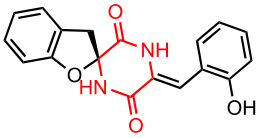

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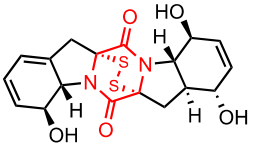

Brocazine G

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Table of Contents

- 1-benzyl 2-methyl (2*S*,3a*R*,7a*R*)-3a-hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (14)
- 1-benzyl 2-methyl (2*S*,3a*R*,7a*R*)-3a-(benzoyloxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (15)
- 1-benzyl 2-methyl (2*S*,3a*R*,7a*R*)-3a-(benzoyloxy)-6-((*tert*-butyldimethylsilyl)oxy)-2,3,3a,7a-tetrahydro-1*H*-indole-1,2-dicarboxylate (28)
- 1-benzyl 2-methyl (2S,3aR,7S,7aR)-3a-(benzoyloxy)-7-hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (51).
- 1-benzyl 2-methyl (2S,3aR,7S,7aR)-3a-(benzoyloxy)-7-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (29).
- 1-benzyl 2-methyl (2S,3aR,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (77).
- 1-benzyl 2-methyl (2S,3aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (83)
- 1-benzyl 2-methyl (2S,3aR,6S,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-((2-nitrophenyl)selanyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (98)
- 1-benzyl 2-methyl (2*S*,3a*S*,4*R*,7*R*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (99)
- 1-benzyl 2-methyl (2*S*,3a*S*,7*R*,7a*S*)-4,7-bis((*tert*-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (121)
- (2*S*,3a*S*,7*R*,7a*S*)-1-((benzyloxy)carbonyl)-4,7-bis((*tert*-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1*H*-indole-2-carboxylic acid (122)
- Methyl (2S,3aS,4R,7R,7aS)-4,7-bis((tert-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-2-carboxylate (123)
- Benzyl (2S,3aS,4R,7R,7aS)-2-((2S,3aS,4R,7R,7aS)-4,7-bis((tert-butyldimethylsilyl)oxy)-2-(methoxycarbonyl)-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carbonyl)-4,7-bis((tert-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carboxylate (124)
- 1-benzyl 2-methyl (2*S*,3a*S*,7*S*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-4-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (100).

- 1-benzyl 2-methyl (2*S*,3a*R*,7a*R*)-3a-acetoxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (56)
- 1-benzyl 2-methyl (2*S*,3a*R*,7a*R*)-3a-acetoxy-6-((*tert*-butyldimethylsilyl)oxy)-2,3,3a,7a-tetrahydro-1*H*-indole-1,2-dicarboxylate (62)
- 1-benzyl 2-methyl (2*S*,3a*R*,7*S*,7a*R*)-3a-acetoxy-7-hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (63)
- 1-benzyl 2-methyl (2*S*,3a*R*,7*S*,7a*R*)-3a-acetoxy-7-((*tert*-butyldimethylsilyl)oxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (64)
- 1-benzyl 2-methyl (2*S*,7*S*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-6-oxo-2,3,5,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (60)
- 1-benzyl 2-methyl (2*S*,7*S*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-6-(((trifluoromethyl)sulfonyl)oxy)-2,3,7,7a-tetrahydro-1*H*-indole-1,2-dicarboxylate (61)
- 1-benzyl 2-methyl (2*S*,7*R*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2,3,7,7a-tetrahydro-1*H*-indole-1,2-dicarboxylate (32)
- 1-benzyl 2-methyl (2S,3aR,7R,7aR)-3a-(benzoyloxy)-7-hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (7)
- 1-benzyl 2-methyl (2S,3aR,7R,7aR)-3a-(benzoyloxy)-7-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (104)
- 1-benzyl 2-methyl (2S,3aR,7R,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (105)
- 1-benzyl 2-methyl (2S,3aR,6R,7R,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (106)
- 1-benzyl 2-methyl (2S,3aR,6S,7R,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-((2-nitrophenyl)selanyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (107)
- 1-benzyl 2-methyl (2S,3aS,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-4-hydroxy-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (109)
- 1-benzyl 2-methyl (2*S*,3a*S*,4*S*,7*S*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (101)

- 1-benzyl 2-methyl (2S,3aS,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-4-oxo-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (103)
- 1-benzyl 2-methyl (2S,7R,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,5,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (110)
- 1-benzyl 2-methyl (2S,7R,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-(((trifluoromethyl)sulfonyl)oxy)-2,3,7,7a-tetrahydro-1H-indole-1,2-dicarboxylate (111)
- 1-benzyl 2-methyl (2S,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,3,7,7a-tetrahydro-1H-indole-1,2-dicarboxylate (103)
- 1-benzyl 2-methyl (2S,3aR,7aR)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (16)
- 1-benzyl 2-methyl (2S,3aR,6S,7aR)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (95)
- 1-benzyl 2-methyl (2S,3aR,6R,7aR)-6-((2-nitrophenyl)selanyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (96)
- 1-benzyl 2-methyl (2S,3aS,7aR)-4-hydroxy-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (97)
- 4-benzyl 5-methyl (3aR,5S,6aS)-2-oxooctahydro-4H-oxireno[2,3-e]indole-4,5-dicarboxylate (67)
- 1-benzyl 2-methyl (2S,3aS,7aR)-4-hydroxy-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (65)
- 1-benzyl 2-methyl (2S,3aS,7aR)-4-oxo-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (70)
- 1-benzyl 2-methyl (2S,3aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-((methylsulfonyl)oxy)-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (84)
- 1-benzyl 2-methyl (2S,3aR,6R,7S,7aR)-3a-(benzoyloxy)-7-((tert-butyldimethylsilyl)oxy)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (30)
- 1-benzyl 2-methyl (2S,3aR,6R,7S,7aR)-6-acetoxy-3a-(benzoyloxy)-7-((tert-butyldimethylsilyl)oxy)-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (31)

- 1-benzyl 2-methyl (2S,3aR,6S,7aR)-3a-acetoxy-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (57)
- 1-benzyl 2-methyl (2S,3aR,6R,7aR)-3a-acetoxy-6-bromo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (58)
- (5aS,10aS)-octahydro-5H,10H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (126)
- (5aR,10aR)-11-(1l4,2l4-trisulfan-1,2-dienylidene)tetrahydro-1H,5H,6H,10H-11l4-5a,10a-epithiodipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (127)
- (5aR,10aR)-tetrahydro-1H,5H,6H,10H-5a,10a-epidithiodipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (128)
- (5aR,10aR)-5a,10a-bis(methylthio)octahydro-5H,10H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (131)
- (5aS,10aS)-octahydro-5H,10H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione-5a,10a-d2 (129)
- (5aS,10aS)-5a,10a-dimethyloctahydro-5H,10H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (130)
- 1-benzyl 2-methyl (2*S*,3a*S*,4*S*,7*S*,7a*S*)-4,7-bis((*tert*-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (132)
- 1-benzyl 2-methyl (2S,3aS,4S,7S,7aS)-4-acetoxy-7-((tert-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (134)
- (2*S*,3a*S*,4*S*,7*S*,7a*S*)-1-((benzyloxy)carbonyl)-4,7-bis((*tert*-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1*H*-indole-2-carboxylic acid (133)
- Methyl (2S,3aS,4S,7S,7aS)-4-acetoxy-7-((tert-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-2-carboxylate (135)
- Benzyl (2S,3aS,4R,7R,7aS)-2-((2S,3aS,4R,7R,7aS)-4,7-bis((tert-butyldimethylsilyl)oxy)-2-(methoxycarbonyl)-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carbonyl)-4,7-bis((tert-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carboxylate (136)

- (1*S*,4*S*,4a*S*,6a*S*,7a*S*,8*S*,11*S*,11a*S*,13a*S*,14a*S*)-4,8,11-tris((*tert*-butyldimethylsilyl)oxy)-6,13-dioxo-4,4a,6a,7,7a,8,11,11a,13,13a,14,14a-dodecahydro-1*H*,6*H*-pyrazino[1,2-*a*:4,5-*a'*]diindol-1-yl acetate (137)

List of Schemes

List of Tables

List of Abbreviations

Boc	tert-Butyloxycarbonyl
BOPCl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Cbz	Carboxybenzyl
DCM	Dichloromethane
DKP	Diketopiperazine
DMP	Dess–Martin Periodinane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMDO	Dimethyldioxirane
DMAP	4-Dimethylaminopyridine
Et_3SiH	Triethylsilane
Et_3N	Triethylamine
HMPT	Hexamethylphosphoramide
*i*PrOH	Isopropyl Alcohol
KHMDS	Potassium bis(trimethylsilyl)amide
MeCN	Acetonitrile
MeOH	Methanol
*m*CPBA	*meta*-Chloroperoxybenzoic acid
NMR	Nuclear Magnetic Resonance
n-BuLi	n-Butyllithium
$NaBH_4$	Sodium Borohydride
$Pd(PPh_3)$	Tetrakis(triphenylphosphine)palladium(0)

$Pd(dba)_3CHCl_3$	Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct
PPh_3	Triphenylphosphine
SeO_2	Selenium Dioxide
SAR	Structure–Activity Relationship
TPP	Thiamine Pyrophosphate
TBSOTf	*tert*-Butyldimethylsilyl Trifluoromethanesulfonate
TIPS	Triisopropylsilane
THF	Tetrahydrofuran
t-BuLi	tert-Butyllithium
TBAI	Tetra-n-butylammonium bromide
TBS	*tert*-Butyldimethylsilyl
TMS	*Tri*methylsilyl
TIPS	Triisopropylsilyl

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My warm thank goes to Dr. Medha Gunawardhana, Dr. Chamitha Weeramange, and Dr. Huafan Fang, Mr. Basantha Acharya for their friendship and support. My special thank goes to my lovely friend late Dr. Aritri Majumdar for her love, friendship, and support.

I am sincerely grateful to all the teachers and everyone who helped me to learn something new and improve myself since I was born.

Last but not least, I would like to show my greatest gratitude to my family: my beloved parents, husband, grandmother, uncle, aunt, and my dog for their unconditional love, trust, care and continuous support.

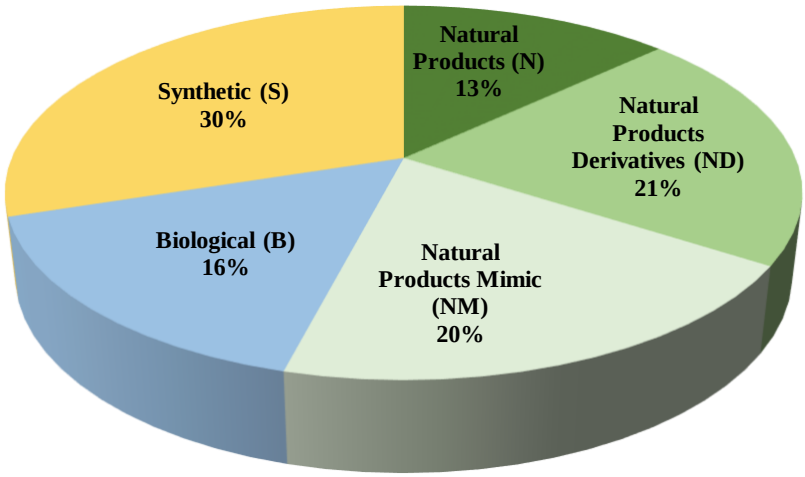
Dedication

I dedicate my work to my ammi (Mrs. Komanthika Nugahapola), apuchchi (Mr. Sunil Hulangamuwa), my loving husband (Dr. Lorne Jordan), teecha (Mrs. Vijalindika Nugahapola), mama (Mr. Ilandranatha Nugahapola), amma (late Mrs. Vimalawathi Kumarihami), and my baby boy (Recon).

Chapter 1 - Isolation of Brocazine Class Natural Products

1.1 Natural Products and the Importance of Total Synthesis

Natural products are mainly secondary metabolites produced by nature to perform specific functions such as self-defense, cell communication, and stress responses; though some natural products have interesting biological properties that can be used as therapeutics.[1-3] Use of natural products for healthcare ranges from using a mixture of natural compounds, isolation of biologically important compounds from the original natural sources, total synthesis, and synthesizing of derivatives from the original natural products.[4,5] 54% of all the drugs that have been approved from 1981 to 2014 are either natural products (N), natural products derivatives (ND), or natural products mimics (NM) (Scheme 1.1.1).[6] 13% of the them were directly originated from natural products, 21% were the derivatives of natural products, and 20% were the mimics of the natural products. Only 46% of the drugs approved were discovered from synthetic and biological based sources. Therefore, it can be concluded that the natural products play a vital role in drug discovery research.

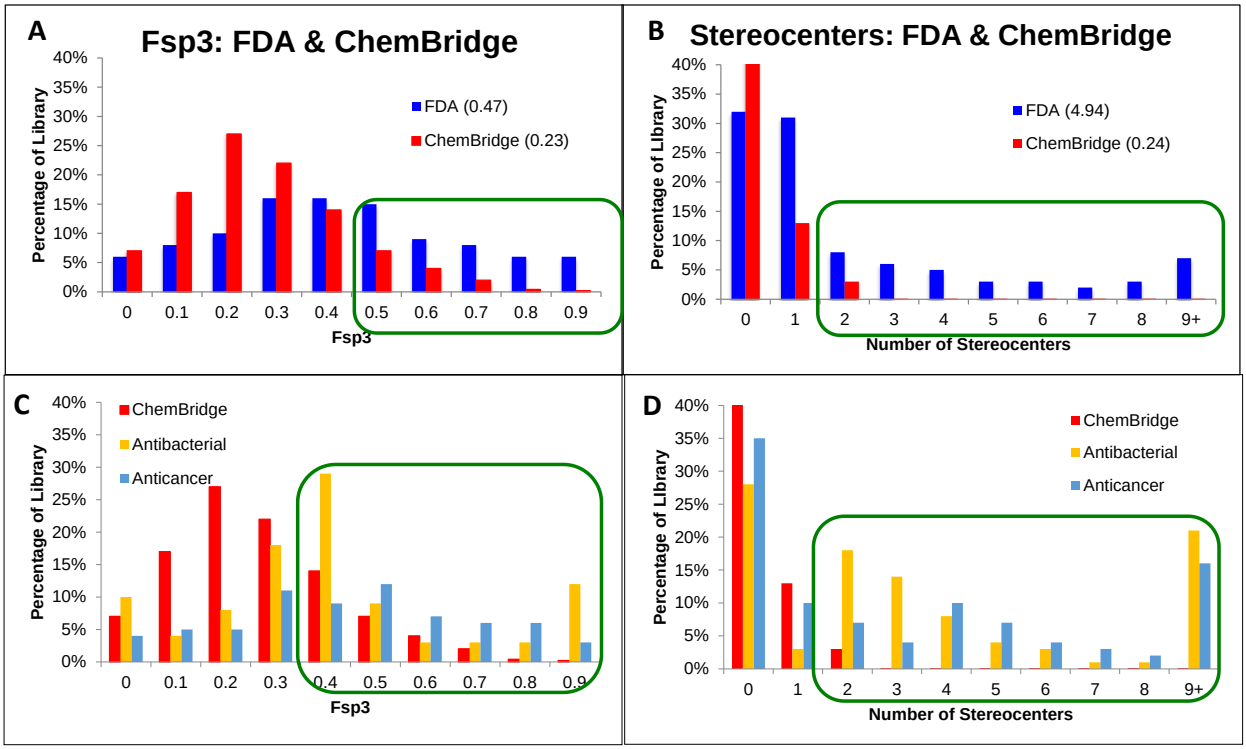


Scheme 1.1.1: All Approved Drugs from 1981-2014

Total synthesis of natural products provides a reliable and sustainable way to access biologically active natural compounds for therapeutic applications. However, they can also be beneficial in opening new areas in drug discovery research.[7-9] Previously, screening libraries were primarily filled with natural products and synthetic dyes. Later, synthetically derived and target-based small molecules were added into screening libraries.[10] With the use of high-throughput screening, it led to the need of more and more compounds for rapid assay screenings. Throughout these years, natural roducts remain to be a great souse to populate screening libraries due to their complex structures. Natural products can be considered as a great source to populate screening libraries, and to construct screening libraries by derivatization to access large number of small molecules, mainly due to their complex structures and the amenability for many chemical reactions (to be discussed later in this chapter).[11] There are many methods that can be used for screening library construction, which include platform-based synthesis and derivatization the original natural product.

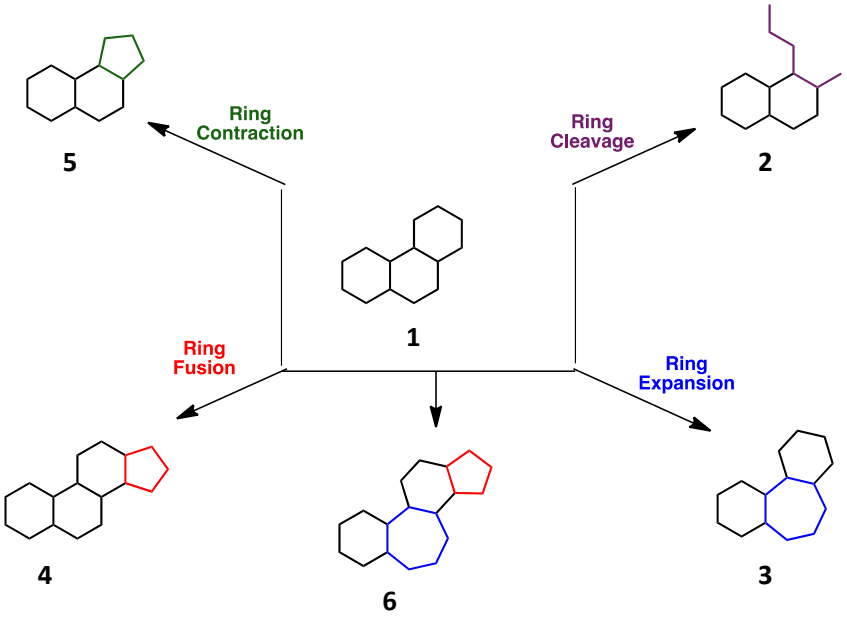
Most commercially available libraries, such as the ChemBridge library (largest chemical screening library), are synthesized via platform-based synthesis. In platform based synthesis, a large number (>10,000) of different molecules can be synthesized in a short period of time using automated methods.[12] As such, these libraries are composed of mainly small molecules that are flat (as evaluated by the percentage/fraction of sp^3-hybridized atoms in the compound) and lacking a large percentage of stereocenters. Multiple drugs have been discovered and approved by the FDA employing the ChemBridge library. A large percentage of these drugs act as kinase inhibitors, and also cause many off target side effects.[13-15] Kinases are very common enzymes that play vital roles in cell growth and metabolism, though the overexpression of kinases can be observed in some disease conditions such as cancer. Therefore, the inhibition of kinases can cause various side effects due to their inhibition of undesired targets. Therefore, discovering bioactive molecules with higher degree of complexity is crucial in drug discovery research to have higher efficiency with lower side effects. Quantifying molecular complexity is no easy task and has been done in a variety of means.[16-18] One such metric to assess molecular complexity can be performed by assessment of the percentage/fraction of sp^3 hybridized carbons (Fsp^3) and the number of stereo centers. Together, Fsp^3 and the number of stereocenters can be an indicator of three-dimensional shape of molecules.[19] In additional to molecular complexity, lipophilicity is also another major point of consideration for library design. Lipophilicity is commonly quantified by cLogP, which explains the absorption and the permeation of the molecule.[20] The complexity and the lipophilicity of molecules directly affect the probability of finding drug candidates, which have higher potency and selectivity towards a particular protein target. Therefore, screening libraries with higher Fsp^3 /stereo centers and lower cLogP values have higher probability of finding drug like molecules. Small molecules in Chembridge library have the average Fsp^3 of 0.23, whereas the average Fsp^3

of FDA approved drugs is 0.47 (Scheme 1.1.2 A). The average number of stereo centers in FDA approved drugs and the Chembridge library are 4.94 and 0.24, respectively (Scheme 1.1.2 B).[18] ChemBridge has been used to discover most of the compounds found in the FDA. However, Fsp^3 of the large percentage of molecules having antibacterial and anticancer activities is significantly higher than the Fsp^3 of the molecules in ChemBridge library (Scheme 1.1.2 C). Moreover, the number of stereocenters of molecules having anticancer and antibacterial activities is significantly higher than that of ChemBridge library (Scheme 1.1.2 D). This means that there is a gap (shown in green boxes) in ChemBridge library that needs to be filled with molecules with higher degree of complexity. Therefore, it is beneficial to construct small molecule screening libraries with higher $Fsp^3$and higher number of stereocenters to increase the probability of discovering molecules with drug like properties.



Scheme 1.1.2: Fsp3 and Stereocenters of Small Molecules in ChemBridge Library

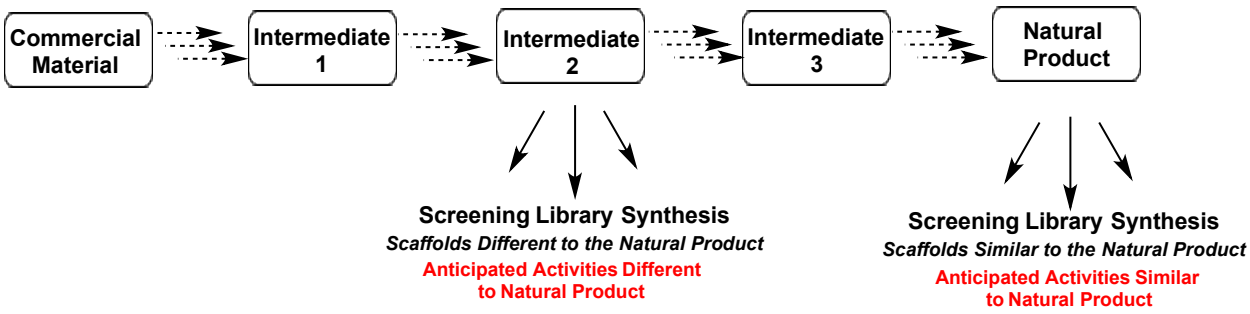
While ChemBridge is the most utilized, commercially available, small molecule screening library, multiple other academic research laboratories are developing new routes to construct their own libraries with targeted properties.[21-24] One example is that of Prof. Paul Hergenrother at the University of Illinois who employs natural products as starting materials for the construction of screening libraries via ring distortions, termed complexity to diversity, in 2013.[18] In this approach, the concept is to diversify a natural product into core scaffolds that differ from the parent natural product. These scaffolds are then further functionalized to provide new libraries for screening purposes that possess complexity imparted from the parent natural product. Accessing the core scaffolds was envisioned to arise from the diversification of the natural product through known synthetic transformations. Scheme 1.1.3 highlights the overview of the core scaffold construction. Starting from a polycyclic system, a natural product, it was envisioned that diversification of **1** could arise from ring cleavage accessing **2**. Furthermore, ring expansion upon **1** could access **3** giving access to different chemical space found in both **1** and **2**. Ring fusion upon **1** could also be performed to give access to **4**, and similarly ring contraction of **1** to **5**. Furthermore, these diversifications could be performed in parallel giving access to core scaffolds such as **6**.



Scheme 1.1.3: General Concept of the Derivatization of Small Molecules

In the complexity to diversity concept, the number of diversification steps could be endless. Therefore, Hergenrother decided to set forth a rule that all diversifications should be done in five synthetic steps or less.[18, 25, 26] Numerous collection of libraries were constructed from various natural products, each possessing high Fsp^3 character, high percentage of stereocenters, and synthetically amendable to allow for construction of targeted clogP properties. Unfortunately, screening of these collections of compounds (>500 compounds) revealed that all the biological activities were highly comparable to the parent natural product. While undesirable for the construction of variable chemical screening libraries, further thought on this matter led to the same conclusion. Each natural product employed in this route was synthesized and refined by nature to perform a particular function, and therefore, synthetic manipulations to the final natural product is less likely to produce molecules with different biological activities. Therefore, synthesis of libraries via a non-bio-inspired synthetic routes could give rise to small molecule libraries, which have a higher probability of finding molecules with different activities.

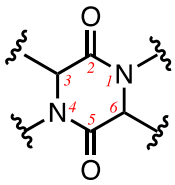
Our lab envisions on a noval way of accessing new complex small molecule screening libraries by derivatizing the intermediates within total synthesis routes of natural products. This could allow the access of complex and diverse small molecule libraries that could potentially have diverse biological activities. We envision that this approach should prevent the activity biased by the natural product due to non-natural synthetic route that is being developed, as long as the route is not bio-inspired. For this endeavor, a natural product, which has a complex chemical structure and amendable for many chemical modifications will be selected as the first candidate for the derivatization. The natural product will be accessed from a commercially available material and many intermediates will be accessed in this synthetic route (Scheme 1.1.4). These intermediates will be derivatized to access screening libraries with scaffolds different to the original natural product, which could also potentially have activities different to the original natural product due to non-natural synthesis. Therefore, the goal of this dissertation is to establish a reliable and reproducible route to access the brocazine family of diketopiperazine (DKP) natural products, from which the intermediates can be amendable for chemical derivatization for complex screening library construction. Furthermore, if the diversification of the intermediates within our brocazine fails to deliver new libraries with complex biological activities, the brocazine natural products accessed (each with wide biological activities) can be diversified via the complexity to diversity strategy for screening library construction.



Scheme 1.1.4: Screening Library Construction through Total Synthesis of Natural Products

1.2 Diketopiperazines

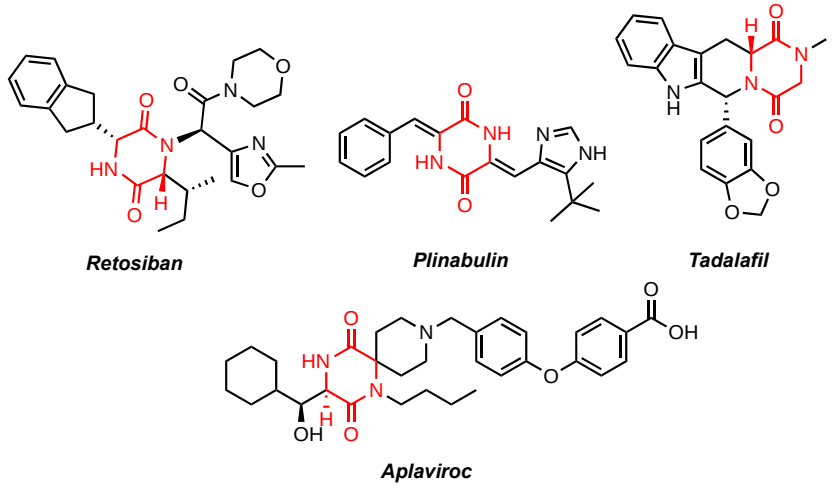
Many of the natural products that possess potent biological activities have 2,5-diketopiperazines (2,5-DKPs) core.[27, 28] Structure of DKPs consists of a six membered cyclic ring with two amide bonds, and are the smallest possible cyclic peptides found in nature (Scheme 1.2.1).[14]



Scheme 1.2.1 General Structure of 2,5-Diketopiperazine

Some examples of naturally occurring bioactive DKPs currently used as therapeutics are Retosiban, Tadalafil, Plinabulin, and Aplaviroc (scheme 1.2.2). Retosiban is an oxytocin receptor antagonist developed by GlaxoSmithKline as a treatment for preterm labour.[27, 29, 30] Plinabulin is a tubulin polymerization inhibitor that is in clinical trial for non-small cell lung cancer.[27, 31] Tadalafil is a phosphodiesterase inhibitor that is used to treat benign prostatic hyperplasia (BPH) and pulmonary arterial hypertension.[27, 32] Aplaviroc is a CCR5 inhibitor developed by GlaxoSmithKline as a treatment for HIV infection.[27, 33, 34] In addition, there are many bioactive DKP natural products that have been recently isolated from marine sources, which includes

epicoccins, brocazines, and spirobrocazines, which will be discussed later in this chapter and chapter 2.[26, 35, 36]

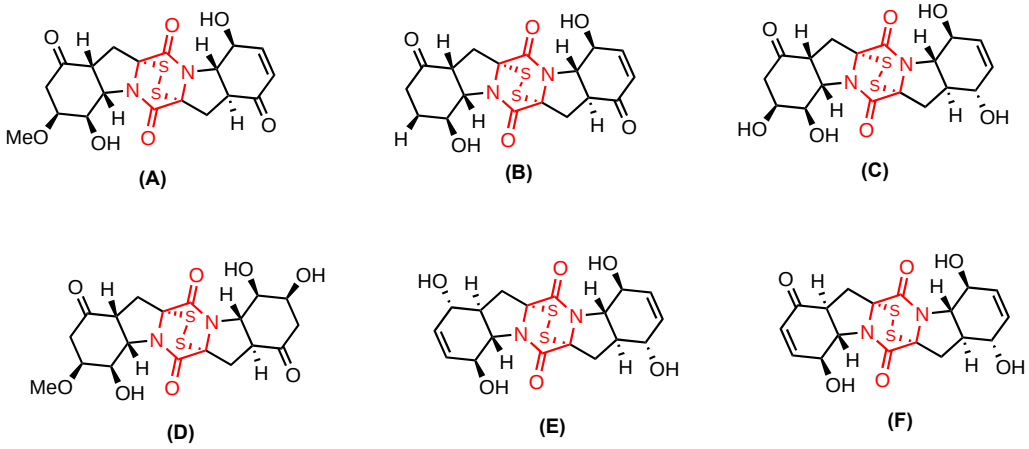


Scheme 1.2.2: Examples of Biologically Active 2,5-Diketopiperazine Therapeutics (DKPs are highlighted in red)

1.3 Isolation and Biological Activity of Brocazine F and G

The brocazines are a new class of DKP natural products were isolated in 2014 by Wang group. These molecules were isolated from a bioassay guided approach to isolate bioactive natural products from marine sources. Brocazine family is a thiodiketopiperazines containing natural products that were isolated from fungal strain *Penicillium brocae* MA-231, which is an endophytic fungus derived from marine mangrove plant *Avicennia marina.*[26] These compounds were isolated from the extracts of *P. brocae* MA-231 with multiple extractions with ethyl acetate and using a combination of column chromatography techniques such as silica gel, sephadex LH-20, and HPLC. Structurally, the brocazine family share a similar DKP carbon framework, highlighted in red, as shown in scheme 1.3.1. All brocazines have a thiodiketopiperazine central core, with one or more alcohol groups attached. Brocazine A and B possess ketone and enone systems, whereas brocazine C possesses a ketone in one side and an allylic diol system in the other side. Brocazine

D has two ketone systems and brocazine E has two allylic diol systems, whereas brocazine F possesses an enone system and an allylic diol system.



Scheme 1.3.1: Structures of Brocazine A-F

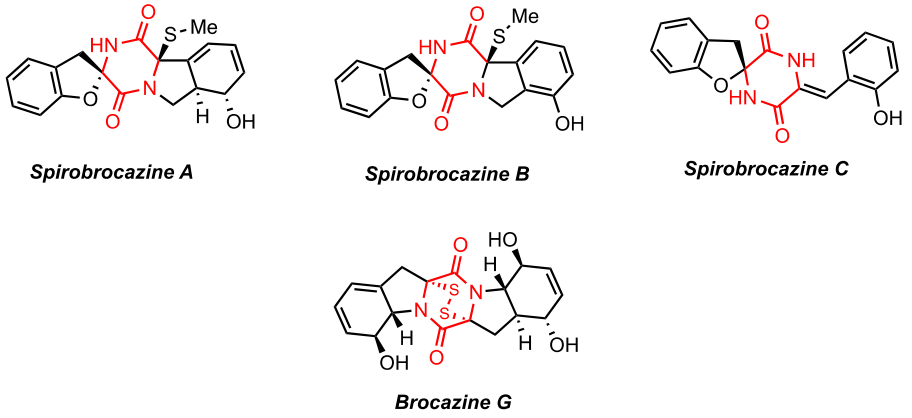
The brocazine cytotoxicity was determined by screening against different types of cancer cell lines: human prostate cancer (Dul45), human cervix carcinoma (HeLa), Human hepatoma cells (HepG2), human breast carcinoma (MCF-7), human large-cell lung carcinoma (NCI-H460), human gastric (SCG-7901), human pancreatic cancer (SWI-990), human colon carcinoma cancer (SW480), and human glioma cells (U251). Brocazine A, B, E, and F showed activity against many cancer cell lines tested.[26] Most notably, it was found that brocazine F possessed an IC_{50} value of 0.89 μM against human large cell lung cancer cell line, NCI-H460. However, brocazine C and D did not show any activity toward none of the cell lines tested. These cytotoxic data suggest that the presence of either enone systems or the presence of more than one allylic diol systems are essential for the activity of brocazines.

Table 1.3.1: Cytotoxicity of Brocazine A-F Against Nine Tumor Cell Lines (IC_{50}, μM)

Human prostate cancer (Dul45), human cervix carcinoma (HeLa), Human hepatoma cells (HepG2), human breast carcinoma (MCF-7), human large-cell lung carcinoma (NCI-H460), human gastric (SCG-7901), human pancreatic cancer (SWI-990), human colon carcinoma cancer (SW480), human glioma cells (U251). --: no activity (>20 μM). N.t.: not tested. Paclitaxel[l], Cisplatin[m], Cefitinib[n], Doxorubicin[o], Gemcitabine[p].)

	DUL45	HELA	HEPG2	MCF-7	NCI-H460	SGC-7901	SWI990	SW480	U251
1	4.2	6.8	6.4	5.5	4.9	2.6	6.0	2.0	5.2
2	3.6	5.3	5.5	6.1	4.0	2.4	6.4	1.2	3.5
3	--	--	--	--	--	--	--	--	--
4	--	--	--	--	--	--	--	--	--
5	11.2	4.3	5.6	9.0	12.4	2.2	2.1	n.t	6.1
6	1.7	6.9	2.9	3.0	0.89	8.0	5.9	n.t	5.3
Positive control	1.5[l]	5.0[l]	5.1[m]	1.8[l]	7.6[n]	2.9[o]	2.2[p]	11.3[m]	10.8[n]

In 2016, Wang group isolated brocazine G and three different types of spirobrocazines (A-C) from fungal strain *Penicillium brocae* MA-231 (Scheme 1.3.2).[35] Among these newly isolated brocazines, brocazine G showed strong activities towards A2780 (human ovarian cancer) and A2780 CisR (cisplatin resistance human ovarian cancer) cell lines with IC_{50} values of 0.664 μM and 0.661 μM respectively. In addition, brocazine G showed strong and selective activity against human pathogen *Staphylococcus aureus* with MIC value of 0.25 μg/mL.



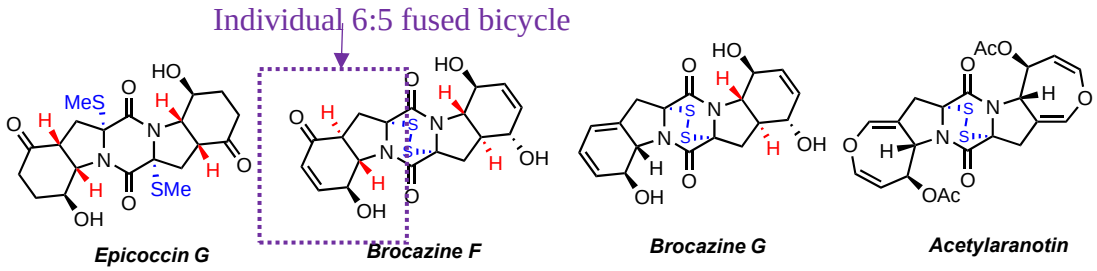
Scheme 1.3.2: Structures of Spirobrocazine (A-C) and Brocazine

Brocazine F/ G were selected for the total synthesis campaign due to their interesting biological activities, which have been discussed previously. Furthermore, brocazine F/G and the intermediates of the proposed synthetic route possess complex structures, which are amendable for many chemical modifications for screening library construction. Therefore, it was envisioned that the total synthesis campaign of brocazines and the screening library construction would open new areas of drug discovery research. Moreover, in the case of failed hypothesis of screening library construction from the intermediates of the route, it would be still possible to access the total synthesis of bioactive natural products, brocazine F and G. Moreover, the derivatization of the final natural products can be performed to access a small molecule screening library with higher degree of complexity.

1.4 Synthetic Challenges of Brocazine's & Similarity and Differences towards the Epicoccin's

To date, no synthesis of the brocazine family, or work towards this family has been reported. Upon selection of this family of natural products a closely related natural product family was found, the epicoccin's. The epicoccin and brocazine families belong to the same thiodiketopiperazine family of natural products. Although both share a similar carbon framework, they do have some

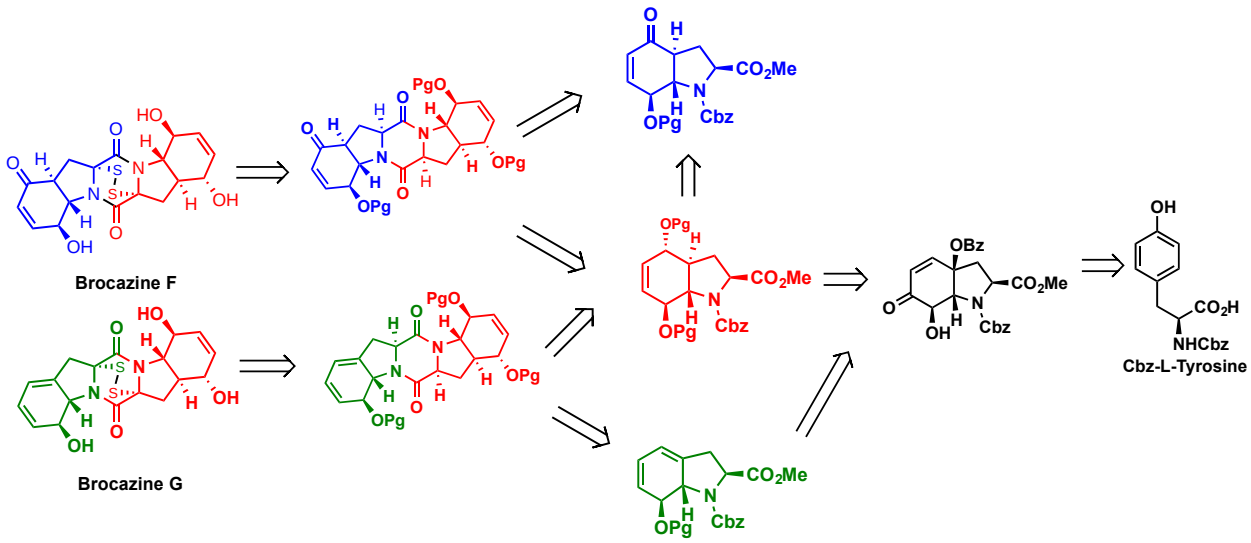
differences, which have been highlighted (Scheme 1.4.1). Epicoccin G contains thiomethyl groups in the central DKP core, whereas, brocazine F and G have disulfide linkages in their central DKP cores. Moreover, epicoccin G has two cis 6:5 fused systems making the compound more puckered, whereas, brocazines have one or two trans 6:5 fused systems which makes their structure planer. Accessing trans 6:5 fused systems is challenging due to their planer conformation, which makes reaction conditions applicable to trans systems unavailable. This is mainly due to the difficult accessibility of the reagents to the reaction site producing the desired products. Moreover, the synthesis of trans 6:5 fused systems has not been reported as much compared to that of cis 6:5 fused systems due to their synthetic challenges. However, the synthesis of cis 6:5 fused system containing natural products such as epicoccin G and acetylaranotin has been reported by many research groups.[37-39] In addition, the synthesis of asymmetrical DKPs are challenging as the functionalities need to be introduced to individual 6:5 fused systems before coupling them together to access DKP cores. However, in symmetrical DKPs, DKP core can be accessed first and the functionalities can be introduced directly to the DKP core (to be discussed in chapter 2). Therefore, some of the chemistry that has been used for symmetrical cis 6:5 systems such as epicoccin G and acetylaranotin cannot be directly used for the synthesis of brocazine F and G, and the development of new routes to access trans 6:5 system need to be explored.



Scheme 1.4.1: Structural Differences of Epicoccin G and Brocazine F and G

1.5 Retrosynthetic Analysis of Brocazine F and G

Proposed retrosynthetic analysis for the synthesis of brocazine F and G (Scheme 1.5.1). The final stages of accessing brocazine F and G are proposed to follow analogous disulfide incorporation upon the respective DKP cores, **7** and **8**. DKP cores **7** and **8** can be accessed from the coupling of **9**/**10** and **10**/**11**, respectively. Diol **10** can be accessed from a palladium catalyzed deoxygenation of α-hydroxy ketone **12**. Enone **9** can be directly accessed via an DMP oxidation of diol **10**. The diene **11** can be accessed via a Zn-catalyzed elimination of the benzyl group of α-hydroxy ketone **12**, followed by the triflate enol ether formation and triflate elimination. The α-hydroxy ketone **12** can be stereo selectively accessed from the spiralization, ring rearrangement, benzoylation, and stereo selective Rubottom oxidation of the commercially available material Cbz-L-tyrosine.

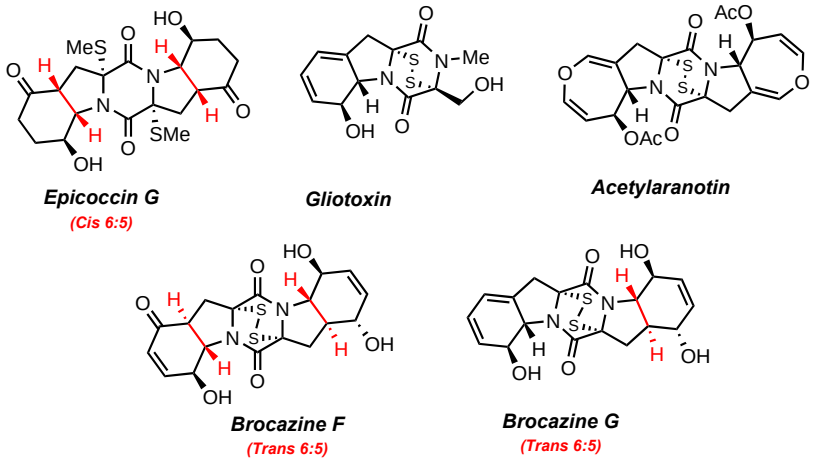


Scheme 1.5.1: Retrosynthetic Analysis of Brocazine F and G

Chapter 2 - Previous Synthetic Work

2.1 Natural Products Similar to Brocazines

Total synthesis of brocazine F and G has not yet been achieved. However, the total syntheses of DKP natural products similar to brocazines have been successfully achieved by several research groups. A literature review of the synthesis strategies that have been used in accessing brocazine like natural products will be discussed in this chapter. Epicoccin G, gliotoxin, and acetylaranotin are some natural products that are similar to brocazines. All of these natural products consist of at least one fused bicycle system, and these fused bicycles can be coupled together to access the DKP core of the natural product (Scheme 2.1.1).

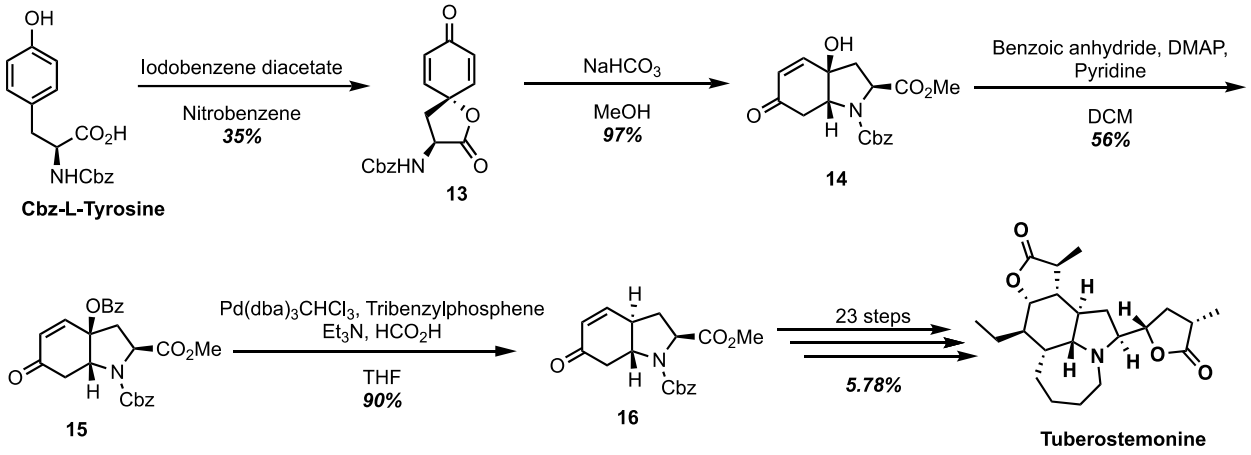


Scheme 2.1.1: Structures of Brocazine F & G and Natural Product Similar to Brocazines

2.2 Accessing Trans Fused Bicycle System Utilizing the Chemistry Developed by Wipf Group

The Wipf group has established a synthetic procedure that have been used by multiple groups for the synthesis of natural products with DKP cores.[40] Wipf's route to gain access to the 6:5 fused ring system commenced with the phenolic oxidation of Cbz-L-tyrosine with iodobenzene diacetate

to access the 6:5 spiral **13** in 35% yield. Subjecting **13** to basic methanol promoted lactone cleavage and subsequent amine addition via 1,4-Michael pathway to access **14** in 97% yield. Compound **14** was benzoylated to obtain **15** in 56% yield, which was in turn transformed through a palladium-catalyzed elimination to access trans-fused bicycle **16** in 90% yield. The final natural product tuberostermonine was obtained after 23 steps from compound **16** with the overall yield of 5.78% (Scheme 2.2.1).[40] This chemistry, developed by Wipf group has laid foundation to multiple natural product total synthesis, which will be discussed later in this chapter.



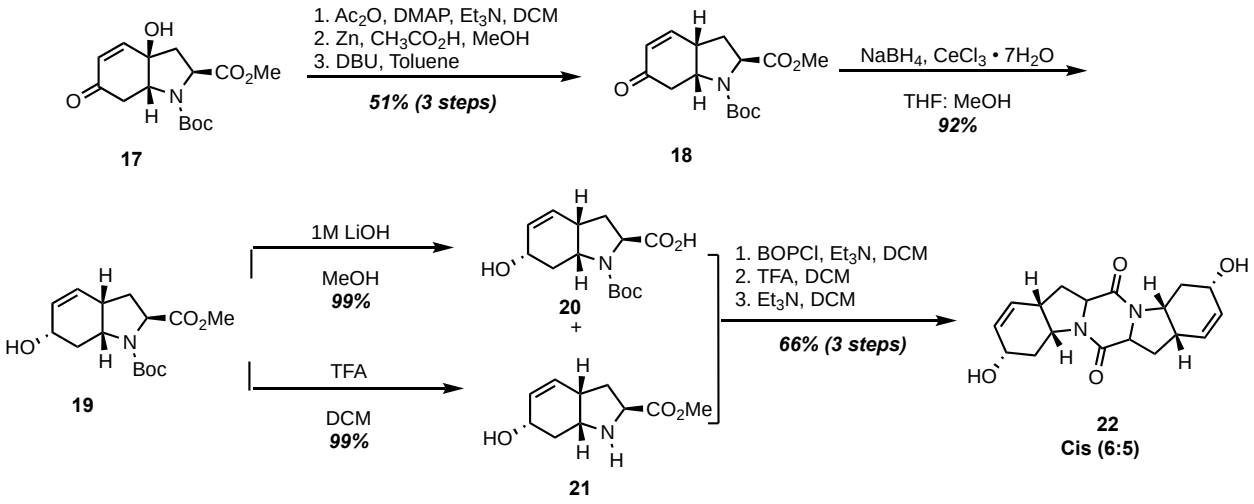
Scheme 2.2.1: Synthesis of trans 6:5 Fused Bicycle Compound **16** from Cbz-L-Tyrosine

2.3 Total Synthesis of Epicoccin G by Nicolaou Group

Epicoccin G, a symmetrical natural product, was isolated from the endophytic fungus *Epicoccum nigrum* by Dan Du and coworkers in 2010.[36] This natural product has shown to exhibits anti-HIV activity in C8166 cells with the IC_{50} value of 13.5 μM. The enantioselective total synthesis of epicoccin G has been achieved by Nicolaou group in 2011.[37] In this synthetic work, they have used some of the chemistry developed by Wipf group, as well as two-directional sulfenylation,

photooxygenation, and Kornblum - DeLaMare rearrangement to allow for enantioselective access the final natural product.

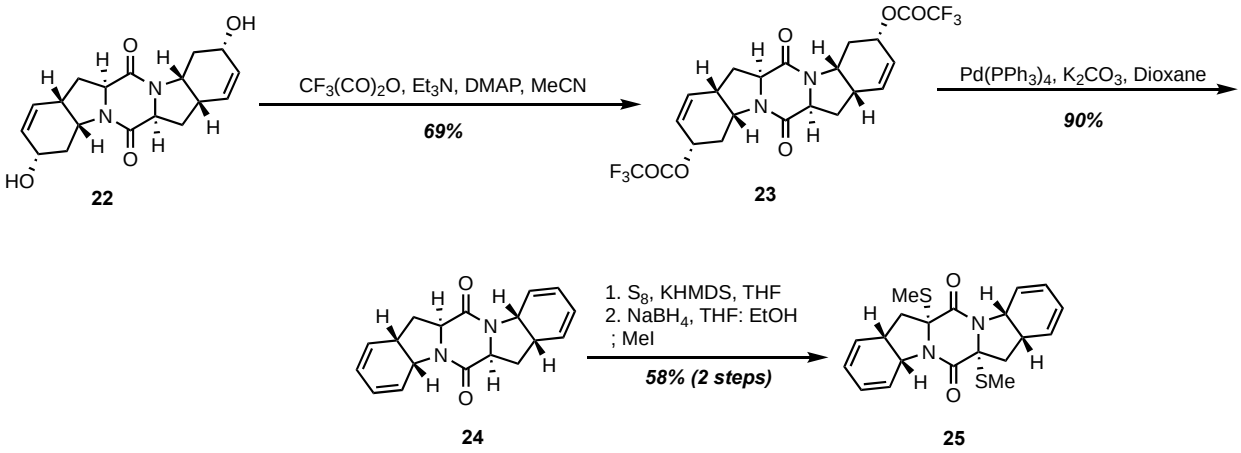
Compound **17** was accessed via the route developed by Wipf group as discussed in subsection 2.2. Cis enone bicycle **18** was accessed via three step procedure, which includes acetylation of the tertiary alcohol of **17**, followed by the zinc facilitated reduction, and base-induced isomerization with the overall yield of 51%. Luche reduction of enone **18** gave access to **19** in 92% yield and the saponification and Boc deprotection of **19** separately gave access to **20** in 99% and **21** in 99% yields, respectively. Coupling of compound **20** and **21** was performed with BOPCl, followed by Boc deprotection and aminolysis to yield DKP compound **22** with the overall yield of 66% over 3 steps (Scheme 2.3.1).[37]



Scheme 2.3.1: Synthesis of DKP Compound **22** from Compound **17**

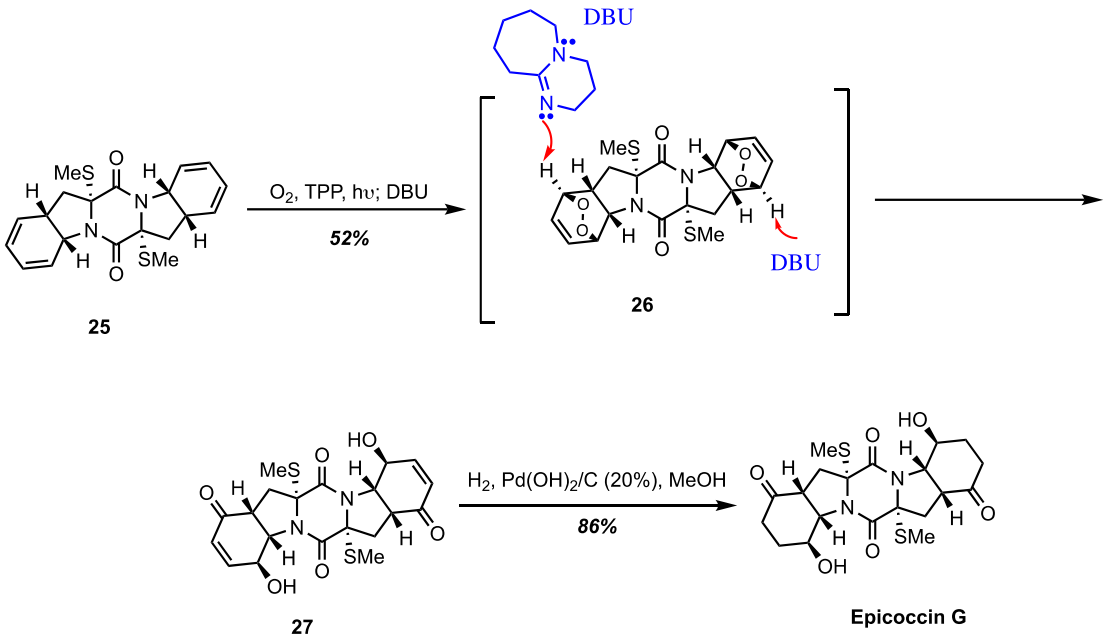
Bistrifluoroacetate **23** was accessed from the trifluoroacetylation of compound **22** using trifluoroacetic anhydride in 69% yield. Treatment of **23** with Pd(PPh3), K_2CO_3 in dioxane promoted the elimination of the trifluoroacetate group to afford diene **24** in 90% yield.

Bismethylsulfonation was achieved with the formation of oligosulfide by using elemental sulfur and KHMDS, followed by the reduction of oligosulfide using $NaBH_4$ with the subsequent quenching of the reaction using MeI to yield **25** in overall yield of 58% (Scheme 2.3.2).[37]



Scheme 2.3.2: Synthesis of Bismethylsulfonated **25** from **22**

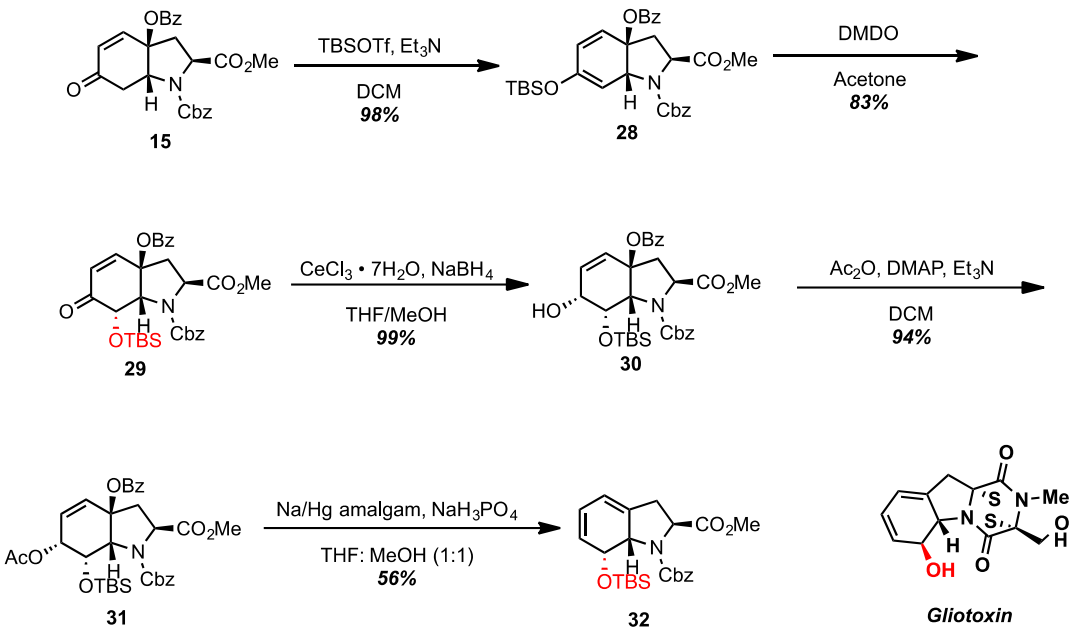
Accessing the oxidized carbon core was accomplished by a [4+2] addition of O_2 (g) to diene **25** to afford **26**, followed by the treatment of DBU to undergo regioselective Kornblum-DeLaMare rearrangement to give rise to **27** in 52% yield. DBU is a large non-nucleophilic bulky base and it can only access the hydrogen adjacent to the thiomethyl group resulting the desired product **27** due to sterics. In this procedure, alcohol enone systems can be stereo selectively introduced in one step procedure. However, this procedure uses O_2 (g), TPP, and hν, which can make the reaction dangerous and non-cost effective. Finally, the compound **27** was reduced by catalytic hydrogenation with $Pd(OH)_2/C$ to afford the natural product epicoccin G in 86% yield (Scheme 2.3.3).[37]



Scheme 2.3.3: Synthesis of Epicoccin G from **25** via Regioselective Kornblum-DeLaMare Rearrangement

2.4 Accessing Diene Bicycle System Utilizing the Chemistry Developed by Sundburg Group

In 1996, Sundburg group developed a method to access the diene fragment of gliotoxin **32** using Rubottom oxidation and mercury amalgam facilitated elimination of a benzyl group.[41] From **15**, accessed by Wipf, TBS enol ether formation was performed using TBSOTf to afford the TBS enol ether **28** in 98% yield.[40, 41] Compound **28** was then subjected to Rubottom oxidation conditions empoying DMDO as the oxidant to obtain **29** in 83% yield. Surprisingly, the crystal structure of compound **29** showed that the resultant alpha hydroxyl group (Shown in red) possessed S configuration compared to that of gliotoxin (R configuration) (Scheme 2.6). Compound **30** was accessed by the Luche reduction of enone **29** in 99% yield, and this material was acetylated to give **31** in 94% yield. Mercury amalgam facilitated elimination of benzyl group of **31** resulted the opposite isomer of the diene system **32** of gliotoxin in 56% yield (Scheme 2.4.1).[41]

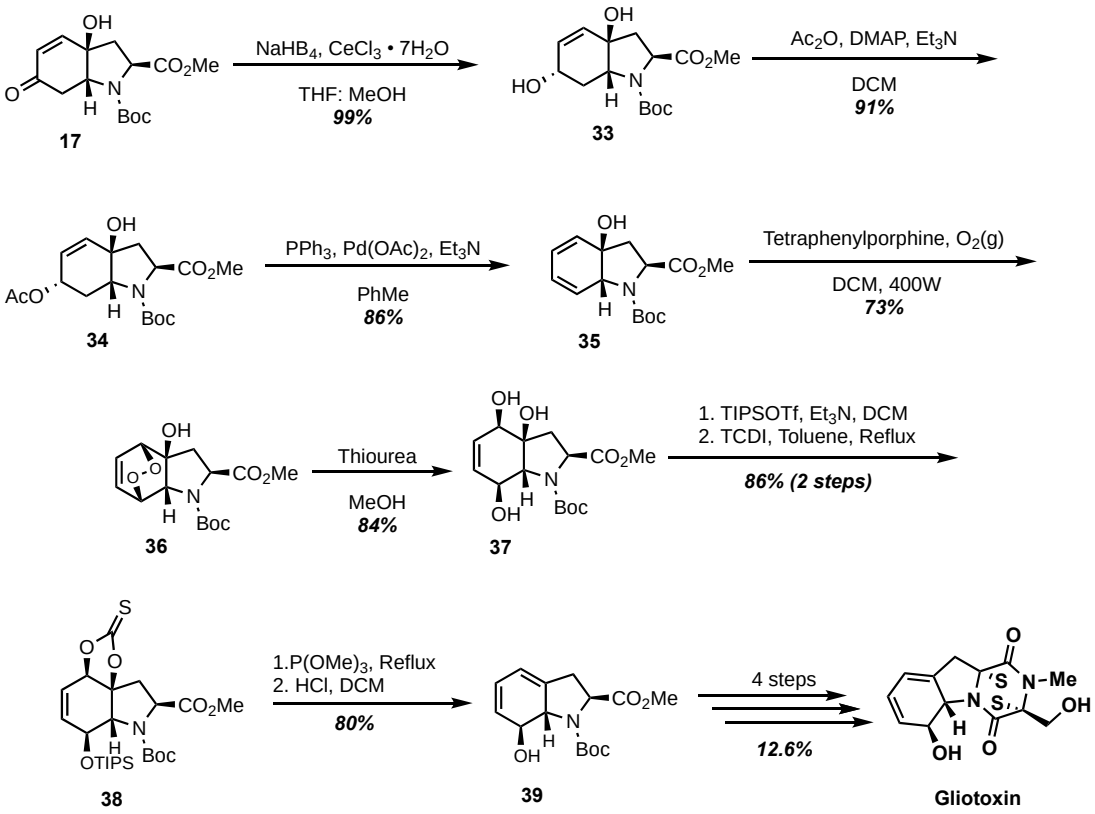


Scheme 2.4.1: Synthesis of Diene Alcohol Compound **32** from Compound **15**

2.5 Accessing Diene Bicycle System Utilizing the Chemistry Developed by Nicolaou Group

In 2012, Nicolaou group developed a synthetic route to access gliotoxin utilizing the chemistry developed by Wipf and some of the chemistry that they have used for their total synthesis of epicoccin G.[38] In this synthetic route, they have used diene formation, photooxidation, and Corey-Winter Olefination to stereo-selectively access gliotoxin. Luche reduction of enone **17** gave the selective reduction of the carbonyl group in enone system to obtain enol **33** in 99% yield. Stoichiometric control of acetylation of **33** only resulted the desired monoacetylated product **34** in 91% yield. Palladium-catalyzed elimination of compound **34** accessed diene **35** in 86% yield, which was then subjected to photochemical addition of O_2 (g) to access **36** in 73% yield. Treatment of compound **36** with thiourea resulted in the formation of the triol **37** in 84% yield. After the selective protection of lower alcohol group with TIPS group, thiocarbonyl group was introduced to 1, 2- diol system to yield compound **38** with the overall yield of 86%. Compound **38** was then

deoxygenated and deprotected to yield compound **39** in overall yield of 80%. Final natural product gliotoxin was obtained after 4 steps from diene **39** with the overall yield of 12.6% (Scheme 2.5.1).

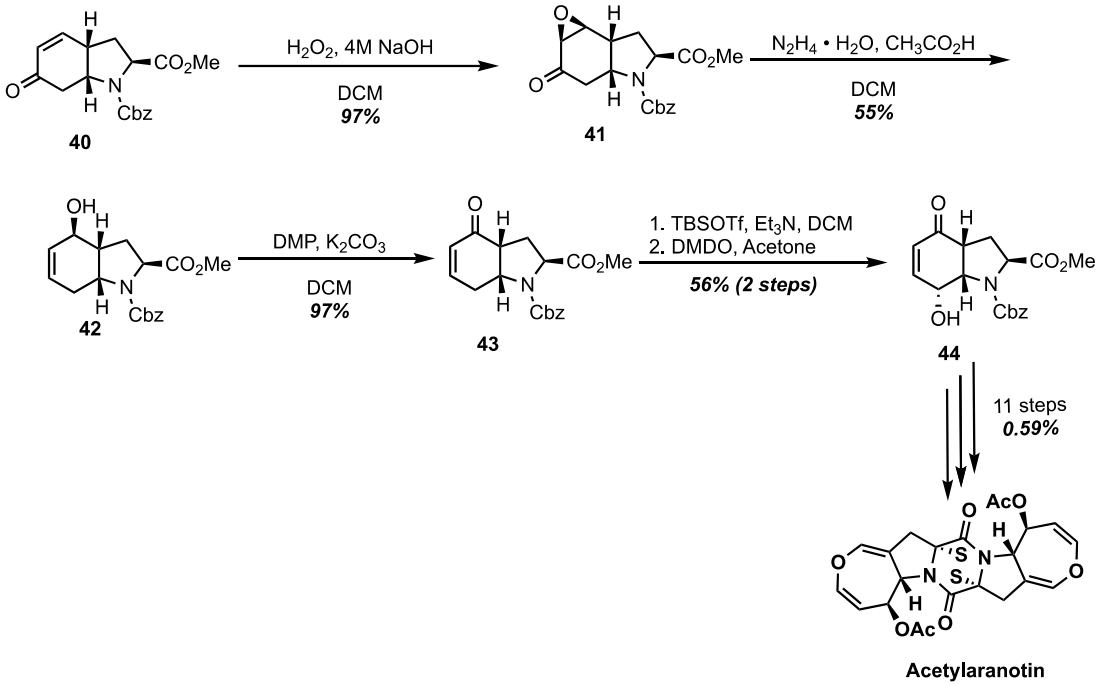


Scheme 2.5.1: Synthesis of Diene Alcohol compound **39** from Compound **17**

2.6 Accessing Enone Allylic Alcohol System Utilizing the Chemistry Developed by Tokuyama Group

In 2012, Tokuyama group published the total synthesis of acetylaranotine, a thiodiketopiperazine natural product.[39] In this paper, they have accessed the cis 6:5 fused allylic alcohol eneone system **40** in their synthetic route to access acetylaranotin. Epoxidation **40** with H_2O_2 and NaOH afforded epoxy ketone **41** in 97% yield. Subjecting **41** to Wharton rearrangement conditions of $N_2H_4 \bullet H_2O$, afforded enol **42** in 55% yield. The secondary alcohol of compound **42** was oxidized by DMP

oxidation to yield enone **43** in 97% yield. Introduction of alcohol group in the allylic position of enone was achieved via extended Rubottom oxidation to obtain the compound **44** with the overall yield of 56%. Surprisingly, the X-ray crystallographic structure showed that the resultant alcohol group possessed the undesired stereochemistry. However, the desired stereochemistry of this alcohol was accessed later via an oxidation-reduction procedure of the DKP core of acetylaranotin. The final natural product acetylaranotin was obtained after 11 steps from compound **44** with the overall yield of 0.59% (Scheme 2.6.1).

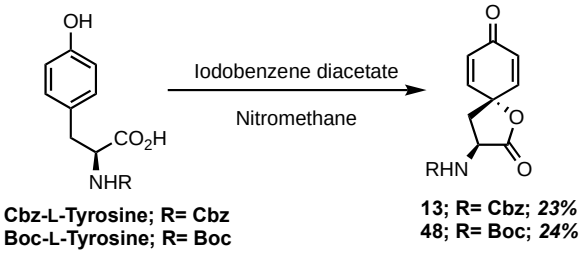


Scheme 2.6.1: Synthesis of Acetylaranotin from Compound **40**

Chapter 3 - Synthetic Efforts Towards Brocazine F and G and Discussion

3.1 Spiral Ring formation

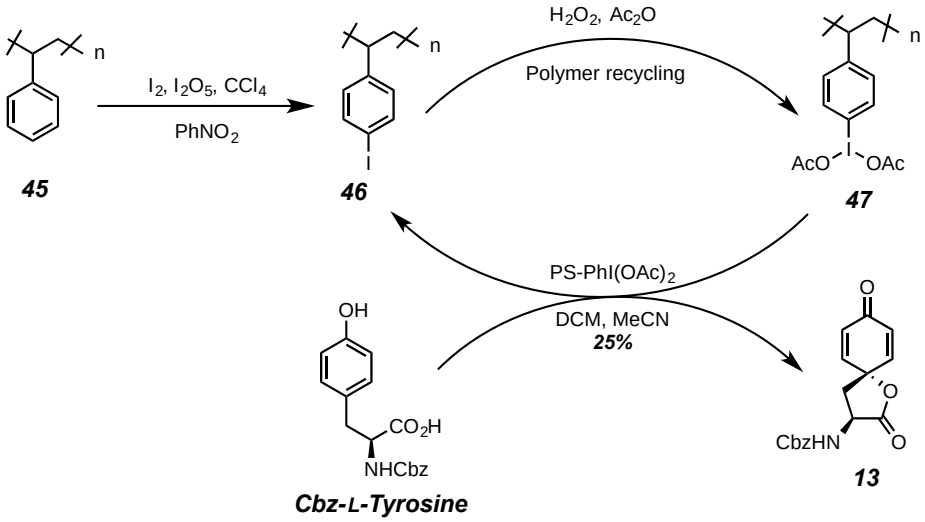
Our synthetic endeavors towards the total synthesis of the brocazine family was commenced from Cbz-L-tyrosine/ Boc-L-Tyrosine and their transformation into the 6:5 spiral ring **13/48**.[40, 42] Cbz-L-tyrosine and Boc-L-Tyrosine were converted to 6:5 spiral **13** and **48** using iodobenzene diacetate in 23% and 24% yields, respectively (Scheme 3.1.1). This reaction proceeds with the coordination of iodobenzene diacetate to the phenolic group of Cbz/Boc-L-tyrosine making the para position more electrophilic, which allows the oxygen of the carboxylic acid to attack the said position producing 6:5 spiral systems **13** and **48**, respectively. Optimization of this reaction while not undertaken by Wipf, was undertaken to enhance access of **13** and **48**.



Scheme 3.1.1: Spiral Ring Formation Reaction

The yield of this reaction was low due to the polymerization of Cbz-L-tyrosine after the coordination with iodobenzene diacetate, which was proved by analyzing the ^{1}H NMR of the sticky brown substance that was collected after quenching the reaction. Therefore, it was decided to use a procedure found in literature which uses polymer supported hypervalent iodine source instead of iodobenzene diacetate to obtain a better yield for the spiralization reaction.[43] The first attempt of the optimization of spiral ring formation reaction was done with polymer assisted material **47**. Polymer **47** was synthesized by iodination of polystyrene **45** with I_2, I_2O_5, and CCl_4 to obtain

iodinated polystyrene **46**, followed by the acetylation with H_2O_2 and Ac_2O to yield polymer **47.**[43] The advantage of this method is the ability to regenerate the polymer with H_2O_2 and Ac_2O once it is used (Scheme 3.2). However, when the polymer **47** was used for the spiral ring formation reaction of Cbz-L-tyrosine, the spiral **13** was obtained in 25% yield (Scheme 3.1.2). Moreover, even after using different amounts of polymer (entry 1-4), time durations (entry 1, 5-7), and extraction methods (entry 9-11), it was unable to optimize the reaction yield higher than 25% (Table 3.1.1). The article that we referred for this procedure has reported 75-100% yields for the spiralization reactions of similar substrates. However, this procedure did not result a higher yield than 25% in the desired system, even after attempting the reaction with several people to test for the human error. Further optimization of the spiralization reaction with the polymer supported material is currently being undertaken.



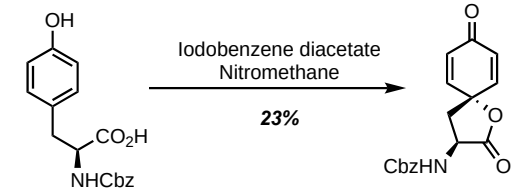
Scheme 3.1.2: Spiral Ring Formation Using Polymer Assisted Material

Table 3.1.1: Optimization of the Spiral Ring Formation Using Polymer Assisted Material

Entry	Scale	Polymer mass	Yield	Note
1	100 mg	250 mg	11 %	20 h
2	100 mg	490 mg	20 %	20 h
3	100 mg	1000 mg	19 %	20 h
4	100 mg	80 mg	13 %	20 h
5	100 mg	250 mg	13 %	6 h
6	100 mg	250 mg	11 %	4 h
7	100 mg	250 mg	4 %	1 h
8	100 mg	250 mg	22 %	10 h
9	100 mg	490 mg	20 %	6 h more solvent for polymer
10	100 mg	490 mg	22 %	20 h extraction before filtering polymer
11	100 mg	490 mg	5 %	1.5 h more solvent for tyrosine

It was decided to further explore the initial methods to improve the yield of the spiralization reaction. Further attempts to optimize the spiral ring formation reaction was performed by using different solvents and temperatures (Table 3.1.2). First, it was decided to investigate the effect on temperature for the reaction yield using 0 ◦C, room temperature, and reflux conditions (entry 1-3, 4-5)). However, it was observed that the temperature had no significant effect on the reaction yield in multiple solvents explored, resulting the yields around 25%. It was also observed that the reaction yield did not have a significant effect on the equivalents of the hypervalent iodine source used (entry 6). It was observed that the solvent had some effect on reaction yield, in which employing *i*PrOH:MeCN (1:4) and MeOH resulted in 45% and 18% yields, respectively (entry 4,7). This increased yield could be due to the better solubility of the reactants and reagents when *i*PrOH:MeCN (1:4) was used. While further optimization is being undertaken, efforts towards the total synthesis of brocazone F and G was continued.

Table 3.1.2: Optimization of Wipf Spiral Ring Formation Reaction; Effect of Different Solvents and Temperatures

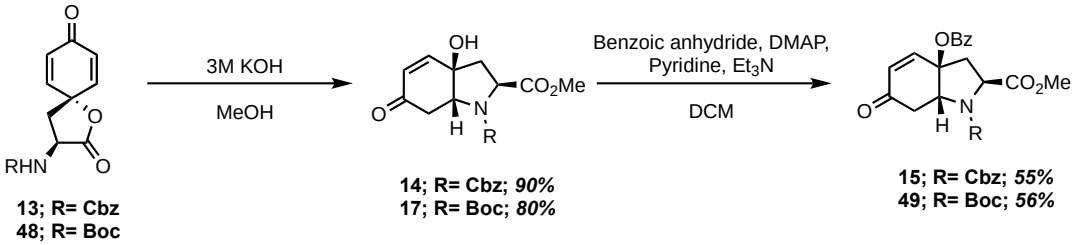


Cbz-L-Tyrosine **13**

Entry	Solvent	$PhI(OAc)_2$ (eq)	Temperature	% Yield
1	Nitromethane (1 M)	1.0	RT	23%
2	Nitromethane (1 M)	1.5	0 ◦C	8%
3	Nitromethane (1 M)	1.5	Reflux	25%
4	iPrOH: MeCN (4:1) (0.1 M)	1.5	RT	45%
5	iPrOH: MeCN (4:1) (0.1 M)	1.5	0 ◦C	20%
6	iPrOH: MeCN (4:1) (0.1 M)	2.0	reflux	44%
7	MeOH (0.1 M)	1.5	RT	18%

3.2 Accessing Benzylated 15 and 49

Accessing **15** (Cbz) and **49** (Boc) were done following a procedure developed by Wipf group.[40] Treating **13** and **48** with 3M KOH at -20 °C promoted the rearrangement to obtain **14** and **17** in 90% and 80% yields, respectively. Treating the tertiary alcohol **14** and **17** with benzoic anhydride, DMAP, and pyridine at reflux conditions afforded the desired compounds **14** and **17** in 55% and 56% yields, respectively (Scheme 3.2.1). Optimization of the benzoylation reaction was necessary as it was challenging to proceed forward with the total synthesis route with this lower yielding reaction in addition to the spiralization step.



Scheme 3.2.1: Accessing Benzylated Compounds **15** and **49** from Compound **13** and **48**, Respectively

DMAP forms an activated compound with benzoic anhydride making the esterification reaction with the alcohol more feasible. Therefore, the optimization of benzoylation reaction was attempted by using different equivalents of DMAP to test the effect of the equivalents of DMAP in reaction yield (Table 3.2.1, entry 1-2). However, the equivalence of DMAP did not have a significant effect on the yield of the reaction. Then, it was decided to use benzoyl chloride instead of benzoic anhydride. It was assumed that the benzoyl chloride would access the tertiary alcohol group more efficiently due to its smaller size. However, when benzoyl chloride was used instead of benzoic anhydride, the reaction yield dropped down to 18% (entry 3). This could be due to the lower stability of the benzoyl chloride, degrading before it reacts with the alcohol **14**. Then it was thought that a smaller base such as Et_3N would more efficiently access the tertiary alcohol group, increasing the reaction yield. However, the yield of the reaction did not have a significant effect when Et_3N was used as the base (entry 4-5). Finally, it was decided to use benzoic anhydride (3 eq), DMAP (0.1 eq), pyridine (5.12 eq), and Et_3N (3 eq) under reflux conditions to test the combination effect of all the reactions in reaction yield. In this case, the yield was optimized to 83% and the reproducible results were obtained in many trials tested (entry 6).

Table 3.2.1: Optimization of Benzoylation Reaction

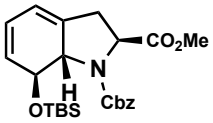
Entry	Reagent (eq)	DMAP (eq)	Base (eq)	% Yield
1	Benzoic anhydride (2.00 eq)	0.05	Pyridine (5.12 eq)	56%
2	Benzoic anhydride (2.00 eq)	0.10	Pyridine (5.12 eq)	55%
3	Benzoyl chloride (2.00 eq)	0.05	Pyridine (5.12 eq)	18%
4	Benzoic anhydride (2.00 eq)	0.10	Et_3N (5.00 eq)	58%
5	Benzoic anhydride (.00 eq)	0.10	Et_3N (5.00 eq)	57%
6	Benzoic anhydride (3.00 eq)	0.10	Pyridine (5.12 eq), Et_3N (3.00 eq)	83%

3.3 Objectives

Accessing the carbon framework of the three main fragments of brocazine F and G was focused at the early stage of the project. The stereoselective access of the fragments would be focused once the main carbon frameworks of the fragments were accessed. The attempts that were undertaken to access the carbon framework of the fragments will be discussed in next sub sections.

3.4 Efforts Towards Accessing Diene System

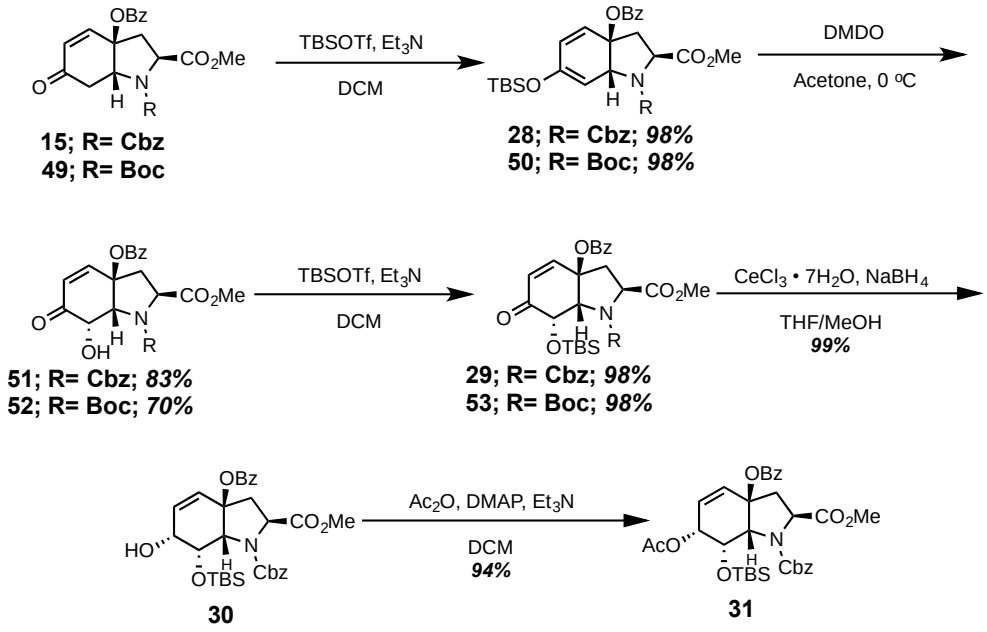
Efforts towards accessing the carbon frameworks of diene system will be discussed in this section, structure shown in Scheme 3.3. Accessing these systems with the desired stereochemistry will be discussed in subsection 3.5.



Scheme 3.4: Structure of Diene System

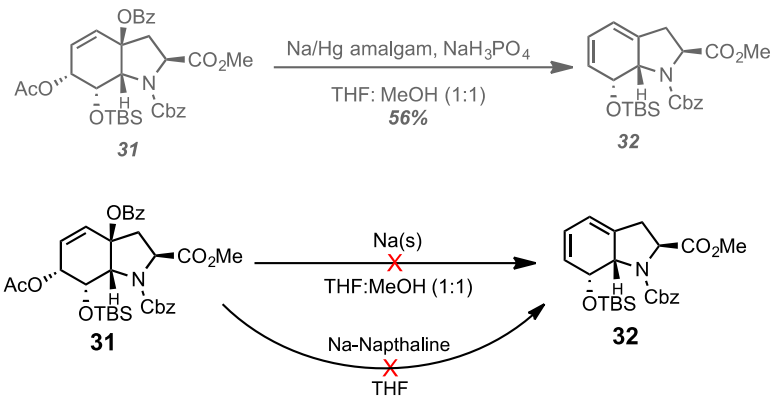
3.4.1 Na Catalyzed Reaction

Accessing diene alcohol **32** was attempted using a synthetic route developed by Sundburg group.[41] TBS enol ether formation of **15** and **49** were accomplished with TBSOTf and Et_3N to obtain **28** and **50** in 98% yields for both Cbz and Boc protected compounds, which were subsequently treated with DMDO to perform a Rubottom oxidation to obtain α-hydroxyl ketones **51** and **52** in 83% and 70% yields, respectively. Moreover, the resultant α- hydroxyl carbonyl ketones **51** had the opposite stereochemistry (S configuration) compared to the desired compound (R configuration). Stereochemistry was confirmed by the comparison with proton NMR of **51** with the published NMR of Sunburg group, where they also have accessed the S configuration. However, at this stage of the project, accessing the carbon framework of the diene alcohol system was considered, therefore, it was decided to continue with the envisioned route. The compounds **51** and **52** were TBS protected with TBSOTf and Et_3N to obatin **29** and **53** in 98% and 85% yields, respectively. Up to this stage, both Cbz and Boc protected compounds were used in the route and both resulted the desired products with similar yields. However, chemo compatibility issues, concluding degradation with the TBS enol ether formation and Rubttom oxidation with the Boc protected nitrogen were observed. Therefore, it was decided to proceed forward with the Cbz protected compounds. Luche reduction of **29** with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ selectively resulted allylic alcohol **30** in 99% yield, followed by the acetylation with Ac_2O, DMAP, and Et_3N to give **31** in 94% yield (Scheme 3.3.1.1).



Scheme 3.4.1.1: Accessing Diene System **31** from Compound **15**

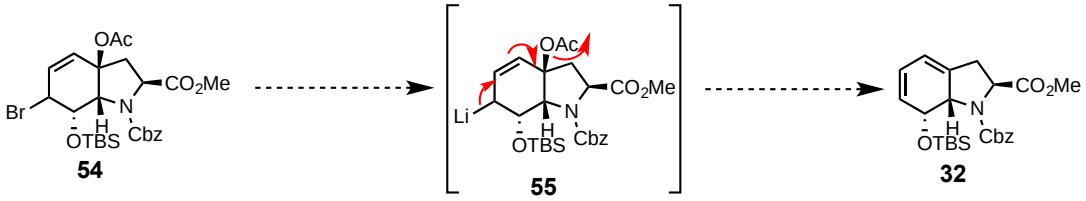
According to the Sunburg's procedure, the elimination of the acetate and the benzoyl groups to access diene system has been achieved using sodium amalgam facilitated reaction. Sodium amalgam needs to be freshly prepared and handling mercury requires special safety precautions. Therefore, we attempted the reaction using Na (s) and Na-naphthalene instead of Na/Hg. However, the Na catalyzed elimination of the acetate and the benzoyl group using Na (s) and Na-naphthalene resulted the degradation of compound **31**. (Scheme 3.3.1.2). These different results could be due to the different strengths of the Na present in Na/Hg, Na(s), and Na-naphthalene. In Na/Hg, Na has better handling properties and it allows Na to be relatively less active compared to that of pure Na(s) and Na-Naphthalene. This could result the degradation of **31** when Na(s) and Na-naphthalene were used instead of Na/Hg. Therefore, milder conditions to introduce diene system needed to be investigated.



Scheme 3.4.1.2: Accessing Diene System **32** from Compound **31**

3.4.2 Lithium/Halogen Exchange Reaction

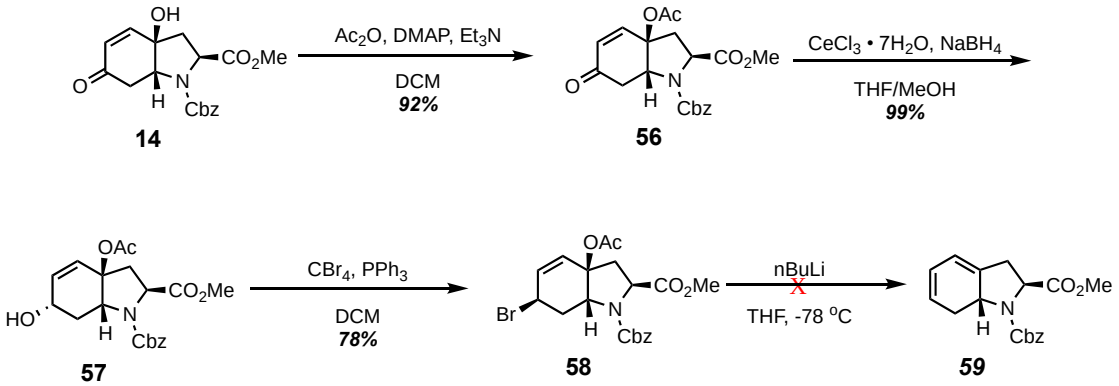
With the failed Na-catalyzed reaction, it was envisioned to use a milder conditions of lithium/halogen exchange facilitated formation of diene to access **32** from **54**. It was hypothesized that the compound **54** upon lithium/halogen exchange with *n*BuLi would afford **55**, and would subsequently undergo the elimination of the acetate to result diene **32** in an internal E2' like reaction (Scheme 3.3.2.1).



Scheme 3.4.2.1: Lithium/ Halogen Exchange Reaction to Access the Diene System

To investigate the synthetic feasibility of the route, it was decided to attempt the proposed lithium/halogen reaction facilitated diene formation with a simpler model system, lacking the OTBS group. Compound **56** was obtained by the acetylation of compound **14** in 92% yield, followed by the Luche reduction conditions to access allylic alcohol **57** in 99% yield.[37] Then the

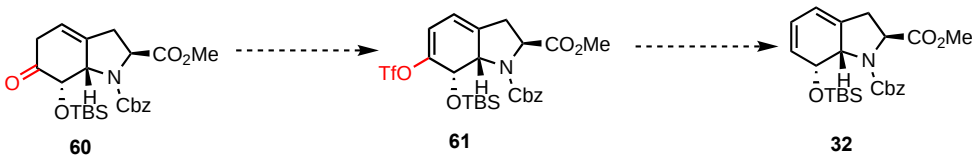
bromination of **57** was performed with Appel reaction conditions to access **58** in 78% yield.[44] Lithium/halogen exchange is usually performed with either *n*-BuLi or *t*-BuLi. Lithium/halogen exchange was attempted by treating compound **58** with *n*BuLi at -78 °C. However, the reaction was unsuccessful with 85% of recovered starting material (Scheme 3.3.2.2). The could be mainly due to the unfavorable exchange of the halide with the *n*-Butyl group. Attempts with *t*-BuLi was not undertaken.



Scheme 3.4.2.2: Accessing Diene System **59** from compound **14**

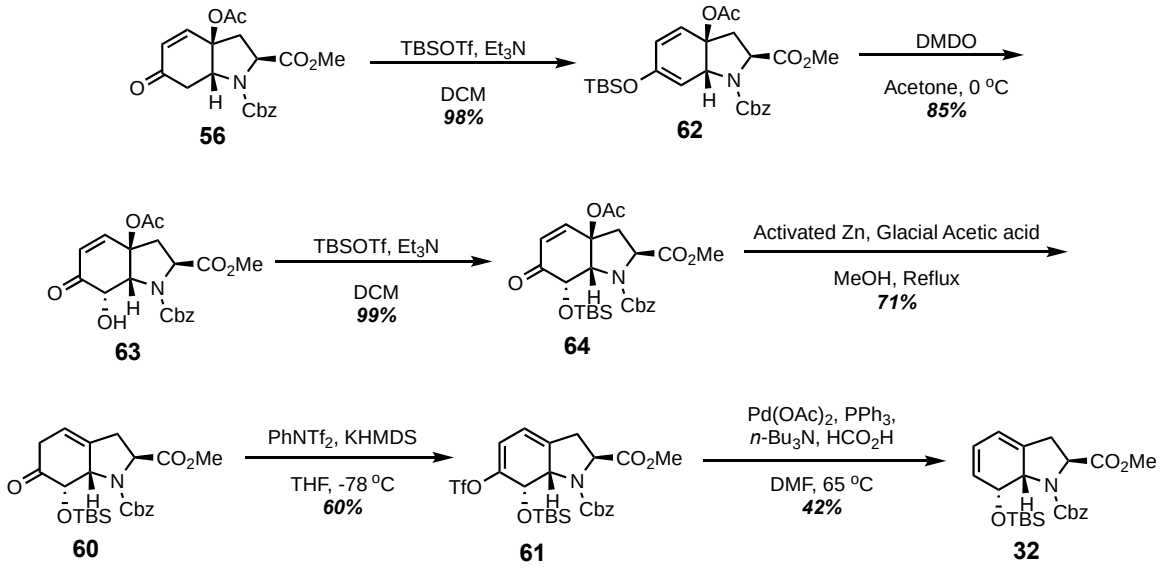
3.4.3 Comin's Reagent

Comin's reagent can be used to convert carbonyl compounds into triflate enolates, and the triflate group can subsequently reductively be eliminated to access the corresponding alkene.[24, 26] Therefore, it was envisioned to use the Comin's reagent on ketone **60** to access the triflate enolate **61** and the subsequent reductive elimination of the triflate group to access the diene **32** (Scheme 3.3.3.1).



Scheme 3.4.3.1: Comin's Reaction to Access the Diene System

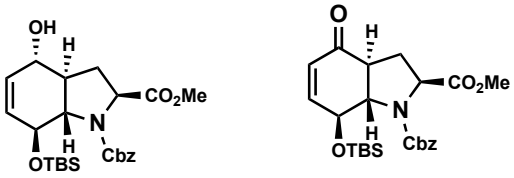
Treating **56** with TBSOTf and Et_3N afforded TBS enol ether **62** in 98% yield. Subsequent treatment with DMDO promoted a Rubottom oxidation to obtain compound **63** in 85% yield.[41] Protection of the free alcohol of **63** with TBSOTf and Et_3N was performed to access **64** in 99% yield. Refluxing **64** under Zn-catalyzed conditions afforded acetate elimination and rearrangement to **60** in 71% yield. Subjecting **60** to Comins' triflation conditions ($PhNTf_2$) gave access to **61** in 60% yield. Treating **61** with $Pd(OAc)_2$ promoted the triflate removal with reductive elimination to access diene **32** in 42% yield. (Scheme 3.3.3.2).[37, 39] Stereochemistry of the diene **32** was confirmed with the direct comparison of the NMRs of the same compound published by Sunburg group.[41] With this route, the carbon framework of the diene system **32** has been successfully accessed.



Scheme 3.4.3.2: Accessing Diene System **32** from Compound **56** Via Comin's Reagent

3.5 Efforts Towards Accessing Diol System and Allylic Alcohol System

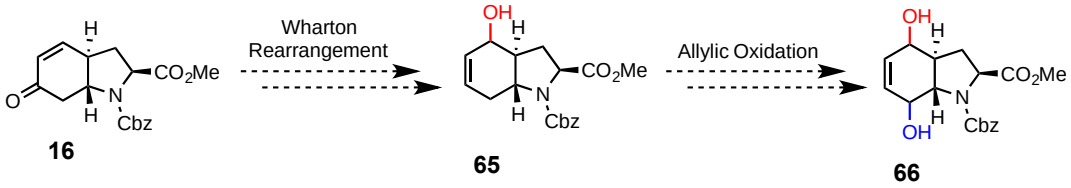
Efforts towards accessing the carbon frameworks of diol and allylic alcohol systems will be discussed in this section, structures shown in Scheme 3.4. Accessing these systems with the desired stereochemistry will be discussed in subsection 3.5.



Scheme 3.5: Structures of Diol System and Allylic Alcohol System

3.5.1 Wharton Rearrangement and Allylic Oxidation

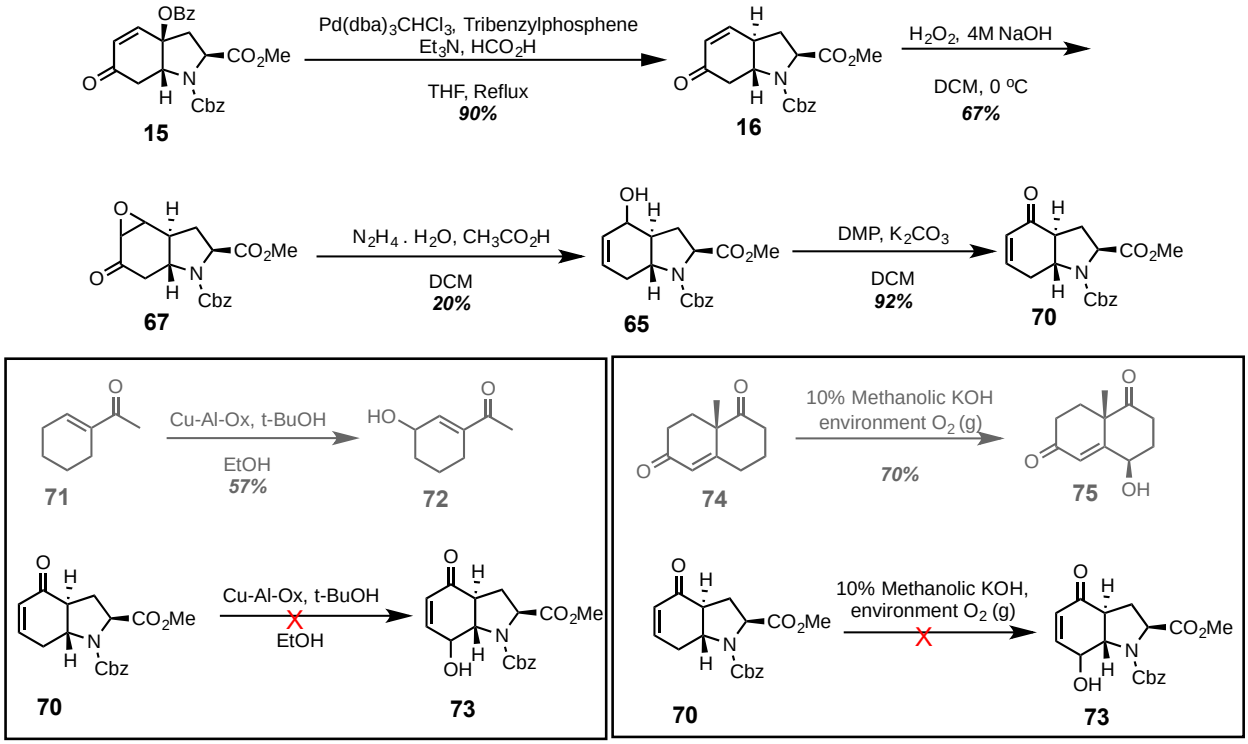
It was envisioned that accessing allylic alcohol **66** could come from a synthetic route consists of Wharton rearrangement (**16** to **65**) and allylic oxidation reactions (**65** to **66**). In this route, trans-fused bicycle **16** would be accessed first and the northern alcohol group, highlighted in red, would be accessed via Wharton rearrangement reaction. Then the southern alcohol group, highlighted in blue, was envisioned to be introduced via an allylic oxidation reaction, as shown in scheme 3.4.1.1.



Scheme 3.5.1.1: Envisioned Route to Access the Diol **66** with Wharton Rearrangement and Allylic Oxidation

Pd-catalyzed deoxygenation of **15** was performed with $Pd(dba)_3CHCl_3$, tribenzylphosphene, Et_3N, and HCO_2H to yield trans-fused 6:5 bicycle **16** in 90% yield.[40] Epoxidation of **16** with H_2O_2 and NaOH afforded epoxy ketone **67** in 67% yield, whose stereochemistry was not determined.

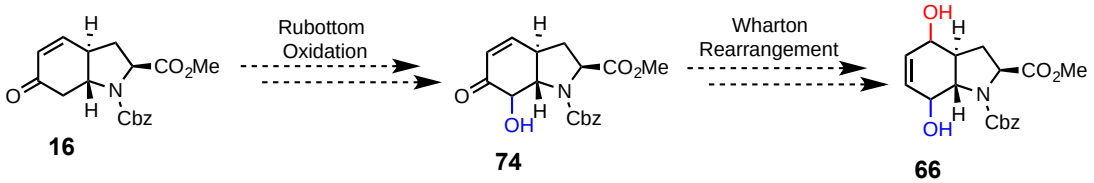
Wharton rearrangement conditions gave access to **65** in 20% yield from **67**. The highest yield reported for the Wharton rearrangement of the cis 6:5 bicycle was 56%.[26] However, the Wharton rearrangement of trans 6:5 bicycle system resulted a lower yield of 20%. This could be due to the difference in the ring conformations of cis (puckered) and trans (flat) systems, making the reagents to access the reaction site of the molecule in different efficiencies. DMP oxidation upon the allylic alcohol in **65** afforded enone **70** in 92% yield.[39] As typical Riley oxidation conditions with SeO_2 did not work for enone systems due to the electrophilic nature of enone double bond, literature reported similar allylic oxidation procedures were attempted. Guerra and coworkers have developed an allylic oxidation protocol of an enone with a Cu-Al-Ox catalyst, in which enone **71** was oxidized to allylic alcohol **72** in 57%.[45] Yoshioka has developed an allylic oxidation of an enone using methanolic KOH with air as the termind odidant, in which enone **74** was oxidized to **75** in 70% yield.[46] However, none of these procedures resulted the desired product upon enone **70** (Scheme 3.4.1.2). This could be mostly due to the nature of the trans fused ring system with many functionalities preventing the allylic oxidation of compound **70**.



Scheme 3.5.1.2: Efforts Towards Accessing Compound **73** from compound **15**

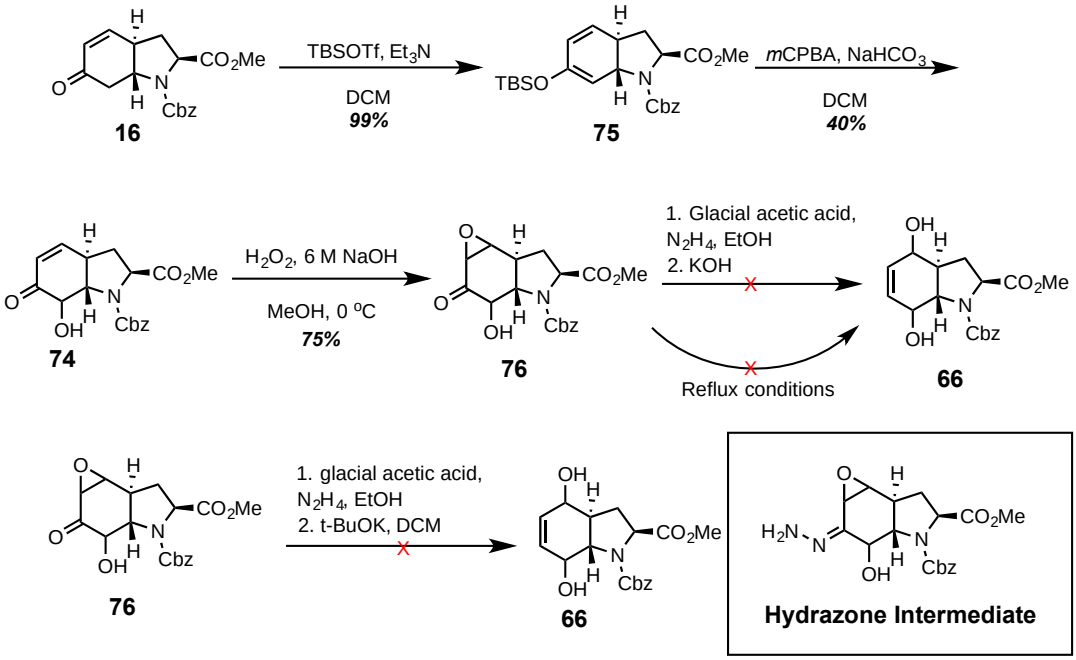
3.5.2 Rubottom Oxidation and Wharton Rearrangement

With the failed allylic oxidation, it was thought to reverse the alcohol installation; southern alcohol (blue) first, with a Rubottom oxidation of **16** to access **74**. Then the northern alcohol; red would be introduced with Wharton rearrangement conditions to access diol **66** (Scheme 3.4.2.1).



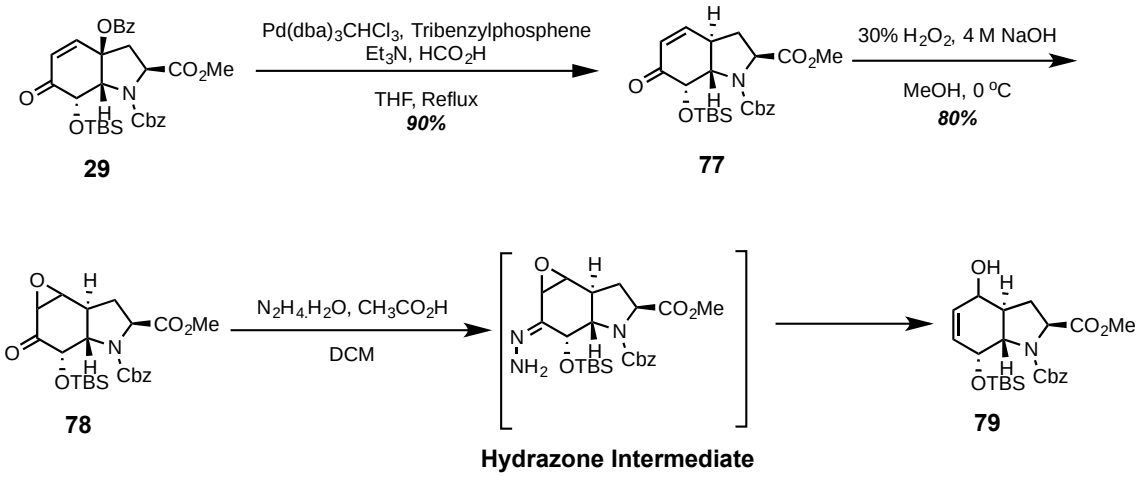
Scheme 3.5.2.1: Envisioned Route to Access the Diol **66** with Rubottom Oxidation and Wharton Rearrangement

Trans fused 6:5 bicycle **16** was converted to TBS enol ether **75** in 99% yield, followed by a Rubottom oxidation with *m*CPBA to give **74** in 40% yield.[47] Stereochemistry of the α-hydroxy ketone was not investigated as the main objective of the project at this stage to access the carbon framework of the diol system. However, it was envisioned to investigate the stereochemistry of all the compounds once a reliable route to access the diol system was established. Epoxidation of **74** with H_2O_2 and 6M NaOH afforded epoxy ketone **76** in 75% yield.[39] Although, the Wharton rearrangement of **76** with $N_2H_4 \bullet H_2O$ was attempted using different bases (KOH and t-BuOK) and different temperatures to obtain the desired product **66**, it only resulted the hydrazone intermediate, as shown in scheme 3.13.[48, 49] This could be due the interference of the sourthern alcohol group of **76** with the formed epoxy hydrazone intermediate preventing the rearrangement reaction. Therefore, to prevent any possible interference with the hydrazine, it was decided to TBS protect the lower alcohol group before attempting the Wharton rearrangement (Scheme 3.4.2.2).



Scheme 3.5.2.2: Accessing Diol System **66** Using Wharton Rearrangement

However, at this stage, another procedure to access α-hydroxy ketone **74** was needed to be investigated as the Rubottom oxidation procedure with *m*CPBA on compound **16** resulted in reproducibility issues. Therefore, the deoxygenation of Rubottom oxidized compound **29** was performed to access **77** in 90% yield.[40] The epoxidation of **77** with H_2O_2, and NaOH resulted epoxy ketone **78** in 80% yield (Scheme 3.4.2.3), and the stereochemistry of the epoxide was not determined.[39]



Scheme 3.5.2.3: Accessing Diol System **79** Using Wharton Rearrangement

Optimization of Wharton rearrangement of **78** needed to be undertaken as it only resulted the hydrazone intermediate (Table 3.4.2.1). It was attempted to improve the yield by changing the equivalents of formic acid (CH_3CO_2H) added (entry 1-4). However, it only resulted the hydrazone intermediate at different temperatures screened. Then, it was decided to use a base instead of an acid for the rearrangement of the hydrazone. Although different bases such as *t*-BuOK and KOH were used in the reaction to facilitate the rearrangement, it only resulted the hydrazone intermediate at different temperatures tested (entry 5-6) After extensive efforts, product **79** was obtained in trace amounts when $N_2H_4 \bullet H_2O$ (5 eq) and CH_3CO_2H (3 eq) were used at reflux

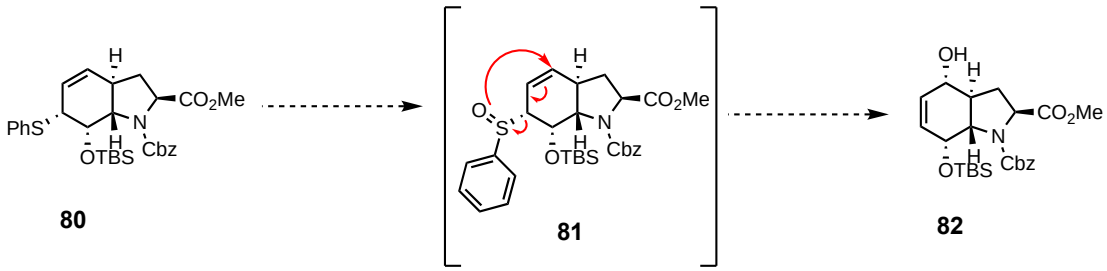
conditions (entry 7).[39] However, another route to access diol system was needed as it was impossible perform multistep total synthesis with trace amount of material.

Table 3.5.2.1: Optimization of Wharton Rearrangement

Entry	Reagents	Acid/Base	Solvent	Temp.	%Yield
1	$N_2H_4 \bullet H_2O$ (2 eq)	CH_3CO_2H (1 eq)	DCM	Zero-RT-reflux	Hydrazone
2	$N_2H_4 \bullet H_2O$ (2 eq)	CH_3CO_2H (2 eq)	DCM	Zero-RT-reflux	Hydrazone
3	$N_2H_4 \bullet H_2O$ (2 eq)	CH_3CO_2H (2 eq)	MeOH	Zero-RT-reflux	Hydrazone
4	$N_2H_4 \bullet H_2O$ (4 eq)	CH_3CO_2H (3 eq)	DCM	Zero-RT-reflux	Hydrazone
5	$N_2H_4 \bullet H_2O$ (4 eq)	*t*-BuOK (1.5 eq)	DCM	Zero-RT-reflux	Hydrazone
6	$N_2H_4 \bullet H_2O$ (2 eq)	KOH (4 eq)	MeOH	Zero-RT-reflux	Hydrazone
7	$N_2H_4 \bullet H_2O$ (5 eq)	CH_3CO_2H (3 eq)	DCM	Zero-RT-reflux	Trace amount of product

3.5.3 Mislow-Evans Reaction

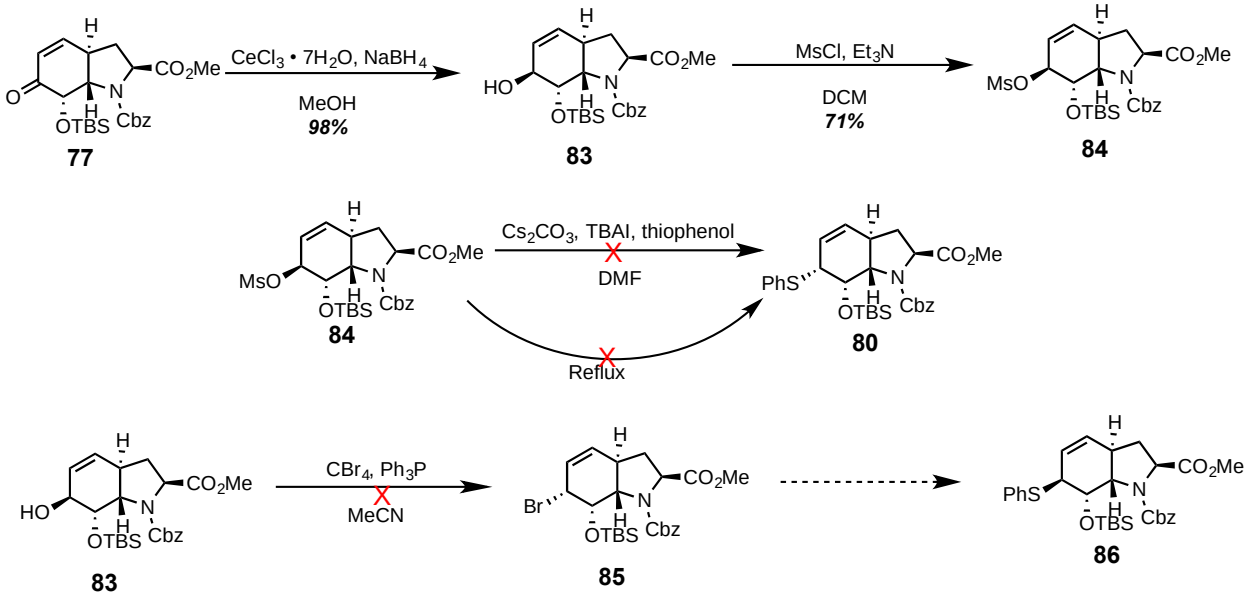
A Mislow-Evans reaction can be used to access allylic alcohols from allylic sulfoxides in [2,3] sigmatropic rearrangement.[50] It was envisioned that addition of **80** would access **81**, which would then primed to undergo the Mislow-Evans rearrangement to **82** (Scheme 3.4.3.1).



Scheme 3.5.3.1: Mislow-Evans Reaction to Access the Diol **82**

Luche reduction of enone **77** was accomplished to obtain allylic alcohol **83** in 98% yield, followed by the mesylation to access **84** in 71% yield. Accessing the thiophenol **80** from **84** with thiophenol,

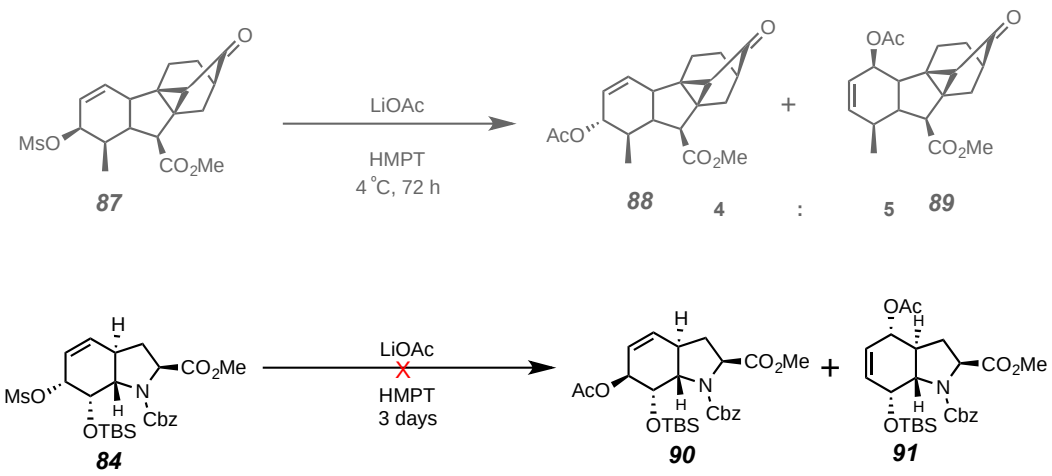
Cs_2CO_3, and TBAI, was unsuccessful, even under reflux conditions (Scheme 3.4.3.2).[50] Therefore, accessing the thiophenol **86** from compound **83** via a brominated intermediate was envisioned. However, the bromination of compound **83** using Appel reaction was unsuccessful with the 98% recovery of the starting material. This could be due to the ring conformation of 6:5 trans-fused system or the steric interference of the adjacent OTBS group making the reaction not feasible.



Scheme 3.5.3.2: Efforts Towards Accessing Diol System **82** with Mislaw-Evans Reaction

3.5.4 Using SN2' Reaction

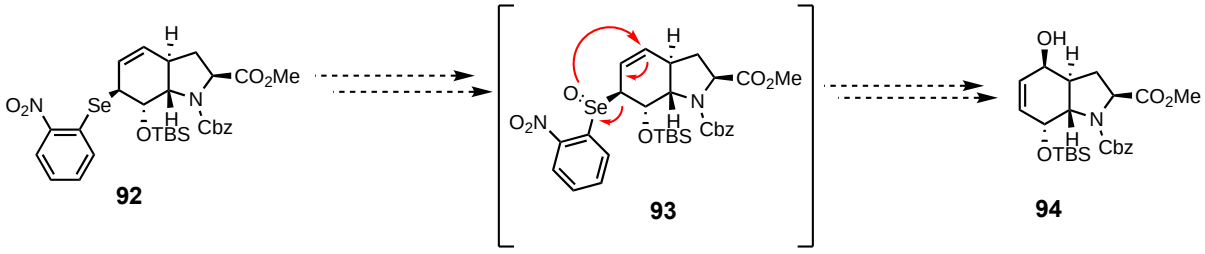
Saunders and coworkers have discussed the use of LiOAc and HMPT for an SN2' type acetate rearrangement to convert mesylate **87** to **88** (SN2) and **89** (SN2') (Scheme 3.4.4.1).[51] Therefore, it was envisioned to attempt this SN2' reaction conditions on the compound **84** to access **91**. However, this procedure was unsuccessful upon system **84** to access 91 and even 90, and gave full recovery of the starting material. This could be due to the ring conformation of **84** and the functionalities around making the reaction sterically not feasible.



Scheme 3.5.4.1: Efforts Towards Accessing Compound **91** Using SN2' Reaction

3.5.5 Grieco Conditions

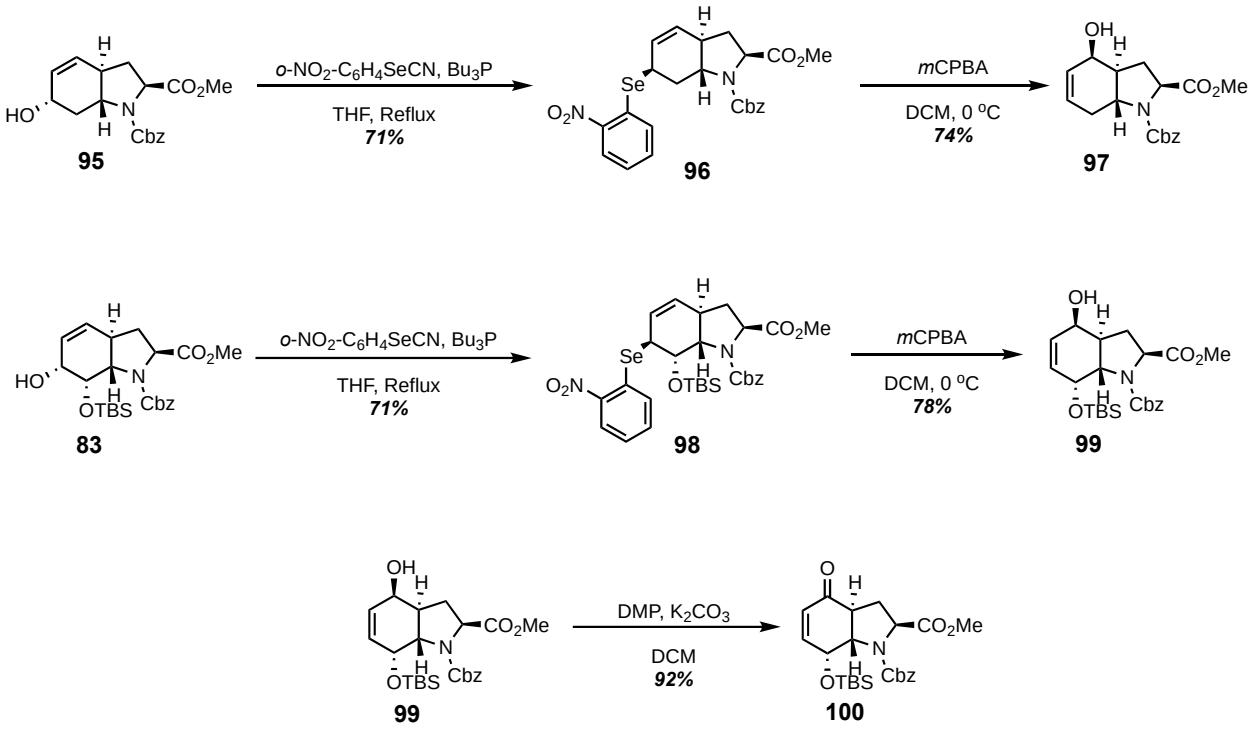
Grieco reaction is very similar to Mislow-Evans reaction as they both undergo [2,3] sigmatropic rearrangement to perform allylic alcohol rearrangements. Therefore, it was envisioned to use Grieco conditions to access selenide **92** and subsequent rearrangement via the oxidized intermediate **93** to access the diol **94** (Scheme 3.4.5.1).



Scheme 3.5.5.1: Grieco Conditions to Access the Diol System **94**

To test the feasibility of the route, it was decided to attempt the procedure in a simpler model system **95**, lacking the OTBS group. Subjecting **95** to Grieco reaction conditions under reflux afforded allylic selenide **96** in 71% yield, with 20% of recovered starting material. The *m*CPBA oxidation facilitated the sigmatropic rearrangement of the selenide was performed to obtain **97** in

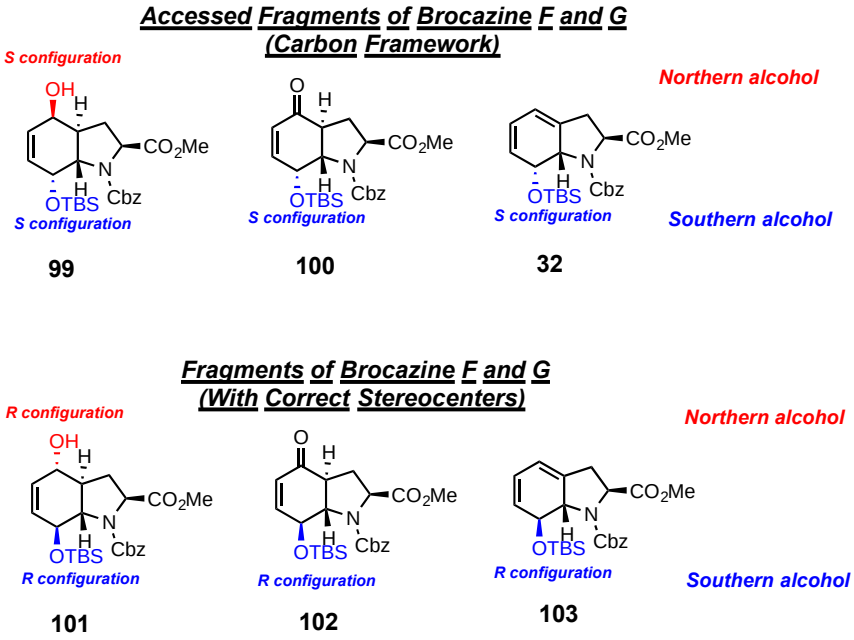
74% yield. Since the reaction worked successfully with the model system, it was decided to attempt the reaction in the actual system **83**. Grieco condition of compound **83** resulted allylic selenide **98** in 71% yield, followed by the *m*CPBA oxidation facilitated sigmatropic rearrangement of selenide group was performed to obtain compound **99** in 78% yield. DMP oxidation of diol **99** gave access to enone **100** in 92% yield (Scheme 3.4.5.2).[52] With this route, the main carbon frameworks of diol system **99** and the enone system **100** have been successfully accessed.



Scheme 3.5.5.2: Accessing Diol System **99** Using Grieco Conditions

3.6 Accessing the Main Fragments with Desired Stereochemistry

The carbon frameworks of all three fragments of brocazine F and G have been successfully accessed. However, in order to synthesize brocazine F and G, these three groups needed to be accessed with desired stereocenters. The desired stereochemistry of the southern alcohol group; blue, needs to be accessed first, and the northern alcohol group; red, needs to be accessed next (Scheme 3.5.1.1).

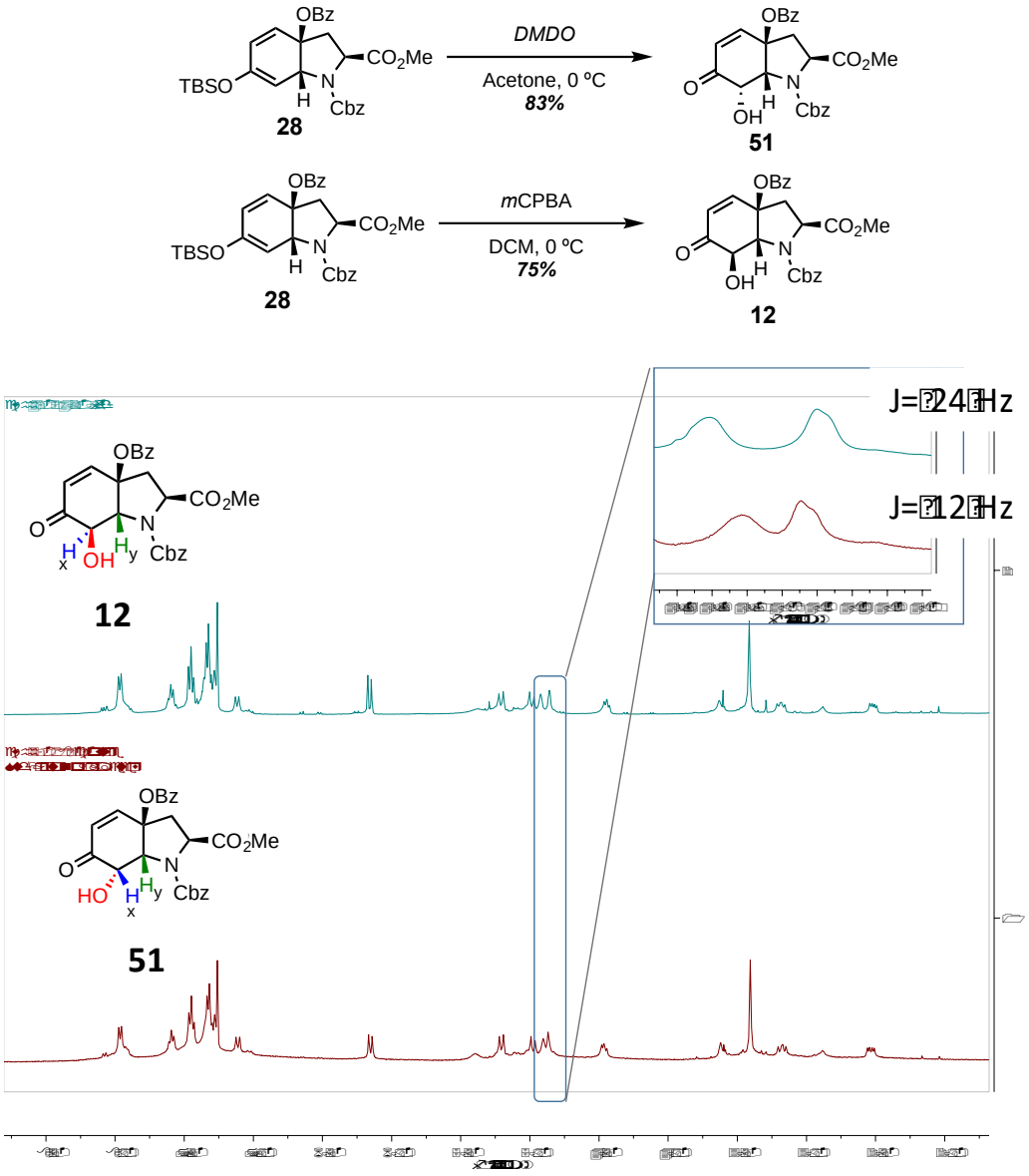


Scheme 3.6.1: The fragments that have been Accessed and Envisioned to be Accessed

3.6.1 Diol System and Enone System

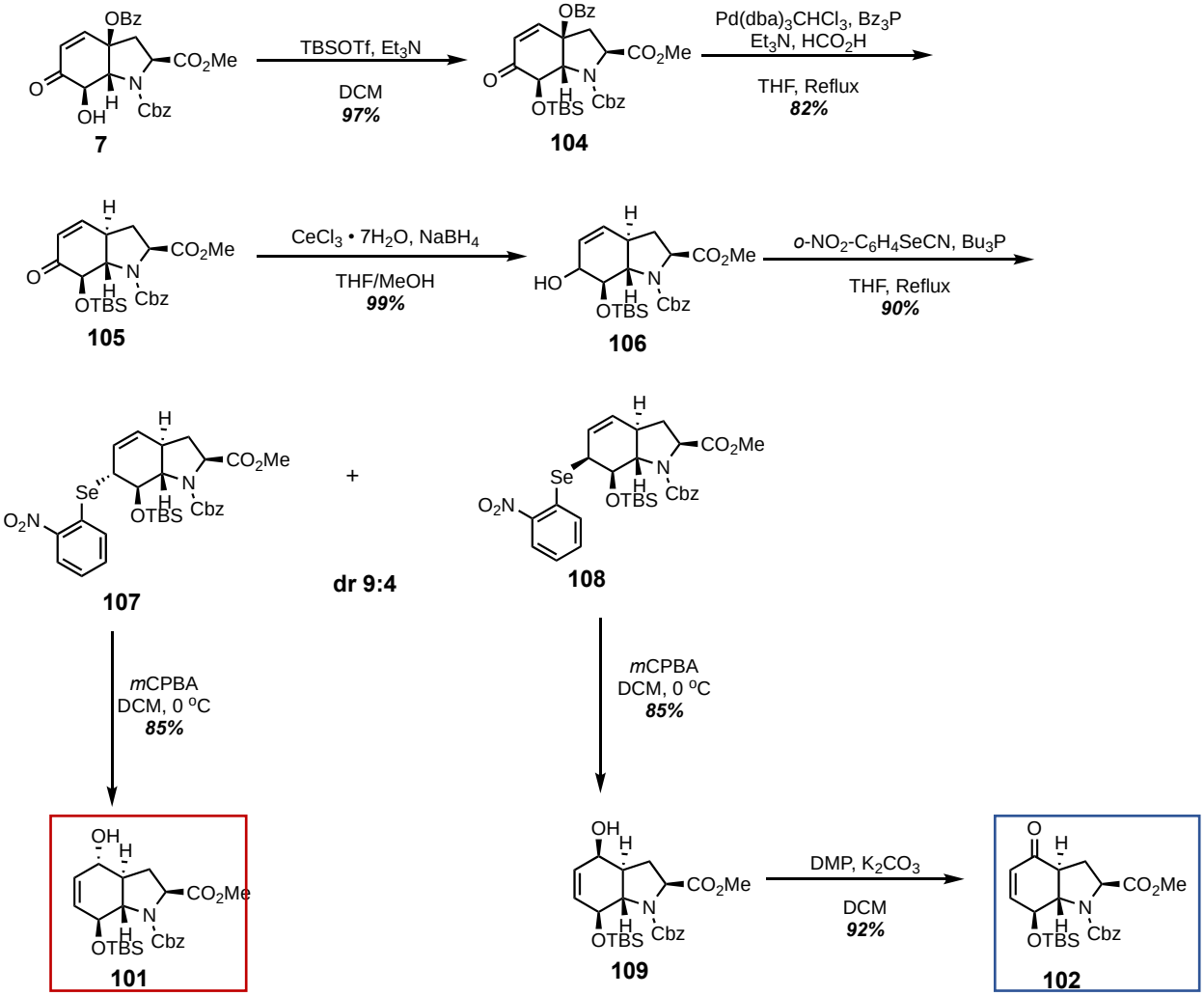
Treatment of **28** with DMDO and *m*CPBA provided two different compounds. DMDO has been shown to afford **51**, and we propose *m*CPBA gives access to the epimer about this alcohol, **12**, accessed in 75% yield. Stereochemistry of the newly introduced alcohol was confirmed by comparing the proton NMRs of DMDO oxidation product **51** with the *m*CPBA oxidation product **12**, as well with 2D NMR analysis. Coupling constant of the H_x and H_y in **12** is 24 Hz, the coupling

constant of the H_x and H_y in **51** is 12 Hz. This indicates that the H_x and H_y are facing the opposite direction (trans) in **12,** whereas H_x and H_y are facing the same direction (cis) in **51** (Scheme 3.5.1.2). These data supported that the obtained α-hydroxy ketone with *m*CPBA reaction possessed the desired stereochemistry (R configuration).



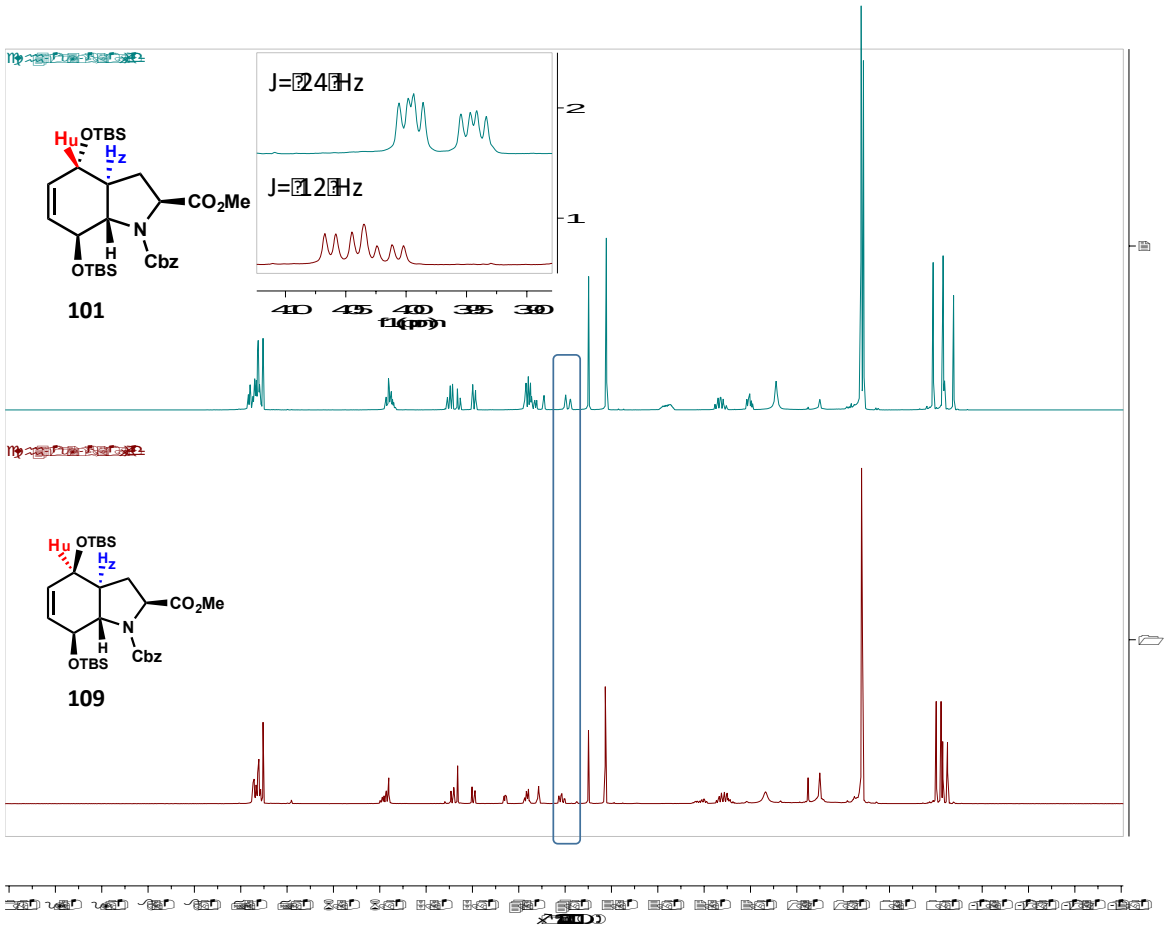
Scheme 3.6.1.1: Rubottom Oxidation to Access α-Hyroxy Ketone and NMR Characterization to Determine the Stereochemistry

Free alcohol group of **7** was TBS protected with TBSOTf and Et_3N to obtain **104** in 99% yield, subsequent Pd-catalyzed deoxygenation afforded trans-fused bicycle **105** in 82% yield.[40, 41] Luche reduction of enone **105** at room temperature produced the allylic alcohol **106** in 99% yield, the mixture of two stereoisomers were carried forward. Treatment of Grieco conditions upon **106** resulted in allylic selenides **107** and **108** in 90% yield (dr- 9:4). The *m*CPBA oxidation facilitated sigmatropic rearrangement of selenide group to diols **101** and **109,** 85% yield for both compounds. Oxidation of diol **109** resulted in enone **102** in 92% yield (Scheme 3.5.1.3).[52]



Scheme 3.6.1.2: Accessing the Diol **101** and enone **102** with Desired Stereochemistry

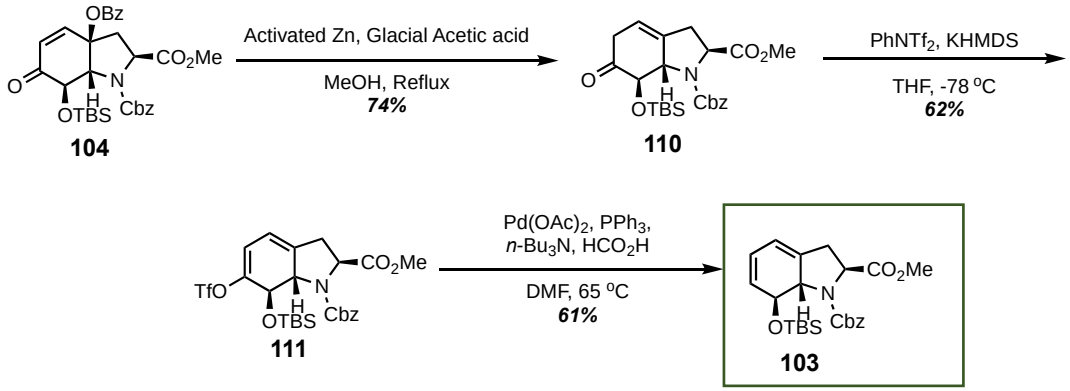
The stereochemistry of the diols **101** and **109** were determined via the comparison of the coupling constants between the H_u and H_z**.** Analysis of the coupling constants between H_u and H_z **in 101** and **109** revealed J= 24 Hz and 12 Hz, respectively (Scheme 3.5.1.4). From this, it can be concluded that **101** is the R configuration and **109** is S configuration with respect to the northern alcohol group. With this route, the diol **101** and the enone **102** have been successfully accessed with the desired stereocenters.



Scheme 3.6.1.3: NMR Characterization to Determined the Stereochemistry of Diols **101** and **109**

3.6.2 Diene System

The desired stereoisomer of the diene **103** was accessed following a route consisting of Comins's reagent. Zn-catalyzed elimination of the benzoyl group of compound **104** under reflux conditions was performed to access compound **110** in 74% yield.[37] Comins' reaction of compound **110** converted the carbonyl group of **110** to a triflate enol ether **111** in 62% yield. The reductive elimination of the triflate group of **111** with a $Pd(OAc)_2$ catalyzed reaction at 65 °C resulted the diene **103** in 61% yield (Scheme 3.5.2.1).[39] with this route, the diene system **103** has been accessed with the desired stereochemistry.



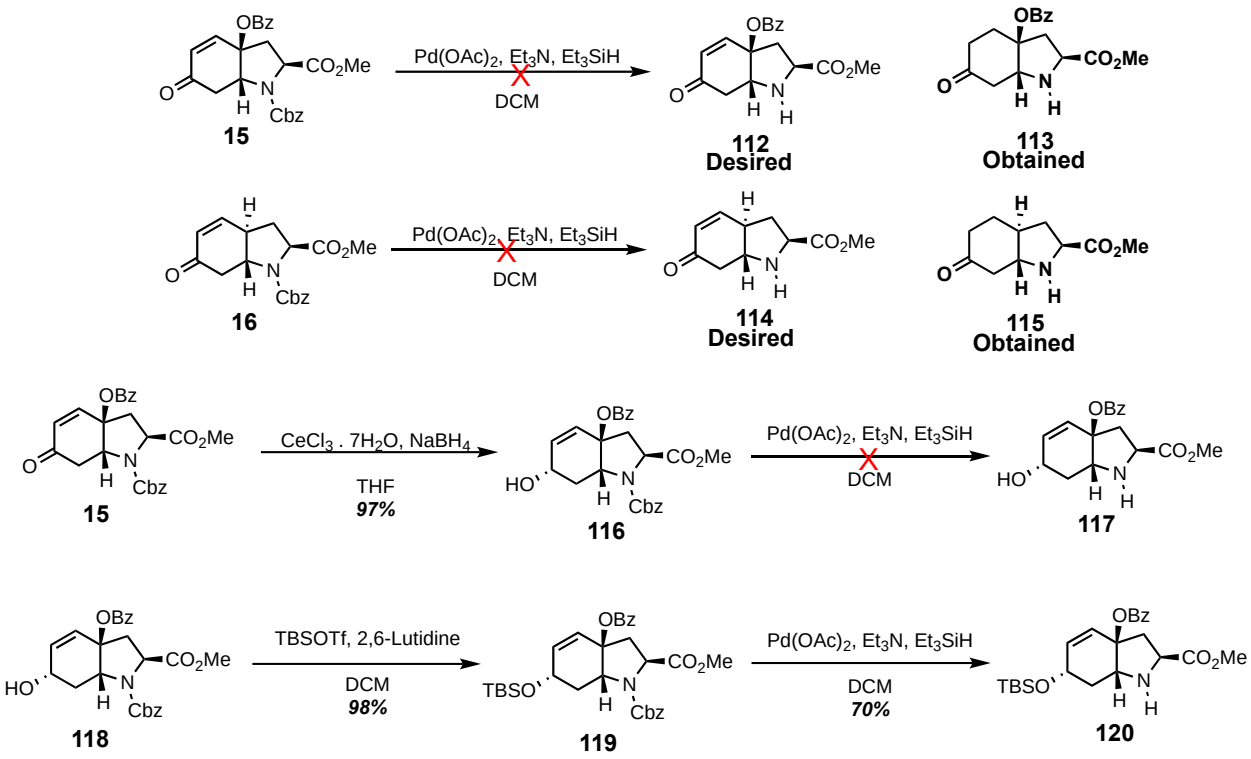
Scheme 3.6.2.1: Accessing Diene System **103** with Desired Stereochemistry

3.7 Investigations into Cbz Deprotection

At this stage, all three fragments of brocazine F and G, with the desired stereochemistry installed has been successfully achieved. Next step of the project is to couple and cyclize the respective fragments to access the DKP cores of brocazine F and G. For this, Cbz deprotection to access the free amine and the saponification to access the free carboxylic acid needs to be performed. Saponification is a simple and straightforward reaction, and it was assumed that it would work well in our systems as they do not have any functionalities intolerable to basic conditions.

However, Cbz deprotection in the presence of enone/ allylic alcohol is challenging, as the double bond can also be reduced concurrent to Cbz deprotection. Therefore, Cbz deprotection conditions suitable for systems containing enone/ allylic alcohol were investigated using model systems.

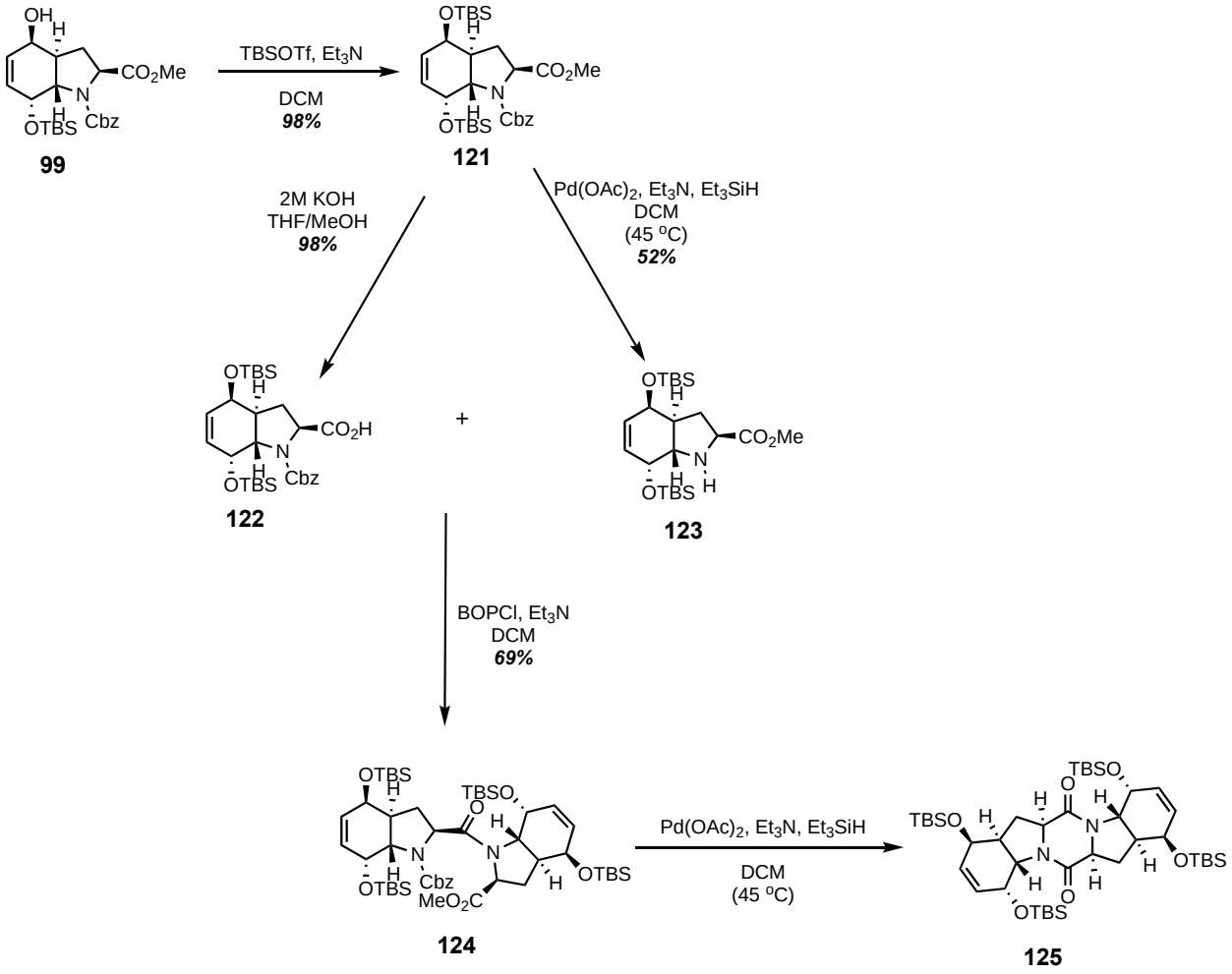
Typical conditions of Cbz deprotection with H_2(g) under high pressure cannot be used for the systems containing double bonds as they can also get reduced along with the Cbz deprotection. Therefore, a literature precedent Cbz deprotection using *in situ* generation of H_2 (g) was attempted with compound **15** and **16** using $Pd(OAc)_2$, Et_3N, and Et_3SiH.[39, 40] However, the desired products were not isolated and the fully reduced products **113** and **115** were obtained, respectively. It was hypothesized that the enone system could be making the double bond more electrophilic, resulting these undesired products. Therefore, compound **15** was reduced using Luche reduction conditions to obtain compound **116** in 97% yield, and Cbz deprotection was attempted. However, the reaction was unsuccessful with the fully recovered starting material **116**. At this point, it was hypothesized that the free alcohol group could be chelating the Pd-catalyst. Therefore, TBS protection of compound **118** was performed to obtain **119** in 98% yield, and the Cbz deprotection was performed to successfully obtain amine **120** in 70% yield (Scheme 3.6.1).



Scheme 3.7.1: Investigations into Cbz Deprotection

3.8 Investigations into Analog Synthesis

It was envisioned to use compound **99** for analog synthesis as it can be used to test the feasibility of Cbz deprotection procedure and the saponification in more similar systems to the main fragments of brocazines. Furthermore, this could also be used to access an analog of brocazine family. First, TBS protection of compound **99** was performed to access **121** in 98% yield.[39] Saponification and Cbz deprotection of compound **121** separately gave carboxylic acid **122** and amine **123** in 98% and 52% yields, respectively. Coupling of **122** and **123** with BOPCl gave compound **124** in 69% yield (Scheme 3.7.1).[39] Although the aminolysis of **124** was attempted, purification was challenging as the scale of the reaction was very low. Therefore, it was decided to mainly focus on the actual system with desired stereochemistry to access the brocazine natural products and revisit the DKP analog synthesis later in the project.

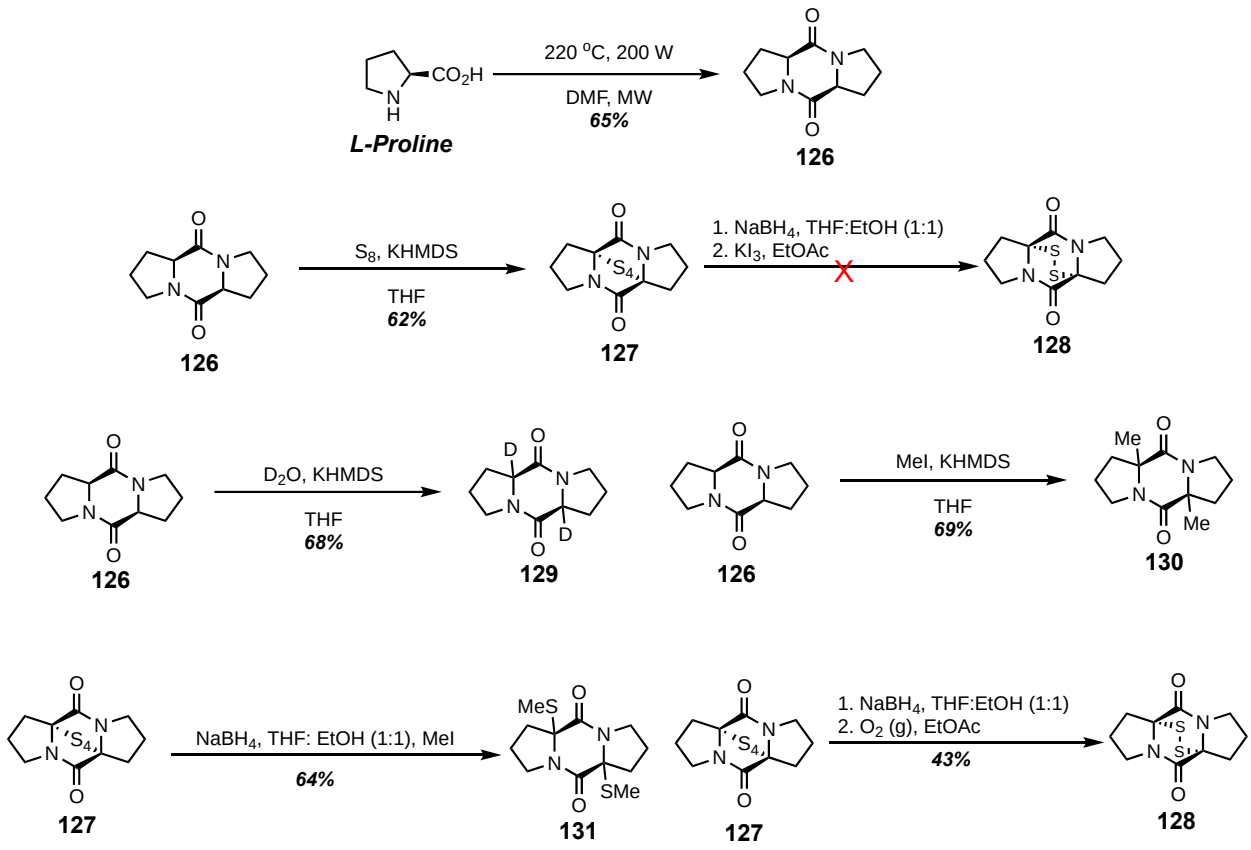


Scheme 3.8.1: Investigations into Analog Synthesis

3.9 Investigations into Disulfide Linkage Incorporation

Investigations into disulfide linkage incorporation into DPK systems are crucial as both brocazine F and G contains a disulfide linkage in their central cores. Even though there are several literature precedencies of procedures for disulfide incorporation into DKP systems, they are well reported to be difficult and requires technical expertise and practice. Therefore, it was decided to use a simpler model system to get the required expertise. L-proline was subjected to a microwave assisted reaction to obtain DKP model system **126** in 65% yield.[53] Treatment of **126** with KHMDS

and S_8 resulted the oligosulfide **127** in 62% yield.[37] Subjecting oligosulfide **127** to conditions of $NaBH_4$ and KI_3 did not result the desired product **128**. Therefore, it was needed to further confirm the formation of the compound **127** by checking the activity of KHMDS on compound **126**. It was decided to use D_2O and MeI instead of S_8 and incorporate deuterium and methyl groups to the compound **126**, respectively. If the reaction was successful, the desired products formation should be clearly visible in ^1H NMR due to the disappearance of the deuterated atoms (with D_2O) and the appearance of the methyl peaks (with MeI) in the NMRs. With this, it can also be confirmed the feasibility of the formation of **127** when S8 was used due to the similarities of the reactions. Compound **126** was treated with KHMDS, followed by the subsequent addition of D_2O to access compound **129** in 68% yield. Compound **126** was treated with KHMDS, followed by the subsequent addition of MeI to access compound **130** in 69% yield. These results showed that the treatment of **126** with S_8 and KHMDS should also have resulted the desired oligosulfide **127**. Then, it was needed to confirm the reduction of the **127** with $NaBH_4$. To explore this, compound **127** was reduced with $NaBH_4$, followed by MeI to access thiomethylate **131** in 64% yield.[54] With this results, further confirmation of **127** was achieved. Then the disulfide linkage formation with KI_3 was attempted again, and it was still not successful. Therefore, it was decided to use O_2 (g) instead of KI_3 for the disulfide incorporation reaction.[37] However, the reaction was still not successful resulting the dimerized DKP product. Therefore, it was envisioned to use very dilute conditions (0.001M) when introducing O_2 (g) to the reaction to prevent the dimerization reaction. Then the reaction was successful and the desired product **128** was accessed in 43% yield (Scheme 3.8.1).[39] With this, a reliable and reproducible procedure to introduce disulfide linkage into DKP cores, which can be used in brocazine DKP cores has been successfully optimized.

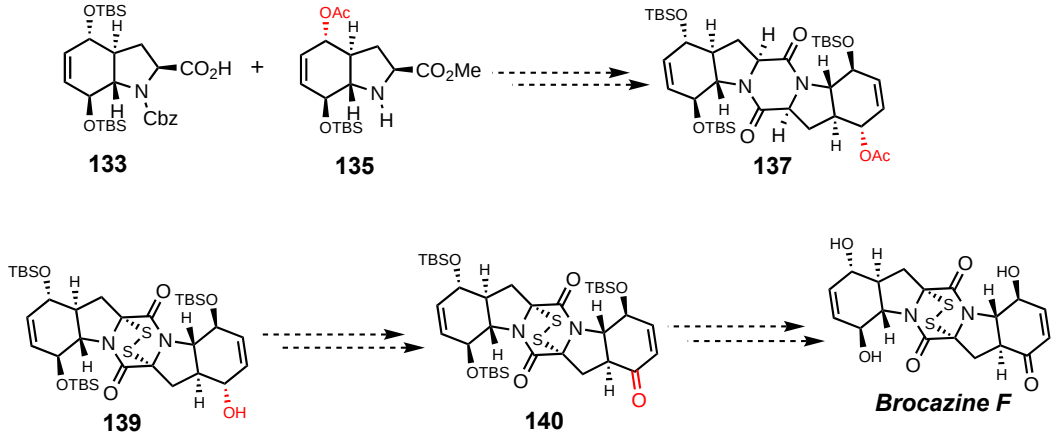


Scheme 3.9.1: Investigations into Disulfide Linkage Incorporation

3.10 Accessing the DKP Core of Brocazine F

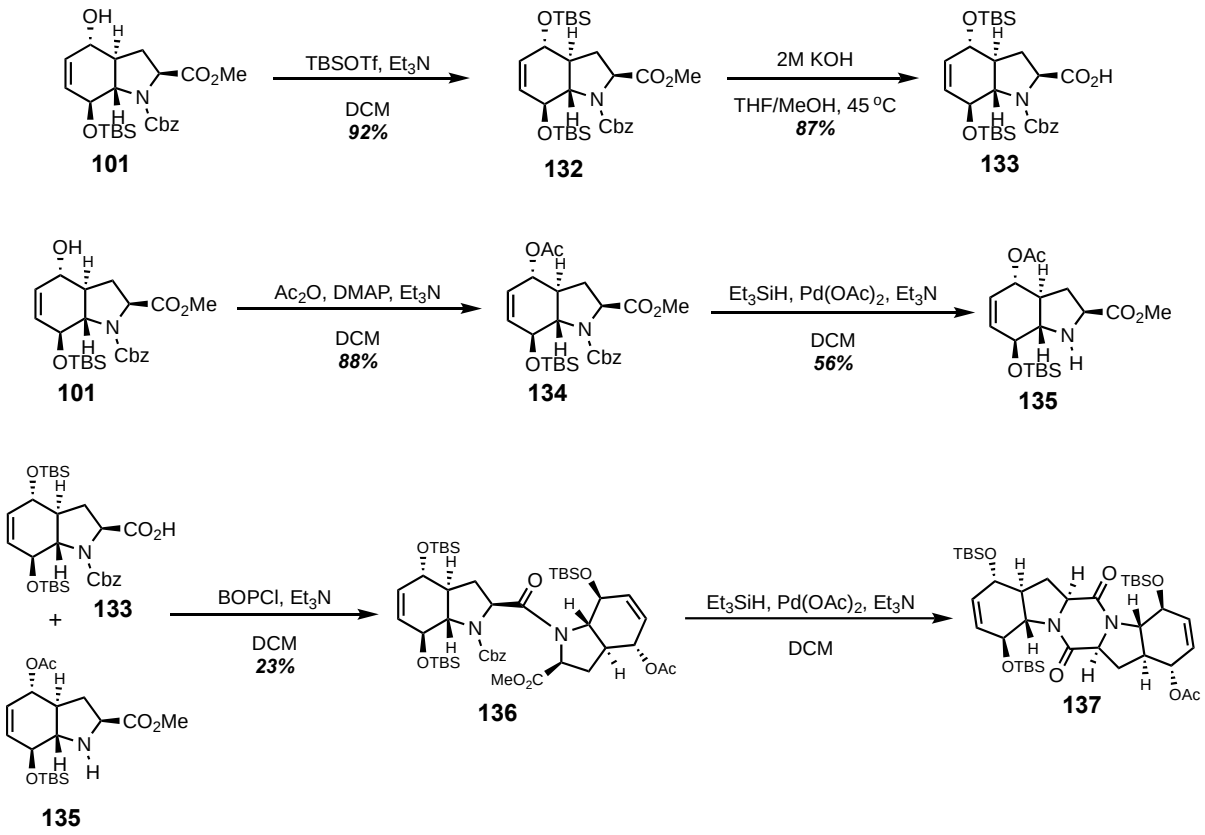
Investigations into accessing the DKP core of brocazine F will be discussed in this section. According to the previous studies (section 3.6) the free alcohol group of **101** needed be protected as it can interfere with the Cbz deprotection reaction. Moreover, the enone **102** cannot be directly used for the Cbz deprotection as it can reduce the enone double bond concurrent to Cbz deprotection. Therefore, it was decided to TBS and acetyl protect the alcohol **101** separately to access **133** and **135**, respectively, and couple them together to access the DKP core **137**. Then the acetyl group can be selectively deprotected to access **139**, and the free alcohol can be oxidized to

access the desired enone system **140**. Brocazine F can then be accessed after the deprotection of all the protecting groups (Scheme 3.9.1).



Scheme 3.10.1: Envisioned route to Access Brocazine F

Treatment of **101** with TBSOTf gave access to **132** in 92% yield, followed by the saponification with 2M KOH at 45 °C to access the carboxylic acid **133** in 87%.[39] Acetylation of **101** was performed with Ac_2O, DMAP, and Et_3N to obtain compound **134** in 88% yield, followed by the Cbz deprotection with $Pd(OAc)_2$, Et_3N, and Et_3SiH to access amine **135** in 56% yield.[38] Coupling of the acid **133** and the amine **135** gave access to **136** in 23% yield (Scheme 3.9.2). The lower yield of the coupling reaction could be due to the steric effects caused by the functionalities and the ring conformation of the reactants. The investigations into the optimization of the reaction yield are currently underway. Aminolysis of **136** was performed in very low scale (9 mg), to access the DKP **137**. However, further purification of **137** is needed for full characterization.



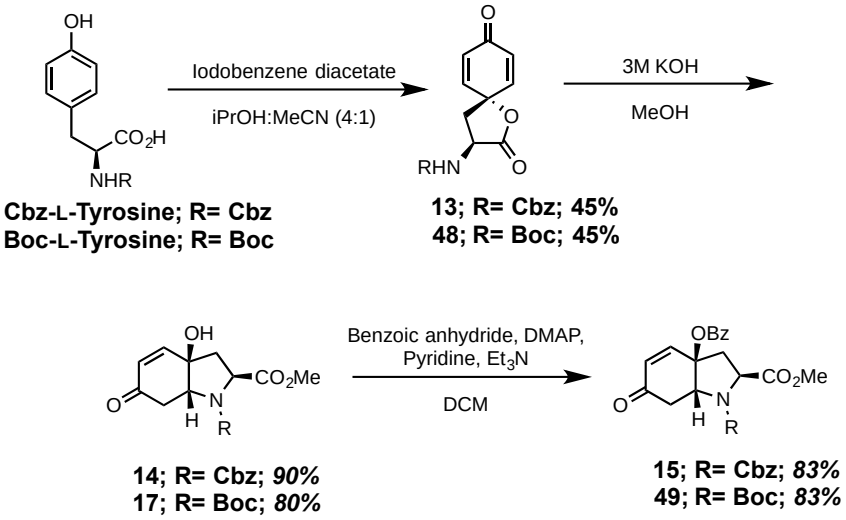
Scheme 3.10.2: Accessing the DKP core of Brocazine F

Chapter 4 - Future Work and Conclusion

Brocazine F and G are natural products bearing a disulfide diketopiperazine core that was isolated by Meng *et al* in 2014 and 2016 from an endophytic fungus derived from the marine mangrove plant *Avicennia marina* named *Penicillium brocae* MA-231. Due to their potent biological activities and the intriguing polycyclic core structure, our laboratory devised a total synthesis route to access this family. We also envisioned on a new way of accessing small molecule screening libraries by derivatizing the intermediates of the total synthesis routes of these natural products. This could allow the access of complex and diverse small molecule libraries which could potentially have diverse biological activities due to non-natural synthetic route that is being developed. Therefore, in this dissertation a reliable and reproducible route to access the brocazine family of diketopiperazine (DKP) natural products, from which the intermediates can be amendable for chemical derivatization for complex screening library construction was discussed.

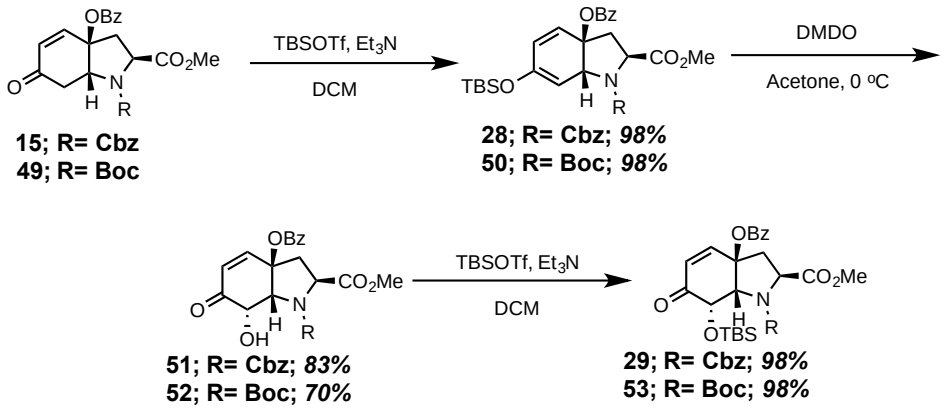
Efforts towards the total synthesis of the brocazine family started from Cbz-L-tyrosine/ Boc-L-tyrosine and its transformation into the 6:5 spiral ring **13/48** in 23% and 24% yields, respectively. After the extensive efforts to optimize the yield of the reaction using polymer assisted reaction conditions and using various temperature/solvent conditions, the reaction yield was optimized to 45%. Treating **13** and **48** with 3M KOH at -20 °C promoted the rearrangement to obtain **14** and **17** in 90% and 80% yields, respectively. Accessing **15** (Cbz) and **49** (Boc) were done by treating the tertiary alcohol **14** and **17** with benzoic anhydride, DMAP, and pyridine at reflux conditions to afford the desired products in 55% and 56% yields, respectively. The optimization of the benzoylation reaction was attempted by using different reagents (benzoic chloride/ benzoic anhydride), different bases, and different equivalences of bases/DMAP/ reagents. The reaction

yield was optimized to 83% when benzoic anhydride (3 eq), DMAP (0.1 eq), pyridine (5.12 eq), and Et_3N (3 eq) were used under reflux conditions (Scheme 4.1).



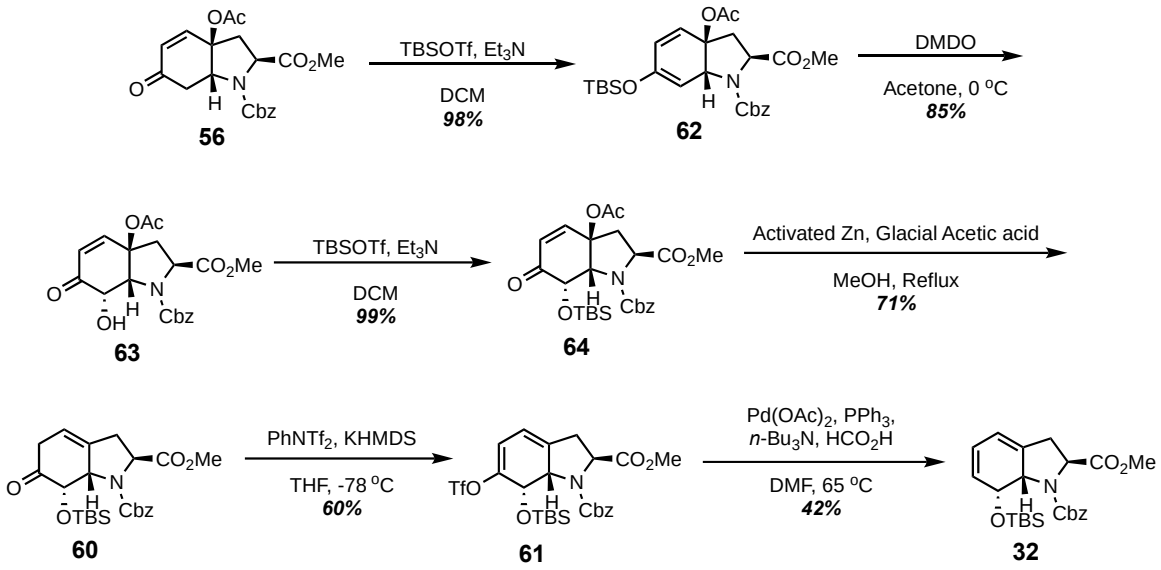
Scheme 4.1: Accessing Benzylated Compounds **15** and **49**

TBS enol ether formation of **15** and **49** were performed with TBSOTf and Et_3N to obtain **28** and **50** in 98% yields in both Cbz and Boc protected compounds, which were subsequently treated with DMDO to perform a Rubottom oxidation to obtain α-hydroxyl ketones **51** and **52** in 83% and 70% yields, respectively. Moreover, the resultant α- hydroxyl carbonyl ketones **51** had the opposite stereochemistry (S configuration) compared to the desired compound (R configuration) (Scheme 4.2). At this stage, the Boc protected compound resulted degradation issues with TBS enol ether formation and Rubottom oxidation reactions. Therefore, it was decided to proceed forward only with the Cbz protected compounds.



Scheme 4.2: Accessing α-hydroxyl ketones **29** and **53**

Extensive efforts towards accessing the diene **32** from the TBS protected α-hydroxyl ketone **29** was taken by using Na-catalyzed reaction and lithium-halogen exchange reaction. However, none of these efforts were successful, resulting either the degraded product or the starting material **29**. Finally, it was decided to attempt the Comin's reagent facilitated triflate enolate formation and the subsequent triflate removal to access the diene **32**. Comins' reaction conditions on **60** gave access to triflate **61** in 60% yield, followed by the elimination of the triflate group by Pd-catalyzed reaction with $Pd(OAc)_2$, PPh_3, and *n*-Bu_3N to access diene **32** in 42% yield. With this approach, we were able to successfully access the carbon framework of the diene **32** (Scheme 4.3).

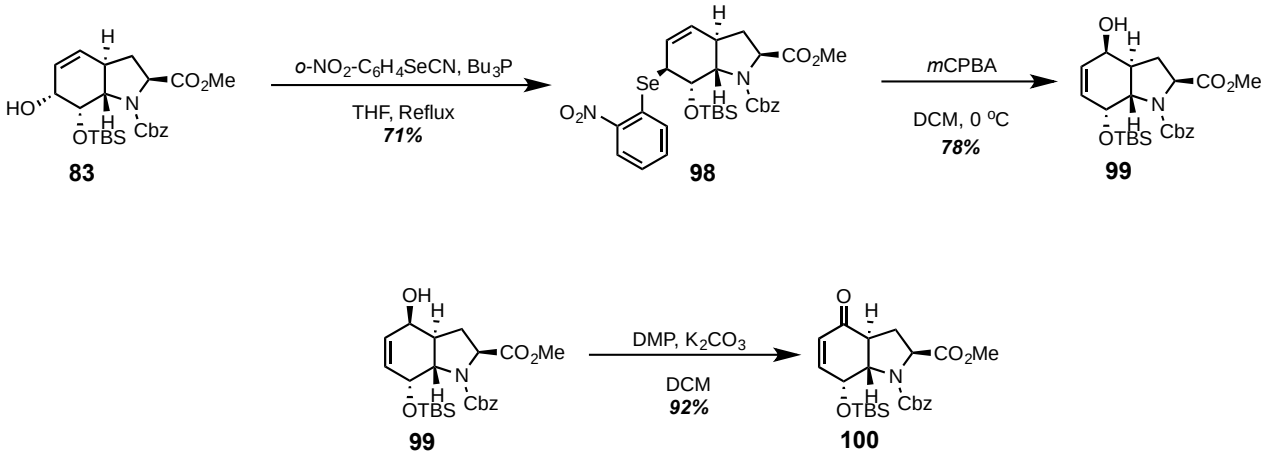


Scheme 4.3: Accessing the Carbon Framework of Diene **32**

Accessing the main carbon framework of the diol system was first attempted with route consists of Wharton rearrangement and allylic oxidation reactions. Wharton rearrangement conditions of **67** gave access to **65** in 20% yield, followed by the DMP oxidation to afford enone **70** in 92% yield. However, the attempts for the allylic oxidation of enone **70** by following literature reported procedures such as using methanolic KOH and Cu-Al-Ox catalyst were unsuccessful resulting degraded product and the starting material, respectively. With the failed allylic oxidation, it was envisioned to reverse the alcohol installation by using Rubottom oxidation followed by Wharton rearrangement. The deoxygenation of Rubottom oxidized compound **29** was performed to access **77** in 90% yield, followed by the epoxidation resulted epoxy ketone **78** in 80% yield. However, the Wharton rearrangement of **78** mainly returned the hydrazone intermediate with trace amount of product even after the extensive efforts to optimize the yield. Therefore, the investigations into another approaches to introduce the diol system were attempted. It was envisioned to attempt Mislow-Evans reaction to access the diol **82**. Accessing the thiophenol **80** from **84** with thiophenol, Cs_2CO_3, and TBAI, was unsuccessful even under reflux conditions. Therefore, accessing the

thiophenol **86** from compound **83** via a brominated intermediate was attempted. However, the bromination of compound **83** using an Appel reaction was unsuccessful with the 98% recovery of the starting material. With the unsuccessful Mislow-Evans reaction, it was envisioned to attempt a S_N2' reaction with LiOAc and HMPT on the mesylate **84** to access diol **91**. However, this procedure was unsuccessful with the full recovery of the starting material.

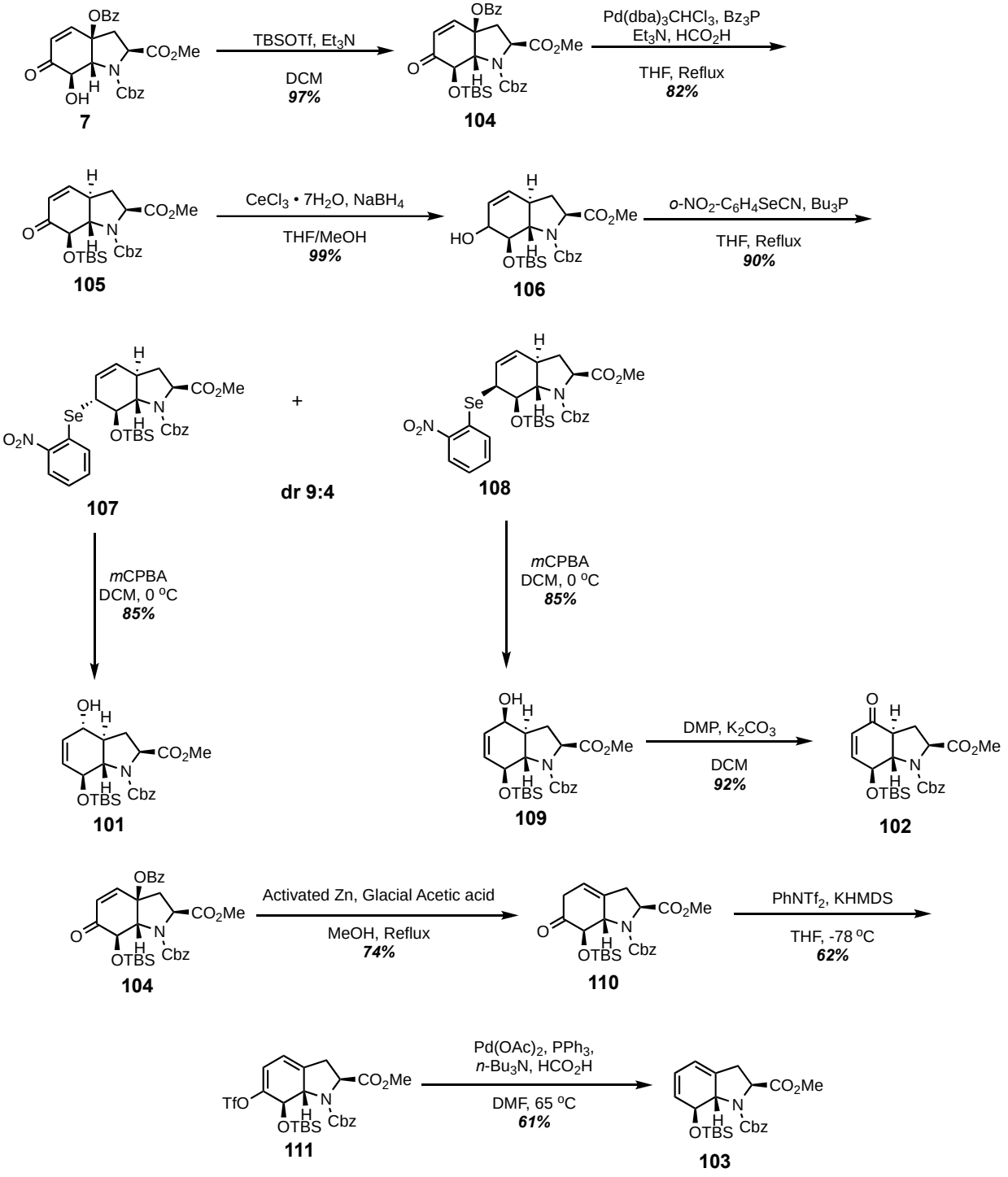
Finally, it was envisioned to attempt Grieco conditions and subsequent rearrangement facilitated access of the diol **94.** Grieco condition of allylic alcohol **83** resulted allylic selenide **98** in 71% yield, followed by the *m*CPBA oxidation facilitated sigmatropic rearrangement of selenide group was performed to obtain compound **99** in 78% yield. DMP oxidation of diol **99** gave access to enone **100** in 92% yield. With this, we have successfully accessed the main carbon frameworks of diol **99** and the enone **100** (Scheme 4.4).



Scheme 4.4: Accessing the Carbon Framework of Diol **99** and Enone **100**

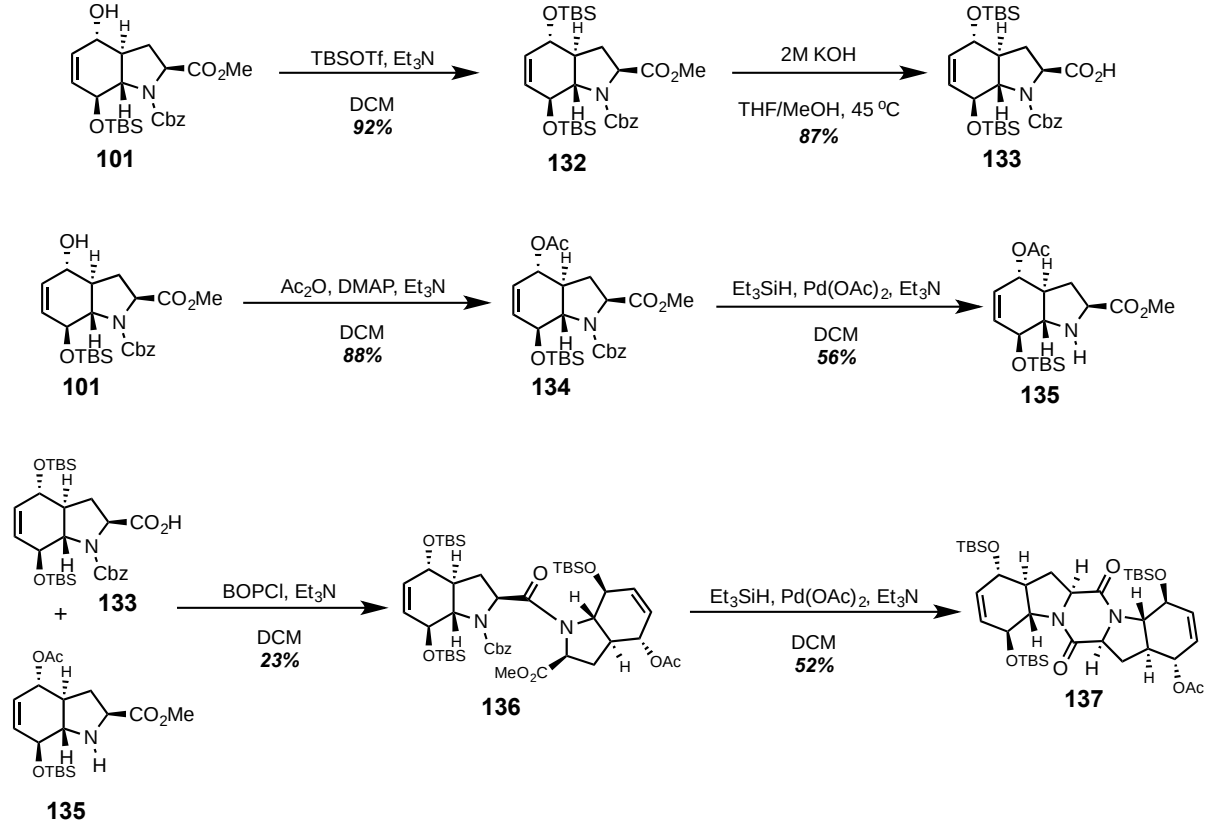
We have successfully accessed the carbon framework of all fragments of brocazine F and G. However, these fragments needed to be accessed with desired sterocenters. The desired stereochemistry of the sorthern alcohol was obtained when *m*CPBA was used rather than DMDO as the oxidant for the Rubottom oxidation reaction. Deoxygenation of TBS protected Rubottom

oxidation product **104** was performed to access trans-fused bicycle **105** in 82% yield, followed by the Luche reduction to access the allylic alcohol **106** in 99% yield. The Grieco conditions of the mixture of two distereomers **106** resulted allylic selenides **107** and **108** with the overall yield of 90% (dr- 9:4). The *m*CPBA oxidation facilitated sigmatropic rearrangement of selenide group gave access to the diols **101** and **109** in the highest yield of 85% for both compounds. The oxidation of diol **109** resulted enone **102** in 92% yield. The desired stereoisomer of the diene **103** was accessed following a route consists of Comins's reagent. Comins' reaction of compound **110** resulted triflate enol ether **111** in 62% yield, followed by the elimination of the triflate group of **111** with a $Pd(OAc)_2$ catalyzed reaction at 65 °C resulted the diene **103** in 61% yield. At this stage, we have successfully accessed all the fragments of brocazine F and G with desired stereochemistry. In the next stage, coupling of the fragments was needed to be performed to access the desired DKP cores of brocazine F and G (Scheme 4.5).



Scheme 4.5: Accessing the Fragments of Brocazine F and G with Desired Stereochemistry

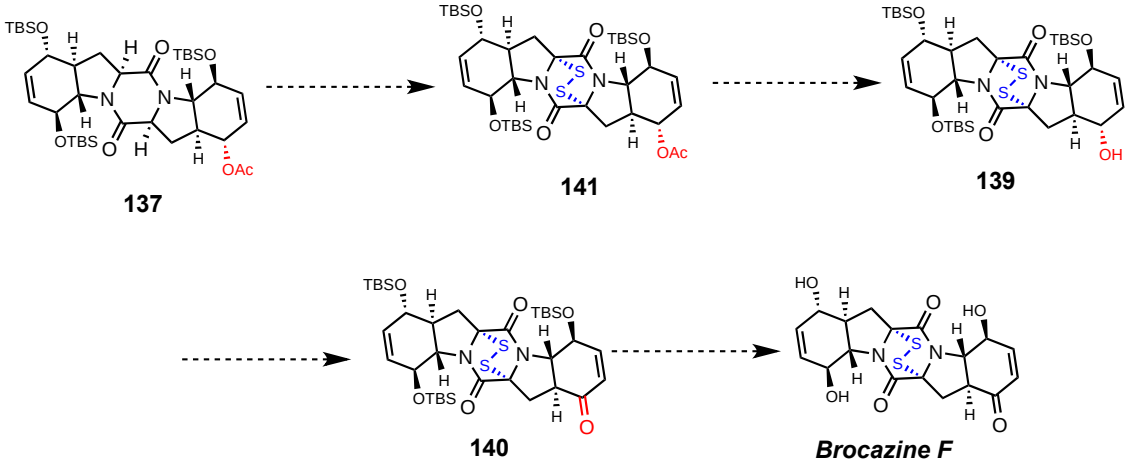
Investigations into the Cbz deprotection showed that the presence of enone or free alcohol groups interfere with the Cbz deprotection reaction conditions. Therefore, all the free alcohol groups needed to be protected before performing the Cbz deprotection. It was decided to TBS and acetyl protect the alcohol **101** separately to access **133** and **135**, respectively, and coupled them together with BOPCl to access **136** in 23% yield. The investigations into the optimization of the reaction yield is currently underway. Aminolysis of **136** was attempted in 9 mg scale and the desired DKP **137** was obtained. However, further purification of the compound is needed in order to fully confirm the presence of the desired DKP **137** (Scheme 4.6).



Scheme 4.6: Accessing the DKP core of Brocazine F

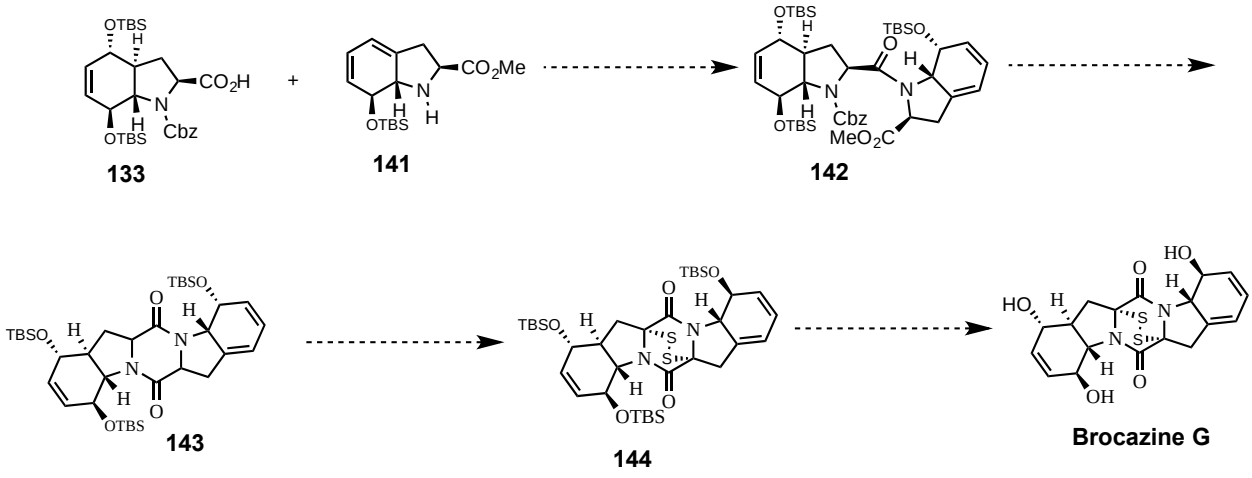
In future work, disulfide incorporation to the DKP core of **137** needs to be performed to access the thiodiketopiperazine **141**. The acetate group of the DKP **137** needs be deprotected to access **139** and the free alcohol group can be selectively oxidized to access the desired enone system **140**.

Finally, brocazine F can then be accessed after the deprotection of all the protecting groups (Scheme 4.7).



Scheme 4.7: Proposed Route to Access Brocazine F

Coupling of carboxylic acid **133** with amine **141** to obtain **142**, followed by the aminolysis will be performed to access the DKP core of brocazine G. Disulfide incorporation to the DKP core of **143** will be performed to access the thiodiketopiperazine **144**. Finally, brocazine F can then be accessed after the deprotection of all the protecting groups (Scheme 4.8).



Scheme 4.8: Proposed Route to Access Brocazine G

Chapter 5 - References

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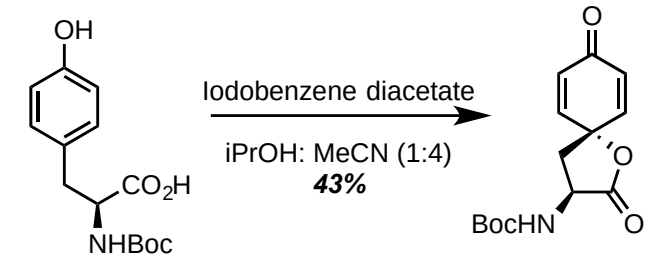
Chapter 6 - Experimental and NMRs

General Methods

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) and the visualization was done using UV light and $KMnO_4$/heat. Sorbtech silica gel (60, particle size 40-63 μm) was used for silica gel chromatography. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity plus and Bruker spectrometer for ^{1}H (400 MHz or 600 MHz) and ^{13}C (101 MHz or 151 MHz) in deuterated chloroform ($CDCl_3$), unless otherwise indicated. Signal patterns are indicated as br, broad peak; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The rotamer peaks were shown in (). All the non-aqueous reactions were performed under an inert atmosphere of aargon in flame-dried glassware, containing a stir bar, unless otherwise noted. Anhydrous diethyl ether (Et_2O), toluene (PhMe), *N*,*N*-dimethylsulforamide (DMF), tetrahydrofuran (THF), dichloromethane (DCM), and acetonitrile (MeCN) were obtained via a dual column solvent purification system (J.C Mayer of Glass Contour). All other solvents and reagents were obtained from commercial sources without further purification unless noted. Organic extracts were dried with NaSO4 (unless otherwise noted) before filtration and concentration under reduced pressure.

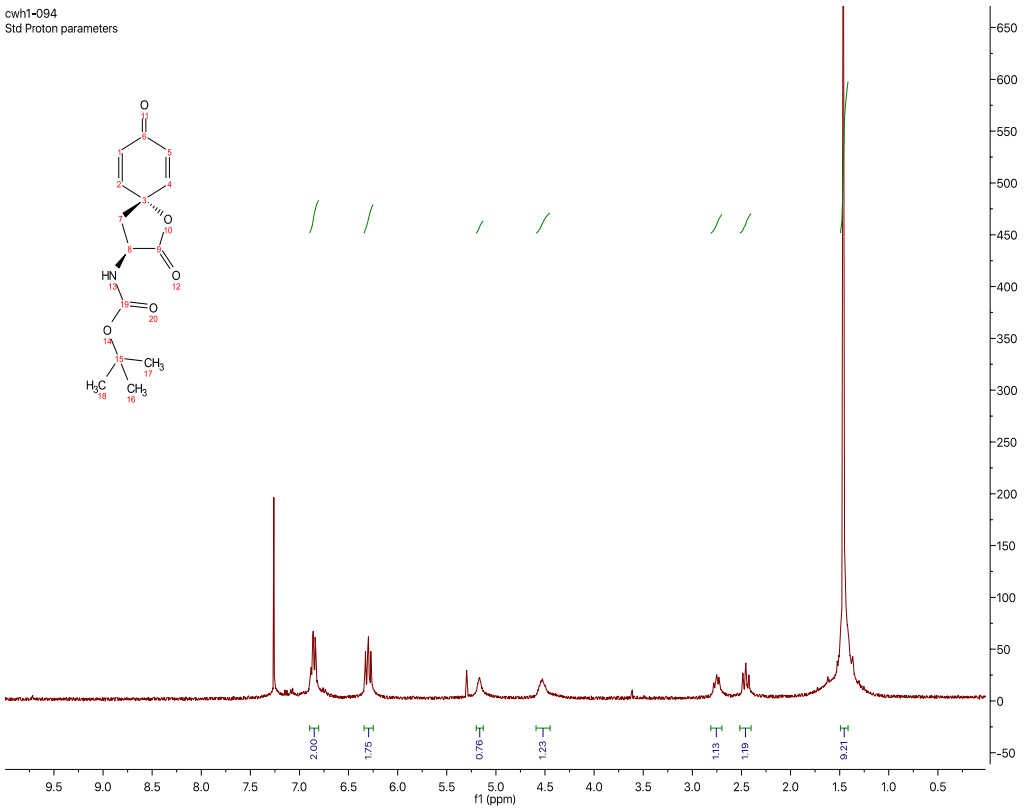
***Tert*-butyl (*S*)-(2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-3-yl)carbamate (48)**



Boc-L-Tyrosine **48**

To a stirred solution of iodobenzene diacetate (4.3 g, 13.3 mmol, 1.5 eq) in *i*PrOH: MeCN (1:4, 0.20 M, 66.5 mL) was added a stirred solution of **Boc-L- tyrosine** (2.5 g, 8.9 mmol, 1 eq) in *i*PrOH: MeCN (1:4, 0.23 M, 39 mL) dropwise over 30 minutes, and then was stirred at room temperature. After 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (× 2), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc: hexanes, 1:1) to give compound **48** as a yellow foam (1.1 g, 43% yield). Rf = 0.58 (silica, EtOAc:hexanes, 1:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 6.90 – 6.80 (m, 2H), 6.34 – 6.25 (m, 2H), 5.17 (s, 1H), 4.59 – 4.45 (brs, 1H), 2.75 (t, J = 11.2 Hz, 1H), 2.45 (t, J = 12.4 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-d) δ 184.08, 173.61, 155.22, 144.22, 143.93, 129.73, 129.14, 81.23, 76.14, 50.19, 38.67, 28.24. Known compound; all the spectral data matches the data reported in reference ***52***.

Notebook Entries:
Procedure – cwh2-015
^{1}H – cwh1-094
^{13}C – cwh2-015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Std Proton parameters
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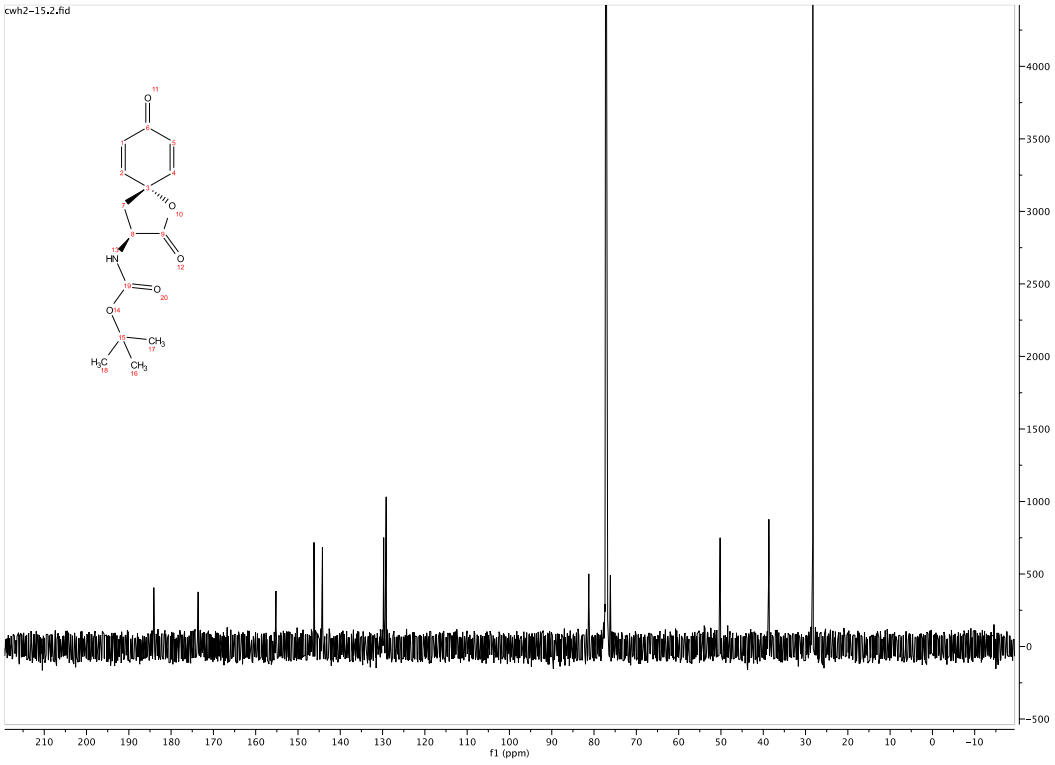
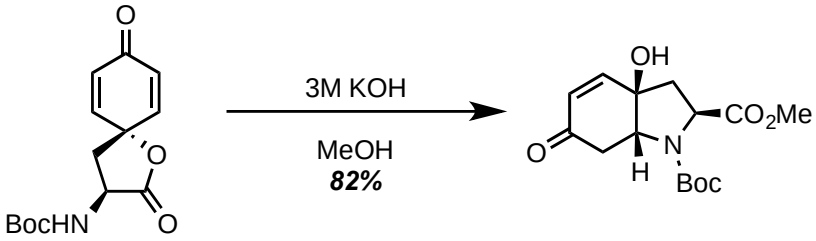
0.76
1.23
1.13
1.19
8.21
f1 (ppm)


cwh2-15.2.fid
f1 (ppm)

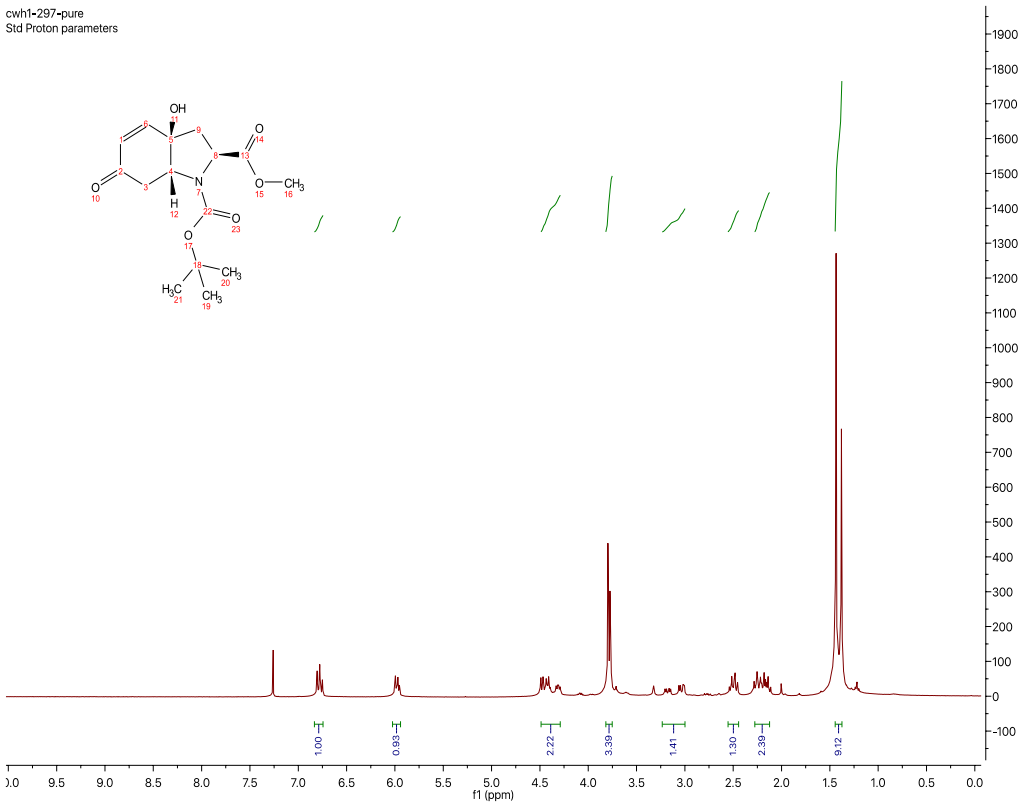
1-(tert-butyl) 2-methyl (2S,3aR,7aR)-3a-hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (17)



48 **17**

To a stirred solution of 3M KOH (120 mL, 0.10 M) and MeOH (120 mL, 0.10 M) at -20 °C was added compound **48** (3.0 g, 10.7 mmol, 1 eq) dissolved in MeOH (100 mL, 0.14 M), and then was stirred at -20 °C. After 30 minutes, the reaction was quenched with 5M HCl until a pH of 2 and was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **17** as a yellow foam (3 g, 82% yield). Rf = 0.24 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.83 – 6.74 (m, 1H), 6.03 – 5.94 (m, 1H), 4.49 – 4.29 (m, 2H), 3.82 + 3.75 (s + s', 3H), 3.10 (m, 1H), 2.49 (m, 1H), 2.29 – 2.12 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ (196.33, 196.31), (175.52, 175.50), (153.65, 153.63) (148.57, 148.19), (129.28, 129.15), (81.75, 81.42), (76.76, 75.74), (65.86, 65.53), (58.82, 58.67), (53.41, 53.05), (42.90, 42.18), (40.71, 39.73), (28.51, 28.38). Known compound; all the spectral data matches the data reported in reference ***38***. The procedure was taken from reference ***40***.

Notebook Entries:
Procedure – cwh1-297
^{1}H – cwh1-297-pure
^{13}C – cwh1-297-pure


cwh1-297-pure
Std Proton parameters
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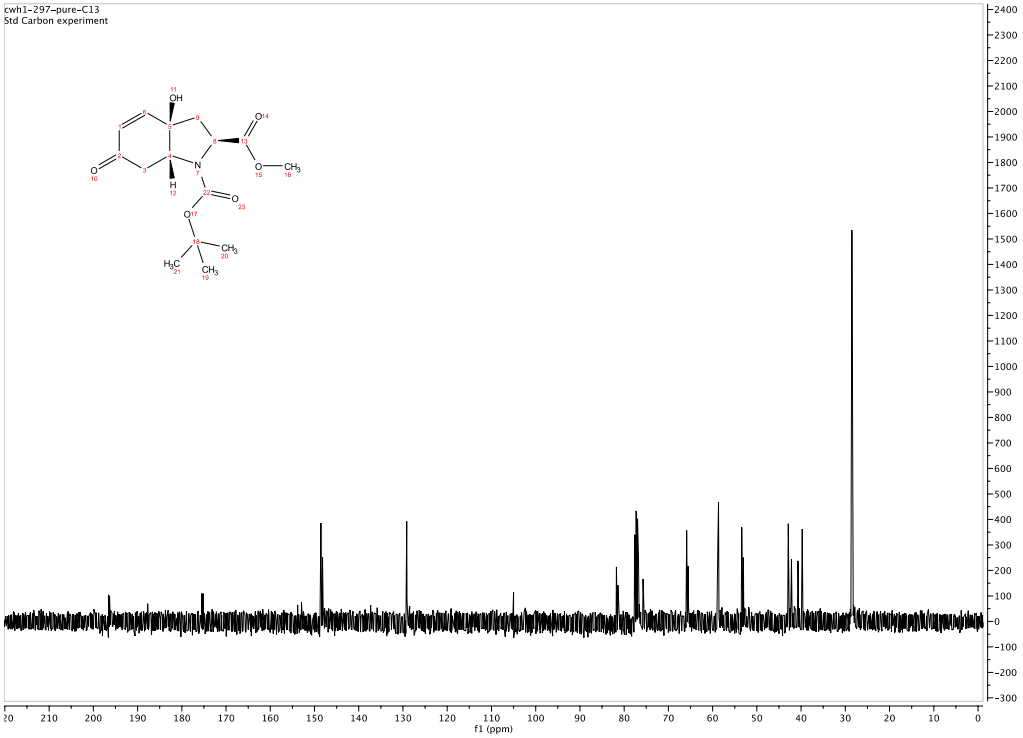
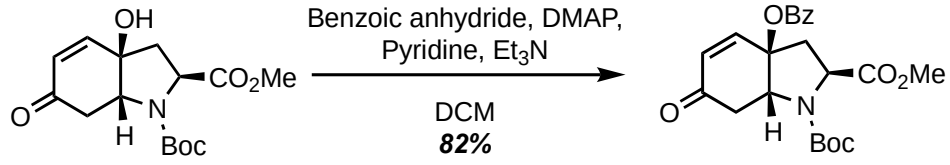
2.22
3.39
1.41
1.30
2.39
9.12
f1 (ppm)


cwh1-297-pure-C13
Std Carbon experiment
f1 (ppm)

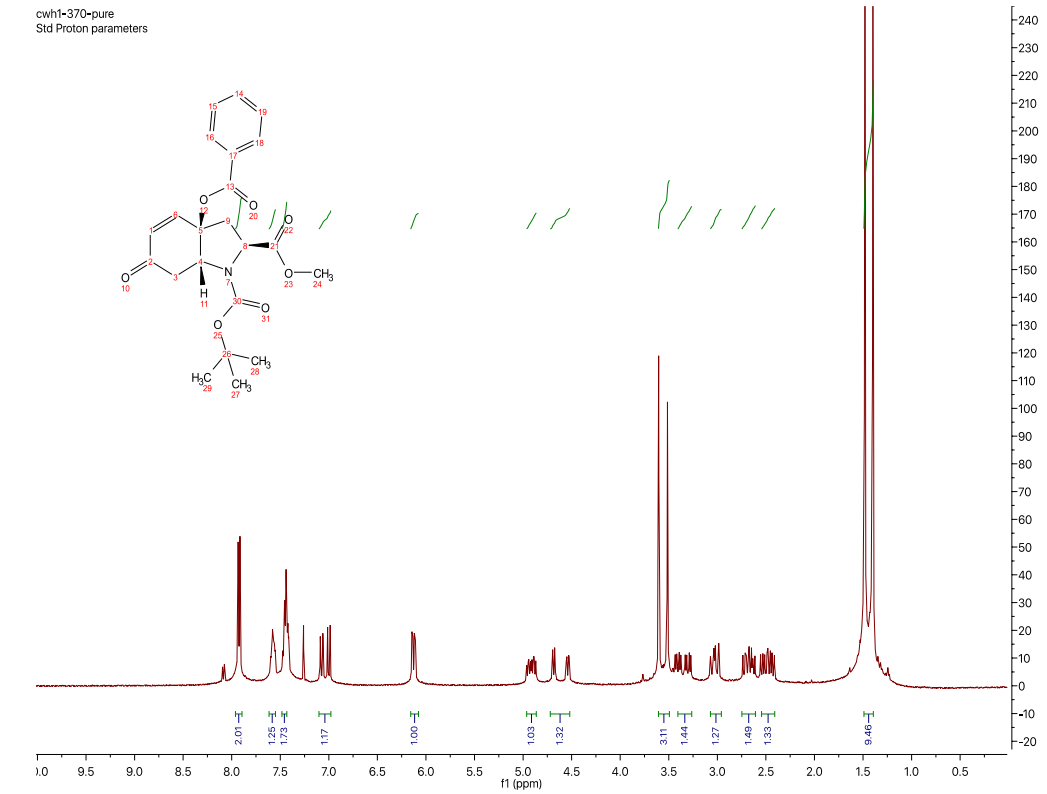
1-(tert-butyl) 2-methyl (2S,3aR,7aR)-3a-(benzoyloxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (49)

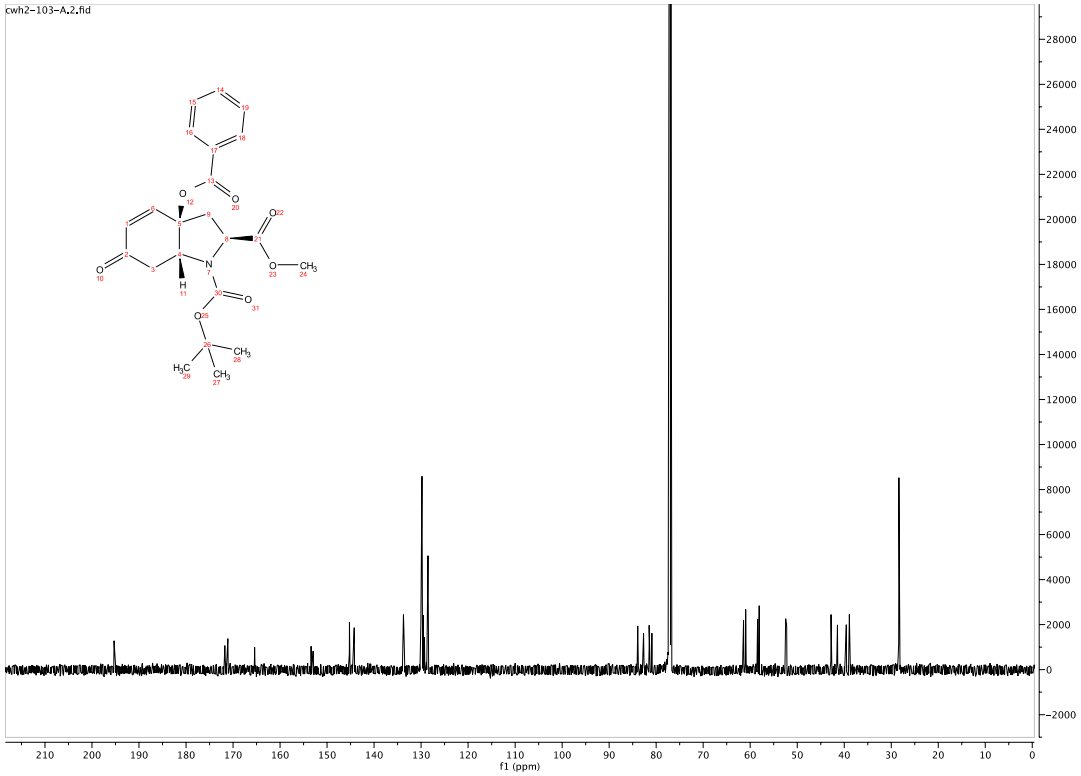


17 **49**

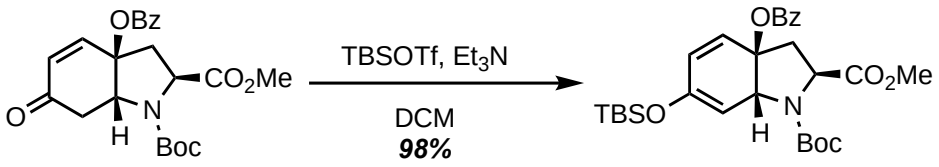
To a stirred solution of compound **17** (920 mg, 2.96 mmol, 1 eq) in DCM (30 mL, 0.10 M) was added benzoic anhydride (2.0 g, 8.87 mmol, 3.0 eq), DMAP (37 mg, 0.30 mmol, 0.1 eq), pyridine (1.25 mL, 15.39 mmol, 5.12 eq), and Et_3N (1.7 mL, 11.84 mmol, 4.0 eq), and then brought to reflux. After 48 h, the reaction was quenched with 1M HCl and the organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:5 and 2:1) to give compound **49** as a light-yellow foam (1.0 g, 82% yield). Rf = 0.54 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-d) δ 7.96 – 7.89 (m, 2H), 7.58 (dt, J = 10.7, 5.7 Hz, 1H), 7.50 –7.39 (m, 2H), 7.04 (dd, J = 30.1, 10.4 Hz, 1H), 6.13 (dd, J = 10.4, 4.5 Hz, 1H), 4.92 (ddd, J = 21.9, 9.7, 6.8 Hz, 1H), 4.61 (ddd, J = 58.4, 9.5, 2.0 Hz, 1H), 3.56 (s+ s', 3H), 3.41 – 3.26 (m, 1H), 3.07 – 2.96 (m, 1H), 2.67 (ddd, J = 26.0, 14.2, 9.5 Hz, 1H), 2.55 – 2.41 (m, 1H), 1.48 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-d) δ (195.32, 195.26), (171.75, 171.11), (165.40, 165.23), (153.39, 152.97), (145.23, 144.23), (133.75, 133.66), (130.06, 129.83), (129.81, 129.54), (129.39, 129.30),(128.53, 128.47), (83.92, 82.69), (81.49, 80.92), (61.42, 60.97), (58.44, 58.09), (52.46, 52.24), (42.80, 41.43), (39.56, 38.90), (28.26, 28.24). . Known compound; all the spectral data matches the data reported in reference ***40***.

Notebook Entries:
Procedure – cwh4-073
^1H – cwh1-370-pure ^{13}C – cwh2-103-A


cwh1-370-pure
Std Proton parameters
f1 (ppm)


cwh2-103-A.2.fid
f1 (ppm)

1-(tert-butyl) 2-methyl (2S,3aR,7aR)-3a-(benzoyloxy)-6-((tert-butyldimethylsilyl)oxy)-2,3,3a,7a-tetrahydro-1H-indole-1,2-dicarboxylate (50)



15 **50**

To a stirred solution of compound **15** (110 mg, 0.26 mmol, 1 eq) in DCM (1.7 mL, 0.156 M) was added Et_3N (0.07 mL, 0.53 mmol, 2.04 eq) and TBSOTf (0.065 mL, 0.286 mmol, 1.1 eq), and then was stirred at room temperature. After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layers were extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **50** as a white foam (129 mg, 98% yield). Rf = 0.47 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.91 (m, 2H), 7.62 – 7.50 (m, 1H), 7.47 – 7.38 (m, 2H), 6.11 – 5.72 (m, 2H), 5.45 – 5.17 (m, 2H), 4.56 – 4.30 (m, 1H), 3.57 (s + s', 3H), 2.90 (m, 1H), 2.50 – 2.38 (m, 1H), 1.50 + 1.40 (s+ s', 9H), 0.93 (s+ s', 9H), 0.22 + 0.13 (s+ s', 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ (172.91, 172.17), (165.60, 165.26) (146.96, 146.57), (133.53, 133.41), (130.27, 130.19), (129.89, 129.88), (129.60, 128.95), (128.58, 128.51), (125.87, 125.35), (103.65, 103.59), (97.90, 97.77), (86.32, 85.00), (80.81, 80.40), (63.52, 63.09), (55.55, 54.99), (52.47, 52.27), (42.46, 41.65), (28.71, 28.51), (25.85, 25.83), (18.30, 18.26), (-4.24, -4.30). New compound; Procedure was taken from reference ***41***.

Notebook Entries:
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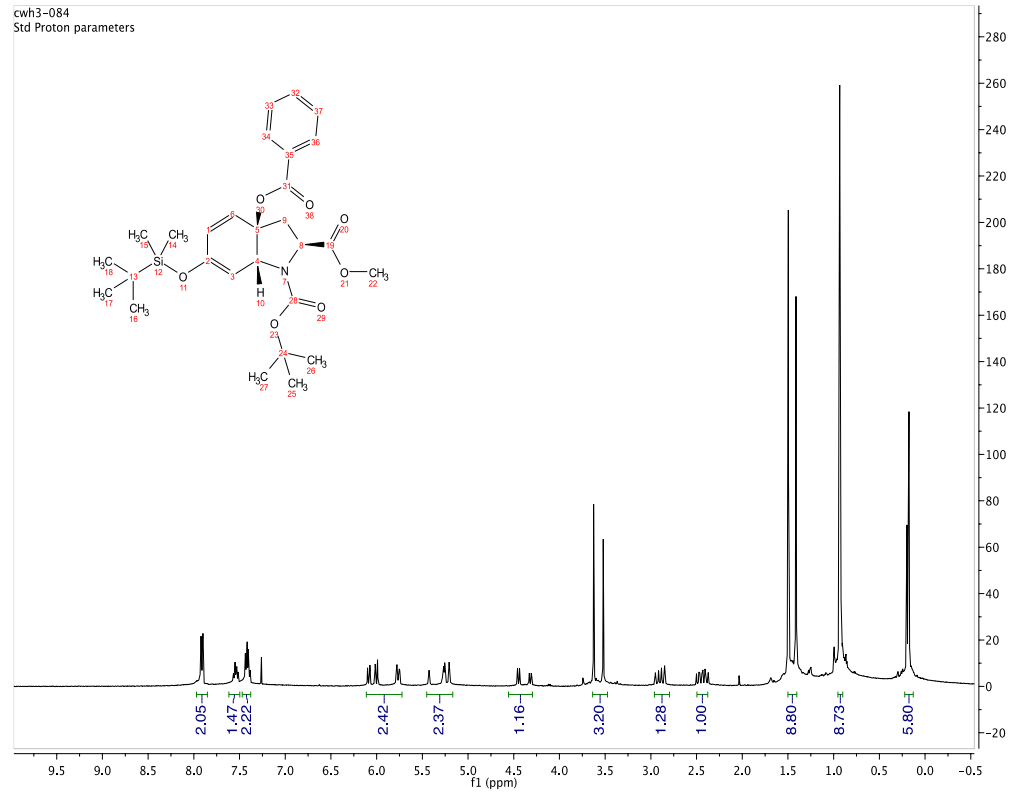
^{1}H – cwh3-084
^{13}C – cwh3-084


cwh3-084
Std Proton parameters
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2.37
1.16
3.20
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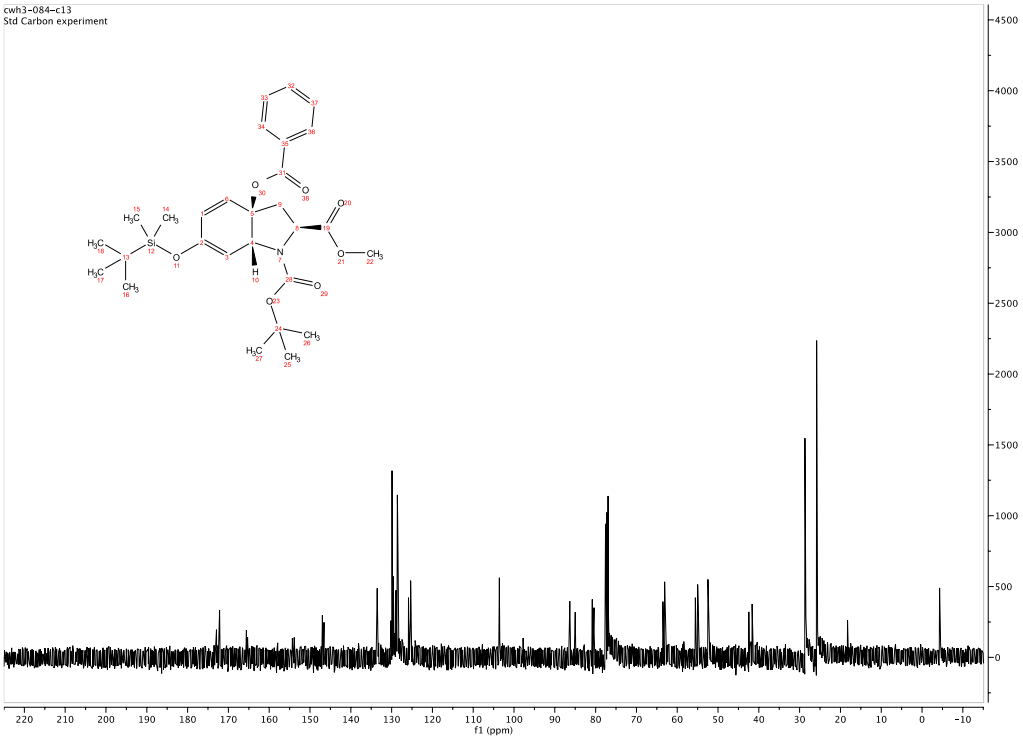
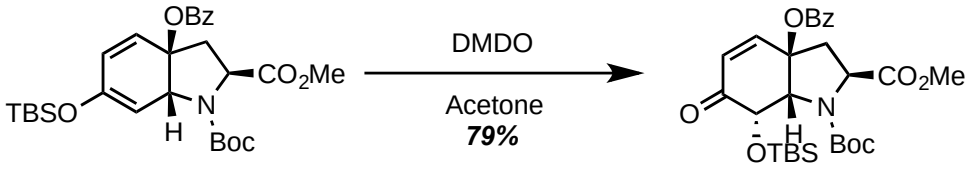
1.00
8.80
8.73
5.80
f1 (ppm)


cwh3-084-c13
Std Carbon experiment
f1 (ppm)

1-(*tert*-butyl) 2-methyl (2*S*,3a*R*,7*S*,7a*R*)-3a-(benzoyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (52)



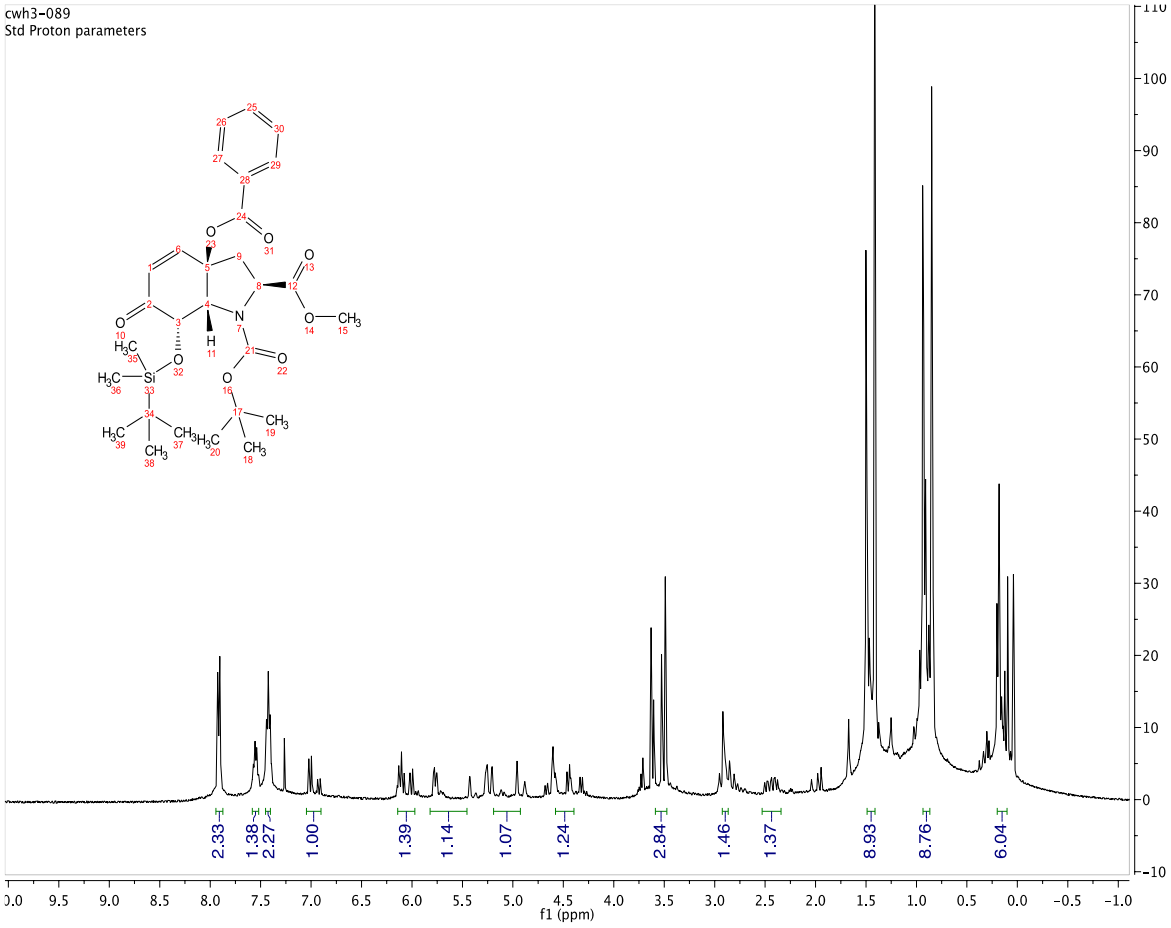
50 **52**

To a stirred solution of compound **50** (60 mg, 0.11 mmol, 1 eq) in acetone (1.3 mL, 0.0875 M) was added freshly prepared DMDO (2.3 mL, 0.15 mmol, 1.34 eq) at 0 °C, and then was stirred at 0 °C. After 1 h, the reaction mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc: hexanes, 1:6) to give compound **52** as a white foam (431 mg, 79% yield). Rf = 0.13 (silica, EtOAc:hexanes, 1:6); Rotamers were shown in ( ). $_1$H NMR (400 MHz, Chloroform-d) δ 7.91 (m, 2H), 7.58 – 7.52 (m, 1H), 7.45 – 7.40 (m, 2H), 6.96 (ddd, J = 34.8, 10.5, 2.0 Hz, 1H), 6.14 – 5.97 (m, 1H), 5.82 – 5.46 (m, 1H), 5.19 – 4.93 (m, 1H), 4.58 – 4.39 (m, 1H), 3.51 (s+ s', 3H), 2.92 – 2.87 (m, 1H), 2.53 – 2.34 (m, 1H), 1.42 (m, 9H), 0.93 – 0.87 (m, 9H), 0.20 – 0.10 (m, 6H). New compound; Procedure was taken from reference ***41***. (Compound was degraded and $_{13}$C was not obtained)

DMDO Preparation

Solution of 24 g of NaHCO3 was stirred in a 1 L RBF containing 20 mL of H2O and 30 mL acetone at 0 ºC. After 20 min, 25 g of oxone was added, the flask is loosely covered and the mixture was vigorously stirred at 0 ºC. After 15 min, the mixture was rotovaped carefully and the rotavaped light yellow solution (DMDO) was collected. Then the DMDO solution was dried with Na2SO4 and used for the reaction immediately.

Notebook Entries:
Procedure – cwh3-089
$_1$H – cwh3-089


cwh3-089
Std Proton parameters
2.33
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2.27
1.00
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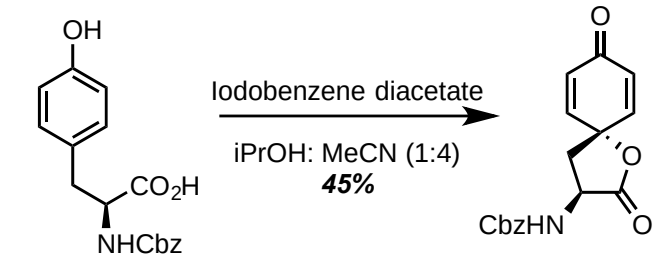
1.14
1.07
1.24
2.84
1.46
1.37
8.93
8.76
6.04
f1 (ppm)

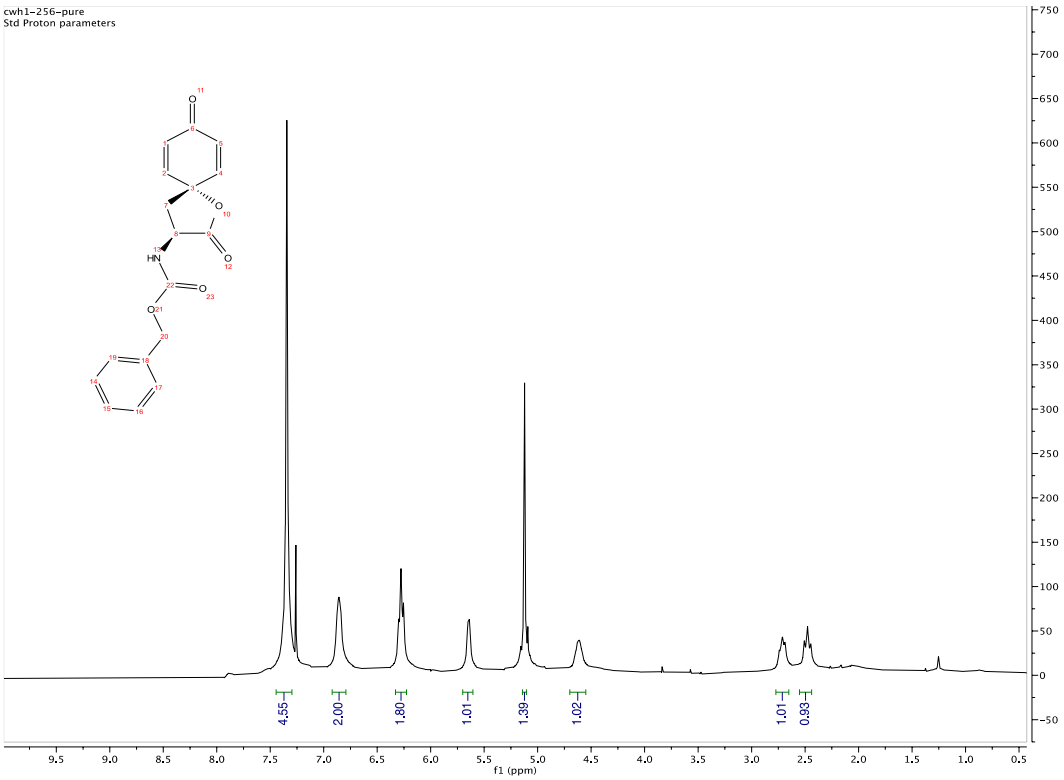
Benzyl (2,8-dioxo-1-oxaspiro [4.5] deca-6,9-dien-3-yl) carbamate (13)

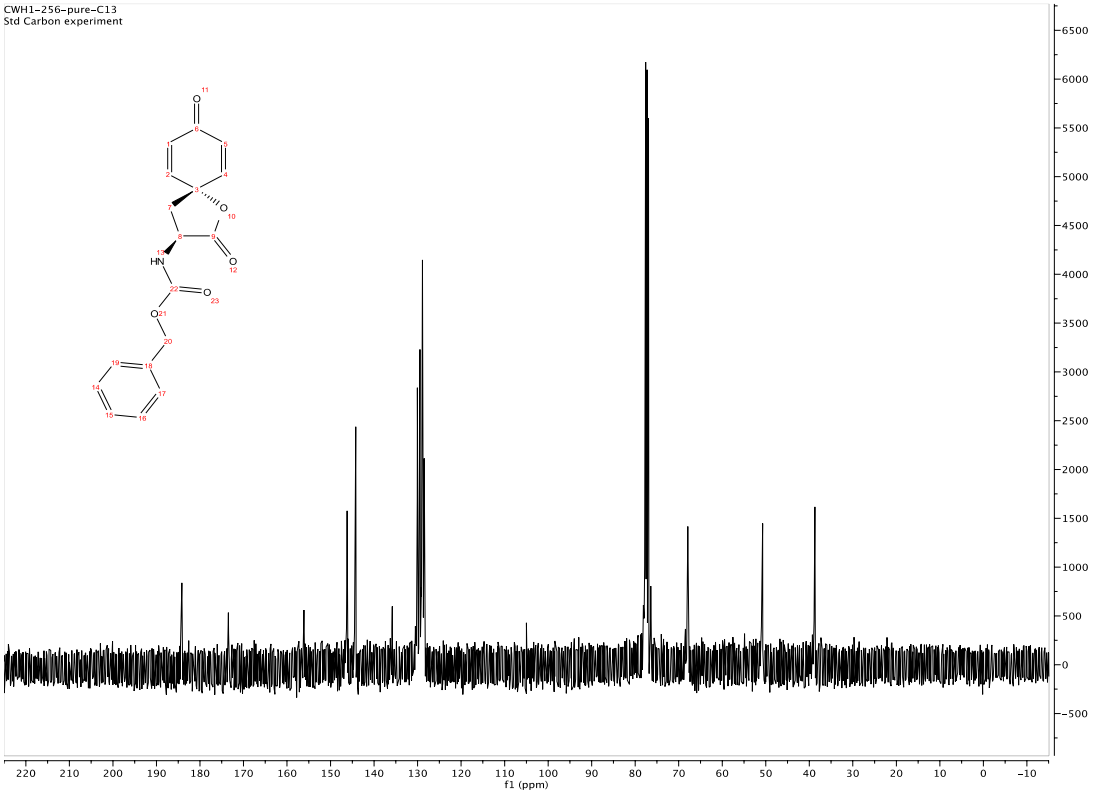


Cbz-L-tyrosine **13**

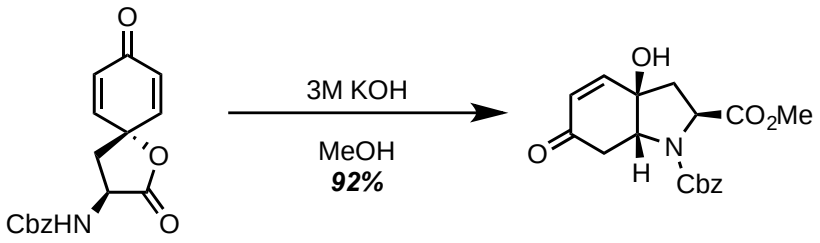
To a stirred solution of iodobenzene diacetate (7.7 g, 23.78 mmol, 1.5 eq) in *i*PrOH: MeCN (1:4, 0.20 M, 80 mL) was added a stirred solution of **Cbz-L- tyrosine** (5g, 15.85 mmol, 1 eq) in *i*PrOH: MeCN (1:4, 0.23 M, 70 mL) dropwise over 30 minutes, and then was stirred at room temperature. After 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the organic layers were extracted with EtOAc (× 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (× 2), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc: hexanes, 1:1) to give compound **13** as a yellow foam (2.23 g, 45% yield). Rf = 0.59 (silica, EtOAc:hexanes, 1:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.45 – 7.30 (m, 5H), 6.86 (s, 2H), 6.28 (t, J = 9.1 Hz, 2H), 5.65 (d, J = 6.3 Hz, 1H), 5.13 (d, J = 2.2 Hz, 1H), 4.61 (s, 1H), 2.70 (d, J = 10.1 Hz, 1H), 2.48 (t, J = 12.1 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 184.17, 173.47, 156.12, 146.19, 144.22, 135.82, 130.06, 129.45, 128.68, 76.43, 67.92, 50.75, 38.73. Known compound; all the spectral data matches the data reported in reference ***40***.

Notebook Entries:
Procedure – cwh4-001
^{1}H – cwh1-256-pure
^{13}C – cwh2-256-pure-c13


cwh1-256-pure
Std Proton parameters
4.55
2.00
1.80
1.01
1.39
1.02
1.01
0.93
f1 (ppm)


CWH1-256-pure-C13
Std Carbon experiment
f1 (ppm)

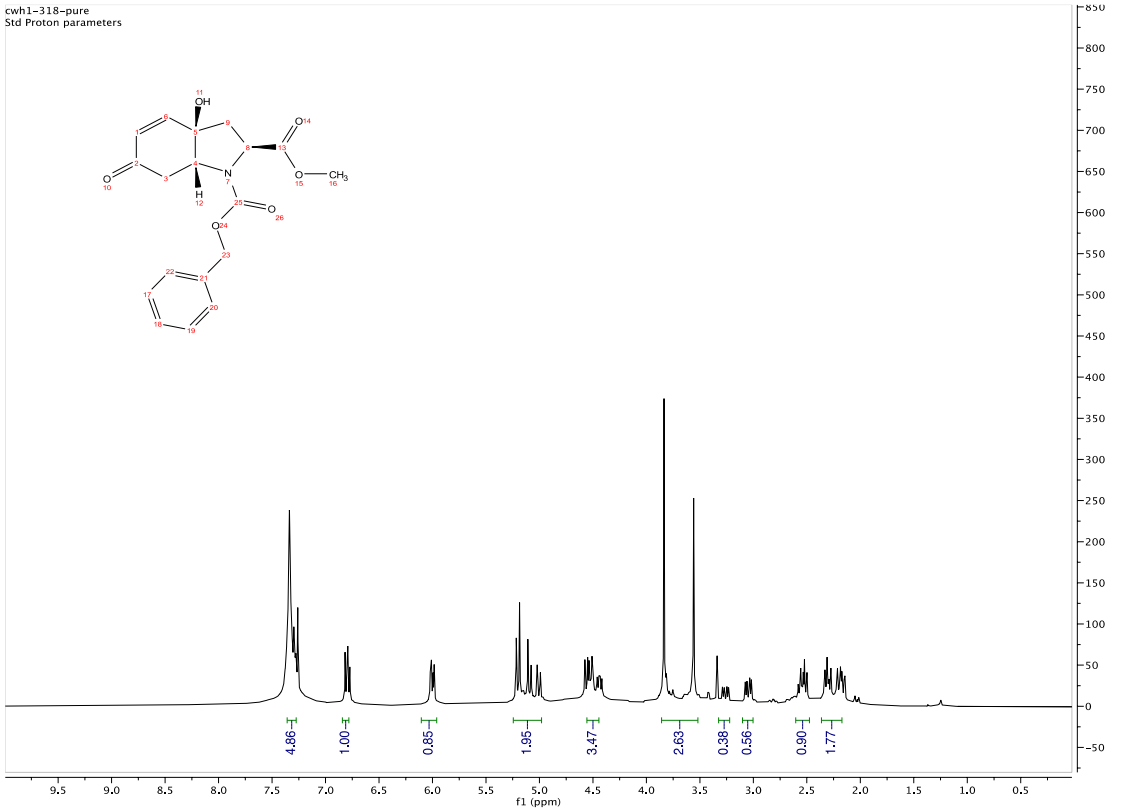
1-benzyl 2-methyl (2*S*,3a*R*,7a*R*)-3a-hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (14)

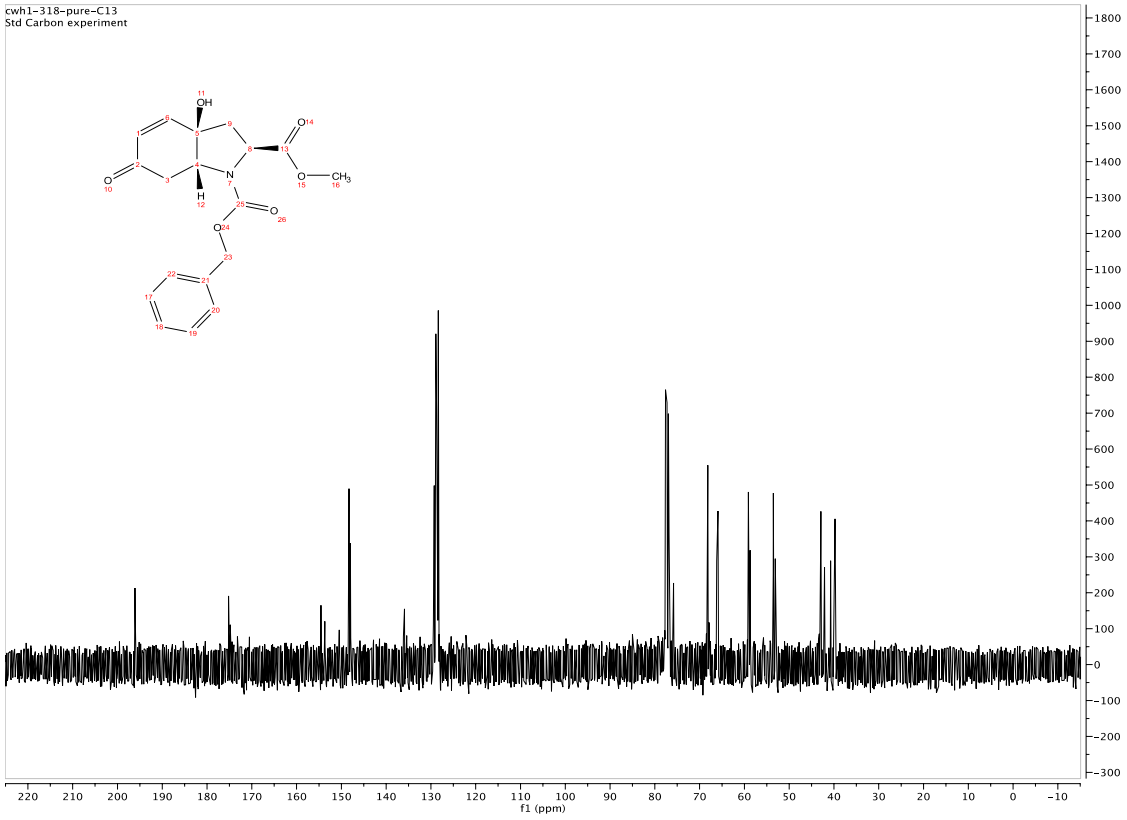


13 **14**

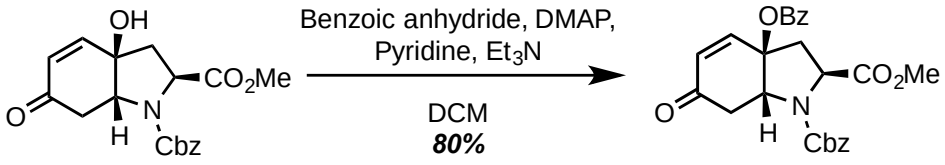
To a stirred solution of 3M KOH (64 mL, 0.10 M) and MeOH (64 mL, 0.10 M) at -20 °C was added compound **13** (2.0 g, 6.38 mmol, 1 eq) dissolved in MeOH (46 mL, 0.14 M), and then was stirred at -20 °C. After 30 minutes, the reaction was quenched with 5M HCl until a pH of 2 and was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **14** as a yellow foam (2 g, 92% yield). Rf = 0.25 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.27 (m, 5H), 6.84 – 6.78 (m, 1H), 6.10 – 5.96 (m, 1H), 5.24 – 4.98 (m, 2H), 4.56 – 4.44 (m, 3H), 3.83+ 3.56 (s + s', 3H), 3.10 – 3.00 (m, 1H), 2.60 – 2.48 (m, 1H), 2.36 – 2.17 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ (196.09, 196.01), (175.20, 175.22), (154.57, 153.87), (148.30, 147.98), (135.95, 135.40), (129.39, 129.25), (128.90, 128.73), (128.64, 128.53), (128.36, 128.32), (76.82, 75.82), (68.16, 67.92), (66.18, 65.91), (59.11, 58.73), (53.55, 53.11), (42.92, 42.12), (40.76, 39.76). Known compound; all the spectral data matches the data reported in reference ***40***.

Notebook Entries:
Procedure – cwh4-003
^{1}H – cwh1-318-pure
^{13}C – cwh1-318-pure-c13


cwh1-318-pure
Std Proton parameters
4.86
1.00
0.85
1.95
3.47
2.63
0.38
0.56
0.90
1.77
f1 (ppm)


cwh1-318-pure-C13
Std Carbon experiment
f1 (ppm)

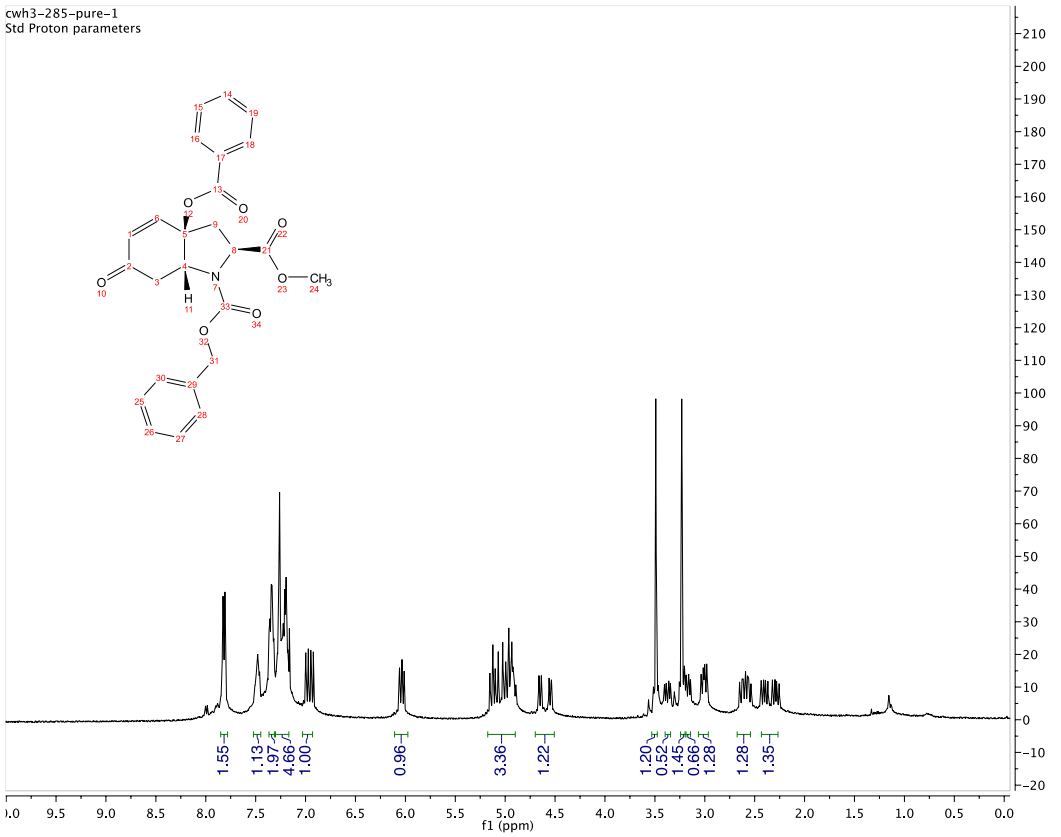
1-benzyl 2-methyl (2*S*,3a*R*,7a*R*)-3a-(benzoyloxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (15)

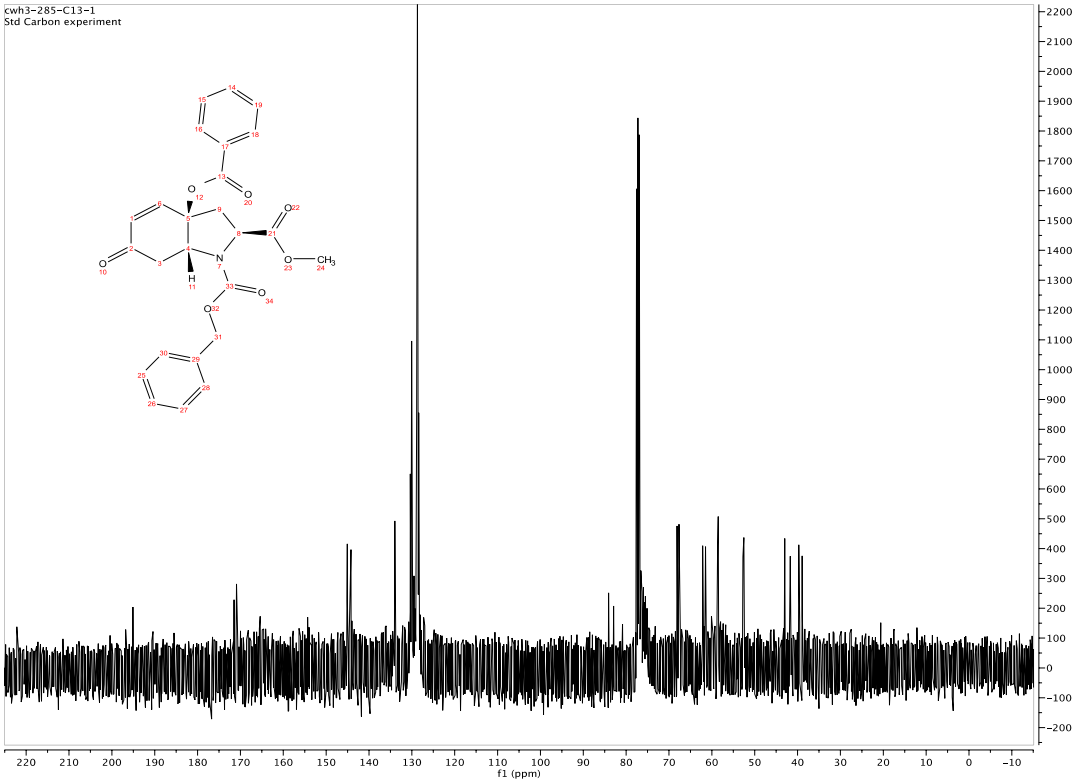


14 **15**

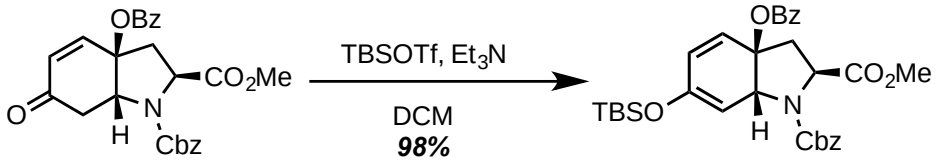
To a stirred solution of compound **14** (2.0 g, 5.79 mmol, 1 eq) in DCM (58 mL, 0.10 M) was added benzoic anhydride (3.9 g, 17.38 mmol, 3 eq), DMAP (71 mg, 0.579 mmol, 0.1 eq), pyridine (2.4 mL, 30.10 mmol, 5,12 eq), and Et_3N (3.2 mL, 23.16 mmol, 4.0 eq) and the reaction mixture was refluxed. After 48 h, the reaction was quenched with 1M HCl and the organic layers were extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:5 and 2:1) to give compound **15** as a light-yellow foam (1.97 g, 82% yield). Rf = 0.54 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.85 – 7.78 (m, 2H), 7.52 – 7.45 (m, 1H), 7.34 (m, 2H), 7.30 – 7.17 (m, 5H),, 7.03 – 6.93 (m, 1H), 6.04 (dd, J = 10.4, 7.8 Hz, 1H), 5.17 – 4.90 (m, 3H), 4.60 (ddd, J = 40.4, 9.6, 1.8 Hz, 1H), 3.49 – 3.26 (s+ s', 3H), 3.40 – 3.23 (m, 1H), 3.06 – 2.96 (m, 1H), 2.68 – 2.54 (m, 1H), 2.43 – 2.27 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ (195.09, 195.06), (171.48, 170.91), (145.06, 144.22), (133.97, 133.95), (130.36, 130.3l5), (130.05, 130.01), (129.84, 129.80), (129.64, 129.62), (129.50, 129.47), (128.88, 128.86), (128.72, 128.70), (128.61, 128.59), (128.53, 128.52), (128.44, 128.43), (84.09, 82.93), (68.13, 67.66), (62.15, 61.47), (58.67, 58.51), (52.74, 52.53), (42.99, 41.71), (39.73, 38.91). Known compound; all the spectral data matches the data reported in reference ***40***.

Notebook Entries: Procedure – cwh4-022 ^{1}H – cwh3-285-pure-1 ^{13}C – cwh3-285-c13-1


cwh3-285-pure-1
Std Proton parameters
1.55
1.13
1.97
4.66
1.00
0.96
3.36
1.22
1.20
0.52
1.45
0.66
1.28
1.28
1.35
f1 (ppm)


cwh3-285-C13-1
Std Carbon experiment
f1 (ppm)

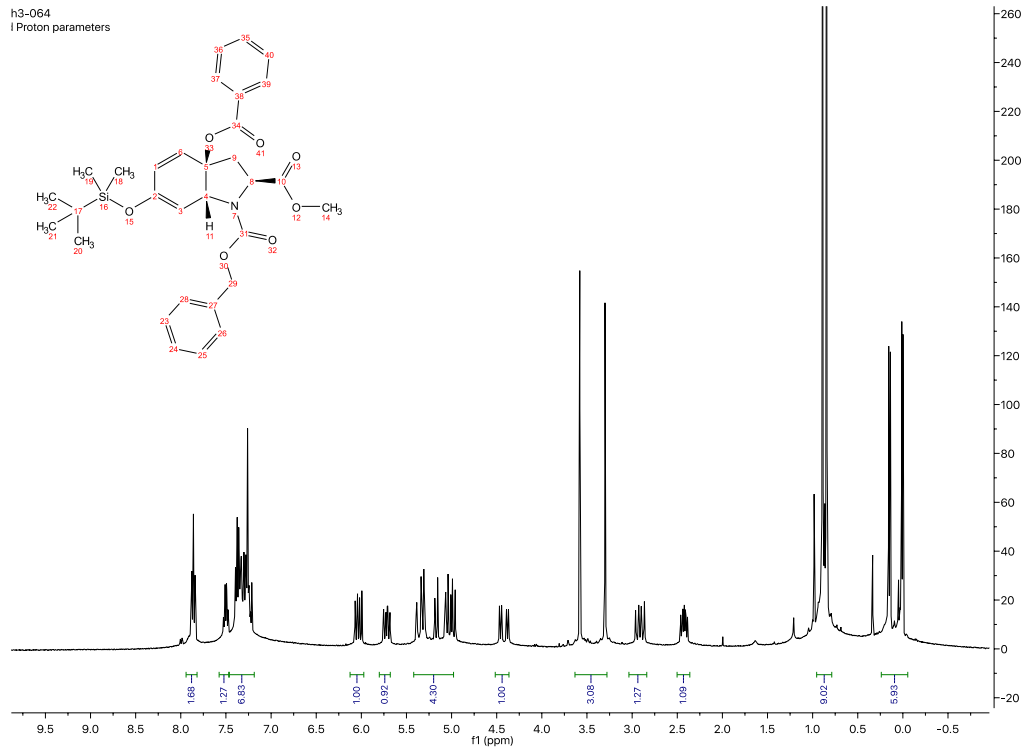
1-benzyl 2-methyl (2*S*,3a*R*,7a*R*)-3a-(benzoyloxy)-6-((*tert*-butyldimethylsilyl)oxy)-2,3,3a,7a-tetrahydro-1*H*-indole-1,2-dicarboxylate (28)

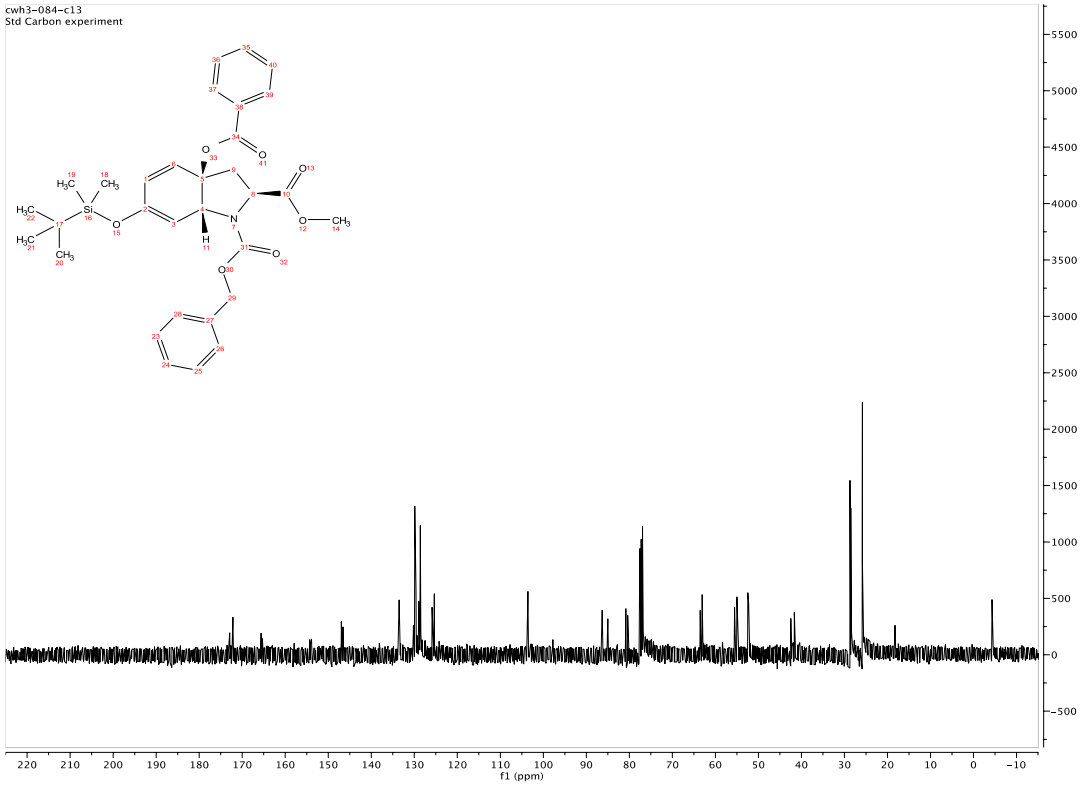


15 **28**

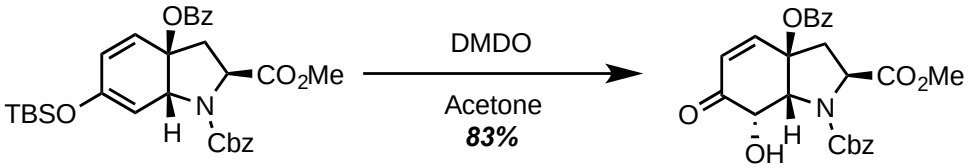
To a stirred solution of compound **15** (191 mg, 0.42 mmol, 1 eq) in DCM (2.7 mL, 0.156 M) was added Et_3N (0.12 mL, 0.87 mmol, 2.04 eq) and TBSOTf (0.14 mL, 0.63 mmol, 1.50 eq), and then was stirred at room temperature. After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **28** as a white foam (232 mg, 98% yield). Rf = 0.48 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.86 (m, 2H), 7.58 – 7.47 (m, 1H), 7.46 – 7.19 (m, 7H)), 6.03 (dd, J = 19.4, 10.2 Hz, 1H), 5.72 (ddd, J = 18.1, 10.2, 2.1 Hz, 1H), 5.42 – 4.98 (m, 4H), 4.42 (dd, J = 30.9, 9.4 Hz, 1H), 3.44 (s +s', 3H), 3.04 – 2.84 (m, 1H), 2.42 (ddd, J = 14.0, 9.6, 6.6 Hz, 1H), 0.96 – 0.79 (m, 9H), 0.15 (m, 6H). ^{13}C (101 MHz, Chloroform-d) δ (172.91, 172.16), (165.60, 165.59), (153.88, 153.82), (146.96, 146.57), (133.53, 133.41), (130.27, 130.19), (130.04, 129.91), (129.89, 129.88), (129.61, 129.60), (129.32, 129.30), (128.96, 128.95), (128.58, 128.51), (125.87, 125.35), (103.65, 103.59), (86.32, 85.00), (80.81, 80.40), (63.52, 63.09), (55.55, 54.99), (52.47, 52.27), (42.45, 41.65), (28.71, 28.51), (25.85, 25.83), (18.26, 18.25), (-4.24, -4.30). Known compound; all the spectral data matches the data reported in reference ***41***.

Notebook Entries:
Procedure – cwh3-064
^{1}H – cwh3-064 ^{13}C – cwh3-084-c13


h3-064
l Proton parameters
1.68
1.27
6.83
1.00
0.92
4.30
1.00
3.08
1.27
1.09
9.02
5.93
f1 (ppm)


cwh3-084-c13
Std Carbon experiment
f1 (ppm)

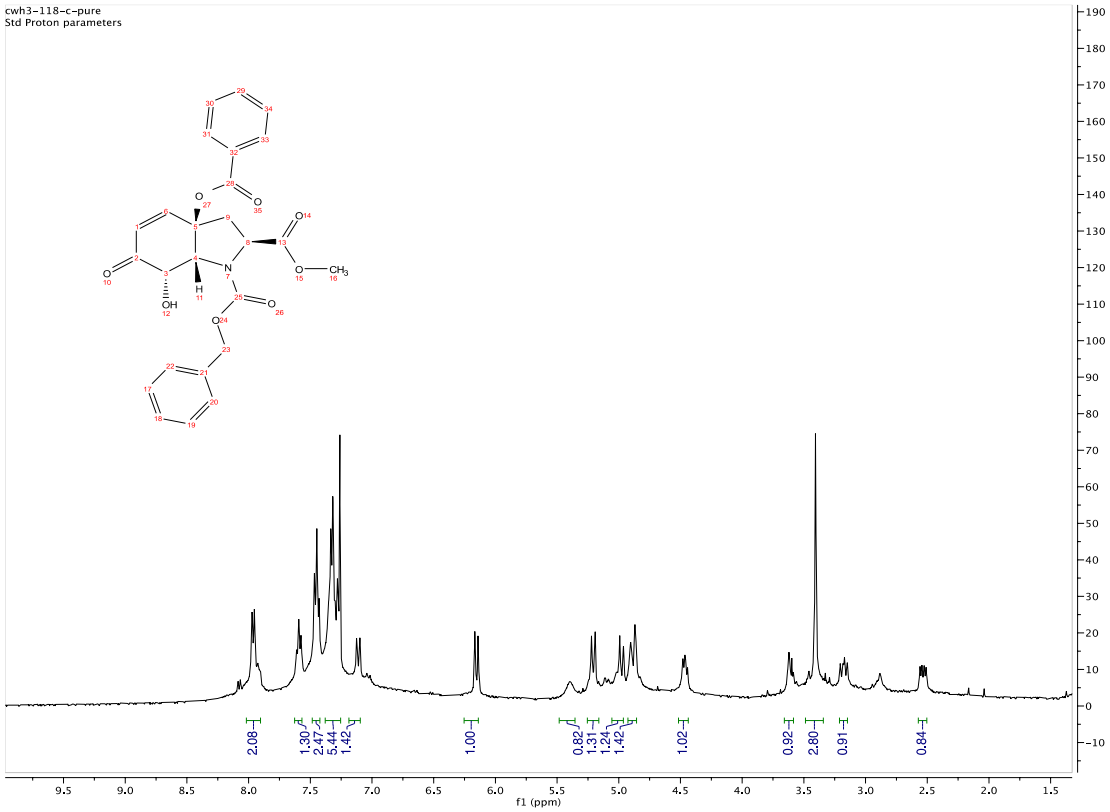
1-benzyl 2-methyl (2S,3aR,7S,7aR)-3a-(benzoyloxy)-7-hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (51)

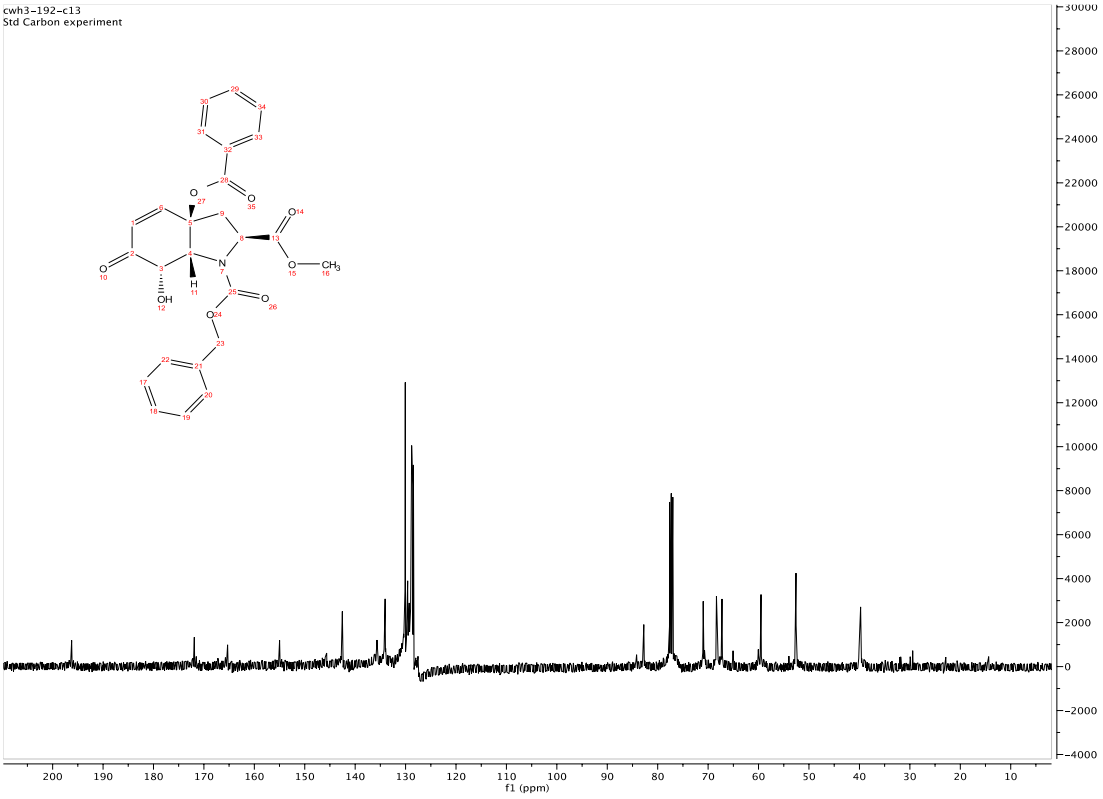


28 **51**

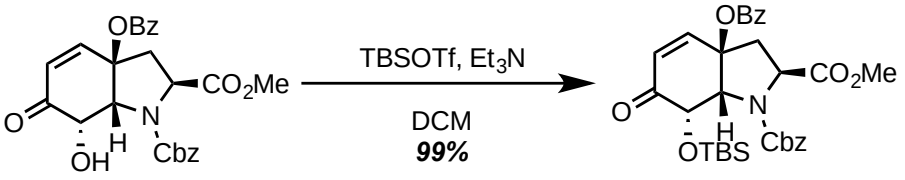
To a stirred solution of compound **28** (700 mg, 1.32 mmol, 1 eq) in acetone (16 mL, 0.0875 M) was added freshly prepared DMDO (30 mL, 1.77 mmol, 1.34 eq) at 0 °C, and then was stirred at 0 °C. After 1 h, the reaction mixture was concentrated in vacuo and the crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **51** as a white foam (472 mg, 83% yield). Rf = 0.43 (silica, EtOAc:hexanes, 1:1); $_{1}$H NMR (400 MHz, Chloroform-d) δ 7.94 (dd, J = 19.6, 7.7 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.38 – 7.25 (m, 5H), 7.11 (d, J = 10.4 Hz, 1H), 6.15 (d, J = 10.3 Hz, 1H), 5.39 (s, 1H), 5.21 (d, J = 12.0 Hz, 1H), 4.99 (s, 1H), 4.93 – 4.86 (m, 1H), 4.46 (dd, J = 9.0, 6.4 Hz, 1H), 3.66 – 3.58 (m, 1H), 3.41 (s, 3H), 3.18 (dd, J = 13.6, 9.1 Hz, 1H), 2.53 (dd, J = 13.6, 6.4 Hz, 1H). $_{13}$C NMR (101 MHz, Chloroform-d) δ 196.22, 171.90, 165.29, 154.98, 142.54, 135.68, 134.05, 130.06, 129.58, 129.27, 128.80, 128.73, 128.58, 128.44, 82.76, 70.98, 68.35, 67.26, 59.52, 52.58, 39.77. Known compound; all the spectral data matches the data reported in reference ***41***.

Notebook Entries:
Procedure – cwh3-118
$_{1}$H – cwh3-118-c-pure
$_{13}$C – cwh3-192-c13


cwh3-118-c-pure
Std Proton parameters
2.08
1.30
2.47
5.44
1.42
1.00
0.82
1.31
1.24
1.42
1.02
0.92
2.80
0.91
0.84
f1 (ppm)


cwh3-192-c13
Std Carbon experiment
f1 (ppm)

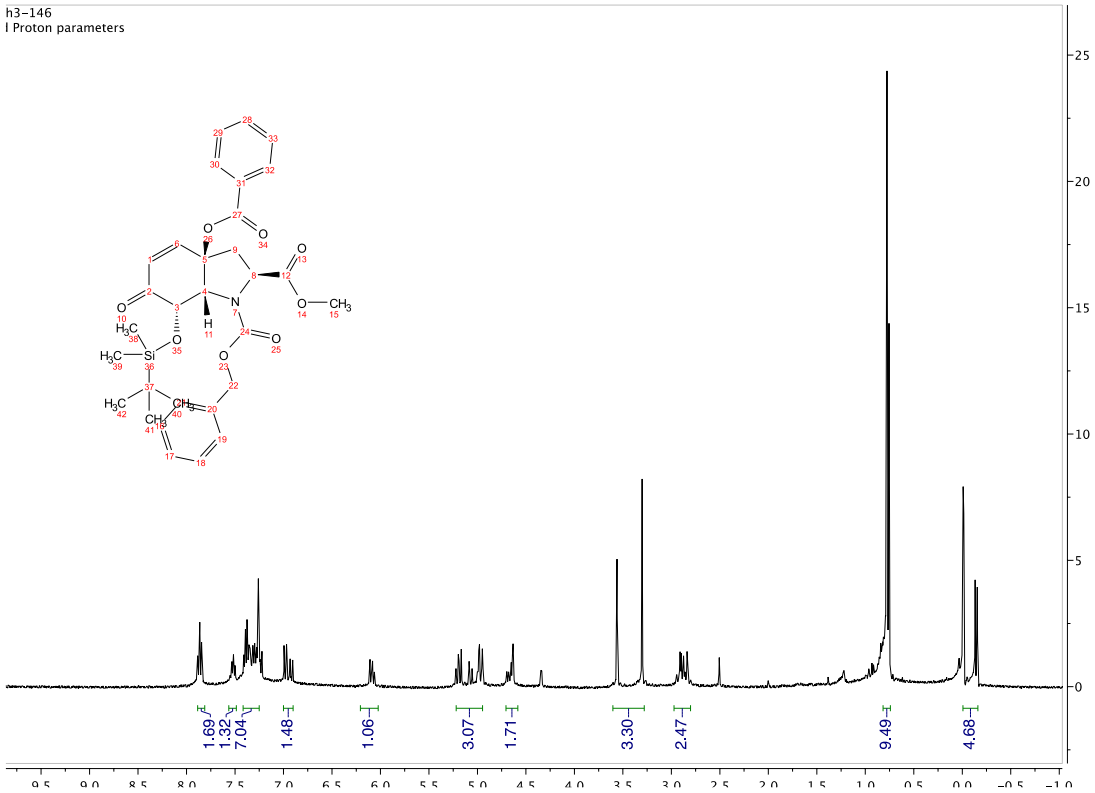
1-benzyl 2-methyl (2S,3aR,7S,7aR)-3a-(benzoyloxy)-7-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (29)

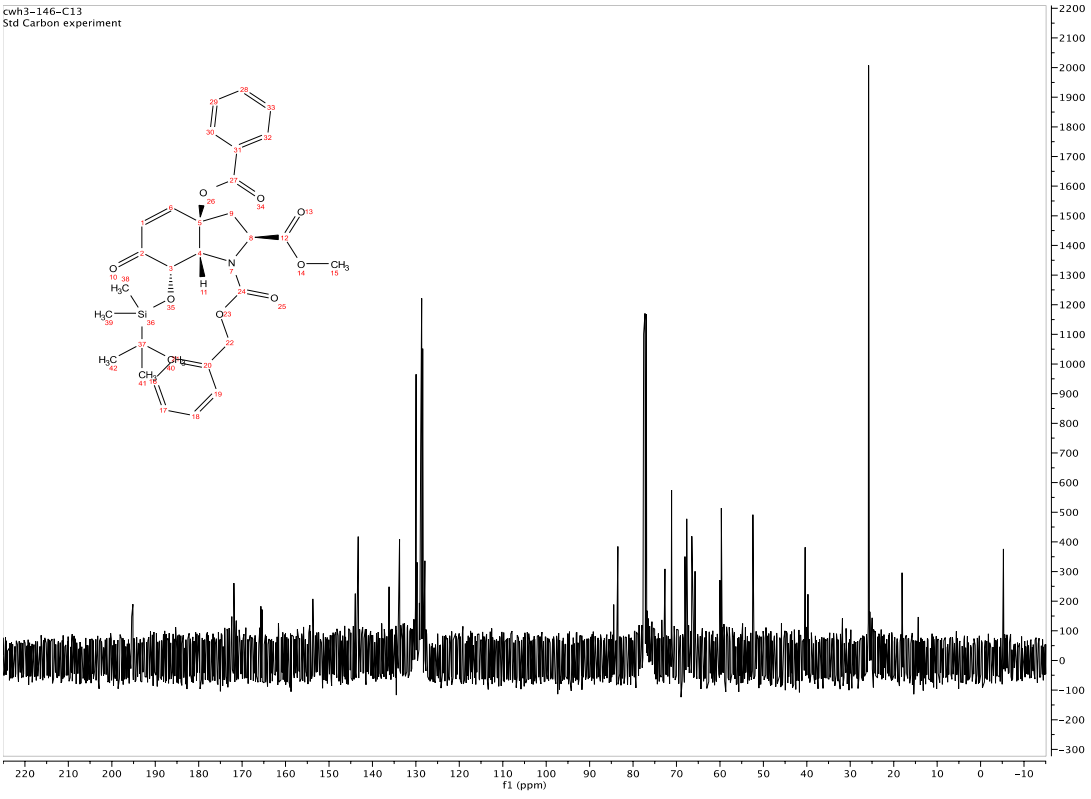


51 **29**

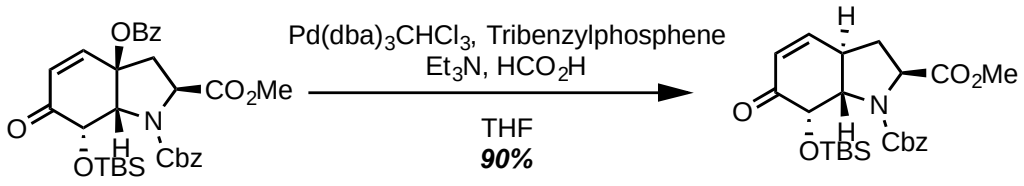
To a stirred solution of compound **51** (240 mg, 0.51 mmol, 1 eq) in DCM (9.0 mL, 0.056 M) was added Et_3N (0.20 mL, 1.70 mmol, 3.3 eq) and TBSOTf (0.13 mL, 0.56 mmol, 1.1 eq), and then was stirred at room temperature. After 4 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:6) to give compound **29** as a white foam (292 mg, 99% yield). Rf = 0.22 (silica, EtOAc:hexanes, 1:6); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-d) δ 7.85 (m, 2H), 7.56 – 7.49 (m, 1H), 7.42 – 7.25 (m, 7H), 7.00 – 6.90 (m, 1H), 6.21 – 6.02 (m, 1H), 5.22 – 4.95 (m, 3H), 4.71 – 4.58 (m, 2H), 3.43 (s+ s', 3H), 2.97 – 2.80 (m, 2H), 0.77 (m, 9H), -0.14 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ (195.14,195.12), (171.90, 170.89), (153.73, 153.70), (143.94, 143.28,) (136.18, 133.79), (133.75, 130.02), (129.95, 129.75), (129.55, 129.53), (128.99, 128.89), (128.70, 128.66), (128.63, 128.61), (128.41, 128.39), (128.36, 127.93), (84.44, 83.49), (72.66, 71.13), (68.04, 67.64), (66.47, 65.73), (60.02, 59.68), (52.59, 52.42), (40.39, 39.73), (25.77, 25.76), (18.08,14.35), (-5.13, -5.26). Known compound; all the spectral data matches the data reported in reference ***41***.

Notebook Entries:
Procedure – cwh3-146
^1H – cwh3-146
^{13}C – cwh3-146-c13


h3-146
l Proton parameters
1.69
1.32
7.04
1.48
1.06
3.07
1.71
3.30
2.47
9.49
4.68


cwh3-146-C13
Std Carbon experiment
f1 (ppm)

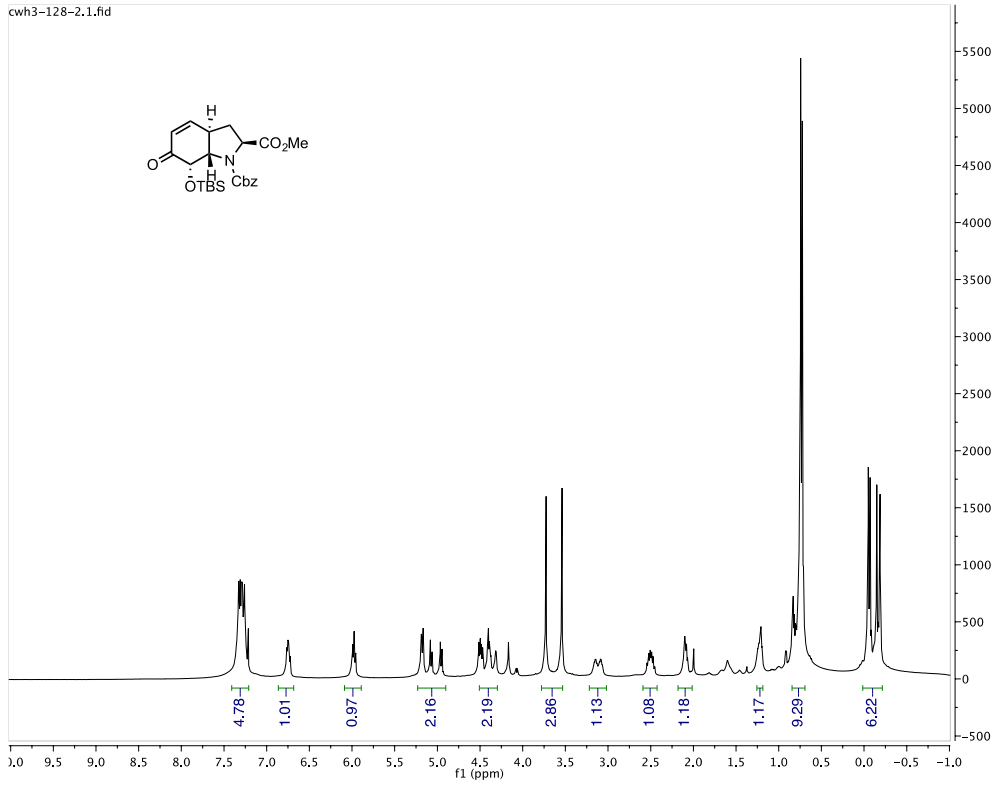
1-benzyl 2-methyl (2S,3aR,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (77)

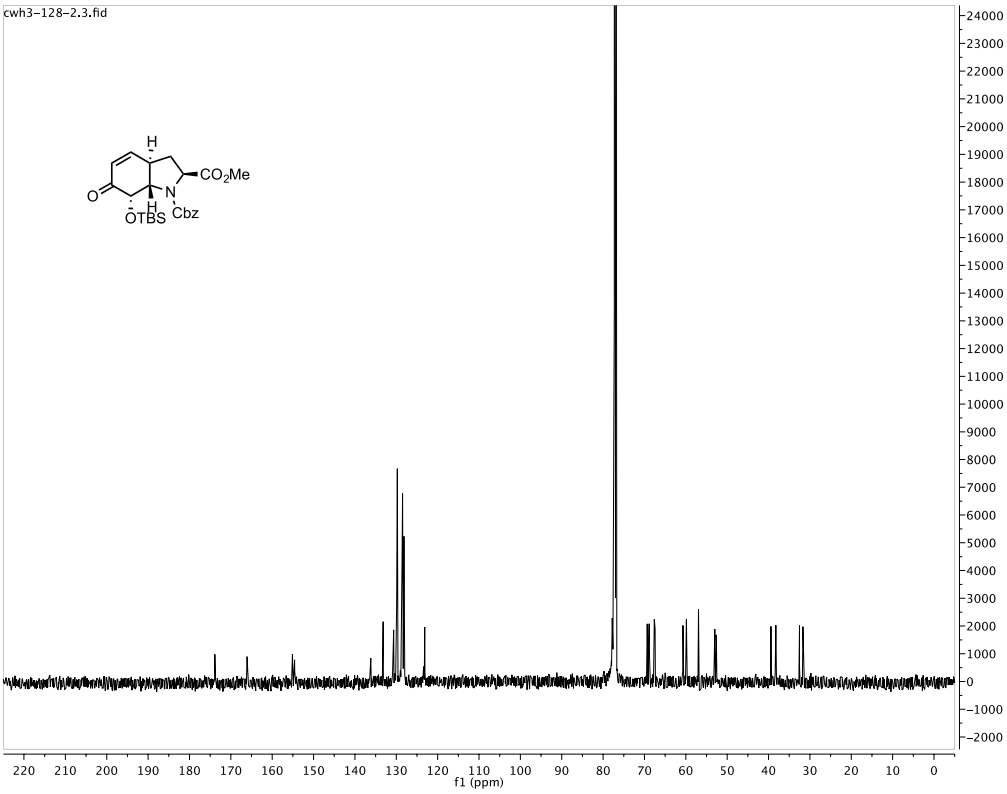


29 **77**

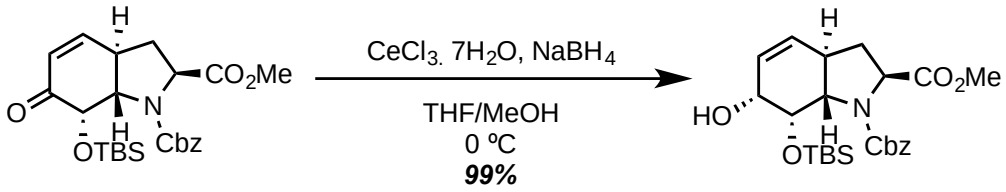
To a stirred solution of compound **29** (150 mg, 0.26 mmol, 1 eq) in THF (1.0 mL, 0.22 M) was added $Pd(dba)_3CHCl_3$ (5 mg, 0.005 mmol, 0.02 eq) and tribenzylphosphene (6 mg, 0.02 mmol, 0.08 eq). After stirring for 1-minute Et_3N (0.13 mL, 0.90 mmol, 3.47 eq) was added immediately followed by the addition of 95% HCO_2H (0.04 mL, 0.90 mmol, 3.47 eq) and the reaction mixture was refluxed. After 12 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc: hexanes, 1:3) to give compound **77** as a light-yellow foam (107 mg, 90% yield). Rf = 0.43 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^1H NMR (600 MHz, Chloroform-d) δ 7.41 – 7.21 (m, 5H), 6.86 – 6.68 (m, 1H), 6.09 – 5.89 (m, 1H), 5.23 – 4.90 (m, 2H), 4.51 – 4.30 (m, 2H), 3.64 (s+ s', 3H), 3.22 – 3.02 (m, 1H), 2.59 – 2.42 (m, 1H), 2.09 (m, 1H), 1.26 – 1.19 (m, 1H), 0.84 – 0.69 (m, 9H), 0.02 – -0.21 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-d) δ (173.85, 173.73), (166.08, 166.07), (155.09, 154.58), (136.14, 133.21), (133.17, 130.62), (129.91, 129.75), (128.61, 128.47), (128.42, 128.25), (128.15, 128.01), (123.36, 123.11), (77.77, 77.75), (69.32, 68.86), (67.60, 67.42), (60.67, 59.86), (56.92,56.91), (52.98, 52.61), (39.42, 38.23), (32.52, 31.68). New compound; Procedure was taken from reference ***40***.

Notebook Entries:
Procedure – cwh3-150 ^1H – cwh3-128 ^{13}C – cwh3-128


cwh3-128-2.1.fid
CO2Me
O
N
H
OTBS
Cbz
4.78
1.01
0.97
2.16
2.19
2.86
1.13
1.08
1.18
1.17
9.29
6.22
f1 (ppm)


cwh3-128-2.3.fid
CO2Me
O
N
H
OTBS
Cbz
f1 (ppm)

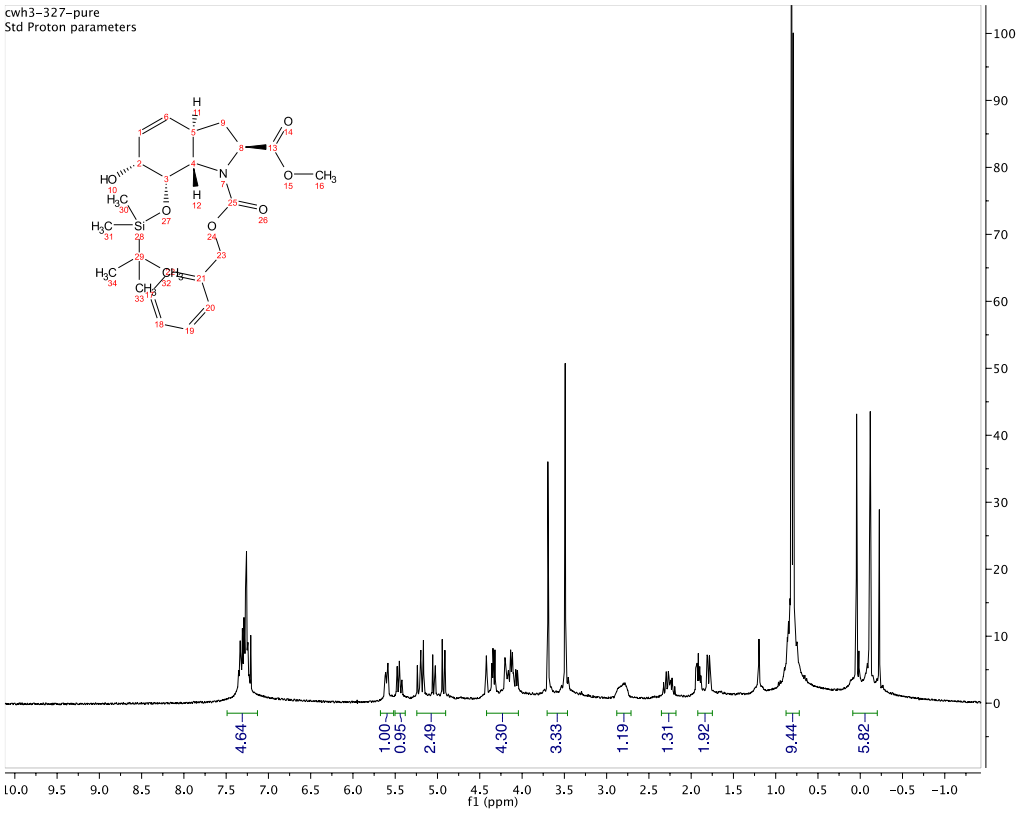
1-benzyl 2-methyl (2S,3aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (83)

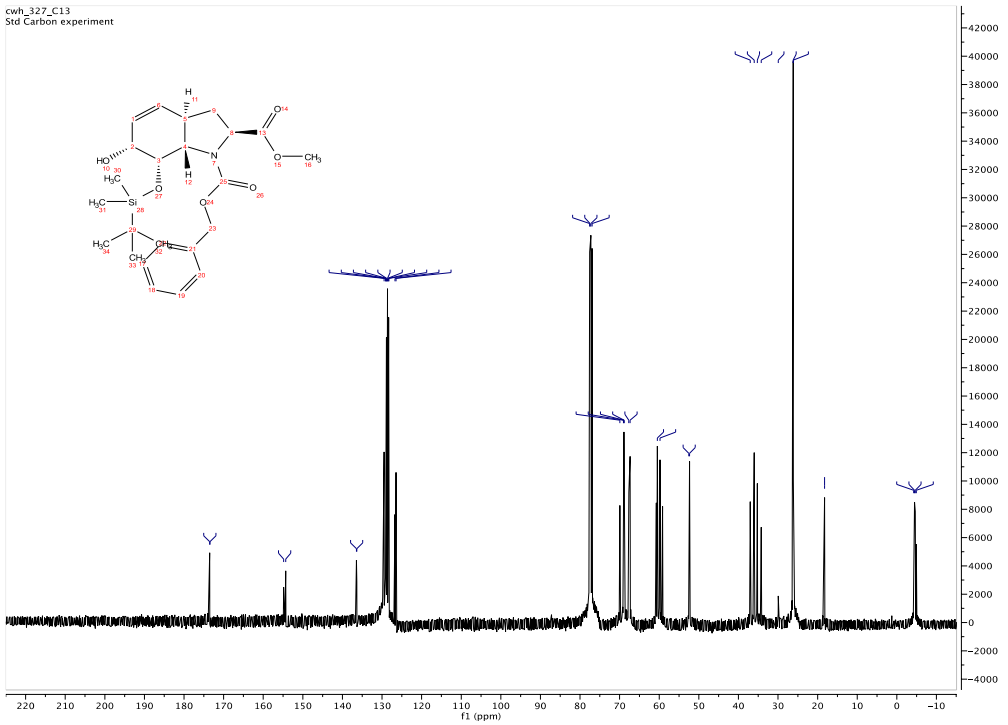


77 **83**

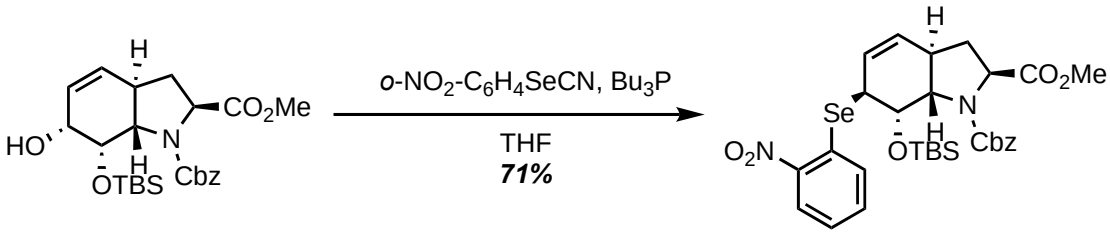
To a stirred solution of compound **77** (30 mg, 0.065 mmol, 1 eq) in THF:MeOH 1:1 (0.75 mL, 0.0875M) was added $CeCl_3 \cdot 7H_2O$ (24 mg, 0.065 mmol, 1 eq) and stirred for 5 mins. Then $NaBH_4$ (2.5 mg, 0.065 mmol, 1 eq) was added portion wise, and then was stirred at 0 °C. After 5 mins, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **83** as a white foam (29 mg, 99% yield). Rf = 0.39 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.49 – 7.13 (m, 5H), 5.67 – 5.52 (m, 1H), 5.50 – 5.38 (m, 1H), 5.24 – 4.90 (m, 2H), 4.39 – 4.11 (m, 4H), 3.59 (s+ s', 3H), 2.35 – 2.18 (m, 1H), 1.85 (m, 2H), 0.80 (m, 9H), -0.11 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ (173.51, 173.44), (154.85, 154.32), (136.45, 136.37), (129.48, 129.10,) (129.06, 128.87), (128.85, 128.62), (128.58, 128.35), (128.33, 128.29), (126.73, 126.45), (69.94, 69.02), (68.90, 68.86), (67.68, 67.35), (60.74, 60.48), (59.80, 59.16), (52.53, 52.34), (37.02, 36.02), (35.23, 34.24), (26.21, 26.17), (18.25, 18.24), (-4.26, -4.92). New compound; Procedure was taken from reference ***41***.

Notebook Entries:
Procedure – cwh3-327 ^{1}H – cwh3-327-pure ^{13}C – cwh3-327-c13


cwh3-327-pure
Std Proton parameters
4.64
1.00
0.95
2.49
4.30
3.33
1.19
1.31
1.92
9.44
5.82
f1 (ppm)


cwh_327_C13
Std Carbon experiment
f1 (ppm)

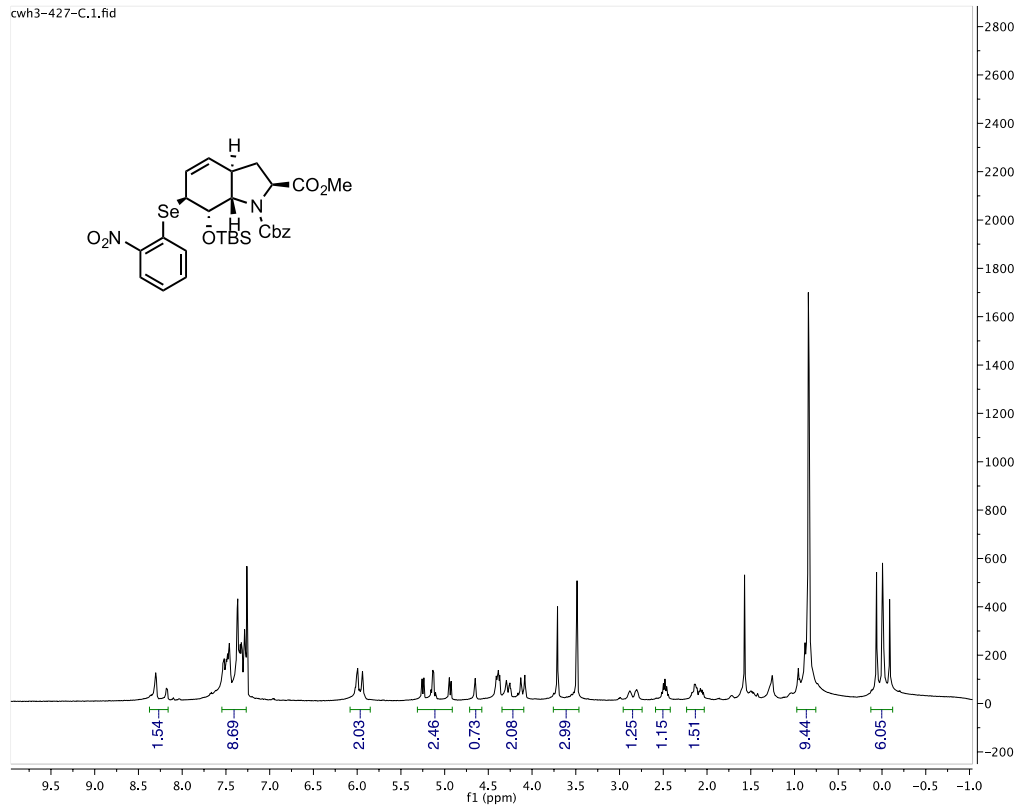
1-benzyl 2-methyl (2S,3aR,6S,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-((2-nitrophenyl)selanyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (98)

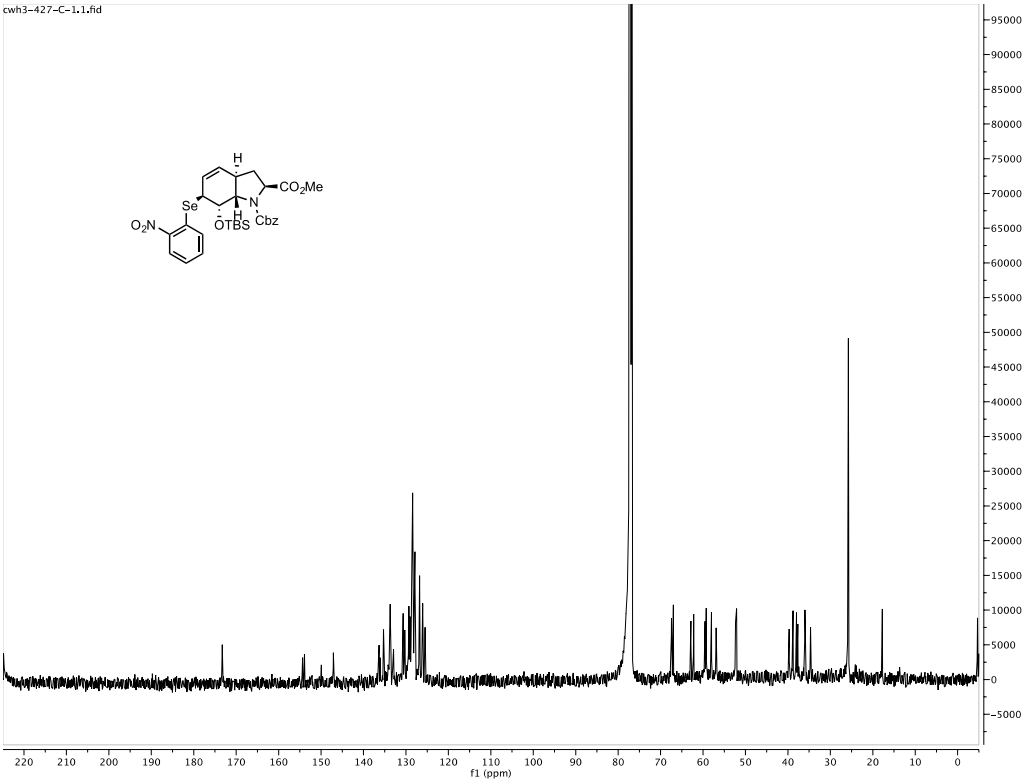


83 **98**

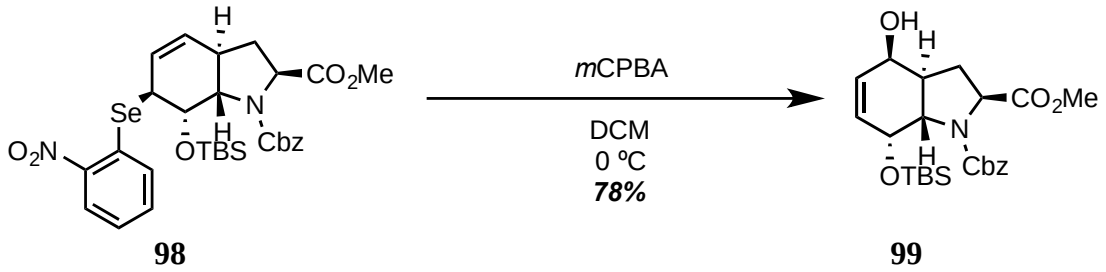
To a stirred solution of compound **83** (60 mg, 0.130 mmol, 1 eq) in THF (1.3 mL, 0.1 M) was added *o*-NO_2-C_6H_4SeCN (59 mg, 0.260 mmol, 2 eq). Then Bu_3P (0.07 mL, 0.286 mmol, 2.2 eq) was added drop wise and the reaction mixture was refluxed. After 16 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:6) to give compound **98** as a white foam (58 mg, 71% yield). Rf = 0.57 (silica, EtOAc:hexanes, 1:6); Rotamers were shown in ( ). ^{1}H NMR (600 MHz, Chloroform-d) δ 8.37 – 7.27 (m, 10H), 5.97 (m, 2H), 5.31 – 4.91 (m, 2H), 4.66 (m, 1H), 4.34 – 4.09 (m, 2H), 3.60 (s+ s', 3H), 2.96 – 2.74 (m, 1H), 2.48 (ddd, J = 22.3, 12.5, 9.5 Hz, 1H), 2.23 – 2.03 (m, 1H), 0.97 – 0.76 (m, 9H), -0.01 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-d) δ (173.30, 173.16), (154.35, 153.92), (149.33, 147.11), (136.33, 135.29), (133.84, 133.73), (133.65, 132.97), (130.68, 130.29), (129.33, 129.07), (128.68, 128.58), (128.42, 128.25), (128.05, 127.98), (127.90, 126.84), (126.07, 125.51), (67.44, 67.00), (62.88, 62.20), (59.51, 59.24), (58.01, 56.90), (52.33, 52.10), (39.70, 38.82), (37.99, 37.67), (35.98, 34.65), (25.75, 25.76), (17.76, 17.75) (-4.67, -4.66). New compound; Procedure was taken from reference ***52***.

Notebook Entries:
Procedure – cwh3-427 ^{1}H – cwh3-427-C ^{13}C – cwh3-427-C


cwh3-427-C.1.fid
H
CO2Me
Se
N
O2N
H
OTBS
Cbz
1.54
8.69
2.03
2.46
0.73
2.08
2.99
1.25
1.15
1.51
9.44
6.05
f1 (ppm)


cwh3-427-C-1.1.fid
H
CO2Me
Se
N
O2N
H
OTBS
Cbz
f1 (ppm)

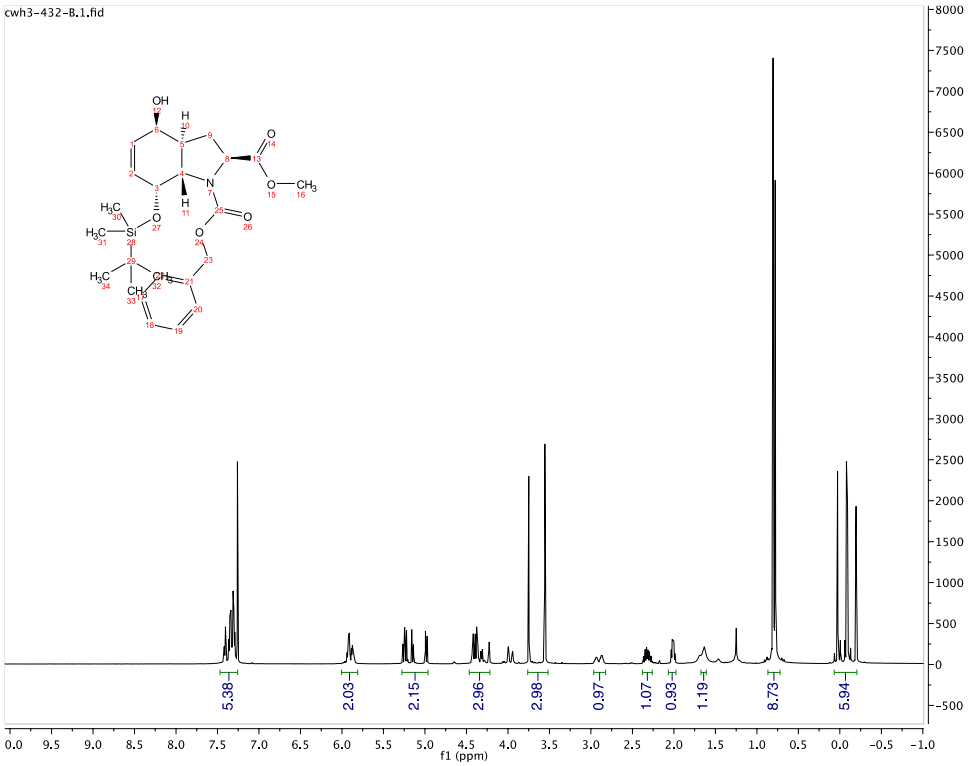
1-benzyl 2-methyl (2*S*,3a*S*,4*R*,7*R*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (99)

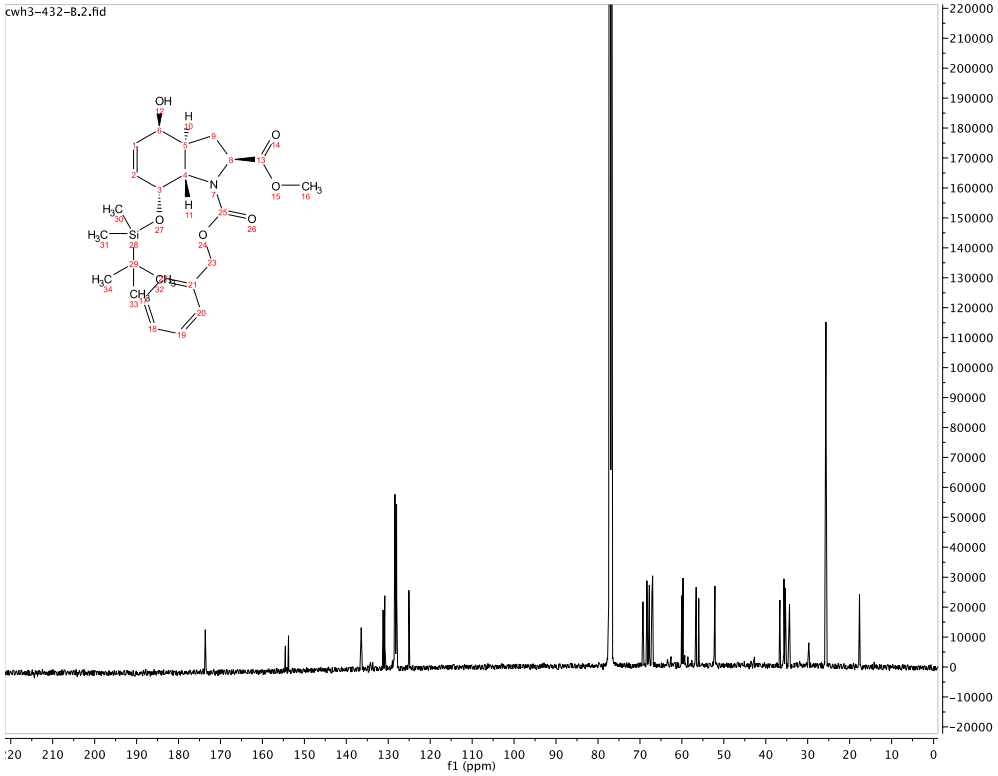


98 **99**

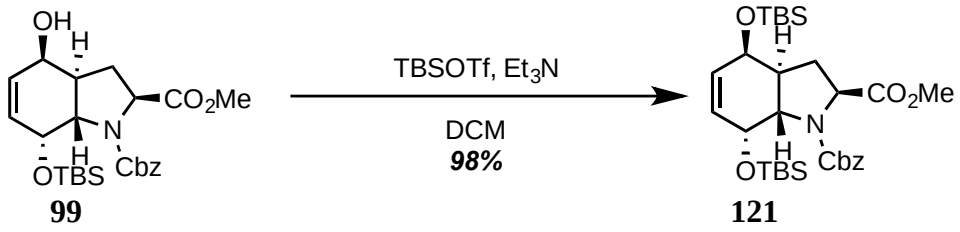
To a stirred solution of compound **98** (20 mg, 0.031 mmol, 1 eq) in DCM (1.2 mL, 0.025 M) was added *m*CPBA (8.3 mg, 0.037 mmol, 1.2 eq) in DCM (0.4 mL, 0.10 M) at -78 °C, and then was stirred at 0 °C. After 5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **99** as a white foam (11.1 mg, 78% yield). Rf = 0.45 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.47 – 7.26 (m, 5H), 6.01 – 5.81 (m, 2H), 5.28 – 4.96 (m, 2H), 4.47 – 4.22 (m, 3H), 3.65 (s +s', 3H), 2.97 – 2.82 (m, 1H), 2.32 (m, 1H), 2.01 (m, 1H), 1.70-1.63 (m, 1H), 0.87 – 0.72 (m, 9H), 0.07 – -0.20 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-d) δ (173.62, 173.56), (154.54, 153.79), (136.48, 136.44), (131.23, 130.83), (128.52, 128.39), (128.26, 128.09), (128.03, 127.99), (125.08, 124.93), (69.44, 69.28), (68.34, 67.91), (67.75, 67.13), (60.03, 59.73), (56.60, 55.98), (52.30, 52.11), (36.63, 35.89), (34.35, 29.73), (25.65, 25.62), (17.65, 17.64). New compound; Procedure was taken from reference ***52***.

Notebook Entries:
Procedure – cwh3-432
^{1}H – cwh3-432-B
^{13}C – cwh3-432-B


cwh3-432-B.1.fid
5.38
2.03
2.15
2.96
2.98
0.97
1.07
0.93
1.19
8.73
5.94
f1 (ppm)


cwh3-432-B.2.fid
f1 (ppm)

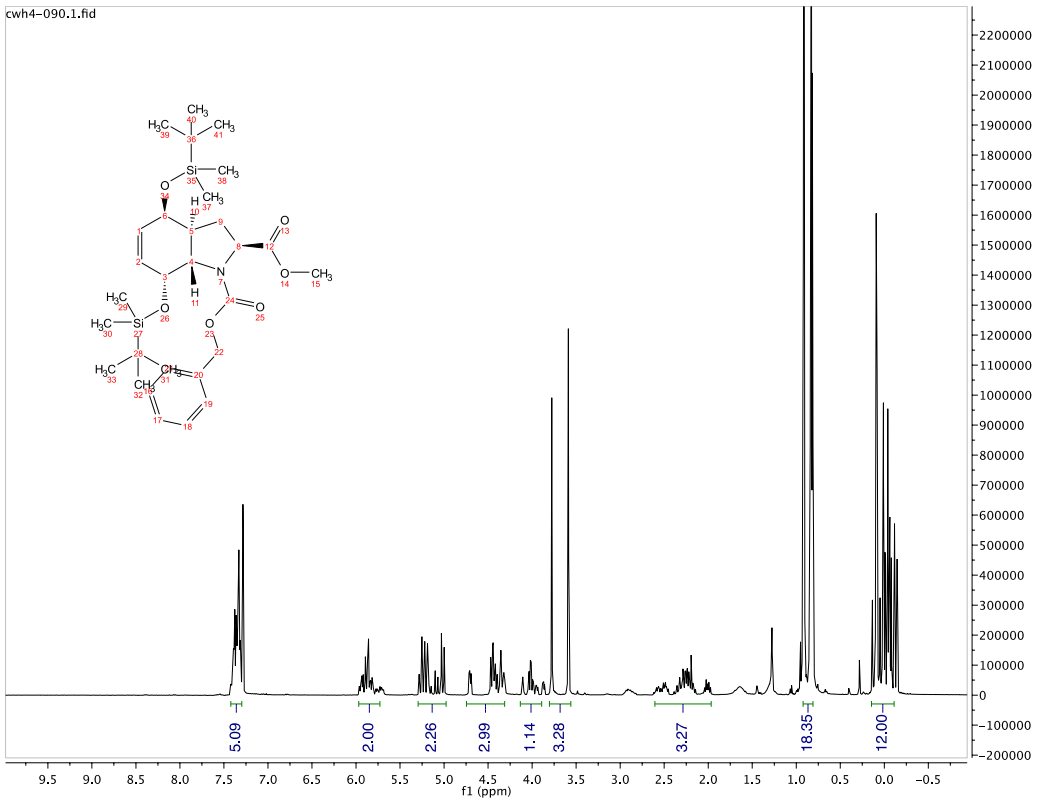
1-benzyl 2-methyl (2*S*,3a*S*,7*R*,7a*S*)-4,7-bis((*tert*-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (121)

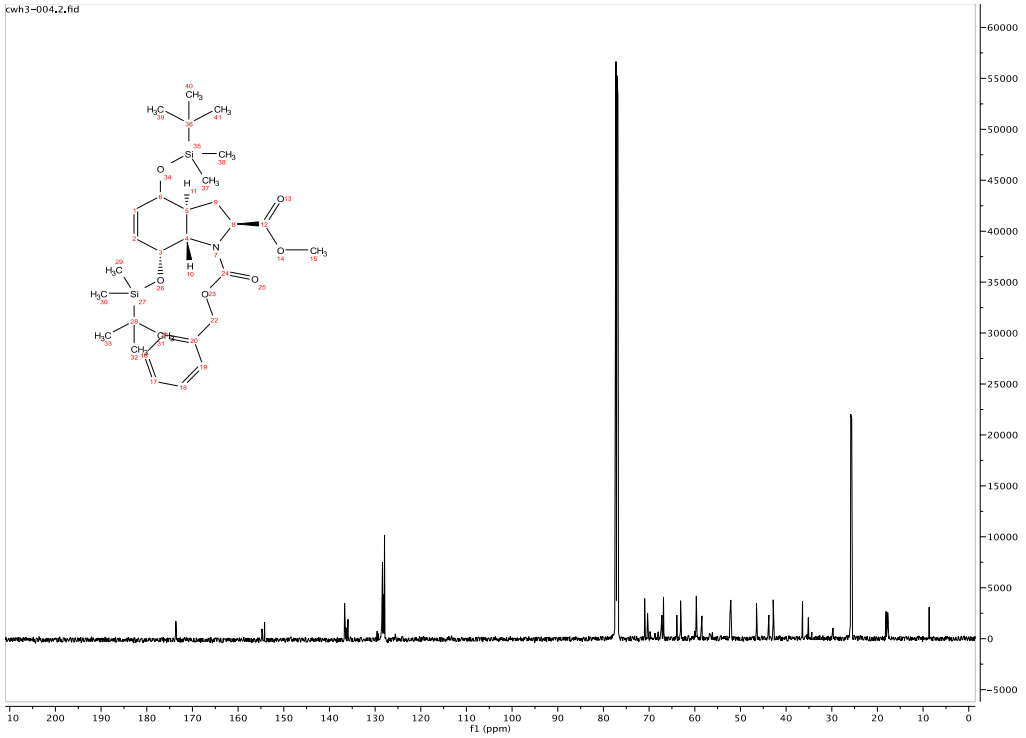


99 **121**

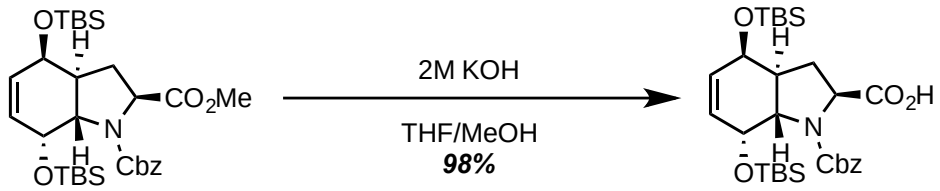
To a stirred solution of compound **99** (22 mg, 0.0476 mmol, 1 eq) in DCM (0.5 mL, 0.10 M) was added Et_3N (0.013 mL, 0.0952 mmol, 2 eq) and TBSOTf (0.013 mL, 0.0571 mmol, 1.2 eq), and then was stirred at room temperature. After 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:6) to give compound **121** as a white foam (26.7 mg, 98% yield). Rf = 0.44 (silica, EtOAc:hexanes, 1:6); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.27 (m, 5H), 5.94 – 5.70 (m, 2H), 5.27 – 4.95 (m, 2H), 4.72 – 4.29 (m, 3H), 4.11 – 3.87 (m, 1H), 3.75 + 3.56 (s +s', 3H), 2.58 – 1.94 (m, 3H), 0.90 – 0.79 (m, 18H), 0.12 – -0.13 (m, 12H).l ^{13}C NMR (151 MHz, Chloroform-d) δ (173.64, 173.50), (154.77, 154.21), (136.67, 136.53), (136.37, 135.93), (129.55, 128.64), (128.53, 128.39), (128.26, 128.11), (127.94, 127.75), (70.98, 70.33), (68.02, 67.38), (67.22, 66.86), (63.92, 63.12), (59.73, 58.43), (52.27, 52.10), (43.77, 42.83), (36.40, 35.13), (25.85, 25.70, 25.64), (18.12, 17.74), (8.69, 8.68), (-4.55, -4.58). New compound; Procedure was taken from reference ***39***.

Notebook Entries:
Procedure – cwh4-004
^1H – cwh4-090
^{13}C – cwh4-004


cwh4-090.1.fid
5.09
2.00
2.26
2.99
1.14
3.28
3.27
18.35
12.00
f1 (ppm)


cwh3-004.2.fid
f1 (ppm)

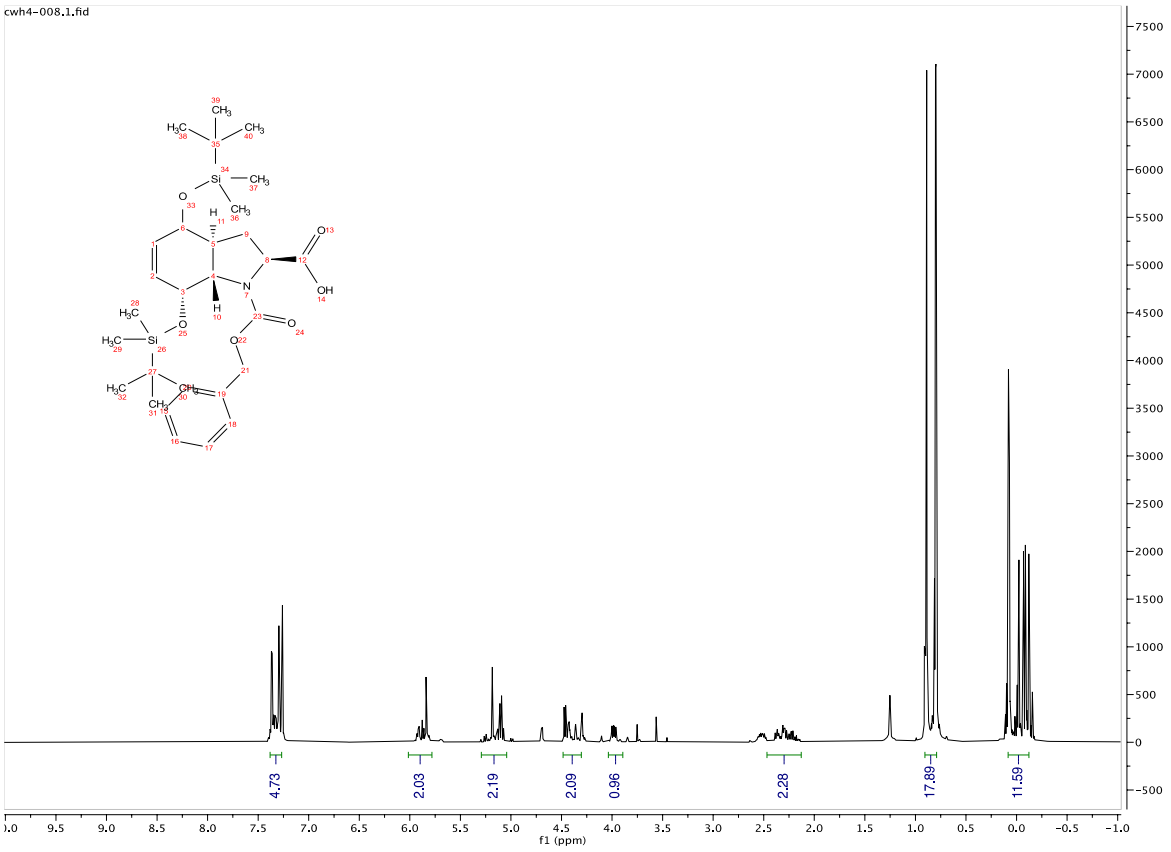
(2*S*,3a*S*,7*R*,7a*S*)-1-((benzyloxy)carbonyl)-4,7-bis((*tert*-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1*H*-indole-2-carboxylic acid (122)



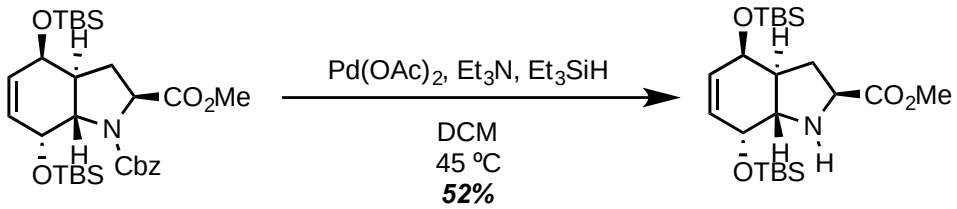
121 **122**

To a stirred solution of compound **121** (27 mg, 0.0467 mmol, 1 eq) in THF:MeOH 1:1 (1.0 mL, 0.05 M) was added 2M KOH (0.5 mL, 0.10 M), and then was stirred at room temperature. After 1 h, the reaction was acidified to pH 2 with 1M HCl and organic layers were extracted with EtOAc (× 3). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo to give compound **122** as a white foam (25.5 mg, 98% yield). Rf = 0.12 (silica, EtOAc:hexanes, 6:1); [Rotamers were shown in ( )]. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.38 – 7.27 (m, 5H), 6.01 – 5.78 (m, 2H), 5.29 – 5.04 (m, 2H), 4.48 – 4.30 (m, 2H), 3.98 (ddd, J = 16.8, 9.2, 3.6 Hz, 1H), 2.47 – 2.13 (m, 2H), 0.92 – 0.79 (m, 18H), 0.12 – -0.12 (m, 12H). Directly used in the next reaction without further purification. New compound; Procedure was taken from reference ***39***.

Notebook Entries:
Procedure – cwh4-008
^{1}H – cwh4-008


cwh4-008.1.fid
4.73
2.03
2.19
2.09
0.96
2.28
17.89
11.59
f1 (ppm)

Methyl (2S,3aS,4R,7R,7aS)-4,7-bis((tert-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-2-carboxylate (123)

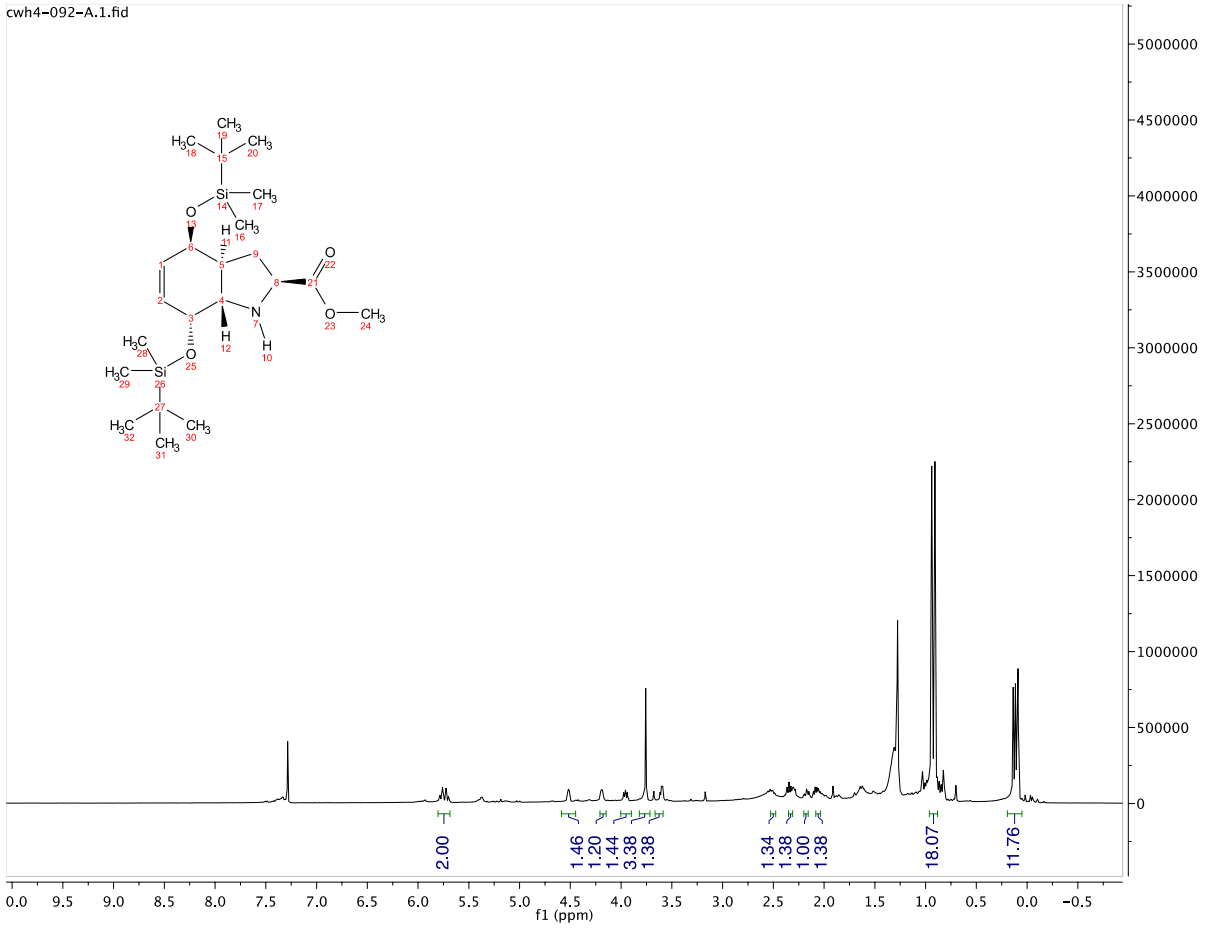


121 **123**

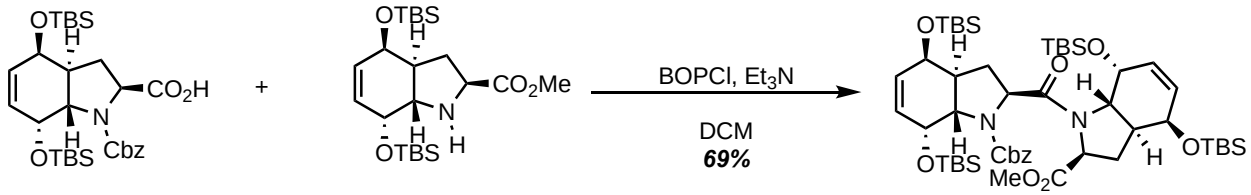
To a stirred solution of compound **121** (31 mg, 0.054 mmol, 1 eq) in DCM (0.54 mL, 0.10 M) was added $Pd(OAc)_2$ (29 mg, 0.130 mmol, 2.4 eq) and Et_3N (0.04 mL, 0.260 mmol, 4.8 eq), was and stirred for 5 mins at 45 °C. Then Et_3SiH (0.18 mL, 1.08 mmol, 20 eq) was added drop wise, and then was stirred at 45 °C. After 20 h, the reaction was filtered through celite pad and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **123** as an oily residue (12 mg, 52% yield). Rf = 0.35 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-*d*) δ 5.80 – 5.69 (m, 2H), 4.52 (m, 1H), 4.21 – 4.15 (m, 1H), 3.96 (m, 1H), 3.76 (s, 3H), 3.67 – 3.59 (m, 1H), 2.50 (m, 1H), 2.35 – 2.31 (m, 1H), 2.20 – 2.16 (m, 1H), 2.08 – 2.04 (m, 1H), 0.92 (m, 18H), 0.19 – 0.05 (m, 12H). New compound; Procedure was taken from reference ***39***.

Notebook Entries:

Procedure – cwh4-092
^1H – cwh4-092


cwh4-092-A.1.fid
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
2.00
1.46
1.20
1.44
3.38
1.38
1.34
1.38
1.00
1.38
18.07
11.76
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

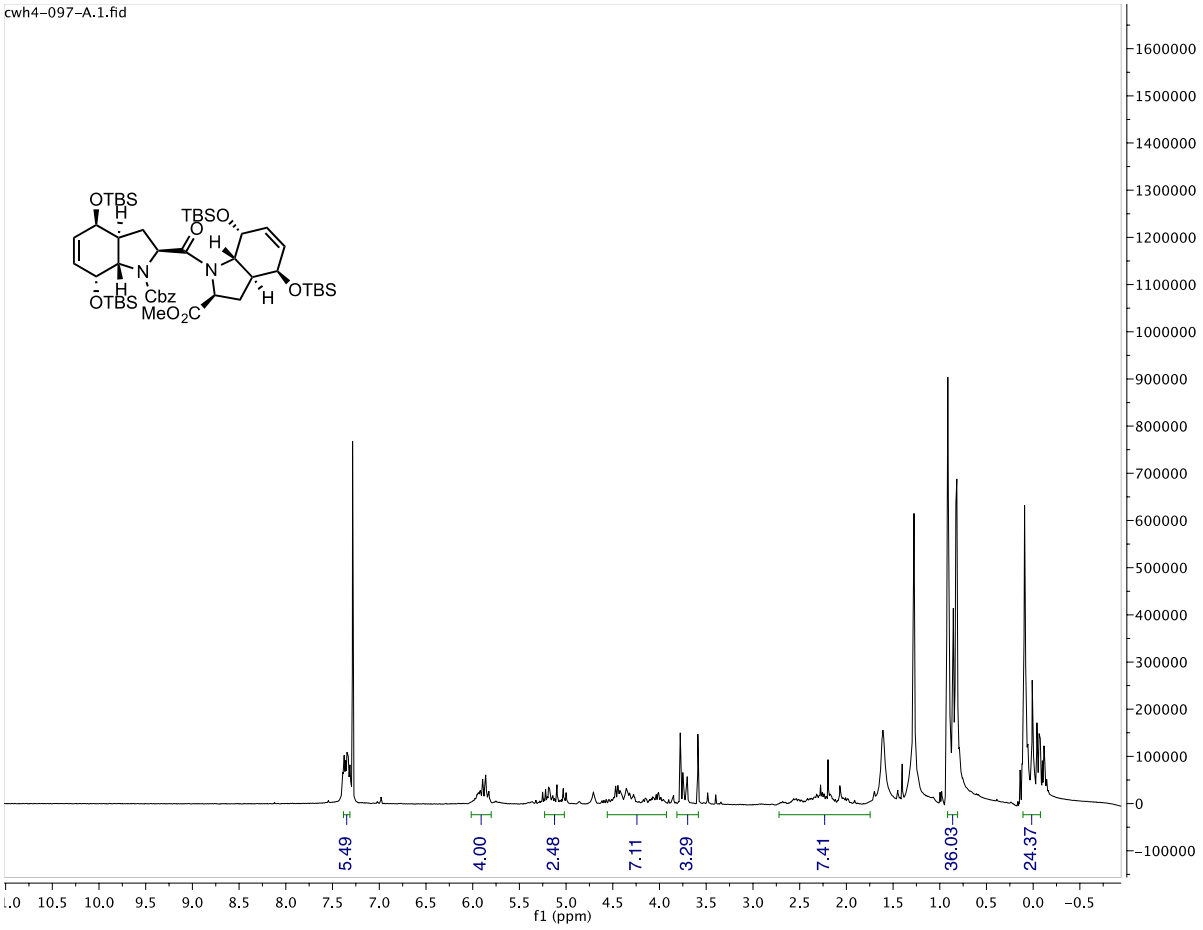
Benzyl (2S,3aS,4R,7R,7aS)-2-((2S,3aS,4R,7R,7aS)-4,7-bis((tert-butyldimethylsilyl)oxy)-2-(methoxycarbonyl)-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carbonyl)-4,7-bis((tert-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carboxylate (124)



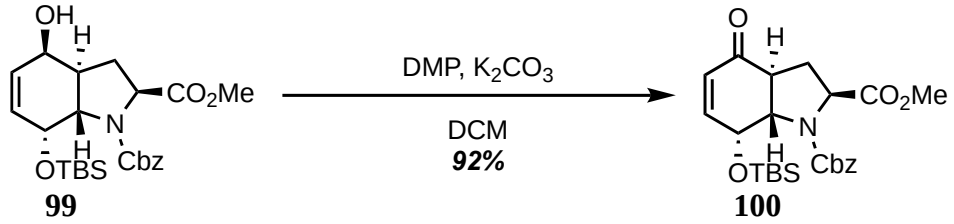
122 **123** **124**

To a stirred solution of carboxylic acid **122** (11 mg, 0.02 mmol, 1 eq) and amine **123** (9 mg, 0.02 mmol, 1 eq) in DCM (0.20 mL, 0.10 M) was cooled to 0 ºC. Then Et_3N (0.008 mL, 0.06 mmol, 3.0 eq) was added and stirred. After 5 mins, BOPCl (5 mg, 0.02 mmol, 1 eq) was added portion wise, and then was stirred at room temperature. After 20 h, the reaction was concentrated in vacuo and the crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 3:1) to give compound **124** as a white foam (13.5 mg, 69% yield). Rf = 0.62 (silica, EtOAc:hexanes, 3:1); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.35 (m, 5H), 5.90 (m, 4H), 5.23 – 5.02 (m, 2H), 4.56 – 3.93 (m, 7H), 3.81 – 3.58 (s+ s', 3H), 2.72 – 1.75 (m, 7H), 0.92 – 0.81 (m, 36H), 0.11 – -0.08 (m, 24H). New compound; Procedure was taken from reference ***39***.

Notebook Entries:
Procedure – cwh4-097
^1H – cwh4-097-A


cwh4-097-A.1.fid
OTBS
H
TBSO
O
H
N
H
OTBS
Cbz
MeO2C
N
H
OTBS
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
−100000
5.49
4.00
2.48
7.11
3.29
7.41
36.03
24.37
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
f1 (ppm)

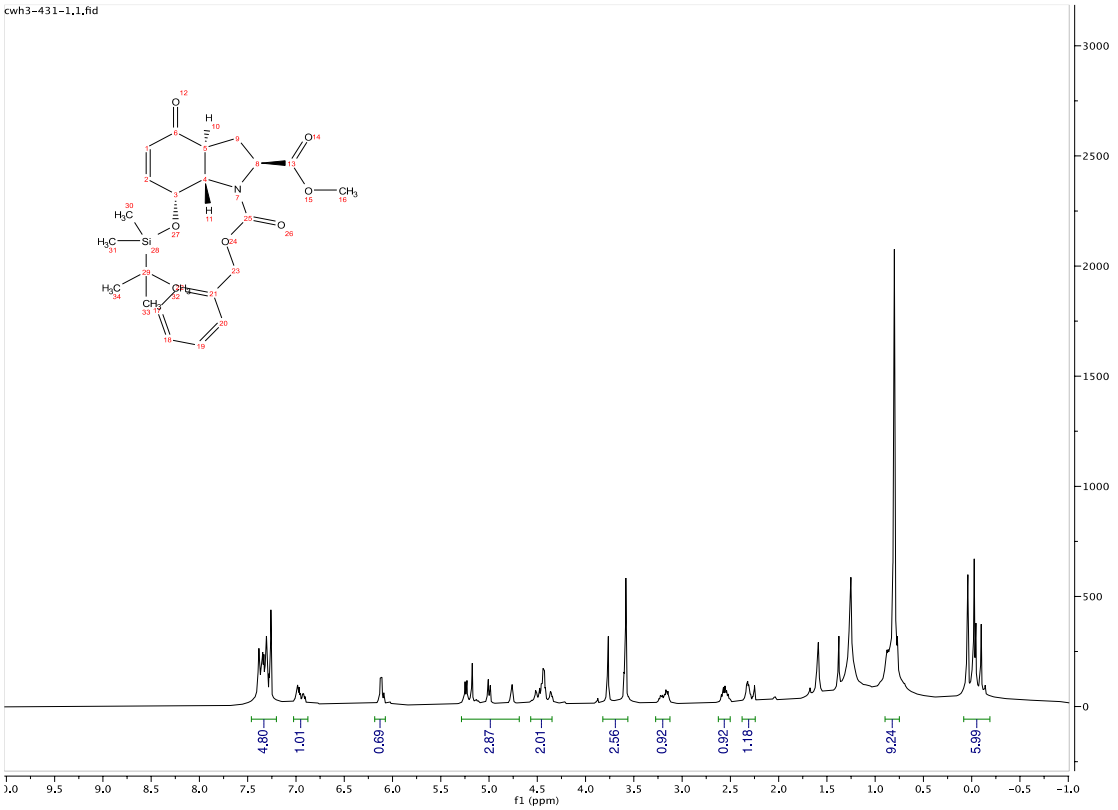
1-benzyl 2-methyl (2*S*,3a*S*,7*S*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-4-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (100)

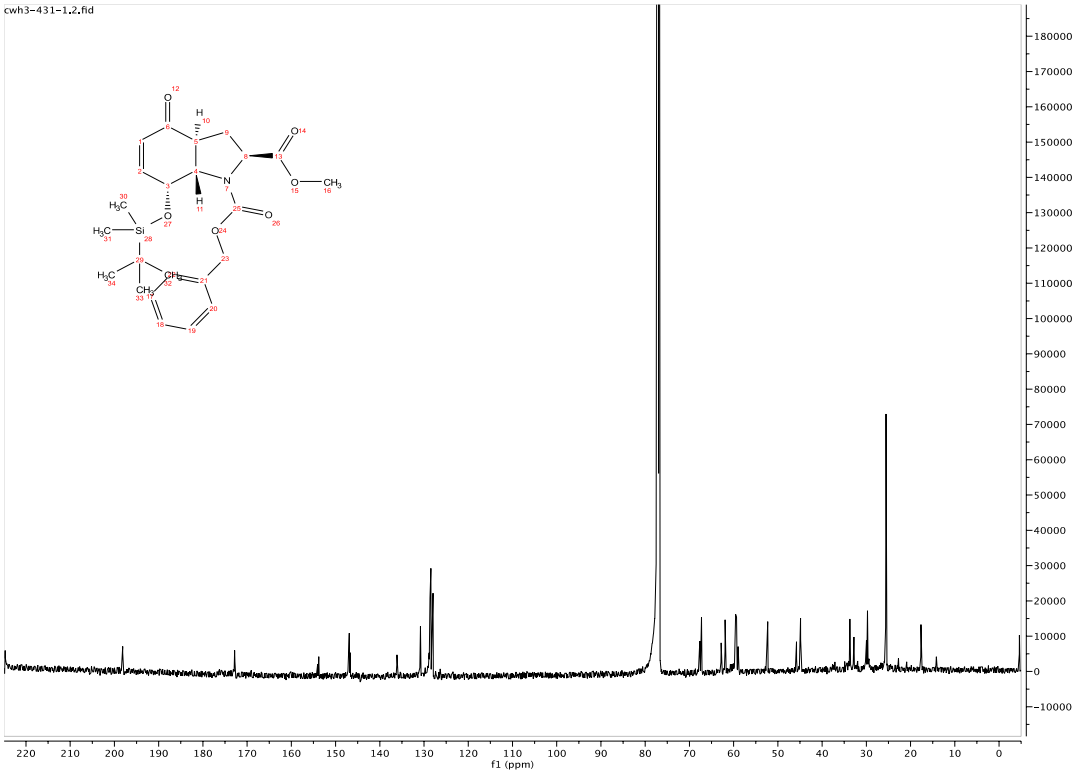


99 **100**

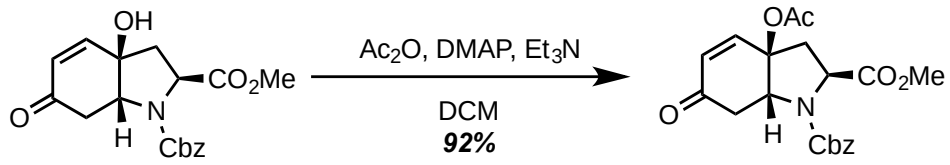
To a stirred solution of compound **99** (10 mg, 0.022 mmol, 1 eq) in DCM (0.23 mL, 0.10 M) was added DMP (14 mg, 0.033 mmol, 1.5 eq) and K_2CO_3 (7.7 mg, 0.056 mmol, 2.6 eq), and then was stirred at room temperature. After 4 h, the reaction was diluted with H_2O and organic layer was extracted with DCM (5 mL × 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **100** as a white foam (9.2 mg, 92% yield). Rf = 0.52 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (600 MHz, Chloroform-d) δ 7.46 – 7.20 (m, 5H), 7.03 – 6.88 (m, 1H), 6.11 (m, 1H), 5.29 – 4.69 (m, 3H), 4.57 – 4.35 (m, 2H), 3.82 + 3.56 (s+ s', 3H), 3.27 – 3.13 (m, 1H), 2.62 – 2.50 (m, 1H), 2.38 – 2.24 (m, 1H), 0.81 (m, 9H), 0.08 – -0.19 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-d) δ (198.13, 198.12), (172.82, 172.81), (153.79, 153.78), (146.90, 146.68), (136.11, 135.98), (130.72, 130.70), (128.66, 128.58), (128.45, 128.13), (128.03, 127.98), (67.66, 67.26), (62.84, 61.93), (59.63, 58.97), (52.49, 52.30), (45.79, 44.87), (33.72, 32.81), (29.97, 29.73), (25.56, 22.74), (17.66, 14.17), (-4.62, -4.61). New compound; Procedure was taken from reference ***39***.

Notebook Entries:
Procedure – cwh3-431
^{1}H – cwh3-431
^{13}C – cwh3-431


cwh3-431-1.1.fid
4.80
1.01
0.69
2.87
2.01
2.56
0.92
0.92
1.18
9.24
5.99
f1 (ppm)


cwh3-431-1.2.fid
f1 (ppm)

1-benzyl 2-methyl (2*S*,3a*R*,7a*R*)-3a-acetoxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (56)

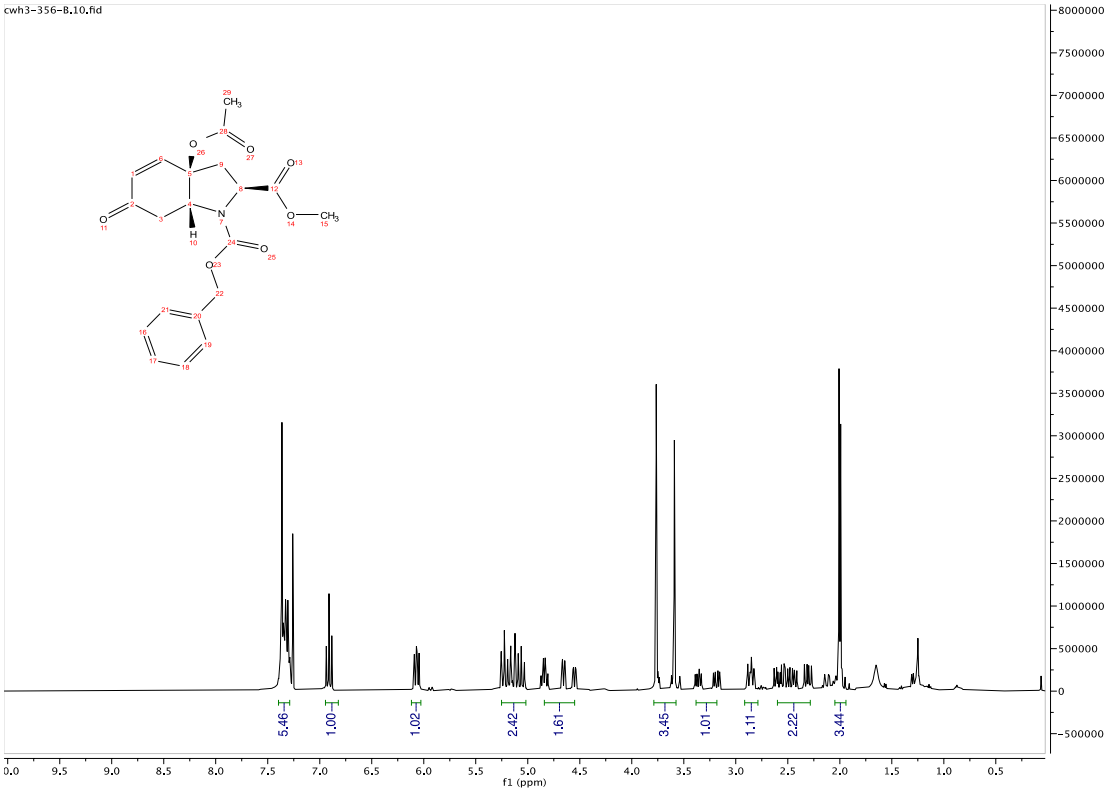


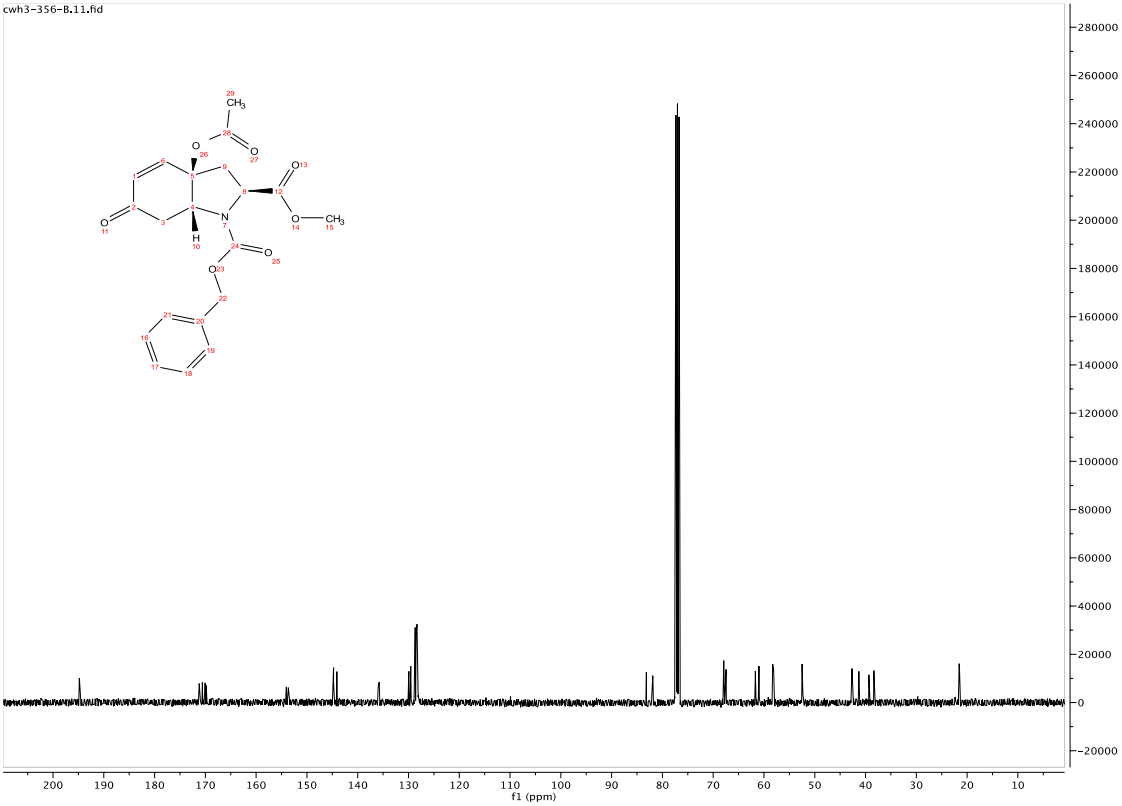
14 **56**

To a stirred solution of compound **14** (800 mg, 2.55 mmol, 1 eq) in DCM (26 mL, 0.10 M) was added acetic anhydride (0.48 mL, 5.10 mmol, 2 eq), DMAP (62 mg, 0.51 mmol, 0.2 eq), and Et_3N (1.1 mL, 7.66 mmol, 3.0 eq), and then was stirred at room temperature. After 15 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:1) to give compound **56** as a light-yellow foam (908 mg, 92% yield). Rf = 0.30 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-d) δ 7.40 – 7.29 (m, 5H), 6.91 (m, 1H), 6.12 – 6.03 (m, 1H), 5.25 – 5.02 (m, 2H), 4.84 – 4.55 (m, 2H), 3.76 + 3.54 (s+ s', 3H), 3.38 – 3.18 (m, 1H), 2.91 – 2.79 (m, 1H), 2.60 – 2.28 (m, 2H), 2.00 (s+ s', 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ (194.89, 194.81), (171.20, 170.59), (170.04, 169.83), (154.06, 153.67), (144.75, 144.11), (135.97, 135.76), (129.93, 129.55), (128.67, 128.49), (128.41, 128.32), (128.22, 128.14), (83.15, 81.89), (67.91, 67.47), (61.68, 60.99), (58.29, 58.10), (52.50, 52.33), (42.68, 41.31), (39.34, 38.35), (21.55, 21.47). New compound; Procedure was taken from reference ***38***.

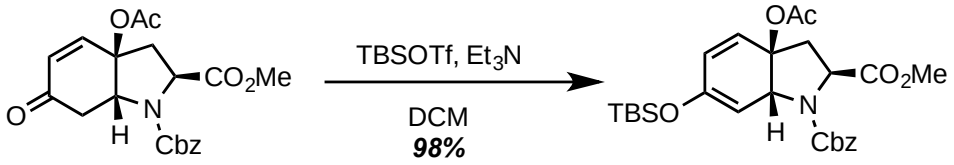
Notebook Entries:

Procedure – cwh4-037
^1H – cwh3-356-B
^{13}C – cwh3-356-B


cwh3-356-B.10.fid
5.46
1.00
1.02
2.42
1.61
3.45
1.01
1.11
2.22
3.44
f1 (ppm)


cwh3-356-B.11.fid
f1 (ppm)

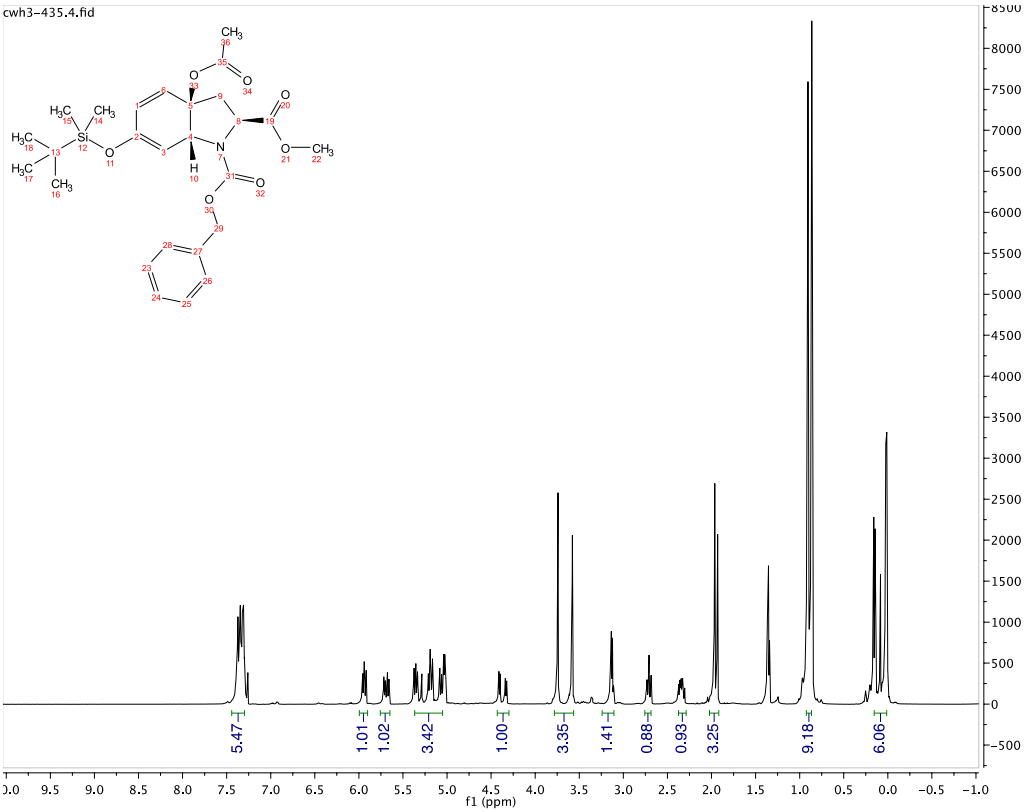
1-benzyl 2-methyl (2*S*,3a*R*,7a*R*)-3a-acetoxy-6-((*tert*-butyldimethylsilyl)oxy)-2,3,3a,7a-tetrahydro-1*H*-indole-1,2-dicarboxylate (62)

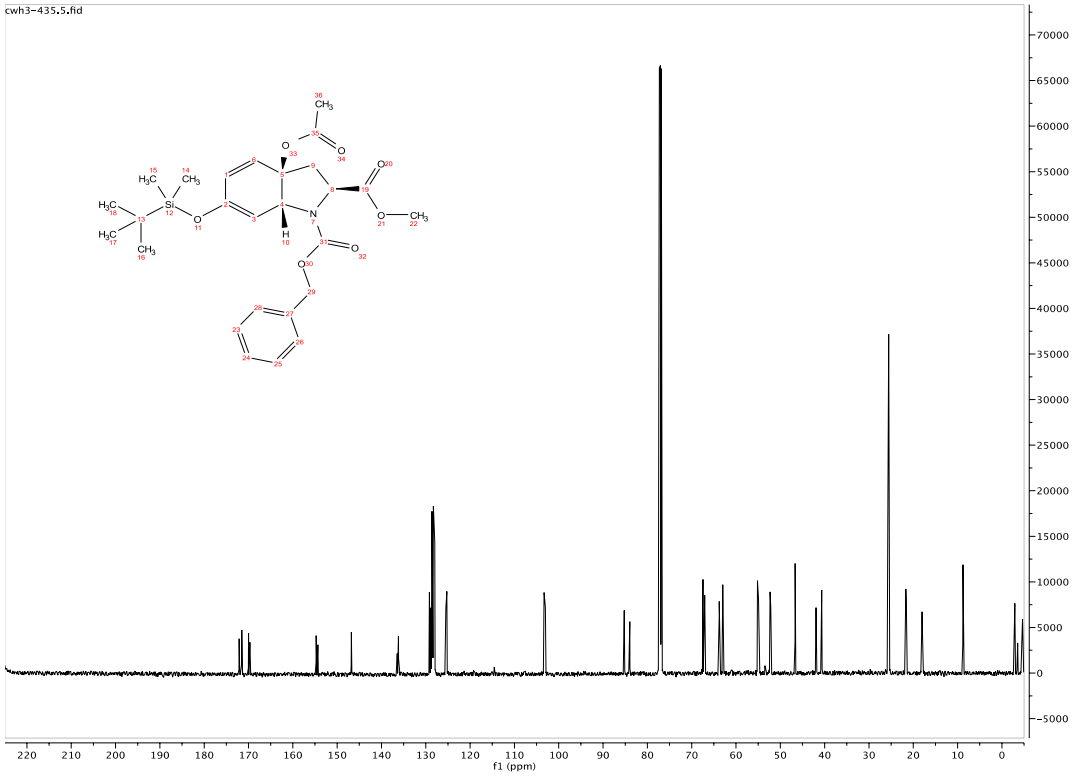


56 **62**

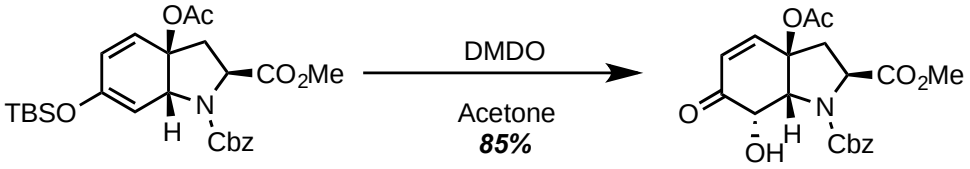
To a stirred solution of compound **56** (700 mg, 1.81 mmol, 1 eq) in DCM (18 mL, 0.10 M) was added Et_3N (0.51 mL, 3.69 mmol, 2.04 eq) and TBSOTf (0.46 mL, 1.99 mmol, 1.1 eq), and then was stirred at room temperature. After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **62** as a white foam (888.86 mg, 98% yield). Rf = 0.43 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^{1}H NMR (600 MHz, Chloroform-d) δ 7.44 – 7.30 (m, 5H), 5.94 (m, 1H), 5.69 (m, 1H), 5.39 – 5.02 (m, 3H), 4.43 – 4.30 (m, 1H), 3.66 (s+ s', 3H), 3.24 – 3.11 (m, 1H), 2.72 (m, 1H), 2.33 (m, 1H), 2.02 + 1.92 (s+ s', 3H), 0.92 – 0.87 (m, 9H), 0.11 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-d) δ (172.10, 171.52), (169.99, 169.68), (154.74, 154.36), (146.79, 146.59), (136.44, 136.16), (129.18, 128.84), (128.61, 128.44), (128.29, 128.22), (128.03, 127.97), (125.48, 125.24), (103.32, 103.00), (85.23, 83.97), (67.46, 67.07), (63.78, 62.98), (55.14, 54.93), (52.32, 52.16), (46.66, 40.67), (25.71, 25.68), (25.60, 25.54), (21.67, 21.57), (17.99, 8.80), (-2.92, -3.56). New compound; Procedure was taken from reference ***41***.

Notebook Entries:
Procedure – cwh4-039
^{1}H – cwh3-435
^{13}C – cwh3-435


cwh3-435.4.fid
5.47
1.01
1.02
3.42
1.00
3.35
1.41
0.88
0.93
3.25
9.18
6.06
f1 (ppm)


cwh3-435.5.fid
f1 (ppm)

1-benzyl 2-methyl (2*S*,3a*R*,7*S*,7a*R*)-3a-acetoxy-7-hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (63)

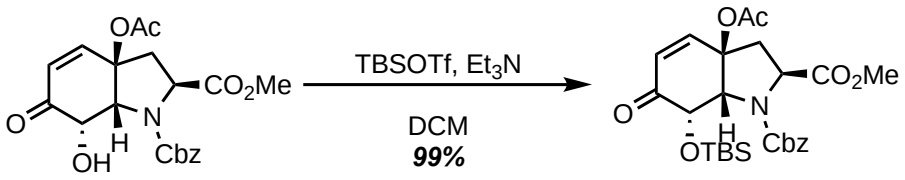


62 **63**

To a stirred solution of compound **62** (900 mg, 1.79 mmol, 1 eq) in acetone (21 mL, 0.0875 M) was added freshly prepared DMDO (40 mL, 2.40 mmol, 1.34 eq, 0.06M) at 0 °C, and then was stirred at 0 °C. After 1 h, the reaction mixture was concentrated in vacuo and the crude residue to give compound **63** as a white foam (472 mg, 85% yield). Rf = 0.40 (silica, EtOAc:hexanes, 1:1); Crude material was used for the next reaction without further purification.

Notebook Entries:
Procedure – cwh4-040

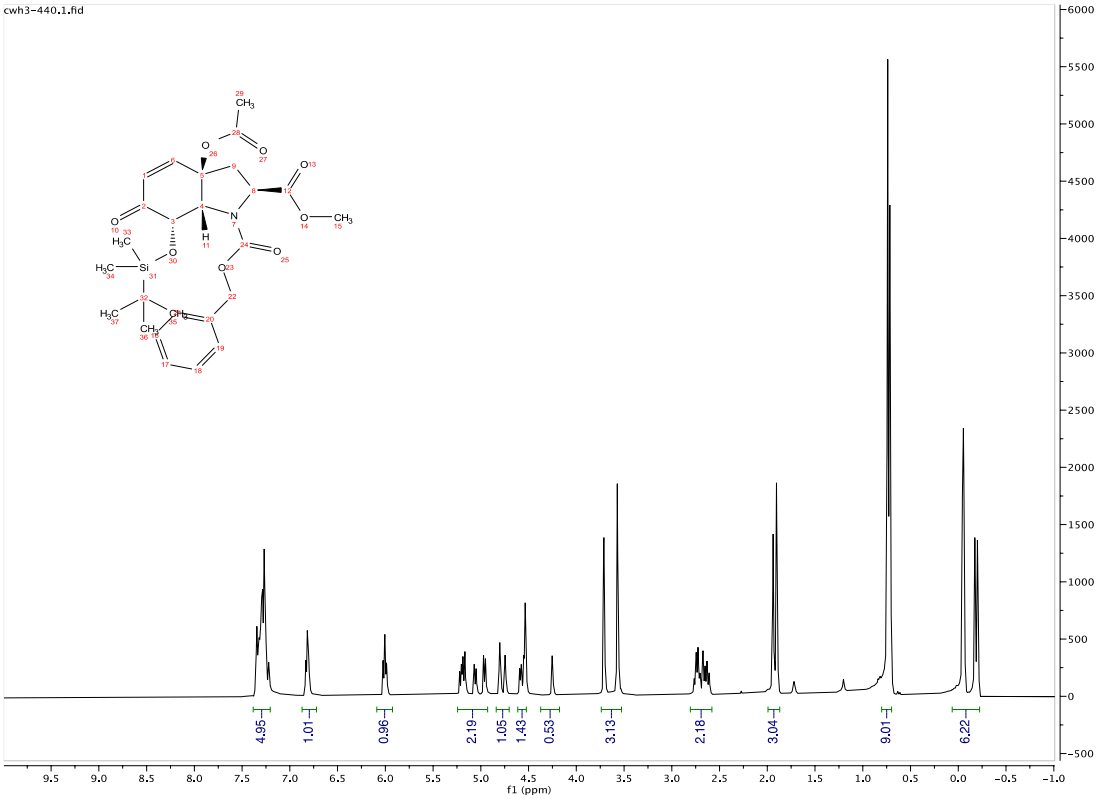
1-benzyl 2-methyl (2*S*,3a*R*,7*S*,7a*R*)-3a-acetoxy-7-((*tert*-butyldimethylsilyl)oxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (64)

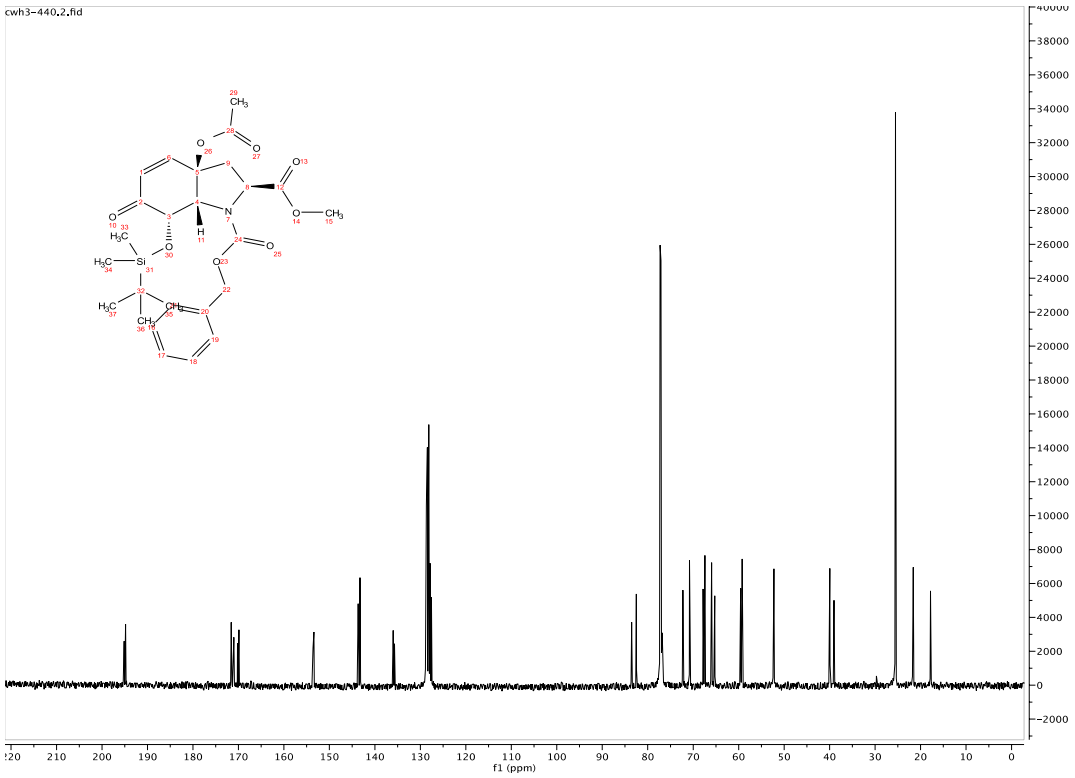


63 **64**

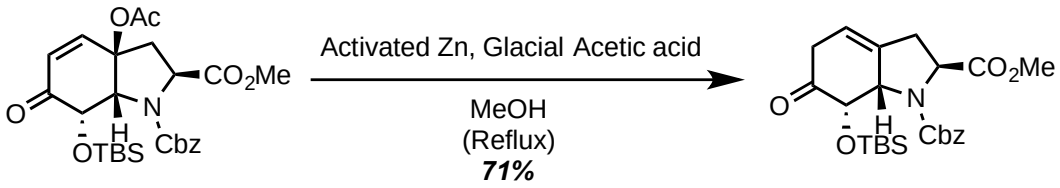
To a stirred solution of compound **63** (720 mg, 1.78 mmol, 1 eq) in DCM (18 mL, 0.10 M) was added Et_3N (0.50 mL, 3.57 mmol, 2 eq) and TBSOTf (0.45 mL, 1.96 mmol, 1.1 eq), and then was stirred at room temperature. After 10 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **64** as a white foam (911.79 mg, 99% yield). Rf = 0.42 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^{1}H NMR (600 MHz, Chloroform-d) δ 7.38 – 7.20 (m, 5H), 6.82 (m, 1H), 6.01 (m, 1H), 5.24 – 4.93 (m, 2H), 4.77 (dd, J = 34.0, 3.9 Hz, 1H), 4.61 – 4.52 (m, 1H), 4.25 (d, J = 4.1 Hz, 1H), 3.74 + 3.53 (s+ s', 3H), 2.69 (m, 2H), 1.92 (s+ s', 3H), 0.73 (m, 9H), 0.06 – -0.22 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-d) δ (195.13, 194.82), (171.59, 171.02), (170.20, 169.89), (153.61, 153.41), (143.66, 143.27), (135.97, 135.69), (128.83, 128.69), (128.51, 128.45), (128.18, 128.15), (127.86, 127.57), (83.53, 82.50), (72.27, 70.82), (67.82, 67.43), (65.96, 65.26), (59.58, 59.24), (52.35, 52.24), (39.96, 39.04), (25.54, 25.52), (21.72, 21.61), (17.83, 17.80). New compound; Procedure was taken from reference ***41***.

Notebook Entries:
Procedure – cwh4-041
^{1}H – cwh3-440
^{13}C – cwh3-440


cwh3-440.1.fid
4.95
1.01
0.96
2.19
1.05
1.43
0.53
3.13
2.18
3.04
9.01
6.22
f1 (ppm)


cwh3-440.2.fid
f1 (ppm)

1-benzyl 2-methyl (2*S*,7*S*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-6-oxo-2,3,5,6,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (60)

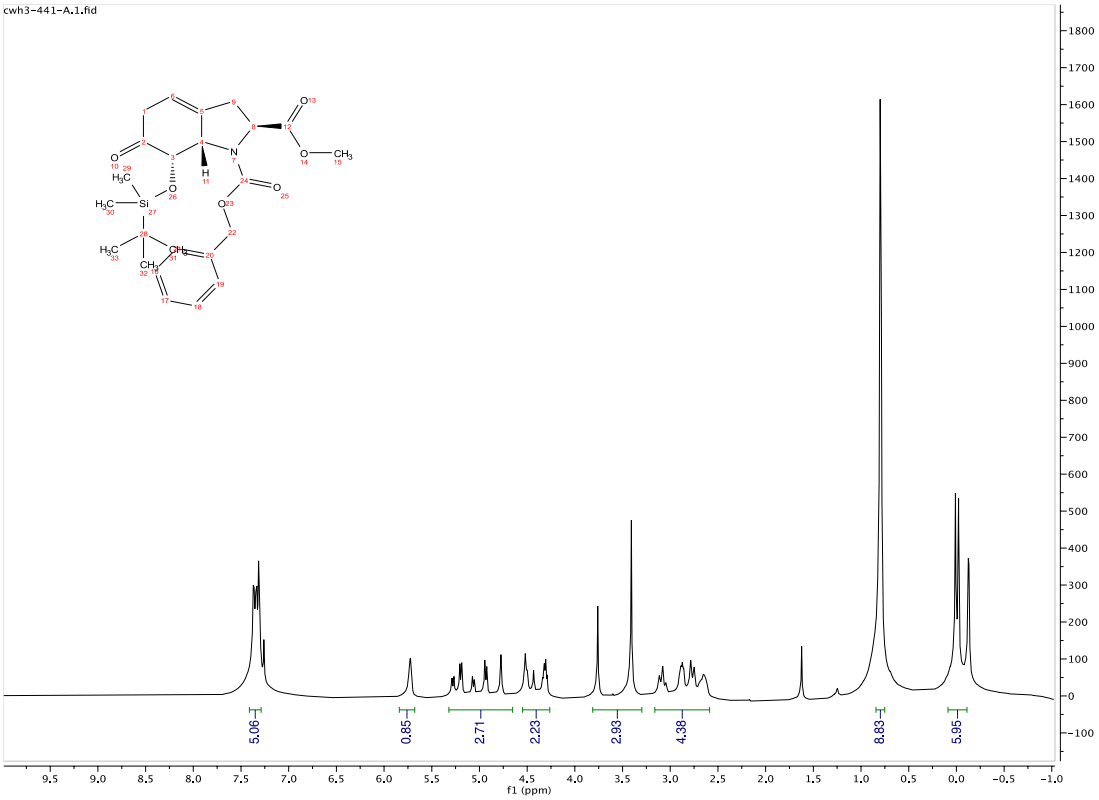


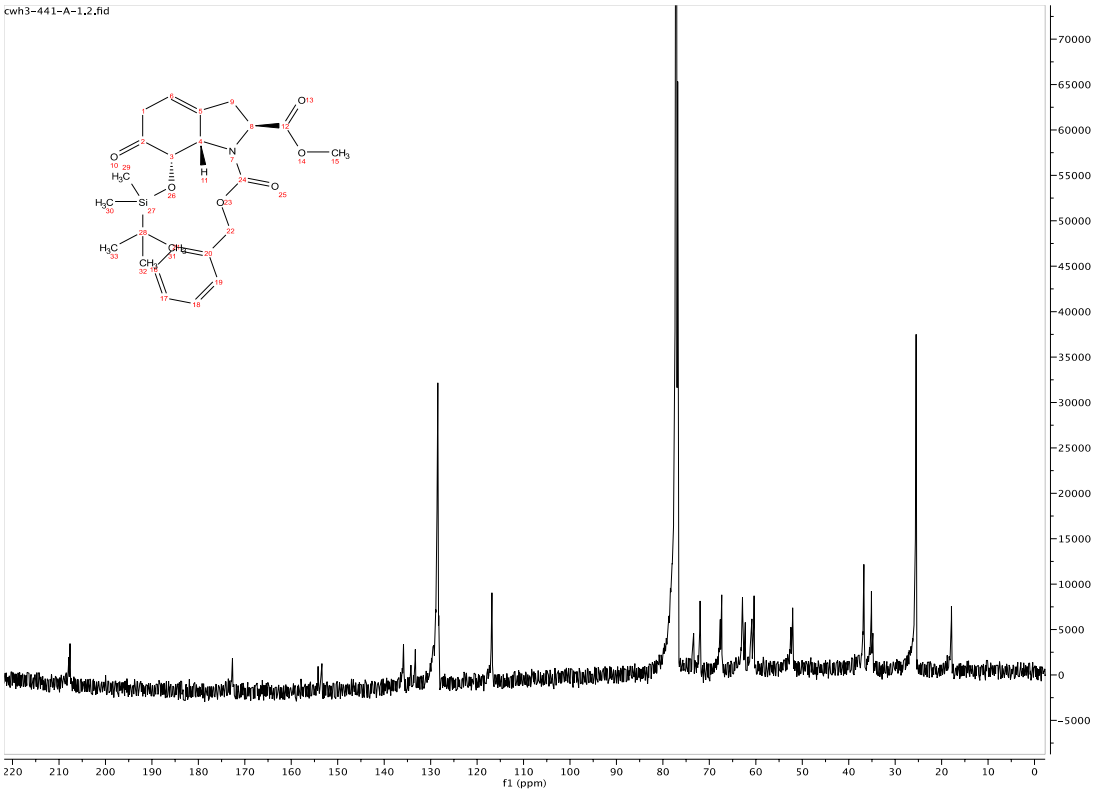
64 **60**

To a stirred solution of compound **64** (300 mg, 0.58 mmol, 1 eq) in MeOH (3 mL, 0.0223 M) was added activated Zn (303, 4.64 mmol, 8 eq) and glacial acetic acid (0.07 mL, 1.16 mmol, 2 eq). The reaction mixture was refluxed for 0.5 h and was filtered through celite pad. The organic layer was concentrated in vacuo and the crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **60** as a white foam (188.86 mg, 71% yield). Rf = 0.44 (silica, EtOAc:hexanes, 1:3) ; Rotamers were shown in ( ); $_{1}$H NMR (600 MHz, Chloroform-d) δ 7.41 – 7.29 (m, 5H), 5.73 (m, 1H), 5.32 – 4.65 (m, 3H), 4.55 – 4.26 (m, 2H), 3.81 + 3.30 (s+ s', 3H), 3.16 – 2.59 (m, 4H), 0.79 (m, 9H), 0.06 (m, 6H). $_{13}$C NMR (151 MHz, Chloroform-d) δ (207.62, 207.61), (172.66, 172.65) (154.21, 153.41), (135.83, 135.82), (134.25, 134.24), (133.28, 133.30), (128.63, 128.44), (128.35, 128.23), (116.82, 116.81), (73.42, 72.01), (67.65, 67.34), (62.87, 62.28), (60.84, 60.39), (52.47, 52.09), (36.74, 36.73), (35.11, 34.81), (25.50, 25.49), (17.89. 17.88). New compound; Procedure was taken from reference ***39***.

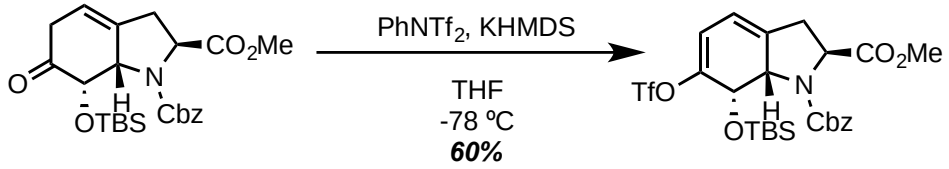
Notebook Entries:

Procedure – cwh4-042
$_{1}$H – cwh3-441-A
$_{13}$C – cwh3-441-A


cwh3-441-A.1.fid
5.06
0.85
2.71
2.23
2.93
4.38
8.83
5.95
f1 (ppm)


cwh3-441-A-1.2.fid
f1 (ppm)

1-benzyl 2-methyl (2*S*,7*S*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-6-(((trifluoromethyl)sulfonyl)oxy)-2,3,7,7a-tetrahydro-1*H*-indole-1,2-dicarboxylate (61)

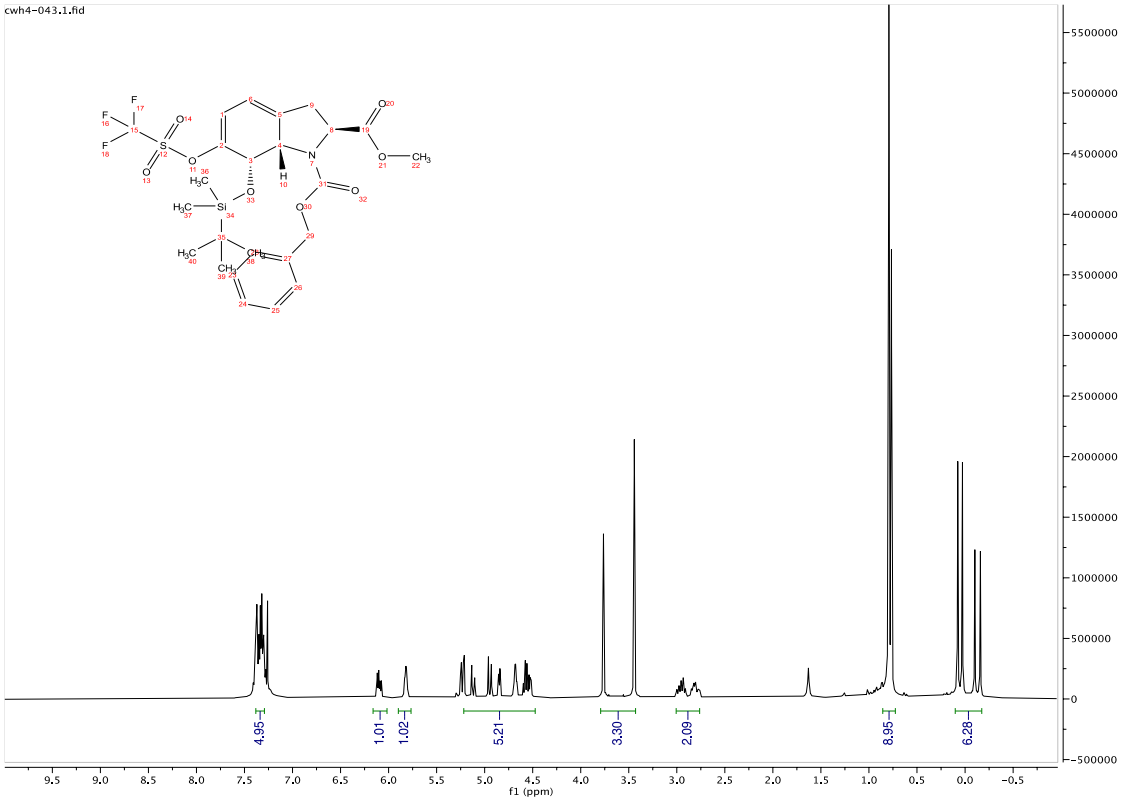


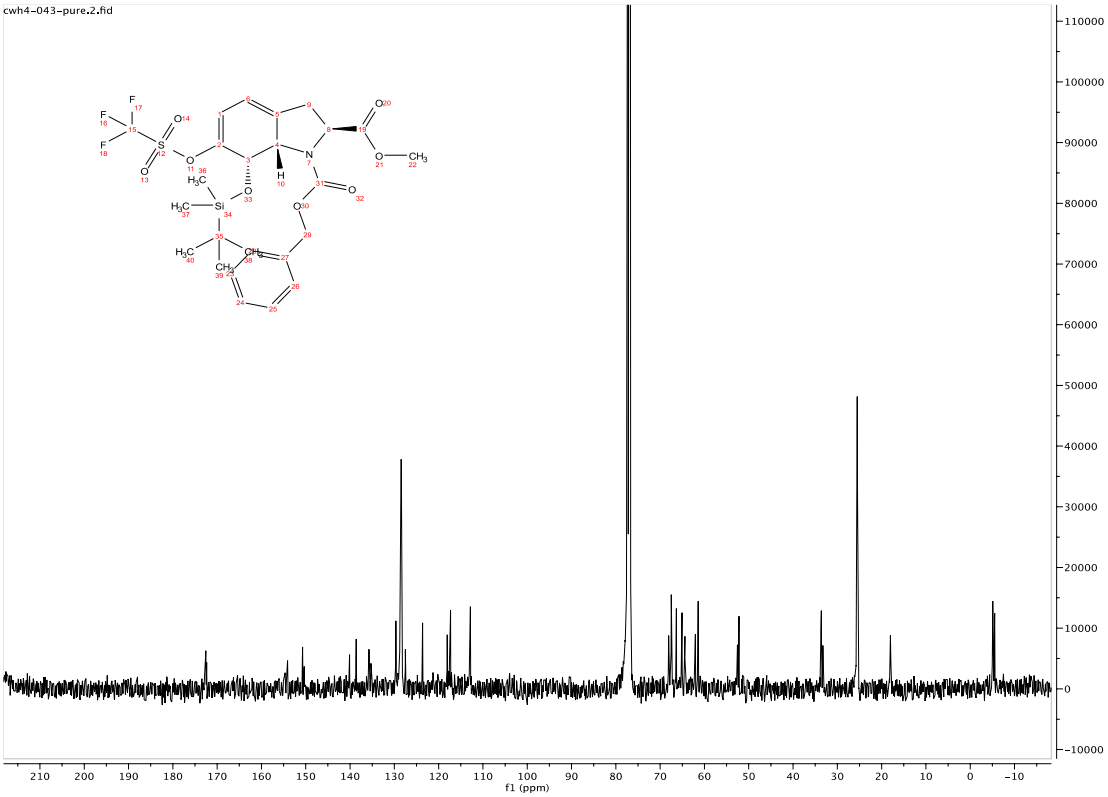
60 **61**

To a stirred solution of compound **60** (140 mg, 0.30 mmol, 1 eq) in THF (3 mL, 0.10 M) was cooled to – 78 °C. Then $PhNTf_2$ (120 mg, 0.335 mmol, 1.1 eq) was added followed by KHMDS (0.72 mL, 0.36 mmol, 1.2 eq), and then reaction mixture was stirred at – 78 °C. After 0.5 h, the reaction was quenched with H_2O and organic layer was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:6) to give compound **61** as a white foam (106 mg, 60% yield). Rf = 0.33 (silica, EtOAc:hexanes, 1:6); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.38 – 7.26 (m, 5H), 6.10 (dd, J = 11.3, 5.8 Hz, 1H), 5.90 – 5.77 (m, 1H), 5.22 – 4.47 (m, 5H), 3.60 (s+ s', 3H), 3.01 – 2.76 (m, 2H), 0.78 (m, 9H), 0.10 – -0.17 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ (172.57, 172.56), (154.16, 154.14), (150.74, 150.73), (140.12, 138.62), (135.74, 133.43), (129.66, 128.66), (128.48, 128.43), (127.50, 123.62), (118.07, 117.32), (112.84, 112.83), (68.08, 67.48), (67.33, 66.33), (65.06, 64.41), (62.05, 61.42), (52.55, 52.21), (33.63, 33.28), (25.52, 25.44), (18.03, 18.02), (-5.10, -5.49). New compound; Procedure was taken from reference ***39***.

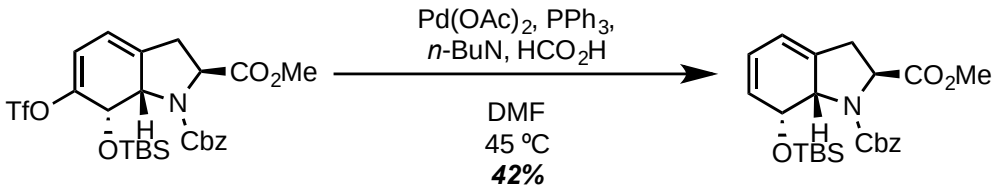
Notebook Entries:

Procedure – cwh4-043
^{1}H – cwh4-043
^{13}C – cwh4-043


cwh4-043.1.fid
4.95
1.01
1.02
5.21
3.30
2.09
8.95
6.28
f1 (ppm)


cwh4-043-pure.2.fid
f1 (ppm)

1-benzyl 2-methyl (2*S*,7*R*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2,3,7,7a-tetrahydro-1*H*-indole-1,2-dicarboxylate (32)

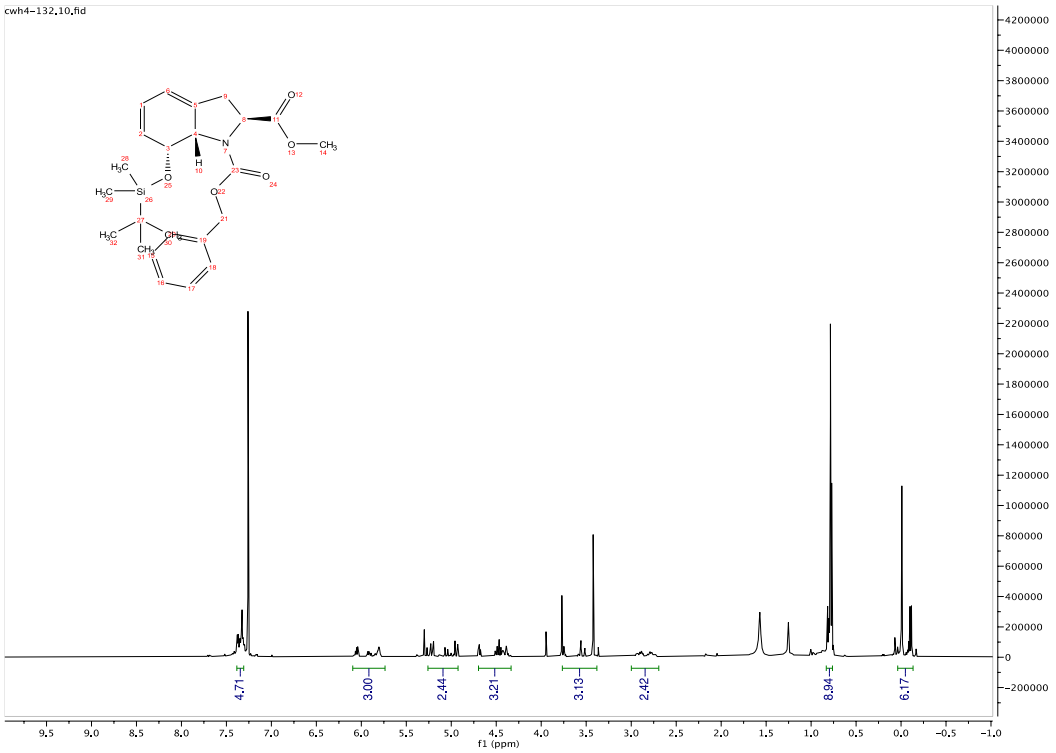


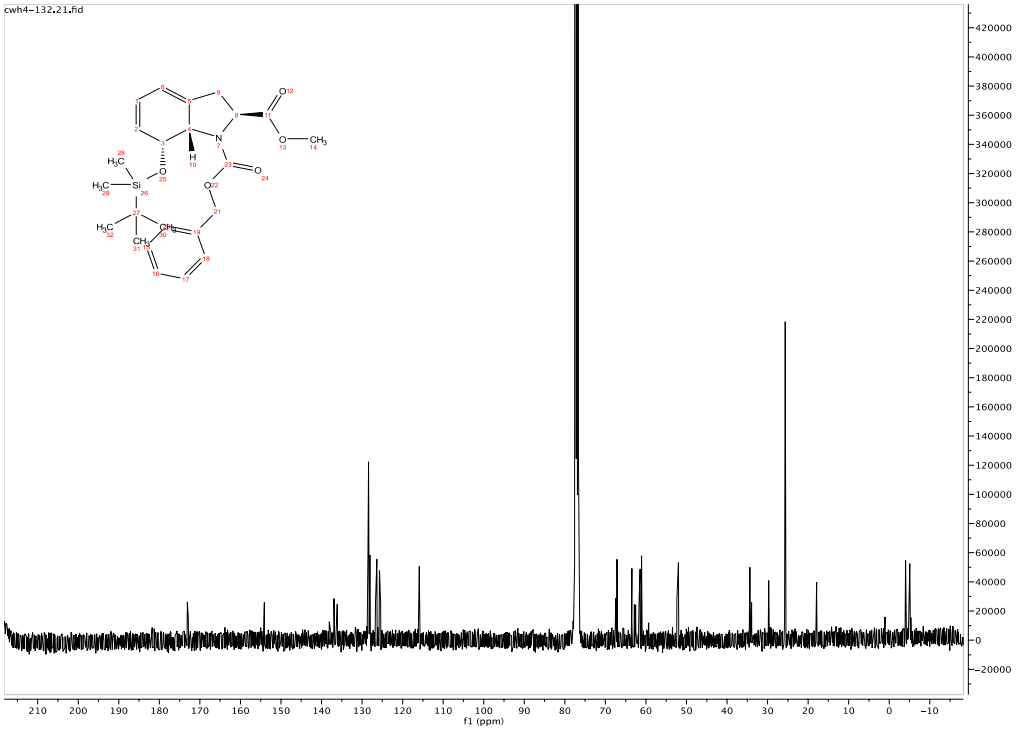
61 **32**

To a stirred solution of compound **61** (31 mg, 0.052 mmol, 1 eq) in DMF (0.5 mL, 0.10 M) was added $Pd(OAc)_2$ (2.4 mg, 0.01 mmol, 0.2 eq) and PPh_3 (5.5 mg, 0.02 mmol, 0.4 eq). Then *n*-Bu_3N (0.062 mL, 0.260 mmol, 5 eq) and HCO_2H (0.006 mL, 0.152 mmol, 3 eq) were added, and then was stirred at 65 °C. After 0.5 h, the reaction was quenched with 1M HCl and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc: hexanes, 1:3) to give compound **32** as a white foam (23 mg, 59% yield). Rf = 0.41 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.38 – 7.31 (m, 5H), 6.10 – 5.74 (m, 3H), 5.26 – 4.92 (m, 2H), 4.70 – 4.34 (m, 3H), 3.77 + 3.38 (s+ s', 3H), 3.00 – 2.69 (m, 2H), 0.83 – 0.76 (m, 9H), 0.04 – -0.13 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ (173.10, 172.85), (154.10, 154.09), (136.93, 136.14), (128.53, 128.41), (128.33, 128.17), (128.14, 128.08), (126.68, 126.34), (125.72, 125.43), (116.01, 115.89), (67.45, 67.14), (63.46, 62.84), (62.54, 61.68), (61.43, 61.09), (52.36, 51.98), (34.37, 33.94), (29.72, 25.69), (25.66, 25.63), (17.91, 17.90), (-3.94, -4.03). Known compound; all the spectral data matches the data reported in ***33***. Procedure was taken from reference ***39***.

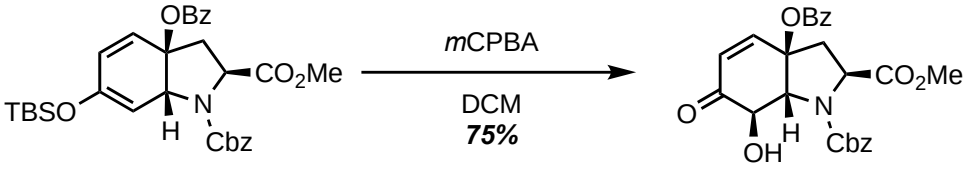
Notebook Entries:

Procedure – cwh4-132
^{1}H – cwh4-132
^{13}C – cwh4-132


cwh4-132.10.fid
4.71
3.00
2.44
3.21
3.13
2.42
8.94
6.17
f1 (ppm)


cwh4-132.21.fid
f1 (ppm)

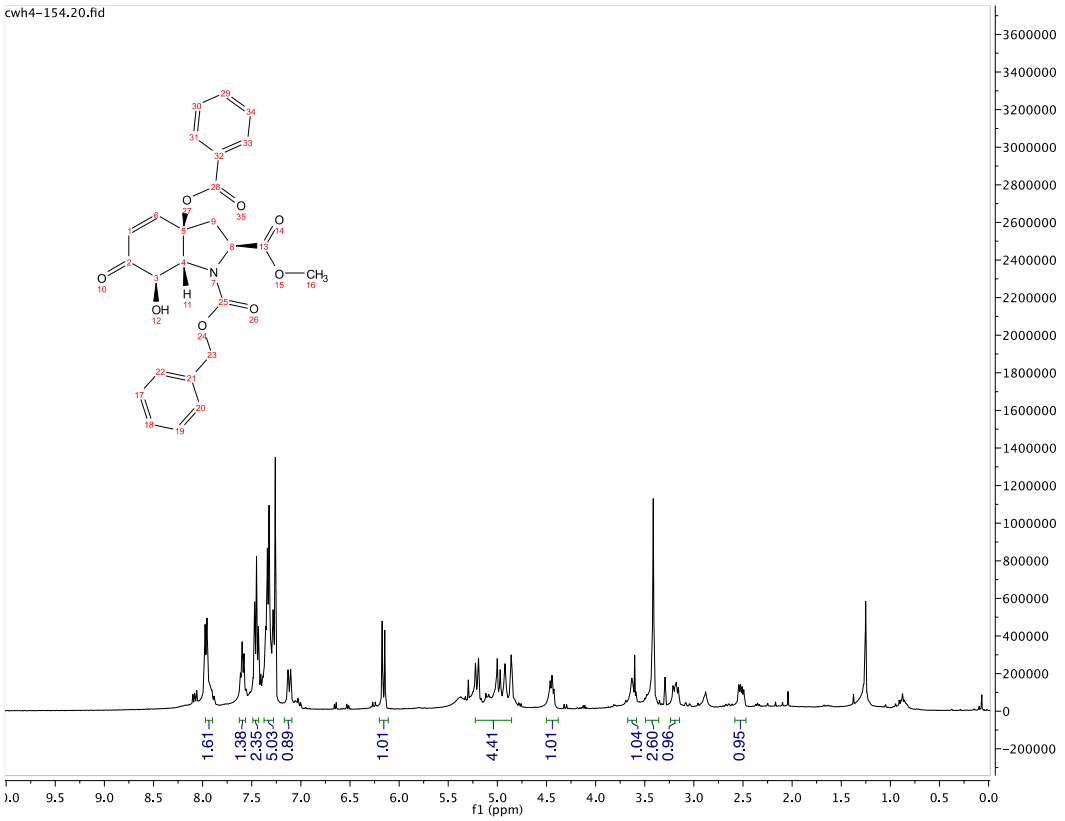
1-benzyl 2-methyl (2S,3aR,7R,7aR)-3a-(benzoyloxy)-7-hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (12)

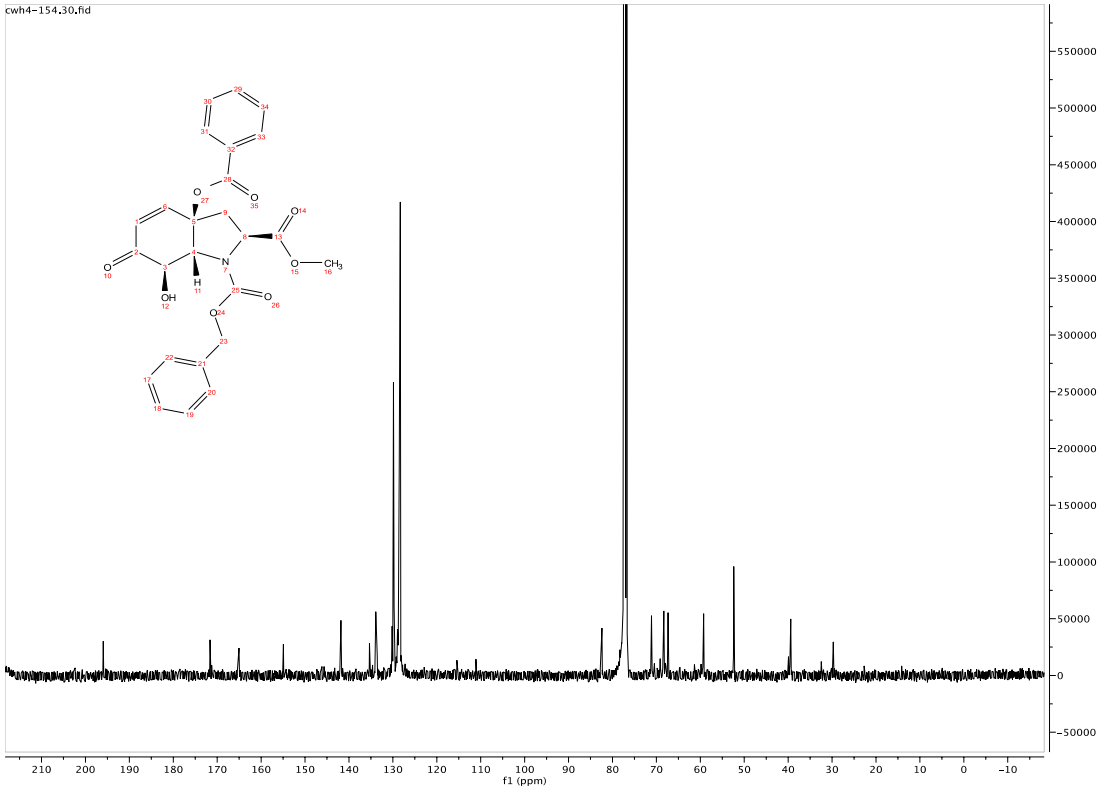


28 **12**

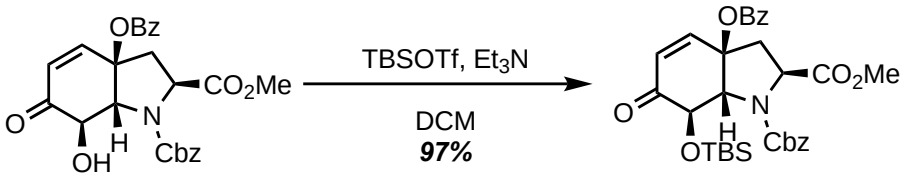
To a stirred solution of compound **28** (1.4 g, 3.01 mmol, 1 eq) in DCM (30 mL, 0.10 M) was added 77% *m*CPBA (743 mg, 3.32 mmol, 1.1 eq) at 0 °C, and then was stirred at 0 °C. After 0.5 h, the reaction mixture was quenched with 1M HCl and extracted the organic layer with DCM (× 3). The combined organic layers were washed with $NaHCO_3$, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **12** as a white foam (1.05 g, 75% yield). Rf = 0.52 (silica, EtOAc:hexanes, 1:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.94 (m, 2H), 7.60 (m, 1H), 7.46 (m, 2H), 7.37 – 7.28 (m, 5H), 7.12 (d, J = 10.3 Hz, 1H), 6.16 (d, J = 10.3 Hz, 1H), 5.22 – 4.86 (m, 4H), 4.50 – 4.38 (m, 1H), 3.67 – 3.58 (m, 1H), 3.41 (s, 3H), 3.24 – 3.15 (m, 1H), 2.52 (dd, J = 13.6, 6.7 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 195.94, 171.63, 165.03, 154.93, 141.82, 135.32, 133.90, 130.17, 129.86, 128.95, 128.61, 128.54, 128.40, 128.31, 82.39, 71.11, 68.30, 67.34, 59.25, 52.39, 39.40, 29.72. New compound; Procedure was taken from reference ***41***.

Notebook Entries:
Procedure – cwh4-220
^{1}H – cwh4-154
^{13}C – cwh4-154


cwh4-154.20.fid
1.61
1.38
2.35
5.03
0.89
1.01
4.41
1.01
1.04
2.60
0.96
0.95
f1 (ppm)


cwh4-154.30.fid
f1 (ppm)

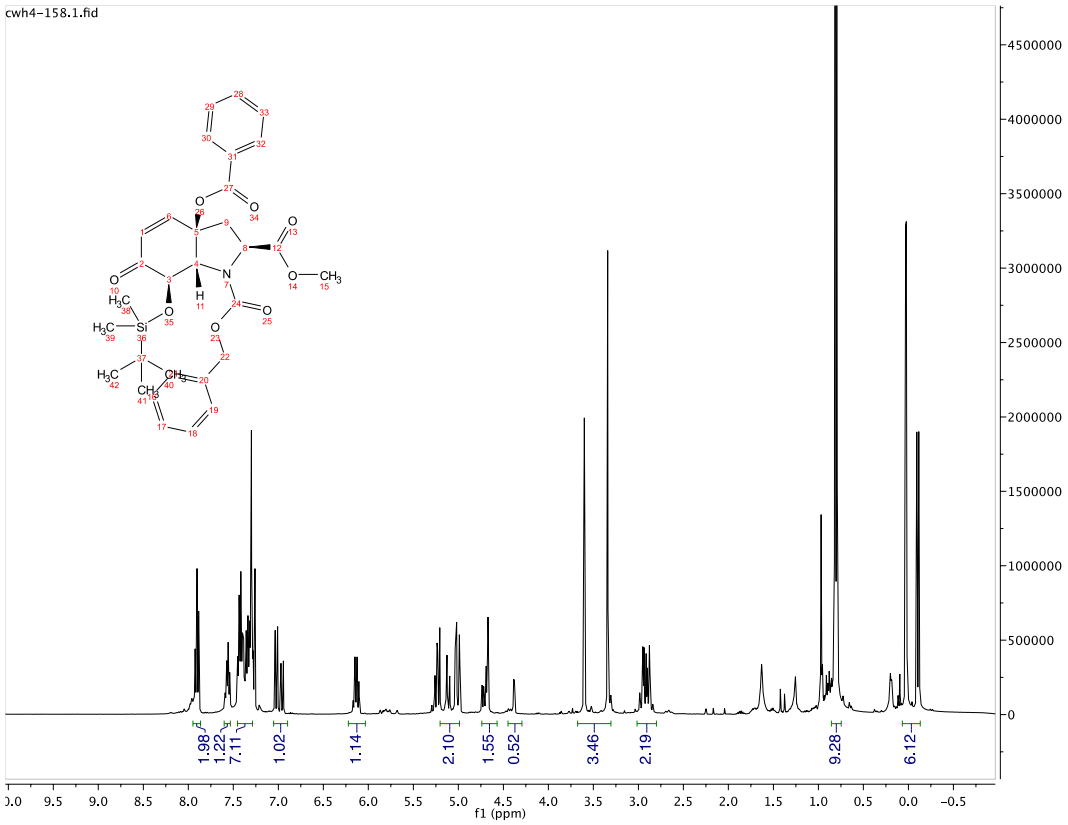
1-benzyl 2-methyl (2S,3aR,7R,7aR)-3a-(benzoyloxy)-7-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (104)

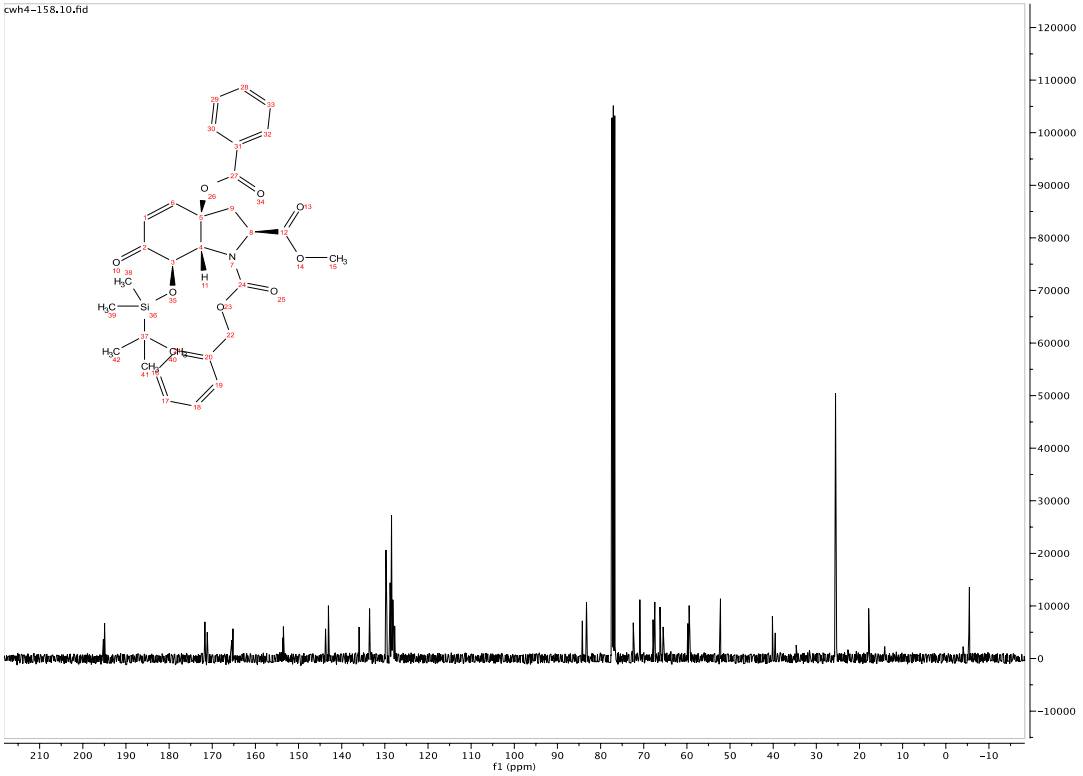


12 **104**

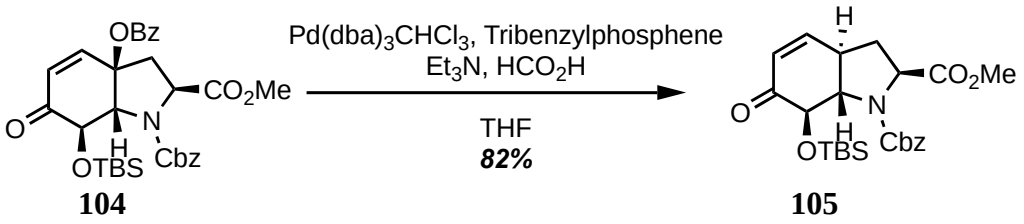
To a stirred solution of compound **12** (450 mg, 0.967 mmol, 1 eq) in DCM (9.7 mL, 0.10 M) was added Et_3N (0.27 mL, 1.934 mmol, 2 eq) and TBSOTf (0.27 mL, 1.064 mmol, 1.1 eq) and then was stirred at room temperature. After 4 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **104** as a white foam (511 mg, 97% yield). Rf = 0.82 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-d) δ 7.90 (td, J = 8.4, 1.3 Hz, 2H), 7.57 (td, J = 7.4, 5.5 Hz, 1H), 7.45 – 7.27 (m, 7H), 6.99 (dd, J = 25.5, 10.5 Hz, 1H), 6.22 – 6.03 (m, 1H), 5.28 – 4.97 (m, 2H), 4.74 – 4.57 (m, 2H), 4.45 – 4.29 (m, 1H), 3.47 (s+ s', 3H), 3.01 – 2.80 (m, 2H), 0.80 (m, 9H), -0.10 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ (195.23, 194.94), (171.70, 171.15), (165.46, 165.19), (153.62, 153.52), (143.74, 143.08), (135.95, 135.93), (133.58, 133.55), (129.81, 129.74), (128.78, 128.68), (128.49, 128.45), (128.42, 128.40), (128.20, 128.18), (128.14, 127.71), (84.22, 83.27), (72.44, 70.91), (67.84, 67.43), (66.25, 65.51), (59.80, 59.47), (52.39, 52.23), (40.18, 39.52), (25.56, 25.56), (17.87, 17.84), (-5.47, -5.49). New compound; Procedure was taken from reference ***41***.

Notebook Entries:
Procedure – cwh4- 158
^1H – cwh4-158
^{13}C – cwh4-158


cwh4-158.1.fid
1.98
1.22
7.11
1.02
1.14
2.10
1.55
0.52
3.46
2.19
9.28
6.12
f1 (ppm)


cwh4-158.10.fid
f1 (ppm)

1-benzyl 2-methyl (2S,3aR,7R,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (105)

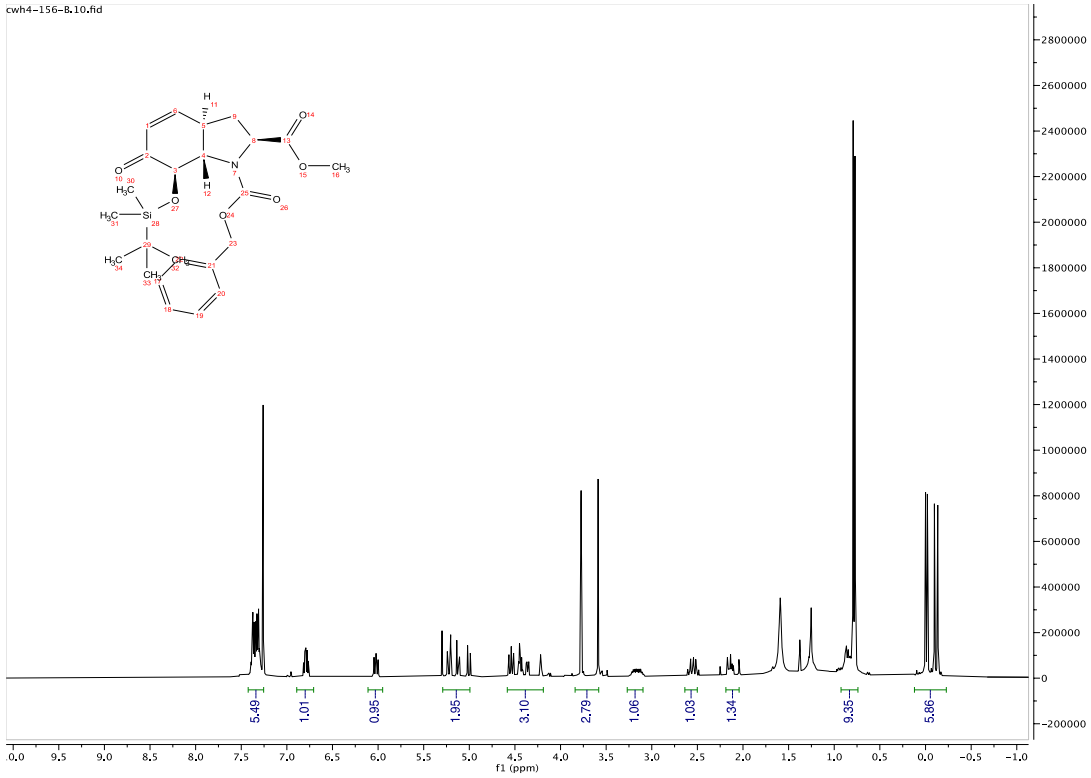


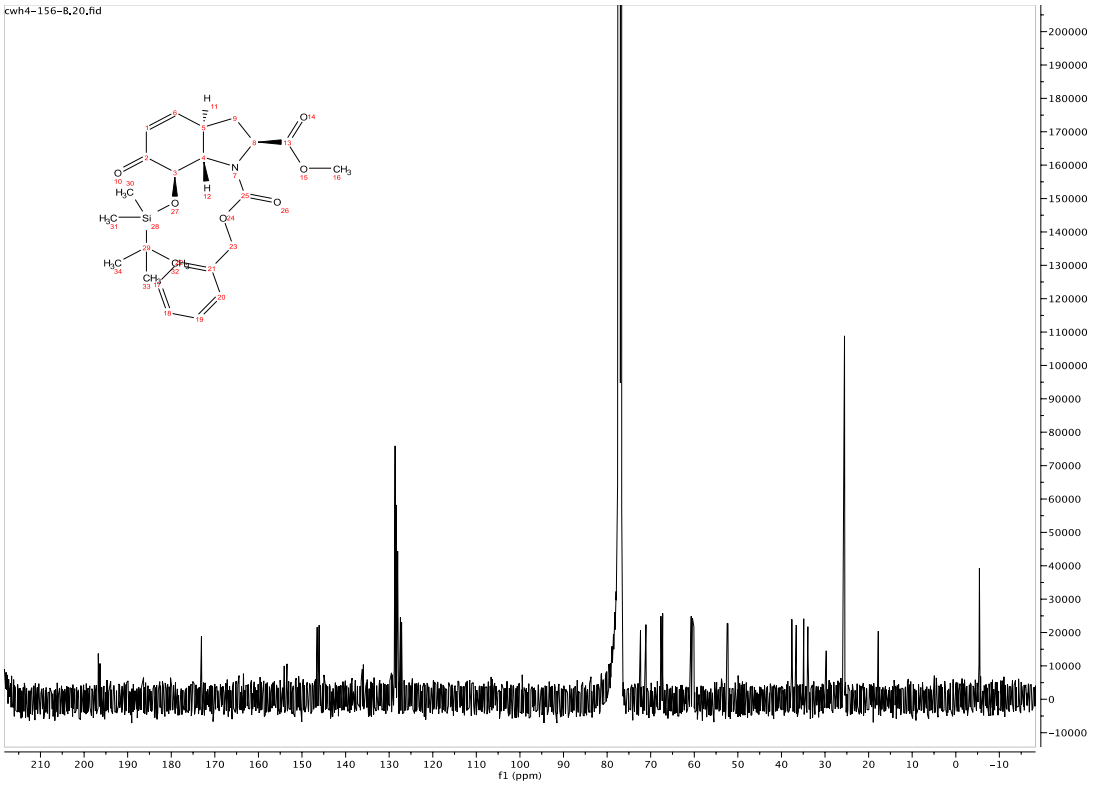
104 **105**

To a stirred solution of compound **104** (400 mg, 0.733 mmol, 1 eq) in THF (3.3 mL, 0.22 M) was added $Pd(dba)_3CHCl_3$ (15 mg, 0.0147 mmol, 0.02 eq) and tribenzylphosphene (17.8 mg, 0.0586 mmol, 0.08 eq). After stirring for 1 minute, Et_3N (0.35 mL, 2.544 mmol, 3.47 eq) was added immediately followed by the addition of 95% HCO_2H (0.10 mL, 2.544 mmol, 3.47 eq), and then was refluxed. After 12 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc: hexanes, 1:1) to give compound **105** as a light-yellow foam (275 mg, 82% yield). Rf = 0.43 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). 1H NMR (400 MHz, Chloroform-d) δ 7.42 – 7.25 (m, 5H), 6.79 (m, 1H), 6.02 (m, 1H), 5.29 – 4.99 (m, 2H), 4.58 – 4.19 (m, 3H), 3.68 (s+ s', 3H), 3.16 (m, 1H), 2.64 – 2.50 (m, 1H), 2.19 – 2.04 (m, 1H), 0.78 (m, 9H), -0.12 (m, 6H). 13C NMR (101 MHz, Chloroform-d) δ (196.73, 196.71), (173.07, 173.05), (146.50, 146.07), (128.64, 128.43), (128.11, 128.04), (127.91, 127.87), (127.41, 127.14), (72.33, 71.09), (67.65, 67.25), (60.75, 60.69), (60.41, 60.08), (52.47, 52.28), (37.62, 36.61), (34.89, 33.94), (29.73, 29.71), (25.53, 25.51), (17.79, 17.78), (-5.43, -5.49).

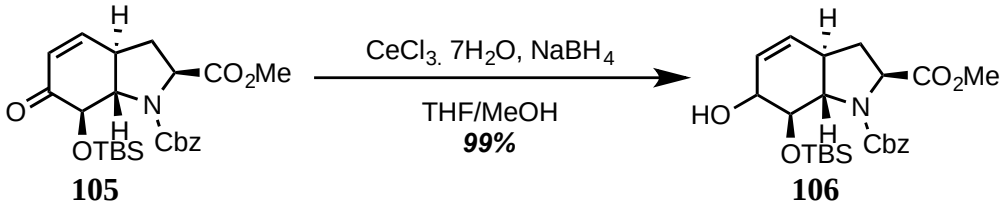
New compound; Procedure was taken from reference ***40***.

Notebook Entries:
Procedure– cwh4-182 ^{1}H – cwh4-156-B ^{13}C – cwh4-156-B


cwh4-156-B.10.fid
5.49
1.01
0.95
1.95
3.10
2.79
1.06
1.03
1.34
9.35
5.86
f1 (ppm)

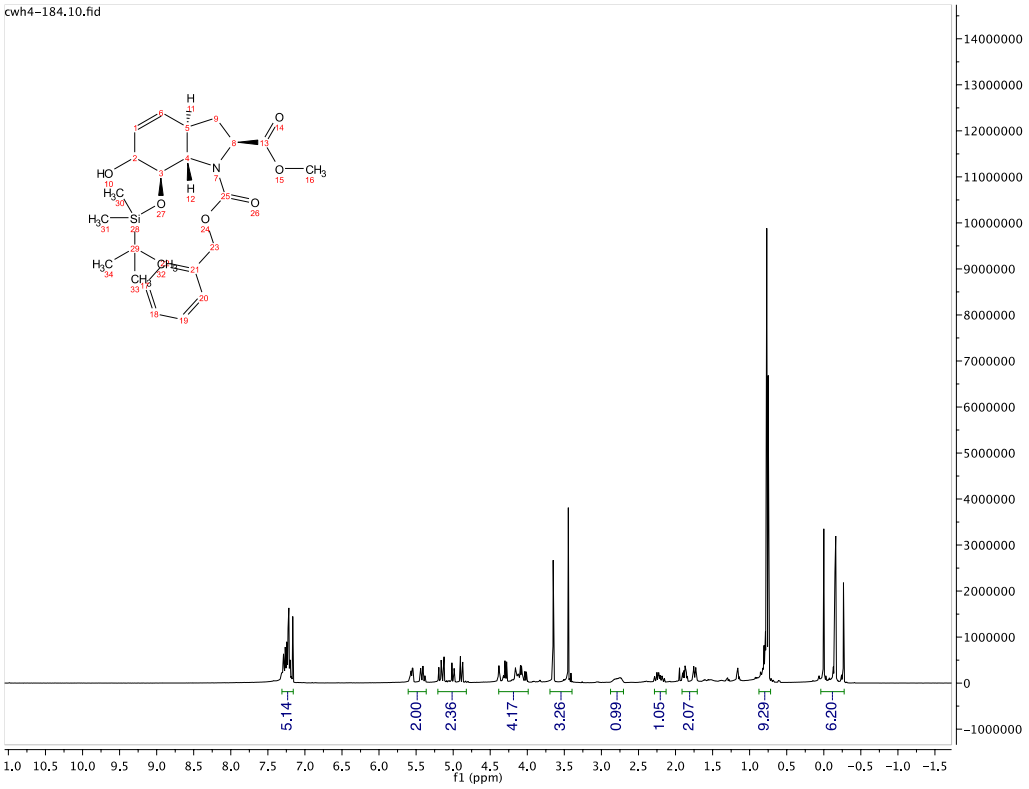

cwh4-156-B.20.fid
f1 (ppm)

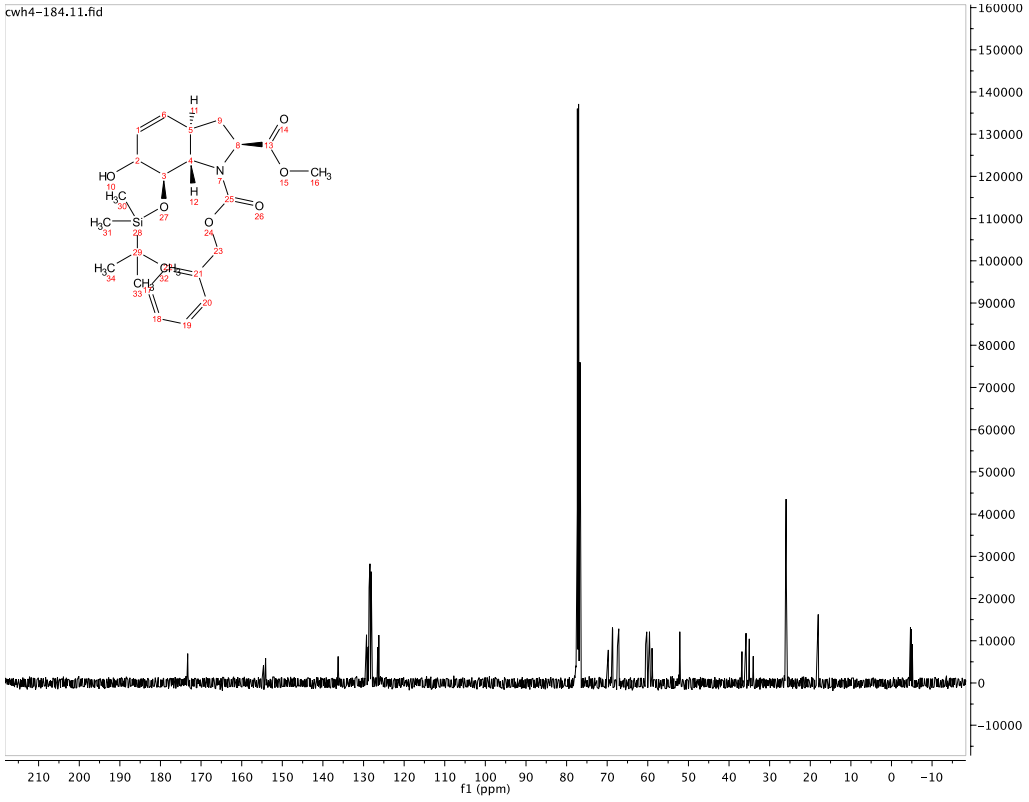
1-benzyl 2-methyl (2S,3aR,6R,7R,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (106)



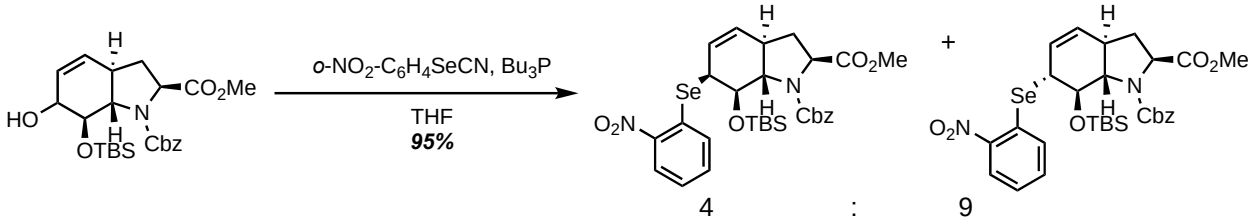
To a stirred solution of compound **105** (55 mg, 0.12 mmol, 1 eq) in THF:MeOH 1:1 (1.4 mL, 0.0875M) was added $CeCl_3 \cdot 7H_2O$ (45 mg, 0.12 mmol, 1 eq) and stirred for 5 mins. Then $NaBH_4$ (4.5 mg, 0.12 mmol, 1 eq) was added portion wise, and then was stirred at room temperature. After 5 mins, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **106** as a white foam (54.5 mg, 99% yield). Rf = 0.39 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.38 – 7.29 (m, 5H), 5.71 – 5.45 (m, 2H), 5.28 – 4.95 (m, 2H), 4.50 – 4.08 (m, 4H), 3.64 (s+ s', 3H), 2.31 (m, 1H), 1.97 (m, 2H), 0.85 (m, 9H), 0.12 – -0.17 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (173.29, 173.22), (154.64, 154.11), (136.24, 136.16), (129.27, 128.85), (128.64, 128.63), (128.40, 128.36), (126.52, 126.24), (69.74, 68.82), (68.70, 68.65), (67.47, 67.14), (60.54, 60.27), (59.59, 58.95), (52.31, 52.12), (36.81, 35.81), (35.01, 34.03), (25.96, 25.93), (18.03, 18.01), (-4.67, -4.87). New compound; Procedure was taken from reference ***41***.

Notebook Entries:
Procedure – cwh4-161
^{1}H – cwh4-184
^{13}C – cwh4-184


cwh4-184.10.fid
5.14
2.00
2.36
4.17
3.26
0.99
1.05
2.07
9.29
6.20
f1 (ppm)


cwh4-184.11.fid
f1 (ppm)

1-benzyl 2-methyl (2S,3aR,6S,7R,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-((2-nitrophenyl)selanyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (107)

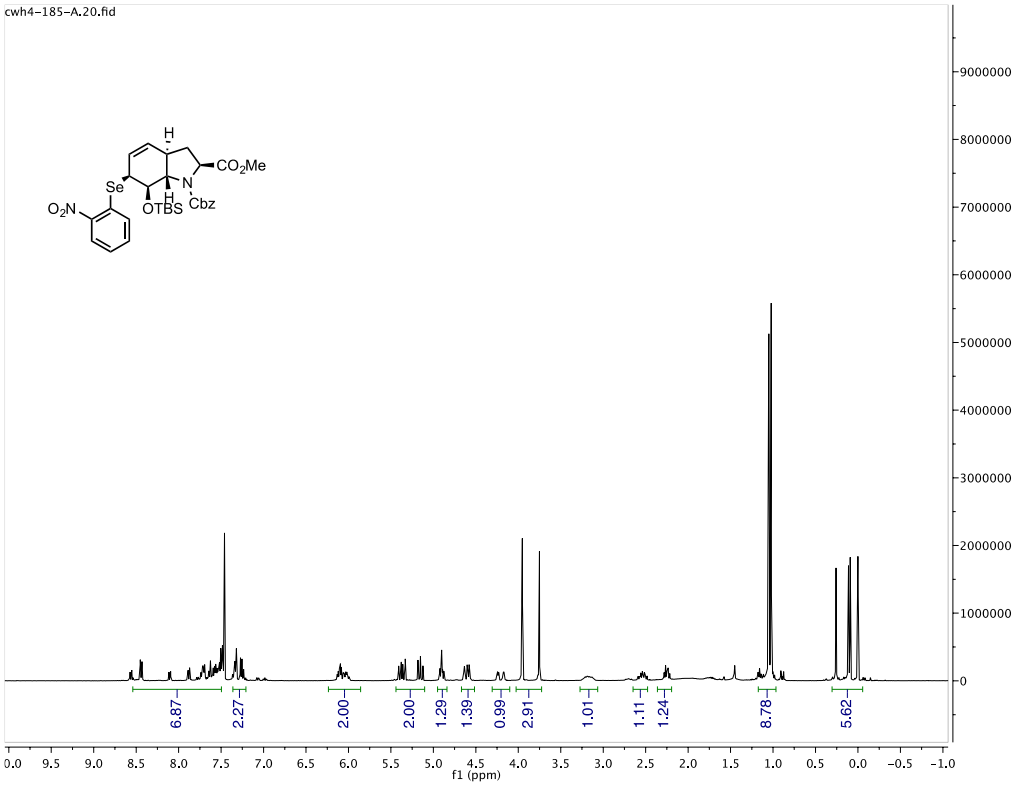


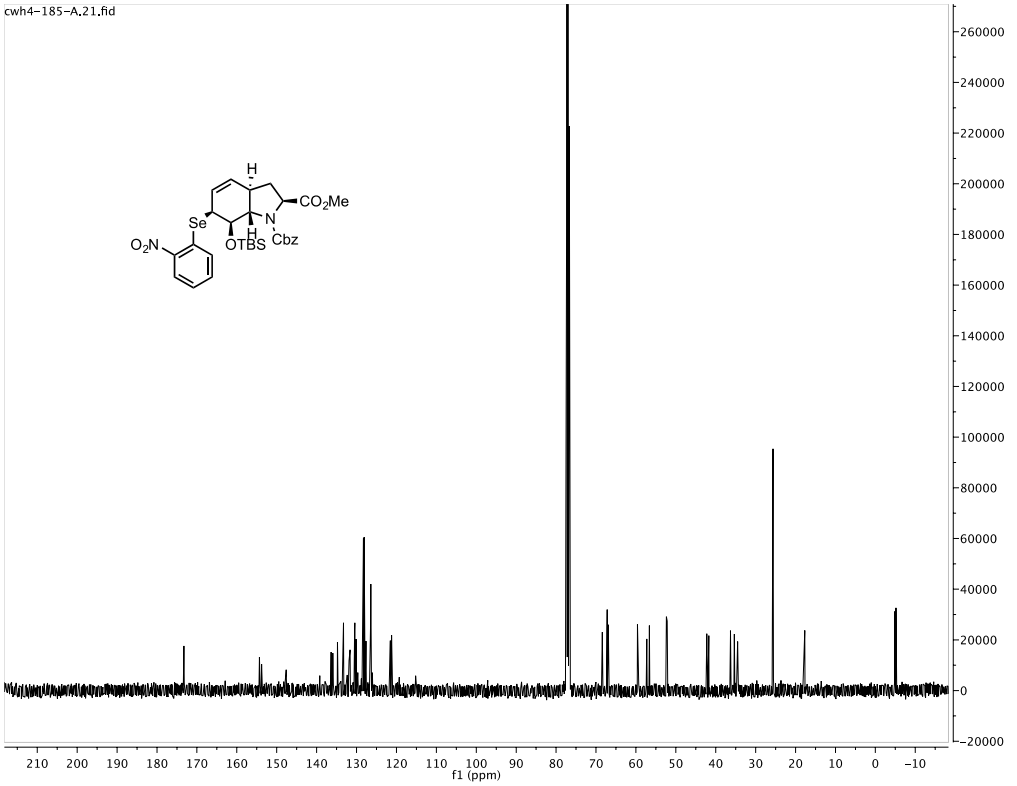
106 **107** **108**

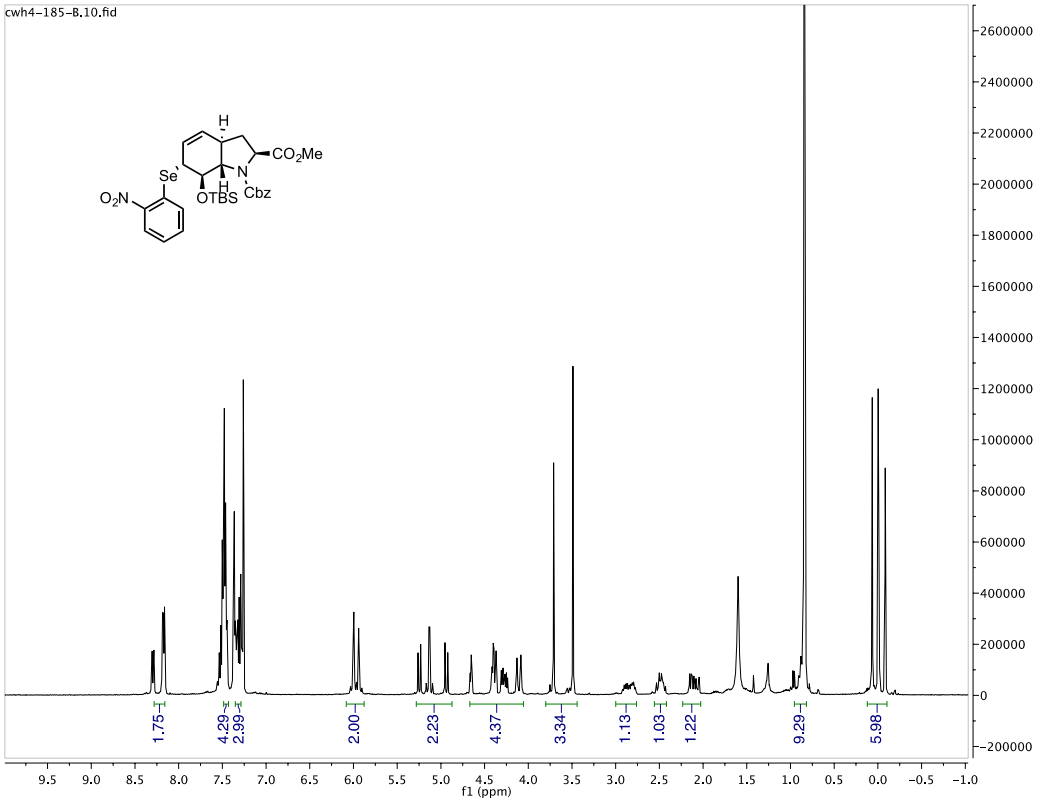
To a stirred solution of compound **106** (100 mg, 0.22 mmol, 1 eq) in THF (2.2 mL, 0.1 M) was added *o*-NO_2-C_6H_4SeCN (98 mg, 0.44 mmol, 2 eq). Then Bu_3P (0.12 mL, 0.48 mmol, 2.2 eq) was added drop wise and the reaction mixture was refluxed. After 16 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **107** as a white foam (40 mg, 29% yield). Rf = 0.77 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 7.50 (m, 7H), 7.36 – 7.21 (m, 2H), 6.24 – 5.86 (m, 2H), 5.44 – 5.10 (m, 2H), 4.95 – 4.16 (m, 4H), 3.85 (s+ s', 3H), 3.17 (m, 1H), 2.54 (m, 1H), 2.25 (m, 1H), 1.17 – 0.97 (m, 9H), 0.30 – -0.06 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (173.40, 173.27), (154.33, 153.80), (147.62, 147.61), (136.36, 135.94), (134.78, 133.38), (131.71, 131.62), (130.41, 130.07), (129.68, 128.41), (128.02, 127.99), (127.97, 127.65), (126.50, 126.42), (126.36, 126.03), (121.54, 121.22), (68.43, 67.30), (67.20, 66.92), (59.60, 59.43), (57.27, 56.62), (52.35, 52.15), (42.24, 41.74), (36.30, 35.53), (35.34, 34.52), (25.68, 25.66), (17.75, 17.70), (-4.80, -5.17).

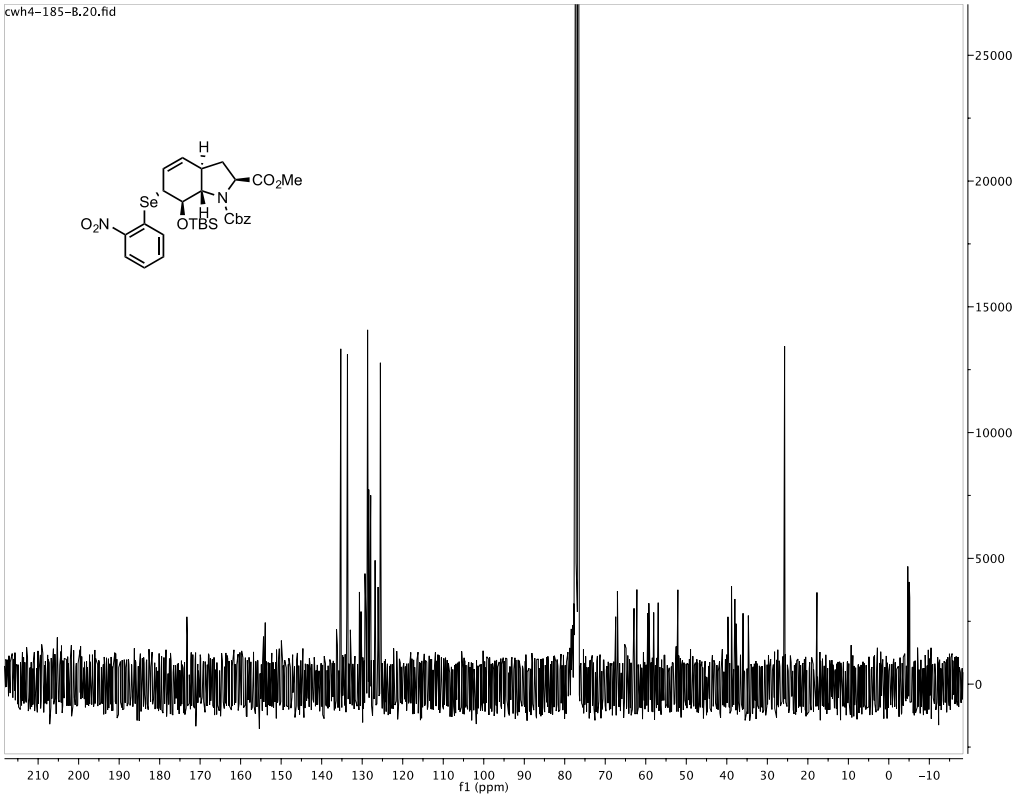
Compound **108** was obtained as a white foam (90 mg, 67% yield). Rf = 0.75 (silica, EtOAc:hexanes, 1:3); [Rotamers were shown in ( )]. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 – 8.16 (m, 2H), 7.49 – 7.43 (m, 4H), 7.35 – 7.29 (m, 3H), 6.08 – 5.88 (m, 2H), 5.28 – 4.87 (m, 2H), 4.67 – 4.06 (m, 4H), 3.60 (s+ s', 3H), 3.00 – 2.76 (m, 1H), 2.48 (m, 1H), 2.23 – 2.03 (m, 1H), 0.84 (m, 9H), -0.01 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (173.29, 173.28), (153.94, 153.93), (147.92, 147.90), (135.30, 135.29), (133.70, 133.63), (130.67, 130.28), (129.32, 129.10), (128.67, 128.58), (128.40, 128.38), (128.24, 128.10), (127.98, 127.90), (126.82, 126.75), (126.07, 125.50), (67.43, 67.01), (62.90, 62.20), (59.51, 59.24), (58.03, 56.92), (52.31, 52.08), (39.71, 38.83), (38.02, 37.70), (35.99, 34.67), (25.75, 25.73), (17.76, 17.75), (-4.68, -5.16). New compounds; Procedure was taken from reference ***52***.

Notebook Entries:
Procedure – cwh4-185
^{1}H – x; cwh4-185-A, y; cwh4-185-A
^{13}C – x; cwh4-185-B, y; cwh4-185-B

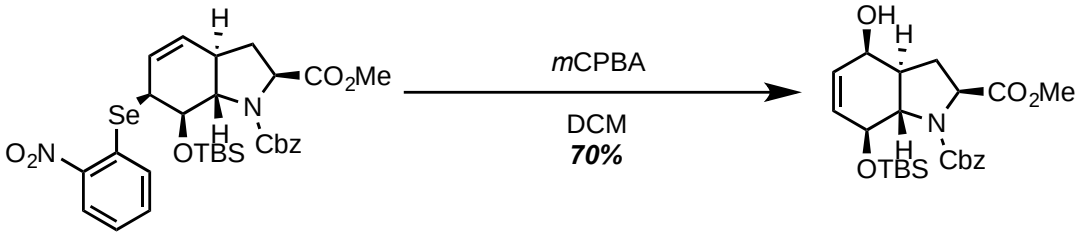

cwh4-185-A.20.fid
H
CO2Me
Se
N
O2N
OTBS
H
Cbz
6.87
2.27
2.00
2.00
1.29
1.39
0.99
2.91
1.01
1.11
1.24
8.78
5.62
f1 (ppm)


cwh4-185-A.21.fid
H
CO2Me
Se
N
O2N
OTBS
H
Cbz
f1 (ppm)


cwh4-185-B.10.fid
CO2Me
Se
O2N
OTBS
Cbz
1.75
4.29
2.99
2.00
2.23
4.37
3.34
1.13
1.03
1.22
9.29
5.98
f1 (ppm)


cwh4-185-B.20.fid
CO2Me
Se
O2N
OTBS
Cbz
f1 (ppm)

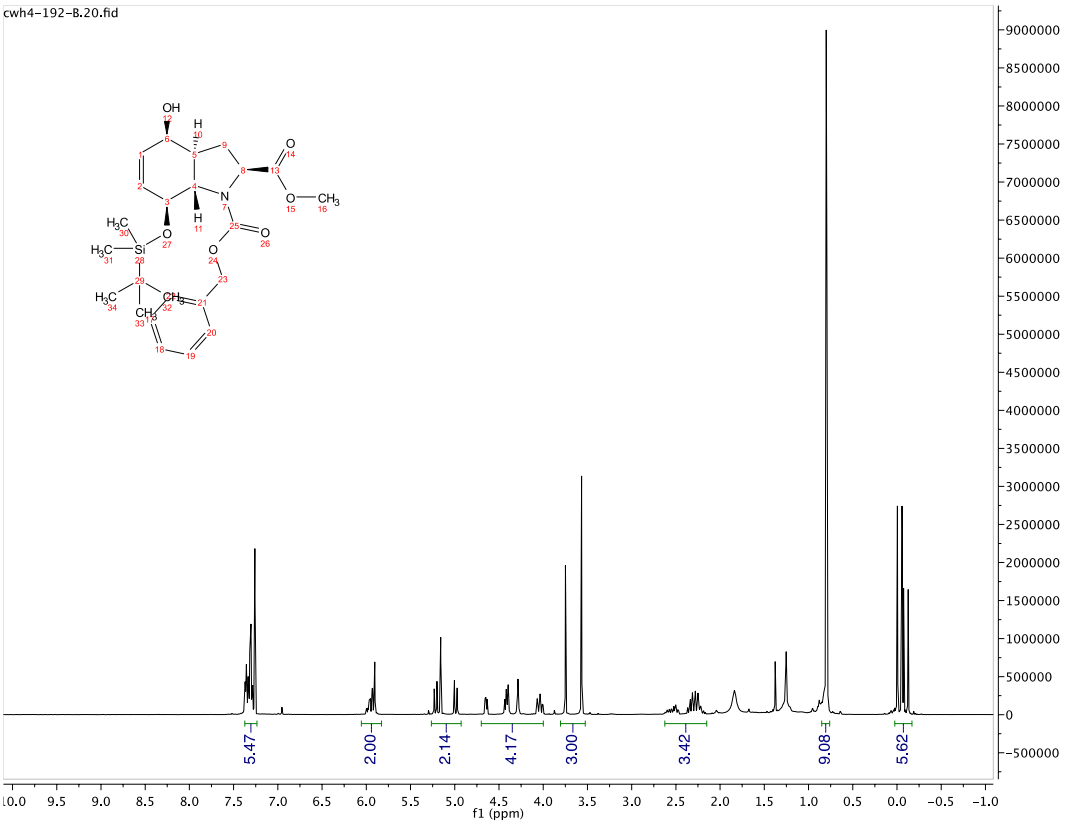
1-benzyl 2-methyl (2S,3aS,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-4-hydroxy-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (109)

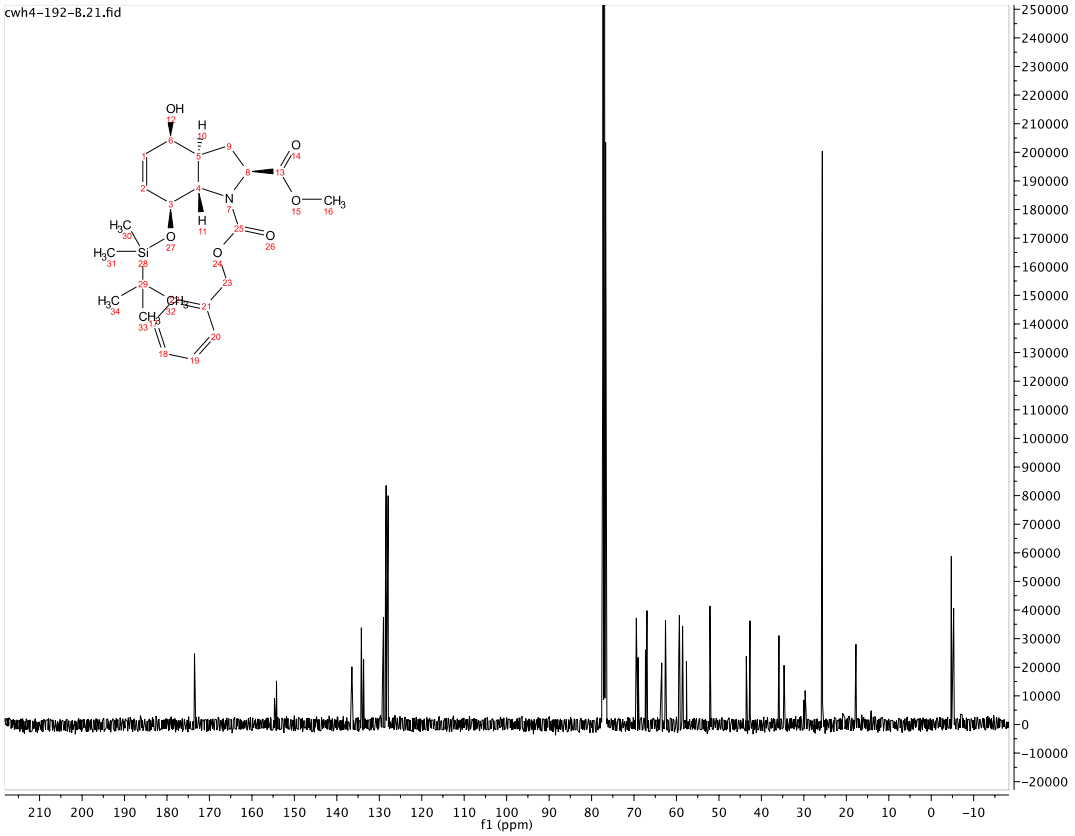


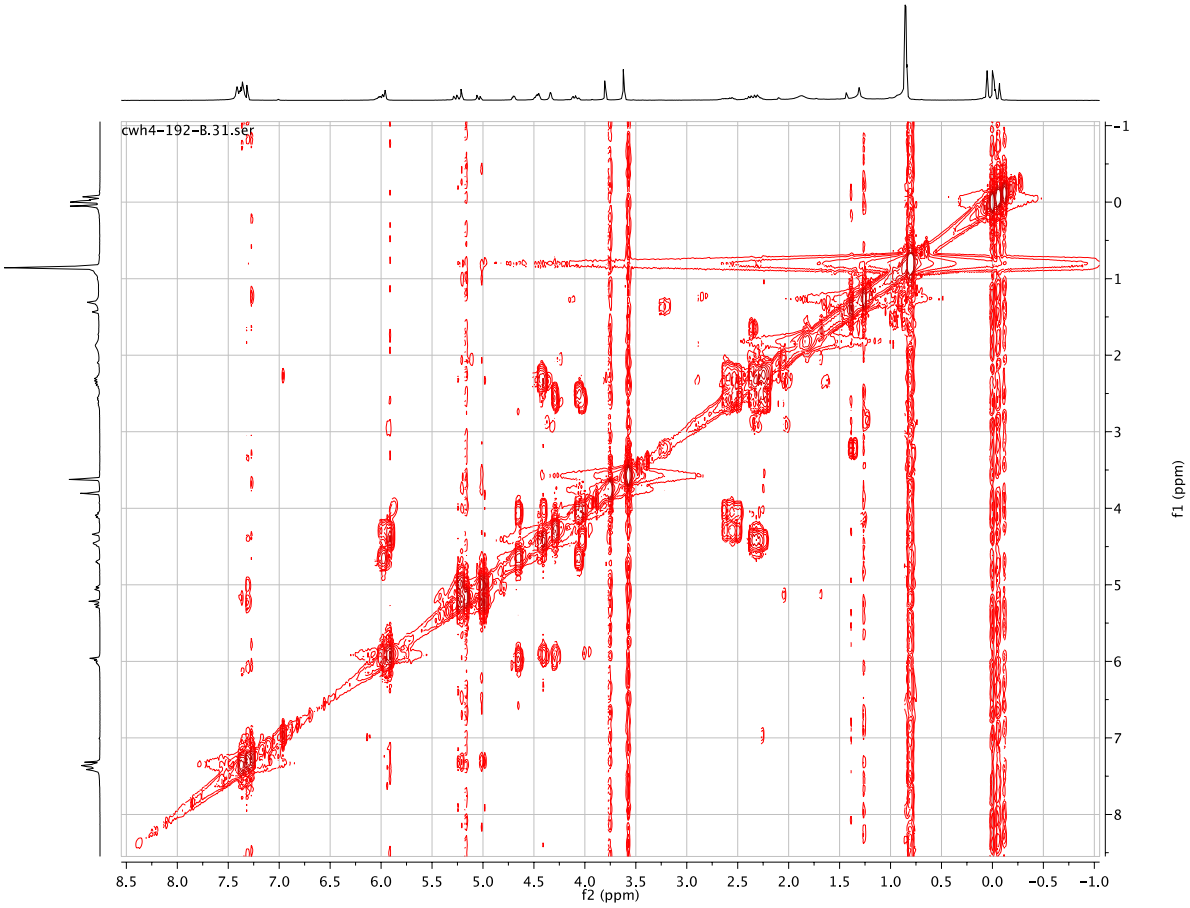
108 **109**

To a stirred solution of compound **108** (41 mg, 0.0635 mmol, 1 eq) in DCM (3.0 mL, 0.025 M) was added 77% *m*CPBA (17 mg, 0.0762 mmol, 1.2 eq) in DCM (0.76 mL, 0.10 M) at -78 °C, and then reaction mixture was stirred at 4 °C. After for 5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **109** as a white foam (20 mg, 70% yield). Rf = 0.45 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.24 (m, 5H), 6.06 – 5.83 (m, 2H), 5.26 – 4.93 (m, 2H), 4.70 – 4.00 (m, 4H), 3.66 (s+ s', 3H), 2.62 – 2.15 (m, 3H), 0.80 (m, 9H), 0.02 – -0.17 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (173.51, 173.41), (154.68, 154.20), (136.45, 136.32), (134.22, 133.69), (129.02, 128.82), (128.54, 128.39), (128.28, 128.16), (127.96, 127.91), (69.44, 69.02), (67.29, 66.95), (63.46, 62.58), (59.46, 59.30), (58.56, 57.65), (52.29, 52.12), (43.55, 42.68), (35.87, 34.66), (29.97, 29.72), (25.65, 25.64), (17.74, 17.71), (-4.72, -5.20). New compound; Procedure was taken from reference ***52***.

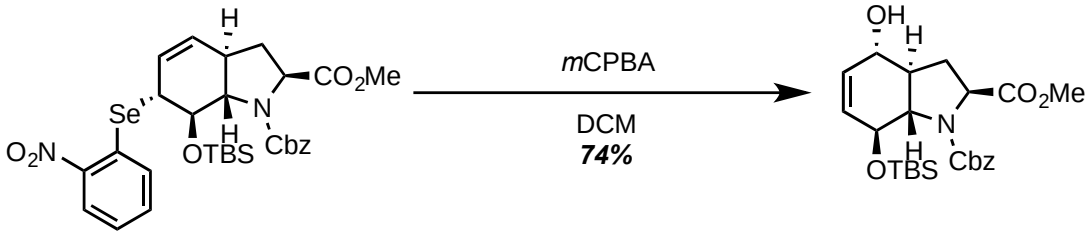
Notebook Entries:
Procedure – cwh4-192
^{1}H – cwh4-192-B
^{13}C – cwh4-192-B


cwh4-192-B.20.fid
5.47
2.00
2.14
4.17
3.00
3.42
9.08
5.62
f1 (ppm)


cwh4-192-B.21.fid
f1 (ppm)


cwh4-192-B.31.ser
f2 (ppm)
f1 (ppm)

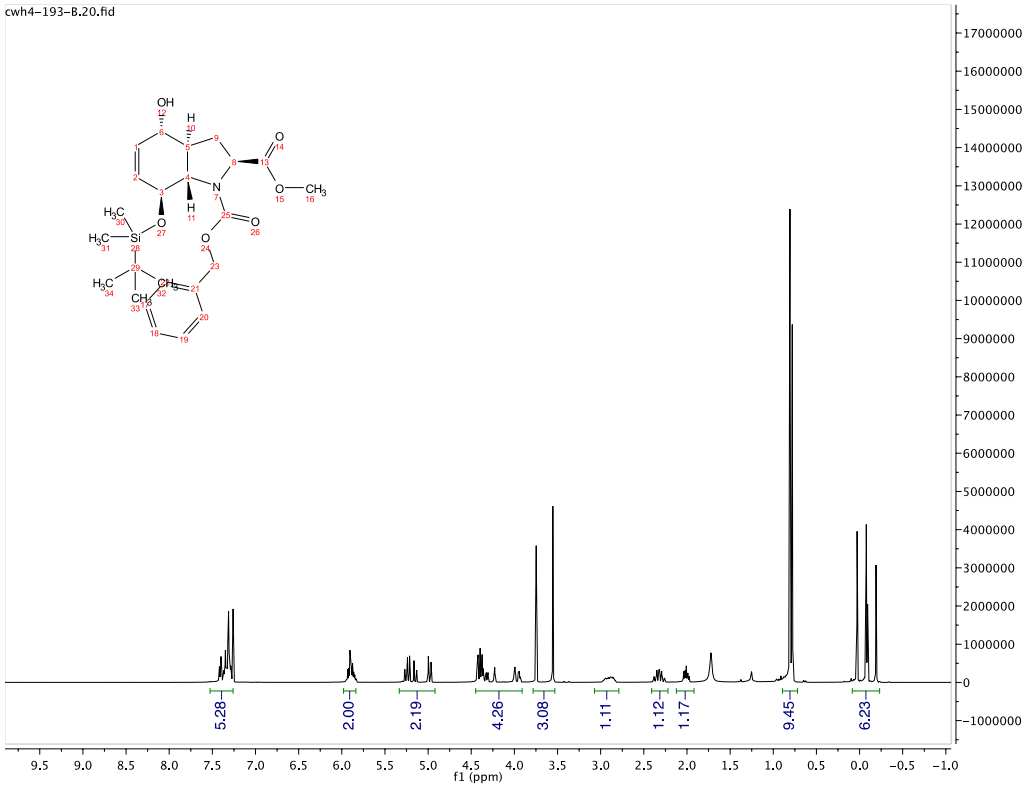
1-benzyl 2-methyl (2*S*,3a*S*,4*S*,7*S*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (101)

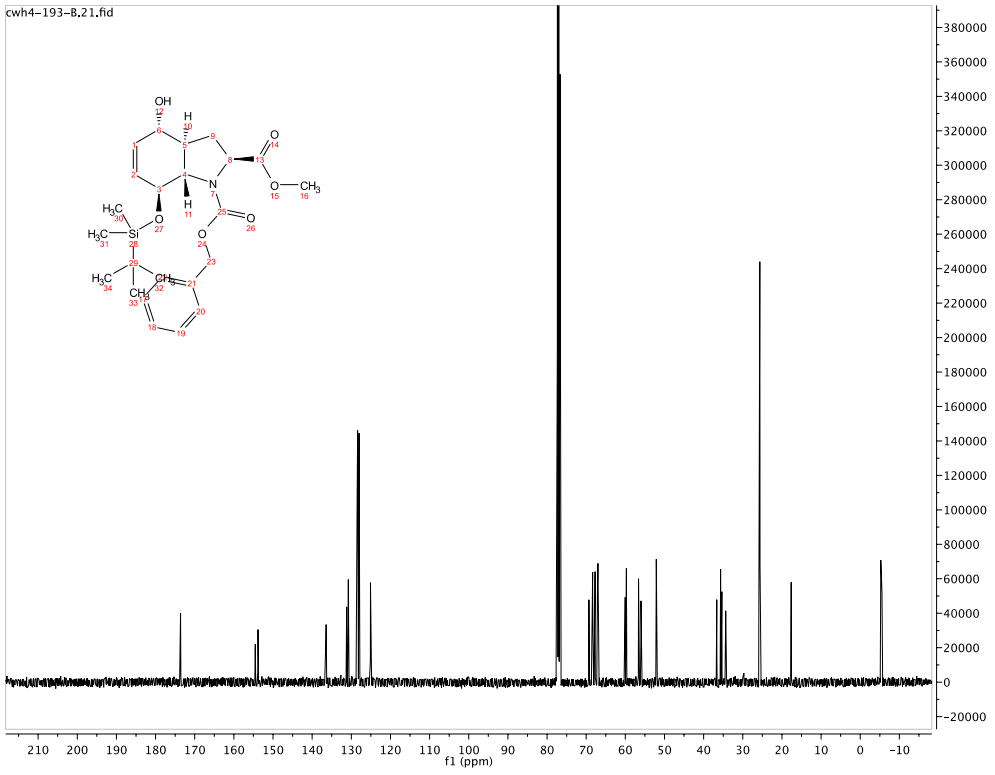


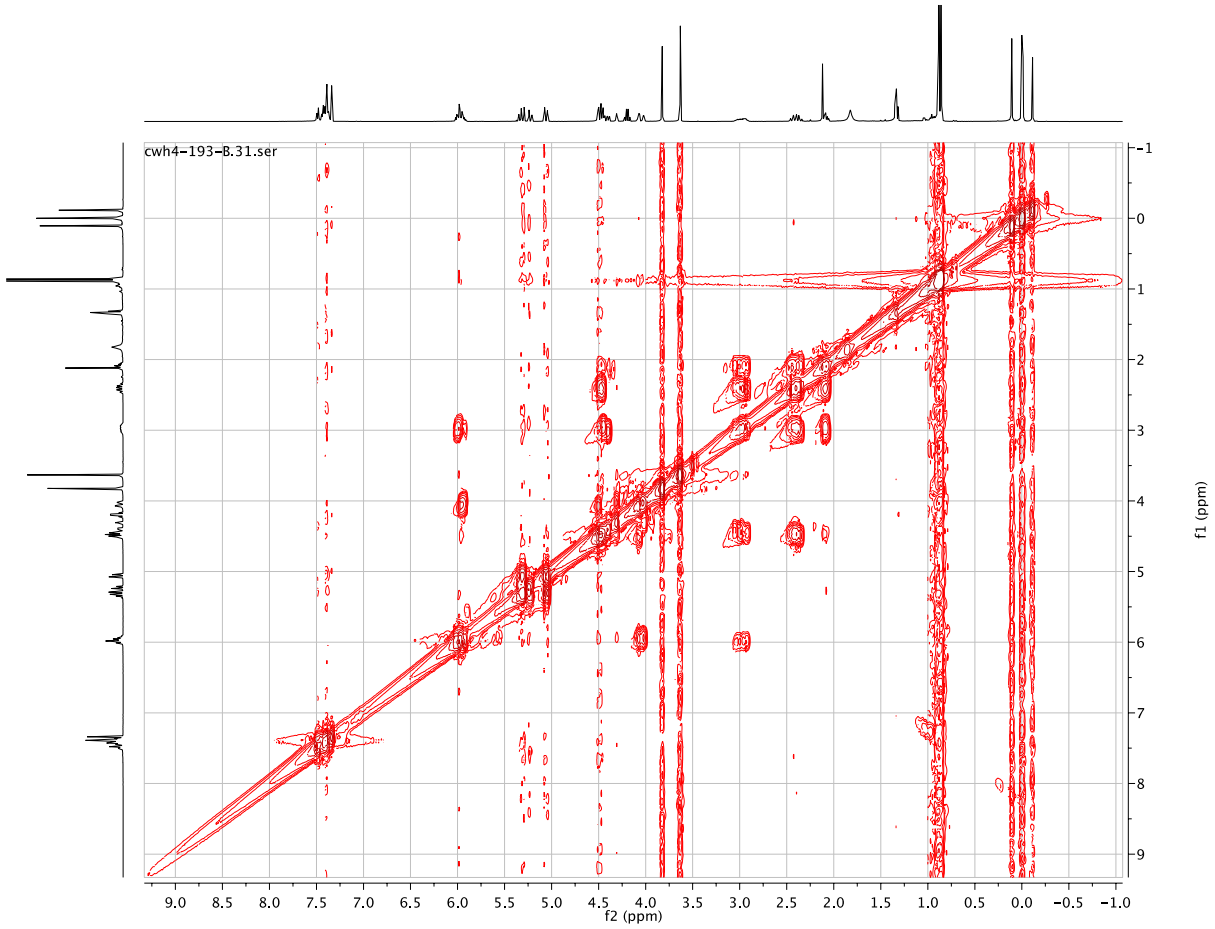
107 **101**

To a stirred solution of compound **107** (78 mg, 0.1209 mmol, 1 eq) in DCM (5.0 mL, 0.025 M) was added 77% *m*CPBA (32 mg, 0.1451 mmol, 1.2 eq) in DCM (1.5 mL, 0.10 M) at -78 °C, and then reaction mixture was stirred at 4 °C. After for 5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **101** as a white foam (41 mg, 74% yield). Rf = 0.46 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.26 (m, 5H), 5.98 – 5.84 (m, 2H), 5.33 – 4.92 (m, 2H), 4.45 – 3.91 (m, 4H), 3.65 (s+ s', 3H), 3.07 – 2.79 (m, 1H), 2.32 (m, 1H), 2.01 (m, 1H), 0.79 (m, 9H), 0.08 – -0.23 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (173.61, 173.57), (154.54, 153.82), (136.48, 136.43), (131.19, 130.76), (128.52, 128.39), (128.25, 128.08), (128.02, 127.98), (125.11, 124.94), (69.31, 68.36), (67.91, 67.73), (67.13, 67.00), (60.04, 59.74), (56.62, 55.99), (52.28, 52.09), (36.64, 35.66), (35.35, 34.35), (25.65, 25.62), (17.64, 17.63), (-5.18, -5.44). New compound; Procedure was taken from reference ***52***.

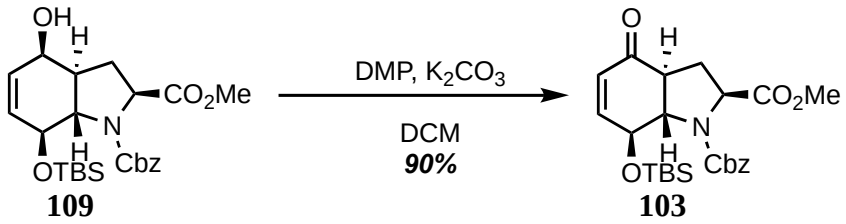
Notebook Entries:
Procedure – cwh4-193
^{1}H – cwh4-193-B
^{13}C – cwh4-193-B


cwh4-193-B.20.fid
5.28
2.00
2.19
4.26
3.08
1.11
1.12
1.17
9.45
6.23
f1 (ppm)


cwh4-193-B.21.fid
f1 (ppm)


cwh4-193-B.31.ser
f2 (ppm)
f1 (ppm)

1-benzyl 2-methyl (2S,3aS,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-4-oxo-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (103)

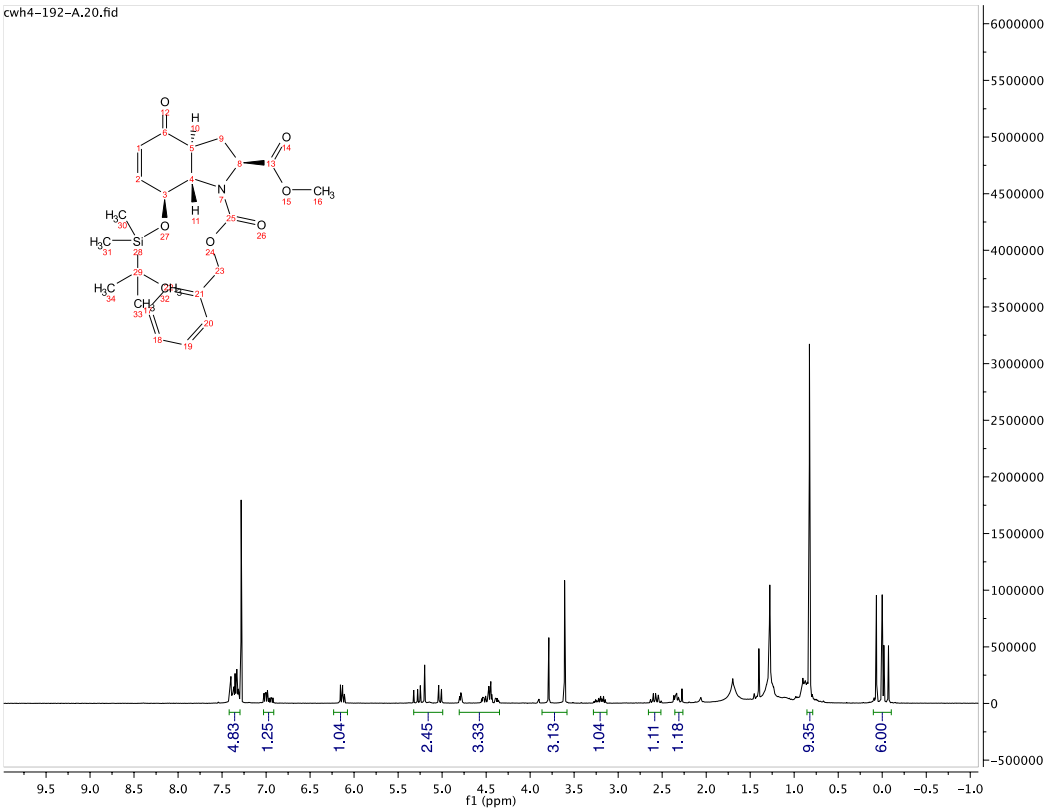


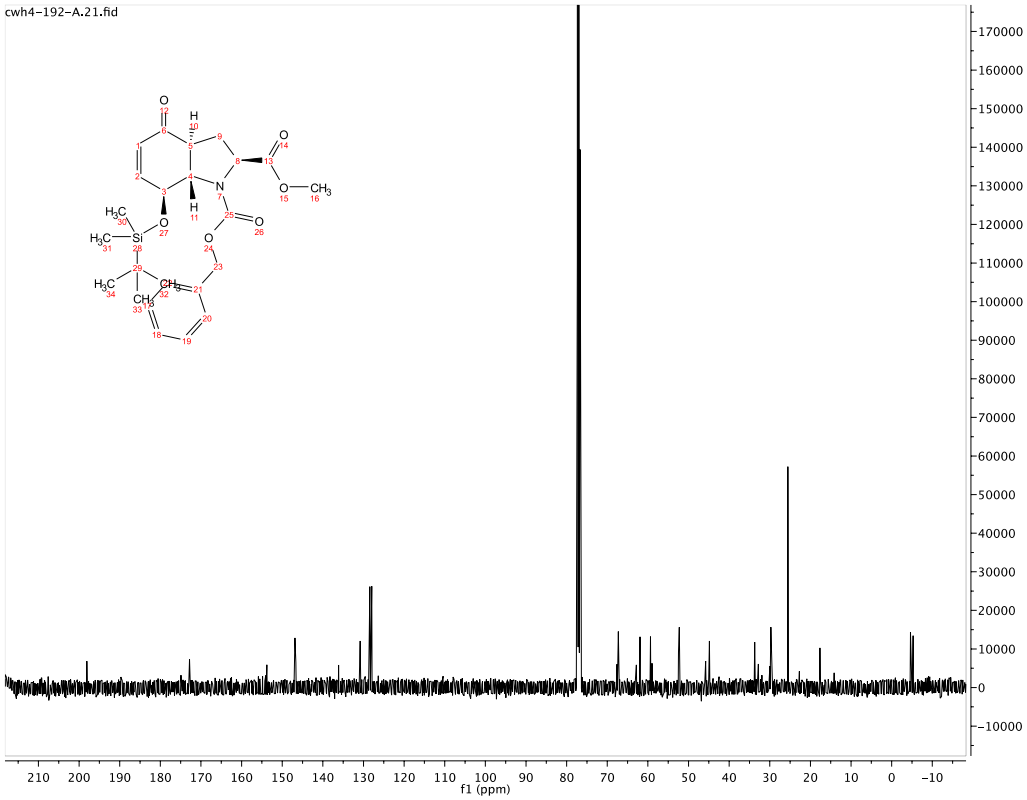
109 **103**

To a stirred solution of compound **109** (20 mg, 0.044 mmol, 1 eq) in DCM (0.45 mL, 0.10 M) was added DMP (37 mg, 0.088 mmol, 2 eq) and K_2CO_3 (18 mg, 0.132 mmol, 3 eq), and then was stirred at room temperature. After for 4 h, the reaction was diluted with H_2O and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **103** as a white foam (18 mg, 90% yield). Rf = 0.53 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.27 (m, 5H), 7.01 – 6.89 (m, 1H), 6.11 (dd, *J* = 10.0, 8.0 Hz, 1H), 5.30 – 4.97 (m, 2H), 4.78 – 4.33 (m, 3H), 3.67 (s+ s', 3H), 3.26 – 3.10 (m, 1H), 2.56 (m, 1H), 2.33 – 2.24 (m, 1H), 0.80 (m, 9H), -0.09 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (198.10, 198.09), (172.81, 72.80), (153.79, 53.78), (146.88, 146.65), (136.11, 136.10), (130.81, 130.73), 128.65), (128.56, 128.44), (128.12, 127.97), (67.65, 67.26), (62.85, 61.94), (59.64, 59.55), (59.36, 58.98), (52.46, 52.28), (45.80, 44.87), (33.71, 32.80), (29.97, 29.72), 25.55, (17.66, 17.65), (-4.62, -5.28). New compound; Procedure was taken from reference ***39***.

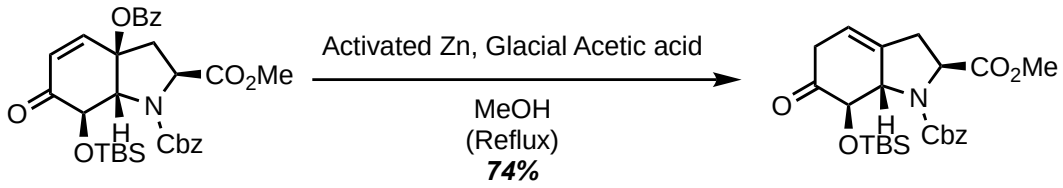
Notebook Entries:

Procedure – cwh4-254
^{1}H – cwh4-192-A
^{13}C – cwh4-192-A


cwh4-192-A.20.fid
4.83
1.25
1.04
2.45
3.33
3.13
1.04
1.11
1.18
9.35
6.00
f1 (ppm)


cwh4-192-A.21.fid
f1 (ppm)

1-benzyl 2-methyl (2S,7R,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,5,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (110)

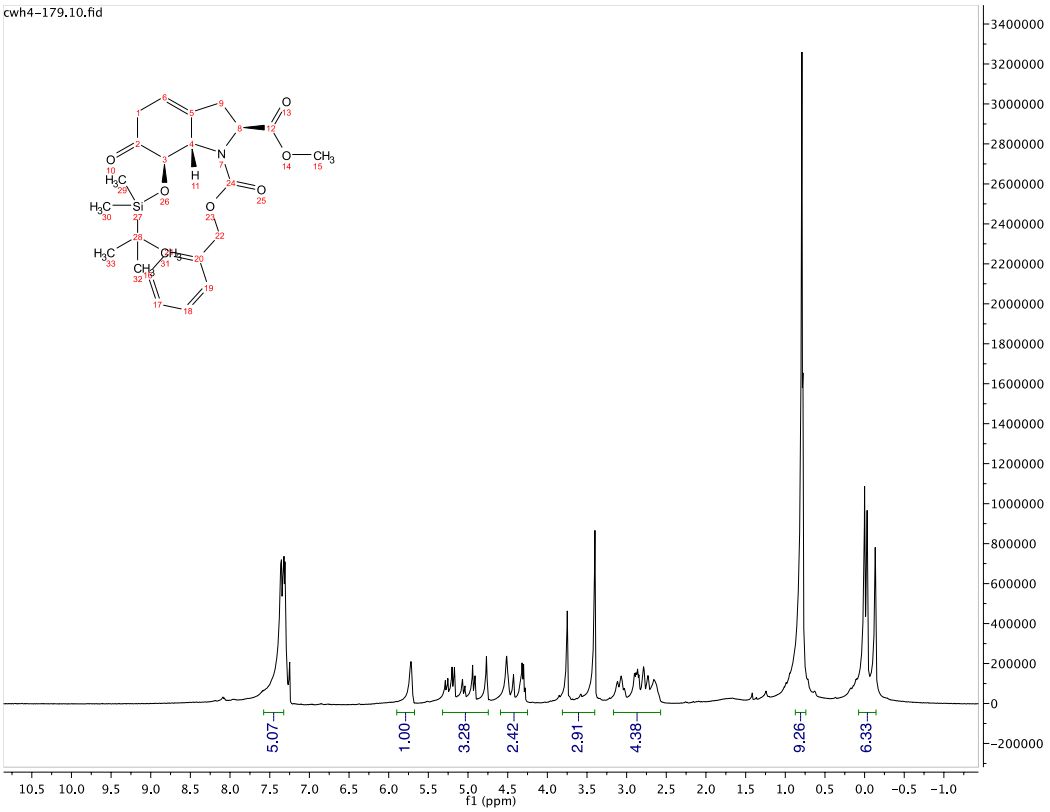


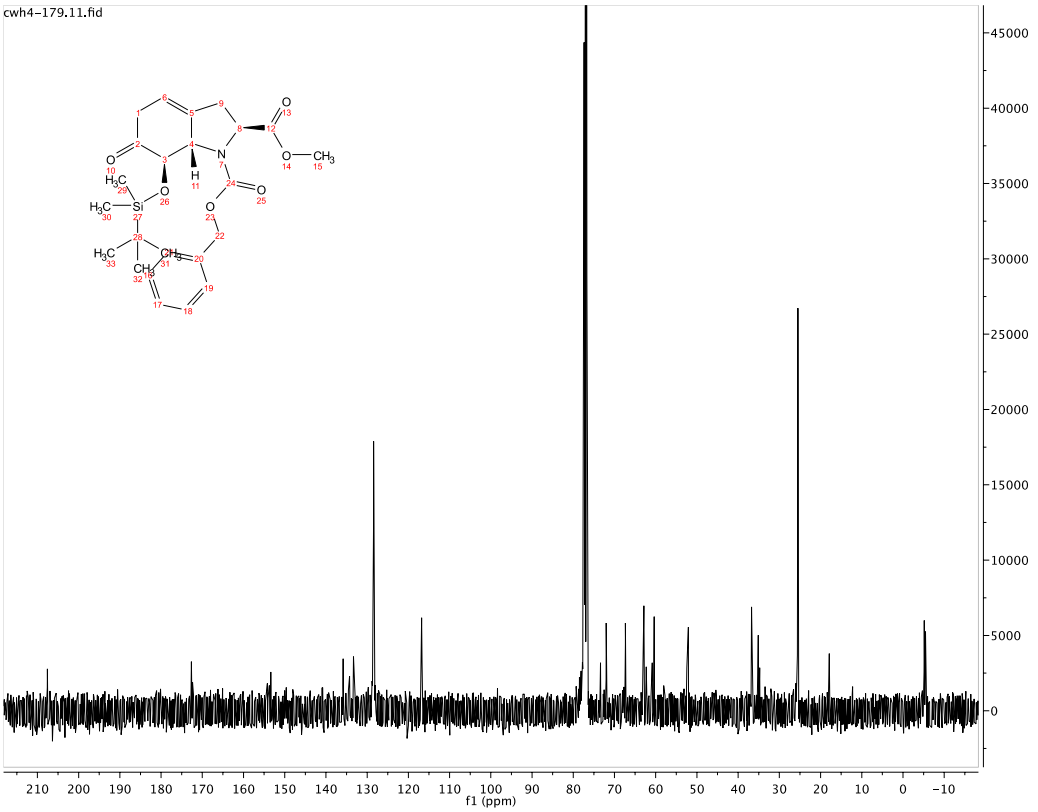
104 **110**

To a stirred solution of compound **104** (260 mg, 0.476 mmol, 1 eq) in MeOH (2 mL, 0.223 M) was added activated Zn (250 mg, 3.812 mmol, 8 eq) and glacial acetic acid (0.06 mL, 0.952 mmol, 2 eq), and was refluxed. After 0.5 h reaction mixture was filtered through celite pad and the organic layer was concentrated in vacuo. Then the crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **110** as a white foam (161 mg, 74% yield). Rf = 0.39 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.32 (m, 5H), 5.72 (m, 1H), 5.32 – 4.74 (m, 3H), 4.59 – 4.25 (m, 2H), 3.81 – 3.40 (s+ s', 3H), 3.17 – 2.57 (m, 4H), 0.87 – 0.74 (m, 9H), 0.08 – -0.14 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (207.58, 207.57), (172.64, 172.63), (154.12, 153.93), (135.84, 133.32, 128.64), (128.45, 128.41), (128.35, 128.22), (116.80, 116.70), (73.39, 72.00), (67.66, 67.36), (62.87, 62.29), (60.85, 60.38), (52.07, 52.06), (36.73, 35.10), (25.49, 25.48), (17.89, 17.88), (-5.15, -5.44). New compound; Procedure was taken from reference ***39***.

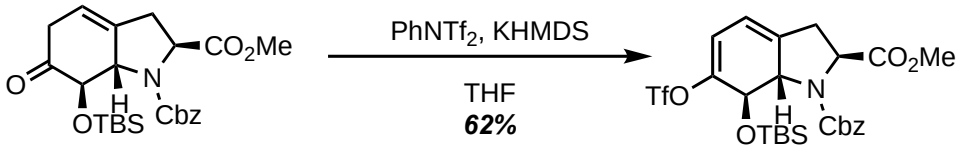
Notebook Entries:

Procedure – cwh4-179
^{1}H – cwh4-179
^{13}C – cwh4-179


cwh4-179.10.fid
5.07
1.00
3.28
2.42
2.91
4.38
9.26
6.33
f1 (ppm)


cwh4-179.11.fid
f1 (ppm)

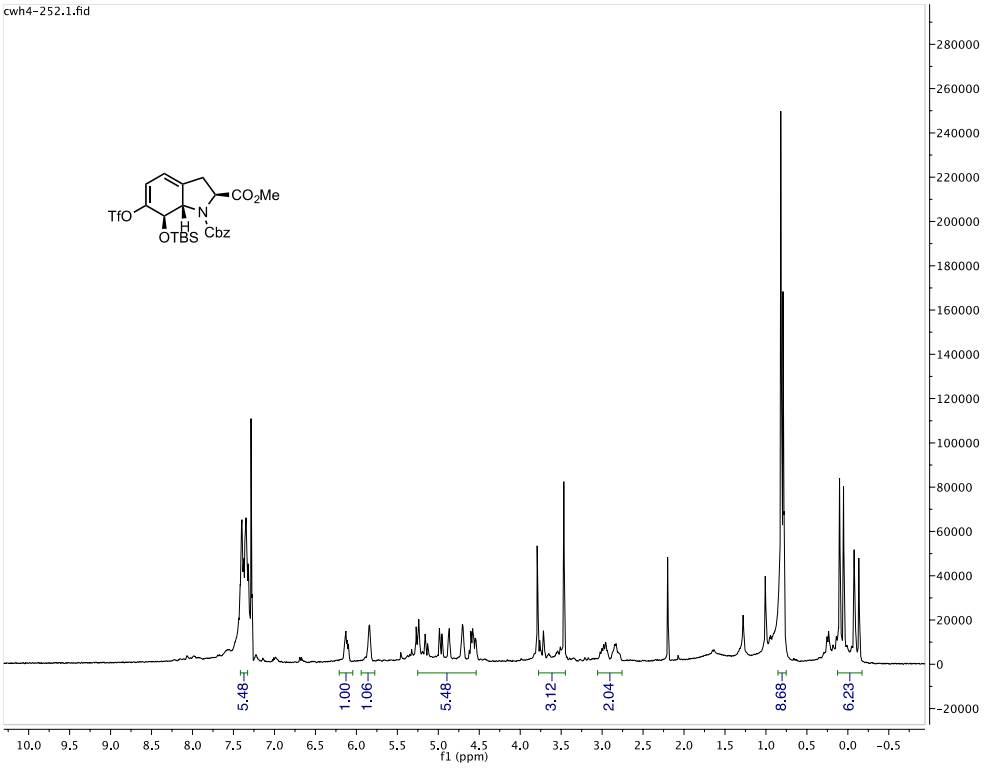
1-benzyl 2-methyl (2S,7R,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-(((trifluoromethyl)sulfonyl)oxy)-2,3,7,7a-tetrahydro-1H-indole-1,2-dicarboxylate (111)

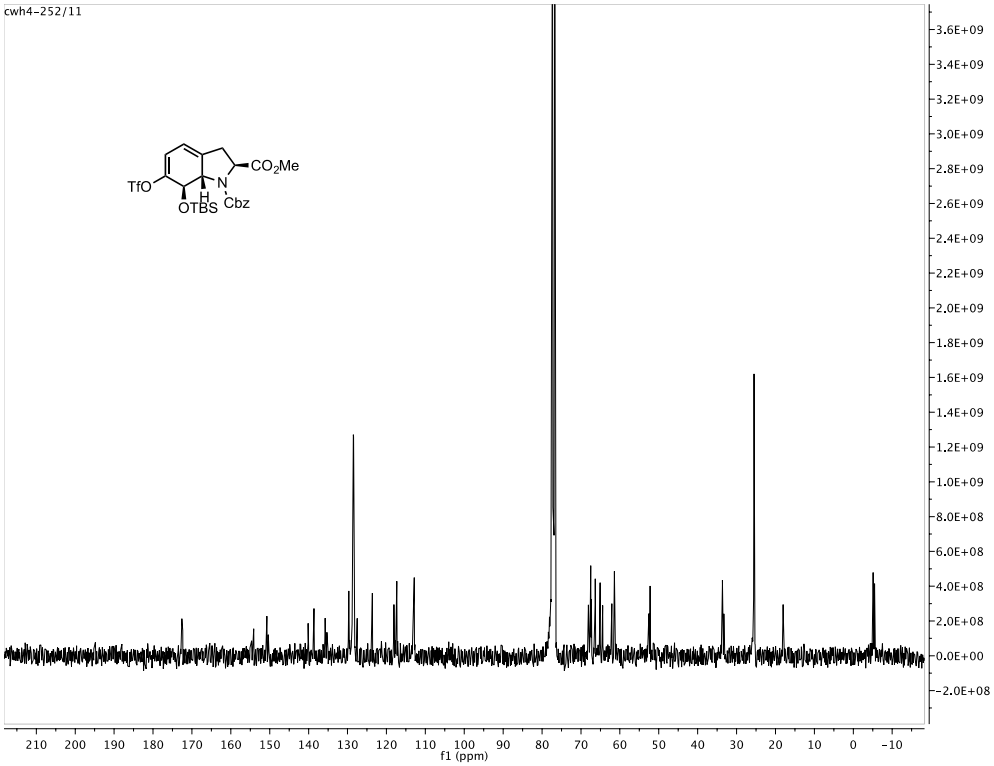


110 **111**

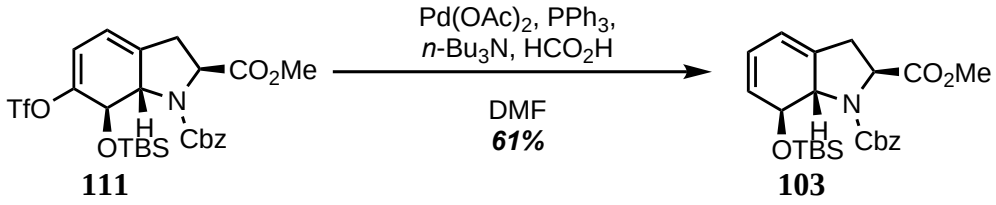
To a stirred solution of compound **110** (48 mg, 0.104 mmol, 1 eq) in THF (1 mL, 0.10 M) was cooled to – 78 °C. Then $PhNTf_2$ (41 mg, 0.115 mmol, 1.1 eq) was added followed by KHMDS (0.25 mL, 0.125 mmol, 1.2 eq), and then was stirred at – 78 °C. After 0.5 h, the reaction was quenched with H_2O and the organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **111** as a white foam (38 mg, 62% yield). Rf = 0.54 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.33 (m, 5H), 6.12 (m, 1H), 5.84 (m, 1H), 5.25 – 4.54 (m, 5H), 3.78 – 3.45 (m, 3H), 3.05 – 2.76 (m, 2H), 0.85 – 0.75 (m, 9H), 0.13 – -0.17 (m, 6H). (172.57, 172.56), (154.16, 154.14), (150.74, 150.73), (140.12, 138.62), (135.74, 133.43), (129.66, 128.66), (128.48, 128.43), (127.50, 123.62), (118.07, 117.32), (112.84, 112.83), (68.08, 67.48), (67.33, 66.33), (65.06, 64.41), (62.05, 61.42), (52.55, 52.21), (33.63, 33.28), (25.52, 25.44), (18.03, 18.02), (-5.10, -5.49). New compound; Procedure was taken from reference ***39***.

Notebook Entries:
Procedure – cwh4-252
^{1}H – cwh4-252
^{13}C – cwh4-252


cwh4-252.1.fid
TfO
OTBS
H
N
Cbz
CO2Me
5.48
1.00
1.06
5.48
3.12
2.04
8.68
6.23
f1 (ppm)


cwh4-252/11
TfO
OTBS
H
N
Cbz
CO2Me
f1 (ppm)

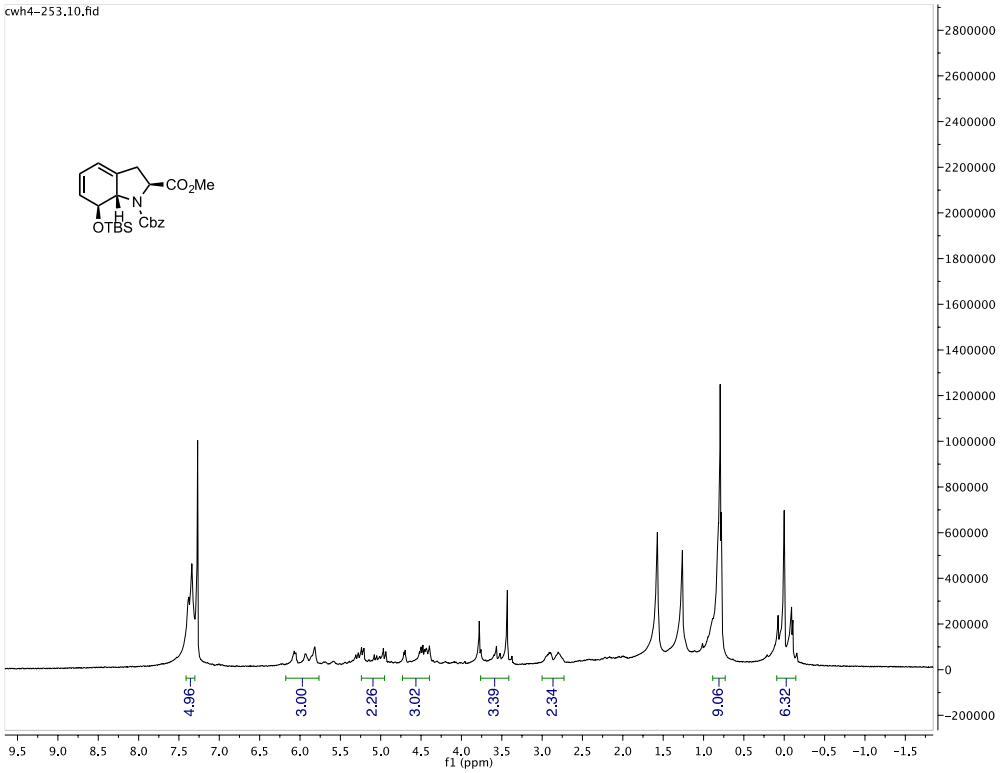
1-benzyl 2-methyl (2S,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,3,7,7a-tetrahydro-1H-indole-1,2-dicarboxylate (103)

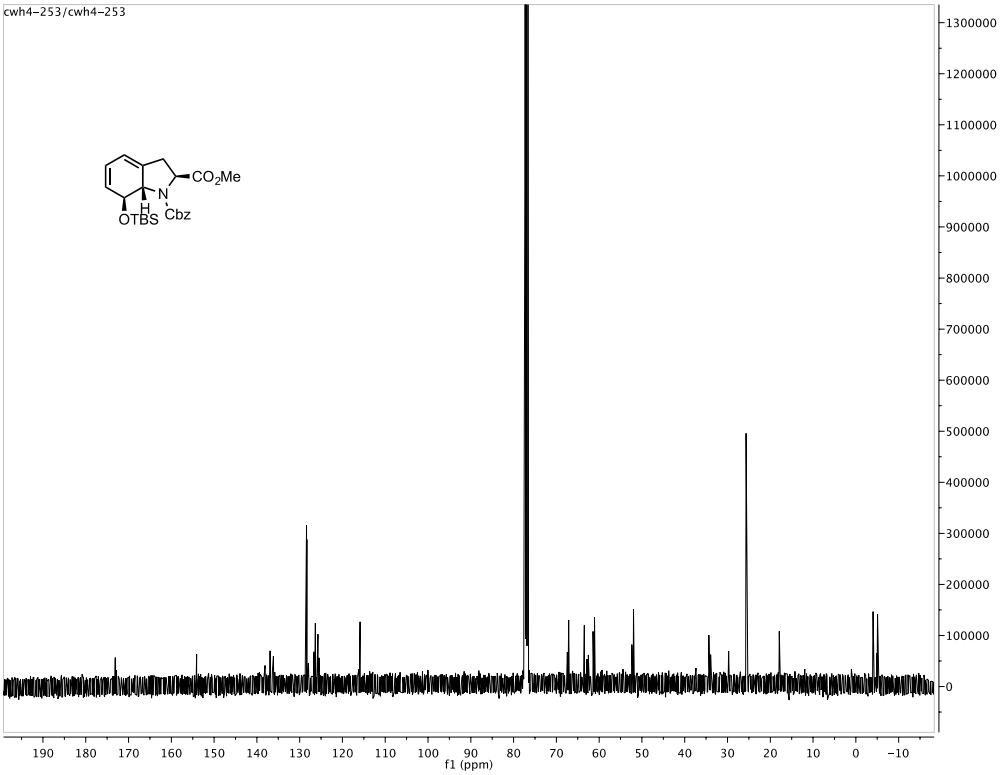


To a stirred solution of compound **111** (25 mg, 0.042 mmol, 1 eq) in DMF (0.5 mL, 0.10 M) was added $Pd(OAc)_2$ (2.0 mg, 0.01 mmol, 0.2 eq) and PPh_3 (4.4 mg, 0.017 mmol, 0.4 eq). Then *n*-Bu_3N (0.05 mL, 0.210 mmol, 5 eq) and HCO_2H (0.005 mL, 0.126 mmol, 3 eq) were added, and then was stirred at 65 °C. After 0.5 h, the reaction was quenched with 1M HCl and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **103** as a white foam (23 mg, 61 % yield). Rf = 0.41 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.30 (m, 5H), 6.18 – 5.76 (m, 3H), 5.24 – 4.95 (m, 2H), 4.73 – 4.40 (s+ s', 3H), 3.76 – 3.41 (m, 3H), 3.00 – 2.73 (m, 2H), 0.89 – 0.73 (m, 9H), 0.09 – -0.14 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (173.10, 172.85), (136.93, 136.91), (128.53, 128.41), (128.32, 128.17), (128.14, 128.08), (126.68, 126.34), (125.72, 125.43), (116.01, 115.89), (67.45, 67.14), (63.46, 62.84), (62.53, 61.68), (61.43, 61.09), (52.36, 51.98), (34.37, 33.94), (29.72, 29.69), (25.66, 25.63), (17.91, 17.90), (-3.94, -5.06). New compound; Procedure was taken from reference ***39***.

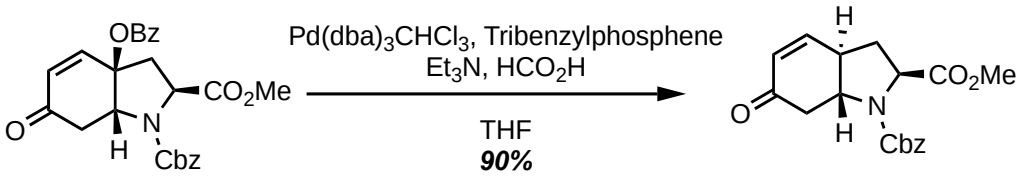
Notebook Entries:

Procedure – cwh4-253
^{1}H – cwh4-253
^{13}C – cwh4-253


cwh4-253.10.fid
CO2Me
N
H
OTBS
Cbz
4.96
3.00
2.26
3.02
3.39
2.34
9.06
6.32
f1 (ppm)


cwh4-253/cwh4-253
CO2Me
N
H
OTBS
Cbz
f1 (ppm)

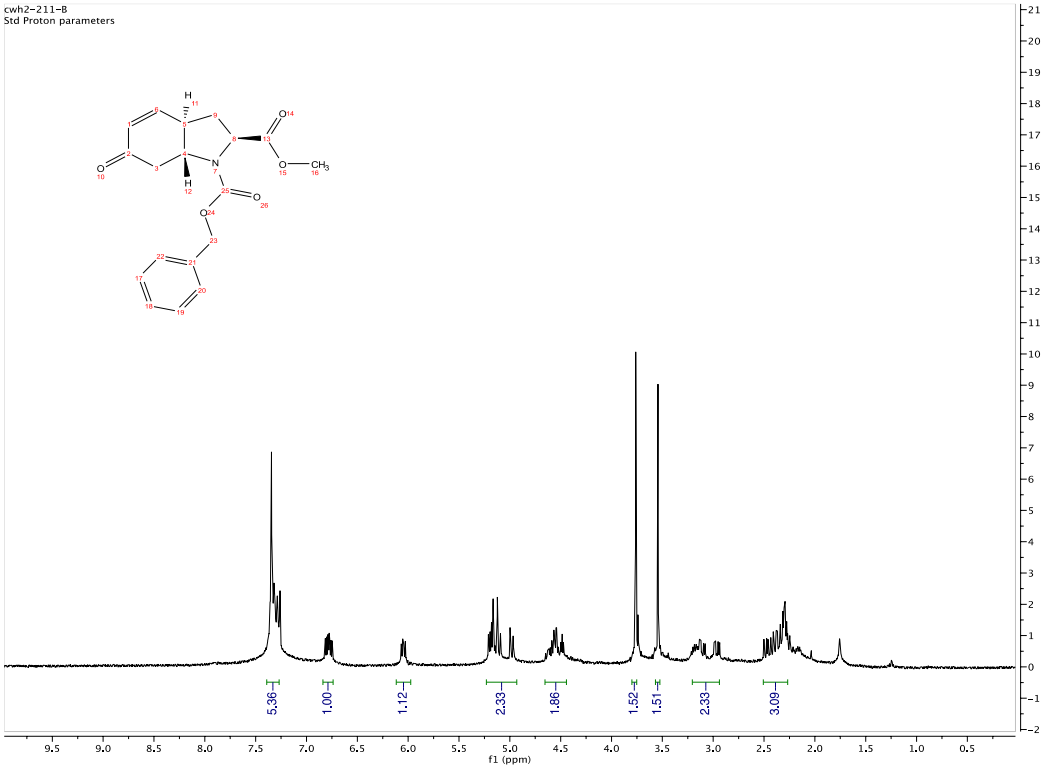
1-benzyl 2-methyl (2S,3aR,7aR)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (16)

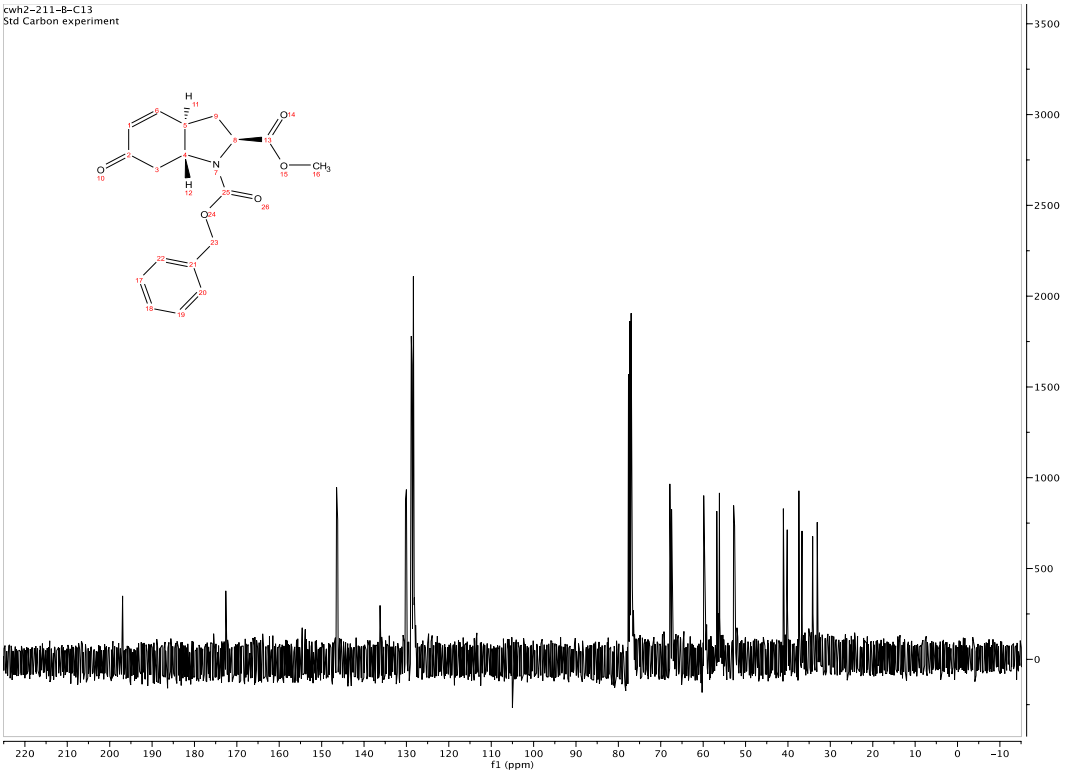


15 **16**

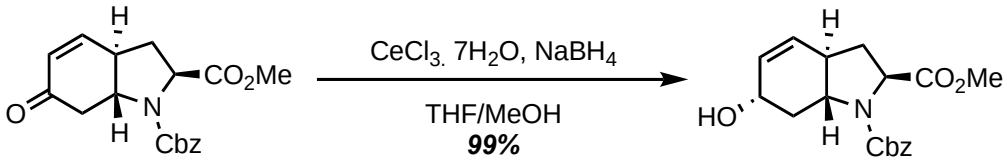
To a stirred solution of compound **15** (900 mg, 2.17 mmol, 1 eq) in THF (10 mL, 0.22 M) was added $Pd(dba)_3CHCl_3$ (45 mg, 0.043 mmol, 0.02 eq) and tribenzylphosphene (52 mg, 0.172 mmol, 0.08 eq). After stirring for 1-minute, Et_3N (1.0 mL, 7.53 mmol, 3.47 eq) was added immediately followed by the addition of 95% HCO_2H (0.3 mL, 7.53 mmol, 3.47 eq), and was refluxed. After 12 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc: hexanes, 1:1) to give compound **16** as a light-yellow foam (643 mg, 90% yield). Rf = 0.44 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.27 (m, 5H), 6.78 (m, 1H), 6.05 (m, 1H), 5.23 – 4.93 (m, 2H), 4.65 – 4.44 (m, 2H), 3.76 + 3.54 (s+ s', 3H), 3.21 – 2.94 (m, 2H), 2.51 – 2.27 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ (196.96, 196.85), (172.76, 172.60), (146.47, 146.21), (136.30, 136.21), (130.21, 130.01), (128.84,128.77), (128.68, 128.52), (128.37, 128.23), (67.86, 67.46), (59.88, 59.64), (56.79, 56.78), (56.50, 56.16), (52.83, 52.58), (41.09, 40.18), (37.43, 36.68), (34.16, 33.09). Known compound; all the spectral data matches the data reported in reference ***40***.

Notebook Entries:
Procedure – cwh2-365
^1H – cwh2-211-B
^{13}C – cwh2-211-B


cwh2-211-B
Std Proton parameters
5.36
1.00
1.12
2.33
1.86
1.52
1.51
2.33
3.09
f1 (ppm)


cwh2-211-B-C13
Std Carbon experiment
f1 (ppm)

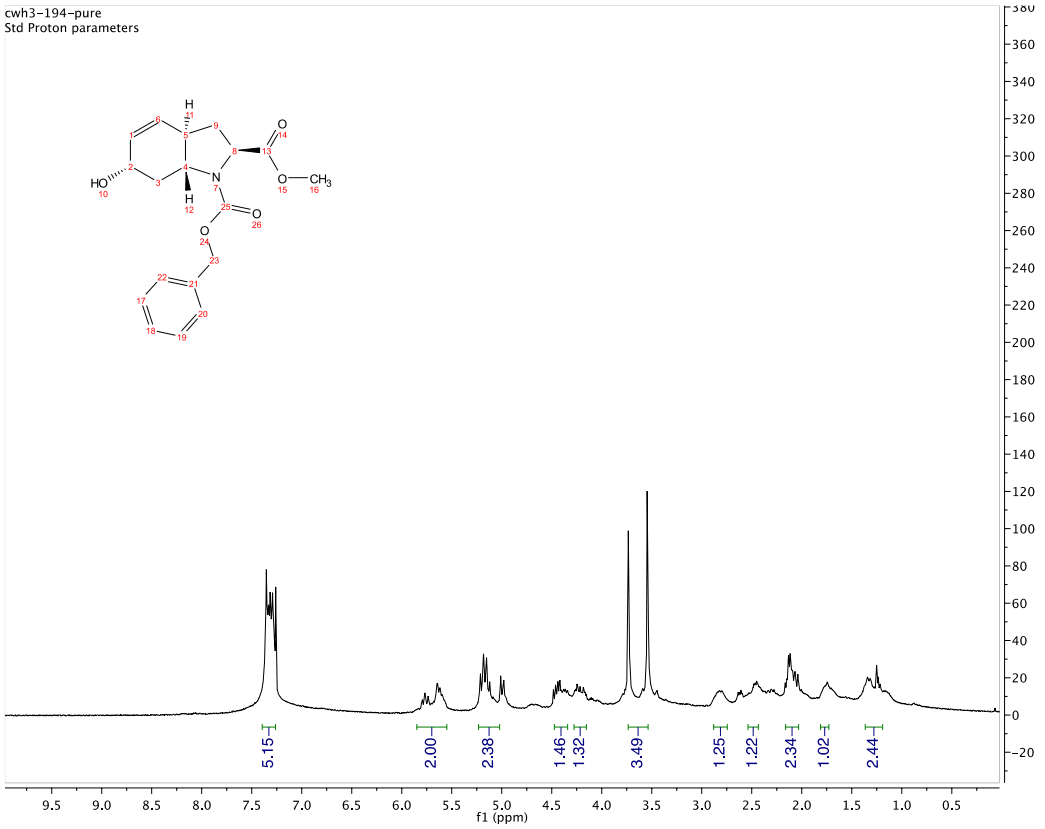
1-benzyl 2-methyl (2S,3aR,6S,7aR)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (95)

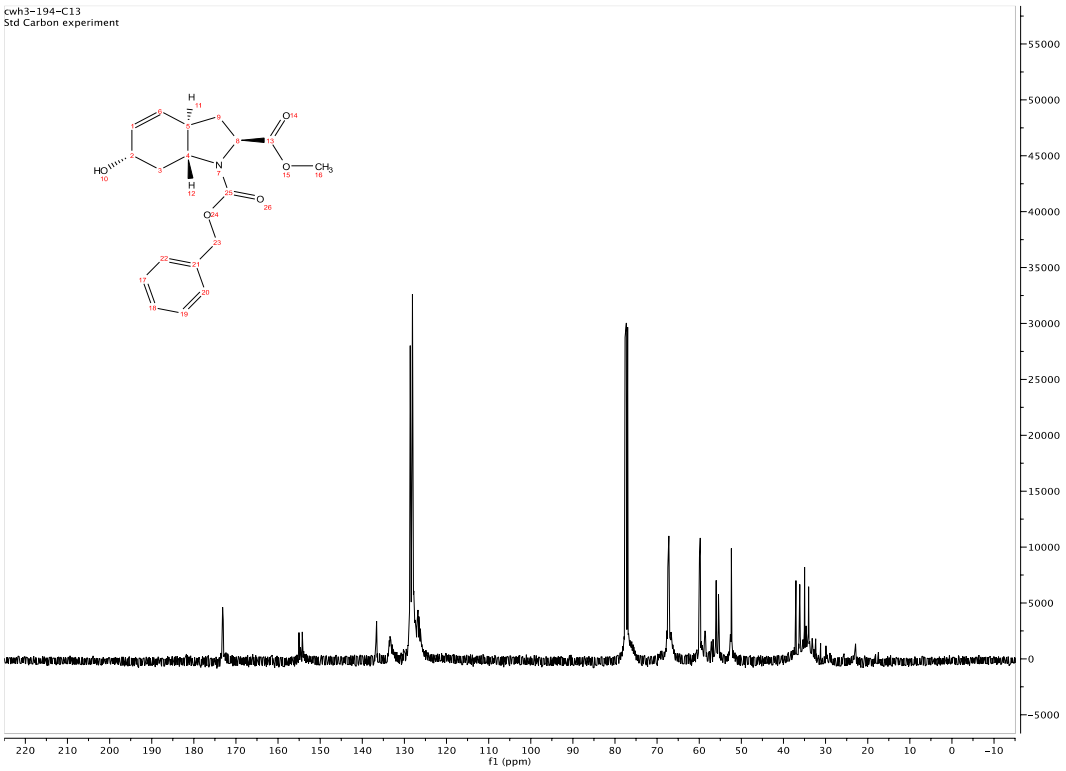


16 **95**

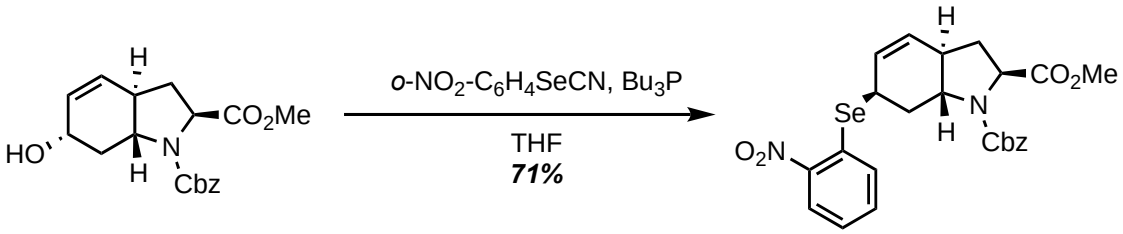
To a stirred solution of compound **16** (50 mg, 0.52 mmol, 1 eq) in THF:MeOH 1:1 (2.0 mL, 0.0875M) was added $CeCl_3 \cdot 7H_2O$ (57 mg, 0.152 mmol, 1 eq), and was stirred. After 5 mins, $NaBH_4$ (6 mg, 0.152 mmol, 1 eq) was added portion wise, and then was stirred at room temperature. After 5 mins, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **95** as a white foam (50 mg, 99% yield). Rf = 0.41 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 (m, 5H), 5.85 – 5.55 (m, 2H), 5.23 – 5.02 (m, 2H), 4.47 – 4.34 (m, 1H), 4.22 (m, 1H), 3.74 – 3.54 (s+ s', 3H), 2.82 (m, 1H), 2.54 – 2.43 (m, 1H), 2.16 – 2.03 (m, 2H), 1.33 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (173.16, 173.02), (155.05, 154.25), (136.60, 136.59), (133.08, 133.07), (128.73, 128.69), (128.62, 128.60), (128.26, 128.22), (128.16, 128.09), (128.01, 126.77), (126.55, 126.54), (67.45, 67.37), (59.78, 59.75), (55.98, 55.44), (52.53, 52.37), (37.05, 36.14), (34.99, 34.82). Known compound; all the spectral data matches the data reported in reference ***40***.

Notebook Entries:
Procedure – cwh3-194
^{1}H – cwh3-194-pure
^{13}C – cwh3-194-pure


cwh3-194-pure
Std Proton parameters
5.15
2.00
2.38
1.46
1.32
3.49
1.25
1.22
2.34
1.02
2.44
f1 (ppm)


cwh3-194-C13
Std Carbon experiment
f1 (ppm)

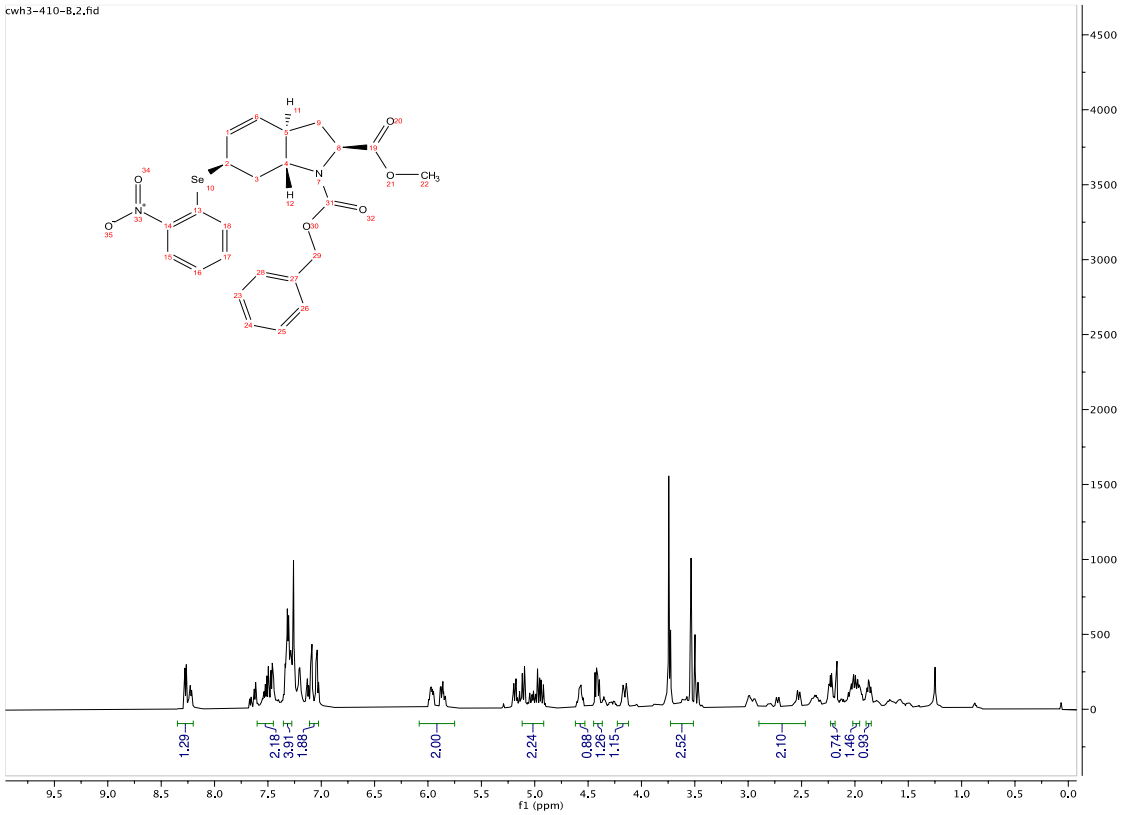
1-benzyl 2-methyl (2S,3aR,6R,7aR)-6-((2-nitrophenyl)selanyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (96)

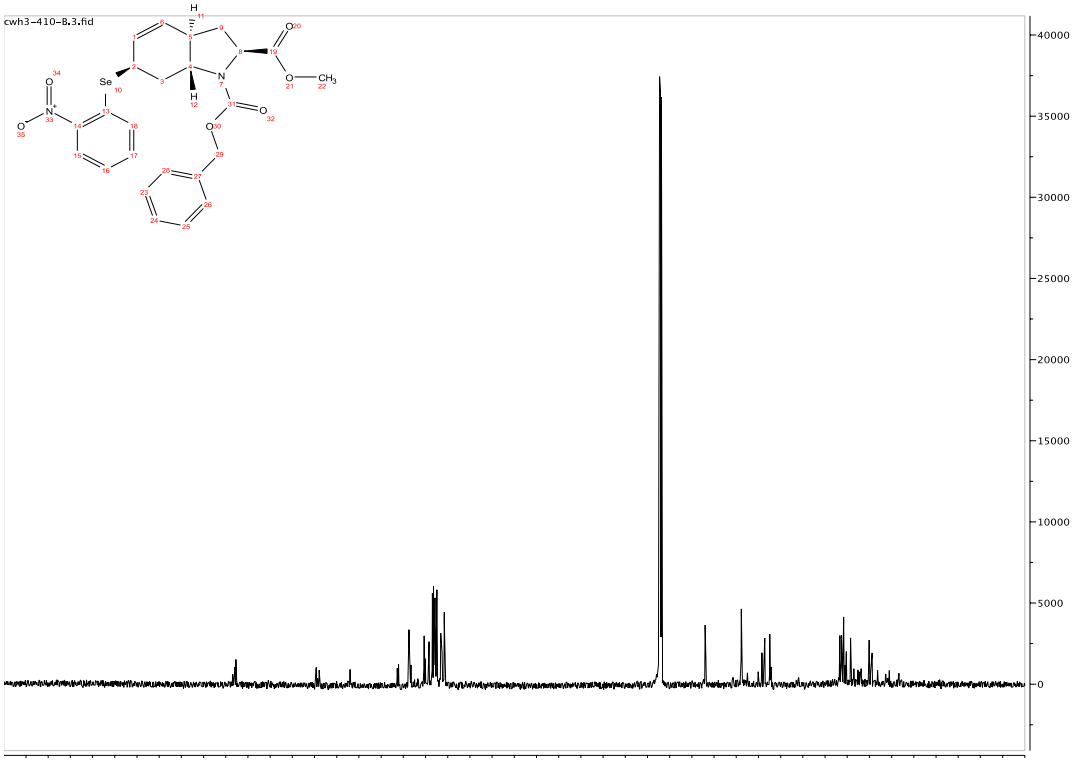


95 **96**

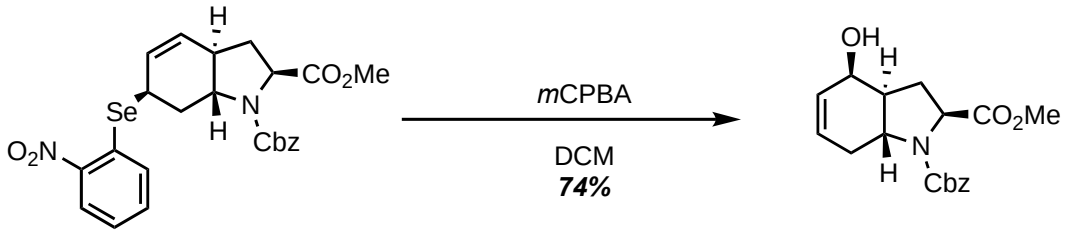
To a stirred solution of compound **95** (60 mg, 0.181 mmol, 1 eq) in THF (1.8 mL, 0.1 M) was added *o*-NO_2-C_6H_4SeCN (82 mg, 0.362 mmol, 2 eq) and Bu_3P (0.10 mL, 0.398 mmol, 2.2 eq) drop wise, and then was refluxed. After 16 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **96** as a white foam (66 mg, 71% yield). Rf = 0.57 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^1H NMR (600 MHz, Chloroform-d) δ 8.35 – 8.20 (m, 1H), 7.60 – 7.45 (m, 2H), 7.32 (m, 4H), 7.07 (m, 2H), 6.08 – 5.75 (m, 2H), 5.12 – 4.92 (m, 2H), 4.58 (m, 1H), 4.41 (m, 1H), 4.23 – 4.12 (m, 1H), 3.73 + 3.51 (s+ s', 3H), 2.90 – 2.46 (m, 2H), 2.23 – 2.19 (m, 1H), 2.02 – 1.96 (m, 1H), 1.90 – 1.85 (m, 1H). ^{13}C NMR (151 MHz, Chloroform-d) δ (172.95, 172.70), (154.06, 153.96), (146.99, 146.98), (136.38, 136.07), (133.85, 133.70), (130.04, 129.84), (129.36, 129.20), (128.48, 128.44), (128.41, 128.19), (128.04, 127.87), (127.43, 126.61), (126.26, 125.98), (125.77, 125.51), (67.02, 66.95), (66.88, 66.83), (58.87, 58.68), (54.22, 53.58), (52.36, 52.23), (36.65, 36.29), (35.80, 35.20), (34.24, 33.52), (30.05, (29.73). New compound; Procedure was taken from reference ***52***.

Notebook Entries:
Procedure – cwh3-410
^1H – cwh3-410-B ^{13}C – cwh3-410-B


cwh3-410-B.2.fid
1.29
2.18
3.91
1.88
2.00
2.24
0.88
1.26
1.15
2.52
2.10
0.74
1.46
0.93
f1 (ppm)


cwh3-410-B.3.fid

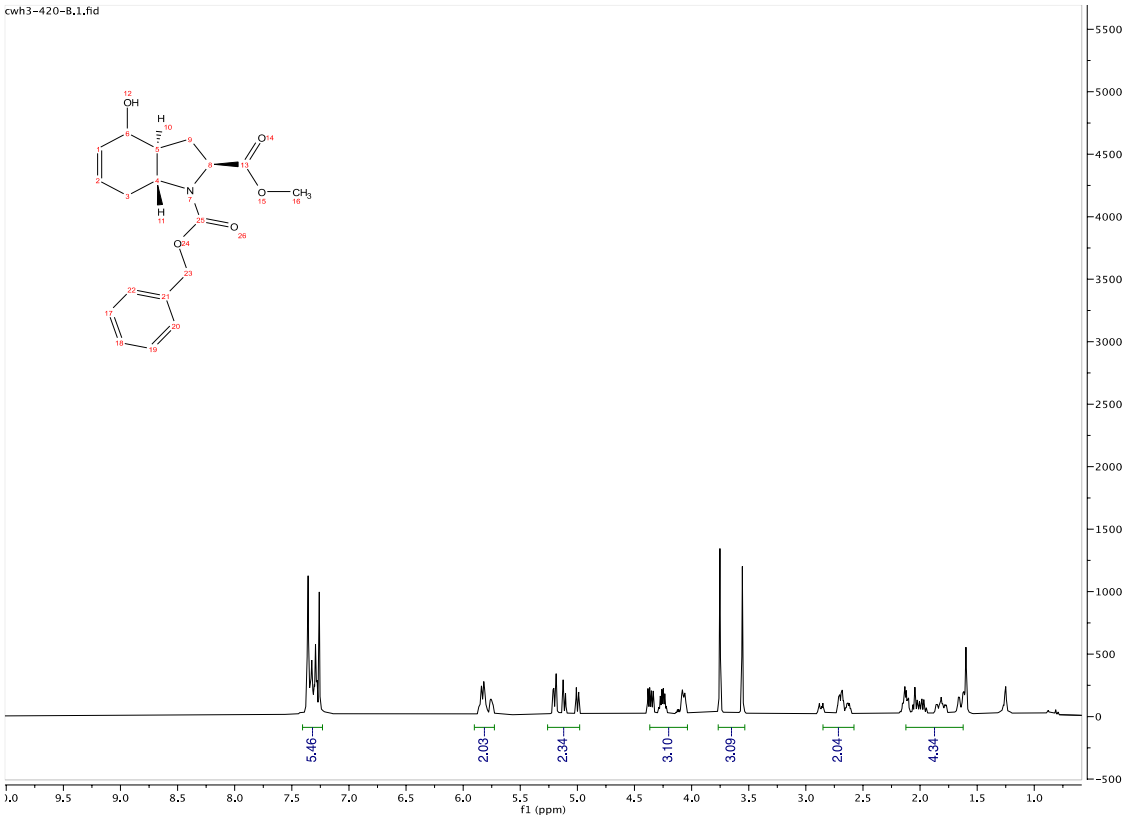
1-benzyl 2-methyl (2S,3aS,7aR)-4-hydroxy-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (97)

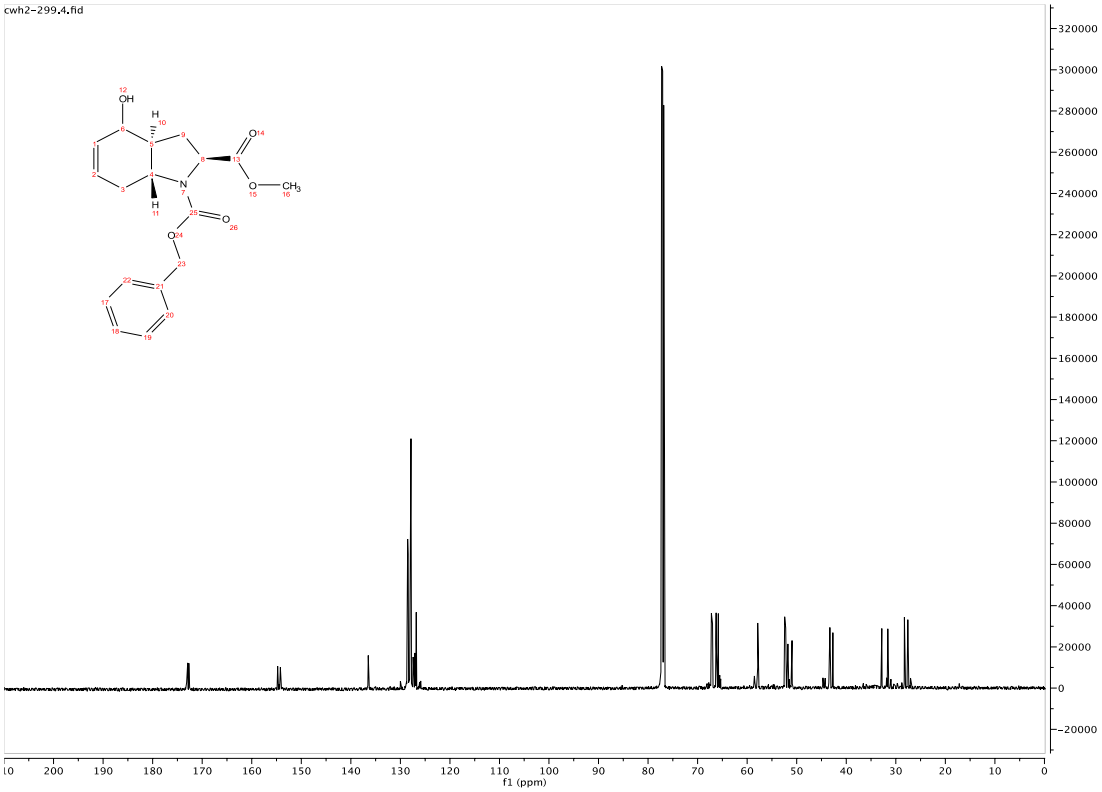


96 **97**

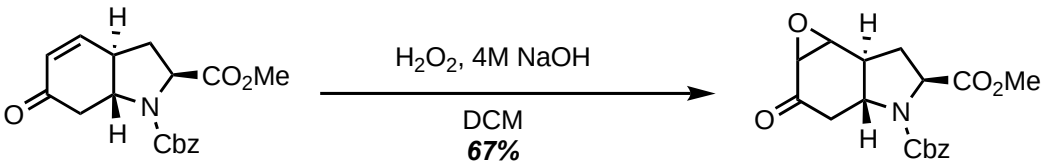
To a stirred solution of compound **96** (40 mg, 0.078 mmol, 1 eq) in DCM (3.0 mL, 0.025 M) was added *m*CPBA (21 mg, 0.093 mmol, 1.2 eq) in DCM (0.9 mL, 0.10 M) at 0 °C, and then was stirred at 4 °C. After 16 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **97** as a white foam (29 mg, 74% yield). Rf = 0.45 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (600 MHz, Chloroform-d) δ 7.41 – 7.23 (m, 5H), 5.90 – 5.73 (m, 2H), 5.26 – 4.98 (m, 2H), 4.37 – 4.04 (m, 3H), 3.65 (s+ s', 3H), 2.85 – 2.58 (m, 2H), 2.12 – 1.62 (m, 4H). ^{13}C NMR (151 MHz, Chloroform-d) δ (172.94, 172.69), (154.76, 154.22), (136.47, 136.40), (128.52, 128.49), (128.42, 128.05), (127.67, 127.64), (127.05, 126.96), (126.78, 126.10), (67.13, 66.98), (66.25, 65.83), (57.86, 57.81), (52.36, 52.21), (51.78, 51.52), (51.09, 50.94), (44.71, 44.25), (43.31, 42.71), (32.82, 31.86), (28.26, 27.57). New compound; Procedure was taken from reference ***52***.

Notebook Entries:
Procedure – cwh3-420
^{1}H – cwh3-420-B
^{13}C – cwh3-420-B


cwh3-420-8.1.fid
5.46
2.03
2.34
3.10
3.09
2.04
4.34
f1 (ppm)


cwh2-299.4.fid
f1 (ppm)

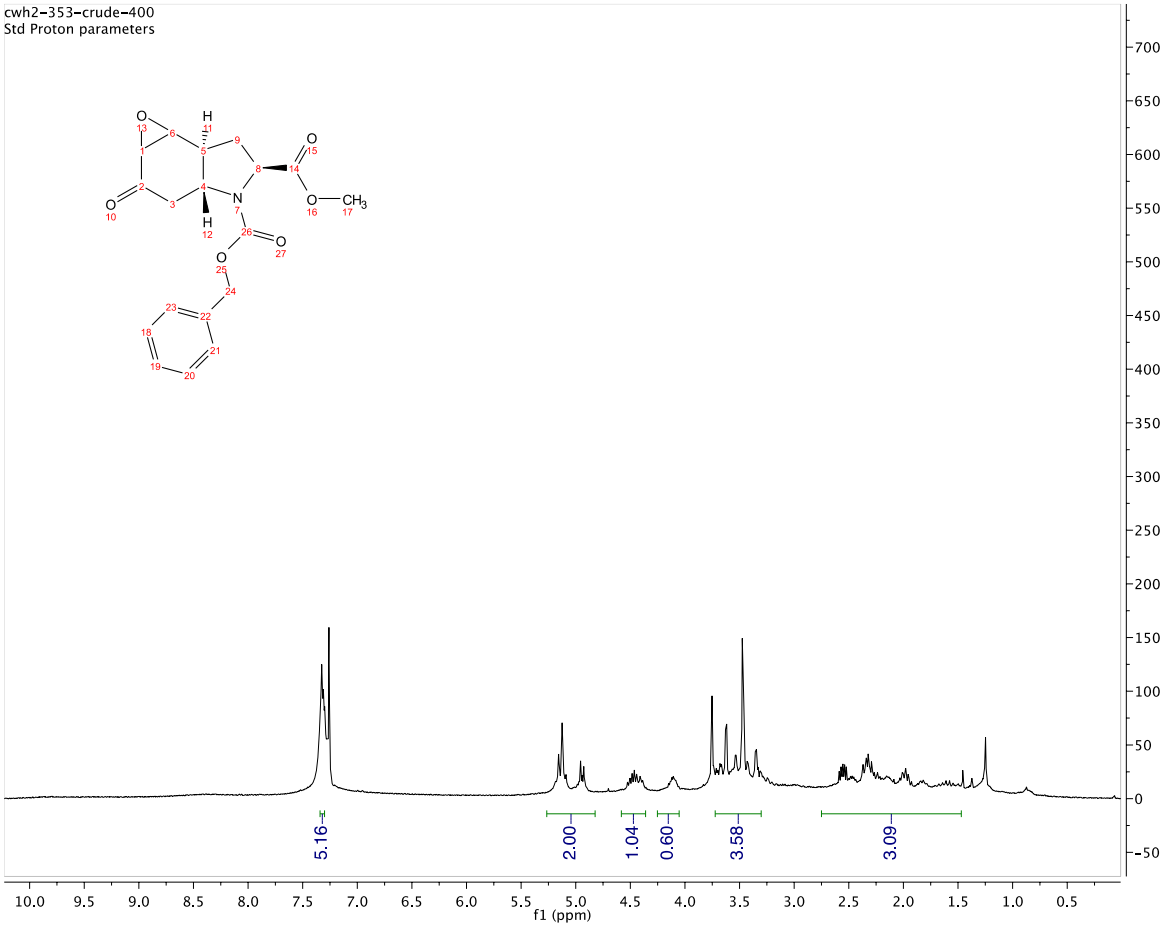
4-benzyl 5-methyl (3aR,5S,6aS)-2-oxooctahydro-4H-oxireno[2,3-e]indole-4,5-dicarboxylate (67)



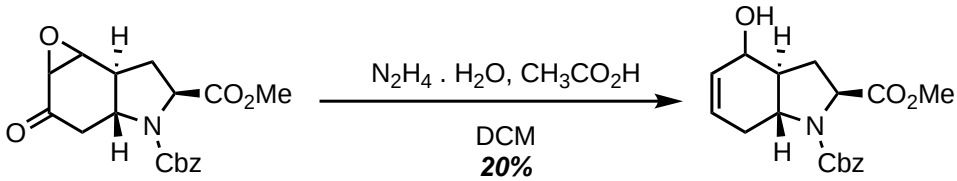
16 **67**

To a stirred solution of compound **16** (383 mg, 1.16 mmol, 1 eq) in DCM (11 mL, 0.10 M) was bubbled with argon for 5 minutes. Then H_2O_2 (20 mL, 6.05 mmol, 5.2 eq) was added followed by 4M NaOH (0.030 mL, 0.116 mmol, 0.1 eq) at 0 °C, and then was stirred at 0 °C. After 0.5 h, the reaction was quenched with 3 drops of glacial acetic acid and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **67** as a white foam (268 mg, 67% yield). Rf = 0.29 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.30 (m, 5H), 5.26 – 4.82 (m, 2H), 4.45 (td, *J* = 19.0, 17.4, 7.1 Hz, 1H), 4.25 – 4.05 (m, 1H), 3.72 – 3.30 (m, 4H), 2.75 – 1.47 (m, 3H). New compound; Procedure was taken from reference ***39***.

Notebook Entries:
Procedure – cwh2-353
^{1}H – cwh2-353-crude


cwh2-353-crude-400
Std Proton parameters
5.16
2.00
1.04
0.60
3.58
3.09
f1 (ppm)

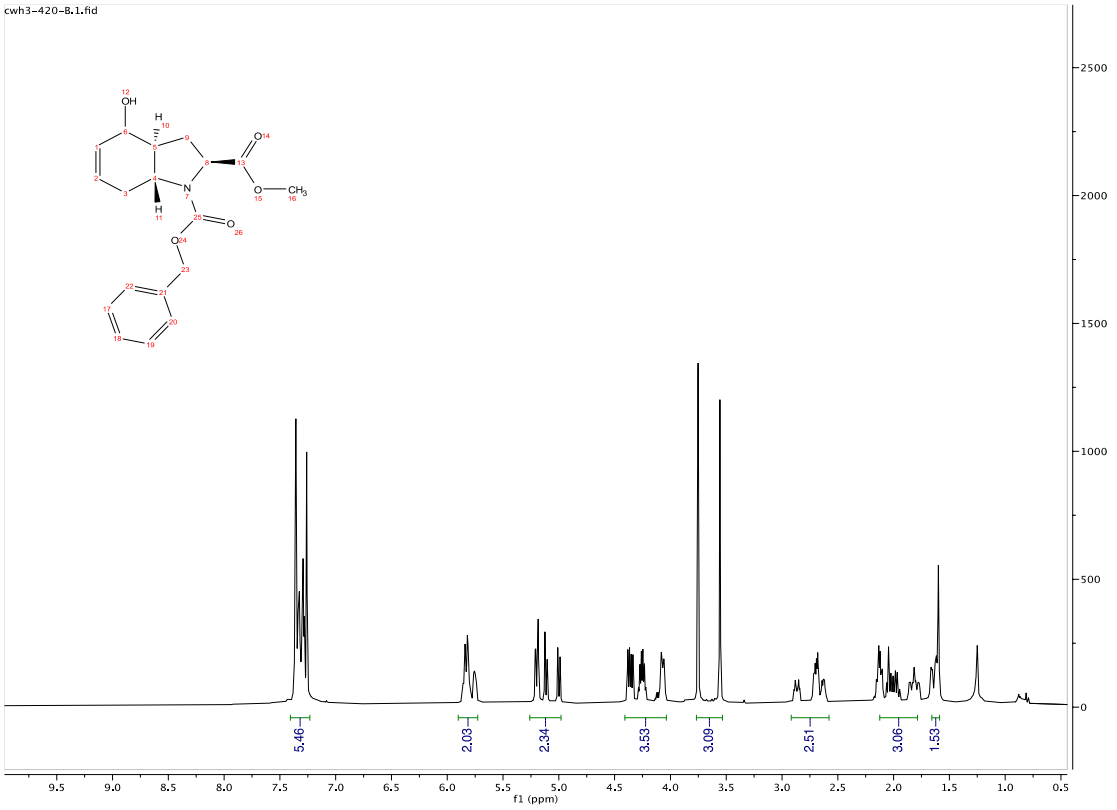
1-benzyl 2-methyl (2S,3aS,7aR)-4-hydroxy-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (65)

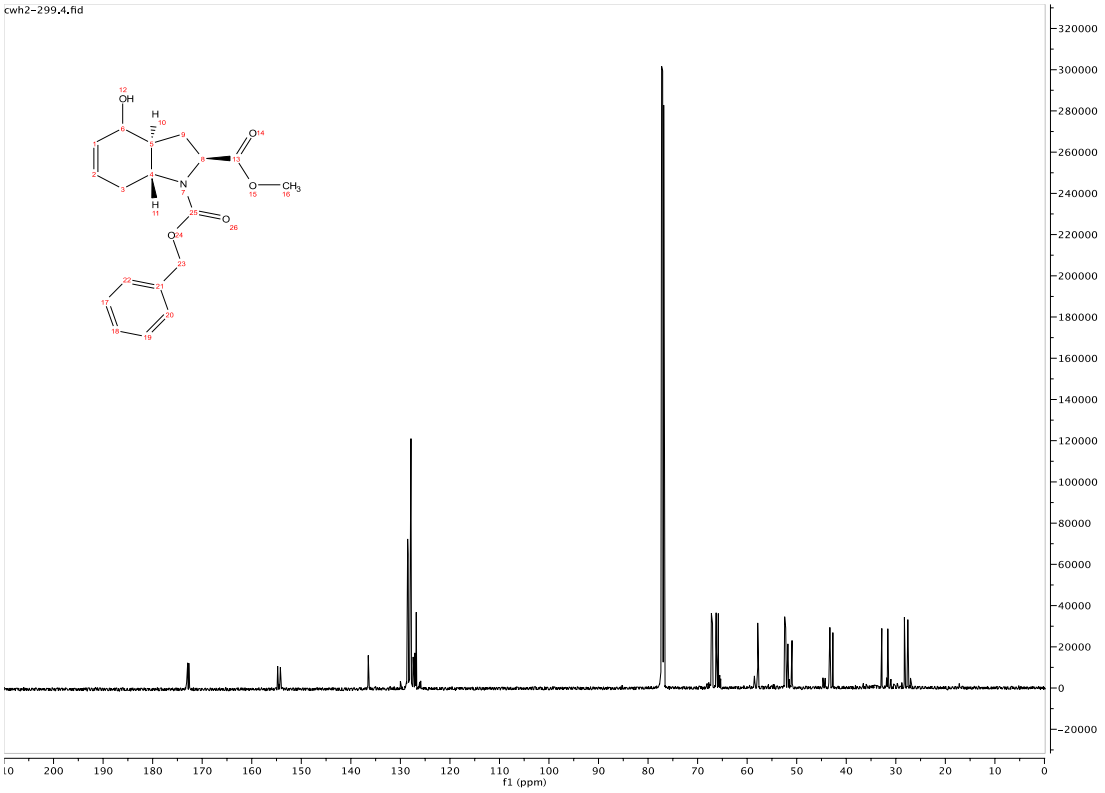


67 **65**

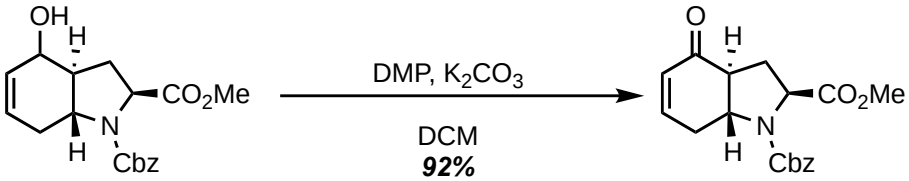
To a stirred solution of compound **67** (213 mg, 0.62 mmol, 1 eq) in DCM (6.2 mL, 0.10 M) was added $N_2H_4.H_2O$ (0.06 mL, 1.23 mmol, 2 eq) followed by 1 drop of glacial acetic acid at 0 °C, and then was stirred at room temperature. After 16 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **65** as a white foam (41 mg, 20% yield). Rf = 0.45 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (600 MHz, Chloroform-d) δ 7.41 – 7.23 (m, 5H), 5.90 – 5.73 (m, 2H), 5.26 – 4.98 (m, 2H), 4.37 – 4.04 (m, 3H), 3.65 (s+ s', 3H), 2.85 – 2.58 (m, 2H), 2.12 – 1.62 (m, 4H). ^{13}C NMR (151 MHz, Chloroform-d) δ (172.94, 172.69), (154.76, 154.22), (136.47, 136.40), (128.52, 128.49), (128.42, 128.05), (127.67, 127.64), (127.05, 126.96), (126.78, 126.10), (67.13, 66.98), (66.25, 65.83), (57.86, 57.81), (52.36, 52.21), (51.78, 51.52), (51.09, 50.94), (44.71, 44.25), (43.31, 42.71), (32.82, 31.86), (28.26, 27.57). New compound; Procedure was taken from reference ***39***.

Notebook Entries:
Procedure – cwh2-367
^{1}H – cwh3-420-B
^{13}C – cwh3-420-B


cwh3-420-B.1.fid
5.46
2.03
2.34
3.53
3.09
2.51
3.06
1.53
f1 (ppm)


cwh2-299.4.fid
f1 (ppm)

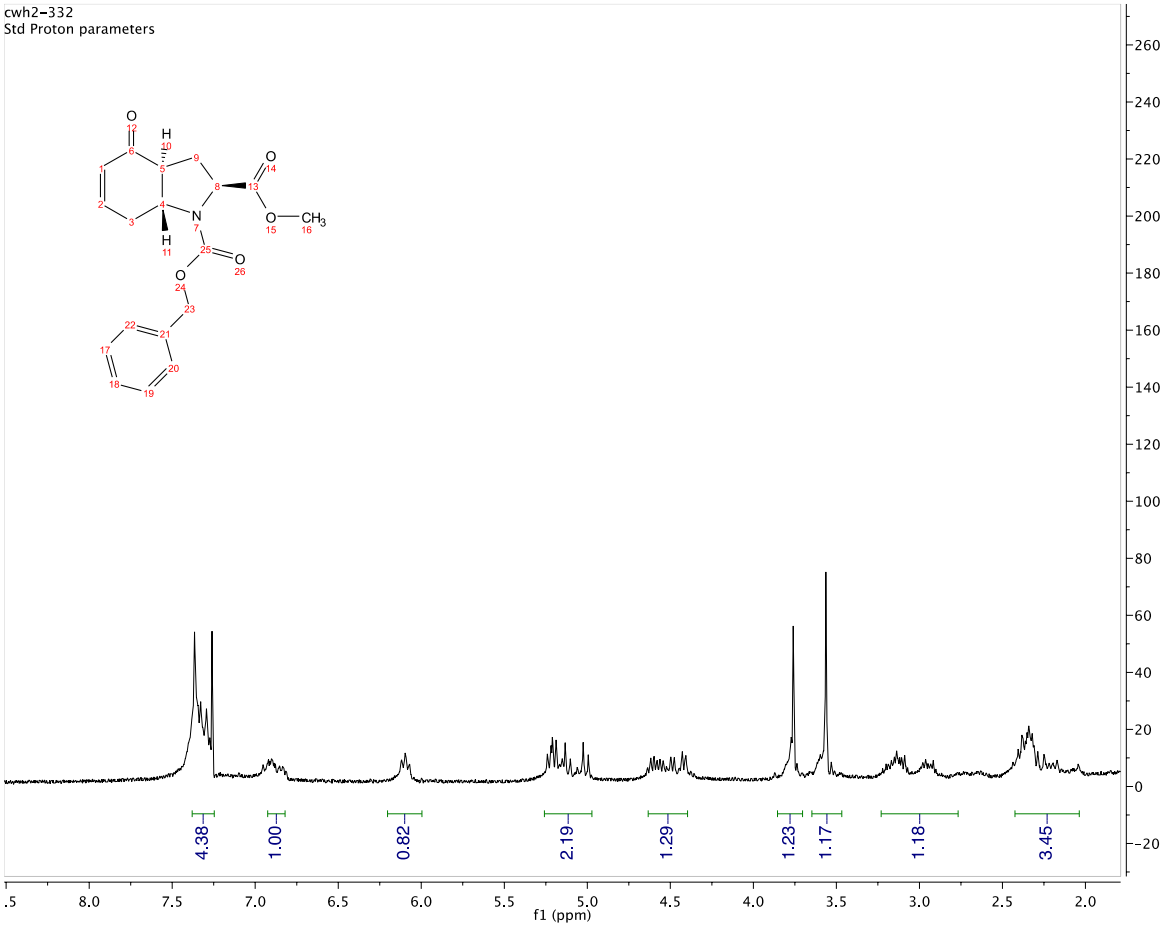
1-benzyl 2-methyl (2S,3aS,7aR)-4-oxo-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (70)



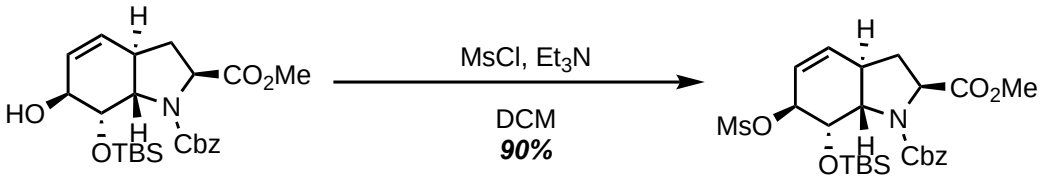
65 **70**

To a stirred solution of compound **65** (11 mg, 0.036 mmol, 1 eq) in DCM (0.4 mL, 0.10 M) was added DMP (15 mg, 0.108 mmol, 2 eq) and K_2CO_3 (48 mg, 0.180 mmol, 3 eq), and was stirred at room temperature. After 4 h, the reaction was diluted with H_2O and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **70** as a white foam (8.3 mg, 83% yield). Rf = 0.52 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). 1H NMR (400 MHz, Chloroform-d) δ 7.48 – 7.27 (m, 5H), 6.95 – 6.81 (m, 1H), 6.16 – 6.06 (m, 1H), 5.34 – 5.01 (m, 2H), 4.59 (dd, J = 14.8, 7.6 Hz, 1H), 4.53 – 4.38 (m, 1H), 3.83 + 3.45 (s+ s', 3H), 3.23 – 3.05 (m, 1H), 2.94 (m, 1H), 2.38 – 2.20 (m, 3H). New compound; Procedure was taken from reference ***39***.

Notebook Entries:
Procedure – cwh2-332`
$_1$H – cwh2-332


cwh2-332
Std Proton parameters
4.38
1.00
0.82
2.19
1.29
1.23
1.17
1.18
3.45
f1 (ppm)

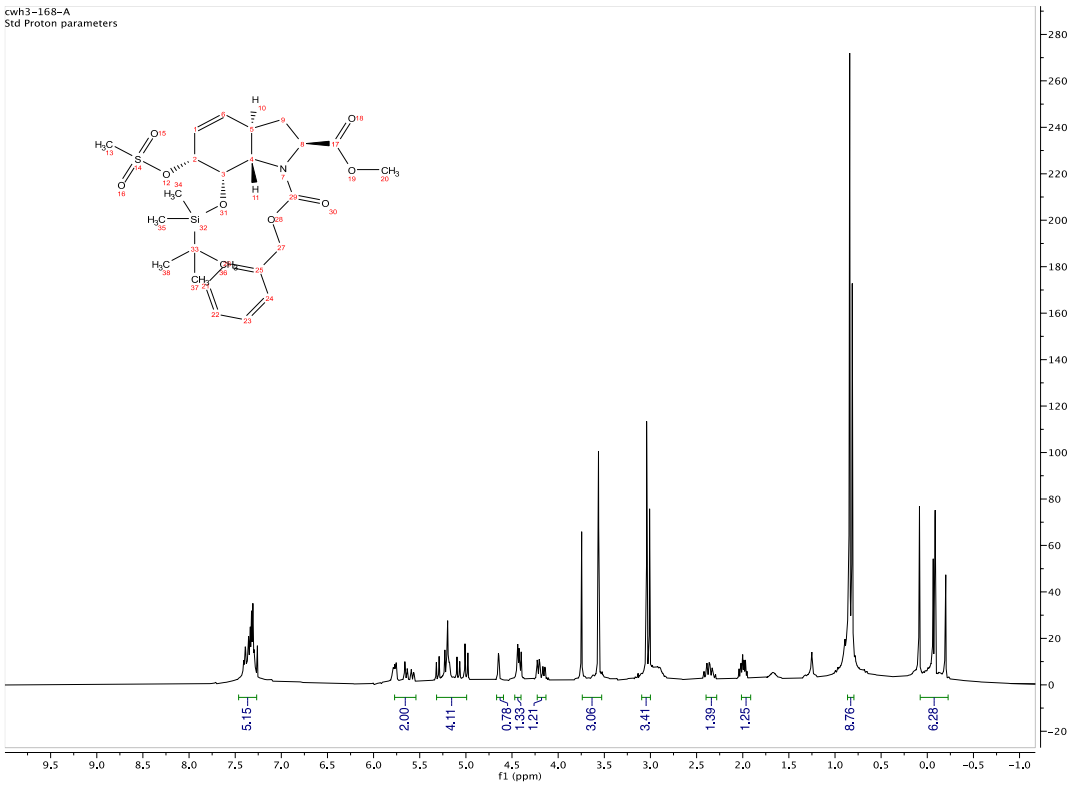
1-benzyl 2-methyl (2S,3aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-6-((methylsulfonyl)oxy)-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (84)

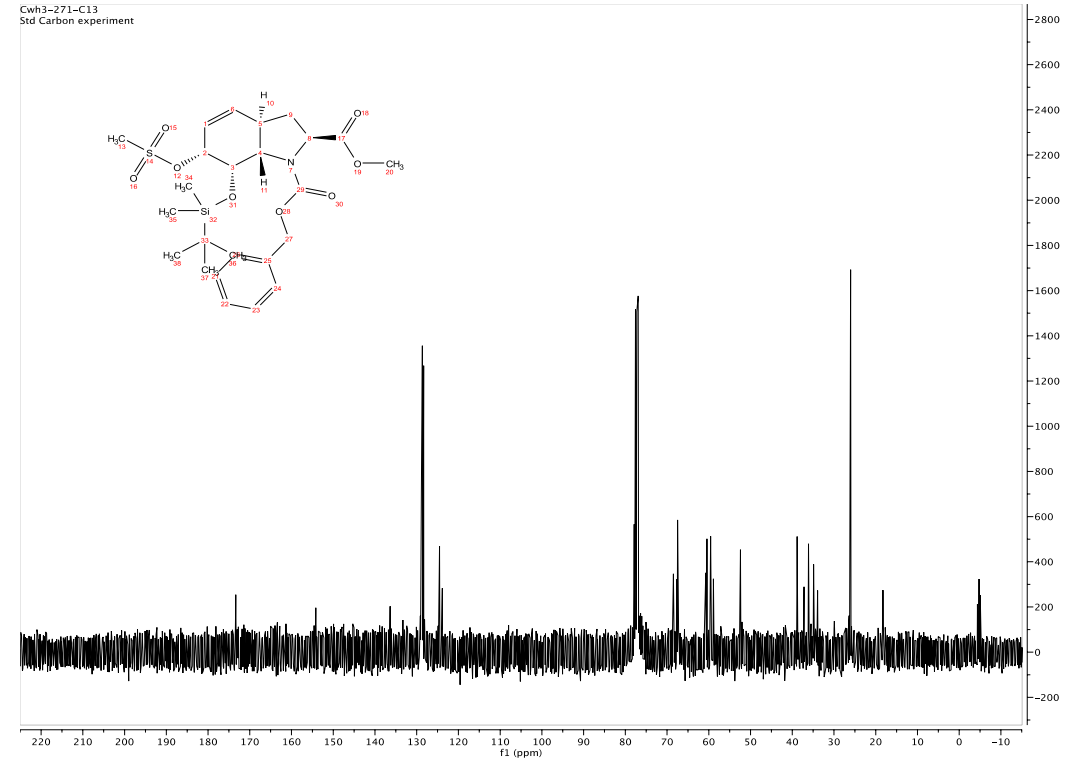


83 **84**

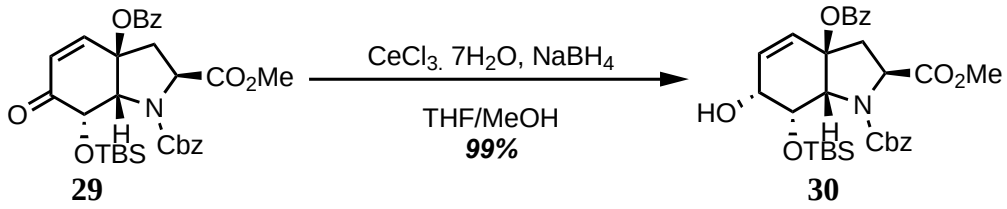
To a stirred solution of compound **83** (89 mg, 0.193 mmol, 1 eq) in DCM (0.7 mL, 0.267 M) was added Et_3N (0.04 mL, 0.290 mmol, 1.5 eq) and MsCl (0.02 mL, 0.232 mmol, 1.2 eq) at -78 °C, and then was stirred at -78 °C. After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **84** as a white foam (93.6 mg, 90% yield). Rf = 0.46 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-d) δ 7.46 – 7.27 (m, 5H), 5.77 – 5.54 (m, 2H), 5.32 – 4.99 (m, 4H), 4.64 (m, 1H), 4.47 – 4.40 (m, 1H), 4.23 – 4.13 (m, 1H), 3.56 (s+ s', 3H), 3.02 (s+ s', 3H), 2.40 – 2.28 (m, 1H), 1.98 (m, 1H), 0.86 – 0.79 (m, 9H), 0.08 – -0.23 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ (173.35, 173.34), (154.18, 154.17), (136.36, 136.35), (129.04, 128.87), (128.81, 128.63), (128.58, 128.34), (124.52, 123.86), (77.88, 77.65), (68.47, 67.73), (67.47, 67.29), (60.73, 60.45), (59.56, 58.90), (52.58, 52.41), (38.83, 38.73), (37.17, 36.12), (34.89, 33.92), (26.03, 26.00), (18.28, 18.27), (-4.36, -5.05). New compound; Procedure was taken from reference ***50***.

Notebook Entries:
Procedure – cwh3-168
^1H – cwh3-168-A
^{13}C – cwh3-271-c13


cwh3-168-A
Std Proton parameters
5.15
2.00
4.11
0.78
1.33
1.21
3.06
3.41
1.39
1.25
8.76
6.28
f1 (ppm)


Cwh3-271-C13
Std Carbon experiment
f1 (ppm)

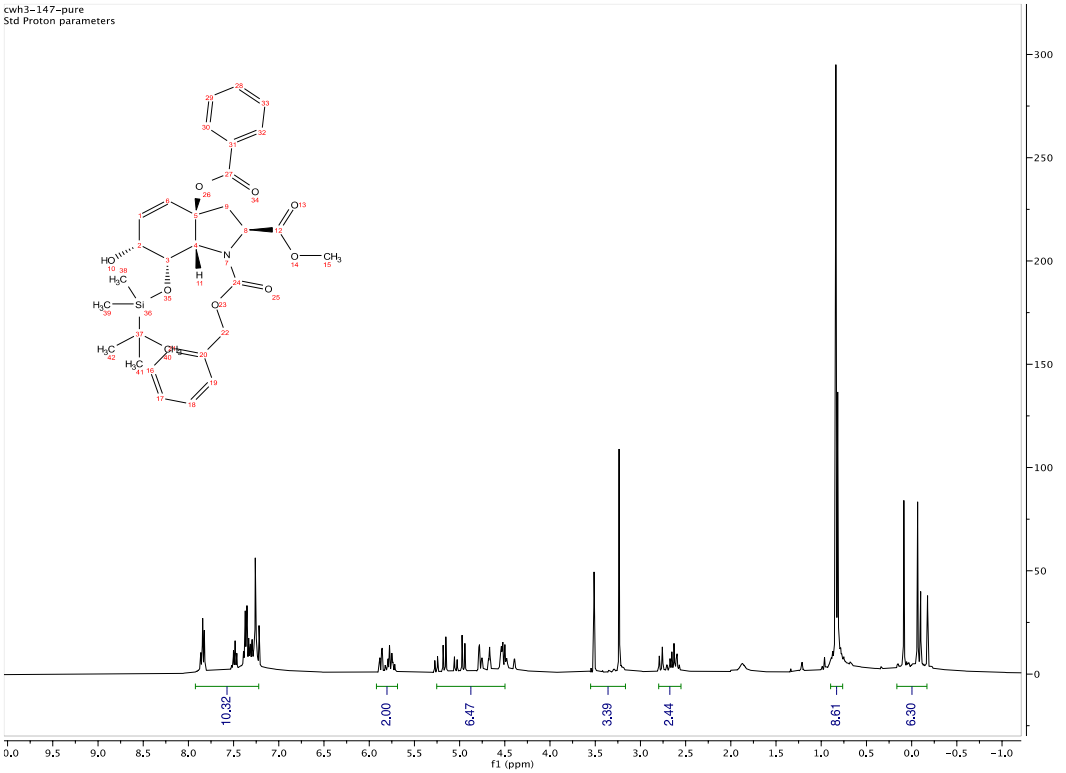
1-benzyl 2-methyl (2S,3aR,6R,7S,7aR)-3a-(benzoyloxy)-7-((tert-butyldimethylsilyl)oxy)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (30)

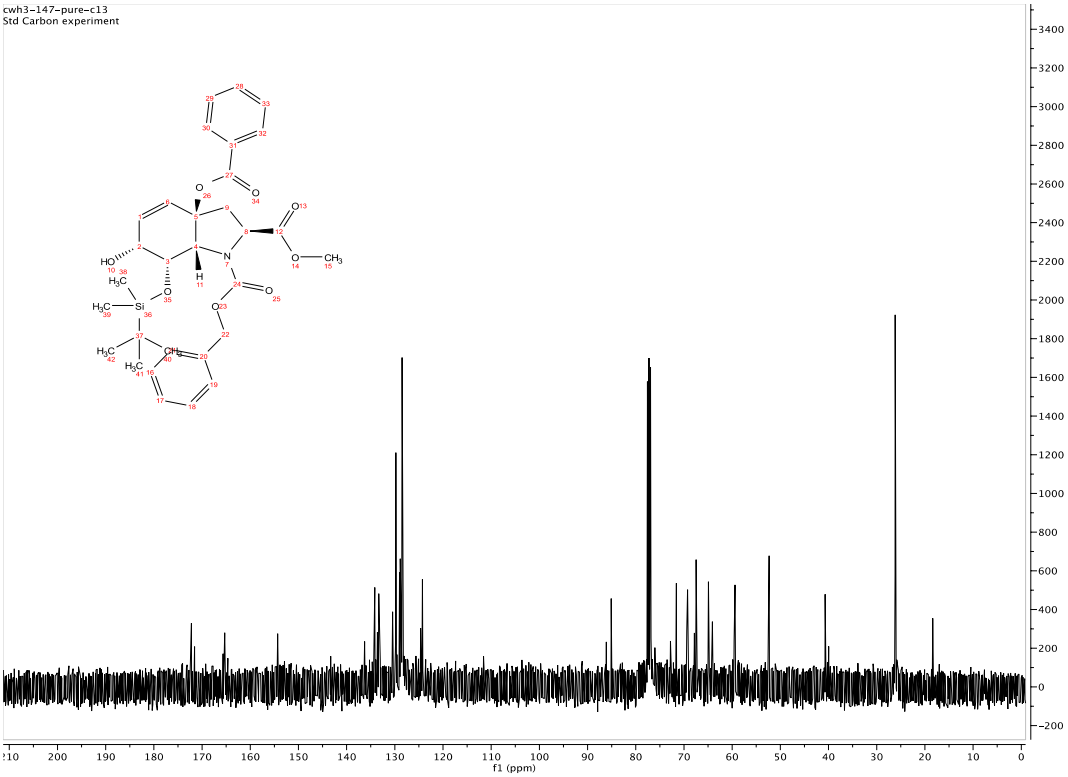


29 **30**

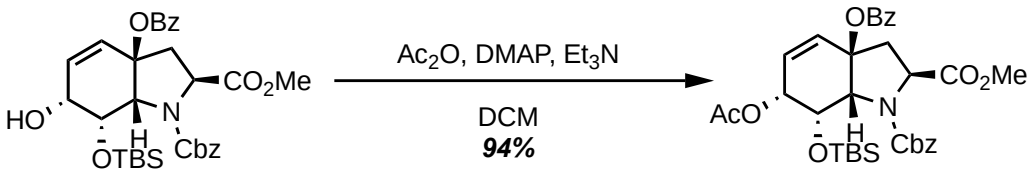
To a stirred solution of compound **29** (37 mg, 0.064 mmol, 1 eq) in THF:MeOH 1:1 (1.0 mL, 0.0875M) was added $CeCl_3 \cdot 7H_2O$ (24 mg, 0.064 mmol, 1 eq), and was stirred for 5 mins. Then $NaBH_4$ (2.4 mg, 0.064 mmol, 1 eq) was added portion wise, and then was stirred at room temperature. After 5 mins, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:3) to give compound **30** as a white foam (36.6 mg, 99% yield). Rf = 0.39 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.92 – 7.22 (m, 10H), 5.92 – 5.69 (m, 2H), 5.25 – 4.50 (m, 6H), 3.37 (s+ s', 3H), 2.80 – 2.55 (m, 2H), 0.83 (s+ s', 9H), 0.16 – -0.17 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ (172.22, 171.55), (165.30, 165.29), (154.31, 154.30), (136.27, 136.26), (134.17, 134.16), (133.62, 133.34), (130.48, 130.47), (129.83, 129.79), (129.03, 128.87), (128.64, 128.50), (128.48, 128.34), (124.65, 124.27), (86.12, 85.10), (72.81, 71.56), (69.42, 69.24), (67.83, 67.48), (64.93, 64.10), (59.60, 59.41), (52.47, 52.32), (40.70, 39.97), (26.17, 26.14), (18.38, 18.37), (-4.23, -4.47). Known compound; all the spectral data matches the data reported in reference ***41***.

Notebook Entries:
Procedure – cwh3-147
^{1}H – cwh3-147-pure
^{13}C – cwh3-147-pure


cwh3-147-pure
Std Proton parameters
10.32
2.00
6.47
3.39
2.44
8.61
6.30
f1 (ppm)


cwh3-147-pure-c13
Std Carbon experiment
f1 (ppm)

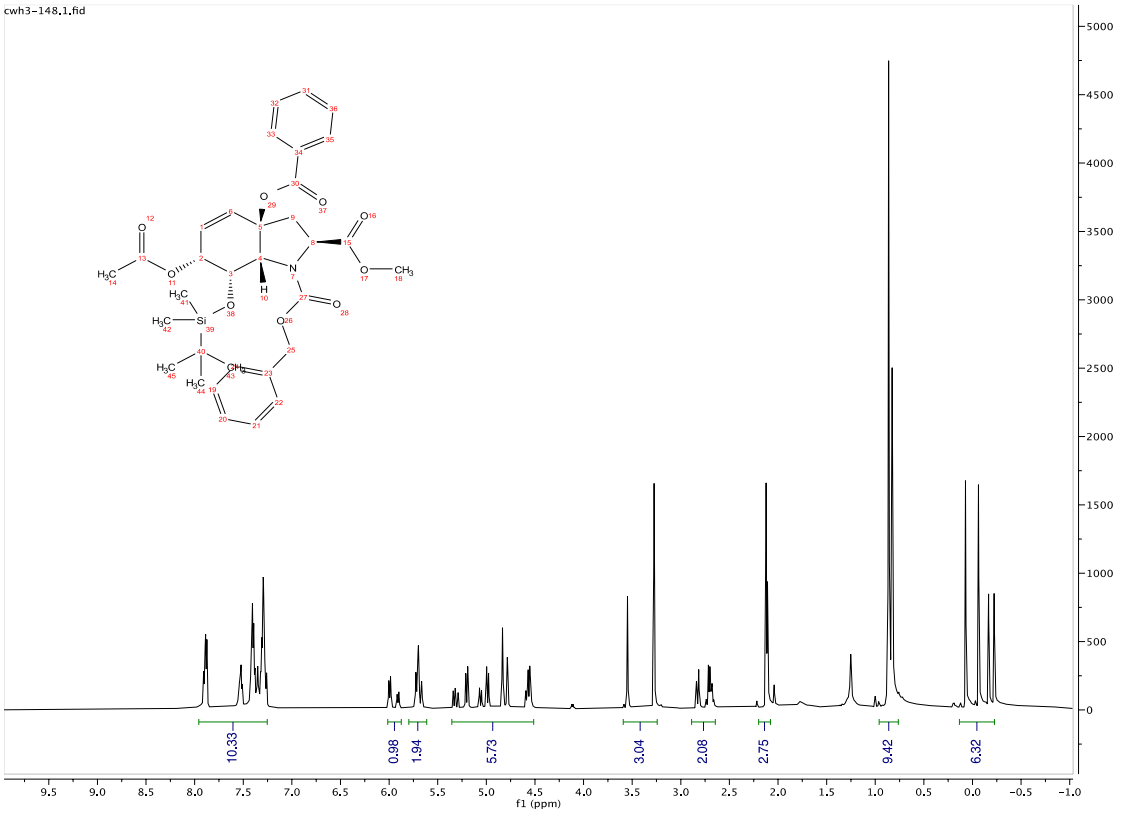
1-benzyl 2-methyl (2S,3aR,6R,7S,7aR)-6-acetoxy-3a-(benzoyloxy)-7-((tert-butyldimethylsilyl)oxy)-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (31)

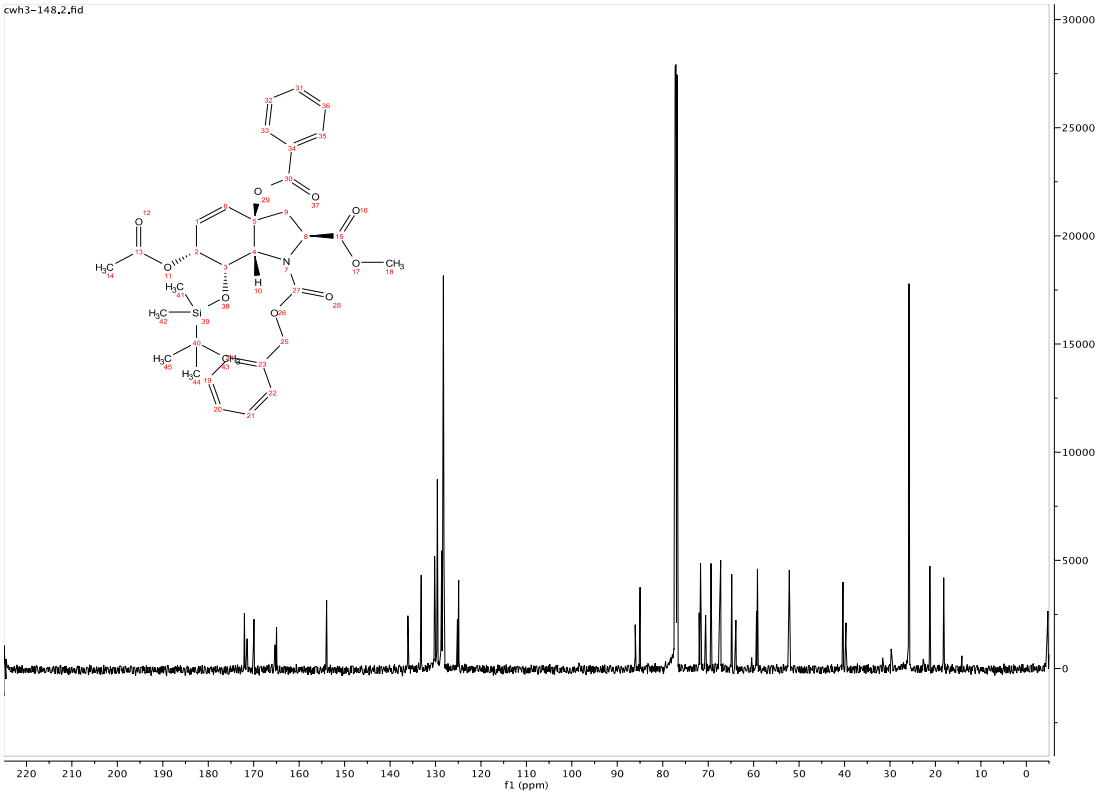


30 **31**

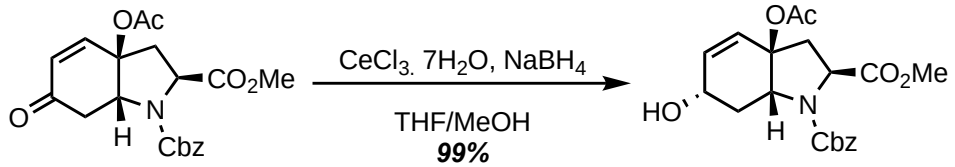
To a stirred solution of compound **30** (37 mg, 0.064 mmol, 1 eq) in DCM (0.6 mL, 0.10 M) was added acetic anhydride (0.02 mL, 0.195 mmol, 3.05 eq), DMAP (0.8 mg, 0.064 mmol, 0.10 eq), and Et_3N (0.03 mL, 0.198 mmol, 3.10 eq), and then was stirred at room temperature. After 4 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:3) to give compound **31** as a light-yellow foam (37.6 mg, 94% yield). Rf = 0.30 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^1H NMR (600 MHz, Chloroform-d) δ 7.96 – 7.25 (m, 10H), 5.95 (m, 1H), 5.80 – 5.61 (m, 2H), 5.36 – 4.51 (m, 6H), 3.59 + 3.24 (s+ s', 3H), 2.89 – 2.64 (m, 2H), 2.12 (s+ s', 3H), 0.96 – 0.76 (m, 9H), 0.09 – -0.25 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-d) δ (172.06, 171.44), (170.03, 169.95), (165.29, 164.98), (153.96, 153.95), (136.08, 136.04), (133.19, 133.15), (130.18, 130.15), (129.64, 129.59), (128.77, 128.64), (128.42, 128.30), (128.28, 128.12), (125.19, 124.89), (86.05, 85.00), (71.97, 71.69), (70.57, 69.37), (67.49, 67.25), (64.82, 63.90), (59.36, 59.16), (52.29, 52.15), (40.34, 39.68), (29.74, 29.73), (25.82, 25.78), (21.30, 21.23), (18.18, 18.15), (-4.60, -4.74). Known compound; all the spectral data matches the data reported in reference ***41***.

Notebook Entries:
Procedure – cwh3-148
^1H – cwh3-148 ^{13}C – cwh3-148


cwh3-148.1.fid
10.33
0.98
1.94
5.73
3.04
2.08
2.75
9.42
6.32
f1 (ppm)


cwh3-148.2.fid
f1 (ppm)

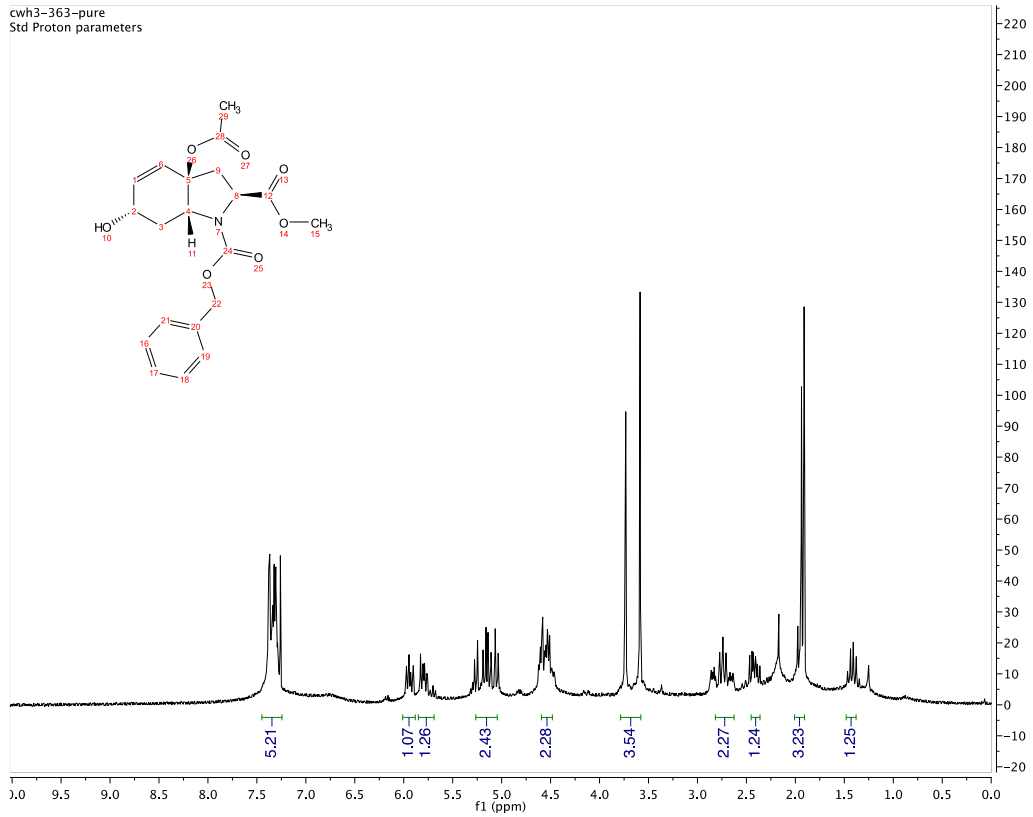
1-benzyl 2-methyl (2S,3aR,6S,7aR)-3a-acetoxy-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (57)

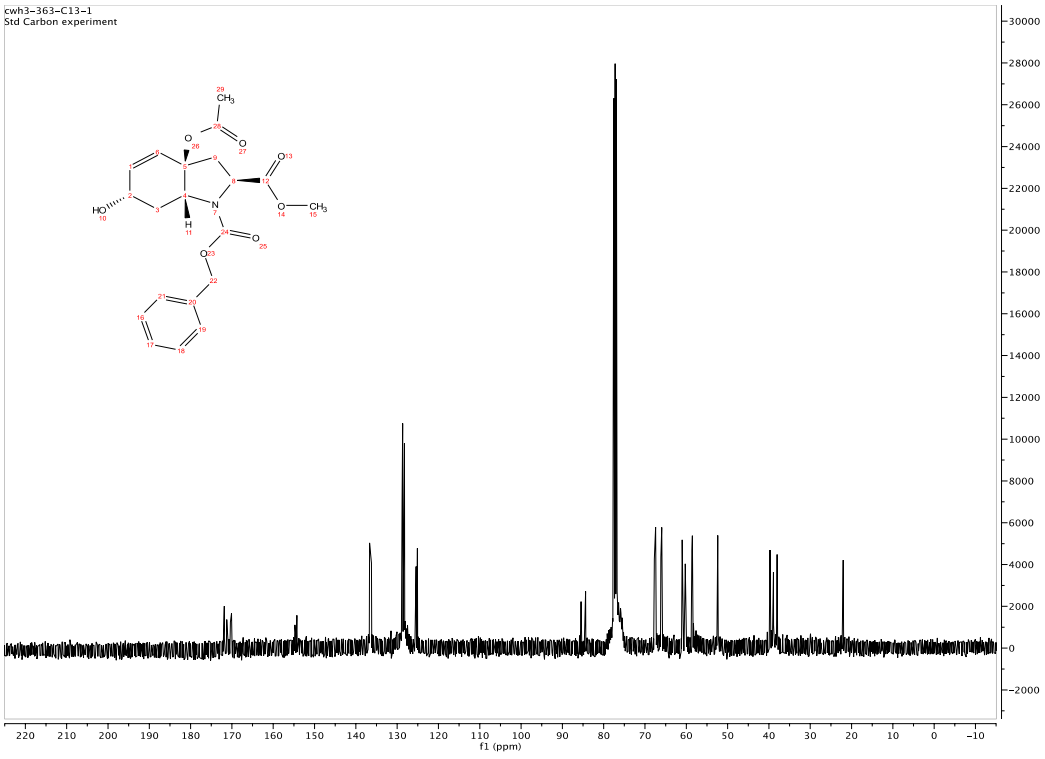


56 **57**

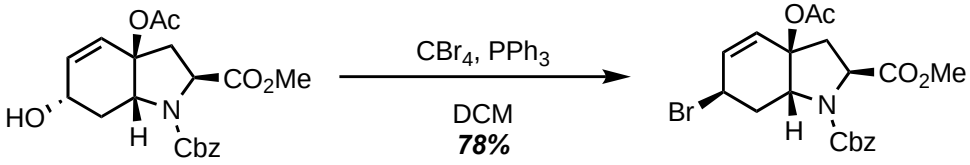
To a stirred solution of compound **56** (70 mg, 0.18 mmol, 1 eq) in THF:MeOH 1:1 (2.0 mL, 0.0875M) was added $CeCl_3 \cdot 7H_2O$ (67 mg, 0.18 mmol, 1 eq), and was stirred for 5 mins. Then $NaBH_4$ (6.7 mg, 0.13 mmol, 1 eq) was added portion wise, and then was stirred at room temperature. After 5 mins, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **57** as a white foam (69.4 mg, 99% yield). Rf = 0.37 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.45 – 7.24 (m, 5H), 6.01 – 5.88 (m, 1H), 5.79 (m, 1H), 5.26 – 5.04 (m, 2H), 4.60 – 4.43 (m, 2H), 3.66 (s+ s', 3H), 2.82 – 2.63 (m, 2H), 2.45 – 2.36 (m, 1H), 1.92 (s+ s', 3H), 1.48 – 1.38 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.84, 171.24, 170.35, 170.09, 154.77, 154.27, 136.68, 136.46, 136.21, 128.80, 128.66, 128.40, 128.33, 128.31, 128.25, 128.18, 125.42, 125.10, 85.47, 84.38, 77.45, 67.75, 67.43, 66.15, 65.95, 60.99, 60.25, 58.66, 58.52, 52.50, 52.38, 43.63, 39.74, 39.04, 38.91, 38.02, 22.11, 22.03. Known compound; all the spectral data matches the data reported in reference ***38***.

Notebook Entries:
Procedure – cwh3-363
^{1}H – cwh3-363-pure
^{13}C – cwh3-363-c13


cwh3-363-pure
Std Proton parameters
5.21
1.07
1.26
2.43
2.28
3.54
2.27
1.24
3.23
1.25
f1 (ppm)


cwh3-363-C13-1
Std Carbon experiment
f1 (ppm)

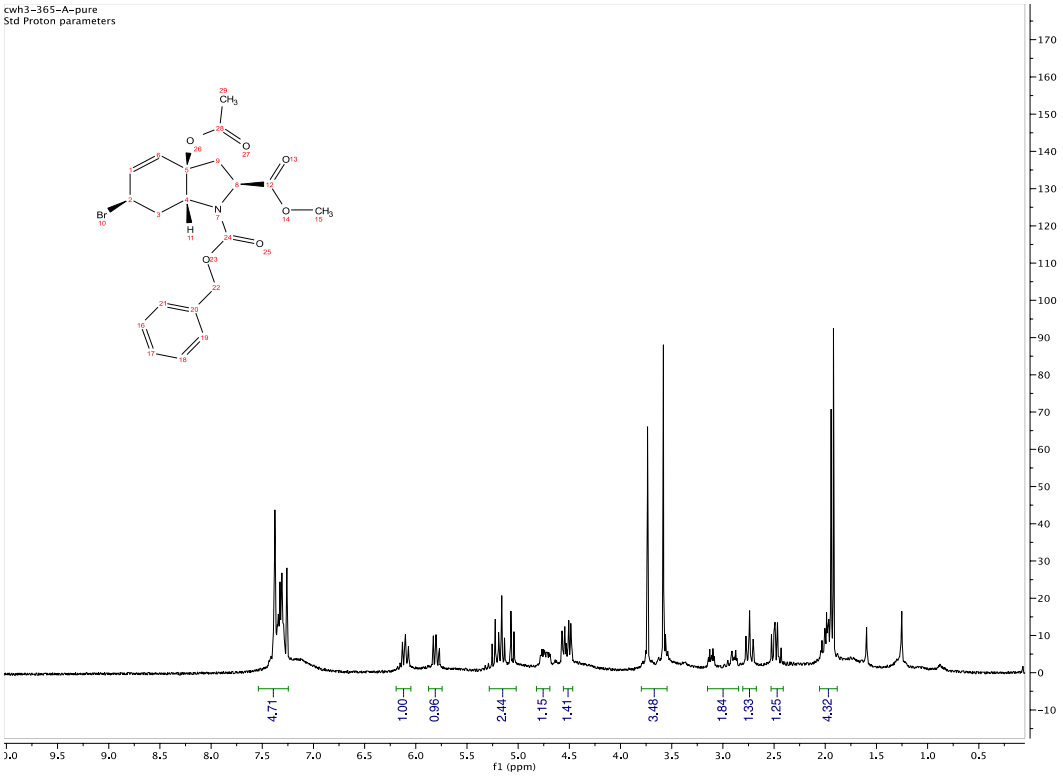
1-benzyl 2-methyl (2S,3aR,6R,7aR)-3a-acetoxy-6-bromo-2,3,3a,6,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (58)

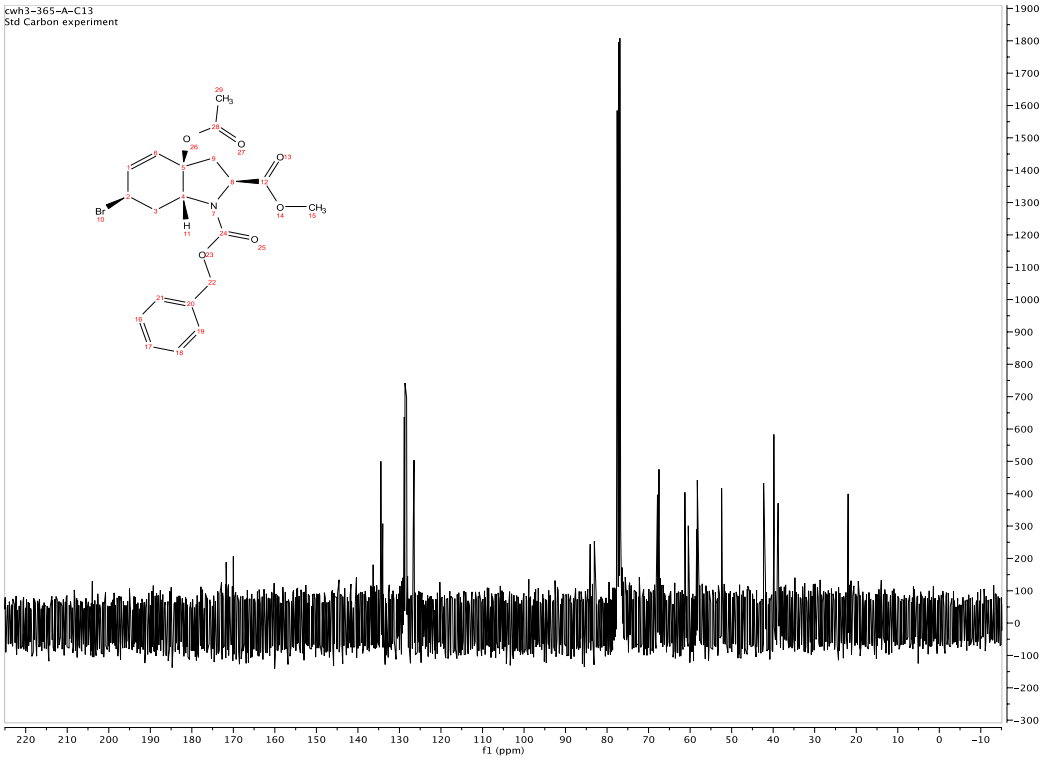


57 **58**

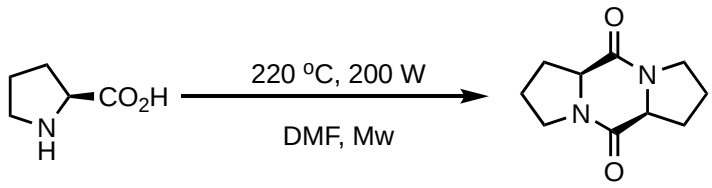
To a stirred solution of compound **57** (63 mg, 0.162 mmol, 1 eq) in DCM (1.6 mL, 0.10 M) was added CBr_4 (59 mg, 0.178 mmol, 1.1 eq) and PPh_3 (47 mg, 0.178 mmol, 1.1), and then was stirred at room temperature. After 16 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **58** as a white foam (57 mg, 78% yield). Rf = 0.45 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.54 – 7.25 (m, 5H), 6.11 (m, 1H), 5.80 (m, 1H), 5.28 – 5.02 (m, 2H), 4.82 – 4.69 (m, 1H), 4.56 – 4.47 (m, 1H), 3.66 (s+ s', 3H), 3.15 – 2.85 (m, 2H), 2.74 (m, 1H), 2.48 (m, 1H), 2.06 – 1.88 (m, 4H). ^{13}C NMR (101 MHz, Chloroform-d) δ (171.73, 171.72), (170.02, 170.01), (152.87, 152.86), (136.33, 136. 32), (134.49, 134.03), (128.83, 128.67), (128.48, 128.40), (128.34, 128.28), (126.67, 126.50), (84.07, 83.06), (67.85, 67.49), (61.26, 60.44), (58.43, 58.26), (52.54, 52.41), (42.29, 42. 28), (39.85, 39.84), (38.95, 38.82), (22.02, 21.95). New compound; Procedure was taken from reference ***44***.

Notebook Entries:
Procedure – cwh3-364
^{1}H – cwh3-365-A-pure
^{13}C – cwh3-365-A-pure


cwh3-365-A-pure
Std Proton parameters
4.71
1.00
0.96
2.44
1.15
1.41
3.48
1.84
1.33
1.25
4.32
f1 (ppm)


cwh3-365-A-C13
Std Carbon experiment
f1 (ppm)

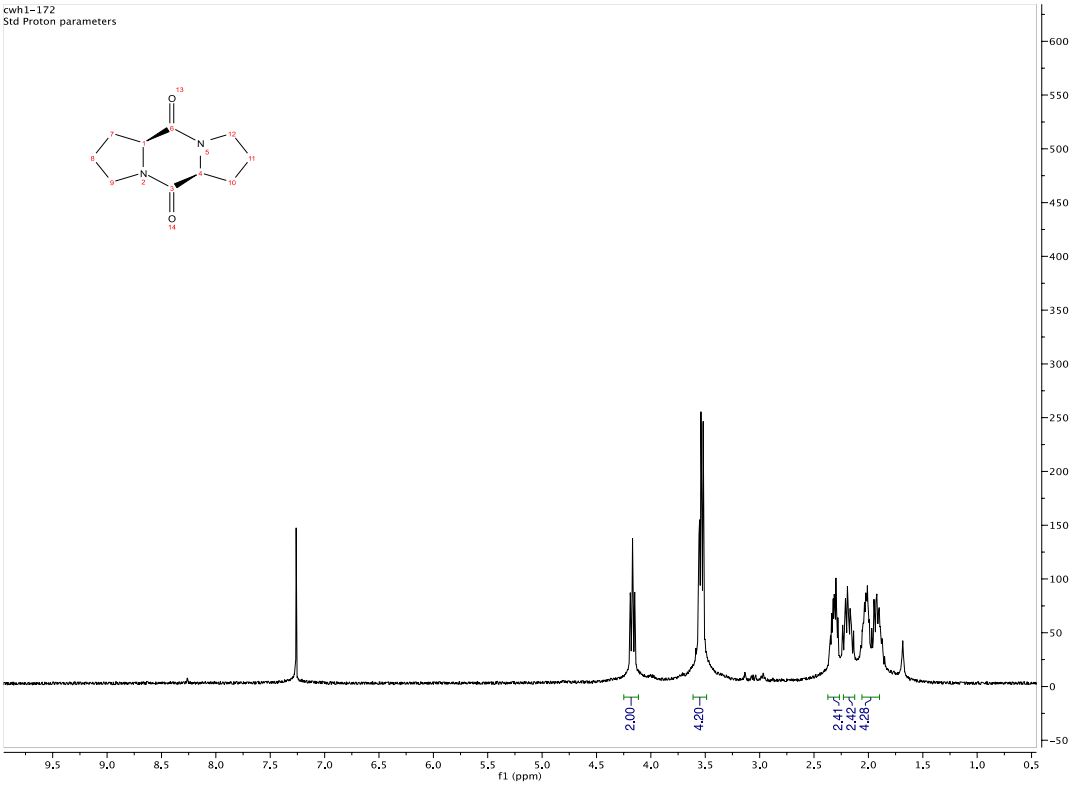
(5aS,10aS)-octahydro-5H,10H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (126)

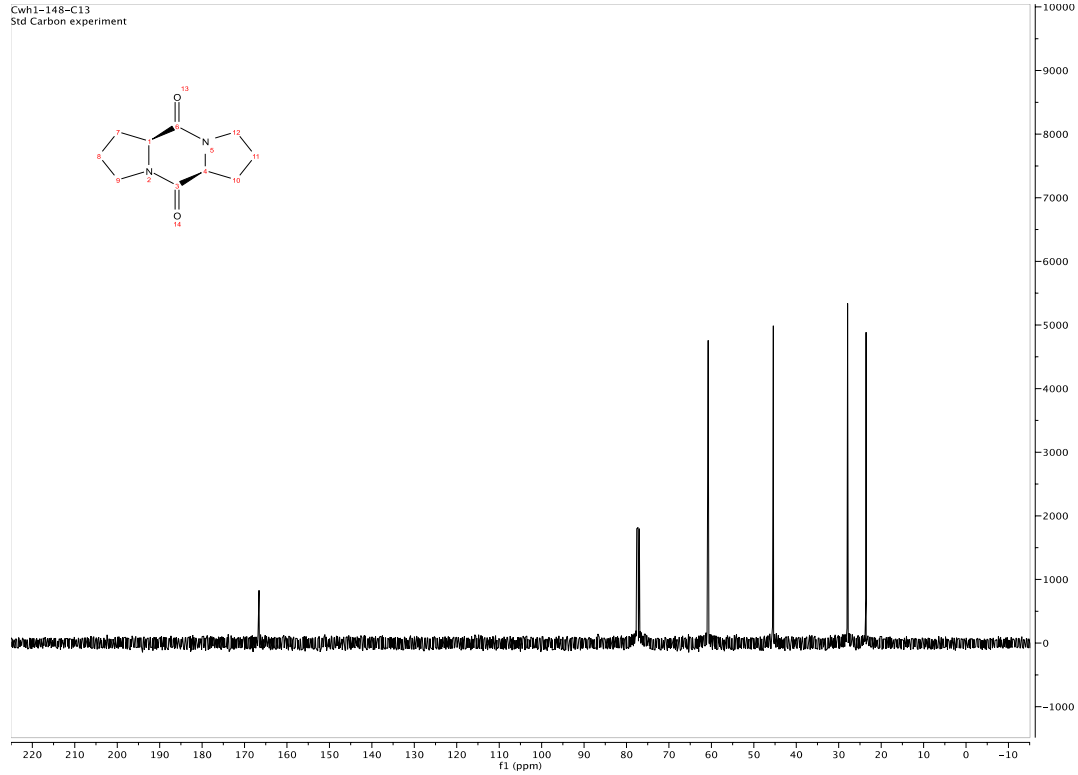


L-Proline **126**

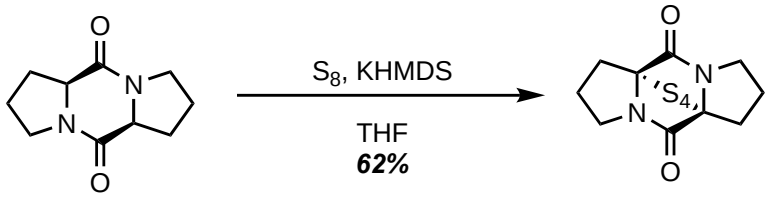
To a stirred solution of **L-Proline** (2.5 g, 21.7 mmol, 1 eq) in DMF (2.0 mL, 10.85 M) was microwaved at 220 °C and 200 W for 25 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo to give compound **126** as a white foam (3.4 g, 80% yield). Rf = 0.55 (silica, EtOAc: MeOH, 9:1); 1H NMR (400 MHz, Chloroform-d) δ 4.17 (t, J = 8.1 Hz, 2H), 3.61 – 3.49 (m, 4H), 2.32 (m, 2H), 2.23 – 2.13 (m, 2H), 2.06 – 1.90 (m, 4H). 13C NMR (101 MHz, Chloroform-d) δ 166.58, 60.75, 45.42, 27.90, 23.56. Known compound; all the spectral data matches the data reported in reference ***53***.

Notebook Entries:
Procedure – cwh1-172
$_1$H – cwh1-172
$_{13}$C – cwh1-148-c13


cwh1-172
Std Proton parameters
2.00
4.20
2.41
2.42
4.28
f1 (ppm)

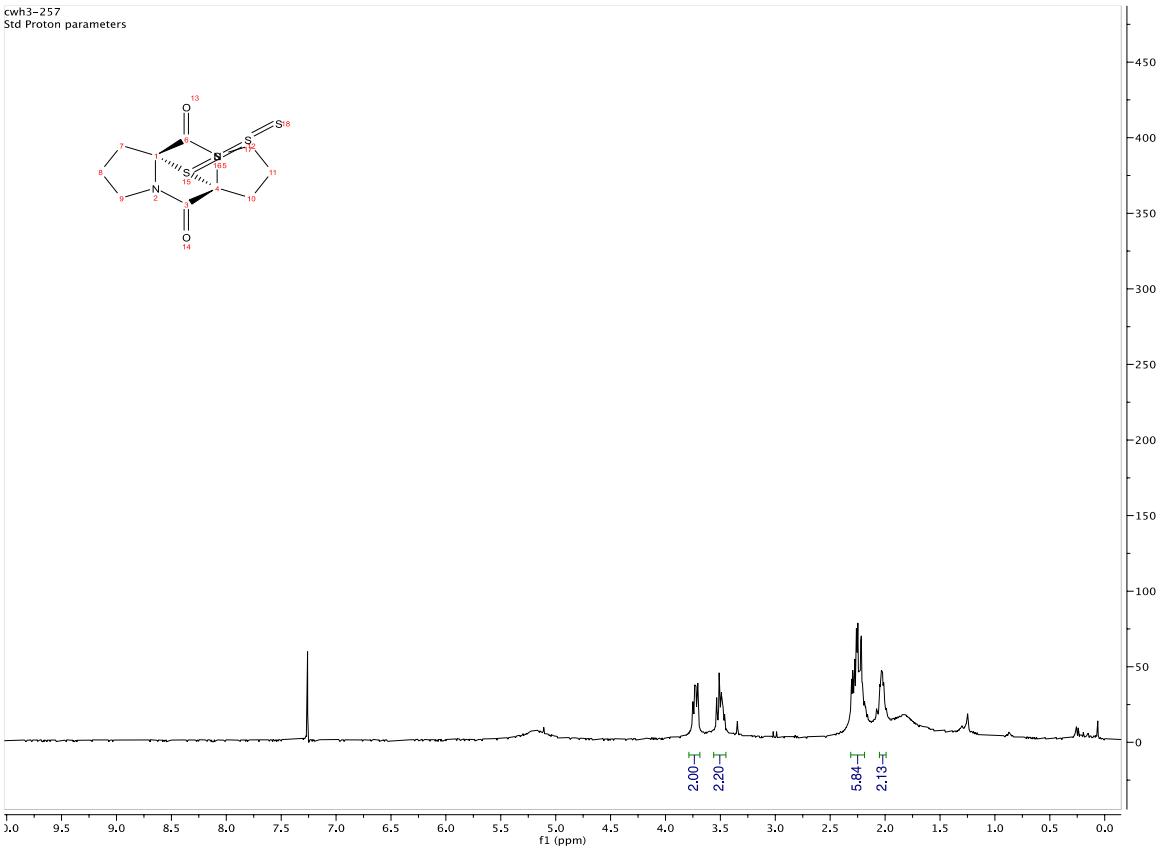

Cwh1-148-C13
Std Carbon experiment
f1 (ppm)

(5aR,10aR)-11-(1l4,2l4-trisulfan-1,2-dienylidene)tetrahydro-1H,5H,6H,10H-11l4-5a,10a-epithiodipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (127)

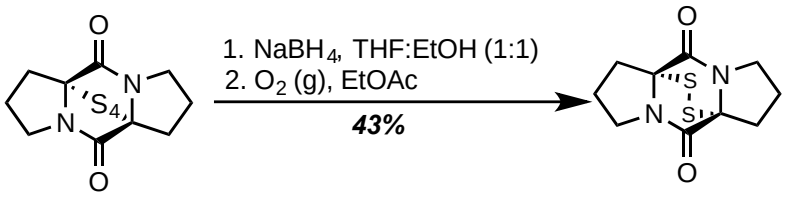


To a stirred solution of S_8 (263 mg, 8.21 mmol, 8 eq) in THF (5 mL, 1.6 M) was added NaHMDS (5 mL, 3.078 mmol, 3 eq) dropwise and stirred for 1 minutes. Then compound **126** (200 mg, 1.026 mmol, 1 eq) dissolved in THF (5 mL, 0.2 M) was added to the reaction mixture drop wise, and then NaHMDS (3.5 mL, 2.052 mmol, 2 eq) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc: MeOH: DCM, 8:1:1) to give compound **127** as a white foam (203 mg, 62% yield). Rf = 0.54 (silica, EtOAc: MeOH: DCM, 8:1:1); 1H NMR (400 MHz, Chloroform-d) δ 3.73 (m, 2H), 3.50 (m, 2H), 2.31 – 2.19 (m, 6H), 2.03 (m, 2H). Known compound; all the spectral data matches the data reported in reference ***54***.

Notebook Entries:
Procedure – cwh3-405
^1H – cwh3-257


cwh3-257
Std Proton parameters
450
400
350
300
250
200
150
100
50
0
2.00
2.20
5.84
2.13
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

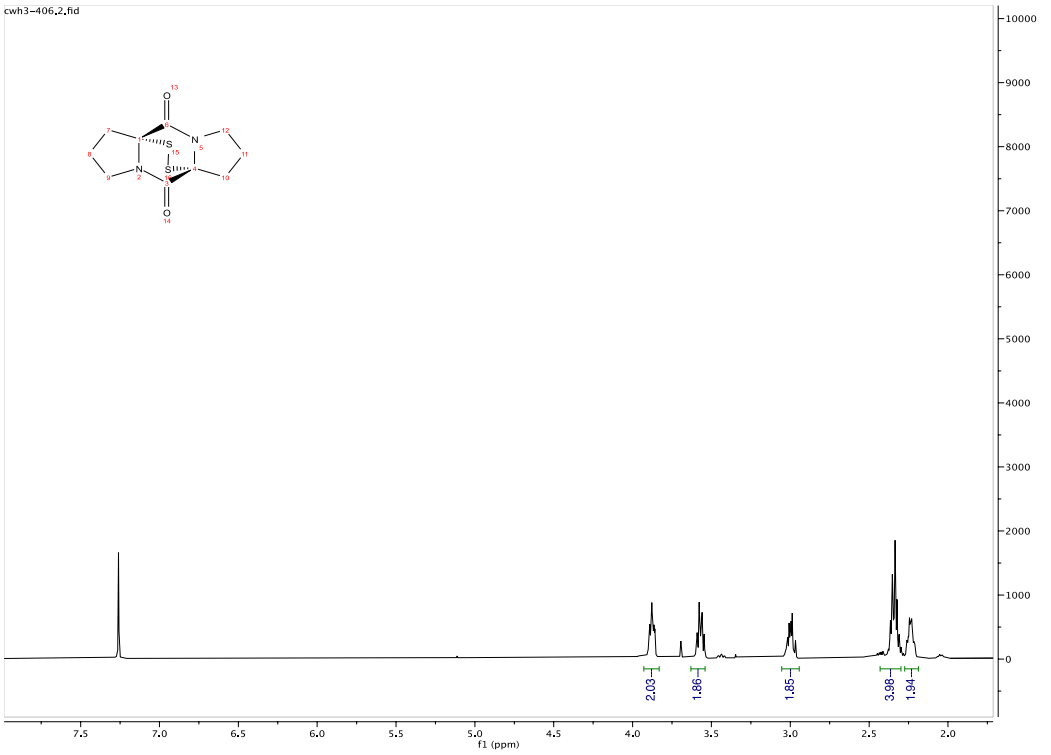
(5aR,10aR)-tetrahydro-1H,5H,6H,10H-5a,10a-epidithiodipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (128)

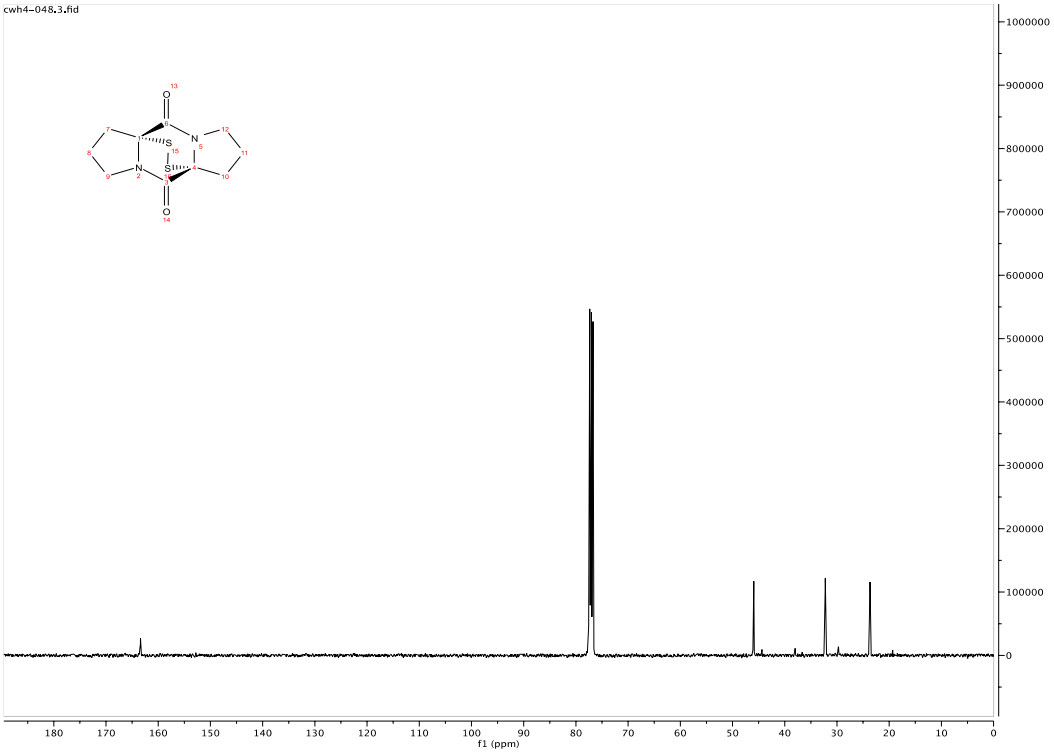


127 **128**

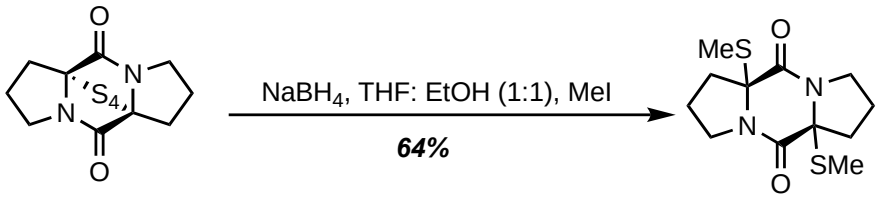
To a stirred solution of compound **127** (328 mg, 1.026 mmol, 1 eq) in THF: EtOH 1:1 (10 mL, 0.10 M) was bubbled with argon for 5 minutes. Then the reaction mixture was cooled to 0 °C and $NaBH_4$ (951 mg, 25.65 mmol, 25 eq) was added portion wise. The reaction mixture was allowed to reach room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and diluted with EtOAc (0.002M). The organic layer was bubbled with O_2 (g) for 15 h and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc) to give compound **128** as a white foam (113 mg, 43% yield). Rf = 0.60 (silica, EtOAc); 1H NMR (600 MHz, Chloroform-d) δ 3.88 (m, 2H), 3.57 (m, 2H), 3.05 – 2.94 (m, 2H), 2.43 – 2.30 (m, 4H), 2.27 – 2.19 (m, 2H). 13C NMR (101 MHz, Chloroform-d) δ 163.40, 45.93, 44.36, 38.02, 32.24, 29.74, 23.68, 19.32. Known compound; all the spectral data matches the data reported in reference ***39***.

Notebook Entries:
Procedure – cwh3-406
^{1}H – cwh3-406
^{13}C – cwh4-048


cwh3-406.2.fid
2.03
1.86
1.85
3.98
1.94
f1 (ppm)


cwh4-048.3.fid
f1 (ppm)

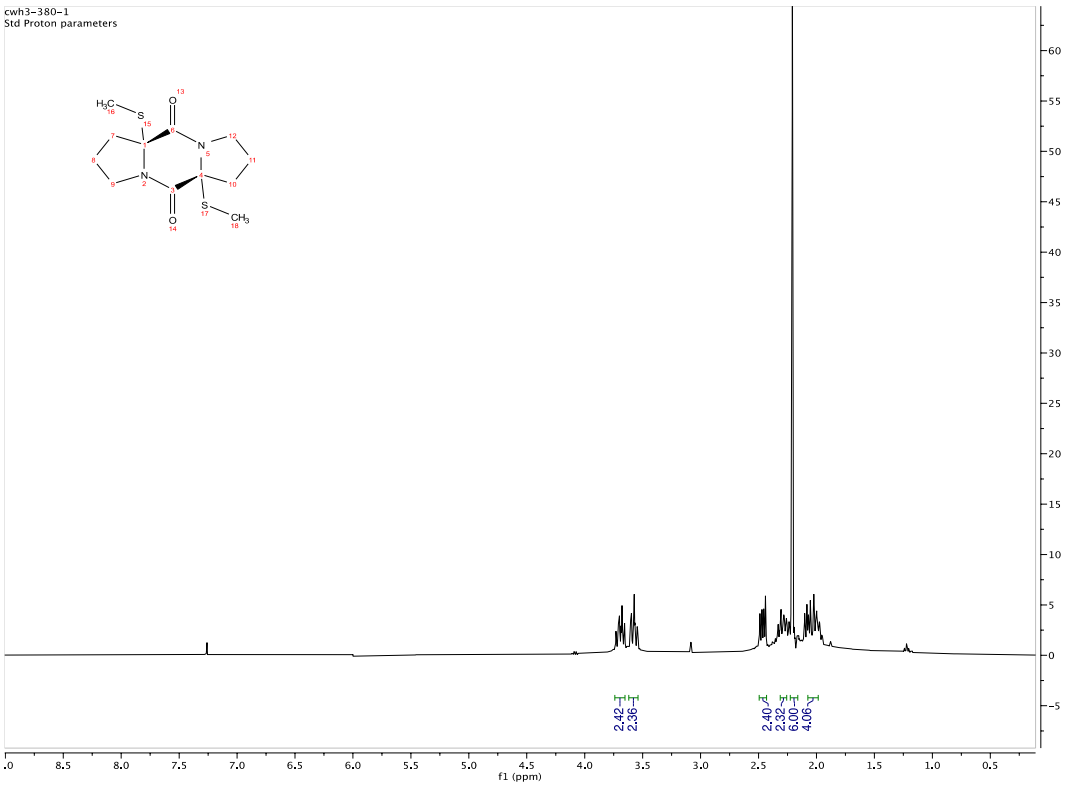
(5aR,10aR)-5a,10a-bis(methylthio)octahydro-5H,10H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (131)

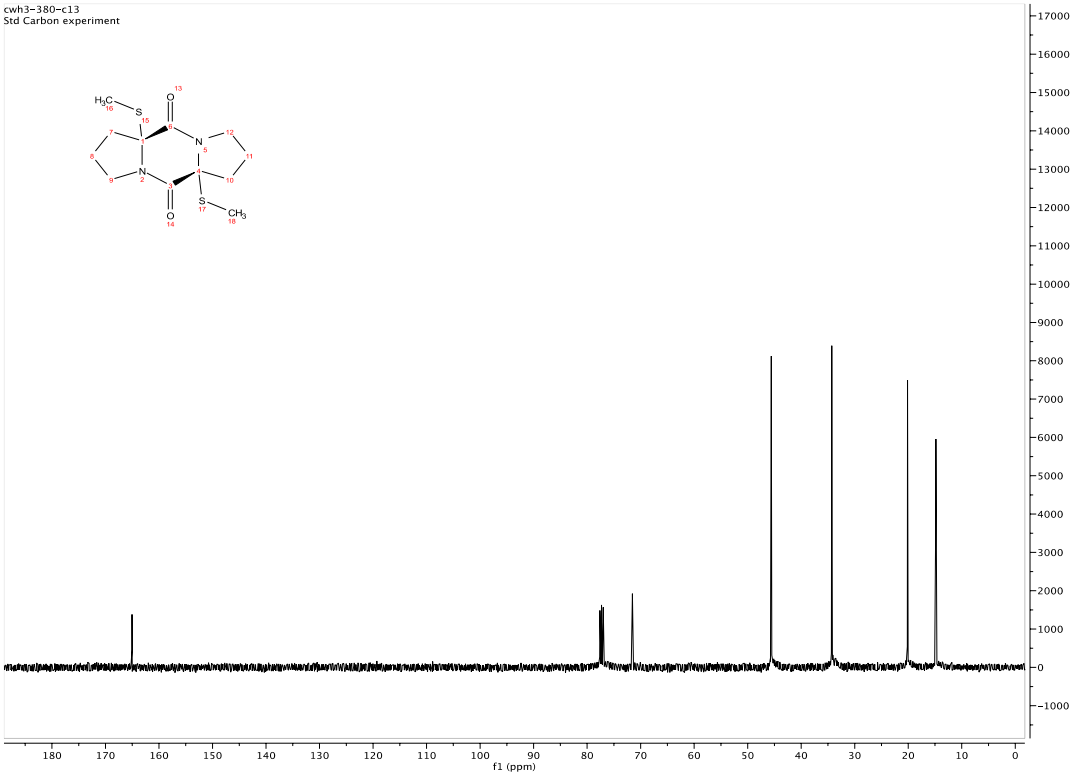


127 **131**

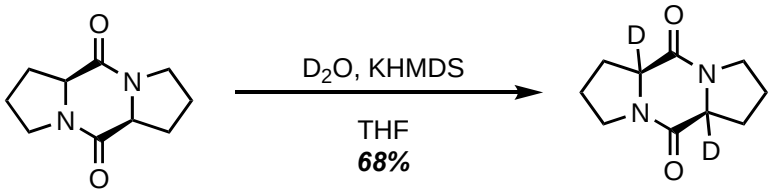
To a stirred solution of compound **127** (165 mg, 0.515 mmol, 1 eq) in THF: EtOH 1:1 (5 mL, 0.10 M) was bubbled with argon for 5 minutes. Then the reaction mixture was cooled to 0 °C and $NaBH_4$ (477 mg, 12.87 mmol, 25 eq) was added portion wise. The reaction mixture was allowed to reach room temperature and stirred for 1 h. Then the reaction was added MeI (1.6 mL, 25.75 mmol, 50 eq), and then was stirred at room temperature. After 12h, the reaction was quenched with saturated aqueous NH_4Cl and organic layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc) to give compound **131** as a white foam (94 mg, 64% yield). Rf = 0.53 (silica, EtOAc); 1H NMR (400 MHz, Chloroform-d) δ 3.74 – 3.65 (m, 2H), 3.57 (ddd, J = 11.8, 9.7, 2.1 Hz, 2H), 2.46 (dd, J = 12.8, 6.6 Hz, 2H), 2.31 – 2.26 (m, 2H), 2.21 (s, 6H), 2.07 – 1.98 (m, 4H). 13C NMR (101 MHz, Chloroform-d) δ 165.03, 71.53, 45.59, 34.28, 20.13, 14.84. Known compound; all the spectral data matches the data reported in reference ***54***.

Notebook Entries:
Procedure – cwh3-380
^{1}H – cwh3-380-1
^{13}C – cwh3-380-c13


cwh3-380-1
Std Proton parameters
2.42
2.36
2.40
2.32
6.00
4.06
f1 (ppm)


cwh3-380-c13
Std Carbon experiment
f1 (ppm)

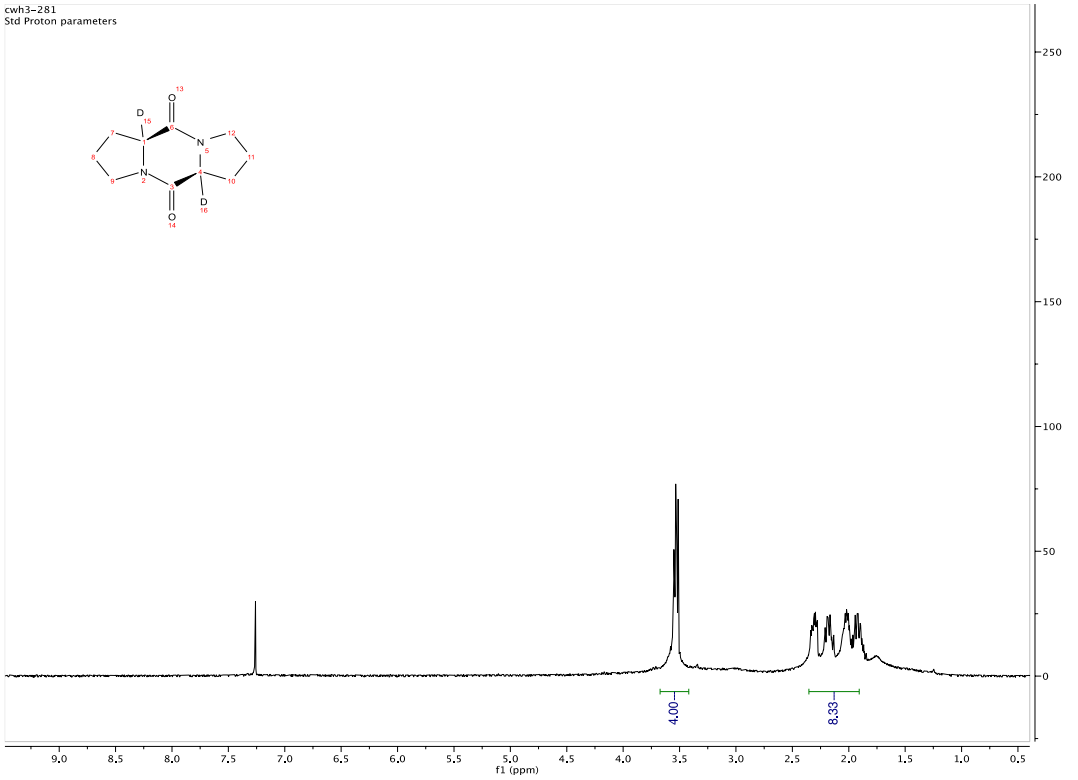
(5aS,10aS)-octahydro-5H,10H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione-5a,10a-d2 (129)

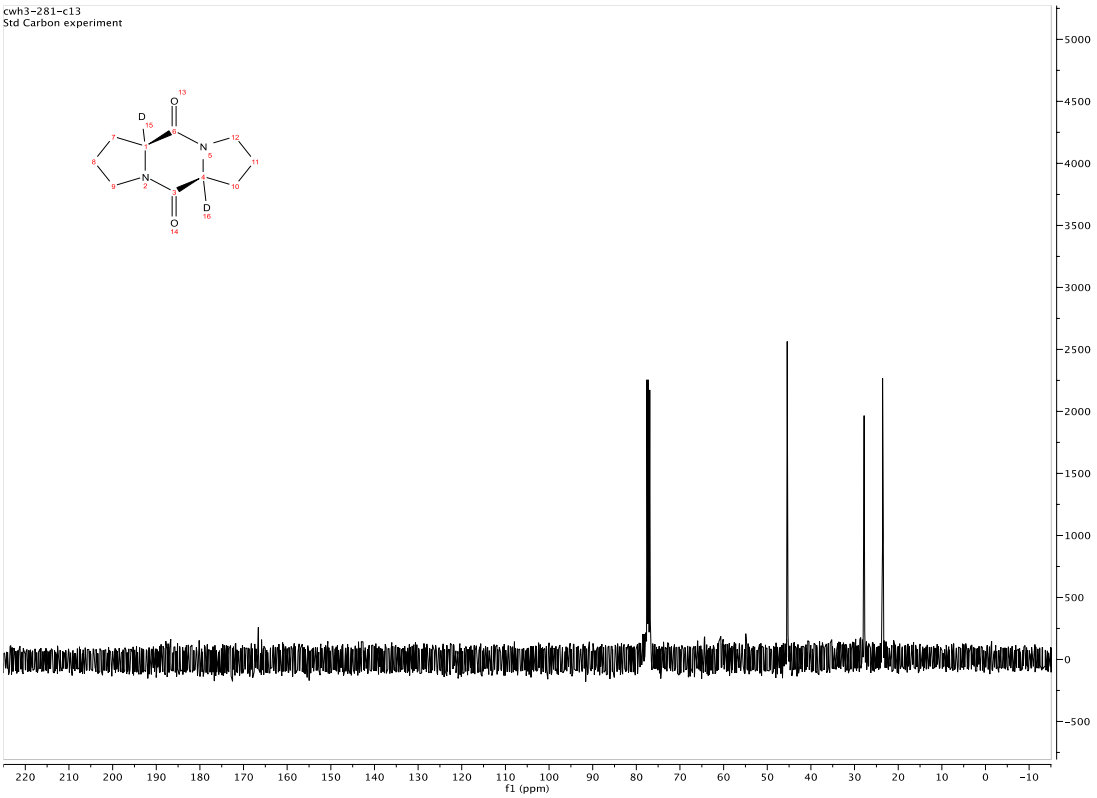


126 **129**

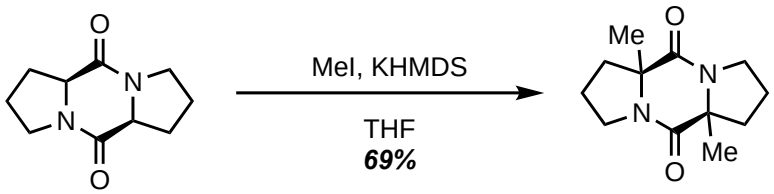
To a stirred solution of compound **126** (100 mg, 0.51 mmol, 1 eq) in THF (17 mL, 0.03 M) was added NaHMDS (3 mL, 3.06 mmol, 6 eq) drop wise at -78 °C, and was stirred at room temperature. After 1h D_2O (3 mL, 0.17 M) was added, and then was stirred at room temperature. After 2 h, the reaction was quenched with saturated aqueous NH_4Cl and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc: MeOH: DCM, 8:1:1) to give compound **129** as a white foam (68.7 mg, 68% yield). Rf = 0.44 (silica, EtOAc: MeOH: DCM, 8:1:1); 1H NMR (400 MHz, Chloroform-d) δ 3.67 – 3.42 (m, 4H), 2.35 – 1.91 (m, 8H). 13C NMR (101 MHz, Chloroform-d) δ 166.61, 45.43, 27.80, 23.57. Known compound; all the spectral data matches the data reported in reference ***54***.

Notebook Entries:
Procedure – cwh3-281
^{1}H – cwh3-281
^{13}C – cwh3-281-c13


cwh3-281
Std Proton parameters
4.00
8.33
f1 (ppm)


cwh3-281-c13
Std Carbon experiment
f1 (ppm)

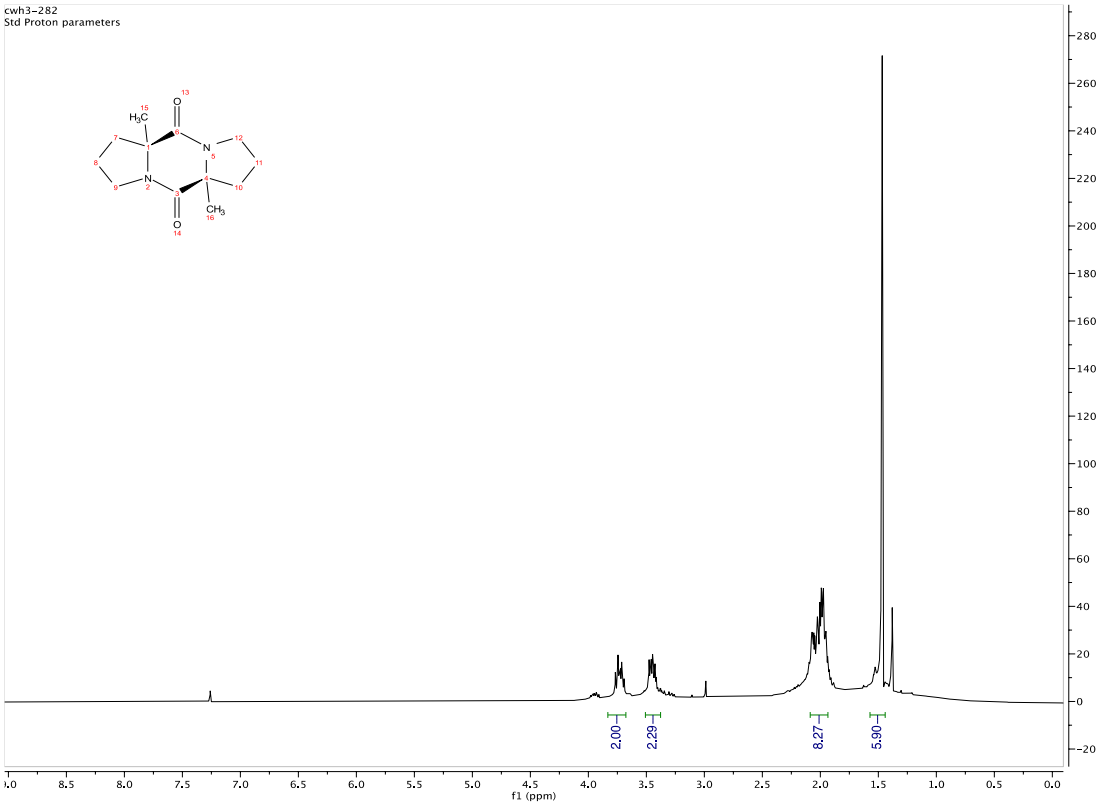
(5aS,10aS)-5a,10a-dimethyloctahydro-5H,10H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (130)



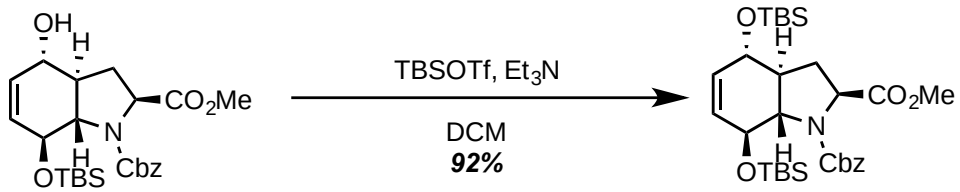
126 **130**

To a stirred solution of compound **126** (100 mg, 0.51 mmol, 1 eq) in THF (17 mL, 0.03 M) was added NaHMDS (3 mL, 3.06 mmol, 6 eq) dropwise at -78 °C. The reaction was stirred for 1 h and MeI (1.6 mL, 25.5 mmol, 50 eq) was added. After 12 h, the reaction was quenched with saturated aqueous NH_4Cl and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc: MeOH: DCM, 8:1:1) to give compound **130** as a white foam (78 mg, 69% yield). Rf = 0.56 (silica, EtOAc: MeOH: DCM, 8:1:1); 1H NMR (400 MHz, Chloroform-d) δ 3.83 – 3.68 (m, 2H), 3.51 – 3.38 (m, 2H), 2.09 – 1.93 (m, 8H), 1.47 (s, 6H). Known compound; all the spectral data matches the data reported in reference ***54***.

Notebook Entries:
Procedure – cwh3-282
^{1}H – cwh3-282


cwh3-282
Std Proton parameters
2.00
2.29
8.27
5.90
f1 (ppm)

1-benzyl 2-methyl (2*S*,3a*S*,4*S*,7*S*,7a*S*)-4,7-bis((*tert*-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1,2-dicarboxylate (132)

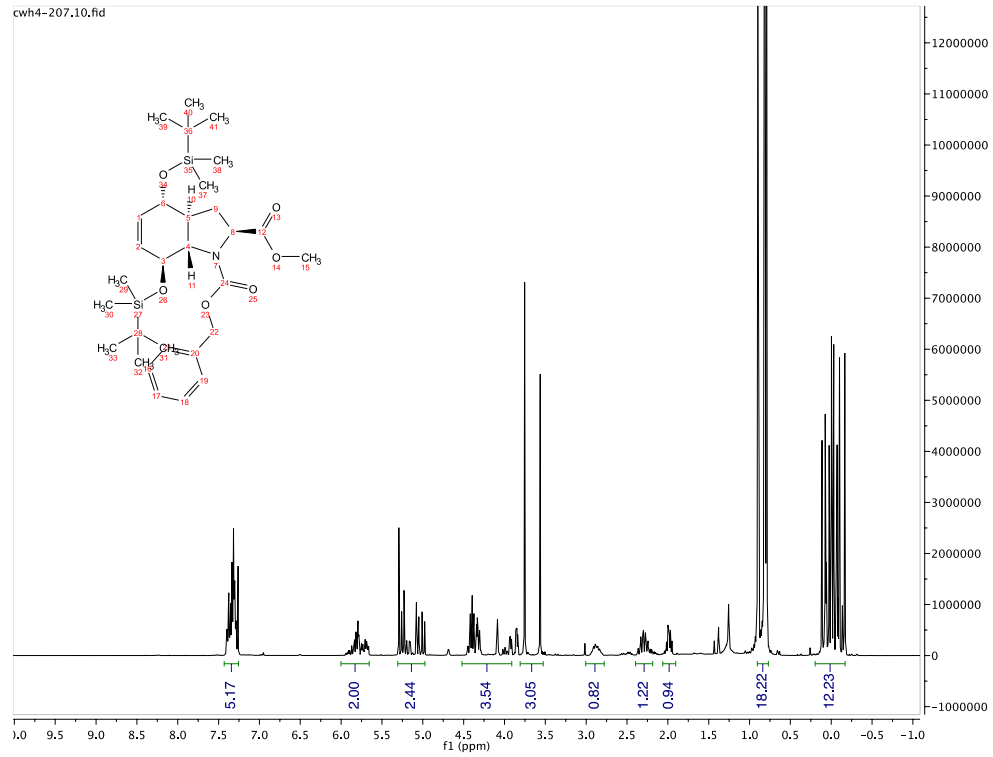


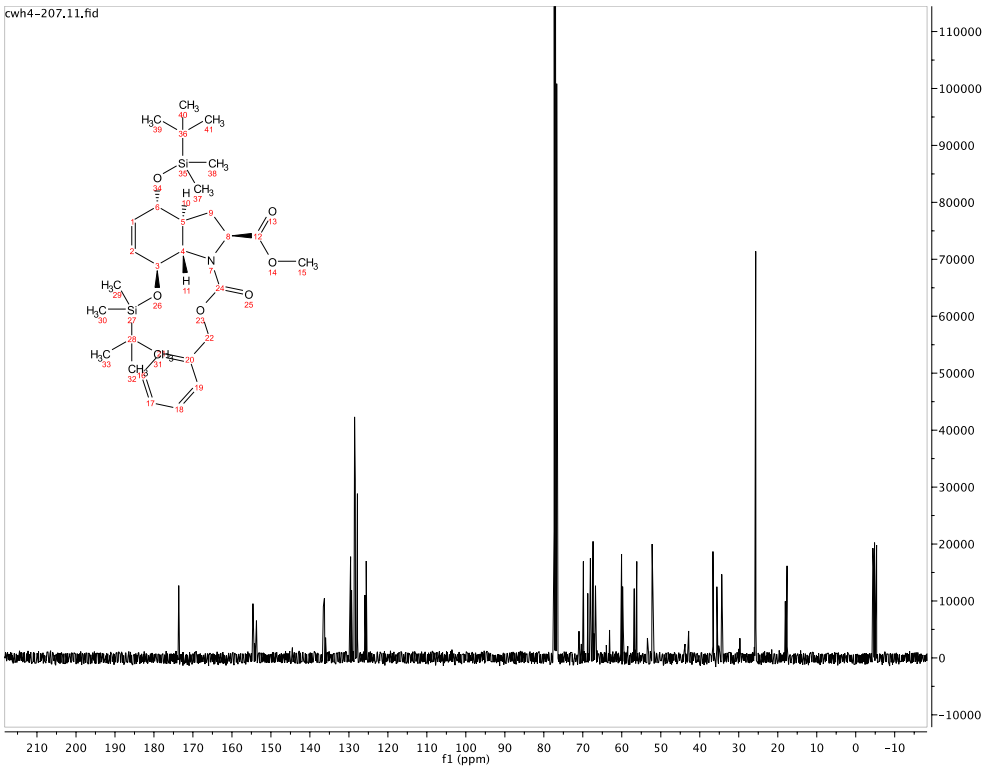
101 **132**

To a stirred solution of compound **101** (30 mg, 0.065 mmol, 1 eq) in DCM (0.65 mL, 0.10 M) was added Et_3N (0.02 mL, 0.130 mmol, 2 eq) and TBSOTf (0.02 mL, 0.078 mmol, 1.2 eq), and then was stirred at room temperature. After 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give compound **132** as a white foam (34 mg, 92% yield). Rf = 0.78 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.26 (m, 5H), 6.00 – 5.66 (m, 2H), 5.31 – 4.97 (m, 2H), 4.52 – 3.91 (m, 4H), 3.66 (s+ s', 3H), 3.01 – 2.78 (m, 1H), 2.40 – 2.19 (m, 1H), 1.98 (m, 1H), 0.93 – 0.76 (m, 18H), 0.20 – -0.17 (m, 12H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (173.74, 173.61), (154.61, 153.71), (136.69, 136.56), (129.56, 129.31), (128.62, 128.51), (127.88, 127.81), (125.90, 125.56), (70.99, 70.37), (69.85, 68.74), (67.37, 67.21), (66.85, 66.76), (59.66, 59.61), (56.80, 56.16), (53.42, 52.21), (36.61, 36.40), (35.61, 35.40), (35.14, 34.36), (25.85, 25.63), (17.92, 17.62), (-4.33, -5.35). New compound; Procedure was taken from reference ***39***.

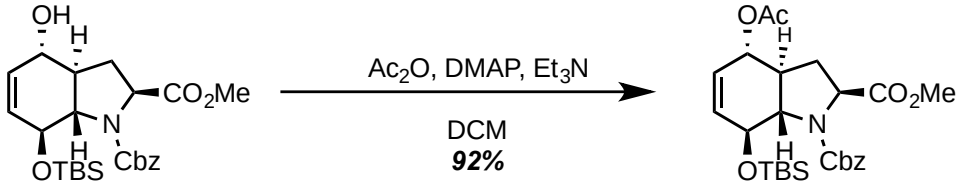
Notebook Entries:

Procedure – cwh4-207
^1H – cwh4-207
^{13}C – cwh4-207


cwh4-207.10.fid
5.17
2.00
2.44
3.54
3.05
0.82
1.22
0.94
18.22
12.23
f1 (ppm)


cwh4-207.11.fid
f1 (ppm)

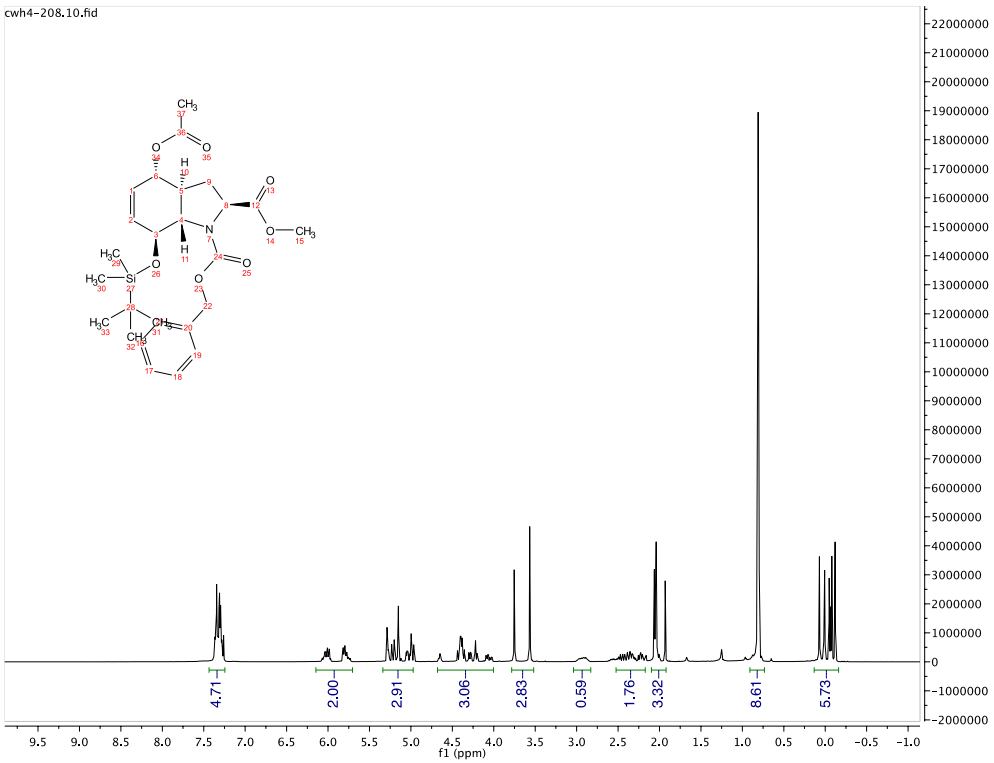
1-benzyl 2-methyl (2S,3aS,4S,7S,7aS)-4-acetoxy-7-((tert-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (134)

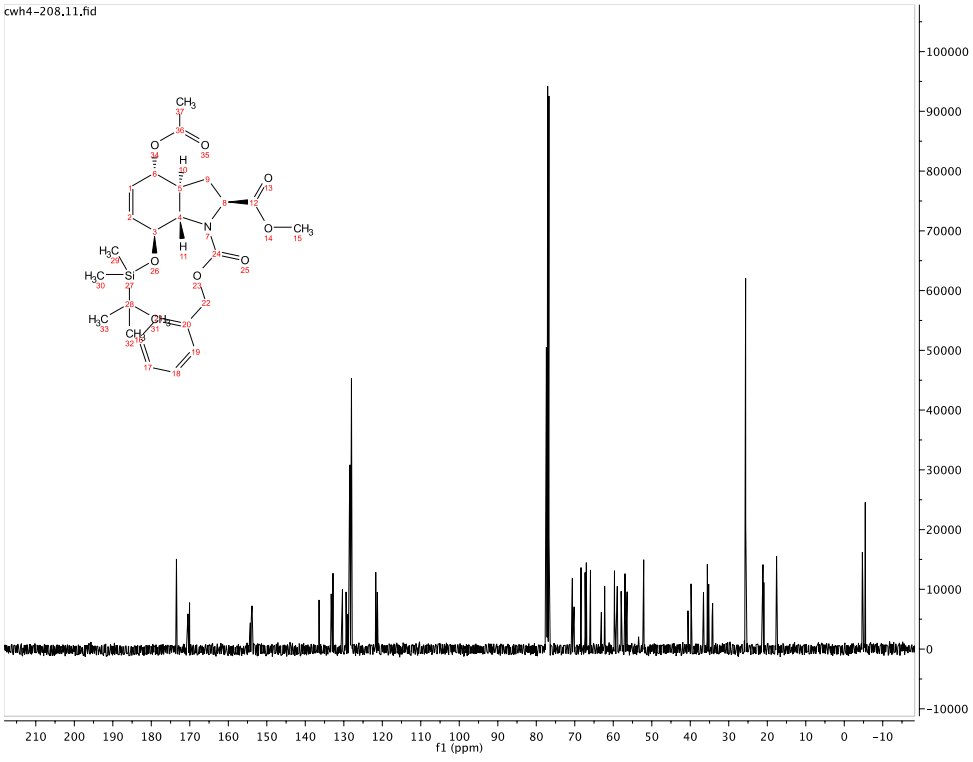


101 **134**

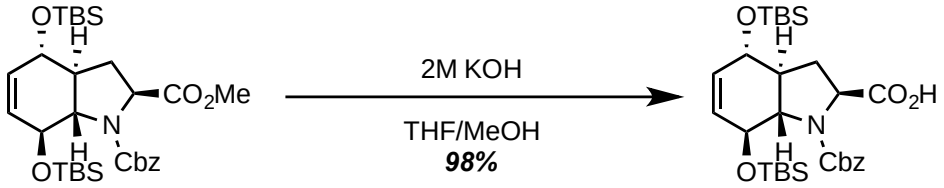
To a stirred solution of compound **101** (48 mg, 0.104 mmol, 1 eq) in DCM (1 mL, 0.10 M) was added acetic anhydride (0.02 mL, 0.208 mmol, 2 eq), DMAP (2.3 mg, 0.021 mmol, 0.2 eq), and Et_3N (0.04 mL, 0.312 mmol, 3.0 eq), and then was stirred at room temperature. After 15 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the organic layer was extracted with DCM (× 3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:1) to give compound **134** as a light-yellow foam (47 mg, 92% yield). Rf = 0.72 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.25 (m, 5H), 6.15 – 5.71 (m, 2H), 5.34 – 4.97 (m, 3H), 4.68 – 4.00 (m, 3H), 3.66 (s+ s', 3H), 2.92 (m, 1H), 2.52 – 2.17 (m, 2H), 2.10 – 1.92 (m, 3H), 0.91 – 0.73 (m, 9H), 0.13 – -0.16 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (173.48, 173.40), (170.48, 169.91), (154.46, 153.84), (136.42, 136.18), (133.28, 132.81), (130.33, 130.21), (129.42, 128.91), (128.12, 128.01), (127.95, 127.91), (121.71, 121.28), (70.64, 70.19), (67.33, 67.01), (66.98, 66.73), (63.09, 62.24), (59.86, 59.11), (58.95, 57.06), (56.97, 56.41), (52.30, 52.08), (40.60, 39.80), (36.56, 35.21), (34.31, 34.20), (25.65, 25.63), (21.22, 20.90), (17.72, 17.59), (-4.71, -5.47). New compound; Procedure was taken from reference ***38***.

Notebook Entries:
Procedure – cwh4-208 ^{1}H – cwh4-208 ^{13}C – cwh4-208


cwh4-208.10.fid
4.71
2.00
2.91
3.06
2.83
0.59
1.76
3.32
8.61
5.73
f1 (ppm)


cwh4-208.11.fid
f1 (ppm)

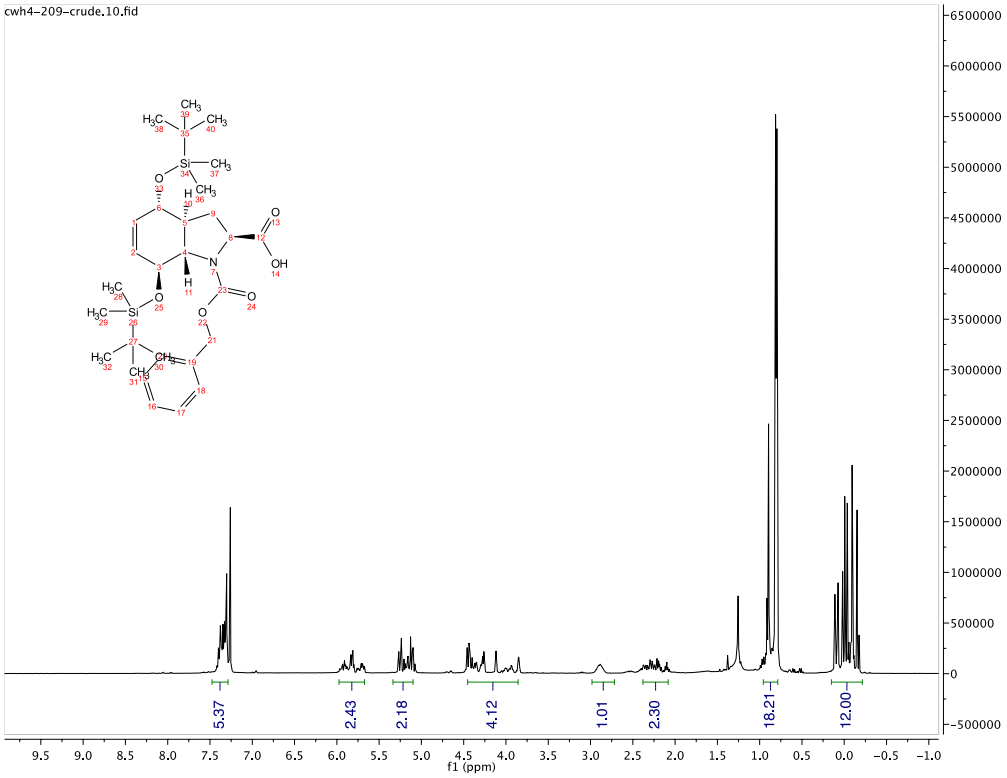
(2*S*,3a*S*,4*S*,7*S*,7a*S*)-1-((benzyloxy)carbonyl)-4,7-bis((*tert*-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1*H*-indole-2-carboxylic acid (133)



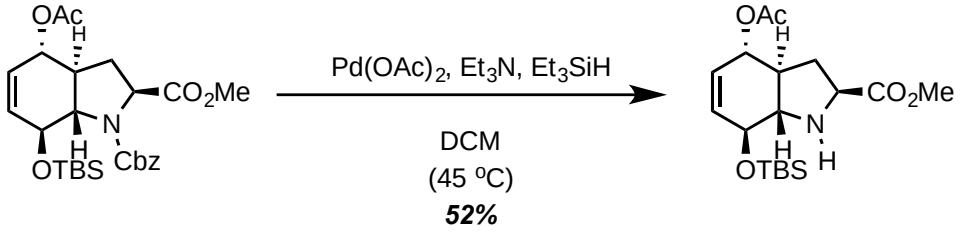
132 **133**

To a stirred solution of compound **132** (75 mg, 0.130 mmol, 1 eq) in THF:MeOH 1:1 (1.3 mL, 0.1 M) was added 2M KOH (1.3 mL, 0.10 M), and then was stirred at 45 °C. After 1 h, the reaction was acidified to pH 2 with 1M HCl and organic layer was extracted with EtOAc (× 3). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo to give compound **133** as a white foam (71 mg, 98% yield). Rf = 0.11 (silica, EtOAc:hexanes, 1:1); Rotamers were shown in ( ). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.29 (m, 5H), 5.97 – 5.67 (m, 2H), 5.34 – 5.10 (m, 2H), 4.45 – 3.86 (m, 4H), 2.88 (t, *J* = 10.1 Hz, 1H), 2.38 – 2.08 (m, 2H), 0.96 – 0.79 (m, 18H), 0.15 – -0.21 (m, 12H). Crude was directly used in next reaction without further purification. New compound; Procedure was taken from reference ***39***.

Notebook Entries:
Procedure – cwh4-232
^{1}H – cwh4-209


cwh4-209-crude.10.fid
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
5.37
2.43
2.18
4.12
1.01
2.30
18.21
12.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

Methyl (2S,3aS,4S,7S,7aS)-4-acetoxy-7-((tert-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-2-carboxylate (135)

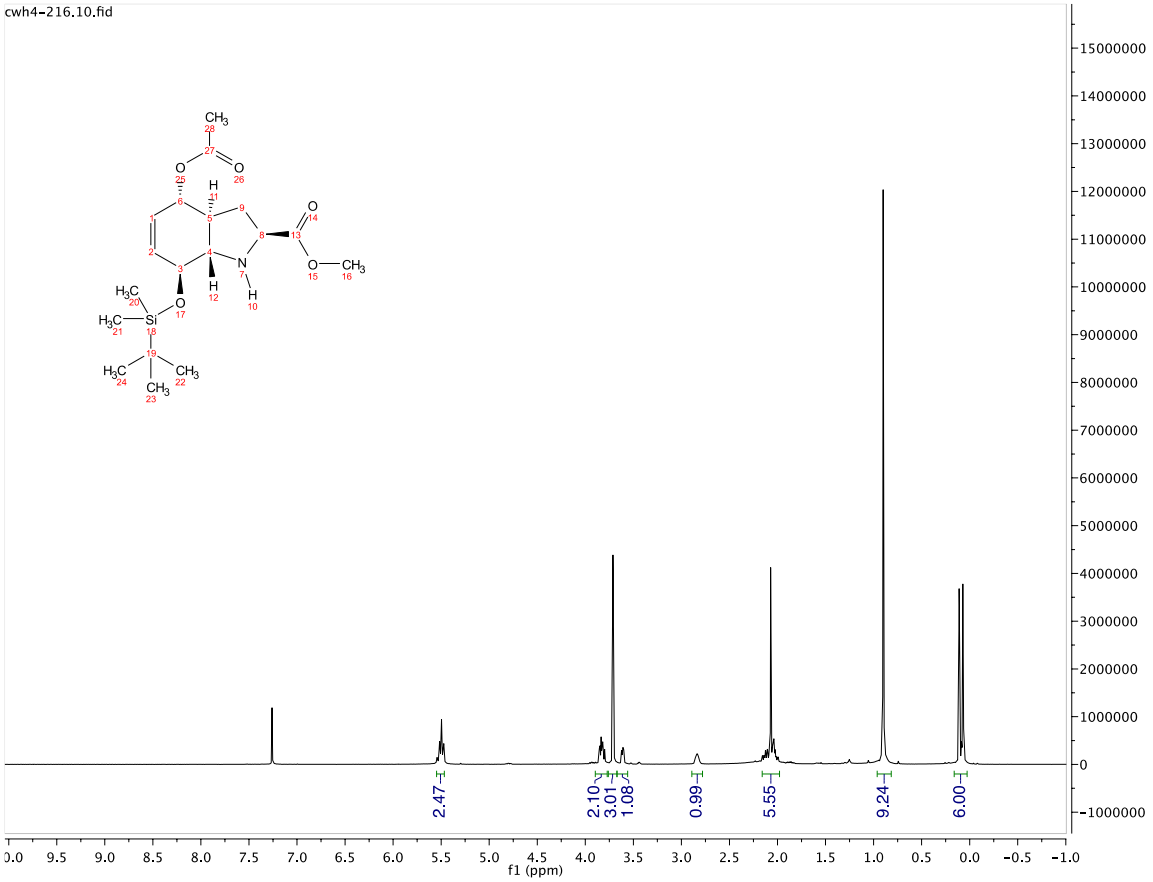


134 **135**

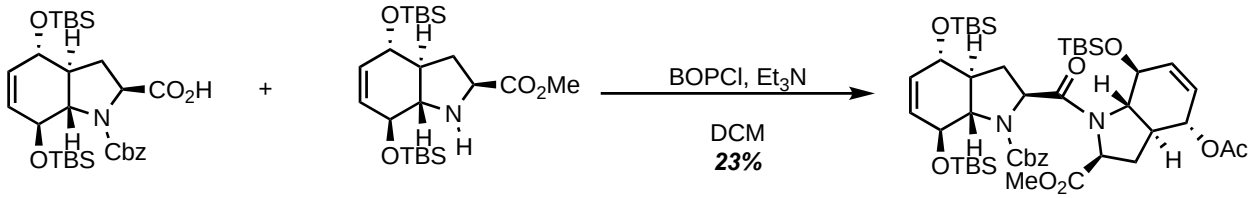
To a stirred solution of compound **134** (35 mg, 0.069 mmol, 1 eq) in DCM (0.70 mL, 0.10 M) was added $Pd(OAc)_2$ (18 mg, 0.083 mmol, 1.2 eq) and Et_3N (0.02 mL, 0.166 mmol, 2.4 eq), and was stirred for 5 mins at 45 °C. Then Et_3SiH (0.10 mL, 0.690 mmol, 10 eq) was added drop wise, and then was stirred at 45 °C. After 20 h, the reaction was filtered through celite pad and concentrated in vacuo to give compound **135** as an oily residue (13 mg, 52% yield). Rf = 0.31 (silica, EtOAc:hexanes, 1:3); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-*d*) δ 5.55 – 5.47 (m, 2H), 3.90 – 3.77 (m, 2H), 3.71 (s, 3H), 3.61 (dd, *J* = 5.8, 3.4 Hz, 1H), 2.84 (td, *J* = 5.9, 3.1 Hz, 1H), 2.16 – 1.98 (m, 6H), 0.90 (s, 9H), 0.09 (d, *J* = 15.4 Hz, 6H). New compound; Procedure was taken from reference ***39***.

Notebook Entries:

Procedure – cwh4-215
^1H – cwh4-216


cwh4-216.10.fid
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
2.47
2.10
3.01
1.08
0.99
5.55
9.24
6.00
f1 (ppm)

Benzyl (2S,3aS,4R,7R,7aS)-2-((2S,3aS,4R,7R,7aS)-4,7-bis((tert-butyldimethylsilyl)oxy)-2-(methoxycarbonyl)-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carbonyl)-4,7-bis((tert-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carboxylate (136)

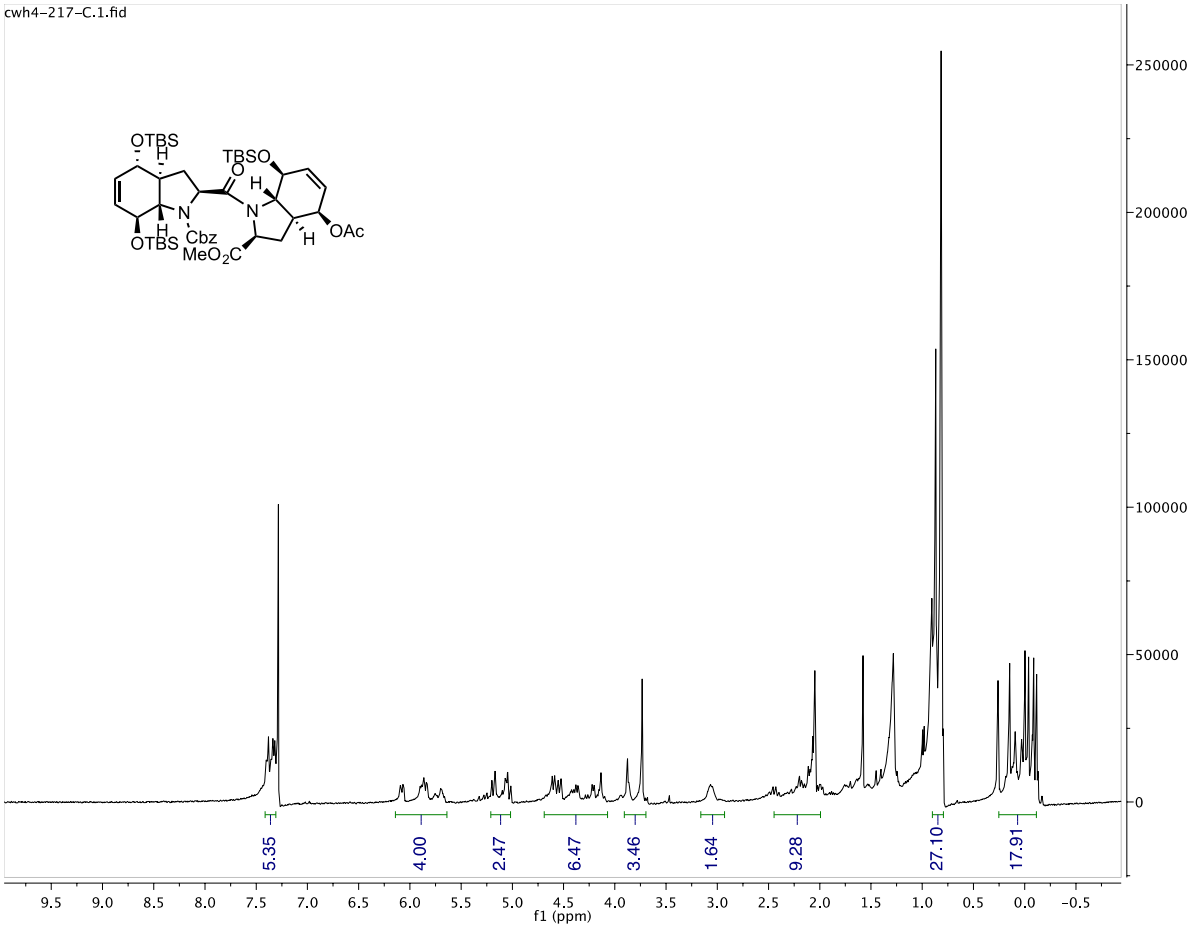


133 **135** **136**

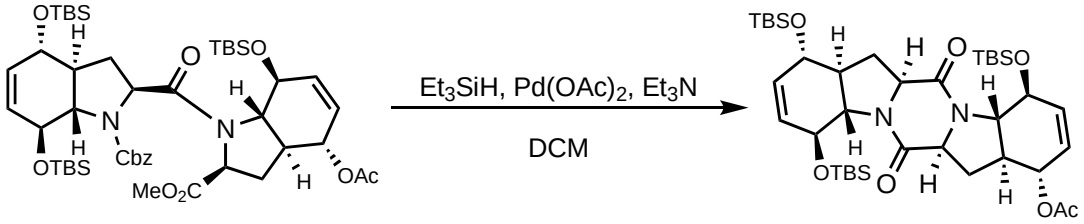
To a stirred solution of carboxylic acid **133** (24 mg, 0.043 mmol, 1 eq) and amine **135** (16 mg, 0.043 mmol, 1 eq) in DCM (0.40 mL, 0.10 M) was cooled to 0 ºC. Then Et_3N (0.02 mL, 0.130 mmol, 3.0 eq) was added and stirred. After 5 mins, BOPCl (13 mg, 0.052 mmol, 1.2 eq) was added portion wise, and then was stirred at room temperature. After 20 h, the reaction was concentrated in vacuo and the crude residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 3:1) to give compound **136** as a white foam (9 mg, 23% yield). Rf = 0.61 (silica, EtOAc:hexanes, 3:1); Rotamers were shown in ( ). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.31 (m, 5H), 6.09 – 5.66 (m, 4H), 5.23 – 5.04 (m, 2H), 4.63 – 4.09 (m, 6H), 3.90 – 3.72 (s+ s', 3H), 3.06 (s, 2H), 2.53 – 1.97 (m, 9H), 0.97 – 0.77 (m, 27H), 0.33 – -0.26 (m, 16H).

New compound; Procedure was taken from reference ***39***.

Notebook Entries:
Procedure – cwh4-217
^1H – cwh4-217-C


cwh4-217-C.1.fid
OTBS
H
TBSO
O
H
N
N
H
OAc
H
OTBS
Cbz
MeO2C
250000
200000
150000
100000
50000
0
5.35
4.00
2.47
6.47
3.46
1.64
9.28
27.10
17.91
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

(1*S*,4*S*,4a*S*,6a*S*,7a*S*,8*S*,11*S*,11a*S*,13a*S*,14a*S*)-4,8,11-tris((*tert*-butyldimethylsilyl)oxy)-6,13-dioxo-4,4a,6a,7,7a,8,11,11a,13,13a,14,14a-dodecahydro-1*H*,6*H*-pyrazino[1,2-*a*:4,5-*a'*]diindol-1-yl acetate (137)

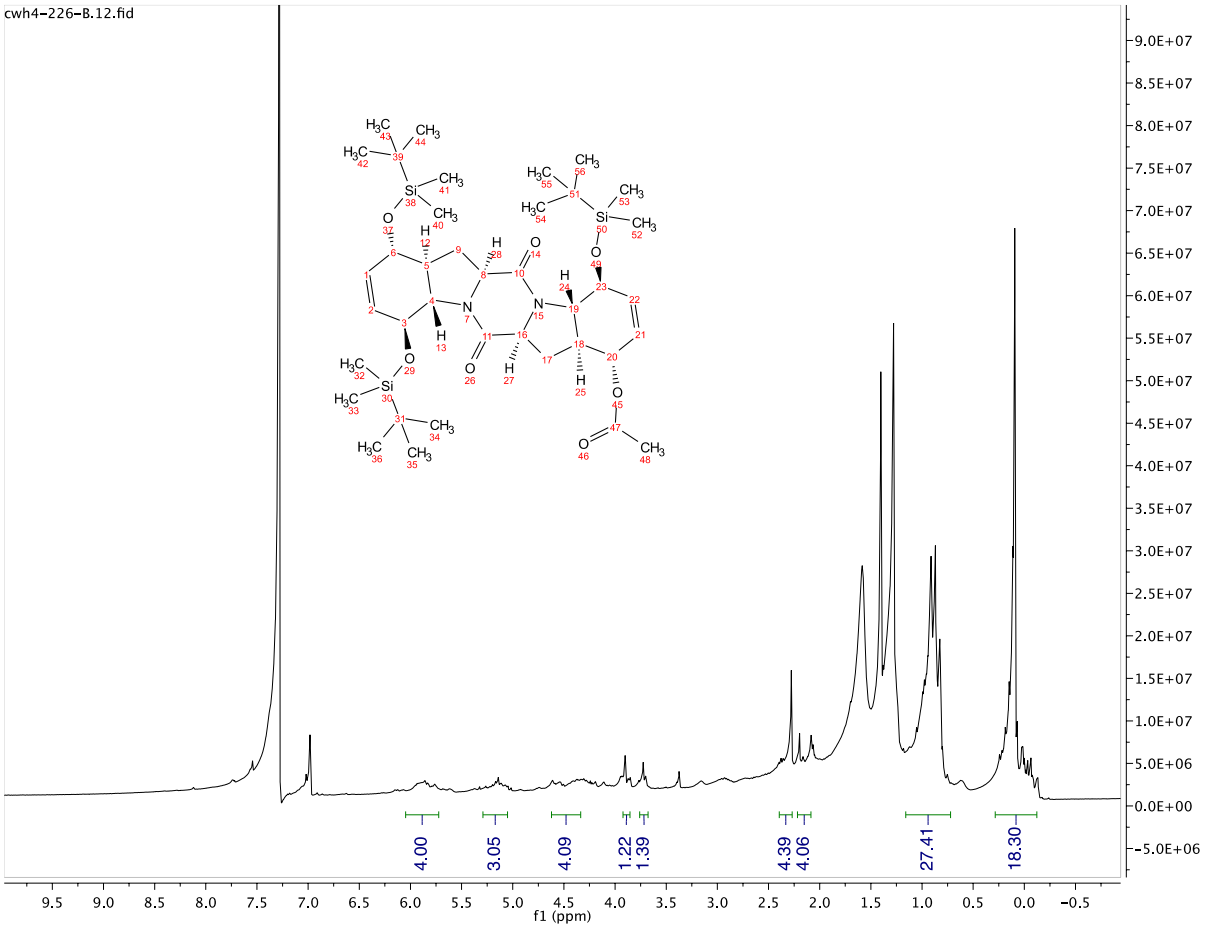


136 **137**

To a stirred solution of compound **136** (9 mg, 0.0098 mmol, 1 eq) in DCM (1.0 mL, 0.01 M) was added $Pd(OAc)_2$ (0.44 mg, 0.002 mmol, 0.2 eq) and Et_3N (0.5 μL, 0.004 mmol, 0.4 eq), and was stirred for 5 mins at 45 °C. Then Et_3SiH (0.01 mL, 0.069 mmol, 7 eq) was added drop wise, and then was stirred at 45 °C. After 2 h, the reaction was filtered through celite pad and concentrated in vacuo to give compound **137** as an oily residue. Rf = 0.63 (silica, EtOAc:hexanes, 1:3); ^1H NMR (400 MHz, Chloroform-*d*) δ 6.22 – 5.84 (m, 4H), 5.45 – 5.08 (m, 3H), 4.80-4.32 (m, 4H), 3.81 (m, 1H), 3.75 (m, 1H), 2.31 – 2.10 (m, 4H), 2.08-1.90 (m, 4H), 0.90 (m, 27H), 0.02 (m, 18H). New compound; Procedure was taken from reference ***39***.

Notebook Entries:

Procedure – cwh4-226
^1H – cwh4-226-B


cwh4-226-B.12.fid
4.00
3.05
4.09
1.22
1.39
4.39
4.06
27.41
18.30
f1 (ppm)

ADDENDUM