STUDIES TOWARD THE TOTAL SYNTHESIS OF RITTERAZINE B: THE INVESTIGATION OF ALKYNYLATION REACTIONS FOR USE IN THE SYNTHESIS OF THE WESTERN FRAGMENT

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ABSTRACT

The ritterazine and cephalostatin natural products have biological activities and structures that are interesting to synthetic organic chemists. These products have been found to exhibit significant cytotoxicity against P388 murine leukemia cells, and therefore have the potential to be used as anticancer drugs. The ritterazines and cephalostatins are steroidal dimers joined by a central pyrazine ring. Given that the steroid halves are unsymmetrical and highly oxygenated, there are several challenges in synthesizing these compounds in an organic laboratory.

Ritterazine B is the most potent derivative in the ritterazine family. Its biological activity is comparable to drugs that are being used to treat cancer today. For this reason, and the fact that there are no reported syntheses of ritterazine B to date, our lab set out to synthesize this natural product.

Herein, efforts toward the synthesis of the western fragment of ritterazine B are described. Two different routes are explored to access a common intermediate. An alkyne conjugate addition reaction was initially investigated due to the success of this key reaction in the synthesis of the eastern fragment. However, it has been found that a propargylation reaction has greater reactivity and yields, and has the potential to reduce the step count of the synthesis of the western fragment of ritterazine B.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
At	benztriazolyl
atm	atmosphere(s)
BHT	2,6-di-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
C	cytosine

c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
^{14}C	carbon-14 isotope
/C	supported on activated carbon charcoal
°C	degrees Celcius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
Cys	cysteine
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCE	1,2-dichloroethane
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMTS	dimethylthexylsilyl
DNA	deoxyribonucleic acid
DPPA	diphenylphosphorylazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTT	dithiothreitol
ee	enantiomeric excess
E	methyl carboxylate (CO_2CH_3)
E^+	electrophile
E	trans (entgegen) olefin geometry
EC_{50}	median effective concentration (50%)
EDC	*N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide
e.g.	for example (Latin: *exempli gratia*)
EI	electron ionization

eq	equation
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
ETP	epipolythiodiketopiperazine
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
G	guanine
h	hour(s)
^{1}H	proton
^{2}H	deuterium
^{3}H	tritium
[H]	reduction
HATU	2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPT	hexamethylphosphoramide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)

IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LD_{50}	median lethal dose (50%)
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
μ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
MM	mixed method

mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
m/*z*	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile
o	ortho
[O]	oxidation
t-Oct	*tert*-octyl (1,1,3,3-tetramethylbutyl)
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
pK_a	acid dissociation constant

PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl
Pro	proline
psi	pounds per square inch
py	pyridine
pyr	pyridine
q	quartet
R	alkyl group
R	rectus
REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
ref	reference
R_f	retention factor
RNA	ribonucleic acid
s	singlet or seconds
s	selectivity factor = $k_{rel(fast/slow)} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
SOD	superoxide dismutase

Su	succinimide
t	triplet
T	thymine
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
temp	temperature
Teoc	trimethylsilylethoxycarbonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
Troc	2,2,2-trichloroethoxycarbonyl

Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry

Chapter 1

Background Information on Ritterazines and Cephalostatins

1.1 ISOLATION AND BIOLOGICAL DATA

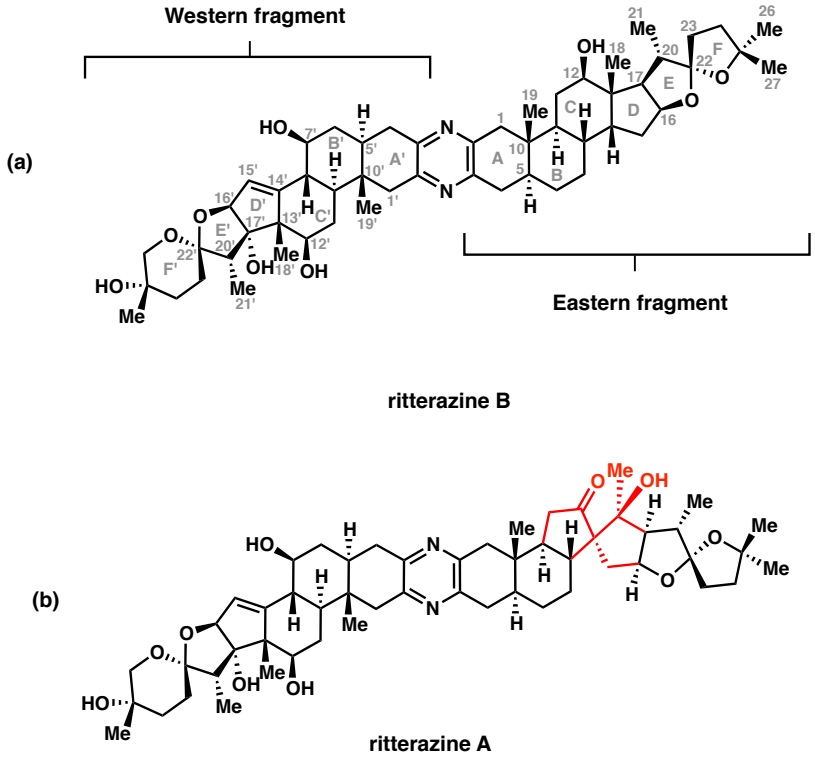
Ritterazines A through Z are natural products that were isolated from the Japanese marine tunicate *Ritterella tokioka* by Fusetani et al, collected at depths of 3–5 m off the Izu Peninsula, 100 km southwest of Tokyo.[1] Tunicates such as *Ritterella tokioka* have found to be a significant source of cytotoxic compounds, including the didemnins, the ecteinascidins, and the patellazoles.[1] Upon isolation via lipophilic extraction, the extracts were found to exhibit potent activity against P388 murine leukemia cells.[1d] Structurally, ritterazines are dimeric steroidal alkaloids strongly resembling the structures of the cephalostatins.[1] However, the cephalostatins were isolated from the East African hemichordate *Cephalodiscus gilchristi* in the Indian Ocean, hundreds of miles away from the Izu Peninsula.[1] Although these natural products come from different parts of the world, their structure and biological activity is very similar.[1]

Ritterazine B (**Figure 1a**) was isolated by Fusetani et al. in 1995, and its structure was found to strongly resemble the previously isolated ritterazine A (**Figure**

[1] a) Fusetani #1 b) Fusetani #2 c) Fusetani #3 d) Fusetani #4

1b).[1] The UV spectrum of ritterazine B contained a peak at λ_{max} 288 nm, which was also found in the spectrum of ritterazine A, indicating that both of these structures include a pyrazine ring.[1b] This pyrazine ring joins the two steroidal moieties, facilitating deconstruction of the ritterazine structures into the western and eastern fragments. The western half of ritterazine B was determined to possess the same connectivity and stereochemistry as that of ritterazine A. This includes a C14'–C15' unsaturation in the D' ring, hydroxyl groups at C7', C12', and C17', and a 5/6 spiroketal system with the E'/F' rings. The eastern half of ritterazine B is slightly less oxidized, containing a hydroxyl group at C12, and a 5/6 spiroketal.

Figure 1. *(a) Structure of western and eastern fragments of ritterazine B with atom labels. (b) Structure of ritterazine A with highlighted differences from ritterazine B.*



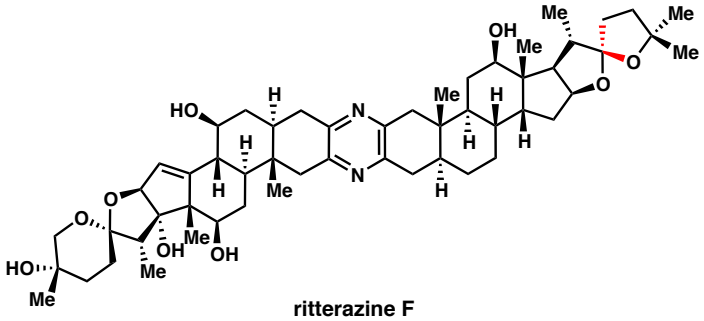
Ritterazine B is the most potent of the ritterazine derivatives isolated to date. Comparison of the various ritterazine structures can provide insight into the structure-activity relationships of ritterazine B that are important for biological activity. **Table 1** shows the cytotoxicity against P388 murine leukemia cells for all ritterazine derivatives. Ritterazines F and G (**Figure 2**) are the two most potent compounds after ritterazine B, and, unsurprisingly, their structures are very similar to ritterazine B. Ritterazine F has the same structure as ritterazine B, except it contains the opposite stereochemistry of the 5/5 spiroketal at C22. Ritterazine G has the same structure as ritterazine B, except that it contains D ring unsaturation.

Ritterazines A, E, and Y (**Figures 1c** and **2**, respectively) are also extremely potent compounds. The western fragments of ritterazines A and E are the same as ritterazines B, F, and G, so therefore, the structural components of the western half must be essential for potent biological activity. However, the structures of ritterazines A and E are distinguished by eastern fragments with rearranged steroid skeletons in which the C and D rings are joined as a 5/5 spirocycle. Lastly, ritterazine Y (**Figure 2**) exhibits the same cytotoxicity as ritterazines A and E, however the structure of ritterazine Y lacks the rearranged steroid. The eastern half is the same as ritterazine F, which was shown not to decrease cytotoxicity substantially. However, the decrease in activity from ritterazine F to ritterazine Y comes from the loss of hydroxyl groups at C7' and C17', and therefore indicating that these functional groups increase cytotoxicity.

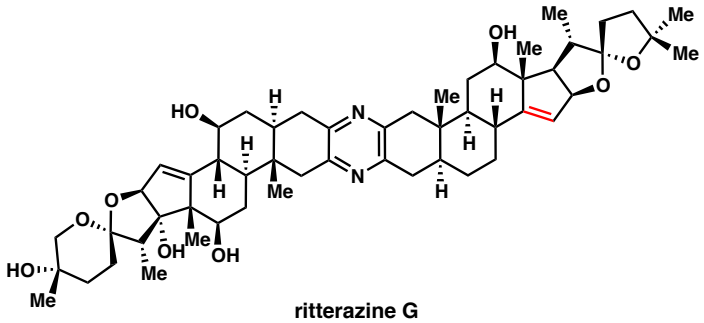
Table 1. *Cytotoxic activity of 26 ritterazine derivatives against P388 murine leukemia cells (IC_{50}, ng/mL).*

Ritterazine	IC_{50} (ng/mL)	Ritterazine	IC_{50} (ng/mL)
A	3.5	N	460
B	0.15	O	2100
C	92	P	710
D	16	Q	570
E	3.5	R	2100
F	0.73	S	460
G	0.73	T	460
H	16	U	2100
I	14	V	2100
J	13	W	3200
K	9.5	X	3000
L	10	Y	3.5
M	15	Z	2000

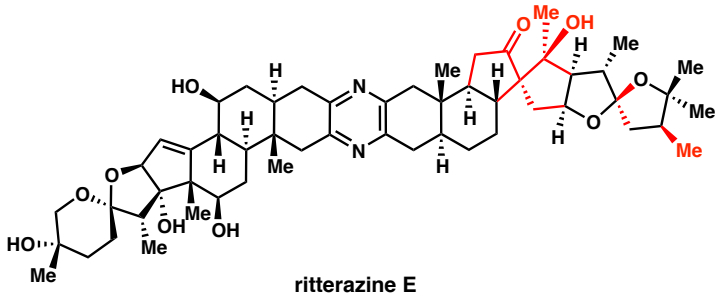
Figure 2. *Structures of ritterazines F, G, E, and Y with highlighted differences from ritterazine B.*



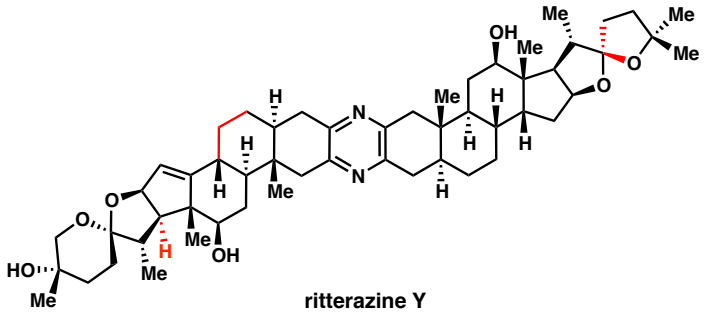
ritterazine F



ritterazine G



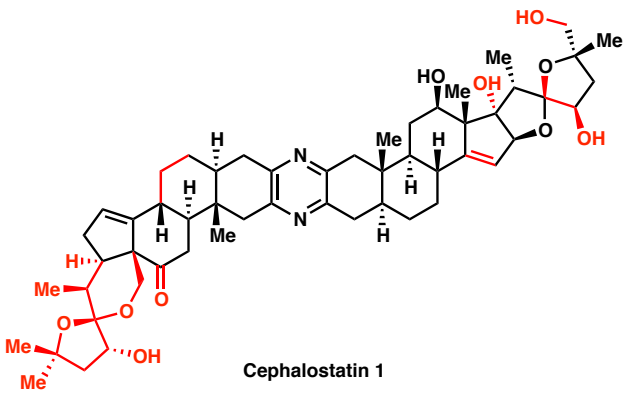
ritterazine E



ritterazine Y

The related natural product cephalostatin 1 (**Figure 3**) also contains the steroidal dimer joined by a pyrazine ring, however there are some significant structural differences. The eastern half of cephalostatin 1 resembles the eastern fragment of ritterazine B, except that cephalostatin 1 possesses an unsaturated D ring, and the opposite stereochemistry of the 5/5 spiroketal at C22. In addition, cephalostatin 1 is further functionalized with hydroxyl groups at C17, C23, and C27. The western half of cephalostatin 1 differs more significantly from the corresponding ritterazine B fragment. Most strikingly, D' and E' rings are fused at C17' and C13', and the E' and F' rings comprise a 6/5 spirocyclic system.

***Figure 3**. Structure of cephalostatin 1 with highlighted differences from ritterazine B.*



Cephalostatin 1

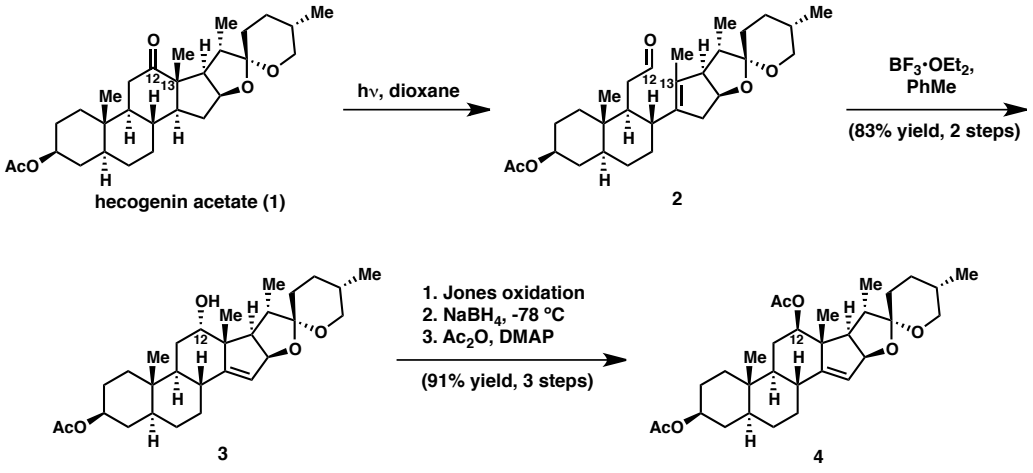
Cephalostatin 1 has more potent biological activity compared to ritterazine B, however analysis of the biological activities indicates that the cellular target and mechanism of action are likely the same. The average GI_{50} values of cephalostatin 1 and ritterazine B against the National Cancer Institute's collection of 60 human cancer cell lines (NCI-60) are 1.8 nM and 3.2 nM, respectively,[2,3] and the COMPARE correlation coefficient against NCI-10 for cephalostatin 1 and ritterazine B is 0.93, where values greater than 0.60 suggest that the two compounds have a related mechanism of action.[4,5] Shair et al. has shown that the cellular target of these compounds is oxysterol binding protein (OSBP), and has demonstrated that cephalostatin 1 and ritterazine B change the cellular localization of OSBP to the Golgi, and also cephalostatin 1 (and, most likely, ritterazine B) reduces levels of OSBP to an antiproliferative level.[5] Shair studied the effects of these natural products on the biosynthesis of sphingomyelin. Ceramide is transported to the Golgi for synthesis of sphingomyelin by ceramide transport protein (CERT), which depends on OSBP and VAP-A.[5] It was further found that high concentrations of cephalostatin 1

and ritterazine B inhibit the biosynthesis of sphingomyelin.[5] Although these experiments have produced interesting results, there are still more questions to be answered, and how these natural products bind to OSBP is unknown.

1.2 PRIOR SYNTHETIC STUDIES

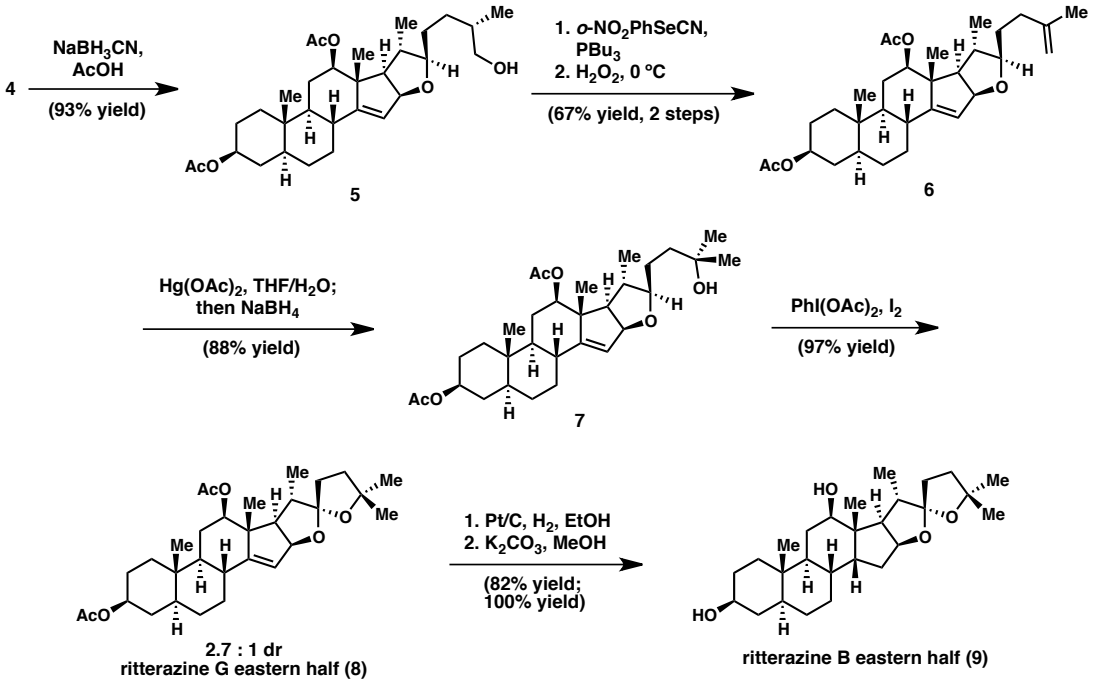
Shair et. al. reported syntheses of the eastern fragments of ritterazines B, F, and G.[3] Beginning with the commercially available steroid, hecogenin acetate (**1**), Norrish type I photolytic cleavage of the C12–C13 bond provides aldehyde **2** (**Scheme 1**), which, when treated with BF_3•OEt_2, undergoes an ene reaction to reclose the six-membered C ring and produce **3**.[3] A three-step procedure involving oxidation to the ketone, diastereoselective reduction to the correctly configured alcohol at C12, and subsequent protection delivers steroid **4**.

Scheme 1. *Initial steps in Shair's syntheses of ritterazines B, F, and G eastern halves.*



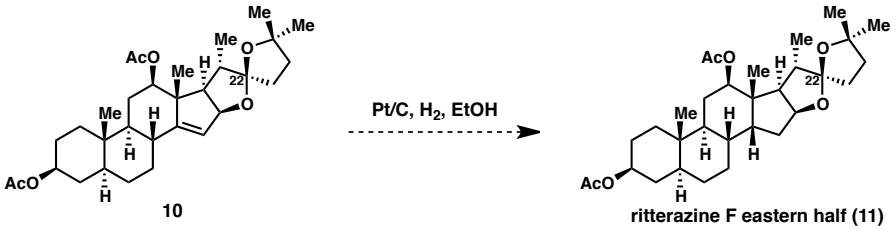
Shair then implements several steps to convert the 5/6 spiroketal of **4** to the desired 5/5 system found in ritterazine G. Reductive opening of the acetal provides primary alcohol **5**, which is subjected to selenation/oxidation following the Grieco protocol to provide alkene **6**. Oxymercuration/demercuration of **6** delivers tertiary alcohol **7**, which is subjected to a Suárez iodine(III)-mediated oxidative ring closure to give the required 5/5 spiroketal. The Suárez reaction produces a 2.5:1 mixture of diastereomers, slightly favoring the desired stereochemistry. After isolating the major diastereomer, Shair uses a two-step procedure to complete the synthesis of the eastern fragment of ritterazine B (**9**). Compound **8** was subjected to hydrogenation with Pt/C in ethanol, and acetyl deprotection to yield the eastern half of ritterazine B (**9**) in 33% overall yield and 11 steps from hecogenin acetate.[3]

Scheme 2. *Completion of Shair's syntheses of ritterazines G and B eastern fragments.*

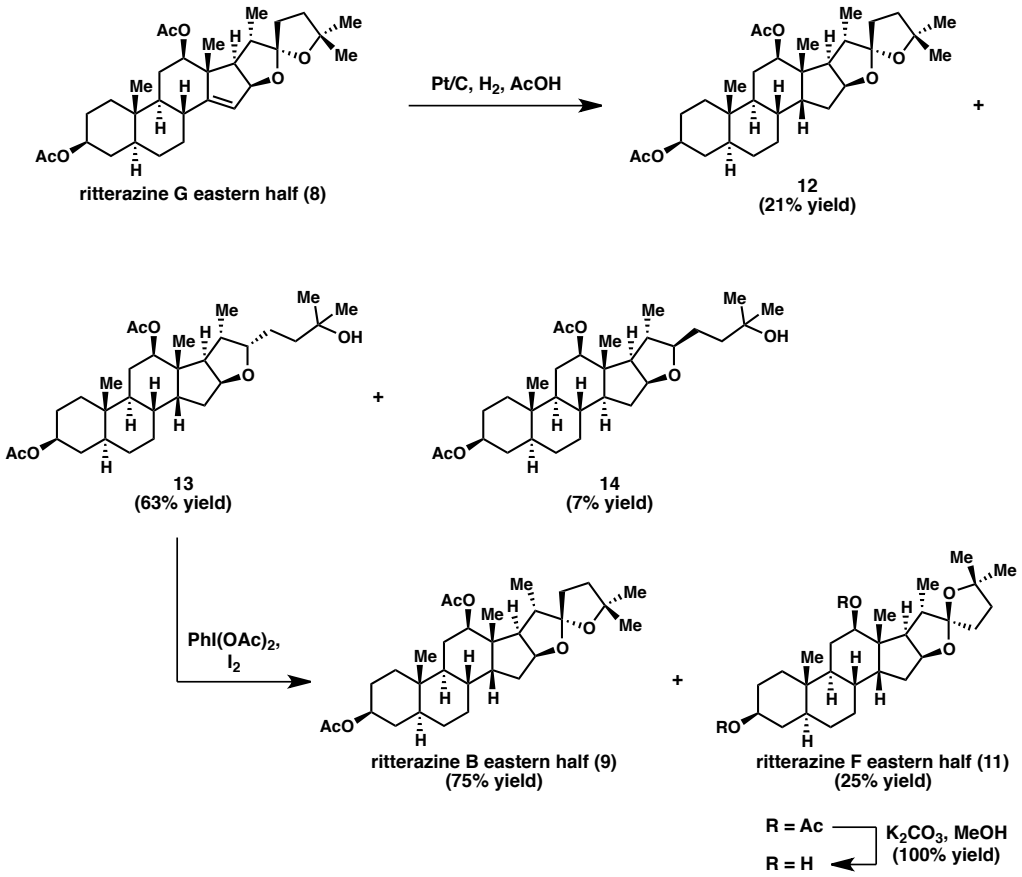


As mentioned previously, the eastern half of ritterazine F has the opposite stereochemistry to ritterazine B at the 5/5 spiroketal, as found in the minor product (**10**) of the Suárez oxidative cyclization. Shair's efforts to reduce the double bond of **10** revealed that the stereochemistry of the spiroketal equilibrates in ethanol, leading to a mixture of products favoring ritterazine G and B (**Scheme 3**).[3] This result indicated that the stereochemistry of the 5/5 spiroketal in ritterazines G and B is the thermodynamic configuration.[3] In order to form the contra-thermodynamic spiroketal of ritterazine F, Shair hydrogenates compound **8** in acetic acid. This reaction produces a mixture of ketal **12** (21% yield), as well as ring opened diastereomers **13** and **14** (**Scheme 4**). Upon Suárez oxidation of **13**, the desired ritterazine F eastern fragment is produced in 25% yield, due to some equilibration of the ketal to compound **9** under the reaction conditions.

Scheme 3. *Shair's attempted hydrogenation to form ritterazine F eastern half.*



Scheme 4. *Shair's endgame for the synthesis of ritterazine F eastern fragment.*

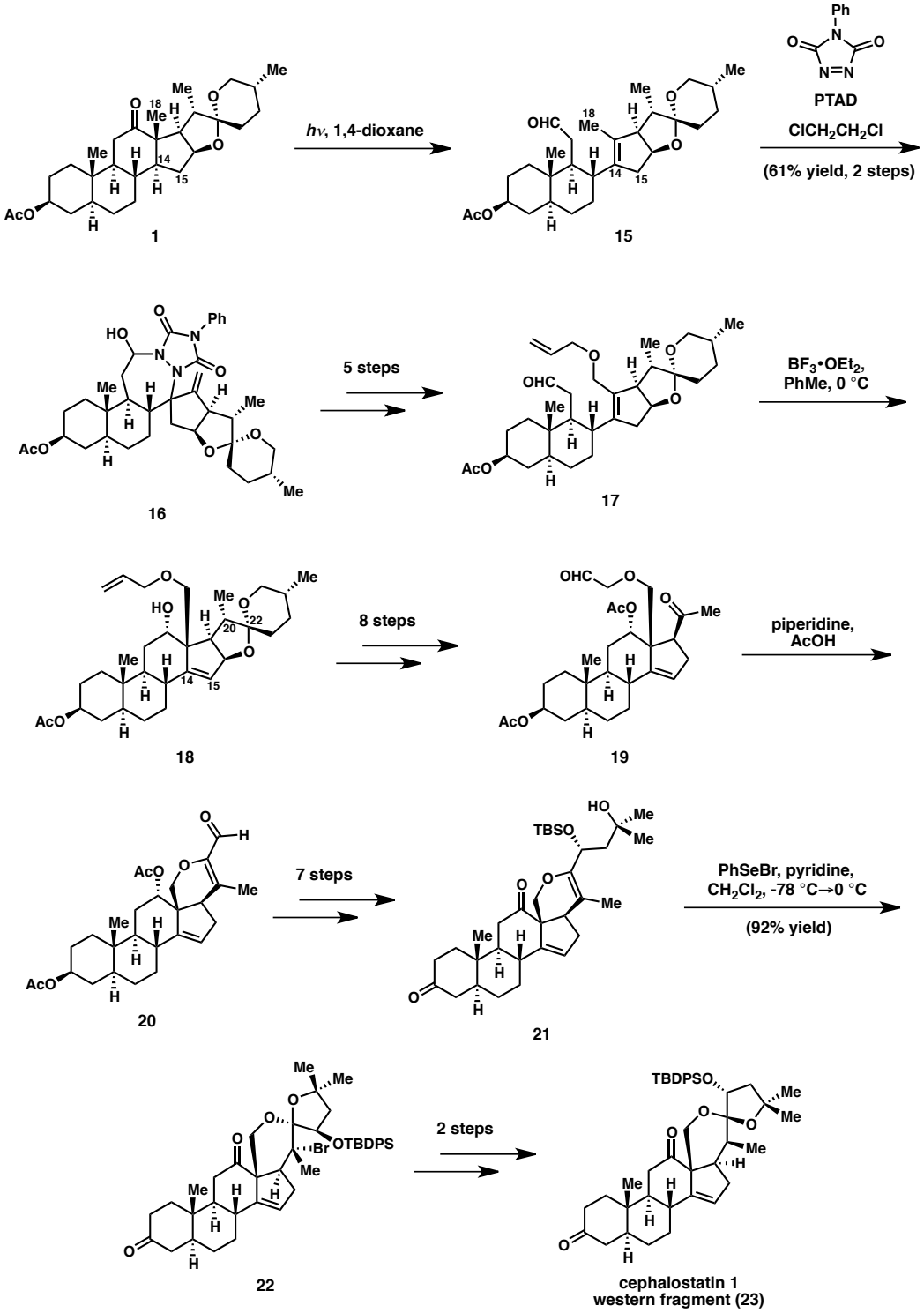


Shair has also reported a total synthesis of the related natural product cephalostatin 1.[2] The synthesis of the western fragment begins from commercially available steroid hecogenin acetate (**1**). The important transformations required to convert this compound to the western fragment of cephalostatin 1 involve installation of the C14–C15 olefin, which is present in the western half of ritterazine B, and rearrangement of the spiroketal. To this end, photolysis of **1** results in type I Norrish reaction to provide aldehyde **15** with a tetra-substituted double bond in the D ring (**Scheme 5**). From here, the synthesis requires selective oxidation of the C18 methyl group and isomerization of the double bond. To achieve these transformations, Shair

employs an unusual allylic oxidation with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), which proceeds through an ene reaction to selectively functionalize the C18 methyl group, forming a 7-membered hemiaminal.[2] Elaboration over five steps delivers aldehyde **17**, which is treated with BF_3•OEt_2 to close the C ring and yield compound **18**. This transformation successfully employs the C14–C15 olefin, which is the desired position for cephalostatin 1.

The final major transformation involves rearrangement of the spiroketal. This requires eight steps and involves oxidative scission of the C20–C22 bond to provide ketone **19**. Intramolecular aldol reaction of **19** produces enal **20**, which is homologated to form tertiary alcohol **21**. The spiroketal in the western fragment of cephalostatin 1 was proposed to be in the thermodynamically stable configuration, and it was predicted that treatment of **21** in mild acid would produce the desired spiroketal.[2] However, this was not the case, and Shair found that the undesired stereoisomer was formed. This was surprising given that the correct stereoisomer was produced by Fuchs et al. in a similar transformation, although Fuchs' substrate lacked the D-ring unsaturation.[2,] In order to resolve this outcome, Shair employed a two-step bromoetherification/reductive debromination sequence. Following bromoetherification of **21** with PhSeBr, compound **22** was subjected to debromination, and then epimerization of the spiroketal with acid to yield the western half of cephalostatin 1.

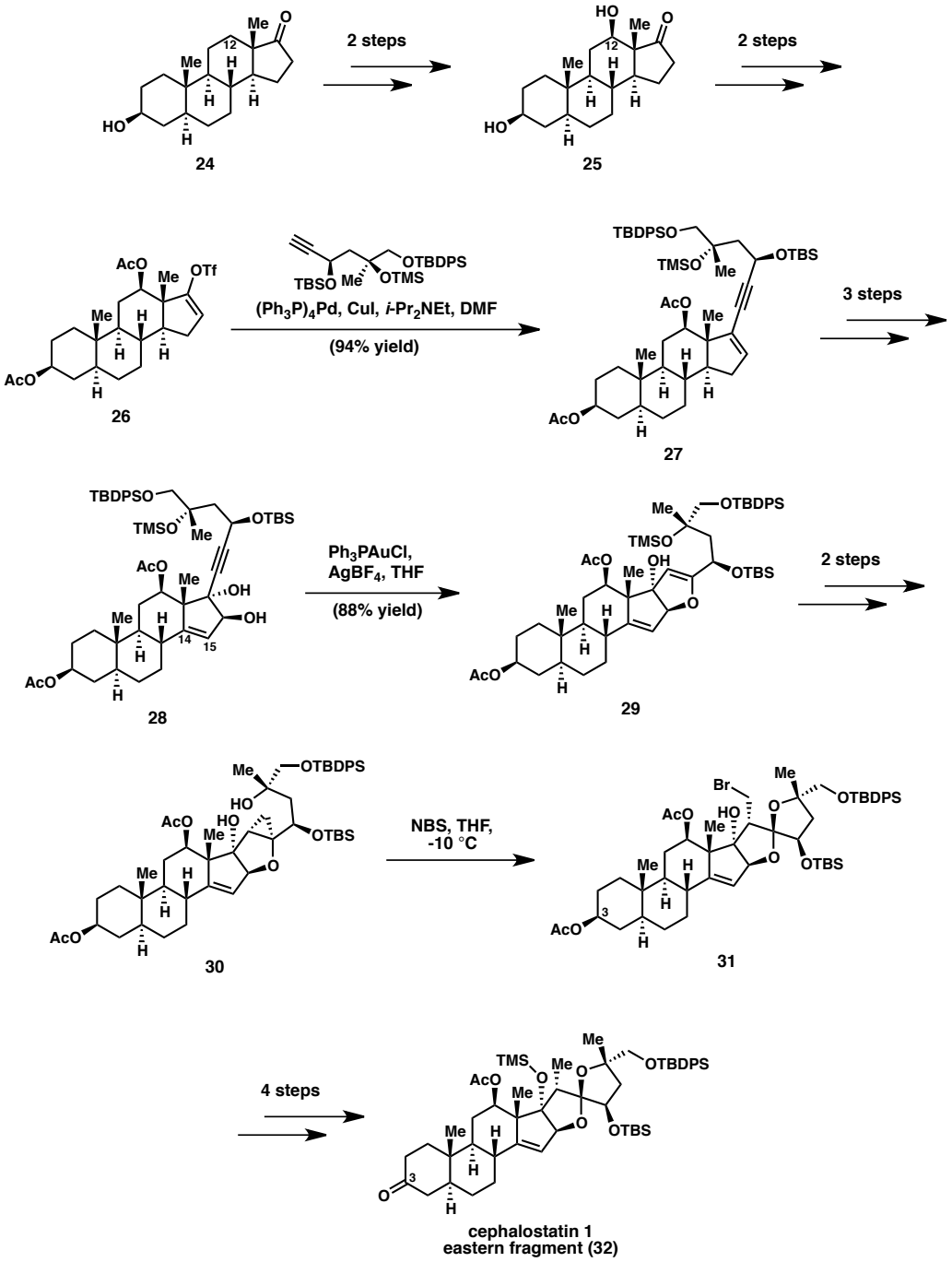
Scheme 5. *Shair's synthesis of the western fragment of cephalostatin 1 from commercially available hecogenin acetate.*



Shair's synthesis of the eastern fragment of cephalostatin 1 begins with commercially available *trans*-androsterone (**24**). In order to oxidize at C12, Shair employs methodology developed by Shönecker et al. that involves condensation of **24** with 2-(aminomethyl)pyridine in catalytic acid, followed by oxidation with stoichiometric $Cu(OTf)_2$ in the presence of molecular oxygen to arrive at diol **25**.[2,7] This second step is rather low yielding (25% yield), and presents the opportunity to develop an improved method for C12 oxidation in the synthesis of ritterazine B. Acetylation of diol **25**, followed by conversion to the corresponding vinyl triflate, provides **26**. This is cross-coupled with a functionalized alkyne fragment using a Pd-catalyzed Sonogashira coupling to produce **27** in 94% yield.

Elaboration of **27** through a three-step sequence provides *trans*-diol **28**, which undergoes a Au(I)-catalyzed 5-endo-dig cyclization to produce **29** in 88% yield. To prepare the precursor for the key spiroketalization, intermediate **29** undergoes Simmons–Smith cyclopropanation, and deprotection of the TMS alcohol to provide **30**. The spiroketal of the eastern half of cephalostatin 1 is the contra-thermodynamic configuration, which required kinetically controlled spiroketalization.[2] This was achieved under neutral reaction conditions using NBS, which decrease equilibration of the spiroketal to yield **31** as the major diastereomer in a 5:1 separable mixture. Completion of the synthesis of cephalostatin 1 eastern fragment involved debromination, TMS protection of the hindered alcohol, selective deacetylation of the C3 alcohol, and oxidation to the ketone.

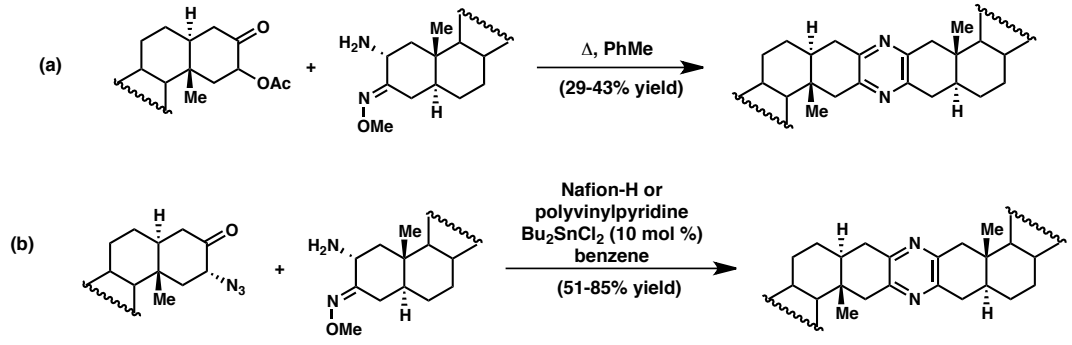
Scheme 6. *Shair's synthesis of the eastern fragment of cephalostatin 1 from commercially available trans-androsterone.*



In order to join the two western and eastern fragments (**23** and **32**, respectively), Shair adapted methodology from Fuchs et al. for unsymmetrical

pyrazine formation.[8,9] Fuchs' initial studies toward the synthesis of cephalostatin 7 led to the desired unsymmetrical product, as well as homocoupling from each of the coupling partners.[8] Heathcock et al. had presented a solution to this problem by coupling α-acetoxy ketones with α-amino methoximes (**Scheme 7a**), however the drawback of this methodology is the low yields (29–43% yield).[10] Fuchs et al. subsequently improved upon this protocol by substituting the α-acetoxy ketone with an α-azido ketone (**Scheme 7b**), which greatly improved yields. In Fuchs' synthesis of 14'α,15'-dihydrocephalostatin 1 analog, he established that the eastern fragment was optimal as the α-amino methoxime, and the western fragment as the α-azido ketone.[8] Therefore, Shair followed this approach to complete the synthesis of cephalostatin 1.[2,8]

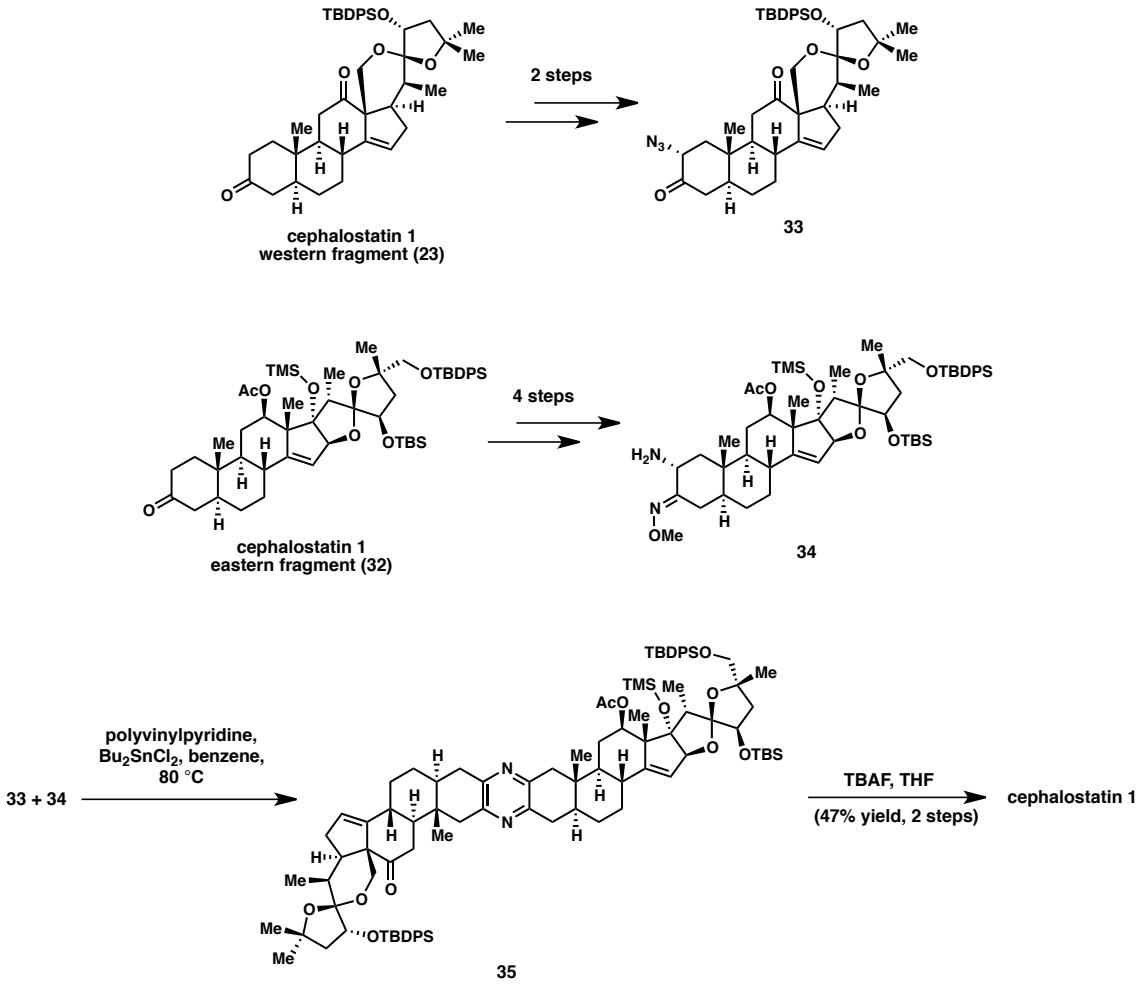
Scheme 7. *(a) Unsymmetrical pyrazine formation by Heathcock et al. (b) Unsymmetrical pyrazine formation by Fuchs et al.*



The western fragment of cephalostatin 1 (**23**) was converted to the α-azido ketone **33** through a two-step process. First, α-bromination was achieved with $PhMe_3NBr_3$, and the bromide was then converted to the desired azide using tetramethylguanidinium azide and $EtNO_2$. The eastern half (**32**) was subjected to the

the same bromination/azidation sequence, which was then followed by formation of the methoxime. Staudinger reduction of the azide moiety to primary amine **33** enabled coupling of intermediates **33** and **34** in the presence of polyvinylpyridine and Bu_2SnCl_2 to produce compound **35**. Completion of the synthesis of cephalostatin 1 was achieved upon global deprotection of the siloxy groups.

Scheme 8. *Completion of Shair's total synthesis of cephalostatin 1.*



Chapter 2

Efforts in Our Laboratory[‡]

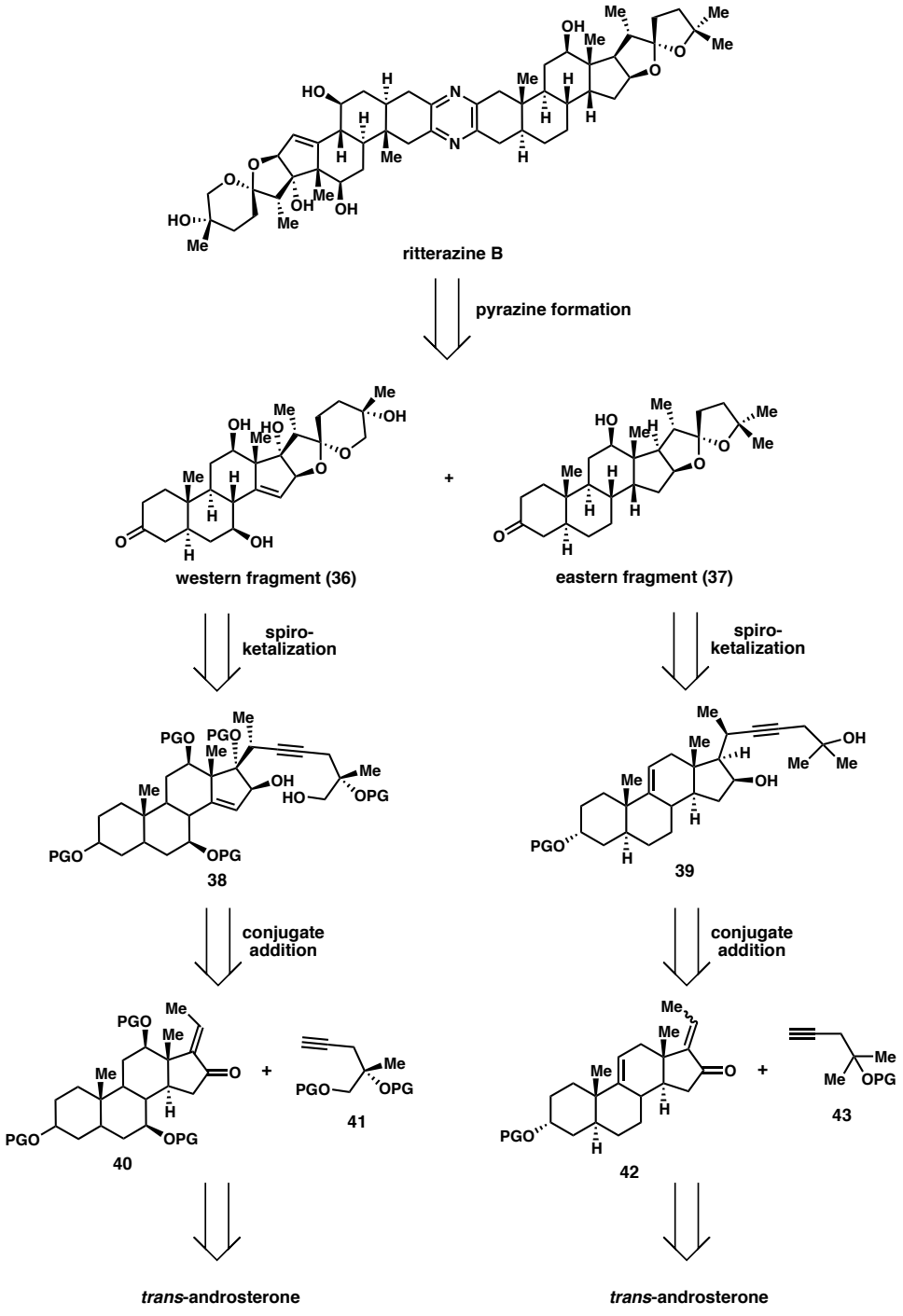
2.1 RETROSYNTHETIC ANALYSIS

Given that conditions for pyrazine formation have been established in prior synthetic reports by Shair and Fuchs,[2,6,8,9] ritterazine B was retrosynthetically simplified to the western (**36**) and eastern (**37**) fragments (**Scheme 9**). From here, our proposed retrosynthesis involves two key reactions, which can be employed for both halves of the natural product. We envision forming the 5/6 spiroketal of the western half and the 5/5 spiroketal of the eastern fragment using a metal-catalyzed alkyne spiroketalization reaction with intermediates **38** and **39**, respectively. These compounds can be produced from an alkyne conjugate addition between **40** and **41** for the western fragment, and between **42** and **43** for the eastern half. It is anticipated that for the western fragment, cyclization of the less hindered primary alcohol will occur to produce the 5/6 spirocycle. Enones **40** and **42** can be formed from commercially available steroid *trans*-androsterone (**24**). Specific issues that need to be addressed include improving upon existing methods to oxidize the C12 position, which is relevant for both halves of ritterazine B. In addition, for the western

[‡] Work conducted in collaboration with Anton Dubrovskiy and Arthur Han.

fragment, new strategies to oxidize carbons C7 and C17 and install the C14–C15 olefin are required.

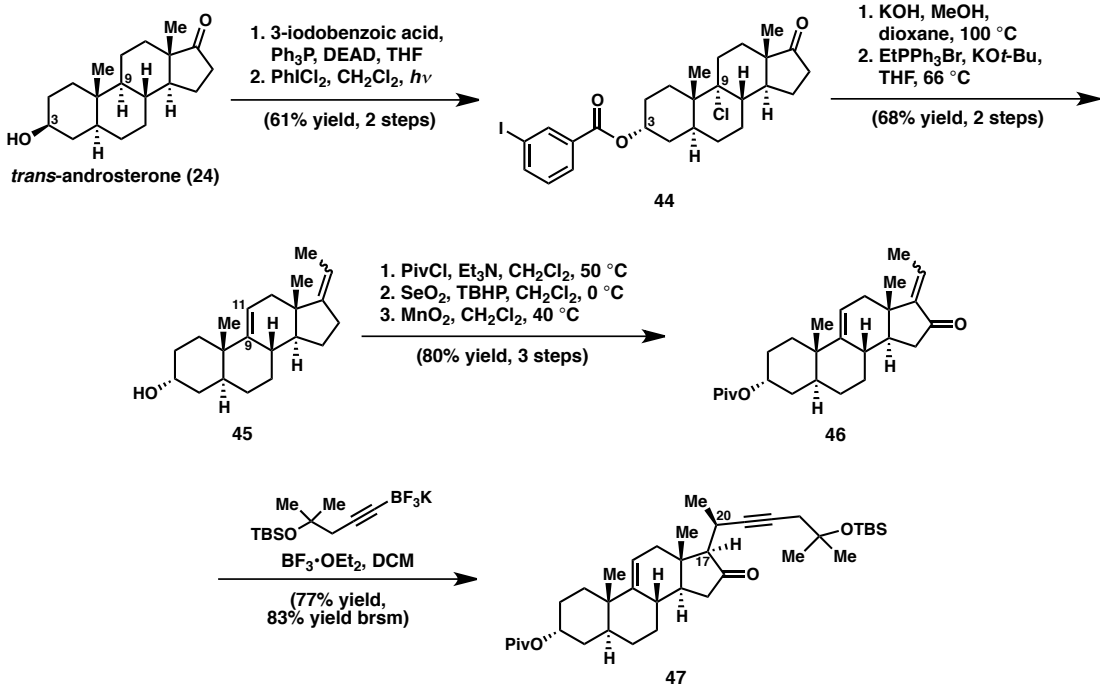
Scheme 9. *Retrosynthetic analysis of ritterazine B.*



2.2 SYNTHESIS OF THE EASTERN FRAGMENT

Initial studies in our laboratory were conducted by Anton Dubrovskiy and focused on the synthesis of the eastern fragment of ritterazine B beginning from commercially available *trans*-androsterone (**24**). The sequence begins with a Mitsunobu reaction between *trans*-androsterone (**24**) and 3-iodobenzoic acid to provide ester **44** with inversion of stereochemistry at C3 (**Scheme 10**). Directed C–H chlorination following the protocol developed by Davitishvili et al. furnished chloride **44** in 61% yield over two steps.[11] Subsequent elimination of the chloride to yield the C9–C11 olefin occurs with concomitant deprotection of the C3 alcohol, which upon Wittig olefination with $EtPPh_3Br$ produces olefin **45** in 68% yield over two steps. Protection of the alcohol as the pivalate ester followed by allylic oxidation with SeO_2 provided the C16–alcohol, which was oxidized with MnO_2 to provide enone **46**. After considerable experimentation, it was determined that addition of the alkynyl trifluoroborate salt to enone **46** in the presence of BF_3•OEt_2 furnished alkyne **47** in 77% yield.[12,13]

Scheme 10. *Initial steps of our synthesis of ritterazine B eastern fragment.*

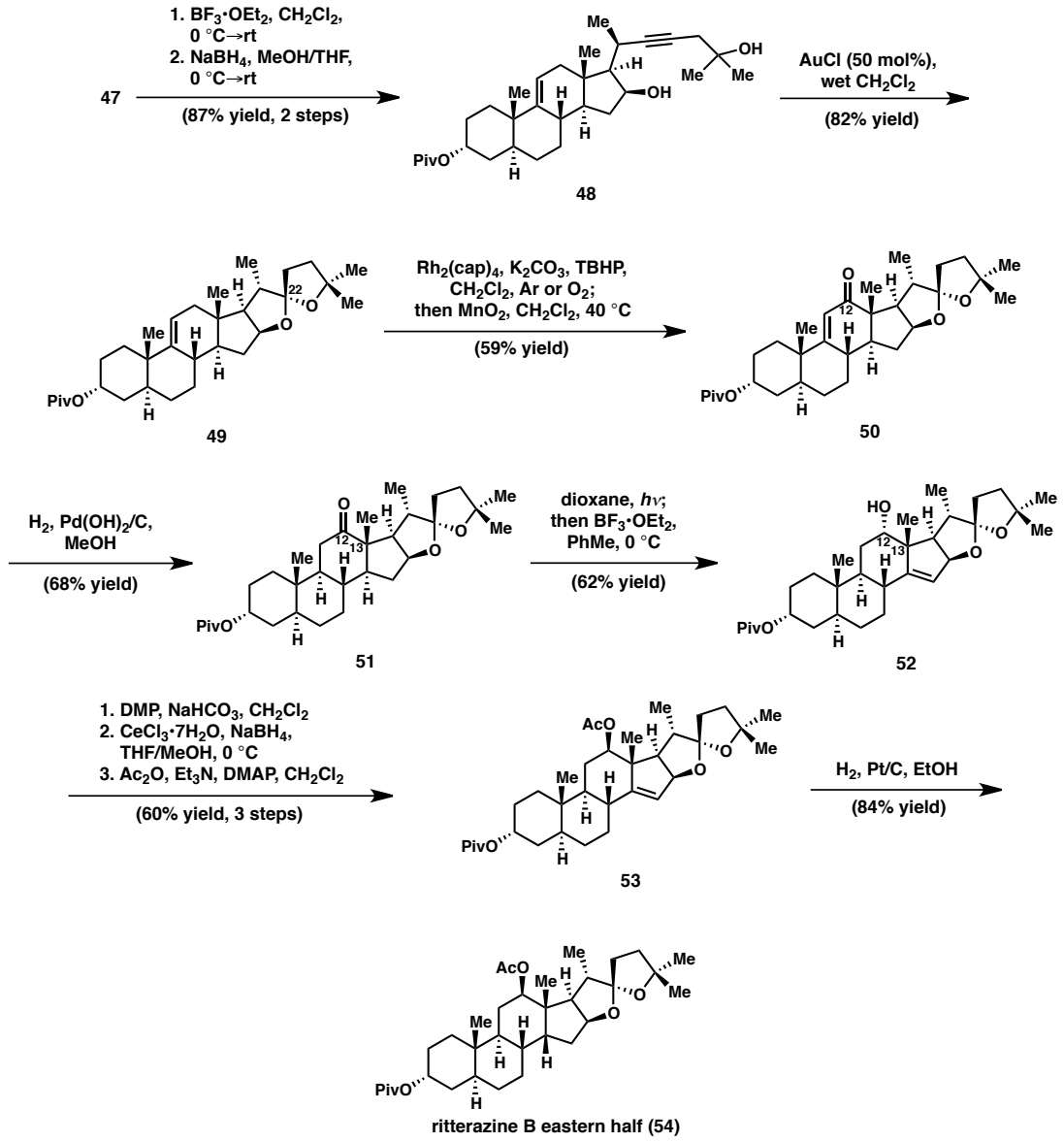


To prepare the spiroketalization precursor, silyl ether **47** was deprotected and the ketone was reduced to the desired β-configured alcohol to give diol **48** (**Scheme 11**). We were pleased to find that spiroketalization of **48** proceeded smoothly with catalytic AuCl to provide **49** with the correct stereochemistry at C20 and C22.[14] Notably, under the reaction conditions, C20 epimerizes to give the correct configuration. An allylic oxidation of **49** using catalytic $Rh_2(cap)_4$, K_2CO_3, and TBHP under argon or O_2 furnished enone **50**.[15] Hydrogenation of the C9–C11 olefin with $Pd(OH)_2/C$ produced **51** in 68% yield.

The final transformation required to complete the synthesis of ritterazine B eastern fragment is conversion of the C/D ring juncture from *trans* to *cis*. Adapting conditions from Shair, Norrish type I fragmentation of the C12–C13 bond and

subsequent closure via a BF_3•OEt_2-mediated ene reaction provided intermediate **52**.[2] Correction of the configuration of the C12 hydroxyl was achieved through oxidation/reduction. Following acetylation of the free hydroxyl group, hydrogenation produced the desired *trans* junction, completing the synthesis of the eastern fragment (**54**) in 15 steps from *trans*-androsterone.

Scheme 11. *Completion of our synthesis of the eastern fragment of ritterazine B.*

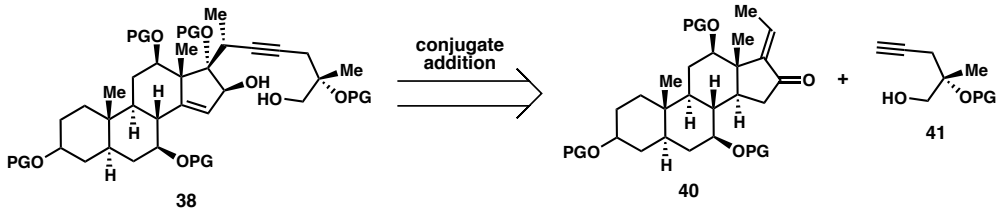


2.3 SYNTHESIS OF THE WESTERN FRAGMENT

2.3.1 Plan 1 – Alkyne Conjugate Addition

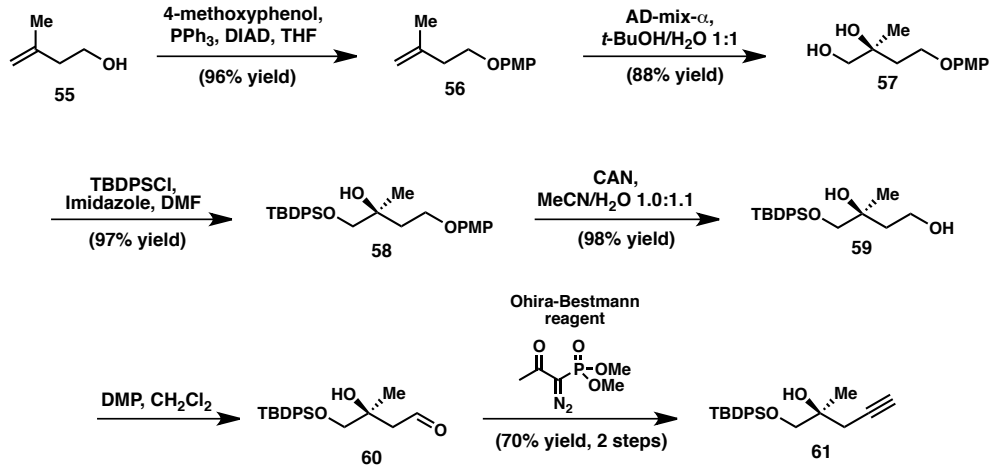
Given our success in preparing the eastern fragment of ritterazine B, my objective was to develop a synthesis of western fragment **38**. The initial goal was to investigate the conjugate addition reaction of alkyne **41**, as this is the first key step in our retrosynthesis (repeated in **Scheme 12**). Although alkyne **41** bears an additional hydroxyl group compared to the alkyne **43** (see **Scheme 9**), we anticipated using a similar sequence to that employed for the preparation of **47** (see **Scheme 10**).

Scheme 12. *Retrosynthetic analysis of first key reaction of the western fragment.*



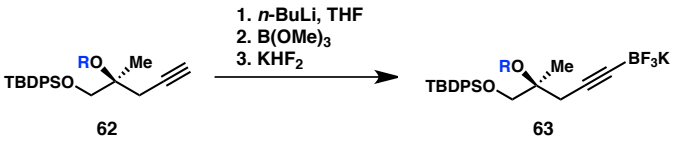
To this end, the desired alkyne **61** was initially prepared by a route adapted from a procedure published by Shair.[2] Starting with 3-methyl-3-buten-1-ol (**55**), protection of the alcohol group as the para-methoxy phenol (PMP) ether gave **56** in 96% yield (**Scheme 13**). Asymmetric dihydroxylation provided diol **57**, and selective protection of the primary alcohol as the *tert*-butyldiphenyl silyl (TBDPS) ether provided **58** in 97% yield. Deprotection of the PMP group, and then DMP oxidation produced aldehyde **60**. Finally, the Ohira-Bestmann reagent was employed to convert the aldehyde to the desired alkyne **61** in 70% yield over two steps.

Scheme 13. *Initial synthesis of alkyne fragment.*



The benefit of intermediate **61** is that several protecting group schemes could be investigated to find the optimal substrate for the conjugate addition reaction. Whereas treatment of **62a** (R = MOM) or **62b** (R = TES) with *n*-BuLi, $B(OMe)_3$, then KHF_2 provided the corresponding trifluoroborates (**Table 2**, entries 1 and 2), we were surprised to find that no reaction occurred under the same conditions with **62c** (R = TBS). The origin of this difference in reactivity is unclear, however it is possible that the increased steric hindrance of TBS is responsible for the lack of reactivity.

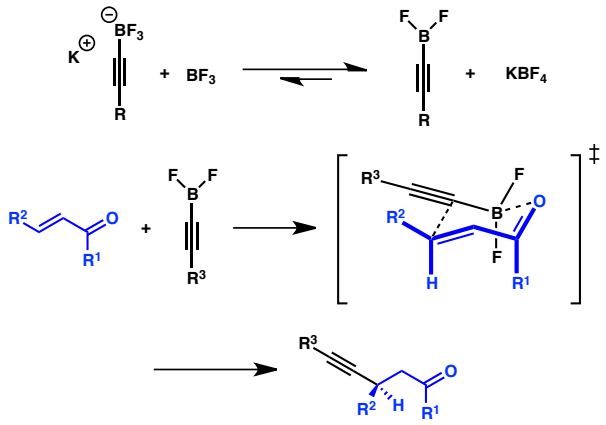
Table 2. *Initial attempts to form alkynyl trifluoroborate salt.*



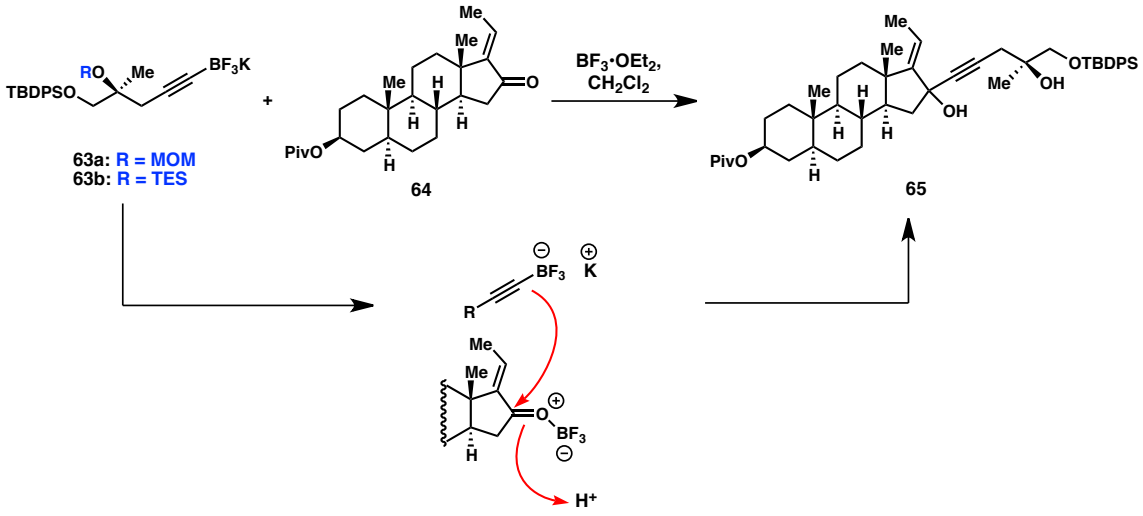
Entry	R	Result	63
1	MOM	82% yield	63a
2	TES	80% yield	63b
3	TBS	SM	63c

With trifluoroborates **63a** and **63b** in hand, the key conjugate addition reaction was investigated. Woodward et al. have shown that conjugate additions of alkynyl trifluoroborates to enones proceed through a closed transition state (**Scheme 14**).[13] In the presence of BF_3, the trifluoroborate salt is in equilibrium with the more active alkynyl BF_2 species, which forms a chair–like closed transition state that facilitates alkyne addition in a 1,4 fashion.[13] Unfortunately, under the previously optimized conditions, treatment of enone **64** with either trifluoroborate salts **63a** or **63b** gave only 1,2–addition product **65a** and **65b** (**Scheme 15**). Interestingly, the tertiary alcohol in the product was deprotected under the reaction conditions in both cases. A possible mechanism to produce **65** involves activation of the ketone with BF_3, followed by nucleophilic attack of the trifluoroborate salt at the carbonyl carbon.

Scheme 14. *Mechanism and transition state of alkyne conjugate addition using trifluoroborate salts.*

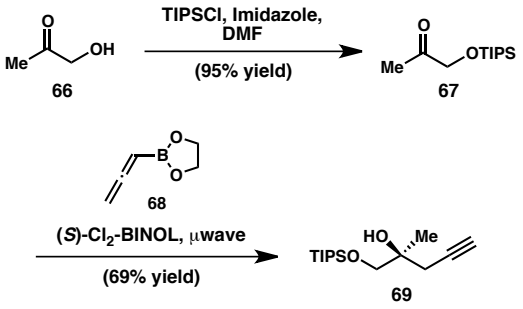


Scheme 15. *First attempt at conjugate addition.*



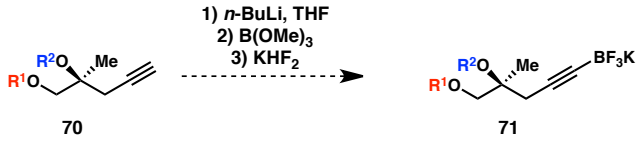
To determine whether the primary alcohol protecting group exerts any influence on the reactivity of the conjugate addition, further alkynyl derivatives were prepared. However, the synthesis of the alkyne fragment (shown in **Scheme 13**) did not lend itself to late stage diversification. Therefore, a more rapid and efficient synthesis of the alkyne fragment was developed based on a catalytic asymmetric reaction reported by Shaus et al. (**Scheme 16**).[16] Beginning with hydroxyacetone (**66**), the free alcohol was protected as the tri-*iso*-propylsilyl (TIPS) ether (**67**). Treatment of **67** with allenylboronate **68** and catalytic BINOL under microwave irradiation produced **69** in 62% yield. This route has proven to be significantly more convenient and has greatly improved the synthesis of the alkyne fragment.

Scheme 16. *Improved synthesis of alkyne fragment.*



After protection of the tertiary alcohol of **69** as the TBS ether, this compound was subjected to the standard conditions for trifluoroborate formation. Unfortunately, no reaction occurred and starting material was recovered (entry 1, **Table 3**). Attempts to change the identity of the tertiary alcohol protecting group of **69** were unsuccessful. Therefore, we turned our attention to altering the primary alcohol protecting group. Disappointingly, efforts to convert the bis-silyl ethers **70b** and **70c** to their corresponding trifluoroborates were also unsuccessful (entries 2 and 3).

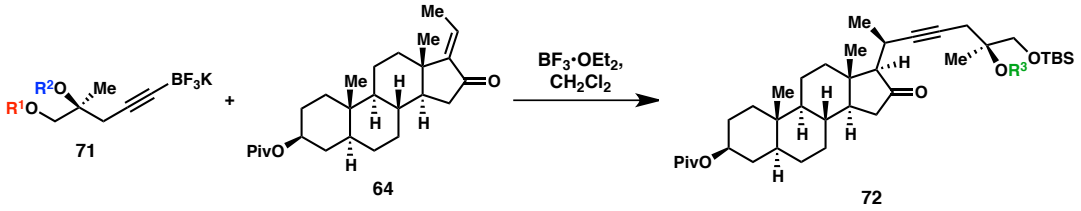
Table 3. *Attempts to form the desired trifluoroborate salt.*



Entry	R^1	R^2	Result	71
1	TIPS	TBS	SM	71a
2	TBS	TIPS	SM	71b
3	TBS	TBS	SM	71c

Concomittant to my own efforts, my co-workers were also preparing alkynyl trifluoroborates with varying protecting groups. This collective effort determined that alkynyl trifluoroborates **71a** and **71b** can be prepared, and that these compounds will undergo the desired conjugate addition reactions in 25% and 56% yield respectively.

Table 4. *Most current results with the conjugate addition reaction.*



Entry	R^1	R^2	Result	72	R^3
1	All	TBS	~25% NMR yield	72a	H
2	PMP	Me	56% isolated yield	72b	Me

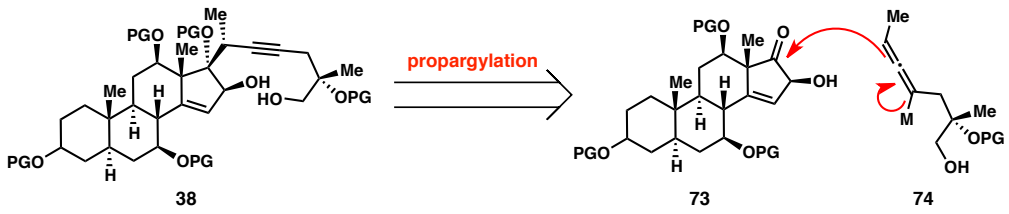
Future directions of this synthetic route involve applying the alkynyl conjugate addition to a fully oxidized western steroid. Most importantly, methods to oxidize at C17 following the conjugate addition reaction must be investigated. One possible approach would involve a Rubottom oxidation of a silyl enol ether derived from **72**. Although this route seems probable, alternative routes with potentially shorter step counts were also pursued.

2.3.2 Plan 2 – Propargylation with Allenes

An alternative route to intermediate **38** has been explored. This approach involves the propargylation of α-hydroxyketone **73** with functionalized allenyl metal

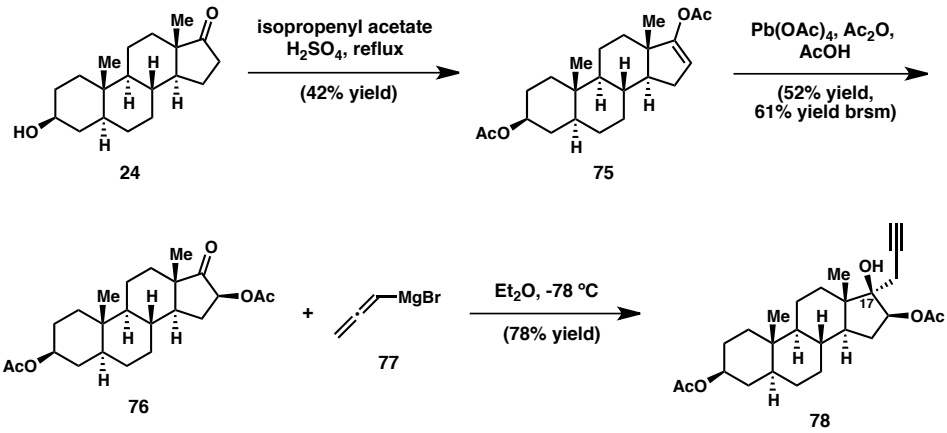
74 (**Scheme 17**). This type of reaction has been developed using a variety of allenyl metal species, including tin,[17] magnesium,[18] lithium,[19] titanium,[20] boron,[21] and zinc,[22] as well as others. Most allenyl metal reagents are unstable, and are therefore generated in situ.[17a] A complicating factor is that these reagents are often in equilibrium with the propargylic species, however sufficient research has been done to favor the propargylic adduct.[17a] Although the diastereoselectivity of the transformation was initially uncertain, this route is attractive in that the C17 alcohol would be installed directly during the propargylation reaction.

Scheme 17. *Revised retrosynthesis of intermediate* ***38*** *using propargylation.*



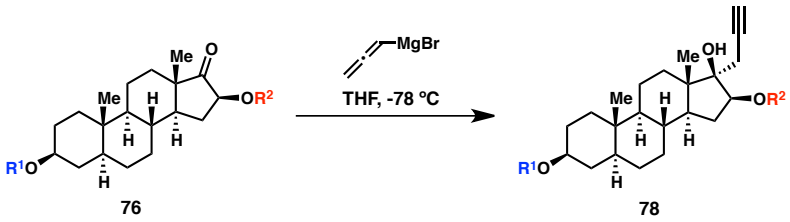
In order to investigate this reaction, model steroid *trans*-androsterone (**24**) was oxidized α to the carbonyl using the two-step procedure reported by Ridley et al. (**Scheme 18**).[23] Treatment of **24** with isopropenyl acetate and catalytic sulfuric acid at reflux produced protected enolate **75**, which upon subsequent oxidation with lead(IV) acetate provided α-acetoxy ketone **76** in 52% yield (61% yield b.r.s.m.). We were pleased to find that exposure of **76** at –78 °C to allenylmagnesium bromide (**77**), generated in situ from propargyl bromide, produced homopropargyl alcohol **78** in 78% yield. Moreover, alcohol **78** was produced as a single diastereomer.

Scheme 18. *Initial hit in propargylation studies with model ketone.*



Unfortunately, stereochemical analysis by 1D- and 2D-NMR determined that **78** possesses the incorrect configuration at C17. In an effort to overturn this diastereoselectivity, a variety of protecting groups capable of directing delivery of the allenyl Grignard were initially pursued. **Table 5** shows the results of substrates bearing different protecting groups with allenyl Grignard. Unfortunately, treatment of the substrates under standard conditions still resulted in allenylation to give the undesired propargylation product.

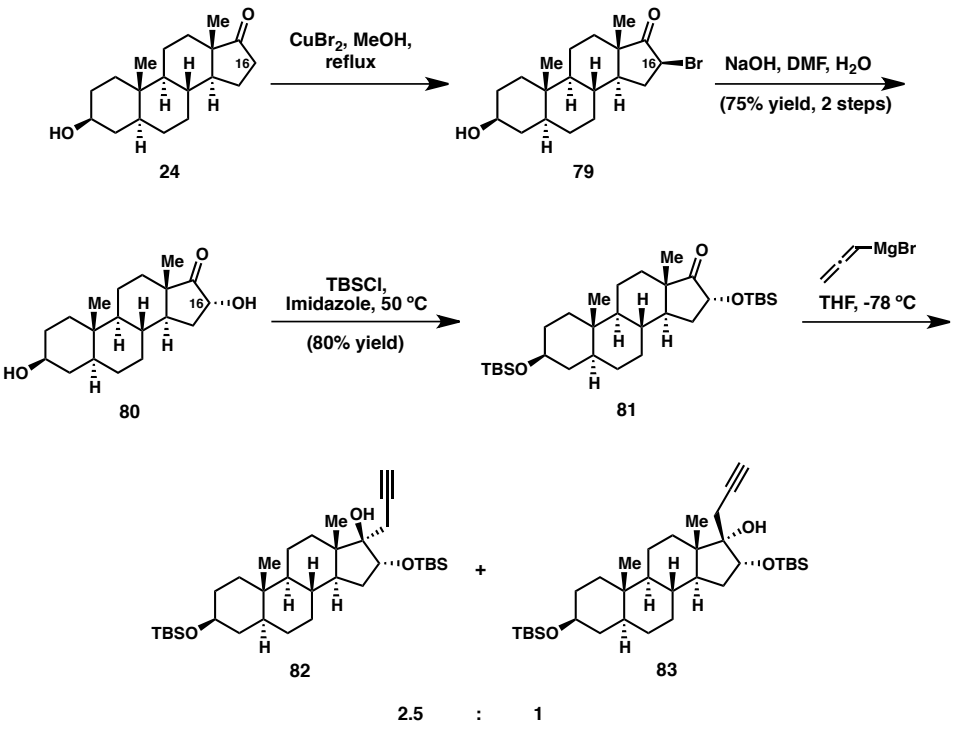
***Table 5**. Reaction of allenyl Grignard with directing protecting groups.*



Entry	R^1	R^2	Result
1	H	H	side product
2	MOM	MOM	78b (72% yield)
3	MEM	MEM	78c (63% yield)

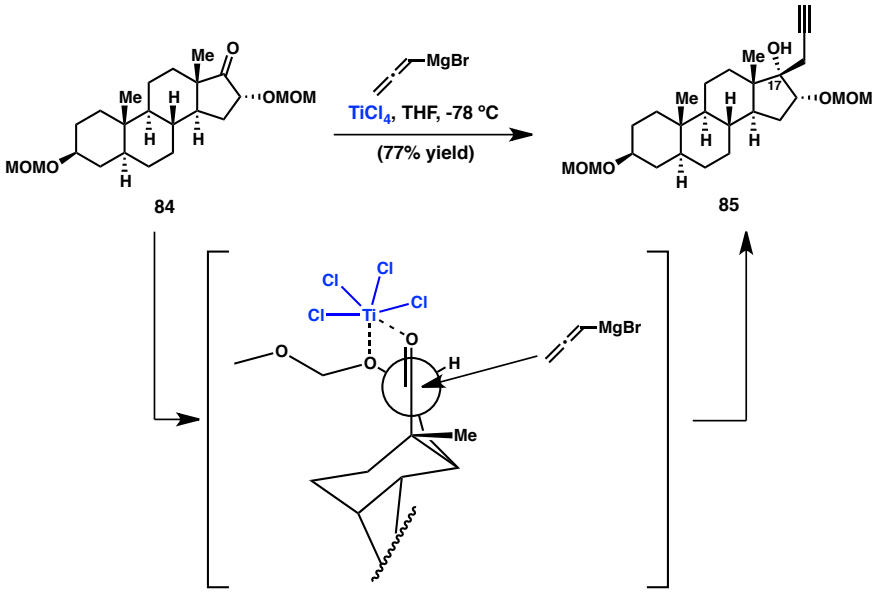
Given the lack of success overturning the diastereoselectivity on the β-disposed C16 hydroxyl, we turned our attention to investigating the propargylation of steroids bearing the inverted stereochemistry at position C16. We hypothesized that a large sterically bulky protecting group would block the α-face, directing propargylation to the β-face. Diol **80** was prepared using a two-step procedure developed by Numazawa and Osawa et al. by performing an α-bromination, followed by S_N2 displacement (**Scheme 19**).[24] After TBS protection to form **81**, propargylation with allenyl Grignard resulted in a mixture of diastereomers **82**/**83** 2.5:1 d.r. Although the major diastereomer **82** is the undesired stereochemistry, formation of the desired product **83** was a promising result.

Scheme 19. *Propargylation with α-configuration at C16.*



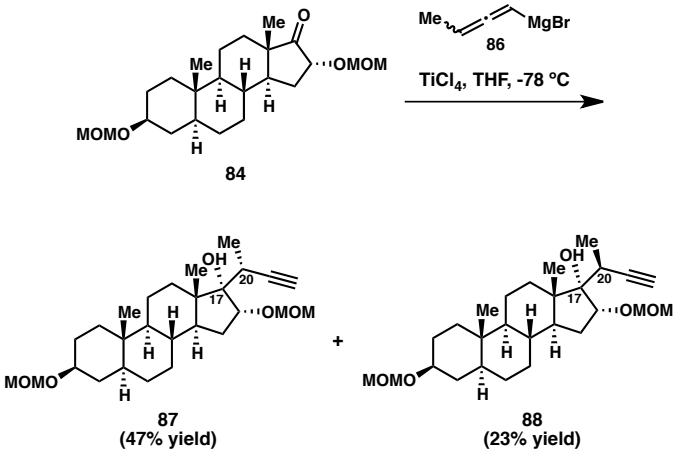
Reetz et al. have demonstrated that diastereoselectivity of propargylation reactions can be influenced by using $TiCl_4$ as an additive.[25] It is proposed that $TiCl_4$ can coordinate to the carbonyl oxygen, as well as oxygen atoms of an ether protecting group, and promote propargylation through an open transition state. Inspired by Reetz's findings, compound **84** was prepared and subjected to allenyl Grignard and $TiCl_4$ in dichloromethane at –78 °C (**Scheme 20**). Much to our pleasure, homopropargyl alcohol **85** was formed in 77% yield as a single diastereomer, with the correct stereochemistry at C17.

Scheme 20. *Propargylation with $TiCl_4$ to form the desired stereochemistry at C17.*



Having achieved the desired stereoselectivity, we turned to investigating more complex allenyl Grignard reagents. Reaction of steroid **84** with methylated allenyl Grignard **86**, prepared from 3-bromo-1-butyne, produced a mixture of two diastereomers **87** and **88** in 47% and 23% yields, respectively (**Scheme 21**). These two diastereomers arise from the fact that Grignard **86** is racemic; it was anticipated that the enantioenriched allene would deliver the desired product with high diastereoselectivity.

Scheme 21. *Initial attempts at propargylation with methylated allenyl Grignard* ***86***.



To investigate the diastereoselectivity with a chiral allene, a protocol was adapted from Marshall et al.[26] Beginning with (S)-(–)-butyn-2-ol (**89**), attempts to isolate chiral bromide **90** were unsuccessful due to volatility of the bromide (**Scheme 22**). As an alternative intermediate, mesylate **91** was formed as a precursor for the chiral allenyl zinc reagent **92**. Upon treatment of steroidal ketone **84** with zinc reagent **92**, homopropargyl alcohol **87** was formed as a single diastereomer, and the structure of **87** was confirmed via X-ray crystallography (**Figure 4**) to verify the stereochemistry at C20.

Scheme 22. *Propargylation with chiral allenyl zinc reagent.*

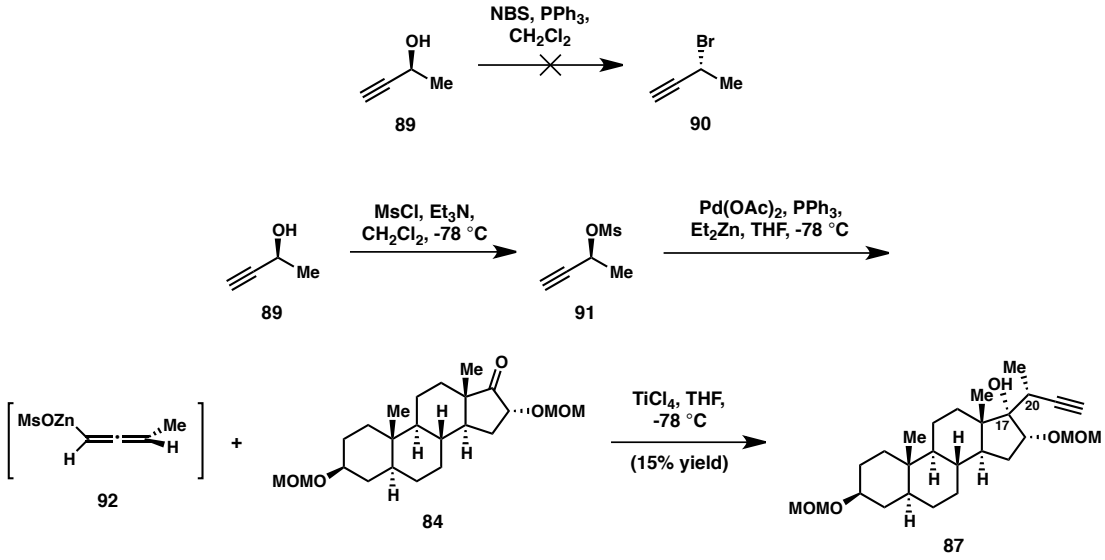
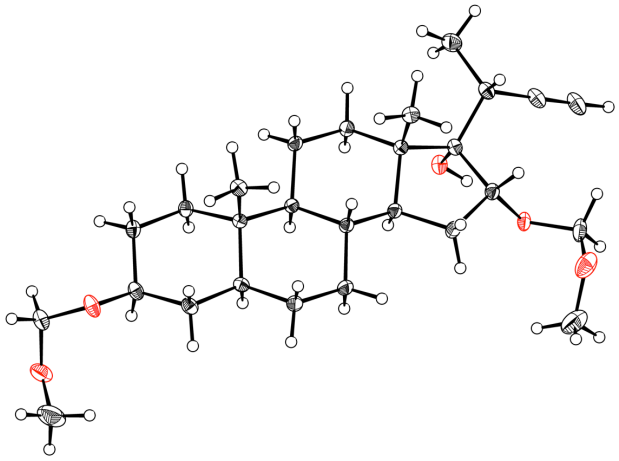


Figure 4. *X-ray structure of alcohol **87**.*

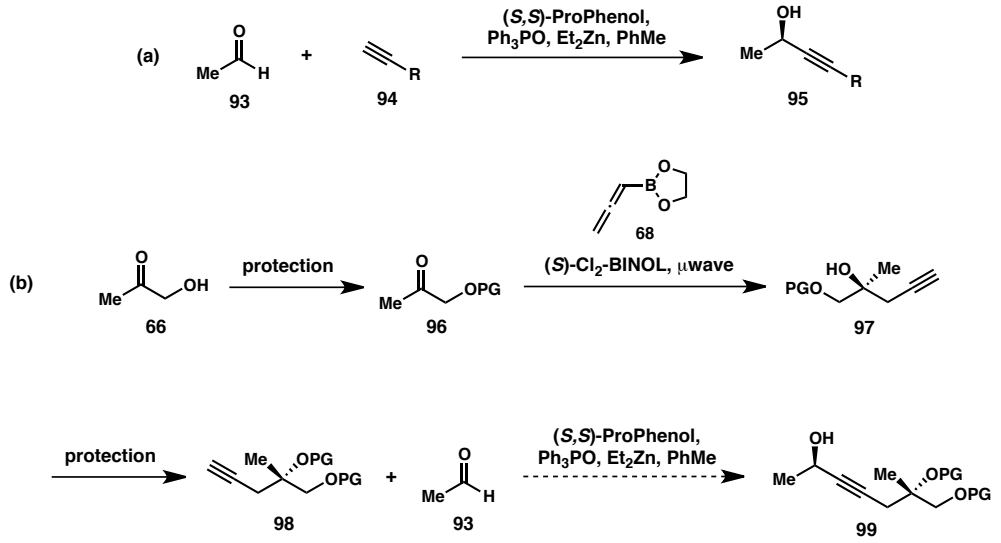


2.4 FUTURE DIRECTIONS

The next step in investigating the synthetic utility of the propargylation reaction in the total synthesis of ritterazine B would be to incorporate the oxygenated aliphatic chain on the alkyne. An efficient method to accomplish this goal involves a

reaction developed by Trost et al. that forms chiral propargyl alcohols **95** from acetaldehyde (**93**) and terminal alkynes **94** (**Scheme 23a**).[27] Using our previously established conditions to form the protected alkyne fragment **98**, the desired chiral homopropargyl alcohol **99** can be synthesized in four steps (**Scheme 23b**).

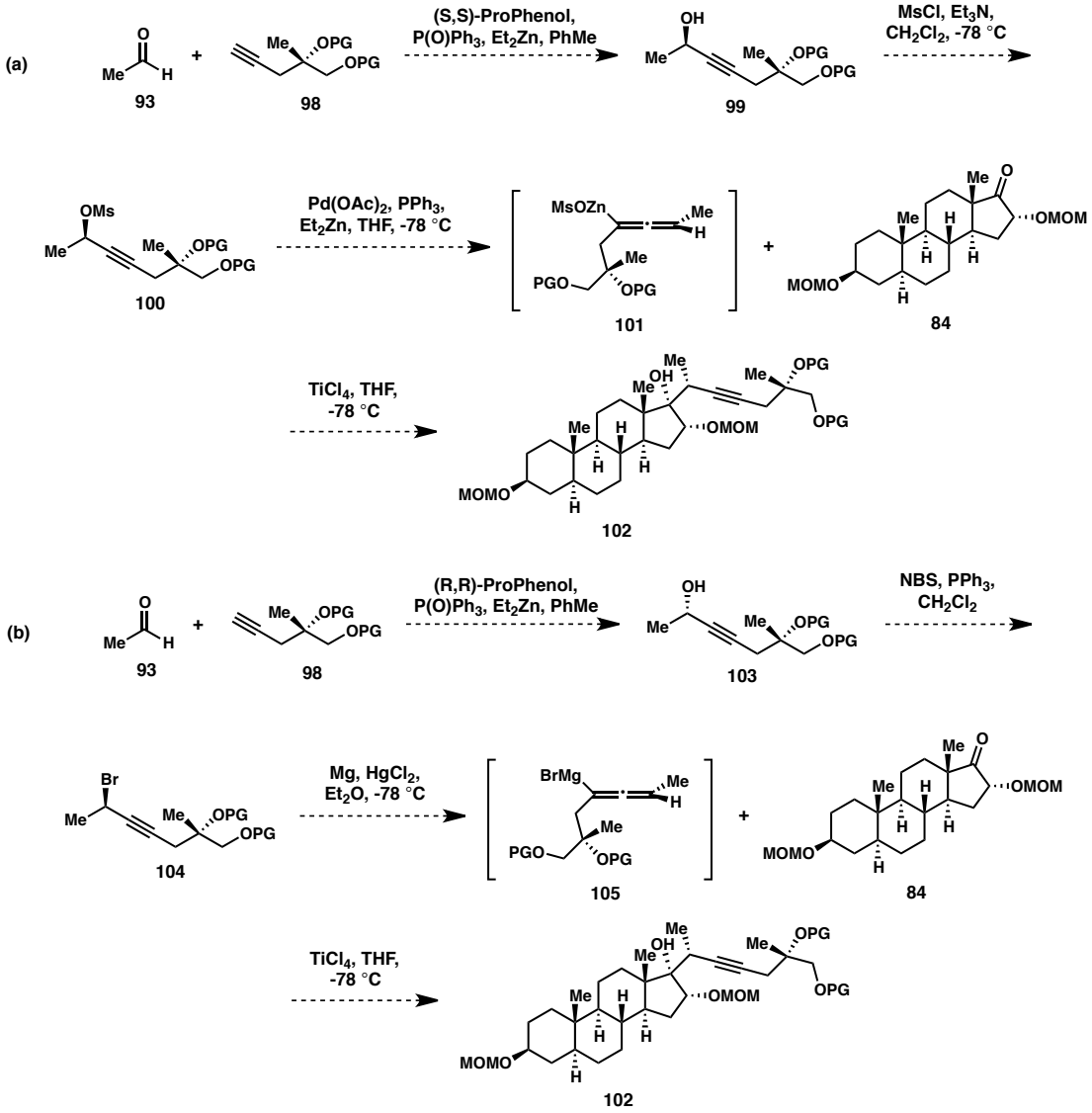
Scheme 23. *(a) Formation of chiral propargyl alcohols by Trost et al. (b) Plan to form desired propargyl alcohol using Trost's method.*



With alcohol **99** in hand, there are two possible conditions for the propargylation reaction with steroid **84** that could deliver the desired product. The first set of conditions utilizes chiral allenyl zinc mesylate **101**, which is formed from the corresponding mesylate **100** (**Scheme 24a**). Treatment of **84** with zinc mesylate **101** will produce homopropargyl alcohol **102**. However, since the yield of the propargylation reaction with allenyl zinc **92** (see **Scheme 22**) was low yielding, either optimization of these conditions or investigation of a different metal are required. Using the (*R*,*R*)-ProPhenol ligand in the Trost reaction with acetaldehyde (**93**) and

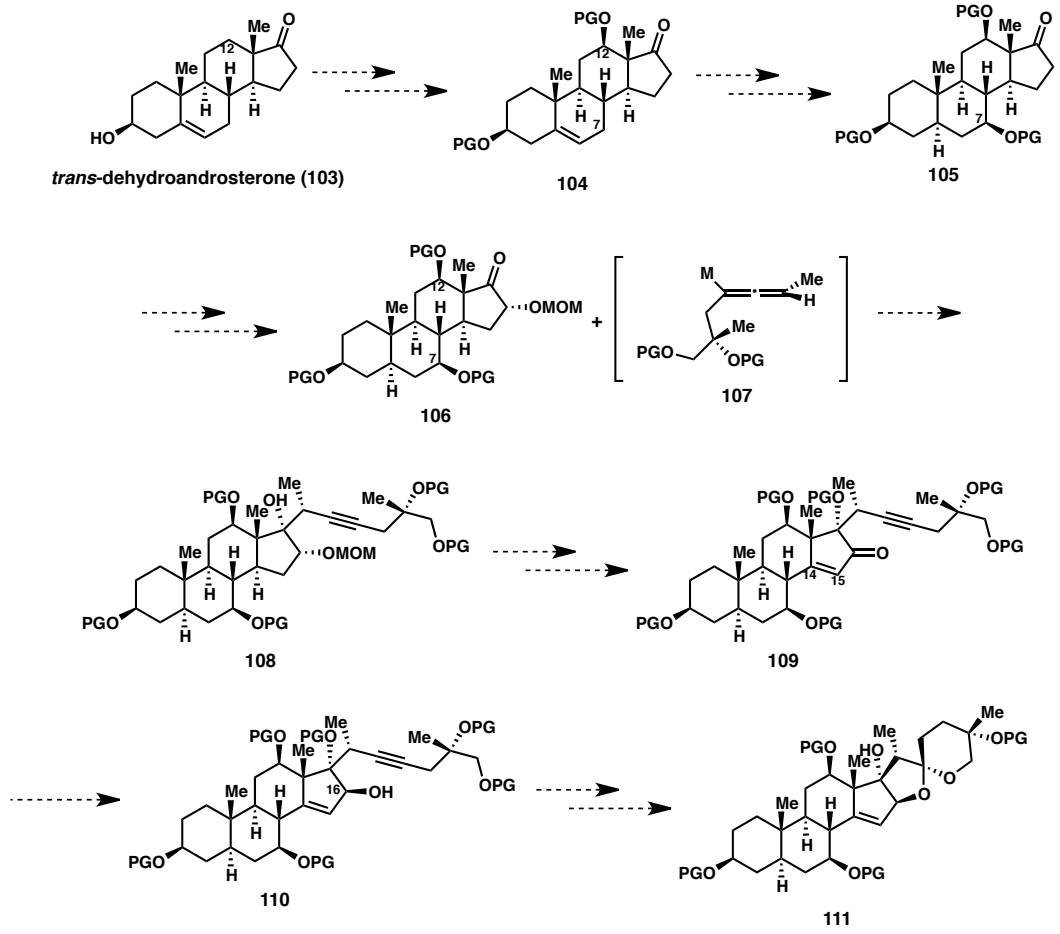
alkyne **98** delivers *R*-alcohol **103**, which will undergo an S_N2 reaction to form bromide **104** as a precursor to the chiral allenyl Grignard **105** (**Scheme 24b**). Treatment of steroid **84** with in situ-generated Grignard **105** should produce the desired homopropargyl alcohol **102**.

Scheme 24. *Plans to produce homopropargyl alcohol **102** (a) using a chiral allenyl zinc mesylate or (b) using a chiral allenyl Grignard.*



In order to utilize the propargylation reaction in the synthesis of the western fragment of ritterazine B, the steroid substrate needs to be oxidized at C7 and C12 prior to the propargylation reaction. *trans*-Dehydroandrosterone **103** will be oxidized at C12 using Shair's two-step procedure to provide **104**,[2] followed by ketone protection, oxidation at C7, hydrogenation, and ketone deprotection to deliver compound **105** (**Scheme 25**). To access propargylation substrate **106**, intermediate **105** undergoes α-bromination and S_N2 displacement, and treatment of **106** with a chiral allene **107** will produce homopropargyl alcohol **108**. To install the double bond at C14–C15, the tertiary alcohol is protected, C16 MOM ether is deprotected, oxidized, and a Mukaiyama reaction will provide enone **109**. Reduction at C16 to alcohol **110**, followed by primary alcohol deprotection and alkyne spiroketalization should produce ritterazine B western fragment **111**. This substrate can be coupled with the eastern half of ritterazine B via pyrazine formation to complete the total synthesis of ritterazine B.

Scheme 25. *Plans to complete the synthesis of ritterazine B western fragment.*



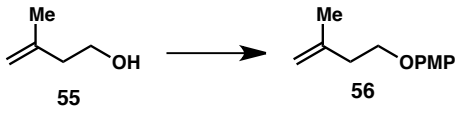
2.5 EXPERIMENTAL SECTION

2.5.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Unless otherwise stated, chemicals and reagents were used as received. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al.[28] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^{1}H, δ = 7.26), MeCN (^{1}H, δ = 1.94), or DMSO (^{1}H, δ = 2.50), and $CDCl_3$ (^{13}C, δ = 77.0), MeCN (^{13}C, δ = 118.26), or DMSO (^{13}C, δ = 40.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer

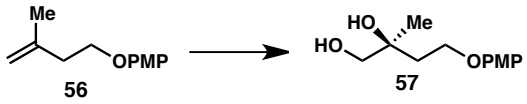
Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode.

2.5.2 Prepartive Procedures and Spectoscopic Data



1-methoxy-4-((3-methylbut-3-en-1-yl)oxy)benzene (56)

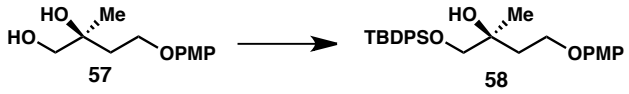
A flask was charged with 4-methoxyphenol (2.54 g, 20.5 mmol) and PPh_3 (2.33 g, 8.87 mmol), and then THF (23 mL) was added. The addition of alcohol **55** (0.588 g, 6.82 mmol) was followed by the addition of diisopropyl azodicarboxylate (1.75 mL, 8.87 mmol), and the reaction was heated to a reflux for 3.5 h. The reaction was cooled to room temperature, and THF was removed under pressure. The resulting residue was loaded unto a column and purified by column chromatography (5% EtOAc/Hex) to produce **56** (1.26 g, 96% yield).



(*S*)-4-(4-methoxyphenoxy)-2-methylbutane-1,2-diol (57)

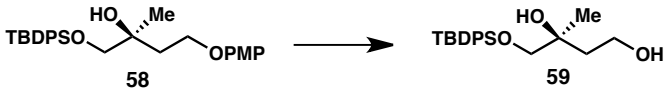
K_2CO_3 (3.49 g, 25.2 mmol), $K_3Fe(CN)_6$ (8.31 g, 25.2 mmol), $K_2OsO_4 \cdot 2H_2O$ (12.4 mg, 0.0336 mmol), and $(DHQ)_2PHAL$ (65.5 mg, 0.0841 mmol) were added all at once to a solution of olefin **56** (1.62 g, 8.41 mmol) in *t*-BuOH (45 mL) and H_2O

(45 mL) at 0 °C. After 5 h at room temperature, Na_2SO_3 (12.7 g, 100 mmol) was added and the mixture was stirred for 5 min. Minimal water was added and the aqueous layer was extracted from EtOAc four times. The combined organics were washed with brine, and dried over $MgSO_4$. The crude was purified by column chromatography (20%→50% EtOAc/Hex) to give **57** (1.68 g, 88% yield).



(*S*)-1-((*tert*-butyldiphenylsilyl)oxy)-4-(4-methoxyphenoxy)-2-methylbutan-2-ol (58)

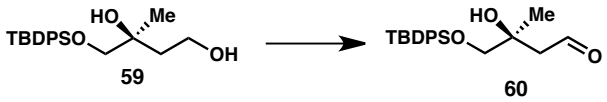
Imidazole (0.247 g, 3.63 mmol), followed by TBDPSCl (0.69 mL, 2.66 mmol), was added to a solution of diol **57** (0.548 g, 2.42 mmol) in DMF (2.7 mL). After stirring overnight at room temperature, the reaction was quenched with sat. NH_4Cl and extracted with ether three times. The combined organic layers were washed with water, then brine, and then dried over $MgSO_4$. The crude product was purified via column chromatography (15%→40% EtOAc/Hex) to give **58** (1.09 g, 97% yield).



(*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-3-methylbutane-1,3-diol (59)

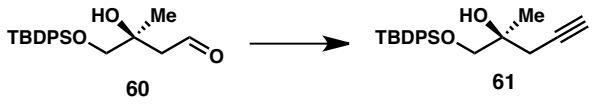
A solution of CAN (2.61 g, 4.76 mmol) in water (11 mL) was added dropwise via an addition funnel to a solution of alcohol **58** (1.09 g, 2.36 mmol) in acetonitrile (9.5 mL) at 0 °C. After 15 min, EtOAc and water was added and the layers were

separated. Aqueous was extracted from EtOAc twice more, and then the combined organics were washed with water, then brine, and then dried over $MgSO_4$. The crude was purified via column chromatography (eluting with CH_2Cl_2 to remove impurities, and then EtOAc to elute product) to give **59** (0.829 g, 98% yield).



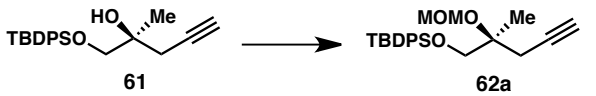
(*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-3-methylbutanal (60)

Dess-Martin periodinane (48.8 mg, 0.115 mmol) was added to a solution of diol **59** (27.5 mg, 0.0767 mmol) in dichloromethane (0.5 mL) and this was stirred overnight. The reaction was quenched with a 1:1 mixture of sat. $NaHCO_3$/1.5 M $Na_2S_2O_3$ and the aqueous layer was extracted from Et_2O three times. The combined organic layers were washed with brine and dried over $MgSO_4$, and crude aldehyde **60** was used in the next step without purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (t, J = 2.4 Hz, 1H), 7.68 – 7.61 (m, 4H), 7.48 – 7.37 (m, 6H), 3.53 (d, J = 1.3 Hz, 2H), 2.88 (s, 1H), 2.73 (dd, J = 15.6, 2.3 Hz, 1H), 2.49 (dd, J = 15.7, 2.6 Hz, 1H), 1.26 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.1, 135.6, 132.8, 123.0, 127.9, 72.2, 70.9, 51.6, 26.9, 24.3, 19.3; IR (NaCl/thin film): 3453, 3071, 3047, 2959, 2931, 2888, 2858, 2739, 1720, 1472, 1461, 1428, 1391, 1362, 1188, 1155, 1112, 824, 741 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{21}H_{28}O_3Si$ $[M–H]^-$ 355.1735, found 355.1736.



(*S*)-1-((*tert*-butyldiphenylsilyl)oxy)-2-methylpent-4-yn-2-ol (61)

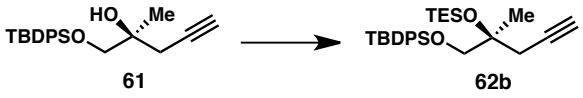
K_2CO_3 (16.6 mg, 0.120 mmol), followed by Ohira–Bestmann reagent (13.8 mg, 0.0719 mmol), was added to a solution of crude aldehyde **60** (25.7 mg, 0.0599 mmol) in MeOH (1 mL), and this was stirred at room temperature overnight. The reaction was quenched with sat. $NaHCO_3$ and diluted with Et_2O. The aqueous layer was extracted from Et_2O three times, and then the combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (5% EtOAc/Hex) to provide alkyne **61** (18.9 mg, 70% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.66 (m, 4H), 7.48 – 7.36 (m, 6H), 3.67 (d, *J* = 9.7 Hz, 1H), 3.54 (d, *J* = 9.8 Hz, 1H), 2.59 (s, 1H), 2.58 – 2.46 (m, 2H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.28 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 129.8, 127.8, 80.8, 72.2, 70.6, 69.5, 29.1, 26.6, 23.0, 19.3; IR (NaCl/thin film): 3561, 3452, 3071, 3050, 2998, 2959, 2931, 2892, 2858, 1590, 1487, 1472, 1464, 1428, 1391, 1362, 1188, 1152, 1113, 1090, 998, 908, 824, 742 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{22}H_{28}O_2Si$ $[M\bullet]^+$ 352.1853, found 352.1832.



(*S*)-5,9,9-trimethyl-8,8-diphenyl-5-(prop-2-yn-1-yl)-2,4,7-trioxa-8-siladecane (62a)

Bu_4NI (3.1 mg, 0.00834 mmol), followed by N,N-diisopropylethylamine (0.02 mL, 0.125 mmol) was added to a solution of alkyne **61** (14.7 mg, 0.0417 mmol) in

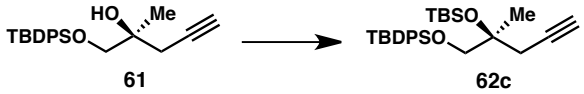
THF (0.5 mL). After dropwise addition of chloromethyl methyl ether (MOMCl, 0.01 mL, 0.167 mmol), the reaction was heated to 80 °C and stirred for 2 h. Upon cooling to room temperature, the reaction was quenched with water and the aqueous layer was extracted from Et_2O three times. The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (5% EtOAc/Hex) to provide **62a** (15.1 mg, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (ddt, *J* = 7.9, 6.2, 1.7 Hz, 4H), 7.46 – 7.35 (m, 6H), 4.81 – 4.76 (m, 2H), 3.73 (d, *J* = 10.2 Hz, 1H), 3.60 (d, *J* = 10.2 Hz, 1H), 3.35 (s, 3H), 2.66 – 2.55 (m, 2H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.35 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.7, 135.5, 129.7, 127.6, 91.6, 81.1, 77.9, 70.2, 68.3, 55.4, 27.4, 26.9, 20.8, 19.3; IR (NaCl/thin film): 3309, 3071, 3050, 2932, 2891, 2858, 1472, 1428, 1390, 1362, 1189, 1144, 1112, 1040, 1007, 996, 918, 824, 739, 702 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{24}H_{32}O_3Si$ $[M+H]^+$ 397.2193, found 397.2182.



(*S*)-8,8-diethyl-2,2,6-trimethyl-3,3-diphenyl-6-(prop-2-yn-1-yl)-4,7-dioxa-3,8-disiladecane (62b)

DMAP (7.6 mg, 0.0618 mmol) and imidazole (16.8 mg, 0.247 mmol) were added to a solution of alkyne **61** (21.8 mg, 0.0618 mmol) in DMF (0.3 mL). Chlorotriethylsilane (TESCl, 0.03 mL, 0.185 mmol) was added and the reaction was heated to 40 °C for 4 h. Upon cooling to room temperature, DMF was extracted from hexanes three times and the combined hexane layers were washed with water, then

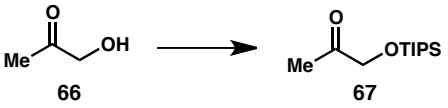
brine, and dried over $MgSO_4$. The crude product was purified by column chromatography (5% EtOAc/Hex) to provide alkyne **62b** (18.2 mg, 63% yield, 85% yield b.r.s.m.). $[\alpha]_D^{25.0}$ = +4 ° (*c* = 0.455, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 4H), 7.45 – 7.35 (m, 6H), 3.58 (d, *J* = 9.6 Hz, 1H), 3.46 (d, *J* = 9.6 Hz, 1H), 2.51 (ddd, *J* = 72.1, 16.4, 2.7 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.31 (s, 3H), 1.06 (s, 9H), 0.90 (t, *J* = 7.9 Hz, 9H), 0.55 (qd, *J* = 7.9, 1.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ135.7, 133.6, 129.6, 127.6, 81.9, 75.3, 70.3, 67.0, 30.0, 26.9, 24.6, 19.3, 6.97, 6.74; IR (NaCl/thin film): 3311, 3071, 3050, 2955, 2932, 2875, 2858, 1472, 1459, 1428, 1239, 1195, 1160, 1112, 1030, 1016, 1009, 821, 740 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{28}H_{42}O_2Si_2$ $[M+H]^+$ 467.2796, found 467.2705.



(*S*)-2,2,3,3,5,9,9-heptamethyl-8,8-diphenyl-5-(prop-2-yn-1-yl)-4,7-dioxa-3,8-disiladecane (62c)

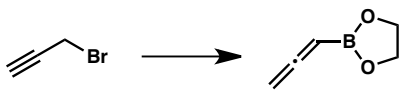
TBSCl (11.5 mg, 0.0766 mmol), imidazole (5.2 mg, 0.0766 mmol) and **61** (13.5 mg, 0.0383 mmol) were heated neat to 120 °C overnight. The reaction was quenched with water and diluted with dichloromethane, and the aqueous layer was extracted from dichloromethane three times. The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by flash chromatography (Hex→5% EtOAc/Hex) to give **62c** (15.9 mg, 89% yield). $[\alpha]_D^{25.0}$ = +2 ° (*c* = 0.795, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.71 (m, 4H), 7.45 – 7.31 (m, 6H), 3.50 (d, *J* = 9.5 Hz, 1H), 3.34 (d, *J* = 9.5 Hz, 1H), 2.45 (dd, *J* = 16.4,

2.7 Hz, 1H), 2.31 (dd, *J* = 16.4, 2.7 Hz, 1H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.11 (s, 3H), 1.03 (s, 9H), 0.85 (s, 9H), -0.03 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2, 135.6, 129.4, 127.4, 82.0, 69.9, 69.2, 29.7, 27.1, 26.9, 25.9, 24.4, 19.5, 18.3, -5.54, -5.61; IR (NaCl/thin film): 3312, 3071, 3050, 2956, 2930, 2894, 2857, 1472, 1463, 1428, 1390, 1361, 1258, 1193, 1159, 1110, 1103, 1039, 1028, 1006, 851, 837, 822, 777, 741, 703 cm^{-1}; HRMS (ESI) calc'd for $C_{28}H_{42}O_2Si_2$ $[M+H]^+$ 467.2713, found 467.2796.



1-((triisopropylsilyl)oxy)propan-2-one (67)

Acetol (2.27 g, 30.6 mmol) was added to a solution of imidazole (4.38 g, 64.3 mmol) in DMF (40 mL), followed by the addition of TIPSCl (7.21 mL, 33.7 mmol). After stirring at room temperature for 1.5 h, the reaction was quenched with sat. NH_4Cl, and the aqueous layer was extracted from diethyl ether four times. The combined organic layers were washed with water, then brine, and finally dried over $MgSO_4$. The crude product was purified by column chromatography (5%→20% EtOAc/Hex) to give **67** (6.72 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (d, *J* = 1.2 Hz, 2H), 2.22 (s, 3H), 1.18 – 0.99 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.1, 69.9, 26.1, 17.9, 17.7, 12.3, 11.8; IR (NaCl/thin film): 3503, 2944, 2893, 2867, 1720, 1464, 1435, 1417, 1384, 1354, 1248,1231, 1123, 1069, 1014, 996, 919, 882, 838, 799 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{12}H_{26}O_2Si$ $[M+H_3O]^+$ 249.1880, found 249.1871.

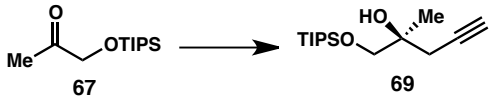


68

2-(propa-1,2-dien-1-yl)-1,3,2-dioxaborolane (68)

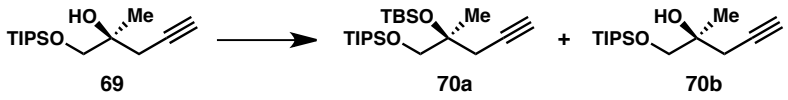
A 2-neck flask was charged with Mg turnings (2.43 g, 100 mmol) and $HgCl_2$ (46.2 mg, 0.170 mmol) and then gently heated while flushing with N_2 to remove excess moisture. Et_2O (15 mL) was added and the reaction flask was fitted with a reflux condenser. Propargyl bromide (10.3 g, 86.8 mmol) in Et_2O (50 mL) was added dropwise, and the reaction was cooled with a salt/ice bath. After stirring for 45 min at room temperature, the Grignard reagent was added dropwise via canula to a solution of trimethyl borate (9.02 g, 86.8 mmol) in Et_2O (100 mL) at –78 °C over about 30 min. The reaction was allowed to warm to room temperature, and then cooled to 0 °C before adding HCl (3M, 100 mL) dropwise using an addition funnel. The mixture was stirred at 0 °C for approximately 25 min and then allowed to warm to room temperature for 5 min. The aqueous layer was extracted from Et_2O (50 mL x 3) and the combined organics were dried over $MgSO_4$. The organic layer was filtered into a flame-dried 500 mL round-bottom flask, and then the solvent was reduced under pressure to leave ~200 mL. Ethylene glycol (8.08 g, 130 mmol) and $MgSO_4$ (100 g) were added and the reaction was stirred using a mechanical stirrer at room temperature for 23 h. The mixture was filtered, washing with Et_2O, and the solvent was reduced under pressure. The crude was dissolved in 150 mL pentane at 0 °C, and excess ethylene glycol as removed as the bottom layer if necessary. If a precipitate

remained, the crude was filtered through oven-dried Celite. The crude product was purified via distillation and stored under inert gas in the fridge.



(*S*)-2-methyl-1-((triisopropylsilyl)oxy)pent-4-yn-2-ol (69)

A mixture of (*S*)-3,3'-Cl-BINOL (35.7 mg, 0.101 mmol) and 2-(propa-1,2-dien-1-yl)-1,3,2-dioxaborolane (0.166 g, 1.501 mmol) was stirred at room temperature for 5 min. To this was added ketone **67** (0.232 g, 1.01 mmol), and the reaction mixture was subjected to microwave irradiation at 10 W for 1.5 h. The next day, the residue was purified via column chromatography (5% EtOAc/Hex) to provide **69** (0.188 g, 69% yield). $[\alpha]_D^{25.0}$ = +2 ° (*c* = 0.435, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (d, *J* = 9.3 Hz, 1H), 3.54 (d, *J* = 9.3 Hz, 1H), 2.62 (s, 1H), 2.50 – 2.37 (m, 2H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.27 (s, 3H), 1.08 (d, *J* = 1.0 Hz, 12H), 1.07 (dd, *J* = 2.3, 1.3 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0, 81.0, 72.1, 70.4, 69.2, 29.0, 22.9, 18.0, 12.0; IR (NaCl/thin film): 3558, 3454, 3314, 2944, 2888, 2867, 1463, 1422, 1383, 1157, 1100, 1069, 1014, 996, 911, 882, 809, 774 cm^{-1}.



TBSCl (0.120 g, 0.799 mmol), imidazole (0.0544 g, 0.799 mmol) and **69** (0.108 g, 0.399 mmol) were heated neat to 120 °C overnight. The reaction was quenched with water and diluted with dichloromethane, and the aqueous layer was

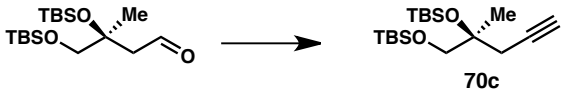
extracted from dichloromethane four times. The combined organic layers were washed with brine and dried over $MgSO_4$. The crude mixture was separated using column chromatography (hexanes) to afford **70a** (27.6 g, 18% yield, 41% yield brsm) and **70b** (13.3 mg, 9% yield, 20% yield brsm).

(*S*)-8,8-diisopropyl-2,2,3,3,5,9-hexamethyl-5-(prop-2-yn-1-yl)-4,7-dioxa-3,8-disiladecane (70a)

$[\alpha]_D^{25.0}$ = +3 ° (*c* = 0.735, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 – 3.44 (m, 2H), 2.49 – 2.34 (m, 2H), 1.94 (td, *J* = 2.7, 1.3 Hz, 1H), 1.29 (d, *J* = 1.5 Hz, 3H), 1.07 (d, *J* = 1.2 Hz, 15H), 1.06 – 1.04 (m, 8H), 0.86 (d, *J* = 1.4 Hz, 9H), 0.12 (d, *J* = 1.4 Hz, 3H), 0.09 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.1, 75.5, 70.2, 69.9, 29.9, 25.8, 24.6, 18.2, 18.0, 12.1, -2.09; IR (NaCl/thin film): 3314, 2944, 2893, 2866, 1472, 1458, 1387, 1254, 1197, 1164, 1108, 1066, 1035, 1016, 1004, 882, 835, 806, 774 cm^{-1}.

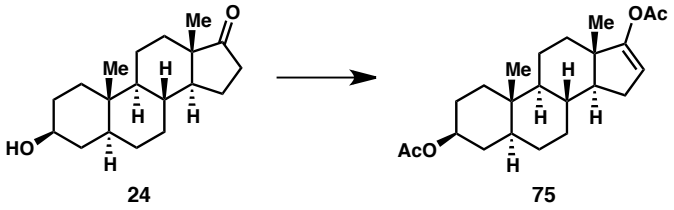
(*S*)-8,8-diisopropyl-2,2,3,3,6,9-hexamethyl-6-(prop-2-yn-1-yl)-4,7-dioxa-3,8-disiladecane (70b)

$[\alpha]_D^{25.0}$ = +3 ° (*c* = 0.460, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51 (dd, *J* = 61.1, 9.4 Hz, 2H), 2.53 – 2.33 (m, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.28 (s, 3H), 1.05 – 1.04 (m, 21H), 0.90 (s, 9H), 0.06 (d, *J* = 1.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.1, 75.1, 69.9, 69.6, 30.0, 25.9, 24.8, 18.3, 13.5, -5.46, -5.51; IR (NaCl/thin film): 3315, 2929, 2866, 2360, 1653, 1559, 1506, 1472, 1464, 1388, 1257, 1197, 1168, 1144, 1103, 1044, 1006, 882, 851, 837, 776 cm^{-1}.



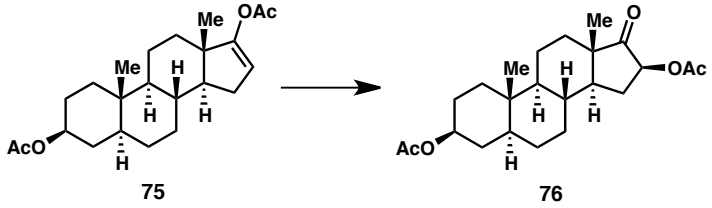
(*S*)-2,2,3,3,5,8,8,9,9-nonamethyl-5-(prop-2-yn-1-yl)-4,7-dioxa-3,8-disiladecane (70c)

K_2CO_3 (78.7 mg, 0.569 mmol), followed by Ohira–Bestmann reagent (65.6 mg, 0.342 mmol), was added to a solution of crude aldehyde (98.7 mg, 0.285 mmol) in MeOH (5 mL), and this was stirred at room temperature overnight. The reaction was quenched with sat. $NaHCO_3$ and diluted with Et_2O. The aqueous layer was extracted from Et_2O three times, and then the combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (hexanes) to provide alkyne **70c** (70.7 mg, 72% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51 (d, *J* = 9.6 Hz, 1H), 3.41 (d, *J* = 9.5 Hz, 1H), 2.42 (dd, *J* = 16.5, 2.7 Hz, 1H), 2.32 (dd, *J* = 16.5, 2.7 Hz, 1H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.25 (s, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.0, 75.4, 69.8, 69.6, 29.8, 25.9, 25.8, 24.4, 18.3, 18.2, –2.26, –5.50; IR (NaCl/thin film): 3315, 2956, 2930, 2887, 2858, 1472, 1464, 1388, 1362, 1310, 1255, 1197, 1165, 1137, 1104, 1043, 1007, 939, 834, 814, 798, 775 cm^{-1}; HRMS (ESI) calc'd for $C_{18}H_{38}O_2Si_2$ $[M+K]^+$ 381.2042, found 381.2170.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17-diyl diacetate (75)

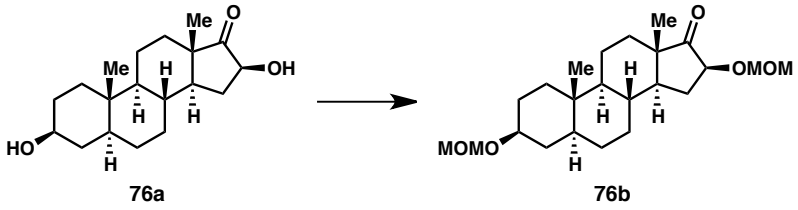
One drop of conc. H_2SO_4 was added to a solution of *trans*-androsterone **24** (0.643 g, 2.21 mmol) in isopropenyl acetate (16 mL) and this was heated to reflux for 4 h. Upon cooling to room temperature, the reaction was quenched with 0.5 M Na_2CO_3 (65 mL). The aqueous layer was extracted from EtOAc (65 mL, then 35 mL) and the combined organics were washed with water (65 mL) and brine (65 mL), and then dried over $MgSO_4$. The crude product was purified via column chromatography (neutral alumina powder, CH_2Cl_2) and then recrystallized from Et_2O to give **75** (0.311 g, 38% yield).



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*S*)-10,13-dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,16-diyl diacetate (76)

Acetic anhydride (0.32 mL, 3.35 mmol) was added to a solution off steroid **75** (0.279 g, 0.745 mmol) and $Pd(OAc)_4$ (0.364 g, 0.820 mmol) in acetic acid (13 mL). After stirring overnight at room temperature, the acetic acid was removed via rotary evaporation. The resulting residue was diluted in Et_2O (20 mL) and water-saturated

Et_2O (20 mL) to decompose the lead complex. The mixture was filtered, and the filtrant was washed with 0.5 M Na_2CO_3 (40 mL), water (40 mL), and brine (40 mL), Upon drying over $MgSO_4$, the crude product was purified via column chromatography (5% EtOAC/95% CH_2Cl_2) to give **76** (0.151 g, 52% yield, 61% b.r.s.m.).

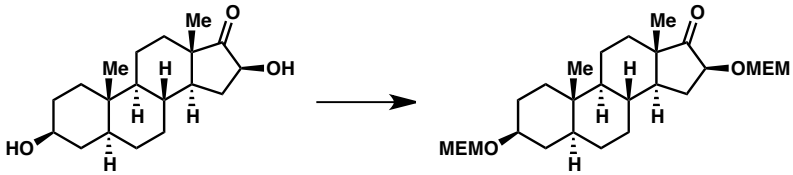


76a **76b**

(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*S*)-3,16-bis(methoxymethoxy)-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17(2*H*)-one (76b)

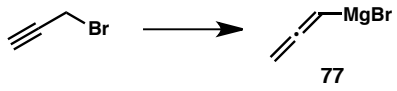
Bu_4NI (35.0 mg, 0.0949 mmol), followed by N,N-diisopropylethylamine (0.33 mL, 1.90 mmol) was added to a solution of steroid **76a** (0.145 g, 0.474 mmol) in THF (4 mL). After dropwise addition of chloromethyl methyl ether (MOMCl, 0.18 mL, 2.37 mmol), the reaction was heated to 50 °C and stirred overnight. Upon cooling to room temperature, the reaction was quenched with water and the aqueous layer was extracted from Et_2O three times. The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (10%→15% EtOAc/Hex) to provide **76b** (0.187 g, 80% yield). $[\alpha]_D^{25.0}$ = –72 ° (*c* = 0.540, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (d, *J* = 6.7 Hz, 1H), 4.73 (d, *J* = 6.7 Hz, 1H), 4.70 – 4.66 (m, 2H), 3.76 (s, 1H), 3.50 (tt, *J* = 11.2, 4.8 Hz, 1H), 3.41 (s, 3H), 3.37 (s, 3H), 2.23 (ddd, *J* = 18.7, 7.7, 1.1 Hz, 1H), 1.96 – 1.90 (m, 1H), 1.91 – 1.69 (m, 3H), 1.64 (ddt, *J* = 16.2, 8.8, 3.4 Hz, 3H), 1.59 – 1.23 (m,

9H), 1.18 – 1.08 (m, 1H), 1.03 – 0.88 (m, 2H), 0.84 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.1, 96.4, 94.6, 89.3, 76.2, 55.5, 55.1, 54.4, 45.3, 44.9, 42.1, 36.9, 36.8, 36.4, 35.9, 35.2, 34.5, 31.8, 28.6, 28.5, 20.5, 12.3, 12.2; IR (NaCl/thin film): 2931, 2849, 1753, 1464, 1449, 1382, 1218, 1146, 1104, 1040, 1009, 916 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{23}H_{38}O_5$ $[M+Na]^+$ 417.2611, found 417.2596.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*S*)-3,16-bis((2-methoxyethoxy)methoxy)-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17(2*H*)-one (76c)

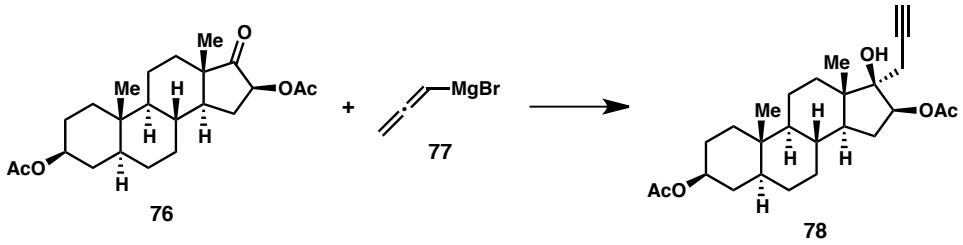
Bu_4NI (8.6 mg, 0.0232 mmol), followed by N,N-diisopropylethylamine (0.08 mL, 0.463 mmol) was added to a solution of steroid **76a** (35.5 mg, 0.116 mmol) in THF (1 mL). After dropwise addition of 2-methoxyethoxymethyl chloride (MEMCl, 0.07 mL, 0.579 mmol), the reaction was heated to 50 °C and stirred overnight. Upon cooling to room temperature, the reaction was quenched with water and the aqueous layer was extracted from Et_2O three times. The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (20%→35% EtOAc/Hex) to provide **76c** (22.7 mg, 41% yield). IR (NaCl/thin film): 3365, 3166, 2930, 2863, 1731, 1451, 1417, 1384, 1298, 1226, 1169, 1132, 1110, 1093, 1046, 930 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{27}H_{46}O_7$ $[M+Na]^+$ 505.3136, found 505.3108.



77

propa-1,2-dien-1-ylmagnesium bromide (77)

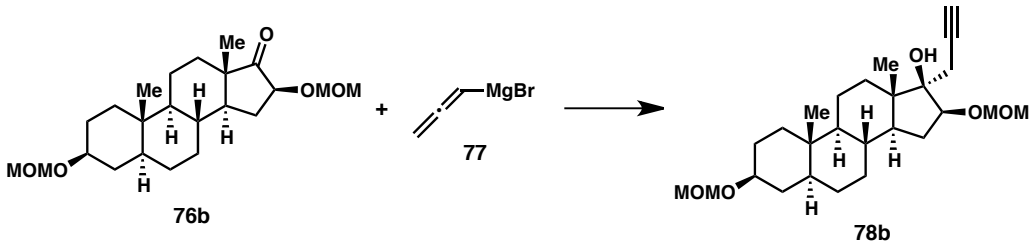
A 2-neck flask was charged with Mg turnings (0.194 g, 7.98 mmol) and $HgCl_2$ (2.2 mg, 0.00798 mmol) and then gently heated while flushing with N_2 to remove excess moisture. Et_2O (2 mL) was added and the reaction flask was fitted with a reflux condenser. Propargyl bromide (0.949 g, 7.98 mmol) was added dropwise while simultaneously adding Et_2O (3 mL) dropwise to maintain reflux. After stirring for 1 h, the reagent was ready to use as is.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*S*,17*R*)-17-hydroxy-10,13-dimethyl-17-(prop-2-yn-1-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,16-diyl diacetate (78)

Allenylmagnesium bromide **77** (0.0259 mmol, 0.02 mL of 1.68 M soln. in Et_2O) was added to a solution of steroid **76** (10.1 mg, 0.0259 mmol) in THF (2 mL) at –78 °C. After 1.5 h, another 0.02 mL (0.0259 mmol, 1 equiv) of allenylmagnesium bromide was added, and this was repeated every 30 min until a total of 4 equiv of allenylmagnesium bromide had been added. After a total of 3.5 h, the reaction was quenched with water, and the aqueous layer was extracted from Et_2O three times. The combined organic layers were washed with brine and dried over $MgSO_4$, which

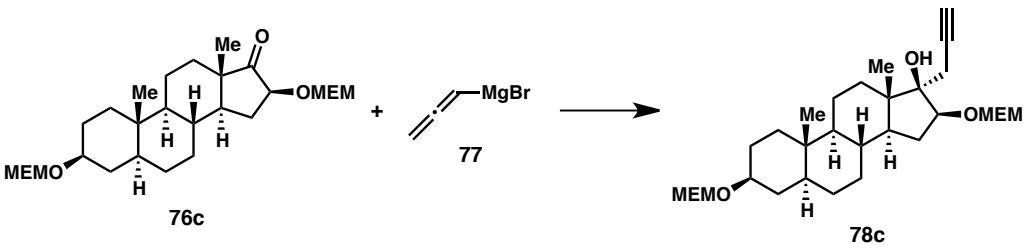
provided pure **78** (8.7 mg, 78% yield) without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (dd, *J* = 8.3, 5.8 Hz, 1H), 4.68 (tt, *J* = 11.4, 4.9 Hz, 1H), 2.61 – 2.49 (m, 2H), 2.41 – 2.26 (m, 2H), 2.10 (s, 3H), 2.02 (s, 3H), 1.86 – 1.78 (m, 1H), 1.73 (dt, *J* = 13.2, 3.6 Hz, 1H), 1.68 – 1.43 (m, 6H), 1.41 – 1.11 (m, 8H), 1.11 – 0.93 (m, 2H), 0.91 (s, 3H), 0.87 (dd, *J* = 12.2, 4.5 Hz, 1H), 0.84 (s, 3H), 0.65 (td, *J* = 11.5, 3.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 169.9, 110.0, 80.7, 80.6, 73.5, 71.2, 54.3, 47.2, 46.0, 44.7, 36.8, 35.8, 35.7, 34.0, 33.2, 32.3, 31.8, 28.4, 27.5, 27.2, 21.4, 21.1, 20.7, 13.8, 12.2; IR (NaCl/thin film): 3305, 3270, 2930, 2853, 1730, 1449, 1377, 1362, 1244, 1155, 1041, 1025 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{26}H_{38}O_5$ $[M–OH]^+$ 413.2692, found 413.2692.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*S*,17*R*)-3,16-bis(methoxymethoxy)-10,13-dimethyl-17-(prop-2-yn-1-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol (78b)

Allenylmagnesium bromide **77** (0.0467 mmol, 0.03 mL of 1.63 M soln. in Et_2O) was added to a solution of steroid **76b** (9.2 mg, 0.0233 mmol) in toluene (0.5 mL) at –78 °C. After 30 min, another 0.03 mL of allenylmagnesium bromide was added. After a total of 1 h, the reaction was quenched with water, and the aqueous layer was extracted from Et_2O three times. The combined organic layers were washed with brine and dried over $MgSO_4$, which provided pure **78b** (7.3 mg, 72% yield)

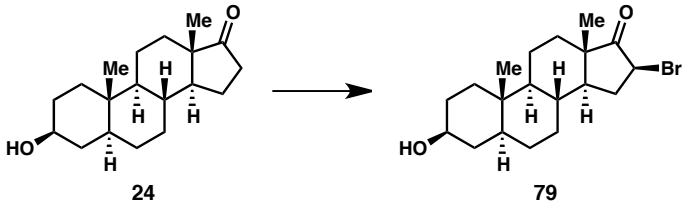
without further purification. $[\alpha]_D^{25.0}$ = –20 ° (*c* = 0.405, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 – 4.72 (m, 2H), 4.69 – 4.65 (m, 2H), 3.48 (tt, *J* = 11.1, 4.8 Hz, 1H), 3.42 (s, 3H), 3.36 (s, 3H), 3.28 (s, 1H), 3.19 – 3.16 (m, 1H), 2.46 – 2.34 (m, 2H), 2.02 – 1.95 (m, 2H), 1.83 (tdd, *J* = 12.4, 6.3, 3.4 Hz, 2H), 1.74 – 1.50 (m, 5H), 1.49 – 1.38 (m, 2H), 1.37 – 1.15 (m, 5H), 1.08 (ddt, *J* = 12.2, 8.7, 3.2 Hz, 1H), 1.03 – 0.90 (m, 2H), 0.89 (s, 3H), 0.88 – 0.82 (m, 1H), 0.81 (s, 3H), 0.65 (ddd, *J* = 12.3, 10.5, 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 97.7, 94.6, 90.3, 81.4, 76.4, 76.3, 69.5, 56.0, 55.1, 54.6, 48.0, 45.0, 43.8, 39.4, 37.8, 37.0, 35.8, 35.32, 34.8, 32.6, 31.7, 28.7, 28.6, 20.5, 12.4, 12.3; IR (NaCl/thin film): 3528, 3305, 3275, 2931, 2849, 1469, 1449, 1379, 1300, 1215, 1177, 1151, 1103, 1043, 1035, 1009, 927, 917 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{26}H_{42}O_5$ $[M+H]^+$ 435.3105, found 435.3078.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*S*,17*R*)-3,16-bis((2-methoxyethoxy)methoxy)-10,13-dimethyl-17-(prop-2-yn-1-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol (78c)

Allenylmagnesium bromide **77** (0.0783 mmol, 0.05 mL of 1.62 M soln. in Et_2O) was added to a solution of steroid **76c** (12.6 mg, 0.0261 mmol) in THF (0.5 mL) at –78 °C. After 30 min, another 0.03 mL (0.0522 mmol) of allenylmagnesium bromide was added. After a total of 45 min, the reaction was quenched with water,

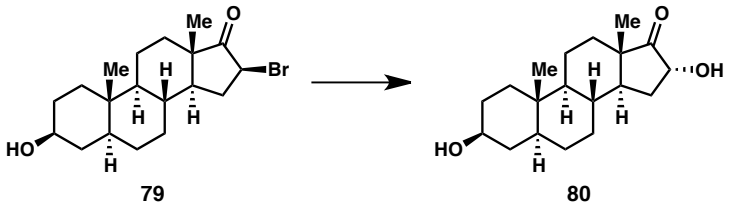
and the aqueous layer was extracted from Et_2O three times. The combined organic layers were washed with brine and dried over $MgSO_4$, which provided pure **78c** (8.6 mg, 63% yield) without further purification. $[\alpha]_D^{25.0}$ = –18 ° (*c* = 0.500, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.87 – 4.80 (m, 2H), 4.78 – 4.74 (m, 2H), 3.77 – 3.74 (m, 2H), 3.72 – 3.68 (m, 2H), 3.58 – 3.54 (m, 4H), 3.54 – 3.48 (m, 1H), 3.39 (s, 6H), 3.29 (s, 1H), 3.25 (s, 1H), 2.42 (qd, *J* = 16.4, 2.6 Hz, 2H), 2.00 (dd, *J* = 13.0, 6.7 Hz, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.87 – 1.76 (m, 2H), 1.73 – 1.48 (m, 5H), 1.47 – 1.36 (m, 2H), 1.36 – 1.13 (m, 6H), 1.12 – 1.03 (m, 1H), 1.02 – 0.90 (m, 2H), 0.87 (s, 3H), 0.80 (s, 3H), 0.65 (ddd, *J* = 12.3, 10.5, 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 96.8, 93.6, 90.8, 81.5, 76.4, 76.3, 71.9, 71.7, 69.5, 67.9, 66.7, 59.0, 59.0, 54.6, 47.9, 44.9, 43.9, 39.4, 37.8, 37.0, 35.8, 35.2, 34.8, 32.5, 31.7, 28.7, 28.6, 20.5, 12.4, 12.3; IR (NaCl/thin film): 3480, 3305, 3262, 2929, 2849, 1466, 1450, 1378, 1367, 1200, 1170, 1130, 1111, 1090, 1047, 984, 930, 849 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{30}H_{50}O_7$ $[M+Na]^+$ 545.3449, found 545.3474.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*S*)-16-bromo-3-hydroxy-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17(2*H*)-one (79)

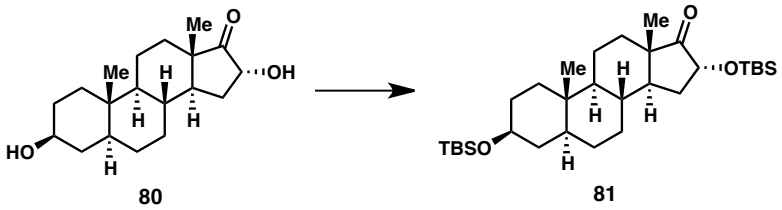
$CuBr_2$ (1.16 g, 5.21 mmol) was added to a solution of *trans*-androsterone **24** (0.505 g, 1.74 mmol) in distilled methanol (20 mL) and this was heated to reflux and stirred overnight. The next day, the reaction was quenched with water, and the

aqueous layer was extracted from chloroform three times. The combined organic layers were washed with brine and dried over $MgSO_4$. The crude bromide **79** was used in the following step without any further purification.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*R*)-3,16-dihydroxy-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17(2*H*)-one (80)

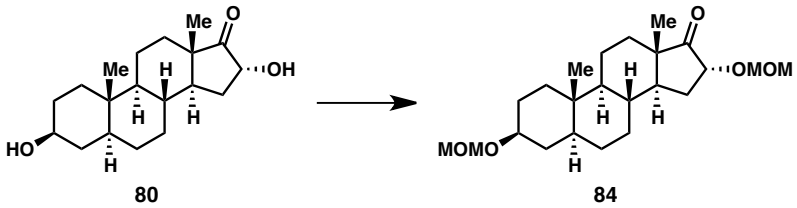
Bromide **79** (0.642 g, 1.74 mmol) was dissolved in 75% aq. DMF (30 mL), and then NaOH (0.0834 g, 2.08 mmol) was added. After 30 min, the reaction was poured into 1% HCl solution and the aqueous was extracted from EtOAc. The organic layer was washed with 5% $NaHCO_3$, then water, and then dried over $MgSO_4$. The crude diol **80** (0.400 g, 75% yield two steps) was clean enough that purification was unnecessary.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*R*)-3,16-bis((*tert*-butyldimethylsilyl)oxy)-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17(2*H*)-one (81)

Imidazole (0.206 g, 3.03 mmol), followed by TBSCl (0.400 g, 2.65 mmol), was added to a solution of **80** (0.387 g, 1.26 mmol) in dichloromethane (10 mL). The

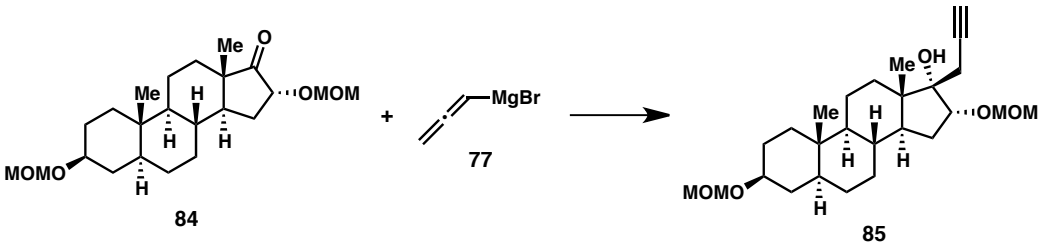
reaction was heated to 50 °C overnight and then quenched water and diluted with dichloromethane. The aqueous layer was extracted from dichloromethane three times, and then the combined organics were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (hexanes) to give **81** (0.539 g, 80% yield). $[\alpha]_D^{25.0}$ = +9 ° (*c* = 0.740, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (d, *J* = 8.1 Hz, 1H), 3.54 (dd, *J* = 11.3, 6.5 Hz, 1H), 1.95 – 1.02 (m, 20H), 0.94 (d, *J* = 8.1 Hz, 2H), 0.92 (s, 1H), 0.89 (d, *J* = 4.9 Hz, 15H), 0.81 (s, 1H), 0.77 (d, *J* = 2.1 Hz, 1H), 0.28 – 0.19 (m, 1H), 0.11 (s, 3H), 0.10 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.6, 72.3, 72.0, 54.5, 48.4, 47.4, 45.1, 38.7, 37.1, 35.7, 35.6, 35.0, 32.8, 31.9, 30.7, 28.5, 25.9, 25.8, 25.7, 25.6, 25.6, 20.2, 14.6, 12.3, -4.53; IR (NaCl/thin film): 2929, 2856, 1754, 1723, 1711, 1693, 1470, 1461, 1454, 1446, 1385, 1360, 1253, 1179, 1150, 1095, 1071, 1004, 870,835, 776 cm^{-1}.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*R*)-3,16-bis(methoxymethoxy)-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17(2*H*)-one (84)

Bu_4NI (14.6 mg, 0.0396 mmol), followed by N,N-diisopropylethylamine (0.14 mL, 0.792 mmol) was added to a solution of steroid **80** (60.7 mg, 0.198 mmol) in THF (1.6 mL). After dropwise addition of chloromethyl methyl ether (MOMCl, 0.08 mL, 0.990 mmol), the reaction was heated to 50 °C and stirred overnight. Upon cooling to room temperature, the reaction was quenched with water and the aqueous

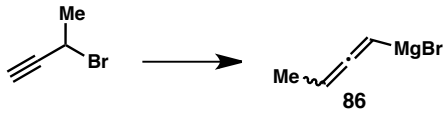
layer was extracted from Et_2O three times. The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (20% EtOAc/Hex) to provide **84** (76.4 mg, 98% yield). $[\alpha]_D^{25.0}$ = +86 ° (*c* = 0.255, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 (d, *J* = 6.7 Hz, 1H), 4.70 – 4.65 (m, 3H), 4.32 (dd, *J* = 7.1, 2.5 Hz, 1H), 3.49 (tt, *J* = 11.2, 4.8 Hz, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 1.92 – 1.68 (m, 5H), 1.68 – 1.60 (m, 2H), 1.59 – 1.38 (m, 4H), 1.38 – 1.23 (m, 5H), 1.11 (ddt, *J* = 15.7, 12.5, 3.4 Hz, 1H), 1.04 – 0.92 (m, 2H), 0.90 (s, 3H), 0.83 (s, 3H), 0.70 (ddd, *J* = 13.7, 7.5, 4.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 217.3, 96.1, 94.6, 76.2, 74.4, 55.6, 55.1, 54.4, 48.8, 47.7, 44.9, 36.9, 35.8, 35.3, 35.0, 31.6, 30.7, 29.7, 28.7, 28.4, 20.2, 14.4, 12.2; IR (NaCl/thin film): 2930, 2856, 1751, 1464, 1449, 1375, 1215, 1146, 1102, 1066, 1043, 1012, 917 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{23}H_{38}O_5$ $[M+H]^+$ 395.2792, found 395.2767.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*R*,17*S*)-3,16-bis(methoxymethoxy)-10,13-dimethyl-17-(prop-2-yn-1-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol (85)

$TiCl_4$ (0.01 mL, 0.0471 mmol) was added to a solution of steroid **84** (9.3 mg, 0.0236 mmol) in THF (0.5 mL) at –78 °C, followed by the addition of allenylmagnesium bromide **77** (0.0707 mmol, 0.04 mL of 1.63 M soln. in Et_2O). After 30 min, the reaction was quenched with water and diluted with Et_2O, and the

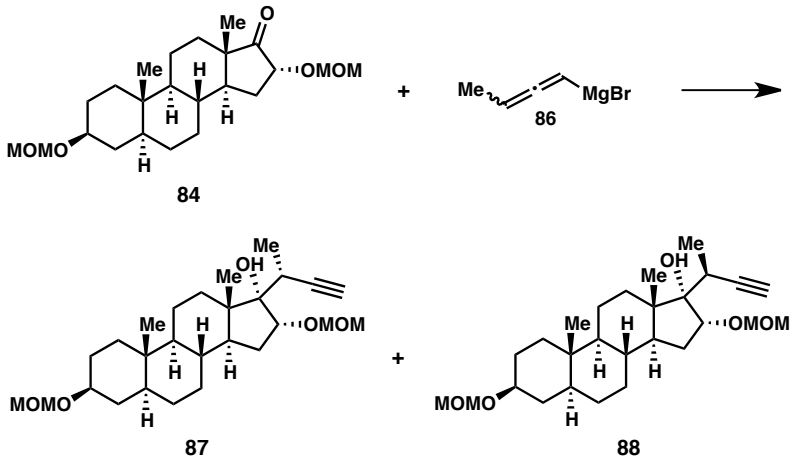
aqueous layer was extracted from Et_2O three times. The combined organic layers were washed with brine and dried over $MgSO_4$ to give pure **85** (7.9 mg, 77% yield) without further purification. $[\alpha]_D^{25.0}$ = –30 ° (*c* = 0.455, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (q, *J* = 6.8 Hz, 2H), 4.67 (d, *J* = 1.2 Hz, 2H), 4.03 (dd, *J* = 8.0, 3.1 Hz, 1H), 3.48 (tt, *J* = 11.2, 4.7 Hz, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 3.21 (s, 1H), 2.49 – 2.39 (m, 2H), 1.87 – 1.80 (m, 1H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.92 (td, *J* = 11.4, 9.0 Hz, 2H), 1.78 – 1.68 (m, 2H), 1.65 – 1.53 (m, 8H), 1.48 – 1.38 (m, 2H), 1.36 – 1.19 (m, 7H), 1.13 – 1.05 (m, 2H), 1.00 – 0.82 (m, 3H), 0.80 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 96.5, 94.6, 81.6, 81.5, 80.2, 76.3, 70.2, 56.0, 55.1, 54.1, 48.4, 47.2, 45.0, 37.0, 35.7, 35.4, 35.3, 32.4, 32.1, 30.5, 28.8, 28.7, 25.8, 20.2, 15.5, 12.3; IR (NaCl/thin film): 3478, 3311, 3264, 2941, 2923, 2898, 2848, 1468, 1450, 1384, 1353, 1219, 1150, 1104, 1076, 1040, 1026, 1013, 989, 960, 916 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{26}H_{42}O_5$ $[M+Na]^+$ 457.2924, found 457.2914.



86

buta-1,2-dien-1-ylmagnesium bromide (86)

86 was prepared from 3-bromobut-1-yne using the same procedure as allenylmagnesium bromide **77**.



$TiCl_4$ (0.01 mL, 0.0542 mmol) was added to a solution of steroid **84** (10.7 mg, 0.0271 mmol) in THF (0.5 mL) at –78 °C, followed by the addition of buta-1,2-dienyl-magnesium bromide **86** (0.0814 mmol, 0.05 mL of 1.50 M soln. in Et_2O). After 30 min, the reaction was quenched with water and diluted with Et_2O, and the aqueous layer was extracted from Et_2O three times. The combined organic layers were washed with brine and dried over $MgSO_4$ to give a mixture of **87** and **88**. The two products were separated by column chromatography (15% EtOAc/Hex) to afford **87** (5.7 mg, 47% yield) and **88** (2.8 mg, 23% yield).

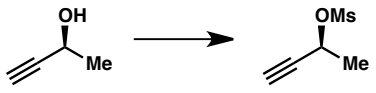
(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*R*,17*S*)-17-((*S*)-but-3-yn-2-yl)-3,16-bis(methoxymethoxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol (87)

$[\alpha]_D^{25.0}$ = +5 ° (*c* = 0.240, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (d, *J* = 6.7 Hz, 1H), 4.71 – 4.65 (m, 3H), 3.96 (dd, *J* = 7.6, 2.5 Hz, 1H), 3.49 (tt, *J* = 11.2, 4.8 Hz, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 3.21 (s, 1H), 2.73 (qd, *J* = 6.9, 2.5 Hz, 1H), 2.01 (d, *J* = 2.4 Hz, 1H), 1.91 – 1.76 (m, 3H), 1.70 (dt, *J* = 13.3, 3.6 Hz, 1H), 1.59 (tddd, *J* = 20.4, 12.4, 9.0, 5.5 Hz, 7H), 1.48 – 1.37 (m, 1H), 1.36 – 1.29 (m, 2H), 1.28 (d, *J* = 6.9

Hz, 3H), 1.25 (t, *J* = 1.3 Hz, 2H), 1.12 – 1.04 (m, 1H), 0.95 (tdd, *J* = 13.0, 8.3, 4.6 Hz, 2H), 0.79 (s, 3H), 0.75 (s, 3H), 0.69 (ddd, *J* = 12.5, 10.4, 3.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 97.9, 94.6, 87.6, 83.2, 82.1, 76.3, 69.5, 56.3, 55.1, 53.8, 49.0, 47.4, 44.9, 37.0, 35.6, 35.3, 35.3, 33.7, 33.3, 32.1, 32.0, 28.7, 28.7, 20.5, 16.7, 15.0, 12.2; IR (NaCl/thin film): 3520, 3306, 3270, 2928, 2849, 1461, 1450, 1383, 1352, 1340, 1296, 1218, 1151, 1104, 1070, 1044, 989, 917 cm^{-1}.

(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*R*,17*S*)-17-((*R*)-but-3-yn-2-yl)-3,16-bis(methoxymethoxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol (88)

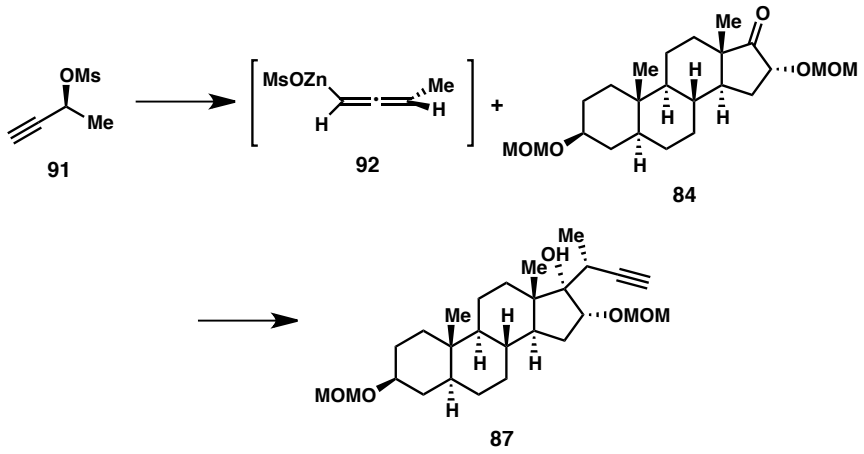
$[\alpha]_D^{25.0}$ = –24 ° (*c* = 0.125, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (d, *J* = 6.8 Hz, 1H), 4.70 – 4.64 (m, 3H), 4.01 (dd, *J* = 8.1, 2.0 Hz, 1H), 3.49 (tt, *J* = 11.2, 4.7 Hz, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 3.13 (s, 1H), 2.68 (qd, *J* = 7.0, 2.5 Hz, 1H), 2.11 (d, *J* = 2.5 Hz, 1H), 2.06 – 2.00 (m, 1H), 1.91 – 1.68 (m, 5H), 1.68 – 1.02 (m, 12H), 1.01 – 0.85 (m, 3H), 0.84 (s, 3H), 0.81 (d, *J* = 0.6 Hz, 3H), 0.74 – 0.65 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 96.1, 94.6, 87.0, 82.3, 80.8, 76.4, 70.7, 56.6, 55.1, 53.9, 49.0, 45.0, 37.0, 35.7, 35.3, 35.3, 32.5, 32.1, 31.9, 31.7, 29.7, 28.8, 28.8, 20.4, 16.3, 15.1, 12.2; IR (NaCl/thin film): 3538, 3231, 2930, 2848, 2819, 1459, 1449, 1377, 1355, 1261, 1219, 1150, 1135, 1103, 1041, 987, 917, 908, 796 cm^{-1}.



89 **91**

(*S*)-but-3-yn-2-yl methanesulfonate (91)

Et_3N (0.09 mL, 0.673 mmol) was added to a solution of alcohol **89** (23.6 mg, 0.337 mmol) in dichloromethane (1.7 mL) at –78 °C, followed by the addition of mesyl chloride (0.04 mL, 0.505 mmol). After 1.25 h at –78 °C, the reaction was quenched with sat. $NaHCO_3$ and allowed to warm to room temperature. The organic layer was separated, washed with brine, and concentrated. The resulting reside was diluted with ether, which was washed twice with water, and then once with brine. The combined aqueous layers were washed with ether twice. The combined organic layers were then dried over $MgSO_4$. The crude mesylate **91** (34.3 mg, 69% yield) was used without further purification.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*R*,17*S*)-17-((*S*)-but-3-yn-2-yl)-3,16-bis(methoxymethoxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol (87)

Triphenyl phosphine (3.5 mg, 0.0134 mmol), followed by mesylate **91** (0.119 g, 0.804 mmol), was added to a solution of $Pd(OAc)_2$ (9.0 mg, 0.0134 mmol) in THF (0.9 mL) at –78 °C. In a separate flask with stir bar, $TiCl_4$ (0.07 mL, 0.536 mmol) was added to a solution of steroid **84** (0.106 g, 0.268 mmol) in THF (0.9 mL) at –78

°C. After stirring for 5 min, the steroid solution was added dropwise to the mesylate solution at –78 °C. Following the dropwise addition of Et_2Zn (1.6 mL, 1.0 M in hexanes, 1.61 mmol), the reaction was warmed to –20 °C and stirred overnight. The reaction was quenched at –20 °C with 10% HCl (caution: evolution of gaseous ethane), and then diluted with ether and warmed to room temperature. Aqueous was extracted from ether twice, and the combined organics were washed with brine and dried over $MgSO_4$. The crude product was purified via flash chromatography (15% EtOAc/Hex) to afford alcohol **87** (18.1 mg, 15% yield, 22% b.r.s.m.). See above for characterization data.

(1) (a) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1994**, *59*, 6164.
(b) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1995**, *60*, 608.
(c) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *Tetrahedron*. **1995**, *51*, 6707.
(d) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1997**, *62*, 4484.

(2) Fortner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 275.

(3) Phillips, S. T.; Shair M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6589.

(4) Komiya, T.; Fusetani, N.; Matsunaga, S.; Kubo, A.; Kaye, F. J.; Kelley, M. J.; Tamura, K.; Yoshida, M.; Fukuoka, M.; Nakagawa, K. *Cancer Chemother. Pharmacol*. **2003**, *51*, 202.

(5) Burgett, A. W. G.; Poulsen, T. B.; Wangkanont, K.; Anderson, D. R.; Kikuchi, C.; Shimada, K.; Okubo, S.; Fortner, K. C.; Mimaki, Y.; Kuroda, M.; Murphy, J. P.; Schwalb, D. J.; Petrella, E. C.; Cornella-Taracido, I.; Schirle, M.; Tallarico, J. A.; Shair, M. D. *Nat. Chem. Biol*. **2011**, *7*, 639.

(6) Bhandaru, S.; Fuchs, P. L. *Tetrahedron Lett*. **1995**, *36*, 8351.

(7) Shönecker, B.; Lange, C.; Zheldakova, T.; Günther, W.; Görls, H.; Vaughan, G. *Tetrahedron*. **2005**, *61*, 103.

(8) Guo, C.; Bhandaru, S.; Fuchs, P. L. *J. Am. Chem. Soc*. **1996**, *118*, 10672.

(9) LaCour, T. G.; Guo, C.; Bhandaru, S.; Boyd, M. R.; Fuchs, P. L.; *J. Am. Chem. Soc*. **1998**, *120*, 692.

(10) Smith, S. C.; Heathcock, C. H. *J. Org. Chem*. **1992**, *57*, 6379.

(11) Davitishvili, M. G. *Khimiko-Farmatsevticheskii Zhurnal*, **1998**, *22*, 1121.

(12) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem*. **2002**, *67*, 8416.

(13) Bertolini, F.; Woodward, S. *Synlett*. **2009**, 51.

(14) (a) Tlais, S. F.; Dudley, G. B.; *Beilstein J. Org. Chem*. **2012**, *8*, 1287. (b) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem. Int. Ed*. **2007**, *46*, 279.

(15) Nakamura, A.; Nakada, M. *Synthesis*. **2013**, *45*, 1421.

(16) Barnett, D. S.; Shaus, S. E. *Org. Lett*. **2011**, *13*, 4020.

(17) (a) Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem*. **1990**, *55*, 4853. (b) Suzuki, M.; Morita, Y.; Yanagisawa, A.; Baker, B. J.; Scheuer, P. J.; Noyori, R. *J. Org. Chem*. **1988**, *53*, 286. (c) Marshall, J. A.; Xie, S. *J. Org. Chem*. **1995**, *60*, 7230.

(18) (a) Roumestant, M. L.; Place, P.; Gore, J. *Tetrahedron*. **1977**, *33*, 1283. (b) Moreau, J.-L.; Frangin, Y.; Gaudemar, M. *Bull. Soc. Chim. Fr*. **1970**, 4511. (c) Wender, P. A.; Harmata, M.; Jeffrey, D.; Mukai, C.; Suffert, J. *Tetrahedron Lett*. **1988**, *29*, 909.

(19) (a) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc*. **1981**, *103*, 5568. (b) Corey, E. J.; Rucker, C. *Tetrahedron Lett*. **1982**, *23*, 719. (c) Michelot, D. *Synth. Commun*. **1989**, *19*, 1705.

(20) (a) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem*. **1982**, *47*, 2225. (b) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn*. **1984**, *57*, 2768.

(21) (a) Zweifel, G.; Backlund, S. J.; Leung, T. *J. Am. Chem. Soc*. **1978**, *100*, 5561. (b) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *Ibid*. **1982**, *104*, 7667. (c) Ikeda, N.; Arai, I.; Yamamoto, H. *Ibid*. **1986**, *108*, 483.

(22) (a) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774. (b) Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565.

(23) McKinney, A. R.; Ridley, D. D.; Turner, P. *Aust. J. Chem.* **2003**, *56*, 829.

(24) Numazawa, M.; Nagaoka, M.; Osawa, Y.; *J. Org. Chem.* **1982**, *47*, 4024.

(25) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556.

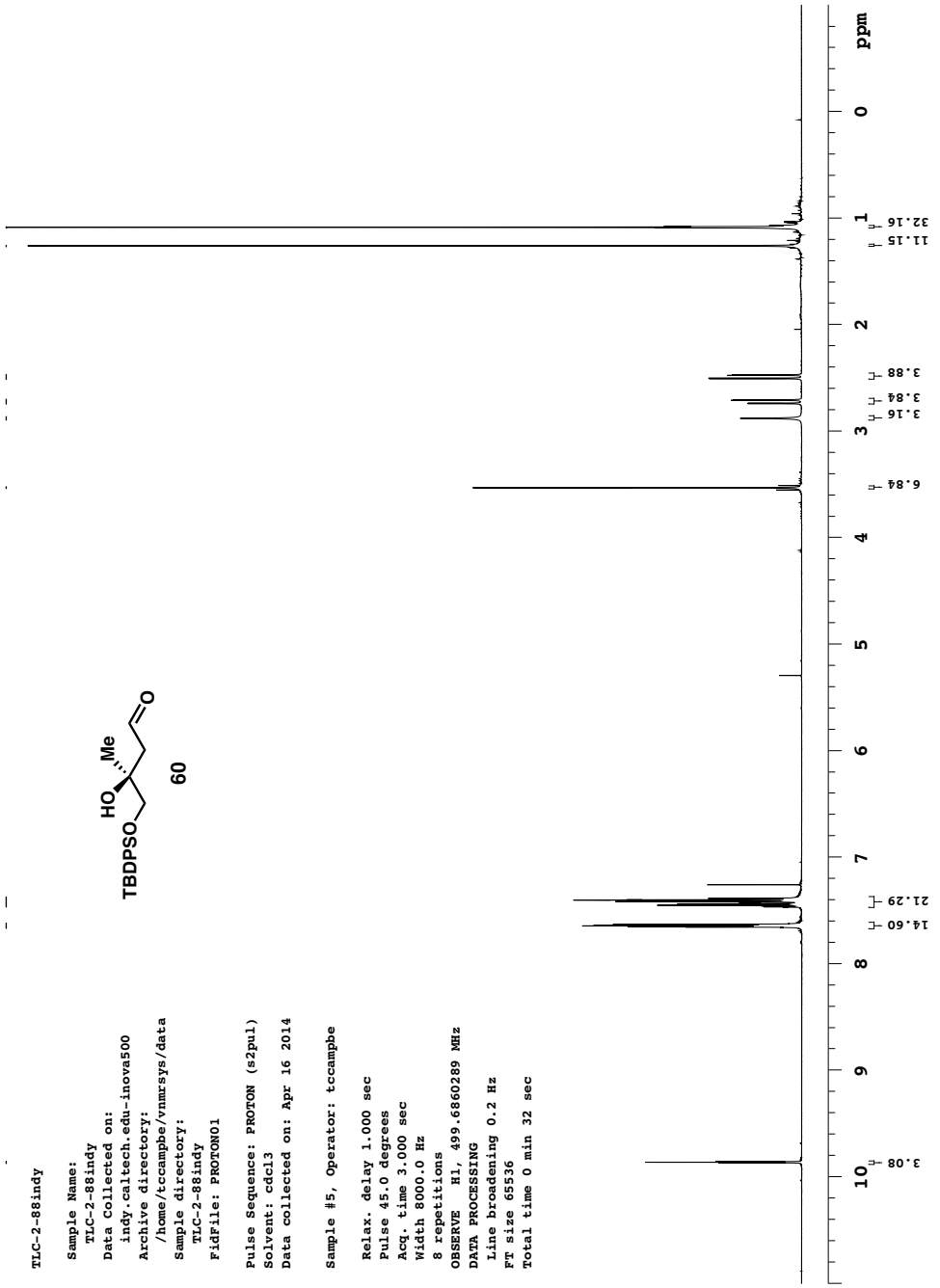
(26) Marshall, J.A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201.

(27) Trost, B. M.; Quintard, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 6704.

(28) Still, W. C., Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Appendix 1

Spectra Relevant to Chapter 2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Solvent: cdcl3
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Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
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DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec
HO
Me
TBDPSO
O
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ppm
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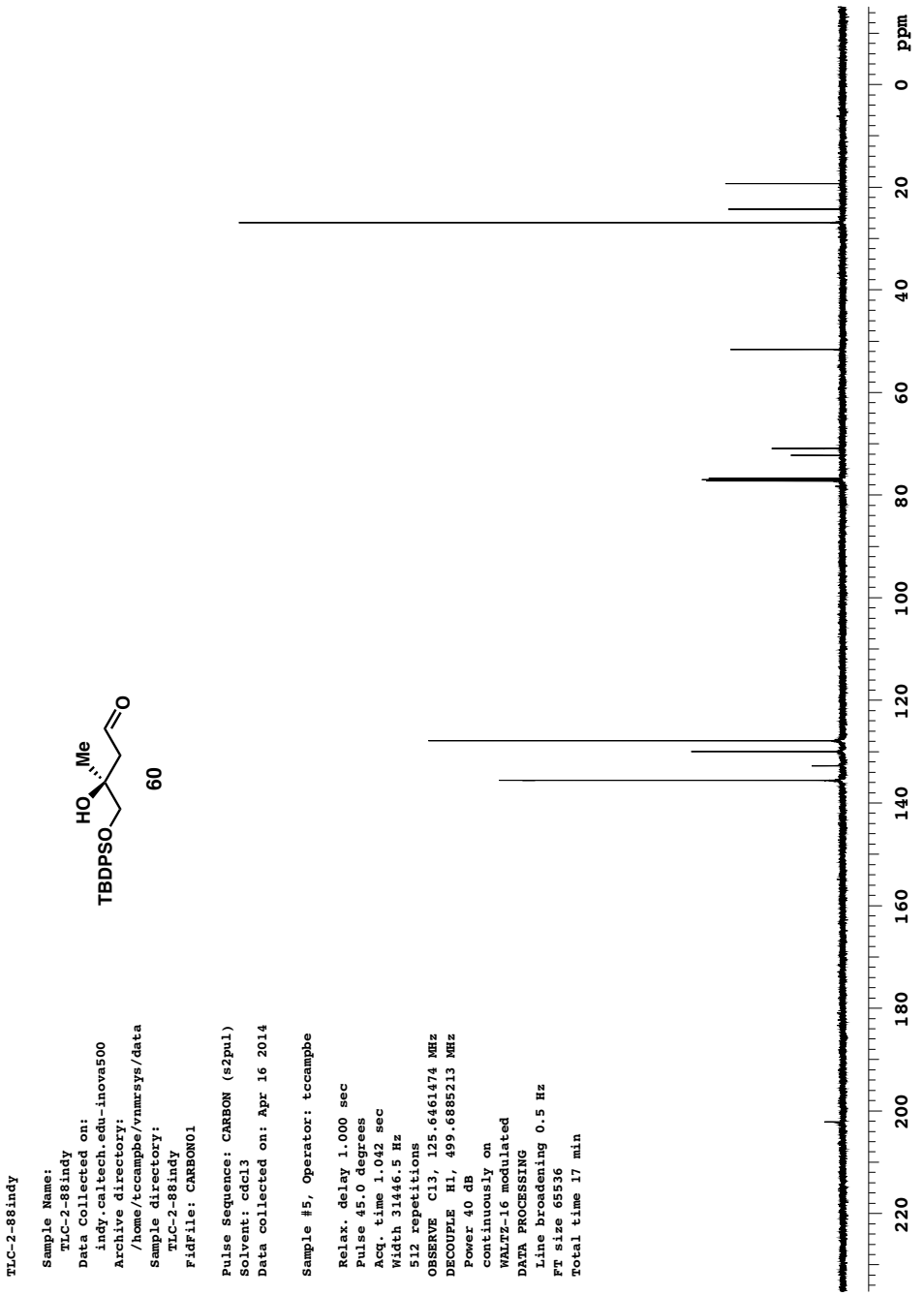
3.16
3.84
3.88
11.15
32.16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Solvent: cdcl3
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Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461474 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
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O
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220
200
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140
120
100
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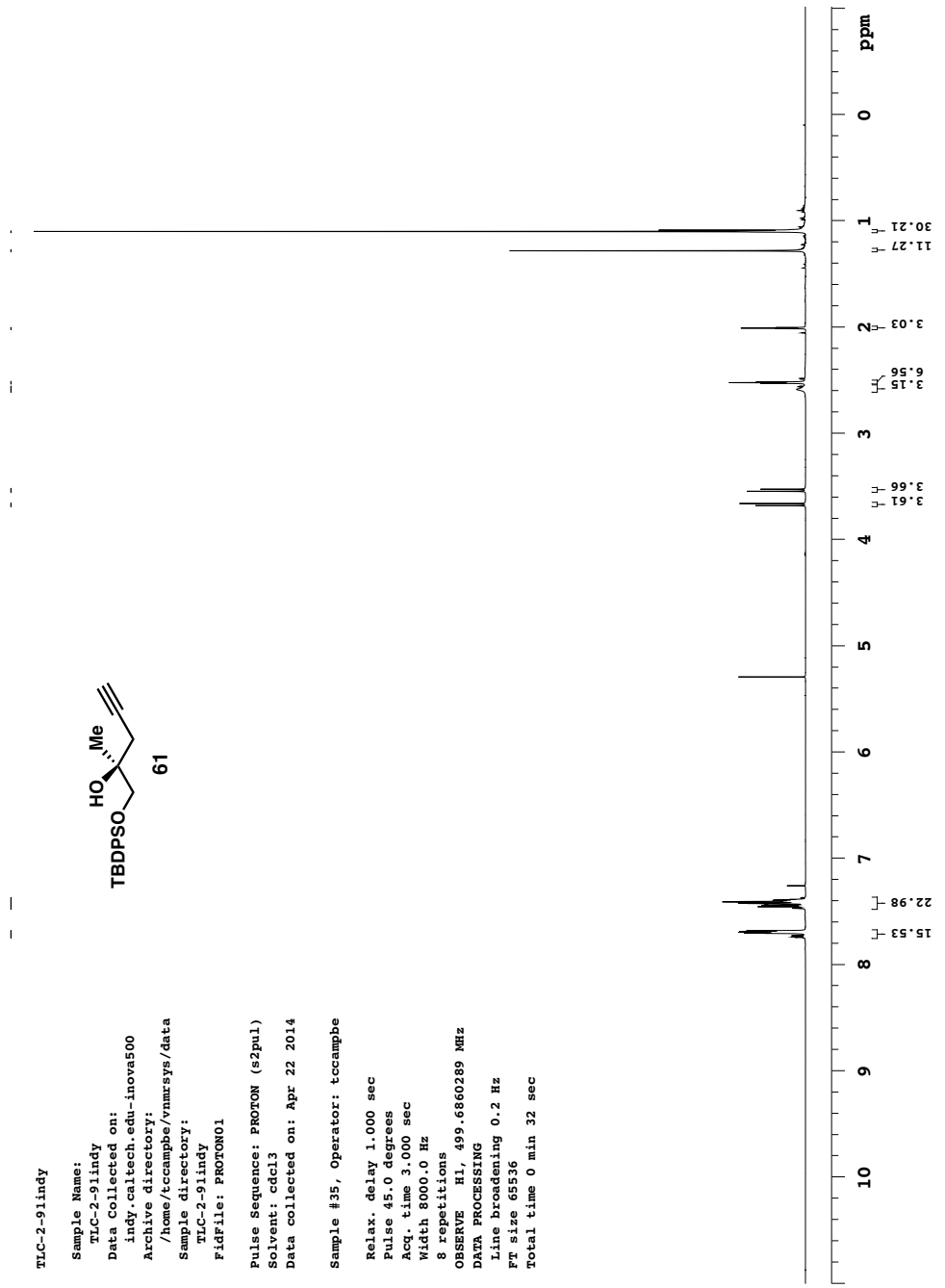
60
40
20
0
ppm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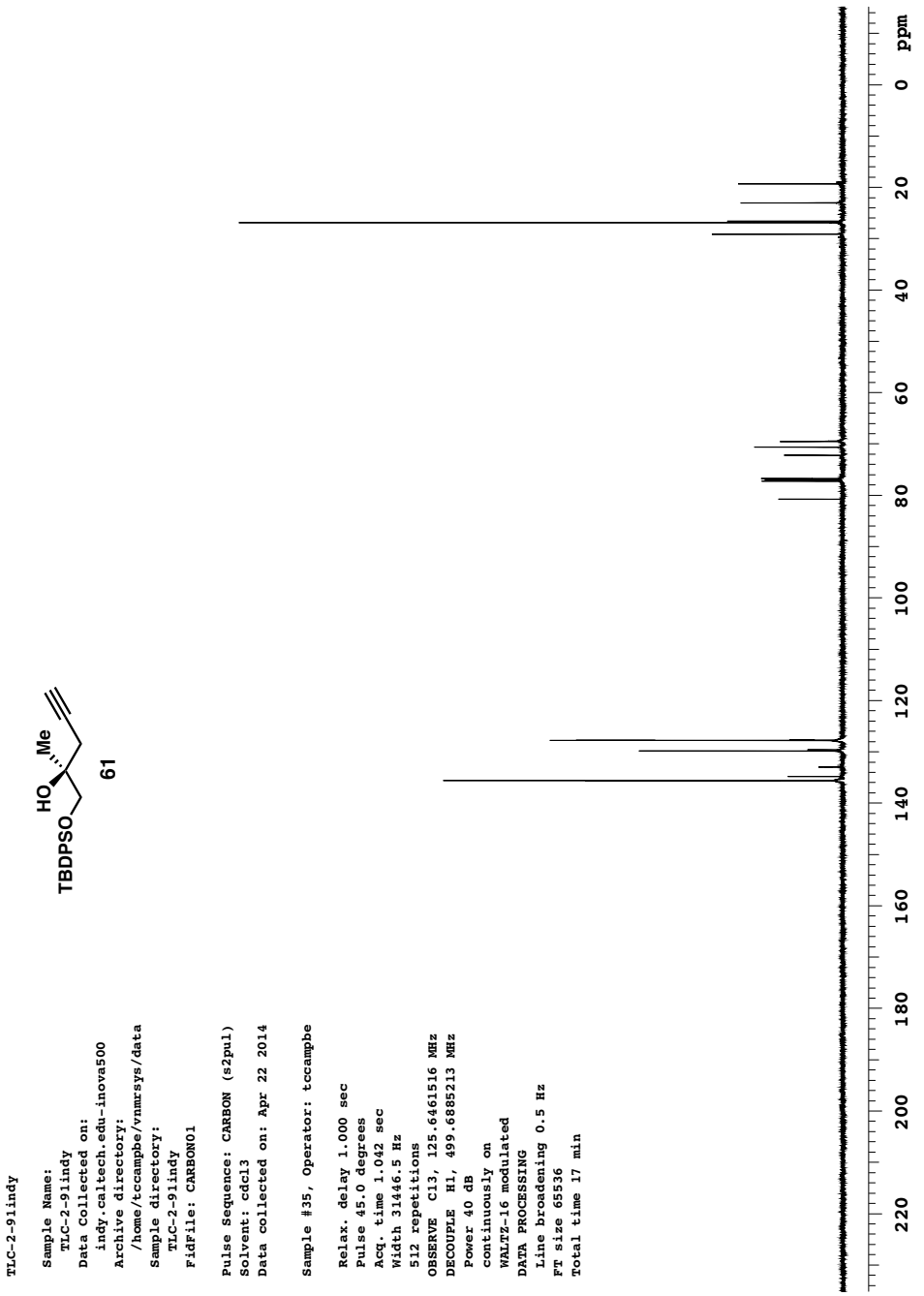
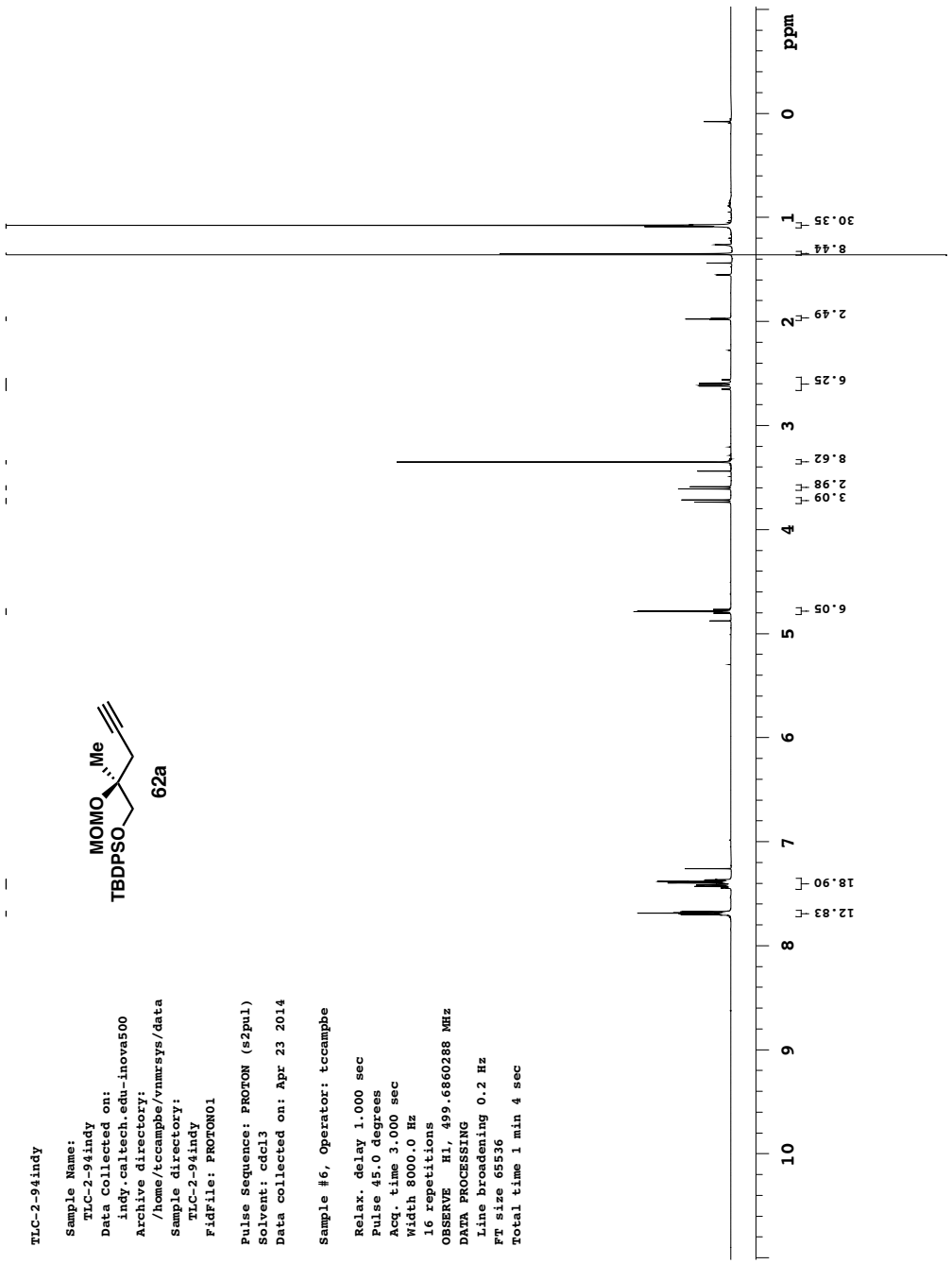
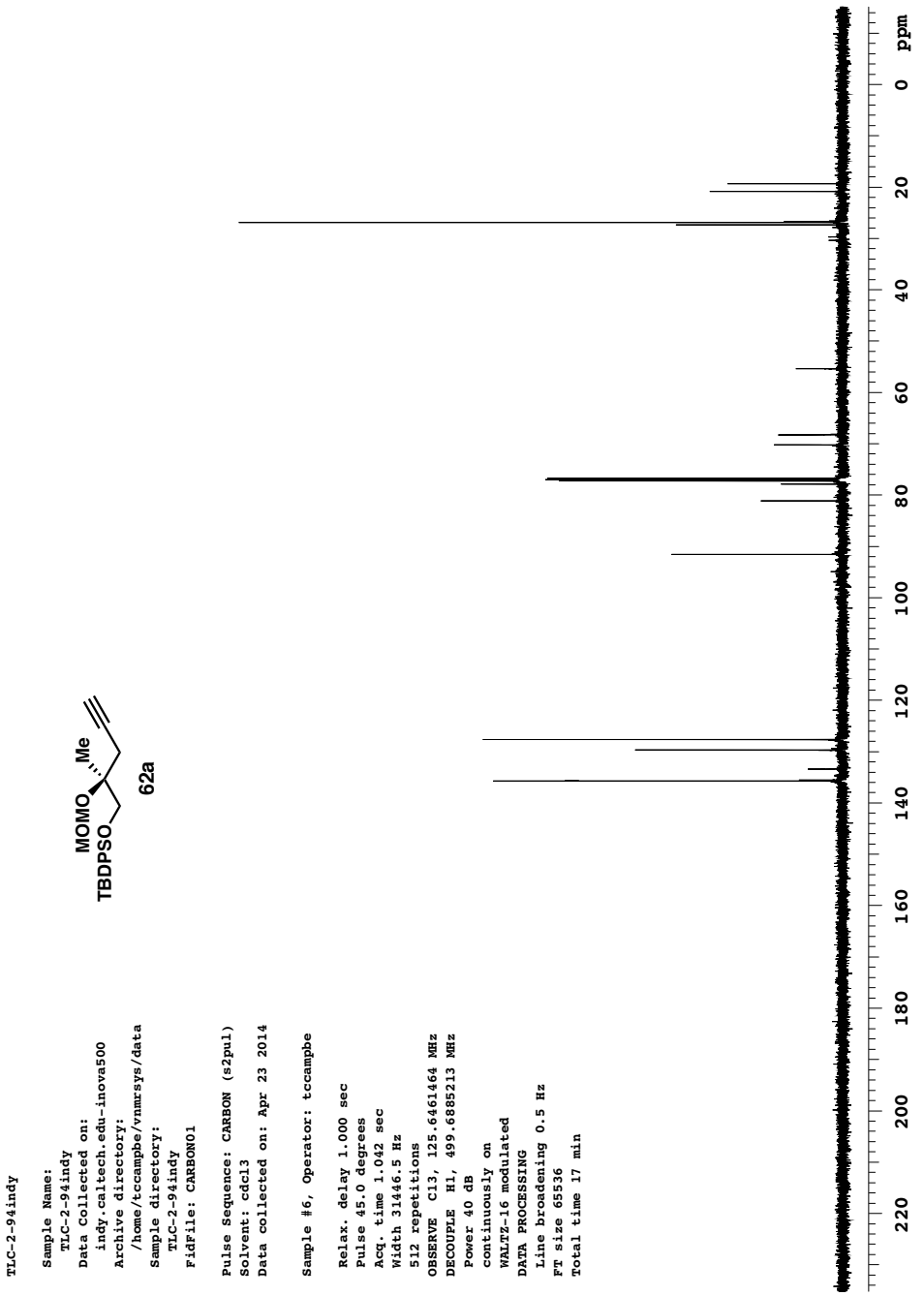
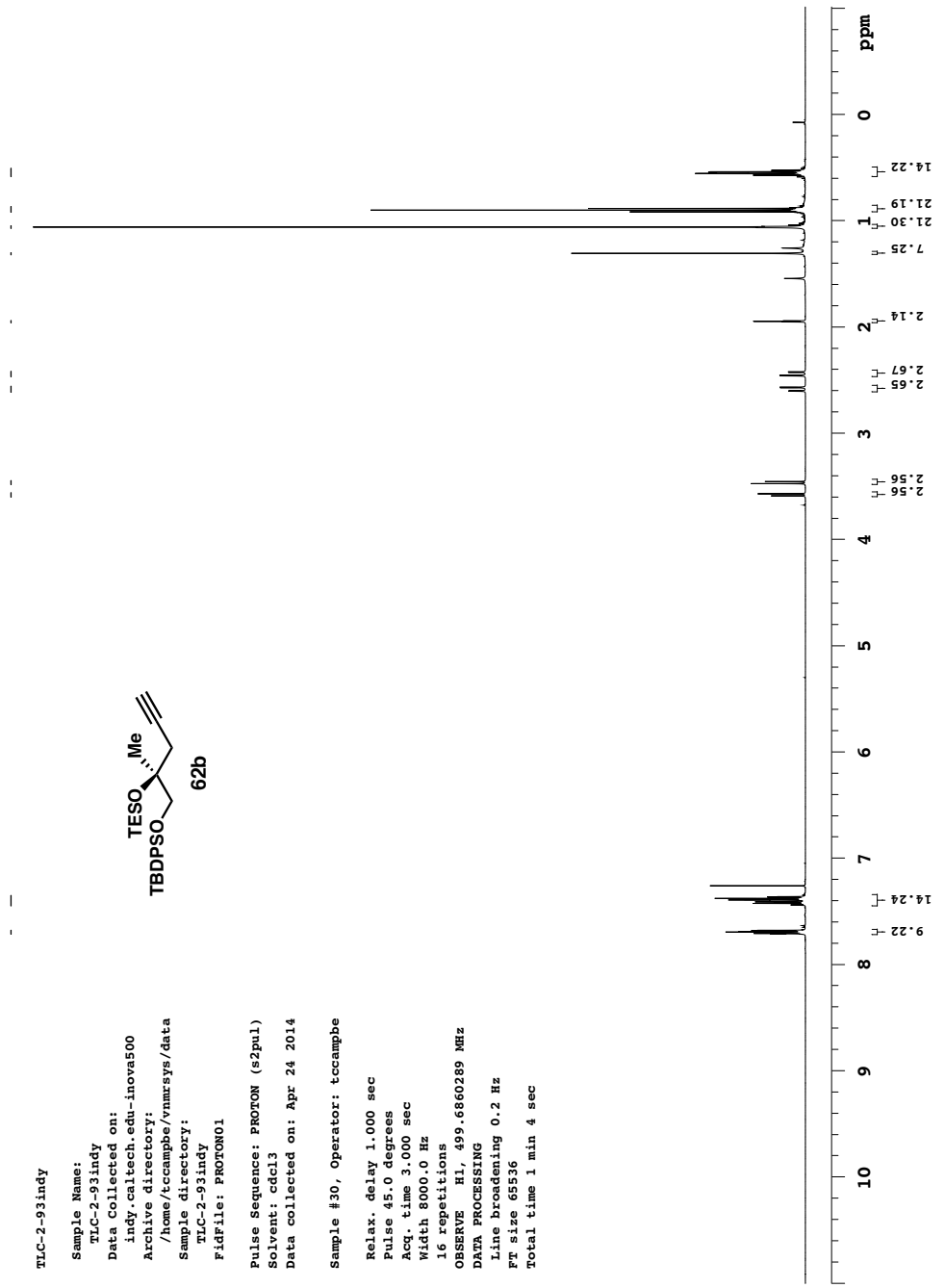
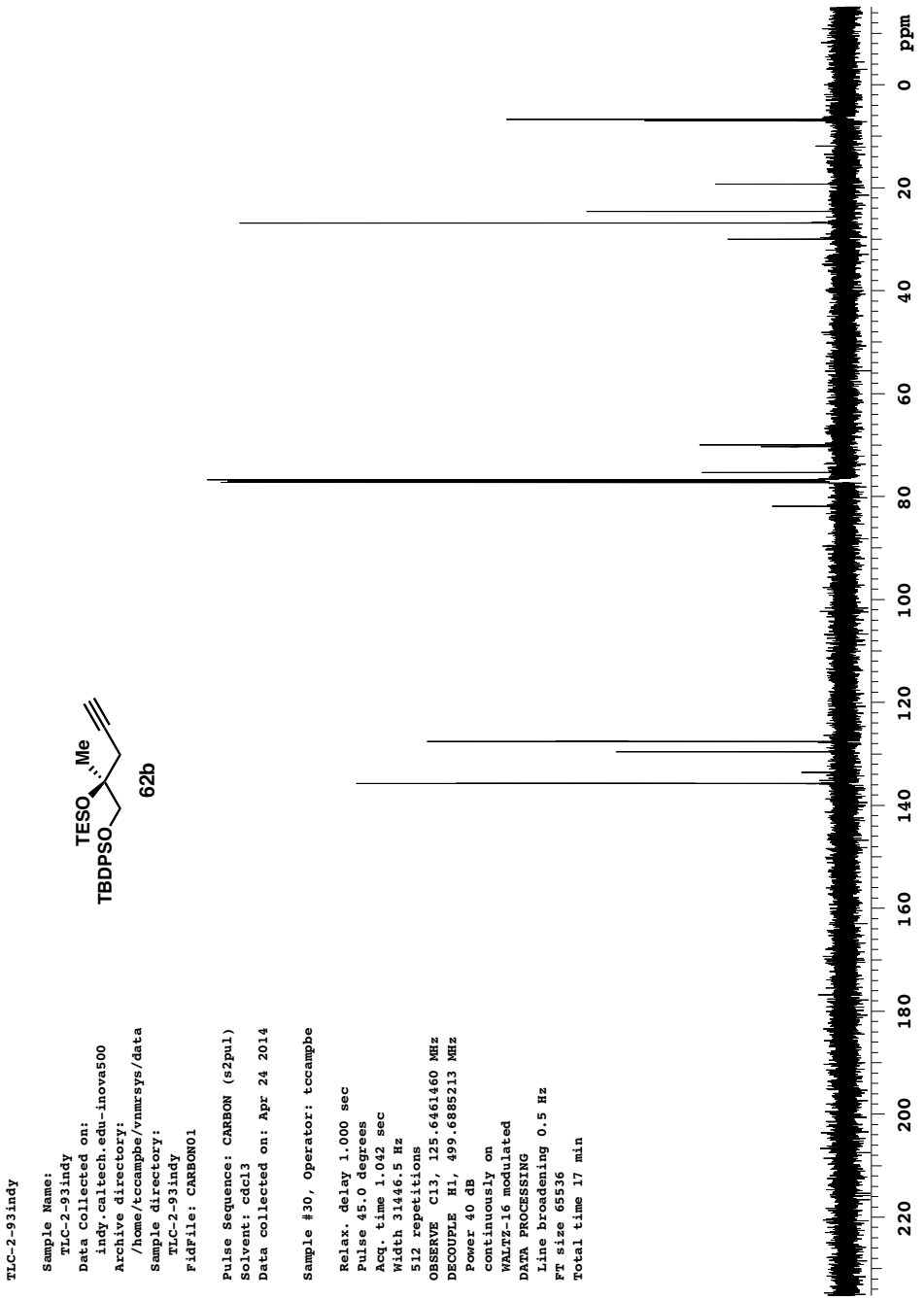
Solvent: cdcl3
Data collected on: Apr 22 2014
Sample #35, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6860289 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec
HO
Me
TBDPSO
61
ppm
30.21
11.27
3.03
6.56
3.15
3.66
3.61
22.98
15.53

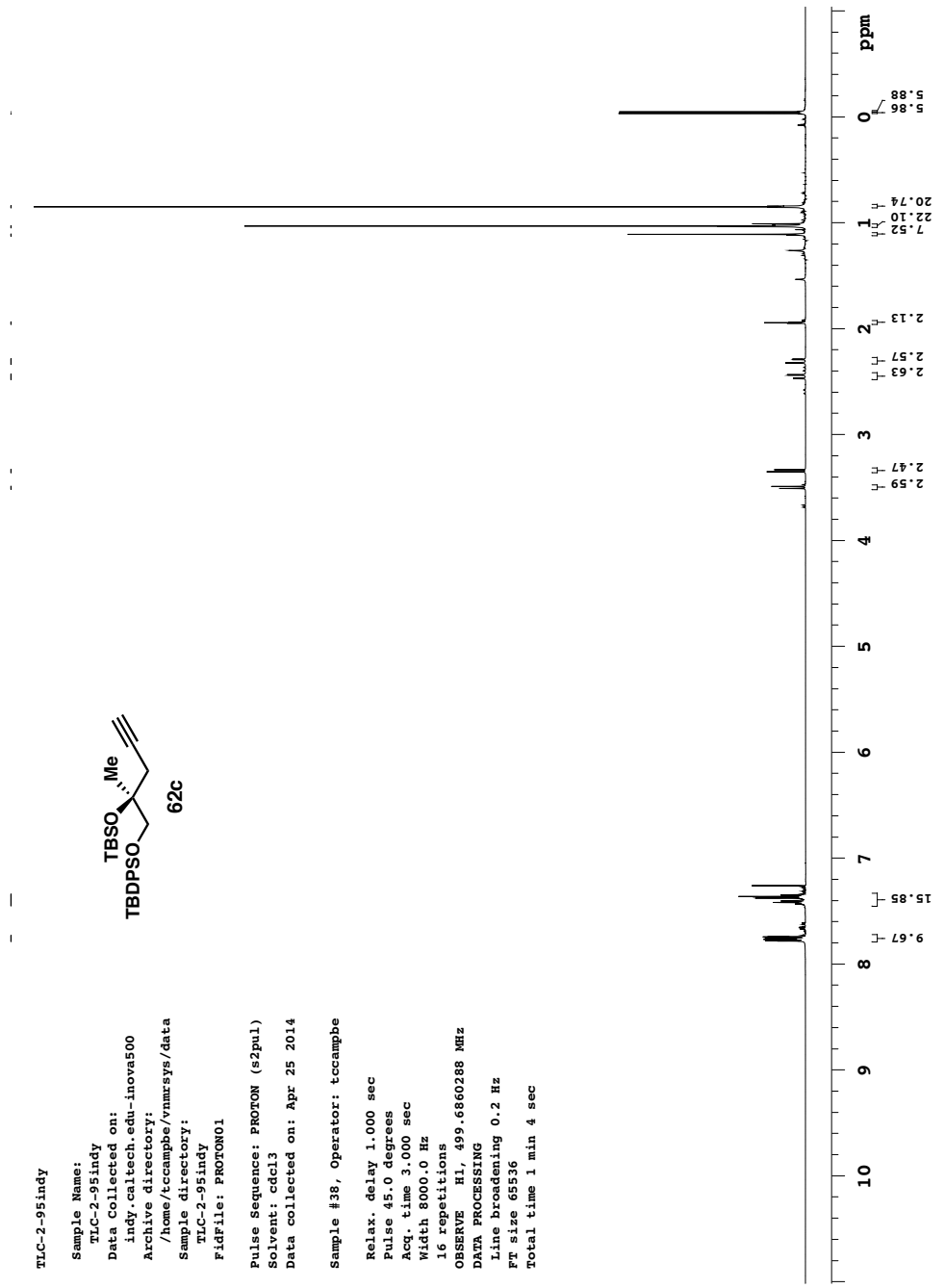

TLC-2-91indy
Sample Name:
TLC-2-91indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-91indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 22 2014
Sample #35, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461516 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
HO
Me
TBDPSO
61
220
200
180
160
140
120
100
80
60
40
20
0
ppm

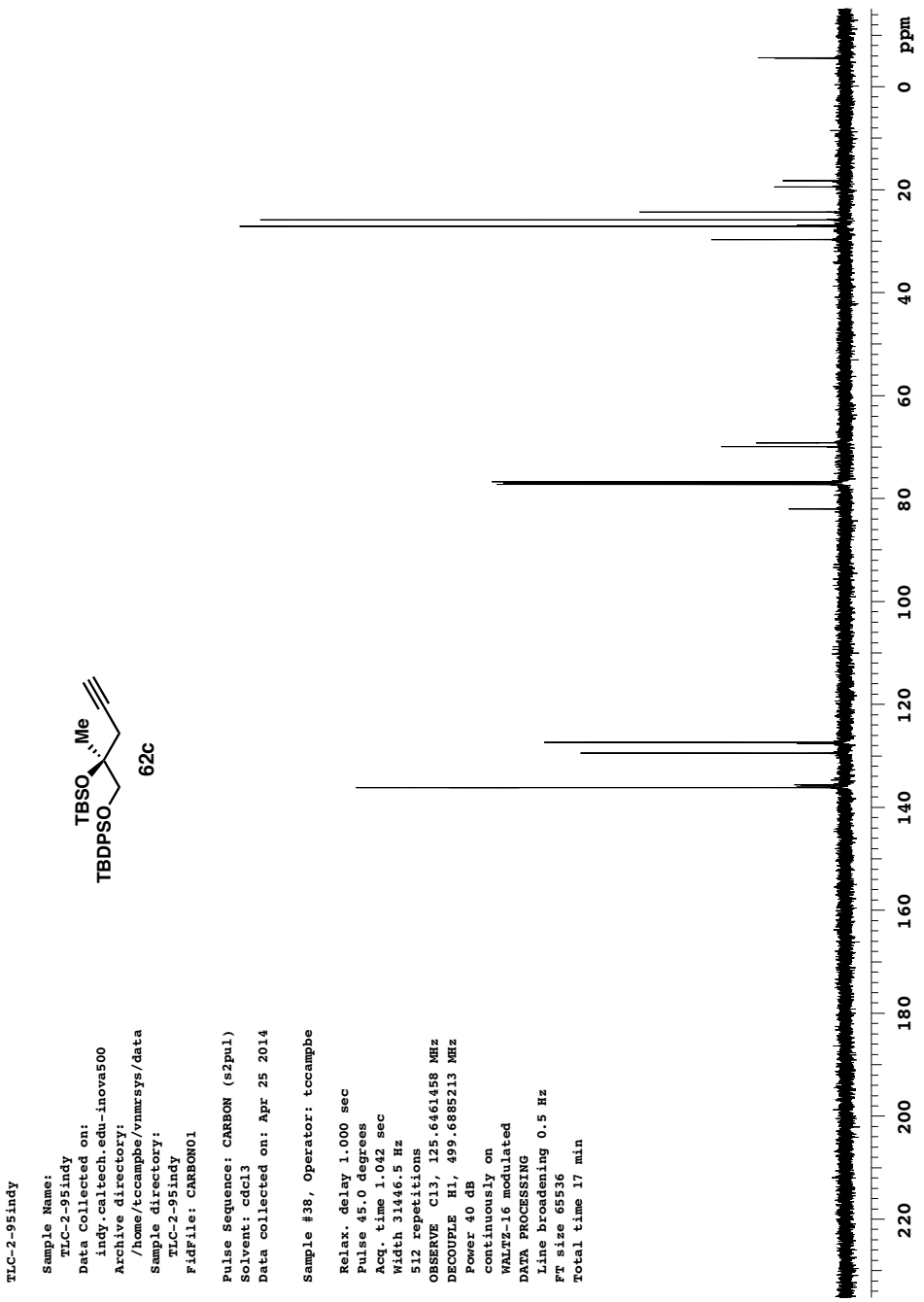

TLC-2-94indy
Sample Name:
TLC-2-94indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-94indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 23 2014
Sample #6, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6860288 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
MOMO
Me
TBDPSO
62a
30.35
8.44
2.49
6.25
8.62
2.98
3.09
6.05
18.90
12.83
ppm

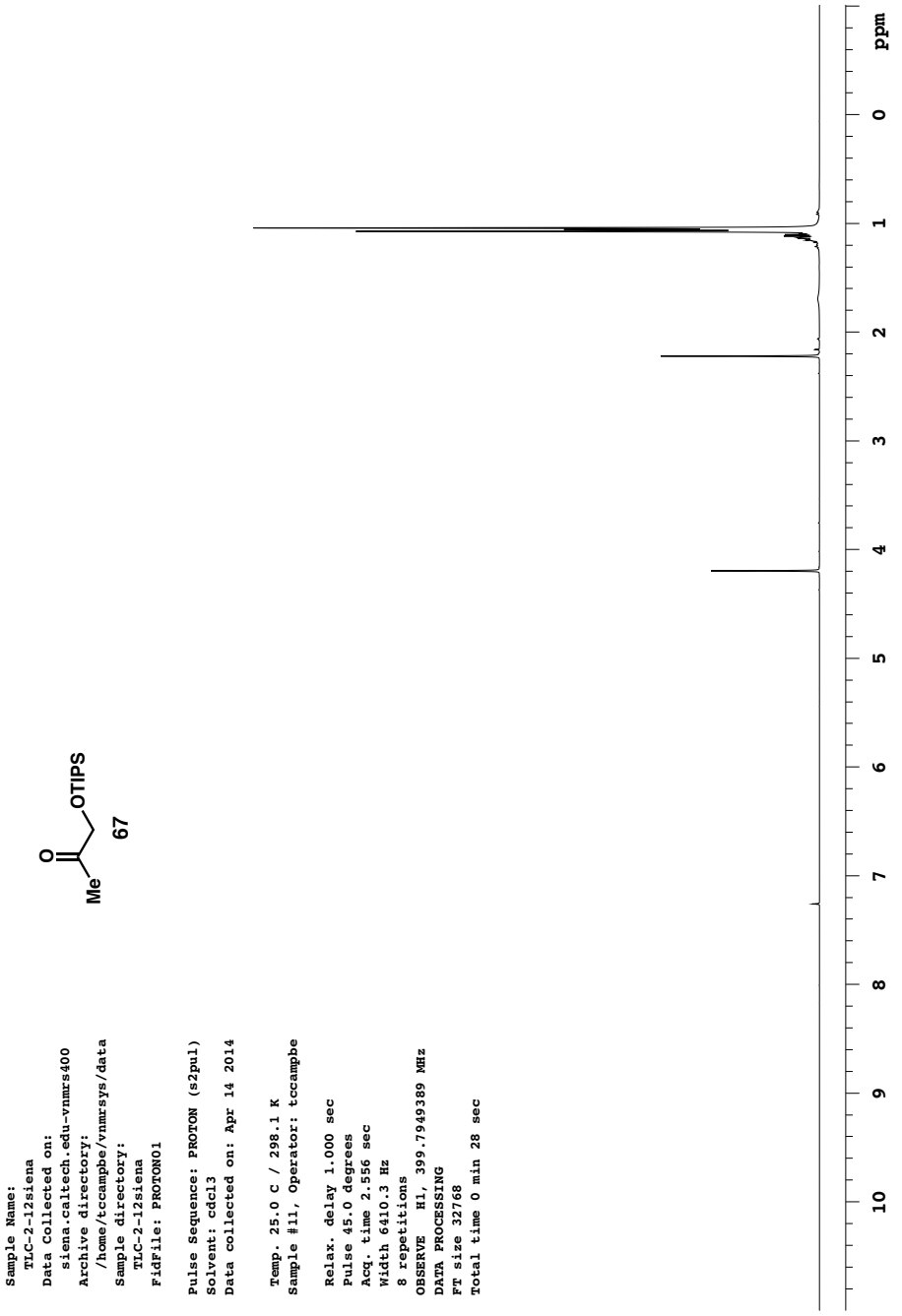

TLC-2-94indy
Sample Name:
TLC-2-94indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-94indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 23 2014
Sample #6, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461464 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
MOMO
Me
TBDPSO
62a
220
200
180
160
140
120
100
80
60
40
20
0
ppm

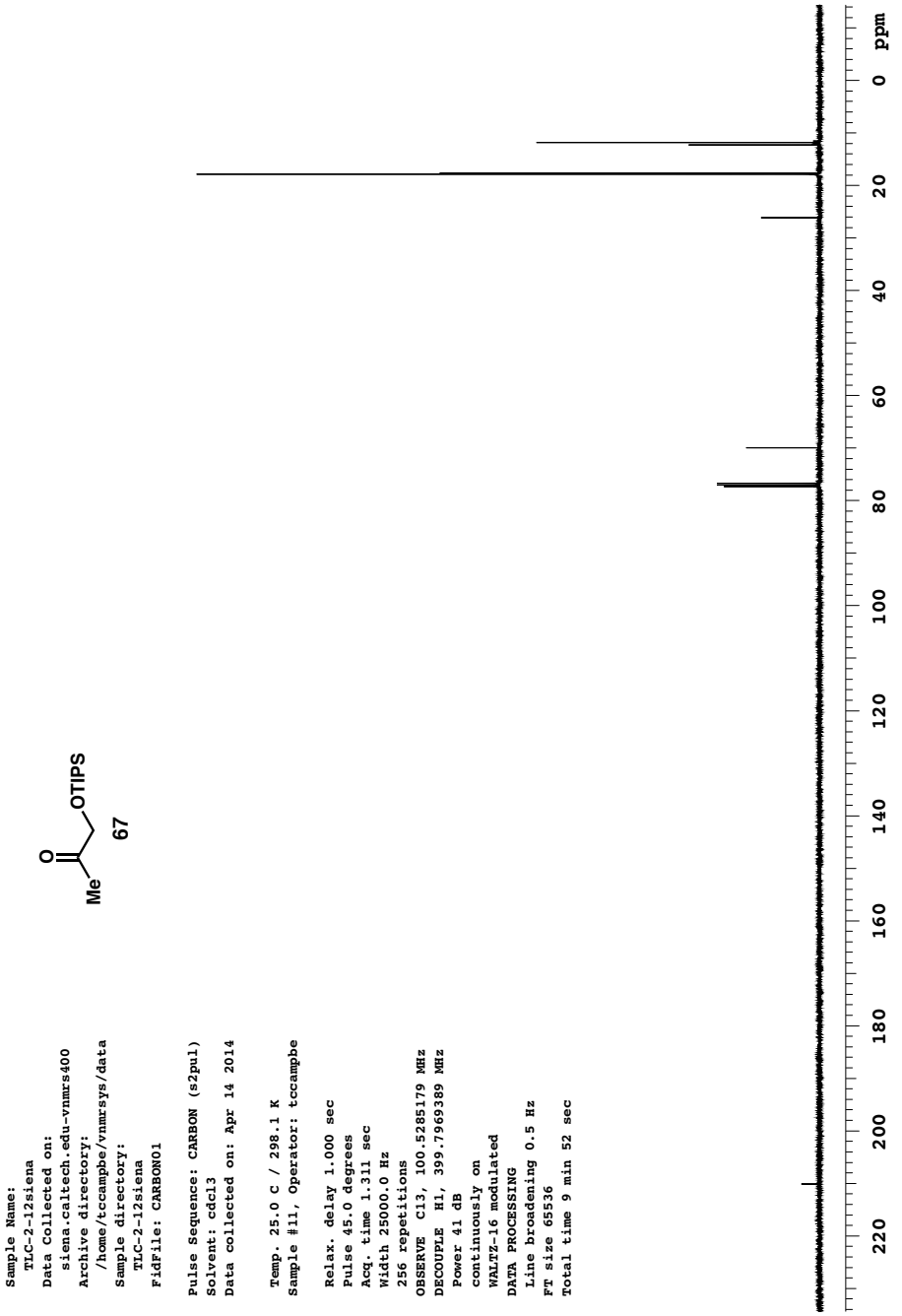

TLC-2-93indy
Sample Name:
TLC-2-93indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-93indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 24 2014
Sample #30, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6860289 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
TESO
Me
TBDPSO
62b
9.22
14.24
7.25
2.56
2.56
2.65
2.67
2.14
21.30
21.19
14.22
10
9
8
7
6
5
4
3
2
1
0
ppm

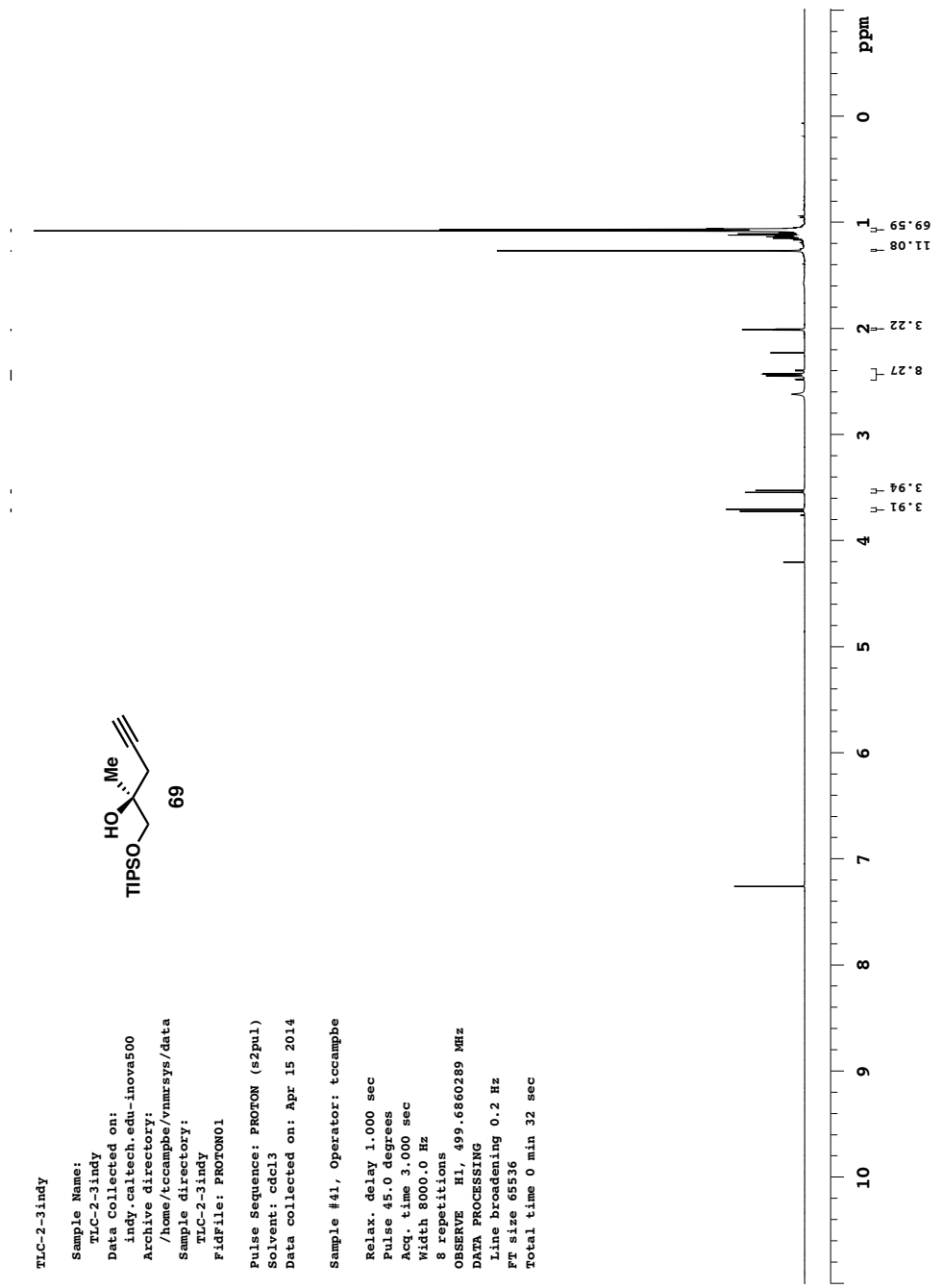

TLC-2-93indy
Sample Name:
TLC-2-93indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-93indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 24 2014
Sample #30, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461460 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
TESO
Me
TBDPSO
62b
220
200
180
160
140
120
100
80
60
40
20
0
ppm

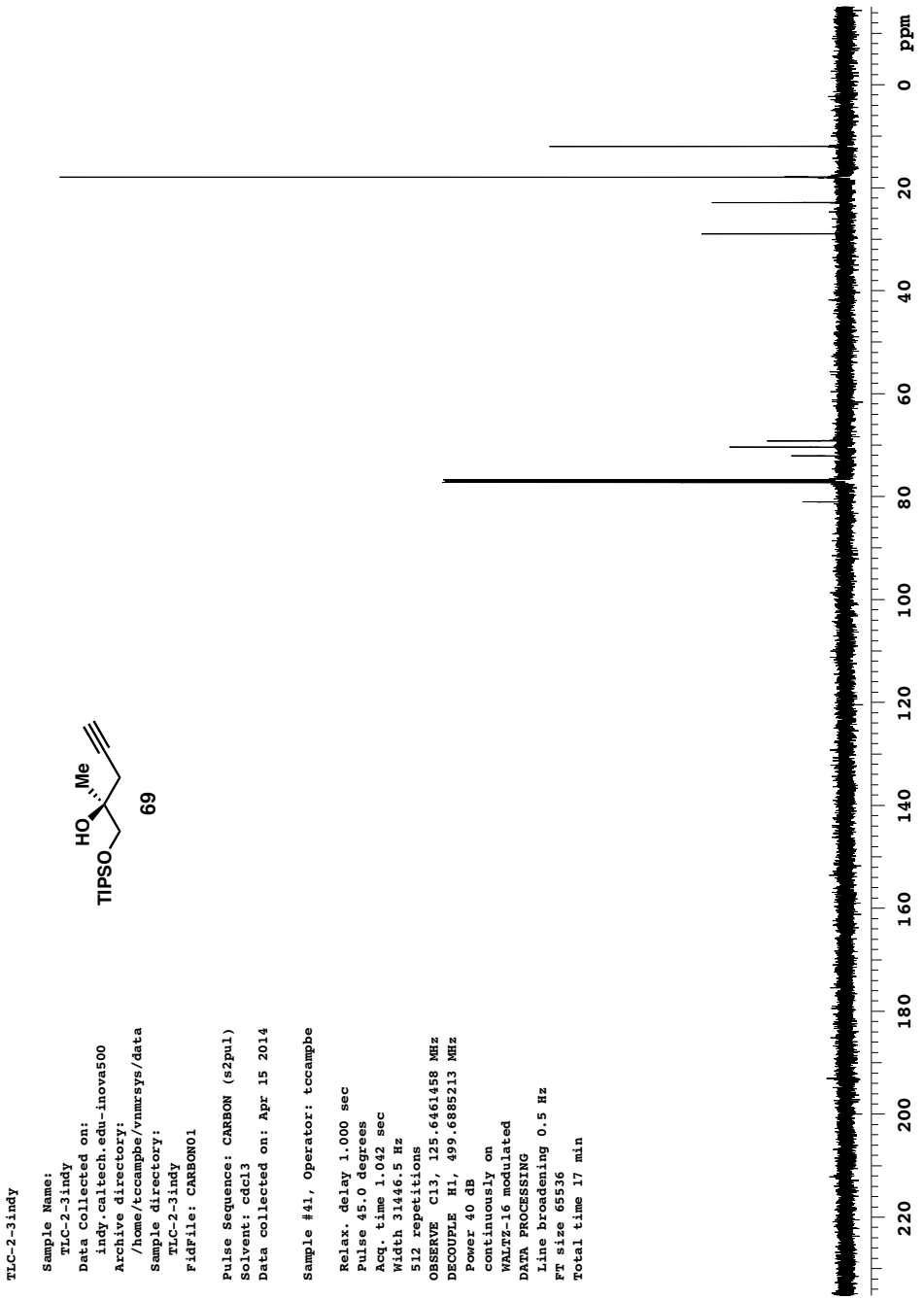

TLC-2-95indy
Sample Name:
TLC-2-95indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-95indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 25 2014
Sample #38, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6860288 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
TBSO
Me
TBDPSO
62c
9.67
15.85
7.52
22.10
20.74
2.13
2.63
2.57
2.59
2.47
5.86
5.88
ppm

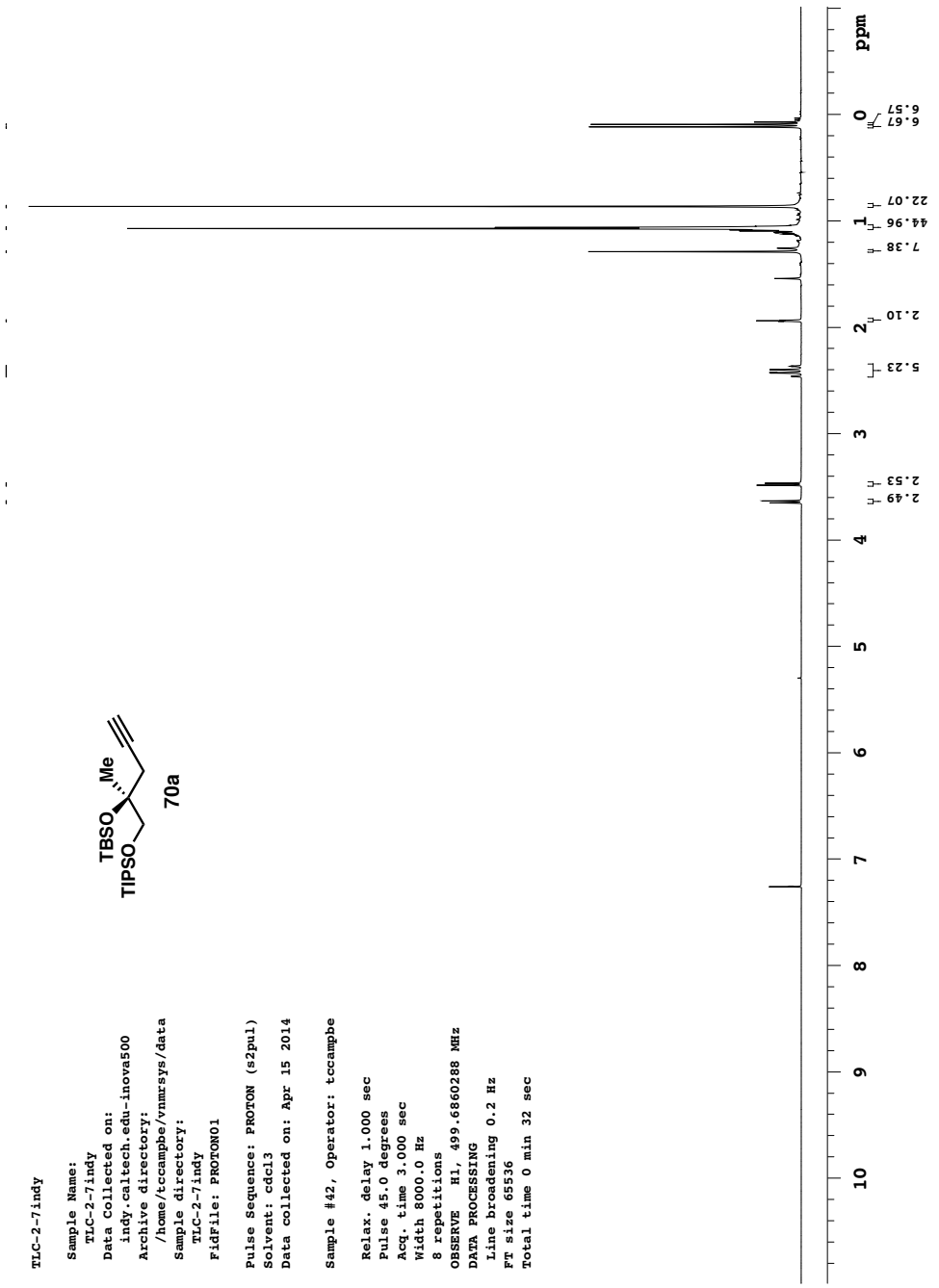

TLC-2-95indy
Sample Name:
TLC-2-95indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-95indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 25 2014
Sample #38, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461458 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
TBSO
Me
TBDPSO
62c
220
200
180
160
140
120
100
80
60
40
20
0
ppm

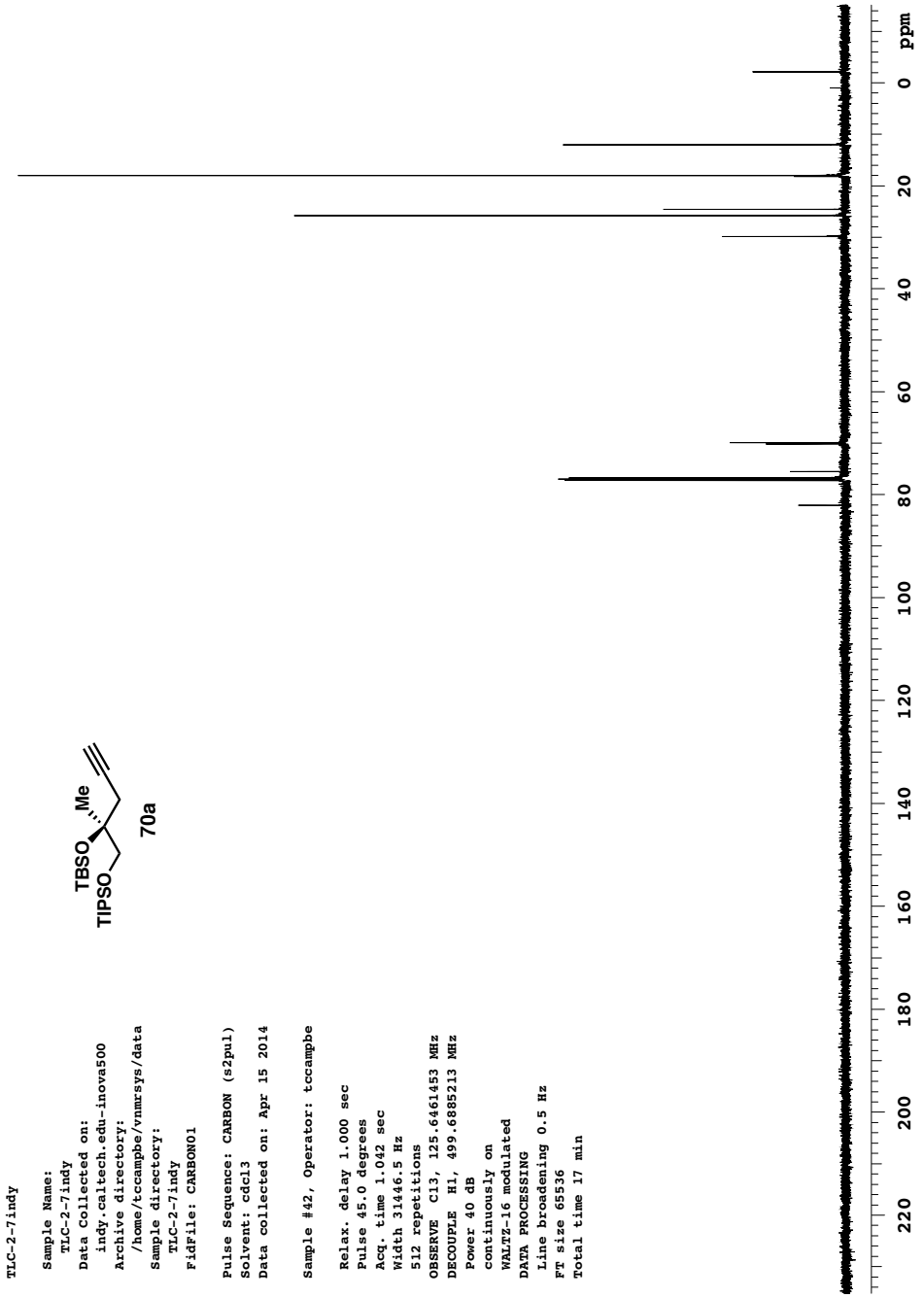

Sample Name:
TLC-2-12siena
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-12siena
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 14 2014
Temp. 25.0 C / 298.1 K
Sample #11, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7949389 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
O
OTIPS
Me
67
10
9
8
7
6
5
4
3
2
1
0
ppm

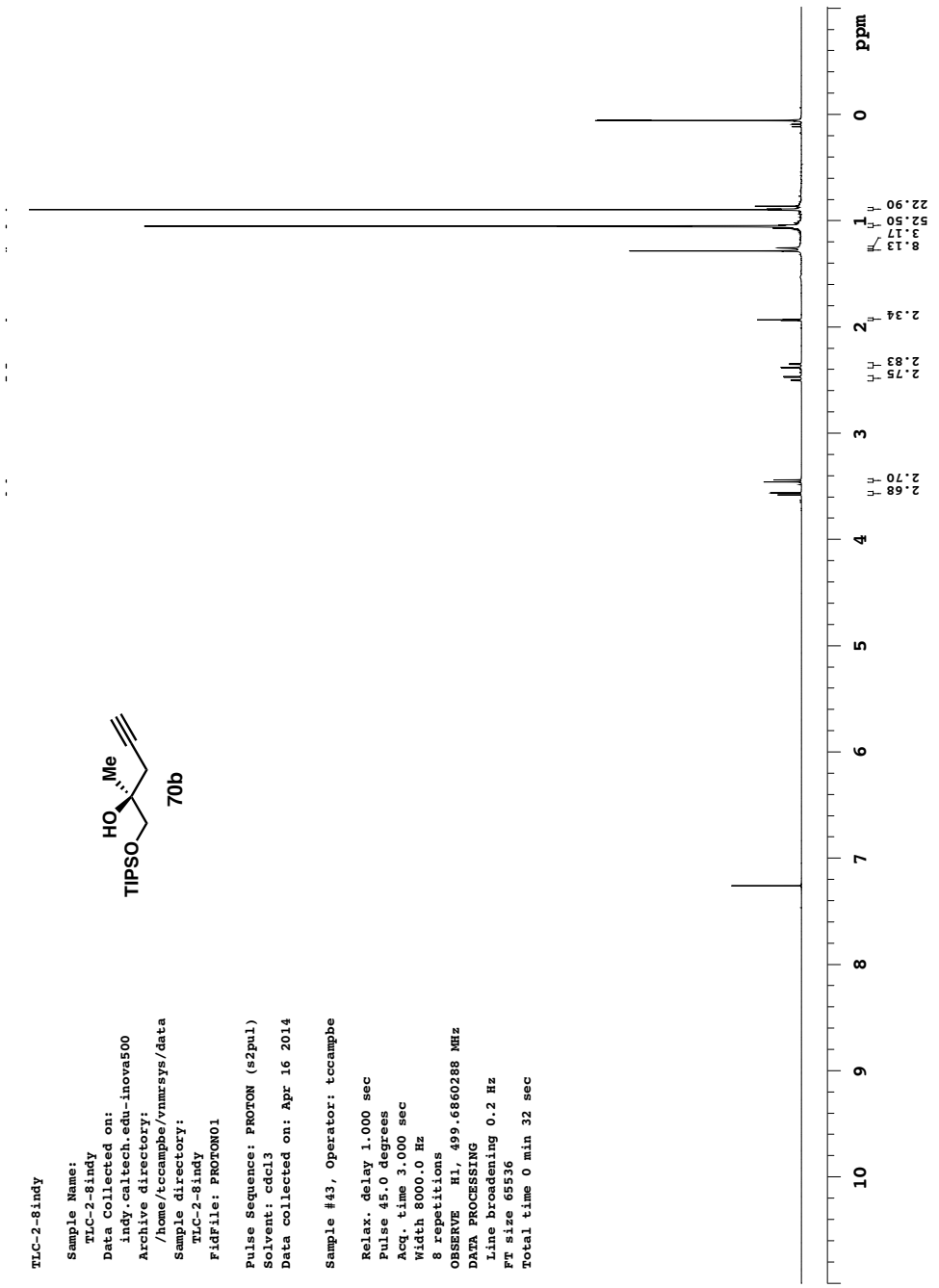

Sample Name:
TLC-2-12siena
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-12siena
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 14 2014
Temp. 25.0 C / 298.1 K
Sample #11, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
256 repetitions
OBSERVE C13, 100.5285179 MHz
DECOUPLE H1, 399.7969389 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 9 min 52 sec
O
OTIPS
Me
67
220
200
180
160
140
120
100
80
60
40
20
0
ppm

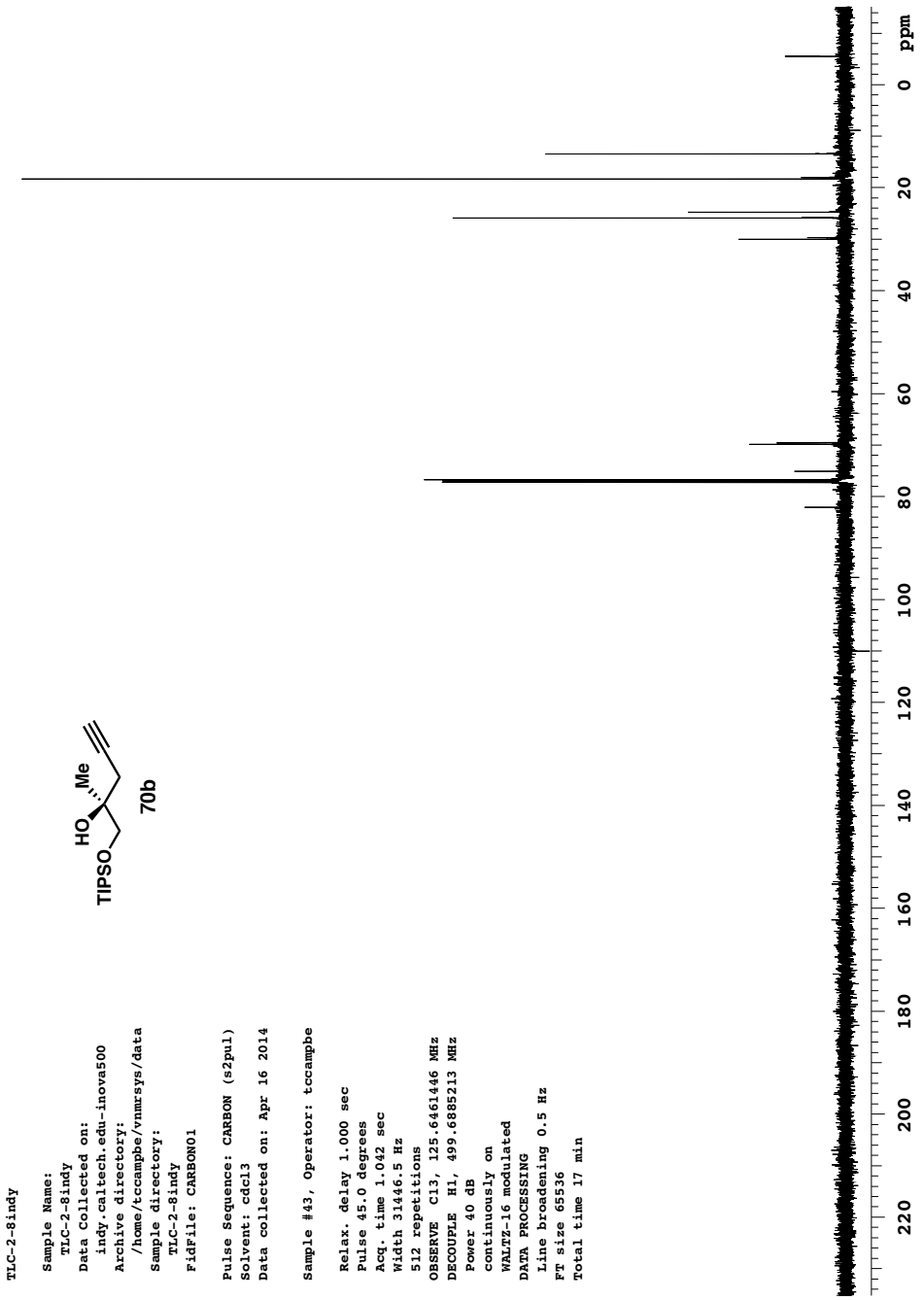

TLC-2-3indy
Sample Name:
TLC-2-3indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-3indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 15 2014
Sample #41, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6860289 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec
HO
Me
TIPSO
69
69.59
11.08
3.22
8.27
3.94
3.91
ppm

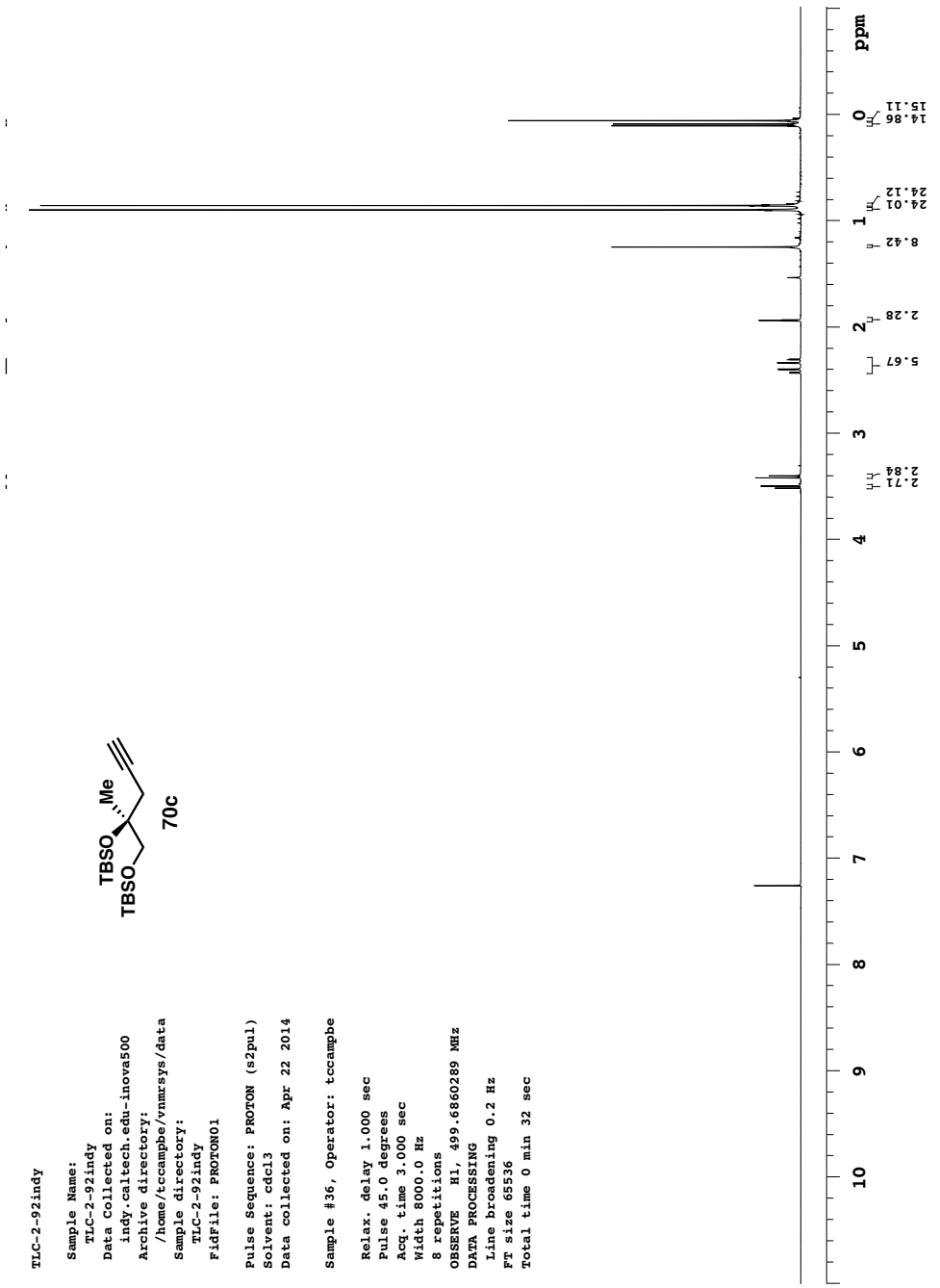

TLC-2-3indy
Sample Name:
TLC-2-3indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-3indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 15 2014
Sample #41, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461458 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
HO
Me
TIPSO
69
220
200
180
160
140
120
100
80
60
40
20
0
ppm

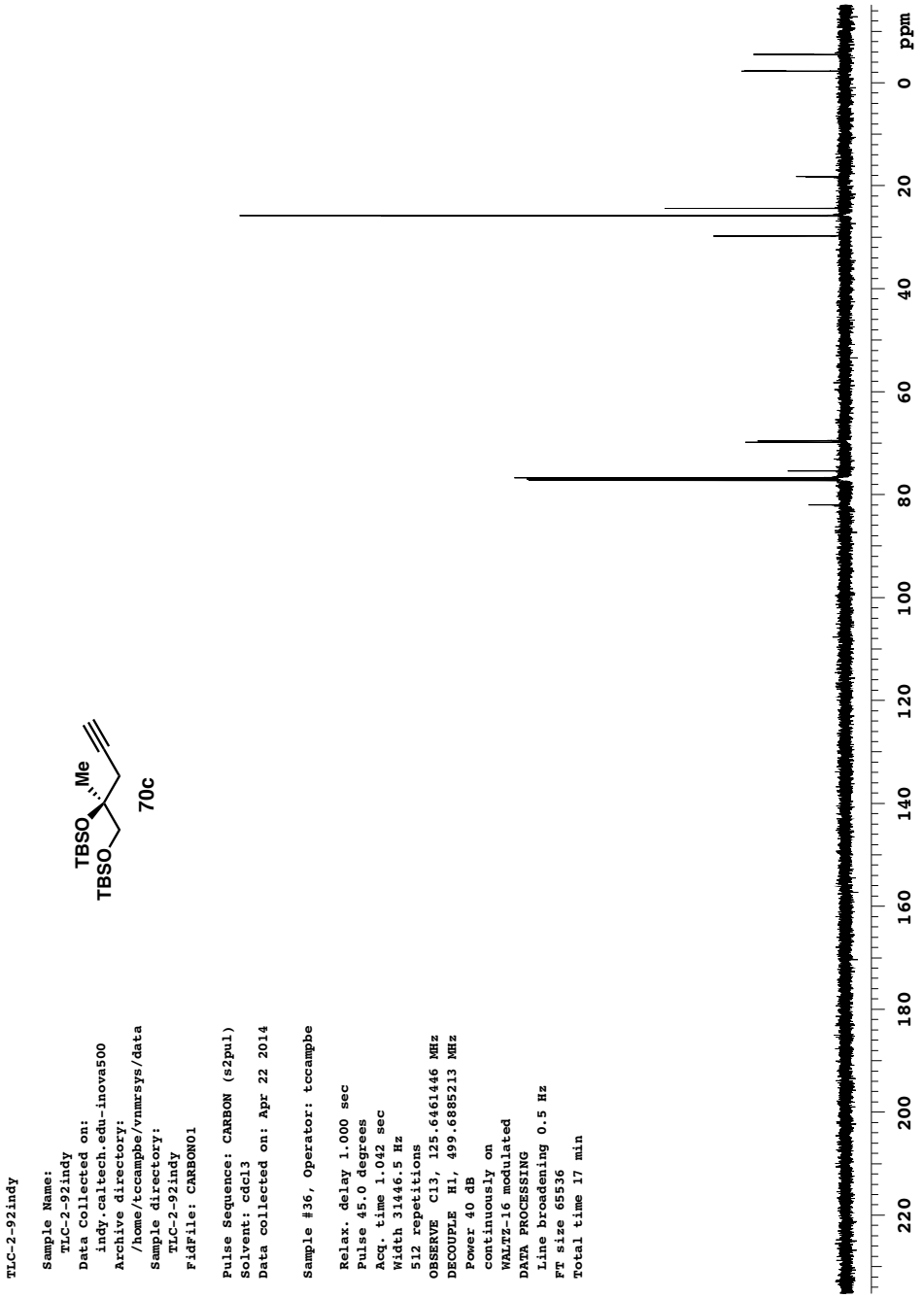

TLC-2-7indy
Sample Name:
TLC-2-7indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-7indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 15 2014
Sample #42, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6860288 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec
TBSO
Me
TIPSO
70a
ppm
6.67
6.57
22.07
44.96
7.38
2.10
5.23
2.53
2.49

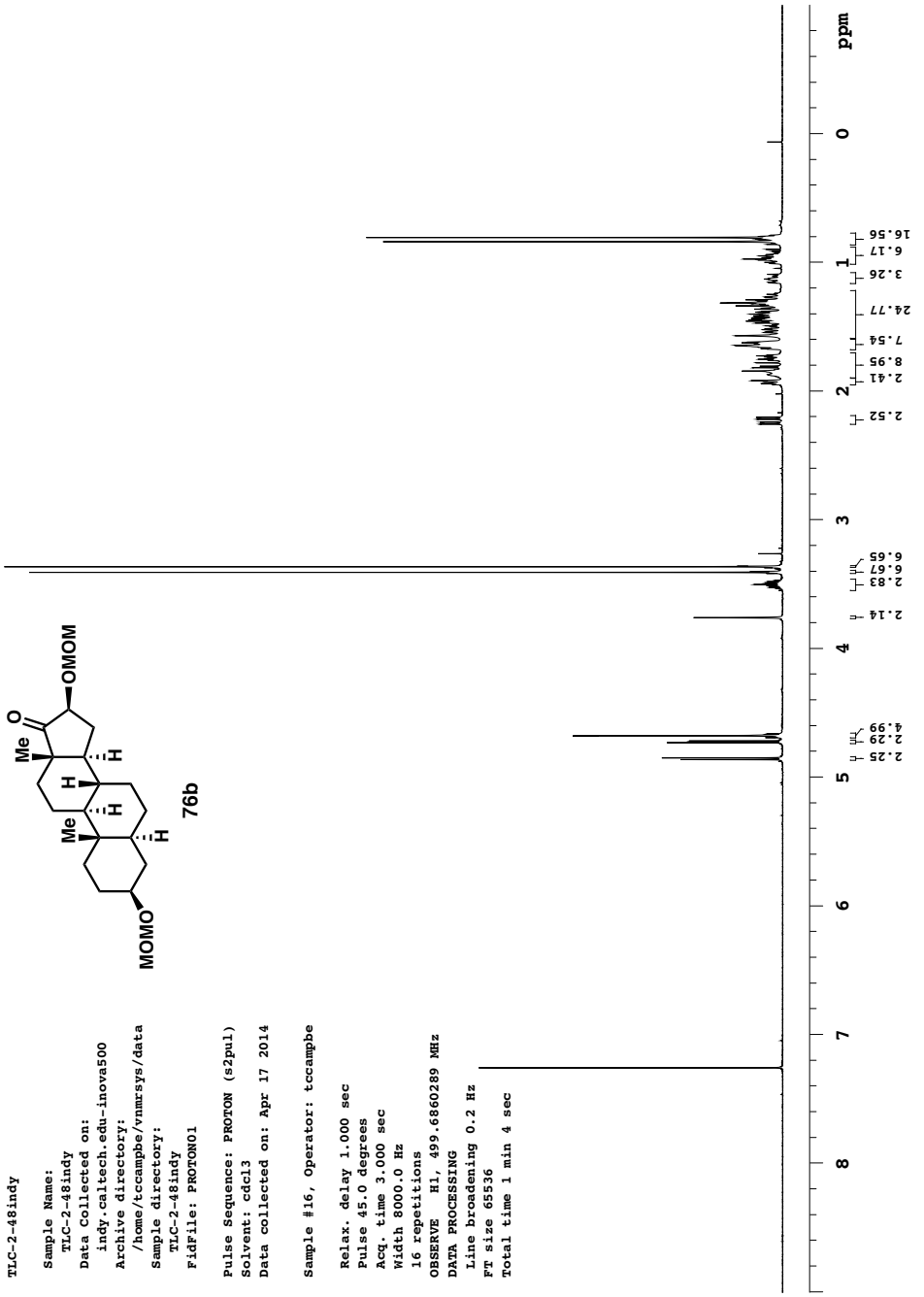

TLC-2-7indy
Sample Name:
TLC-2-7indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-7indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 15 2014
Sample #42, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461453 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
TBSO
Me
TIPSO
70a
220
200
180
160
140
120
100
80
60
40
20
0
ppm

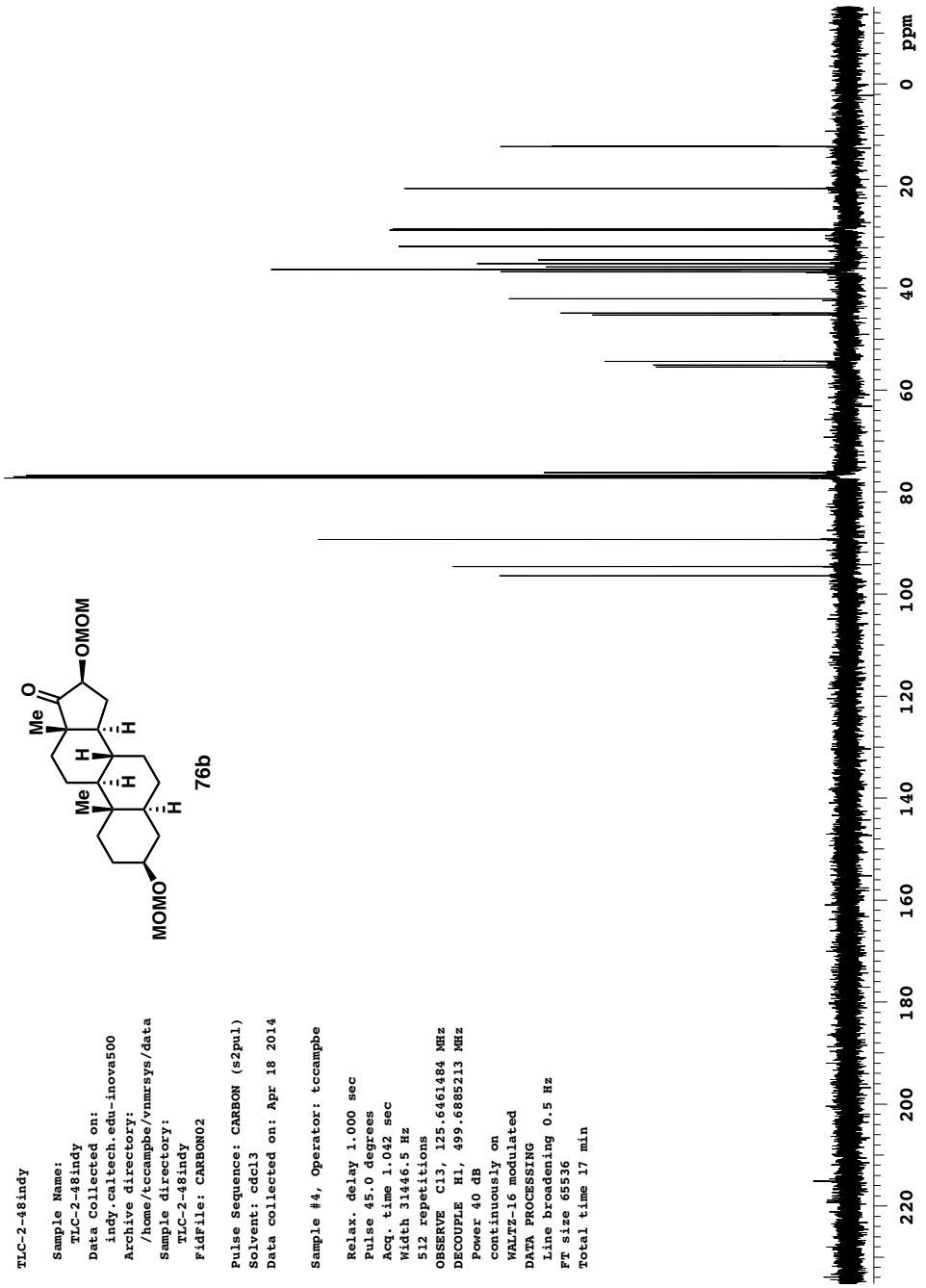

TLC-2-8indy
Sample Name:
TLC-2-8indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-8indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #43, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6860288 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec
HO
Me
TIPSO
70b
8.13
3.17
52.50
22.90
2.34
2.75
2.83
2.68
2.70
10
9
8
7
6
5
4
3
2
1
0
ppm

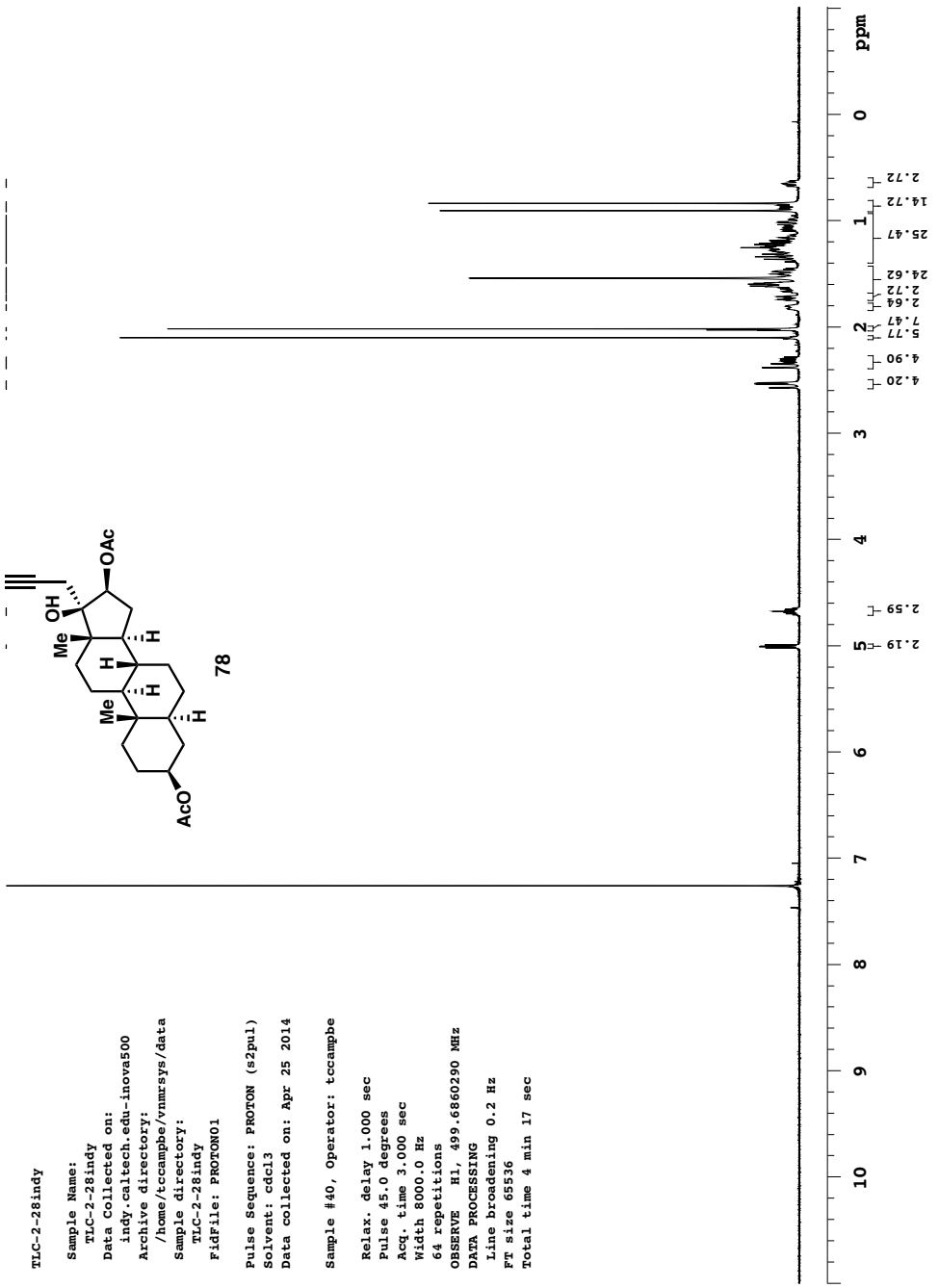

TLC-2-8indy
Sample Name:
TLC-2-8indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-8indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #43, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461446 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
HO
Me
TIPSO
70b
220
200
180
160
140
120
100
80
60
40
20
0
ppm

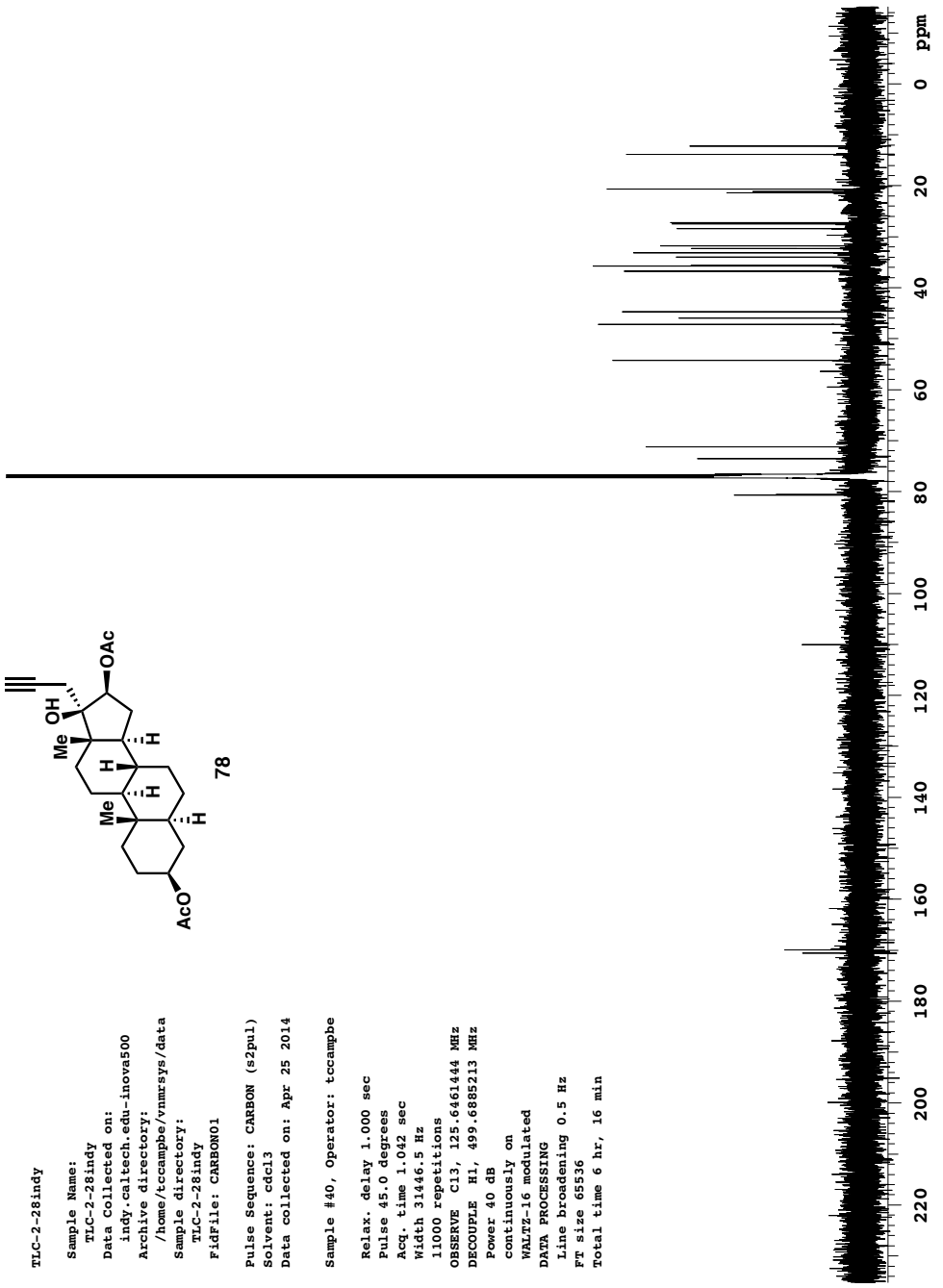

TLC-2-92indy
Sample Name:
TLC-2-92indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-92indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 22 2014
Sample #36, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6860289 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec
TBSO
Me
TBSO
70c
2.71
2.84
5.67
2.28
8.42
24.01
24.12
14.86
15.11
ppm

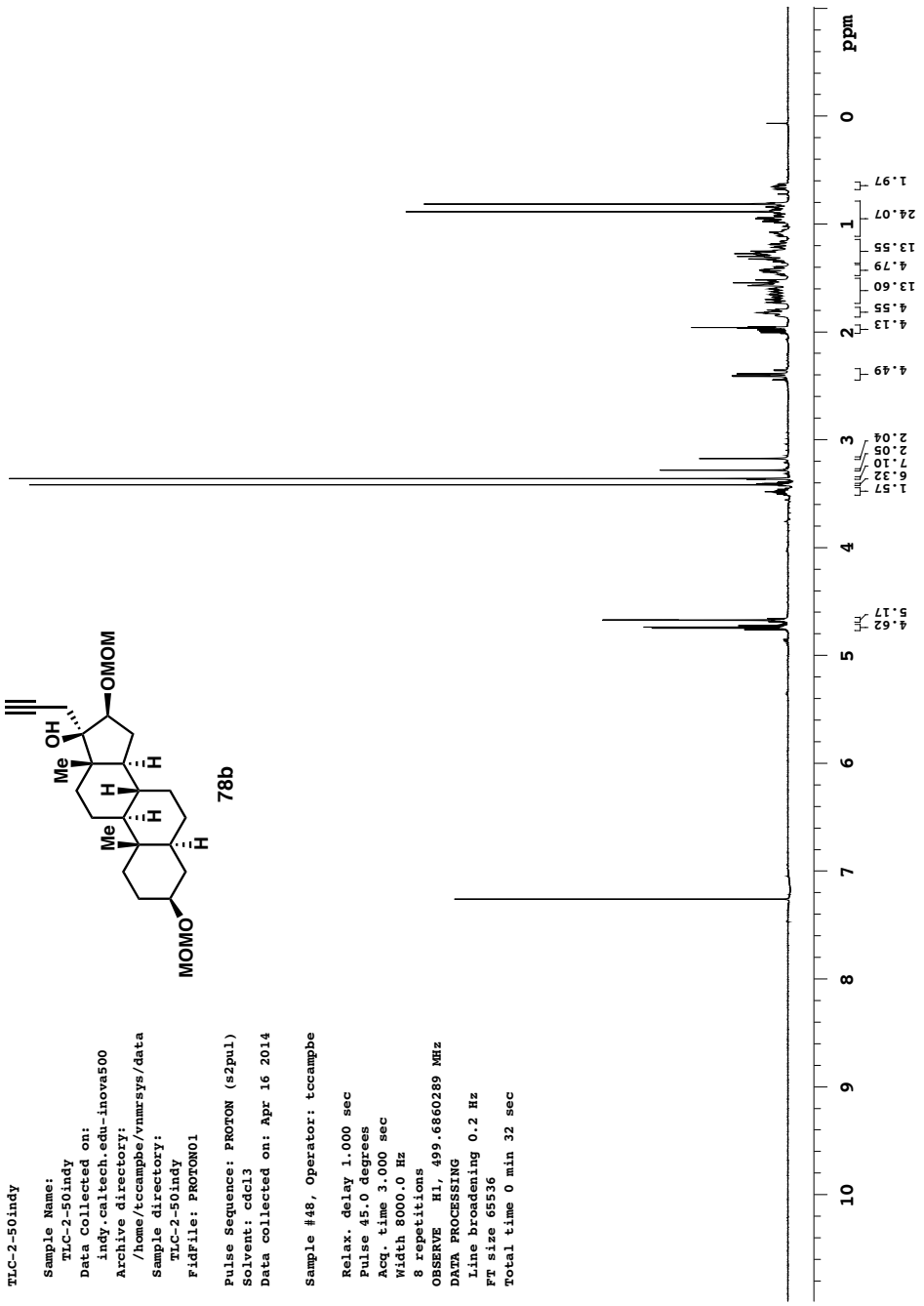

TLC-2-92indy
Sample Name:
TLC-2-92indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-92indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 22 2014
Sample #36, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461446 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
TBSO
Me
TBSO
70c
220
200
180
160
140
120
100
80
60
40
20
0
ppm

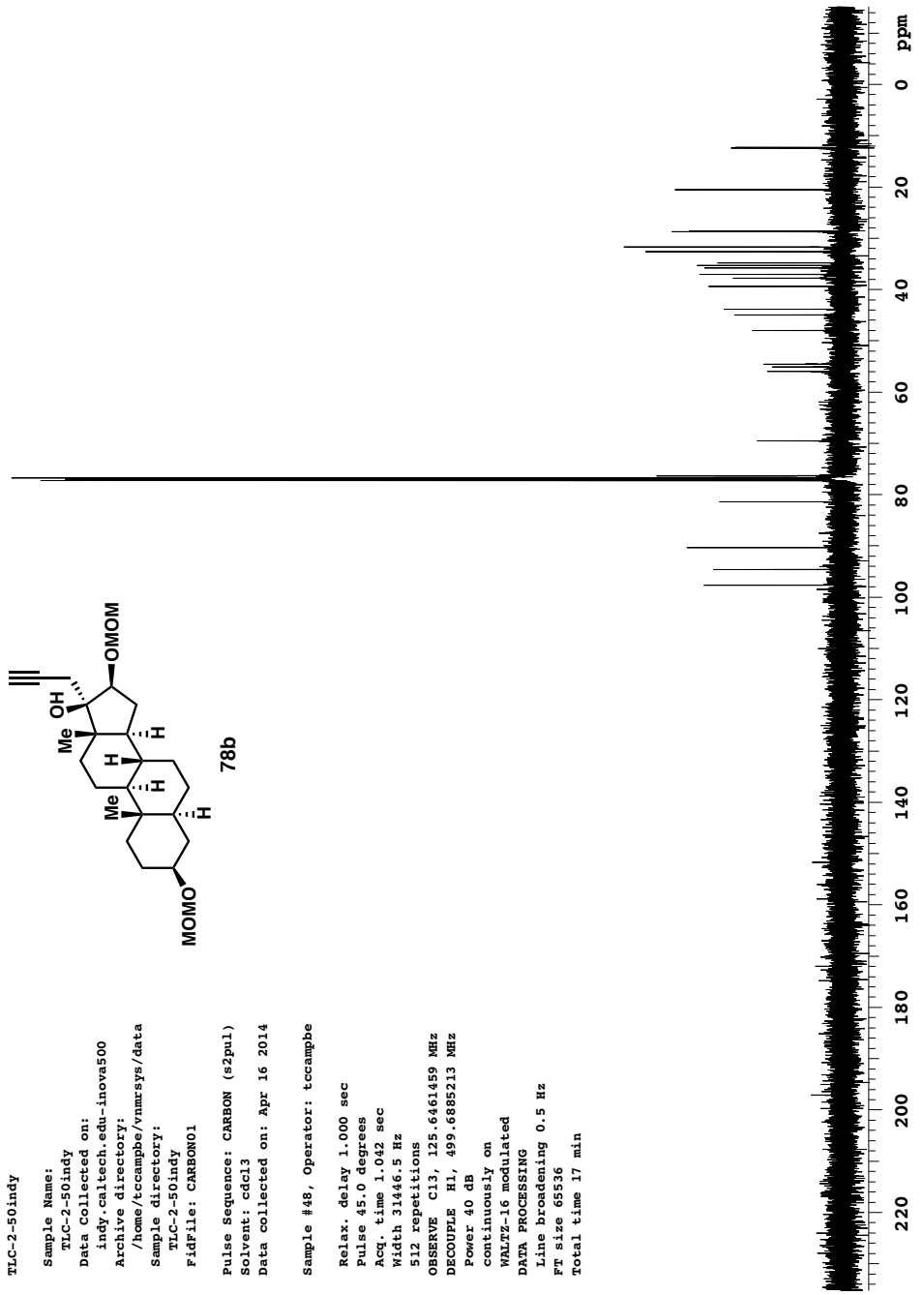

TLC-2-48indy
Sample Name:
TLC-2-48indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-48indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 17 2014
Sample #16, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6860289 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
Me
O
OMOM
H
H
H
Me
H
MOMO
76b
2.25
2.29
4.99
2.14
2.83
6.67
6.65
2.52
2.41
8.95
7.54
24.77
3.26
6.17
16.56
8
7
6
5
4
3
2
1
0
ppm

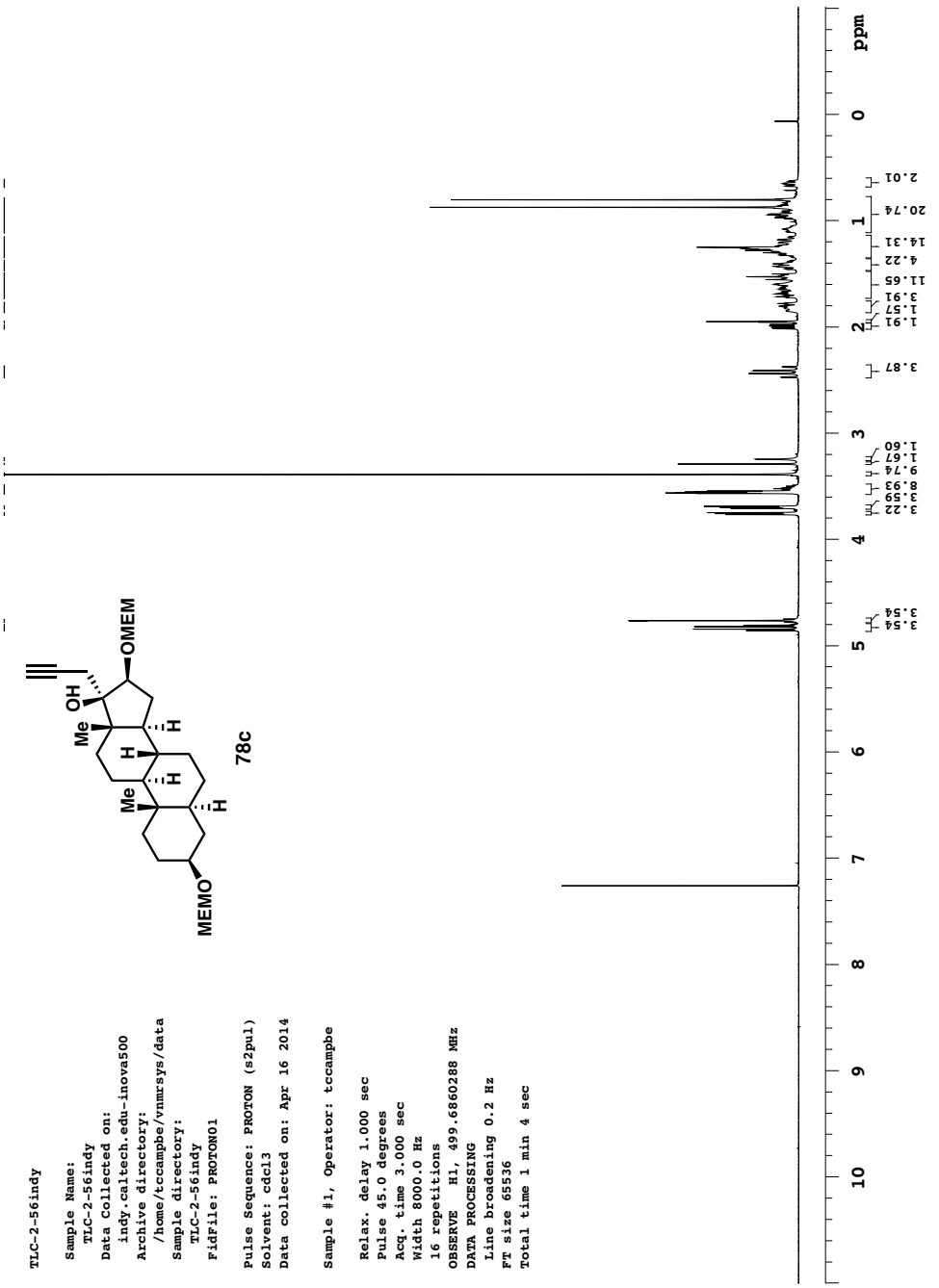

TLC-2-48indy
Sample Name:
TLC-2-48indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-48indy
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 18 2014
Sample #4, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461484 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
Me
O
OMOM
H
H
Me
H
H
H
MOMO
76b
220
200
180
160
140
120
100
80
60
40
20
0
ppm

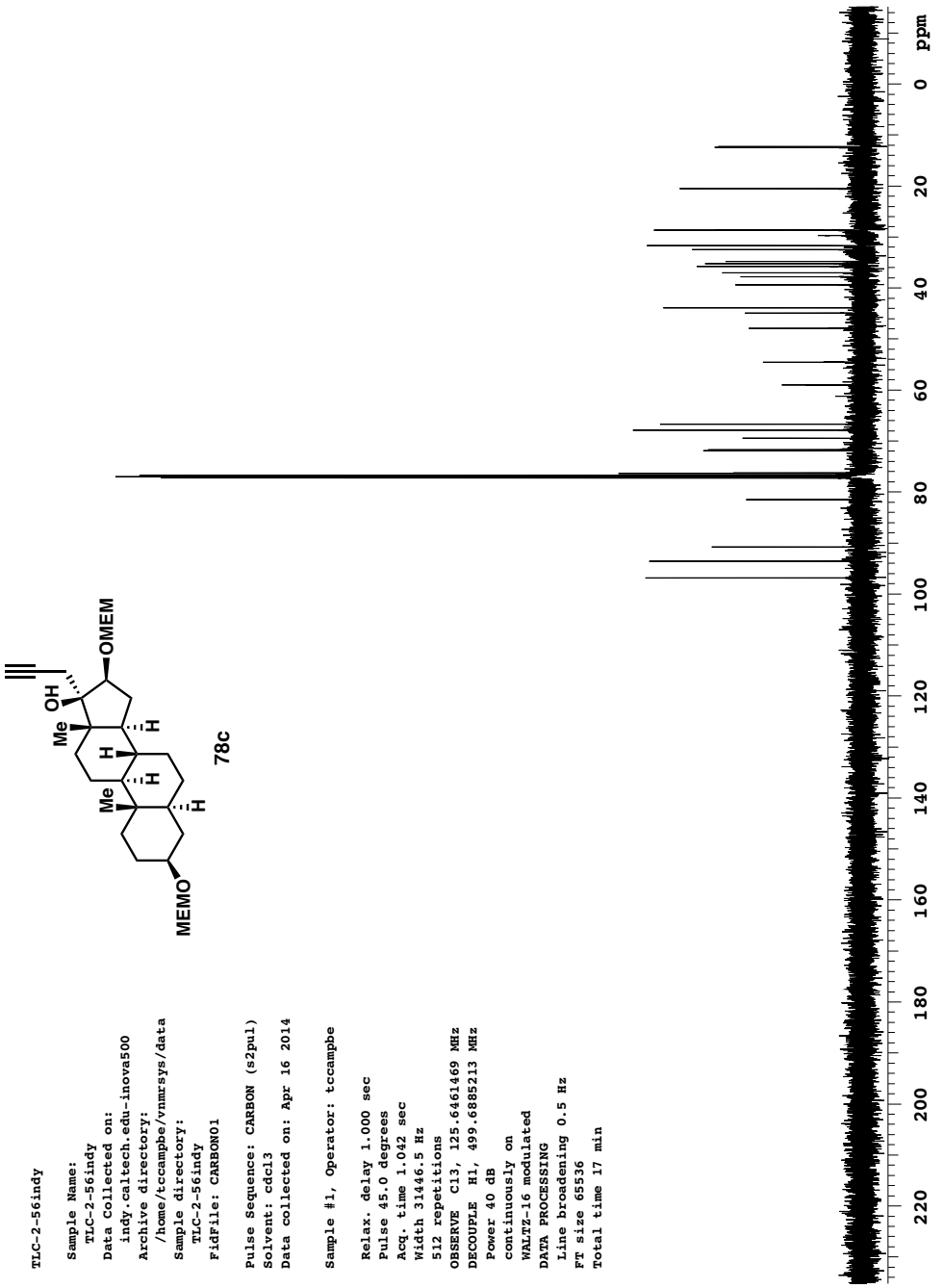

TLC-2-28indy
Sample Name:
TLC-2-28indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-28indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 25 2014
Sample #40, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.6860290 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 4 min 17 sec
OH
Me
OAc
H
H
Me
H
H
AcO
78
ppm
2.59
2.19
4.20
4.90
5.77
7.47
2.64
2.72
24.62
25.47
14.72
2.72

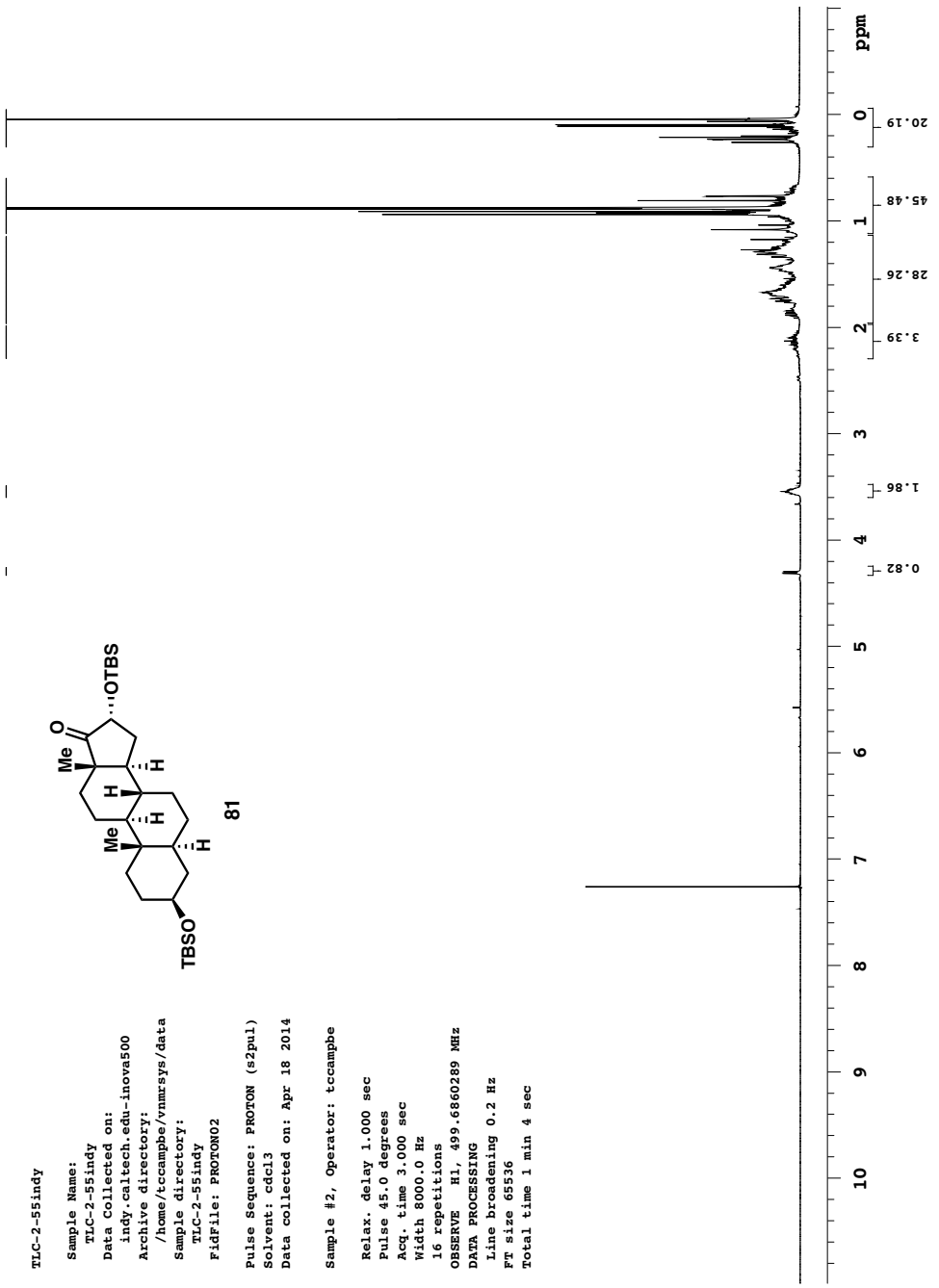

TLC-2-28indy
Sample Name:
TLC-2-28indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-28indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 25 2014
Sample #40, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
11000 repetitions
OBSERVE C13, 125.6461444 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 6 hr, 16 min
OH
Me
OAc
H
Me
H
H
H
H
AcO
78
220
200
180
160
140
120
100
80
60
40
20
0
ppm

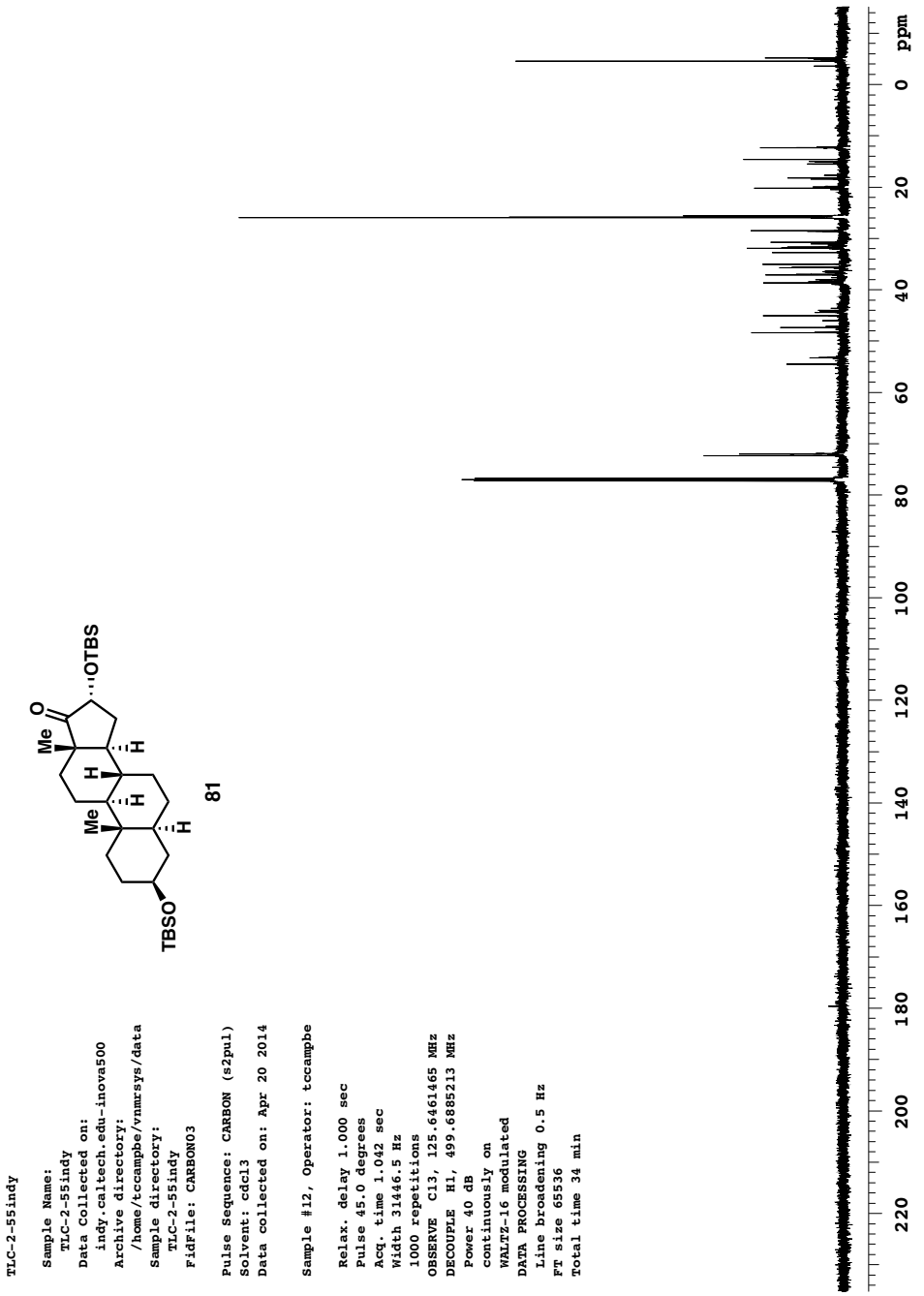

TLC-2-50indy
Sample Name:
TLC-2-50indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-50indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #48, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6860289 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec
OH
Me
OMOM
Me
H
H
H
H
MOMO
78b
ppm
10
9
8
7
6
5
4
3
2
1
0
1.97
24.07
13.55
4.79
13.60
4.55
4.13
4.49
1.57
6.32
7.10
2.05
2.04
4.62
5.17

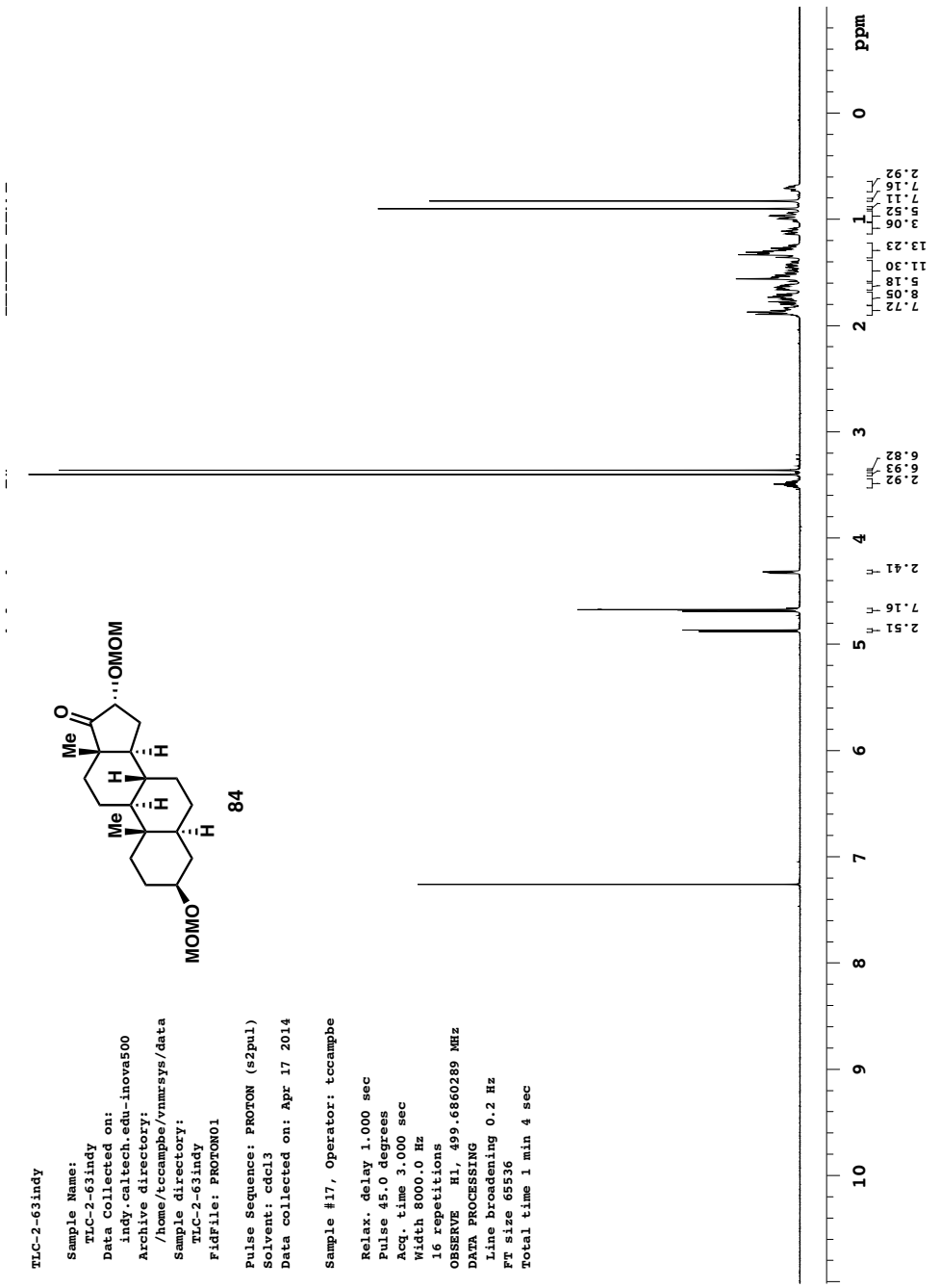

TLC-2-50indy
Sample Name:
TLC-2-50indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-50indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #48, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461459 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
OH
Me
OMOM
H
H
Me
H
H
MOMO
H
78b
220
200
180
160
140
120
100
80
60
40
20
0
ppm

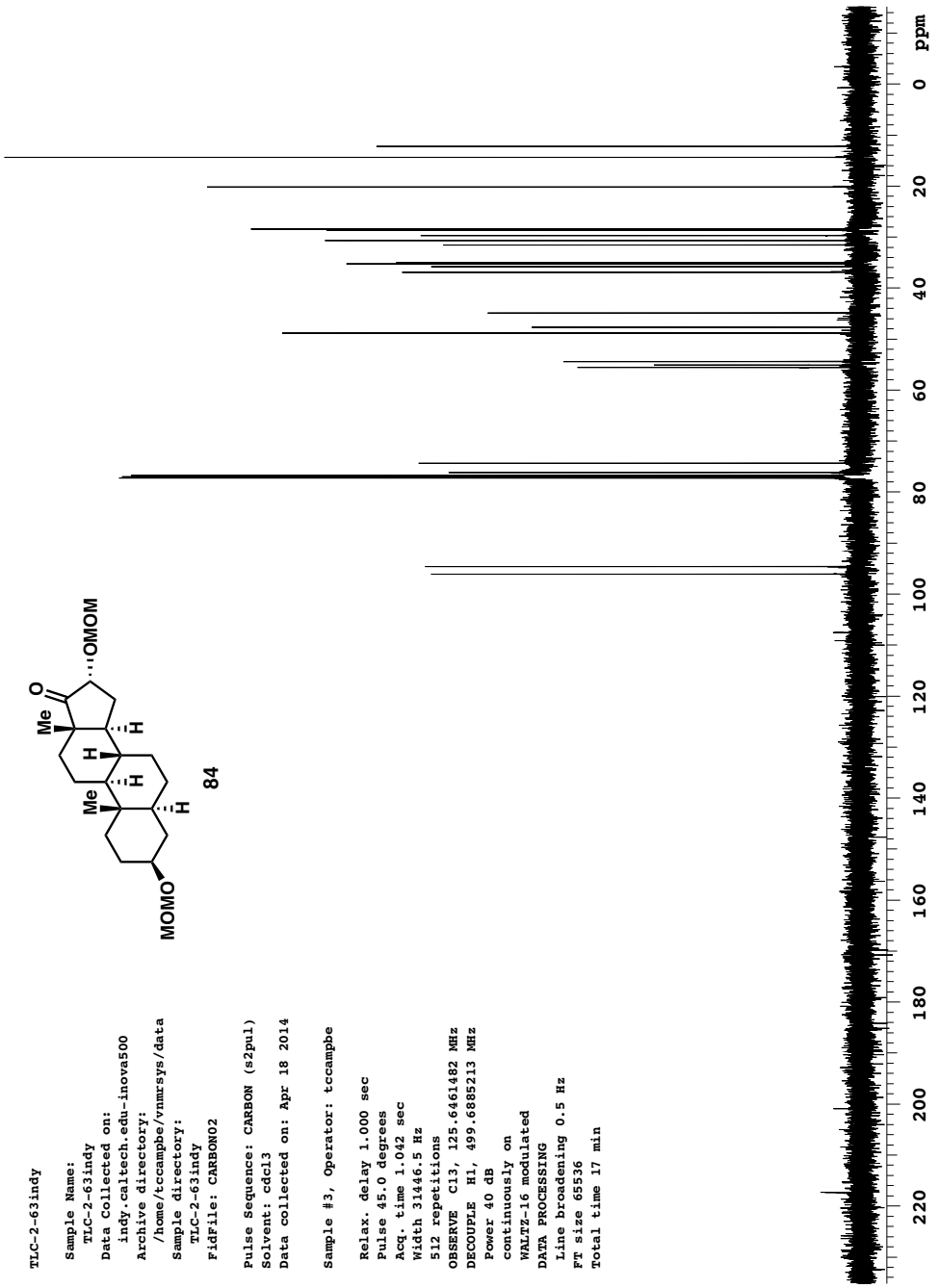

TLC-2-56indy
Sample Name:
TLC-2-56indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-56indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #1, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6860288 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
Me
OH
OMEM
H
Me
H
H
H
MEMO
78c
ppm
10
9
8
7
6
5
4
3
2
1
0
3.54
3.54
3.22
3.59
8.93
9.74
1.67
1.60
3.87
1.91
1.57
3.91
11.65
4.22
14.31
20.74
2.01

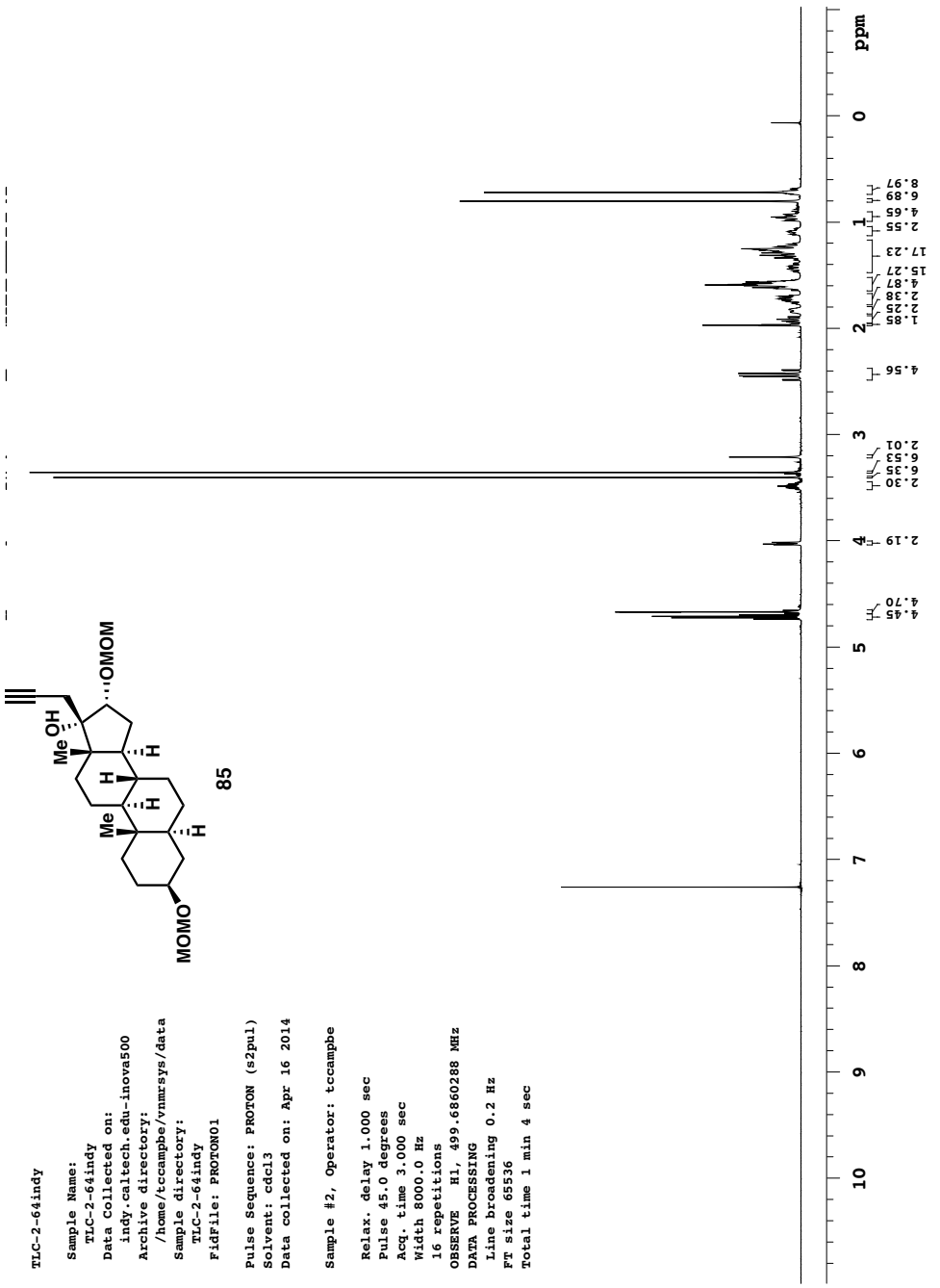

TLC-2-56indy
Sample Name:
TLC-2-56indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-56indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #1, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461469 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
OMEM
OH
Me
Me
MEMO
H
H
H
H
H
78c
220
200
180
160
140
120
100
80
60
40
20
0
ppm

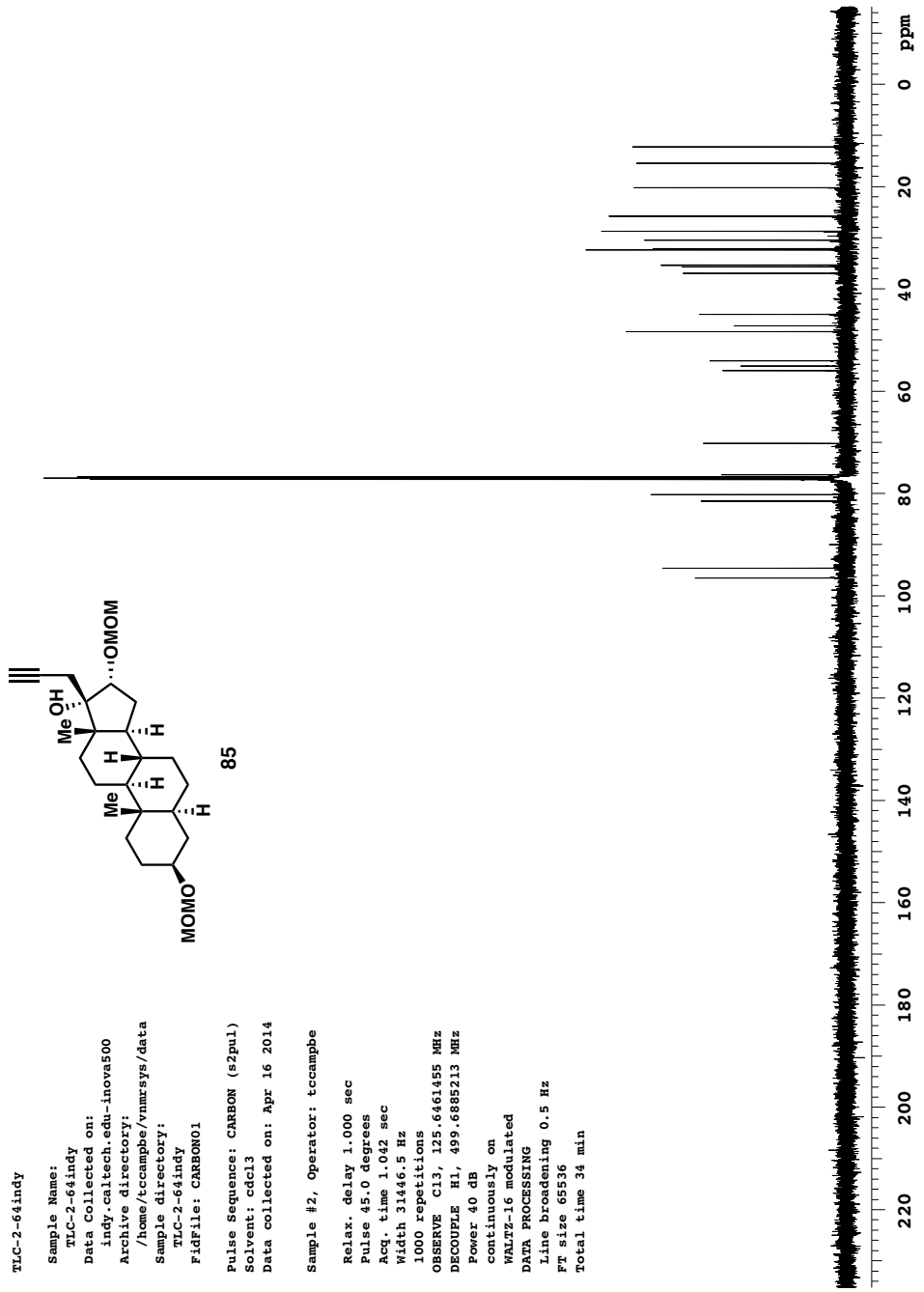

TLC-2-55indy
Sample Name:
TLC-2-55indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-55indy
FidFile: PROTONO2
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 18 2014
Sample #2, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6860289 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
Me
O
OTBS
H
Me
H
H
H
TBSO
H
81
10
9
8
7
6
5
4
3
2
1
0
ppm
20.19
45.48
28.26
3.39
1.86
0.82

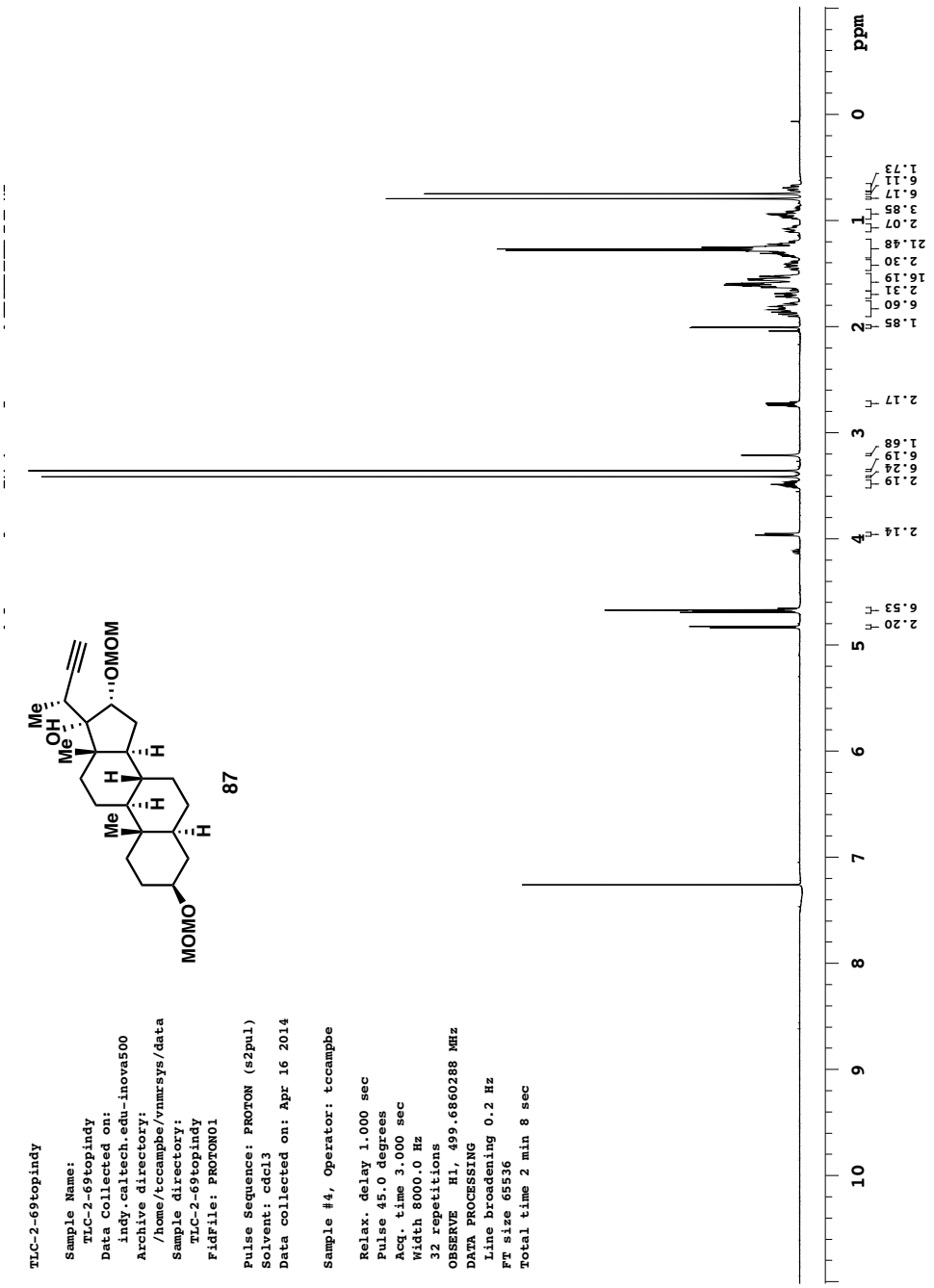

TLC-2-55indy
Sample Name:
TLC-2-55indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-55indy
FidFile: CARBON03
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 20 2014
Sample #12, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6461465 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
Me
O
OTBS
H
Me
H
H
H
TBSO
H
81
220
200
180
160
140
120
100
80
60
40
20
0
ppm

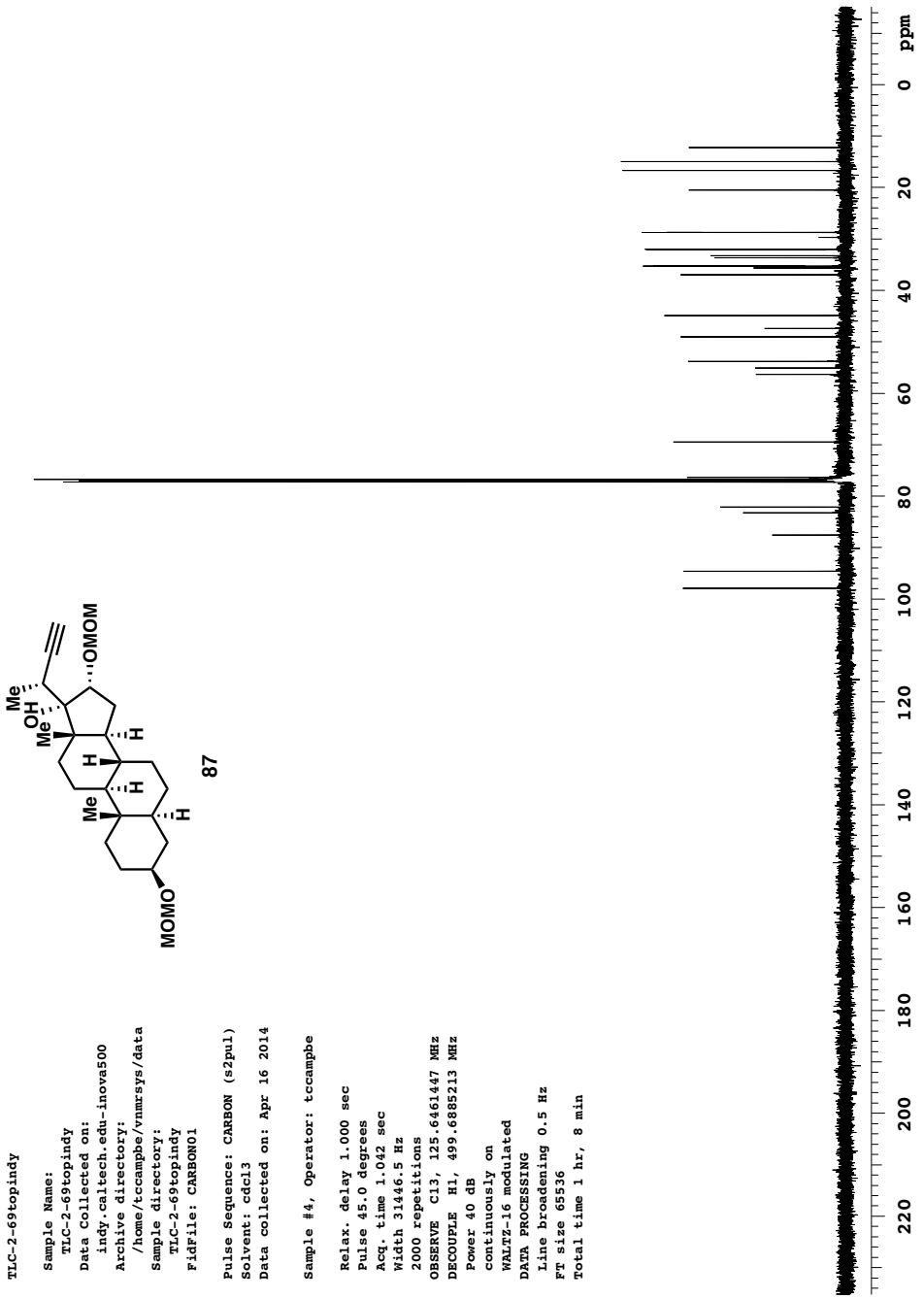

TLC-2-63indy
Sample Name:
TLC-2-63indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-63indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 17 2014
Sample #17, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6860289 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
Me
O
OMOM
H
Me
H
H
H
MOMO
84
ppm
10
9
8
7
6
5
4
3
2
1
0
2.51
7.16
2.41
2.92
6.93
6.82
7.72
8.05
5.18
11.30
13.23
3.06
5.52
7.11
7.16
2.92

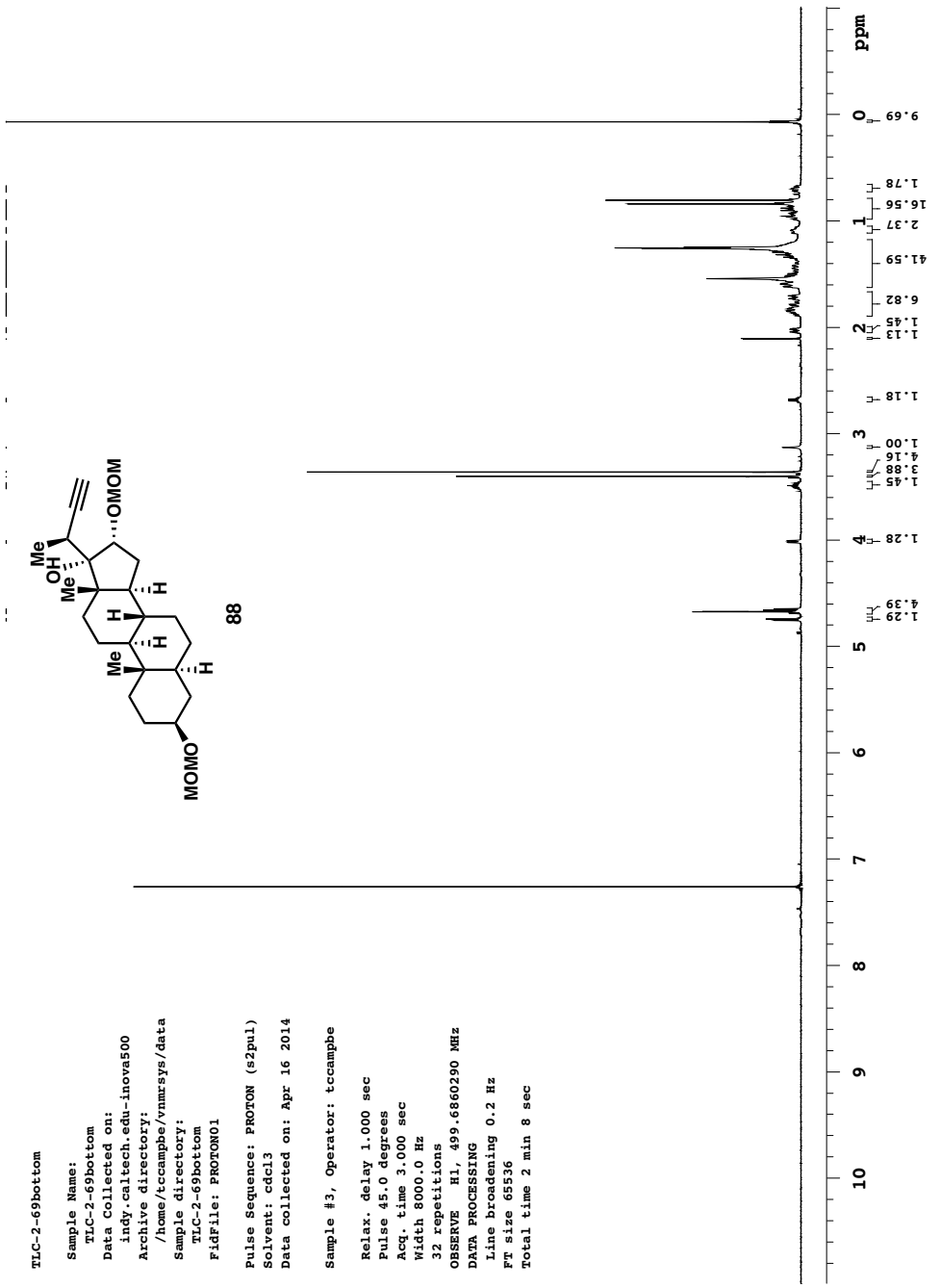

TLC-2-63indy
Sample Name:
TLC-2-63indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-63indy
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 18 2014
Sample #3, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6461482 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
Me
O
OMOM
H
Me
H
H
H
MOMO
84
220
200
180
160
140
120
100
80
60
40
20
0
ppm

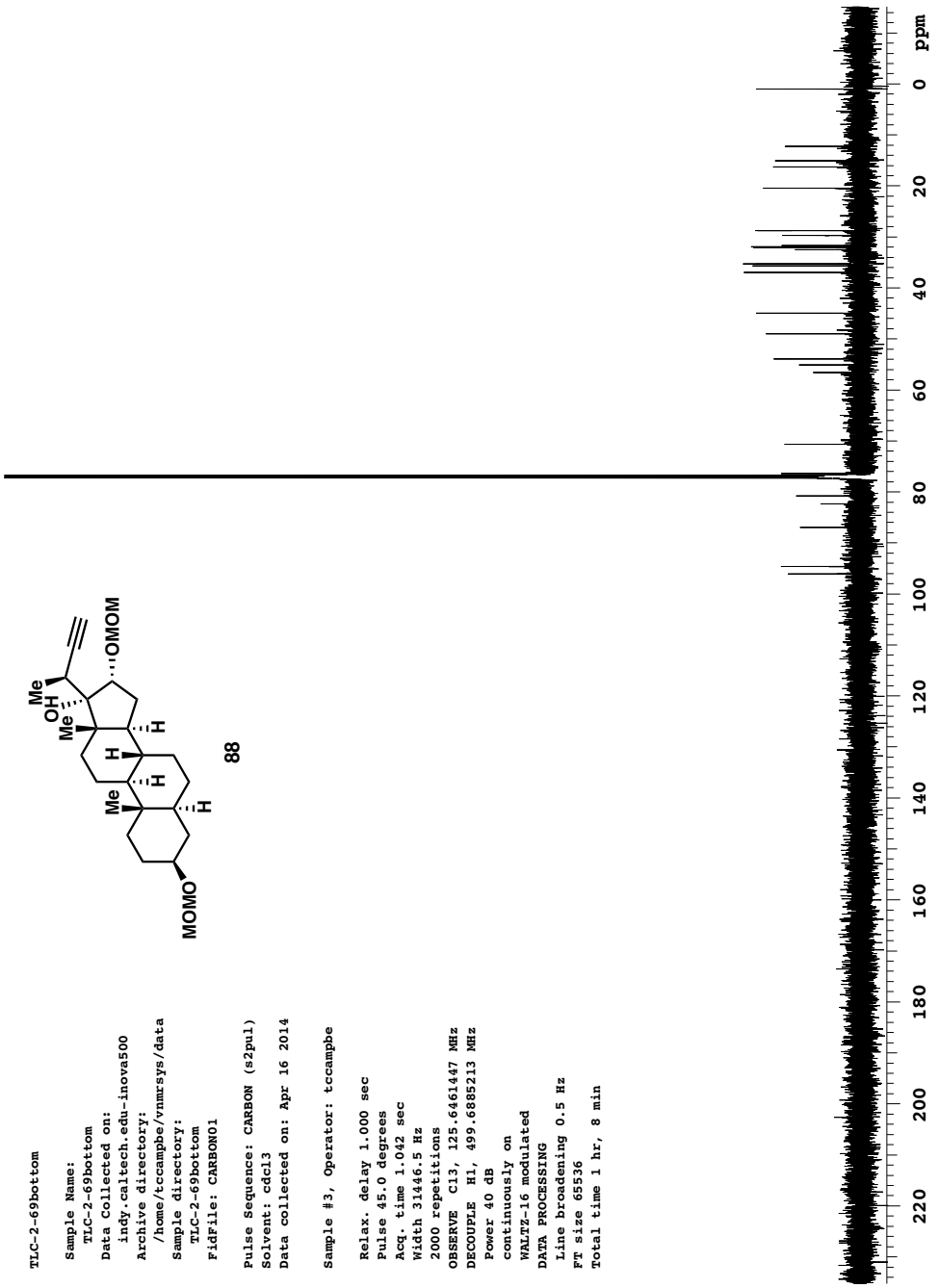

TLC-2-64indy
Sample Name:
TLC-2-64indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-64indy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #2, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6860288 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
OMOM
OH
Me
Me
H
H
H
H
MOMO
85
ppm
8.97
6.89
4.65
2.55
17.23
15.27
4.87
2.38
2.25
1.85
4.56
2.01
6.53
6.35
2.30
2.19
4.70
4.45


TLC-2-64indy
Sample Name:
TLC-2-64indy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-64indy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #2, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6461455 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
Me
OH
H
H
H
Me
H
H
MOMO
OMOM
85
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TLC-2-69topindy
Sample Name:
TLC-2-69topindy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-69topindy
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #4, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.6860288 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
Me
OH
Me
OMOM
Me
H
H
H
H
MOMO
87
ppm
10
9
8
7
6
5
4
3
2
1
0
2.20
6.53
2.14
2.19
6.24
6.19
1.68
2.17
1.85
6.60
2.31
16.19
2.30
21.48
2.07
3.85
6.17
6.11
1.73


TLC-2-69topindy
Sample Name:
TLC-2-69topindy
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-69topindy
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #4, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6461447 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 8 min
Me
OH
Me
H
H
H
Me
H
OMOM
MOMO
87
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TLC-2-69bottom
Sample Name:
TLC-2-69bottom
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-69bottom
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #3, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.6860290 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
OMOM
Me
OH
Me
H
H
H
Me
H
MOMO
88
ppm
9.69
1.78
16.56
2.37
41.59
6.82
1.45
1.13
1.18
1.00
4.16
3.88
1.45
1.28
4.39
1.29


TLC-2-69bottom
Sample Name:
TLC-2-69bottom
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/tccampbe/vnmrsys/data
Sample directory:
TLC-2-69bottom
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 16 2014
Sample #3, Operator: tccampbe
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6461447 MHz
DECOUPLE H1, 499.6885213 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 8 min
Me
OH
Me
OMOM
Me
H
H
H
H
MOMO
88
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Appendix 2

X-Ray Crystallography Reports Relevant to Chapter 2

Figure 4. *X-ray structure of alcohol* ***87***.

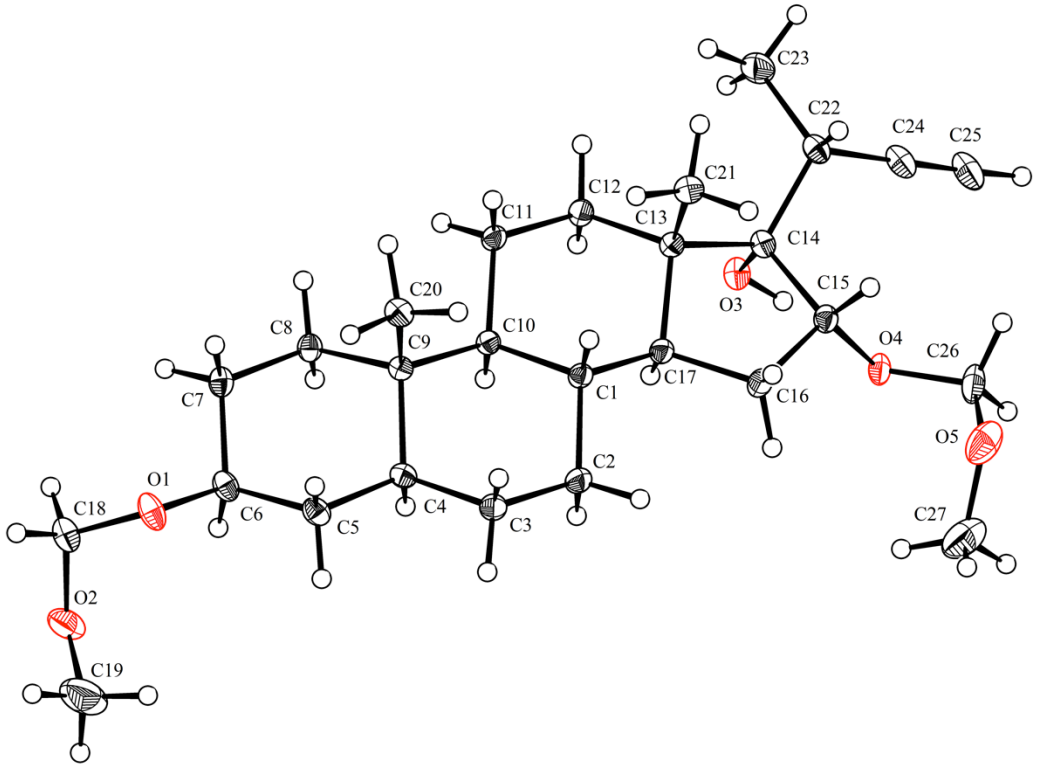


Table 1. Crystal data and structure refinement for a14213.

Identification code	a14213	
Empirical formula	$C_{27}H_{44}O_5$	
Formula weight	448.62	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	P 41 21 2	
Unit cell dimensions	a = 12.1458(4) Å	a= 90°
	b = 12.1458(4) Å	b= 90°
	c = 34.4196(16) Å	g = 90°
Volume	5077.6(4) $Å^3$	
Z	8	
Density (calculated)	1.174 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	

F(000)	1968
Crystal size	0.53 x 0.40 x 0.19 mm^3
Theta range for data collection	1.778 to 37.056°.
Index ranges	-20<=h<=20, -20<=k<=19, -58<=l<=57
Reflections collected	233885
Independent reflections	12739 [R(int) = 0.0650]
Completeness to theta = 25.000°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.9201
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12739 / 0 / 409
Goodness-of-fit on F^2	1.059
Final R indices [I>2sigma(I)]	R1 = 0.0384, wR2 = 0.1003
R indices (all data)	R1 = 0.0461, wR2 = 0.1047
Absolute structure parameter	-0.12(14)
Extinction coefficient	n/a
Largest diff. peak and hole	0.375 and -0.224 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^5) and equivalent isotropic displacement parameters ($Å^2$x 10^4) for a14213. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	129946(8)	149003(7)	56096(2)	195(2)
O(2)	135140(9)	157278(8)	50225(3)	265(2)
O(3)	90398(7)	75451(7)	53158(2)	162(1)
O(4)	68988(6)	79928(7)	53810(2)	163(1)
O(5)	51853(8)	86741(11)	55854(3)	329(2)
C(1)	95261(8)	107761(8)	57862(3)	131(2)
C(2)	89567(9)	117708(9)	56012(3)	173(2)
C(3)	95505(9)	128430(8)	56965(3)	169(2)
C(4)	107604(9)	127728(8)	55763(3)	138(2)
C(5)	113396(9)	138808(8)	56244(3)	164(2)
C(6)	125280(9)	138611(8)	54868(3)	156(2)
C(7)	131681(9)	128993(9)	56614(3)	159(2)

C(8)	125595(8)	117994(8)	56125(3)	143(2)
C(9)	113794(8)	118157(8)	57802(3)	121(1)
C(10)	107635(8)	107272(8)	56784(3)	122(1)
C(11)	113061(8)	96825(8)	58470(3)	143(2)
C(12)	106897(8)	86081(8)	57478(3)	142(2)
C(13)	94677(8)	86716(8)	58659(3)	125(1)
C(14)	86905(8)	77591(8)	57015(3)	134(2)
C(15)	75328(8)	83374(9)	57110(3)	145(2)
C(16)	77380(8)	95900(9)	57160(3)	168(2)
C(17)	89837(8)	96998(8)	56619(3)	134(2)
C(18)	138626(10)	152948(10)	53821(3)	197(2)
C(19)	127984(18)	166497(16)	50724(7)	479(5)
C(20)	114429(9)	119834(9)	62240(3)	158(2)
C(21)	93401(9)	87327(9)	63099(3)	161(2)
C(22)	86402(9)	66577(9)	59331(3)	166(2)
C(23)	97569(11)	60829(10)	59779(4)	242(2)
C(24)	78585(11)	59023(9)	57405(3)	206(2)
C(25)	72478(12)	52766(11)	55777(4)	257(2)
C(26)	57925(10)	77554(12)	54678(3)	239(2)
C(27)	49571(14)	94156(19)	52751(6)	400(4)

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