Strategic Applications of Tandem Reactions in Complex Natural Product Synthesis: Rapid Access to the (Iso)Cyclocitrinol Core

Christopher W. Plummer

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Abstract

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This thesis describes the efforts of Professor James Leighton and myself toward the synthesis of the tetracyclic core of a class of steroidal natural products known as the cyclocitrinols. Our initial work in this area was performed on racemic model systems in order to validate our ring contraction-Cope rearrangement strategy. Novel chemistry was then identified to access the functionalized core in enantio-enriched form. Finally, in line with our efforts to probe the transition state of our key tandem Claisen-Cope reaction, additional substrates were prepared supporting our proposed transition state and improving the efficiency of this transformation.

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Lastly and most importantly, I would like to thank my parents for their love and support throughout my life.

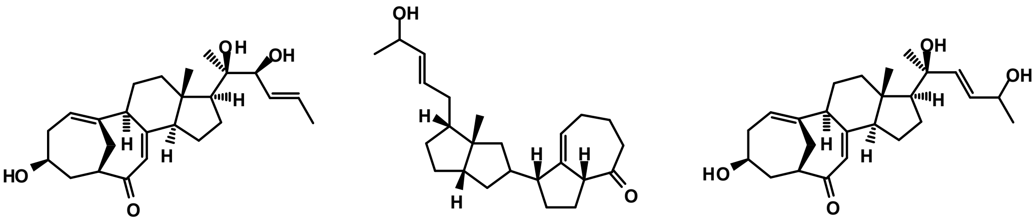
for Walter Wainwright Sr.

I

Background

1.1: Isolation and Characterization of the Cyclocitrinols

In 2003 Philip Crews and coworkers isolated Isocyclocitranol A **1.1** from a terrestrial *Penicillium Citrinum* and reported antibacterial activity against *Staphylococcus epidemidis* (MIC=100ug/mL) and *Enterococcus durans* (MIC=100ug/mL).[1] The absolute and relative configuration was established based on NMR and single crystal X-Ray crystallography. This work also led to the structural revision of previously reported[2] cyclocitrinol **1.2** to structure **1.3** (Figure 1.1).



Isocyclocitrinol A (1.1)

Cyclocitrinol (1.2)
(Original Structure)

Cyclocitrinol (1.3)
(Revised Structure)

Figure 1.2: Isocyclocitrinol **1.1** and structural revision of **1.2** to **1.3**

Later in 2008, Weiming Zhu and coworkers reported the isolation, characterization, and effects on GPR-12 activation of eleven new C25 steroid isomers in the cyclocitrinol family.[3] This unique class of steroids possess an unprecedented bicyclo[4.4.1]undecene ring system containing a bridgehead olefin (Figure 1.2).

---

[1] Amagata, T.; Amagata, A.; Tenney, K.; Valeriote, F.A.; Lobkovsky, E.; Clardy, J.; Crews, P. *Org. Lett.* **2003**, 5, 4393-4396.

[2] Kozlovsky, A.G.; Zhelifonova, V.P.; Ozerskaya, S.M.; Vinokurova, N.G.; Adanin, V.M.; Grafe, U. *Pharmazie* **2000**, *55*, 470-471.

[3] Du, L.; Zhu, T.; Fang, Y.; Gu, Q.; Zhu, W. *J. Nat Prod* **2008**, 71, 1343-1352.

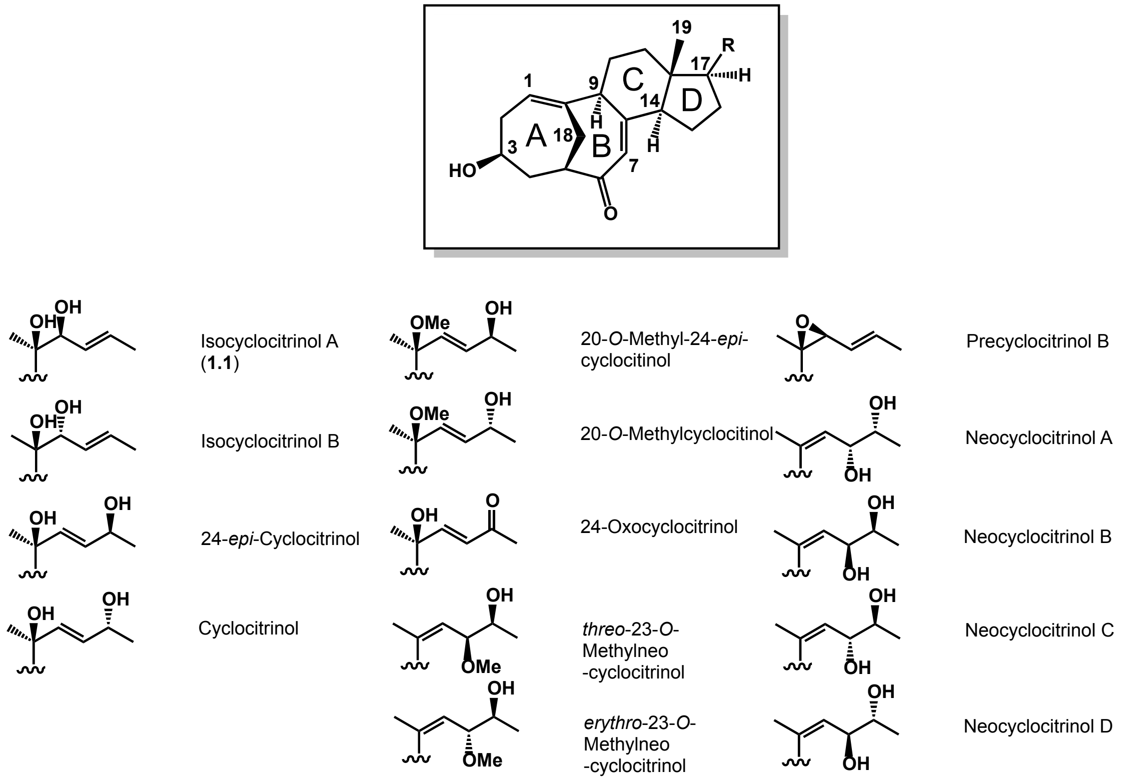

19
R
17
H
1
9
C
14
D
3
A
18
B
H
H
7
HO
O
Isocyclocitrinol A (1.1)
Isocyclocitrinol B
24-epi-Cyclocitrinol
Cyclocitrinol
20-O-Methyl-24-epi-cyclocitinol
20-O-Methylcyclocitinol
24-Oxocyclocitrinol
threo-23-O-Methylneo-cyclocitrinol
erythro-23-O-Methylneo-cyclocitrinol
Precyclocitrinol B
Neocyclocitrinol A
Neocyclocitrinol B
Neocyclocitrinol C
Neocyclocitrinol D
OH
OMe
O

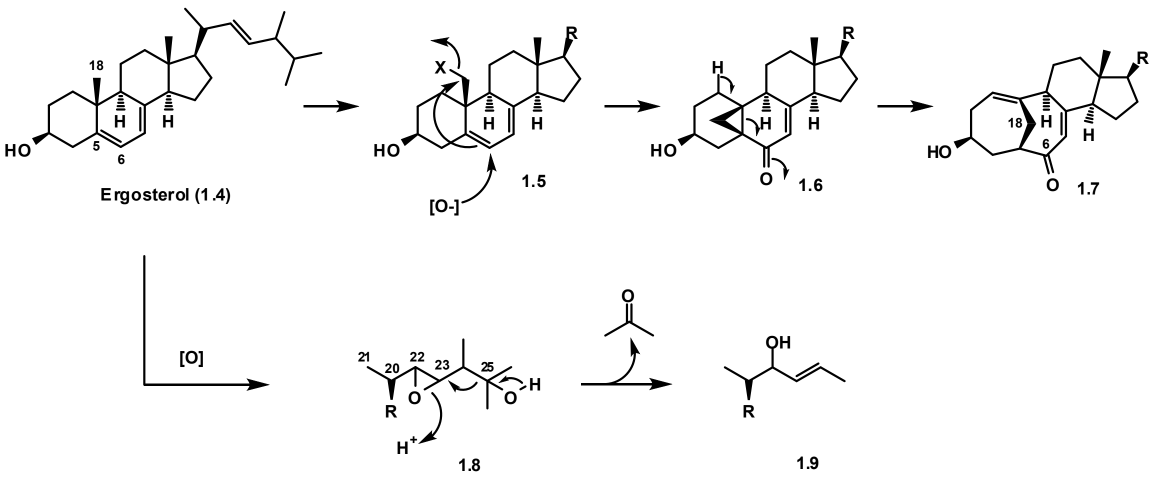
Figure 1.1: Cyclocitrinol family of steroids

1.2: Biosynthesis and Previous Synthetic Approach

A biosynthesic route originating from ergosterol **1.4** was proposed to explain the origins of the bicyclic system and the sidechain.[4] These researchers invoke the intermediacy of cyclopropane structure **1.6** via enzyme-mediated oxidative events. Rupture of this ring system then generates the [4.4.1] bicycle AB core. The side chain of these steroids can also originate from ergosterol. Thus, oxidations at C22 and C25 of **1.4** produce intermediate **1.8**, which then eliminates acetone. Further oxidations and rearrangements would lead to the cyclocitrinols (Scheme 1.1).

---

[4] Marinho, A.M.dR.; Rodrigues-Filho, E.; Ferreira, A.G.; Santos, L. S. *J. Braz. Chem. Soc.* **2005**, *6B*, 1342-1346.

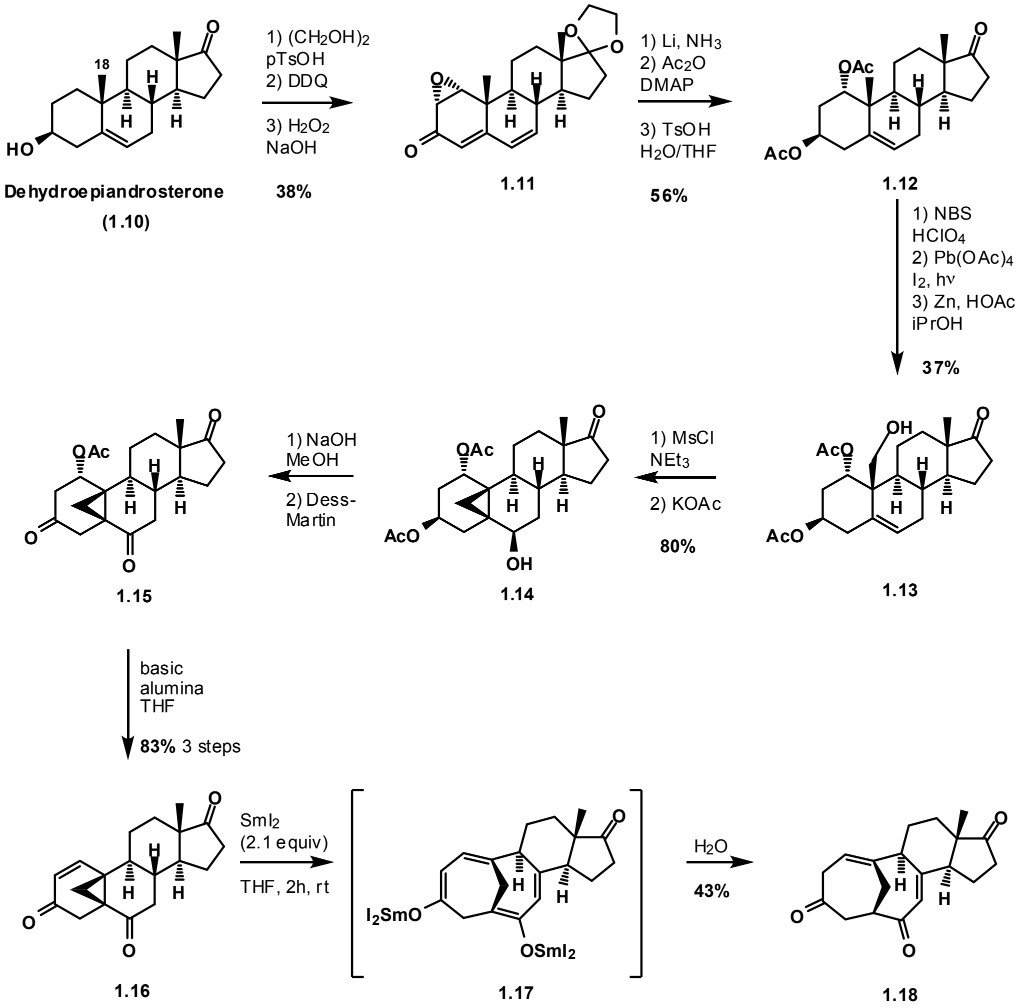


Scheme 1.1: Biosynthesis proposed by Santos and Coworkers

To date, only one group has reported an approach toward the core structure.[5] Perhaps inspired by the biosynthesis, Schmalz demonstrated a samarium diiodide-mediated reductive ring-expansion of cyclopropyltrione **1.15** (Scheme 1.2). Known steroid **1.8** was elaborated into bis-acetate **1.10** in six routine transformations. To prepare for cyclopropanation, C18 had to be functionalized. This was achieved using bromohydrin formation, radical-mediated remote functionalization via hypoiodite reaction, and reductive cleavage of the intermediary cyclic ether with zinc in isopropanol. Mesylation followed by cyclopropanation via solvolysis delivered cyclopropyl carbinol **1.13**. Selective hydrolysis, oxidation, and elimination gave **1.15**, which performed as planned in the key step, delivering the targeted [4.4.1] undecene ring system in 43% yield after aqueous work up.

---

[5] Sheikh, S. E.; zu Greffen, A. M.; Lex, L.; Neudorfl, J.-M.; Schmalz, H.-G. *Synlett* **2007**, *12*, 1881-1884.

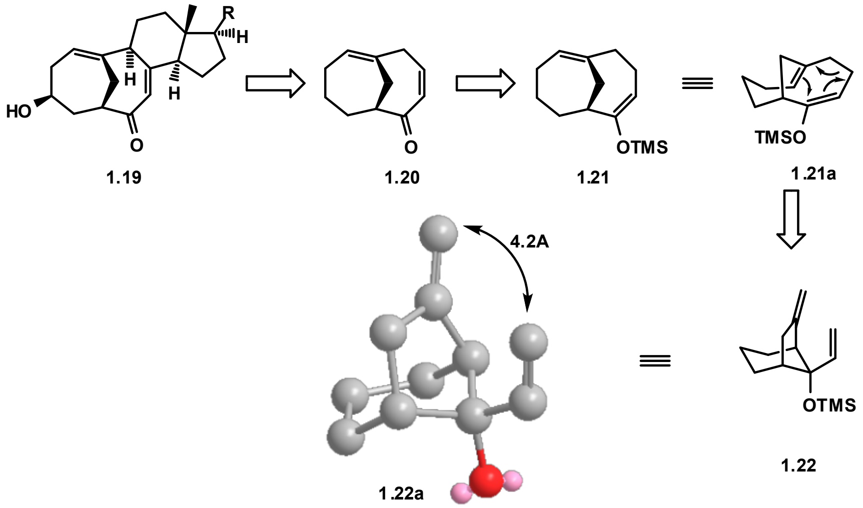

18
HO
Dehydroepiandrosterone
(1.10)
1) (CH2OH)2
pTsOH
2) DDQ
3) H2O2
NaOH
38%
1.11
1) Li, NH3
2) Ac2O
DMAP
3) TsOH
H2O/THF
56%
OAc
AcO
1.12
1) NBS
HClO4
2) Pb(OAc)4
I2, hν
3) Zn, HOAc
iPrOH
37%
OH
AcO
1.13
1) MsCl
NEt3
2) KOAc
80%
1.14
1) NaOH
MeOH
2) Dess-Martin
1.15
basic
alumina
THF
83% 3 steps
1.16
SmI2
(2.1 equiv)
THF, 2h, rt
I2SmO
OSmI2
1.17
H2O
43%
1.18
H
O

Scheme 1.2: Schmalz's approach to the cyclocitrinol core structure

Schmalz's 15-step approach to the core structure proceeds in roughly 2% overall yield. Additionally, it is not clear how trione **1.18** could be chemoselectively functionalized at the C-17 position for side chain installation or how the C-3 ketone might be stereoselectively reduced to the carbinol. While Schmalz has provided a clever first entry into this ring system from a known steroid, we recognize a need for a *de novo* synthesis that meets these remaining challenges.

1.3 Retrosynthetic Analysis

The primary synthetic challenge in accessing this series of unusual steroids is the construction of the [4.4.1] AB ring system with a bridgehead olefin at C1-C10. Bridgehead olefins are relatively rare in natural products and the available preparative strategies are likewise limited. Our retrosynthetic analysis began with simplifying the cyclocitrinol structure down to its most challenging component: the AB bicyclo[4.4.1]undecene ring system **1.20**. Redrawing the enone as its silyl enol ether equivalent (perhaps by way of a Saegusa oxidation) led retrosynthetically to bicyclic structre **1.21** which may be drawn suggestively revealing an oxy Cope product **1.21a**, leading us further to [3.2.1] bicyclic retron **1.22** (Scheme 1.3).



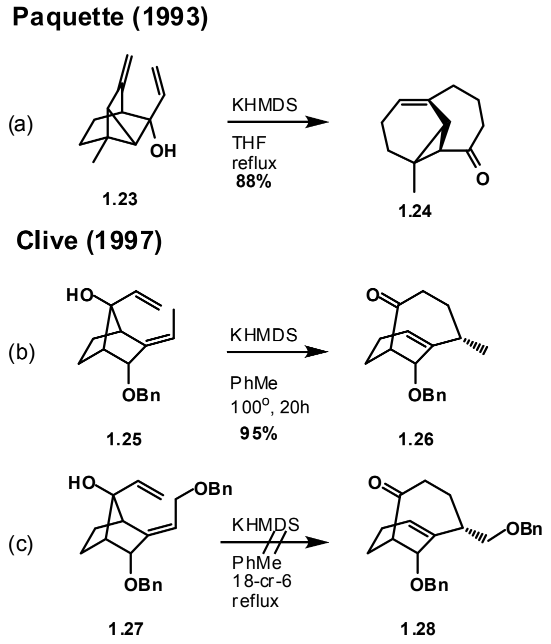
Scheme 1.3: Proposed siloxy Cope reaction to form the AB ring system

The anionic oxy Cope rearrangement has been shown to deliver rate accelerations of up to 10^{17} as compared to the parent Cope[6] and it is this version of the Cope that has found the most extensive application in the context of synthesizing complex molecules. A search of the literature, however, revealed no examples of the planned Cope rearrangement to access the AB core in an anionic oxy context or otherwise.[7] Examination of models and simple mechanics accounts for this lack of precedent: the termini of the reacting alkenes in the conformation that maximizes pi overlap are over four angstroms apart (see 3D structure **1.22a**, scheme 1.3).

---

[6] Evans, D.A.; Golob, A.M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

While the transformation of **1.23** to **1.24** reported by Paquette does closely resemble the targeted transformation, the cyclopropane constitutes a nontrivial alteration in the electronic and steric structure of **1.23** and likely renders direct comparisons largely meaningless (Scheme 1.4, equation (a)).[8] More relevant precedents may be found in the work of Clive, who showed that **1.25** could be transformed into **1.26** (equation (b))by way of an anionic oxy-Cope rearrangement.[9] It is noteworthy, however, both that this reaction required unusually harsh conditions and that more elaborate substrates failed to deliver any Cope product (equation (c)). Wood later corroborated these results.[10]


Paquette (1993)
(a)
OH
1.23
KHMDS
THF
reflux
88%
O
1.24
Clive (1997)
(b)
HO
OBn
1.25
KHMDS
PhMe
100°, 20h
95%
O
OBn
1.26
(c)
HO
OBn
OBn
1.27
KHMDS
PhMe
18-cr-6
reflux
O
OBn
OBn
1.28

Scheme 1.4: Anionic oxy-Cope reactions of bridging carbocycles to form bridgehead olefin

---

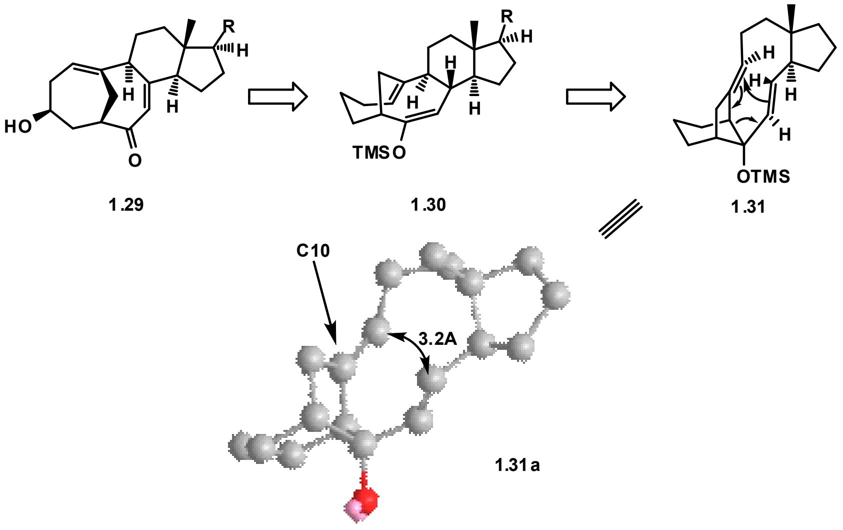
[7] Paquette, L.A. *Tetrahedron* **1997**, *53*, 13971.

[8] Paquette, L.A.; Poupart, M.-A.; *J. Org. Chem* **1993**, *58*, 4245

[9] Sgarbi, P.W.M.; Clive, D.L.J. *Chem. Commun.* **1997**, 2157.

[10] Njardarson, J.T.; Wood, J.L. *Org. Lett.* **2001**, *3*, 2431.

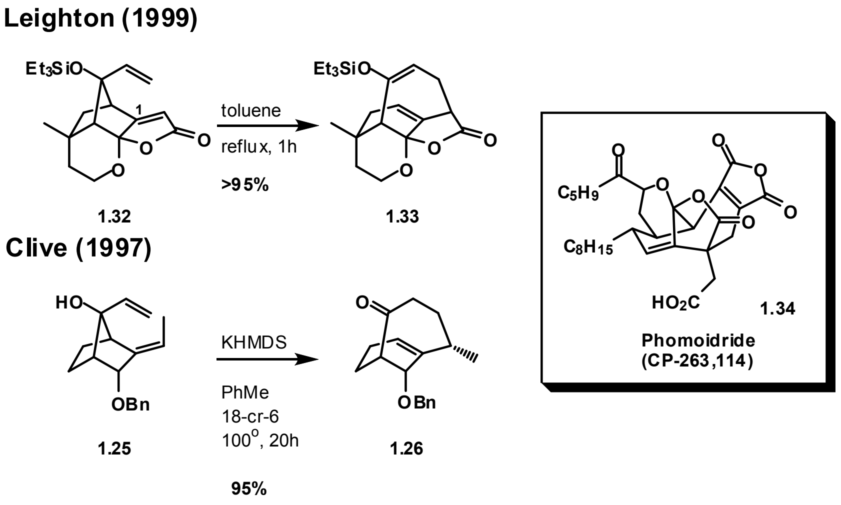
We then considered an alternative to anionic rate enhancement. By installing an additional element of stain into our Cope substrate, perhaps we could force the reacting carbons closer together and drive the reaction through release of strain. Ideally, this additional element of strain would be something we could use for the synthesis of the targeted system, specifically closure of the C ring cyclohexane. This line of reasoning led to 10-membered ring retron **1.31** (Scheme 1.5). Simple molecular mechanics revealed that the two reacting carbons are forced an anstrom closer than the simplified Cope substrate **1.22** (see Scheme 1.3), giving this system a reasonable chance of undergoing the planned sigmatropic rearrangement.



Scheme 1.5: Proposed transannular Cope reaction on 10-membered ring

Ten-membered rings are strained and often difficult to prepare under the best of circumstances, and **1.31** is no exception. In fact, modeling suggests that C10 of [3.2.1] bicycle Cope substrate **1.31** is not trigonal planar, as would be expected of an sp^2 hybridized carbon atom, but is in fact substantially pyramidalized due to the significant torque placed on this position by the medium-sized ring system locked into the bridging ocata[3.2.1]bicycle. While we feel this contributes greatly to the probability of such a system undergoing the planned sigmatropic rearrangement, it also makes accessing such a ten-membered ring extraordinarily difficult. It would be fair to say that we have transferred the problem of forging the AB bicyclo[4.4.1]undecene to one of accessing a particularly strained ten-membered ring.

The strain-release Cope strategy has precedent in the Leighton group in the context of natural product synthesis with the work on Phomoidride.[11] The Phomoidride approach provides an instructive example for our purposes as the lactone ring in **1.32** forces the reacting olefin closer to the vinyl group, also rendering carbon **1** pyramidal and building considerable strain in the reacting substrate (Scheme 1.6). These effects result in a remarkably facile siloxy Cope rearrangement, producing rate acceleration roughly as great as the anionic version of this transformation.


Leighton (1999)
Et3SiO
1
O
O
O
toluene
reflux, 1h
>95%
Et3SiO
1.32
1.33
Clive (1997)
HO
OBn
KHMDS
PhMe
18-cr-6
100°, 20h
95%
O
OBn
1.25
1.26
C5H9
C8H15
HO2C
1.34
Phomoidride
(CP-263,114)

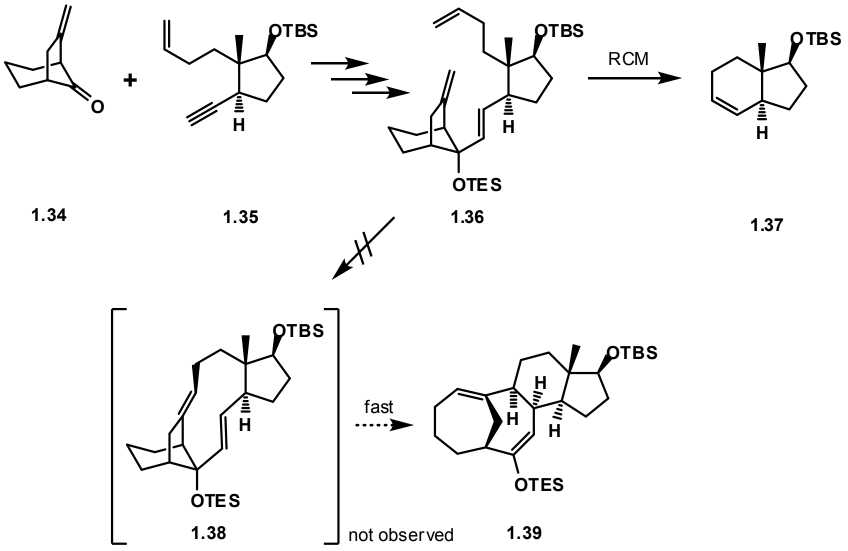
Scheme 1.6: Cope Reaction for the [3.4.1] CP-263,114 core structure

---

[11] Bio, M.; Leighton, J.L. *J. Am. Chem. Soc.* **1999**, 121, 890-891.

1.4: Previous synthetic efforts in the Leighton laboratory towards 10-membered ring Cope substrate

Once the structural requirements for a viable Cope substrate were in place, the considerable synthetic obstacles towards accessing such a molecule became apparent. Former Leighton group member Dr. Arash Soheili attempted a variety of strategies directed toward the direct preparation of the 10-membered ring with the [3.2.1] bicycle and cyclopentane moieties already in place.[12] The first series of attempts relied upon ring-closing metathesis (RCM) to forge the challenging medium-sized ring. Novel chemistry was identified for the preparation of chiral coupling fragments [3.2.1] bicycloketone **1.34** and cyclopentyl moiety **1.35** followed by elaboration to RCM substrate **1.36** (Scheme 1.7). It was hoped that the Cope reaction would then proceed faster than the retro-RCM (ROMP). Unfortunately, ring closure under a variety of conditions failed and hydrindane **1.37** was the only isolable product.

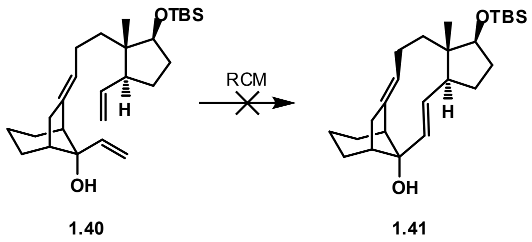


Scheme 1.7: RCM Approach to 10-membered ring followed by Cope

---

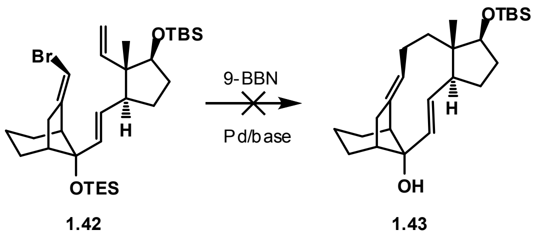
[12] Unpublished results from the PhD thesis of Arash Soheili, Columbia University, **2008**

Disconnecting at the other olefin, an alternative RCM substrate was prepared. Unfortunately, this failed to undergo productive RCM and the strategy was abandoned on the basis that the ten-membered ring was too strained to be closed by this method (Scheme 1.8).



Scheme 1.8: 2nd RCM Approach

Encouraging literature precedent for macrocyclic *B*-Alkyl Suzuki couplings in the context of forming strained medium-sized rings[13] inspired the preparation of vinyl bromide **1.42** (Scheme 1.9). Again macrocycliaztion was not observed and a series of probe experiments implicated oxidative insertion by palladium into the vinyl bromide as the problematic step on the reaction coordinate.

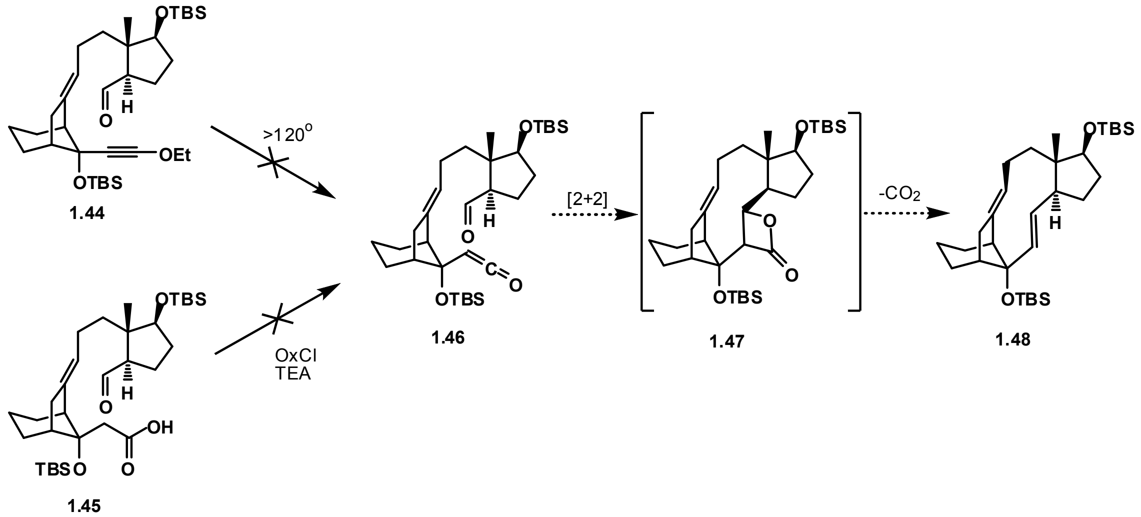


Scheme 1.9: Macrocyclic *B*-Alkyl Suzuki Approach

---

[13] Mohr, P.J.; Halcomb, R.L. *J. Am. Chem. Soc.* **2003**, *123*, 1712.

The considerable strain built into the targeted cyclodecadiene core containing a bicycle moiety prompted a revision of the cyclization strategies. Ring closure at one of the rigid olefins would have to be accompanied by a massive energetic driving force in order to render this process favorable. This line of reasoning led to the notion of ring closure via ketene-aldehyde [2+2] cycloaddition followed by expulsion of CO_2 to drive the process. Substrates **1.44** and **1.45** were prepared and expected to deliver the ketene aldehyde by thermal ene and acylchloride activation, respectively (Scheme 1.10). Unfortunately the [2+2] substrate was not accessed, presumably due to substrate sensitivity issues.



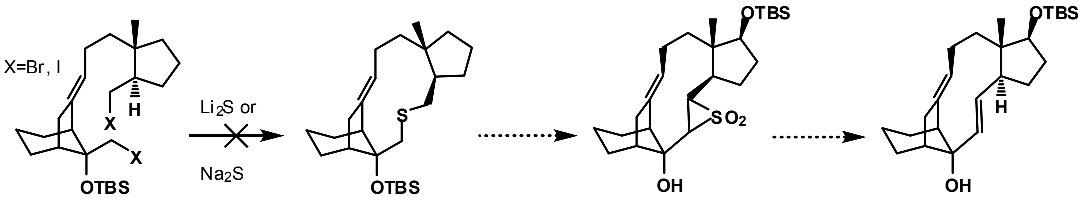
Scheme 1.10: Ketene-Aldehyde [2+2] Approach

It was at this phase of the program that rather than attempting the direct formation of the 10-membered ring, a different approach was pursued. Incremental incorporation of strain through ring contraction was then considered as a potentially viable method for constructing the highly strained system. The Ramberg-Backlund rearrangement has been demonstrated as a method for making strained medium-sized rings in complex total synthesis.[14] Therefore dihalide

---

[14] Boeckman, R.K.; Yoon, S.K.; Heckendorn, D.K. *J. Am. Chem. Soc.* **1991**, *113*, 9682.

1.50 was prepared and subjected to a variety of displacement conditions (Scheme 1.11). Unfortunately, the desired cyclic thioether was not observed and the key transformation could not be attempted.


X=Br, I
X
H
X
OTBS
Li2S or
Na2S
S
OTBS
OTBS
SO2
OH
OTBS
H
OH

1.50 **1.51** **1.52** **1.53**

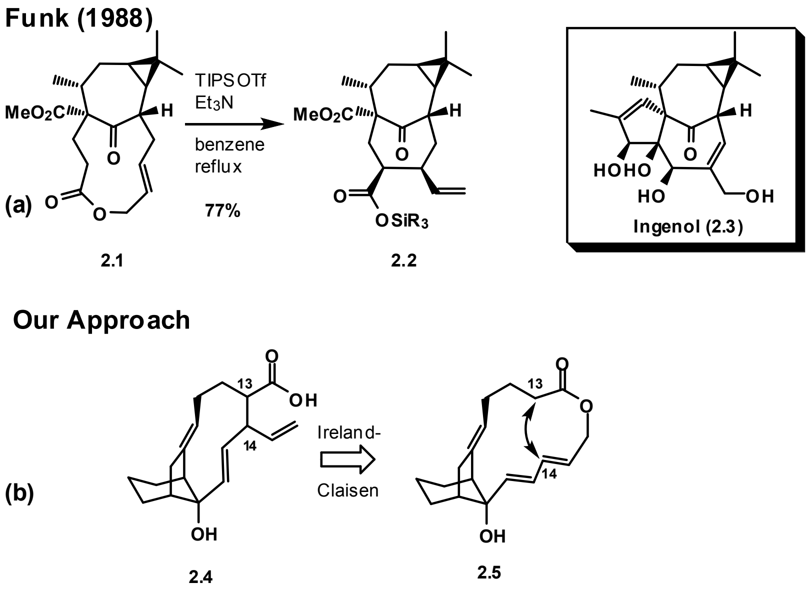
Scheme 1.11: Ramberg-Backlund Approach

II

Model Studies

2.1: First Generation Macrolactone Approach

Thanks to the pioneering contributions of Dr. Soheili, we now had a realistic sense of what we were up against in terms of accessing this very challenging Cope substrate. Related to the ring-contraction concept central to the Ramberg-Backlund approach, we endeavored to synthesize a larger macrolactone and perform an Ireland-Claisen[15] ring contraction. We reasoned that this should force the reacting carbons 13 and 14 into close proximity, unlike the previous approaches, and improve our chances of forming the ten-membered ring. A similar approach was successfully exploited by Funk and coworkers in their efforts toward the challenging core structure of Ingenol **2.3** through the employment of the Ireland-Claisen rearrangement (Scheme 2.1, equation (a)).[16] For our purposes, this approach would require the preparation of a 14-membered model macrolactone such as **2.5** (equation (b)).


Funk (1988)
(a)
MeO2C
H
O
TIPSOTf
Et3N
benzene
reflux
77%
OSiR3
2.1
2.2
HO
HO
HO
OH
Ingenol (2.3)
Our Approach
(b)
13
14
OH
Ireland-
Claisen
OH
2.4
2.5

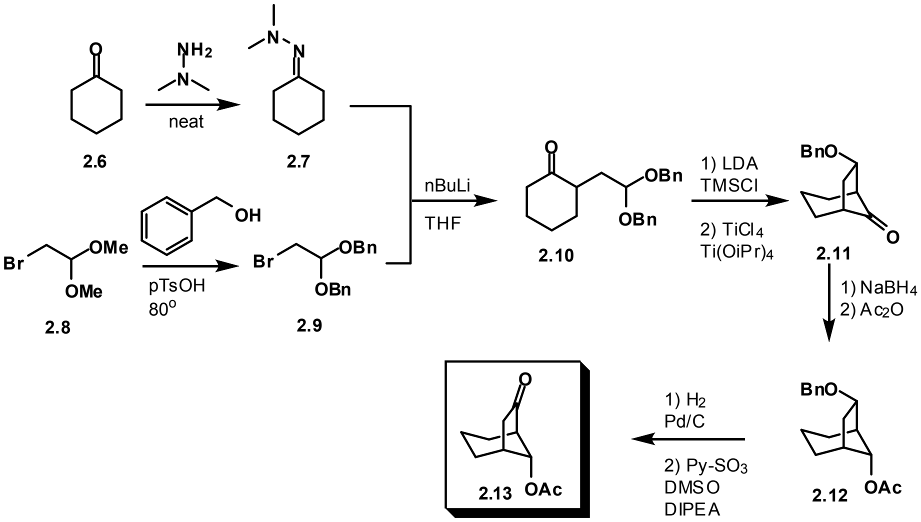
---

[15] Ireland, R.E.; Mueller, R.H. *J. Am. Chem. Soc.* **1972**, *94*, 5897.

[16] Funk, R.L.; Olmstead, T.A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298.

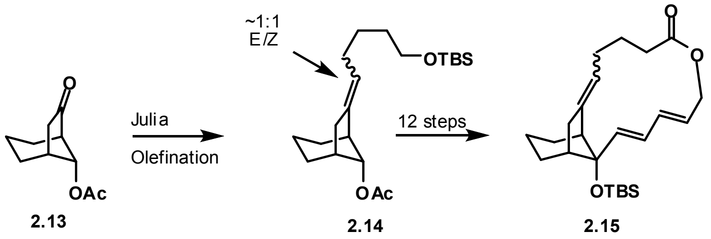
Scheme 2.1: Ireland-Claisen Ring Contractions

Dr. Soheili identified chemistry for the preparation of bicylcoketone **2.13** (Scheme 2.2). This concise and scalable process enabled all of our early stage validation studies and was highlighted by a Mukaiyama acetal aldol cyclization[17] to forge the bridging [3.2.1] carbocycle.


neat
2.6
2.7
Br
OMe
OMe
2.8
OH
pTsOH
80°
Br
OBn
OBn
2.9
nBuLi
THF
OBn
OBn
2.10
1) LDA
TMSCl
2) TiCl4
Ti(OiPr)4
BnO
O
2.11
1) NaBH4
2) Ac2O
BnO
2.12
OAc
1) H2
Pd/C
2) Py-SO3
DMSO
DIPEA
O
2.13
OAc

Scheme 2.2: Synthesis of bicycloketone **2.13** by Dr. Soheili

He then elaborated this intermediate into the Ireland Claisen substrate macrolactone **2.15** (scheme 2.3). Unfortunately, a nonselective Julia olefination[18] resulted in a mixture of C9-C10 alkene isomers which were inseparable.

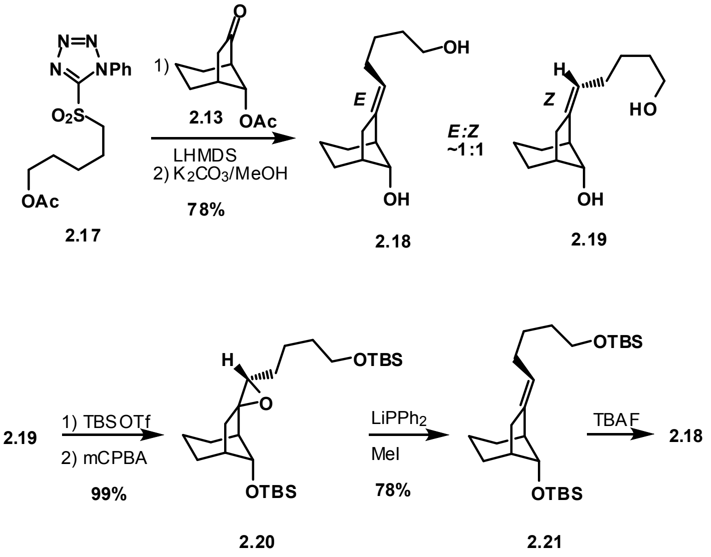

O
OAc
2.13
Julia
Olefination
~1:1
E/Z
OTBS
OAc
2.14
12 steps
O
O
OTBS
2.15

Scheme 2.3: 1st Generation synthesis of Macrolactone **2.16** by Dr. Soheili

---

[17] Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, *12*, 1043.
[18] Blakemore, P.R.; Cole, W.J.; Kocienski, P.J.; Morley, A. *Synlett* **1998**, 26.

My first task on the project was improving this route with an eye toward conciseness and a stereoselective olefiniation (scheme 2.4). We found that coupling of sulfone **2.17** with **2.13** followed by deprotection resulted in a mixture of diols **2.18** and **2.19** which could be separated using a chloroform-acetone system, commonly utilized in natural products isolation for molecules of medium polarity. The wrong (*Z*) isomer could then be inverted via phosphide addition/quaternization on the corresponding epoxide.[19]

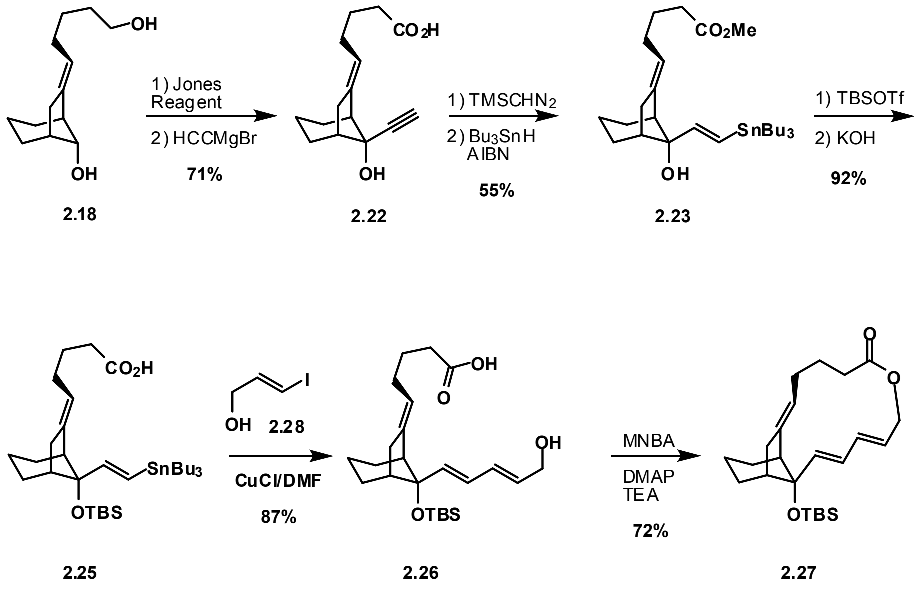

N=N
NPh
N
O2S
OAc
2.17
1)
O
2.13
OAc
LHMDS
2) K2CO3/MeOH
78%
OH
E
OH
2.18
E:Z
~1:1
H
Z
HO
OH
2.19
2.19
1) TBSOTf
2) mCPBA
99%
H
OTBS
O
OTBS
2.20
LiPPh2
MeI
78%
OTBS
OTBS
2.21
TBAF
2.18

Scheme 2.4: Nonselective Julia olefination and inversion of *Z* isomer

Treatment of **2.18** with excess Jones' Reagent converted the primary alcohol to the carboxylic acid with concomitant oxidation of the secondary alcohol to the ketone (Scheme 2.5). This was followed by stereoselective addition by ethynylmagnesium bromide which delivered hydroxy acid **2.22**. Treatment of this material with $TMSCHN_2$ in methanol cleanly delivered the methyl ester which then underwent hydrostannylation to deliver vinyltin species **2.23** in 40% yield over four steps. TBS protection of the tertiary alcohol followed by saponification of the methyl ester gave the acid **2.25**. A variety of standard palladium-mediated cross-coulding experiments were conducted with vinyl iodide **2.28**. Unfortunately none of the desired coupled product was observed and only unreacted starting material or destannylated byproduct was recovered. We presumed that the demanding steric environment crowding the vinyltin species prohibited facile oxidative insertion by a bulky palladium complex. We then turned to Liebskind's stoichiometric copper(I) Stille conditions,[20] which presumably exchanges the vinyltin species to a vinyl copper electrophile. After some optimization, this protocol delivered the desired dienyl hydroxy acid in 87% yield and the stage was set for macrocyclization. After considerable experimentation, 2-methyl-6-nitrobenzoic anhydride (MNBA)[21] was found to mediate macrolactonization very efficiently at elevated temperatures and extended reaction times in toluene, delivering the 14-membered ring **2.27** in 72% yield.

---

[19] Vedejs, E.; Fuchs, P.L. *J. Am. Chem. Soc.* **1971**, *93*, 4070.


OH
OH
2.18
1) Jones Reagent
2) HCCMgBr
71%
CO2H
OH
2.22
1) TMSCHN2
2) Bu3SnH AIBN
55%
CO2Me
SnBu3
OH
2.23
1) TBSOTf
2) KOH
92%
CO2H
SnBu3
OTBS
2.25
I
OH 2.28
CuCl/DMF
87%
OH
O
OH
OTBS
2.26
MNBA
DMAP
TEA
72%
O
O
OTBS
2.27

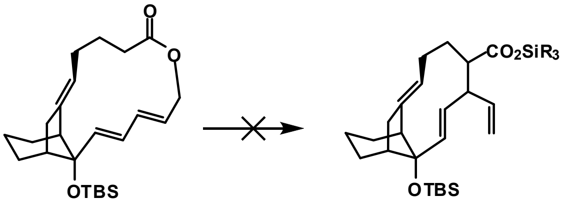
Scheme 2.5: Second Generation Macrolactone Synthesis

Unfortunately, all of our attempts at the Ireland-Claisen rearrangement on this substrate led to degradation products (primarily opening of the macrocycle) or no reaction. We were able to establish some evidence for formation of the silyl ketene acetal intermediate in d8-THF with LDA and TMSCl at -78 °C, observing a resonance at 4.1 ppm (dd), consistent with the vinyl proton of a silyl ketene acetal. Heating of this material to 60 °C, however, led to no reaction and further heating up to 90 °C resulted in recovery of starting material.

---

[20] Allred, G.D.; Liebskind, L.S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

[21] Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535.

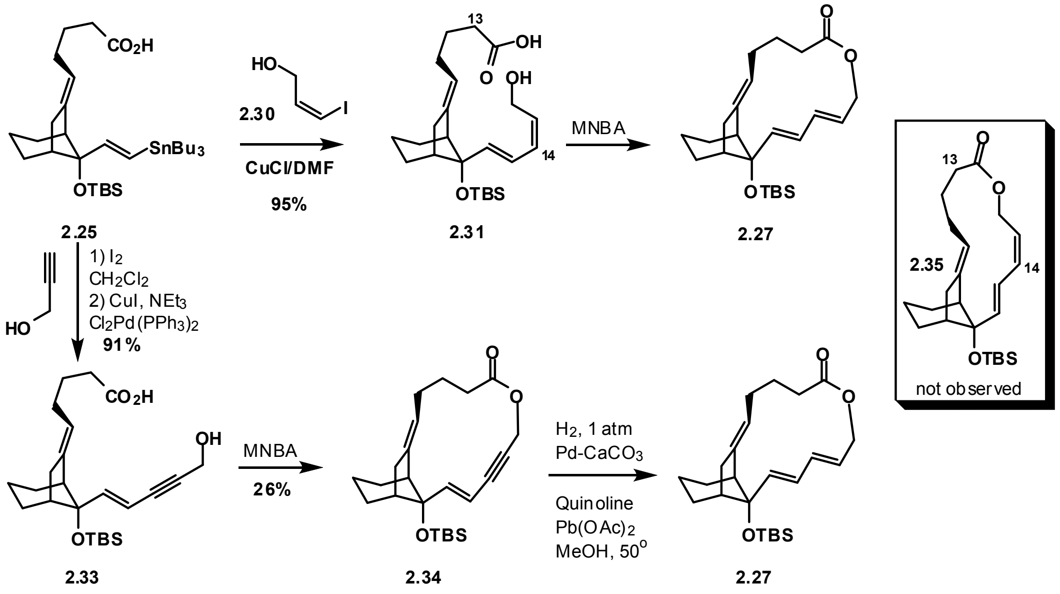


2.27 **2.28**

Scheme 2.6: Attempted Ireland-Claisen on macrolactone **2.27**

2.2: Second Generation Macrolactone Approach

We hypothesized that the Ireland-Claisen transformation on this particular substrate may be difficult due to the relatively rigid macrocycle; most of the carbons in this 14-membered ring are locked in place due to the [3.2.1] bicycle and conjugated *trans-trans* dienyl fragments of the ring. Therefore, we briefly considered a readily accessible substrate (*trans-cis* macrolactone **2.35**) through established chemistry that might drastically change the conformation of the ring and bring the reacting carbons C13 and C14 closer together, greatly enhancing the probability of achieving the rearrangement (Scheme 2.7). Two approaches were attempted in the preparation of this substrate. Vinyliodide **2.30** was coupled to the vinyltin intermediate **2.25** using stoichiometric copper(I) followed by our previously optimized MNBA protocol. Surprisingly, the *trans-trans* macrocycle **2.27** was isolated. We assumed that the targeted trans-cis macrolactone isomerized under the reaction conditions to relieve strain and considered *syn* reduction of an enyne to forge the C14-C15 *Z* olefin. Sonogashira[22] cross coupling of the **2.25**-derrived vinyliodide with propargyl alcohol proceeded in high yield and set the stage for macrocyclization, which gave the cyclic enyne **2.34** in 26% yield. Lindlar[23] reduction of this substrate again led to isolation of the *trans-trans* macrolactone and we have concluded that the desired *trans-cis* dienyl macrocycle **2.35** is a transient species at room temperature and rapidly isomerizes to relieve ring strain.


CO2H
SnBu3
OTBS
2.25
HO
2.30
CuCl/DMF
95%
13
OH
O
OH
14
OTBS
2.31
MNBA
O
O
OTBS
2.27
13
2.35
14
OTBS
not observed
HO
1) I2
CH2Cl2
2) CuI, NEt3
Cl2Pd(PPh3)2
91%
CO2H
OH
OTBS
2.33
MNBA
26%
OTBS
2.34
H2, 1 atm
Pd-CaCO3
Quinoline
Pb(OAc)2
MeOH, 50°
OTBS
2.27

Scheme 2.7: Synthesis of C14-C15 *cis* (*Z*) macrolactone

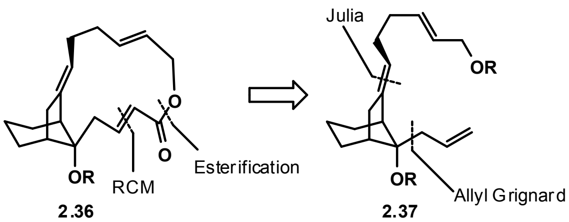
2.3: Third Generation Macrolactone Approach

We then considered the possibility of inverting the polarity of the Ireland-Claisen rearrangement and moving the C7-C8 double bond over 1 carbon (to C8-C14) for better ring flexibility. Swapping the positions of the allylic and ester linkages within the macrocycle revealed target structure **2.36**, which we planned to close via macrolactonization or ring-closing metathesis (Scheme 2.8).

---

[22] Sonogashira, K. in *Comp. Org. Synth.* (eds. Trost, B.M.; Fleming, I.) *3*, 521 (pergamon, Oxford, **1991**)

[23] Lindlar, H.; Dubuis, R. *Org. Synth.* **1973**, *5*, 880



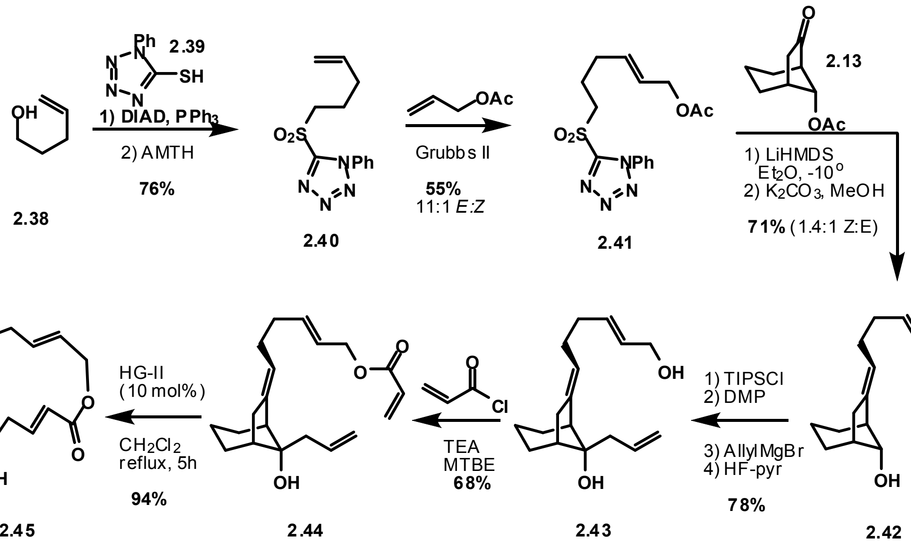
2.36 **2.37**

Scheme 2.8: Retrosynthesis of macrolactone **2.36**

The Julia coupling fragment **2.41** was accessed in three routine transformations: Mitsunobu[24] coupling of 4-pentenol **2.38** and thiol **2.39**, oxidation to the sulfonate, and cross metathesis with allyl acetate (Scheme 2.9). Julia olefination proceeded cleanly with poor selectivity, giving primarily the undesired (*Z*) olefin in a 1.4:1 ratio of **2.42*Z*** to **2.42*E***. Deprotection of the acetates was followed by selective silylation of the primary alcohol. Dess-Martin[25] oxidation of the secondary alcohol cleanly delivered the ketone to which was added allylmagnesium bromide. The crude material was treated with HF-pyridine to remove the TIPS protecting group and diol **2.43** was isolated in 78% yield over 4 steps (one column). Esterification with acryloyl chloride delivered enoate **2.44** which cleanly underwent Hoveyda-Grubbs II-catalyzed ring-closing metathesis under dilution to close the macrocyclic ring system **2.45**.

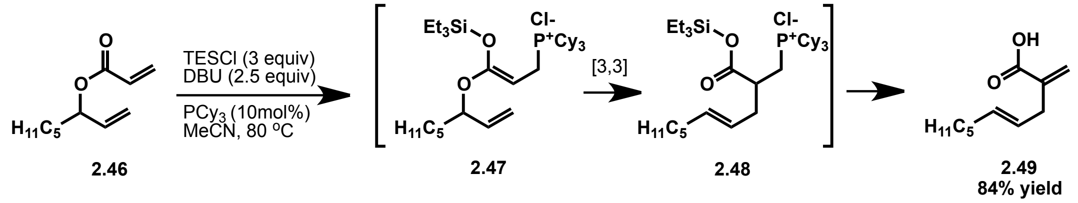
---

[24] Mitsunobu, O. *Synthesis* **1981**, 1-28.
[25] Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155.


2.38
2.39
1) DIAD, PPh3
2) AMTH
76%
2.40
Grubbs II
55%
11:1 E:Z
2.41
2.13
1) LiHMDS
Et2O, -10°
2) K2CO3, MeOH
71% (1.4:1 Z:E)
2.42
1) TIPSCl
2) DMP
3) AllylMgBr
4) HF-pyr
78%
2.43
TEA
MTBE
68%
2.44
HG-II
(10 mol%)
CH2Cl2
reflux, 5h
94%
2.45

Scheme 2.9: Sythesis of macrolactone **2.45**

After extensive experimentation, we were unable to identify conditions for the formation of the desired silyl ketene acetal of 2.45 under standard soft (R_3SiOTf, Et_3N) or hard (LDA or MHMDS, R_3SiCl in THF/HMPA)) enolization conditions. We then took note of a report by Inanaga[26] for phosphine-catalyzed Ireland-Claisen rearrangements. Conjugate addition of tricyclohexylphosphine and subsequent trapping as the silyl ketene acetal phosphonium salt is followed by [3,3] rearrangement and $E1_{CB}$ elimination of the phosphine.

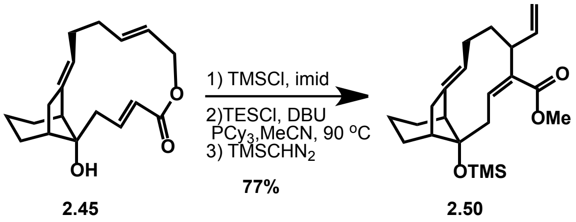

2.46
TESCl (3 equiv)
DBU (2.5 equiv)
PCy3 (10mol%)
MeCN, 80 °C
2.47
[3,3]
2.48
2.49
84% yield

Scheme 2.10: Phosphine-catalyzed Ireland-Claisen rearrangement by Inanaga

Delightfully, subjection of the TMS ether of **2.45** to these conditions followed by esterification with TMS-diazomethane delivered enoate **2.50** in high yield (Scheme 2.11). This was a particularly exciting phase of the program since this was the first time we were able to access the targeted 10-membered ring system.

---

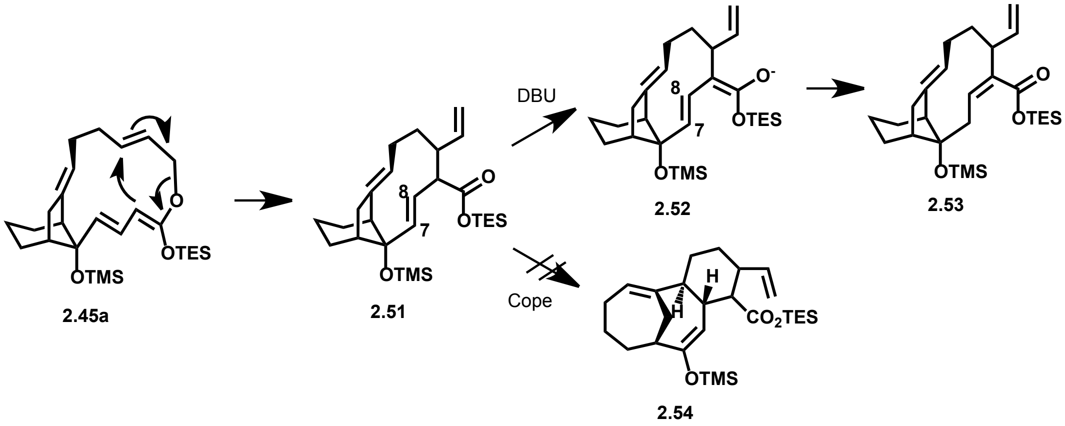
[26] Hanamoto, T.; Baba, Y.; Inanaga, J. *J. Org. Chem.* **1993**, *58*, 299.



OH
2.45
1) TMSCl, imid
2)TESCl, DBU
PCy3,MeCN, 90 °C
3) TMSCHN2
77%
OTMS
OMe
2.50

Scheme 2.11: Claisen ring contraction to give ten-membered ring **2.50**

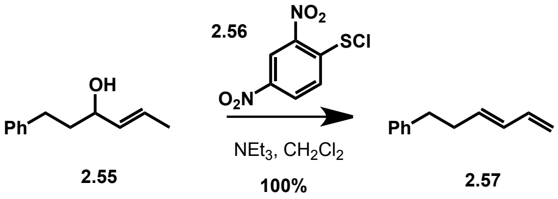
A series of control experiments on the Ireland-Claisen ring contraction rearrangement (**2.45** to **2.50**) later revealed the reaction proceeds cleanly in the absence of phosphine, implicating a γ-deprotonation pathway through the action of DBU, a previously unreported method for the formation of silyl ketene acetals. This means that the C7-C8 double bond is (at least momentarily) in the necessary position for a viable Cope reaction, but instead slides back into conjugation with the ester, presumably via enolization of the silyl ester by DBU followed by γ proton capture (Scheme 2.12). This enticing realization led us to consider the possibility of a tandem Claisen-Cope cascade proceeding directly from the macrolactone to deliver the tricyclic ABC core.



OTMS
OTES
2.45a
8
7
OTES
OTMS
2.51
DBU
Cope
8
7
O-
OTES
OTMS
2.52
OTES
OTMS
2.53
H
H
CO2TES
OTMS
2.54

Scheme 2.12: Alkene isomerization versus Cope reaction of intermediate **2.51**

In order to test the critical Cope rearrangement, unsaturation was required at C7-C8. Attempts to deconjugate enoate **2.50** with a variety of bases and addition-elimation protocols failed to deliver a viable Cope substrate. We then took note of a method first reported by Reich[27] for the preparation of 1,3-dienes from allylic alcohols via [2,3] rearrangement followed by elimination (Scheme 2.13).

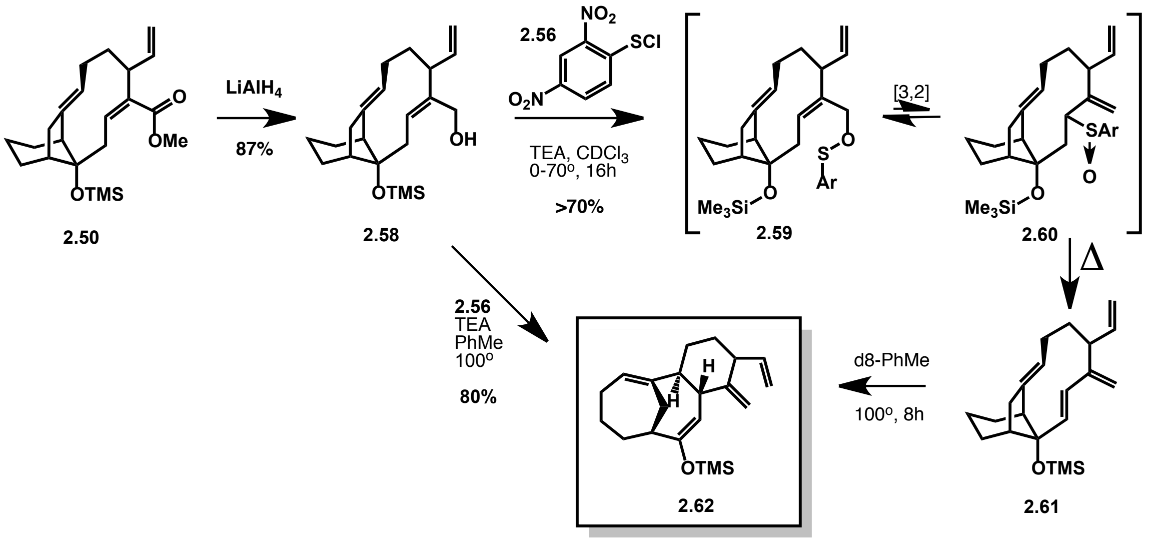


Scheme 2.13: Net 1,4-dehydration reaction to give 1,3-diene **2.57** reported by Reich

Reduction of the methyl ester **2.50** with $LiAlH_4$ gave allylic alcohol **2.58** (Scheme 2.14**).** Subjection of this material to 2,4-dinitrobenzenesulfenyl chloride **2.56** cleanly delivered the sulfenate ester **2.59**. Heating of **2.59** induced reversible [3,2] Mislow-Evans-type rearrangement to give exo-methylene intermediate **2.60**, observable by ^{1}H NMR. Continued heating of this mixture resulted in the desired elimination to give conjugated diene **2.61** (as well as trace **2.62**). Isolation of this intermediate and further heating in toluene resulted in smooth conversion to [3,3] rearranged product **2.62**. The direct conversion of **2.58** to **2.62** was achieved by subjecting allylic alcohol **2.58** to arylsulfenyl chloride **2.56** and triethylamine in toluene at 100 °C for 18 hours, demonstrating a tandem sulfenylation-[3,2]rearrangement-elimination-Cope rearrangement cascade.

---

[27] Reich, H.J.; Wollowitz, S. *J.Am. Chem. Soc.* **1982**, *104*, 7051.

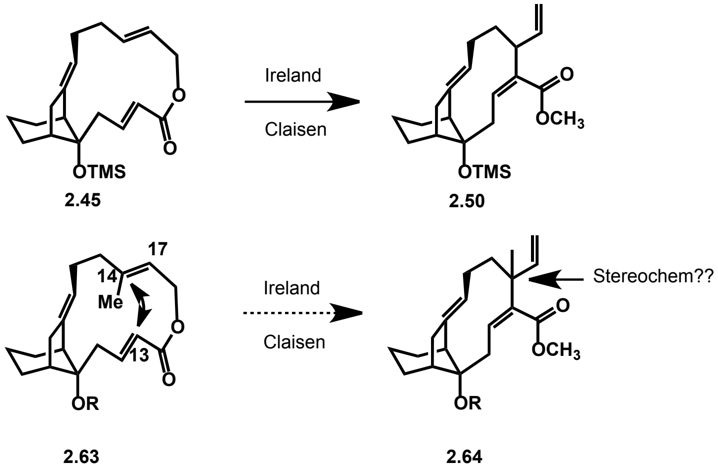

OMe
OTMS
2.50
LiAlH4
87%
OH
OTMS
2.58
2.56
NO2
SCl
O2N
TEA, CDCl3
0-70°, 16h
>70%
S
O
Ar
Me3Si
2.59
[3,2]
SAr
O
Me3Si
2.60
Δ
2.56
TEA
PhMe
100°
80%
H
H
OTMS
2.62
d8-PhMe
100°, 8h
OTMS
2.61

Scheme 2.14: Cope Rearrangement to give ABC ring system

This gratifying result established proof of concept in our proposed strain-driven Cope strategy to forge the ABC ring system of the cyclocitrinol class of steroids. The observation that some Cope product is forming (albeit slowly) at 70 ^{o}C demonstrates massive rate acceleration as compared to a typical Cope rearrangement. This is in line with our initial analysis (Chapter 1, section 3) that the strain caused by the medium sized ring, specifically bringing C8 and C9 into close proximity and pyramidalization at C10, renders this process favorable and delivers an instructive example of a particularly facile siloxy Cope rearrangement.

2.4: Fourth Generation Macrolactone Approach

With proof of concept for our Cope strategy firmly established, we turned our attention to the next major hurdles in the synthesis of the cyclocitrinol core ring system: namely, stereoslective incorporation of the C-19 quaternary methyl, construction of the D ring cyclopentane, and installation of the C-6 enone. Initially, we wished to see if our current macrolactone-Claisen approach could be utilized in meeting these challenges. Ireland-Claisen rearrangements have been shown to set quaternary centers stereoselectively.[28] It was with this notion in mind that we set out to design a macrolactone with a trisubstituted double bond in place at C13-C17 (cyclocitrinol numbering) that would deliver the angular methyl group and at the same time form the 10-membered ring (Scheme 2.15). This strategy then brought into question the nontrivial issue of stereochemistry at the newly formed quaternary center, which would be determined by the C14-C13 bond-forming step.



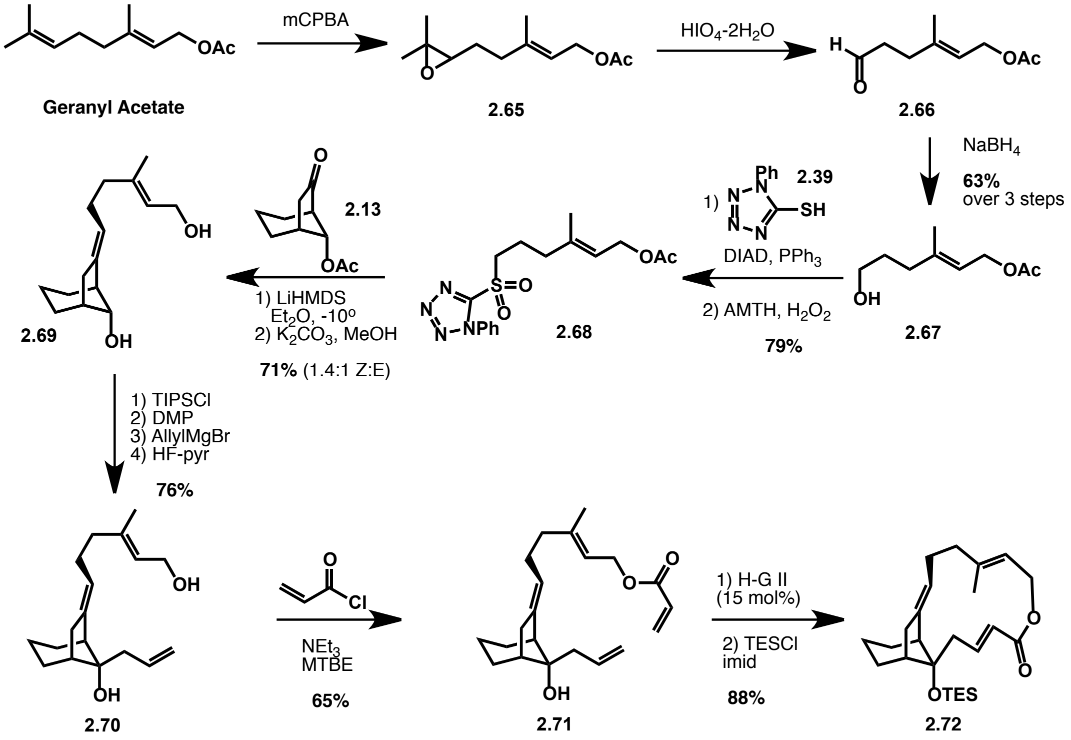
Scheme 2.15: Incorporation of trisubstitued C14-C-17 alkene to install angular (C19) Methyl

Sulfone **2.68** was prepared in a five-step sequence from geranyl acetate in good overall yield. Site selective epoxidation through the controlled addition of mCPBA followed by oxidative cleavage delivered aldehyde **2.66** (Scheme 2.16). This was reduced to the primary alcohol with sodium borohydride to provide **2.67** in 63% yield over 3 steps.[29] Mitsonobu coupling followed by oxidation of the sulfide gave sulfone **2.68** which underwent Julia olefination with [3.2.1]bicyclo ketone **2.13** to deliver a mixture of alkene isomers. This was elaborated into macrocycle **2.72** in the manner previously described (see Scheme 2.9).

---

[28] Gilbert, J.C.; Selliah, R.D. *J. Org. Chem*. **1993**, *58*, 6255.

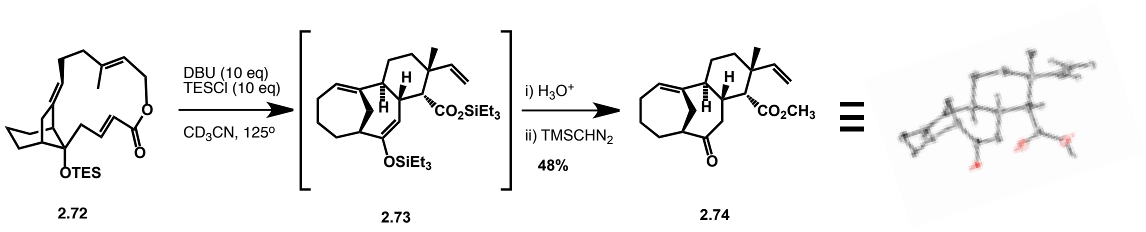
[29] Ukanik, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 5649.



mCPBA
OAc
Geranyl Acetate
2.65
HIO4-2H2O
H
O
2.66
NaBH4
63% over 3 steps
2.67
OH
1) Ph N-N 2.39 SH
DIAD, PPh3
2) AMTH, H2O2
79%
2.68
S=O
NPh
2.13
1) LiHMDS Et2O, -10°
2) K2CO3, MeOH
71% (1.4:1 Z:E)
2.69
1) TIPSCl
2) DMP
3) AllylMgBr
4) HF-pyr
76%
2.70
NEt3
MTBE
65%
Cl
2.71
1) H-G II (15 mol%)
2) TESCl imid
88%
OTES
2.72

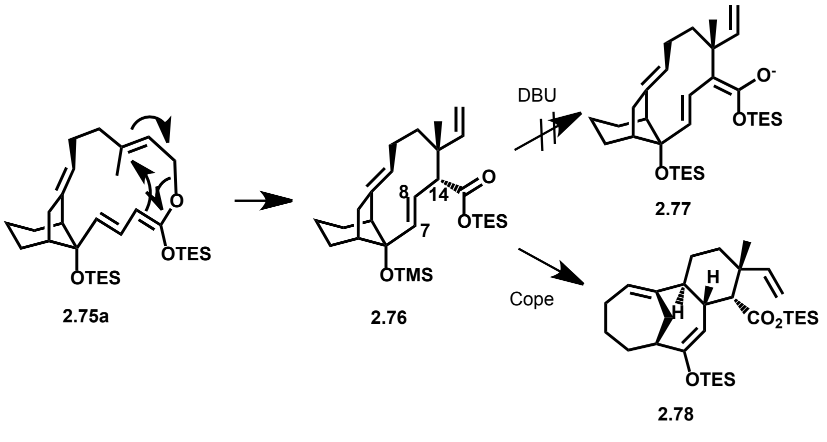
Scheme 2.16: Synthesis of trisubstiruted macrolactone

Upon subjecting this substrate to the Claisen conditions, it was apparent that the reaction was converting to a vinylated species, but required higher temperatures to proceed at a meaningful rate. Interestingly, the new species did not appear to be the desired enoate 10-membered ring analogous to **2.50**. Furthermore, monitoring the reaction by ^{1}H NMR indicated the C-9 trisubstituted olefin proton had shifted significantly upfield, characteristic of the [4.4.1]bicyclo ring system. A doublet at 4.6ppm (corresponding to the silyl enol ether proton in **2.73**) further indicated conversion to the Cope product, implicating a Claisen-Cope cascade of rearrangements to establish the ABC tricyclic core of the natural product had occurred in one pot (Scheme 2.17). Aqueous workup and treatment with TMSCHN$_2$ delivered methyl ester **2.74**.


DBU (10 eq)
TESCl (10 eq)
CD3CN, 125°
i) H3O+
ii) TMSCHN2
48%
H
H
CO2SiEt3
OSiEt3
CO2CH3
O
OTES
O
O
2.72
2.73
2.74

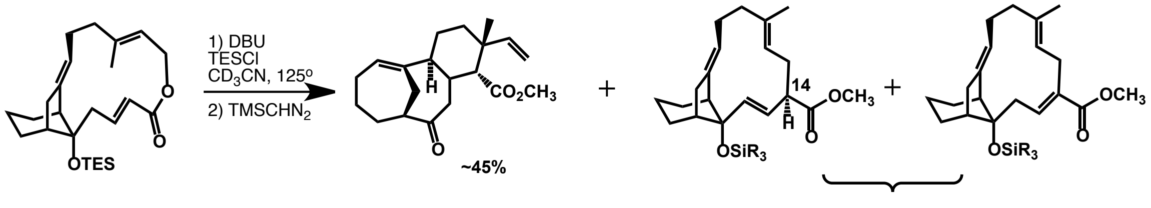
Scheme 2.17: Tandem Claisen-Cope to form ABC tricycle **2.74**

Macrolactone **2.72** undergoes the tandem Claisen-Cope because the C7-C8 double bond that is established during γ-deprotonation by DBU during silyl ketene acetal formation is unable to slide back into conjugation and instead undergoes the Cope to relieve strain. Unlike macrolactone **2.45** (which does not undergo the tandem Claisen-Cope under these reaction conditions), the ten-membered ring **2.76** formed immediately following Claisen rearrangement of **2.75a** cannot be deprotonated at C14 (Scheme 2.18). The silyl ester moiety in this intermediate cannot achieve the required orthogonality with the C14 methine proton in order to render it acidic due to a steric interaction with the adjacent newly formed C13 quaternary center.


OTES
OTES
O
2.75a
8
14
7
O
OTES
OTMS
2.76
DBU
O-
OTES
OTES
2.77
Cope
H
H
CO2TES
OTES
2.78

Scheme 2.18: Tandem Claisen-Cope reaction versus alkene isomerization

The stereochemistry at the putative CD ring junction was determined by a series of 2D NMR experiments and later verified by single crystal X-Ray crystallography.[30] The desired configuration at the C13 quaternary center had been achieved, however, the undesired configuration had been set at C14 and would have to be inverted prior to closure of the D Ring. The *syn* relationship between the vinyl and ester moieties implicates a boat-like transition state in the Ireland-Claisen rearrangement. Furthermore, the decreased yield in this transformation as compared to the Ireland-Claisen rearrangement of substrate **2.45** (see Scheme 2.11) was notable and 12-membered ring byproducts **2.79** and **2.80** were isolated and characterized, accounting for the mass balance.



Scheme 2.19: Byproducts from tandem reaction

Interestingly the configuration at C14 of byproduct **2.79** was *opposite* of that in the Cope product **2.74**. Our initial hypothesis to account for this series of findings was that apparently two boat-like transition states are accessible in the Ireland Claisen rearrangement (**2.81** and **2.83**, Scheme 2.20). Chair-like transition states appear unlikely due to unfavorable 1,3-interactions between the siloxy moiety of the ketene acetal and the allylic methyl group. One of the operable boat TS's delivers a viable Cope substrate which immediately undergoes subsequent rearrangement to deliver the desired ring system **2.78** in order to relieve the considerable strain in the 10-membered ring as planned. The other undergoes a 1,3-shift to relieve strain in the 10-

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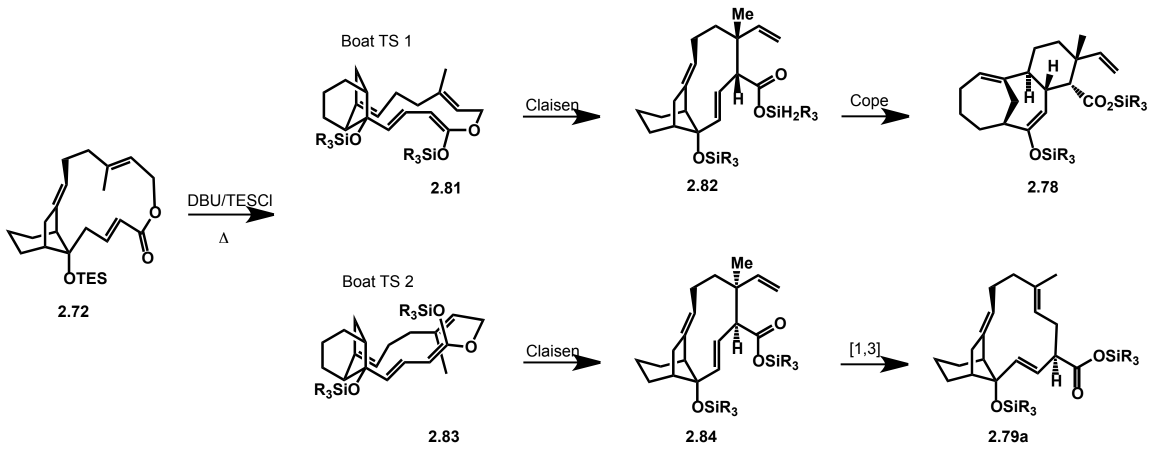
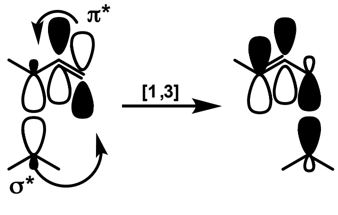
[30] Solved by Aaron Sattler, Columbia University, **2009.**

membered intermediate to deliver byproduct **2.79**. Some of this byproduct is then isomerized to an enoate, accounting for the presence of **2.80**.


Boat TS 1
R$_3$SiO
R$_3$SiO
2.81
Claisen
Me
O
H
OSiH$_2$R$_3$
OSiR$_3$
2.82
Cope
H
H
CO$_2$SiR$_3$
OSiR$_3$
2.78
O
O
OTES
2.72
DBU/TESCl
Δ
Boat TS 2
R$_3$SiO
O
R$_3$SiO
2.83
Claisen
Me
O
H
OSiR$_3$
OSiR$_3$
2.84
[1,3]
OSiR$_3$
H
O
OSiR$_3$
2.79a

Scheme 2.20: Possible Claisen transition states leading to mixture of products

There is another explanation for the inverted configuration at C14 of byproduct **2.79**. The proposed concerted 1,3 sigmatropic shift proceeding with inversion at the migrating carbon is expected due to frontier molecular orbital theory.[31] In order to achieve σ* overlap with the simultaneously shifting π* bond, antarafacial migration is required. This is not possible in our system, so in order to satisfy these stereoelectronic requirements, the migrating carbon C13 shifts *suprafacially* with inversion at C14 (Scheme 2.21). This notion of [1,3] versus [3,3] sigmatropic rearrangements and how it might be impacted to improve the efficiency of this tandem reaction will be revisited in Chapter Four.



Scheme **2.21**: Suprafacial [1,3] sigmatropic shift with inversion at migrating carbon

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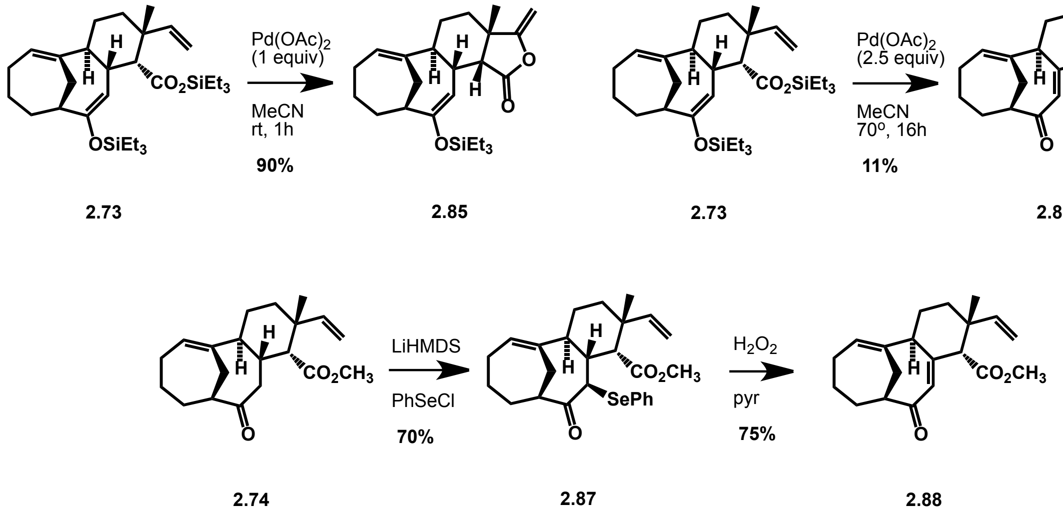
[31] Berson, J.A. *Acc. Chem. Res.* **1968**, *1*, 152.

With **2.74** in hand, we conducted exploratory chemistry that might be applied to the real system. We had originally planned to isolate the silyl enol ether **2.73** arising from the Cope rearrangement and subject it to Pd(OAc)$_2$ in hopes of performing a Saegusa[32] oxidation to install the C6 enone. Unfortunately, Wacker-type activation of the vinyl substituent occurs much more readily and cyclic enol acetate **2.85** was isolated (Scheme 2.22). Forcing conditions did deliver the enone **2.86** in low yield in addition to formation of the enol acetate. Fortunately, we were able to install the C6 enone in reasonable overall yield from **2.74** proceeding through the selenide **2.87** followed by oxidative elimination.



Pd(OAc)2
(1 equiv)
MeCN
rt, 1h
90%
OSiEt3
CO2SiEt3
2.73
2.85
Pd(OAc)2
(2.5 equiv)
MeCN
70°, 16h
11%
2.86
LiHMDS
PhSeCl
70%
H2O2
pyr
75%
CO2CH3
SePh
2.74
2.87
2.88

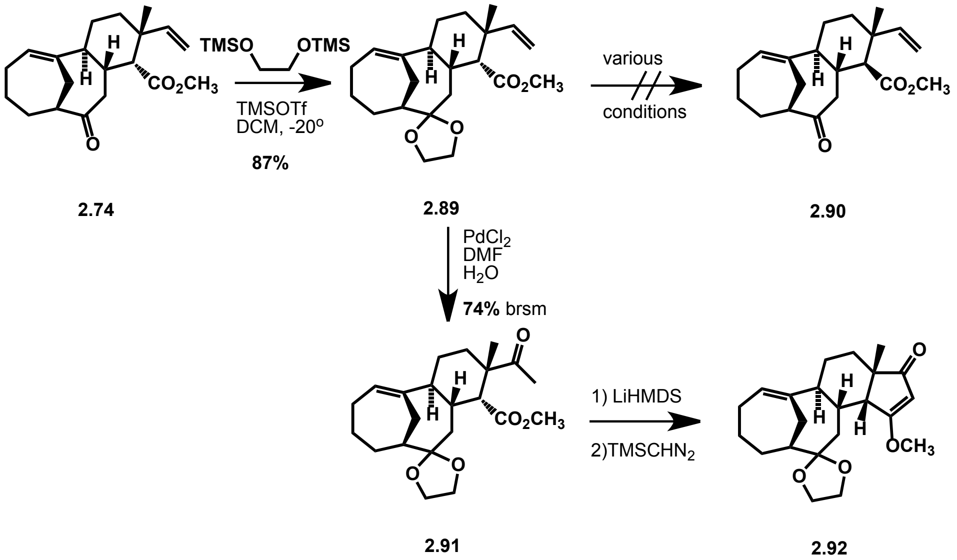
Scheme 2.22: C6 enone installation

Ultimately it was decided that installing the C6 enone would be best performed following D-ring closure and we sought conditions for masking the C6 ketone function. Protection of the ketone using the Nyori protocol[33] was executed in high yield to deliver ketal **2.89**. All attempts at epimerization at C14 failed on this substrate. Based on our attempted Saegusa studies above, we were confident that a Wacker-cyclization sequence should give ready access to D ring closure. This was realized using standard Wacker conditions to give ketone **2.91** (Scheme 2.23). Treatment of this intermediate with LiHMDS followed by $TMSCHN_2$ delivered the vinylagous ester tetracyle **2.92**, epimeric at C14 from the targeted ring system.

---

[32] Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

[33] Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Letters* **1980**, *21*, 1357.


2.74
TMSO OTMS
TMSOTf
DCM, -20°
87%
2.89
various
conditions
2.90
PdCl2
DMF
H2O
74% brsm
2.91
1) LiHMDS
2)TMSCHN2
2.92
H
CO2CH3
O
OCH3

Scheme 2.23: Exploratory C6 and D ring chemistry

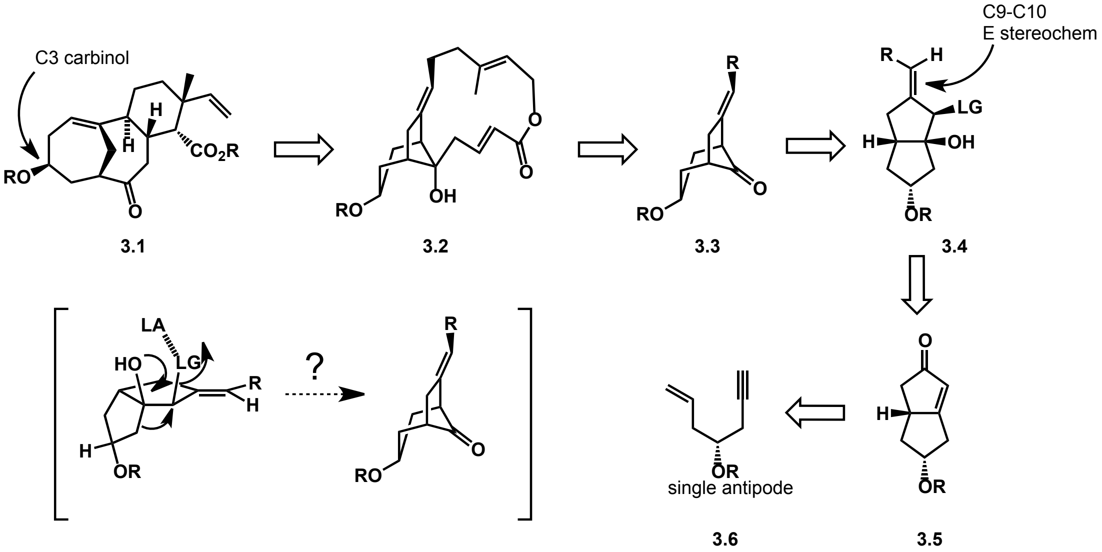
Armed with our newly developed tandem reaction sequence and exploratory results, we endeavored to launch a full assault directed towards securing the fully functionalized tetracycle possessing all of the naturally occurring stereochemistry.

III

2nd Generation Synthesis of [3.2.1] Bicycloketone

3.1: Challenges and Retrosynthetic Analysis

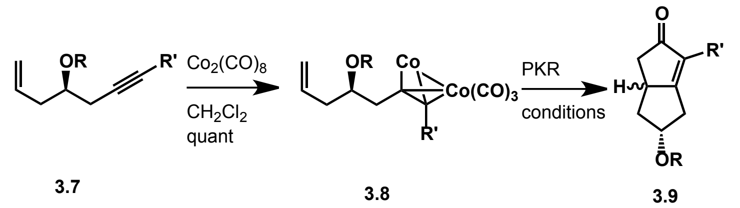
Having secured proof of concept for the tandem Claisen-Cope cascade to construct the ABC core ring system of the cyclocitrinol steroids, we turned our attention to the development of chemistry directed towards synthesizing the real system. We immediately identified several early stage problems that would have to be solved in order to fully capitalize on the results from our validation studies: incorporation of the C-3 carbinol, a stereoselective olefination reaction to form the C9-C10 alkene, and establishment of asymmetry early in the sequence (Scheme 3.1). All of these considerations pointed toward the need for an entirely new synthesis of the bicyclo[3.2.1]octan-8-one.


C3 carbinol
RO
H
H
CO2R
O
3.1
RO
OH
O
O
3.2
R
RO
O
3.3
C9-C10
E stereochem
R
H
LG
H
OH
OR
3.4
LA
HO
LG
R
H
?
H
OR
R
RO
O
OR
single antipode
3.6
O
H
OR
3.5

Scheme 3.1: Retrosynthetic analysis – bicyclo[3.2.1]ketone via pinacol rearrangement

3.2: Pauson-Khand Reaction to establish [3.3.0] enone

When a survey of known methods for the synthesis of bridging carbocycles of this type failed to provide any leads with proper functionalization at the desired positions, we recognized an opportunity to identify new chemistry. The key insight simplifying our retrosynthetic analysis was that a pinacol-type rearrangement of [3.3.0] alkene **3.4** could be expected to deliver the desired bicyclo[3.2.1]ketone **3.3** with the C9-C10 alkene geometry already set. We hoped an olefination reaction on a ketone derived from **3.5** would proceed with the desired E selectivity. The targeted [3.3.0] ring system appeared readily accessible from enyne **3.6** by way of a Pauson-Khand (PKR) reaction.

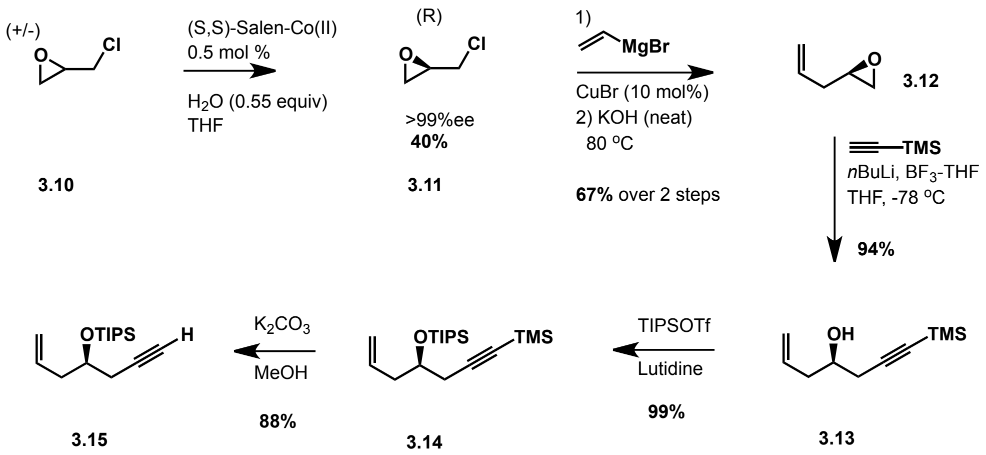


Scheme 3.2: Pauson-Khand Reaction (PKR) cyclocarbonylation

In the event, we were able to obtain (R)-epichlorohydrin **3.11** in very high enantio purity via hydrolytic kinetic resolution (HKR) using Jacobsen's cobalt (II) Salen catalyst (Scheme 3.3).[34] Opening of the epoxide ring with vinylmagnesium bromide in the presence of catalytic amounts of copper (I) bromide was followed by distillation of the crude chlorohydrin product over KOH to give allyl epoxide **3.12** in 67% yield.[35] A second epoxide opening with lithium TMS acetylide provided enynol **3.13** in high yield. TIPS protection of the secondary alcohol was followed by TMS removal to give the enyne PKR substrates **3.13** and **3.14**, respectively.

---

[34] Furrow, M.E.; Schaus, S.E.; Jacobsen, E.N. *J. Org. Chem.* **1998**, *63*, 6776.
[35] De Camp Schuda, A.; Mazzocchi, P.H.; Fritz, G.; Morgan, T. *Synthesis* **1986**, 309.


(+/-)
Cl
O
(S,S)-Salen-Co(II)
0.5 mol %
H2O (0.55 equiv)
THF
(R)
>99%ee
40%
1)
MgBr
CuBr (10 mol%)
2) KOH (neat)
80 °C
67% over 2 steps
3.10
3.11
3.12
TMS
nBuLi, BF3-THF
THF, -78 °C
94%
OTIPS
H
K2CO3
MeOH
88%
TMS
TIPSOTf
Lutidine
99%
OH
3.15
3.14
3.13

Scheme 3.3: Synthesis of Enynes for PKR reaction

All three enyne intermediates (**3.13**, **3.14**, and **3.15**) were complexed with one equivalent of $Co_2(CO)_8$ and subjected to a screen of standard PKR conditions. Attempted cyclocarbonylation of enynol **3.13** after complexation with $Co_2(CO)_8$ did not lead to any PKR product under any of the conditions examined (Scheme 3.4). We reasoned that a large protecting group on the alcohol might provide some angle compression, forcing the alkene closer to the cobalt-complexed alkyne, leading to cyclization. It was also thought that perhaps the bulky TMS group was slowing the rate of cyclocarbonylation. Consistnet with this line of reasoning, both substrates **3.14** and **3.15** underwent cyclocarbonylation in warm acetonitrile[36] to give a mixture of diastereomeric enones. We observed a slight improvement in isolated yield when the reaction was run under a balloon pressure of CO. Terminal alkyne **3.15** proceeded more efficiently to enones **3.21a** and **3.21b** but surprisingly showed no diastereoselectivity in the cyclocarbonylation reaction while TMS-enyne **3.14** showed some selectivity for the undesired exo diastereomer.

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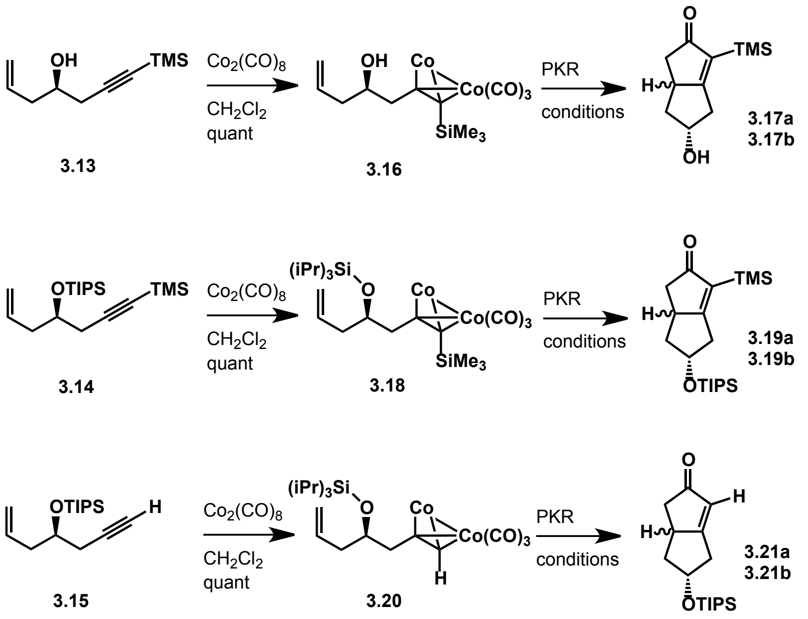
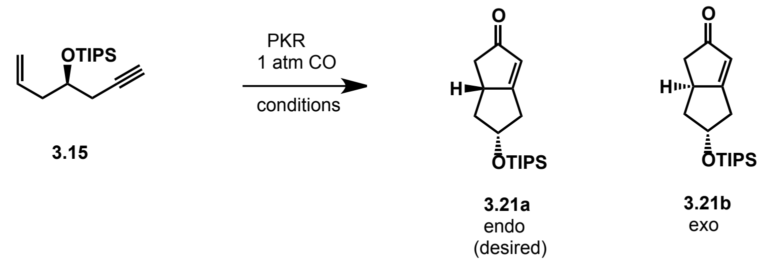
[36] Hoye, T.R.; Suriano, J.A. *J. Org. Chem.* **1993**, *58*, 1659.


OH
TMS
Co$_2$(CO)$_8$
CH$_2$Cl$_2$
quant
3.13
OH
Co
Co(CO)$_3$
SiMe$_3$
3.16
PKR
conditions
O
TMS
H
OH
3.17a
3.17b
OTIPS
TMS
Co$_2$(CO)$_8$
CH$_2$Cl$_2$
quant
3.14
(iPr)$_3$Si
O
Co
Co(CO)$_3$
SiMe$_3$
3.18
PKR
conditions
O
TMS
H
OTIPS
3.19a
3.19b
OTIPS
H
Co$_2$(CO)$_8$
CH$_2$Cl$_2$
quant
3.15
(iPr)$_3$Si
O
Co
Co(CO)$_3$
H
3.20
PKR
conditions
O
H
H
OTIPS
3.21a
3.21b

Conditions	Yield	endo/exo (a/b)
MeCN, 60 °C 4 A mol sieves	0	NA
CH$_2$Cl$_2$, NMO rt, 16h	0	NA
DME, 1 atm CO 55 °C 16h	0	NA
CH$_2$Cl$_2$, NMO rt, 16h	0	NA
MeCN, 55 °C 18 h	10	1 : 2.5
MeCN, 65 °C 44 h	50	1 : 1.6
CH$_2$Cl$_2$, NMO rt, 16h	66	1 : 1
MeCN, 55 °C 16 h	64	1 : 1
MeCN, 55 °C 16 h, 1 atm CO	**83**	**1 : 1**

Scheme 3.4: PKR of various enynes following complexation by Co$_2$(CO)$_8$

With an efficient PKR protocol in hand we set out to further improve the reaction for scalability with an eye towards rendering the transformation catalytic in metal (i.e. circumvention of the pre-complexation step) and improving the diastereomeric ratio. It remained an open question how we might force the large siloxy group into the concave face of the [3.3.0] ring system but we were optimistic we might find a lead with a screen of transition metals known to catalyze such cyclocarbonylations and apply chiral ligands to induce reagent control of diastereoselectivity.



3.15

3.21a endo (desired)

3.21b exo

entry	catalyst-mol%	solvent	additive(equiv)	temp	exo/endo	yield
1	$Co_2(CO)_8$-100	MeCN	none	50	1.0	81
2	$Co_2(CO)_8$-10	DME	none	70	1.8	37
3	$Co_2(CO)_8$-10	DME	$CyNH_2$ (0.2)	70	1.2	20
4	$Co_2(CO)_8$-10	DME	$P(OPh)_3$ (0.3)	85	1.4	32
5	$Co_2(CO)_8$-10	PhH	Bu_3PS (0.2)	70	1.0	50
6	$Co_2(CO)_8$-10	PhH	TMTU (0.4)	70	1.0	78
7	$Co_2(CO)_8$-10	PhH	TMTU (0.6)	70	1.0	82
8	**$Co_2(CO)_8$-5**	**PhH**	**TMTU (0.3)**	**70**	**1.0**	**82**
9	$Co_2(CO)_8$-20	DME	(S)BINAP (0.2)	70	1.2	30
10	$Co_2(CO)_8$-10	PhH	TETRATU (0.6)	70	1.0	42
11	$Co_2(CO)_8$-10	PhH	(S)BINAP (0.2)	70	3.0	30

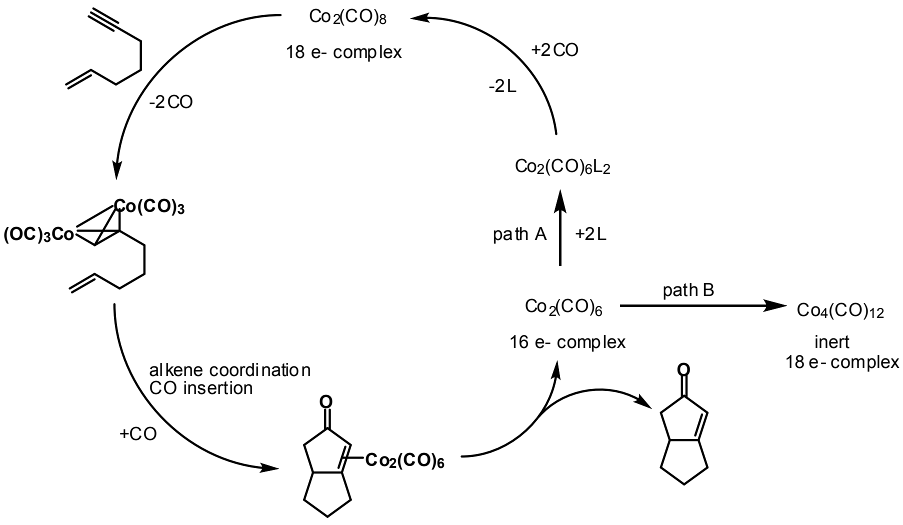
Table 3.1: One-Pot catalytic Pauson-Khand reactions

Since we were able to achieve high efficiency in the Cobalt-mediated PKR, we initially examined a series of known additives combined with catalytic Co loading (Table 3.1).[37] The fundamental issue at hand is identifying a transient ligand that will prevent decomposition of the cobalt to a tetrameric inert species (path B, Scheme 3.5), occupying a coordination site long enough for another CO to complex the cobalt metal center and regenerate the active dicobalt octacarbonyl complex. Yang's method[38] worked perfectly in this regard as tetramethyl thiourea in benzene provided products in excellent yields, but poor d.r. Unfortunately, employment of BINAP or the chiral thiourea TETRATU failed to improve the diastereoselectivity. This was expected as the ligand is presumably not coordinated to the metal during the C-C bond-forming step so we considered other transition metals to which chiral phosphines are known to tightly coordinate.

---

[37] (a)Belanger, D.B.; Mahony, D.J.; Livinghouse, T. *Tetrahedron Lett.* **1998**, *39*, 7637. (b) Jeong, N.; Hwang, S.H.; Lee, Y.; Chung, Y.K. *J. Am Chem. Soc.* **1994**, *116*, 3159. (c) Kraft, M.E.; Bonaga, V.R.; Hirosawa, C. *Tetrahedron Lett.* **1999**, *40*, 9171. (d) Hayashi, M.; Hashimoto; Y.; Yamamoto, Y.; Usuki, J.; Saigo, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 631.

[38] Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 593.



Scheme 3.5: PKR catalytic cycle: achieving turnover of $Co_2(CO)_8$

Palladium[39], rhodium[40], and iridium[41] complexes were screened, identifying a lead in the $(RhCl[cod])_2$ dimer which delivered a modest yield of bicyclic enone products.[42] We determined that the low yield for the Rh-mediated PKR-type reactions was likely due to a competing alkyne polymerization pathway and sought to shut this down through the employment of TMS substrate **3.14** (Scheme 3.6). Delightfully this enyne underwent cyclocarbonylation reasonably efficiently when mediated by a cationic rhodium (I) catalyst (generated from $[RhCl(CO)_2]_2$ and AgOTf)[39b] to give 67% product with just 5 mol % loading of the catalyst. Unfortunately this system delivered the product in very high (16:1) d.r. favoring the wrong diastereomer **3.19b**. We were unable to over turn the resident facial bias through the employment of chiral phosphines.

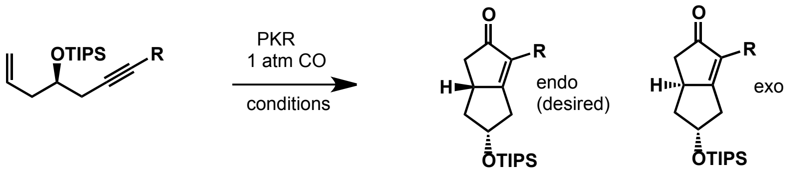
---

[39] Deng, L.J.; Jing, L.; Huang, J.Q.; Yanhe, H.; Chen, M.; Lan, Y.; Chen, J.H.; Lei, A.; Yang, Z. *Synthesis* **2007**, 2565.

[40] (a) Jeong, N.; Lee, S.; Sung, B. *Organometallics* **1998**, *17*, 3642 (b) Jeong, N.; Sung, B.K.; Yoon, K.C. *J. Am. Chem. Soc.* **2000**, *122*, 6771.

[41] Shibata, T.; Takagi, K. *J. Am. Chem. Soc.* **2000**, *122*, 9852.

[42] Experiments performed by summer REU student Andrew Neel, Columbia University, **2010**



3.14 (R = TMS)
3.15 (R = H)

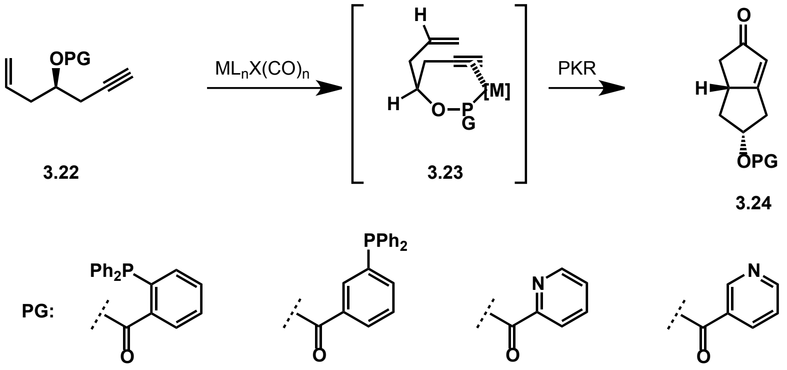
3.19a (R = TMS)
3.21a (R = H)

3.19b (R = TMS)
3.21b (R = H)

entry	R	catalyst-mol%	solvent	additive(equiv)	temp	exo/endo	yield
1	H	PdCl2 - 3	THF	TMTU, LiCl	60	-	trace
2	H	$[RhCl(cod)]_2$ - 5	PhMe	dppp	100	1.5	26
3	H	$[IrCl(cod)]_2$ - 10	PhMe	PPh_3	110	-	trace
4	TMS	$[RhCl(CO)_2]_2$ - 5	PhMe	none	100	1.5	40
5	TMS	$[RhCl(CO)_2]_2$ - 5	PhMe	AgOTf	70	16	67
6	TMS	$[RhCl(CO)_2]_2$ - 5	PhMe	AgOTf/(S)BINAP	70	>20	62

Table 3.2: PKR-type reactions with catalytic Pd, Rh, Ir

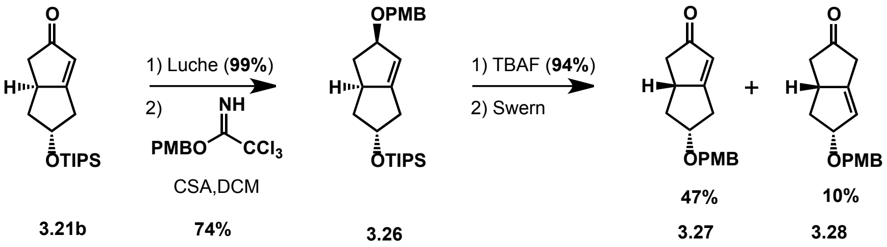
Next we examined the possibility of directing the metal into the alkyne with a coordinating substituent on the C3 carbinol which would necessarily place the coordinating group on the concave face of the bicyclic ring system (see proposed transition state **3.23**, Scheme 3.6). Several substrates were prepared, unfortunately none of them underwent productive PK-type reaction, generally returning nearly all of the starting material. We concluded that the metal sits on the coordinating heteroatom in a conformation pointing away from the alkyne and is unavailable to participate in the cyclocarbonylation.



3.22 **3.23** **3.24**

Scheme 3.6: *Endo*-selective PKR via directing sustituents

Since we were unable to direct the selective formation of the desired enone diastereomer through either substrate or reagent control, we considered inversion of the undesired diastereomer, noting an element of pseudo-symmetry. Luche[43] reduction of exo enone **3.21b** gave a single diastereomeric allylic alcohol which was protected as the PMB ether **3.26** (Scheme 3.7)**.** TBAF removal of the TIPS protecting group revealed a secondary alcohol which was oxidized under Swern conditions. The resulting β−γ unsaturated ketone **3.28** was mostly isomerized to the desired **3.27**, presumably through the action of triethylamine in the Swern reaction. This unoptimized sequence provides proof of concept that the exo diastereomer can be utilized in the synthesis, though a more concise and efficient method is desired.



Scheme 3.7: Inversion of *exo* diastereomer

3.3: Pinacol Rearrangement to forge bicyclo[3.2.1]octan-8-one

Diastereoslectivity issues aside, we were delighted to have a concise and scalable process in place for the decagram preparation of enone **3.21a** and turned our attention to converting this species into the aforementioned pinacol rearrangement substrate (Scheme 3.8). Dihydroxylation of enone **3.21a** followed by acetonide formation delivered ketone **3.30**. Attempted Julia olefination on this substrate returned only starting material. We reasoned that the trajectory of the lithio-sulfone nucleophile from the convex face into the ketone was blocked by one of the acetonide methyl groups of **3.30** and instead prepared benzylidine acetal derivative **3.32**, which proceeded in poor yield. These results combined with the realization that the planned dihydroxylation-protection-olefination-deprotection-tosylation-pinacol sequence was something less than concise, we endeavored to design a more direct sequence.

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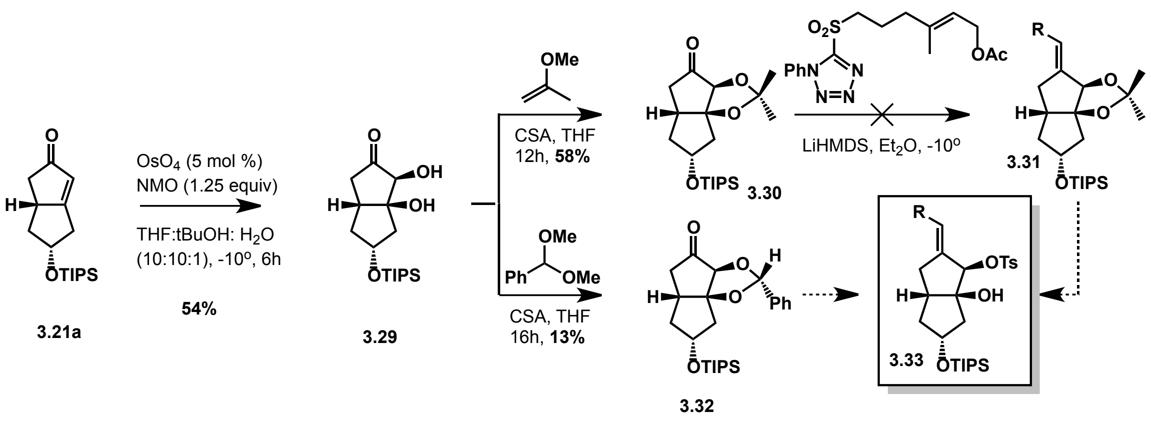
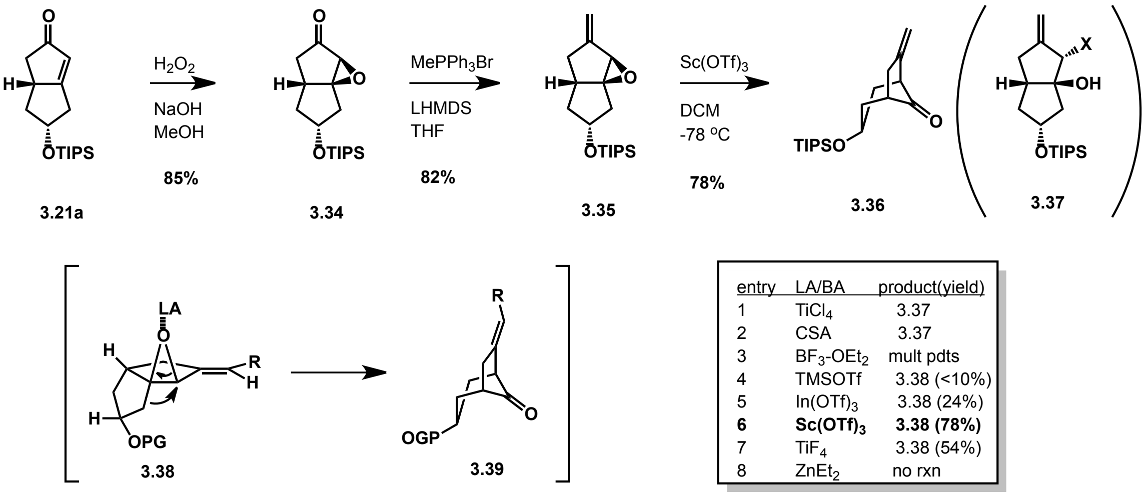
[43] Luche, J.L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.


OsO4 (5 mol %)
NMO (1.25 equiv)
THF:tBuOH: H2O (10:10:1), -10°, 6h
54%
3.21a
3.29
OTIPS
OH
OMe
CSA, THF 12h, 58%
Ph
OMe
CSA, THF 16h, 13%
3.30
3.32
PhN
N=N
O2S
OAc
LiHMDS, Et2O, -10°
3.31
3.33
R
OTs
Ph

Scheme 3.8: Attempted route to pinacol substrate **3.33**

It seemed reasonable that a similar rearrangement might be possible on an epoxide of type **3.38**, which had the added virtue of being readily accessible from enone **3.21a**. Enone epoxidation with alkaline hydrogen peroxide followed by Wittig methenylation delivered **3.35** in high yield (Scheme 3.9). Our initial attempts at the proposed Lewis acid-mediated rearrangement were not encouraging as $TiCl_4$ resulted in chlorohydrin product **3.37** and BF_3-OEt_2 returned a complex mixture. Fortunately, a more extensive screen of Lewis acids revealed that $Sc(OTf)_3$ in CH_2Cl_2 at -78 °C effected clean rearrangement to the desired bridging [3.2.1] ketone **3.36**.

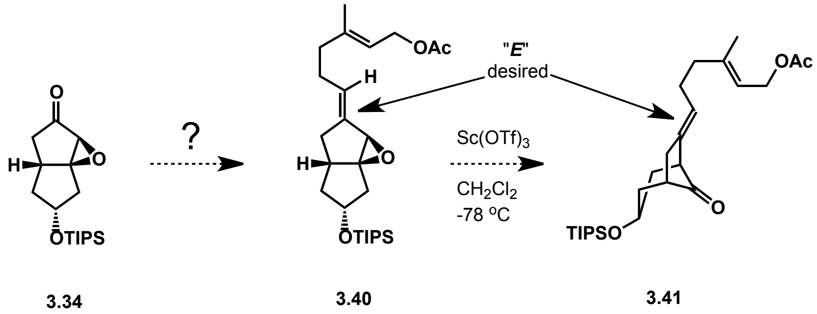

3.21a
H₂O₂
NaOH
MeOH
85%
3.34
MePPh₃Br
LHMDS
THF
82%
3.35
Sc(OTf)₃
DCM
-78 °C
78%
3.36
3.37
TIPSO
OTIPS
X
OH
LA
OPG
R
3.38
OGP
3.39

entry	LA/BA	product(yield)
1	$TiCl_4$	3.37
2	CSA	3.37
3	BF_3-OEt_2	mult pdts
4	TMSOTf	3.38 (<10%)
5	$In(OTf)_3$	3.38 (24%)
6	**$Sc(OTf)_3$**	**3.38 (78%)**
7	TiF_4	3.38 (54%)
8	$ZnEt_2$	no rxn

Scheme 3.9: Synthesis of bicycle[3.2.1]ketone **3.36** via epoxide rearrangement

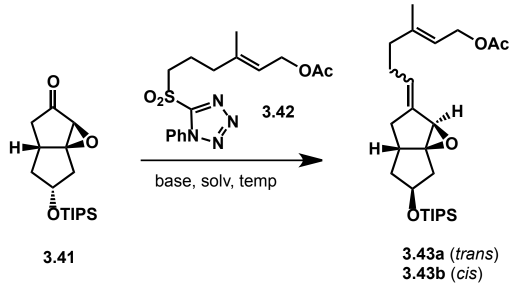
3.4: Carbonyl olefination reactions to establish C9-C10 alkene

With encouraging proof of concept for the key scandium triflate-mediated epoxide rearrangement forging the bicyclo [3.2.1] octane ring system, we turned our attention to the nontrivial problem of stereoselective olefination of epoxyketone **3.34** to fashion the *trans* ("*E*") C9-C10 trisubstitued olefin (Scheme 3.10)


3.34
?
3.40
OAc
"E"
desired
Sc(OTf)₃
CH₂Cl₂
-78 °C
3.41
OTIPS
TIPSO

Scheme 3.10: Selective C9-C10 Olefination-Rearrangement Sequence

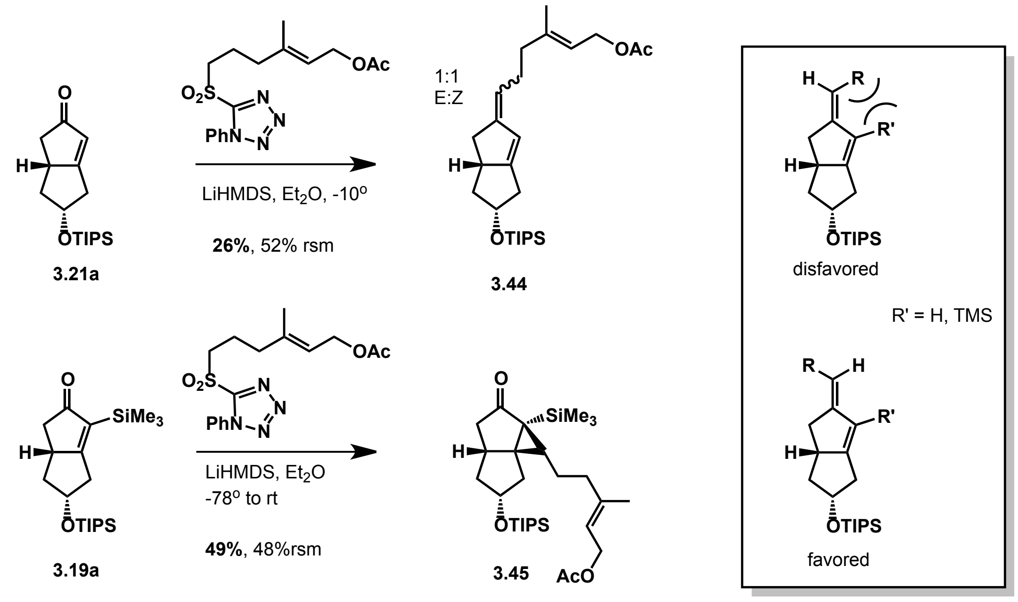
Julia-Kochenski olefination under standard conditions (LiHMDS, Et_2O) proceeded efficiently but slightly favored the undesired *Z* olefin. An extensive screen of conditions varying counterion, solvent polarity, and additives failed to improve the overall yield of the desired E vinyl epoxide **3.43a** (Table 3.3). Additionally, unreacted starting material was recovered in each run, presumably due to competing enolization of the keto epoxide.



entry	base	solv	temp	Z/E	yield	rsm	additive
1	LiHMDS	Et_2O	-78	1.5	68	24	
2	KHMDS	Et_2O	-78	1.5	25	24	
3	LiHMDS	THF/DMF	-78	2.2	49	43	
4	NaHMDS	DMF/DMPU	-78	0.9	60	17	
5	KHMDS	THF/DMPU	-10	0.7	9	72	
6	KHMDS	DMF/DMPU	-78	0.6	28	38	
7	LiHMDS	THF	-78	1.4	59	23	LiCl (5x)
8	LiHMDS	THF	-78	1.3	66	17	$MgBr_2$ (2x)
9	KHMDS	THF	-78	1.0	76	21	HMPA (4x)
10	KHMDS	THF	0	1.0	72	26	

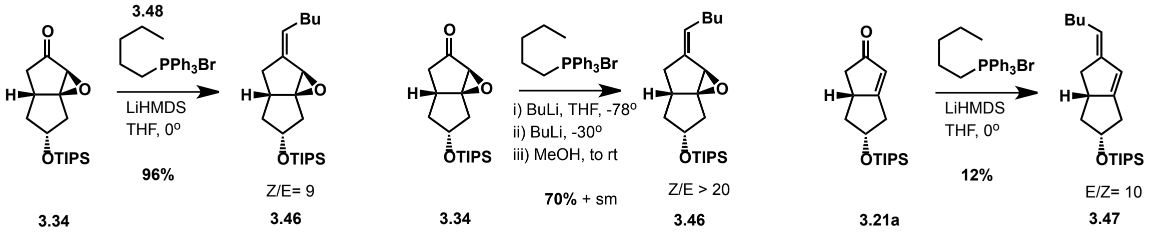
Table 3.3: Julia-Kocienski reaction on keto epoxide to form C9-C10 olefin

Apparently the epoxide function was not providing sufficient steric bias to favor the desired *E* olefin. We reasoned that the vinyl proton in enone **3.21a** might provide enough steric interaction to promote formation of the desired E olefin and if so, we might effect a selective epoxidation on the resulting diene (Scheme 3.11). Unfortunately, no selectivity was observed in the Julia olefination of this substrate and we sought to further enhance this steric interaction by subjecting TMS substrate **3.19a** to the reaction conditions. Surprisingly, attempted Julia-Kocienski olefination of this enone resulted in cyclopropanation to give **3.45**. Apparently this ketone is too hindered to undergo olefination adjacent to the bulky TMS group.


OAc
O_2S
PhN
N
LiHMDS, Et_2O, -10°
26%, 52% rsm
1:1
E:Z
OAc
O
H
ŌTIPS
3.21a
H
ŌTIPS
3.44
H
R
R'
H
ŌTIPS
disfavored
R' = H, TMS
R
H
R'
H
ŌTIPS
favored
O
$SiMe_3$
H
ŌTIPS
3.19a
OAc
O_2S
PhN
N
LiHMDS, Et_2O
-78° to rt
49%, 48%rsm
O
$SiMe_3$
H
ŌTIPS
3.45
AcO

Scheme 3.11: Julia-Kocienski reaction on enones to form C9-C10 olefin

Having exhausted numerous possible Julia substrates and conditions we considered other carbonyl-olefination reactions. Wittig olefination on epoxy ketone **3.34** with a model phosphonium salt **3.38** proceeded very efficiently but with high *Z* selectivity (Scheme 3.12). Schlosser-Wittig olefination on the same substrate surprisingly returned exclusively the *Z* isomer. We did, however, observe very high E selectivity for the Wittig reaction on enone **3.21a** but isolated the desired diene **3.47** in unacceptably low yield.


3.48
PPh_3Br
LiHMDS
THF, 0°
96%
O
H
O
ŌTIPS
3.34
Bu
H
O
ŌTIPS
Z/E= 9
3.46
O
H
O
ŌTIPS
3.34
PPh_3Br
i) BuLi, THF, -78°
ii) BuLi, -30°
iii) MeOH, to rt
70% + sm
Bu
H
O
ŌTIPS
Z/E > 20
3.46
O
H
ŌTIPS
3.21a
PPh_3Br
LiHMDS
THF, 0°
12%
Bu
H
ŌTIPS
E/Z= 10
3.47

Scheme 3.12: Wittig olefination with model phosphoium salt

3.5: Cross-Metathesis to Establish C9-C10 Alkene

After the combined failures of the Julia and Wittig-related protocols in stereoselectively forming the desired *E* trisubstituted olefin, and with ready access to vinylepoxide **3.35** we decided to examine the possibility of establishing the C9-C10 trisubstitued double bond by way of a cross metathesis. Metathesis coupling partners **3.50** and **3.52** were accessed from geranyl acetate in three and six routine transformations, respectively.

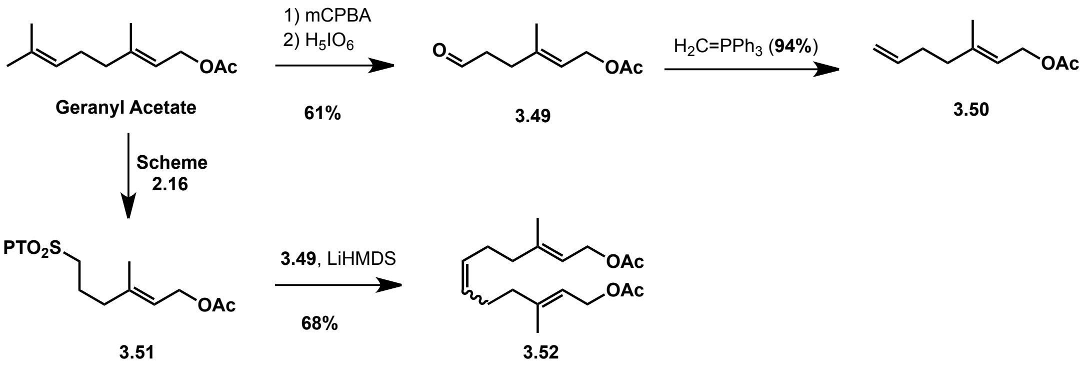
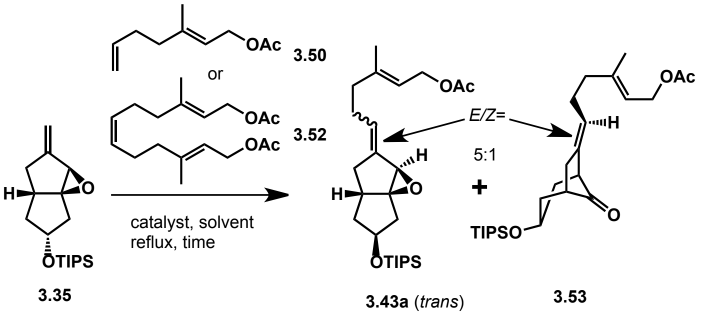


Table 3.13: Synthesis of metathesis coupling partners **3.50** and **3.52**

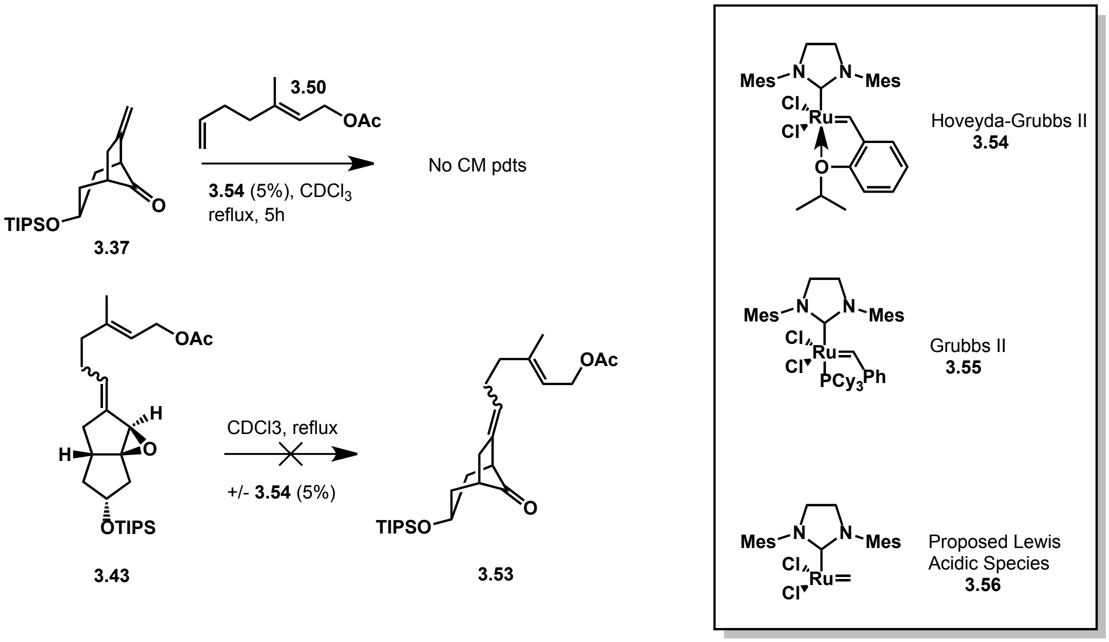
Using high catalyst loads of Grubbs 2nd generation catalyst, cross-metathesis of **3.35** and dienyl acetate **3.50** delivered a mixture of vinyl epoxides **3.43** as well as rearranged product **3.53**, both demonstrating acceptable levels of *E/Z* selectivity. To our delight (after some optimization), we found that cross-metathesis of **3.35** with **3.50** with 5 mol % Hoveyda-Grubbs 2nd generation (HG-II) catalyst delivered exclusively the rearranged [3.2.1] bicyclic ketone in 75% yield as a 4.7:1 (*E/Z*) mixture of alkene isomers. Hence, not only had we identified a stereoslective method for setting the C9-C10 alkene geometry, but we had also stumbled upon a new tandem CM-epoxide rearrangement reaction to generate the targeted bridging ring system, effectively skipping the planned $Sc(OTf)_3$-mediated rearrangement.



Alkene	cat/load (mol%)	solv	time	yield of **7.3**
3.50	G2 / 20	DCM	14	48
3.52	G2 / 10	DCM	20	27
3.50	HG2 / 10	DCM	16	67
3.52	HG2 / 10	DCM	16	58
3.50	**HG2 / 5**	**$CHCl_3$**	**5**	**75**

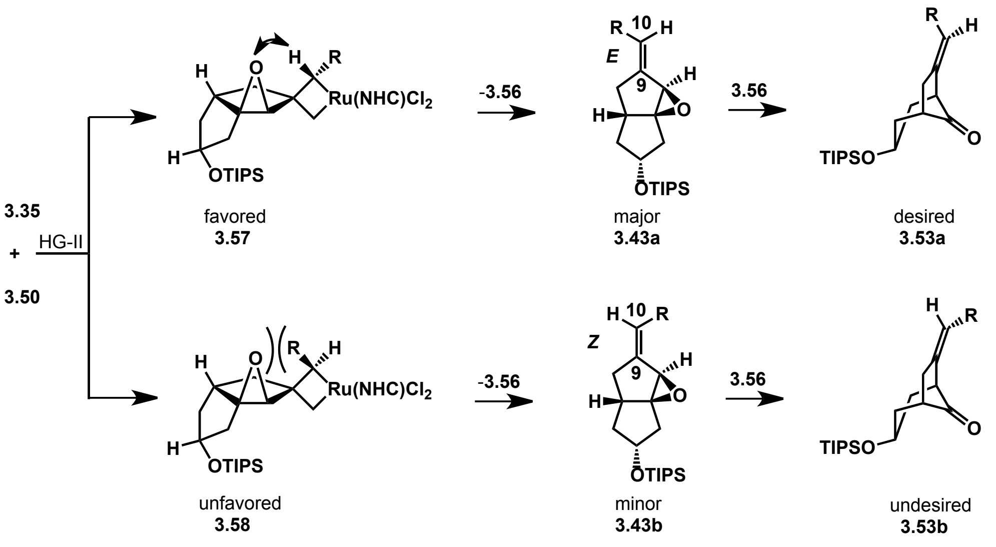
Table 3.4: Tandem cross-metathesis-epoxide rearrangement

A series of control experiments were then conducted to elucidate the precise mechanism of this very interesting tandem reaction (Scheme 3.15). Attempted cross-metathesis of the bicyclo[3.2.1]ketone **3.37** resulted in complete recovery of the starting bicycle (only dimerization of **3.50** was observed), indicating that cross metathesis of vinyl epoxide **3.35** occurs first. Heating of vinyl epoxide **3.43** in chloroform with or without Hoveyda-Grubbs II does not induce rearrangement. This led us to the conclusion that an active Lewis-acidic ruthenium species is responsible for the rearrangement step and is generated in situ *after* initiation of the cross metathesis step. The improved performance of Hoveya-Grubbs II versus Grubbs II in this transformation strongly suggests the identity of the Lewis acidic catalyst to be alkylidene species **3.56** which can accept electrons owing to its empty d orbital.


3.50
OAc
TIPSO
O
3.37
3.54 (5%), CDCl3
reflux, 5h
No CM pdts
OAc
H
H
O
OTIPS
3.43
CDCl3, reflux
+/- 3.54 (5%)
OAc
TIPSO
O
3.53
Mes
N
N
Mes
Cl
Ru
Cl
O
Hoveyda-Grubbs II
3.54
Grubbs II
3.55
PCy3
Ph
Proposed Lewis
Acidic Species
3.56

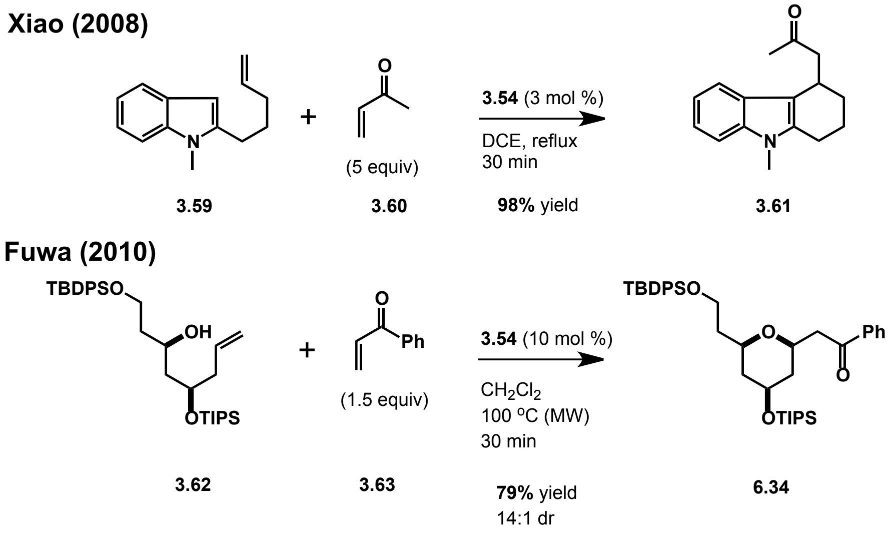
Scheme 3.14: Tandem reaction control experiments

Examination of the two possible metalocyclobutanes **3.57** and **3.58** formed during CM accounts for this observed improvement in *E* seteroselectivity of the C9-C10 trisubstituted olefin (Scheme 3.16). Unfavorable steric interactions between the epoxide oxygen and the alkyl chain of coupling partner **3.50** is minimized in intermediate **3.57**, leading preferentially to the *E* (desired) trisubstituted alkene **3.43a**.


3.35
+
HG-II
3.50
Ru(NHC)Cl2
OTIPS
favored
3.57
-3.56
E
10
9
major
3.43a
3.56
TIPSO
desired
3.53a
unfavored
3.58
Z
minor
3.43b
undesired
3.53b

Scheme 3.15: Possible steric interaction during CM to give improved *E* selectivity

There are recent examples in the literature of this so-called "tandem catalysis" in the context of cross-metathesis of electron-deficient olefins followed by a presumed Lewis acid-mediated cyclization event (Scheme 3.17). The authors invoke a decomposed ruthenium complex as the Lewis acidic species.[44]


Xiao (2008)
3.54 (3 mol %)
DCE, reflux
30 min
(5 equiv)
3.59
3.60
98% yield
3.61
Fuwa (2010)
TBDPSO
OH
OTIPS
Ph
3.54 (10 mol %)
CH2Cl2
100 °C (MW)
30 min
(1.5 equiv)
3.62
3.63
79% yield
14:1 dr
6.34

Scheme 3.16: Examples of "tandem catalysis" with Hoveyda-Grubbs II

---

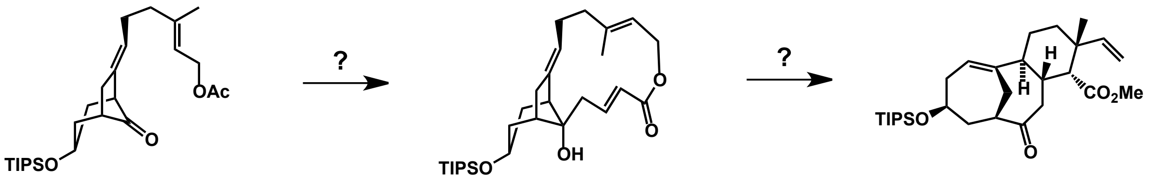
[44] (a) Chen, J.C.; Chang, F.L.; An, X.L.; Zhang, J.J.; Zhu, X.Y.; Xiao, W.J. *Angew. Chem. Int. Ed.* **2008**, *47*, 2489 (b) Fuwa, H.; Noto, K.; Makoto, S. *Org. Lett.* **2010**, *12*, 1636.

IV

Completion of the ABCD Tetracyclic Core of the Cyclocitrinol Steroids

4.1: Macrocycle synthesis and tandem Claisen-Cope applied to the real system

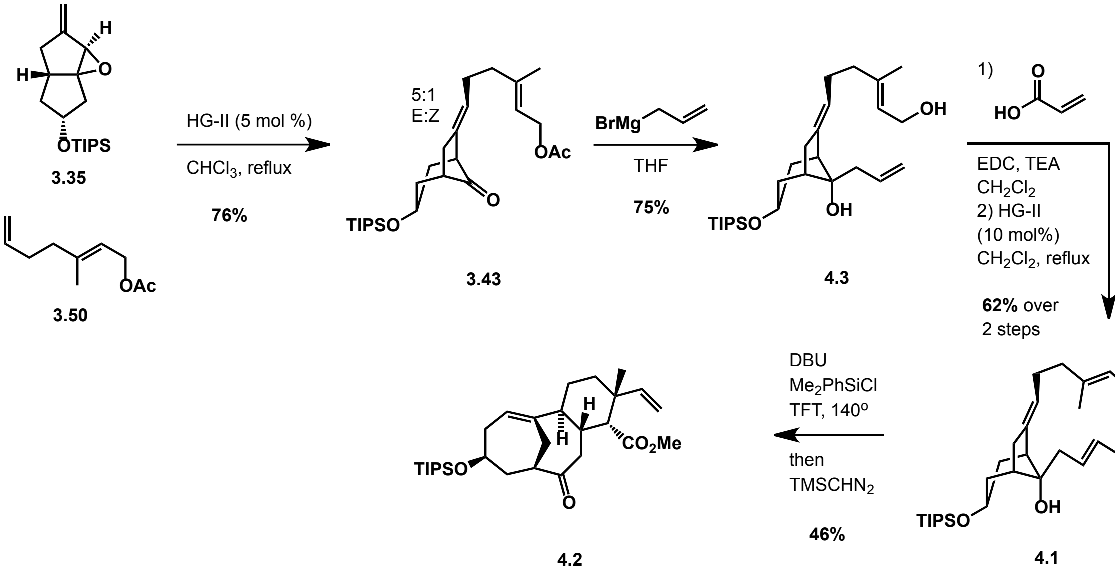
In order to fully capitalize on the substantial gains secured with our direct entry into vinyl epoxide **3.35** and its tandem CM-rearrangement conversion to bicyclo ketoacetate **3.53** (see Scheme 3.14, chapter 3), we had to demonstrate rapid elaboration of **3.53** to the macrolactone **4.1** and prove that this macrocycle also performs in the Claisen-Cope about as well as the model (see Scheme 2.17, chapter 2).



3.53 4.1 4.2

Scheme 4.1: Elaboration to Claisen-Cope product

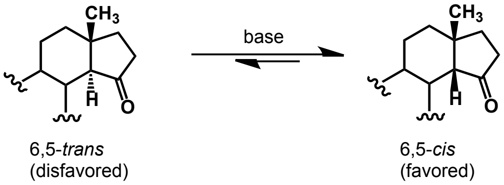
This proved straight forward as allylmagnesium bromide added into the ketone to deliver a single detectable diastereomer with concomitant removal of the acetate to give diol **4.3** (Scheme 4.2). The C9-C10 alkene isomers from the CM reaction were separable at this stage, providing pure **4.3** in 75% yield. EDC-mediated esterification with acrylic acid was followed by ring-closing metathesis with HG-II to give the macrolactone **4.1** in 62% yield over 2 steps. In the key Ireland-Claisen-Cope rearrangement, this substrate performed about as well as the model. **4.1** was transformed into **4.2** in 43% isolated yield after aqueous acidic workup and treatment of the crude acid with TMS-diazomethane. It is worth noting at this point that building blocks **3.35** and **3.50** are transformed to the ABC tricyclic core of the natural product in just 5 steps. This remarkable step economy is due principally to the two tandem reactions, which together account for a complex and extensive series of bond reorganizations.


3.35
3.50
HG-II (5 mol %)
CHCl3, reflux
76%
5:1
E:Z
3.43
BrMg
THF
75%
4.3
1)
EDC, TEA
CH2Cl2
2) HG-II
(10 mol%)
CH2Cl2, reflux
62% over
2 steps
4.1
DBU
Me2PhSiCl
TFT, 140°
then
TMSCHN2
46%
4.2

Scheme 4.2: Concise synthesis of ABC core

4.2: Inversion of Configuration at C14

We determined that in order to elaborate intermediate **4.2** to the ABCD tetracyclic core structure, our best probability of success required epimerization at C14 *prior* to closure of the D ring (Scheme 4.3). This reasoning was based on the thermodynamic preference of *cis* (6,5) hyndrindane ring systems over their *trans*-fused counterpart, meaning epimerization following cyclization would be unfavorable.[45]

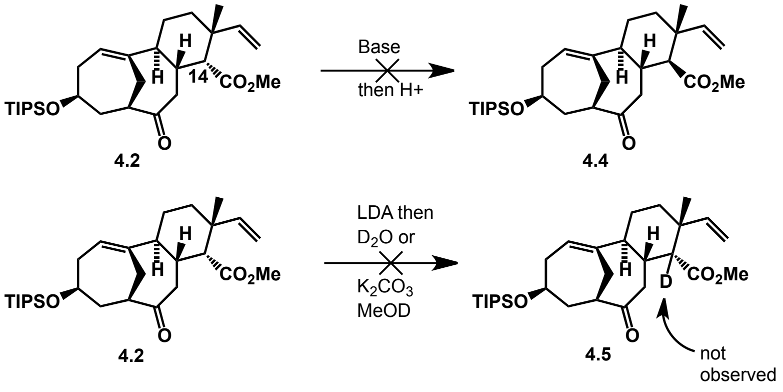

base
6,5-*trans*
(disfavored)
6,5-*cis*
(favored)

Scheme 4.3: Epimerization of (6,5)-CD ring system

---

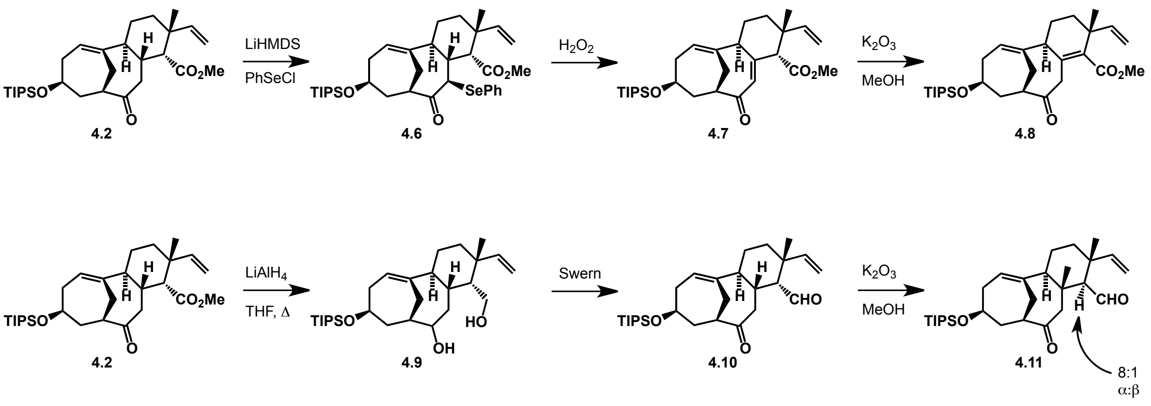
[45] Jankowski, P.; Marczak, S.; Wicha. *Tetrahedron* **1998**, *54*, 12071

Unfortunately, epimerization at C14 of ester intermediate **4.2** returned only starting material under a variety of conditions. Control experiments indicated that deprotonation of the methine proton α to the ester carbonyl was not occurring (Scheme 4.4). We reasoned that in the crowded steric environment adjacent to the quaternary center, perhaps the ester was unable to achieve the required orthogonality with the adjacent proton in order to render it acidic.



Scheme 4.4: Attempted deprotonation at C14

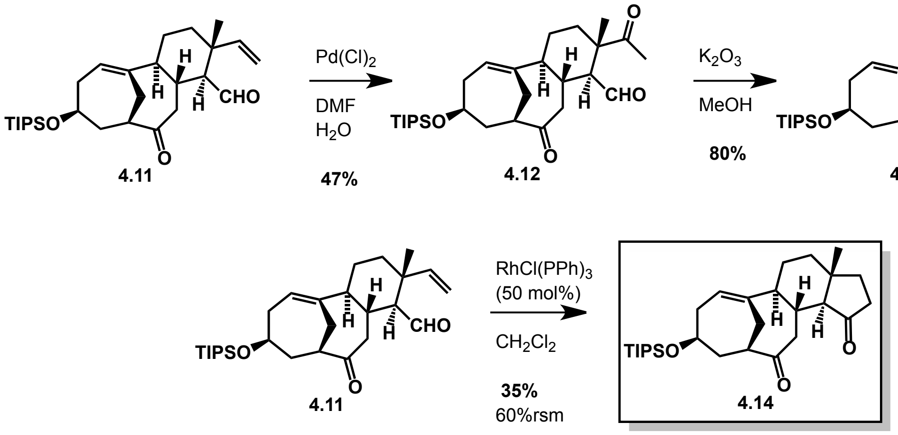
Hence, we sought other substrates possessing an acidic C14 proton that might be epimerized. Enone **4.7** was prepared in two steps (selenide formation followed by oxidative elimination) and subjected to epimerizing conditions such as K_2CO_3 in methanol. Unfortunately we observed migration of the double bond into conjugation with the ester to give enoate **4.8**. Next we examined keto aldehyde **4.10**, reasoning that a smaller and more acidic carbonyl function may be more easily deprotonated at C14. **4.10** was prepared in two steps from **4.2**: $LiAlH_4$ reduction to diol **4.9** followed by double Swern oxidation. Upon subjection of this material to K_2CO_3 in methanol, an ~8:1 mixture of epimers was isolated, favoring the desired configuration (**4.11**).


TIPSO
4.2
CO₂Me
LiHMDS
PhSeCl
4.6
SePh
H₂O₂
4.7
K₂O₃
MeOH
4.8
LiAlH₄
THF, Δ
4.9
OH
HO
Swern
4.10
CHO
4.11
8:1
α:β

Scheme 4.5: C14 Epimerization

4.3: First Generation D-Ring Cyclization

With a solution to the C14 stereocenter in hand, we examined options for closure of the D ring from keto aldehyde **4.11**. Wacker oxidation (notably at a neopentyl center) delivered diketone **4.12**, which underwent aldol condensation to close the 5-membered D ring but also epimerized C14 (Scheme 4.6). We then turned to Larock hydroacylation[46] using Wilkinson's catalyst, which proved competent in the cyclization, delivering **8.15** efficiently but with poor conversion despite high catalyst loading.

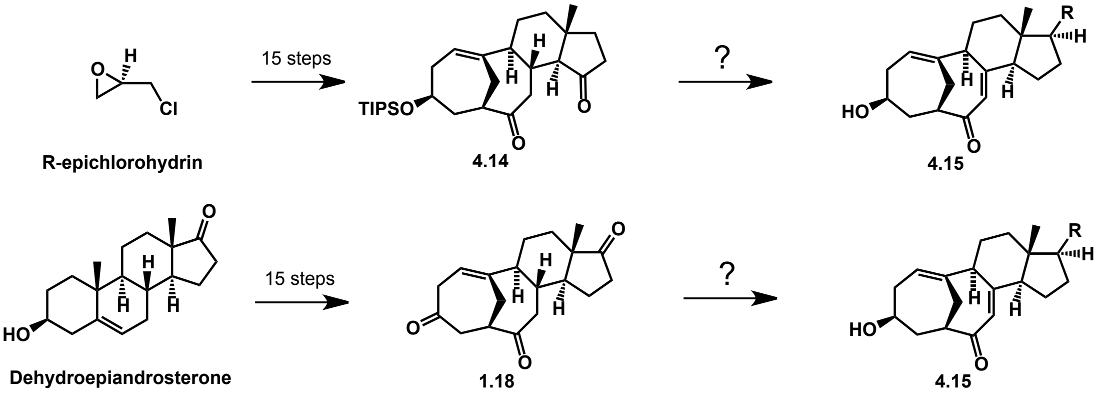

TIPSO
4.11
CHO
Pd(Cl)₂
DMF
H₂O
47%
4.12
K₂O₃
MeOH
80%
4.13
RhCl(PPh)₃
(50 mol%)
CH₂Cl₂
35%
60%rsm
4.14

Scheme 4.6: D-Ring Cyclizations

---

[46] Larock, R.C.; Oertle, K.; Potter, G.F. *J. Am. Chem. Soc.* **1980**, *102*, 190.

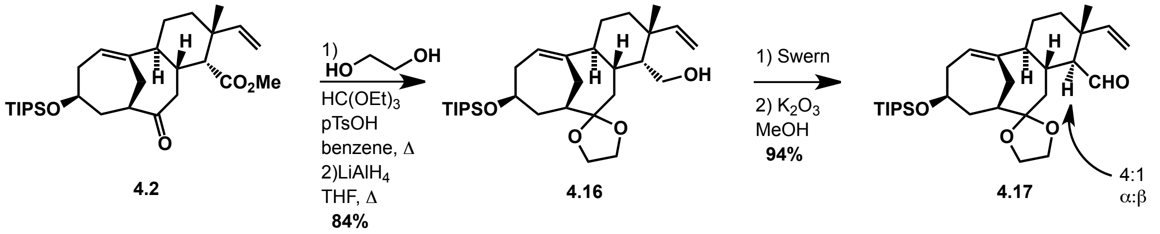
This constituted the first synthesis of the ABCD core structure of this class of natural products that did not start from a known steroid (see chapter 1) and matched up reasonably well against Schmalz's approach (see Scheme 1.2, chapter 1) to the core structure in terms of overall step count from R-epichlorohydrin (Scheme 4.7). The obvious criticism with both approaches is that it is unclear how these advanced intermediates might be elaborated into the naturally occurring system. **4.14** lacks functionality at C17 for the ready installation of the sidechain while **1.18** possesses three ketone functions, which may be difficult to differentiate.



Scheme 4.7: Our initial approach to the ABCD tetracyclic core versus Schmalz's Approach

4.4: Second Generation D-Ring Cyclization

It is with these considerations in mind that we set out to develop a concise sequence to close the D ring, differentiate the C6 ketone, and provide a handle at C17 for sidechain installation. It seemed most practical to protect the C6 ketone and then proceed via aldehyde **4.17β**, since it was at this intermediate that configuration at C14 could be corrected, based on our previous epimerization studies. Surprisingly, the Nyori ketalization protocol failed on the real system, though a screen of known methods proved that excess ethylene glycol and triethylorthoformate with catalytic pTsOH in hot benzene[47] was competent in this regard (Scheme 4.8). Reduction of the ester with $LiAlH_4$ and Swern oxidation to the aldehyde was followed by epimerization under the same conditions as **4.11** above, although interestingly we observe only a 4:1 thermodynamic mixture of C14 aldehyde epimers (favoring the desired configuration) with the ketone protected as the ketal, as compared to 8:1 above.


TIPSO
H
H
CO2Me
O
4.2
1) HO OH
HC(OEt)3
pTsOH
benzene, Δ
2)LiAlH4
THF, Δ
84%
TIPSO
H
H
OH
O
O
4.16
1) Swern
2) K2O3
MeOH
94%
TIPSO
H
H
H
CHO
O
O
4.17
4:1
α:β

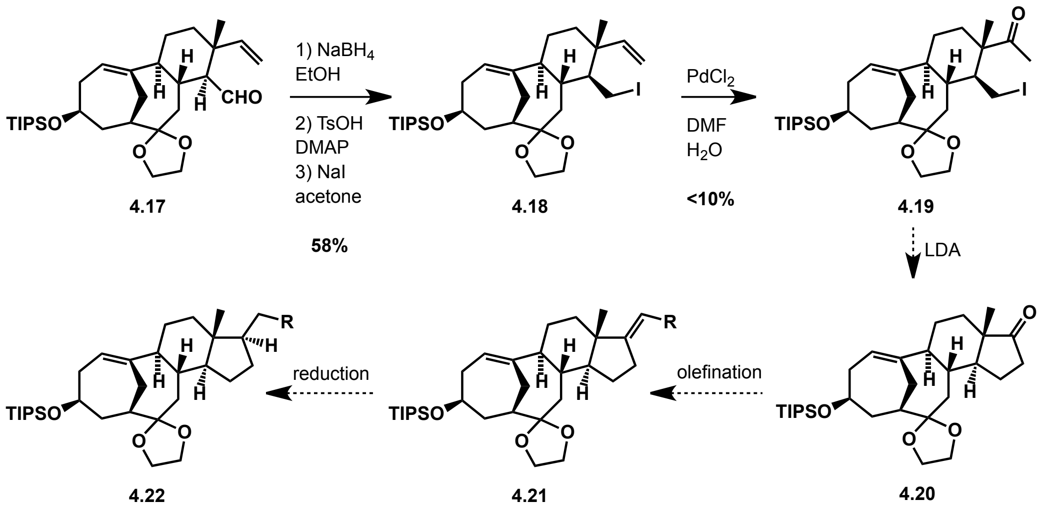
Scheme 4.8: C6-ketalization, C14-epimerization sequence

We first considered closure of the D-ring via an intramolecular enolate alkylation reaction on a keto-iodide of type **4.19**. This was appealing because C17-keto steroids are common intermediates when C17-β sidechain installation is desired.[48] The planned olefination-reduction sequence could be expected to deliver the desired configuration due to direction of the reduction event by the C19 angular methyl group. In the event, Wacker oxidation of iodo olefin **4.18** proceeded inefficiently.

---

[47] Caserio, F.F.; Roberts, J.D. *J. Am. Chem. Soc.* **1958**, *80*, 5837.

[48] Ibuk, T.; Taga, T.; Nishii, S.; Yamamoto, Y.; *J. Chem. Soc., Chem. Comm.* **1988**, *5*, 342.


1) NaBH4
EtOH
2) TsOH
DMAP
3) NaI
acetone
58%
PdCl2
DMF
H2O
<10%
LDA
olefination
reduction
TIPSO
CHO
4.17
4.18
4.19
4.20
4.21
4.22

Scheme 4.9: Attempted intramolecular enolate alkylation to close D ring

B-Alkyl Suzuki[49] reaction on vinyl triflate **4.25** was then examined, reasoning that hydroboration-oxidation of the cyclization product **4.26** should set the desired configuration at C17 (Scheme 4.10). The substrate was accessed from aldehyde **4.17** in 3 steps: Wacker oxidation of the δ−ε unsaturated aldehyde and selective Wittig methenylation was followed by vinyl triflate formation of the methyl ketone **4.24** with KHMDS/Comins reagent to give cyclization substrate **4.25**. Attempted *B*-alkyl Suzuki reaction using 9-BBN and palladium tetrakis/K_3PO_4 failed to proceed under normal conditions and additional reagents/heat lead to hydroboration of the bridgehead olefin.

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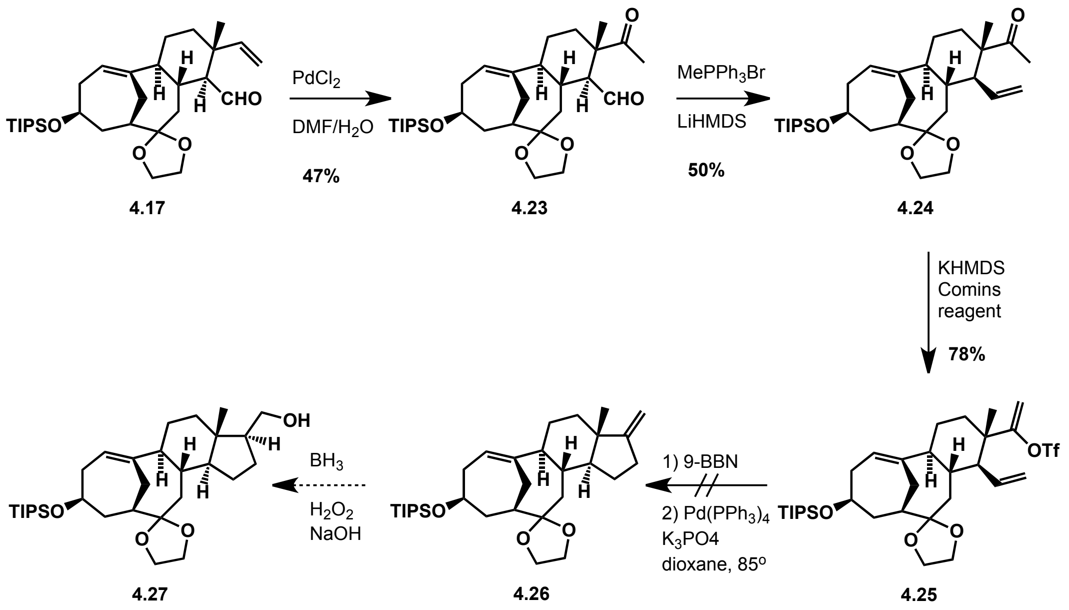
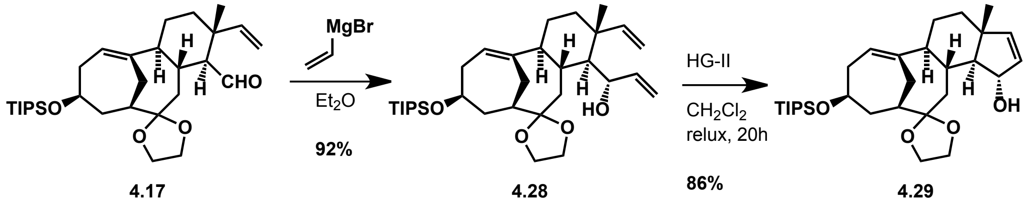
[49] Ohe, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.


4.17
PdCl2
DMF/H2O
47%
4.23
MePPh3Br
LiHMDS
50%
4.24
KHMDS
Comins
reagent
78%
4.25
1) 9-BBN
2) Pd(PPh3)4
K3PO4
dioxane, 85°
4.26
BH3
H2O2
NaOH
4.27
TIPSO
CHO
OTf
OH

Scheme 4.10: Attempted *B*-Alkyl Suzuki to close D ring

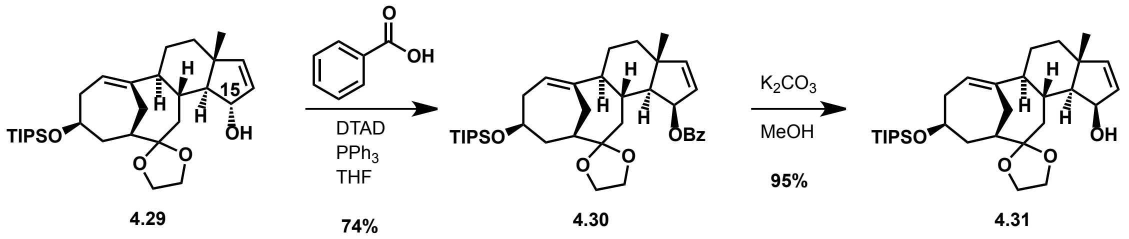
We then considered forging the D ring via RCM. Vinylmagnesium bromide added into the aldehyde **4.17** very efficiently and the resulting mixture of diatereomers (from epimerization at C14) were separated by flash chromatography. Interestingly, the desired (S) aldehyde leads to a single allylic alcohol isomer **4.28** while the (R)-configured epimer delivers a mixture of C-15 cabinols upon addition by vinylmagnesium bromide. Subjection of allylic alcohol **4.28** to RCM with 10 mol% HG-II resulted in sluggish but efficient RCM to give tetracycle **4.29**.


4.17
MgBr
Et2O
92%
4.28
HG-II
CH2Cl2
relux, 20h
86%
4.29
TIPSO
CHO
HO
OH

Scheme 4.11: RCM to close D ring

4.5: Sigmatropic Rearrangements to Establish C17 Side Chain

With tetracyclic allylic alcohol **4.29** in hand, we considered potential methods for stereoselective installation of the C17 side chain. Controlling C17 stereochemistry in steroidal targets is a classical problem in synthetic organic chemistry and the notion of a sigmatropic rearrangement on allylic substrates derived from the C15 β carbinol was appealing on the basis that such transformations could be expected to deliver the side chain handle stereospecifically from the β face. Inversion of the C15 carbinol center was achieved under Mitsunobu conditions with benzoic acid (Scheme 4.12). The resulting benzoate **4.30** was converted to the desired β allylic alcohol **4.31** with potassium carbonate in MeOH at 100° in a sealed tube.



Scheme 4.12: Inversion of C15 carbinol

This material was then subjected to Johnson orthoester Claisen[50] conditions as well as converted to Ireland-Clasien substrates **4.33** and **4.35** (Scheme 4.13). The parent thermal Claisen[51] was also examined after converting **4.31** to the allyl vinyl ether **4.37** under standard mercury acetate/ethyl vinyl ether conditions. Finally, stannyl ether **4.40** was accessed via alkylation of **4.31** with iodomethylstanane **4.39** to set up a [2,3] Still-Wittig rearrangement.[52]

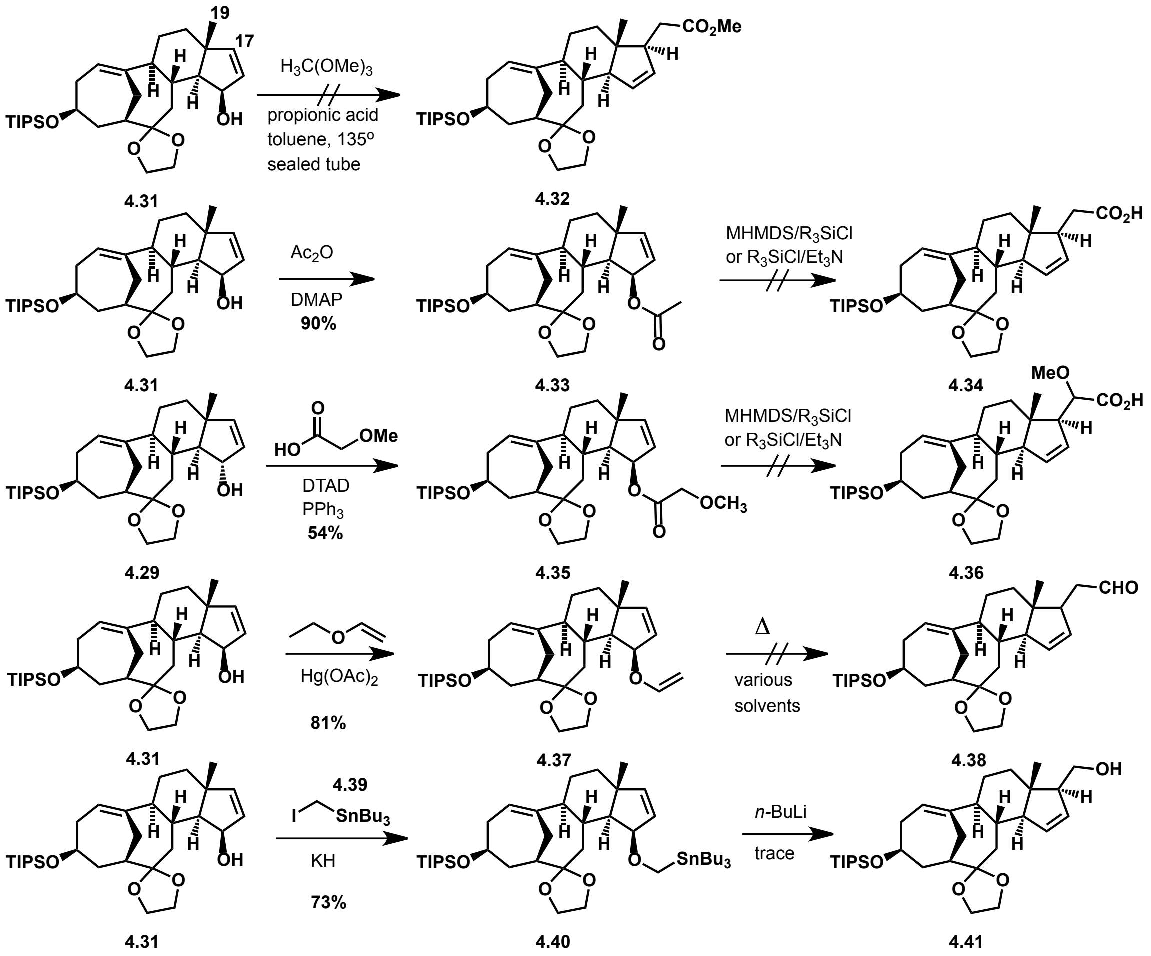
---

[50] Johnson, W.S.; Werthemann, L.; Bartlett, W.R.; Brocksom, T.J.; Li, T.T.; Faulkner, D.J.; Petersen, M.R. *J. Am Chem. Soc.* **1970**, *92*, 741.

[51] Grieco, P.A.; Brandes, E.B.; McCann, S. *J. Org. Chem* **1989**, *54*, 5849.

[52] Still, W.S.; Mitra, A. J. *Am. Chem. Soc.* **1978**, *100*, 1927.

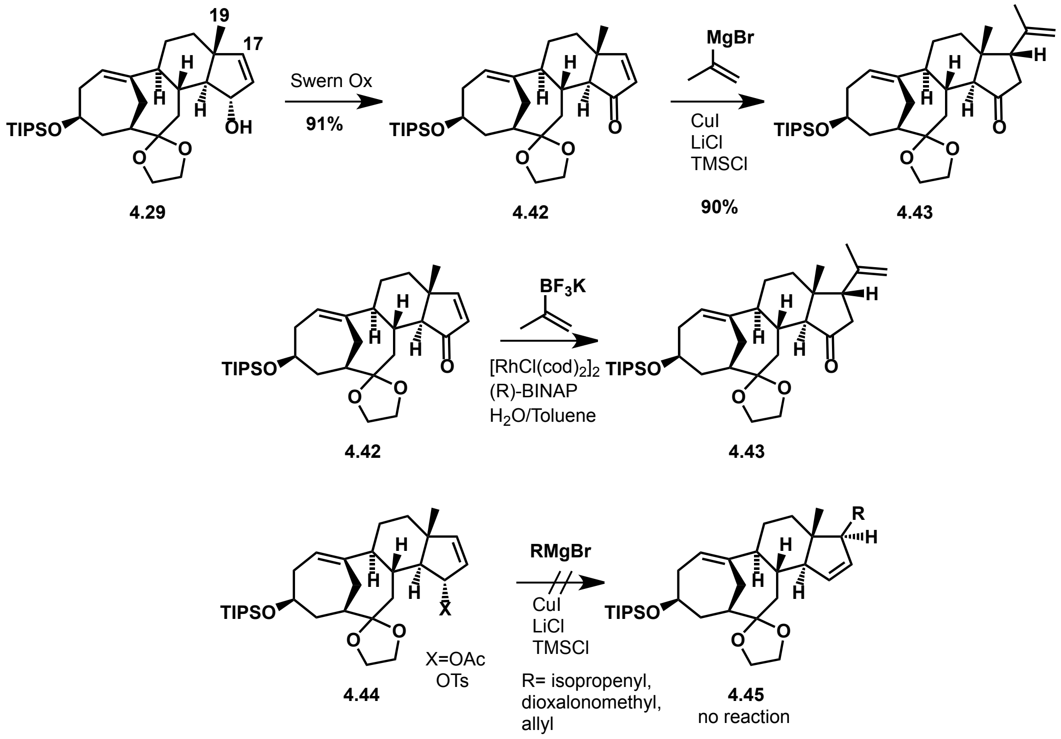
Unfortuantely all of these substrates failed to deliver more than trace amounts of the desired rearranged products under a variety of conditions. We speculate that this is due to steric shielding by the C19 angular methyl group of C17.


19
17
H
H
H
OH
TIPSO
4.31
H3C(OMe)3
propionic acid
toluene, 135°
sealed tube
CO2Me
4.32
Ac2O
DMAP
90%
4.33
MHMDS/R3SiCl
or R3SiCl/Et3N
CO2H
4.34
OMe
HO
DTAD
PPh3
54%
4.29
OCH3
4.35
MeO
CO2H
4.36
Hg(OAc)2
81%
4.37
Δ
various
solvents
CHO
4.38
4.39
I
SnBu3
KH
73%
4.40
n-BuLi
trace
OH
4.41

Scheme 4.13: Attempted Sigmatropic rearrangements to install C17 side chain

4.6: 1,4-Addition Reactions to Establish C17 Side Chain

Next we examined conjugate addition reactions into the enone **4.42**, which was accessed efficiently under Swern conditions from tetracyclic allylic alcohol **4.29** (Scheme 4.14). Unsurprisingly, standard isopropenyl cuprate addition into this substrate proceeded efficiently but with the undesired (R) diastereomer. We attempted to overturn the resident facial bias through the action of chiral ligands using Corey's protocol.[53] This reaction failed to proceed at room temperature and gentle heating again led to primarily the undesired diastereomer. SN2' reaction of allylic system **4.44** with copper nucleophiles was also examined, noting the 1,4-*anti* stereochemical preference for these transformations.[54] Again we met defeat as these substrates proved unreactive under the conditions examined.


19
17
TIPSO
H
OH
4.29
Swern Ox
91%
4.42
MgBr
CuI
LiCl
TMSCl
90%
4.43
BF3K
[RhCl(cod)2]2
(R)-BINAP
H2O/Toluene
4.42
4.43
X
X=OAc
OTs
4.44
RMgBr
R= isopropenyl,
dioxalonomethyl,
allyl
R
4.45
no reaction

Scheme 4.14: 1,4-addition reactions to install side chain handle

4.7: C13-C17 Tetrasubstituted Macrolactone to Establish C17 Side Chain

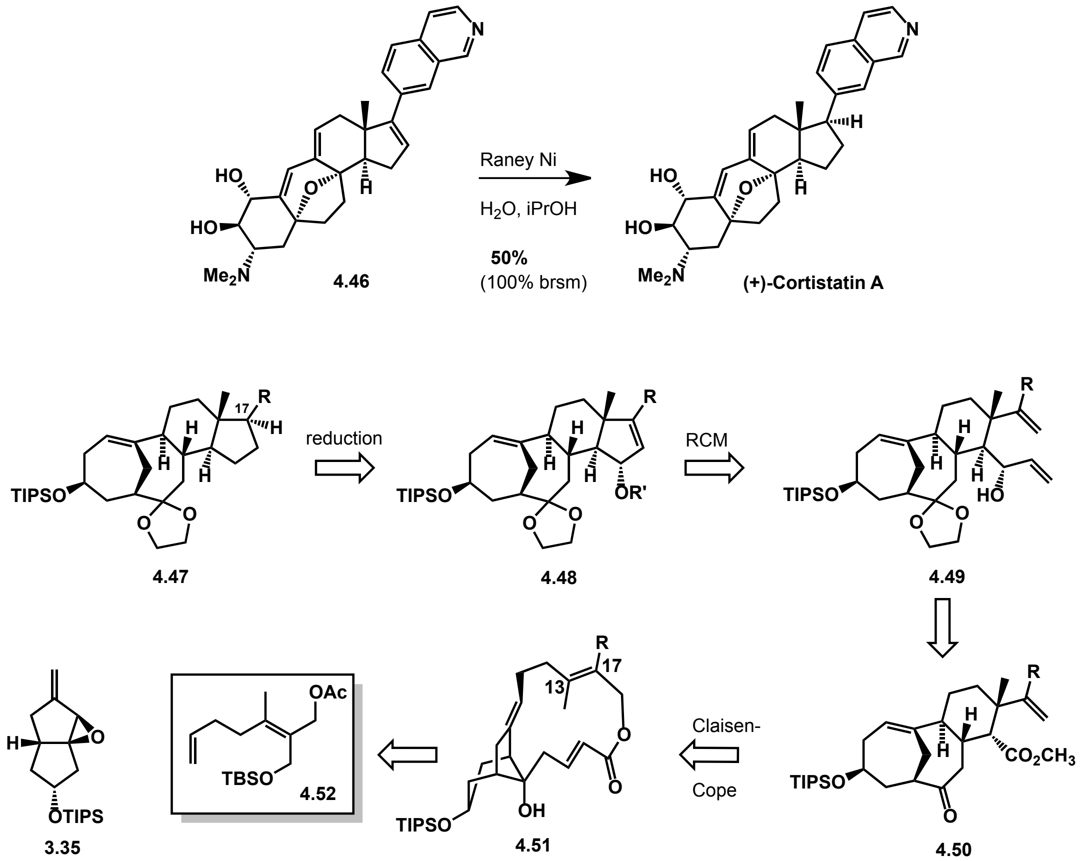
Reduction of unsaturated substrates such as **4.46**[55] have been shown to deliver products favoring "β" orientation of the side chain, presumably due to direction of the incoming reducing agent from the most accessible face opposite the C19 angular methyl group. This precedent led us to consider the possibility of designing a new tetrasubstituted alkene CM coupling partner **4.52** with a versatile substituent already in place at C17. Following the established sequence, this would lead us to a tetracycle of type **4.48** which may be reduced from the α face, establishing the desired configuration at the C17 stereocenter.

---

[53] Lalic, G.; Corey, E.J. *Tetrahedron Lett.* **2008**, *49*, 4894.

[54] Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* **1985**, *25*, 3063.

[55] Shenvi, R.A.; Guerro, C.A.; Shi, J.; Li, C.C.; Baran, P.S. *J. Am. Chem. Soc.* **2008**, *130*, 7241.



4.46
Raney Ni
H_2O, iPrOH
50%
(100% brsm)
(+)-Cortistatin A
4.47
reduction
4.48
RCM
4.49
4.50
Claisen-
Cope
4.51
4.52
3.35

Scheme 4.15: Reduction to set C17 stereocenter

In the event, the tetrasubstituted double bond was set in a titanium-mediated Knoevenagel condensation[56] between 5-hexen-2-one and diethyl malonate followed by exhaustive reduction with excess DIBAL-H. Mono silylation resulted in a seperable mixture of alcohols **4.57** and **4.58**. Each was acetylated and nOe NMR experiments were conducted to distinguish these intermediates. **4.52** then underwent CM-rearrangement with vinyl epoxide **3.35** as planned (see Scheme 3.14, chapter 3), delivering [3.2.1] bicylo ketone **4.60** in 86% yield as a 5:1 mixture of *E/Z* isomers. This was elaborated into the macrocyclic Claisen-Cope substrate **4.61** in the previously described manner, generally performing about as well as the trisubstituted series.

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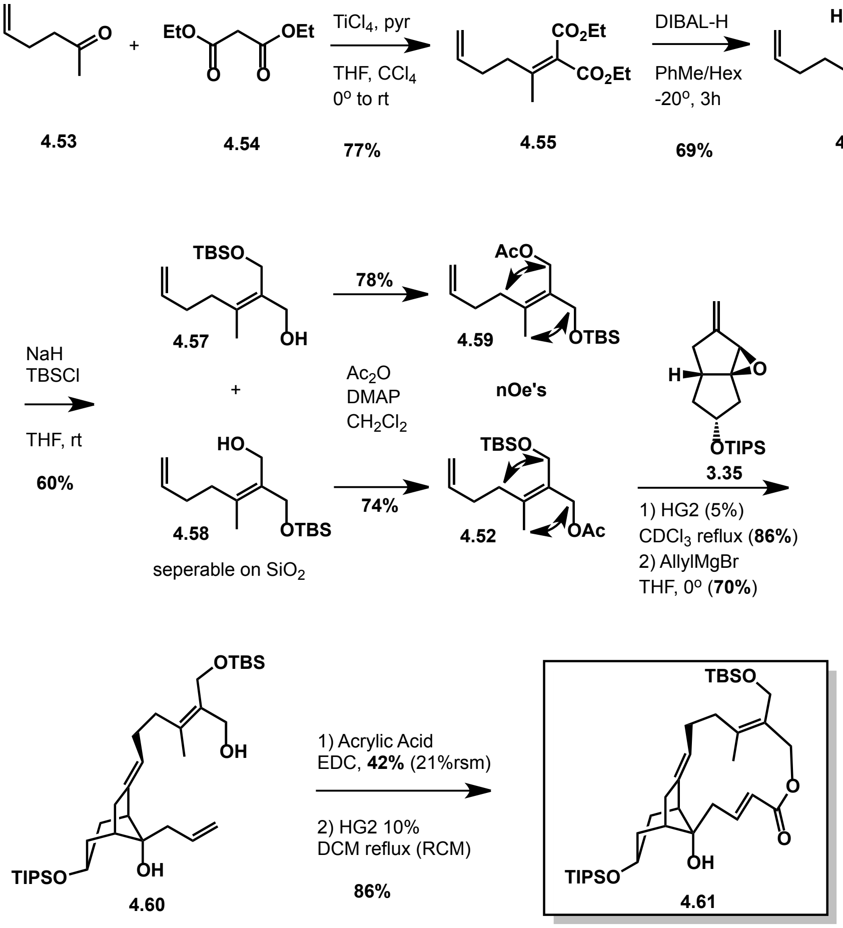
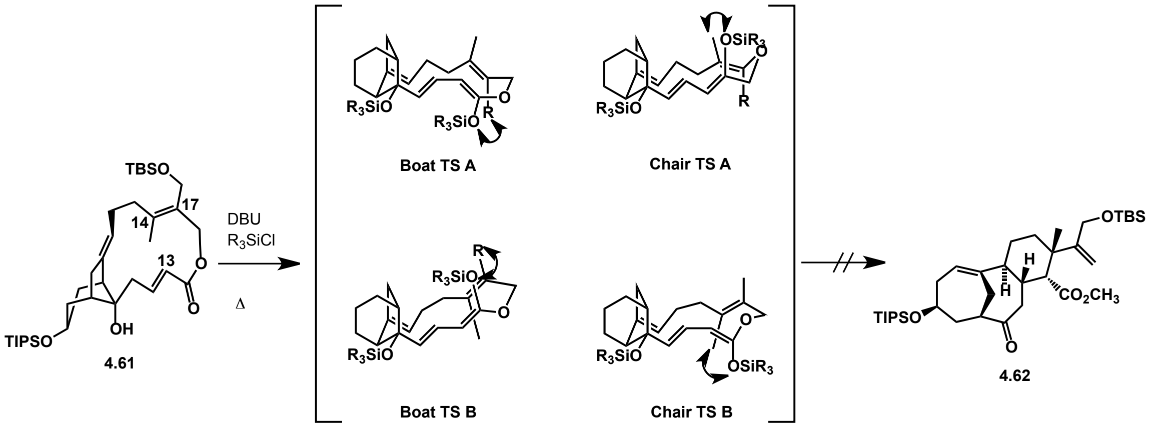
[56] Lehnert, W. *Tetrahedron* **1973**, *29*, 635.


4.53
+
EtO
OEt
4.54
TiCl4, pyr
THF, CCl4
0° to rt
77%
CO2Et
CO2Et
4.55
DIBAL-H
PhMe/Hex
-20°, 3h
69%
HO
OH
4.56
NaH
TBSCl
THF, rt
60%
TBSO
OH
4.57
+
HO
OTBS
4.58
seperable on SiO2
78%
Ac2O
DMAP
CH2Cl2
74%
AcO
OTBS
4.59
nOe's
TBSO
OAc
4.52
H
O
OTIPS
3.35
1) HG2 (5%)
CDCl3 reflux (86%)
2) AllylMgBr
THF, 0° (70%)
OTBS
OH
TIPSO
OH
4.60
1) Acrylic Acid
EDC, 42% (21%rsm)
2) HG2 10%
DCM reflux (RCM)
86%
TBSO
O
O
TIPSO
OH
4.61

Scheme 4.16: Synthesis of C13-C17 tetrasubstituted macrolactone **4.61**

Unfortunately, in the key tandem Claisen-Cope reaction, this intermediate failed to deliver any detectable desired product **4.62**, delivering instead a complex mixture. This result, though disappointing, is consistent with our analysis of the transition state for the Ireland-Claisen reaction to forge the C13-C14 bond (Scheme 4.17). Substitution at C17 effectively locks out all possible transition states in terms of minimizing unfavorable 1-3 interactions, even it were to proceed via a boat-like transition state.

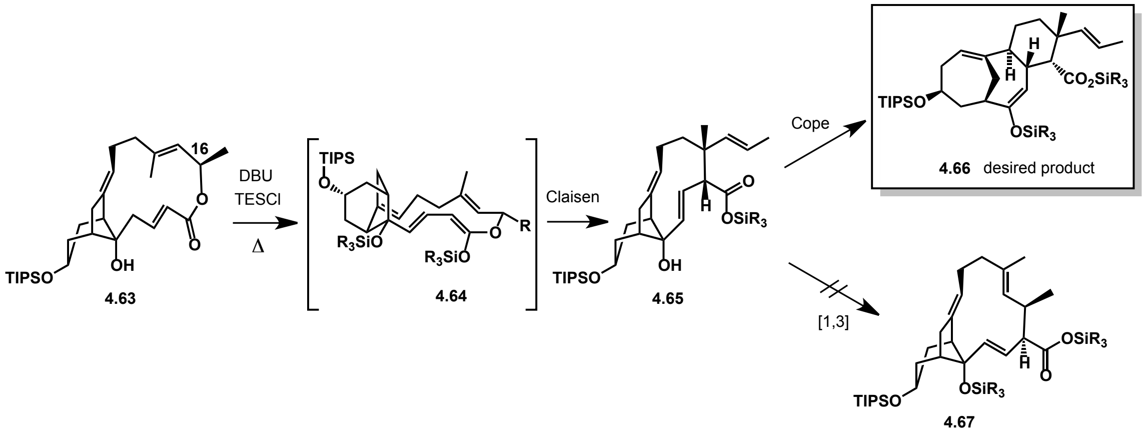

TBSO
17
14
13
TIPSO
OH
4.61
DBU
R3SiCl
Δ
R3SiO
R3SiO
R
O
Boat TS A
OSiR3
O
R
R3SiO
Chair TS A
R
R3SiO
O
R3SiO
Boat TS B
R3SiO
O
OSiR3
Chair TS B
OTBS
H
H
CO2CH3
TIPSO
O
4.62

Scheme 4.17: Unfavorable 1-3 interactions in attempted Claisen-Cope of **4.61**

4.8: Improving the efficiency of the Claisen-Cope reaction

We have established that the key Claisen-Cope tandem reaction that generates the ABC core likely proceeds through a boat-like transition state and also results in the formation of 12-membered ring byproducts **2.79** and **2.80** (see Scheme 2.19, chapter 2). Considering that the total mass balance of this transformation is very high, we realized that if there were some way to shut down the formation of the undesired byproducts, we might drastically improve the overall efficiency of the key reaction in delivering the desired tricyclic ring system. Our initial analysis of two operable boat-like pathways (one leading to desired product, one leading to 12-membered ring) was revised based on consideration of FMO theory. The proposed suprafacial [1,3] sigmatropic shift proceeding with inversion at the migrating carbon could be expected due to stereoelectronic considerations, as mentioned in chapter 2, scheme 2.21. This would then mean that *both products* **4.66** and **4.67** arise from boat-like Claisen intermediate **4.67** (Scheme 4.18).

Improving the efficiency of the overall process then became a matter of slowing the [1,3] pathway in order to realize a higher overall yield of the desired tricyclic Claisen-Cope product. It seemed reasonable that increasing the steric bulk at position C16 should slow the undesired pathway without impacting the desired Cope rearrangement, provided that the substituent installed at C16 was configured so as to avoid unfavorable 1,3-interactions in the Claisen transition state **4.64**. Combining this reasoning with our D-Ring RCM strategy led to the notion of installing an *erasable transition-state controlling substituent* at C16 of the macrocycle.


16
TIPSO
OH
4.63
DBU
TESCl
Δ
TIPS
O
R
R_3SiO
R_3SiO
4.64
Claisen
TIPSO
OH
H
$OSiR_3$
4.65
Cope
TIPSO
H
H
CO_2SiR_3
$OSiR_3$
4.66 desired product
[1,3]
TIPSO
$OSiR_3$
$OSiR_3$
H
4.67

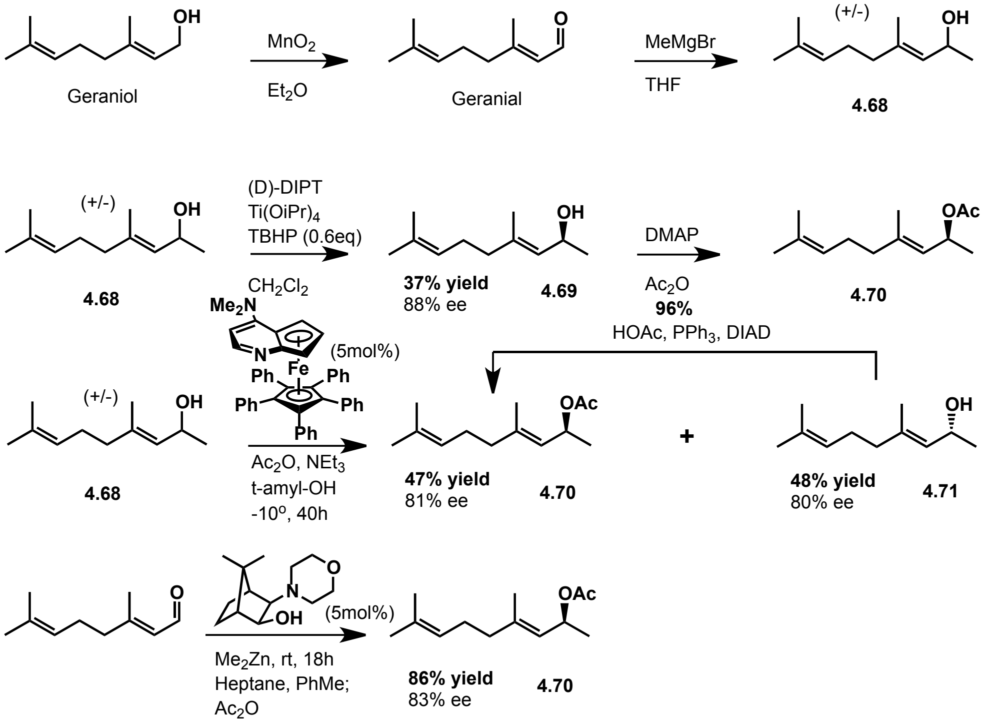
Scheme 4.18: Improving Claisen-Cope efficiency by slowing [1,3] pathway

Testing this hypothesis required the synthesis of a macrolactone of type **4.63** which seemed accessible through our established route, provided we could synthesize chiral acetate **4.70** (Scheme 4.19). This was initially achieved via Sharpless resolution[57] of the racemic secondary alcohol **4.68** resulting from MeMgBr addition into geranial. The low overall yield of this reaction prompted us to consider Fu's chiral DMAP catalyst[58], reasoning that the unacylated allylic alcohol **4.69** could undergo Mitsunobu reaction with acetic acid to converge on the targeted chiral allylic acetate, provided both **4.70** and **4.71** were isolated in reasonable (>80%) ee. The expense of this catalyst combined with the chriogenic conditions and long reaction time further prompted us to seek a better solution in terms of scalability and convenience. Taking note of Noyori's asymmetric method for the addition of diethylzinc into benzaldehyde[59], we were able to achieve acceptable enantioinduction through the action of (+)-MIB[60] in the addition of dimethylzinc into geranial followed by Ac_2O quench of the zinc alkoxide to deliver chiral allylic acetate **4.70** in a single pot.

---

[57] Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

[58] Ruble, J.C.; Latham, H.A.; Fu, G.C. *J. Am. Chem. Soc.* **1997**, *119*, 1492.



Geraniol
MnO2
Et2O
Geranial
MeMgBr
THF
(+/-)
4.68
(D)-DIPT
Ti(OiPr)4
TBHP (0.6eq)
CH2Cl2
37% yield
88% ee
4.69
DMAP
Ac2O
96%
4.70
HOAc, PPh3, DIAD
Me2N
(5mol%)
Ac2O, NEt3
t-amyl-OH
-10°, 40h
47% yield
81% ee
4.70
48% yield
80% ee
4.71
(5mol%)
Me2Zn, rt, 18h
Heptane, PhMe;
Ac2O
86% yield
83% ee
4.70

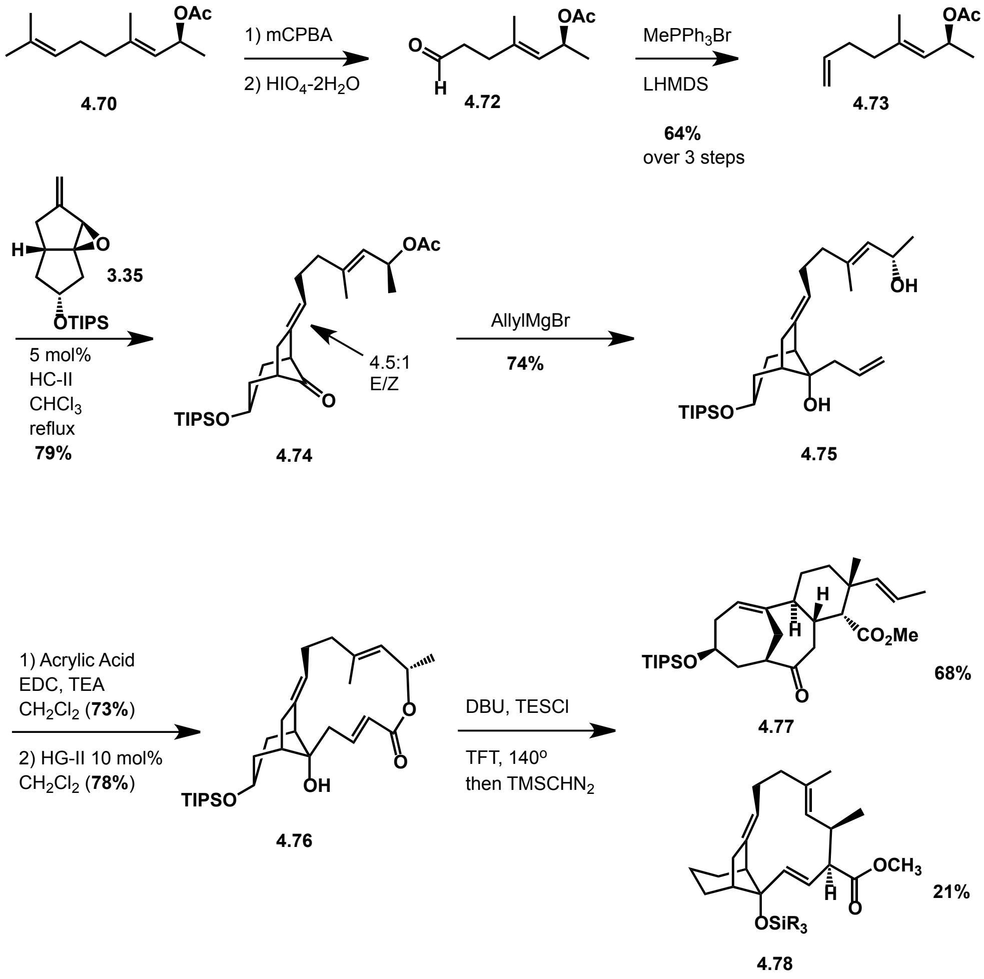
Scheme 4.19: Enantioselective synthesis of 2°-allylic acetate **4.70**

Chiral allylic acetate **4.70** was then converted to the terminal alkene **4.73** through the usual sequence of selective epoxidation, oxidative cleavage, and Wittig olefination (Scheme 4.20). Cross metathesis-rearrangement of terminal alkene **4.73** and vinyl epoxide **3.35** proceeded efficiently to give ketone **4.74**. This intermediate was then elaborated into macrolactone **4.74** in the usual manner: allyl Grignard addition, acrylation, and RCM. When subjected to $Me_2PhSiCl$ and DBU in TFT at 140 °C, this substrate proceeded to the desired Claisen-Cope trycyclic product **4.77** more efficiently than the des-15-methyl derivative **4.1** (see Scheme 4.2). Claisen-Cope product **4.77** was isolated in 68% yield as compared to 43% yield from the 15-unsubstituted ring system **4.1**. Interestingly, we still observe a significant amount (21%) of 12-membered ring product **4.78**.

---

[59] Kitamura, M.; Suga, K.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986***, 108*, 6071.

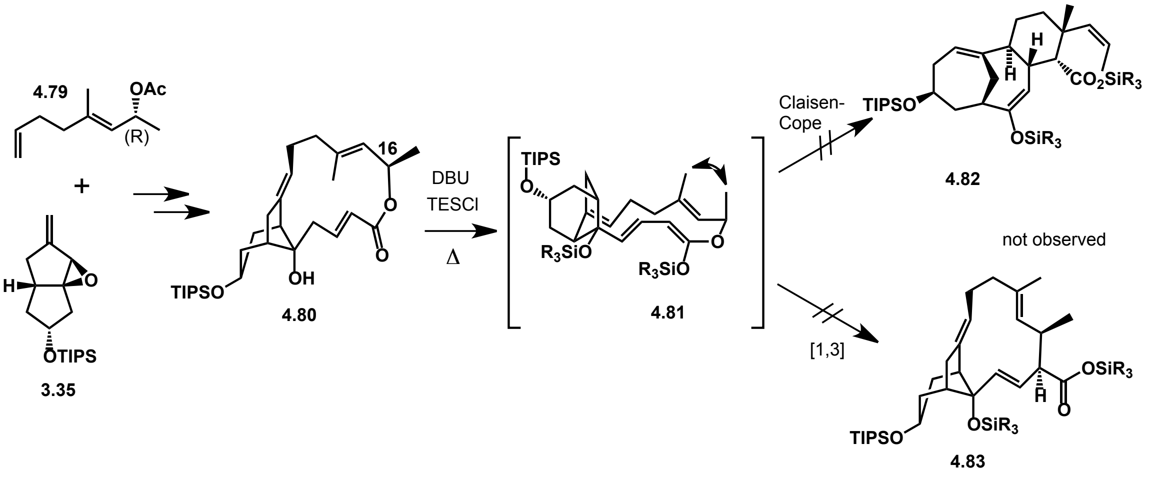
[60] Nugent, W.A. *Chem. Comm.* **1999**, 1369.


OAc
4.70
1) mCPBA
2) HIO_4-$2H_2O$
O
H
OAc
4.72
$MePPh_3Br$
LHMDS
64%
over 3 steps
OAc
4.73
H
O
3.35
OTIPS
5 mol%
HC-II
$CHCl_3$
reflux
79%
OAc
4.5:1
E/Z
TIPSO
O
4.74
AllylMgBr
74%
OH
TIPSO
OH
4.75
1) Acrylic Acid
EDC, TEA
CH_2Cl_2 (73%)
2) HG-II 10 mol%
CH_2Cl_2 (78%)
O
O
TIPSO
OH
4.76
DBU, TESCl
TFT, 140°
then $TMSCHN_2$
H
H
CO_2Me
TIPSO
O
4.77
68%
OCH_3
H
O
$OSiR_3$
4.78
21%

Scheme 4.20: Synthesis of keto ester **4.77**

The presence of **4.78** as a product from this experiment was disappointing since we were unable to shut down the [1,3] pathway entirely, however, the substantially improved yield of Cope product **4.77** demonstrates proof of concept that substitution at C16 does in fact retard the undesired [1,3] sigmatropic shift. This result at least suggests that other substituents (instead of methyl) at C16 might further impact these competing pathways, potentially shutting down the [1,3] shift entirely.

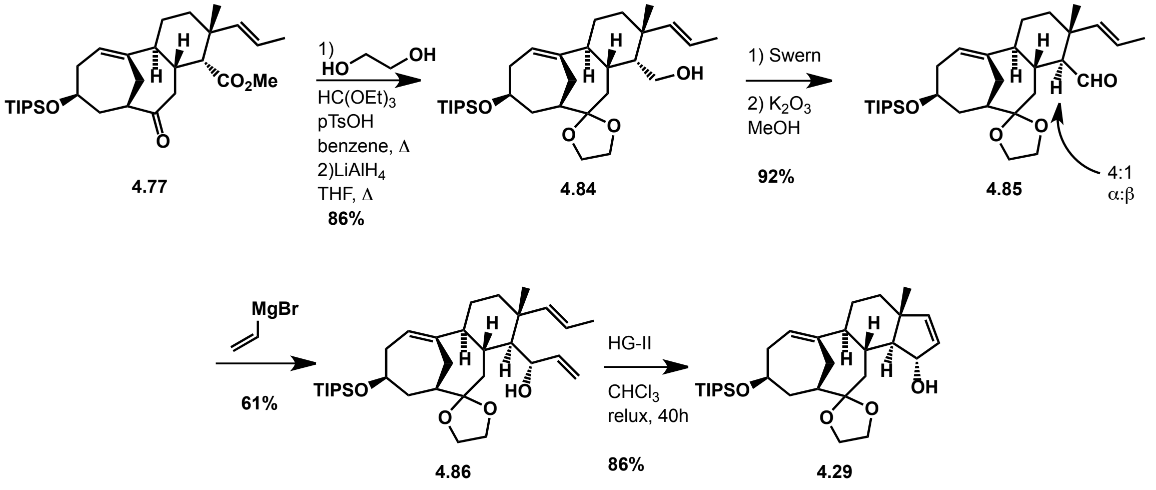
Next we examined the diastereomeric macrolactone C16-(R)-derivative **4.80** in order to further confirm our understanding of the operable transition state. This substrate was accessed through the same chemistry as **4.76** in comparable yield (Scheme 4.21). When subjected to the tandem reaction conditions, however, it returned a complex mixture. That it did not deliver any Claisen-Cope product or 12-membered ring is consistent with our analysis of the Ireland-Claisen transition state; unfavorable 1,3 interactions prevent it from accessing the requisite boat intermediate **4.81**. The alternative boat TS is apparently totally inaccessible for this ring system.



Scheme 4.21: Unfavorable 1,3 interaction preventing Clasien of 16-*R*-Macrolactone **4.80**

Having improved the efficiency of the tandem Claisen-Cope reaction, we set out to demonstrate that the methyl substituent installed at C16 to slow the formation of the 12-

membered ring could be effectively removed so that this improvement could be used in the synthesis of the tetracycle. Since we intended to follow the established route (see Schemes **4.8** and **4.11**), we hoped that RCM to forge the D ring would effectively "erase" the allylic methyl of the propenyl unit. Fortunately the chemistry performed essentially the same as in the des-methyl series. Hence, protection of the ketone in **4.77** followed by LAH reduction of the ester gave primary alcohol **4.84** in 86% yield over two steps (Scheme 4.22). Swern oxidation followed by epimerization with K_2CO_3 in methanol delivered a 3.7:1 mixture of aldehyde epimers **4.85** favoring the desired configuration in a combined 92% yield. Vinyl Grignard addition into the mixture of aldehydes and separation of the allylic alcohol diastereomers delivered pure **4.86** in 61% yield. RCM with 10 mol % HG-II in refluxing chloroform gave the desired cyclization product **4.29** in 86% yield, effectively removing the transition state control element.


TIPSO
H
H
CO2Me
O
4.77
1) HO OH
HC(OEt)3
pTsOH
benzene, Δ
2)LiAlH4
THF, Δ
86%
TIPSO
H
H
OH
O
O
4.84
1) Swern
2) K2O3
MeOH
92%
TIPSO
H
H
H
CHO
O
O
4.85
4:1
α:β
MgBr
61%
TIPSO
H
H
H
HO
O
O
4.86
HG-II
CHCl3
relux, 40h
86%
TIPSO
H
H
H
OH
O
O
4.29

Scheme 4.22: Synthesis of tetracycle **4.29** from Claisen-Cope product **4.77**

V

Conclusion

Over the decades we, as synthetic chemists, have delivered value to the greater scientific community through our ability to build molecules. Certainly over the past 20 years we have demonstrated that given enough time and resources we can access nearly any natural product from commodity reagents through an iterative, deliberate advancement toward the target. In an effort to improve the efficiency with which we execute these syntheses, this work has been primarily directed toward the demonstration of tandem reaction strategies to access complex targets in a rapid buildup of complexity through the creative engineering of cascade sequences.

I hope that this work not only delivers the goods in this regard but also demonstrates some willingness to investigate how these transformations work and explore the greater implications by examining some nontrivial mechanistic considerations that are not only instructive but also applicable to systems beyond these specific cases.

Appendix I

Experimental

General Information: All reactions were conducted under an atmosphere of nitrogen in flame-dried or oven-dried glassware unless otherwise indicated. High pressure reactions were carried out in a Pyrex sealed tube with a Teflon screw cap. Flash chromatography was performed as described by Still[61] on EM silica gel 60 (230-240 mesh). Benzene, toluene, methylene chloride, tetrahydrofuran, and diethyl ether were purchased from Fisher and purified by degassing with argon followed by passage through both an activated neutral alumina column and Q5 reactant column. Triethylamine, diisopropylamine, N,N-diisopropylethylamine, pyridine, and trimethylsilyl chloride were distilled over CaH_2 and stored under nitrogen. All other commercially available reagents were used as received. ^{1}H NMR were recorded on a Bruker DPX-300NB (300 MHz) or DRX-400 (400 MHz) spectrometers. ^{1}H NMR chemical shifts (δ) are reported in parts per million from $CDCl_3$ (δ 7.28 ppm), C_6D_6 (δ 7.15 ppm) or internal standard (tetramethylsilane). Data are reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad; integration, coupling constant(s) in Hz; assignment). Proton decoupled ^{13}C NMR spectra were recorded on a Bruker DRX-400 (100 MHz) and are reported in ppm from $CDCl_3$ (δ 77.0 ppm) or tetramethylsilane internal standard. Infared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR or Nicolet Avatar 370 DTGS spectrometers. Optical rotations were recorded on a JASCO DIP-1000 digital polarimeter; the concentration c is reported in g/100 mL. Low resolution mass spectra were obtained on a JOEL HX110 (APCI) mass spectrometer in the Columbia University Mass Spectrometry Laboratory.

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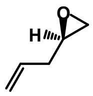
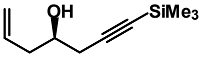
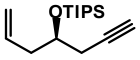
[61] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.



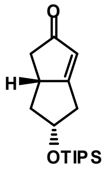
Allyl Epoxide 3.12: To a cooled (-78 °C) solution of copper (I) bromide (6.2 g, 43 mmol) in diethyl ether (600 mL) was added vinylmagnesium bromide (860 mL, 1N in THF, 860 mmol) over 30 min. After 10 min, *R*-epichlorohydrin (39 g, 430 mmol) was added. The solution was then warmed to 0 °C over 1 h with vigorous stirring. The reaction mixture was then poured into saturated aqueous ammonium chloride (1000 mL) and extracted with diethyl ether (2 x 500 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give 65 g of the crude chlorohydrin as an orange oil. Potassium hydroxide (25 g, 450 mmol) was added to the oil and a distillation head was attached to the flask. The mixture was heated with stirring to 80 °C (oil bath, external temperature) under nitrogen and wet epoxide **3.12** was collected by distillation. This was then dried with $MgSO_4$ and decanted to give 28 g (76 %) of **3.12** as a clear liquid: $[\alpha]^{23}_{D}$= -0.30° (c 3.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.11(M, 2H), 2.96 (m, 1H), 2.73 (dd, *J* = 5.0 Hz, 4.0 Hz, 1H), 2.48 (dd, *J* = 5.0 Hz, 2.6 Hz, 1H), 2.30 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 133.0, 117.5, 51.1, 46.4, 36.4; IR (NaCl, neat) 2995, 1647, 1410 cm^{-1}; LRMS (APCI) calcd for C_5H_8O ($[M+H]^+$) 85.1, found 85.0.



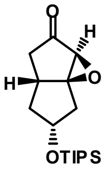
TMS enynol 3.13: To a cooled (-78 °C) solution of ethynyltrimethylsilane (44 g, 450 mmol) in tetrahydrofuran (1500 mL) was added *n*BuLi (110 mL, 2.5 M in hexanes, 270 mmol) over ~25 min. After 10 min, BF_3-THF (30 mL, 270 mmol) was added followed by dropwise addition of epoxide **3.12** (19 g, 220 mmol) over approximately 25 min. After 1 h, the reaction was quenched by the addition of 1.0 liter saturated aqueous sodium bicarbonate. The mixture was extracted with diethyl ether (2 x 500 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (10-20% ethyl acetate in hexanes) to give 38 g (94%) of **3.13** as a clear oil: $[\alpha]^{23}_{D} = +1.3^{o}$ (c 5.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.18 (m, 2H), 3.82 (m, 1H), 2.41 (m, 4H), 2.04 (d, *J* = 5.0 Hz, 1H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 134.3, 118.0, 103.1, 88.0, 69.2, 40.4, 29.2, 1.0; IR (NaCl, neat) 3400, 2960, 2915, 1640, 1420 cm^{-1}; LRMS (APCI) calcd for $C_{10}H_{18}OSi$ ($[M+H]^+$) 182.1, found 182.0.



TIPS Enyne 3.15: To a cooled (0 °C) solution of enynol **3.13** (12.1 g, 66.0 mmol) in dichloromethane (300 mL) was added 2,6-lutidine (12.0 mL, 99.0 mmol). After 1 min, TIPSOTf (22.4 mL, 82.5 mmol) was added dropwise over ~5 min. The solution was warmed to room temperature. After 12 h, triethylamine (10 mL) was added. The mixture was then poured into water (500 mL) and extracted with dichloromethane (2 x 200 mL). The organics were dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in ether / methanol (50 mL : 200 mL) and potassium carbonate (27.6 gm, 200 mmol) was added. The resulting slurry was stirred vigorously for 12 h and then poured into water (300 mL). The aqueous phase was extracted with methylene chloride (2 x 200 mL). The combined organic layers were dried over (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (20% dichloromethane in hexanes) to give enyne 16.1 g (92%) of **3.15** as a clear oil: $[\alpha]^{23}_{D} = +2.20^{o}$ (c 10.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.11 (m, 2H), 4.04 (m, 1H), 2.36-2.50 (m, 4H), 1.99 (t, J = 1.2 Hz, 1H), 1.09 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 134.3, 118.0, 103.1, 88.0, 69.2, 40.4, 29.2, 1.0; IR (NaCl, neat) 3400, 2960, 2915, 1640, 1420 cm^{-1}; LRMS (APCI) calcd for $C_{10}H_{18}OSi$ ([M+H]$^+$) 267.1, found 267.2.

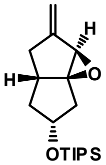


Enone 3.21a: To a solution of enyne **3.15** (6.00 g, 22.5 mmol) in benzene (450 mL) was added dicobalt octacarbonyl (400 mg, 1.15 mmol). After 10 min, tetramethylthiourea (900 mg, 6.75 mmol) was added in a single portion and the reaction vessel was sealed. The vessel was evacuated and then backfilled with carbon monoxide before heating to 70 °C (oil bath, external temperature) under a balloon of CO. After 3 h, the reaction was vented in the hood and filtered through a pad of celite. The mixture was concentrated and then purified by flash chromatography (15 – 25% ethyl acetate in hexanes) to give 2.71 g (41%) of the higher *exo* diastereomer **3.21b** and 2.84 g (43%) of the lower *endo* (desired) diastereomer **3.21a** as clear viscous oils. **3.21a** (desired): $[\alpha]^{23}_{D} = +16.1^{\circ}$ (c 5.7, CH_2Cl_2); ^{1}H NMR (400 MHz, CDCl3) δ 5.72 (s, 1H), 4.29 (m, 1H), 2.54 (dd, *J* = 18.7, 9.0 Hz, 1H), 2.39 (dd, *J* = 17.4, 6.5 Hz, 1H), 2.25 (m, 1H) 2.18 (dd, *J* = 18.7, 6.5 Hz, 1H), 2.13 – 1.99 (m, 1H), 1.90 (dd, *J* = 17.4, 3.5 Hz, 1H), 1.24 – 0.92 (m, 22H).; ^{13}C NMR (100 MHz, $CHCl_3$) δ 210.2, 187.9, 125.3, 73.7, 44.5, 42.1, 42.0, 37.9, 17.9, 12.0; IR (NaCl, neat) 2943, 2866, 1710, 1634 cm^{-1}; LRMS (APCI) calcd for $C_{17}H_{30}O_2Si$ ([M+H]$^+$) 295.2, found 295.2.

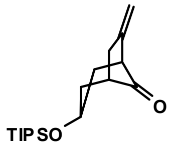


Epoxy Ketone 3.34: To a cooled (-10 °C) solution of enone **3.21a** (1.16 g, 3.95 mmol) in methanol (40 mL) was added hydrogen peroxide (30 wt% in water, 1.20 mL, 12.0 mmol) and

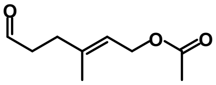
NaOH (2 N solution in water, 50.0 μL, 0.100 mmol). After 30 min, the reaction was quenched with acetic acid (0.5 mL). The resulting mixture was poured into dichloromethane (100 mL). The layers were partitioned and the aqueous phase extracted with dichloromethane (100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography to give 1.06 g (86%) white crystalline solid: $[\alpha]^{23}_{D} = -0.5^{o}$ (c 5.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (m, 1H), 3.34 (s, 1H), 2.53 (m, 4H), 2.17 (d, *J* = 17.5, 1H), 1.98 (dd, *J* = 14.5, 4.4 Hz, 1H) 1.46 (m, 1H), 1.09 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 210.0, 75.9, 70.9, 61.7, 41.3, 40.0, 36.5, 35.0, 17.9, 12.0; IR (NaCl, neat) 2943, 2866, 1747, 1463 cm^{-1}; LRMS (APCI) calcd for $C_{17}H_{30}O_3Si$ ($[M+H]^+$) 311.2, found 311.2.



Vinyl Epoxide 3.35: To a cooled (0 ^{o}C) slurry of $MePPh_3Br$ (4.00 g, 11.2 mmol) in tetrahydrofuran (50 mL) was added LiHMDS (1N in THF, 11.2 mL, 11.2 mmol). After 30 min, ketone **3.34** (1.73 g in 5 mL THF, 5.58 mmol) was added. After 30 min, the reaction was poured into water. The layers were partitioned and the aqueous phase was extracted with diethyl ether (50 mL). The combined organic layers were were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (40% DCM in hexanes) to give 1.47 g (85%) of **3.35** as a clear oil: $[\alpha]^{23}_{D} = +77^{o}$ (c 5.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.12 (s, 1H), 4.51 (m, 1H), 3.57 (s, 1H), 2.35 (m, 5H) 1.89 (dd, *J* = 14.5, 4.4 Hz, 1H), 1.33 (m, 1H) 1.09 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 147.9, 113.3, 71.3, 66.3, 40.3, 40.1, 35.5, 33.5, 17.9, 12.0; IR (NaCl, neat) 2943, 2866, 1463 cm^{-1}; LRMS (APCI) calcd for $C_{18}H_{32}O_2Si$ ($[M+H]^+$) 309.2, found 309.2.

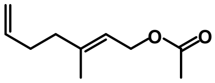


[3.2.1] bicyclo ketone 3.36: To a cooled (-78 °C) solution of vinyl epoxide **3.35** (100 mg, 0.32 mmol) in dichloromethane (3 mL) was added Sc(OTf)$_3$ (160 mg, 0.32 mmol). After 30 min, triethylamine (0.30 mL) was added. The reaction was then allowed to warm to room temperature. The reaction mixture was then poured into saturated aqueous sodium bicarbonate (10 mL) and extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give 78 mg (78%) clear oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.09 (s, 1H), 4.89 (s, 1H), 4.15 (m, 1H), 3.22 (d, *J* = 16.5, 1H), 2.68 (m, 1H) 2.43 (m, 5H) 1.09 (m, 21H).

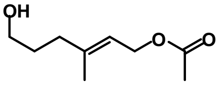


Aldehyde 2.66: To a cooled (-10 °C) solution of geranyl acetate (20.0 g, 102 mmol) in dichloromethane (500 mL) was added mCPBA (77% wt, 22.8 g in 200 mL dichloromethane, 102 mmol) dropwise over 2 h. The resulting slurry was then stirred to room temperature over 2 h and then poured into 2N NaOH (500 mL). The layers were separated and the aqueous phase extracted with dichloromethane (500 mL). The combined organics were then dried (Na$_2$SO$_4$) and concentrated. The resulting clear oil was taken up in diethyl ether (20 mL). The ether solution of crude epoxide was then added dropwise to a cold (0 °C) solution of HIO$_4$-H$_2$O (23.1 g, 102 mmol) in THF (50 mL). After 30 min, the reaction was poured into saturated sodium bicarbonate (250 mL) and extracted with diethyl ether (2 x 250 mL). The combined organic layers were washed with brine, dried (MgSO$_4$), concentrated, and purified by flash

chromatography (10-20% ethyl acetate in hexanes) to give 12.3 g (71%) of aldehyde **2.66** as a clear oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.79 (t, *J* = 1.3, 1H), 5.37 (ddd, *J* = 8.4, 5.7, 1.3 Hz, 1H), 4.59 (d, *J* = 7.0 Hz, 2H), 2.61 (t, 2H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.06 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (100 MHz, CHCl$_3$) δ 201.7, 171.0, 140.0, 119.2, 61.0, 41.7, 31.3, 21.0, 16.5.

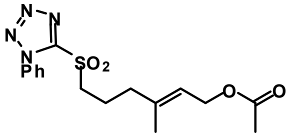


Acetate 3.50: To a cooled (0 °C) slurry of MePPh$_3$Br (15.7 g, 44.0 mmol) in tetrahydrofuran (400 mL) was added LiHMDS (1N in THF, 44.0 mL, 44.0 mmol). After 30 min, aldehyde **2.66** (7.45 g in 10 mL THF, 43.8 mmol) was added to the ylide solution. After 30 min at 0 °C, the mixture was poured into water (500 mL). The layers were partitioned and the aqueous phase extracted with diethyl ether (2 x 300 mL). The combined organics were washed with brine (500 mL), dried (MgSO$_4$), filtered, and concentrated. The residue was purified by flash chromatography (5-10% ethyl acetate in hexanes) to give 6.91 g (94%) of **3.50** as a clear oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.81 (ddt, *J* = 16.6, 10.2, 6.4 Hz, 1H), 5.37 (ddd, *J* = 8.4, 5.9, 1.3 Hz, 1H), 5.11 – 4.93 (m, 2H), 4.60 (d, *J* = 7.1 Hz, 2H), 2.28 – 2.10 (m, 4H), 2.07 (s, 3H), 1.72 (s, 3H).

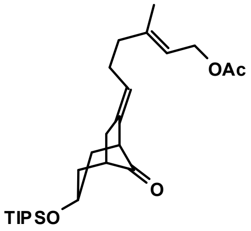


Primary Alcohol 2.67: To a cooled (0 °C) solution of aldehyde **2.66** (10 g, 58.8 mmol) in ethanol (200 mL) was added NaBH$_4$ (2.25 g, 59 mmol) in 3 portions over 5 min. After 1 h, the reaction was quenched with 1N HCl (100 mL). The resulting emulsion was extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with brine (200 mL), dried (MgSO$_4$), filtered, and concentrated. The residue was purified by flash chromatography (40% ethyl acetate in hexanes) to give 9.5 g (94%) of primary alcohol **2.67** as a clear oil: ^{1}H NMR

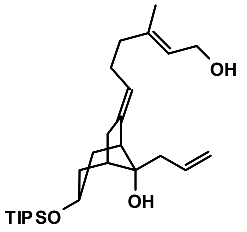
(400 MHz, $CDCl_3$) δ 5.38 (t, *J* = 7.1, 1H), 4.59 (d, *J* = 7.1, 2H), 3.64 (t, *J* = 6.5, 2H), 2.13 (t, *J* = 7.7 Hz, 2H), 2.06 (s, 3H), 1.89 (br s, 1H), 1.72 (s, 3H), 1.71 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 171.1, 141.8, 118.5, 62.2, 61.2, 35.7, 30.4, 20.9, 16.3; IR (NaCl, neat) 3540, 2935, 2865, 1730, 1660, 1463 cm^{-1}.



Sulfone 2.68: To a cooled (0 °C) solution of primary alcohol **2.67** (4.00 g, 23.2 mmol) in tetrahydrofuran (200 mL) was sequentially added 5-thio-4-phenyl-(1,2,3,4)-tetrazole **2.39** (4.50 g, 25.6 mmol), triphenylphosphine (6.08 g, 25.6 mmol), and diisopropylazodicarboxylate (5.08 mL, 25.6 mmol). After 12 h, the reaction mixture was poured into water (300 mL) and extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$), filtered, and concentrated to give a semisolid residue, which was triturated with ether/hexanes to remove triphenylphosphine oxide and the DIAD reduction product. The resulting clear oil was dissolved in ethanol and cooled to 0 °C. Hydrogen peroxide (11.3 mL, 100 mmol) and ammonium molybdate tetrahydrate (494 mg, 0.40 mmol) were sequentially added to the solution. After 12 h, the resulting yellow solution was quenched with saturated aqueous $Na_2S_2O_3$ (50 mL). The mixture was then partitioned between ethyl acetate (200 mL) and water (200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (20-30% ethyl acetate in hexanes) to give 6.70 g sulfone **2.68** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.54 (m, 5H), 5.43 (t, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 7.0 Hz, 2H), 3.72 (t, *J* = 6.4, 2H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.22 – 2.11 (m, 2H), 2.08 (s, 3H), 1.75 (s, 3H); LRMS (APCI) calcd for $C_{16}H_{20}O_4S$ ($[M+H]^+$) 365.1, found 365.0.

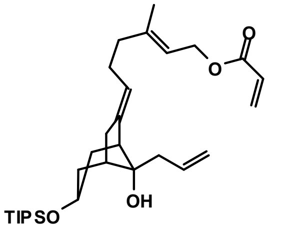


Ketone 3.53: To a solution of vinyl epoxide **3.35** (2.00 g, 6.49 mmol) and acetate **3.50** (1.64 g, 9.75 mmol) in chloroform (32 mL) was added Hoveyda-Grubbs II (200 mg, 0.319 mmol) catalyst. The resulting solution was then heated to reflux on an oil bath. After 4 h, the mixture was cooled to room temperature and then concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give 1.62 g (56%) ketone **3.53** as a 4.5:1 mixture of *E/Z* isomers: $[\alpha]^{23}_{D}$ = -34° (c 4.9, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (m, 2H), 4.57 (d, *J* = 7.1, 2H), 4.10 (m, 1H), 3.09 (d, *J* = 16.0, 1H), 2.67 (br s, 1H) 2.39 (m, 5H), 2.07 (m, 5H) 2.04 (s, 3H), 1.69 (s, 3H), 1.04 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 220.5, 171.2, 141.9, 136.0, 121.8, 118.4, 65.3, 61.3, 53.5, 52.7, 48.4, 45.3, 38.8, 30.4, 26.1, 21.0, 18.1, 16.3, 12.0; IR (NaCl, neat) 3450, 2943, 2866, 1742, 1463 cm^{-1}; LRMS (APCI) calcd for $C_{26}H_{44}O_4Si$ ($[M+H]^+$) 449.3, found 449.2.



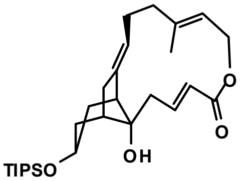
Diol 4.3: To a cooled (0 °C) solution of ketone **3.53** (2.50 g, 5.58 mmol) in tetrahydrofuran (50 mL) was added allylmagnesium bromide (20.0 mL, 1M in THF, 20.0 mmol). After 30 min, the mixture was quenched with saturated aqueous ammonium chloride (50 mL). The layers were separated and the aqueous phase extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (100 mL) then dried ($MgSO_4$), filtered, and concentrated.

The residue was purified by flash chromatography (25% ethyl acetate in hexanes) to give 1.76 g (71%) of **4.3** as a single isomer and 320 mg (13%) lower *Z* isomer: $[\alpha]^{23}_{D}$ = +11° (c 6.3, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.43 (t, *J* = 6.6 Hz, 1H), 5.30 (s, 1H), 5.26 – 5.13 (m, 2H), 4.18 (t, *J* = 7.2 Hz 2H), 4.10 (m, 1H), 2.76 (d, *J* = 16.9 Hz, 1H), 2.33 (ddd, *J* = 13.8, 5.1, 2.8 Hz, 2H), 2.22 (m, 4H), 2.07 (m, 4H), 1.96 (br d, *J* = 6.2 Hz, 1H), 1.71 (s, 3H) 1.81 – 1.66 (m, 2H), 1.06 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 142.9, 139.9, 133.8, 123.3, 120.5, 119.5, 77.2, 65.5, 59.3, 48.6, 42.7, 39.8, 39.1, 37.7, 35.8, 31.2, 26.8, 18.2, 16.2, 12.1; IR (NaCl, neat) 3381, 2940, 2865 cm^{-1}; LRMS (APCI) calcd for $C_{27}H_{48}O_3Si$ ($[M+H]^+$) 449.2, found 431.2 ($-H_2O$).

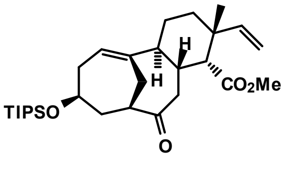


Acrylate 4.3a: To a solution of diol **4.3** (1.85 g, 4.13 mmol), triethylamine (3.51 mL, 25.0 mmol) and acrylic acid (0.550 mL, 8.26 mmol) in dichoromethane (40 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.31 g, 12.4 mmol) in a single portion. After 12 h, the resulting orange slurry was poured into water. The layers were separated and the aqueous phase was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (10-30% ethyl acetate in hexanes) to give 1.68 g **4.3a** (81%) and 120 mg (6%) of **4.3**: $[\alpha]^{23}_{D}$= +11° (c 6.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.16 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.88 (m, 1H), 5.81 (d, *J* = 10.4, 1H), 5.39 (t, *J* = 6.6 Hz, 1H), 5.29 (br s, 1H), 5.20 (ddd, *J* = 19.2, 13.6, 2.1 Hz, 2H), 4.71 (d, *J* = 7.1 Hz, 2H), 4.10 (m, 1H), 2.76 (d, *J* = 16.8 Hz, 1H), 2.33 (ddd, *J* = 13.6, 5.1, 2.9 Hz, 2H), 2.22 (m, 4H), 2.15 – 2.02 (m, 3H), 1.96 (d, *J* = 6.4 Hz, 1H),

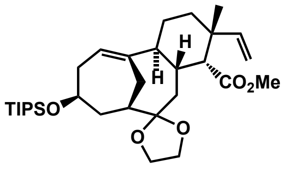
1.65-1.80 (m, 2H), 1.69 (s, 3H), 1.06 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.1, 143.1, 142.5, 133.7, 130.6, 128.6, 120.4, 119.5, 118.1, 65.5, 61.5, 48.6, 42.7, 39.8, 39.1, 37.7, 35.8, 31.2, 26.7, 18.2, 16.4, 12.1; IR (NaCl, neat) 3470, 2941, 2865, 1726, 1407 cm^{-1}; LRMS (APCI) calcd for $C_{30}H_{50}O_4Si$ ($[M+H]^+$) 503.4, found 485.2 ($-H_2O$).



Macrolactone 4.1: To a solution of acrylate **4.3a** (2.00 g, 3.98 mmol) in dichloromethane (500 mL) was added Hoveyda-Grubbs II catalyst (250 mg, 0.399 mmol) and the mixture was heated at reflux. After 4 h, the mixture was cooled and ethyl vinyl ether (1 mL) was added. The resulting mixture was stirred open to the air for 1 h, and then concentrated. The residue was purified by flash chromatography (20% ethyl acetate in hexanes) to give 1.44 g (76%) of macrolactone **4.1** as a clear oil: $[\alpha]^{23}_D = +100^o$ (c 3.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (ddd, *J* = 11.7, 9.3, 5.9 Hz, 1H), 5.87 (d, *J* = 11.8 Hz, 1H), 5.40 (t, *J* = 6.8, 1H), 5.16 (d, *J* = 8.6 Hz, 1H), 4.97 (dd, *J* = 11.3, 9.6 Hz, 1H), 4.34 (dd, *J* = 11.3, 6.4 Hz, 1H), 4.05 (t, *J* = 5.1 Hz, 1H), 3.09 (ddd, *J* = 15.7, 9.4, 1.1 Hz, 1H), 2.68 (d, *J* = 16.5 Hz, 1H), 2.44 (ddd, *J* = 15.7, 5.9, 1.9 Hz, 1H), 2.33 – 1.87 (m, 9H), 1.78 (s, 3H), 1.76 – 1.55 (m, 3H), 1.03 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.9, 144.4, 143.7, 142.0, 122.5, 120.6, 118.8, 77.8, 65.0, 59.9, 49.5, 39.2, 38.8, 38.6, 37.8, 35.7, 31.2, 27.4, 18.1, 16.9, 12.1; IR (NaCl, neat) 3446, 2941, 2865, 1692 cm^{-1}; LRMS (APCI) calcd for $C_{28}H_{46}O_4Si$ ($[M+H]^+$) 475.3, found 457.2 ($-H_2O$).

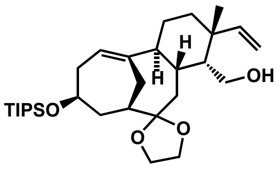


Ketoester 4.2: To a solution of macrolactone **4.1** (700 mg, 1.43 mmol) in triflurotoluene (35.8 mL) in a high pressure Pyrex tube was added 1,8-diazabicylco[5.4.0]undec-7-ene (2.21 mL, 14.7 mmol) and $Me_2PhSiCl$ (2.50, 14.7 mmol). The vessel was sealed with a Teflon screw cap and heated to 140 °C (oil bath, external temperature). After 14 h, the solution was cooled and then was poured into aqueous 1N HCl (50 mL). The mixture was then extracted with dichlormethane (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in diethyl ether (5 mL) and methanol (20 mL), and the resulting solution was treated with TMS-diazomethane (2N solution in hexanes, 3.50 mL, 7.00 mmol). After 1 h, the solution was concentrated and the residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give 322 mg (45%) ketoester **4.2** as a clear oil: $[\alpha]^{23}_{D} = +25^{\circ}$ (c 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, J = 17.5, 10.8 Hz, 1H), 5.65 (t, J = 8Hz, 1H), 5.09 - 4.90 (m, 2H), 3.60 (s, 3H), 3.49 (tt, J = 10.2, 3.4 Hz, 1H), 2.80 (ddd, J = 14.9, 10.1, 5.7 Hz, 2H), 2.68 (d, J = 13.0 Hz, 1H), 2.63 - 2.42 (m, 5H), 2.38 (d, J = 17.3 Hz, 1H), 2.34 - 2.13 (m, 3H), 1.74 (ddd, J = 13.2, 10.3, 4.7 Hz, 1H), 1.63 - 1.52 (m, 3H), 1.39 (d, J = 13.5 Hz, 1H), 1.21 (s, 3H), 1.06 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 212.9, 173.4, 146.0, 145.9, 123.9, 112.3, 65.8, 54.3, 51.0, 49.5, 48.5, 45.7, 45.1, 38.8, 37.1, 32.3, 30.1, 26.2, 26.0, 24.8, 18.1, 12.2; IR (NaCl, neat) 2940, 2860, 1730, 1685, 1441 cm^{-1}; LRMS (APCI) calcd for $C_{29}H_{48}O_4Si$ ($[M+H]^+$) 489.3 found 489.3.



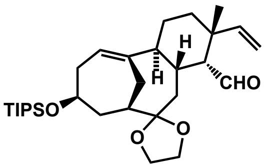
Ketal 4.2a: To a solution of ketone **4.2** (152 mg, 0.311 mmol) in benzene (2 mL) was added ethylene glycol (174 μL, 3.10 mmol), triethylorthoformate (325 μL, 1.55 mmol), and *para*-

toluenesulfonic acid (1 mg). The solution was then heated to 60 °C (oil bath, external temperature). After 10 h, the mixture was poured into saturated aqueous sodium bicarbonate (5 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (8% ethyl acetate in hexanes) to give 151 mg (92%) ketal **4.2a**: $[\alpha]^{23}_{D} = +62^{o}$ (c 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (dd, *J* = 15.6, 10.8 Hz, 1H), 5.48 (dd, *J* = 7.9, 4.9 Hz, 1H), 4.97 (ddd, *J* = 15.2, 11.0, 1.1 Hz, 2H), 4.26 - 4.13 (m, 1H), 3.99 - 3.84 (m, 4H), 3.58 (s, 3H), 2.76 - 2.64 (m, 1H), 2.61 - 2.49 (m, 2H), 2.43 (d, *J* = 4.0 Hz, 1H), 2.41 - 2.30 (m, 2H), 2.24 - 2.13 (m, 2H), 2.08 (dt, *J* = 6.2, 5.8, 1H), 1.83 (dt, *J* = 13.9, 5.8 Hz, 1H), 1.65 (dd, *J* = 13.9, 9.7 Hz, 2H), 1.56 - 1.47 (m, 2H), 1.38 - 1.24 (m, 3H), 1.21 (s, 3H), 1.10 – 1.06 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.9, 147.1, 143.2, 122.8, 112.8, 112.8, 111.4, 65.5, 64.5, 64.0, 56.7, 50.8, 44.6, 38.9, 38.3, 36.8, 35.6, 33.7, 32.9, 31.1, 29.7, 28.9, 25.0, 24.6, 18.1, 12.3 ; IR (NaCl, neat) 2939, 2865, 1724, 1456, 1150, 1083 cm^{-1}; LRMS (APCI) calcd for $C_{31}H_{52}O_5Si$ ($[M+H]^+$) 533.3 found 533.3.



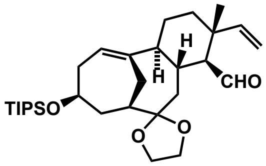
Primary Hydroxyl 4.16: To a solution of ester **4.2a** (151 mg, 0.286 mmol) in tetrahydrofuran (2 mL) was added $LiAlH_4$ (60.0 mg, 1.50 mmol) and heated to 55 °C on an oil bath. After 3 h, the reaction was diluted with diethyl ether (4 mL) and cooled to 0 °C. The resulting mixture was then slowly quenched by the dropwise addition of methanol. Rochelle's salt (saturated, aqueous, 5 mL) was then added. The resulting mixture was then stirred vigorously for 2 h until both layers appeared homogenous. The layers were separated and the aqueous phase extracted with diethyl ether (2 x 10 mL). The combined organic layers were then washed with brine, dried

($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to give 128 mg (89%) of **4.16** as a white crystalline solid: $[\alpha]^{23}_D = +12^o$ (c 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (dd, *J* = 18.0, 10.6 Hz, 1H), 5.37 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.07 (dd, *J* = 14.3, 2.4 Hz, 2H), 4.27 - 4.17 (m, 1H), 3.99 - 3.86 (m, 4H), 3.70 (dd, *J* = 11.8, 7.4 Hz, 1H), 3.47 (d, *J* = 10.5 Hz, 1H), 2.59 - 2.47 (m, 2H), 2.35 (ddd, *J* = 12.4, 8.2, 3.8 Hz, 2H), 2.20 (d, *J* = 13.3 Hz, 1H), 2.09 (dt, *J* = 10.9, 5.4 Hz, 1H), 1.90-1.70 (m, 5H), 1.55 - 1.34 (m, 6H), 1.22 (s, 3H), 1.09 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 149.5, 143.2, 122.2, 113.0, 111.2, 65.2, 64.4, 64.2, 60.9, 54.8, 47.1, 39.8, 38.8, 37.2, 35.9, 33.5, 32.9, 30.1, 29.9, 29.2, 26.4, 25.0, 18.1, 12.3; IR (NaCl, neat) 3446, 2928, 2865, 1449, 1085 cm^{-1}; LRMS (APCI) calcd for $C_{30}H_{52}O_4Si$ ($[M+H-H_2O]^+$) 505.3, found 487.3.

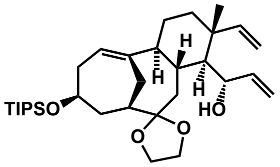


Aldehyde 4.17a: To a cooled (-78 °C) solution of oxalyl chloride (43 μL, 0.50 mmol) in dichloromethane (3 mL) was added DMSO (53 μL, 0.75 mmol). After 10 min, primary hydroxyl **4.16** (130 mg, 0.25 mmol in 0.5 mL dichloromethane) was added by syringe. After 30 min, triethylamine (0.17 mL, 1.2 mmol) was added and the reaction was warmed to room temperature. The mixture was then poured into water and extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give 120 mg (94%) of aldehyde **4.17a** as a clear oil: $[\alpha]^{23}_D = +74.3^o$ (c 10.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 4.4 Hz, 1H), 5.84 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.43 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.09 - 4.96 (m, 2H), 4.26 - 4.13 (m, 1H), 3.91 (dd, *J* = 10.6, 5.1 Hz, 4H), 2.60 - 2.50 (m, 2H), 2.49 -

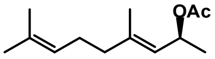
2.21 (m, 4H), 2.21 - 2.14 (m, 1H), 2.11 - 1.93 (m, 2H), 1.85 (dt, *J* = 14.1, 5.8 Hz, 1H), 1.75 (dd, *J* = 14.3, 10.0 Hz, 1H), 1.36 (d, *J* = 14.3 Hz, 2H), 1.23 (s, 3H), 1.08 (m, 21H); ^{13}C NMR (100 MHz, CHCl$_3$) δ ; IR (NaCl, neat) 2940, 2866, 1716, 1463 cm^{-1}; LRMS (APCI) calcd for $C_{30}H_{50}O_4Si$ ([M+H]$^+$) 503.4, found 503.3.



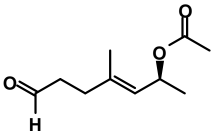
Aldehyde 4.17b: To a solution of aldehyde **4.17a** (145 mg, 0.23 mmol) in methanol was added potassium carbonate (95 mg, 0.69 mmol). The resulting slurry was stirred vigorously. After 12 h, the reaction was poured into saturated aqueous ammonium chloride (5 mL) and extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give 120 mg (100 %) of aldehydes **4.17b** : **4.17a** as a 3.7 : 1 mixture by ^{1}H NMR: ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.55 (d, *J* = 5.1 Hz, 1H), 5.80 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.45 (dd, *J* = 7.8, 4.9 Hz, 1H), 5.08 - 4.90 (m, 2H), 4.27 - 4.15 (m, 1H), 3.97 - 3.80 (m, 4H), 2.65 - 2.47 (m, 3H), 2.41 - 2.33 (m, 1H), 2.28 (d, *J* = 12.8 Hz, 1H), 2.22 - 2.05 (m, 2H), 2.01 (dd, *J* = 11.7, 5.1 Hz, 1H), 1.86 (dt, *J* = 14.2, 6.1 Hz, 2H), 1.66 - 1.53 (m, 3H), 1.53 - 1.42 (m, 2H), 1.25 (s, 3H), 1.08 (m, 21H); ^{13}C NMR (100 MHz, CHCl$_3$) δ ; IR (NaCl, neat) 2940, 2866, 1716, 1463 cm^{-1}; LRMS (APCI) calcd for $C_{30}H_{50}O_4Si$ ([M+H]$^+$) 503.4, found 503.3.



Allylic Alcohol 4.86: To a solution of aldehydes **4.17a** and **4.17b** (1 : 3.7 mixture; 152 mg, 0.294 mmol) in diethyl ether (3 mL) at 0 ^{o}C was added vinylmagnesium bromide (1N in THF; 0.588 mL, 0.588 mmol). After 30 min, the reaction was quenched with saturated aqueous ammonium chloride (5 mL). The resulting mixture was extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (10-20% ethyl acetate in hexanes) to give 95.0 mg (60%) allylic alcohol **4.86** and 26.0 mg (16%) lower diastereomers: $[\alpha]^{23}_{D}$ = +40° (c 10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (ddd, *J* = 17.2, 10.6, 2.9 Hz, 1H), 5.54 – 5.38 (m, 2H), 5.23 (ddd, *J* = 17.3, 7.8, 1.8 Hz, 2H), 5.00 (ddd, *J* = 10.6, 2.6, 1.9 Hz, 1H), 4.28 (dd, *J* = 11.6, 2.7 Hz, 1H), 4.17 (dd, *J* = 8.2, 4.0 Hz, 1H), 4.03 (ddd, *J* = 6.9, 6.0, 3.7 Hz, 1H), 3.93 (ddd, *J* = 7.1, 5.7, 3.7 Hz, 1H), 3.90 – 3.74 (m, 2H), 3.44 (d, *J* = 11.6 Hz, 1H), 2.55 (ddd, *J* = 24.3, 13.5, 6.8 Hz, 2H), 2.38 (dt, *J* = 15.9, 4.0 Hz, 1H), 2.30 (d, *J* = 13.4 Hz, 1H), 2.19 (dd, *J* = 19.8, 11.2 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.95 (d, *J* = 13.4 Hz, 2H), 1.81 (dt, *J* = 20.2, 6.4 Hz, 1H), 1.68 (dd, *J* = 6.3, 1.3 Hz, 3H), 1.59 – 1.31 (m, 7H), 1.16 (s, 3H), 1.07 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 147.5, 144.0, 143.0, 122.7, 122.5, 113.3, 110.8, 71.4, 65.6, 64.8, 64.1, 53.6, 52.6, 40.9, 40.6, 37.3, 37.0, 36.0, 33.9, 31.7, 28.7, 25.0, 18.3, 18.1, 12.2; IR (NaCl, neat) 3486, 2940, 2865, 1463 cm^{-1}; LRMS (APCI) calcd for $C_{32}H_{54}O_4Si$ ($[M+H-H_2O]^+$) 531.4, found 513.3.

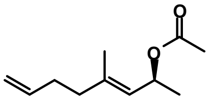


Secondary Acetate 4.70: To a solution of geranial (8.00 g, 52.6 mmol) and (2S)-3-exo-(Morpholino)isoborneol (750 mg, 3.13 mmol) in toluene (50 mL) was added dimethylzinc (1 M in heptane, 100 mL, 100 mmol). After 18 h, the solution was quenched with acetic anhydride (25.0 mL, 265 mmol) and stirred an additional 18 h. The reaction mixture was then poured into saturated aqueous ammonium chloride (200 mL) and extracted with diethyl ether (2 x 150 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give 9.4 g (85%) of acetate **4.70** as a clear oil, 83% ee by chiral GC analysis. $[\alpha]^{23}_D = -31.9^o$ (c 14.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.59 (dq, *J* = 8.8, 6.4 Hz, 1H), 5.15 (d, *J* = 8.8 Hz, 1H), 5.07 (t, *J* = 7.0 Hz, 1H), 2.15 – 2.05 (m, 2H), 2.01 (s, 3H), 2.05 – 1.95 (m, 2H) 1.70 (s, 3H) 1.68 (s, 3H), 1.60 (s, 3H), 1.25 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 170.4, 139.4, 131.7, 124.7, 123.8, 68.1, 39.4, 26.3, 25.7, 21.4, 20.9, 17.7, 16.6; IR (NaCl, neat) 2969, 2924, 1732, 1441, 1367, 1240 cm^{-1}; LRMS (APCI) calcd for $C_{13}H_{22}O_2Si$ ($[M+H]^+$) 211.1, found 211.1

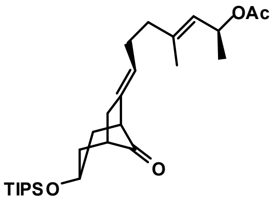


Aldehyde 4.72: To a cooled (-10 °C) solution of acetate **4.70** (13.0 g, 61.9 mmol) in dichloromethane (300 mL) was added mCPBA (77% by wt, 14.2 g, 61.9 mmol) in dichloromethane (100 mL) dropwise over 2 h. The resulting slurry was then warmed to room temperature and stirred for an additional 2 h. The mixture was then poured into 2N NaOH (500 mL). The layers were separated and the aqueous phase extracted with dichloromethane (2 x 250 mL). The combined organic layers were then dried (Na_2SO_4), filtered, concentrated, and taken up in THF (40 mL). The THF solution of crude epoxide was then added dropwise to a cold (0 °C) solution of HIO_4-H_2O (14.1 g, 61.9 mmol) in water (50 mL). After 30 min, the reaction was quenched with saturated sodium bicarbonate (200 mL) and extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (10-20% ethyl acetate in

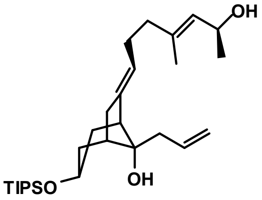
hexanes) to give 7.64 g of aldehyde **4.72** (67%) as a clear oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.78 (t, *J* = 1.5 Hz, 1H), 5.59 (dq, *J* = 8.8, 6.4 Hz, 1H), 5.19 (dd, *J* = 8.6, 1.1 Hz, 1H), 2.64 – 2.53 (m, 62H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.03 (s, 3H), 1.74 (d, *J* = 1.0 Hz, 3H), 1.26 (d, *J* = 6.4 Hz, 3H).



Acetate 4.73: To a cold (0 °C) slurry of MePPh$_3$Br (12.4 g, 34.7 mmol) in tetrahydrofuran (200 mL) was added LiHMDS (1N in THF, 34.7 mL, 34.7 mmol). After 30 min, aldehyde **4.72** (6.40 g in 5 mL THF, 34.8 mmol) was added. After an additional 30 min, the resultant mixture was poured into water. The layers were partitioned and the aqueous phase extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine, dried (MgSO$_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (5-10% ethyl acetate in hexanes) to give 5.0 g (77%) of **4.73** as a clear oil: $[\alpha]^{23}_D$ = -33° (c 10, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.62 (dq, *J* = 8.7, 6.4 Hz, 1H), 5.20 (dd, *J* = 8.8, 1.1 Hz, 1H), 5.09 – 4.93 (m, 2H), 2.19 (ddd, *J* = 10.7, 5.2, 1.3 Hz, 2H), 2.09 (dd, *J* = 13.8, 6.2 Hz, 2H), 2.04 (s, 3H), 1.73 (d, *J* = 1.1 Hz, 3H), 1.28 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CHCl$_3$) δ 170.4, 138.8, 138.1, 124.9, 114.6, 68.1, 38.7, 31.9, 21.4, 20.9, 16.6; IR (NaCl, neat) 2977, 2924, 1732, 1642, 1441, 1367, 1240 cm^{-1}; LRMS (APCI) calcd for C$_{11}$H$_{18}$O$_2$ ([M+H]$^+$) 183.1, found 183.1.

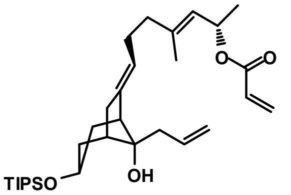


Ketone 4.74: To a solution of vinyl epoxide **3.35** (380 mg, 1.23 mmol) and acetate **4.73** (340 mg, 1.85 mmol) in chloroform (6.15 mL) was added Hoveyda-Grubbs II (38.5 mg, 0.0615 mmol) catalyst. The solution was then heated to reflux. After 4 h, the mixture was concentrated. The brownish residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give 449 mg (79%) of ketone **4.74** as a 4.7:1 mixture of *E/Z* isomers: $[\alpha]^{23}_{D}$ = -52.8° (c 7.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (dq, *J* = 8.8, 6.3 Hz, 1H), 5.36 (br s, 1H), 5.16 (dd, *J* = 8.8, 1.0 Hz, 1H), 4.13 (t, *J* = 3.0 Hz, 1H), 3.11 (d, *J* = 16.0 Hz, 1H), 2.69 (s, 1H), 2.61 – 2.42 (m, 2H), 2.42 – 2.33 (m, 6H), 2.19 – 1.98 (m, 4H), 2.03 (s, 3H), 1.73 (s, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.06 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 220.1, 170.4, 139.2, 136.0, 128.3, 124.9, 121.9, 68.0, 65.4, 52.8, 48.4, 45.4, 38.8, 30.4, 26.1, 21.4, 20.9, 18.1, 16.5, 12.0; IR (NaCl, neat) 2943, 2866, 1759, 1735 1462 cm^{-1}; LRMS (APCI) calcd for $C_{27}H_{46}O_4Si$ ($[M+H]^+$) 463.3, found 463.2.



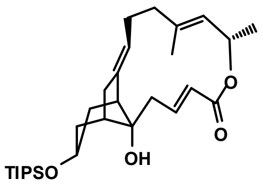
Diol 4.75: To a cooled (0 °C) solution of ketone **4.74** (1.50 g, 3.25 mmol) in tetrahydrofuran (50.0 mL) was added allylmagnesium bromide (13.0 mL, 1M in THF, 13.0 mmol). After 30 min, the reaction was quenched with saturated aqueous ammonium chloride (50 mL). The layers were separated and the aqueous phase back extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (50 mL) then dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (25% ethyl acetate in hexanes) to give 1.11 g (75%) of **4.75** as a single isomer and 210 mg (14%) lower *Z* isomer: $[\alpha]^{23}_{D}$ = +0.11° (c 5.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.5, 10.1, 7.5 Hz, 1H),

5.36 – 5.13 (m, 4H), 4.60 (dq, *J* = 8.3, 6.2 Hz, 1H), 4.10 (t, *J* = 5.1 Hz, 1H), 2.77 (d, *J* = 16.6 Hz, 1H), 2.34 (ddd, *J* = 13.6, 5.1, 2.9 Hz, 2H), 2.30 – 2.17 (m, 4H), 2.15 – 1.93 (m, 5H), 1.80 – 1.61 (m, 3H), 1.71 (s, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.07 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 142.9, 137.8, 133.7, 129.1, 128.3, 120.6, 119.5, 65.5, 64.8, 48.7, 42.8, 39.9, 39.0, 37.8, 35.9, 31.3, 26.9, 23.6, 18.2, 16.4, 12.1; IR (NaCl, neat) 3366, 2926, 2866, 1463 cm^{-1}; LRMS (APCI) calcd for $C_{28}H_{50}O_3Si$ ([M+H-H_2O]$^+$) 463.3, found 445.2.

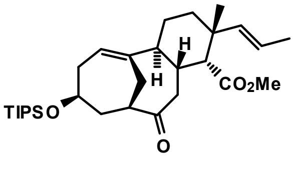


Acrylate 4.75a: To a solution of diol **4.75a** (1.30 g, 2.81 mmol), triethylamine (3.94 mL, 28.1 mmol) and acrylic acid (0.610 mL, 8.43 mmol) in dichoromethane (15 mL) was added EDC (2.16 g, 11.2 mmol) in a single portion. After 12 h, the resulting orange slurry was poured into water (20 mL). The layers were separated and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (10-30% ethyl acetate in hexanes) to give 1.17 g **4.75a** (73%) and 300 mg (21%) **4.75** unreacted starting material. $[\alpha]^{23}_D$ = -4.3° (c 5.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (dd, *J* = 17.3, 1.6 Hz, 1H), 6.12 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.85 (m, 1H), 5.76 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.71 (dq, *J* = 8.8, 6.3 Hz, 1H), 5.21 (m, 4H), 4.09 (t, *J* = 5.2 Hz, 1H), 2.75 (d, *J* = 16.3 Hz, 1H), 2.44 – 2.28 (m, 2H), 2.28 – 2.14 (m, 4H), 2.02 (m, 5H), 1.81 – 1.65 (m, 2H), 1.73 (s, 3H), 1.57 (br d, *J* = 9.6 Hz, 1H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.05 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.7, 142.9, 140.0, 133.7, 130.2, 129.1, 124.4, 120.4, 119.5, 68.4, 65.5, 48.6, 42.8, 39.8, 39.0, 37.8, 35.8, 31.3, 26.8, 21.0,

18.2, 16.6, 12.1; IR (NaCl, neat) 3493, 2940, 2866, 1722, 1638, 1462, 1405 cm^{-1}; LRMS (APCI) calcd for $C_{31}H_{52}O_4Si$ ($[M+H-H_2O]^+$) 517.4, found 499.3

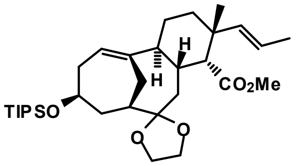


Macrolactone 4.76: To a solution of acrylate **4.75a** (660 mg, 1.25 mmol) in dichloromethane (125 mL) was added Hoveyda-Grubbs 2nd generation catalyst (78.3 mg, 0.125 mmol). The mixture was then heated to reflux on an oil bath. After 4 h, the reaction was cooled to room temperature. The reaction was then quenched with ethyl vinyl ether (1 mL) and stirred open to the air for 1 h. The resulting black solution was concentrated and purified by flash chromatography (20% ethyl acetate in hexanes) to give 410 mg (72%) macrolactone **4.76** as a clear oil. $[\alpha]^{23}_D = +120^o$ (c 3.5, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 6.36 (ddd, *J* = 11.6, 9.1, 5.9 Hz, 1H), 5.88 (d, *J* = 11.7 Hz, 1H), 5.72 (dq, *J* = 9.7, 6.3 Hz, 1H), 5.17 (d, *J* = 9.7 Hz, 2H), 4.07 (t, *J* = 5.1 Hz, 1H), 3.10 (ddd, *J* = 16.1, 9.1, 1.4 Hz, 1H), 2.67 (d, *J* = 16.4 Hz, 1H), 2.51 (ddd, *J* = 16.1, 5.9, 2.2 Hz, 1H), 2.28 – 2.10 (m, 5H), 2.04 – 1.92 (m, 3H), 1.88 (s, 1H), 1.78 (s, 3H), 1.77 – 1.66 (m, 2H), 1.41 (s, 1H), 1.34 (d, *J* = 6.3 Hz, 3H), 1.04 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ166.2, 143.7, 141.8, 140.5, 126.2, 122.6, 121.0, 77.9, 67.2, 65.1, 49.4, 39.5, 39.1, 38.8, 37.8, 35.6, 31.1, 26.5, 20.7, 18.1, 16.2, 12.1; IR (NaCl, neat) 3465, 2941, 2866, 1687, 1462 cm^{-1}; LRMS (APCI) calc'd for $C_{29}H_{48}O_4Si$ ($[M+H-H_2O]^+$) 489.4, found 471.3



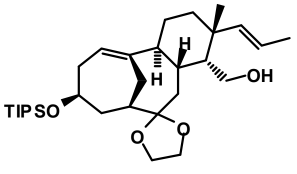
Ketoester 4.77: To a solution of macrolactone **10.17** (260 mg, 0.50 mmol) in triflurotoluene (12 mL) in a high pressure Pyrex tube was added 1,8-diazabicylco[5.4.0]undec-7-ene (0.75 mL, 5.0

mmol) and $Me_2PhSiCl$ (0.84 mL, 5.0 mmol). The vessel was sealed with a Teflon screw cap and heated to 140 °C (oil bath, external temperature). After 14 h, the solution was cooled to room temperature and then poured into aqueous 1N HCl (20 mL). The mixture was extracted with dichlormethane (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and dissolved in diethyl ether (5 mL) and methanol (20 mL). The mixture was then treated with TMS-diazomethane (2N solution in hexanes, 1.0 mL, 2.0 mmol). After 1 h, the solution was concentrated and the residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give ketoester **4.77** (172 mg, 68% yield) as a clear oil. $[\alpha]^{23}_{D} = +15^{\circ}$ (c 3.5, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (t, *J* = 7.3 Hz, 1H), 5.51 – 5.35 (m, 2H), 3.58 (s, 3H), 3.49 (tt, *J* = 10.2, 3.3 Hz, 1H), 2.88 – 2.72 (m, 2H), 2.67 (d, *J* = 13.1 Hz, 1H), 2.63 – 2.11 (m, 9H), 1.74 (ddd, *J* = 13.2, 10.2, 4.7 Hz, 1H), 1.65 (d, *J* = 4.9 Hz, 3H), 1.56 (td, *J* = 8.2, 2.7 Hz, 2H), 1.35 (dd, *J* = 10.7, 2.8 Hz, 1H), 1.18 (s, 3H), 1.06 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 212.6, 173.5, 146.7, 139.3, 123.9, 122.3, 65.9, 54.9, 50.8, 49.5, 48.6, 45.7, 45.1, 38.0, 37.2, 32.6, 31.0, 18.2, 18.1, 18.0, 12.3; IR (NaCl, neat) 3451, 2943, 2865, 1733, 1686 cm^{-1}; LRMS (APCI) calcd for $C_{30}H_{50}O_4Si$ ($[M+H]^+$) 503.4, found 503.3

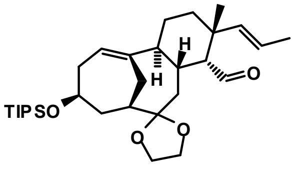


Ketal 4.77a: To a solution of ketone **4.77** (300 mg, 0.598 mmol) in benzene (3 mL) was added ethylene glycol (0.334 mL, 5.98 mmol), triethylorthoformate (0.497 mL, 2.99 mmol), and *para*-toluenesulfonic acid (1mg). The solution was heated to 60 °C on an oil bath. After 10 h, the mixture was poured into saturated aqueous sodium bicarbonate (10 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give 404 mg (quant) crude ketal

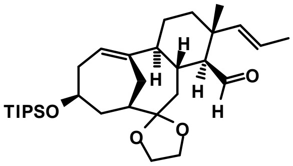
4.77a, which was carried into the subsequent reaction without further purification. $[\alpha]^{23}_{D} = +76^{o}$ (c 7.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (dd, *J* = 7.8, 4.7 Hz, 1H), 5.43 – 5.33 (m, 2H), 4.25 – 4.13 (m, 1H), 4.01 – 3.80 (m, 4H), 3.55 (s, 3H), 2.69 (dd, *J* = 16.6, 10.4 Hz, 1H), 2.60 – 2.44 (m, 2H), 2.40 – 2.25 (m, 3H), 2.25 – 1.98 (m, 3H), 1.81 (dt, *J* = 13.7, 5.7 Hz, 1H), 1.69 – 1.56 (m, 3H), 1.54 – 1.41 (m, 3H), 1.28-1.23 (m, 4H), 1.17 (s, 3H), 1.06 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 174.1, 143.3, 139.9, 122.8, 121.8, 112.8, 65.5, 64.5, 64.0, 57.2, 50.7, 44.5, 38.3, 38.1, 36.8, 35.5, 33.7, 32.9, 31.8, 29.1, 25.5, 24.6, 18.2, 18.1, 12.2; IR (NaCl, neat) 2943, 2866, 1734, 1462, 1438 cm^{-1}; LRMS (APCI) calcd for $C_{32}H_{54}O_5Si$ ($[M+H]^{+}$) 547.4, found 547.3



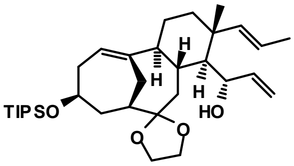
Primary Hydroxyl 4.84: To a solution of ester **4.77a** (105 mg, 0.192 mmol) in tetrahydrofuran (2 mL) was added $LiAlH_4$ (36.5 mg, 0.960 mmol) and heated to 55 ^{o}C on an oil bath. After 3 h, the reaction was diluted with diethyl ether (4 mL) and cooled to 0 ^{o}C. The mixture was then slowly quenched by the dropwise addition of methanol. Rochelle's salt (saturated, aqueous, 5 mL) was then added. The mixture was then stirred vigorously for 2 h until both layers appeared homogenous. The layers were separated and the aqueous phase extracted with diethyl ether (2 x 10 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to give 86.0 mg (86%) of **4.84** as a white crystalline solid. $[\alpha]^{23}_{D} = +66^{o}$ (c 11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (dd, *J* = 15.9, 1.2 Hz, 1H), 5.48 (dq, *J* = 15.8, 6.3 Hz, 1H), 5.36 (dd, *J* = 8.0, 4.7 Hz, 1H), 4.20 (dd, *J* = 5.2, 4.0 Hz, 1H), 4.00 – 3.86 (m, 4H), 3.68 (dd, *J* = 11.8, 7.6 Hz, 1H), 3.44 (d, *J* = 11.5 Hz, 1H), 2.60 – 2.46 (m, 2H), 2.40 – 2.27 (m, 2H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.75 (d, *J* = 6.3, 3H), 1.77 – 1.69 (m, 5H), 1.55 – 1.27 (m, 6H), 1.19 (s, 3H), 1.08 (m, 21H); ^{13}C NMR (100 MHz, CHCl$_3$) δ 143.7, 142.0, 122.0, 121.5, 113.2, 65.5, 64.4, 64.0, 60.9, 55.0, 46.8, 39.1, 38.8, 36.8, 35.9, 33.9, 33.1, 31.0, 29.1, 25.8, 24.5, 18.3, 18.1, 12.3; IR (NaCl, neat) 3433, 2940, 2866, 1464 cm^{-1}; LRMS (APCI) calcd for $C_{31}H_{54}O_4Si$ ([M+H-H$_2$O]$^+$) 519.4, found 501.3



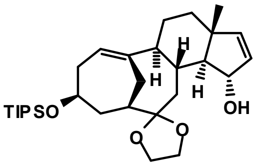
Aldehyde 4.85a: To a cooled (-78 °C) solution of oxalyl chloride (69 μL, 0.80 mmol) in dichloromethane (3 mL) was added DMSO (85 μL, 1.2 mmol). After 10 min, primary hydroxyl **4.84** (205 mg in 0.5 mL dichloromethane, 0.40 mmol) was added. After 30 min, triethylamine (0.28 mL, 2.0 mmol) was added. The reaction was warmed to room temperature. The mixture was then poured into water (10 mL) and extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give 194 mg (96%) aldehyde **4.85a** as a clear oil. $[\alpha]^{23}_{D}$= +74° (c 10, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.78 (d, *J* = 4.7 Hz, 1H), 5.50 – 5.33 (m, 3H), 4.26 – 4.12 (m, 1H), 3.99 – 3.82 (m, 4H), 2.54 (dt, *J* = 16.2, 6.7 Hz, 2H), 2.44 – 2.22 (m, 3H), 2.18 (d, *J* = 13.4 Hz, 1H), 2.11 (t, *J* = 4.3 Hz, 1H), 2.09 – 1.90 (m, 2H), 1.83 (dt, *J* = 13.6, 5.8 Hz, 1H), 1.76 – 1.55 (m, 7H), 1.38 – 1.24 (m, 2H), 1.19 (s, 3H), 1.07 (m, 21H); ^{13}C NMR (100 MHz, CHCl$_3$) δ 206.8, 142.9, 139.7, 122.8, 122.5, 112.7, 65.4, 64.4, 64.0, 62.4, 47.4, 38.2, 37.9, 36.8, 35.8, 34.4, 33.0, 32.9, 29.4, 26.2, 24.4, 18.2, 18.1, 18.1, 12.2; IR (NaCl, neat) 2940, 2866, 1716, 1463 cm^{-1}; LRMS (APCI) calcd for $C_{31}H_{52}O_4Si$ 516.4, found 517.3 ([M+H]$^+$)



Aldehyde 4.85b: To a solution of aldehyde **4.85a** (190 mg, 0.36 mmol) in methanol (4 mL) was added potassium carbonate (152 mg, 1.1 mmol). The resulting slurry was stirred vigorously. After 12 h, the reaction was poured into saturated aqueous ammonium chloride (10 mL) and extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give 192 mg (100 %) of aldehydes **4.85b** : **4.85a** as a 3.7 : 1 mixture by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 5.0 Hz, 1H), 5.53 – 5.34 (m, 3H), 4.30 – 4.11 (m, 1H), 4.03 – 3.75 (m, 4H), 2.67 – 2.42 (m, 3H), 2.37 (d, *J* = 12.0 Hz, 1H), 2.27 (d, *J* = 13.4 Hz, 1H), 2.14 – 2.03 (m, 1H), 1.98 (dd, *J* = 11.7, 5.0 Hz, 1H), 1.85 (dd, *J* = 13.1, 7.1 Hz, 2H), 1.72 – 1.40 (m, 8H), 1.25-1.10 (m, 3H), 1.22 (s, 3H), 1.08 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 206.7, 142.9, 140.5, 123.1, 122.0, 112.4, 65.4, 64.5, 64.1, 62.6, 52.2, 40.4, 39.4, 37.7, 36.8, 36.0, 33.1, 31.6, 29.1, 25.1, 18.1, 12.2; IR (NaCl, neat) 2940, 2866, 1716, 1463 cm^{-1}; LRMS (APCI) calcd for $C_{31}H_{52}O_4Si$ ($[M+H]^+$) 517.4, found 517.3

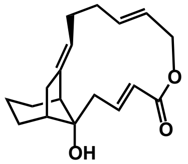


Allylic Alcohol 4.86: To a cooled (0 °C) solution of aldehydes **4.85a** and **4.85b** (1 : 3.7 mixture; 192 mg, 0.372 mmol) in diethyl ether (3 mL) was added vinylmagnesium bromide (1N in THF; 0.744 mL, 0.744 mmol). After 30 min, the reaction was quenched with saturated aqueous ammonium chloride (5 mL). The resulting mixture was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (10-20% ethyl acetate in hexanes) to give 129 mg (64%) allylic alcohol **4.86** and 39 mg (19%) lower diastereomers. $[\alpha]^{23}_{D}$= +39.8° (c 10.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (ddd, *J* = 17.2, 10.6, 2.9 Hz, 1H), 5.54 – 5.38 (m, 2H), 5.23 (ddd, *J* = 17.3, 7.8, 1.8 Hz, 2H), 5.00 (ddd, *J* = 10.6, 2.6, 1.9 Hz, 1H), 4.28 (dd, *J* = 11.6, 2.7 Hz, 1H), 4.17 (dd, *J* = 8.2, 4.0 Hz, 1H), 4.03 (ddd, *J* = 6.9, 6.0, 3.7 Hz, 1H), 3.93 (ddd, *J* = 7.1, 5.7, 3.7 Hz, 1H), 3.90 – 3.74 (m, 2H), 3.44 (d, *J* = 11.6 Hz, 1H), 2.55 (ddd, *J* = 24.3, 13.5, 6.8 Hz, 2H), 2.38 (dt, *J* = 15.9, 4.0 Hz, 1H), 2.30 (d, *J* = 13.4 Hz, 1H), 2.19 (dd, *J* = 19.8, 11.2 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.95 (d, *J* = 13.4 Hz, 2H), 1.81 (dt, *J* = 20.2, 6.4 Hz, 1H), 1.68 (dd, *J* = 6.3, 1.3 Hz, 3H), 1.59 – 1.31 (m, 7H), 1.16 (s, 3H), 1.07 (m, 21H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 147.5, 144.0, 143.0, 122.7, 122.5, 113.3, 110.8, 71.4, 65.6, 64.8, 64.1, 53.6, 52.6, 40.9, 40.6, 37.3, 37.0, 36.0, 33.9, 31.7, 28.7, 25.0, 18.3, 18.1, 12.2; IR (NaCl, neat) 3486, 2940, 2865, 1463 cm^{-1}; LRMS (APCI) calcd for $C_{33}H_{56}O_4Si$ ($[M+H-H_2O]^+$) 545.4, found 527.3

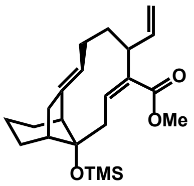


ABCD Tetracyclic Allylic Alcohol 4.29: To a solution of allylic alcohol **4.86** (130 mg, 0.24 mmol) in chlororform (20 mL) was added Hoveyda-Grubbs II catalyst (15 mg, 0.025 mmol). The mixture was then heated to reflux on an oil bath. After 20 h, the reaction was cooled to room temperature. The reaction was then quenched with ethyl vinyl ether (0.1 mL). The resulting mixture was then stirred open to the air for 1 h. The resulting black solution was concentrated. The residue was purified by flash chromatography (20-30% ethyl acetate in hexanes) to give 103 mg (86%) cyclopentenol **4.29** as a brown oil. $[\alpha]^{23}_{D}$= +150° (c 5.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 5.7, 1.3 Hz, 1H), 5.67 (dd, *J* = 5.7, 1.1 Hz,

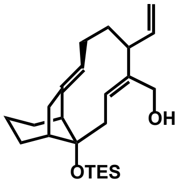
1H), 5.40 (dd, *J* = 7.8, 5.1 Hz, 1H), 4.62 (d, *J* = 8.7 Hz, 1H), 4.27 – 4.19 (m, 1H), 4.04 – 3.84 (m, 4H), 2.56 (ddd, *J* = 21.9, 12.9, 7.3 Hz, 2H), 2.38 (dt, *J* = 15.9, 4.0 Hz, 1H), 2.32 – 2.21 (m, 2H), 2.18 – 2.03 (m, 2H), 1.98 – 1.83 (m, 2H), 1.72 – 1.58 (m, 3H), 1.55 – 1.31 (m, 5H), 1.08 (m, 21H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 144.1, 143.5, 134.1, 122.4, 112.9, 78.2, 65.6, 64.3, 63.9, 55.7, 46.9, 36.8, 36.4, 36.2, 35.6, 33.8, 33.1, 29.9, 25.8, 20.8, 18.1, 18.1, 12.3; IR (NaCl, neat) 3401, 2939, 2866, 1463, 1367 cm^{-1}; LRMS (APCI) calcd for $C_{33}H_{56}O_4Si$ 502.4, found 485.3 ($[M+H-H_2O]^+$)



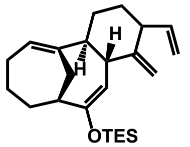
Macrolactone 2.45: To a solution of acrylate **2.44** (25 mg, 0.087 mmol) in dichloromethane (40 mL) was added Hoveyda-Grubbs II catalyst (11 mg, 0.017 mmol). The mixture was then heated at reflux on an oil bath. After 4 hours, the reaction was cooled to room temperature. The reaction was then quenched with ethyl vinyl ether (0.1 mL). The mixture was stirred open to the air for 1 h. The resulting black solution was concentrated. The residue was purified by flash chromatography (25% ethyl acetate in hexanes) to give 21 mg (94%) of macrolactone **2.45** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (ddd, *J* = 11.8, 9.3, 6.1 Hz, 1H), 5.95 – 5.77 (m, 2H), 5.71 – 5.57 (m, 1H), 5.23 – 5.10 (m, 1H), 4.72 (dd, *J* = 11.6, 8.5 Hz, 1H), 4.41 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.04 (ddd, *J* = 15.5, 9.4, 1.7 Hz, 1H), 2.52 (ddd, *J* = 15.5, 6.1, 1.7 Hz, 1H), 2.40 – 2.24 (m, 2H), 2.24 – 1.79 (m, 12H), 1.76 – 1.58 (m, 2H), 1.53 – 1.32 (m, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ IR (NaCl, neat) 3467, 2919, 2855, 1695, 1442, 1401, 1280, 1229, 1194 cm^{-1}; LRMS (APCI) calcd for $C_{18}H_{24}O_3$ 288.2 found 271.3 ($[M+H-H_2O]^+$)



Enoate 2.50: To a solution of macrolactone **2.45** (10 mg, 0.035 mmol) in d3-acetonitrile (0.8 mL) was added 1,8-diazabicylco[5.4.0]undec-7-ene (11 μL, 0.087 mmol) and TESCl (15 μL, 0.11 mmol) in a J-Young tube in an argon glove box. The tube was then sealed and heated to 90 ^{o}C (oil bath, external temperature). After 10 h, conversion to the vinyl species was complete by ^{1}H NMR. The reaction mixture was then poured into 1N HCl (3 mL) and extracted with dichloromethane (3 x 5mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in MeOH/diethyl ether (2 mL) and treated with $TMSCHN_2$ (2N in hexanes, 50 μL). After 1 h, the mixture was concentrated. The residue was purified by flash chromatography (30% dichloromethane in hexanes) to give 11 mg enoate **2.50** (77%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 13.3, 4.8 Hz, 1H), 6.19 – 6.08 (m, 1H), 5.02 (d, *J* = 12.0 Hz, 1H), 4.95 – 4.84 (m, 2H), 3.74 (s, 3H), 3.04 (t, *J* = 8.3 Hz, 1H), 2.71 – 2.51 (m, 2H), 2.41 – 2.17 (m, 4H), 2.14 – 1.85 (m, 8H), 1.81 (d, *J* = 13.8 Hz, 1H), 1.55 – 1.41 (m, 2H), 1.40 – 1.20 (m, 7H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 167.5, 143.3, 138.7, 138.4, 137.9, 127.7, 113.3, 78.8, 51.7, 51.5, 46.0, 43.3, 40.9, 34.5, 31.6, 29 .1, 26.6, 26.3, 18.1, 7.6, 7.2; IR

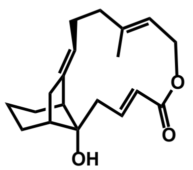


Allylic Alcohol 2.58: To a cooled (-78 ^{o}C) solution of enoate **2.50** (22 mg, 0.053 mmol) in dichloromethane (2 mL) was added DIBAL-H (1N in hexanes, 0.16 mL, 0.16 mmol). After 90 min, the reaction was diluted with diethyl ether (4 mL). The mixture was quenched with saturated aqueous Rochelle's salt (5 mL) and stirred vigorously until both phases appeared homogenous. The layers were then partitioned and the aqueous phase was extracted with diethyl ether (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (20% diethyl ether in hexanes) to give 18 mg (87%) clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 – 5.71 (m, 2H), 5.10 – 4.87 (m, 3H), 4.12 (dd, *J* = 29.6, 13.0 Hz, 2H), 3.12 (dd, *J* = 8.8, 7.2 Hz, 1H), 2.64 (dd, *J* = 17.0, 6.7 Hz, 1H), 2.47 (dd, *J* = 15.4, 12.8 Hz, 1H), 2.41 – 2.26 (m, 1H), 2.19 (dd, *J* = 15.4, 4.7 Hz, 1H), 2.13 – 1.93 (m, 6H), 1.92 – 1.75 (m, 2H), 1.55– 1.24 (m, 5H), 1.03 (t, *J* = 7.9 Hz, 9H), 0.71 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 144.0, 143.2, 139.3, 126.9, 123.1, 113.7, 78.5, 64.6, 51.1, 45.9, 43.1, 39.7, 32.3, 31.5, 30.1, 29.0, 26.6, 26.4, 18.2, 7.7, 7.2

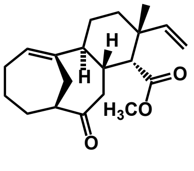


Silyl enolether 2.62: To a cooled (0 °C) solution of allylic alcohol **2.58** (8.0 mg, 0.021 mmol) in d8-toluene (0.5 mL) was added triethylamine (6.7 μL, 0.046) and 2,4-dinitrobenzenesulfenyl chloride (8.1 mg, 0.035 mmol). The solution was then warmed to room temperature. After 30 min, the starting material had completely converted to the sulfenate ester by ^{1}H NMR. The reaction was then heated to 100 °C (oil bath, external temperature). After 3 h, ^{1}H NMR indicated complete conversion to silyl enol ether **2.62**. The reaction mixture was then poured into saturated aqueous ammonium chloride (5 mL) and extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (20% ether in hexanes) to give 4.4 mg (75%) ketone as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 - 5.88 (m, 1H), 5.68 - 5.59 (t, *J* = 5.9 Hz, 1H), 5.34 (d, *J*

= 5.1 Hz, 1H), 5.18 - 5.01 (m, 3H), 4.97 (s, 1H), 3.00 (d, *J* = 7.0 Hz, 1H), 2.69 (s, 2H), 2.52 (s, 1H), 2.37 (ddd, *J* = 32.5, 16.8, 10.2 Hz, 4H), 1.99 (d, *J* = 7.1 Hz, 1H), 1.81 (s, 1H), 1.65 (s, 2H), 1.62 - 1.50 (m, 3H), 1.49 - 1.18 (m, 4H), 1.08 (t, *J* = 7.9 Hz, 9H), 0.77 (dd, *J* = 11.7, 4.6 Hz, 6H).



Macrolactone 2.72: To a solution of acrylate **2.71** (790 mg, 2.39 mmol) in dichloromethane (1200 mL) was added Hoveyda Grubbs II catalyst (150 mg, 0.24 mmol). The mixture was then heated at reflux on an oil bath. After 4 h, the reaction was quenched with ethyl vinyl ether (1 mL) and then stirred open to the air for one hour. The resulting black solution was concentrated. The residue was purified by flash chromatography (15 - 25% ethyl acetate in hexanes) to give 636 mg (88%) macrolactone **2.72** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (ddd, *J* = 11.7, 9.2, 6.3 Hz, 1H), 5.87 (dd, *J* = 11.8, 1.4 Hz, 1H), 5.41 (dd, *J* = 8.6, 7.3 Hz, 1H), 5.15 (d, *J* = 8Hz, 1H), 4.96 (dd, *J* = 11.3, 9.8 Hz, 1H), 4.36 (dd, *J* = 11.3, 6.2 Hz, 1H), 2.99 (dd, *J* = 15.4, 6.3, 1H), 2.49 (ddd, *J* = 15.4, 6.3, 1.8 Hz, 1H), 2.39 - 1.83 (m, 10H), 1.80 (s, 3H), 1.72 (s, 1H), 1.55 - 1.31 (m, 4H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 167.3, 144.2, 143.7, 142.7, 122.8, 121.6, 119.5, 78.6, 60.3, 50.7, 40.2, 39.3, 39.0, 31.6, 28.4, 27.4, 26.7, 17.1, 16.7; IR (NaCl, neat) 3446, 2941, 2865, 1692 cm^{-1}



Ketoester 2.74: To a solution of macrolactone **2.72** (95 mg, 0.31 mmol) in actonitrile (6 mL) in a high pressure Pyrex tube was added 1,8-diazabicylco[5.4.0]undec-7-ene (0.26 mL, 1.7 mmol) and TESCl (0.35, 2.1 mmol). The vessel was sealed with a Teflon screw cap and heated to 125

^{o}C (oil bath, external temperature). After 12 h, the solution was poured into aqueous 1N HCl (20 mL). The mixture was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in diethyl ether (2 mL) and methanol (8 mL). The solution was treated with TMS-diazomethane (2N solution in hexanes, 1.0 mL, 2.0 mmol). After 1 h, the solution was concentrated and the resulting residue was purified by flash chromatography (10 - 30% ethyl acetate in hexanes) to give 46 mg (47%) keto ester **2.74** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 - 5.71 (m, 2H), 5.00 (dd, *J* = 24.5, 5.8 Hz, 2H), 3.59 (s, 3H), 2.80 (dd, *J* = 16.2, 10.2 Hz, 1H), 2.70 - 2.59 (m, 1H), 2.55 - 2.16 (m, 9H), 2.08 (dd, *J* = 8.9, 5.7 Hz, 1H), 1.78 - 1.66 (m, 1H), 1.57 (m, 3H), 1.38 (d, *J* = 13.3 Hz, 1H), 1.20 (s, 3H).; ^{13}C NMR (100 MHz, $CHCl_3$) δ 212.9, 173.7, 146.9, 144.1, 129.2, 112.2, 55.1, 51.3, 48.9, 48.5, 46.1, 39.1, 35.9, 33.0, 30.9, 26.9, 26.6, 25.3, 22.5; IR (NaCl, neat) 2940, 2860, 1730, 1685, 1441 cm^{-1}; LRMS (APCI) calcd for $C_{20}H_{28}O_3$ 316.2 found 317.2 ($[M+H]^+$)

Appendix II

List of Abbreviations

Ac	acetyl
AMTH	ammonium molybdate tetrahydrate
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Bn	benzyl
Bu	butyl
DBU	1,8-diazabicycloundec-7-ene
CM	cross metathesis
CSA	10-camphorsulfonic acid
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropylazodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyl tartaric acid
DMAP	*N,N*-dimethylaminopyridine
DTAD	di-*tert*-butylazodicarboxylate
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N,N*-dimethylpropyleneurea
DMS	dimethylsulfide

DMSO	dimethyl sulfoxide
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide
Et	ethyl
G-II	Grubbs' 2nd generation catalyst
GC	gas chromatography
HG-II	Hoveyda-Grubbs 2nd generation catalyst
HMDS	hexamethyldisilazane
IBX	*o*-iodoxybenzoic acid
IC_{50}	concentration at 50% inhibition
Imid	imidazole
LRMS	low resolution mass spectroscopy
IR	infared
LA	Lewis acid
LDA	lithium diisopropylamide
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
Ms	methylsulfonate
Mes	mesityl
MTBE	methyl *tert*-butyl ether
NMO	*N*-morpholine-*N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
PG	protecting group

Ph	phenyl
PKR	Pauson-Khand reaction
PMB	*p*-methoxybenzyl
Pr	propyl
Pt	phenyltetrazole
Py	pyridine
RCM	ring-closing metathesis
Rt	room temperature
TBAF	tetrabutylammonum fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMTU	tetramethylthiourea
Ts	*p*-toluenesulfonate