Studies of the Kaneda Reaction in the Synthesis of Oocydin A/Haterumalide NA and Polyurethanes from Renewable Resources: Polyols from Soybean Oil

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Abstract

This thesis is broken down into two main projects. First, studies of the Kaneda reaction in the synthesis of oocydin A/haterumalide NA and, second, polyurethanes from renewable resources: polyols from soybean oil. In Chapter I, the stereoselectivity of the Kaneda reaction was studied. The driving interest stemmed from the hypothesis that one epimer of an acyclic precursor could give the desired bicyclic core of oocydin A/haterumalide NA. In Chapter II, the work toward new polyols from soybean oil is discussed. Renewable content in polyurethanes on the market is still low because of economics and performance. Our ideas for new polyol systems are presented.

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List of Abbreviations

Ac	Acetyl
AcOH	Acetic acid
ADMET	Acyclic diene metathesis
AIBN	Azobisisobutyronitrile
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl ($C_6H_5CH_2$-)
n-Bu or ^{n}Bu	normal-Butyl
tert-Bu or ^{t}Bu	tertiary-Butyl
° C	degrees Celsius
CH_2Cl_2	Dichloromethane
CM	Cross metathesis
COSY	Correlated spectroscopy
δ	Chemical shift, in NMR spectroscopy
d	Doublet, in NMR spectroscopy
DBU	1,8-Diazabicylco[5.4.0]undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DCU	Dicyclohexylurea
DET	Diethyl tartrate
DIC	*N*,*N*-diisopropylcarbodiimide
DIPT	Diisopropyl tartrate
DIBAL	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DMF	Dimethylformamide
DMPA	2,2-Dimethoxy-2-phenylacetophenone
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide

DPEN	Diphenylethylenediamine
dr	Diastereomeric ratio
EDCI	1-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide
ESBO	Epoxidized soybean oil
ESI	Electrospray Ionization
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
equiv	Equivalent(s)
ee	Enantiomeric excess
er	Enantiomeric ratio
g	Gram(s)
G1	The first generation Grubbs initiator
G2	The second generation Grubbs initiator
GC-MS or GCMS	Capillary gas chromatography-mass spectrometry
GPC	Gel permeation chromatography
HMBC	Hetero-nuclear multiple bond correlation
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear multiple quantum coherence
HPLC	High pressure (or performance) liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz (cycles per second)
IC_{50}	50% of the concentration for complete inhibition of cellular viability
IR	Infrared
J	Coupling constant (NMR)

KHMDS	Potassium *bis*(trimethylsilyl)amide
λ	wavelength
LAH	Lithium aluminum hydride
LC-MS or LCMS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamide
LiHMDS	Lithium *bis*(trimethylsilyl)amide
m	Multiplet, in NMR spectroscopy
MALDI-MS	Matrix-assisted laser desorption/ionization-mass spectrometry
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeOH	Methanol
MHz	Megahertz
mL	milliliter(s)
mmol	millimole
mol	Mole(s)
mp	Melting point
MPLC	Medium pressure liquid chromatography
MPM	Methoxyphenylmethyl
4Å MS	4-angstrom molecular sieves
MTPA	α-Methoxytrifluoromethylphenylacetyl
NaHMDS	Sodium *bis*(trimethylsilyl)amide
NCS	*N*-chlorosuccinimide
ng	nanogram(s)
nm	nanometer(s)
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
No-D	No deuterium (NMR)

NOE	Nuclear Overhauser Effect/Enhancement
Ph	Phenyl
Ph_3P	Triphenylphosphine
PivCl	Pivaloyl chloride or trimethylacetyl chloride
PMB	*para*-Methoxybenzyl
ppm	Parts per million
i-Pr or *i*Pr	Isopropyl
q	Quartet, in NMR spectroscopy
R	Rectus (configurational)
RCM	Ring-closing metathesis
RRCM	Relay Ring-closing metathesis
RT or rt	Room temperature
S	Sinister (configurational)
s	Singlet, in NMR spectroscopy
SAE	Sharpless asymmetric epoxidation
SBO	Soybean oil
t	Triplet, in NMR spectroscopy
TBAF	Tetrabutylammonium fluoride
TBDPS (BPS)	*tertiary*-Butyldiphenylsilyl
TBDPSCl	*tertiary*-Butyldiphenylsilyl chloride
TBHP	*tertiary*-Butylhydroperoxide
TBS	*tertiary*-Butyldimethylsilyl
TBSCl	*tertiary*-Butyldimethylsilyl chloride
TBSOTf	*tertiary*-Butyldimethylsilyl trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography

TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
t_r	Retention time
Tr	trityl or triphenylmethane
Ts	Tosyl or 4-toluenesulfonyl
TS	Transition state

Chapter I. Oocydin A/Haterumalide NA

I.A. Introduction

The Hoye group has been involved in natural product synthesis for many years. The substrates are chosen for a variety of reasons, but, in general, the two main drivers are to synthesize a specific compound (because of biological activity or structural complexity) or apply a unique approach to a compound. The work done by the Hoye group on oocydin A / haterumalide NA became a project that involved both what was being synthesized and how we were approaching it. As will be discussed in this chapter, the Hoye group was able to complete the first total synthesis of the natural product while also using a novel approach. As is often the case, this led to new ideas and hypotheses about the chemistry, which were tested and analyzed in the following sections.

I.B. Isolation, Biological Activity and Characterization

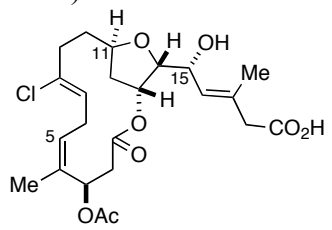
In 1999 two groups independently isolated and reported the natural products oocydin A[1] and haterumalide NA[2], which were eventually found to be the same compound. Oocydin A (**1**, Figure I-1) was isolated from *Serratia marcescens*, a bacterium growing on an aquatic plant, *Rhynocholacis pedicillata*, in a Venezuelan river. Haterumalide NA (along with analogs) was isolated from the Okinawan sponge *Ircinia* sp. off the coast of Japan. The natural product was reported again in 2001, when it was

[1] "Oocydin A, a chlorinated macrocyclic lactone with potent anti-oomycete activity from *Serratia marcescens*," Strobel, G.; Li, J.-Y.; Sugawara, F.; Koshino, H.; Harper, J.; Hess, W. M. *Microbiology* **1999**, *145*, 3557-3564.

[2] "Isolation and Structures of Haterumalides NA, NB, NC, ND, and NE, Novel Macrolides from an Okinawan Sponge *Ircinia* sp." Takada, N.; Sato, H.; Suenaga, K.; Arimoto, H.; Yamada, K.; Ueda, K.; Uemura, D. *Tetrahedron Lett*. **1999**, *40*, 6309-6312.

isolated from a soil bacterium, *Serratia plymuthica*, in Sweden.[3] It is interesting that such a complex compound is found in unrelated organisms around the globe. One explanation could be that bacteria in the sponge made the natural product. For simplicity, the compound will be referred to as oocydin A, except in cases where the authors call it haterumalide NA (previous syntheses).

Figure I-1: Oocydin A / Haterumalide NA (**1**), a natural product isolated from a variety of organisms (shown as the revised structure).



oocydin A/haterumalide NA
(**1**)

Oocydin A displayed a range of biological activities. The macrolide showed toxicity toward oomycetes (water molds) with MICs of approximately 30 ng/mL for various *Phytophthora* spp.[1] As a result, the compound has potential as an antifungal in agricultural and crop protection applications. It also exhibited cytotoxicity against breast cancer cell lines (BT-20 and MCF-7 with IC_{50} values of 20 and 40 ng/mL, respectively)[1] and leukemia cells (P388 with an IC_{50} of 32 ng/mL)[2].

Initial structures for oocydin A / haterumalide NA were proposed by the Strobel and Uemura groups in 1999, however all the stereochemical details were not resolved until 2003. The Strobel group's structure of oocydin A was assigned using (1D and 2D) NMR and IR spectroscopy techniques and they predicted the relative configuration of the stereocenters, which was later confirmed to be correct.[1] The Uemura group correctly

[3] "Suppression of *Sclerotinia sclerotiorum* apothecial formation by the soil bacterium *Serratia plymuthica*: identification of a chlorinated macrolide as one of the causal agents," Thaning, C.; Welch, C. J.; Borowicz, J. J.; Hedman, R.; Gerhardson, B. *Soil Biol. Biochem*. **2001**, *33*, 1817-1826.

determined the absolute configuration of the C15 (Figure I-1) side chain hydroxyl using modified Mosher ester analysis. Coupling constant and NOE data were used to predict the relative configurations at C3, C11, C13 and C14. Then, they (incorrectly) assigned the relationship between C14–C15 to be *threo* in the MTPA-ester derivatives, which led to the prediction of the absolute configuration of haterumalide NA to be 3*S*, 11*S*, 14*S* and 15*R*.[2] The Kigoshi group revised the absolute stereochemical features, wherein each stereocenter has the *R* configuration as shown in Figure I-1, in 2003, upon synthesis of *ent*-haterumalide NA methyl ester.[4]

Making the storyline even more intriguing (or complicated), was the isolation of FR177391 from *Serratia liquefaciens* No. 1821 (a bacterium) in 2005.[5] It was discovered while screening for anti-hyperlipidemic agents (useful in lipid lowering drugs) from microbial products. A single crystal x-ray structure determination of the propylamide derivative showed the natural product had the same connectivity as oocydin A and haterumalide NA. The x-ray structure gives the same relative configuration in FR177391 as the relative configuration in (revised) oocydin A / haterumalide NA. The conundrum now is that there are three natural products with the same connectivity and relative configuration, but only a pair of enantiomers is possible, so which two isolated compounds are identical?

One way to answer that would be specific rotation, which has not been mentioned to this point. There is a discrepancy in the reported data. All three isolation papers publish specific rotations but a clear conclusion cannot be drawn from the data. As stated

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[4] "Enantioselective Synthesis of 15-*epi*-Haterumalide NA Methyl Ester and Revised Structure of Haterumalide NA," Kigoshi, H.; Kita, M.; Ogawa, S.; Itoh, M.; Uemura, D. *Org. Lett*. **2003**, *5*, 957-960.
[5] "FR177391, A New Anti-hyperlipidemic Agent from *Serratia*," Sato, B.; Nakajima, H.; Fujita, T.; Takase, S.; Yoshimura, S.; Kinoshita, T.; Terano, H. *J. Antibiot*. **2005**, *58*, 634-639.

in the FR177391 isolation paper, "the optical rotation of FR177391 (+32 : c0.85, MeOH) was distinct from those of haterumalide NA (–3.0 : c0.053, MeOH) and oocydin A (+18.2 : c0.22, MeOH), indicating that the absolute structure of FR177391 is different from those of haterumalide NA and oocydin A".[5] The three values would imply that they are all different, which cannot be the case since, as stated above, there can only be a pair of enantiomers, having opposite optical rotations. Questions arise about reported concentrations as well since 0.85 is very high if reported in g/mL. The concentration listed in the above quote for oocydin A is incorrect; the isolation paper "measured on 2.2 mg of the compound dissolved in 1 mL methanol", which would give a concentration of 0.0022 g/mL.[1] The issue comes up again in reported total syntheses. In 2005, the Hoye group synthesized (–)-haterumalide NA/(–)-oocydin A but did not report a specific rotation for the synthesized natural product.[6] In 2008, Roulland[7] synthesized the same compound (including absolute configuration) as the Hoye group, but referred to it as (+)-oocydin A, and reported a positive specific rotation that was similar to the reported value of isolated oocydin A. Because of the details included in the rotation data by Roulland and the Hoye group's lack of reporting a rotation value for the final product, the Roulland data and naming should be considered correct. Although this brings about some confusion, it has no bearing on the chemistry to be discussed in the rest of this chapter.

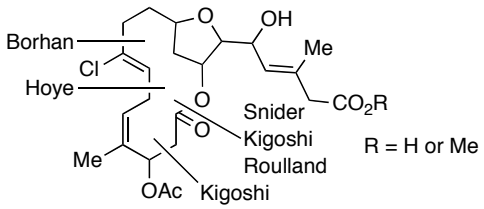
I.C. Previous Syntheses

The interesting structural features contained within oocydin A made it a target for natural product synthesis. Those features include a 14-membered lactone that is strapped

[6] "Alkyne Haloallylation [with Pd(II)] as a Core Strategy for Macrocycle Synthesis: A Total Synthesis of (–)-Haterumalide NA/(–)-Oocydin A," Hoye, T. R.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 6950-6951.
[7] "Total Synthesis of (+)-Oocydin A: Application of the Suzuki-Miyaura Cross-Coupling of 1,1-Dichloro-1-alkenes with 9-Alkyl 9-BBN," Roulland, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3762-3765.

across a THF ring, an endocyclic, skipped diene and 5 stereogenic centers. A number of groups have worked on this molecule and efforts have continued (as discussed below), even following the first total synthesis in 2005 by the Hoye group[6]. A common thread among the syntheses is the issue of fashioning the bicyclic core. This seems to be a result of inherent strain within the molecule, resulting in low-yielding steps when forming the macrocycle, specifically with an intact THF ring. The previous syntheses will be presented and although it is not always the key (most interesting) step of the route, only the macrocyclization step will be highlighted. Illustrated below in Figure I-2 are the bonds constructed (along with the group name) to yield the bicyclic core. No stereochemical information is shown since some routes accomplished syntheses of the enantiomer, while others made the natural product. Also, note some groups were unable to form the desired acid and therefore, reported a synthesis of the methyl ester.

Figure I-2: The bonds constructed in previous syntheses to yield the bicyclic core of **1**.

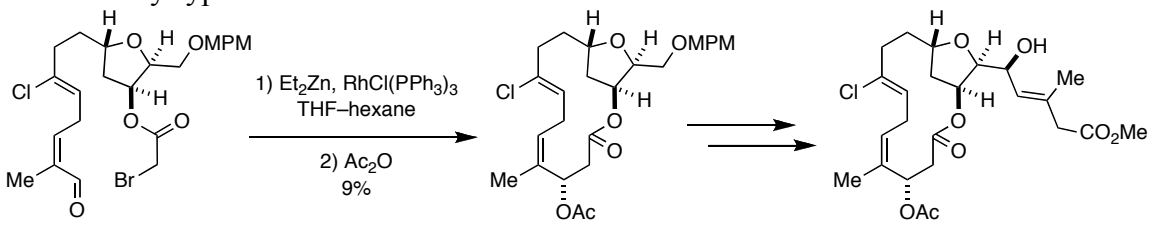


I.C.1. Reformatsky-type Reaction

The first synthesis, reported in 2003 by Kigoshi, detailed the efforts to *ent*-haterumalide NA methyl ester (**4**, Scheme I-1) and lead to the revision of the originally proposed structure of haterumalide NA.[4] The macrolide **3** was formed (along with other stereoisomers) and isolated in a 9% yield using an intramolecular Reformatsky-type

reaction on aldehyde **2**. The macrolactone **3** was carried forward to complete the total synthesis of **4** in 26 steps with a 0.22% overall yield.

Scheme I-1: Kigoshi's approach to bicyclic intermediate **3** using an intramolecular Reformatsky-type reaction.



2 **3** **4**

I.C.2. Macrolactonization Strategies

A few groups constructed the 14-membered ring through macrolactonization as shown in Scheme I-2, albeit in modest yields. The success of this approach hinged on the type of protecting groups employed. Although the Kigoshi group succeeded via the route described above, they also reported failed attempts at macrolactonization on acid *ent*-**5a** under Yamaguchi, Keck, and Mukaiyama-Corey conditions.[4]

Later in 2003, the Snider group afforded the macrolactone *ent*-**6b** in 65% yield (along with dimer and trimer) under Yamaguchi conditions on acid *ent*-**5b** (varying only in protecting groups from Kigoshi's acid).[8] The Snider group also completed the synthesis of **4** (Scheme I-1) in a similar number of steps to Kigoshi but by a more efficient route.

In 2008, Kigoshi reported a 2nd generation synthesis.[9] Macrolide formation failed on an acetonide (at C15) derivative. The protecting groups were changed to give the

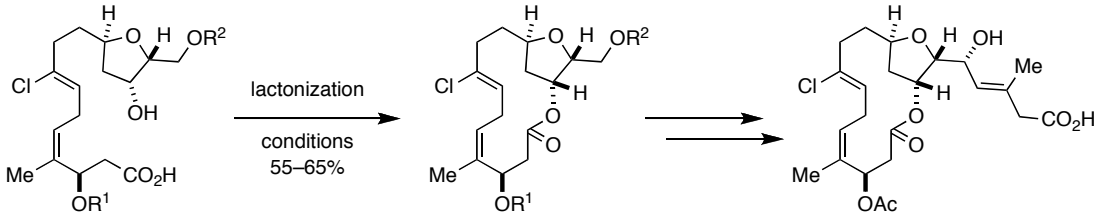
[8] "Synthesis of *ent*-Haterumalide NA (*ent*-Oocydin A) Methyl Ester," Gu, Y.; Snider, B. B. *Org. Lett.* **2003**, *5*, 4385-4388.

[9] (a) "Second-Generation Total Synthesis of Haterumalide NA Using *B*-Alkyl Suzuki-Miyaura Coupling," Hayakawa, I.; Ueda, M.; Yamaura, M.; Ikeda, Y.; Suzuki, Y.; Yoshizato, K.; Kigoshi, H. *Org. Lett.* **2008**, *10*, 1859-1869. (b) "Total Synthesis and Cytotoxicity of Haterumalides NA and B and Their Artificial

enantiomer (having the desired absolute configuration) of the acid used by Snider. With intermediate **5b** in hand, bicycle **6b** was achieved in 61% yield. The (second) total synthesis of haterumalide NA (**1**) was achieved in 33 steps with an improved overall yield of 1.2%.

Another report in 2008, by Roulland, realized a total synthesis of oocydin A (**1**).[7] The key steps made this route noteworthy. However, the macrolactone was again realized (in a 55% yield) by submitting an acid, **5c,** to Yamaguchi conditions. A more efficient, convergent route, making the natural product in 18 steps and 6.1% overall yield, was achieved.

Scheme I-2: Bicycle **6** constructed by various groups under lactonization conditions.



5a R^1 = Ac R^2 = TBDPS
5b R^1 = OTBS R^2 = Tr or Ph_3C
5c R^1 = TBS R^2 = MPM or $CH_2C_6C_4OMe$

I.C.3. Alkyne Haloallylation Reaction

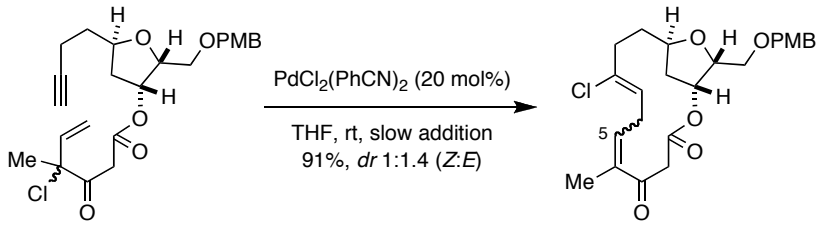
In 2005, the Hoye group completed the first total synthesis of haterumalide NA (**1**).[6] The macrocycle was formed using an alkyne haloallylation reaction first described by Kaneda.[10] As shown in Scheme I-3, the allylic chloride **7** was submitted to $PdCl_2(PhCN)_2$-catalyzed conditions and gave the desired 1-Cl-1,4-diene **8** in a 91% yield. Although the yield was excellent, the C4–C5 bond was a mixture of *Z*:*E* isomers (1:1.4),

Analogues," Ueda, M.; Yamaura, M.; Ikeda, Y.; Suzuki, Y.; Yoshizato, K.; Hayakawa, I.; Kigoshi, H. *J. Org. Chem*. **2009**, *74*, 3370-3377.

[10] "Selective Codimerization of Acetylenes and Allyl Halides Catalyzed by Palladium Complexes," Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55-63.

favoring the undesired *E*-alkene. More details about this chemical transformation will follow in Section I.I.

Scheme I-3: Formation of bicycle **8** via alkyne aloallylation with Pd(II) by the Hoye group.

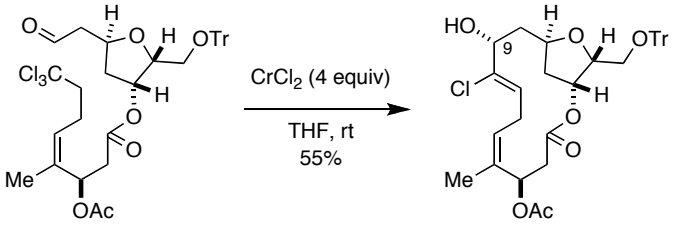


7 **8**

I.C.4. Chromium-mediated Macrolactonization

In 2008 the Borhan group reported a formal synthesis of haterumalide NA by breaking a bond different from those in previous syntheses.[11] They used a $CrCl_2$-mediated coupling on aldehyde **9** to form the C8-C9 bond shown in Scheme I-4 and obtained bicycle **10** in 55% yield. To complete the formal synthesis, a deoxygenation of the C9-OH was afforded. This route was geared toward the C9-oxygenated analog, haterumalide NC, but again shows the moderate yields obtained in forming the bicyclic core of haterumalide NA.

Scheme I-4: A chromium-mediated macrocyclization to **10** by the Borhan group.



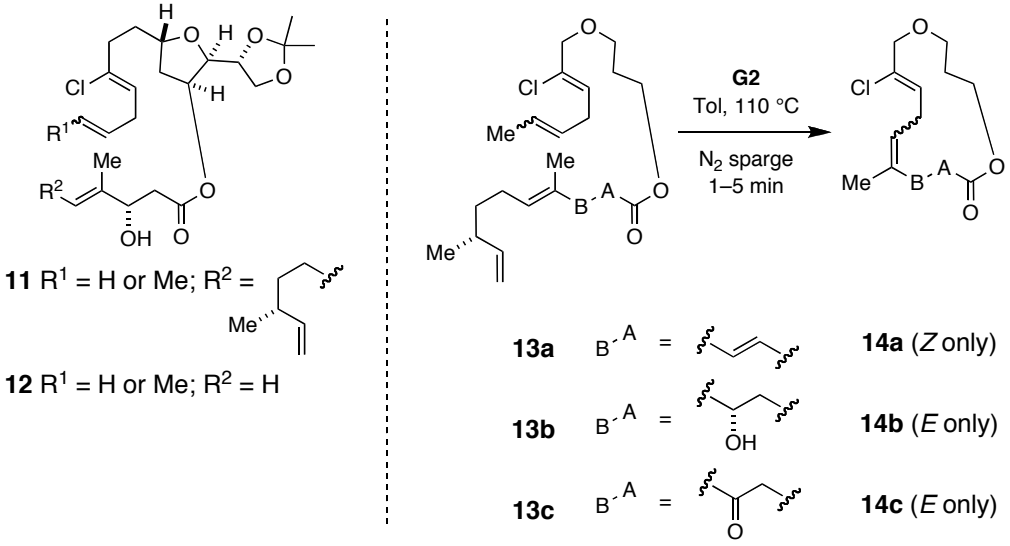
9 **10**

[11] "Total Synthesis of Haterumalides NA and NC via a Chromium-Mediated Macrocyclization," Schomaker, J. M.; Borhan, B. *J. Am. Chem. Soc.* **2008**, *130*, 12228-12229.

I.C.5. RRCM

As an aside within the total synthesis paper,[6] the Hoye group noted that attempts using relay ring closing metathesis (RRCM)[12] also failed. The relay substrates **11** only gave truncated products **12** when treated with Grubbs metathesis initiator **G2**. However, under the same conditions, the relaxed models **13a-c**, lacking the intact THF ring, cyclized to the desired skipped dienes **14** (but only **13a** gave the desired *Z*-alkene).

Scheme I-5: Relay ring closing metathesis (RRCM) studies on the oocydin A core and a model compound by Hoye and Wang.



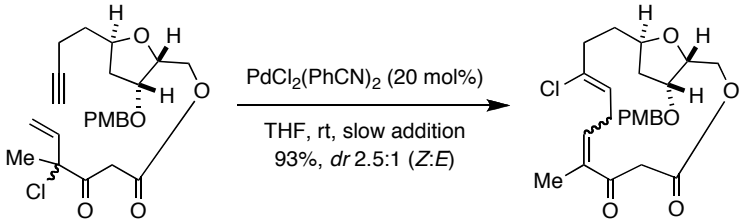
I.D. Hoye Group Synthetic Strategy Toward Oocydin A

After achieving the first total synthesis of oocydin A, the Hoye group continued to think about a more efficient route. The first synthetic strategy had the THF ring intact when submitted to the chloroallylation conditions. The precursor's inherent strain could have played a role in the stereoselectivity of the C4-C5 bond formation (see Scheme I-3). This is displayed in the results shown in Scheme I-6, published by Hoye and Wang in

[12] "Relay Ring-Closing Metathesis (RRCM): A Strategy for Directing Metal Movement Throughout Olefin Metathesis Sequences," Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.*, **2004**, *126*, 10210-10211.

their total synthesis paper.[6] A more relaxed isomer of desired precursor **7** is substrate **15**, which has the THF ring intact, afforded 15-membered lactone **16** in good yield (93%) and favored the desired *Z*-alkene 2.5:1. The more relaxed substrate favored formation of the desired stereoisomer while the more strained 14-membered lactone favored the undesired *E*-alkene. Would reversing the order of the cyclization (macrocycle followed by THF ring formation) improve the selectivity/yield?

Scheme I-6: Alkyne haloallylation to form the more relaxed bicycle **16**.

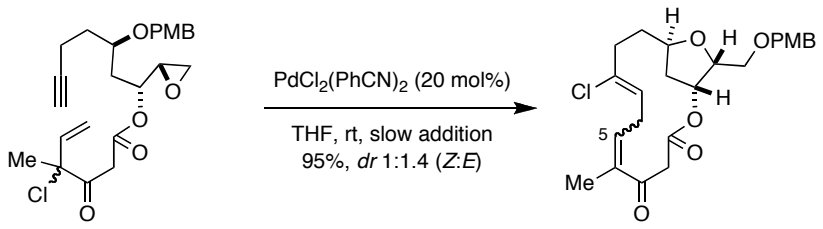


15 **16**

Toward this end Jizhou Wang (a former graduate student) synthesized acyclic precursor **17** and submitted it to the Kaneda reaction conditions.[13] Surprisingly, the product was the same bicyclic compound **8** (Scheme I-3) obtained when starting with the monocyclic precursor **7**. In this reaction (Scheme I-7), the Kaneda cyclization had occurred along with closure of the THF ring and *para*-methoxybenzyl (PMB) migration. The same C4-C5 alkene geometry ratio was obtained as stated above (Z:*E* ~ 1:1.4). Therefore, it was postulated that the THF ring was closed prior to the haloallylation reaction. From these results, many ideas and questions arose about an improved second-generation synthesis.

[13] Unpublished results.

Scheme I-7: The Kaneda reaction on acyclic precursor **17**.



17 **8**

One consideration of a second-generation approach is altering the protecting group. The PMB group underwent migration under the Pd(II) – catalyzed conditions. A different protecting group should allow the closure of the macrocycle before the THF ring is formed. Simple model studies completed in the Hoye group determined that the benzyl ether rearranges at a slightly slower rate than the PMB ether. It was also found that the *tert*-butyldimethylsilyl (TBS) ether did not undergo this migration upon exposure to the same conditions. Therefore, the reactivity of the protecting group can be dialed in to allow for the desired order of cyclizations, *i.e.*, macrocycle formation followed by THF ring closure.

The selectivity and mechanism of the Kaneda reaction is also interesting. The alkene isomer ratios obtained in the haloallylation reactions are noteworthy because both precursors **7** and **17** are an epimeric mixture (at the chlorine-bearing stereocenter). The possibility that each epimer leads to a single C4-C5 alkene geometry exists, which would mean that the Kaneda reaction is stereospecific. (More details about the mechanism of the Kaneda reaction and the importance of having each epimer of the allylic chloride will be presented in Section I-I.) If this proved to be the case, selectivity to give the desired alkene geometry would greatly improve the synthesis of oocydin A and a better

understanding of the Kaneda reaction would help make it a unique tool in the synthesis of other natural products with a similar motif.

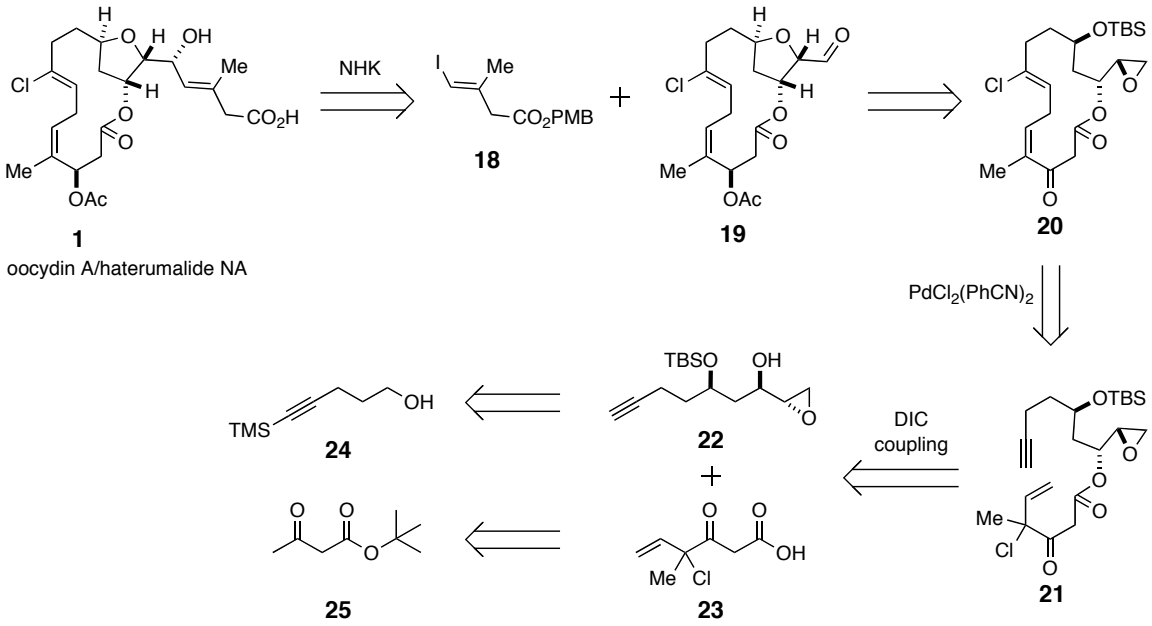
With this knowledge, the goal was to synthesize each of the enantiopure allylic chloride precursors and submit them to Pd(II) - catalyzed conditions. As stated above, the migration did not occur with the TBS ether so TBS will be used as a protecting group to ensure that the macrocycle is closed prior to THF ring formation.

I.E. Retrosynthetic Analysis (Improved Strategy)

The retrosynthetic plan, shown in Scheme I-8, would allow us to test our ideas to improve the synthetic route. The completion of the synthesis would be realized, after deprotection, through a Nozaki-Hiyama-Kishi (NHK) reaction[14] between vinyl iodide **18** and aldehyde **19**. Bicycle **19** would be formed through closure of the THF ring in intermediate **20**, along with other functional group manipulations. In the key step, under palladium(II)-catalyzed conditions, the macrocycle **20** would be constructed from allylic chloride **21**, as one epimer at the chlorine-bearing stereocenter. The acyclic precursor **21** would be assembled via DIC coupling of alcohol **22** and acid **23**. Epoxide **22** can be derived from commercially available trimethylsilyl-4-pentynol (**24**). *tert*-Butylacetoacetate (**25**) will be used to generate each of the enantiopure allylic chlorides ***R-*** and ***S*-23**.

[14] "Reactions of alkenylchromium reagents prepared from alkenyl trifluoromethanesulfonates (triflates) with chromium(II) chloride under nickel catalysis," Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048-6050.

Scheme I-8: Retrosynthesis of oocydin A / haterumalide NA (**1**).



I.F. Synthetic Efforts to Enantiopure Allylic Chlorides

To test the stereoselectivity of the Kaneda reaction and the applicability of our route, both enantiopure allylic chlorides ***R*-** and ***S*-23** need to be in hand. Each enantiomer of **23** will be coupled with epoxide **22** to give the two desired allylic chlorides ***R*-** and ***S*-21**, epimeric at the chlorine-bearing stereocenter. Recall that Jizhou performed a reaction on an epimeric mixture of a different allylic chloride substrate and obtained both olefin isomers (Scheme I-7). Therefore, if we submitted **21** (as an epimeric mixture at the chlorine-bearing stereocenter) to the Kaneda reaction conditions, we would expect to isolate similar amounts of both ***Z,Z*-** and ***E,Z*-20** (C4–C5 olefin isomers, Scheme I-8). However, that would not be a beneficial experiment since we want to study the stereoselectivity of the Kaneda reaction. Therefore we need to submit each epimer, ***R*-** and ***S*-21**, independently and analyze the C4–C5 olefin isomers formed in product **20**. If the reaction is stereospecific, one epimer, say ***R*-21**, would provide one olefin geometry,

such as desired ***Z,Z*-20**. We are not able to predict which epimer of **21** would give rise to the desired diene ***Z,Z*-20**. As a result we want to synthesize each allylic chloride ***R*-** and ***S*-23** so that we can submit each diastereomer ***R*-** and ***S*-21** to the Kaneda reaction. The results obtained from each epimer would give valuable information about the mechanism and selectivity of the Kaneda reaction.

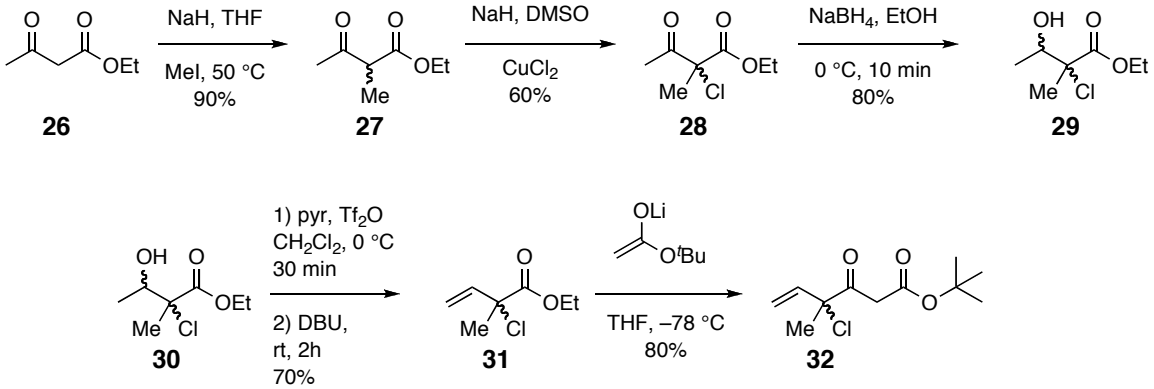
We also need allylic chloride **23** to be enantiopure. For example, if ***R*-23** contained a small amount of its enantiomer ***S*-23**, coupling the material with epoxide **22** would provide a sample of ***R*-21** contaminated with the undesired epimer ***S*-21**. After submitting precursor **21** to the Kaneda reaction, the ratio of C4–C5 isomers in **20** would be analyzed. We would not be able to determine if the minor olefin isomer was formed from epimer ***S*-21** or if ***R*-21** resulted in formation of both olefin isomers (*i.e.,* the reaction is not highly stereospecific). For this reason it is vital that both ***R*-** and ***S*-23** are enantiopure and, as a result, samples of ***S*-21** and ***R*-21** do not have any trace of their epimers (at the chlorine-bearing stereocenter). Efforts toward making the enantiopure allylic chlorides will now be presented. Some routes will be abandoned because of modest stereoselectivity, which is not good enough for our case. The section starts with asymmetric reduction studies, then chlorination studies and, finally, the current route.

I.F.1. Asymmetric Reduction Studies

Asymmetric reduction of β-keto esters was an initial route to the desired enantiopure allylic chlorides. Many catalyst systems are known to provide good yields and stereoselectivity on a variety of substrates. Shown below in Scheme I-9 is the route

(used by Wang[15] in the construction of **17**, Scheme I-7) to racemic allylic chloride **32**, wherein substrates used in this section are also made. Starting with ethyl acetoacetate (**26**), treatment with NaH and methyl iodide provided known α-methyl ester **27**.[16] Chlorination to known ester **28** was achieved in modest yield (60%) using NaH and cupric chloride.[17] Reduction with $NaBH_4$ at low temperature provided β-hydroxy ester **29**. Elimination to allylic chloride **31** was realized through formation of the triflate (pyr, Tf_2O) followed by treatment with DBU. Although crude mass recovery, of both the triflate and the eliminated product, was good, chromatographic separation of **31** from excess DBU usually resulted in an isolated yield of 70%. Claisen condensation with the lithium enolate of *tert*-butyl acetate gave β-keto ester **32** (as a racemic mixture).

Scheme I-9: Synthetic route to racemic chlorinated intermediates.



In the above scheme are a number of β-keto esters that were used in the efforts to access enantiopure allylic chlorides through asymmetric reduction. Beginning with racemic β-keto esters like **28** or **32**, the configuration of the β-hydroxyl group would be

[15] Wang, J. Part I: Formal Synthesis of Haterumalide NA/Oocydin A. Ph.D. Dissertation, University of Minnesota, Minneapolis, MN, 2005.
[16] "An enantioselective synthesis of β^2-amino acid derivatives," Elaridi, J.; Thaqi, A.; Prosser, A.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1309-1319.
[17] "Mild Halogenation of Stabilized Ester Enolates by Cupric Halides," Shi, X.-X.; Dai, L.-X. *J. Org. Chem*. **1993**, *58*, 4596-4598.

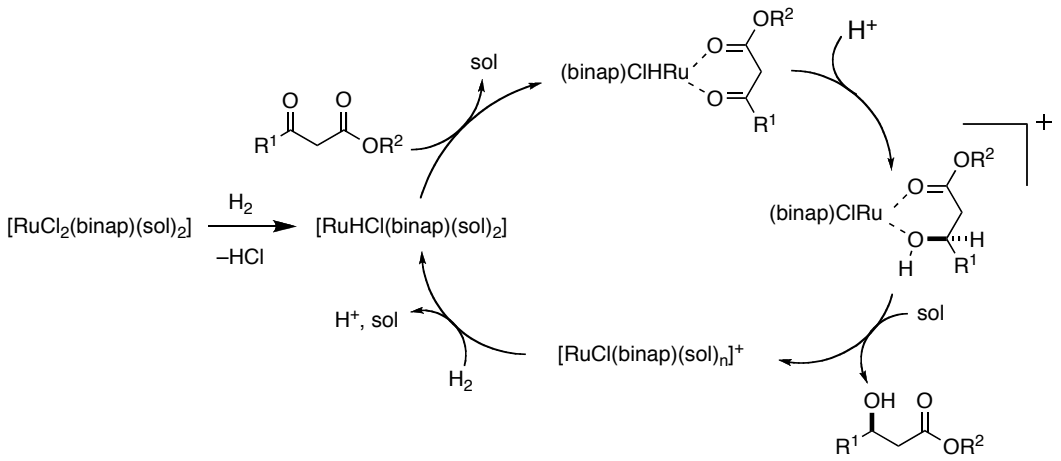
set via reduction resulting in the formation of (hopefully separable) diastereomers. Carrying forward each diastereomer would yield the desired allylic chlorides, ***R*-** and ***S*-23**.

I.F.1.a. BINAP-Ruthenium Route

Noyori's BINAP-ruthenium(II) catalyst has been shown to hydrogenate a variety of β-keto esters to β-hydroxy esters with high enantioselectivities.[18] The catalytic cycle is shown in Figure I-3. The Ru complex reacts with H_2 to form a strong acid (HCl) and a Ru hydride (RuHCl) species, which coordinates to the substrate via carbonyl oxygens. Protonation (by the acid formed in the system) of the ketone oxygen occurs first to facilitate the next step, hydride transfer from the catalyst, affording the alcohol product. As shown, the ester functionality is important for the stereoselectivity since it is able to interact with the Ru center. With BINAP as a ligand, two diastereomeric transition states (TSs) are available. One TS has an unfavorable interaction between a phenyl group (in BINAP) and R^1 (in the substrate). Therefore, formation of the *R*-configuration of the carbinol is achieved when (*R*)-BINAP is used.

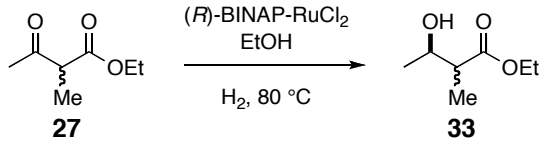
[18] (a) "Asymmetric Catalysis: Science and Opportunities (Nobel Lecture)," Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008-2022. (b) "Toward efficient asymmetric hydrogenation: Architectural and functional engineering of chiral molecular catalysts," Noyori, R.; Kitamura, M.; Ohkuma, T. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5356-5362.

Figure I-3: Catalytic cycle of Noyori's BINAP-Ru(II) system.



As shown in Scheme I-9, there are a few accessible β-keto ester substrates. Two substrates were submitted to the BINAP-Ru(II) system. These reactions were carried out in a Parr bomb to obtain hydrogen pressures around 1400 psi. The α-methyl ester **27** did show evidence of known[19] desired product **33** but the reaction suffered from low conversion (around 50%). The carbinol center is predicted to have the *R*-configuration (as drawn), based on TS structures when (*R*)-BINAP is used. Analysis was not done on **33** to determine if that was the case. Hoping for better results, a more relevant starting material, having the chlorine atom present, was tested.

Scheme I-10: BINAP-Ru(II) reduction of α-methyl β-keto ester **27**.



The α-disubstituted ethyl ester **28** was tested. Reduction to the alcohol products was realized, however, the conversions varied and usually the reaction failed to go to

[19] "Asymmetric Hydrogenation of 3-oxo carboxylates using BINAP-Ruthenium Complexes: (*R*)-(–)-methyl 3-hydroxybutanoate," Kitamura, M. Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth*. **1993**, *71*, 1-7.

completion. Even when full conversion was achieved, the ^{1}H NMR showed a 3:1 (expected 1:1) ratio of the diastereomeric alcohols. Further analysis was required to determine the configuration of the carbinol center and why we saw the unexpected *dr*.

Mosher ester analysis[20] was used to assign the configuration of the newly formed stereocenter. The *syn* and *anti* isomers were separated by HPLC and then converted to the (*R*)- and (*S*)-Mosher esters. Each of the Mosher ester derivatives of the more nonpolar fraction gave a ^{1}H NMR containing one diastereomer. The more polar fraction, after conversion to the Mosher ester derivatives, contained two diastereomers in a 2:1 ratio, which implied that the asymmetric reduction was not highly stereoselective.

The assignment of the carbinol stereocenter in the products can be determined by preparing each of the Mosher esters. Shown below in Figure I-4a, is the modified Mosher ester analysis of the more nonpolar fraction (having one diastereomer). This confirmed that the expected (*R*)-hydroxyl was formed. The more polar fraction is more complicated since it has two diastereomers. The modified Mosher ester analysis of this fraction gives two diastereomers with the minor component having the undesired (*S*) configuration and the major having the expected (*R*)-hydroxyl (Figure I-4b and c, respectively).

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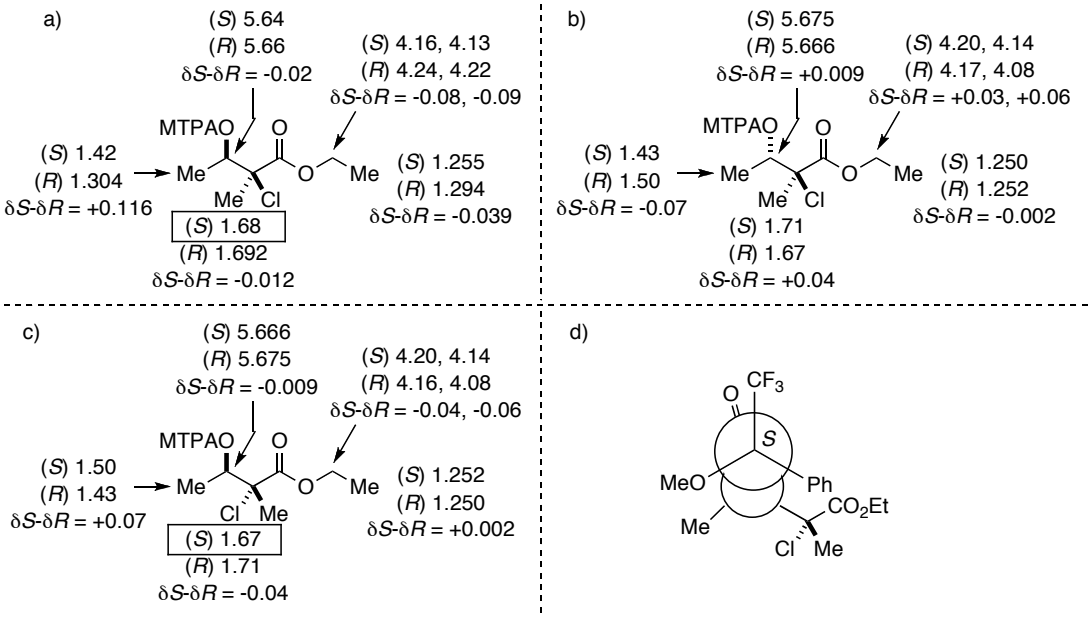
[20] (a) "Mosher ester analysis for the determination of absolute configuration of stereogenic (chiral) carbinol carbons," Hoye. T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451-2458. (b) "Nuclear magnetic resonance enantiomer reagents. Configurational correlations *via* nuclear magnetic resonance chemical shifts of diastereomeric mandelate, *o*-methylmandelate, and α-methoxy-α-trifluoro-methylphenylacetate (MTPA) esters," Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.

Figure I-4: Modified Mosher ester analysis of the (*R*)-BINAP-Ru(II) reduction products.



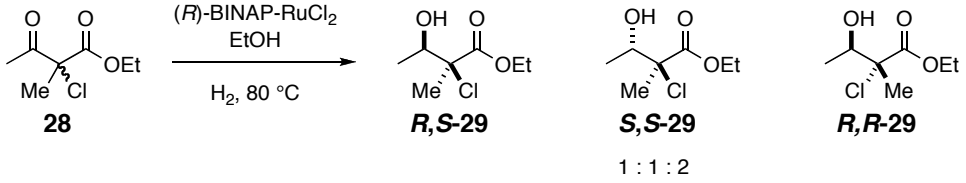
These data were also used to propose the configuration of the chlorine-bearing stereocenters. The phenyl group of the MTPA-ester has a shielding effect. In the representation[21] shown in Figure I-4d, the (*R*) configuration at the chlorine-bearing carbon would result in a more shielded methyl group. The methyl group chemical shift of the (*S*)-MPTA ester (in box, Figure I-4c) is upfield (more shielded) than the methyl group of its C2-epimer (in box, Figure I-4a). From this it was determined that the chlorinated stereocenter has the (*R*) configuration as drawn in Figure I-3c, which then allows assignment of the chlorine-bearing stereocenter in the other products (assumed to be as drawn). *Note that this is not a definitive way to determine the configuration at the chlorine-bearing stereocenter. This doesn't affect the results that will be presented in this section since the wrong assignment would only require changing the configuration of that stereocenter. Throughout this section, the reader should remain aware that Mosher ester

[21] Adapted from representations drawn in reference 17a.

analysis can give the carbinol center configuration but that this analysis cannot definitively define the configuration of the chlorine-bearing stereocenter. Structures will show the proposed configuration at the chlorine-bearing center based on the above analysis.

To summarize the above results, reduction of ester **28** using the (*R*)-BINAP Ru system gave three stereoisomeric products (Scheme I-11) in a 1:1:2 ratio. An interesting (although unwanted) outcome was that the reduction of (*S*)-**28** was not stereoselective, giving a 2:1 mixture of the (*R*)- and (*S*)-hydroxyl products. On the other hand, reduction of (*R*)-**28** gave exclusively the desired product ***R,R*-29**. An uncanny consequence is that although (*R*)-**28** undergoes highly stereoselective reduction, the product is isolated as a mixture of enantiomers (***R,R*-** and ***S,S*-29**), while (*S*)-**28** leads to a mixture at the carbinol stereocenter but an enantiopure compound (***R,S*-29**) can be isolated.

Scheme I-11: Asymmetric reduction products afforded with BINAP-Ru(II) system.



There are a few mechanistic reasons the BINAP-Ru(II) complex is not optimal in this case. There is evidence that selective reduction is not highly effective on α-substituted substrates or on substrates with halogens in close proximity to the reactive carbonyl.[22] These substituents have the ability to coordinate to the catalyst and change the proposed transition state structure, thereby destroying the stereoselectivity. There is

[22] (a) "Asymmetric Hydrogenation of Ketones," Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345-350. (b) "New Chiral Phosphorous Ligands for Enantioselective Hydrogenation," Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029-3070.

precedent that heating can improve the enantioselectivity. However, in that case chlorine was in the gamma position and the reaction proceeded at a much lower pressure.[23] It has also been reported[24] that the addition of acid can be beneficial, resulting in better reproducibility, since it sequesters endogenous amine (from synthesis of the catalyst). This would promote protonation of the carbonyl, which is required prior to hydride transfer, as shown in Figure I-2. This was attempted without much success. Routes using this catalyst system were discontinued due to inconsistent conversions and less than desirable stereoselectivity.

I.F.1.b. TsDPEN Ruthenium Route

Asymmetric transfer hydrogenation using another catalyst by Noyori was also investigated. The purple catalyst, (*S*,*S*)-Ru[N-(tosyl)-1,2-diphenylethylenediamine](*p*-cymene) (**34**), was prepared in our laboratory by Dorian Nelson following the literature procedure.[25] Formic acid-triethylamine was used in an azeotropic mixture as the hydrogen source, which allows for higher conversions than previous methods (such as isopropanol).[26] As shown in Scheme I-12, catalyst **34** reacts with formic acid to generate

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[23] "Asymmetric Synthesis of (+)-Negamycin," Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1996**, *7*, 1919-1922.

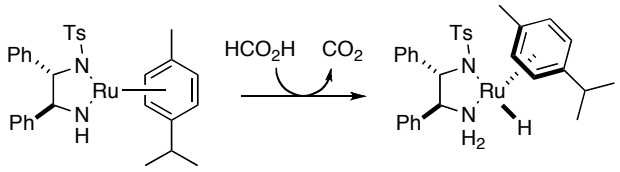
[24] (a) "An Improved Procedure for the Synthesis and Use of $[RuCl_2(BINAP)_2]\bullet NEt_3$. Dependence of the Ru(II)-BINAP Catalyzed Asymmetric Hydrogenation of β-Keto Esters on Trace Amounts of Acid," King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689-6691. (b) "Synthesis of (–)-Haliclonadiamine," Taber, D. F.; Wang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 22-26.

[25] "The Catalyst Precursor, Catalyst, and Intermediate in the Ru^{II}-Promoted Asymmetric Hydrogen Transfer between Alcohols and Ketones," Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285-288.

[26] "Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Ketones Using a Formic Acid–Triethylamine Mixture," Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521-2522.

amine hydrido Ru complex **35** and carbon dioxide, which can be removed from the system to drive the reaction forward.[27]

Scheme I-12: Formation of ruthenium hydride **35** using formic acid.

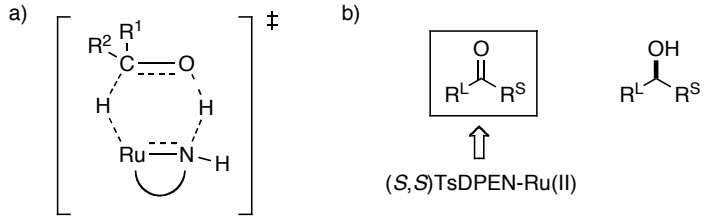


34 **35**

The TsDPEN Ru(II) system does not coordinate to the ester carbonyl like the BINAP Ru(II) complex, which results in the *R*-configuration of the β-hydroxyl ester when (*R*)-BINAP is the chiral ligand. A proposed reaction TS is shown in Figure I-5a.[28] The configuration of the carbinol center, when using the diamine ligand (*S,S*)-TsDPEN, is predicted based on the model shown in Figure I-5b, where sterics play an important role; electronics can play a role but presumably aren't significant in our studies.[29] As a result, the configuration of the product alcohols will vary in the following examples, even though the same chiral ligand [(*S*,*S*)-TsDPEN] is used in all cases. For our purposes, preparation of either configuration of the carbinol center is acceptable as long as the stereoselectivity of the reduction is good.

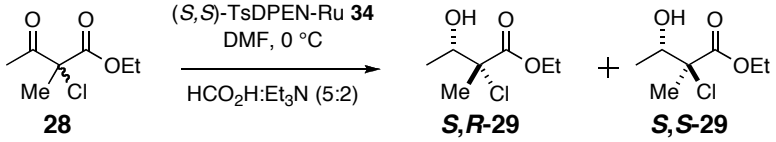
[27] "Asymmetric Transfer Hydrogenation of Ketones with Bifunctional Transition Metal-Based Molecular Catalysts," Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300-1308.
[28] "Asymmetric Transfer Hydrogenation Catalyzed by Chiral Ruthenium Complexes," Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97-102.
[29] "Highly Enantioselective Transfer Hydrogenation of Fluoroalkyl Ketones," Sterk, D.; Stephan, M.; Mohar, B. *Org. Lett.* **2006**, *8*, 5935-5938.

Figure I-5: Proposed TS and stereoselection model for (*S,S*)-TsDPEN Ru(II) complex.



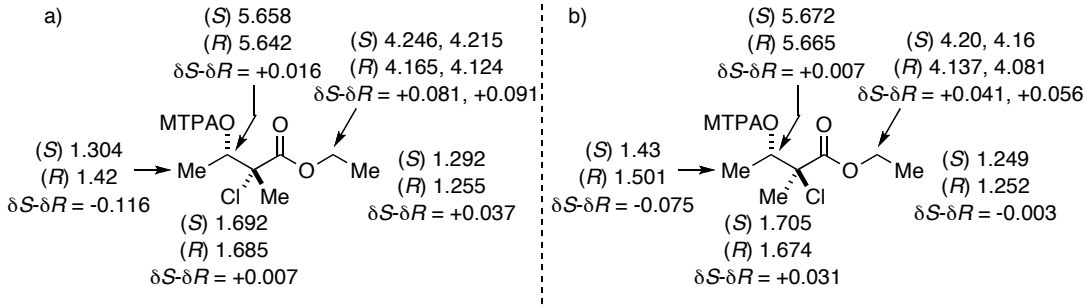
The α-disubstituted ethyl ester **28** was submitted to asymmetric transfer hydrogenation conditions with good results (Scheme I-13). Two diastereomers were obtained in similar quantities, which were separated by HPLC and analyzed (by

Scheme I-13: Asymmetric transfer hydrogenation products of β-keto ester **28**.



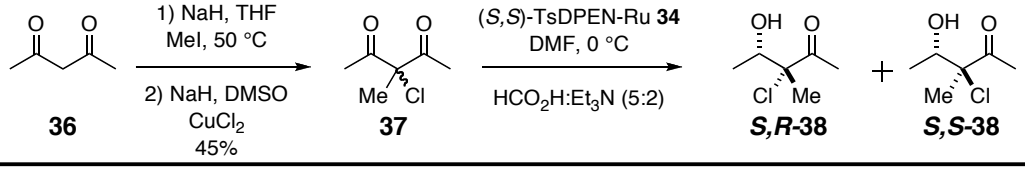
modified Mosher ester analysis, Figure I-5). Both isomers had the expected *S* configuration at the carbinol stereocenter, which is the opposite configuration obtained (in the major stereoisomers) with (*R*)-BINAP (Scheme I-11). The TsDPEN Ru(II) complex gave better enantioselectivity than the BINAP-Ru system, wherein three stereoisomers were formed. The configuration of the chlorine-bearing stereocenters was predicted in a similar manner as described above using Figure I-3d, but more importantly, ***S,S*-29** is formed by both catalyst systems and the ^{1}H NMR spectra of the (*R*)- and (*S*)-Mosher esters are identical (Figure I-4b and I-6b). The asymmetric reduction was successful, but the separation of the stereoisomers proved difficult. Although they could be isolated to give pure compound, scaling up and separating would be hard, especially since both sides of the substrate need to be further manipulated.

Figure I-6: Modified Mosher ester analysis of asymmetric reduction products from α-disubstituted β-keto ester.



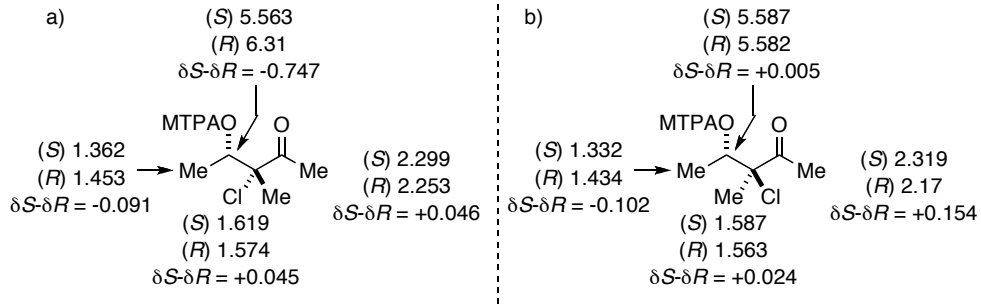
The diketone **37** also proved to be a suitable substrate for transfer hydrogenation (Scheme I-14). 2,4-Pentanedione (**36**) was submitted to the same methylation / chlorination conditions as ethyl acetoacetate (Scheme I-9) to give substituted diketone **37**. After reduction to **38**, the above methods were used to determine that each of the two

Scheme I-14: Synthesis and asymmetric reduction of 1,3-diketone substrate **37**.



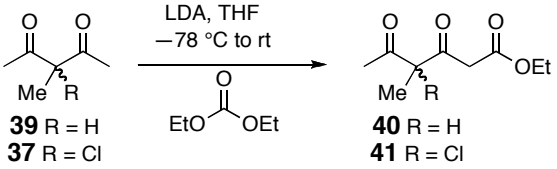
diastereomers formed was enantiopure. In Figure I-7, modified Mosher ester analysis led us to assign the (*S*) configuration to the carbinol center while the chlorine-bearing stereocenters are assumed to be as drawn in Scheme I-14.

Figure I-7: Modified Mosher ester analysis of asymmetric reduction products from diketone substrate.



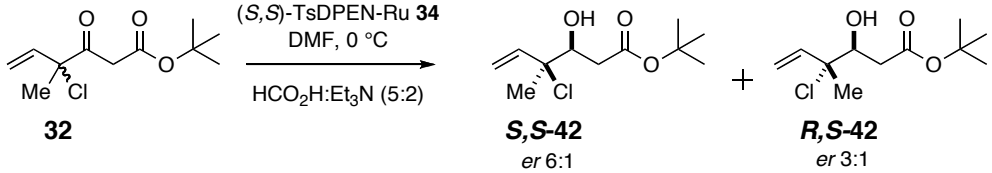
The plan, after separation of the diastereomers, was to alkylate the right hand side of the molecule as well as to eliminate the (newly formed) alcohol to give our desired allylic chloride. Treatment of α-methyl diketone **39** with LDA and diethylcarbonate in THF gave ester **40** in modest yield (Scheme I-15). Attempts to do ethoxycarbonylation on α-disubstituted diketone **37** were not successful. Other substrates applicable to the route were not tested since the diketone showed no hint of product formation.

Scheme I-15: Studies to carry diketone compounds forward via ethoxycarbonylation.



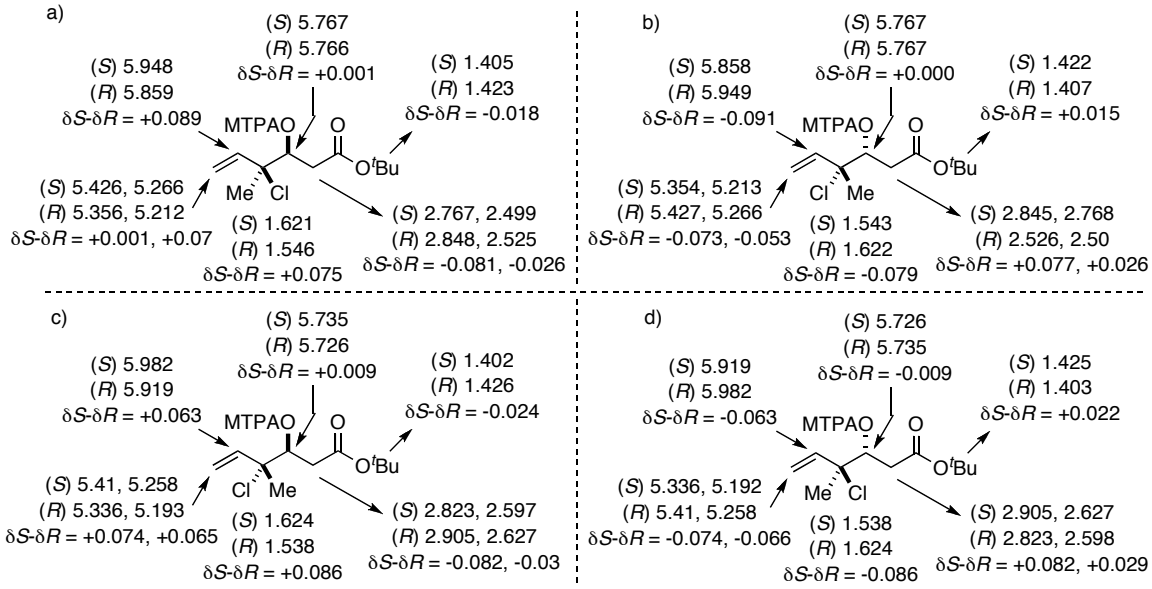
The difficulties encountered when attempting to separate and further manipulate the reduced compounds thus far led us to consider the reduction of a substrate that had the carbon backbone intact. Therefore, the β-keto ester **32** was submitted to asymmetric reduction. Unfortunately, neither of the diastereomers formed was enantiopure (Scheme I-16). The chlorine-bearing stereocenter having the (*S*)-configuration gave a 6:1 *er* (favoring the *S* carbinol), while the C4-epimer gave a 3:1 *er*. The stereocenters were

Scheme I-16: Asymmetric transfer hydrogenation of late stage allylic chloride **32**.



assigned using analysis of the Mosher esters (Figure I-8). If the reduction had been stereoselective, oxidation of the alcohol and removal of the *tert*-butyl group would have given each of the desired enantiopure allylic chlorides.

Figure I-8: Modified Mosher ester analysis of the four stereoisomers obtained via reduction of the β-keto ester having the allylic chloride intact.



I.F.2. Chlorination Studies

Stereoselective chlorination is an alternative approach to the enantiopure allylic chlorides. Although more is known about fluorination, catalytic asymmetric chlorination of 1,3-dicarbonyl compounds[30] or β-keto esters[31] has allowed for moderate success (up to 88% ee). These results are suitable for some applications but higher selectivities would be needed for our studies. This section will discuss attempts to chlorinate a variety of compounds under suitable conditions.

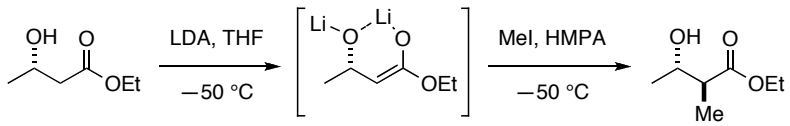
[30] "Organocatalytic Asymmetric α-Halogenation of 1,3-Dicarbonyl Compounds," Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem.* **2005**, *117*, 6375-6378.

[31] (a) "Catalytic Asymmetric Bromination and Chlorination of β-Ketoesters," Marigo, M.; Kumaragurubaran, N.; Jorgensen, K. A. *Chem.–Eur. J.* **2004**, *10*, 2133-2137. (b) "Enantioselective halogenation reactions," Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147-1155. (c) "Strategies for Catalytic Asymmetric Electrophilic α Halogenation of Carbonyl Compounds," Oestreich, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2324-2327.

I.F.2.a. Frater-Seebach Type Reaction

The Frater-Seebach reaction is a stereoselective alkylation of a β-hydroxy ester (Scheme I-17).[32] Lithium bases (LDA or LiHMDS) are used to coordinate the two oxygen atoms and thereby shield one face of the molecule. Typically, the configuration of the carbinol center is set prior to the alkylation step, as in (*S*)-**43**, which would result in one diastereomer of the product (***S,S*-33**).

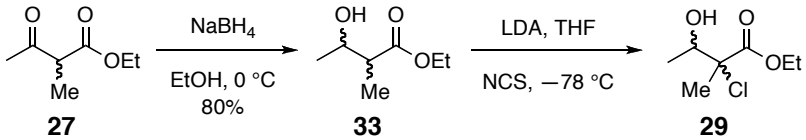
Scheme I-17: Frater-Seebach alkylation of an α-hydroxy ester.



***S*-43** ***S,S*-33**

Racemic β-hydroxy ester **33** (synthesized from **27** via $NaBH_4$ reduction) was deprotonated with LDA at low temperature, then treated with NCS to give two diastereomers of the product alcohol **29** (Scheme I-18). If the chlorination had been selective, we would have obtained either the *syn* or *anti* product (as a racemic mixture). Since the chlorination was not selective, further studies having the carbinol configuration in **33** set (using BINAP Ru, Scheme I-10) would likely be fruitless.

Scheme I-18: Synthesis and chlorination of α-hydroxy ester **33**.



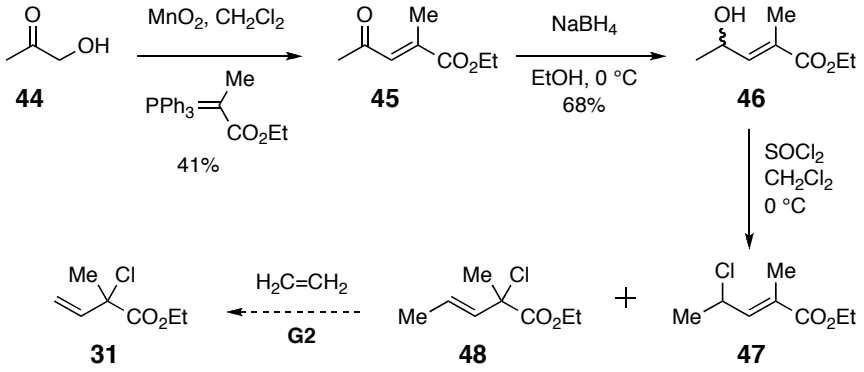
27 **33** **29**
dr 1:1

[32] "The stereoselective α-alkylation of chiral β-hydroxy esters and some applications thereof," Frater, G.; Muller, U.; Gunther, W. *Tetrahedron* **1984**, *40*, 1269-1277.

I.F.2.b. Thionyl Chloride Rearrangement

Addition of the chlorine could be accomplished by reacting thionyl chloride with an allylic alcohol, which upon rearrangement would yield an allylic chloride. Different conditions ($SOCl_2$ in Et_2O vs. NCS in DMS) have been shown to favor retention (allylic rearrangement) or inversion (when starting with one stereoisomer), respectively.[33] The desired allylic alcohol **46** was synthesized as shown in Scheme I-19 to test this approach. Starting from hydroxyacetone (**44**), an *in situ* oxidation-Wittig reaction yielded known unsaturated ester **45**.[34] Reduction with $NaBH_4$ gave alcohol **46**. The reaction with thionyl chloride was not regioselective and gave about a 1:1 ratio of the two allylic chlorides **47** and **48**. If we had gotten better results, the next steps would have been cross metathesis of **48** with ethylene to give the desired terminal alkene **31** followed by conversion of the right hand side of the molecule to the desired β-keto ester **32** (Scheme I-9).

Scheme I-19: Synthesis of allylic alcohol intermediate and thionyl chloride rearrangement products.

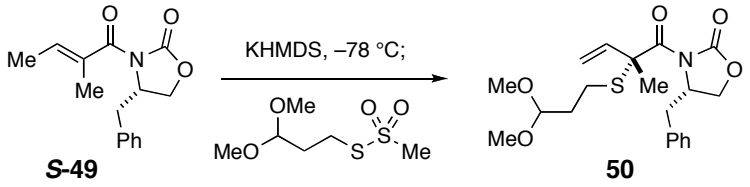


[33] "Reactions of (Organostannyl)- and (Organogermyl)lithium Reagents with Some (Allylic) Cyclohex-2-enyl Chlorides," Wickham, G.; Young, D.; Kitching, W. *J. Org. Chem.* **1982**, *47*, 4884-4895.
[34] "The *in situ* oxidation-Wittig reaction of α-hydroxyketones," Runcie, K.; Taylor, R. J. K. *Chem. Commun.* **2002**, 974-975.

I.F.2.c. Halogenation Studies

Another method used a chiral auxiliary to direct the chlorination to one face of the molecule. Ohata and Terashima[35] used this type of approach to accomplish asymmetric deconjugative α-sulfenylation as shown in Scheme I-20, while others have made a similar enolate with NaHMDS followed by alkylation.[36] Unsaturated imide **49** is a good

Scheme I-20: Asymmetric deconjugation α-sulfenylation by Ohata and Terashima.

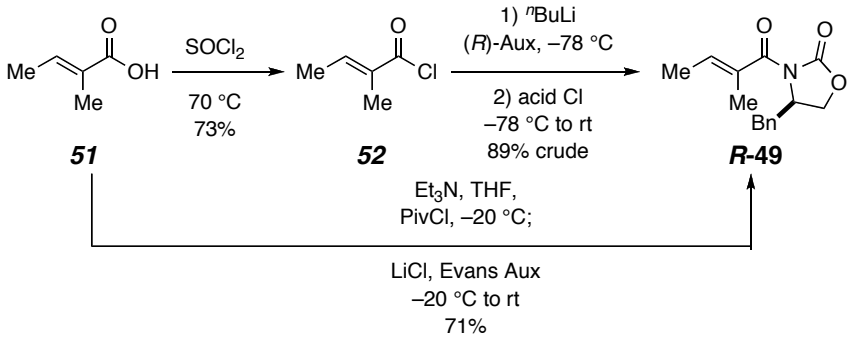


***S*-49** **50**

substrate for our studies since, after chlorination, derivatization of the auxiliary to the β-keto ester should be easily accomplished. The substrate ***R*-49** was first made (Scheme I-21) by conversion of tiglic acid (**51**) to acid chloride **52**, which was subsequently reacted with the lithium anion of (*R*)-4-benzyl-oxazolidin-2-one.[37] A more efficient, one-pot synthesis converted **51** to the mixed anhydride, upon addition of pivaloyl chloride, followed by the addition of LiCl and the oxazolidinone to give ***R*-49** in good yield (80%).[38] Various bases and chlorine sources were tested on this derivative as described below.

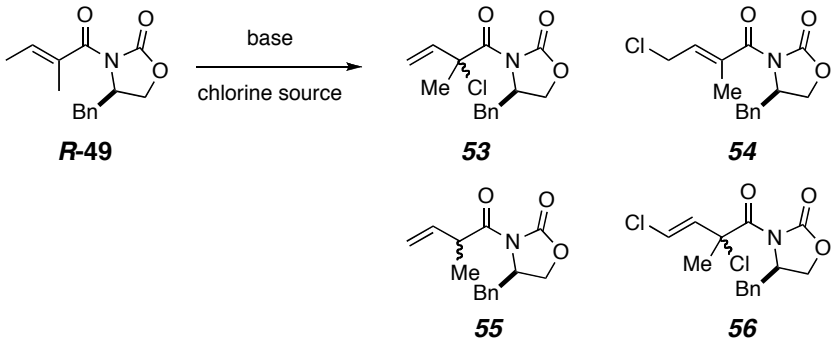
[35] "Synthesis and biological activity of enantiomeric pairs of 5-vinylthiolactomycin congeners," Ohata, K.; Terashima, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4070-4074.
[36] (a) "Stereoselective construction of a quaternary carbon substituted with multifunctional groups: application to the concise synthesis of (+)-ethosuximide," Abe, T.; Suzuki, T.; Sekiguchi, K.; Hosokawa, S. Kobayashi, S. *Tetrahedron Lett.* **2003**, *44*, 9303-9305. (b) "Novel stereoselective construction of a quaternary carbon: application to the synthesis of the cyclopentendione moiety of madindolines," Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6429-6433.
[37] "Asymmetric Diels-Alder Cycloaddition Reactions with α,β-Unsaturated *N*-Acyloxazolidinones," Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.*, **1988**, *110*, 1238-1256.
[38] "Lithium-Initiated Imide Formation. A Simple Method for N-Acylation of 2-oxazolidinones and Borane-2,10-Sultam," Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271-2273.

Scheme I-21: Synthesis of oxazolidinone derivative ***R*-49** by a 2 step or one pot route.



Auxiliary derivative ***R*-49** was deprotonated with three bases followed by chlorination with NCS. The major products were desired allylic chloride **53**, primary chloride **54**, olefin impurity **55**, and dichlorinated byproduct **56** as shown in Scheme I-22.

Scheme I-22: Chlorination products afforded using various bases and chlorine sources.



The product ratios are shown in Table I-1 (using 2 equivalents of base), along with the selectivity (*dr*) for allylic chloride **53**. When LDA was used as the base all 4 products were formed, with desired **53** as the major component, even though full conversion wasn't reached; similar results were obtained with both 1.2 and 2 equivalents of base. Use of the base KHMDS or NaHMDS resulted in conversion of all the starting material and neither reaction led to the formation of olefin impurity **55**. However, when either KHMDS or NaHMDS was used as the base in the reaction, a greater amount of dichlorinated byproduct was formed (when compared to using LDA as the base). A

similar amount of dichloro impurity **56** and desired allylic chloride **53** were produced when NaHMDS was used as the base.

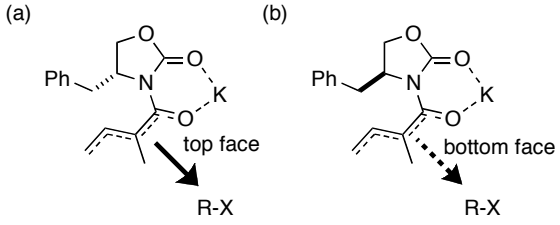
Table I-1: Results of chlorination studies using NCS and different bases.[a]

Base	**Product Ratio 53 : 54 : 55 : 56**	***dr* of 53**	**Conversion**
LDA	24 : 15 : 4 : 1	5 : 1	80%
KHMDS	5 : 1 : 0 : 1	1.5 : 1	100%
NaHMDS	2 : 0 : 0 : 1 [b]	2:1	100%

a) base (2 equiv), NCS (1.2 equiv), THF (0.8 M) at –78 °C
b) contains 20% of another impurity

The stereoselection isn't so important as long as the diastereomers are separable. As shown in Table I-1, LDA gave a moderate *dr* while the other bases did not show much facial selectivity. As shown in Scheme I-20 Ohata and Terashima used the (*S*)-N-acyloxazolidin-2-one to give the (*R*)-configuration at the newly formed center, which was confirmed through derivatization and comparison to a known compound. This was presumed to arise via the chelated dienolate in Figure I-9a.[35] Given the configurations of the newly formed stereocenters in the papers using NaHMDS, the same interpretation is applicable.[36] A similar analysis for our studies would result in attack of chlorine from the bottom face, as shown in Figure I-9b, and would give the (*S*)-configuration at the chlorine-bearing stereocenter as the major diastereomer in **53**.

Figure I-9: Chelated dienolate intermediates to predict configuration of newly formed stereocenter.

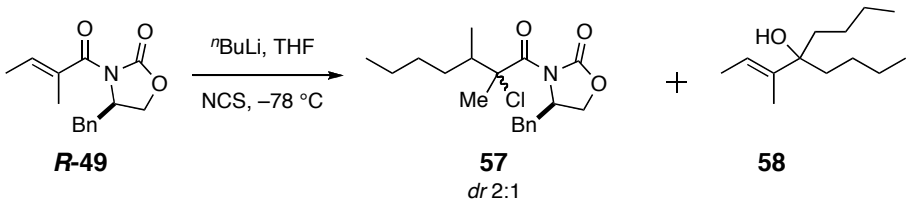


The problems with this route arose when trying to separate and purify the stereoisomers by MPLC. While the two desired products **(*R,R*)-** and **(*S,R*)-53** could be separated from each other, the major diastereomer **[(*S,R*)-53**] eluted along with the dichlorinated products **56** (also a diastereomeric mixture) and could not be isolated cleanly.

Attempts to form the boron enolate by reaction of ***R*-49** with dicyclohexylboron chloride were unsuccessful. Addition of NCS to the mixture of the imide ***R*-49** and the boron compound gave recovered starting material. Presumably, the boron enolate was not formed, although no tests were done to confirm this.

Unexpected products were obtained when ^{n}BuLi was used as the base. This reaction was plagued with products from nucleophilic addition of the *n*-butyl group. Although it was not isolated, the main product observed in the ^{1}H NMR spectrum of the crude product mixture appeared to be the dibutyl alcohol **58**, which also led to the presence of cleaved auxiliary. The other product was purified and determined to be **57**.

Scheme I-23: Chlorination attempt using n-butyl lithium as a base.



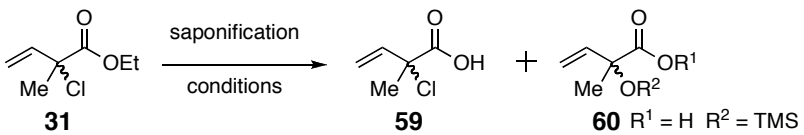
***R*-49** **57** *dr* 2:1 **58**

I.F.3. Synthesis of Enantiopure Allylic Chlorides

The above routes taught us a lot about the reactivity of the substrates. The chlorination chemistry with the chiral auxiliary allowed us to discover that the two allylic chloride diastereomers were separable by MPLC. Therefore, to get the enantiopure allylic chlorides, we needed to synthesize an epimeric mixture of **53**, then separate and carry each diastereomer forward.

As shown above in Scheme I-21, tiglic acid was converted to the oxazolidinone derivative in one pot. Saponification of allylic chloride ethyl ester **31** (Scheme I-9) would yield the acid that would be transformed into the desired imide product. However, formation of the acid from the ethyl ester was problematic. Submitting the ethyl esters to various conditions did not give clean formation of acid **59** (Scheme I-24). GCMS analysis suggested byproducts (such as **60**) that did not contain chlorine (replaced by an oxygen) but these products weren't fully characterized. Isolation of the desired product **59**, in low yield (30%), could only be accomplished by treatment with NaOH. The following were also tried: LiOH, KOH and potassium trimethylsilanoate ($KOSi(CH_3)_3$). Both ^1H NMR and GCMS data showed evidence for loss of chlorine (replaced by a OH or OTMS). The difficulties encountered in forming the acid from the ethyl ester resulted in the use of *tert*-butyl ester.

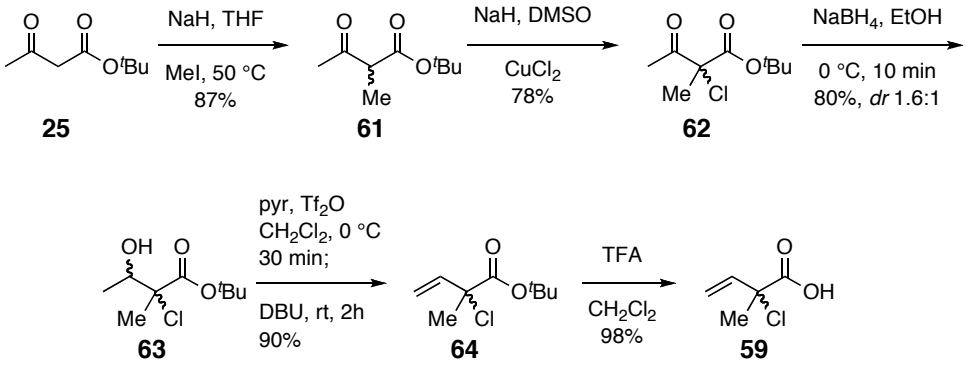
Scheme I-24: Results of saponification of ethyl ester **31**.



31 **59** **60** $R^1 = H$ $R^2 = TMS$ $R^1 = H$ $R^2 = H$

The synthesis of acid **59** was carried out as shown in Scheme I-25. The first four steps were the same as the ethyl ester case (Scheme I-9), but the starting material was *tert*-butyl acetoacetate (**25**). Methylation to **61** followed by chlorination gave disubstituted ester **62** in good yield (68%). Transformation to allylic chloride **64** proceeded smoothly via reduction to **63** and formation / elimination of the triflate. The *tert*-butyl ester was treated with TFA realizing clean conversion to desired acid **59** in a higher yield (quantitative crude) than achieved from the ethyl ester (30%).

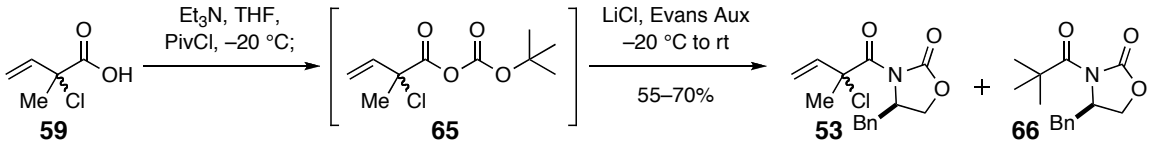
Scheme I-25: Racemic allylic chloride synthetic route using *tert*-butyl ester.



Conversion of the acid to the benzyl-oxazolidinone derivative is shown in Scheme I-26. The intermediate mixed anhydride (**65**) was formed by reacting acid **59** with pivaloyl chloride, but was never isolated. In the same pot, upon treatment with LiCl and (*R*)-4-benzyl-2-oxazolidinone (as shown with tiglic acid in Scheme I-21), **65** was transformed into the desired oxazolidinone derivative **53**. Byproduct **66** was also formed as a result of the lithium anion of the auxiliary attacking the undesired carbonyl of mixed anhydride **65**. Steric bulk could be added to the ester (adamantyl vs. *tert*-butyl) and would probably improve the selectivity but pivaloyl derivative **66** wasn't the major product and was separable from desired product **53** by MPLC. The two diastereomers of

53 were separated (from each other and byproduct **66**) by MPLC. Now, each diastereomer can be carried forward to the enantiopure allylic chlorides.

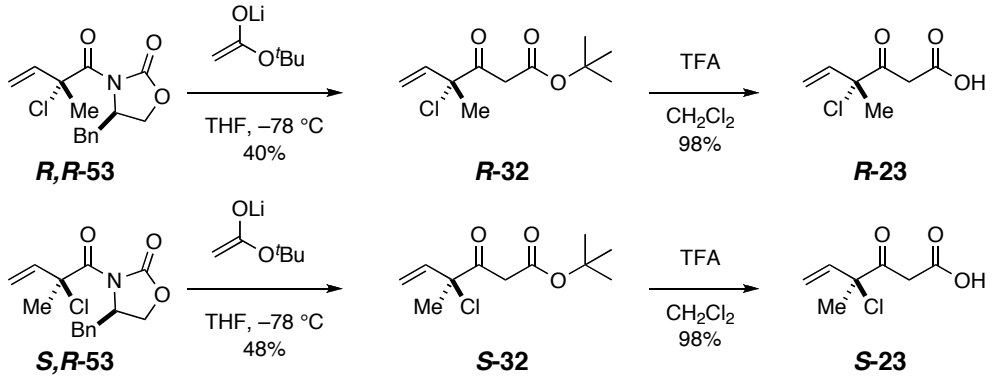
Scheme I-26: Conversion of the acid to oxazolidinone derivative **53**.



Throughout the rest of this chapter, the configuration of the chlorine-bearing stereocenter is assumed (for the ease of discussion) to be as drawn in each diastereomer (and later, enantiomer). Allylic chloride **53** was synthesized previously via chlorination (Scheme I-22) and the configuration of the chlorine-bearing stereocenter in the major diastereomer was determined based on the chelated dienolate shown in Figure I-9b. The major diastereomer resulting from chlorination, (*S,R*)-**53**, was more polar than the minor diastereomer, (*R,R*)-**53**. A new route yielded the same two diastereomers and assignment of the configuration is based on the previous analysis; the more nonpolar (*R,R*)-**53** eluted from silica gel followed by (*S,R*)- **53**. As stated before, this is not a definitive method to assign that stereocenter. An x-ray structure of one diastereomer of the oxazolidinone derivative **53** would confirm (or not) the assigned configuration. Thus far, attempts to get an x-ray quality crystal have not been successful. Derivatives using (*R*)-4-phenyl-2-oxazolidinone were also synthesized in an attempt to get an x-ray structure. For the chemistry that will be studied, it is not vital to know the configuration since each enantiomer will be tested. If the wrong configuration of the chlorine-bearing stereocenter were assumed, the results would be for the epimer. At this point, it is more important to have each enantiopure allylic chloride than to know, precisely, the correct configuration.

Each enantiopure allylic chloride (***R*-** and ***S*-23**) was constructed (Scheme I-27). This was accomplished by Claisen condensation of each diastereomer of **53** with the lithium enolate of *tert*-butyl acetate to give the β-keto *tert*-butyl esters ***R*-** and ***S*-32**. Material was usually stored at this point and converted to the acids ***R*-** and ***S*-23** with TFA immediately before coupling with the epoxide.

Scheme I-27: Transformation of each epimer of the chlorinated compound to the enantiopure acids via Claisen condensation and deprotection.



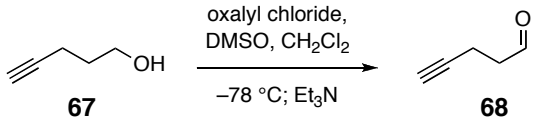
Many studies using asymmetric reduction and chlorination were attempted to give, selectively, one diastereomer. In the end, this could not be accomplished because of problems involving stereoselectivity, regioselectivity, purification, or further derivatization. Finally, the two diastereomers of the auxiliary derivative were synthesized, separated, and then converted to the desired acids. Now, with enantiopure allylic chloride acids ***R*-** and ***S*-23** in hand, discussion of the coupling partner, alcohol **22**, will begin.

I.G. Synthetic Studies to Epoxide Fragment

The synthesis of the southern-half of acyclic precursor ***R*-21** (Scheme I-8) has been achieved so now we move on to the formation of the northern portion, epoxide **22**. The synthesis of the epoxide fragment resulted in a couple of routes as well. Initially, the

starting material was 4-pentynol (**67**). Swern oxidation gave the known[39] aldehyde **68**, which, because of its volatility, was isolated with residual solvent in ~80% yield (Scheme I-28). From here, the route diverged to either an asymmetric route or one where an epimeric mixture was synthesized.

Scheme I-28: Swern oxidation of 4-pentynol (**67**).



To set the carbinol center to the desired *R* configuration, an asymmetric allylation was performed using a titanium catalyst reported by Maruoka.[40] The bis-μ-oxo titanium catalyst (*S,S*-**73**) was generated *in situ* by premixing titanium tetrachloride (**69**) with titanium tetraisopropoxide (**70**), in a 1:3 ratio, to form intermediate **71**. Addition of silver(I) oxide afforded bis-titanium **72**, which upon treatment with (*S*)-binaphthol, gave desired catalyst **(*S,S*)-73** (Scheme I-29). Allylation of aldehyde **68** with allyltributylstannane (**74**) in the presence of the catalyst gave desired alcohol ***R*-75** in good yield and selectivity (93% *ee*, Mosher ester analysis, Figure I-10). The enantiopure compound was carried forward through many of the following steps. However, since setting that stereocenter was not required to study the details of the Kaneda reaction, many of the following procedures will be described using the racemic alcohol.

[39] "Aminoalkynyldithianes. A new class of calcium channel blockers," Adams, T. C.; Dupont, A. C.; Carter, J. P.; Kachur, J. F.; Guzewska, M. E.; Rzeszotarski, W. J.; Farmer, S. G.; Noronha-Blob, L.; Kaier, C. *J. Med. Chem.* **1991**, *34*, 1585-1593.

[40] "Bis(((*S*)-binaphthoxy)(isopropoxy)titanium) Oxide as a μ-Oxo-Type Chiral Lewis Acid: Application to Catalytic Asymmetric Allylation of Aldehydes," Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708-1709.

Scheme I-29: Titanium catalyst synthesis and asymmetric allylation to alcohol **(*R*)-75**.

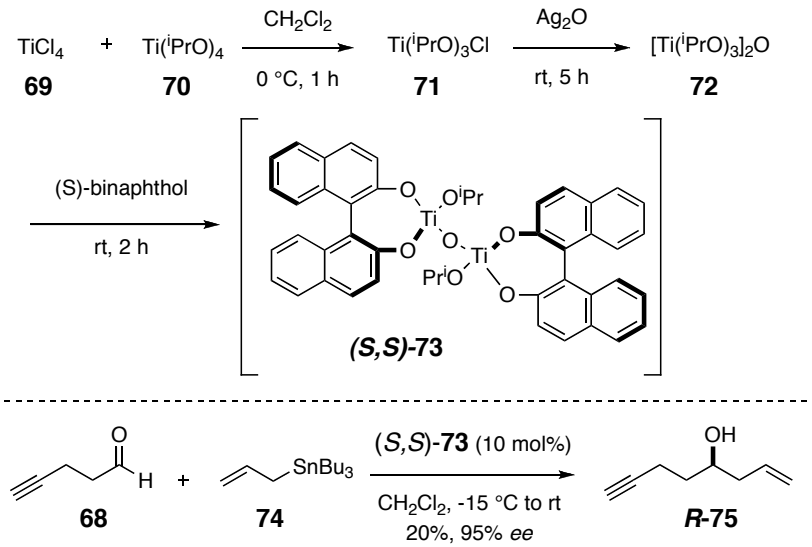
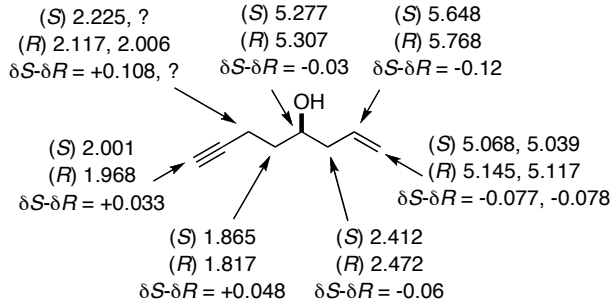
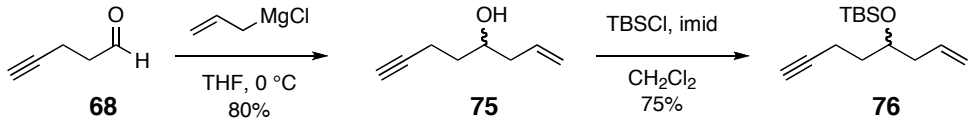


Figure I-10: Modified Mosher ester analysis of the desired enyne alcohol.



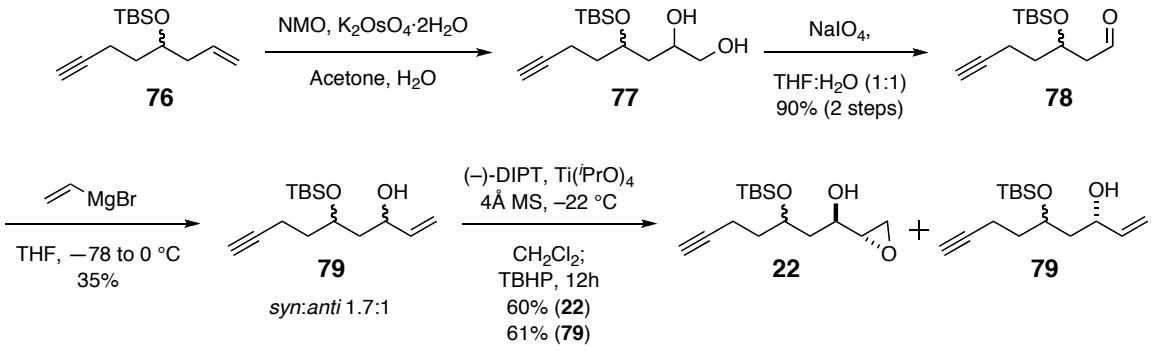
Instead of submitting the aldehyde to asymmetric allylation as described above, the racemic alcohol **75** was obtained by reacting aldehyde **68** with the allyl Grignard reagent (Scheme I-30). Protection as the TBS ether gave **76**. The bis-TBS ether was also formed as an impurity in the reaction but could be removed by distillation.

Scheme I-30: Racemic synthesis of TBS ether **76**.



Problems arose when trying to convert the alkene to an aldehyde. The Johnson-Lemieux[41] one-pot procedure using $K_2OsO_4 \bullet 2H_2O$ and $NaIO_4$ gave low yields (25%) of allylic alcohol **79**, after treatment of aldehyde **78** with vinyl Grignard. Addition of 2,6-lutidine has been shown to improve yields but only gave slight improvements in our studies.[42] The yield could also be increased to 32%, using a two-step procedure (isolating but not purifying diol **77**). The allylic alcohol **79** was obtained as a *syn*:*anti* mixture of 1.7:1.

Scheme I-31: Construction of epoxide **22** by oxidative cleavage of the diol intermediate.



The desired *erythro* configuration of the alcohol epoxide was achieved using Sharpless asymmetric epoxidation (SAE).[43] Kinetic resolution of the alcohols resulted in isolation of desired epoxide **22**, along with recovery of the undesired allylic alcohol **79** by MPLC (Scheme I-31). Usually the recovered alcohol was obtained in a lower yield than the epoxide, presumably a consequence of water-solubility. (*S*)-Alcohol **79** could be converted to the (*R*)-hydroxyl under Mitsunobu conditions. Instead, the undesired

[41] "Osmium Tetroxide-Catalyzed Periodate Oxidation of Olefinic Bonds," Pappo, R.; Alen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478-479.
[42] "Improved Procedure for the Oxidative Cleavage of Olefins by OsO_4–$NaIO_4$," Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217-3219.
[43] "Catalytic Asymmetric Epoxidation and Kinetic Resolution: Modified Procedures Including in Situ Derivatization," Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

substrate was carried forward since reacting with the tartrate enantiomer, (+)-DIPT, would still give the erythro configuration of the alcohol epoxide and this stereoisomer could be coupled with the allylic chloride and tested as well.

Some problems with the SAE reaction were encountered. Paying attention to some of the details that will be described here resulted in an improved and more consistent yield as well as allowed for isolation of the pure epoxide. It is beneficial to stir the reaction so to keep it at low temperatures as well as allow for mixing, it was carried out in a portable cooler (rather than placed in a freezer, which resulted in lower conversion). The reaction is usually accomplished with catalytic amounts of the tartrate (10 mol%), titanium isopropoxide (15 mol%) and TBHP (0.7 equiv) but in our case the reaction was very slow and had low conversions. Sharpless reported similar issues with a secondary allylic alcohol having an alkyl chain and terminal alkene, which required 6-12 days to achieve the desired 50% conversion.[43] In order to improve the reaction time and maintain the selectivity, these reagents were used in at least a stoichiometric amount. The use of stoichiometric diisopropyltartrate caused problems in the workup / isolation procedure. A workup is well documented by Sharpless[43] but a few important details helped give better yields and more pure products (since we used more titanium isopropoxide and tartrate than used in the reference). When the reaction is complete, the excess TBHP is reduced with ferrous sulfate while the excess titanium isopropoxide is reacted with tartaric acid. The mixture is then filtered through celite before it is extracted with CH_2Cl_2 (the reaction solvent). Sharpless recommends Et_2O for extraction but the CH_2Cl_2 worked better at this point because of emulsions that formed in our case (which was why the celite filtration was done). Saponification of the remaining tartrate was

accomplished by stirring the mixture with a (fresh) 30% sodium hydroxide solution for 1 h at 0 °C. However, better results were obtained when CH_2Cl_2 was replaced with Et_2O before treatment with the sodium hydroxide solution. When CH_2Cl_2 was used as a solvent, it appeared to form an emulsion as a milky-colored layer in the sodium hydroxide solution and after extraction the tartrate remained in the sample even after extended stirring (and extended stirring would result in a low recovery of the desired epoxide product). When Et_2O was used as the solvent, the solution was clearer and the tartrate was saponified within an hour. Some residual tartrate may not seem like it is worth all the trouble to remove but it is very important in this case. Any remaining DIPT was unacceptable since, unfortunately, it eluted with desired epoxide **22** when purified by MPLC. Other tartrates, like DET, were easier to saponify and would likely be separable from the epoxide, but decreasing the size of the alkyl groups has been shown to slow the rate of the reaction[44], which was already 12 to 18 hours with stoichiometric reagents. The reaction yields were acceptable after careful attention to the details described above, specifically paying attention to saponification of the tartrate.

In the route shown in Scheme I-31, low yields were obtained when converting the alkene to the aldehyde and, subsequently, the allylic alcohol. Another sequence, using a nitrile group in place of the alkene, was tried. Acetonitrile was deprotonated with LDA and upon addition of the aldehyde gave (known but not characterized)[45] nitrile **81** (Scheme I-32). Along with the desired product, the two to one (aldehyde to nitrile)

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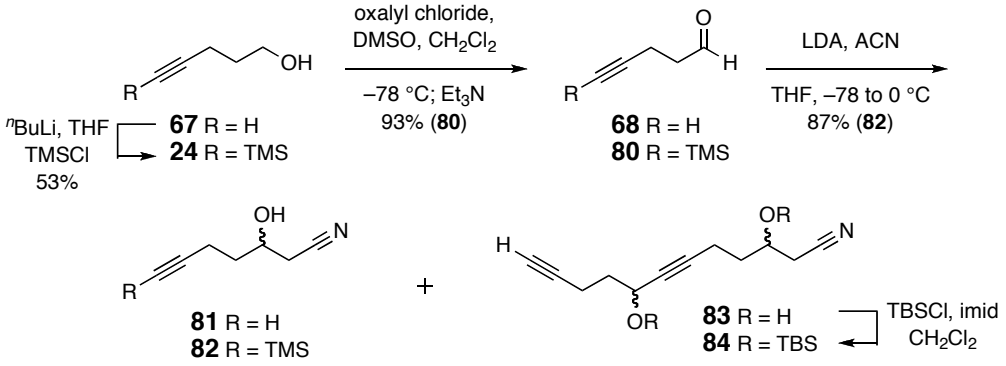
[44] "Kinetic Resolution of Racemic Allylic Alcohols by Enantioselective Epoxidation. A Route to Substances of Absolute Enantiomeric Purity?" Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237-6240.

[45] "Ruthenium-Catalyzed Hydrative Cyclization of 1,5-Enynes," Chen, Y.; Ho, D. M.; Lee, C. *J. Am. Chem. Soc.* **2005**, *127*, 12184-12185.

adduct **83** was formed (via deprotonation of the alkyne, which added to the aldehyde). This byproduct became apparent after the crude mixture was treated with TBSCl and imidazole, resulting in formation and isolation of bis-TBS ether **84**. Based on these results and the volatility issues of 4-pentynal (**68**) described above, we decided to protect the alkyne with TMS. Although trimethylsilyl-4-pentynol (**24**) could be synthesized using *n*BuLi and TMSCl (Scheme I-32), it was also found to be commercially available. Swern oxidation of protected alkyne **24** gave aldehyde **80** in higher purity and yield (93%). Alkylation of the protected alkyne aldehyde gave alcohol **82** as the sole product.

Scheme I-32: Route to the nitrile compounds having a free or TMS-protected alkyne.

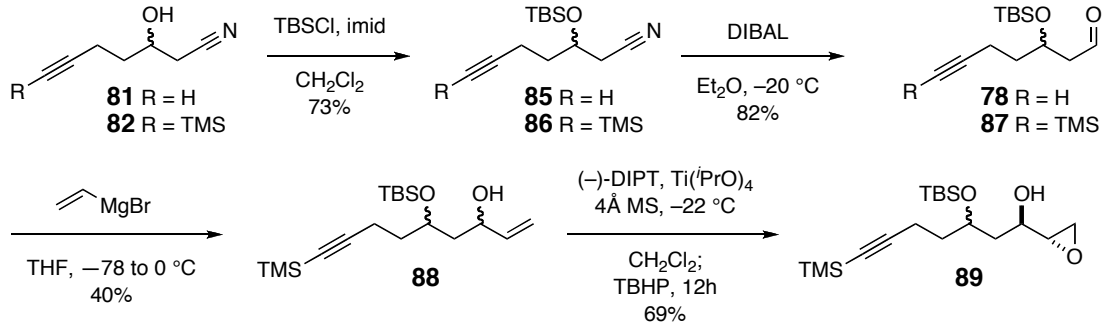


With some steps similar to the sequence above, the nitrile substrate was converted to the desired epoxide. Protection of the alcohol was accomplished. During the protection, bis-TBS ether is also formed but is easily separated from nitrile **86** by distillation. The isolated yields of the next step were similar whether the nitrile had been purified by distillation or was taken forward from the crude pot (discolored but clean by ^{1}H NMR) after distilling off the bis-TBS ether impurity. Conversion of nitrile **86** to the aldehyde was done at low temperature using DIBAL and an acidic workup.[46] If the

[46] (a) "Development of New Chiral Building Blocks for Synthesis of Bicyclo[3.3.0]octane Compounds," Subburaj, K.; Okamoto, S.; Sato, F. *J. Org. Chem.* **2002**, *67*, 1024-1026. (b) "Total Synthesis of

reaction warmed, some reduction of the alkyne was evident and without an acidic workup, another product, presumably an imine complex, was isolated. With aldehyde **87** in hand, the TMS-protected alkynes undergo the same chemistry (Grignard addition and SAE) as shown in Scheme I-31. The advantage of SAE on protected alkyne **88** was that the product epoxide was more nonpolar (compared to the free alkyne) and therefore, was separable from remaining tartrate. Deprotection of alkyne **89** would provide the desired epoxide fragment for coupling with the allylic chloride.

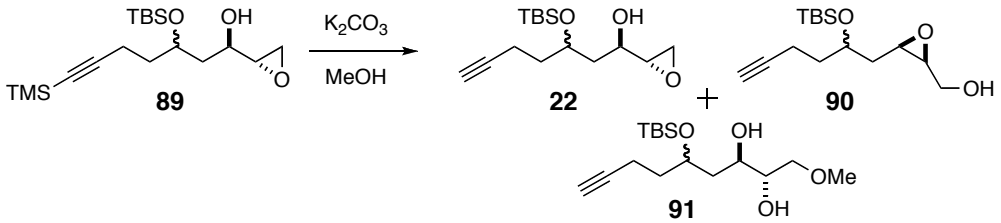
Scheme I-33: Use of nitrile as aldehyde equivalent in synthesis of protected epoxide **89**.



Deprotection was attempted with K_2CO_3 in methanol. However, 3 products, all having the free alkyne, were obtained. The desired epoxide **22** was evident under shorter reaction times (2 hours) but starting compound **89** was still present (Scheme I-34). When left under basic conditions overnight the only products were epoxide **90**, which arises via Payne rearrangement and diol **91**, a result of epoxide opening with methanol. Other conditions ($AgNO_3$/KCN) were tried but gave low yields. Since the epoxide functionality appears to be the issue, a better option was deprotection before SAE.

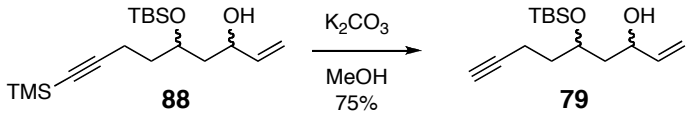
Macquarimicins Using an Intramolecular Diels-Alder Approach Inspired by a Biosynthetic Pathway," Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2004**, *126*, 11254-11267.

Scheme I-34: Substrates obtained in the deprotection of epoxide **89**.



Alkyne **79** was realized from allylic alcohol **88** with K_2CO_3 in methanol (Scheme I-35). As shown previously in Scheme I-31, SAE of the allylic alcohol gave the desired alcohol **22**, which was to be coupled with each of the enantiopure allylic chlorides. The details of the coupling strategies follow in the next section.

Scheme I-35: Successful deprotection of allylic alcohol **88**.



I.H. Coupling Reaction of Acid and Alcohol

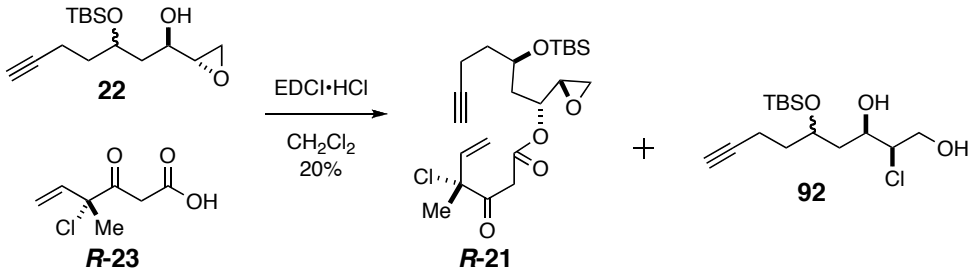
The next step was to obtain the acyclic Kaneda precursors via coupling the alcohol with each of the enantiopure allylic chlorides. The first thought was to use DCC (dicyclohexylcarbodiimide) coupling. As described earlier in Section I.F.1.a., the alcohol products of asymmetric reduction were coupled with the Mosher acids using DCC. This carbodiimide, a crystalline solid mass at rt, can be chipped apart or, alternatively, melted before use but it crystallizes very quickly. There is also a safety concern since DCC is a known allergen and sensitizer, causing skin rashes (even in areas without direct contact to the chemical). Although coupling with DCC is known to work well, another disadvantage is that the urea byproduct, dicyclohexylurea (DCU), formed is not water-soluble and therefore has to be removed by chromatography if it isn't all removed by

filtration. This led to the use of a similar coupling agent, EDCI•HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide).

Using EDCI•HCl has advantages over DCC and is increasingly seen in the literature. As a white crystalline material, it is much easier to manage than DCC. The urea formed is water-soluble and as a result, the desired product can be extracted from the byproduct. The yields should be comparable as well and so this reagent was used for our coupling.

Coupling of alcohol **22** with acid ***R*-23** was accomplished in modest yields (40-50%) to give enyne ***R*-21** (Scheme I-36), although a higher yield was anticipated. At this point, both starting compounds are precious and adding an excess of one is not optimal. Upon purification by MPLC on a larger scale, byproduct **92** was discovered, resulting from opening of the epoxide with chlorine. There was also evidence of the coupled product having the epoxide opened by chlorine. The fact that EDCI is sold as the HCl salt was affecting the chemistry so we considered some solutions.

Scheme I-36: Coupling reaction of the alcohol and acid using EDCI•HCl.

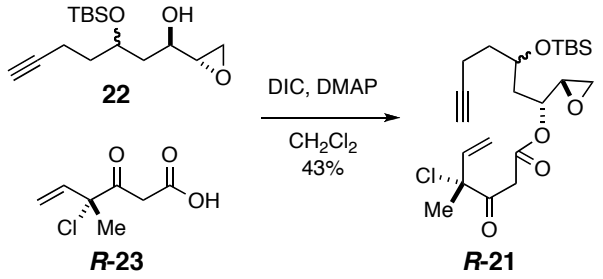


One idea to was to freebase the EDCI and use it in the coupling reaction. This was accomplished using a NaOH solution and extraction, yielding a clear oily product as

described in literature.[47] However, when free-based EDCI was used in the coupling, starting epoxide was recovered and the ^{1}H NMR spectrum of the crude product mixture was very complex, showing only a hint of coupled product. Addition of DMAP is used to accelerate the coupling of acids and alcohols in DCC reactions, while also suppressing the formation of undesired (inactive) *N*-acylureas.[48] When a catalytic amount of DMAP was added to reactions with EDCI or EDCI•HCl, only the latter showed evidence of the desired coupling and both gave recovered epoxide. Using a stoichiometric amount of DMAP with EDCI•HCl did not improve the results. Therefore, another coupling agent was tried.

As a coupling agent, DIC (diisopropylcarbodiimide) is more similar to DCC than EDCI. As a liquid at rt, DIC is easier to transfer and does not have the sensitivity issues of DCC. As far as byproduct formation, it is more similar to DCC and doesn't offer the advantages that EDCI does in removal of the urea byproduct. Coupling acid **22** and alcohol ***R*-23** using DIC and catalytic DMAP (Scheme I-37) allowed for higher isolated yields (60-70%) of the desired ester ***R*-21**.

Scheme I-37: Formation of ester **21** using DIC coupling.



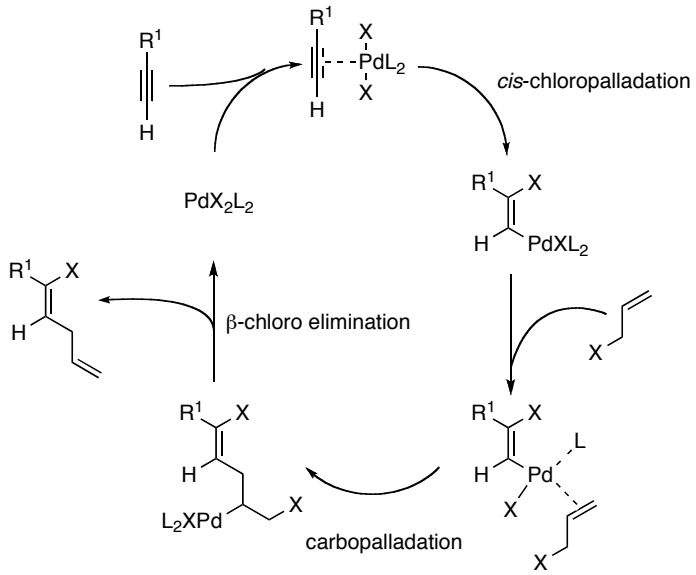
[47] "The Mechanism of Action of Ethanolamine Ammonia-Lyase, an Adenosylcobalamin-dependent Enzyme," Kopczynski, M. G.; Babior, B. M. *J. Biol. Chem*. **1984**, *259*, 7652-7654.
[48] "Simple Method for the Esterification of Carboxylic Acids," Neises, B.; Steglich, W. *Angew. Chem., Int. Ed.* **1978**, *17,* 522-524.

After trial of the above coupling strategies, DIC was found to be the best choice because of ease of handling, safety and lack of side reactions. With the acyclic precursor in hand, the substrates were submitted to the Kaneda reaction conditions.

I.I. Kaneda Studies

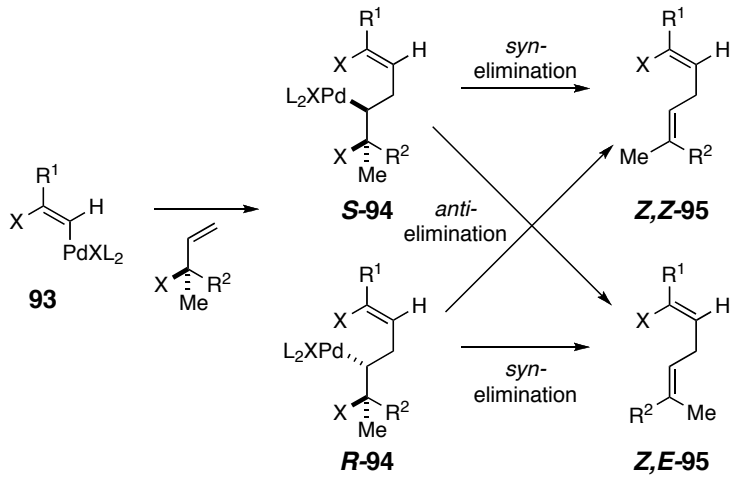
In 1979 Kaneda reported a study on the intramolecular coupling of alkynes with allyl halides to give 1-halo-1,4-dienes.[10] The proposed mechanism is shown below in Figure I-11. The first step is *cis*-chloropalladation of the terminal alkyne. When R^1 is an electron-donating group, (which is the case in our studies), the palladium adds to the terminal carbon of the alkyne. However, if R^1 is an electron-withdrawing group, as in some studies done by Kaneda, the opposite regioselectivity is obtained. The vinyl-palladium intermediate undergoes ligand exchange with an allylic chloride, followed by regioselective addition to yield a vicinal β-chloroalkyl palladium species. Ejection of the catalyst PdX_2L_2 produces the desired halogenated skipped diene.

Figure I-11: Catalytic cycle of Kaneda's alkyne haloallylation reaction with Pd(II).



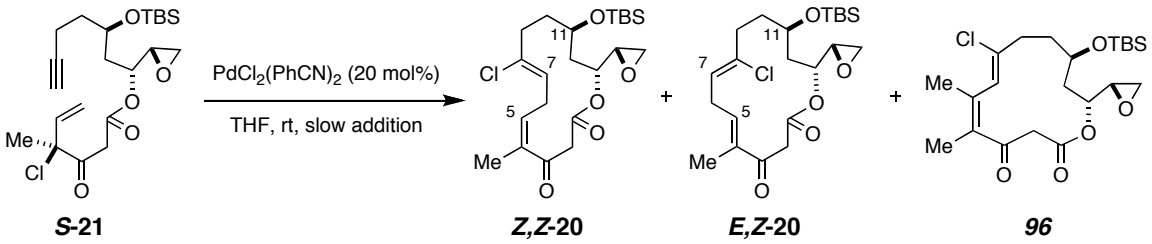
There are some stereoselectivity questions to consider in this reaction, especially for our studies. Kaneda only studied intermolecular coupling, using almost all primary chlorides (one secondary). We are using this chemistry to do an intramolecular version and are using a tertiary allyl chloride. As shown in Scheme I-38, there is more to consider when comparing our studies to the mechanism shown above. When coupling a tertiary allylic chloride, the diastereoselectivity of coordination of vinyl palladium species **93** to one face (*re* versus *si*) of the alkene plays an important role, which would give either ***R*-** or ***S*-94** (referring to the configuration of the palladium-substituted carbon) after carbopalladation. After this, the vicinal β-chloroalkylpalladium intermediate **94** may undergo either *syn*- or *anti*- elimination to produce chloro-1,4-diene **95**. The stereoselectivity of the β-halogen elimination is also important. Therefore, if the coordination / carbopalladation step is stereoselective, giving one diastereomer of **94**, and the elimination was stereoselective for either *syn* or *anti*, only one product, ***Z,Z*- or *Z,E*-95**, would be isolated. As stated above, initial studies by Wang and Hoye used substrates containing an epimeric mixture at the chlorine center. The results "raised the intriguing possibility that these intramolecular haloallylations are stereospecific–that each of the epimeric allylic chlorides engenders a single C4-C5 alkene geometry".[6] Now, with each of the enantiopure allylic chloride acyclic precursors in hand, submitting each one to the Kaneda reaction conditions and analyzing the results, specifically the alkene geometry, will tell a lot about the mechanistic details of the reaction.

Scheme I-38: Stereochemical considerations in mechanistic steps of the Kaneda reaction.



Each epimer of the enantiopure acyclic precursors was submitted to the Kaneda reaction conditions. Initially, this was done on substrates having the TBS ether stereocenter set to the desired (*R*) configuration (through asymmetric allylation, Scheme I-29). The catalyst, bis(benzonitrile)palladium(II) chloride, was dissolved in THF. Addition of the acyclic precursor, such as ***S*-21**, (in THF) was accomplished via syringe pump. Slow addition of the substrate, along with dilute concentrations, minimized the amount of dimerization. From the acyclic starting material, 3 products, separated by MPLC, were isolated and found to have the same mass. As shown below in Scheme I-39, the desired 14-membered lactone product was constructed. Two of the products were stereoisomers, both containing the *Z* isomer of C7-C8 (oocydin A skeleton numbering) alkene as well as each of the C4-C5 alkene isomers. The other product was a constitutional isomer, showing a dimethyl product by ^{1}H NMR, and eventually assigned to be **96**. The characterization of byproduct **96** will be discussed later.

Scheme I-39: Kaneda reaction of acyclic precursor **21**.



At first, the connectivity of the byproduct was not known. In order to obtain more material for analysis, the configuration at the TBS ether carbon was not set (synthesis in Scheme I-30). Because of the distance from the reactive center, we hope that this doesn't affect any stereoselectivity preferences in the Kaneda reaction. When substrates containing a mixture of epimers at C11 (oocydin A skeleton numbering) were submitted to the palladium-catalyzed conditions, the same three products shown in Scheme I-39 were isolated. The crude recovery was modest and only products containing the desired (*R*) configuration at C11 (OTBS center) were isolated (and subsequently found to exactly match those obtained when starting with one diastereomer). The fate of the starting material containing the undesired OTBS configuration was not obvious.

Studies were still done starting with each epimer of the allylic chloride. The results, determined by analysis of the ^{1}H NMR spectrum of the crude product mixture, are shown below in Table I-2. Different C4-C5 alkene ratios were obtained, as well as the amount of byproduct formed, for each of the (*R*)- and (*S*)-allylic chlorides. The undesired constitutional isomer **96** was a major product in all cases, as shown in the last column of Table I-2. It is interesting that the ratio of the alkene isomers is different for the two epimers. When starting with ***R*-21**, the undesired *E* isomer (of the C4-C5 alkene) is slightly favored (1.5 : 1 over the *Z* isomer). The selectivity is similar for the epimer, ***S*-**

21, but now the desired *Z* isomer is favored. Also, note that these alkene isomer ratios are similar in the crude material whether the OTBS stereocenter is set to the desired (*R*) configuration or formed as a mixture (compare ratios in entries 1 and 3 or 2 and 4, Table I-2).

Table 1-2: Results of the Kaneda reaction with different stereoisomers of the acyclic precursor.

Entry	Chlorine center config.	TBS ether center config.	% conversion	Product Ratio *Z,Z*-20:*E,Z*-20:96
1	*R*	*R* + *S*	100	1 : 1.5 : 2
2	*S*	*R* + *S*	100	1.3 : 1 : 1.5
3	*R*	*R*	90	1 : 1.5 : 3
4	*S*	*R*	80	1.4 : 1 : 1.4

The presence of both alkene isomers means that the overall reaction is not stereospecific. Since the product ratios do change depending on the starting material configuration, there is some selectivity present. One step of the reaction (carbopalladation or β-Cl elimination in Scheme I-38) may still be stereospecific, while the other step doesn't have much preference. Determining more details of the reaction using the current substrates would be difficult. Experiments like adding steric bulk to one face of the alkene and analyzing the results might be more useful.

The desired selectivity for the formation of the *Z* alkene at C4-C5 was not achieved but the presence of a byproduct needs to be considered, especially since it was always a major component. The byproduct could be formed via a rearrangement of one (or both) of the desired products, which would change the C4-C5 alkene ratios. The

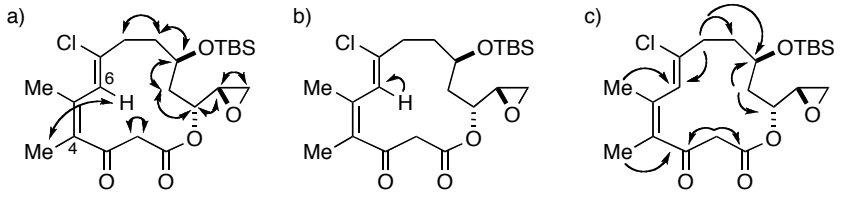
byproduct could also be formed at the expense of one alkene isomer. The assignment of the byproduct structure and a mechanism of formation were important to figure out.

The structure of conjugated diene **96** was determined using various methods. As stated above, the products could be (carefully) separated to give pure samples of each. The desired product, ***Z,Z*-20** eluted from the column with byproduct **96**, but cutting fractions of the peak allowed for isolation of each substrate with **96** being the more polar of the two. The crude mixture, as well as pure samples, could be analyzed using LCMS. This showed that they were all isomers having the same molecular formula. However, the ^{1}H NMR spectrum of the impurity showed the presence of two methyl groups. Various 2D NMR techniques, including COSY, HMQC, and HMBC, were used to assign the connectivity, as well as NOE studies to determine alkene configuration. The chemical shifts of the two methyl groups of **96** (1.92 and 1.89 ppm) in $CDCl_3$ made analysis difficult. Doing the same studies in C_6D_6 helped resolve the two methyl peaks (1.64 and 1.35 ppm).

The 2D NMR analysis of byproduct **96** is shown in Figure I-12. The COSY spectrum showed all the expected correlations and confirmed that the right hand side of the molecule had the same connectivity as the desired product **20**. The only questionable correlation was between the C4 methyl group and the vinyl hydrogen at C6. Since the two methyl peaks were so close, it was hard to be certain about the interpretation but performing the COSY in C_6D_6, where the methyl peaks were more distinguished, yielded the same results. From HMBC (Figure I-12b), it was determined that the methyl group showing a COSY correlation to the vinyl hydrogen was alpha to the carbonyl (C3) group, since the methyl hydrogens gave a correlation to the carbonyl carbon (C3). Also of note

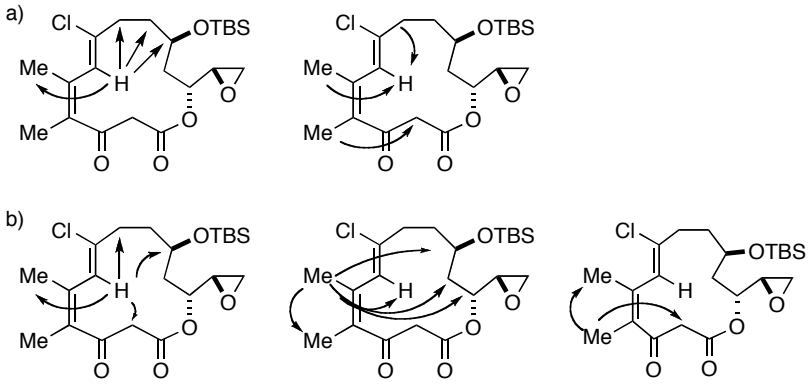
from HMBC is the correlation of the C5 methyl hydrogens to the alkene carbon (C6) bearing the only vinyl hydrogen (allowing assignment of that carbon by HMQC as shown in Figure I-12b). As stated before, the methyl groups in $CDCl_3$ had very similar chemical shifts, but our confidence increased by performing the same studies in C_6D_6 and observing the same correlations.

Figure I-12: 2D-NMR data of byproduct **96**: a) COSY b) HMQC c) HMBC.



The use of both solvents was more beneficial when performing the NOE studies than it had been in the 2D analysis discussed above. In Figure I-13a are the NOE enhancements from the irradiated protons in $CDCl_3$. Irradiating the vinyl hydrogen enhances the methyl at C5 along with other peaks. We can also see the enhancement of that vinyl hydrogen by irradiation of the C5 methyl hydrogens. If we irradiate the C4 methyl hydrogens, slight enhancement of one of the C2 hydrogens occurs. More data were obtained when NOE studies were done in C_6D_6 (Figure I-13b). Irradiating the vinyl hydrogen gave similar results in both solvents. It was the irradiation of the two methyls at C4 and C5 that guided our determination of the structure. We saw enhancement of one methyl when the other methyl was irradiated, implying that the two methyls are on the same side of the alkene. Based on these results, the structure was determined to be **96**.

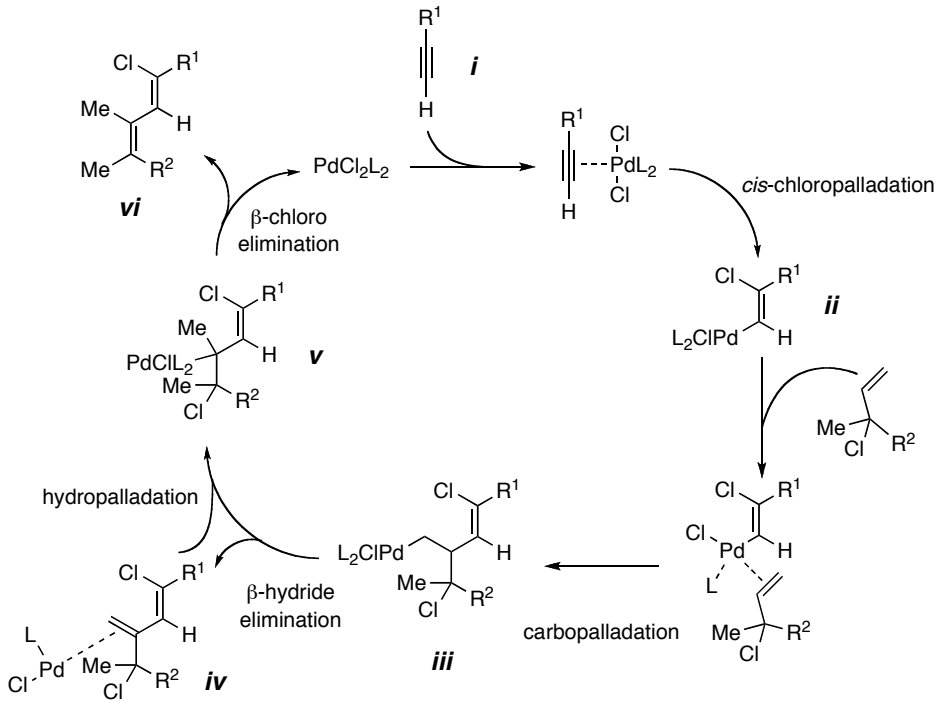
Figure I-13: NOE data of byproduct **96** in a) $CDCl_3$ and b) C_6D_6.



After assigning the structure of product **96**, we began to think more about how it arises. The catalytic cycle for the desired pathway was shown above in Figure I-11. Our proposed mechanism for the formation of **96** is shown below in Figure I-14. The first step, *cis*-chloropalladation, is the same as in the usual Kaneda reaction and the intermediate (**ii**) coordinates to the allylic chloride. However, to form the byproduct, we believe carbopalladation occurs to form a C-C bond between the terminal alkyne carbon and the internal alkene carbon to yield a methylene palladium species (**iii**). In the desired pathway (Figure I-11), the terminal alkyne carbon forms a bond with the terminal alkene carbon, resulting in a methyne palladium species that has a β-chlorine, which does β-chloro elimination to give the desire product and regenerate the catalyst. In Figure I-14, alkyl palladium species **iii** does not have a β-halogen and, as a result, undergoes β-hydride elimination generating a 1-chloro-1,3-diene intermediate (**iv**) with an exocyclic methylene and a palladium hydride complex. Kaneda did report formation of a 1,3-diene product when an alkene lacking an allylic halogen was used in the reaction system, albeit

on simpler substrates and doing intermolecular reactions.[49] Once formed, the palladium hydride could add back into the exocyclic methylene with the opposite regioselectivity, generating a palladium intermediate (**v**) with a β-chlorine. Upon β-chloro elimination of intermediate **v**, the 1-chloro-1,3-diene moiety (**vi**) present in **96** would be formed and the Pd(II) catalyst is regenerated. A dichlorinated 1,3-diene product was not isolated from the reaction mixture and may be evident in the crude NMR but is hard to pick out without having a pure sample for comparison.

Figure I-14: Proposed catalytic cycle for the formation of byproduct **96**.

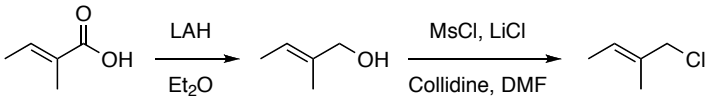


To test the above mechanism, we wanted to make an allylic chloride that could enter the undesired pathway, but was a disubstituted alkene so that if β-hydride elimination occurred, the product would not be able to reenter the catalyst cycle, as we

[49] "Catalytic Codimerization of Styrene and Various Acetylenic Compounds to 1,3-dienes using Palladium Halide-Lithium Halide System," Kaneda, K.; Uchiyama, T.; Kobayashi, H.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *Tetrahedron Lett.* **1977**, *18*, 2005-2008.

proposed above. The synthesis of disubstituted alkene **98** is shown in Scheme I-40. Tiglic acid (**51**) is reduced with LAH to known[50] allylic alcohol **97**, along with a small amount of the fully saturated alcohol. Allylic alcohol **97** is converted to the desired allylic chloride **98** using methanesulfonyl chloride, lithium chloride and collidine in DMF following Albizati's method.[51]

Scheme I-40: Synthetic approach to allylic chloride **98**.

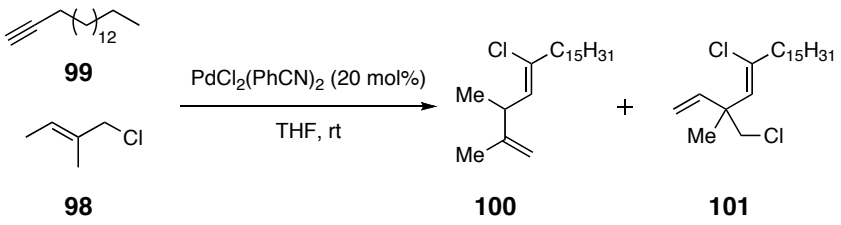


51 **97** **98**

An intermolecular Kaneda coupling reaction was tested using allylic chloride **98** and heptadecyne (**99**) in Scheme I- 41. We would expect to form 1-chloro-1,4-diene **100** from the desired pathway and dichlorinated substrate **101** via the undesired β-hydride elimination. The allylic chloride **98** is volatile, making it more difficult to handle. It also seems to react much slower than previous substrates we've used. As a result, no conclusive results could be drawn from the initial studies. Optimizing the synthesis of allylic chloride **98** and the Kaneda conditions for this reaction as well as monitoring the progress *in situ* by no-D NMR[52] would be the next steps to testing our proposed mechanism.

[50] "Toward the Development of a General Chiral Auxiliary. Enantioselective Alkylation and a New Catalytic Asymmetric Addition of Silyloxyfurans: Application to a Total Synthesis of (–)-Rasfonin," Boeckman, R. K., Jr.; Pero, J. E.; Boehmler, D. J. *J. Am. Chem. Soc.* **2006**, *128*, 11032-11033.
[51] "Chemistry of Dioxenium Cations. Synthetic and Mechanistic Studies on the Stereocontrolled Formation of Tetrahydropyrans from Homoallylic Alcohols and Ortho Esters," Perron-Sierra, F.; Promo, M. A.; Martin, V. A.; Albizati, K. F. *J. Org. Chem.* **1991**, *56*, 6188-6199.
[52] "No-D NMR (No-Deuterium Proton NMR) Spectroscopy: A Simple Yet Powerful Method for Analyzing Reaction and Reagent Solutions," Hoye, T. R.; Eklov, B. M.; Ryba, T. D.; Voloshin, M.; Yao, L. J. *Org. Lett.* **2004**, *6*, 953-956.

Scheme I-41: Expected products of Kaneda reaction using allylic chloride **98**.

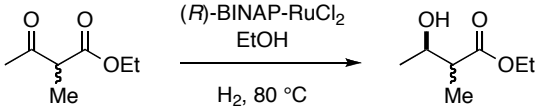


I.J. Conclusion

In conclusion, each enantiopure allylic chloride was synthesized using an oxazolidinone auxiliary. The attempted methods, asymmetric reduction and chlorination, did not achieve the desired stereoselectivity but taught us a lot about the reactivity of the substrate, specifically the influence of the chlorine atom. The enantiopure allylic chlorides were coupled with the epoxide fragment to construct each epimer (at the chlorine center) of the acyclic precursor. When submitted to the Kaneda reaction conditions, it was discovered that the reaction is not completely stereoselective. There does seem to be some selectivity since ***R*-21** favors the *E* geometry of the C4-C5 alkene, while ***S*-21** favors the desired *Z* isomer. During the course of these studies, another interesting byproduct was formed. It was isolated and the structure was determined to be 1,3-diene **96** by 2D NMR analysis. The mechanism of formation is intriguing and although we have proposed how it is made, we were not able to obtain experimental evidence that supports our idea.

I.K. Experimental

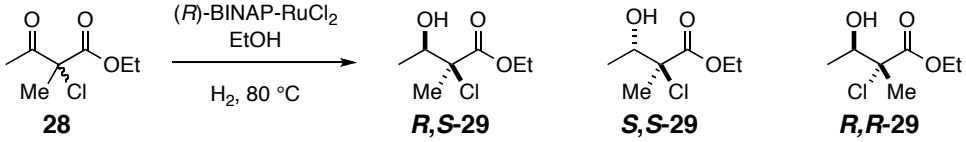
(3*R*)-Ethyl 3-hydroxy-2-methylbutanoate (33)



A culture tube was charged with β-keto ester **27** (500 mg, 3.5 mmol) and EtOH (1 mL). This mixture was degassed by three freeze-pump-thaw cycles and placed under a N_2 atmosphere. Dichloro[(*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium (II) (3 mg) was added. The reaction was placed in the Parr bomb, pressurized with hydrogen gas to 1000 psi and then the pressure was released by opening the stop value. This was repeated three times before the reaction was pressurized to 1000 psi, heated to 80 °C, and left to stir for 18 h. The reaction was concentrated under reduced pressure to yield crude **33** (^{1}H NMR spectrum showed less than 50% conversion).

^{1}H NMR (500 MHz, $CDCl_3$, MB2p290 and MB2p293): Matched literature data.[53]

Ethyl 2-chloro-3-hydroxy-2-methylbutanoate (29)



dr 1 : 1 : 2

A culture tube was charged with β-keto ester **28** (1.0 g, 5.6 mmol) and EtOH (2 mL). This mixture was degassed by three freeze-pump-thaw cycles and placed under a N_2 atmosphere. The (*R*)-BINAP-Ru(II) complex (5 mg) was added. The reaction was placed in the Parr bomb, filled with hydrogen gas to 1400 psi and then the stop valve was

[53] "Asymmetric Reduction of Ethyl 2-methyl 3-oxobutanoate by *Chlorella*," Kuramoto, T.; Iwamoto, K.; Izumi, M.; Kirihata, M.; Yoshizako, F. *Biosci., Biotechnol., Biochem.* **1999**, *63*, 598-601.

opened to drop the pressure back to 1 atm. This was repeated three times before the Parr bomb was pressurized to 1400 psi. The reaction was heated to 80 °C and left to stir for 18 h. After concentration under reduced pressure, the products were purified by HPLC (6:1 hex:EtOAc) to give a 1:3 ratio of two fractions. Fraction 1 contained (***R,S*)-29** while fraction 2 was a mixture of enantiomers (***S,S*)-29** and (***R,R*)-29** (in a 1:2 ratio by Mosher ester analysis as shown in Figure I-4).

(2*S*,3*R*)-ethyl 2-chloro-3-hydroxy-2-methylbutanoate **(*R,S*-29)** (MB2p131A)

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.27 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.20 (dq, *J* = 6.4 and 6.4 Hz, 1H, C*H*OH), 2.53 (d, *J* = 6.3 Hz, 0.9H, O*H*), 1.70 (s, 3H, C(Cl)C*H*$_3$), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$) and 1.25 (d, *J* = 6.4 Hz, 3H, CH(OH)C*H*$_3$).

***S,S*-29** and ***R,R*-29** (*er* 1:2 by Mosher ester analysis) (MB2p131B)

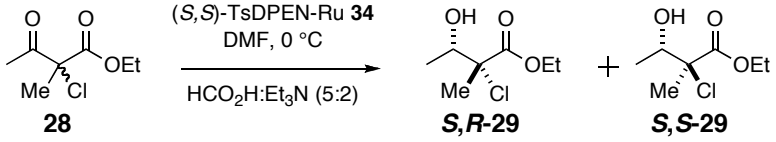
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.27 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.23 (dq, *J* = 6.5 and 6.5 Hz, 1H, C*H*OH), 2.44 (d, *J* = 6.8 Hz, 0.8H, O*H*), 1.75 (s, 3H, C(Cl)C*H*$_3$), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$) and 1.30 (d, *J* = 6.4 Hz, 3H, CH(OH)C*H*$_3$).

GCMS (MB2p118B, 5022014): t_r = 5.98 and 6.00 min; *m/z* 136 (M^+–OCH_2CH_2, 50), 108 (M^+–CO_2Et, 100) and 90 (40).

Mosher ester formation (general)

(*S*)-MTPA (3 equiv) was weighed into a vial. The alcohol (1 equiv) was dissolved in CH_2Cl_2 (0.05 M) and added to the acid. To the stirring mixture was added DCC (7 mg, 0.03 mmol, 3 equiv) and DMAP (5 mg, 0.03 mmol, 3 equiv). The progress was monitored by TLC on silica gel (4:1 Hex:EtOAc). Once complete, the crude mixture was filtered through a cotton plug and purified by MPLC (40:1 Hex:EtOAc).

(3*S*)-Ethyl 2-chloro-3-hydroxy-2-methylbutanoate (29)



β-Keto ester **28** (179 mg, 1 mmol) was weighed into culture tube. A DMF (1 mL) solution of (*S,S*)-TsDPEN-Ru(II) complex (3 mg) was added. In a vial cooled to 0 °C, Et_3N (280 μL, 2 mmol) and HCO_2H (190 μL, 5 mmol) are combined and added to the reaction tube. The reaction was partitioned between Et_2O (20 mL) and H_2O (10 mL). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by HPLC (6:1 Hex:EtOAc) to give two diastereomers, **(*S,R*)-29** and **(*S,S*)-29**.

(2*R*,3*S*)-ethyl 2-chloro-3-hydroxy-2-methylbutanoate **(*S,R*-29)** (MB2p251D and MB2p284E)

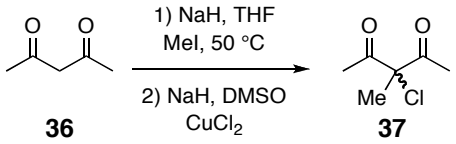
^{1}H NMR (500 MHz, $CDCl_3$): δ Matched above data for enantiomer (p 59, ***R,S*-29**).

(2*S*,3*S*)-ethyl 2-chloro-3-hydroxy-2-methylbutanoate **(*S,S*-29)** (MB2p251E and MB2p284F)

^{1}H NMR (500 MHz, $CDCl_3$): δ Matched above data (p 59).

GCMS MB2p279F

3-Chloro-3-methylpentane-2,4-dione (37)



36 **37**

Pentane-2,4-dione (2 g, 20 mmol) was dissolved in THF (30 mL). Sodium hydride (60% dispersion, 879 mg, 22 mmol) was added in portions and the solution stirred for 15 minutes. Iodomethane (1.37 mL, 22 mmol) was added and the reaction was refluxed for 10 h. The reaction was quenched with H_2O (30 mL), extracted with Et_2O (3x) and the organic layer was washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave known[54] 3-methyl-2,4-dione (1.15 g, 50% yield), which matched literature data.

Sodium hydride (60% dispersion, 425 mg, 10.6 mmol) was added to DMSO (40 mL). 3-Methyl-2,4-dione (1.1 g, 9.6 mmol) in DMSO (10 mL) was added to the mixture dropwise. After stirring for 1 h, $CuCl_2$ (3.24 g, 24.1 mmol) was added in portions and stirred for 18 h. The reaction was quenched with 5% HCl aqueous solution (60 mL) and extracted with Et_2O (3x). The organic layer was washed with 5% HCl aqueous solution (2x 10 mL), DI H_2O, brine, and dried over $MgSO_4$. Concentration under reduced pressure yielded **37** as an oil (640 mg, 45%).

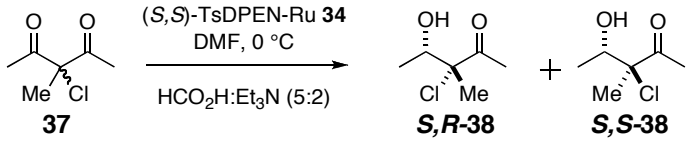
MB2p277

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 6H, COC*H*$_3$) and 1.76 (s, 3H, C(Cl)C*H*$_3$).

GCMS (MB2p277F, 5022014): t_r = 4.30 min; *m/z* 106 (M^+–C(O)CH_3, 100) and 71 (50).

[54] "Selective sequential demasking of ester functions of 1-methyl-3,4,5-tri(methoxycarbonyl)pyrazole," Chambers, D.; Denny, W. A.; Buckleton, J. S. Clark, G. R. *J. Org. Chem.* **1985**, *50*, 4736-4738.

(4*S*)-3-Chloro-4-hydroxy-3-methylpentane-2,4-dione (38)



Diketone **37** (300 mg, 2 mmol) was dissolved in DMF (1 mL) in a culture tube. A DMF (1 mL) solution of (*S,S*)-TsDPEN-Ru(II) complex (5 mg) was added. In a vial cooled to 0 °C, Et_3N (560 μL, 4 mmol) and HCO_2H (380 μL, 10 mmol) are combined and added to the reaction tube. Once complete, the reaction was partitioned between Et_2O (20 mL) and H_2O (10 mL). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by HPLC (6:1 Hex:EtOAc) to give two diastereomers ***S,R*-38** and ***S,S*-38**.

(3*R*,4S)-3-chloro-4-hydroxy-3-methylpentane-2,4-dione **(*S,R*-38)** (MB2p289Gf1)

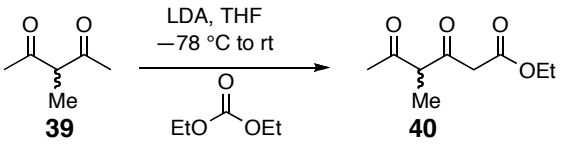
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.20 (dq, *J* = 6.1 and 6.1 Hz, 1H, C*H*OH), 2.41 (s, 3H, COCH_3), 2.52 (d, *J* = 5.9 Hz, 0.9H, O*H*), 1.67 (s, 3H, C(Cl)CH_3) and 1.28 (d, *J* = 6.3 Hz, 3H, CH(OH)CH_3).

(3*S*,4*S*)-3-chloro-4-hydroxy-3-methylpentane-2,4-dione **(*S,S*-38)** (MB2p289Hf2)

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.18 (dq, *J* = 6.6 and 6.6 Hz, 1H, C*H*OH), 2.41 (s, 3H, COCH_3), 2.38 (d, *J* = 7.0 Hz, 1H, O*H*), 1.61 (s, 3H, C(Cl)CH_3) and 1.26 (d, *J* = 6.3 Hz, 3H, CH(OH)CH_3).

GCMS (MB3p45F, 5022014): t_r = 4.71 min; *m/z* 106 (M^+–C(O)CH_3, 100), 90 (70), 71 (85) and 55 (50).

Ethyl 4-methyl-3,5-dioxohexanoate (40)



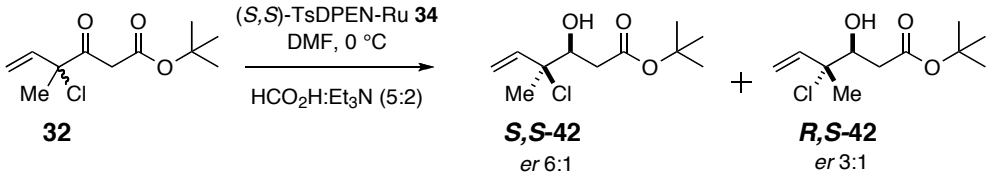
DIPA (876 μL, 6.2 mmol) was dissolved in THF (500 μL) and cooled to –78 °C. The solution was charged with n-butyllithium (274 μL, 6 mmol) and stirred for 15 min. 3-Methyl-2,4-pentanedione (228 μL, 2 mmol) was added and stirred while warming to rt for 4 h. The reaction is cooled back down to –78 °C and diethyl carbonate (254 μL, 2.1 mmol) was added. The mixture stirred and warmed to rt over 14 h and then was partitioned between 10% HCl aqueous solution (40 mL) and EtOAc. Extraction with EtOAc (2x), followed by washing the organic layer with H_2O, brine, drying over Na_2SO_4 and concentrating under reduced pressure gave 380 mg of crude oil. Purification of 100 mg of crude product by MPLC (6:1 Hex:EtOAc) yielded 60 mg of **40** (known[55] but no reported data) in a keto:enol ratio of 1:1.

MB3p16Gf6-8

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21 (q, J = 7.1 Hz, 2H, $OCH_2CH_{3\_keto}$), 4.19 (q, J = 7.1 Hz, 2H, $OCH_2CH_{3\_enol}$), 3.88 (q, J = 7.1 Hz, 1H, $CHCH_{3\_keto}$), 3.55 (d, J = 16.0 Hz, 1H, $C(O)CH_aHC(O)_{\_enol}$), 3.51 (d, J = 16.0 Hz, 1H, $C(O)CHH_bC(O)_{\_enol}$), 3.33 (s, 2H, $C(O)CH_2C(O)_{\_keto}$), 2.23 (s, 3H, $C(O)CH_{3\_keto}$), 2.16 (s, 3H, $C(O)CH_{3\_enol}$), 1.85 (s, 3H, $C{=}CCH_{3\_enol}$), 1.36 (d, J = 7.1 Hz, 3H, $CHCH_{3\_keto}$), 1.29 (t, J = 7.1 Hz, 3H, $CH_2CH_{3\_keto}$) and 1.29 (t, J = 7.1 Hz, 3H, $CH_2CH_{3\_enol}$).

[55] "A Convenient Synthesis of Alkylated 4-Hydroxy-2pyrones," Suzuki, E.; Sekizaki, H.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1973**, 568-568.

(3*S*)-*tert*-Butyl 4-chloro-3-hydroxy-4-methylhex-5-enoate (42)



Diketone **32** (170 mg, 0.73 mmol) was dissolved in DMF (500 μL) in a culture tube. A DMF (500 μL) solution of (*S,S*)-TsDPEN-Ru(II) complex (3 mg) was added. In a vial cooled to 0 °C, Et_3N (280 μL, 2 mmol) and HCO_2H (190 μL, 5 mmol) are combined and added to the reaction tube. Once complete, the reaction was partitioned between Et_2O (20 mL) and H_2O (10 mL). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by MPLC (19:1 Hex:EtOAc) to give two diastereomers ***S,S*-42** and ***R,S*-42**.

(3*S*,4*S*)-*tert*-butyl 4-chloro-3-hydroxy-4-methylhex-5-enoate **(*S,S*-42)** (MB2p265If7-8) (*er* 6:1 by Mosher ester analysis, Figure I-8)

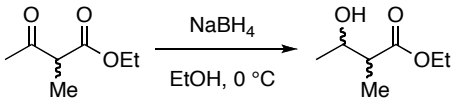
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.05 (dd, *J* = 17.1 and 10.7 Hz, 1H, H_2C=C*H*), 5.42 (d, *J* = 17.1, 1H, CH=CH_{trans}H), 5.26 (d, *J* = 10.7, 1H, CH=CHH_{cis}), 4.12 (ddd, *J* = 10.1, 3.8 and 2.5 Hz, 1H, C*H*OH), 3.18 (d, *J* = 3.9 Hz, 1H, O*H*), 2.61 (dd, *J* = 16.3 and 2.5 Hz, 1H, CH_aHC(O)O), 2.37 (dd, *J* = 16.2 and 10.1 Hz, 1H, CHH_bC(O)O), 1.68 (s, 3H, C(Cl)CH_3) and 1.47 (s, 9H, C(CH_3)$_3$).

(3*S*,4*R*)-*tert*-butyl 4-chloro-3-hydroxy-4-methylhex-5-enoate **(*S,S*-42)** (MB2p265If12-15) (*er* 3:1 by Mosher ester analysis, Figure I-8)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02 (dd, *J* = 17.1 and 10.7 Hz, 1H, H_2C=C*H*C), 5.42 (d, *J* = 17.1, 1H, CH=CH_{trans}H), 5.25 (d, *J* = 10.7, 1H, CH=CHH_{cis}), 4.06 (ddd, *J* = 10.0, 4.8

and 2.6 Hz, 1H, C*H*OH), 3.06 (d, *J* = 4.8 Hz, 1H, O*H*), 2.62 (dd, *J* = 16.2 and 2.6 Hz, 1H, CH_aHC(O)O), 2.42 (dd, *J* = 16.2 and 9.9 Hz, 1H, CHH_bC(O)O), 1.69 (s, 3H, C(Cl)CH_3) and 1.47 (s, 9H, C(CH_3)$_3$).

Ethyl 3-hydroxy-2-methylbutanoate (33)



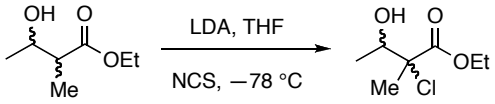
27 **33**

Sodium borohydride (131 mg, 3.5 mmol) was added to a cooled (0 °C) solution of β-keto ester **27** (1 g, 6.9 mmol) in EtOH (35 mL). The reaction was monitored by TLC. After 5 min, saturated aqueous NH_4Cl was added to quench the reaction, followed by extraction with CH_2Cl_2 (3x). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give 795 mg (80% crude yield) of **33**, which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): Matched literature data.[56]

TLC: R_f = 0.3; 6:1 Hex:EtOAc.

Ethyl 2-chloro-3-hydroxy-2-methylbutanoate (29)



33 **29**
dr 1:1

β-Hydroxy ester **33** (100 mg, 0.7 mmol) in THF (1 mL) was added to a mixture of DIPA (213 μL, 1.5 mmol) and ^{n}BuLi (756 μL, 1.43 mmol) in THF (6 mL) at –78 °C. The reaction was charged with NCS (96 mg, 0.7 mmol) in THF (1 mL) and left to stir at

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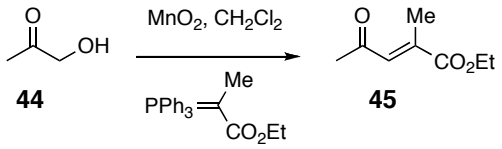
[56] "Asymmetric Reduction of Ethyl 2-methyl 3-oxobutanoate by *Chlorella*," Kuramoto, T.; Iwamoto, K.; Izumi, M.; Kirihata, M.; Yoshizako, F. *Biosci., Biotechnol., Biochem.* **1999**, *63*, 598-601.

–78 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3x). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give **29** (25% conversion by ^{1}H NMR) as a *syn*/*anti* mixture (1:1).

^{1}H NMR (500 MHz, $CDCl_3$): Matched data reported above (p 59).

(*E*)-Ethyl 2-methyl-4-oxopent-2-enoate (45)



44 **45**

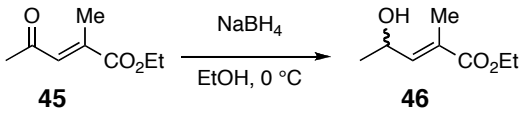
A mixture of hydroxy acetone (**44**) (100 mg, 1.35 mmol), Wittig reagent (587 mg, 1.62 mmol) and MnO_2 (1.33 g, 13.5 mmol) in CH_2Cl_2 (45 mL) was stirred at rt for 30 min. The mixture was filtered through celite, concentrated under reduced pressure and purified by MPLC (9:1 Hex:EtOAc) to give **45** (85 mg, 41% yield).

MB3p94

^{1}H NMR (500 MHz, $CDCl_3$): Matched literature data.[57]

GCMS: MB3p96G

(*E*)-Ethyl 4-hydroxy-2-methylpent-2-enoate (46)



45 **46**

A solution of enone **45** (80 mg, 0.5 mmol) in EtOH (2 mL) was cooled to 0 °C. Sodium borohydride (10 mg, 0.3 mmol) was added and the reaction stirred for 5 min before quenching with saturated aqueous NH_4Cl. The mixture was extracted with

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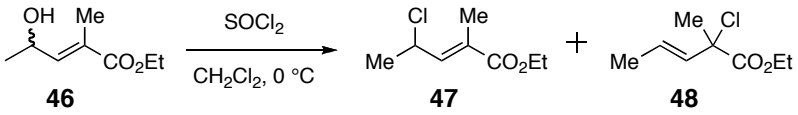
[57] "Highly Enantioselective Transfer Hydrogenation of α,β-Unsaturated Ketones," Martin, N. J. A.; List B. *J. Am. Chem. Soc.* **2006**, *128*, 13368-13369.

CH_2Cl_2 (3x), dried over Na_2SO_4 and concentrated under reduced pressure to yield 55 mg (68% yield) of alcohol **46**.

^{1}H NMR (500 MHz, $CDCl_3$, MB3p98E): δ 6.69 (dq, *J* = 8.3 and 1.4 Hz, 1H, C=C*H*), 4.68 (dqd, *J* = 8.2, 6.4 and 3.8 Hz, 1H, C(OH)*H*), 4.21 (dq, *J* = 10.8 and 7.1 Hz, 1H, OCH$H_a$$CH_3$), 4.19 (dq, *J* = 10.8 and 7.1 Hz, 1H, OCH$H_b$$CH_3$), 1.88 (d, *J* = 1.4 Hz, 3H, C=CCH_3), 1.59 (br d, *J* = 3.6 Hz, 1H, O*H*), 1.32 (d, *J* = 6.4 Hz, 3H, CH(OH)CH_3) and 1.31 (t, *J* = 7.1 Hz, 3H, CH_2CH_3).

(*E*)-Ethyl 2-chloro-2-methylpent-3-enoate (48)



Thionyl chloride (30 μL, 0.4 mmol) was added dropwise to a stirred solution of ester **46** (55 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 3 h, the reaction was concentrated under reduced pressure to give 52 mg of crude oil containing **47** and **48**. Purification by MPLC (19:1 Hex:EtOAc) yielded desired ester **48** (more polar), followed by elution of ester **47**.

^{1}H NMR (500 MHz, $CDCl_3$, MB3p103Ef3): δ 5.90-5.81 (m, 2H, H_3CC*H*=C*H*), 4.25 (dq, *J* = 10.9 and 7.1 Hz, 1H, OC$H_a$$HCH_3$), 4.23 (dq, *J* = 10.8 and 7.1 Hz, 1H, OCH$H_b$$CH_3$), 1.86 (s, 3H, C(Cl)C$H_3$), 1.71 (d, *J* = 4.8 Hz, 3H, C=CHCH_3) and 1.32 (t, *J* = 7.1 Hz, 3H, CH_2CH_3).

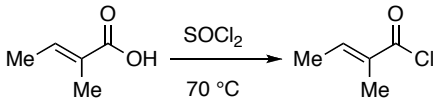
(*E*)-ethyl 4-chloro-2-methylpent-2-enoate **(47)** (MB3p103Ef6)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 (dq, *J* = 9.9 and 1.5 Hz, 1H, C=C*H*), 4.81 (dq, *J* = 10 and 6.6 Hz, 1H, H_3C(Cl)C*H*), 4.23 (q, *J* = 7.1 Hz, 2H, OC$H_2$$CH_3$), 1.91 (d, *J* = 1.5 Hz,

3H, CH=CC*H*$_3$), 1.63 (d, *J* = 6.6 Hz, 3H, CH(Cl)C*H*$_3$) and 1.31 (t, *J* = 7.1 Hz, 3H, CH_2CH_3).

GCMS (MB3p103Ef6, 5022014): t_r = 6.29 min; *m/z* 176 (M^+, 30), 141 (M^+–Cl, 50), 131 (M^+–OEt, 45) and 113 (100).

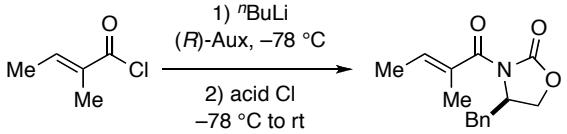
(*E*)-2-Methylbut-2-enoyl chloride (52)



51 ***52***

Thionyl chloride (1.09 mL, 15 mmol) was added to (neat) tiglic acid (**51**) (1 g, 10 mmol) and heated to 70 °C for 14 h. The reaction was concentrated under reduced pressure to give 850 mg (73% yield) of tigaloyl chloride (**52**, known and commercially available), which was used without further purification.

(2*E*,4*R*)-4-benzyl-3-(2-methylbut-2-enoyl)oxazolidin-2-one (*R*-49)



52 ***R*-49**

To a solution of (*R*)-4-benzyl-1,3-oxazolidin-2-one (738 mg, 4.17 mmol) in THF (15 mL) at –78 °C was added *n*-butyllithium (2.32 mL, 4.17 mmol). After 15 min, acid chloride **52** (541 mg, 4.58 mmol) was added. The mixture was stirred at –78 °C for 30 min and then at 0 °C for 15 min before quenching with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (3x) and the organic layers were washed with saturated aqueous $NaHCO_3$ (2x) and brine (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude *N*-acyl oxazolidinone (1.06 g,

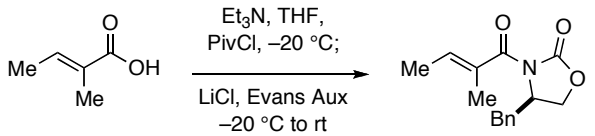
89% crude yield), which was recrystallized from hexanes to give known (but no reported data)[58] ***R*-49**.

^{1}H NMR (500 MHz, $CDCl_3$, MB3p137B): δ 7.35–7.31 (m, 2H, Ar-H_{meta}), 7.30–7.27 (m, 1H, Ar-H_{para}), 7.22–7.18 (m, 2H, Ar-H_{ortho}), 6.21 (qq, J = 6.9 and 1.4 Hz, 1H, C=C*H*), 4.71 (dddd, J = 9.1, 8.1, 5.5 and 3.5 Hz, 1H, $PhCH_2CH$), 4.24 (dd, J = 8.8 and 8.1 Hz, 1H, $PhCH_aH$), 4.15 (dd, J = 9.0 and 5.5 Hz, 1H, $PhCHH_b$), 3.35 (dd, J = 13.5 and 3.5 Hz, 1H, C(O)OCH_aH), 2.81 (dd, J = 13.5 and 9.3 Hz, 1H, C(O)OCHH_b), 1.91 (dq, J = 1.3 and 1.3 Hz, 3H, CH=CCH_3) and 1.82 (dq, J = 7.0 and 1.2 Hz, 3H, C=CHCH_3).

GCMS (MB3p112F, 5022014): t_r = 12.40 min; *m/z* 259 (M^+, 15), 244 (M^+–CH_3, 30) and 83 (100).

HPLC-MS (MB3p112G, Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 277.3 $(M+NH_4)^+$; t_r = 9.72 min.

(2*E*,4*R*)-4-benzyl-3-(2-methylbut-2-enoyl)oxazolidin-2-one (*R*-49)



51 ***R*-49**

To the solution of tiglic acid (**51**) (1 g, 10 mmol) and Et_3N (3.48 mL, 25 mmol) in THF (60 mL) was added pivaloyl chloride (1.48 mL, 12 mmol) at –20 °C. A white solid formed and mixing was continued at –20 °C for 1 h. The reaction was charged with LiCl (466 mg, 11 mmol) and (*R*)-4-benzyl-1,3-oxazolidin-2-one (1.42 g, 8 mmol) and allowed to warm to rt while stirring for 14 h. Addition of 0.2 M HCl (50 mL) quenched the reaction, followed by extraction with EtOAc (3x). The organic layer was washed with

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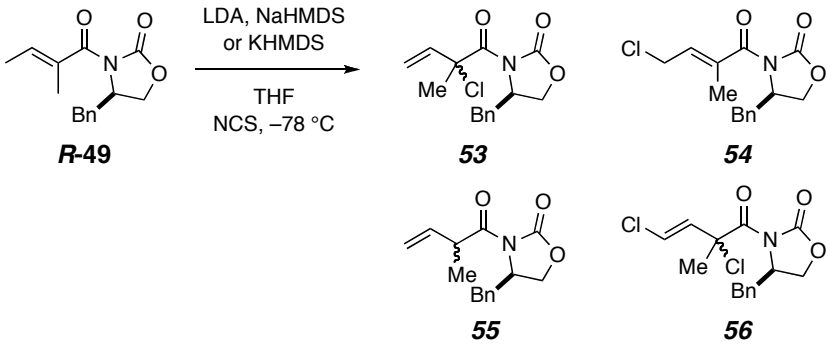
[58] "Synthesis and biological activity of enantiomeric pairs of 5-vinylthiolactomycin congeners," Ohata, K.; Terashima, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4070-4074.

0.2 M HCl, saturated aqueous $NaHCO_3$, and brine. The solution was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield crude product, which was recrystallized with hexanes to give ***R*-49** (1.5 g, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$): Matched above data.

(*R*)-4-benzyl-3-(2-chloro-2-methylbut-3-enoyl)oxazolidin-2-one (53)



R*-49** ***53 ***54*** ***55*** ***56***

LDA and NCS

A solution of DIPA (323 mL, 2.42 mmol) in THF (1.5 mL), was charged with *n*-butyllithium (926 mL, 2.31 mmol) at 0 °C and stirred for 15 min. After cooling to –78 °C, the reaction was treated with chiral imide ***R*-49** (300 mg, 1.15 mmol) in THF (8 mL). After 90 min, NCS (309 mg, 2.31 mmol) was added and stirring was continued for an additional 30 min at –78 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 330 mg of crude product containing **53**, **54**, **55**, and **56** in a 24:15:4:1 ratio (at 80% conversion). The compounds were separated by MPLC (6:1 Hex:EtOAc) eluting off in the following order: **53** (diastereomer 1) **56** (diastereomer 1), **53** (diastereomer 2), **56** (diastereomer 2), **55**, and remaining **49**. Primary chloride **54** was not isolated.

KHMDS and NCS

A solution of chiral imide ***R*-49** (100 mg, 0.4 mmol) in THF (3 mL) was charged with (0.5 M in toluene) KHMDS (1.54 mL, 0.77 mmol) at –78 °C and stirred for 90 min. NCS (103 mg, 0.77 mmol) in THF (1.2 mL) was added and stirred for another 30 min. Workup and product isolation was the same as described above for the LDA/NCS reaction, which gave 110 mg of crude product containing **53**, **54**, and **56** in 5:1:1 ratio.

NaHMDS and NCS

A solution of chiral imide ***R*-49** (100 mg, 0.4 mmol) in THF (3 mL) was charged with (0.84 M in THF) NaHMDS (917 μL, 0.77 mmol) at –78 °C and stirred for 90 min. NCS (103 mg, 0.77 mmol) in THF (1.2 mL) was added and stirred for another 30 min. Workup and product isolation was the same as described above for the LDA/NCS reaction, which gave 50 mg crude product containing **53** and **56** in 2:1 ratio.

(*R*)-4-benzyl-3-((*R*)-2-chloro-2-methylbut-3-enoyl)oxazolidin-2-one **(53)** (MB5p48Hf11-16) (less polar diastereomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.32 (m, 2H, Ar-H_{meta}), 7.31–7.27 (m, 1H, Ar-H_{para}), 7.24–7.21 (m, 2H, Ar-H_{ortho}), 6.54 (dd, J = 17.5 and 10.8 Hz, 1H, H_2C=CH), 5.27 (d, J = 10.8 Hz, 1H, C=CHH_{cis}), 5.24 (d, J = 17.5 Hz, 1H, C=CHH_{trans}), 4.70 (dddd, J = 9.8, 7.4, 3.4 and 2.2 Hz, 1H, $PhCH_2C$$H$), 4.25 (ddd, J = 9.0, 7.4 and 0.9 Hz, 1H, PhCHH_a), 4.17 (dd, J = 9.1 and 2.2 Hz, 1H, PhCHH_b), 3.30 (dd, J = 13.3 and 3.3 Hz, 1H, C(O)OCHH_a), 2.79 (dd, J = 13.3 and 9.8 Hz, 1H, C(O)OCHH_b) and 2.00 (s, 3H, ClCCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 150.9, 139.2, 135.3, 129.7 (2), 129.2 (2), 127.7, 115.8, 68.6, 66.3, 57.7, 37.7 and 29.7.

$[\alpha]^{25}_D = -17$ (*c* 0.00346 g/mL, $CHCl_3$).

HPLC-MS (MB3p113Hf6, Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 311.0 $(M+NH_4)^+$; t_r = 11.13 min.

(4*R*)-4-benzyl-3-((*S*)-2-chloro-2-methylbut-3-enoyl)oxazolidin-2-one **(53)** (MB5p48Hf17-25) (more polar diastereomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.32 (m, 2H, Ar-H_{meta}), 7.31–7.28 (m, 1H, Ar-H_{para}), 7.25–7.22 (m, 2H, Ar-H_{ortho}), 6.45 (dd, *J* = 17.5 and 10.8 Hz, 1H, H_2C=C*H*), 5.24 (d, *J* = 17.4 Hz, 1H, C=CHH_{trans}), 5.23 (d, *J* = 10.8 Hz, 1H, C=CHH_{cis}), 4.73 (dddd, *J* = 9.8, 7.2, 3.3 and 3.3 Hz, 1H, $PhCH_2$C*H*), 4.23 (dd, *J* = 9.0 and 7.6 Hz, 1H, PhCHH_a), 4.18 (dd, *J* = 9.1 and 2.9 Hz, 1H, PhCHH_b), 3.28 (dd, *J* = 13.4 and 3.5 Hz, 1H, C(O)OCHH_a), 2.81 (dd, *J* = 13.4 and 9.6 Hz, 1H, C(O)OCHH_b) and 2.01 (s, 3H, ClCCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 150.9, 139.3, 135.2, 129.7 (2), 129.2 (2), 127.6, 115.4, 68.5, 66.3, 57.4, 37.6 and 29.4.

$[\alpha]^{25}_D = -60$ (*c* 0.00438 g/mL, $CHCl_3$).

HPLC-MS (MB3p113H2p10, Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 311.0 $(M+NH_4)^+$; t_r = 11.16 min.

(2*E*,4R)-4-benzyl-3-(4-chloro-2-methylbut-2-enoyl)oxazolidin-2-one (**54**) (MB3p117G)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.06 (tq, *J* = 7.7 and 1.4 Hz, 1H, C=C*H*).[59]

(4*R*)-4-benzyl-3-(2-methylbut-3-enoyl)oxazolidin-2-one **(55)** (MB3p131Gf17-20)

^{1}H NMR (500 MHz, $CDCl_3$): Matched reported data.[60]

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[59] This is the only distinguishable peak in the crude NMR and used it to obtain ratios of the products from the ^{1}H NMR of the crude reaction mixture. We were not able to isolate this product.

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 277.0 $(M+NH_4)^+$; t_r = 10.81 min.

(3*E*,4R)-4-benzyl-3-(2,4-dichloro-3-methylbut-2-enoyl)oxazolidin-2-one **(56)** (MB3p116Gf9) (less polar diastereomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.33 (m, 2H, Ar-H_{meta}), 7.31–7.29 (m, 1H, Ar-H_{para}), 7.22–7.19 (m, 2H, Ar-H_{ortho}), 6.71 (d, *J* = 13.6 Hz, 1H, C=C(Cl)*H*), 6.36 (d, *J* = 13.5 Hz, 1H, ClCH=C*H*), 4.70 (dddd, *J* = 9.8, 7.4, 3.3 and 2.3 Hz, 1H, $PhCH_2CH$), 4.29 (br dd, *J* = 9.0 and 7.1 Hz, 1H, PhCHH_a), 4.21 (dd, *J* = 9.0 and 2.4 Hz, 1H, PhCHH_b), 3.25 (dd, *J* = 13.5 and 3.3 Hz, 1H, C(O)OCHH_a), 2.85 (dd, *J* = 13.4 and 9.4 Hz, 1H, C(O)OCHH_b) and 2.03 (s, 3H, C(Cl)CH_3).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 345.0 $(M+NH_4)^+$; t_r = 11.53 min.

(3*E*,4R)-4-benzyl-3-(2,4-dichloro-3-methylbut-2-enoyl)oxazolidin-2-one **(56)** (MB3p116Gf12) (more polar diastereomer, as a 1:2 mixture with ***S,R*-53**)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.32 (m, 2H, Ar-H_{meta}), 7.31–7.27 (m, 1H, Ar-H_{para}), 7.24–7.19 (m, 2H, Ar-H_{ortho}), 6.58 (d, *J* = 13.5 Hz, 1H, C=C(Cl)*H*), 6.37 (d, *J* = 13.5 Hz, 1H, ClCH=C*H*), 4.74–4.70 (m, 1H, $PhCH_2CH$), 4.27 (br dd, *J* = 9.2 and 7.3 Hz, 1H, PhCHH_a), 4.21 (dd, *J* = 9.0 and 3.0 Hz, 1H, PhCHH_b), 3.26 (dd, *J* = 13.3 and 3.4 Hz, 1H, C(O)OCHH_a), 2.83 (dd, *J* = 13.4 and 9.6 Hz, 1H, C(O)OCHH_b) and 2.05 (s, 3H, ClCCH_3).

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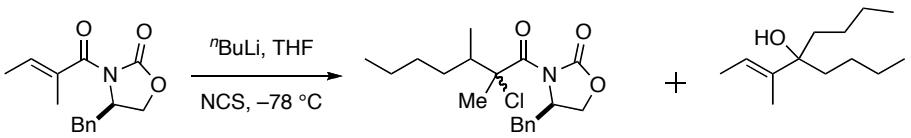
[60] "Synthesis of Novel Enantiopure Fluorinated Building Blocks from Acyclic Chiral Allylsilanes," Tredwell, M.; Tenza, K.; Pacheco, M. C.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 4495-4497.

(*R*)-4-benzyl-3-(2-chloro-2,3-dimethylheptanoyl)oxazolidin-2-one (57)



***R*-49** **57** *dr* 2:1 **58**

A solution of chiral imide ***R*-49** (100 mg, 0.4 mmol) in THF (3 mL) was charged with (2.5 M in hexanes) *n*-butyllithium (308 μL, 0.77 mmol) at –78 °C and stirred for 90 min. NCS (103 mg, 0.77 mmol) in THF (1.2 mL) was added and stirred for another 30 min. Workup and product isolation was the same as described above for the LDA/NCS reaction, which gave 129 mg crude product containing **57** and **58** in similar amounts.

(*R*)-4-benzyl-3-(2-chloro-2,3-dimethylheptanoyl)oxazolidin-2-one **(57)** (MB3p115G2f6) (less polar diastereomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.32 (m, 2H, Ar-H_{meta}), 7.31–7.28 (m, 1H, Ar-H_{para}), 7.26–7.23 (m, 2H, Ar-H_{ortho}), 4.70 (dddd, J = 10.5, 7.3, 3.3 and 2.4 Hz, 1H, $PhCH_2CH$), 4.22 (ddd, J = 9.0, 7.2 and 0.9 Hz, 1H, C(O)OCH_aH_b), 4.15 (dd, J = 9.0 and 2.4 Hz, 1H, C(O)OCH_aH_b), 3.35 (dd, J = 13.2 and 3.4 Hz, 1H, PhCH_aH_b), 3.15 (dqd, J = 9.2, 6.8 and 2.3 Hz, 1H, H_3CCH), 2.73 (dd, J = 13.2 and 10.4 Hz, 1H, PhCH_aH_b), 1.78 (s, 3H, C(Cl)CH_3), 1.45–1.11 (m, 6H, $H_3C(CH_2)_3C$), 0.95 (d, J = 6.8 Hz, 3H, $CHCH_3$) and 0.92 (t, J = 7.0 Hz, 3H, CH_2CH_3).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 369.3 $(M+NH_4)^+$; t_r = 13.72 min.

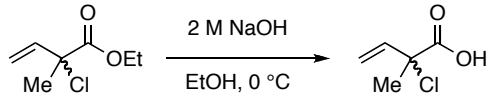
(*R*)-4-benzyl-3-(2-chloro-2,3-dimethylheptanoyl)oxazolidin-2-one **(57)**

(MB3p115Gf7) (more polar diastereomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.32 (m, 2H, Ar-H_{meta}), 7.30–7.27 (m, 1H, Ar-H_{para}), 7.26–7.24 (m, 2H, Ar-H_{ortho}), 4.75 (dddd, *J* = 10.1, 7.3, 3.4 and 2.9 Hz, 1H, $PhCH_2CH$), 4.21 (ddd, *J* = 9.1, 7.3 and 0.9 Hz, 1H, C(O)OCH_aH_b), 4.17 (dd, *J* = 9.0 and 2.9 Hz, 1H, C(O)OCH_aH_b), 3.34 (dd, *J* = 13.4 and 3.6 Hz, 1H, PhCH_aH_b), 3.04–2.99 (m, 1H, H_3CCH), 2.75 (dd, *J* = 13.3 and 10.1 Hz, 1H, PhCH_aH_b), 1.86 (s, 3H, C(Cl)CH_3), 1.41–1.20 (m, 6H, $H_3C(CH_2)_3C$), 1.07 (d, *J* = 6.6 Hz, 3H, $CHCH_3$) and 0.89 (t, *J* = 7.0 Hz, 3H, CH_2CH_3).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 369.3 $(M+NH_4)^+$; t_r = 13.60 min.

2-Chloro-2-methylbut-3-enoic acid (59)



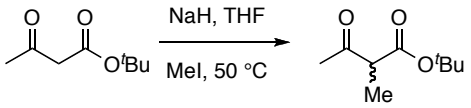
31 **59**

Ethyl ester **31** (465 mg, 2.86 mmol) was dissolved in EtOH (40 mL) at 0 °C. Freshly prepared 2 M NaOH (1.43 mL, 2.86 mmol) was added. The reaction was stirred while monitoring progress by GCMS. After addition of 1 M HCl, the EtOH was removed under reduced pressure and the product was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give acid **59** (140 mg, 30% yield).

MB3p144G

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.21 (dd, *J* = 17.1 and 10.6 Hz, 1H, H_2C=C*H*), 5.51 (d, *J* = 17.0 Hz, 1H, CH=CHH_{trans}), 5.34 (d, *J* = 10.6 Hz, 1H, CH=CHH_{cis}) and 1.90 (s, 3H, C(Cl)CH_3).

***tert*-Butyl-2-methyl-3-oxobutanoate (61)**



25 **61**

tert-Butyl acetoacetate (**25**, 18.3 g, 116 mmol) was dissolved in THF (115 mL). The solution was charged with sodium hydride, 60% dispersion in oil, (5.1 g, 127 mmol) in portions, followed by stirring for 15 min. After addition of iodomethane (7.94 mL, 127 mmol), the reaction was heated to 50 °C for 15 h. The reaction was quenched with DI H_2O and the THF was removed by concentration under reduced pressure. The solution was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give known compound **61** as an oil (17.3 g, 87% yield), which was used without purification.

^{1}H NMR (500 MHz, $CDCl_3$, MB5p34): Matched literature data.[61]

GCMS: MB3p56F

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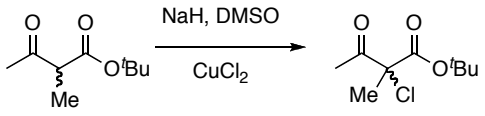
[61] "Studies on the Nactins: Total Synthesis of (+/–)-*tert*-Butyl 8-*O*-(*tert*-Butyldimethylsilyl)nonactate," Barrett, A. G.; Sheth, H. G. *J. Org. Chem.* **1983**, *48*, 5017–5022.

***tert*-Butyl-2-chloro-2-methyl-3-oxobutanoate (62)**

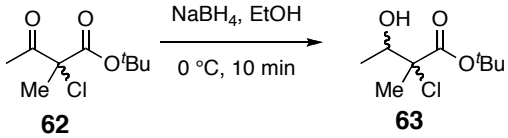


Sodium hydride, 60% dispersion, (4.4 g, 110 mmol) was massed in a flask and washed with hexanes (2x50 mL) prior to addition of DMSO (480 mL). β-Keto ester **61** (17.2 g, 100 mmol) in DMSO (20 mL) was added dropwise via syringe and stirred at rt for 1h before charging with $CuCl_2$ (33.6 g, 250 mmol). After 14 h, the reaction was quenched with 1 M HCl (200 mL) and extracted with Et_2O (3x). The combined organic layers were washed with 1 M HCl and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give known **62** as an oil (16 g, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$, MB3p160F): Matched literature data.[62]

GCMS: MB3p57F

***tert*-Butyl-2-chloro-3-hydroxy-2-methylbutanoate (63)**



β-Keto ester **62** (16.8 g, 81.5 mmol) was dissolved in absolute ethanol (270 mL) and cooled to 0 °C. Sodium borohydride (1.54 g, 40.7 mmol) was added in portions. After 10 min, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and

[62] "Umpolung of halide reactivity: efficient (diacetoxyiodo)benzene-mediated electrophilic α-halogenation of 1,3-dicarbonyl compounds," Akula, R.; Galligan, M.; Ibrahim, H. *Chem. Commun.* **2009**, 6991–6993.

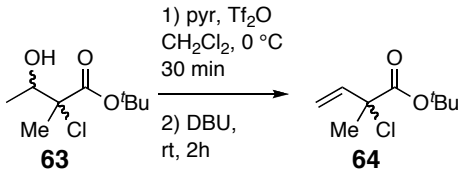
concentrated under reduced pressure to provide (4 stereoisomers of) alcohol **63** (13.5 g, 80%) in a *dr* of 1.6:1.

^{1}H NMR (500 MHz, $CDCl_3$, MB3p255E): δ 4.16 (dq, *J* = 6.4 and 6.4 Hz, 1.5H, HOC*H*$_{\_diast1/diast2}$), 2.56 (d, *J* = 6.1 Hz, 1H, CHO*H*$_{\_diast1}$), 2.45 (d *J* = 7.1 Hz, 0.5H, CHO*H*$_{\_diast2}$), 1.71 (s, 1.5H, CClC*H*$_{3\_diast2}$), 1.65 (s, 3H, CClC*H*$_{3\_diast1}$), 1.50 (s, 13H, C(C*H*$_{3\_diast1/diast2}$), 1.29 (d, *J* = 6.4 Hz, 1.5H, CH(OH)C*H*$_{3\_diast2}$) and 1.24 (d, *J* = 6.4 Hz, 3H, CH(OH)C*H*$_{3\_diast1}$).

GCMS (MB3p58E, 5022014): t_r = 6.19 and 6.24 min; *m/z* 193 (M^+–Me, 5), 173 (M^+–$O(CH_3)_3$, 5), 108 (15) and 57 (100).

R_f = 0.3; 6:1 Hex:EtOAc.

***tert*-Butyl-2-chloro-2-methylbut-3-enoate (64)**



The stereoisomeric mixture of alcohol **63** (8.5 g, 40.7 mmol) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. Pyridine (8.2 mL, 102 mmol) and trifluoromethanesulfonic anhydride (8.56 mL, 50.9 mmol) were added and the solution stirred at 0 °C for 30 min. The reaction was charged with DBU (24.3 mL, 163 mmol) and warmed to rt over 2h. Addition of 1 M HCl quenched the reaction followed by extraction with CH_2Cl_2 (2x50 mL). The combined organic layers were washed with 1 M HCl, H_2O, saturated aqueous $NaHCO_3$ and brine, followed by drying over Na_2SO_4, filtering, and concentrating under reduced pressure to give the crude allylic alcohol.

Purification by flash chromatography (9:1 Hex:EtOAc) provided allylic chloride **64** (7 g, 90%).

^{1}H NMR (500 MHz, $CDCl_3$, MB3p334Ef4-6): δ 6.18 (dd, *J* = 17.1 and 10.6 Hz, 1H, H_2C=C*H*), 5.41 (d, *J* = 17.1 Hz, 1H, CH=CHH_{trans}), 5.24 (d, *J* = 10.6 Hz, 1H, CH=CHH_{cis}), 1.82 (s, 3H, C(Cl)CH_3) and 1.49 (s, 9H, C(CH_3)$_3$).

GCMS (MB3p60E, 5022014): t_r = 5.12 min; *m/z* 175 (M^+–Me, 5), 89 (M^+–C(O)O$(CH_3)_3$, 25) and 57 (100).

R_f = 0.4; 9:1 Hex:EtOAc.

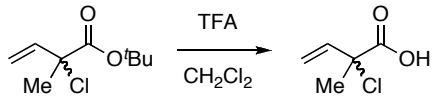
Characterization of the crude triflate intermediate when isolated in 2-step procedure:

(*dr* 1.3:1)

^{1}H NMR (500 MHz, $CDCl_3$, MB3p177F2): δ 5.49 (q, *J* = 6.3 Hz, 0.7H, TfOC$H_{_diast2}$), 5.39 (q, *J* = 6.4 Hz, 1H, TfOC$H_{_diast1}$), 1.76 (s, 2.1H, CClCH_{3_diast2}), 1.71 (s, 3H, CClCH_{3_diast1}), 1.63 (d, *J* = 6.4 Hz, 2.1H, C(OTf)CH_{3_diast2}), 1.55 (d, *J* = 6.4 Hz, 3H, C(OTf)CH_{3_diast1}), 1.52$^+$ (s, 6.3H, C(CH_3)$_{3\_diast2}$) and 1.52$^-$ (s, 9H, C(CH_3)$_{3\_diast1}$).

GCMS (MB3p59G2, 5022014): t_r = 6.95 and 7.16 min; *m/z* 325 (M^+–Me, 10), 239 (M^+–C(O)O$(CH_3)_3$, 10) and 57 (100).

2-Chloro-2-methylbut-3-enoic acid (59)



64 **59**

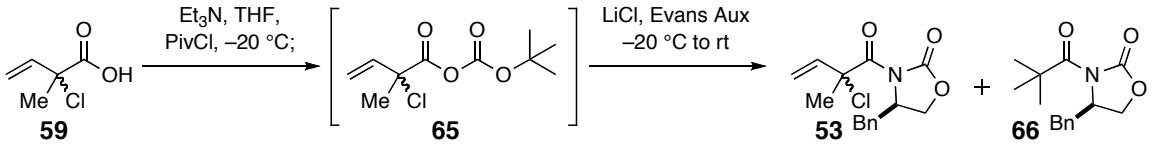
Trifluoroacetic acid (1.73 mL, 23 mmol) was added to a solution of *tert*-butyl ester **64** (1.48 g, 7.7 mmol) in CH_2Cl_2 (60 mL) and stirred at rt for 14 h. The reaction was concentrated under reduced pressure to give crude acid **59** in quantitative yield, which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$, MB3p144G): Matched above data (p 75).

GCMS (MB3p79F4, 5022014): t_r = 4.61 min; *m/z* 98 (M^+–HCl, 100), 69 (95) and 53 (10).

R_f = 0.5; 2:1 Hex:EtOAc.

(*R*)-4-Benzyl-3-(2-chloro-2-methylbut-3-enoyl)oxazolidin-2-one (53)



To the solution of acid **59** (3.1 g, 23 mmol) and triethylamine (6.18 mL, 44.3 mmol) in THF (120 mL) was added pivaloyl chloride (2.62 mL, 21.2 mmol) at 0 °C. A white solid formed immediately and stirring was continued for 1 h. The reaction was charged with lithium chloride (826 mg, 19.5 mmol) and (*R*)-4-benzyl-1,3-oxazolidin-2-one (2.51 g, 14.2 mmol), followed by warming to rt and stirring for 14 h. Addition of 0.2 M HCl quenched the reaction and THF was removed under reduced pressure. The mixture was partitioned between EtOAc and 0.2 M HCl. The organic layer was washed with 0.2 M HCl, saturated aqueous $NaHCO_3$ and brine. The EtOAc was removed under reduced pressure after drying over Na_2SO_4 and filtering. Purification by MPLC (9:1 Hex:EtOAc) provided ***R,R*-53** (1.44 g, 69%) and ***S,R*-53** (1.14 g, 55%).

***R,R*-53** and ***S,R*-53**

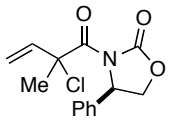
^{1}H NMR (500 MHz, $CDCl_3$): Matched above data (p 71–72).

(*R*)-4-benzyl-3-pivaloyloxazolidin-2-one **(66)**

^{1}H NMR (500 MHz, $CDCl_3$, MB3p154Hf9-10): δ 7.35–7.31 (m, 2H, Ar-H_{meta}), 7.29–7.27 (m, 1H, Ar-H_{para}), 7.24–7.21 (m, 2H, Ar-H_{ortho}), 4.70 (dddd, *J* = 9.7, 7.5, 3.0 and 3.0

Hz, 1H, $PhCH_2CH$), 4.21 (ddd, J = 8.9, 7.5 and 0.8 Hz, 1H, $PhCH_aH_b$), 4.15 (dd, J = 9.0 and 2.8 Hz, 1H, $PhCH_aH_b$), 3.24 (dd, J = 13.2 and 3.3 Hz, 1H, $C(O)OCH_aH_b$), 2.77 (dd, J = 13.3 and 9.6 Hz, 1H, $C(O)OCH_aH_b$) and 1.41 (s, 9H, $C(CH_3)_3$).

(*R*)-4-Phenyl-3-(2-chloro-2-methylbut-3-enoyl)oxazolidin-2-one



The phenyl derivatives were synthesized in the same manner as above using (*R*)-4-phenyl-1,3-oxazolidin-2-one and purified by MPLC (6:1 Hex:EtOAc).

<u>(less polar diastereomer)</u>

^{1}H NMR (300 MHz, $CDCl_3$, MB5p66S): δ 7.43–7.27 (m, 5H, Ar-*H*), 6.48 (dd, J = 17.6 and 10.8 Hz, 1H, $H_2C=CH$), 5.46 (dd, J = 8.4 and 3.4 Hz, 1H, $PhCH$), 5.20 (d, J = 10.8 Hz, 1H, $H_2C=CH_{cis}H$), 5.02 (d, J = 17.6 Hz, 1H, $H_2C=CH_{trans}H$), 4.73 (dd, J = 8.7 and 8.7 Hz, 1H, $C(O)OCH_aH_b$), 4.27 (dd, J = 8.8 and 3.4 Hz, 1H, $C(O)OCH_aH_b$) and 1.89 (s, 3H, $C(Cl)CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$, MB5p66S1): δ 169.0, 151.3, 139.4, 139.1, 129.4 (2), 129.1, 125.9 (2), 115.5, 70.1, 68.1, 59.8 and 29.8.

$[\alpha]^{25}_D$ = –56 (*c* 0.00408 g/mL, $CHCl_3$).

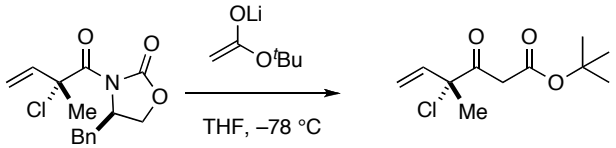
<u>(more polar diastereomer)</u>

^{1}H NMR (500 MHz, $CDCl_3$, MB5p66I): δ 7.43–7.33 (m, 5H, Ar-*H*), 6.46 (dd, J = 17.5 and 10.8 Hz, 1H, $H_2C=CH$), 5.49 (dd, J = 8.7 and 4.7 Hz, 1H, $PhCH$), 5.22 (d, J = 10.8 Hz, 1H, $H_2C=CH_{cis}H$), 5.17 (d, J = 17.5 Hz, 1H, $H_2C=CH_{trans}H$), 4.72 (dd, J = 8.8 and 8.8 Hz, 1H, $C(O)OCH_aH_b$), 4.25 (dd, J = 8.9 and 4.8 Hz, 1H, $C(O)OCH_aH_b$) and 1.88 (s, 3H, $C(Cl)CH_3$).

^{13}C NMR (125 MHz, $CDCl_3$, MB5p66I): δ 169.3, 151.3, 139.1, 138.5, 129.5 (2), 129.0, 125.8 (2), 115.6, 70.1, 68.6, 59.7 and 29.8.

$[\alpha]^{25}_D$ = –96 (*c* 0.0038 g/mL, $CHCl_3$).

(*R*)-*tert*-Butyl 4-chloro-4-methyl-3-oxohex-5-enoate (*R*-32)



***R,R*-53** ***R*-32**

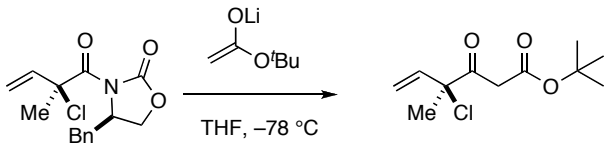
Fresh LDA was prepared by adding *n*-butyllithium (1.29 mL, 2.32 mmol) to a solution of diisopropylamine (417 μL, 3.33 mmol) in THF (2.5 mL) at 0 °C and stirring for 15 min. After cooling to –78 °C, *tert*-butyl acetate (303 μL, 2.26 mmol) was added. After 1 h, the mixture was treated with chiral imide **53** (316 mg, 1.07 mmol) in THF (1 mL) and stirring continued for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by MPLC (19:1 Hex:EtOAc) gave *tert*-butyl ester **32** (100 mg, 40%).

^{1}H NMR (500 MHz, $CDCl_3$, MB3p184Gf6-8): δ 6.00 (dd, *J* = 16.9 and 10.6 Hz, 1H, H_2C=C*H*), 5.55 (d, *J* = 16.9 Hz, 1H, CH=CHH_{trans}), 5.38 (d, *J* = 10.6 Hz, 1H, CH=CHH_{cis}), 3.70 (d, *J* = 16.1 Hz, 1H, C(O)CHH_aC(O)), 3.64 (d, *J* = 16.1 Hz, 1H, C(O)CHH_bC(O)), 1.77 (s, 3H, C(Cl)CH_3) and 1.46 (s, 9H, C(CH_3)$_3$).

$[\alpha]^{25}_D$ = +76 (*c* 0.00436 g/mL, $CHCl_3$).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc, MB2p267A): *m/z* = 250.0 $(M+NH_4)^+$; t_r = 12.31 min.

(*S*)-*tert*-Butyl 4-chloro-4-methyl-3-oxohex-5-enoate (*S*-32)



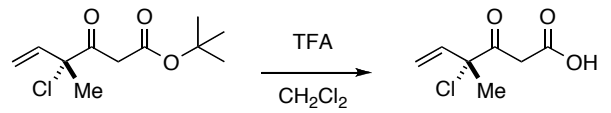
***S,R*-53** **S-32**

Following the above procedure using ***S,R*-53** (233 mg, 0.8 mmol), *tert*-butyl ester **32** (89 mg, 48%) was provided after purification by MPLC (19:1 Hex:EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$, MB3p243Gf3-7): δ 6.00 (dd, *J* = 16.9 and 10.6 Hz, 1H, H_2C=C*H*), 5.55 (d, *J* = 16.9 Hz, 1H, CH=CH_{trans}), 5.37 (d, *J* = 10.6 Hz, 1H, CH=CH_{cis}), 3.70 (d, *J* = 16.1 Hz, 1H, C(O)CH_aC(O)), 3.64 (d, *J* = 16.1 Hz, 1H, C(O)CH_bC(O)), 1.77 (s, 3H, C(Cl)CH_3) and 1.46 (s, 9H, C(CH_3)$_3$).

$[\alpha]^{25}_D$ = –77 (*c* 0.0044 g/mL, $CHCl_3$).

(*R*)-4-Chloro-4-methyl-3-oxohex-5-enoic acid (*R*-23)



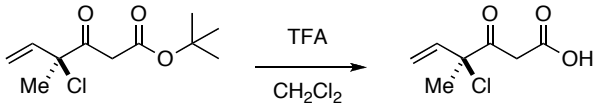
***R*-32** ***R*-23**

Trifluoroacetic acid (182 μL, 2.45 mmol) was added to a solution of *tert*-butyl ester **32** in CH_2Cl_2 (2 mL) and left to stir while monitoring by TLC. The reaction was concentrated under reduced pressure to give crude acid **23** (132 mg, 92%), which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$, MB5p13E): δ 5.99 (dd, *J* = 16.9 and 10.6 Hz, 1H, H_2C=C*H*), 5.60 (d, *J* = 16.9 Hz, 1H, CH=CH_{trans}), 5.43 (d, *J* = 10.6 Hz, 1H, CH=CH_{cis}), 3.89 (d, *J* = 16.9 Hz, 1H, C(O)CH_aC(O)), 3.79 (d, *J* = 16.9 Hz, 1H, C(O)CH_bC(O)) and 1.78 (s, 3H, C(Cl)CH_3).

R_f=0.4 (2:1 Hex:EtOAc)

(*S*)-4-Chloro-4-methyl-3-oxohex-5-enoic acid (*S*-23)

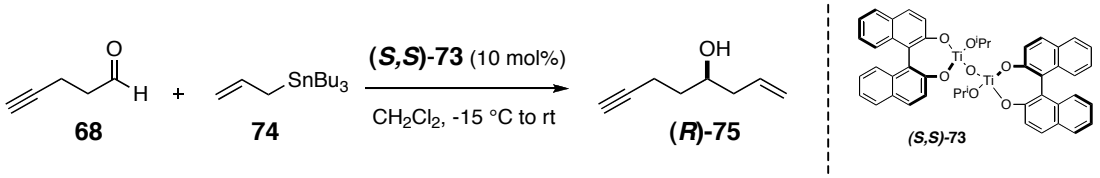


***S*-32** ***S*-23**

Following the same procedure as above using ***S*-32** (68 mg, 0.29 mmol) provided ***S*-23** (63 mg, 92%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$, MB4p28E): Matched above data of enantiomer ***R*-23**.

(*R*)-Oct-1-en-7-yn-4-ol (*R*-75)



68 **74** **(*R*)-75**

To a flask containing CH_2Cl_2 (30 mL) cooled to 0 °C was added titanium tetrachloride (165 μL, 1.5 mmol) and titanium isopropoxide (1.32 mL, 4.5 mmol). After warming to rt and stirring for 1h, silver (I) oxide (695 mg, 3.0 mmol) was added. The mixture was stirred for 5 h under exclusion of direct light. The solution was diluted with CH_2Cl_2, treated with (*S*)-binaphthol (1.72 g, 6.0 mmol) and stirred for 12 h to furnish **(*S,S*)-73** *in situ*. The catalyst solution was cooled to –15 °C and charged with aldehyde **68** (2.45 g, 30 mmol) and allyltributylstannane (11.08 mL, 36 mmol). The reaction was warmed to 0 °C and stirred for 4 h before quenching with saturated aqueous $NaHCO_3$. The combined organic layers from extraction with Et_2O (3x) were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Addition of hexanes followed by filtration removed some binaphthol impurity. Purification by MPLC (6:1 Hex:EtOAc) gave **(*R*)-75** (3.3 g, 88%, containing binaphthol and

allyltributylstannane impurities). Further purification by distillation gave pure **(*R*)-75** (720 mg, 20%).

^{1}H NMR (500 MHz, $CDCl_3$, MB2p20D or MB1p181D): δ 5.88–5.78 (m, 1H, H_2C=C*H*), 5.18–5.13 (m, 2H, C=CH_2), 3.82 (ddddd, *J* = 8, 8, 4, 4 and 4 Hz, 1H, HOC*H*), 2.36 (ddd, *J* = 7.5, 6.7 and 2.7 Hz, 2H, HC≡CCH_2), 2.34–2.29 (m, 1H, H_2C=CHCHH_a), 2.19 (dddt, *J* = 13.9, 7.9, 7.9 and 1.4 Hz, 1H, C=CHCHH_b), 1.98 (t, *J* = 2.7 Hz, 1H, C≡C*H*), 1.77 (dd, *J* = 4.1 and 2.8 Hz, 1H, CO*H*), 1.72 (dtd, *J* = 13.8, 7.6 and 3.8 Hz, 1H, HC≡CCH_2CHH_a) and 1.69–1.62 (m, 1H, HC≡CCH_2CHH_b).

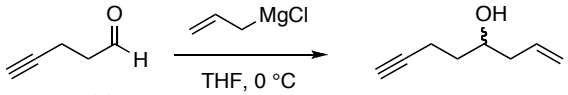
^{13}C NMR (125 MHz, $CDCl_3$): δ 134.6, 118.7, 84.3, 69.6, 68.9, 42.1, 35.3 and 15.2.

Bp: 70-75 °C at 4.3 mm Hg.

TLC: R_f = 0.5 (2:1 Hex:EtOAc).

Mosher ester analysis Figure I-10 (p 38).

Oct-1-en-7-yn-4-ol (75)



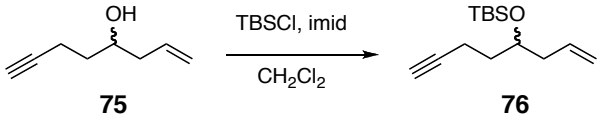
68 **75**

To a solution of aldehyde **68** (3.1 g, 37 mmol) in THF (90 mL) was added allylmagnesium chloride (2.0 M in THF, 37.3 mL, 75 mmol) at 0 °C. After 2 h, saturated aqueous NH_4Cl was added to quench the reaction followed by extraction with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give alcohol **75** (3.65 g, 80%).

^{1}H NMR (500 MHz, $CDCl_3$, MB2p58A1H and MB2p58A13C): Matched above data for (***R*-75**).

GCMS (MB3p174E, 5027016): t_r = 4.61 min; *m/z* 124 (M^+, 5), 83 (M^+–$CH_2CH{=}CH_2$, 100) and 55 (100).

***tert*-Butyldimethyl(oct-1-en-7-yn-4-yloxy)silane (76)**



A solution of *tert*-butyldimethylsilyl chloride (2.91 g, 19.3 mmol) in CH_2Cl_2 (30 mL) was treated with imidazole (2.19 g, 32 mmol) and stirred at rt for 1 h. The mixture was charged with alcohol **75** (2 g, 16.1 mmol) in CH_2Cl_2 (10 mL) and stirred for 3 h. The reaction was quenched with H_2O (40 mL) and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude ether **76** (2.86 g, 75%). Portions of the crude product were purified by distillation or MPLC (19:1 Hex:EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$, MB3p176H2 or MB2p209H): δ 5.85–5.75 (m, 1H, $H_2C{=}CH$), 5.08–5.03 (m, 2H, $CH{=}CH_2$), 3.83 (dddd, *J* = 7.6, 5.7, 5.7 and 4.4 Hz, 1H, TBSOC*H*), 2.26–2.21 (m, 4H, $HC{\equiv}CCH_2$ and $H_2C{=}CHCH_2$), 1.94 (t, *J* = 2.7 Hz, 1H, $C{\equiv}CH$), 1.71–1.58 (m, 2H, $HC{\equiv}CCH_2CH_2$), 0.89 (s, 9H, $C(CH_3)_3$), 0.07$^+$ (s, 3H, $SiCH_{3\_a}$), and 0.07$^-$ (s, 3H, $SiCH_{3\_b}$).

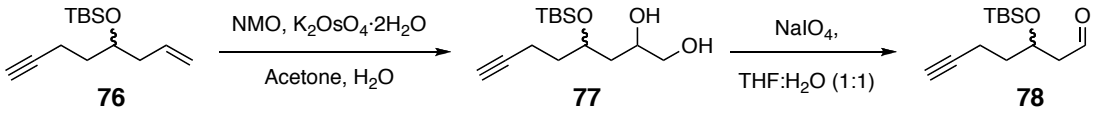
^{13}C NMR (125 MHz, $CDCl_3$, MB2p108D13C): δ 134.9, 117.3, 70.5, 68.9, 68.5, 42.1, 35.5, 26.1 (3), 14.8 and –4.5 (2).

GCMS (MB2p107G2, 5022014): t_r = 7.50 min; *m/z* 197 (M^+–$CH_2CH{=}CH_2$, 25), 181 (M^+–$C(CH_3)_3$, 25), 75 (100) and 59 (20).

TLC: R_f = 0.8 (9:1 Hex:EtOAc).

Bp: 79–92 °C at 10 Torr.

3-(*tert*-Butyldimethylsilyloxy)hept-6-ynal (78)



76 **77** **78**

Alkene **76** (2.45 g, 10.3 mmol) was dissolved in acetone and H_2O (3:1, 60 mL), followed by addition of potassium osmate dihydrate (60 mg, 0.16 mmol) and 4-methylmorpholine *N*-oxide (2.21 g, 18.9 mmol) and stirred for 14 h. The reaction was quenched by addition of 0.5 M aqueous solution of sodium thiosulfate and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude diol **77** that was used without further purification.

Crude diol **77** was dissolved in THF and H_2O (1:1, 70 mL), charged with sodium periodate (4.5 g, 21 mmol) and stirred for 1 h. The reaction was quenched by addition of H_2O and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and concentration under reduced pressure to provide aldehyde **78** (2.2 g, 90%), which was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$, MB3p163F): δ 9.82 (t, *J* = 2.5 Hz, 1H, C(O)*H*), 4.34 (dddd, *J* = 6.9, 5.5, 5.5 and 5.5 Hz, 1H, TBSOC*H*), 2.59 (ddd, *J* = 15.9, 5.5 and 2.1 Hz, 1H, HC(O)CHH_a), 2.55 (ddd, *J* = 15.9, 5.9 and 2.7 Hz, 1H, HC(O)CHH_b), 2.30–2.25 (m, 2H, HC≡CCH_2), 1.97 (t, *J* = 2.7 Hz, 1H, CH_2C≡C*H*), 1.82–1.70 (m, 2H, HC≡CCH_2CH_2), 0.88 (s, 9H, C(CH_3)$_3$), 0.11 (s, 3H, SiCH_{3_a}) and 0.08 (s, 3H, SiCH_{3_b}).

GCMS (MB3p163E, 5025015): t_r = 8.00 min; *m/z* 183 (M^+– C(CH_3)$_3$, 90), 101 (100), 75 (50) and 59 (25).

TLC: R_f = 0.5 (9:1 Hex:EtOAc).

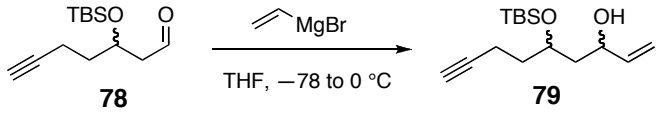
Characterization files for diol intermediate

^{1}H NMR: MB3p152Gf24-28

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc, MB3p148G): *m/z* = 273.0 $(M+H)^+$; t_r = 12.59 min.

GCMS: MB3p147H2

5-(*tert*-Butyldimethylsilyloxy)non-1-en-8-yn-3-ol (79)



78 **79**

To a solution of aldehyde **78** (2.2 g, 9.1 mmol) in THF (90 mL) cooled to –78 °C is added vinylmagnesium bromide (1 M in THF, 27 mL, 27 mmol). The mixture is warmed to 0 °C and stirred for 1 h. The reaction is quenched by addition of saturated aqueous NH_4Cl, followed by extraction with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by MPLC (9:1 Hex:EtOAc) provided allylic alcohol **79** (860 mg, 34%) in a *syn:anti* ratio of 1.7:1.

*Reaction was performed starting with *R*-**78**, *S*-**78**, and (+/–)-**78**, which all gave similar ratios (~1.7:1) of *syn*-**79** to *anti*-**79**.

***syn*-79**

^{1}H NMR (500 MHz, $CDCl_3$, MB4p248Ef10-11 or MB4p234Ef11-14): δ 5.87 (ddd, *J* = 17.2, 10.5 and 5.8 Hz, 1H, H_2C=C*H*), 5.27 (ddd, *J* = 17.2, 1.5 and 1.5 Hz, 1H, C=CHH_{trans}), 5.10 (ddd, *J* = 10.5, 1.4 and 1.4 Hz, 1H, C=CHH_{cis}), 4.31–4.26 (m, 1H, HOC*H*), 4.07 (dddd, *J* = 7.5, 5.7, 5.7 and 5.7 Hz, 1H, TBSOC*H*), 2.70 (br s, 1H, O*H*), 2.27 (dddd, *J* = 17.0, 7.3, 7.3 and 2.7 Hz, HC≡CCHH_a), 2.21 (dddd, *J* = 17.0, 7.5, 7.5 and

2.7 Hz, HC≡CCHH_b), 1.95 (dd, *J* = 2.7 and 2.7 Hz, 1H, $CH_2C{\equiv}CH$), 1.79–1.74 (m, 2H, (HO)CHCH_2), 1.72–1.62 (m, 2H, (TBSO)CHCH_2CH_2), 0.91 (s, 9H, C(CH_3)$_3$) and 0.12 (s, 6H, Si(CH_3)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$, MB4p256Hf2-3): δ 141.0, 114.5, 84.2, 71.5, 70.7, 68.8, 43.2, 36.3, 26.0 (3), 18.1, 14.3, -4.0 and -4.4.

GCMS (MB4p234Ef11-14, 5029021): t_r = 7.87 min; *m/z* 211 (M^+– $C(CH_3)_3$, 5), 157 (90) and 75 (100).

***anti*-79** (*anti:syn* 3:1)

^{1}H NMR (500 MHz, $CDCl_3$, MB4p270Hf3 or MB4p236Hf2-3): δ 5.86 (ddd, *J* = 17.2, 10.4 and 5.7 Hz, 1H, $H_2C{=}CH$), 5.26 (ddd, *J* = 17.2, 1.5 and 1.5 Hz, 1H, C=CHH_{trans}), 5.09 (ddd, *J* = 10.4, 1.4 and 1.4 Hz, 1H, C=CHH_{cis}), 4.42–4.38 (m, 1H, HOC*H*), 4.13 (dddd, *J* = 5.8, 5.8, 5.8 and 4.2 Hz, 1H, TBSOC*H*), 3.02 (br s, 1H, O*H*), 2.31–2.18 (m, 2H, HC≡CCH_2), 1.96 (dd, *J* = 2.7 and 2.7 Hz, 1H, $CH_2C{\equiv}CH$), 1.89–1.62 (m, 4H, (HO)CHCH_2 and (TBSO)CHCH_2CH_2), 0.91 (s, 9H, C(CH_3)$_3$), 0.13 (s, 3H, SiCH_{3_a}) and 0.12 (s, 3H, SiCH_{3_b}).

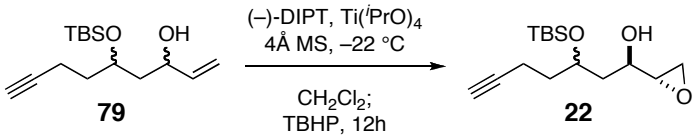
^{13}C NMR (125 MHz, $CDCl_3$, MB4p270Hf3): δ 141.2, 114.4, 84.1, 69.9, 69.7, 69.0, 42.2, 35.2, 26.0 (3), 18.2, 14.9, -4.4^+ and -4.4^-.

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc, MB3p191f6-8): *m/z* = 269.0 $(M+H)^+$; t_r = 13.50 min.

TLC: R_f = 0.2 (9:1 Hex:EtOAc).

IR: MB4p269Hf3

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-((*S*)-oxiran-2-yl)hept-6-yn-1-ol (22)



A vial was charged with 4Å molecular sieves (20 mg) and CH_2Cl_2 (10 mL). *D*-(–)-diisopropyl tartrate (833 μL, 3.98 mmol), titanium tetraisopropoxide (982 μL, 3.3 mmol) and alcohol **79** (890 mg, 3.3 mmol) were added and the reaction cooled to –22 °C with a portable cooler and isopropanol. After stirring for 30 min, the mixture was treated with *tert*-butyl hydroperoxide (6 M in CH_2Cl_2, 1.1 mL, 6.6 mmol) and stirred at –22 °C for another 14 h. The reaction was quenched by adding to a solution of ferrous sulfate heptahydrate (1.1 g, 4.0 mmol) and tartaric acid (1.5 g, 10 mmol) in DI H_2O (30 mL) cooled to 0 °C. The mixture was filtered through celite, followed by extraction with CH_2Cl_2. Most of the CH_2Cl_2 was removed under reduced pressure and the residual mixture (10 mL) was diluted with Et_2O (10 mL). This mixture was added to a solution of 30% NaOH in H_2O cooled to 0 °C and stirred for 1 h. After dilution with H_2O (20 mL), the solution is extracted with Et_2O (3x). The combined organic layers are dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by MPLC (3:1 Hex:EtOAc) provided desired epoxide **22** (283 mg, 60% (based on max 50% yield)) and recovered allylic alcohol **(3*S*)-79** (288 mg, 61% (based on max 50% yield).

*This reaction was performed starting with (5*R*)-**79** and (+/–)-**79** (*dr* 1.7:1). It was also done using *L*-(+)-DIPT starting with (5*S*)-**79**, (3*S*)-**79**, (3*S*,5*R*)-**79** and (+/–)-**79**. The reactions starting with an epimeric mixture at C3 (carbinol center) resulted in recovery of the unreacted allylic alcohols (3*S*,5*R*)-**79**, (3*S*-**79**), (3*R*,5*S*)-**79** and (3*R*)-**79**, which could be submitted to SAE with the appropriate enantiomer of DIPT.

***syn,anti*-22** (*e.g.*, (3*R*-**22**)

^{1}H NMR (500 MHz, $CDCl_3$, MB4p236Hf8-13_2 or MB4p270Hf5-6): δ 4.10 (ddt, *J* = 6.7, 5.7 and 5.7 Hz, 1H, (TBSO)C*H*), 3.83 (ddd, *J* = 9.2, 3.6 and 3.6 Hz, 1H, (HO)C*H*), 2.98 (ddd, *J* = 4.0, 4.0 and 2.8 Hz, 1H, (HO)CHC*H*), 2.80 (dd, *J* = 5.1 and 2.8 Hz, 1H, HCOCHH_a), 2.77 (dd, *J* = 5.1 and 3.9 Hz, 1H, HCOCHH_b), 2.68 (s, 1H, O*H*), 2.32–2.20 (m, 2H, HC≡CCH_2), 1.96 (dd, *J* = 2.7 and 2.7 Hz, 1H, CH_2C≡C*H*), 1.81 (ddd, *J* = 14.2, 5.5 and 3.0 Hz, 1H, (HO)CHCHH_a), 1.78 (ddd, *J* = 7.3, 7.3 and 5.9 Hz, 2H, HC≡CCH_2CH_2), 1.68 (ddd, *J* = 14.2, 9.3 and 6.9 Hz, 1.1H, (HO)CHCHH_b), 0.90 (s, 9H, C(CH_3)$_3$), 0.12 (s, 3H, SiCH_{3_a}) and 0.11 (s, 3H, SiCH_{3_b}).

^{13}C NMR (125 MHz, $CDCl_3$, MB4p270Hf5-6): δ 84.2, 70.2, 68.9, 68.3, 54.6, 44.6, 39.9, 36.0, 26.0 (3), 18.1, 14.5, –4.2 and –4.4.

COSY, HMQC: MB4p270Hf5-6

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-((*R*)-oxiran-2-yl)hept-6-yn-1-ol **(*ent*-22)**

(as 1.5:1 mixture of (1*S*,3S)- and (1*S*,3*R*)-*ent*-**22**)

^{1}H NMR (500 MHz, $CDCl_3$, MB4p187If9 or MB4p293Hf7-10): δ 4.18 (tdd, *J* = 5.9, 5.9 and 4.0 Hz, 0.7H, (TBSO)C$H_{_min}$), 4.10 (ddt, *J* = 6.8, 5.8 and 5.8 Hz, 1H, (TBSO)C$H_{_maj}$), 3.88 (dddd, *J* = 9.5, 4.0, 4.0 and 1.5 Hz, 0.7H, (HO)C$H_{_min}$), 3.83 (dddd, *J* = 8.7, 4.1, 3.0 and 1.3 Hz, 1H, (HO)C$H_{_maj}$), 2.98 (ddd, *J* = 4.0, 4.0 and 2.8 Hz, 1H, (HO)CHC$H_{_maj}$), 2.96 (ddd, *J* = 4.4, 3.3 and 3.3 Hz, 0.7H, (HO)CHC$H_{_min}$), 2.79 (dd, *J* = 5.1 and 2.8 Hz, 1H, HCOCHH_{a_maj}), 2.80–2.76 (m, 2.4H, HCOCHH_{b_maj} and HCOCH_{2_min}), 2.69 (d, *J* = 1.6 Hz, 1H, O*H*), 2.32–2.18 (m, 3.4H, HC≡CC$H_{2_maj/min}$), 1.96^{+} (dd, *J* = 2.6 and 2.6 Hz, 0.7H, CH_2C≡C$H_{_min}$), 1.96^{-} (dd, *J* = 2.6 and 2.6 Hz, 1H, CH_2C≡C$H_{_maj}$), 1.86–1.64 (m, 6.8H, HOCHC$H_{2_maj/min}$ and HC≡CCH_2C$H_{2_maj/min}$), 0.90^{+}

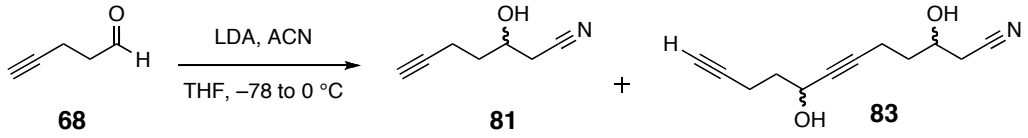
(s, 6.3H, C(CH_3)$_{3\_min}$), 0.90$^-$ (s, 9H, C(CH_3)$_{3\_maj}$), 0.13 (s, 2.1H, SiC$H_{3_a_min}$), 0.12 (s, 5.1H, SiC$H_{3_b_min}$ and SiC$H_{3_a_maj}$) and 0.11 (s, 3H, SiC$H_{3_b_maj}$).

^{13}C NMR (125 MHz, $CDCl_3$, MB4p293Hf7-10): δ 84.2$_{_maj}$, 84.0$_{_min}$, 70.2$_{_maj}$, 69.3$_{_min}$, 69.0$_{_min}$, 68.9$_{_maj}$, 68.2$_{_maj}$, 67.3$_{_min}$, 54.8$_{_min}$, 54.7$_{_maj}$, 44.6$_{_min}$, 44.5$_{_maj}$, 40.0$_{_maj}$, 39.0$_{_min}$, 36.0$_{_maj}$, 35.5$_{_maj}$, 26.0$_{_maj/min}$ (3), 18.1$_{_maj/min}$, 14.7$_{_min}$, 14.5$_{_maj}$, –4.2$_{_maj}$, –4.4$_{_maj/min}$ and –4.5$_{_min}$.

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc, MB4p102F): *m/z* = 285.3 $(M+H)^+$; t_r = 13.14 min.

TLC: R_f = 0.2 (4:1 Hex:EtOAc)

3-Hydroxyhept-6-ynenitrile (81)



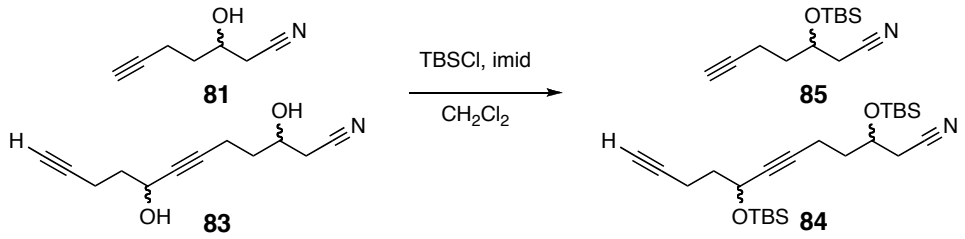
Diisopropylamine (2.41 mL, 18 mmol) in THF (16 mL) cooled to 0 °C was treated with *n*-butyllithium (2.5 M in Hex, 7.25 mL, 18 mmol) and stirred for 15 min. The mixture was cooled to –78 °C and charged with acetonitrile (946 μL, 18 mmol) in THF (8 mL). After 30 min, aldehyde **68** (1.64 g, 20 mmol) was added and the reaction was stirred at –78 °C for 30 min, then allowed to warm to rt and stir for an additional hour. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3x). The combined organic layers were washed with 2 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford alcohol **81** (1.66 g) as a crude mixture containing impurity **83** (~2:1 ratio).

81 and **83** (2:1)

^{1}H NMR (500 MHz, $CDCl_3$, MB3p281G2 or MB3p295G): δ 4.18 (dddd, *J* = 6.1, 6.1, 6.1 and 6.1 Hz, 1H, HOC*H*$_{\_prod/imp}$), 2.62 (dd, *J* = 16.7 and 5.0 Hz, 2H, N≡CCH*H*$_{a\_prod/imp}$), 2.55 (dd, *J* = 16.7, 6.5 Hz, 2H, N≡CCH*H*$_{b\_prod/imp}$), 2.43–2.30 (m, 6H, HC≡CC*H*$_{2\_prod/imp}$ and C(OH)C≡CC*H*$_{2\_imp}$), 2.03 (t, *J* = 2.7 Hz, 1H, $CH_2C{\equiv}CH$), 1.95 (t, *J* = 2.7 Hz, 0.6H, C≡C*H*$_{\_imp}$), 1.90 (ddd, *J* = 7.3, 7.3 and 5.2 Hz, 3H, HC≡CCH$_2$CH*H*$_{a\_prod/imp}$ and C(OH)C≡CCH$_2$CH*H*$_{a\_imp}$) and 1.81 (ddd, *J* = 7.2, 6.4 and 6.4 Hz, 3H, HC≡CCH$_2$CH*H*$_{b\_prod/imp}$ and C(OH)C≡CCH$_2$CH*H*$_{b\_imp}$).

GCMS (MB3p295G2, 5025015): t_r = 5.36 min; *m/z* 123 (M^+, 5), 104 (25), 83 (50) and 55 (100).

3-(*tert*-Butyldimethylsilyloxy)hept-6-ynenitrile (85)



To a solution of *tert*-butyldimethylsilyl chloride (2.44 g, 16.1 mmol) in CH_2Cl_2 (30 mL) was added imidazole (1.84 g, 27 mmol) and stirred at rt for 1 h. The mixture was charged with the crude mixture of alcohols **81** and **83** (~2:1, 1.66 g) in CH_2Cl_2 (5 mL) and stirred for 3 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude TBS ether products **84** and **85**. Purification by MPLC (9:1 Hex:EtOAc) provided desired nitrile **85** (835 mg) and bis-TBS ether **84** (659 mg).

^{1}H NMR (500 MHz, $CDCl_3$, MB3p296Ff2): δ 4.12 (dddd, *J* = 7.7, 4.8, 4.8 and 4.8 Hz, 1H, TBSOC*H*), 2.55 (dd, *J* = 16.6 and 5.6 Hz, 1H, N≡CCHH_a), 2.49 (dd, *J* = 16.6 and 5.1 Hz, 1H, N≡CCHH_b), 2.29 (ddd, *J* = 7.4, 6.4 and 2.7 Hz, 2H, HC≡CCH_2), 1.99 (t, *J* = 2.7 Hz, 1H, CH_2C≡C*H*), 1.87–1.74 (m, 2H, HC≡CCH_2CH_2), 0.91 (s, 9H, C(CH_3)$_3$), 0.14 (s, 3H, SiCH_{3_a}), and 0.12 (s, 3H, SiCH_{3_b}).

^{1}H NMR (500 MHz, C_6D_6, MB3p296Ff2): δ 3.61 (dddd, *J* = 7.8, 5.3, 5.3 and 5.3 Hz, 1H, TBSOC*H*), 1.93 (dddd, *J* = 17.0, 8.3, 6.8 and 2.7 Hz, 1H, HC≡CCHH_a), 1.85 (dddd, *J* = 17.0, 6.7, 6.0 and 2.7 Hz, 1H, HC≡CCHH_b), 1.68 (t, *J* = 2.7 Hz, 1H, CH_2C≡C*H*), 1.67 (dd, *J* = 16.7 and 5.5 Hz, 1H, N≡CCHH_a), 1.62 (dd, *J* = 16.7 and 5.6 Hz, 1H, N≡CCHH_b), 1.43 (dddd, *J* = 13.7, 7.7, 6.7 and 6.0 Hz, 1H, HC≡CCH_2CHH_a), 1.30 (dddd, *J* = 13.5, 8.4, 6.8 and 4.4 Hz, 1H, HC≡CCH_2CHH_b), 0.90 (s, 9H, C(CH_3)$_3$), 0.01 (s, 3H, SiCH_{3_a}) and -0.02 (s, 3H, SiCH_{3_b}).

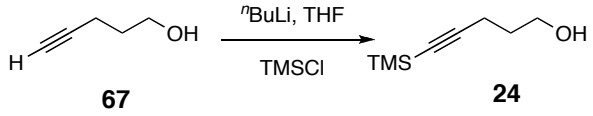
GCMS (MB3p296Ff2, 5025015): t_r = 7.56 min; *m/z* 180 (M^+– $C(CH_3)_3$, 100), 139 (25), 98 (50) and 75 (25).

3,8-bis(*tert*-butyldimethylsilyloxy)dodeca-6,11-diynenitrile (84)

^{1}H NMR (500 MHz, $CDCl_3$, MB3p296Ff1f8-9): δ 4.50–4.46 (m, 1H, C≡CC(OTBS)*H*), 4.11–4.05 (m, 1H, N≡CH_2C(OTBS)*H*), 2.53 (ddd, *J* = 16.6, 5.6 and 1.0 Hz, 1H, N≡CCHH_a), 2.47 (ddd, *J* = 16.7, 5.2 and 2.6 Hz, 1H, N≡CCHH_b), 2.35–2.27 (m, 4H, HC≡CCH_2 and TBSOCC≡CCH_2), 1.95 (t, *J* = 2.7 Hz, 1H, CH_2C≡C*H*), 1.89–1.73 (m, 4H, CH_2(TBSO)CHC≡CCH_2), 0.91 (s, 9H, C(CH_3)$_3$), 0.90 (s, 9H, C(CH_3)$_3$), 0.13$^+$ (s, 3H, SiCH_3), 0.13$^-$ (s, 3H, SiCH_3), 0.12 (s, 3H, SiCH_3), and 0.11 (s, 3H, SiCH_3).

HPLC-MS (no column, APCI/ESI, 95% MeOH:H_2O + 0.05% NH_4OAc, MB3p296Ff1f8-9): *m/z* = 451.2 $(M+NH_4)^+$.

5-(Trimethylsilyl)pent-4-yn-1-ol (24)

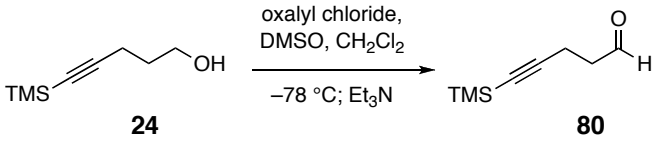


A solution of 4-pentynol (**67**, 1 g, 11.9 mmol) in THF (24 mL) cooled to –78 °C was treated with *n*-butyllithium (2.5 M in hexanes, 9.51 mL, 23.8 mmol). The reaction was stirred for 30 min at –78 °C, warmed to 0 °C and stirred for 1h, and cooled back down to –78 °C. The mixture was charged with trimethylsilyl chloride (3.17 mL, 25 mmol) and allowed to warm to rt while stirring for 2 h. The reaction was quenched with 10% aqueous HCl and stirred for 30 min before extraction with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by MPLC (3:1 Hex:EtOAc) provided known alcohol **24** (988 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$, MB4p76Ff8-14): δ Matched literature data.[63]

GCMS: MB4p25G

5-(Trimethylsilyl)pent-4-ynal (80)



To a solution of oxalyl chloride (3.25 mL, 38 mmol) in CH_2Cl_2 (75 mL) at –78 °C, DMSO (5.23 mL, 73.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise followed by stirring the reaction for 30 min. The mixture was charged with alcohol **24** (5.1 g, 32 mmol) in CH_2Cl_2 (45 mL) and stirred at –78 °C for 40 min. The reaction was treated

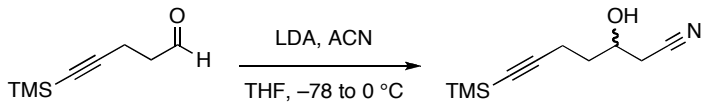
[63] "New Cobalt-Catalyzed Cycloisomerization of ε-Acetylenic β-Keto Esters. Application to a Powerful Cyclization Reactions Cascade," Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699–2708.

with triethylamine (22 mL, 160 mmol) and warmed to rt while stirring for 30 min before diluting with Et_2O (250 mL). The organic layer was washed with saturated aqueous NH_4Cl (100 mL), saturated aqueous $CuSO_4$ (100 mL) and brine (100 mL). The Et_2O layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give aldehyde **80** (4.6 g, 93%). Purification by MPLC (9:1 Hex:EtOAc) has been done but generally **80** was carried forward as the crude product.

^{1}H NMR (500 MHz, $CDCl_3$, MB4p58Gf6-11): δ Matched literature data.[64]

GCMS (MB4p43E, 5025015): t_r = 4.41 min; *m/z* 139 (M^+– CH_3, 100), 109 (50) and 83 (25).

3-Hydroxy-7-(trimethylsilyl)hept-6-ynenitrile (82)



80 **82**

Diisopropylamine (4.72 mL, 33.4 mmol) in THF (30 mL) cooled to 0 °C was treated with *n*-butyllithium (2.5 M in Hex, 12.2 mL, 30.4 mmol) and stirred for 15 min. The mixture was cooled to –78 °C and charged with acetonitrile (1.75 mL, 33.4 mmol) in THF (15 mL). After 30 min, aldehyde **80** (4.62 g, 31.9 mmol) was added and stirring was continued at –78 °C for 30 min followed by warming to rt while stirring for an additional hour. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3x). The combined organic layers were washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced

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[64] "Biomimetic Polyene Cyclizations. Participation of the (Trimethylsilyl)acetylenic Group and the Total Synthesis of the *D*-Homosteroid System," Johnson, W. S.; Yarnell, T. M.; Myers, R. F.; Morton, D. R.; Boots, S. G. *J. Org. Chem*. **1980**, *45*, 1254-1259.

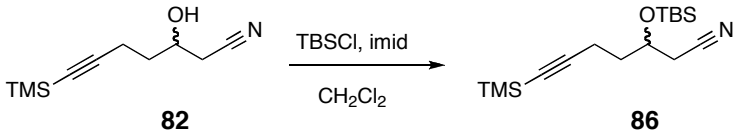
pressure to afford alcohol **82** (5.1 g, 87%). The product is used crude but has been purified by MPLC (2:1 Hex:EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$, MB4p253Gpump): δ 4.15 (dddd, *J* = 6.6, 5.2, 5.2 and 5.2 Hz, 1H, HOC*H*), 2.62 (dd, *J* = 16.7 and 5.2 Hz, 1H, N≡CCHH_a), 2.56 (dd, *J* = 16.7 and 6.3 Hz, 1H, N≡CCHH_b), 2.46 (dt, *J* = 17.3 and 7.1 Hz, 1H, TMSC≡CCHH_a), 2.40 (dt, *J* = 17.3 and 6.4 Hz, 1H, TMSC≡CCHH_b), 1.83–1.78 (m, 2H, TMSC≡CCH$_2$CH_2) and 0.16 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (125 MHz, $CDCl_3$, MB4p288Gf6-7): δ 117.5, 105.5, 87.0, 67.4, 34.7, 26.2, 16.5, and 0.2 (3).

GCMS (MB4p253Gpump, 5027016): t_r = 7.16 min; *m/z* 180 (M^+– CH_3, 100), 162 (50), 139 (40) and 75 (50).

3-(*tert*-Butyldimethylsilyloxy)-7-(trimethylsilyl)hept-6-ynenitrile (86)



82 **86**

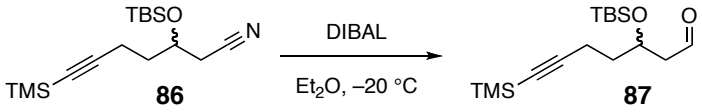
To a solution of *tert*-butyldimethylsilyl chloride (5.55 g, 36.8 mmol) in CH_2Cl_2 (50 mL) was added imidazole (4.18 g, 61.4 mmol) and stirred at rt for 1 h. The mixture was charged with alcohol **82** (5.1 g, 26.1 mmol) in CH_2Cl_2 (5 mL) and stirred for 2 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude TBS ether **86**. The *bis*-TBS ether (TBSOTBS) was distilled away to leave **86** (5.9 g, 73%).

^{1}H NMR (500 MHz, $CDCl_3$, MB4p289Fpotf2): δ 4.12 (dddd, *J* = 7.5, 5.1, 5.1 and 5.1 Hz, 1H, TBSOC*H*), 2.56 (dd, *J* = 16.6 and 5.5 Hz, 1H, N≡CCHH_a), 2.49 (dd, *J* = 16.6 and 5.2 Hz, 1H, N≡CCHH_b), 2.37–2.27 (m, 2H, TMSC≡CCH_2), 1.85–1.71 (m, 2H, TMSC≡CCH$_2$CH_2), 0.91 (s, 9H, Si(CH$_3$)$_2$C(CH_3)$_3$), 0.15 (s, 9H, C≡CSi(CH_3)$_3$), 0.14 (s, 3H, SiCH_{3_a}), and 0.13 (s, 3H, SiCH_{3_b}).

^{13}C NMR (125 MHz, $CDCl_3$, MB4p289Fpotf2): δ 117.6, 105.9, 86.1, 66.9, 35.5, 26.5, 25.9 (3), 18.2, 16.0, 0.3 (3), –4.5$^+$ and –4.5$^-$.

GCMS (MB4p254Fdpot, 5027016): t_r = 8.85 min; *m/z* 294 (M^+– CH_3, 10), 252 (M^+–$C(CH_3)_3$, 100), 211 (25) and 155 (25).

3-(*tert*-Butyldimethylsilyloxy)-7-(trimethylsilyl)hept-6-ynal (87)



To a solution of nitrile **86** (4.6 g, 14.8 mmol) in Et_2O (70 mL) was added diisobutylaluminum hydride (1.5 M in toluene, 15 mL, 22.3 mmol) at –20 °C. After stirring for 2 h at –20 °C, the mixture was warmed to rt and stirred for 30 min. The reaction was poured into mixture of hexanes (50 mL) and 1 M HCl (50 mL). After mixing for a short time, the solution was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide aldehyde **87** (3.8 g, 82%), which was carried forward as the crude product.

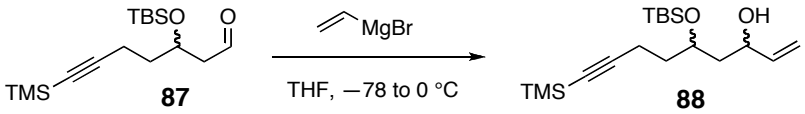
^{1}H NMR (500 MHz, $CDCl_3$, MB4p290Ef3): δ 9.82 (dd, *J* = 2.8 and 2.1 Hz, 1H, C(O)*H*), 4.33 (dddd, *J* = 7.0, 5.5, 5.5 and 5.5 Hz, 1H, TBSOC*H*), 2.60 (ddd, *J* = 15.8, 5.3 and 2.1 Hz, 1H, H(O)CCHH_a), 2.53 (ddd, *J* = 15.8, 5.9 and 2.9 Hz, 1H, H(O)CCHH_b), 2.32 (ddd,

J = 17.2, 7.3 and 7.3 Hz, 1H, TMSC≡CCHH_a), 2.28 (ddd, J = 17.1, 6.9 and 6.9 Hz, 1H, TMSC≡CCHH_b), 1.81–1.68 (m, 2H, TMSC≡CCH_2CH_2), 0.88 (s, 9H, Si(CH_3)$_2$C(CH_3)$_3$), 0.15 (s, 9H, C≡CSi(CH_3)$_3$), 0.11 (s, 3H, SiCH_{3_a}) and 0.08 (s, 3H, SiCH_{3_b}).

^{13}C NMR (125 MHz, $CDCl_3$, MB4p290E): δ 202.0, 106.5, 81.0, 67.0, 50.9, 36.4, 26.0 (3), 18.2, 16.2, 0.3 (3), -4.3 and -4.5.

GCMS (MB4p255E2, 5027016): t_r = 8.54 min; *m/z* 255 (M^+–C(CH_3)$_3$, 40), 181 (30), 147 (100) and 73 (50).

5-(*tert*-Butyldimethylsilyloxy)-9-(trimethylsilyl)non-1-en-8-yn-3-ol (88)



To a solution of aldehyde **87** (4.0 g, 12.8 mmol) in THF (65 mL) cooled to –78 °C was added vinylmagnesium bromide (0.8 M in THF, 32 mL, 26 mmol). The mixture was warmed to 0 °C and stirred for 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl, followed by extraction with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (9:1 Hex:EtOAc) provided allylic alcohol **88** (1.7 g, 39%) in a *syn:anti* ratio of 1.5:1.

88 (*syn:anti* 1.5:1)

^{1}H NMR (500 MHz, $CDCl_3$, MB4p291Ef6-11): δ 5.86 (ddd, J = 17.2, 10.5 and 5.7 Hz, 1H, H_2C=C$H_{_syn}$), 5.84 (ddd, J = 17.2, 10.4 and 5.5 Hz, 0.6H, H_2C=C$H_{_anti}$), 5.27 (dd, J = 17.2 and 1.5 Hz, 1H, CH=CHH_{trans_syn}), 5.26 (dd, J = 17.2 and 1.5 Hz, 0.7H, CH=CHH_{trans_anti}), 5.10 (dd, J = 10.4 and 1.4 Hz, 1H, CH=CHH_{cis_syn}), 5.09 (dd, J = 10.4 and 1.4 Hz, 0.7H, CH=CHH_{cis_anti}), 4.43–4.38 (m, 0.7H, HOC$H_{_anti}$), 4.31–4.26 (m, 1H,

HOC$H_{_syn}$), 4.16–4.11 (m, 0.7H, TBSOC$H_{_anti}$), 4.09–4.04 (m, 1H, TBSOC$H_{_syn}$), 3.11 (d, J = 2.7 Hz, 0.6H, O$H_{_anti}$), 2.73 (d, J = 2.4 Hz, 1H, O$H_{_syn}$), 2.34–2.20 (m, 4H, TMSC≡CC$H_{2_syn/anti}$), 1.87–1.61 (m, 8H, HOCHC$H_{2_syn/anti}$ and C≡CCH$_2$C$H_{2_syn/anti}$), 0.91 (s, 18H, Si(CH$_3$)$_2$C(CH_3)$_{3\_syn/anti}$), 0.15 (s, 18H, C≡CSi(CH_3)$_{3\_syn/anti}$), 0.13 (s, 9H, SiC$H_{3_a_syn/anti}$ and SiC$H_{3_b_syn}$) and 0.12 (s, 3H, SiC$H_{3_b_anti}$).

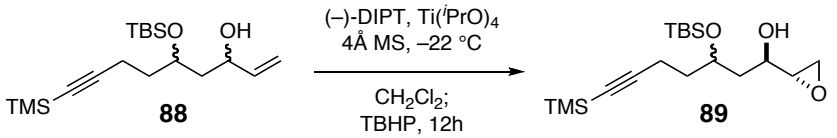
^{13}C NMR (125 MHz, $CDCl_3$, MB4p291Ef6-11): δ 141.2$_{syn}$, 141.1$_{anti}$, 114.5$_{syn}$, 114.3$_{anti}$, 106.9$_{syn}$, 106.8$_{anti}$, 85.4$_{anti}$, 85.2$_{syn}$, 71.6, 70.9, 69.9$^+$, 69.9$^-$, 43.2$_{syn}$, 42.1$_{anti}$, 36.4$_{syn}$, 35.1 $_{anti}$, 26.1 (3)$_{syn/anti}$, 18.2$_{syn/anti}$, 16.4$_{anti}$, 15.9$_{syn}$, 0.3 (3)$_{syn/anti}$, -3.9, -4.3, -4.4$^+$ and -4.4$^-$.

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc, MB4p72Ef7-10): *m/z* = 341.3 $(M+H)^+$; t_r = 14.80 min.

GCMS: MB4p72Ef7-10

TLC: R_f = 0.42 (6:1 Hex:EtOAc).

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-((*S*)-oxiran-2-yl)-7-(trimethylsilyl)hept-6-yn-1-ol (89)



A vial was charged with 4Å molecular sieves (5 mg) and CH_2Cl_2 (1 mL). *D*-(–)-diisopropyl tartrate (74 μL, 0.35 mmol), titanium tetraisopropoxide (87 μL, 0.29 mmol) and alcohol **88** (100 mg, 3.3 mmol) were added and the reaction cooled to –22 °C with a portable cooler and isopropanol. After stirring for 30 min, the mixture was treated with *tert*-butyl hydroperoxide (6 M in CH_2Cl_2, 147 μL, 0.59 mmol) and stirred at –22 °C for another 14 h. The reaction was quenched by adding to a solution of ferrous sulfate heptahydrate (98 mg, 0.35 mmol) and tartaric acid (131 mg, 0.87 mmol) in DI H_2O (10

mL) cooled to 0 °C. The mixture was filtered through celite, followed by extraction with CH_2Cl_2. Most of the CH_2Cl_2 was removed under reduced pressure and the residual mixture (5 mL) was diluted with Et_2O (10 mL). This mixture was added to a solution of 30% NaOH in H_2O (10 mL) cooled to 0 °C and stirred for 1 h at 0 °C. After dilution with H_2O (20 mL), the solution is extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by MPLC (6:1 Hex:EtOAc) provided desired epoxide **89** (36 mg, 69% (based on max 50% yield)) and recovered allylic alcohol (3*S*)-**88** (28 mg, 56% (based on max 50% yield).

***R,R,S*-89** and ***S,R,S*-89** (*dr* 1.5:1)

^{1}H NMR (500 MHz, $CDCl_3$, MB4p75Hf5-8): δ 4.19 (dddd, *J* = 6.2, 6.2, 4.8 and 4.8 Hz, 0.7H, TBSOC$H_{_diast2}$), 4.10 (dddd, *J* = 6.8, 5.9, 5.9 and 5.9 Hz, 1H, TBSOC$H_{_diast1}$), 3.87 (dddd, *J* = 6.2, 6.2, 4.5 and 1.7 Hz, 0.7H, HOC$H_{_diast2}$), 3.82 (dddd, *J* = 9.0, 4.4, 3.0 and 1.6 Hz, 1H, HOC$H_{_diast1}$), 3.08 (d, *J* = 1.7 Hz, 0.7H, O$H_{_diast2}$), 2.98 (ddd, *J* = 4.0, 4.0 and 2.8 Hz, 1H, HOCHCHO$_{_diast1}$), 2.95 (ddd, *J* = 4.5, 3.3 and 3.3 Hz, 0.7H, HOCHCHO$_{_diast2}$), 2.80 (dd, *J* = 5.1 and 2.8 Hz, 1H, HC(O)CHH_{a_diast1}), 2.78–2.75 (m, 0.7H, HC(O)CHH_{a_diast2}), 2.77$^+$ (dd, *J* = 5.1 and 3.3 Hz, 0.7H, HC(O)CHH_{b_diast2}), 2.77$^-$ (dd, *J* = 5.1 and 3.9 Hz, 1H, HC(O)CHH_{b_diast1}), 2.71 (d, *J* = 1.6 Hz, 1H, O$H_{_diast1}$), 2.31 (ddd, *J* = 17.1, 7.1 and 7.1 Hz, 1H, TMSC≡CCHH_{a_diast1}), 2.29 (ddd, *J* = 16.9, 7.1 and 7.1 Hz, 0.7H, TMSC≡CCHH_{a_diast2}), 2.26 (ddd, *J* = 17.1, 7.3 and 7.3 Hz, 1H, TMSC≡CCHH_{b_diast1}), 2.25 (ddd, *J* = 17.1, 7.0 and 7.0 Hz, 0.7H, TMSC≡CCHH_{b_diast2}), 1.83 (ddd, *J* = 14.3, 5.4 and 3.0 Hz, 1.7H, HOCHCH$H_{a_diast1/diast2}$), 1.80–1.71 (m, 4H, TMSC≡CCH$_2$C$H_{2_diast1/diast2}$), 1.67 (ddd, *J* = 14.2, 9.2 and 6.7 Hz, 1.7H,

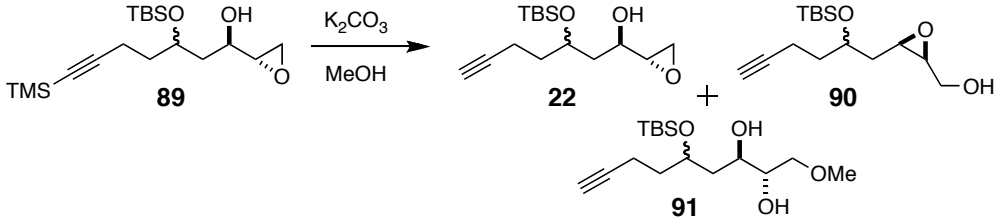
HOCHCH$H_{b_diast1/diast2}$), 0.90^{+} (s, 9H, Si$(CH_3)_2$C(CH_3)$_{3\_diast2}$), 0.90^{-} (s, 9H, Si$(CH_3)_2$C(CH_3)$_{3\_diast1}$), 0.15^{+} (s, 9H, C≡CSi(CH_3)$_{3\_diast1}$), 0.15^{-} (s, 9H, C≡CSi(CH_3)$_{3\_diast2}$), 0.13 (s, 3H, SiCH_{3_a}), 0.12 (s, 6H, SiCH_{3_a} and SiCH_{3_b}) and 0.11 (s, 3H, SiCH_{3_b}).

^{13}C NMR (125 MHz, $CDCl_3$, MB4p75Hf5-8): δ 106.9$_{_diast1}$, 106.7$_{_diast2}$, 85.4$_{_diast2}$, 85.3$_{_diast1}$, 70.4$_{_diast1}$, 69.5$_{_diast2}$, 68.3$_{_diast1}$, 67.5$_{_diast2}$, 54.8$_{_diast2}$, 54.7$_{_diast1}$, 44.7$_{_diast2}$, 44.6$_{_diast1}$, 40.0$_{_diast1}$, 39.0$_{_diast2}$, 36.2$_{_diast1}$, 35.3$_{_diast2}$, 26.0 (6) $_{\_diast1/diast2}$, 18.2$_{_diast2}$, 18.1$_{_diast1}$, 16.3$_{_diast2}$, 16.0$_{_diast1}$, 0.3^{+}(3)$_{\_diast1}$, 0.3^{-}(3)$_{\_diast2}$, –4.1$_{_diast1}$, –4.3$_{_diast2}$, –4.4$_{_diast1}$ and –4.5$_{_diast2}$.

TLC: R_f = 0.25 (4:1 Hex:EtOAc).

*Also synthesized a mixture of *R,S,R*- and *S,S,R*-**89** (1:1.5) using the above procedure with (+)-DIPT (MB4p58Hf5-8, 1H and 13C).

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-((*S*)-oxiran-2-yl)hept-6-yn-1-ol (22)



A solution of epoxide **89** (20 mg, 0.05 mmol) in MeOH (500 μL) was charged with K_2CO_3 (23 mg, 0.17 mmol). The reaction was stirred at rt and monitored by TLC for the disappearance of starting material. Upon completion the reaction was partitioned between H_2O and EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The products were purified by MPLC (3:1 Hex:EtOAc) for characterization.

22

Characterization data listed above (p 88-89).

(2*S*,3*R*)-3-(2-(*tert*-butyldimethylsilyloxy)hex-5-ynyl)oxrian-2-yl)methanol **(90)**

^{1}H NMR (500 MHz, $CDCl_3$, MB4p173Ef5-6): δ 4.05–3.99 (m, 1H, TBSOC*H*), 3.93 (dd, *J* = 12.6 and 2.4 Hz, 1H, HOCHH_a), 3.64 (dd, *J* = 12.7 and 3.7 Hz, 1H, HOCHH_b), 3.10 (ddd, *J* = 6.9, 5.2 and 2.4 Hz, 1H, TBSOCHCH_2C*H*(O)$_{\_diast1}$), 3.08 (ddd, *J* = 7.0, 4.7 and 2.3 Hz, 1H, TBSOCHCH_2C*H*(O)$_{\_diast2}$), 2.95–2.91 (m, 1H, HOCH_2C*H*(O)), 2.29–2.23 (m, 2H, HC≡CCH_2), 1.95 (t, *J* = 2.7 Hz, 1H, C≡C*H*), 1.80–1.69 (m, 3H, HC≡CCH_2CH_2 and TBSOCHCHH_aCH(O)), 1.64 (ddd, *J* = 14.1, 7.0 and 5.1 Hz, 1H, TBSOCHCHH_bCH(O)), 0.90 (s, 9H, Si$(CH_3)_2$C$(CH_3)_3$), 0.89 (s, 6H, C≡C$(CH_3)_3$), 0.10 (s, 1.5H, SiCH_3), 0.94 (s, 3H, SiCH_3) and 0.71 (s, 1.5H, SiCH_3).

COSY: MB4p173Ef5-6

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc, MB4p173Ef5-6): *m/z* = 385.3 $(M+H)^+$; t_r = 13.04 min.

TLC: R_f = 0.3 (3:1 Hex:EtOAc).

(2*S*,3*R*)-5-(*tert*-butyldimethylsilyloxy)-1-methoxynon-8-yne-2,3-diol **(91)** (*dr* 1.5:1)

^{1}H NMR (500 MHz, $CDCl_3$, MB4p173Ef12-13): δ 4.20 (dddd, *J* = 6.3, 6.3, 4.1 and 4.1 Hz, 0.6H, TBSOC$H_{_diast2}$), 4.10 (dddd, *J* = 7.5, 5.5, 5.5 and 5.5 Hz, 1H, TBSOC$H_{_diast1}$), 3.93 (ddd, *J* = 9.0, 5.9 and 2.8 Hz, 0.6H, HOC$H_{_diast2}$), 3.80 (ddd, *J* = 8.9, 5.8 and 2.7 Hz, 1H, HOC$H_{_diast1}$), 3.65 (dd, *J* = 6.1 and 3.7 Hz, 1H, MeOCHH_{a_diast1}), 3.63 (dd, *J* = 6.0 and 3.5 Hz, 1H, MeOCHH_{b_diast1}), 3.59–3.50 (m, 3.7H, MeOCH_{2_diast2} and HOC$H_{diast1/diast2}$), 3.40$^+$ (s, 3H, OCH_{3_diast1}), 3.40$^-$ (s, 1.6H, OCH_{3_diast2}), 2.31–2.18 (m, 3.4H, HC≡CC$H_{2_diast1/diast2}$), 1.96 (t, *J* = 2.7 Hz, 0.6H, C≡CH_{diast2}), 1.95 (t, *J* = 2.7 Hz, 1H,

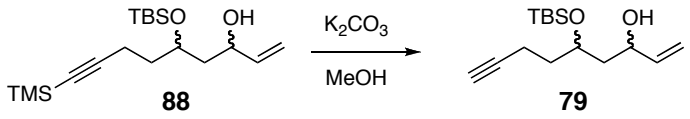
C≡CH_{diast1}), 1.90–1.63 (m, 4H, HC≡CCH$_2$C$H_{2_diast1/diast2}$ and HOCHC(OH)HCH_{2_diast2}), 1.82 (ddd, J = 14.4, 5.0 and 2.6 Hz, 1H, HOCHC(OH)HCHH_{a_diast1}), 1.60 (ddd, J = 14.4, 9.8 and 7.5 Hz, 2H, HOCHC(OH)HCH$H_{b_diast1/diast2}$), 0.90$^+$ (s, 9H, Si(CH$_3$)$_2$C(CH_3)$_{3\_diast1}$), 0.90$^-$ (s, 9H, C≡CSi(CH_3)$_{3\_diast2}$), 0.13 (s, 9H, SiC$H_{3_a_diast1/diast2}$ and SiCH_{3_b}) and 0.12 (s, 3H, SiCH_{3_b}).

COSY: MB4p173Ef12-13

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H$_2$O + 0.05% NH$_4$OAc, MB4p173Ef12-13): m/z = 317.3 (M+H)$^+$; t$_r$ = 12.78 min.

TLC: R$_f$ = 0.2 (3:1 Hex:EtOAc).

5-(*tert*-Butyldimethylsilyloxy)non-1-en-8-yn-3-ol (79)

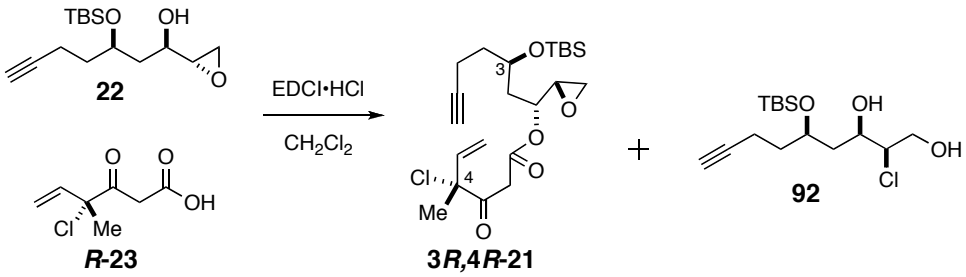


Protected alkyne **88** (1.5 g, 4.4 mmol) was dissolved in MeOH (40 mL) and treated with K$_2$CO$_3$ (792 mg, 5.7 mmol). After 2 h, the reaction was partitioned between H$_2$O and EtOAc followed by extraction with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to provide crude alcohol **79** (830 mg, 75%).

79

Characterization data listed above (p 86-87).

(4*R*)-((1*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-((*S*)-oxiran-2yl)hept-6ynyl) 4-chloro-4-methyl-3-oxohex-5-enoate (*R,R*-21)



To a solution of alcohol **22** (96 mg, 0.34 mmol) in CH_2Cl_2 (14 mL) was added acid ***R*-23** (66 mg, 0.37 mmol) and EDCI•HCl (77 mg, 0.4 mmol). The mixture was stirred at rt for 12 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by MPLC (6:1 Hex:EtOAc) provided ester ***R*-21** (30 mg, 20%) followed by elution of diol **92** (30 mg).

^{1}H NMR (500 MHz, $CDCl_3$, MB3p251Ff5-6): δ 5.99 (dd, *J* = 16.9 and 10.6 Hz, 1H, H_2C=C*H*), 5.57 (d, *J* = 16.9 Hz, 1H, CH=CH_{trans}), 5.41 (d, *J* = 10.6 Hz, 1H, CH=CH_{cis}), 4.91 (ddd, *J* = 8.7, 5.0 and 4.6 Hz, 1H, C(O)OC*H*), 3.94 (dddd, *J* = 7.4, 7.4, 4.3 and 4.3 Hz, 1H, TBSOC*H*), 3.82 (d, *J* = 16.4 Hz, 1H, C(O)CH_aC(O)O), 3.73 (d, *J* = 16.4 Hz, 1H, C(O)CH_bC(O)O), 3.00 (ddd, *J* = 5.3, 3.9 and 2.6 Hz, 1H, H_2C(O)C*H*), 2.77 (dd, *J* = 5.1 and 3.9 Hz, 1H, CH(O)CH_a), 2.73 (dd, *J* = 5.1 and 2.6 Hz, 1H, CH(O)CH_b), 2.27 (dddd, *J* = 14.1, 6.3, 6.3 and 2.7 Hz, 1H, HC≡CCH_a), 2.23 (dddd, *J* = 14.9, 7.5, 7.5 and 2.7 Hz, 1H, HC≡CCH_b), 1.94 (dd, *J* = 2.7 and 2.7 Hz, 1H, C≡C*H*), 1.89 (ddd, *J* = 14.3, 8.4 and 4.4 Hz, 1H, C(O)OCHCH_a), 1.84 (ddd, *J* = 14.4, 7.3 and 4.5 Hz, 1H, C(O)OCHCH_b), 1.77 (s, 3H, C(Cl)CH_3), 1.72 (dddd, *J* = 13.7, 7.8, 7.8 and 4.1 Hz, 1H, HC≡CCH_2CH_a), 1.63 (dddd, *J* = 13.8, 7.6, 7.6 and 6.3 Hz, 1H,

HC≡CCH$_2$CHH_b), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 3H, SiCH_{3_a}) and 0.07 (s, 3H, SiCH_{3_b}).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H$_2$O + 0.05% NH$_4$OAc, MB4p34Ff2-3): *m/z* = 443.2 $(M+H)^+$; t_r = 14.38 min.

(*S*)-((1*S*)-3-(*tert*-butyldimethylsilyloxy)-1-((*R*)-oxiran-2yl)hept-6ynyl) 4-chloro-4-methyl-3-oxohex-5-enoate (*ent*-***R,R*-21** and its 3*S* epimer)

(*dr* 1.8:1, 3*S*:3*R*)[65]

^{1}H NMR (500 MHz, C_6D_6, MB4p285Gf4): δ 5.60$^+$ (dd, *J* = 16.9 and 10.6 Hz, 0.8H, H$_2$C=C$H_{_diast2}$), 5.60$^-$ (dd, *J* = 16.9 and 10.6 Hz, 1H, H$_2$C=C$H_{_diast1}$), 5.22 (d, *J* = 16.9 Hz, 1.8H, CH=CH$H_{trans_diast1/diast2}$), 5.09 (ddd, *J* = 7.4, 5.0 and 5.0 Hz, 0.8H, C(O)OC$H_{_diast2}$), 5.04 (ddd, *J* = 8.8, 5.3 and 4.4 Hz, 1H, C(O)OC$H_{_diast1}$), 4.89 (d, *J* = 10.6 Hz, 1H, CH=CHH_{cis_diast1}), 4.88 (d, *J* = 10.6 Hz, 0.8H, CH=CHH_{cis_diast2}), 4.02 (ddd, *J* = 7.5, 7.5, 4.4 and 4.4 Hz, 1H, TBSOC$H_{_diast1}$) 4.01–3.95 (m, 0.8H, TBSOC$H_{_diast2}$), 3.59 (d, *J* = 16.3 Hz, 0.8H, C(O)CHH_aC(O)O$_{_diast2}$), 3.54 (d, *J* = 16.3 Hz, 1H, C(O)CHH_aC(O)O$_{_diast1}$), 3.48 (d, *J* = 16.3 Hz, 0.8H, C(O)CHH_bC(O)O$_{_diast2}$), 3.43 (d, *J* = 16.3 Hz, 1H, C(O)CHH_bC(O)O$_{_diast1}$), 2.79 (ddd, *J* = 5.2, 3.9 and 2.5 Hz, 0.8H, H$_2$C(O)C$H_{_diast2}$), 2.75 (ddd, *J* = 5.3, 3.9 and 2.5 Hz, 1H, H$_2$C(O)C$H_{_diast1}$), 2.55 (dd, *J* = 5.2 and 2.5 Hz, 0.8H, CH(O)CHH_{a_diast2}), 2.53 (dd, *J* = 5.2 and 2.5 Hz, 1H, CH(O)CHH_{a_diast1}), 2.34 (dd, *J* = 5.2 and 3.9 Hz, 0.8H, CH(O)CHH_{b_diast2}), 2.32 (dd, *J* = 5.2 and 3.9 Hz, 1H, CH(O)CHH_{b_diast1}), 2.26–2.17 (m, 1.8H, HC≡CCH$H_{a_diast1/diast2}$), 2.14 (dddd, *J* = 17.3, 8.0, 6.8 and 2.7 Hz, 1H, HC≡CCHH_{b_diast1}), 2.02 (dddd, *J* = 17.6, 8.1, 6.8 and 2.6 Hz, 0.8H, HC≡CCHH_{b_diast2}), 1.87 (ddd, *J* = 14.4, 8.7 and 4.6 Hz, 1H,

[65] Note the major diastereomer (diast1) is the enantiomer of the compound characterized prior to this data set.

C(O)OCHCHH_{a_diast1}), 1.78–1.57 (m, 5H, C(O)OCHCHH_{b_diast1}, C(O)OCHCH_{2_diast2} and HC≡CCH$_2$C$H_{2_diast1/diast2}$), 1.49 (s, 3H, C(Cl)CH_{3_diast2}), 1.48 (s, 3H, C(Cl)CH_{3_diast1}), 0.96 (s, 9H, SiC(CH_3)$_{3\_diast2}$), 0.95 (s, 9H, SiC(CH_3)$_{3\_diast1}$), 0.17 (s, 3H, SiC$H_{3_a_diast2}$), 0.11 (s, 3H, SiC$H_{3_a_diast1}$) 0.10$^+$ (s, 3H, SiC$H_{3_b_diast2}$) and 0.10$^-$ (s, 3H, SiC$H_{3_b_diast1}$).

^{13}C NMR (125 MHz, $CDCl_3$, MB4p285Gf4): δ 197.1$_{diast1/diast2}$, 166.3$_{diast1/diast2}$, 136.8$_{diast1/diast2}$, 118.7$_{diast1/diast2}$, 84.4$_{diast1/diast2}$, 73.0$_{diast1/diast2}$, 72.2$_{diast2}$, 71.5$_{diast1}$, 68.8$_{diast1}$, 68.7$_{diast2}$, 67.4$_{diast1}$, 67.3$_{diast2}$, 52.4$^+_{diast1}$, 52.4$^-_{diast2}$, 46.0$_{diast2}$, 45.8$_{diast1}$, 43.9$_{diast1}$, 38.6$_{diast1}$, 38.2$_{diast2}$, 36.6$_{diast2}$, 35.3$_{diast1}$, 26.1$_{diast2}$, 26.0$^+_{diast1}$, 26.0$^-$(3)$_{diast1/diast2}$, 18.2$_{diast1/diast2}$, 14.6$^+_{diast2}$, 14.6$^-_{diast1}$, –4.0$_{diast2}$, –4.3$_{diast1}$, –4.5$_{diast1}$ and –4.6$_{diast2}$.

COSY, HMQC and HMBC: MB4p285Gf4

(*S*)-((1*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-1-((*S*)-oxiran-2yl)hept-6ynyl) 4-chloro-4-methyl-3-oxohex-5-enoate (**3*R*,4*S*-21**)

^{1}H NMR (500 MHz, $CDCl_3$, MB3p236Ff6-7 or MB3p199Ff6): δ 5.98 (dd, *J* = 16.9 and 10.6 Hz, 1H, H_2C=C*H*), 5.57 (d, *J* = 16.9 Hz, 1H, CH=CHH_{trans}), 5.41 (d, *J* = 10.6 Hz, 1H, CH=CHH_{cis}), 4.91 (ddd, *J* = 9.0, 4.9 and 4.7 Hz, 1H, C(O)OC*H*), 3.95 (dddd, *J* = 7.8, 7.8, 4.1 and 4.1 Hz, 1H, TBSOC*H*), 3.86 (d, *J* = 16.4 Hz, 1H, C(O)CHH_aC(O)O), 3.69 (d, *J* = 16.4 Hz, 1H, C(O)CHH_bC(O)O), 3.00 (ddd, *J* = 5.3, 3.9 and 2.6 Hz, 1H, H_2C(O)C*H*), 2.76 (dd, *J* = 5.0 and 4.0 Hz, 1H, CH(O)CHH_a), 2.73 (dd, *J* = 5.0 and 2.6 Hz, 1H, CH(O)CHH_b), 2.32–2.19 (m, 2H, HC≡CCH_2), 1.94 (dd, *J* = 2.7 and 2.7 Hz, 1H, C≡C*H*), 1.90 (ddd, *J* = 14.5, 8.7 and 4.5 Hz, 1H, C(O)OCHCHH_a), 1.84 (ddd, *J* = 14.5, 7.5 and 4.4 Hz, 1H, C(O)OCHCHH_b), 1.77 (s, 3H, C(Cl)CH_3), 1.73 (dddd, *J* = 13.8, 7.8, 7.8 and 4.0 Hz, 1H, HC≡CCH$_2$CHH_a), 1.64 (dddd, *J* = 13.8, 7.7, 7.7 and 6.3 Hz, 1H,

HC≡CCH$_2$CHH_b), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 3H, SiCH_{3_a}) and 0.07 (s, 3H, SiCH_{3_b}).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H$_2$O + 0.05% NH$_4$OAc, MB3p204Ff4-7): *m/z* = 443.0 $(M+H)^+$; t_r = 14.34 min.

(*S*)-((1*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-1-((*S*)-oxiran-2yl)hept-6ynyl) 4-chloro-4-methyl-3-oxohex-5-enoate (**3*S*,4*S*-21**)

^{1}H NMR (500 MHz, CDCl$_3$, MB3p199Ff4): δ 5.99 (dd, *J* = 16.9 and 10.6 Hz, 1H, H$_2$C=CH), 5.57 (d, *J* = 16.9 Hz, 1H, CH=CHH_{trans}), 5.41 (d, *J* = 10.6 Hz, 1H, CH=CHH_{cis}), 4.88 (ddd, *J* = 8.8, 5.1 and 4.0 Hz, 1H, C(O)OCH), 3.95–3.90 (m, 1H, TBSOCH), 3.84 (d, *J* = 16.4 Hz, 1H, C(O)CHH_aC(O)O), 3.72 (d, *J* = 16.3 Hz, 1H, C(O)CHH_bC(O)O), 3.00 (ddd, *J* = 5.0, 3.8 and 2.5 Hz, 1H, H$_2$C(O)CH), 2.78 (dd, *J* = 5.1 and 3.9 Hz, 1H, CH(O)CHH_a), 2.74 (dd, *J* = 5.1 and 2.6 Hz, 1H, CH(O)CHH_b), 2.30–2.15 (m, 2H, HC≡CCH_2), 1.95 (dd, *J* = 2.7 and 2.7 Hz, 1H, C≡CH), 1.81–1.70 (m, 4H, C(O)OCHCH_2 and HC≡CCH$_2$CH_2), 1.77 (s, 3H, C(Cl)CH_3), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 3H, SiCH_{3_a}) and 0.05 (s, 3H, SiCH_{3_b}).

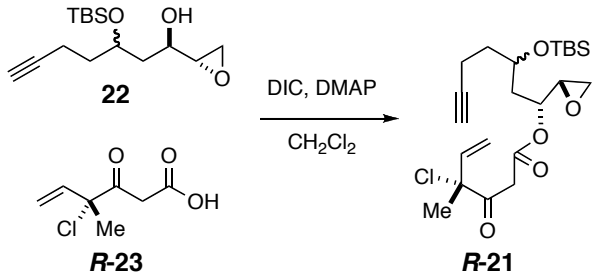
(2*R*,3*R*)-5-(*tert*-butyldimethylsilyloxy)-2-chlorononon-8-yne-1,3-diol **(92)** (*dr* 1.4:1)

^{1}H NMR (500 MHz, CDCl$_3$, MB4p246Ef8-11): δ 4.15–4.90 (m, 1.6H, TBSOC$H_{_diast1/diast2}$), 3.83–3.77 (m, 1.6H, HOC$H_{_diast1/diast2}$), 3.80 (dd, *J* = 11.2 and 3.5 Hz, 1.6H, HOCH$H_{a_diast1/diast2}$), 3.73 (dd, 11.2 and 6.8 Hz, 1.6H, HOCH$H_{b_diast1/diast2}$), 3.66 (ddd, *J* = 6.6, 5.2 and 3.3 Hz, 1H, ClC$H_{_diast1}$), 3.64 (ddd, *J* = 6.6, 5.2 and 3.3 Hz, 0.6H, ClC$H_{_diast2}$), 3.29^+ (s, 0.6H, O$H_{_diast2}$), 3.29^- (s, 1H, O$H_{_diast1}$), 2.52 (s, 0.6H, O$H_{_diast2}$), 2.51 (s, 1H, O$H_{_diast1}$), 2.29 (dddd, *J* = 16.9, 8.3, 6.1 and 2.7 Hz, 1.6H, HC≡CCH$H_{a_diast1/diast2}$), 2.23 (dddd, *J* = 17.0, 7.7, 7.7 and 2.7 Hz, 1.6H,

HC≡CCH$H_{b_diast1/diast2}$), 1.96^{+} (t, J = 2.7 Hz, 1.6H, C≡C$H_{diast1/diast2}$), 1.96^{-} (ddd, J = 14.3, 4.2 and 2.2 Hz, 1.6H, C(Cl)HC(OH)HCH$H_{a_diast1/diast2}$), 1.85–1.70 (m, 4H, HC≡CCH_2C$H_{2_diast1/diast2}$), 1.56 (ddd, J = 14.3, 9.5 and 8.7 Hz, 1.4H, C(Cl)HC(OH)HCH$H_{b_diast1/diast2}$), 0.91 (s, 14H, SiC(CH_3)$_{3\_diast1/diast2}$) and 0.14 (s, 7H, Si(CH_3)$_{2\_diast1/diast2}$).

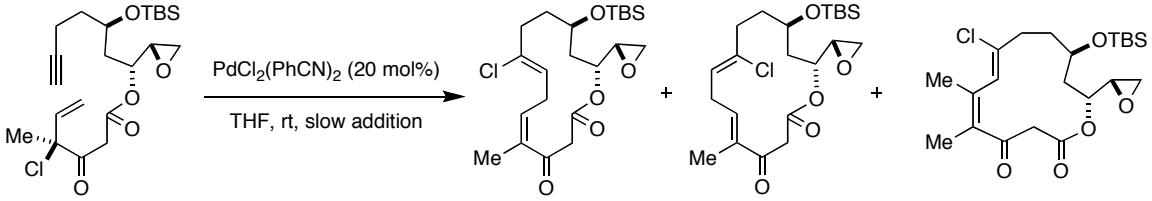
HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc, MB4p246Ff8-11): m/z = 321.0 $(M+H)^{+}$; t_r = 14.69 min.

(4*R*)-((1*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-((*S*)-oxiran-2yl)hept-6ynyl) 4-chloro-4-methyl-3-oxohex-5-enoate (*R*-21)



To a solution of alcohol (60 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) was added acid ***R*-23** (56 mg, 0.32 mmol) in CH_2Cl_2 (1 mL). The reaction was charged with 4-dimethylaminopryidine (5 mg, 0.04 mmol) and *N*,*N*'-diisopropylcarbodiimide (53 μL, 0.34 mmol) and left to stir at rt for 12 h. The mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. After extraction, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by MPLC (6:1 Hex:EtOAc) provided ester ***R*-21** (40 mg, 43%). Characterization of **21** and its stereoisomers are described above in the previous reaction.

(5*Z*,8*Z*,12*R*,14*R*)-12-(*tert*-butyldimethylsilyloxy)-9-chloro-5-methyl-14-((*S*)-oxiran-2-yl)oxacyclotetradeca-5,8-diene-2,4-dione (*Z*,*Z*-20)



S*-21** ***Z,Z*-20** ***E,Z*-20** ***96

A solution of acyclic ester ***S*-21** (16 mg, 0.036 mmol) in THF (6 mL) was added via syringe pump to a flask containing *bis*(benzonitrile)palladium(II) chloride (7 mg, 0.02 mmol) in THF (35 mL) over 2 h. After all the starting material was consumed (by ^{1}H NMR analysis), the reaction was concentrated under reduced pressure to leave 5 mL THF. Petroleum ether (10 mL) was added to the mixture followed by filtering through a pad of silica gel (3:1 Hex:EtOAc). The crude product mixture was purified by MPLC (6:1 Hex:EtOAc) and provided undesired alkene isomer ***E*,*Z*-20** (2 mg), desired macrocycle ***Z*,*Z*-20** (2 mg, containing some byproduct) and byproduct **96** (1 mg), in order of elution.

***Z*,*Z*-20** (contains trace amount of impurity **96**)

^{1}H NMR (500 MHz, $CDCl_3$, MB3p238Ef10 or MB4p257Ef8): δ 5.93 (ddq, *J* = 7.7, 7.7 and 1.4 Hz, 1H, C(O)C=C*H*), 5.17 (dd, *J* = 7.0 and 5.9 Hz, 1H, (Cl)C=C*H*), 4.76 (ddd, *J* = 10.0, 5.5 and 3.1 Hz, 1H, C(O)OC*H*), 3.81 (dddd, *J* = 8.1, 8.1, 4.2 and 4.2 Hz, 1H, TBSOC*H*), 3.64 (d, *J* = 13.2 Hz, 1H, C(O)CHH_aC(O)O), 3.57 (d, *J* = 13.2, 1H, C(O)CHH_bC(O)O), 3.21 (ddd, *J* = 15.7, 8.8 and 8.8 Hz, 1H, C=CHCHH_aCH=C), 3.08-3.03 (m, 1H, C=CHCHH_bCH=C), 3.06 (ddd, *J* = 5.6, 3.9 and 2.6 Hz, 1H, H_2C(O)C*H*), 2.79 (dd, *J* = 5.1 and 3.9 Hz, 1H, CH(O)CHH_a), 2.74 (dd, *J* = 5.1 and 2.6 Hz, 1H, CH(O)CHH_b), 2.46–2.31 (m, 2H, CH=C(Cl)CH_2), 2.02 (s, 3H, C=CCH_3), 1.99–1.91 (m,

1H, OCHCHH_a), 1.81–1.67 (m, 2H, OCHCHH_b and C=C(Cl)CH_2CHH_a), 1.63–1.57 (m, 1H, C=C(Cl)CH_2CHH_b), 0.90 (s, 9H, SiC(CH_3)$_3$) and 0.10 (s, 6H, Si(CH_3)$_2$).

NOE (1D goesy): MB3p238Ef10

Irradiation of proton at 5.93 ppm resulted in enhancement of protons at 2.02 ppm.

Irradiation of methyl protons at 2.02 ppm resulted in enhancement of protons at 5.93 and 3.57 ppm.

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc, MB3p209Ef8): *m/z* = 443.0 $(M+H)^+$; t_r = 14.51 min.

(5*E*,8*Z*,12*R*,14*R*)-12-(*tert*-butyldimethylsilyloxy)-9-chloro-5-methyl-14-((*S*)-oxiran-2-yl)oxacyclotetradeca-5,8-diene-2,4-dione **(*E*,*Z*-20)**

^{1}H NMR (500 MHz, $CDCl_3$, MB3p238Ef8 or MB4p180Ef7-8): δ 6.43 (ddq, *J* = 7.9, 6.5 and 1.3 Hz, 1H, C(O)C=C*H*), 5.69 (dd, *J* = 8.2 and 7.9 Hz, 1H, (Cl)C=C*H*), 4.64 (ddd, *J* = 9.3, 5.8 and 3.5 Hz, 1H, C(O)OC*H*), 3.74–3.68 (m, 1H, TBSOC*H*), 3.73 (d, *J* = 15.5 Hz, 1H, C(O)CHH_aC(O)O), 3.58 (d, *J* = 15.5, 1H, C(O)CHH_bC(O)O), 3.14 (ddd, *J* = 14.7, 7.8 and 7.8 Hz, 1H, C=CHCHH_aCH=C), 2.99–2.92 (m, 1H, C=CHCHH_bCH=C), 2.96 (ddd, *J* = 6.1, 3.9 and 2.5 Hz, 1H, H_2C(O)C*H*), 2.75 (dd, *J* = 5.1 and 3.8 Hz, 1H, CH(O)CHH_a), 2.71 (dd, *J* = 5.1 and 2.6 Hz, 1H, CH(O)CHH_b), 2.49 (ddd, *J* = 13.9, 10.9 and 2.7 Hz, 1H, CH=C(Cl)CHH_a), 2.40 (ddd, *J* = 13.7, 6.4 and 2.8 Hz, 1H, CH=C(Cl)CHH_b), 2.01–1.94 (m, 1H, OCHCHH_a), 1.86 (br s, 3H, C=CCH_3), 1.79 (dddd, *J* = 14.0, 10.9, 2.6 and 2.6 Hz, 1H, C=C(Cl)CH_2CHH_a), 1.76 (ddd, *J* = 14.1, 9.3 and 3.5 Hz, 1H, OCHCHH_b), 1.58 (dddd, *J* = 14.4, 8.7, 6.4 and 2.8 Hz, 1H, C=C(Cl)CH_2CHH_b), 0.91 (s, 9H, SiC(CH_3)$_3$) and 0.10 (s, 6H, Si(CH_3)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$, MB4p251E13C): δ 198.7, 167.5, 140.5, 138.7, 137.2, 122.4, 72.3, 65.6, 52.2, 46.7, 46.3, 39.1, 35.0, 33.3, 29.9, 28.1, 26.0(3), 11.7, -3.5 and -3.8.

NOE (1D goesy): MB3p238Ef8

Irradiation of proton at 6.43 ppm results in enhancement of protons at 3.73, 3.58 and 3.14 ppm.

^{1}H NMR (500 MHz, C_6D_6, MB3p238Ef8_benzene): δ 6.17 (ddq, *J* = 8.1, 6.7 and 1.4 Hz, 1H, C(O)C=C*H*), 5.36 (dd, *J* = 8.5 and 7.2 Hz, 1H, (Cl)C=C*H*), 4.70 (ddd, *J* = 9.6, 5.7 and 3.8 Hz, 1H, C(O)OC*H*), 3.71 (dddd, *J* = 8.6, 7.5, 4.8 and 2.5 Hz, 1H, TBSOC*H*), 3.41 (d, *J* = 15.4 Hz, 1H, C(O)CHH_aC(O)O), 3.30 (d, *J* = 15.4 Hz, 1H, C(O)CHH_bC(O)O), 2.73 (ddd, *J* = 14.2, 7.8 and 7.8 Hz, 1H, C=CHCHH_aCH=C), 2.59 (ddd, *J* = 6.0, 3.8 and 2.5 Hz, 1H, H_2C(O)C*H*), 2.53 (ddd, *J* = 14.8, 7.8 and 7.8 Hz, 1H, C=CHCHH_bCH=C), 2.39 (dd, *J* = 5.2 and 2.5 Hz, 1H, CH(O)CHH_a), 2.33 (ddd, *J* = 13.7, 10.6 and 2.7 Hz, 1H, CH=C(Cl)CHH_a), 2.23–2.18 (m, 1H, CH=C(Cl)CHH_b), 2.21 (dd, *J* = 5.2 and 3.7 Hz, 1H, CH(O)CHH_b), 1.96 (ddd, *J* = 14.2, 9.6 and 4.9 Hz, 1H, OCHCHH_a), 1.81 (s, 3H, C=CCH_3), 1.66–1.59 (m, 1H, C=C(Cl)CH_2CHH_a), 1.61 (ddd, *J* = 14.0, 8.8 and 3.9 Hz, 1H, OCHCHH_b), 1.40 (dddd, *J* = 14.6, 7.1, 7.1 and 2.8 Hz, 1H, OCHCHH_b), 0.98 (s, 9H, SiC(CH_3)$_3$), 0.10 (s, 3H, SiCH_{3_a}) and 0.06 (s, 3H, SiCH_{3_b}).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc, MB3p209Ef6): *m/z* = 443.0 $(M+H)^+$; t_r = 14.57 min.

(5*Z*,7*Z*,11*R*,13*R*)-11-(*tert*-butyldimethylsilyloxy)-8-chloro-5,6-dimethyl-13-((*S*)-oxiran-2-yl)oxacyclotrideca-5,7-diene-2,4-dione **(96)**

^{1}H NMR (500 MHz, $CDCl_3$, MB4p180Ef11 or MB3p249Ef9): δ 6.24 (s, 1H, C=C*H*), 4.69 (ddd, *J* = 10.8, 5.3 and 2.6 Hz, 1H, C(O)OC*H*), 3.75 (dddd, *J* = 9.1, 6.9, 3.2 and 3.2 Hz, 1H, TBSOC*H*), 3.65 (d, *J* = 12.2 Hz, 1H, C(O)CHH_aC(O)O), 3.45 (d, *J* = 12.2, 1H, C(O)CHH_bC(O)O), 3.02 (ddd, *J* = 5.4, 3.9 and 2.6 Hz, 1H, H_2C(O)C*H*), 2.78 (dd, *J* = 5.1 and 3.9 Hz, 1H, CH(O)CHH_a), 2.74 (dd, *J* = 5.1 and 2.6 Hz, 1H, CH(O)CHH_b), 2.42–2.32 (m, 2H, C=C(Cl)CH_2), 1.98 (ddd, *J* = 14.3, 10.9 and 3.4 Hz, 1H, OCHCHH_a), 1.92 (br s, 3H, (Cl)C=CCH_3), 1.89 (br s, 3H, C(O)C(CH_3)=C), 1.78 (ddd, *J* = 14.4, 9.3 and 2.7 Hz, 1H, OCHCHH_b), 1.74–1.69 (m, 1H, C=C(Cl)CH_2CHH_a) 1.61–1.57 (m, 1H, C=C(Cl)CH_2CHH_b), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.18 (s, 3H, SiCH_{3_a}) and 0.17 (s, 3H, SiCH_{3_b}).

^{13}C NMR (75 MHz, $CDCl_3$, MB4p180Ef11 or MB4p181Ef8 or MB4p266Ff10): δ 198.3, 165.2, 136.7, 136.2, 135.8, 126.9, 72.1, 66.3, 52.3, 48.2, 46.2, 38.0, 35.5, 33.2, 29.9, 26.0(3), 18.8, 14.9, –4.2 and –4.3.

NOE (1D goesy): MB4p296Ff8-9

Irradiation of protons at 2.42–2.32 ppm resulted in enhancement of the proton at 6.24 ppm.

Irradiation of methyl protons at 1.92 ppm resulted in enhancement of the proton at 6.24 ppm.

Irradiation of methyl protons at 1.89 ppm resulted in enhancement of the proton at 3.65 ppm.

Irradiation of the proton at 6.24 ppm resulted in enhancement of protons at 3.75, 2.42–2.32, 1.92, 1.74–1.69 and 0.17 ppm.

COSY: MB4p181Ef8, MB4p180Ef11

HMQC: MB4p296Ff8-9 or MB4p266Ff10

HMBC: MB4p296Ff8-9 or MB4p266Ff10 or MB4p181Ef8

^{1}H NMR (500 MHz, C_6D_6, MB5p28Ef7): δ 6.28 (s, 1H, C=C*H*), 4.70 (ddd, *J* = 11.0, 5.3 and 2.7 Hz, 1H, C(O)OC*H*), 3.85 (dddd, *J* = 10.6, 8.0, 3.3 and 3.3 Hz, 1H, TBSOC*H*), 3.29 (d, *J* = 11.4 Hz, 1H, C(O)CHH_aC(O)O), 3.03 (d, *J* = 11.5 Hz, 1H, C(O)CHH_bC(O)O), 2.77 (ddd, *J* = 5.8, 3.5 and 2.9 Hz, 1H, H_2C(O)C*H*), 2.46 (dd, *J* = 5.1 and 2.4 Hz, 1H, CH(O)CHH_a), 2.35 (ddd, *J* = 14.5, 10.7 and 3.0 Hz, 1H, C=C(Cl)CHH_a), 2.27 (dd, *J* = 5.2 and 3.9 Hz, 1H, CH(O)CHH_b), 2.13 (ddd, *J* = 15.0, 6.5 and 3.0 Hz, 1H, C=C(Cl)CHH_b), 2.00 (ddd, *J* = 14.2, 11.2 and 3.2 Hz, 1H, OCHCHH_a), 1.74–1.64 (m, 2H, OCHCHH_b and C=C(Cl)CH_2CHH_a), 1.67 (s, 3H, (Cl)C=CCH_3), 1.46 (dddd, *J* = 14.3, 7.6, 6.7 and 3.1 Hz, 1H, C=C(Cl)CH_2CHH_b), 1.37 (s, 3H, C(O)C(CH_3)=C), 1.01 (s, 9H, SiC(CH_3)$_3$), 0.34 (s, 3H, SiCH_{3_a}) and 0.32 (s, 3H, SiCH_{3_b}).

^{13}C NMR (125 MHz, C_6D_6, MB5p28Ef7): δ 197.1, 164.6, 136.2, 135.2, 127.3, 123.1, 72.3, 66.3, 51.9, 48.0, 45.5, 38.4, 35.6, 33.5, 27.8, 26.1(3), 18.1, 14.2, –4.1 and –4.3.

NOE (1D goesy): MB4p28Ef7

Irradiation of methyl protons at 1.67 ppm resulted in enhancement of protons at 6.28, 4.70, 3.85, 2.00 and 1.37 ppm.

Irradiation of methyl protons at 1.37 ppm resulted in enhancement of protons at 3.29 and 1.67 ppm.

Irradiation of the proton at 6.28 ppm resulted in enhancement of protons at 4.70, 3.03, 2.46, 2.35, 1.74–1.64 and 1.67 ppm.

COSY, HMQC and HMBC: MB5p28Ef7

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc, MB3p238Ef11): *m/z* = 443.0 $(M+H)^+$; t_r = 14.65 min.

Chapter II: Polyols from Soybean Oil

II.A. Introduction

The Hoye group is involved in collaborative efforts with groups in other areas of chemistry (e.g., polymers, materials, computational) as well as other departments (e.g., chemical engineering, medicinal chemistry). This project is a joint venture between a number of groups in chemistry and chemical engineering and material science (CEMS). In this chapter, the discussion will focus primarily on our contribution toward making polyols from soybean oil. Our knowledge of chemical reactions and our ability to analyze the products (and byproducts) help guide the route to making polyols from renewable resources, which we hope will be able to compete with petrochemical polyols.

II.B. Background

Polyurethanes are polymers containing urethane linkages between polyols and isocyanates. The major applications are flexible (*e.g.*, seating and bedding) and rigid foams (*e.g.*, thermal insulators) but use in coatings, adhesives, sealants, and elastomers (CASE) applications are also common. As we try to move away from our dependence on petrochemicals (because of cost and limited feedstock), there has been increasing interest in making vegetable oil polyols. Vegetable oil is readily available, renewable and inexpensive. However, to be used as a polyol, hydroxyl group functionality needs to be incorporated. To compete with petrochemical polyols, natural oil polyols need to have certain molecular weights (MWs) and number of hydroxyl groups (f_n). For flexible

foams MWs between 3-6 kg/mol and f_n around 2-3 are needed while application in rigid foams generally require lower MWs of *ca.* 1-2 kg/mol but higher f_n (*e.g.*, 4-6).[66]

We propose to use soybean oil (SBO) as our renewable resource to make polyols for use in polyurethanes. Soybean oil is a readily available, inexpensive starting material. In general, vegetable oils (triglycerides) are comprised of a glycerol unit and 3 fatty acid chains. The triglycerides in soybean oil (Figure II-1) typically comprise a combination of 5 fatty acid moieties: palmitic (11%), stearic (4%), oleic (23.4%), linoleic (53.3%) and linolenic (7.8%).[67] Palmitc and stearic acid are fully saturated chains of 16 and 18 carbons, respectively. Oleic, linoleic, and linolenic acid all contain *cis*-alkenes in the 18-carbon chain. Oleic acid has one unsaturation unit (lipid number is 1) and is an ω-9 fatty acid (counting in from the chain end, contrary to IUPAC naming). Linoleic acid, an ω-6 fatty acid, is the most abundant in SBO and has a skipped diene unit. Linolenic acid, a skipped triene, has 3 *cis*-alkenes and is an ω-3 fatty acid. As a result of having 5 different fatty acids for the 3 chains of the triglyceride, soybean oil varies molecule to molecule. Based on the percentages given above for the different fatty acids and the fact that there are 3 chains per molecule, the calculated average number of double bonds per molecule is 4.6 ((0.234+(0.533x2)+(0.078x3))x3) and the average molecular weight is 868.7 g/mol. The percentages can change based on the growing season, climate, region, processing, etc. and as a result, different averages are reported. Although we can analyze our sample of soybean oil and determine more accurate values, we used 4.4 as the

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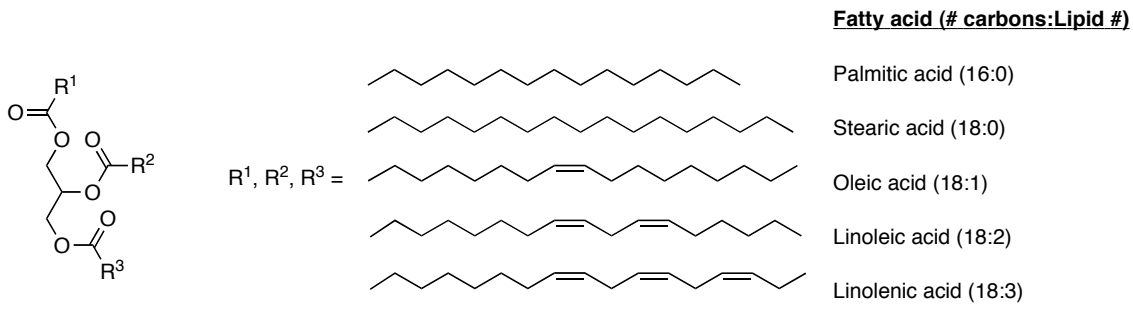
[66] "Polyurethanes from Vegetable Oils," Petrovic, Z. S. *Polym. Rev.*, **2008**, *48*, 109-155.
[67] "Vegetable oil-based polymeric materials: synthesis, properties, and applications," Xia, Y.; Larock, R. C. *Green Chem.* **2010**, *12*, 1893-1909.

average number of double bonds per molecule and a molecular weight of 872.5 g/mol for all the experiments that will be discussed.

Figure II-1: The triglyceride structure and fatty acid chains of soybean oil.



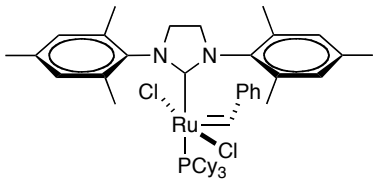
Polyols have already been prepared from soybean oil. The required hydroxyl groups can be introduced in a variety of ways.[66] Epoxidation (ESBO is commercially available) of the double bonds followed by opening with a nucleophile (such as MeOH) gives secondary hydroxyls (in the middle of long fatty chains), which are not as reactive with isocyanates. One product of this method, BiOH®, has been successful as a polyol in polyurethane synthesis, but, in order to maintain product performance, the renewable content is only 5-20%.[68] Another technique is hydroformylation followed by reduction of the aldehyde, which gives (more reactive) primary hydroxyls. Other chemistry performed on soybean oil, such as metathesis and esterification of the ester bonds, has been used to make renewable polyols. We will use known reactions to transform soybean oil into new polyols. We want to improve the amount of renewable content in polyurethane formulations by making polyols with properties that will compete (both in properties and price) with petrochemical polyols.

[68] BiOH® A Cargill Innovation. Our Story. http://www.bioh.com/bioh_story.html (accessed May 24, 2011).

II.C. Results

A suitable polyol would need certain molecular weight ranges and the desired hydroxyl functionality (for specific applications). To transform soybean oil into a polyol, we plan to increase the molecular weight first, which will be accomplished by metathesis chemistry using Grubbs' 2nd generation catalyst, **G2** (Figure II-2).[69] The remaining alkenes will be functionalized using the thiol-ene reaction.[70] This method incorporates the desired primary hydroxyl groups, which are more reactive than the secondary hydroxyls and therefore more similar to petrochemical polyols. The stoichiometry of the reaction should allow us to control the functionality, *i.e.*, the number of hydroxyls incorporated (f_n). Our approach, using oligomerized soybean oil, will allow for more distance between the reactive alcohols, which we propose will give better properties when incorporated into polyurethanes.

Figure II-2: Grubbs' 2nd generation catalyst, **G2**.



II.C.1. Metathesis Studies

Acyclic diene metathesis (ADMET) polymerization has been studied on a variety of substrates with different metathesis catalysts. Larock's group has reported ADMET of model compounds and vegetable oil, including soybean oil, using Grubbs' 1st generation

[69] "Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands," Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.
[70] "Thiol-Ene Click Chemistry," Hoyle, C. E.; Bowman, C. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 1540-1573.

catalyst (**G1**, having another tricyclohexylphosphine (PCy_3) in place of the *N*-heterocyclic carbene in **G2**).[71] Following their lead, we set out to metathesize the fatty esters (as models) and soybean oil using **G2**. We had the aim of constructing soybean oil oligomers having desired molecular weights and taking the oligomers forward using thiol-ene chemistry. We also hoped to add to the understanding and analysis of the metathesized products.

Metathesis of methyl oleate (*cis*-**201**) should form diester **202** and hydrocarbon **203** in the same ratio (Scheme II-1). With only one alkene in the center of the fatty ester chain, the ruthenium alkylidene species formed will have 9 carbons with either an ester or methyl end. Since the products can undergo metathesis as well, we would expect a statistical mixture of products and starting material (1:1:2 of **202**:**203**:**201**). Monitoring by GCMS was a convenient method since aliquots could be submitted at various time points and GCMS allowed us to see starting material and products as well as their *cis/trans* isomers. As an aside, the *cis* isomers eluted first and became further separated from the *trans* isomers at longer retention times. Analysis by ^{1}H NMR spectroscopy is not as useful in this case since the protons in the starting material and products are very similar.

Methyl oleate (***cis*-201**) was treated with **G2** (0.3-0.9 mol%) and gave the expected products **202** and **203** along with monoester **201** (Scheme II-1), all in a *cis/trans* mixture (1:6), using GCMS. In the ^{1}H NMR spectrum we could see alkene isomerization via the slight downfield shift of the vinyl protons and slight upfield shift of the allylic

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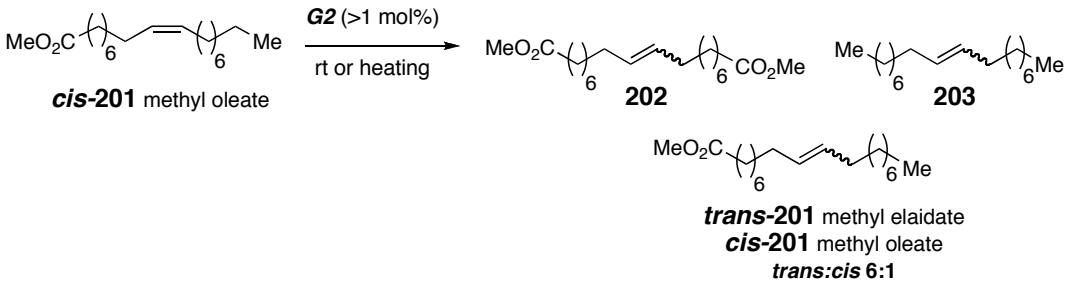
[71] (a) "Model Studies and the ADMET Polymerization of Soybean Oil," Tian, Q.; Larock, R. C. *J. Am. Oil Chem. Soc.* **2002**, *79*, 479-488. (b) "Ruthenium-Catalyzed Metathesis of Vegetable Oil," Refvik, M. D.; Larock, R. C.; Tian, Q. *J. Am. Oil Chem. Soc.* **1999**, *76*, 93-98.

protons. Using technical grade (75%) starting material, we noticed a pattern of peaks (almost quintet-like) around each of the 3 major components (**201**, **202**, and **203**). The peaks differed by masses of (+ or –) 14 (a CH_2 unit) and were found to be products obtained by migration of the double bond along the fatty acid chain. This has been reported previously and can be suppressed by addition of benzoquinone, which reacts with the suspected culprit, a ruthenium-hydride species.[72] Interestingly, when a more pure sample (99%) of ***cis*-201** was used, the only products were diester **202** and hydrocarbon **203** (along with *Z* to *E* isomerization of the starting material) at room temperature or when heated to 45 °C. Upon heating to 100 °C, the double bond migrates and the analogues (varying by 14) of starting material and products are apparent. Adding more catalyst and heating to a higher temperature yields an even greater array of products. This would imply that both impurities in the starting material and the temperature play a role in formation of the undesired ruthenium-hydride species. This is potentially significant because these byproducts may correlate with catalyst lifetime – an important factor impacting the economic validity of the reaction.

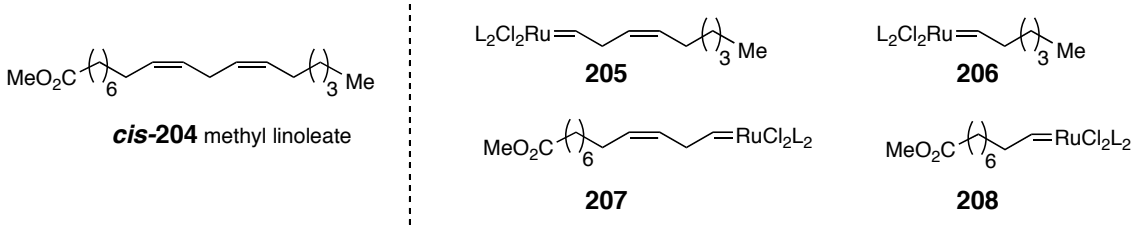
Scheme II-1: Self-metathesis of methyl oleate (***cis*-201**) with **G2**.



[72] "Studying and Suppressing Olefin Isomerization Side Reactions During ADMET Polymerizations," Fokou, P. A.; Meier, M. A. R. *Macromol. Rapid Commun.* **2010**, *31*, 368-373.

The metathesis of methyl linoleate (***cis*-204**, Figure II-3) is more complicated due to the presence of the skipped diene. Now, there are twice as many ruthenium alkylidene species to consider. The 6-carbon chain alkylidene **206** must have a methyl end group. However, the alkylidene having a 9-carbon chain can contain either a methyl, as in **205**, or ester, yielding **208**, end group. With species like **205** in play, cross metathesis (CM) could construct a product containing a skipped diene. Intermediate **207** is also possible, having a 12-carbon chain and an ester end group.

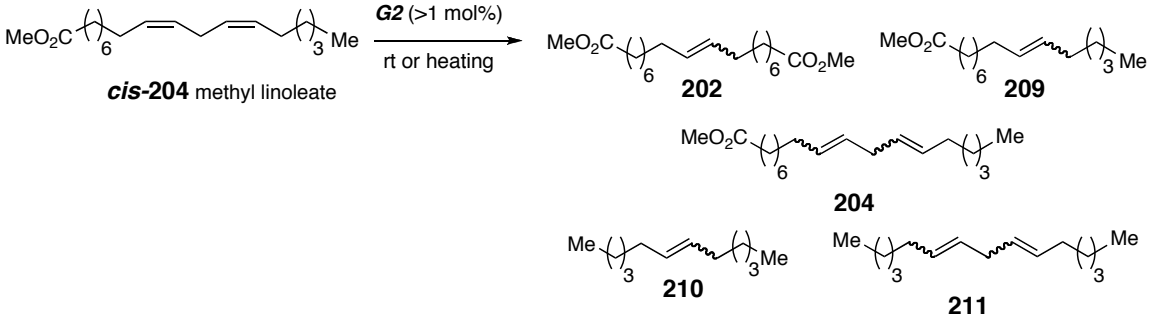
Figure II-3: Possible ruthenium alkylidene species when methyl linoleate (**205**) is treated with **G2**.



With these considerations, the reaction of methyl linoleate with **G2** gave a more complicated GC chromatogram displaying 5 major products (as *cis/trans* mixtures) as shown in Scheme II-2 in a 1:1:4:2:2 ratio of **210**:**211**:**209**:**204**:**202** (by GCMS integration). The major product is monoester **209**, a 15-carbon compound from CM of a 9-carbon ester fragment and a 6-carbon hydrocarbon chain. Some of the products still contain a skipped diene (like **211**) from ruthenium alkylidene **205**. In very small amounts, products containing 3 double bonds are present (like an 18-carbon skipped triene from the CM of two 9-carbon chains like the one on ruthenium in **205**). Analysis by ^{1}H NMR spectroscopy again indicates *cis*/*trans* isomerization. Also evident are two singlets that were assigned to be 1,4-cyclohexadiene. Metathesis of linoleic and linolenic

esters has been reported to yield cyclohexa-1,4-diene.[73] To drive the equilibrium further toward the products and eventually eliminate the skipped diene units, we would need to remove the smaller, more volatile hydrocarbons.

Scheme II-2: Self-metathesis of methyl linoleate (***cis*-204**) with **G2**.



If we took the next linear step, we would perform the metathesis of methyl linolenate, a skipped triene. Since we've added another double bond, we would have to consider two more ruthenium alkylidene species, giving 6 total. Instead, we moved on to the desired substrate, soybean oil. At the outset, we had a few goals in studying the metathesis of SBO. We wanted to understand the equilibrium and then expand our studies to drive the reaction to completion by removing the smaller hydrocarbons along with all the skipped dienes in the fatty acid chains.

Soybean oil was reacted with **G2** both neat and in C_6D_6 in an NMR tube and analyzed over time. In this case, the materials are too big to analyze by GCMS (unless we esterify to the fatty esters prior to analysis) so we turn to ^{1}H NMR spectroscopy. In C_6D_6, 11 mol% of catalyst was added to soybean oil and within an hour the peak corresponding to the bis-allyic protons was gone and a substantial amount of dihydrobenzene was formed (as described above in methyl linoleate metathesis).

[73] "Formation of Cyclohexa-1,4-diene by Metathesis of Linoleic and Linolenic esters," Verkuijlen, E. Boelhouwer, C. *Chem. Comm.* **1974**, 793-794.

Isomerization (*Z* to *E*) of the double bonds was also noted, favoring the *trans* configuration. Neat soybean oil was treated with **G2** (0.3 mol%) and the reaction was monitored by No-D[52] NMR. After 24 hours a small amount of dihydrobenzene and *cis/trans* isomerization were evident. The importance of catalyst load was already apparent in the first couple of experiments.

At this point, the study of the metathesis reaction was taken over by another member of the Hoye group, Senthil Gurusamy-Thangavelu. Through his studies we have successfully metathesized soybean oil to form oligomers. The best results are obtained with 0.1 mol% catalyst, heating to 100 °C and applying a vacuum (to remove the small hydrocarbons and drive the reaction toward our desired products of higher molecular weights). Various methods were used to analyze the oligomers, mainly GPC, NMR and MALDI-MS.[74] The biggest challenge has become economics. Impurities in the starting material or catalyst decomposition have kept us from being successful at catalyst load levels below 0.05 mol%. Due to the required high catalyst loads, the material produced by this process is unlikely to be competitively priced with other polyols from renewable resources such as BiOH®.

II.C.2. Thiol-ene Chemistry

The thiol-ene reaction has been studied on a variety of substrates, has gained notoriety as a "click" reaction,[75] and is seeing greater use in polymer[76] and even biobased

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[74] (a) "Rapid characterization of edible oils by direct matrix-assisted laser desorption/ionization time-of-flight mass spectrometry analysis using triacylglycerols," Lay, J. O., Jr.; Liyanage, R.; Durham, B.; Brooks, J. *Rapid Commun. Mass Spectrom.* **2006**, *20*, 952-958. (b) "Reducing fragmentation observed in the matrix-assisted laser desorption/ionization time-of-flight mass spectrometric analysis of triacylglycerols in vegetable oils," Gidden, J.; Liyanage, R.; Durham, B.; Lay, J. O., Jr. *Rapid Commun. Mass Spectrom.* **2007**, *21*, 1951-1957.

[75] "Click Chemistry: Diverse Chemical Function from a Few Good Reactions," Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004-2021.

polymer[77] and polyol[78] synthesis. The thiol-ene reaction can be initiated under thermal or photochemical conditions, which forms the thiyl radical that adds to the alkene, yielding a carbon radical (Figure II-4). The carbon-centered radical abstracts a hydrogen atom from another alkylthiol to construct the thioether (thiol-ene adduct) and a thiyl radical, propagating the radical chain.[79] The rate-determining step is the abstraction of the thiol hydrogen by a carbon radical and as a result the thiol structure is relevant.[79] Termination occurs when two thiyl radicals combine to give a disulfide, two carbon radicals form oligomers or a thiyl radical combines with a carbon radical. (This last issue is why some would argue against calling this a "click" reaction.) The thiol-ene reaction has regioselectivity issues to consider since the thiyl radical can add to either carbon (with the R^2 or R^3 substituent) of the alkene. These problems are compounded in substrates like methyl linoleate, where regioselectivity between carbons of the alkene and the different alkenes in the chain become relevant. The reader should keep this in mind and the array of products will be portrayed as best as possible in the schemes below. Both thermal and photochemical initiation of the thiol-ene reaction will be discussed in the following sections.

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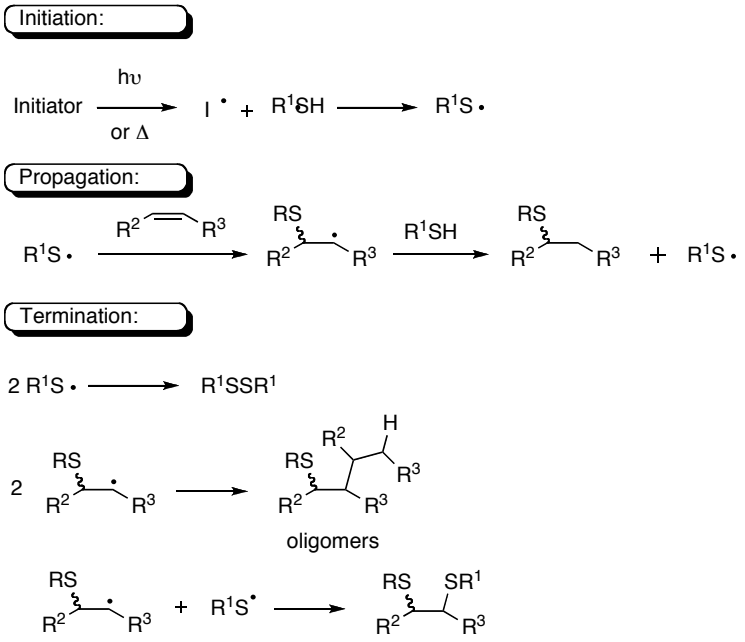
[76] "Thiol-ene "click" reactions and recent applications in polymer and materials synthesis," Lowe, A. B. *Polym. Chem.* **2010**, *1*, 17-36.
[77] "Thiol-ene *vs*. ADMET: a complimentary approach to fatty acid-based biodegradable polymers," Turunc, O.; Meier, M. A. R. *Green Chem.* **2011**, *13*, 314-320.
[78] "Synthesis of Biobased Polyols by Thiol-ene Coupling from Vegetable Oils," Desroches, M.; Caillol, S.; Lapinte, V.; Auvergne, R.; Boutevin, B. *Macromolecules* **2011**, *44*, 2489-2500.
[79] "Reactivity and Reversibility in the Reaction of Thiyl Radicals with Olefins," Walling, C.; Helmreich, W. *J. Am. Chem. Soc.* **1959**, *81*, 1144-1148.

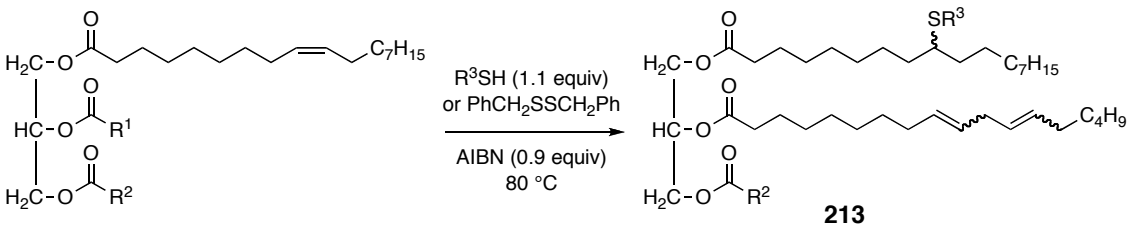
Figure II-4: Chain propagation of the thiol-ene reaction.



II.C.2.a. Thermal Conditions

Initially, we used thermal conditions for initiation of the thiol-ene. Early results were not promising. Soybean oil (**212**) was treated with two different thiols (benzenethiol and octanethiol) and AIBN, heated to 80 °C and monitored by ^{1}H NMR spectroscopy (Scheme II-3). Since the aim was to functionalize a few alkenes, the alkene to thiol ratio was ~4:1 (soybean oil has an average number of 4.4 double bonds per molecule). There was evidence of a desired thiol-ene adduct like **213**, but there appeared to be a lot of unproductive side reactions as well as incomplete conversion (remaining thiol). Isomerization of the double bonds (all *cis* in starting material) occurred very quickly, eventually reaching an equilibrium ratio of ~6:1 (*trans*:*cis*). This occurs through

Scheme II-3: Thermal thiol-ene reaction of soybean oil with thiols using AIBN.

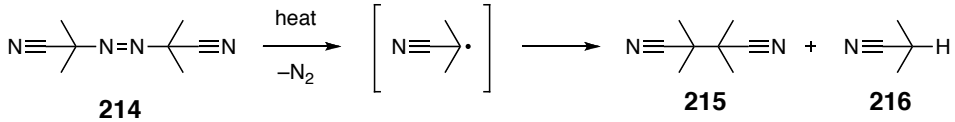


212 Soybean oil
R^1 and R^2 = palmitic, stearic, oleic, linoleic, or linolenic

213
R^1 and R^2 = palmitic, stearic, oleic, linoleic, or linolenic
$R^3 = (CH_2)_7CH_3$ or CH_2Ph

a reversible addition of the thiyl radical to an alkene carbon.[80] The fate of AIBN was also relevant. The 2-cyanoprop-2-yl radical (from AIBN) underwent dimerization to a slightly greater extent than proton abstraction (preferably from thiol) to give **215** and **216** respectively (Scheme II-4). Maybe AIBN is not the best initiator since the resulting radical is dimerizing instead of abstracting the thiol proton.

Scheme II-4: Byproducts formed from AIBN.



214
AIBN

215

216

To study the reaction more, we ran a few experiments. One idea was to cleave a disulfide bond to form thiyl radicals. Soybean oil was treated with benzyl disulfide and AIBN and heated. There was little (if any) hint of alkene isomerization and the starting disulfide remained. As expected, we saw undesired byproducts from AIBN, mostly formation of dimer **215**, but isobutyronitrile (**216**) was also present. The 2-cyanoprop-2-yl radical must have abstracted a proton, likely a bis-allylic proton, from soybean oil since the disulfide (and not thiol) was used.

[80] "The Elaidinization of Methyl Oleate with Mercaptans," Kircher, H. W. *J. Am. Oil Chem. Soc.* **1964**, *41*, 351-354.

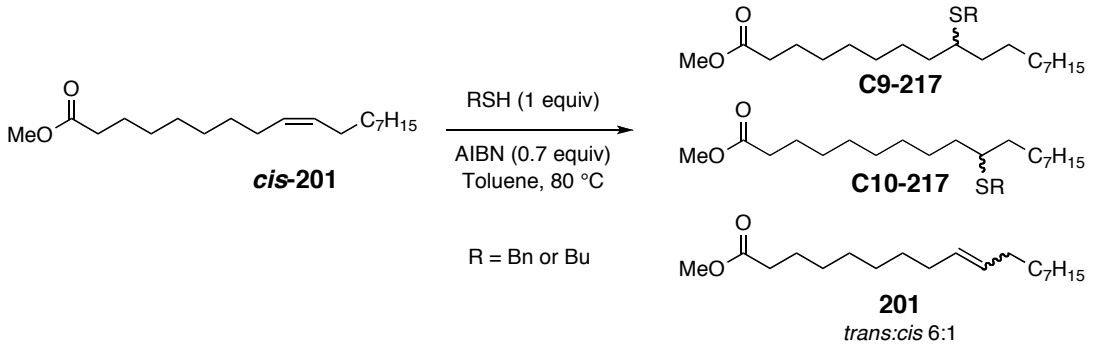
This result prompted us to consider the ease of abstracting the bis-allylic protons (in the linoleate and linolenate chains). To study this, we treated soybean oil with AIBN at various temperatures. At 50 and 65 °C, formation of isobutyronitrile (**216**) was not evident. Even after extended heating at 50 °C, AIBN was still present. Within an hour at 100 °C, dimer **215** and a trace amount of isobutyronitrile (**216**) are realized. The cyanopropyl radical does abstract bis-allylic protons from soybean oil but this only occurs after prolonged heating at high temperatures.

In order to learn more about the optimal thermal conditions, methyl oleate and methyl linoleate were studied. Starting with the simpler of the two, methyl oleate (***cis*-201**), having only one unsaturation unit, was treated with a full equivalent of thiol (benzyl and butanethiol) and AIBN (70 mol%) in toluene (Scheme II-5). Solvent was used in this case because previous results suggested there were solubility problems with AIBN. Heating this mixture gave the desired thiol-ene adducts (**C9-** and **C10-217**). However, even though a full equivalent of thiol was added, half the starting material alkene remained as a (1:6) mixture of *cis* (methyl oleate) and *trans* (methyl elaidate) isomers. There was some disulfide byproduct but only a hint of starting thiol remained. There was also a greater amount of isobutyronitrile (**216**) produced compared to dimer **215**. The butanethiol adduct of methyl oleate **217**, along with the remaining alkene **201**, was purified by MPLC and analyzed by NMR and GCMS. Mass spectrometry showed similar amounts of the 2 regioisomeric C9 and C10-**217** adducts (based on different fragmentations[81]). Starting with methyl linoleate (two unsaturation units), the thiol-ene

[81] "Determination of Double Bond Position in Mono-Unsaturated Acetates by Mass Spectrometry of Dimethyl Disulfide Adducts," Buser, H.-R.; Arn, H.; Guerin, P.; Rauscher, S. *Anal. Chem.* **1983**, *55*, 818-822.

chemistry was not as clean. Based on side products, incomplete conversion (even with an equivalent of thiol) and the amount of AIBN (almost a full equivalent) needed for these reactions, we decided to move from thermal to photochemical conditions.

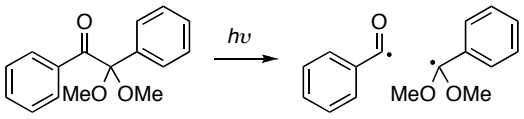
Scheme II-5: Thermal thiol-ene reaction of methyl oleate with thiols using AIBN.



II.C.2.b. Photochemical Conditions

Thiol-ene reactions under photochemical conditions have been reported and most relevant is a study using butanethiol and vegetable oil.[82] Bantchev irradiated the reactions ($\lambda < 325$ nm), used a photoinitiator, 2,2-dimethoxy-2-phenylacetophenone (DMPA, Scheme II-6) for some reactions and, for the best results, used a 6:1 ratio of thiol to double bond. We wanted to use their methodology but noted that they wanted to functionalize all the alkenes, while our goal was to react only a portion. We began looking at the reaction with simpler starting materials (the alkene and the thiol) and moved on to our desired system (soybean oil and mercaptoethanol).

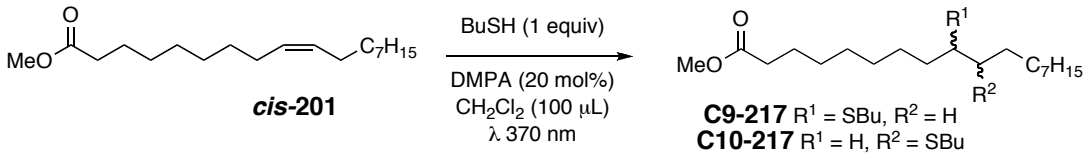
Scheme II-6: DMPA and the radicals formed by photoinitiation.



[82] "Free Radical Addition of Butanethiol to Vegetable Oil Double Bonds," Bantchev, G. B.; Kenar, J. A.; Biresaw, G.; Han, M. G. *J. Agric. Food Chem.* **2009**, *57*, 1282-1290.

The thiol-ene addition of butanethiol to methyl oleate was studied under a variety of conditions. Full conversion to our desired adducts, C9- and C10-**217,** was achieved upon exposure to black light (λ ~370 nm) in the Rayonet for 2 hours, using DMPA (20 mol%) as the photoinitiator (Scheme II-7). A minimal amount of solvent, CH_2Cl_2, was used to solubilize the DMPA. Cutting back the amount of DMPA to 2 mol% still resulted in formation of thioether **217** but after 2 hours about 15% of (isomerized) alkene remained along with a small amount of thiol. This reaction (using 2 mol% DMPA) was repeated without the use of solvent and after 2 hours, 25% of the double bonds were still present. A minimal amount of solvent is beneficial and the amount of DMPA is important for conversion.

Scheme II-7: Thiol-ene reaction of methyl oleate and butane thiol.



To see if the photoinitiator was needed, we tried reactions without DMPA but still exposed to black lights. There was evidence of thiol-ene addition as well as *cis/trans* isomerization. After 24 hours, there was a 1.5:1 ratio of thioether **217** to remaining alkene **201**, having a *cis:trans* ratio of 1:5. The photoinitiator is important since it leads to more efficient formation of the thiyl radical.

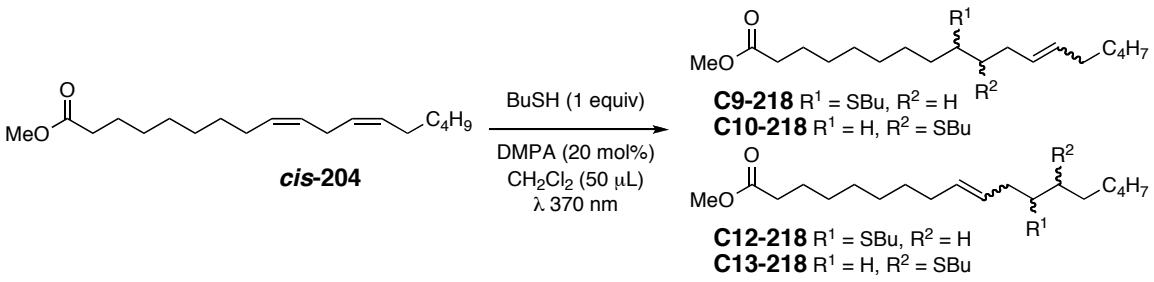
In an early experiment it was noted that isomerization and product formation were visible in the ^{1}H NMR spectrum after the reaction sat under hood light for a few hours prior to exposure to black lights. Reactions were set up with and without DMPA (20 mol% when added) and then left out in room light or placed in a dark cabinet covered in

foil. After 24 hours, the reaction with initiator and light exposure had a ratio of 1:9 thioether to alkene (1:2 *cis:trans*). The mixture placed in a dark cabinet had a lower conversion (16:1 alkene:thioether) and contained mostly *cis* alkene (2:1). Without DMPA, there was evidence of alkene isomerization and the thio-ene adduct, albeit in a smaller proportion than with the photoinitiator. As expected, the conversion was greater when exposed to light versus left in the dark.

From the above reactions, we took away a few helpful hints about moving toward our desired substrates. Although radical formation could be initiated by room light, the reaction was faster when exposed to the higher energy black lights. Both light sources are capable of forming the thiyl radical since we saw thioether formation in the absence of photoinitiator. Solvent wasn't necessary but better results were obtained when the DMPA was solubilized.

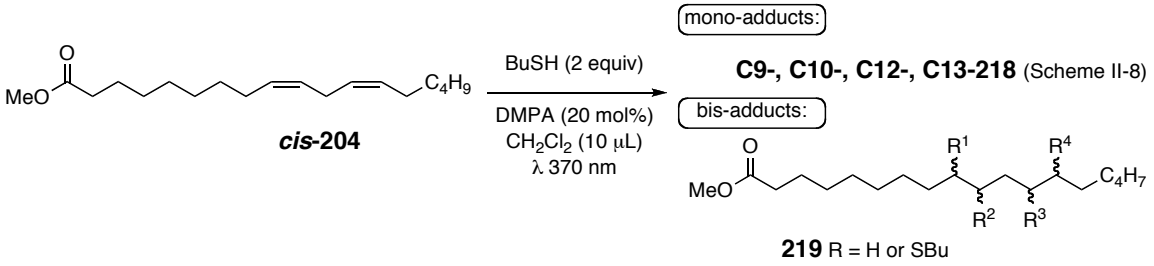
The reaction using methyl linoleate, having a skipped diene, led to more complicated data. A similar procedure as described above was followed. A mixture of methyl linoleate (***cis*-204**), DMPA, and butanethiol was placed under black lights (Scheme II-8). When 2 mol% DMPA was used, there was evidence of double bond isomerization but not any thioether. The use of more photoinitiator (20 mol%) led to a greater amount of the *trans* alkene and showed evidence of mono-thioether **218** by ^{1}H NMR, GCMS and LCMS analyses. The products were hard to purify by MPLC since alkene **204** and the four regioisomeric thioether products (**218**) eluted together on silica gel.

Scheme II-8: Photochemical thiol-ene of methyl linoleate and butanethiol.



Almost all (90%) of the alkenes were functionalized when more butanethiol (2 equivalents) was added (Scheme II-9). These conditions led to the formation of bis-thioether **219** (4 possible regioisomers) as well as the mono adducts (**218**) described above. The products eluted together when purified by MPLC and could be analyzed by ^{1}H NMR, GCMS and LCMS. There were many peaks that had a mass corresponding to the bis-thioether (**219**) by GC since there are regio- and stereoisomers to consider.

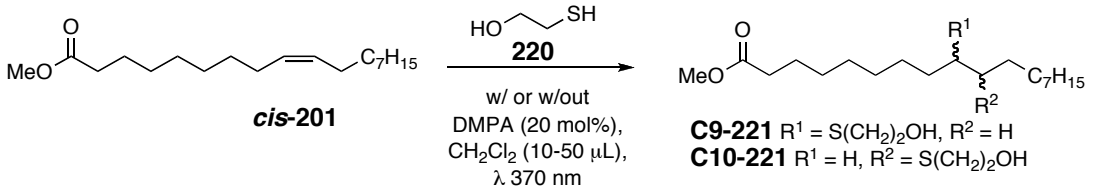
Scheme II-9: Adding 2 equivalents of butanethiol to methyl linoleate.



The thiol-ene chemistry was working well with butanethiol but we wanted to use the reaction to install primary hydroxyls. To accomplish this, we tested mercaptoethanol. Shown in Scheme II-10, methyl oleate (***cis*-201**) was treated with mercaptoethanol (**220**, 1 equiv) in CH_2Cl_2 (to solubilize the thiol and DMPA) and placed under black lights both with and without photoinitiator (DMPA, 20 mol%). Better results were obtained with DMPA and after 24 hours the ratio of thioether:alkene was 13:1. Without initiator, in the same timeframe, the ratio was only 1:1. In the latter experiment, starting thiol remained

even after 3 days of irradiation. In order to achieve full conversion, 2 equivalents of mercaptoethanol were needed. Since the thioether products are now more polar (having a hydroxyethyl instead of butyl chain), they were retained on the silica gel. As a result, the C9 and C10 regioisomeric adducts of **221** could be enhanced in the fractions by splitting the product peak (C9-**221** eluted first).

Scheme II-10: Thiol-ene of methyl oleate with mercaptoethanol.



Using disulfides was unsuccessful in the AIBN chemistry but it was worth trying under photochemical conditions. 2-Hydroxyethyl disulfide (0.5 equiv) was added to methyl oleate both with (20 mol%) and without photoinitiator. No thiol-ene product was observed after irradiation. The experiments were repeated having mercaptoethanol (**220**, 0.5 equiv) added as well as the disulfide. This resulted in formation of the desired adducts, but once the thiol starting material was gone, no further reaction was evident, which implied that the disulfide was not participating.

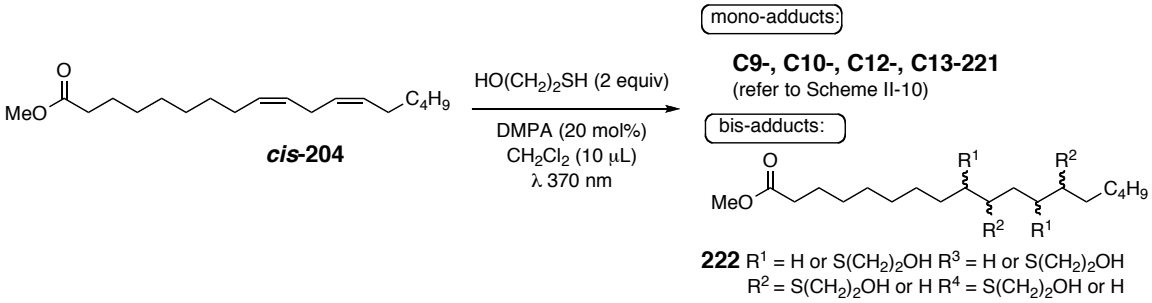
Since methyl oleate required two equivalents of mercaptoethanol to achieve full conversion and butanethiol only needed one, we did a competition experiment. Methyl oleate (***cis*-201**), DMPA (2 mol%), CH_2Cl_2, and both thiols (1.5 equiv each) were mixed and placed in the Rayonet reactor for 17 hours (Scheme II-11). By ^1H NMR analysis, the thiol-ene adducts were obtained in a similar ratio of 1.15:1, slightly favoring butylthioether **217**. However, GC only showed a small amount of the hydroxyethylthioether **221**. Acetylation of the product mixture allowed for better

interpretation in the ^{1}H NMR spectrum since the peaks moved apart. However, the GC chromatogram showed that even the acetate did not ionize well, giving a much different ratio than ^{1}H NMR integration.

Scheme II-11: Competition experiment between butanethiol and mercaptoethanol.

Methyl linoleate was also reacted with mercaptoethanol. Using 2 equivalents of thiol, both the mono- and bis-thioether products **221** and **222**, respectively, were formed (Scheme II-12). To obtain the mono-adducts (4 regioisomers), MPLC was performed with 3:1 hexanes:ethyl acetate. The more polar bis-adducts (4 regioisomers) were isolated using a 1:1 hexanes:ethyl acetate system. The adducts are formed and can be isolated but there are still issues to consider as we move to our desired system.

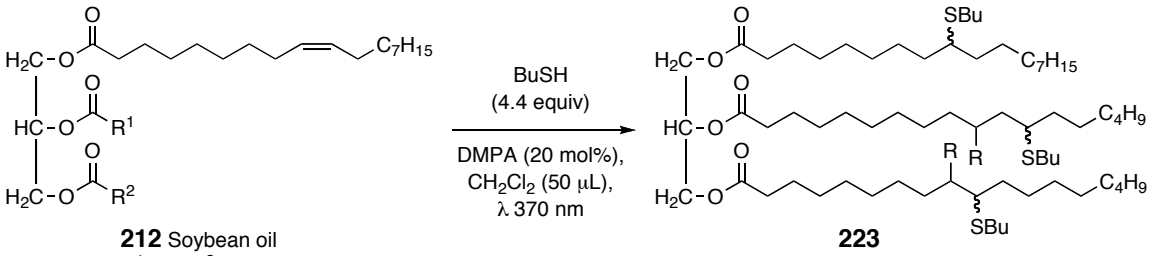
Scheme II-12: Methyl linoleate and mercaptoethanol adducts from thiol-ene.



The end goal is to use thiol-ene chemistry on soybean oil oligomers (from metathesis chemistry, Section II.C.1.) but we hoped to begin learning by starting with soybean oil. Soybean oil, having an average of 4.4 alkenes per molecule, is more complicated because of all the skipped dienes and regioisomers that would result from

the thiol-ene. Recall that metathesized soybean oil (Section II.C.1) would have no more than one alkene per chain (the number of alkenes per molecule is dependent on the size of oligomer formed by metathesis). Although, the final plan is to functionalize a few alkenes in a molecule (or oligomer), we started by reacting all the double bonds. Soybean oil (**212**) was treated with DMPA (20 mol%), CH_2Cl_2, and butanethiol (various equivalents) followed by exposure to black lights (Scheme II-13). The reaction was monitored by ^{1}H NMR spectroscopy and showed that the vinyl protons were gone in 6 hours with 4.4 equivalents of thiol. The peak pertaining to the bis-allylic protons is not visible either. Thioether **223** was purified by MPLC. By ^{1}H NMR integration, we calculated an average of 3 butane thioethers per molecule of SBO (using the glycerol methylene protons). This would lead us to believe that some carbon-centered radicals are adding to double bonds or terminating by reacting with another carbon radical (inter- and/or intramolecularly). Interestingly, when 2.2 equivalents of thiol (to react half of the double bonds) were used, a fraction isolated by MPLC gave integrations of 1.7 thioethers and 1.3 alkenes per molecule. This would again imply some C-C bond formation in the reaction.

Scheme II-13: Thiol-ene addition of butanethiol to soybean oil.



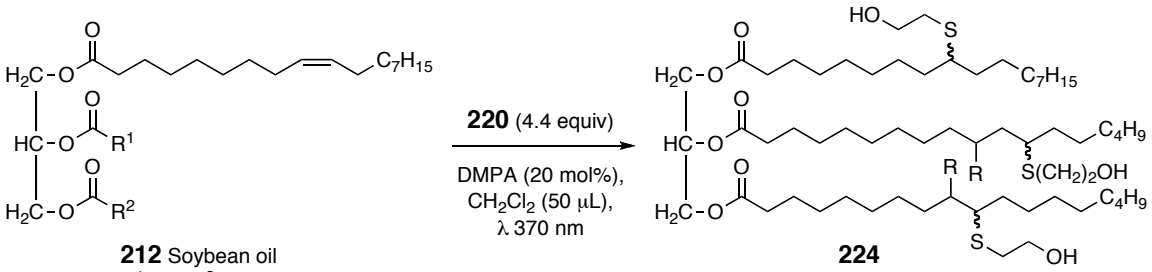
212 Soybean oil
R^1 and R^2 = palmitic, stearic, oleic, linoleic, or linolenic

223
R = C (inter- or intramolecular)

To move toward the final goal, a few more studies were conducted. Since the photoinitiator leads to some unwanted products that are difficult to separate from the desired products, it would be beneficial to use less photoinitiator. In some of the above experiments, 20 mol% DMPA was required because of the amount of thiol being used to functionalize all the double bonds. When 2 mol% of DMPA was used with butanethiol (4.4 equivalents), only starting materials (alkene and thiol) were observed, without a trace of thiol-ene adduct. When reactions with soybean oil were performed on smaller scales, even 20 mol% of DMPA did not give full conversion. Impurities in soybean oil or the thiol could be reacting with some of the DMPA making small-scale reactions difficult.

Incorporating the primary hydroxyls with mercaptoethanol led to more difficulties than encountered with butanethiol. Solubility is an issue since mercaptoethanol is only soluble in soyoil to the extent of a 1:1 molar ratio (by ^{1}H NMR analysis). Soybean oil (**212**) was treated with DMPA (20 mol%) in CH_2Cl_2 along with mercaptoethanol (**220**, 4.4 equiv) and irradiated to yield the desired thioether **224** (Scheme II-14). A

Scheme II-14: Thiol-ene adduct of soybean oil (**212**) and mercaptoethanol (**220**).



major component of the crude mixture was a thioester formed by combination of the benzoyl radical (from DMPA, Scheme II-6) to the thiyl radical (of mercaptoethanol). This side reaction may become a bigger problem as we try to reduce the amount of thiol

used in order to functionalize a fraction of the double bonds since we will have to consider the amount of thiol forming this byproduct as well as the role the byproduct will play in the final product mixture. As with butanethiol, stepping down to 2 mol% DMPA was unsuccessful. Using 10 mol% DMPA, the thiol-ene reaction occurred, but conversion was low and a substantial amount of mercaptoethanol remained, even after 17 hours of irradiation.

Since we only desire to functionalize a portion of the double bonds, we reduced the amount of both thiol and DMPA. Using 2.2 equivalents of mercaptoethanol (to react half of the double bonds in soybean oil), adduct formation occurred at 20, 10 and 1 mol% of DMPA. At 20 and 10 mol%, the product was a yellow viscous material. Some alkene remained, but the resonances for bis-allylic protons along with most of the linolenate chain end methyl groups were gone. However, at 1 mol% DMPA, only a small amount of conversion to the desired adduct had occurred and most of the mercaptoethanol remained. As a comparison, the same study using 10 and 1 mol% DMPA, along with 2.2 equivalents of mercaptoethanol was done on methyl oleate. This simpler alkene formed the desired product (**221**, Scheme I-10) with only 1 mol% DMPA. It appears that there are complications when soybean oil is used as a substrate, which requires higher loads of the photoinitiator. These issues are not fully understood at this point but may be related to the labile doubly allylic protons present in the dienic and trienic fatty acid moieties.

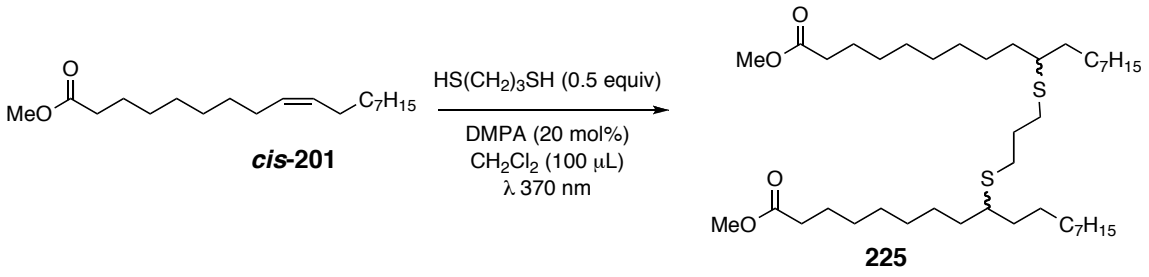
A problem was also discovered with mercaptoethanol. As time went on, there seemed to be more disulfide formed in the crude mixtures. It could be detected even at very early time points. We found that the mercaptoethanol sample had formed more of the disulfide over time. This is a problem, especially when using limiting amounts of

thiol to functionalize some of the alkenes, if the amount of disulfide is not considered. For this reason, some reactions, especially when limiting thiol, should be repeated. Mercaptoethanol should be looked at periodically to adjust for the amount of disulfide.

Crosslinking Experiments

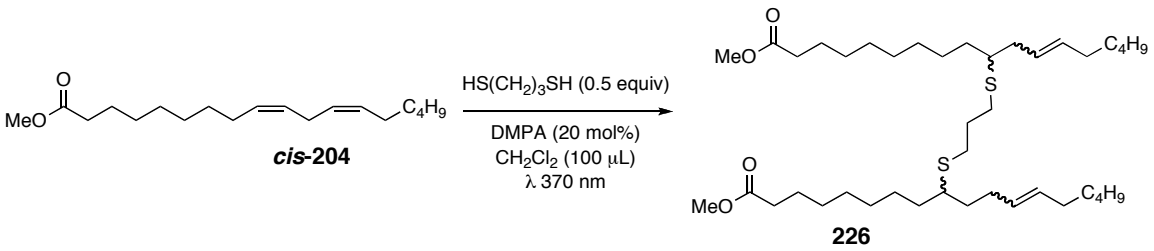
Since the metathesis chemistry did not work as well as planned and the thiol-ene chemistry worked well in some cases, we decided to try some crosslinking experiments with a dithiol to increase molecular weight and form soybean oil oligomers. The first experiment was on methyl oleate with DMPA (20 mol%) in CH_2Cl_2 and propane dithiol (0.5 equiv), which was irradiated for 15 hours. The desired 2:1 (methyl oleate:propanedithiol) adduct **225** was formed (Scheme II-15). This reaction is complete within 2 hours. Recall, there are still regioisomers present and the product drawn in Scheme II-15 is a representation of one regioisomer (having a thioether at C9 of one chain and C10 of the other). Cutting back to 0.25 equivalents (to react half the alkenes) was also successful. The chemistry is clean and full conversion of the dithiol was observed. MPLC allowed separation of the remaining alkene fatty esters (now mostly *trans*) from crosslinked material. The product was slightly viscous and did not smell like thiol, even prior to purification.

Scheme II-15: Crossinglinking of methyl oleate using propanedithiol.



The promising results using methyl oleate led us to move on to methyl linoleate. Methyl linoleate, propanedithiol (0.5 equiv), and DMPA (20 mol%) in CH_2Cl_2, upon irradiation, gave a viscous (pleasant smelling) material with broadened peaks in the ^1H NMR spectrum (Scheme II-16). The LCMS showed the correct mass (714, M+18) for a 2:1 adduct such as **226** (again recall the regioselectivity choices). By NMR integration, there were fewer vinyl protons than expected, implying some C-C bond formation. There is also the possibility of a 3:2 adduct, although there wasn't evidence to confirm its formation.

Scheme II-16: Crosslinking methyl linoleate with propanedithiol.



We also attempted crosslinking experiments on soybean oil. Propanedithiol (1 equiv) and DMPA (20 mol%) in CH_2Cl_2 was added to soybean oil and placed in the Rayonet reactor. We obtained a very viscous material that did not smell of thiol. Based on the amount of dithiol about half of the double bonds should have reacted. The product is harder to interrogate by ^1H NMR spectroscopy because the starting thiol peaks are similar to the thioether product peaks. Also when starting with soybean oil, there are many regioisomers possible. The thioether product could have a sulfur substituent that is allylic, bis-allyic, or in the middle of a long alkyl chain, which all result in slight chemical shift changes of the methine protons attached to the sulfur-bearing carbons. Stereoisomers also contribute to chemical shift differences. The peak shape in the ^1H

NMR spectrum and lack of odor suggests all the starting dithiol has reacted. The alkene integrations are close to the expected values if 45% of the double bonds are reacted. Another problem is the formation of 1,2-dithiolane, which has resonances that overlap with the bis-allylic and the allylic proton peaks. When less dithiol (0.2 equiv) was used with the same amount of DMPA, a slightly viscous material was formed and did not smell of thiols. The ^{1}H NMR spectrum of the crude product mixture is similar to the experiment just described, but there are fewer vinyl protons than expected. Less thiol was used in this case, so if the initiator does abstract bis-allylic protons, it would lead to more carbon-carbon bond formation.

Overall, the crosslinking experiments with propanedithiol seem to be working well. The starting dithiol reacts and there isn't any residual smell in the crude mixtures. This reaction could be a promising way to increase molecular weight. We need to find better ways to analyze the products (like GPC or MALDI-MS) since the NMR spectrum becomes more broad and complicated. The compounds are too large for GCMS and they do not behave well on LCMS (even soybean oil itself does not behave well). There are ongoing studies in the laboratory to use the thiol-ene reaction to crosslink (using dithiols) and add hydroxyl functionality (using a hydroxyl substituted thiol) in a single pot.

II.D. Conclusion

A variety of things were learned when performing metathesis on both the fatty acid methyl esters and on soybean oil itself. The *cis*/*trans* isomerization is rapid. The formation of 1,4-cyclohexadiene is interesting, because it removes the skipped dienes and the volatility of the byproduct allows us to remove it by vacuum. Removal of the smaller hydrocarbons during reaction by vacuum allows us to increase the molecular weight and

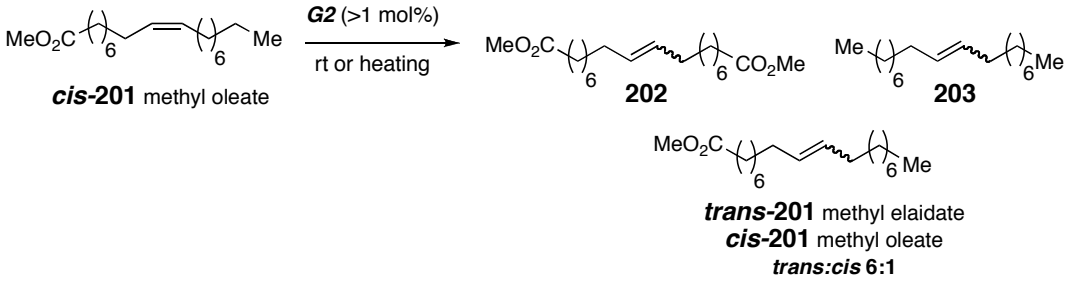
form larger oligomers. The largest hurdle is the amount of catalyst needed for consistent results. We would need to make large strides for metathesis to be an economically feasible option at this point. We could make attempts to clean up the soybean oil but likely that would not be enough.

The thiol-ene chemistry works well for some substrates. The problems arise as we move to more complicated substrates, like soybean oil, having impurities and bis-allylic protons. Not only is the ene starting material an issue, moving to our desired thiol, mercaptoethanol, introduced additional problems. We encounter solubility issues with this more polar thiol. Also, the S-H bond in mercaptoethanol is stronger than in other thiols used. Adding more initiator to form the thiyl radical resulted in a thioester byproduct from the initiator and thiol. This is a problem since we want to limit the amount of thiol added to the reaction in the first place. Similarly, disulfide formation is another roadblock since we know it will not react under our conditions. All of the byproducts left in the polyol will have an impact on the properties when it is used in a polyurethane formulation.

Using dithiols and thiol-ene chemistry to crosslink seems to be a viable idea. The chemistry works well and the products do not smell of thiol. Economics come into play again because now we are using a catalyst (DMPA) and a dithiol to form oligomers, which can impact cost significantly. The amount of dithiol needed to obtain certain molecular weights would depend on how often we were crosslinking molecules of soybean oil versus linking two chains within one molecule of soybean oil. Learning more about these issues using better analysis methods will help confirm whether this method should be pursued further.

II.E. Experimental

Dimethyl octadec-9-enedioate (202)



A vial was charged with methyl oleate (***cis*-201**, 100 mg, 0.34 mmol) and **G2** (3 mg, 0.003 mmol). The reaction was heated to 50 °C in an oil bath for 1 h. The crude reaction mixture was analyzed and is detailed below.

Characterization of crude product mixture (*cis:trans* 1:3) (File MB4p261D)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.40–5.36 (m, 2H, *H*C=C*H*$_{trans}$), 5.36–5.33 (m, 0.5H, *H*C=C*H*$_{cis}$), 3.67 (s, 3.7H, C(O)OC*H*$_{3\_trans/cis}$), 2.30 (t, *J* = 7.5 Hz, 2.8H, MeOC(O)C*H*$_{2\_trans/cis}$), 2.04–1.98 (m, 1H, C*H*$_2$CH=CHC*H*$_{2\_cis}$), 1.99–1.93 (m, 4H, C*H*$_2$CH=CHC*H*$_{2\_trans}$), 1.62 (dddd, *J* = 7.2, 7.2, 7.2 and 7.2 Hz, 2.8H, MeOC(O)CH$_2$C*H*$_{2\_trans/cis}$), 1.36–1.25 (m, 25H, Me(C*H*$_2$)$_{6\_trans/cis}$ and MeOC(O)CH$_2$CH$_2$(C*H*$_2$)$_{4\_trans/cis}$), 0.88 (t, *J* = 6.9 Hz, 3.9H, CH$_2$C*H*$_{3\_trans/cis}$).

Methyl octadec-9-enoate **(201)** (*cis:trans* 1:6)

GCMS (5027027): t_r = 17.72 min (*cis*) and 17.78 min (*trans*); *m/z* 296 (M^+, 25), 264 (M^+–MeOH, 100), 222 (M^+–CH_2=C(OH)OCH_3, 50), 180 (30), 97 (60), 83 (60), 69 (60) and 55 (90).

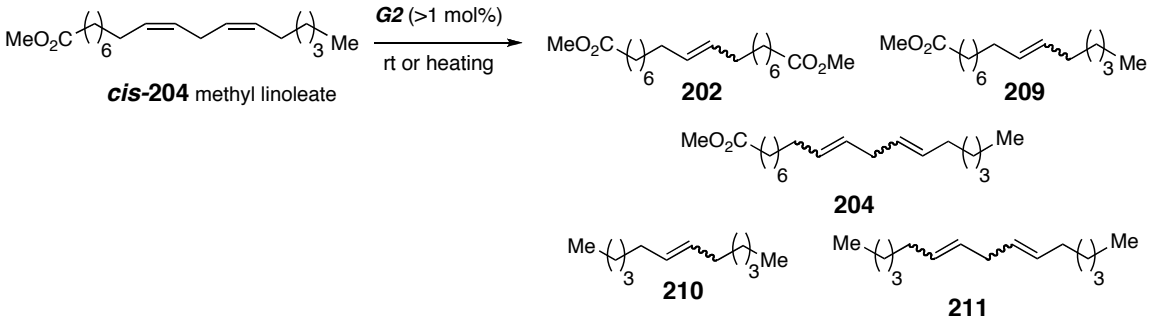
Dimethyl octadec-9-enedioate **(202)**

GCMS (5027027): t_r = 20.49 min (*cis*) and 20.57 min (*trans*); *m/z* 340 (M^+, 10), 308 (M^+–MeOH, 70), 276 (100), 248 (15), 95 (30), 81 (60) and 55 (75).

Octadec-9-ene **(203)**

GCMS (5027027): t_r = 14.55 min (*cis*) and 14.62 min (*trans*); *m/z* 252 (M^+, 75), 224 (M^+–$H_2C{=}CH_2$, 10), 125 (40), 111 (60), 97 (100), 83 (100), 69 (75) and 55 (100).

Dimethyl octadec-9-enedioate (202)



A vial was charged with methyl linoleate (***cis*-204**, 100 mg, 0.34 mmol) and **G2** (1 mg, 0.3mol%). The reaction was heated to 100 °C in an oil bath for 1 h. The crude reaction mixture was analyzed and is detailed below.

Characterization of crude product mixture (File MB5p44)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.44–5.32 (m, 2H, *H*C=C*H*$_{trans/cis}$), 3.67 (s, 3H, C(O)OC*H*$_{3\_trans/cis}$), 2.31 (t, *J* = 7.5 Hz, 3H, MeOC(O)C*H*$_{2\_trans/cis}$), 2.07–1.93 (m, 4H, C*H*$_2$CH=CHC*H*$_{2\_trans/cis}$), 1.66–1.57 (m, 3H, MeOC(O)CH$_2$C*H*$_{2\_trans/cis}$), 1.40–1.23 (m, 17H), 0.91–0.86 (m, CH$_2$C*H*$_{3\_trans/cis}$).

Dimethyl octadec-9-enedioate **(202)**

Characterization is listed in above experiment.

Methyl octadeca-9,12-dienoate **(204)**

GCMS (5027016): t_r = 10.17 min; *m/z* 294 (M^+, 70), 363 (M^+–OMe, 30), 109 (60), 95 (90), 81 (100) and 67 (85).

Methyl pentadec-9-enoate **(209)**

GCMS (5027016): t_r = 8.73 min; *m/z* 254 (M^+, 20), 222 (M^+–MeOH, 60), 180 (M^+–CH_2=C(OH)OCH_3, 50), 96 (60), 69 (75) and 55 (100).

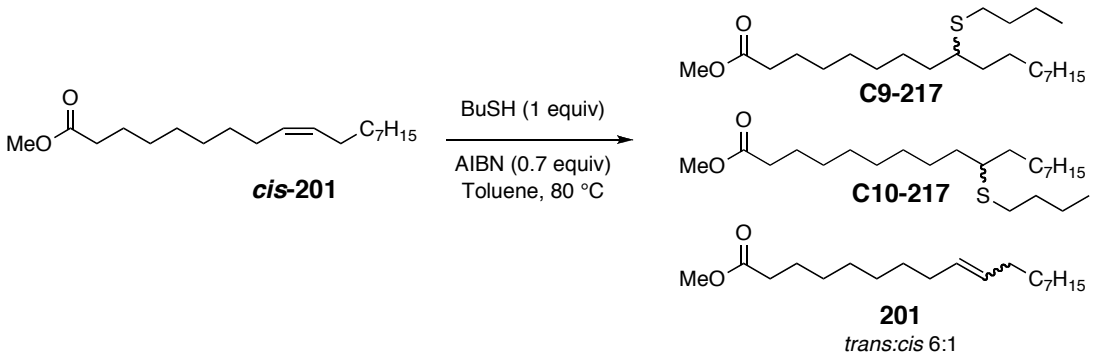
Dodeca-3,6-diene **(210)**

GCMS (5027016): t_r = 4.83 min; *m/z* 168 (M^+, 75), 83 (40), 69 (100) and 55 (75).

Pentadeca-6,9-diene **(211)**

GCMS (5027016): t_r = 6.86 min; *m/z* 208 (M^+, 40), 96 (50), 81 (40) and 67 (100).

Methyl 9-(butylthio)octadecanoate (C9-217)



A vial was charged with methyl oleate (***cis*-201**, 200 mg, 0.67 mmol), butanethiol (73 μL, 0.67 mmol) and AIBN (77 mg, 0.47 mmol). Toluene (1.2 mL) was added to solubilize the reaction before heating to 80 °C for 24 h. The mixture was concentrated under reduced pressure. Purification of a fraction of the crude material (120 mg) by MPLC (19:1 Hex:EtOAc) provided a mixture of **201** and **217** (66 mg, 1:1).

C9-217 and C10-217 (File MB4p200)

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.67 (s, 3H, C(O)OC*H*$_3$), 2.55 (dddd, *J* = 6.4, 6.4, 6.4 and 6.4 Hz, 1H, CH_2SC*H*), 2.48 (t, *J* = 7.4 Hz, 2H, CHSC*H*$_2$), 2.30 (t, *J* = 7.5 Hz, 2H, MeOC(O)C*H*$_2$), 1.65–1.59 (m, 2H, MeOC(O)CH_2C*H*$_2$), 1.58–1.48 (m, 6H,

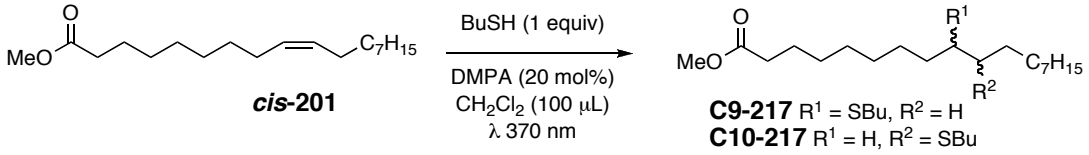
$CH_2CH_2SCH(CH_2)_2$), 1.45–1.37 (m, 6H, $CH_2(CH_2)_2SCH(CH_2CH_2)_2$), 1.33–1.25 (m, 18H), 0.92 (t, J = 7.3 Hz, 3H, $S(CH_2)_3CH_3$) and 0.88 (t, J = 7.1 Hz, 3H, $(CH_2)_4CH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 51.7, 46.0, 35.1^+, 35.1^-, 35.0, 34.3^+, 34.3^-, 32.3, 32.1^+, 32.1^-, 30.2, 29.9, 29.8^+, 29.8^-, 29.7, 29.6, 29.5^+, 29.5^-, 29.4^+, 29.4^-, 29.3, 27.0^+, 27.0, 27.0^-, 25.2, 22.9, 22.4, 14.3 and 13.9.

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 387.3 $(M+H)^+$; t_r = 20.0 min.

GCMS (5029021): t_r = 12.90 min; m/z 386 (M^+), 329, 297, 273, 259, 229 and 215.

Methyl 9-(butylthio)octadecanoate (C9-217)

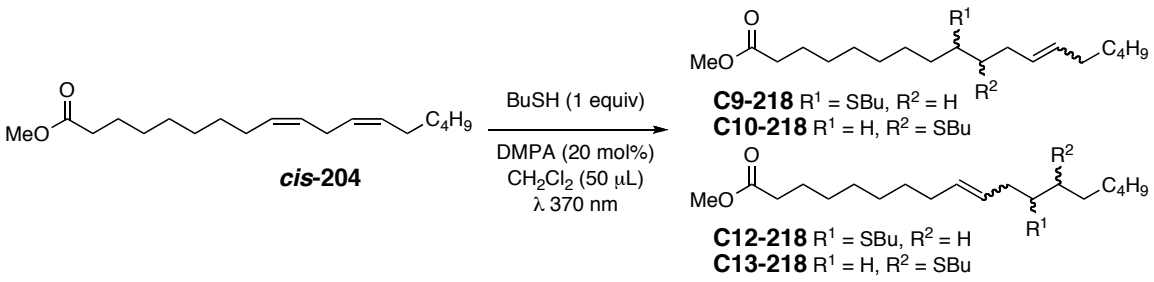


A vial is charged with methyl oleate (***cis*-201**, 200 mg, 0.67 mmol), butanethiol (73 μL, 0.67 mmol) and 2,2-dimethoxy-2-phenylacetophenone (DMPA, 34 mg, 0.13 mmol). The reaction is solubilized by addition of CH_2Cl_2 (100 μL). The vial is placed in the Rayonet reactor and irradiated with black lights (λ 370 nm) for 2 h. Half of the crude mixture was flushed through a bed of silica gel (19:1 Hex:EtOAc) to provide regioisomeric products **C9-217** and **C10-217** (67 mg).

C9-217 and **C10-217**

Characterization data listed in previous reaction.

Methyl 9-(butylthio)octadec-12-enoate (C9-218)



A vial is charged with methyl linoleate (***cis*-204**, 100 mg, 0.34 mmol), butanethiol (36 μL, 0.34 mmol) and 2,2-dimethoxy-2-phenylacetophenone (DMPA, 17 mg, 0.06 mmol). The reaction is solubilized by addition of CH_2Cl_2 (50 μL). The vial is placed in the Rayonet reactor and irradiated with black lights (λ 370 nm) for 5 h. The crude mixture was flushed through a bed of silica gel (19:1 Hex:EtOAc) to provide regioisomeric adducts **218** (30 mg).

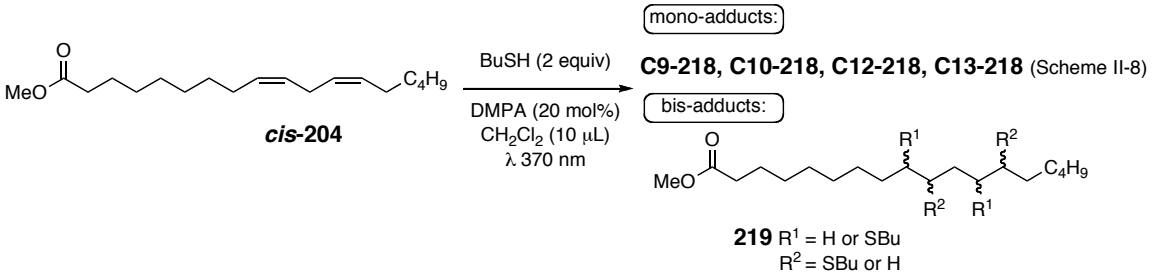
218 (mixture of regioisomers) (File MB4p205)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50–5.34 (m, 2H, *H*C=C*H*), 3.67 (s, 3H, C(O)OC*H*$_3$), 2.79–2.75 (m, 0.1H, CH_2SCH), 2.74–2.70 (m, 0.2H, CH_2SCH), 2.68–2.65 (m, 0.5H, CH_2SCH), 2.64–2.54 (m, 1H, CHSC*H*$_2$), 2.53–2.45 (m, 2H, CHSC*H*$_2$), 2.30 (t, *J* = 7.5 Hz, 2H, MeOC(O)C*H*$_2$), 2.17–1.95 (m, 4H, C*H*$_2$CH=CHC*H*$_2$), 1.64–1.50 (m, 8H, $MeOC(O)CH_2CH_2$ and SCH_2CH_2 and SCHC*H*$_2$), 1.45–1.23 (m, 26H), 0.91 (t, *J* = 7.3 Hz, 3H, $S(CH_2)_3CH_3$) and 0.88 (t, *J* = 7.2 Hz, 3H, $(CH_2)_4CH_3$).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 385.3 $(M+H)^+$; t_r = 19.1 min.

GCMS (5029021): t_r = 12.87 min; *m/z* 327 (M^+–butyl, 25), 273 (50), 259 (15), 241 (25) and 187 (100).

Methyl 9,12-bis(butylthio)octadecanoate (C9,C12-219)



Followed the above procedure using 2 equivalents of butanethiol.

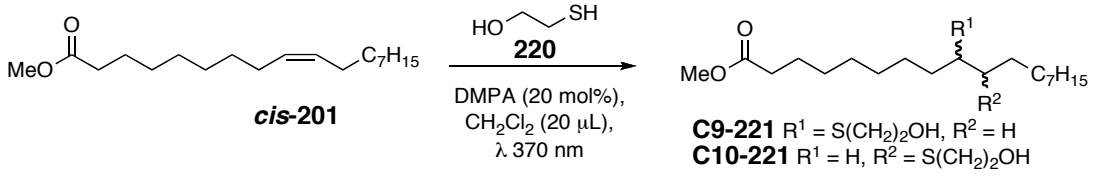
218 and 219 (mixture of regioisomers) (File MB4p225)

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.67 (s, 3H, C(O)OC*H*$_3$), 2.60–2.53 (m, 1.5H, CH_2SC*H*), 2.52–2.45 (m, 4H, CHSC*H*$_2$), 2.30 (t, *J* = 7.5 Hz, 2H, MeOC(O)C*H*$_2$), 1.70–1.50 (m, 10H, MeOC(O)CH_2C*H*$_2$ and SCH_2C*H*$_2$ and SCHC*H*$_2$), 1.45–1.37 (m, 8H, S$(CH_2)_2$C*H*$_2$ and SCHCH_2C*H*$_2$), 1.33–1.24 (m, 14H), 0.92 (t, *J* = 7.4 Hz, 6H, S$(CH_2)_3$C*H*$_3$) and 0.89 (t, *J* = 7.0 Hz, 3H, $(CH_2)_4$C*H*$_3$).

GCMS (5029021): t_r = 14.66–15.14 min; *m/z* 474 (M^+, 10), 417 (M^+–butyl, 100), 385 (10), 327 (20), and 273 (10).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 475.3 $(M+H)^+$; t_r = 21.6 min.

Methyl 9-(2-hydroxyethylthio)octadecanoate (C9-221)



A vial is charged with methyl oleate (***cis*-201**, 200 mg, 0.67 mmol), mercaptoethanol (96 μL, 1.34 mmol) and 2,2-dimethoxy-2-phenylacetophenone (DMPA, 40 mg, 0.13 mmol). The reaction is solubilized by addition of CH_2Cl_2 (20 μL). The vial

is placed in the Rayonet reactor and irradiated with black lights (λ 370 nm) for 19 h. Purification by MPLC (4:1 Hex:EtOAc) provided samples of **C9-221** and **C10-221**.

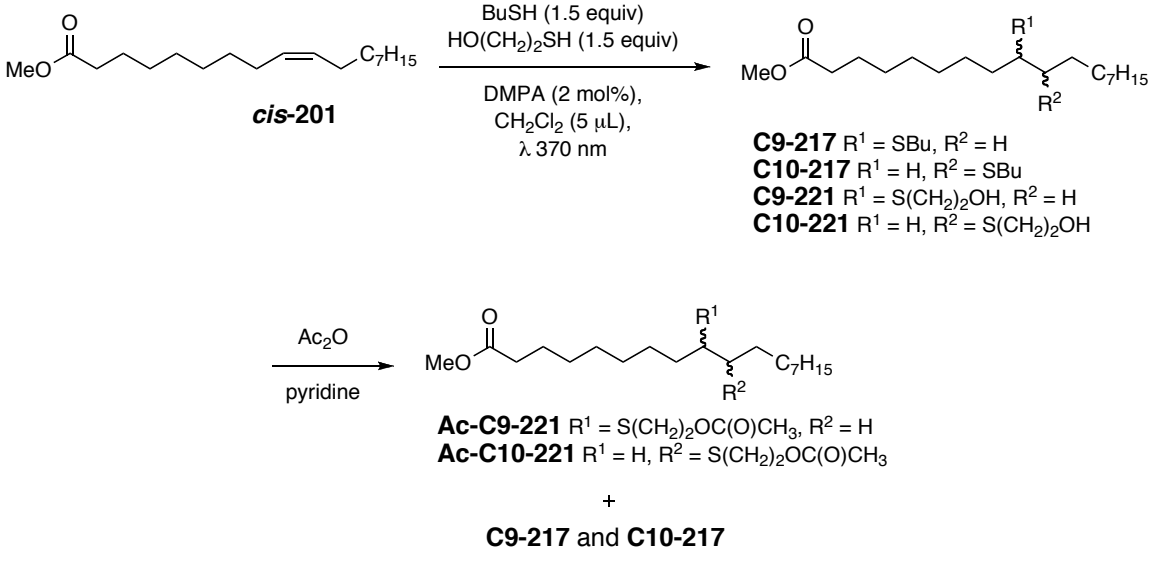
C9-221 and C10-221 (File MB4p212 and MB4p228)

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.70 (br t, *J* = 5.7 Hz, 2H, HOC*H*$_2$), 3.67 (s, 3H, C(O)OC*H*$_3$), 2.72 (t, *J* = 6.0 Hz, 2H, CHSC*H*$_2$), 2.59 (dddd, *J* = 6.6, 6.6, 6.6 and 6.6 Hz, 1H, CH_2SC*H*), 2.31 (t, *J* = 7.5 Hz, 2H, MeOC(O)C*H*$_2$), 1.65–1.59 (m, 2H, MeOC(O)CH_2C*H*$_2$), 1.58–1.46 (m, 4H, SCH(C*H*$_2$)$_2$), 1.45–1.36 (m, 4H, SCH(CH_2C*H*$_2$)$_2$), 1.33–1.25 (m, 18H) and 0.88 (t, *J* = 6.9 Hz, 3H, $(CH_2)_4$C*H*$_3$).

GCMS (5029021): t_r = 13.30 min; *m/z* 356 (M^+–H_2O, 5), 329 (M^+–CH_2CH_2OH, 10), 297 (M^+–SCH_2CH_2OH, 20), 203 (20), and 55 (100).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 392.3 $(M+NH_4)^+$; t_r = 16.5 min.

Methyl 9-(2-acetoxyethylthio)octadecanoate (Ac-C9-221)



A vial is charged with methyl oleate (***cis*-201**, 100 mg, 0.34 mmol), mercaptoethanol (36 μL, 0.51 mmol), butanethiol (55 μL, 0.51 mmol) and 2,2-

dimethoxy-2-phenylacetophenone (DMPA, 2 mg, 0.7 mol%). The reaction is solubilized by addition of CH_2Cl_2 (5 μL). The vial is placed in the Rayonet reactor and irradiated with black lights (λ 370 nm) for 17 h. The ^{1}H NMR spectrum of the crude product mixture showed a 1.15:1 ratio of products **217**:**221**. (Data for these compounds are on pages 140 (**217**) and 143 (**221**).

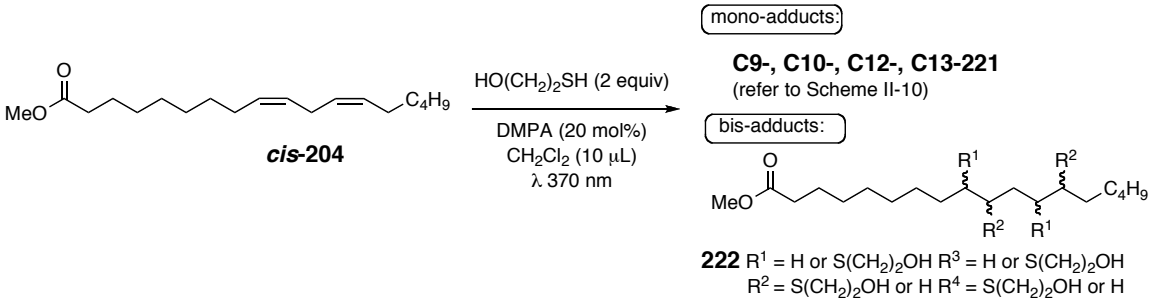
The crude product mixture of **217** and **221** (28 mg) was treated with acetic anhydride (10 μL) and pyridine (20 μL). The reaction was concentrated under reduced pressure to provide a mixture (20 mg) of **217** and acetylated product **Ac-221**.

217 and acetylated 221 (1.15:1, both as a mixture of C9 and C10 regioisomers) (File MB4p241)

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.19 (t, J = 7.2 Hz, 1.8H, $H_3C(O)OCH_{2\_Ac\text{-}221}$), 3.67 (s, 5H, $C(O)OCH_{3\_217/Ac\text{-}221}$), 2.71 (t, J = 7.2 Hz, 2H, $CHSCH_{2\_Ac\text{-}221}$), 2.61 (dddd, 0.9H, $CH_2SCH_{\_Ac\text{-}221}$), 2.55 (dddd, J = 6.4, 6.4, 6.4 and 6.4 Hz, 1H, $CH_2SCH_{\_217}$), 2.47 (t, J = 7.4 Hz, 2H, $CHSCH_{2\_217}$), 2.31 (t, J = 7.5 Hz, 3.6H, $MeOC(O)CH_{2\_217/Ac\text{-}221}$), 2.07 (s, 2.5H, $OC(O)CH_{3\_Ac\text{-}221}$), 1.65–1.58 (m, 4H, $MeOC(O)CH_2CH_{2\_217/Ac\text{-}221}$), 1.58–1.48 (m, 10H, $SCH(CH_2)_{2\_217/Ac\text{-}221}$ and $CH_2CH_2SCH_{\_217}$), 1.45–1.37 (m, 10H, $SCH(CH_2CH_2)_{2\_217/Ac\text{-}221}$ and $S(CH_2)_2CH_{2\_217}$), 1.33–1.23 (m, 35H), 0.91 (t, J = 7.4 Hz, 3H, $S(CH_2)_3CH_{3\_217}$) and 0.88 (t, J = 7.1 Hz, 5H, $(CH_2)_4CH_{3\_217/Ac\text{-}221}$).

GCMS (5029021): t_r = 13.56 min; *m/z* 385 (M^+–OMe, 5), 356 (M^+–HOC(O)Me, 15), 327 (70), 297 (20), 265 (30), and 55 (100).

Methyl 9,12-bis(2-hydroxyethylthio)octadecanoate (C9,C12-222)



A vial is charged with methyl linoleate (***cis*-204**, 120 mg, 0.41 mmol), mercaptoethanol (58 μL, 0.82 mmol) and 2,2-dimethoxy-2-phenylacetophenone (DMPA, 21 mg, 0.08 mmol). The reaction is solubilized by addition of CH_2Cl_2 (10 μL). The vial is placed in the Rayonet reactor and irradiated with black lights (λ 370 nm) for 15 h. Purification by MPLC (3:1 Hex:EtOAc) provided a sample of mono-adducts **221** (4 mg), whereas the more polar solvent system (1:1 Hex:EtOAc) gave a sample of bis-adducts **222** (4 mg).

C9-, C10-, C12- and C13-221 (File MB4p226Hf4)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.52–5.32 (m, 2H, *H*C=C*H*), 3.72–3.67 (m, 2H, HOCH_2), 3.67 (s, 3H, C(O)OCH_3), 2.77–2.70 (m, 2H, CHSCH_2), 2.66–2.57 (m, 1H, CH_2SC*H*), 2.30 (t, J = 7.5 Hz, 3H, MeOC(O)CH_2), 2.26 (t, J = 6.5 Hz, 1H, SCHCH_2CH=CH), 1.64–1.59 (m, 4H, MeOC(O)CH_2CH_2 and SCHC$H_2$$CH_2$CH=CH), 1.35–1.22 (m, 23H) and 0.88 (t, J = 7.1 Hz, 3H, $(CH_2)_4$CH_3).

GCMS (5029021): t_r = 13.27 min; *m/z* 327 (M^+–CH_2CH_2OH, 35), 243 (75), 169 (90), and 55 (100).

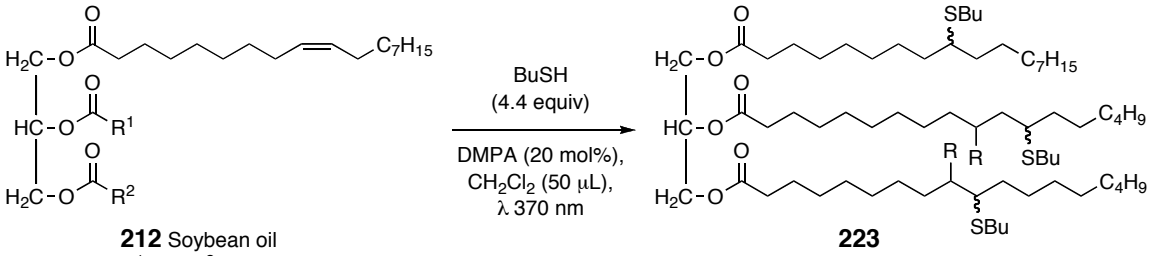
HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 390.3 $(M+NH_4)^+$; t_r = 16.0 min.

222 (mixture of 4 regioisomers) (MB4p226If7-9)

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.77–3.69 (m, 4H, HOCH_2), 3.67 (s, 3H, C(O)OCH_3), 2.76–2.70 (m, 4H, CHSCH_2), 2.63–2.57 (m, 2H, CH_2SC*H*), 2.31 (t, *J* = 7.6 Hz, 2H, MeOC(O)CH_2), 1.65–1.59 (m, 4H, MeOC(O)CH_2CH_2 and SCHCH_2CHS), 1.57–1.50 (m, 4H, SCH(CH_2)$_2$), 1.46–1.37 (m, 4H, SCH(CH_2CH_2)$_2$), 1.34–1.24 (m, 14H) and 0.91–0.87 (m, 3H, $(CH_2)_4$CH_3).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 468.3 $(M+NH_4)^+$; t_r = 15.0 min.

Butylthio-modified soybean oil (223)



212 Soybean oil
R^1 and R^2 = palmitic, stearic, oleic, linoleic, or linolenic

223
R = C (inter- or intramolecular)

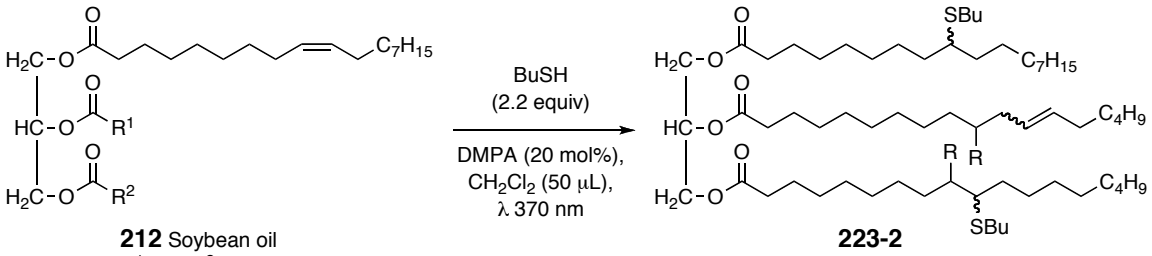
A vial is charged with soybean oil (**212**, 400 mg, 0.45 mmol), butanethiol (217 μL, 2.02 mmol) and 2,2-dimethoxy-2-phenylacetophenone (DMPA, 103 mg, 0.4 mmol). The reaction is solubilized by addition of CH_2Cl_2 (50 μL). The vial is placed in the Rayonet reactor and irradiated with black lights (λ 370 nm) for 6 h. Purification by MPLC (19:1 Hex:EtOAc) provided a sample of **223**.

File MB4p215

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.26 (app quintet, *J* = 5.4 Hz, 1H, C(O)OC*H*), 4.29 (dd, *J* = 11.9 and 4.0 Hz, 2H, (C(O)OCHH_a)$_2$), 4.14 (dd, *J* = 11.9 and 5.9 Hz, 2H, (C(O)OCHH_b)$_2$), 2.59–2.53 (m, 3H, CH_2SC*H*), 2.51–2.45 (m, 8H, CHSCH_2), 2.34–2.29

(m, 6H, OC(O)CH_2), 1.65–1.48 (m, 30H, SCH_2CH_2 and SCHCH_2 and OC(O)CH_2CH_2), 1.45–1.37 (m, 18H, $SCH_2CH_2CH_2$ and $SCHCH_2CH_2$), 1.33–1.24 (m, 55H), 0.91 (t, J = 7.3 Hz, 12H, $S(CH_2)_3CH_3$) and 0.91–0.86 (m, 6H, CH_2CH_3).

Butylthio-modified soybean oil (223-2)



212 Soybean oil
R^1 and R^2 = palmitic, stearic, oleic, linoleic, or linolenic

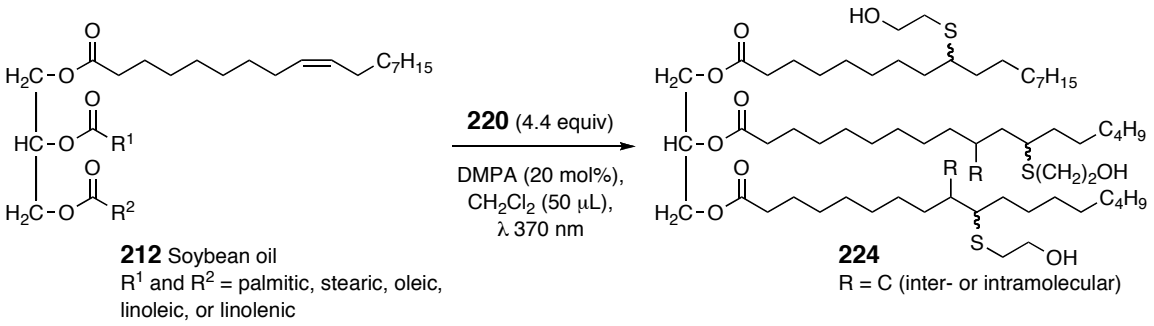
223-2
R = C (inter- or intramolecular)

Followed above procedure with less butanethiol (2.2 equiv).

File MB4p217

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.47–5.33 (m, 2.6H, *H*C=C*H*), 5.26 (app quintet, J = 5.4 Hz, 1H, C(O)OC*H*), 4.29 (dd, J = 11.9 and 4.2 Hz, 2H, $(C(O)OCH_aH_b)_2$), 2.59–2.53 (m, 1.7H, CH_2SCH), 2.51–2.45 (m, 4.5H, CHSCH_2), 2.34–2.29 (m, 7H, OC(O)CH_2), 2.06–1.94 (m, 4H, CH=CHCH_2CH=CH), 1.64–1.49 (m, 21H, SCH_2CH_2 and SCHCH_2 and OC(O)CH_2CH_2), 1.45–1.37 (m, 11H, $SCH_2CH_2CH_2$ and $SCHCH_2CH_2$), 1.33–1.24 (m, 57H), 0.91 (t, J = 7.3 Hz, 8H, $S(CH_2)_3CH_3$) and 0.88 (t, J = 7.0 Hz, 9H, CH_2CH_3).

Hydroxyethylthio-modified soybean oil (224)



212 Soybean oil
R^1 and R^2 = palmitic, stearic, oleic, linoleic, or linolenic

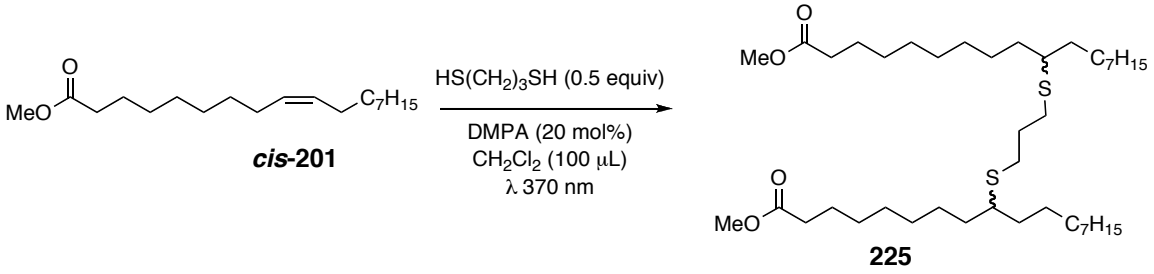
224
R = C (inter- or intramolecular)

Followed above photochemical procedures.

File MB4p216

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.26 (app quintet, *J* = 5.4 Hz, 1H, C(O)OC*H*), 4.29 (dd, *J* = 11.9 and 4.0 Hz, 2H, (C(O)OCHH_a)$_2$), 4.14 (dd, *J* = 11.9 and 5.9 Hz, 2H, (C(O)OCHH_b)$_2$), 3.72–3.67 (m, 4H, HOCH_2), 2.74–2.70 (m, 4H, CHSCH_2), 2.63–2.57 (m, 2H, CH_2SC*H*), 2.34–2.29 (m, 6H, MeOC(O)CH_2), 1.64–1.50 (m, 15H, MeOC(O)CH_2CH_2 and SCHCH_2CHS and SCH(CH_2)$_2$), 1.46–1.37 (m, 8H, SCH(CH_2CH_2)$_2$), 1.33–1.24 (m, 50H) and 0.89 (t, *J* = 7.1 Hz, 3H, CH_2CH_3).

Methyl 10-(3-(1-methoxy-1-oxooctadecan-9-ylthio)propylthio)octadecanoate (225)



***cis*-201**

225

A vial is charged with methyl oleate (***cis*-201**, 200 mg, 0.67 mmol), propanedithiol (34 μL, 0.34 mmol), DMPA (40 mg, 0.134 mmol) and CH_2Cl_2 (100 μL). The vial is placed in the Rayonet reactor and irradiated with black lights (λ 370 nm) for 2 h. The crude product **225** was obtained as a slightly viscous, pleasant smelling material.

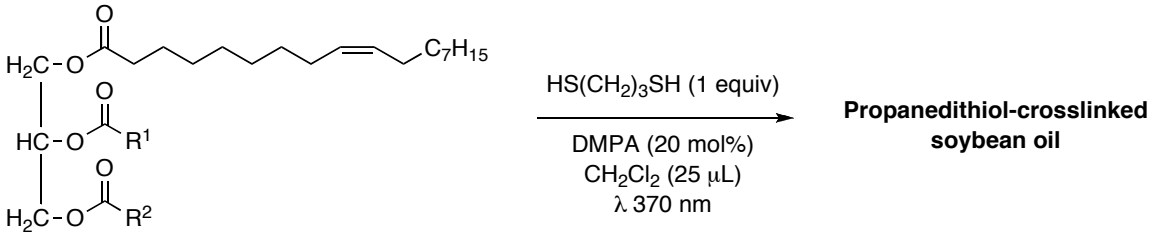
(In cases when a limited amount of propanedithiol was used, crosslinked product **225** could be separated from remaining starting material (**201**) by MPLC (19:1 Hex:EtOAc).

File MB5p20

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.67 (s, 6H, C(O)OC*H*$_3$), 2.58 (t, *J* = 7.2 Hz, 4H, SC*H*$_2$CH$_2$C*H*$_2$S), 2.58–2.52 (m, 2H, *H*CS(CH$_2$)$_3$SC*H*), 2.30 (t, *J* = 7.5 Hz, 4H, MeOC(O)C*H*$_2$), 1.82 (app quintet, *J* = 7.2 Hz, 2H, SCH$_2$C*H*$_2$CH$_2$S), 1.65–1.59 (m, 4H, MeOC(O)CH$_2$C*H*$_2$), 1.57–1.48 (m, 8H, SCH(C*H*$_2$)$_2$), 1.45–1.35 (m, 8H, SCH(CH$_2$C*H*$_2$)$_2$), 1.34–1.24 (m, 36H) and 0.88 (t, *J* = 7.0 Hz, 6H, (CH$_2$)$_4$C*H*$_3$).

^{1}H NMR (500 MHz, C_6D_6): δ 3.36 (s, 6H, C(O)OC*H*$_3$), 2.65–2.54 (m, 4H, SC*H*$_2$CH$_2$C*H*$_2$S), 2.51–2.44 (m, 2H, *H*CS(CH$_2$)$_3$SC*H*), 2.13 (t, *J* = 7.5 Hz, 4H, MeOC(O)C*H*$_2$), 1.96–1.85 (m, 2H, SCH$_2$C*H*$_2$CH$_2$S), 1.64–1.42 (m, 20H, MeOC(O)CH$_2$C*H*$_2$, SCH(C*H*$_2$)$_2$ and SCH(CH$_2$C*H*$_2$)$_2$), 1.37–1.18 (m, 36H) and 0.92 (t, *J* = 7.0 Hz, 6H, (CH$_2$)$_4$C*H*$_3$).

Propanedithiol-crosslinked soybean oil



212 Soybean oil
R^1 and R^2 = palmitic, stearic, oleic, linoleic, or linolenic

Followed above procedure for photochemical reactions.

File MB5p39, MB5p40

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.45–5.32 (m, 5.3H, *H*C=C*H*), 5.29–5.24 (m, 1H, C(O)OC*H*), 4.29 (dd, *J* = 11.9 and 4.2 Hz, 2H, (C(O)OCH*H*$_a$)$_2$), 4.14 (dd, *J* = 11.9 and

5.9 Hz, 2H, (C(O)OCHH_b)$_2$), 2.79–2.65 (t, J = 7.2 Hz, 3H, SCH_2CH$_2$CH_2S and HCS(CH$_2$)$_3$SCH), 2.31 (t, J = 7.5 Hz, 6H, MeOC(O)CH_2), 2.08–1.94 (m, 8H, SCH$_2$CH_2CH$_2$S and H_2CCH=CHCH_2), 1.65–1.56 (m, 8H, MeOC(O)CH$_2$CH_2 and SCH(CH_2)$_2$), 1.38–1.24 (m, 49H) and 0.91–0.86 (m, 7H, CH$_2$CH_3).

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