Strategies and Discoveries Leading to the Synthesis of Trichoaurantianolide Natural Products

David R. Williams[1]

Department of Chemistry, Indiana University, Bloomington, Indiana, USA

[1]*Corresponding Author: E-Mail:* williamd@indiana.edu

Chapter Outline

Abstract: Studies directed towards strategies for construction of neodolastane diterpenes have culminated in the total synthesis of trichoaurantianolides C and D. This account describes the most challenging aspects of the proposed lines of inquiry, and unanticipated results, encountered in the pursuit of these ideas. Methodology development defined new knowledge of reactivity and stereoselectivity for advancements in organic synthesis. Efforts explore issues of stereocontrol in the formation of highly substituted cycloheptane ring systems Regioselective oxidation reactions are also described. Several cyclization processes are examined in the course of the study.

Keywords: Natural products, Total synthesis, Neodolastanes, Diterpenes, Stereoselective cyclizations, Regiocontrolled oxidations, π-Allyl Stille reactions, Trichoaurantianolides

1. INTRODUCTION

Several years ago, a small family of diterpenoid natural products attracted our attention as novel targets for synthesis studies. Initially, four compounds were independently characterized by the research teams of Vidari[1] and Steglich.[2] Trichoaurantianolides A–D (**1**–**4** of Figure 1) were isolated from fruiting bodies of the mushrooms *Tricholoma aurantium* and *Tricholoma fracticum* in 1995.

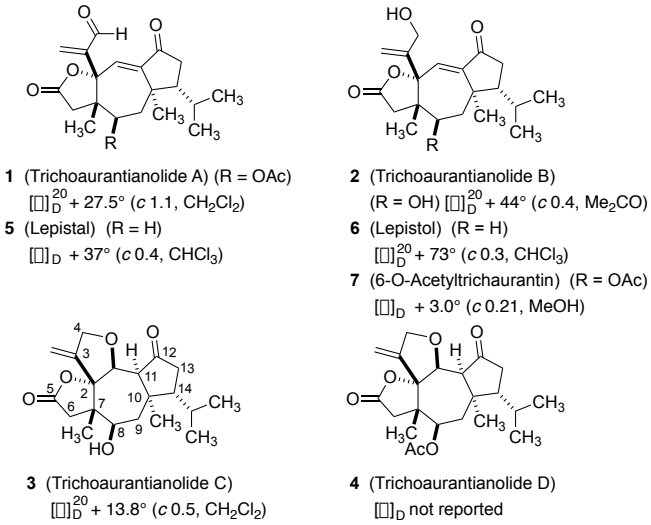


FIGURE 1 Trichoaurantianolides A–D and related metabolites.

Subsequent efforts of Stermer and coworkers[3] described the isolation of the closely-related lepistal (**5**) and lepistol (**6**) of Figure 2 as the corresponding C_8 deoxygenated compounds of this family. In addition, the corresponding acetate of trichoaurantianolide B was discovered and named as 6-O-aetyltrichoaurantin (**7**).[2] Structure assignments were based upon extensive NMR studies, and the features of relative stereochemistry were confirmed by an X-ray crystallographic analysis of trichoaurantianolide B (**2**).[1b,2] These original investigators described the trichoaurantianolides as examples of a new class of diterpenes named as neodolastanes that signified a structural relationship to the tricyclic metabolites of marine origins known as dolastanes as represented by dolatriol (**8**)[4] and the clavularane **9**[5] of Figure 2. Neodolastanes were defined as substances in

which the bridgehead methyl substituent appears in a vicinal relationship with respect to the isopropyl group as exemplified in 4,5-deoxyneodolabelline (**10**) of Figure 2, a related class of marine natural products.[6]

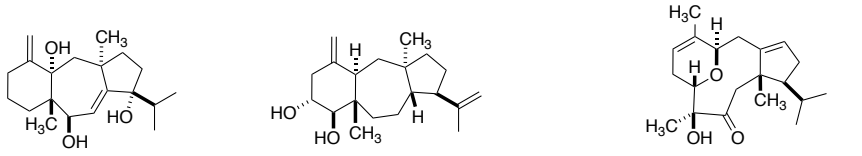


FIGURE 2 Examples of related marine natural products.

Steglich and coworkers[2] also indicated an assignment of absolute stereochemistry for **2** that was based on Hamilton's applications of linear-hypothesis testing of crystallographic data. This seldom-used technique was in agreement with the proposed absolute configuration of **2** that was advanced by Vidari, based on an assessment of the observed Cotton effects in CD spectroscopy. In 2003, Ohta and coworkers[7] reported the discovery of related neodolastanes tricholomalides A, B, and C (structures **11**, **12**, and **13** of Figure 3) from *Tricholoma sp.* They concluded that the tricholomalides possessed the opposite absolute configuration claimed for the trichoaurantianolides. This conclusion was based upon the independent analysis of their circular dichroism studies.

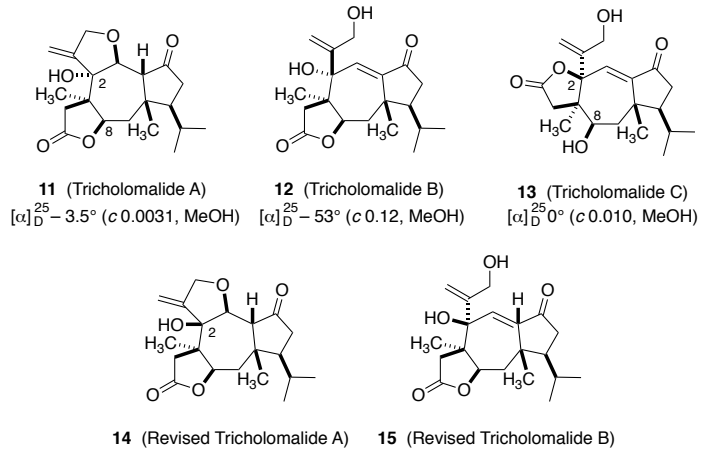


FIGURE 3 Tricholomalide structures and revisions.

By application of the octant rule for substituent effects on cisoid α,β-unsaturated ketones,[8] Ohta and coworkers suggested a revision of the prior assignment of absolute configuration for the trichoaurantianolides. This assertion was advanced in spite of the consistently positive specific rotations recorded in different solvents for trichoaurantianolides A, B, and C[1,2] versus the negative values of tricholomalides A (**11**) and B (**12**) (compare values in Figure 1 and Figure 3). Note that tricholomalide C (**13**) only differs from trichoaurantianolide B (**2**) as a C-8 diastereomeric alcohol, presented in the antipodal series. The specific rotation of **13** was of little value since it was recorded as $[\alpha]_D^{25}$ 0° (*c* 0.01, MeOH).[7] In 2006, Danishefsky described a pathway for the total synthesis of racemic tricholomalides A and B, and this effort led to a revision of the relative C-2 stereochemistry (Figure 3; revised structures **14** and **15**).[9] It seemed rather unusual that genetically similar fungi would produce closely related metabolites as enantiomers, but certainly this is not unprecedented. As a starting point, this issue lacked clarity, and we concluded that our synthesis plans must unambiguously address the issues of absolute configuration.

The chemistry of dolabellane and dolastane diterpenes has been reviewed.[10] The proposed pathway for biosynthesis of the trichoaurantianolides and related compounds (Figure 4) follows an established sequence from geranylgeranyl pyrophosphate (**16**) which undergoes π-cation cyclization to initially form the eleven-membered ring of **17**. The event is followed by a second cyclization to form the dolabellane cation **18**, and this [9.3.0]cyclotetradecane skeleton is central to several families of natural products. Direct capture or elimination from **18** leads to the 3,7-dolabelladiene **19**, which presents the most common pattern of unsaturation within this class. Compounds within this group are traditionally numbered beginning with C-1 as the bridgehead carbon bearing the methyl group rather than following the connectivity presented in geranylgeranyl **16**. The cation **18** also undergoes a 1,2-hydrogen migration and elimination which

leads to a transannular cyclization yielding the 5-7-6 tricyclic dolastane **20**. The secodolastanes, represented by **21**, are a small collection of marine natural products which arise from oxidative cleavage of C_{10}–C_{14} in the parent tricycle **20**. In analogous fashion, the neodolabellane structure **22** is produced from **18** by stereospecific backbone migrations that result in the vicinal placement of the bridgehead methyl and isopropyl substituents. Transannular cyclizations, stemming from **22**, yield the class of neodolastane diterpenes (**23**). Trichoaurantianolides and the related lepistal A (**5**) are the result of oxidations and cleavage of the C-ring (C4–C5) of **23**, which leads to the features of an unusual butyrolactone system.

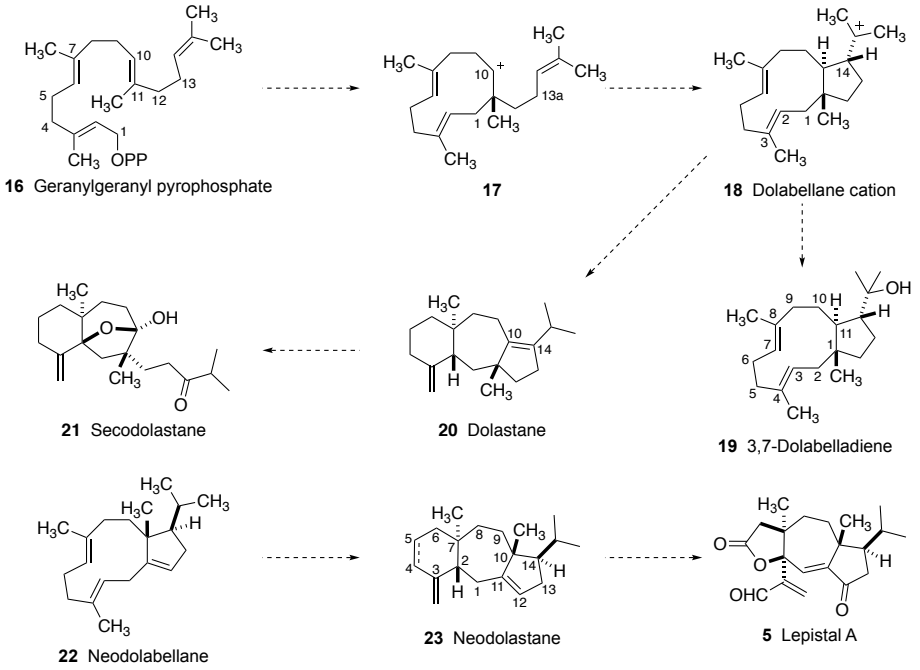


FIGURE 4 Biogenetic origins of neodolastanes.

The guanacastepenes, such as **24**,[11] and heptemerones, such as **25**,[12] are primary examples of the 5-7-6 neodolastane family and these metabolites have also been isolated from fungi sources. A characteristic structural feature is the vicinal, *syn*-relationship of the bridgehead methyl and isopropyl substituents as compared to the 1,3-*trans* relationship found in dolastanes (Figure 2, structures **8** and **9**). Guanacastepenes have proven to be attractive targets for synthesis studies.[11,13]

However, these fungal metabolites exhibit the antipodal, absolute stereochemistry as compared to neodolastanes from marine origins, such as sphaerostanol (**26**) (Figure 5).[14]

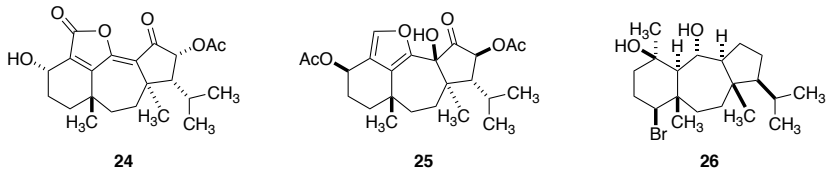
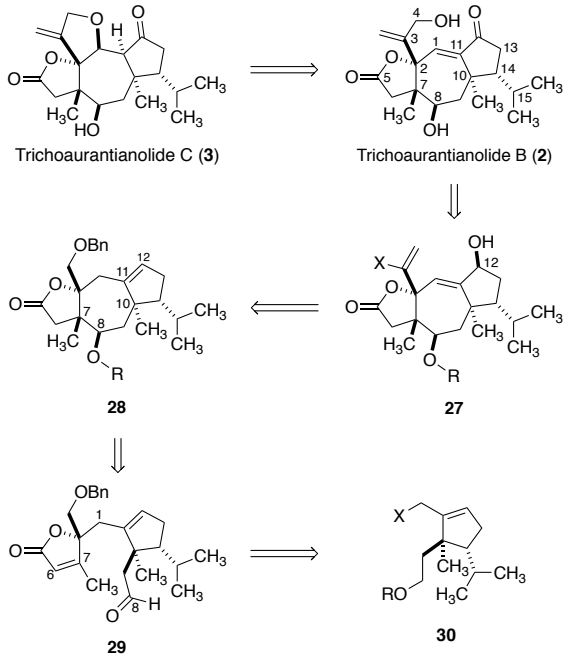


FIGURE 5 Stereochemical comparison of guanacastepenes and neodolastanes of marine origin.

2. RETROSYNTHETIC ANALYSIS

Trichoaurantianolides C and D present a significant challenge for synthesis because the carbon framework is densely functionalized by a number of oxidation events that have occurred in late stages of the biosynthesis. The skeleton has seven contiguous asymmetric centers, six of which are contained within the seven-membered carbocycle. In addition, three of these chiral carbons are fully substituted, and the bridgehead positions at C-7 and C-10 are quaternary carbons. We devised the retrosynthetic analysis of Scheme 1 as our initial strategy, noting that it assumed that formation of trichoaurantianolide B (**2**) would readily provide for the intramolecular conjugate addition to achieve the production of trichoaurantianolide C (**3**). Thus, the stereochemistry at C-1 and C-11 would be anticipated by thermodynamic control. The allylic alcohol of **27** was recognized as a stable intermediate where a standard oxidation to the cyclopentanone would serve to trigger the planned conjugate addition. Furthermore, the inclusion of a vinylic bromide or iodide (X in **27**) or the corresponding triflate (X = OTf) would suggest a mild cross-coupling to produce the reactive alcohol of **2**. We chose to simplify intermediate **27** in two ways. First, the trisubstituted alkene of **28** could be utilized as a suitable precursor to generate the unsaturated alcohol of **27** via a variety of known oxidation processes, and the selective removal of the benzyl group in **28** would permit elaboration to the activated alkenyl species of the planned cros-coupling reaction.

A significant aspect of our analysis sought to establish the desired *anti* stereochemistry for the fully substituted stereogenic centers at C-7 and C-10 of the cycloheptane in **28**. It is at this point that a conceptual basis of our strategy is truly revealed. We have illustrated two five-membered rings in structure **29**, which are attached via a short (one-carbon) linker. Our proposal will examine the formation of the central, seven-membered ring of **28** with stereoselectivity that is controlled by the elements of chirality within the smaller rings. The idea would use the intact five-membered rings of **29**, and especially the asymmetry of C-2 and C-10 to achieve selective formation of the *anti*-dimethyl arrangement. We chose the butenolide and aldehyde of **29** as the motif for advancing a reductive cyclization, and this concept was reinforced by modeling that predicted a minimization of steric interactions leading to the desired outcome. We were confident of a route for preparation of **30**, but preliminary studies would be necessary to design an efficient approach to attach the nonracemic butenolide moiety of **29**.

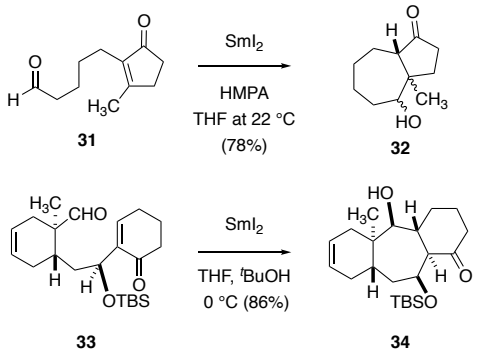


SCHEME 1 Retrosynthetic analysis.

3. PRELIMINARY INVESTIGATIONS

3.1. A Modest Beginning

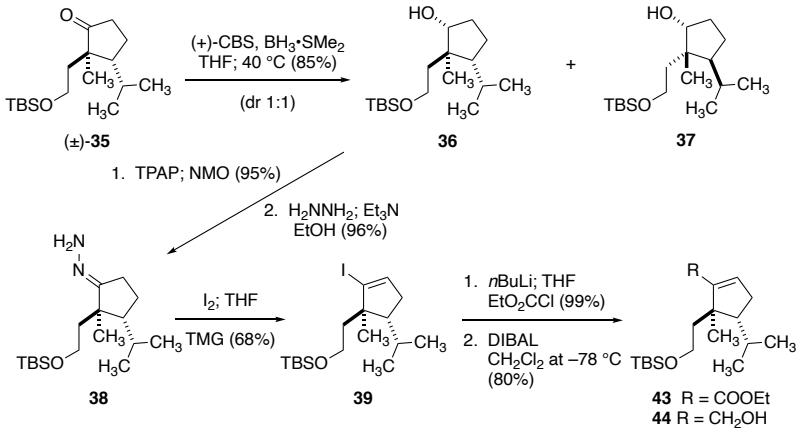
The rationale of Scheme 1 was particularly appealing because we readily found literature precedents for the proposed intramolecular reductive cyclization. Although relatively few studies had reported reductive coupling reactions to yield seven- and eight-membered rings,[15] Tori and coworkers[16] had described the SmI_2 reduction of the unrestricted enone of **31** to produce approximately equal amounts of four diastereomers of **32**, whereas Arimoto and coworkers [17] had illustrated high stereoselectivity for the conversion of **33** to **34**.



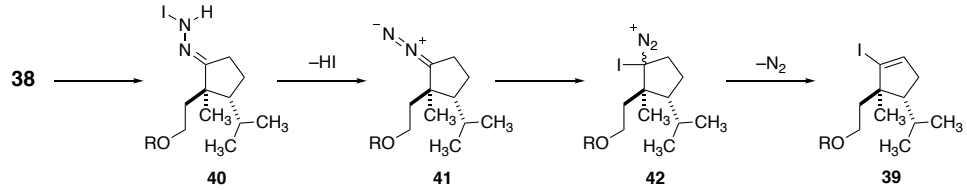
31 **32** **33** **34**

In support of Scheme 1, we also recognized a convenient route for the preparation of the nonracemic cyclopentane component **30**, which had been explored in our prior studies for the synthesis of (+)-4,5-deoxyneodolabelline.[6] This sequence is illustrated in Scheme 2, utilizing the racemic ketone **35**, which we had prepared on a large scale. Application of the CBS reduction[18] afforded a separable 1:1 mixture of diastereomeric alcohols **36** and **37**, and the desired **36** was submitted to the Ley oxidation[19] for conversion to the chiral hydrazone derivative **38**. Decomposition of **38** with iodine in the presence of tetramethylquanidine (TMG) produced the alkenyl iodide **39** following a concept introduced by Barton and coworkers.[20] The hydrazone **38** is oxidized by iodine to produce the diazo intermediate **41** and the elimination of nitrogen in **42** gives the enantioenriched alkene **39**. Reactions are run under anhydrous conditions to avoid formation of ketone caused by hydrolysis of **42**. Thus, we had access to multigram quantities of a

significant building block that contained two chiral centers including the important, quaternary C-10 asymmetry. The iodide **39** proved to be a useful intermediate for cross-coupling reactions and for halogen-metal exchange processes. In this case, the transformation of **39** to the allylic alcohol 44 of Scheme 2 was especially effective by the halogen-metal exchange using *n*-butyllithium.



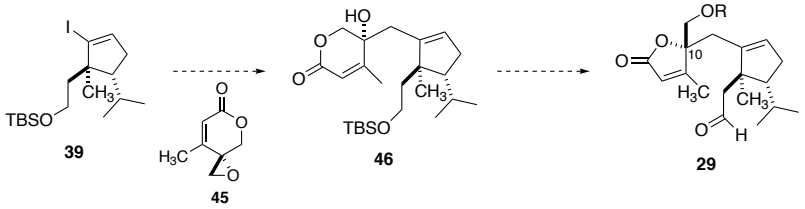
Mechanism of vinyl iodide formation:



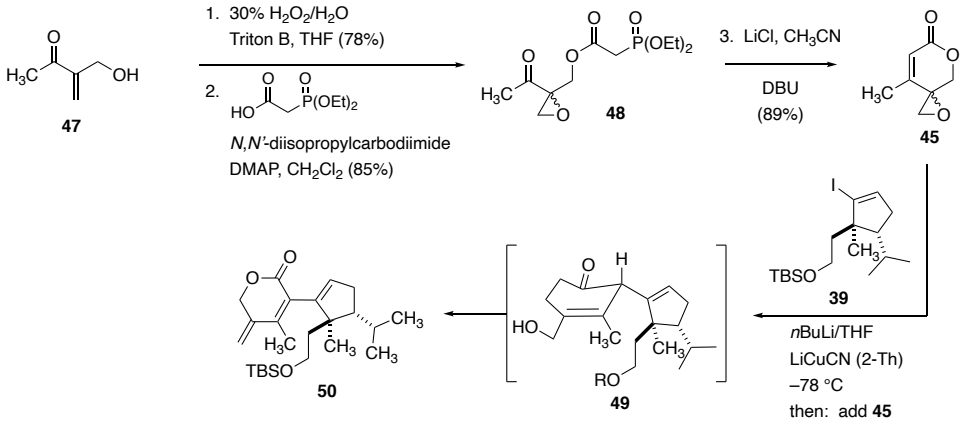
SCHEME 2 Preparation of enantioenriched cyclopentene **41**.

Preliminary studies explored a convergent route toward the preparation of nonracemic lactone **29** of Scheme 1 using the facile metalation of iodide **39**. In fact, the reorganization of the readily available, six-membered lactone of **46** to the desired butenolide **29**, illustrated in Scheme 3, appeared plausible. It also advantageously secured the correct C-10 stereochemistry via opening of the terminal epoxide of **45**. The idea was initially explored with racemic epoxylactone **45**, which was prepare by the three-step route shown in Scheme 4. This effort could be readily adapted toward a nonracemic synthesis. However, subsequent experiments, which transformed the alkenyl iodide **39** into the higher order cuprate to facilitate oxirane ring-opening, resulted in the exclusive

formation of the novel triene **50**. This unanticipated product arose from a surprising S_N2' reaction with **45**, and subsequent dehydration of **49**. The use of the organolithium species of **39** was totally ineffective.



SCHEME 3 Attachment of the unsaturated lactone.

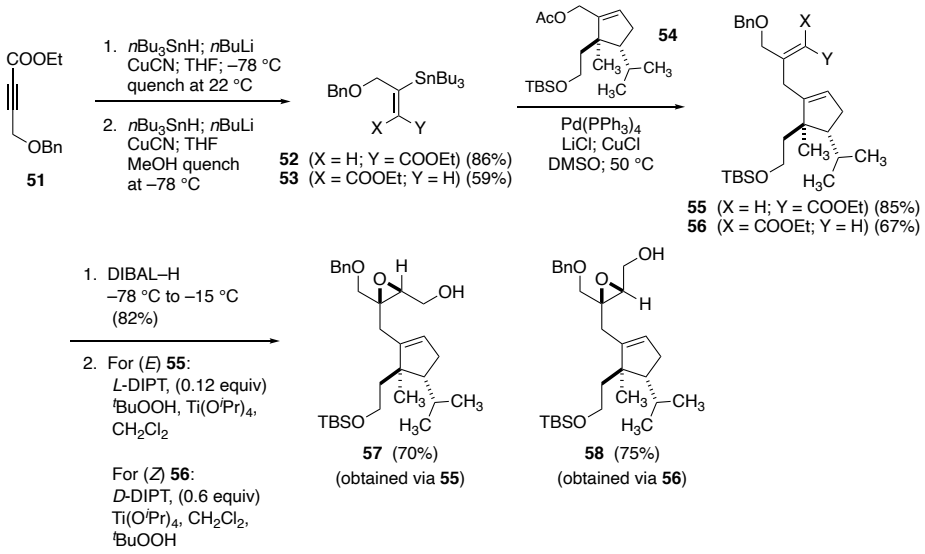


SCHEME 4 Preparation of **45** and the cuprate addition reaction yielding **50**.

3.2. The π-Allyl Stille Reaction

Concomitantly, alternative routes to incorporate the C-10 chirality proved more profitable. We planned to use the allyl alcohol **44** (Scheme 2) to extend the carbon framework, and then introduce the desired C-10 stereochemistry via the asymmetric Sharpless epoxidation.[21] These efforts were advanced by studies of the π-allyl Stille cross-coupling reaction.[22] As summarized in Scheme 5, the conjugate addition of tri-*n*-butylstannyl cuprate with alkynyl ester **51** yielded the (*Z*)-α,β-unsaturated **52** (>98% stereoselectivity) when reactions were quenched after warming to 22 °C. Conversely, the (*E*)-product **52** (<99% stereoselectivity) was obtained by *syn* addition of the cuprate and a kinetic quench at –78 °C by inclusion of methanol.[23] Thus, the pure *Z*- and *E*-isomers

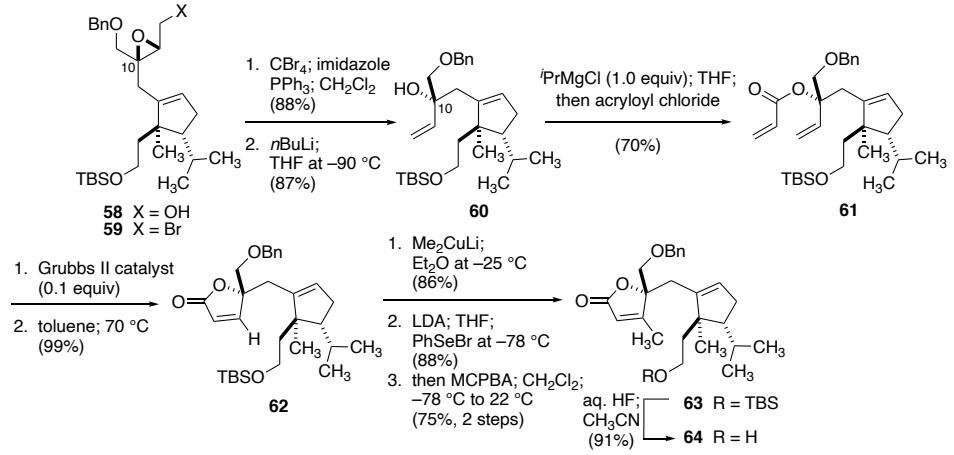
52 and **53** were available and examined in the Stille cross-coupling with the allylic acetate **54**. To our delight, stereocontrol was observed in both cases using $Pd(PPh_3)_4$ to provide good yields of the trisubstituted olefins **55** (85%) and **56** (67%). The DIBAL reductions to the corresponding nonconjugated 2,5-diene-1-ols proceeded smoothly. However, the Sharpless asymmetric epoxiodation (SAE) of the *E*-allylic alcohol resulted in poor diastereofacial selectivity (dr 65:35) under optimized conditions using L-diisopropyl tartrate (0.12 equiv) and $Ti(O^iPr)_4$ (0.1 equiv). On the other hand, the *Z*-allylic alcohol from **56** afforded the epoxide **58** in 75% (dr 92:8).



SCHEME 5 Preparation of (*E*)- and (*Z*)-epoxy alcohols **57** and **58**.

The assignment of epoxide stereochemistry in our experiments was assumed based upon the Sharpless model for predicting these outcomes,[24] but was unambiguously clarified in the subsequent reactions leading to the tricyclic core of trichoaurantiolide C. Further efforts toward this goal are diagrammed in Scheme 6 and set the stage for our planned cyclization of the seven-membered ring. A classic technique was employed for generation of the C-10 alcohol by conversion to the epoxybromide **59** followed by reductive opening via treatment with *n*-BuLi at –90 °C. This two-step process cleanly resulted in the 1,3-transposition to yield the tertiary allylic

alcohol of **60**, and the acylation of the hindered alkoxide of **60** with freshly distilled acryloyl chloride afforded the ester **61** (70%). This material was immediately subjected to conditions for ring-closing metathesis (RCM).[25] As anticipated, the Grubbs II catalyst[26] was especially effective for the production of the five-membered lactone **62** (>95% yield) with mild heating at 70 °C. With the butenolide **62** in hand, we devised conditions to introduce the remaining vinylic methyl group by utilizing a standard tactic that involved the conjugate addition of dimethylcuprate with lactone **62** followed by selenylation of the resulting enolate. Oxidative elimination created the fully substituted lactone of **63**, and fluoride deprotection gave **64**.



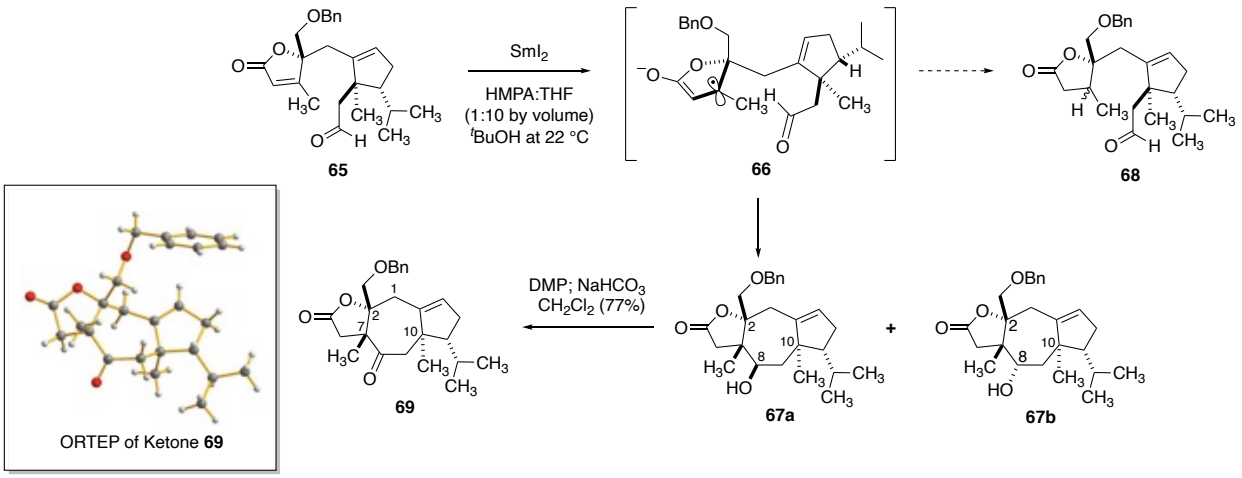
SCHEME 6 Formation of butenolide **64**.

3.3. The Reductive Cyclization

The investigations of reductive cyclizations, focused on the use of samarium diiodide.[27,28] These studies required diligent efforts to identify the appropriate reaction conditions because small changes were known to greatly alter reaction outcomes based on the influence of proton sources, substrates, and the presence of various additives. For example, Proctor and coworkers[29] found that changing the proton source from methanol to *tert*-butanol produced different reaction pathways. Salts, such as LiCl and NiI_2, and cosolvents, including hexamethylphosphoramide (HMPA), *N*-methyl-2-pyrrolidinone (NMP), and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

(DMPU), effectively altered the oxidation/reduction potential of the medium.[30,31] As shown in Scheme 7, the aldehyde **65** was generated by a mild Dess–Martin oxidation[32] of **64** (92% yield); however, initial attempts for SmI_2 cyclization in anhydrous THF containing methanol (2.2 equiv) led only to recovered starting material. Subsequent use of HMPA as a cosolvent (THF/HMPA, 10:1 by volume) gave the desired products **67a** and **67b** (dr 85:15) in 30% yield accompanied by an equal amount of the reduced butyrolactone **68** as a mixture of diastereomers. The fact that the aldehyde had not been reduced in **68** led us to conclude that reactions were initiated by introducing an electron into the butenolide with subsequent protonation. SmI_2 cyclizations were then examined in the absence of a proton source. Under these conditions, an excess of SmI_2 (6 equiv) was required for consumption of the starting material at 0 °C, but substantial amounts of byproducts were also observed. With the introduction of anhydrous *tert*-butanol, in addition to HMPA, the yield of the desired cyclization was increased to 63% (dr 67:33) with a significant reduction in side products. The cycloheptanols were purified via flash chromatography and characterized by 2D NMR analysis. Significantly, the 2D-NOESY studies of the major isomer **67a** provided key correlations between the C-7 methyl and the C-2 methylene substituents to support the assignment of the *cis*-fused lactone. The stereochemistry of the C-8 hydrogen and C-10 methyl as well as the α-hydrogen at C-1 was also established by 2D-NOESY. The minor product **67b** displayed the expected correlations of the β-hydrogen at C-8 with the C-2 and C-7 alkyl groups. The tethered arrangement of **65** provided a conformational bias for facial selectivity via initial production of the ketyl radical **66**. Thus, the 7,10-*anti*-dimethyl substitution pattern in **67a** and **67b** is enforced by a minimization of steric requirements and ring strain leading these *cis*-fused lactones. Oxidation of the mixture of alcohols yielded the ketone **69** as a crystalline solid, and X-ray analysis unambiguously confirmed the relative stereochemistry of the tricyclic system.[33]

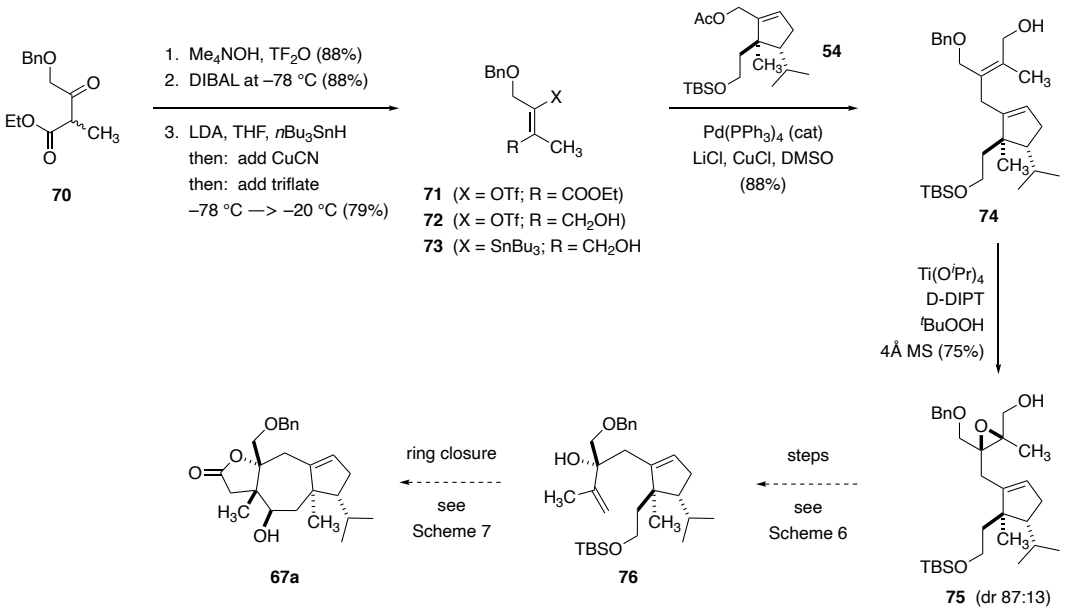
These data also established the absolute configuration at C-2 arising from the Sharpless epoxidation of Scheme 6.[34]



SCHEME 7 Formation of the tricyclic core of the trichoaurantianolides.

Encouraged by the information gathered from these studies, we sought improvements in the efficiency of our approach, and we also initiated studies to explore chemistry for the formation of the bridging furanyl ring system as featured in trichoaurantianolide C. Three steps had been used to introduce the β-methyl substituent of the butanolide prior to cyclization. As summarized in Scheme 8, these three steps were readily eliminated by incorporation of the methyl group from the outset. The known ketoester[35] **70** was exclusively converted to the *E*-vinyl **71** triflate as a single stereoisomer in 88% yield.[36] However, subsequent experiments to replace the triflate with tri-*n*-butylstannyl or trimethylstannyl substitution using palladium catalysis were met with a lack of reactivity of the vinyl triflate. The ester of **71** was readily reduced to give the alcohol **72** using DIBAL, and stannylation was then achieved by reaction with the higher order stannylcuprate[37] to yield **73** as a single stereoisomer. It was notable that this reaction not only proceeded with complete stereoretention at low temperatures, but it was also highly reproducible and amenable to

the large-scale production of **73**. This stannane proved to be an excellent substrate for the π-allyl Stille cross-coupling and gave the tetrasubstituted alkene **74** in 88% yield with net retention of olefin geometry. In fact, this effective cross-coupling may be the methodology of choice for the preparation of highly substituted, stereodefined 1,4-dienes. Furthermore, the application of the SAE showed improvements of stereo- and regioselectivity for the production of the epoxy alcohol **75** (dr 87:13). Subsequent steps culminating in the RCM with the Grubbs II catalyst were uneventful based on the prior efforts of Schemes 6 and 7. Thus, the robust synthesis pathway of Scheme 8 afforded significant quantities of the tricyclic **67a** and encouraging prospects for a rapid completion of the total synthesis.

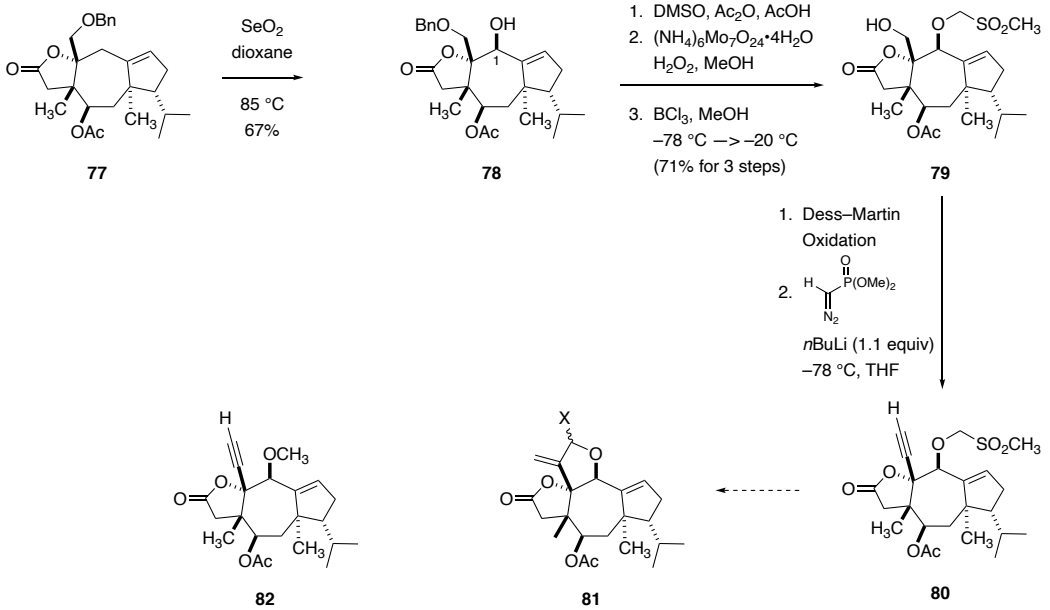


SCHEME 8 Streamlined preparation of tricyclic **67a**.

4. TACTICS FOR FUNCTIONALIZATION OF THE BRIDGEHEAD SUBSTITUENT

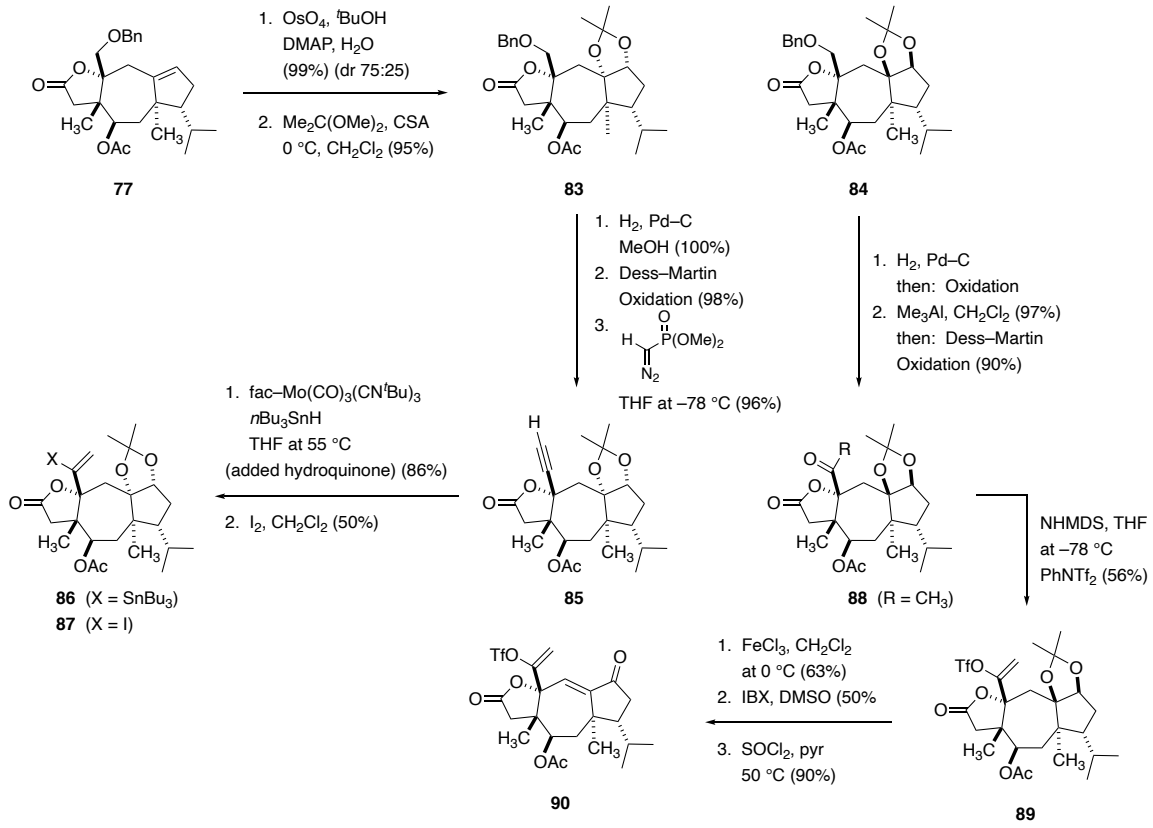
Two objectives remained for completion of the synthesis. The first task required creation of the appropriately functionalized, vinylic C-2 substitution, and the second, seemingly straightforward, objective would be to devise an oxidation protocol to transform the cyclopentane into the desired enone. The efforts of Scheme 9 began with studies of the allylic oxidation of acetate **77**, which

led to the β-alcohol **78** using SeO_2. This reaction occurred with excellent regiocontrol and resulted in a small amount of the epimeric C-1 α-alcohol (11%). The *O*-alkylation of alcohol **78** was achieved by treatment with Ac_2O and acetic acid in DMSO for the generation of the electrophilic intermediate of a Pummerer rearrangement[38] with subsequent nucleophilic capture by the C-1 hydroxy group. This reaction was essentially a quantitative conversion, and the resulting thiomethyl acetal was immediately oxidized to the corresponding sulfone using ammonium molybdate tetrahydrate[39] under mild conditions with subsequent deprotection to give the primary alcohol **79** (71% over 3 steps). Oxidation of **79** using the Dess–Martin periodinane[32] and introduction of the Gilbert–Seyferth reagent,[40] dimethyl(diazomethyl)phosphonate, resulted in the terminal alkyne **80** in a quantitative conversion (>96% yield). This effective four-step sequence led to exploration of five-exo-digonal cyclizations using **80** in accordance with Baldwin's rules for ring closures.[41] Attempts of carbanion or radical-mediated cyclizations of **80** failed to produce **81** (X = SO_2CH_3 or H). Reductive conditions using SmI (THF, HMPA) at –78 °C led to further disappointment and the isolation of methyl ether **82**.



SCHEME 9 Formation of alkyne **80**.

Several experiments examined other oxidations of the cyclopentane moiety of **77**. For example, epoxidations of various protected derivatives of tricycle **77** were followed by typical reagents for base-induced isomerization of the resulting β-epoxide to an allylic alcohol.[42] However, these attempts led to the backbone migration of the bridgehead methyl substituent. Subsequently, dihydroxylation of **77** (Scheme 10) required DMAP for activation of OsO_4,[43] and produced a separable mixture of β-diol (75%) and α-diol (25%) derivatives. These isomers were individually advanced upon conversion to their corresponding acetonides **83** and **84**. Hydrogenolysis of **83**, oxidation, and the use of the Gilbert–Seyferth reaction[40] gave the alkyne **85**. Furthermore, a noteworthy, regioselective, molybdenum-catalyzed hydrostannylation[44] proceeded in high yield to give **86**. This route also permitted easy access to the corresponding vinyl iodide **87**. Similar advances were recorded with the β-acetonide **84** via conversion to the methyl ketone **88** for low temperature deprotonation leading to isolation of the enol triflate **89**. The triflate was transformed into the enone **90** via mild hydrolysis, IBX oxidation[45] to the α-hydroxyketone, and facile elimination using $SOCl_2$ and pyridine. Thus, we were within striking distance of our goal, which required the addition of a single methylene (C-4). Considerable efforts to execute various cross-coupling reactions[46] and carbonylations[47] of **86**, **87**, **89**, and **90** using a variety of catalysts failed miserably. Rapid destruction of these starting materials indicated the absence of the butyrolactone moiety via a palladium-induced elimination of the allylic ester functionality.

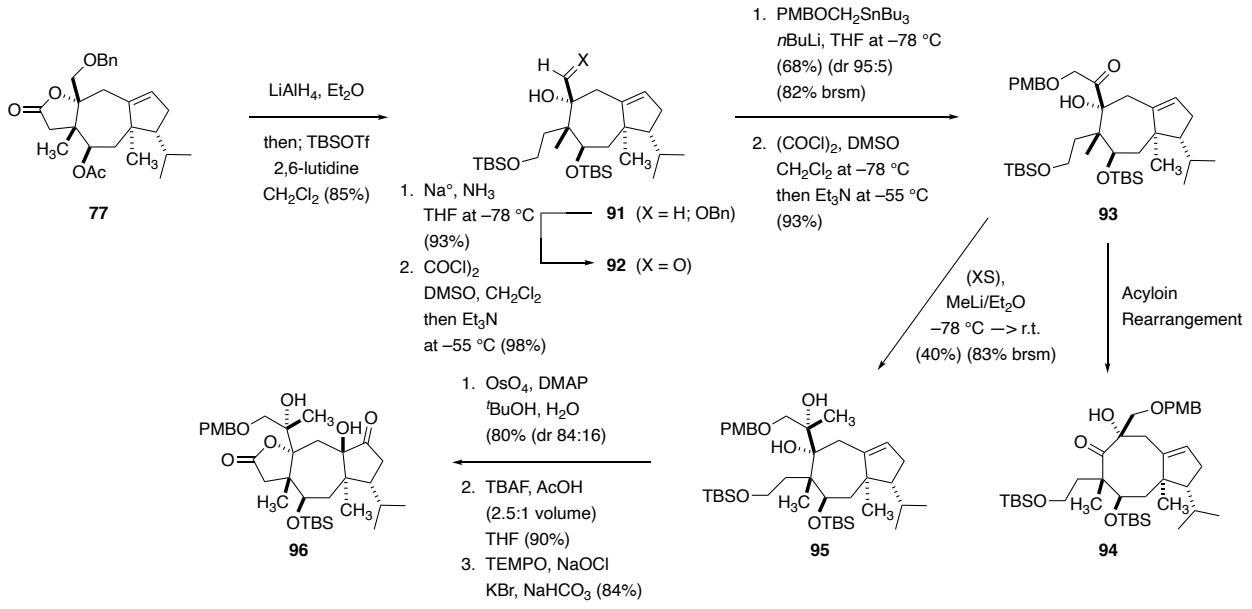


SCHEME 10 Formation of C-3 vinylic derivatives.

5. REVISITING THE ORIGINAL PLAN

A straightforward element of our retrosynthetic analysis (Scheme 1) was based on the intramolecular 1,4-conjugate addition for conversion of **2** into trichoaurantianolide C (**3**). Studies were undertaken to set the stage for this ring closure by creating the Michael acceptor enone and the allylic alcohol simultaneously via a dehydration reaction. The appropriate elaboration of the C-2 substituent of **77** was explored in the double elimination approach of Scheme 11. $LiAlH_4$ reduction of **77** was followed by TBS protection to yield the tertiary alcohol **91** (85%). Subsequent removal of the benzyl protecting group and Swern oxidation[48] led to the unstable α-hydroxy aldehyde **92**, which was converted into the α-hydroxy ketone **93** in two standard operations. The addition of the lithium carbanion, generated from $PMBOCH_2SnBu_3$, was first carried out at –78 °C to avoid a competing Wittig rearrangement[49] and subsequent Swern oxidation gave the

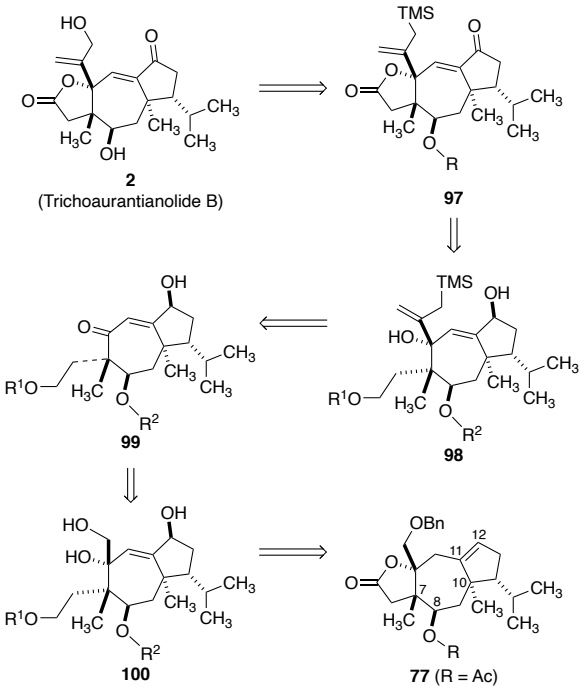
expected ketone **93**. Secondly, methylmagnesium bromide was added to the hindered ketone, resulting in the unanticipated acyloin rearrangement to yield varying amounts of **94** as a single diastereomer. The alternative use of methylcerium reagent (CH_3Li, $CeCl_3$) favored formation of the eight-membered **94**, which was produced by a selective migration of the neighboring methylene in **93**. After these initial frustrations, we found that newly purchased bottles of methyllithium in ether afforded the desired diol **95** in moderate yields (40% yield, 83% brsm) without accompanying amounts of ketone **94**. The stereochemistry of **95** has been illustrated with the expectations of a chelation-controlled addition since a single isomer was obtained, but this detail could not be unambiguously determined using NMR techniques. Indeed, this is a very challenging task since the diol **95** has incorporated three contiguous fully substituted carbons. Dihydroxylation of **95** was followed by selective removal of the primary silyl ether and TEMPO oxidation[50] to produce the key intermediate **96**. We were positioned to complete the total synthesis upon the elimination of two equivalents of water only to face disappointment once again as a variety of procedures for dehydration, including the use of Martin sulfurane,[51] Burgess reagent[52] or mesyl chloride, led to a multitude of products.



SCHEME 11 The double elimination approach.

6. NEW PLAN AND RENEWED OPPORTUNITIES

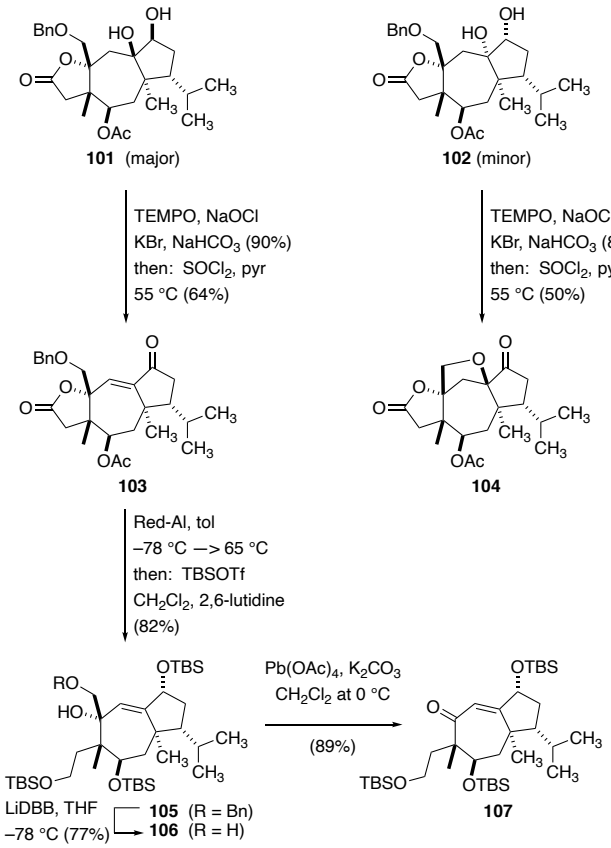
It was time to revise the original retrosynthetic analysis to accommodate this body of results. An alternative plan is illustrated in Scheme 12, and it includes two significant features that are based on positive and negative results of the prior studies. These plans recognize trichoaurantianolide B (**2**) as a logical precursor of an internal conjugate addition, reasonably incorporating the advantages of the efficient and stereocontrolled assembly of the tricyclic core of **77**. Secondly, our revised plan generates the C-2 stereochemistry using ketone **99** for nucleophilic addition of 1-trimethylsilyl-2-propenyllithium as an ideal synthon for the allylic alcohol. Thus, a key transformation toward construction of trichoaurantianolide B effects a late-stage oxidation of allylsilane **97** to produce the desired alcohol for conjugate addition.



SCHEME 12 The revised retrosynthetic approach.

Refocused studies began with the cyclopentane of **77** in efforts to access the allylic alcohol **100** of Scheme 12. These experiments revealed independent pathways for dehydration processes

stemming from major β-diol **101**, and α-diol **102**, (Scheme 13). TEMPO oxidation[50] of the diol **101** led to *syn*-elimination upon treatment with thionyl chloride in pyridine to yield the expected enone **103** (64%), whereas the application of these same steps to the diastereomeric **102** gave the *trans*-fused cyclopentanone **104**. This divergent reactivity was attributed to the facile internal backside displacement of a reactive sulfonyl ester, produced by reaction of the α-hydroxyketone with thionyl chloride. The novelty of this transformation has illustrated seemingly disfavored characteristics that involve the nucleophilic attack of a benzyl ether at a fully substituted carbon via a crowded transition state and the production of a *trans*-fused five-membered ring system. Nevertheless, sufficient quantities of the desired enone **103** were available from the major diol **101**, and these efforts were advanced by hydride reduction and protection as previously described in Scheme 11. Although the use of Birch conditions led to the reductive cleavage of the allylic silyl ether of **105**, debenzylation to give **106** was smoothly accomplished by use of the radical anion of 4,4′-di-*tert*-butylbiphenyl (LiDBB).[53] Subsequently, the oxidative cleavage of the intermediate diol **106** provided the expected cycloheptenone **107**.

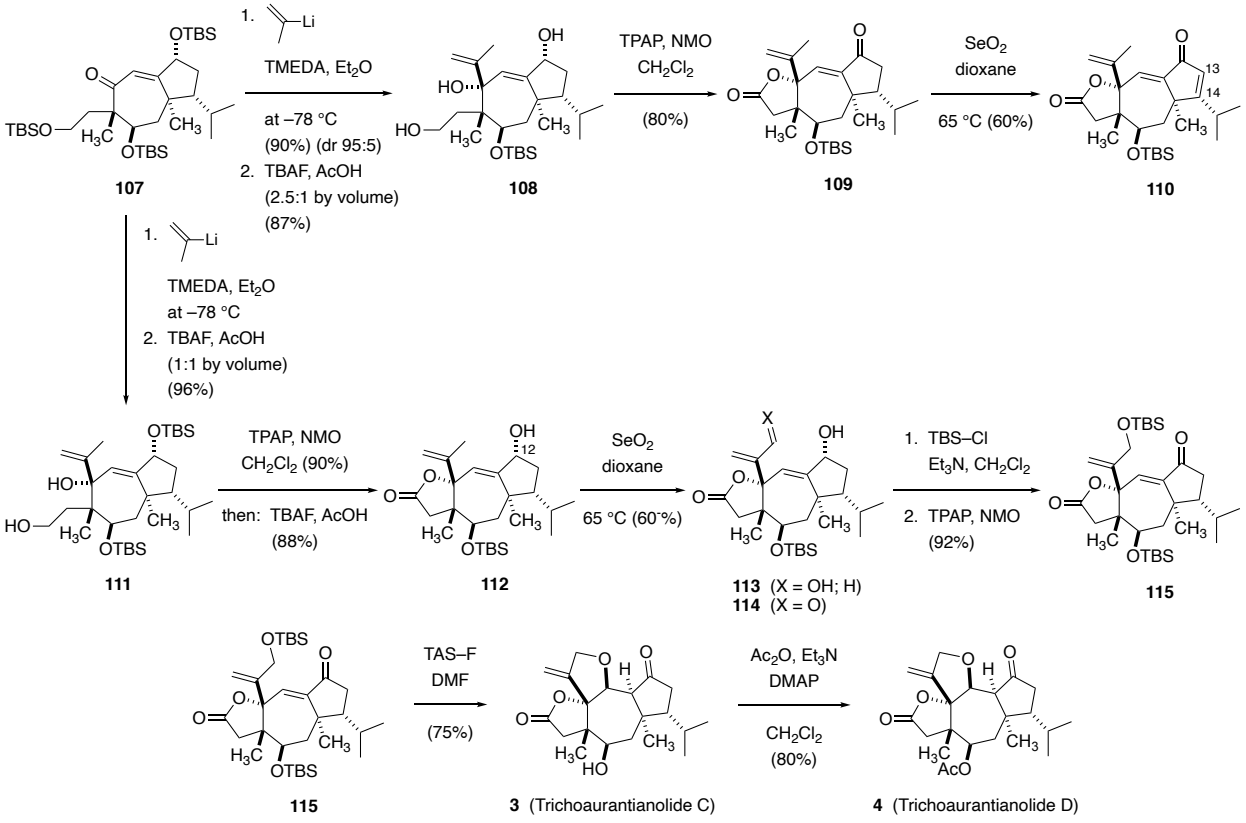


SCHEME 13 Studies leading to ketone **107**.

7. COMPLETION OF THE TOTAL SYNTHESIS

Once again, we were standing on the threshold of finalizing steps for completion of the total synthesis. Our revised approach (Scheme 12) called for nucleophilic addition of a functionalized allylic alcohol equivalent to the C-3 carbonyl of **107**. A primary concern was the diastereofacial selectivity of a reaction generating three contiguous, fully substituted carbons (C-2, C-3, and C-7). In the event, our attempts for addition of excess Grignard reagent (20 equiv), derived from (2-bromoallyl)trimethylsilane, completely failed, even at elevated temperatures. Had we misjudged the steric hinderance involved in the proposed reaction? As shown in Scheme 14, enone **107** reacted with 2-propenyllithium (15 equiv) at –78 °C to give a mixture of C-2 diastereomeric alcohols (dr 2:1) in a modest 30% yield. A significant improvement in the formation of the C-2

tertiary alcohol was then achieved by precomplexation of the lithium reagent with tetramethylenediamine (TMEDA).[54] At –78 °C in ether, this procedure afforded the desired alcohol in 90% yield with impressive stereocontrol (dr 95:5) followed by deprotection with TBAF to give the triol **108**. Oxidation yielded lactone **109** by using the Ley TPAP procedure, and final allylic oxidation was required to reach our goal.



SCHEME 14 The end-game approach for total synthesis of trichoaurantianolides C and D.

Unfortunately, the SeO_2 oxidation of **109** was problematic because it readily introduced the cyclopentenone unsaturation of **110**.[55] Formation of the C-13-C-14 double bond occurred at a faster rate than the desired allylic hydroxylation. This reaction was attributed to the ease of enolization of the starting cyclopentanone, and the stereochemistry of the selenoxide intermediate that facilitates the *syn*-elimination. We overcame these issues by selective deprotection of the primary OTBS ether of **107** following the addition of organolithium reagent to give **111**. TPAP

oxidation[19] of **111** yielded the butyrolactone, and cleavage of the less hindered TBS ether led to the allylic alcohol **112**. The SeO_2 oxidation of **112** gave the desired **113** (X = H; OH) with considerable amounts of overoxidation to the aldehyde **114** (X = O) These reactions were quenched at the first signs of the observation of a slower oxidation of the C-12 alcohol leading to the enone. For the sake of efficiency, crude product mixtures were directly quenched by a Luche reduction[56] which provided diol **113** in 60% yields (93% brsm) with recovery of starting **112** (33%). The introduction of the TBS silyl ether in **113** followed by mild oxidation gave the penultimate enone **115** as we planned for conditions to trigger the internal conjugate addition of trichoaurantianolide B (**2**) to produce trichoaurantianolide C (**3**) and D (**4**). Indeed, this highly anticipated reaction did not evolve as we had expected. In fact, the selective cleavage of the TBS ether of **115** immediately led to conjugate addition and ring closure under all conditions. Global deprotection with TAS-F[57] cleanly produced trichoaurantianoide C (**3**) in 75% yield, and trichoaurantianolide D (**4**) was obtained from synthetic **3** via acetylation using acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP).[58] Finally, the total synthesis had been achieved, and the structures of **3** and **4** were confirmed by comparisons with proton and carbon NMR data and optical rotations generously supplied by Professor Vidari.

8. CONCLUSION

This contributed chapter is specifically authored with students in mind, and all who aspire to master the art of total synthesis. Our studies, culminating in the total synthesis of trichoaurantianolide natural products began with an understanding of the value of the reported structural characterizations as well as inconsistencies and missing pieces of crucial information. The logic of our retrosynthetic plan was developed with particular goals in mind to explore concepts of strategy and methodology. Of course, it is far more stimulating to assume the calculated risk of a

proposed reaction than to repeat published preparations of the literature. The value of studies of natural product synthesis is measured by the new information acquired in the course of this journey. In our account, we have described strategies and several unsuccessful tactics. In general, the obstacles and the resolution of these problems in the course of our lines of inquiry are at least as interesting as the achievement of the total synthesis itself. A well-crafted retrosynthesis is insightful, but, more importantly, it is a hypothesis, and frequently, it does not proceed according to plan. Lessons learned from experimentation give rise to adjustments and revisions. Through these efforts, the π-allyl Stille cross coupling emerged as a general reaction protocol for the stereocontrolled preparation of nonconjugated 1,4-skipped dienes using tri- and tetrasubstituted alkene components. On the other hand, the unexpected and chemoselective S_N2' reaction of a higher-order cuprate resulted in the formation of the complex, conjugated triene by the unusual nucleophilic addition at the alpha carbon of a conjugated ester. Our general strategy for construction of the polycyclic system, proved highly successful. Two small rings were connected via a linker for subsequent closure of a larger, central ring. This concept established the relative stereochemistry of two asymmetric quaternary carbons of a cycloheptane with 1,4-*trans*-dimethyl substitution at the bridgehead positions. When the proposed cross-coupling failed to introduce the allylic alcohol of trichoauratianolide B, we devised and examined several tactics to circumvent the problem. These efforts led to the discovery of an unusual cyclization of a benzyl ether to produce a polycyclic tetrahydrofuran containing a *trans*-fused cyclopentanone. We also uncovered a facile acyloin rearrangement affording a highly substituted cyclooctenone by ring expansion. Molecules speak to practitioners of the art in various ways, and the message was clear. We altered a failing strategy and achieved the first total synthesis of the trichoaurantianolides C and D. In the final effort, laboratory experimentation demonstrated improved reactivity and stereoselectivity in the

course of nucleophilic addition of isopropenyllithium by precomplexation with TMEDA and we uncovered fine distinctions of functional group reactivity in the oxidation profile of selenium dioxide. In summary, trichoaurantianolide C was prepared in 21 steps from the known allylic acetate, and these studies confirmed the original assignment of absolute configuration by Steglich and Vidari. More importantly, these efforts enriched our knowledge of organic chemistry and provided new insights to broadly advance studies to address the challenging projects of the future.

ACKNOWLEDGEMENTS

These studies are the result of talented and dedicated individuals. I gratefully acknowledge the efforts and intellect of Dr. Paul T. Gladen and Dr. Joseph R. Pinchman in these investigations. This publication is based upon work supported by the National Science Foundation under Grant Nos. CHE-1055441 and CHE-1665356. We thank Professor Vidari for comparisons of our NMR spectra for synthetic **3** and **4** with spectra of authentic material.

REFERENCES

1. (a) Invernizzi, A. G.; Vidari, G.; Via-Finzi, P. V. *Tetrahedron Lett*. **1995**, *36*, 1905–1908. (b) Benevelli, F.; Carugo, O.; Invernizzi, A. G.; Vidari, G. *Tetrahedron Lett*. **1995**, *36*, 3035–3038.
2. Knops, L.; Nieger, M.; Steffan, B.; Steglich, W. *Liebigs Ann*. **1995**, *1995*, 77–80.
3. Mazur, X.; Becker, U.; Anke, T.; Sterner, O. *Phytochemistry*, **1996**, *43*, 405–407.
4. Pettit, G. R.; Ode, R. H.; Herald, C. L.; VonDreele, R. B.; Michel, C. *J. Am. Chem. Soc.* **1976**, *98*, 4677–4678.
5. For synthesis of clavularanes: Williams, D. R.; Coleman, P. J.; Henry, S. S. *J. Am. Chem. Soc.* **1993**, *115*, 11654–11655.

6. For synthesis of [9.3.0]-neodolabellanes: (a) Williams, D. R.; Heidebrecht, R. W. Jr. *J. Am. Chem. Soc.* **2003**, *125*, 1843–1850. (b) Williams, D. R.; Coleman, P. J.; *Tetrahedron Lett*. **1995**, *36*, 35–38.
7. Tsukamoto, S.; Macabalang, A. D.; Nakatani, K.; Obara, Y.; Nakahata, N.; Ohta, T. *J. Nat. Prod*. **2003**, *66*, 1578–1581.
8. Kirk, D. N. *Tetrahedron* **1986**, *42*, 777–818.
9. Wang, Z.; Min, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 10848–10849.
10. For an overview: Hiersemann, M.; Helmboldt, H. *Top. Curr. Chem*. **2005**, *243*, 73–136.
11. Marković, D.; Kolympadi, M.; Deguin, B.; Porée, F.-H.; Turks, M. *Nat Prod. Rep.* **2015**, *32*, 230–255.
12. Heptemerone isolation: Valdivia, C.; Kettering, M.; Anke, N.; Thines, E.; Sterner, O. *Tetrahedron* **2005**, *61*, 9527–9532.
13. For a review of synthesis: (a) Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095–13101. (b) Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025–7035. (c) Miller, A. K.; Hughes, C. C.; Kennedy-Smith, J. J.; Gradl, S. N.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 17057–17062. (d) Gampe, C. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 2962–2965. (e) Peng, S.-Z.; Sha, C.-V. *Org. Lett.* **2015**, *17*, 3486–3489.
14. Smyrniotopoulos, V.; Vagias, C.; Bruyere, C.; Lamoral-Theys, D.; Kiss, R.; Roussis, V. *Bioorg. Med. Chem.* **2010**, *18*, 1321–1330.
15. For examples of seven and eight-membered ring formation: (a) Monovich, L. G.; Le Huérou, Y.; Rönn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52–57. (b)

Fukuzawa, S.-i.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, S. *Chem. Commun.* **1987**, 920–921. (c) Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533–9540.

16. Sono, M.; Sugimoto, Y.; Tatara, H.; Ise, N.; Takaoka, S.; Tori, M. *Tetrahedron* **2008**, *64*, 11096–11104.
17. Sato, A.; Masuda, T.; Arimoto, H.; Uemura, D. *Org. Biomol. Chem.* **2005**, *3*, 2231–2233.
18. For a general review: Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.
19. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
20. Barton, D. H. R.; Bushiardes, G.; Fourrey, J. L. *Tetrahedron Lett.* **1983**, *24*, 1605–1608.
21. (a) For an overview: Johnson, R. A.; Sharpless, K. B. in *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; pp. 231–285. (b) For an example: Balasubramaniam, R. P.; Moss, D. K.; Wyatt, J. K.; Spence, J. D.; Gee, A.; Nantz, M. H. *Tetrahedron* **1997**, *53*, 7429–7444.
22. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.
23. For examples and discussion: (a) Williams, D. R.; Fromhold, M. G.; Earley, J. D. *Org. Lett.* **2001**, *3*, 2721–2724. (b) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923–1925.
24. For a review of models for substrate-directed epoxidations: (a) Johnson, R. A.; Sharpless, K. B. in *Comprehensive Organic Synthesis*; Trost, B. M. and Fleming, I., Eds.; Elsevier: Oxford, 1991, Vol. 7, pp. 389–436. (b) Sawano, T.; Yamamoto, H. *Eur. J. Org. Chem.* **2020**, 2369–2378.

25. (a) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204–2207. (b) Bassetti, M.; D'Annibale, A.; Fanfoni, A.; Minissi, F. *Org. Lett.* **2005**, *7*, 1805–1808. (c) Albrecht, U.; Langer, P. *Tetrahedron* **2007**, *63*, 4648–4654.

26. (a) Grubbs, R. H.; Trnka, T. M. in *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004, pp. 153–178. (b) Mizutani, H.; Watanabe, M.; Honda, T. *Tetrahedron* **2002**, *58*, 8929–8936.

27. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338.

28. For specific examples: (a) Kang, H.-Y.; Koh, H. Y.; Chang, M. H.; Hwang, J.-T.; Shim, S. C. *Bull. Korean Chem. Soc.* **1994**, 15, 710–712. (b) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, 133, 14964–14967. (c) Sono, M.; Onishi, S.; Tori, M. *Tetrahedron* **2003**, *59*, 3385–3395. (d) Tamiya, M.; Jäger, C.; Ohmori, K.; Suzuki, K. *Synlett* **2007**, *2007*, 780–784. (e) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140–7165.

29. Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811–4814.

30. Machrouhi, F.; Hamann, B.; Namy, J.-L.; Kagan, H. B. *Synlett* **1996**, *1996*, 633–634.

31. (a) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968. (b) Shabangi, M.; Sealy, J. M.; Fuchs, J. R.; Flowers, R. A. II, *Tetrahedron Lett.* **1998**, *39*, 4429–4432.

32. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

33. The ketone **66** ($C_{25}H_{32}O_4$) is isolated as colorless needles (from Hexanes/EtOAc), monoclinic, $P2_1$, a = 10.6858(4) Å, b = 6.5912(3) Å, c = 15.6583(7) Å, β = 100.169(3) Å, V = 1085.52(8) Å^3. A single crystal was mounted and data collection was carried out at

150K using CuKα radiation. Final residues were R1 = 0.0421 and wR2 = 0.0842 (F^2, all data). The structure was solved with direct methods and refined with full-matrix least squares/difference Fourier cycles. All non-hydrogen atoms were refined with anisotropic displacement parameters.

34. Williams, D. R.; Pinchman, J. R. *Can. J. Chem.* **2013**, *91*, 21–37.
35. Ethyl 4-(benzyloxy)-2-methyl-3-oxobutanoate was prepared from 4-chloro acetoethylacetate. See: (a) Seebach, D.; Eberle, M. *Synthesis*, **1986**, *1986*, 37–40. (b) Knobloch, E.; Brückner, R. *Synthesis*, **2008**, 2229–2246.
36. Babinski, D.; Soltani, O.; Fantz, D. E. *Org. Lett*. **2008**, *10*, 2901–2904.
37. Gilbertson, S. R.; Cahllener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett*. **1988**, *29*, 4795–4798.
38. Pojer, P. M.; Angyal, S. J. *Tetrahedron Lett.* **1976**, *17*, 3067–3068.
39. (a) Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291–2294. (b) Williams, D. R.; Clark, M. P.; Emde, U.; Berliner, M. A. *Org. Lett.* **2000**, *2*, 3023–3026.
40. (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379–1386. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837–1845.
41. Baldwin, J. E. *Chem. Commun.* **1976**, 734 and 738.
42. For a comprehensive review: Crandall, J. K.; Apparu, M. *Org. React.* (NY), **1983**, *29*, 345–443.
43. He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772.
44. (a) Kazmaier, U.; Schauss, D.; Pohlman, M. *Org. Lett.* **1999**, *1*, 1017–1019. (b) Kazmaier, U.; Pohlman, M.; Schauss, D. *Eur. J. Org. Chem.* **2000**, 2761–2766.

45. Wirth, T. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2812–2814.

46. For related examples: (a) Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563–6579. (b) Cook, G. K.; Hornback, W. J.; Jordan, C. L.; MacDonald, J. H. III; Monroe, J. E. *J. Org. Chem.* **1989**, *54*, 5828–5830. See also, reference 6a.

47. (a) For a review: Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133. (b) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452–461.

48. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

49. For a review: Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105–209.

50. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562.

51. Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 5003–5010.

52. Burgess, E. M.; Penton, H. R. Jr; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26–31.

53. Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854–860.

54. For an overview of the role of TMEDA in complexation of organolithium species: Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448–454.

55. For a review of allylic oxidations in natural product synthesis: Nakamura, A.; Nakada, M. *Synthesis* **2013**, *45*, 1421–1451.

56. Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

57. Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436–6437.

58. For a full account of this work: Williams, D. R.; Gladen, P. T.; Pinchman, J. R. *J. Org. Chem.* **2015**, *80*, 5474–5493.