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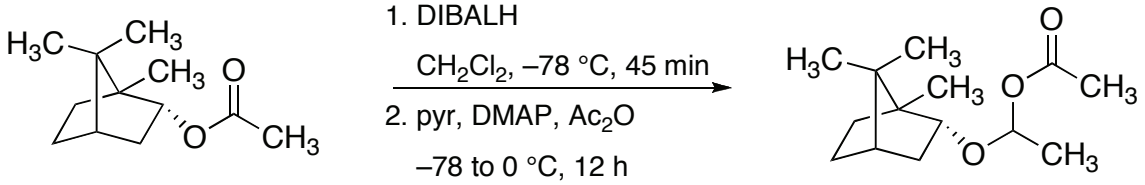
Discussion Addendum for: Preparation of α-Acetoxy Ethers by the Reductive Acetylation of Esters: *endo*-1-Bornyloxyethyl Acetate



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Original Article: Kopecky, D. J.; Rychnovsky, S. D. *Org. Synth*. **2003**, *80*, 177.

Reductive acetylation has proven to be a powerful methodology primarily because its products are excellent substrates for carbon-carbon bond forming reactions. Since 2003, the *Organic Syntheses* article and the primary references have been cited over 100 times. This discussion addendum aims to provide a brief overview of recent developments in this methodology. Improvements and variations of α-acetoxy ether formation, as well as the synthetic utility of α-acetoxy ethers will be discussed. Recent applications in the context of the total synthesis of complex natural products are also included.

Improvements and Variations of α-Acetoxy Ether Formation

The original reductive acetylation protocol involves the addition of diisobutylaluminum hydride (DIBALH) as a 1.0 M solution in hexanes to the ester at –78 °C. The resulting aluminum alkoxide is then treated with pyridine, 4-dimethylaminopyridine (DMAP), and acetic anhydride (Ac_2O) sequentially. The internal temperature during these additions should not exceed –72 °C in order to maximize the yield and prevent undesired side reactions.[2] While this method is general, recent developments include the use of asymmetric electrophiles in order to generate more complex acyl ethers and the extension of reductive acetylation to lactams and imides.

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Shortly after the original article, Rovis and Zhang reported the use of acid fluorides as competent reagents for the trapping of such aluminum alkoxides, the results of which are summarized in Figure 1.[3] Aryl, vinyl, and alkyl acid fluorides are all effective trapping reagents (67-97% yield) and steric bulk is well tolerated (pivaloyl fluoride = 92% yield). This development allows access to more complex acyl acetal derivatives without sacrificing a full equivalent of the acid, which represents an improvement in atom economy over the use of symmetric anhydrides.

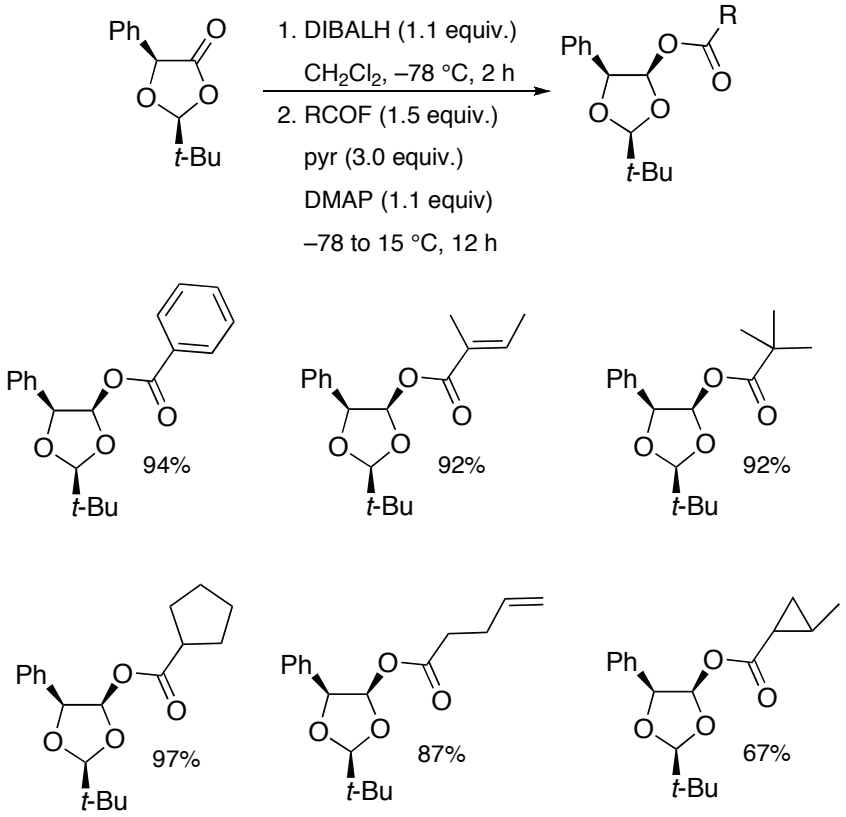
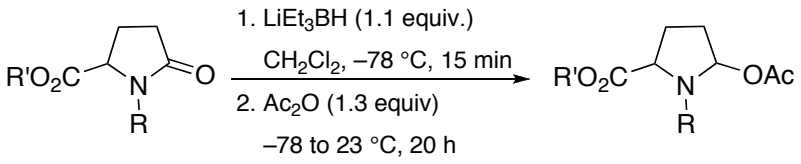


Figure 1. Acid Fluorides as Trapping Reagents.

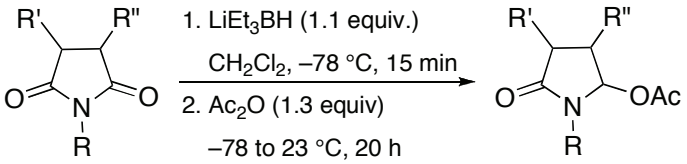
More recently, Dalla and co-workers have extended reductive acetylation strategy to the formation of α-acetoxy pyrrolidines (Figure 2).[4] While DIBALH will reduce imides, the resultant aluminum alkoxide is not nucleophilic enough to react with acetic anhydride. Therefore, the reductant of choice for the preparation of α-acetoxy amines is lithium triethylborohydride ($LiEt_3BH$), whose lithium alkoxide is sufficiently nucleophilic for effective trapping with acetic anhydride.



R	R'	% yield
Boc	Me	100
Boc	*t*-Bu	96
CBz	*t*-Bu	77

Figure 2. Formation of α-Acetoxy Pyrrolidines.

A variety of *N*-alkylated imides, shown in Figure 3, afford α-acetoxy lactams in high yields (75-100%), with the notable exception of cases where there is α-branching with respect to the nitrogen substituent (e.g. the imide of α-methylbenzylamine, MeBn). Steric bulk on the imide also limits the conversion to the α-acetoxy lactams, as shown by the modest yield for the *bis*-OTBS imide. Despite these limitations, this reductive acetylation strategy offers rapid entry into *N*-acylimium ions for use in Mannich reactions.



R	R'	R"	% yield	cis:trans[a]
PMB	H	OAc	88	100:0
Allyl	H	OAc	79	100:0
Bn	H	OTBS	75	100:0
PMB	H	OTBS	75	8:92
Bn	OAc	OAc	95	0:100
Allyl	OAc	OAc	80	0:100
Bn	OTBS	OTBS	30	0:100
MeBn	H	H	0	

a: refers to stereochemistry between R" and the newly formed acetate.

Figure 3. α-Acetoxy Lactams from Imides.

Synthetic Utility of α-Acetoxy Ethers

Treatment of α-acetoxy ethers with a Lewis acid (commonly $BF_3{\cdot}OEt_2$, $MgBr_2{\cdot}OEt_2$, TMSOTf, $SnCl_4$ or $TiCl_4$) results in the formation of

an oxocarbenium ion, which can be intercepted by a variety of nucleophiles to afford a new carbon-carbon or carbon-heteroatom bond adjacent to an ether linkage. The scope of such transformations has been investigated in the context of diastereoselective nucleophilic additions. α-Acetoxy ethers are also useful substrates for cascade sequences, such as oxonia Cope–Prins and Sakurai–Prins–Ritter cyclizations. The use of α-acetoxy ethers in enantioselective organocatalytic oxa-Pictet Spengler reactions have also been examined.

The use of α-(trimethylsilyl)benzyl alcohol as a chiral auxiliary has been investigated by Rychnovsky and Crossrow for diastereoselective additions to oxocarbenium ions generated from α-acetoxy ethers.[5] This chiral auxiliary was chosen due to the ease of preparation of both enantiomers and facile deprotection or conversion to the benzyl ether. Treatment of the α-acetoxy ether with a variety of nucleophiles, including allyl silanes, silyl enol ethers, and silyl ketene acetals, in the presence of TMSOTf proceed in high yields (87-98%) and high diastereoselectivities (20:1 to 80:1), as shown in Figure 4. Similarly, (*E*)-crotyltrimethylsilane affords the *syn* product in high yield and diastereoselectivity (82%, 27:2.4:1). The addition of cyanide and ethyl nucleophiles proceed in high yields (97% and 75% respectively), albeit with modest diastereoselectivity (5:1 and 4:1).

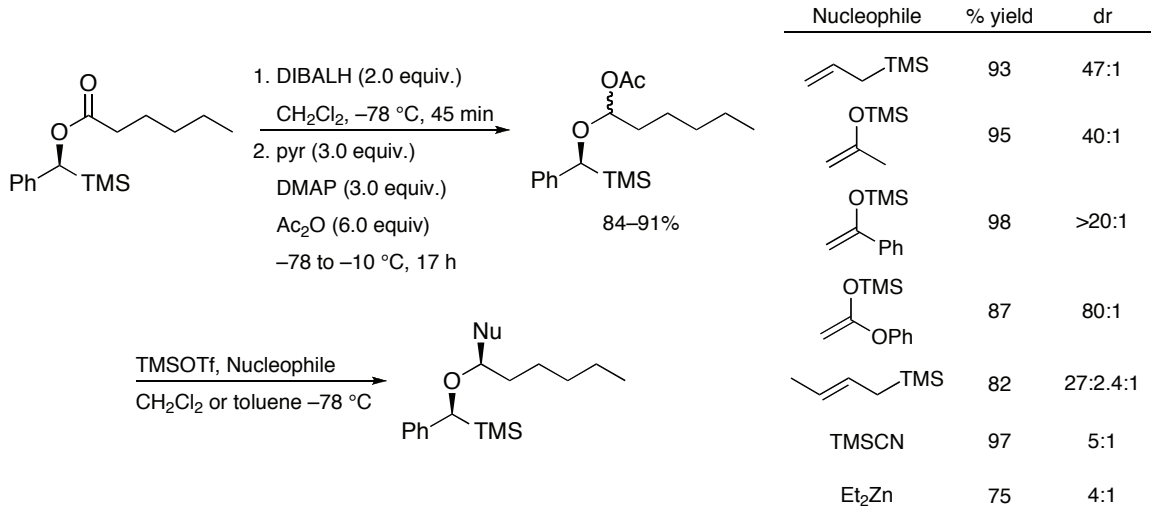


Figure 4. Diastereoselective Additions of Nucleophiles.

Rychnovsky and Dalgard have reported on the expedient synthesis of tetrahydropyranones through an oxonia Cope–Prins cyclization.[6] This strategy, outlined in Figure 5, involves a reductive acetylation of an ester **1**,

followed by treatment with TMSOTf to generate oxocarbenium ion **3**. The pendant allyl moiety participates in a 2-oxonia Cope rearrangement to generate oxocarbenium ion **4**, which is poised for a Prins cyclization (intramolecular Mukaiyama aldol reaction) with the silyl enol ether to afford tetrahydropyranone **5**. This transformation is effective for a variety of substrates (Figure 6) affording the tetrahydropyranone product in high yields (77-99%), including those bearing quaternary centers adjacent to the ketone.

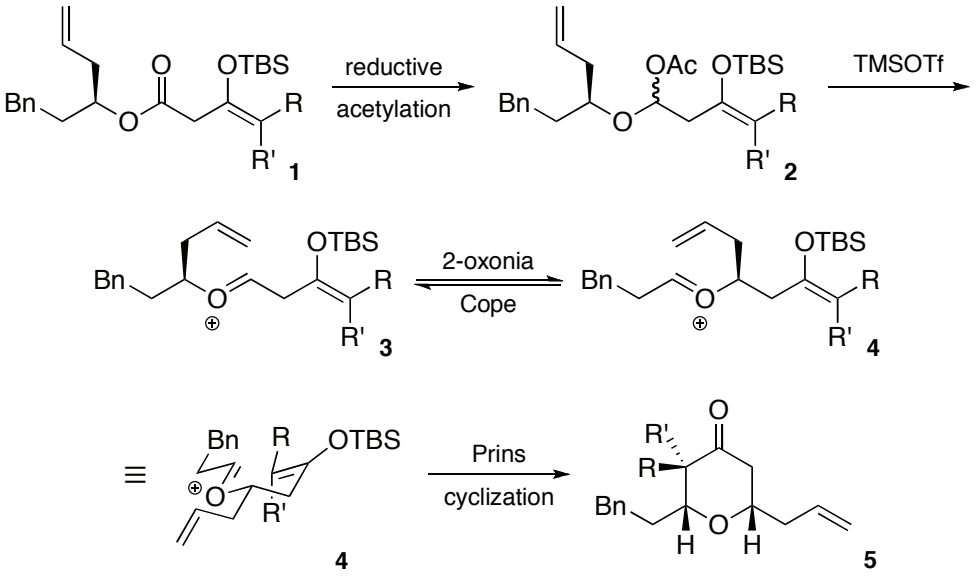


Figure 5. 2-Oxonia Cope–Prins Cyclization.

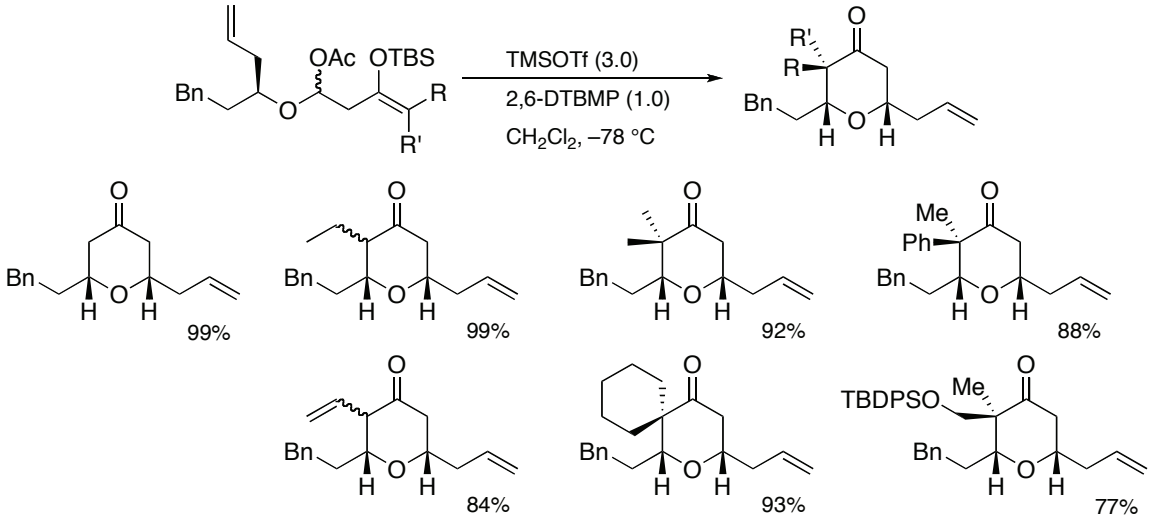


Figure 6. Synthesis of Tetrahydropyranones.

Rovis and Epstein have also utilized α-acetoxy ethers in a cascade sequence to provide 4-amino tetrahydropyrans through a Sakurai–Prins–Ritter cyclization.[7] As shown in **Figure 7**, treatment of 4-acetoxy-1,3-

dioxane **6** with TMSOTf generates oxocarbenium ion **7**, which upon treatment with allyl silane affords alkene **8**. In the presence of TfOH, acetal cleavage results in formation of oxocarbenium ion **9**, which undergoes a Prins cyclization to give carbocation **10**. Addition of a nitrile to the carbocation affords 4-amino tetrahydropyran **11** after hydrolysis.

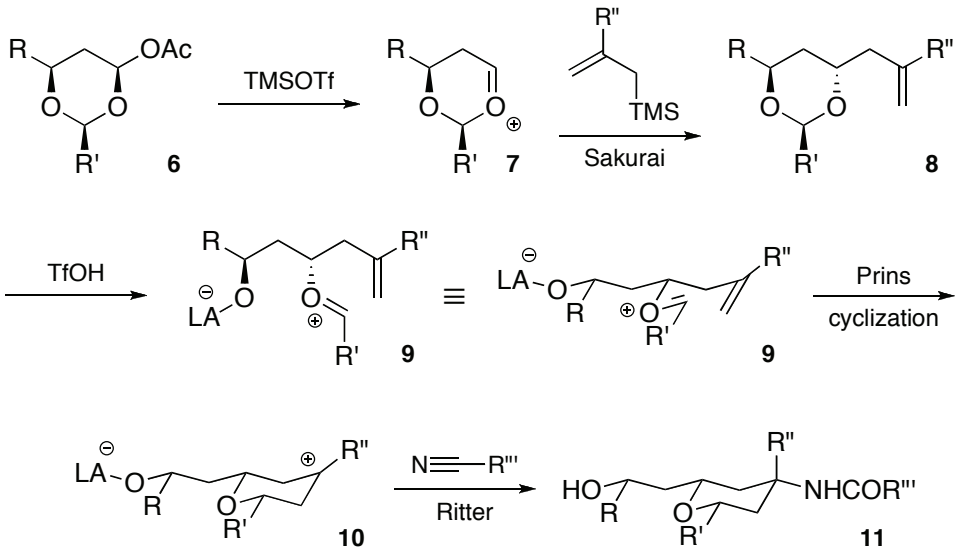


Figure 7. Sakurai–Ritter–Prins Cyclization.

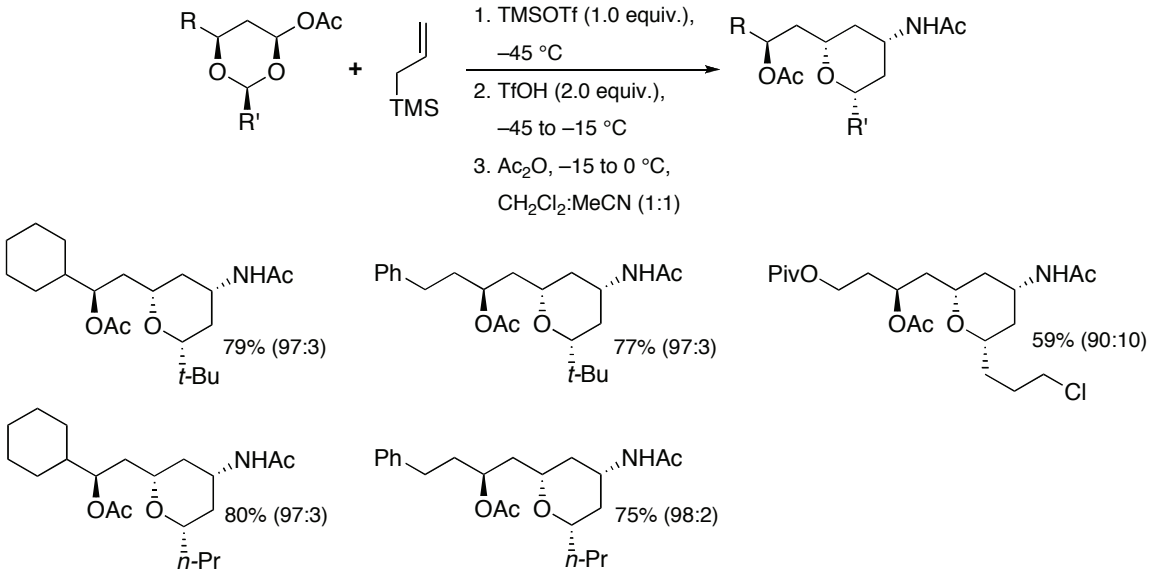


Figure 8. Synthesis of 4-Amino Tetrahydropyrans.

The Sakurai–Ritter–Prins reaction is effective for a variety of dioxane derivatives, as shown in Figure 8. This transformation affords the 4-amino tetrahydropyran products in good yields (59-88%) and high

diastereoselectivies (90:10 to 99:1). It should be noted that 2-substituted allyl silanes (Figure 9) and a variety of nitriles are effective partners in this transformation.[7]

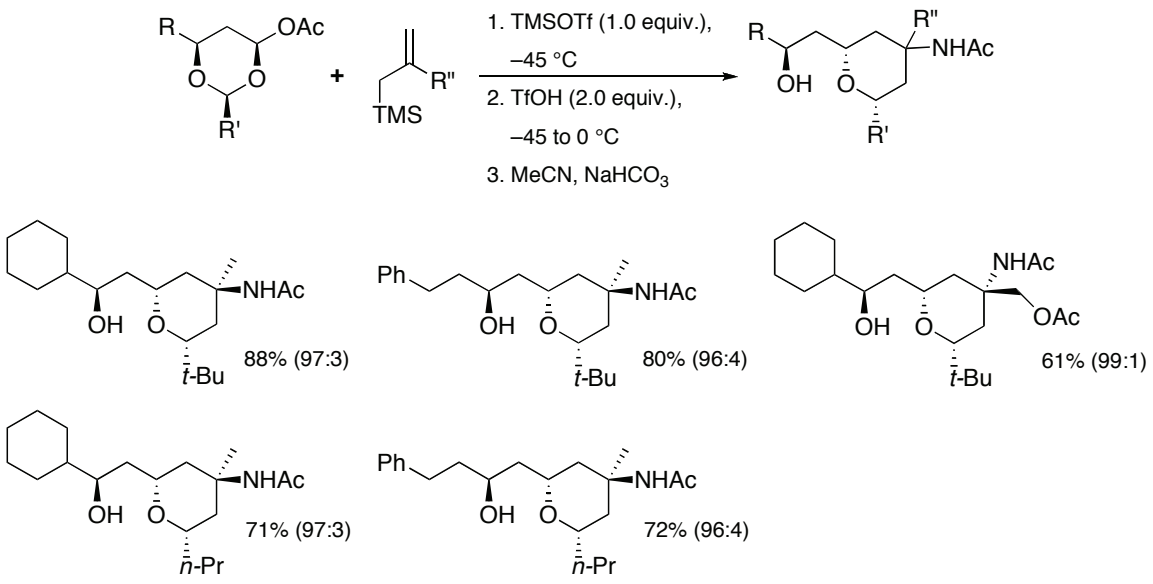


Figure 9. Synthesis of Quaternary 4-Amino Tetrahydropyrans.

Jacobsen and Doyle have utilized α-acetoxy ethers as substrates in the development of enantioselective organocatalytic oxa-Pictet–Spengler reactions (Figure 10).[8] An ester derivative of tryptophol was reduced and trapped to give α-acetoxy ether **12**. In the presence of a thiourea catalyst **13**, TMSCl, and BaO, oxocarbenium ion formation and subsequent ring closure afforded tetrahydropyrano-indole **14** in good yield (82%) and good enantiomeric excess (79%).

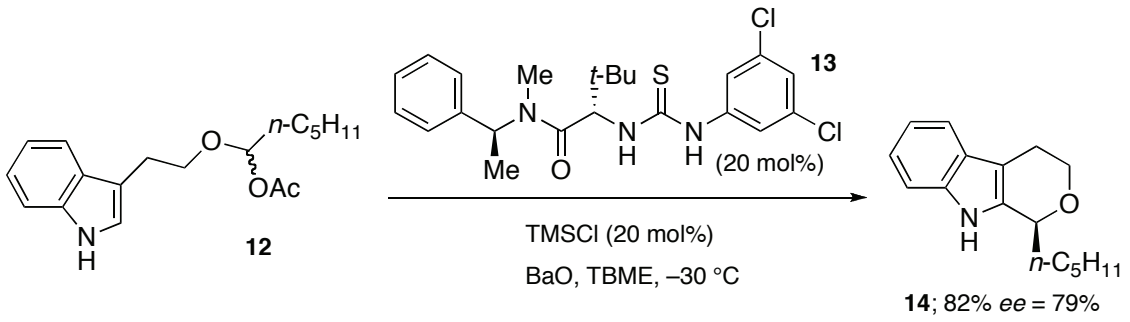
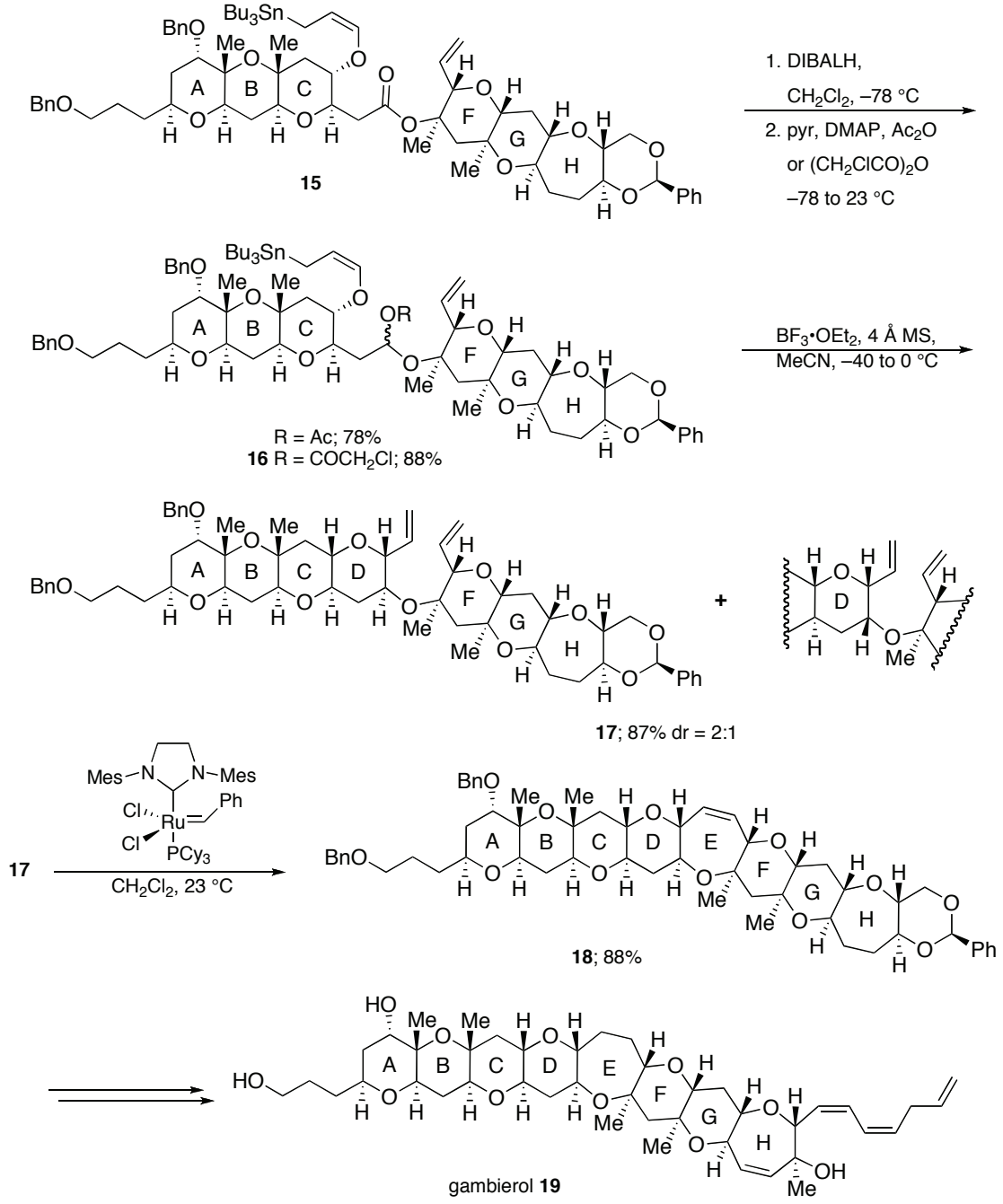


Figure 10. Organocatalytic Asymmetric Oxa-Pictet–Spengler Cyclization.

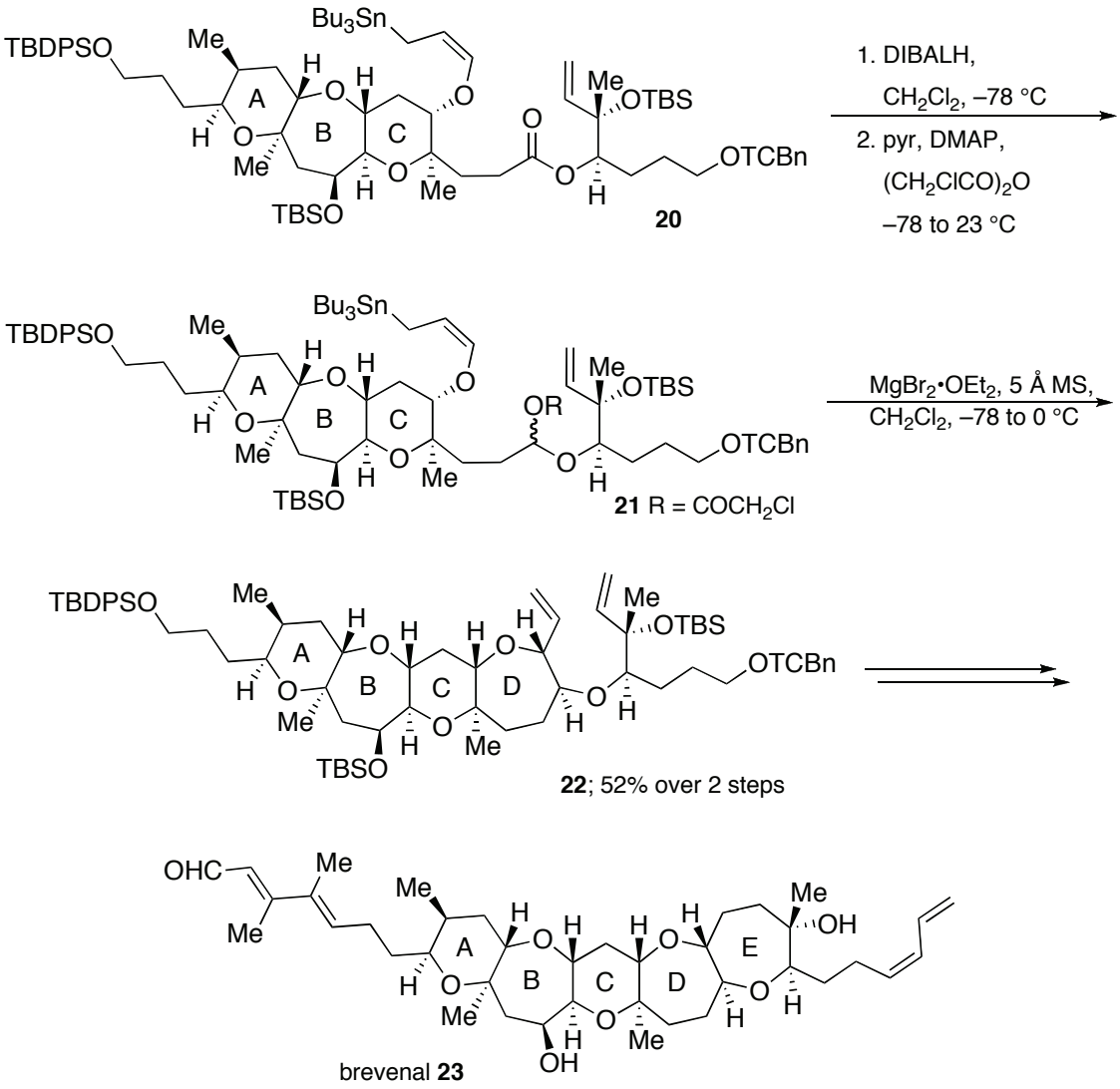
Highlighted Applications in the Total Synthesis of Complex Natural Products: Intramolecular Allylation of α-Acetoxy Ethers

Kadota, Yamamoto and co-workers utilized reductive acetylation to unite two complex fragments in their highly convergent synthesis of marine neurotoxin gambierol (**19**).[9] The strategy, shown in Scheme 1, begins with the coupling of ABC acid to FGH alcohol *via* Yamaguchi esterification. The resulting ester **15** is then subjected to reductive acetylation conditions. While



Scheme 1. Kadota and Yamamoto's Total Synthesis of Gambierol.

Ac_2O is an effective trapping reagent, chloroacetic anhydride provided increased yield and proper diastereoselectivity for the subsequent ring closure. Treatment of the resulting α-acetoxy ether **16** with boron trifluoride etherate in the presence of 4 Å molecular sieves afforded effective closure of the 6-membered D ring in high yield (87%) and modest diastereoselectivity (2:1) with respect to the acyclic ether. The resulting diene **17** is primed for a ring closing metathesis to forge the 7-membered E ring. The complex polycyclic ether framework **18** was then further elaborated to gambierol (**19**).

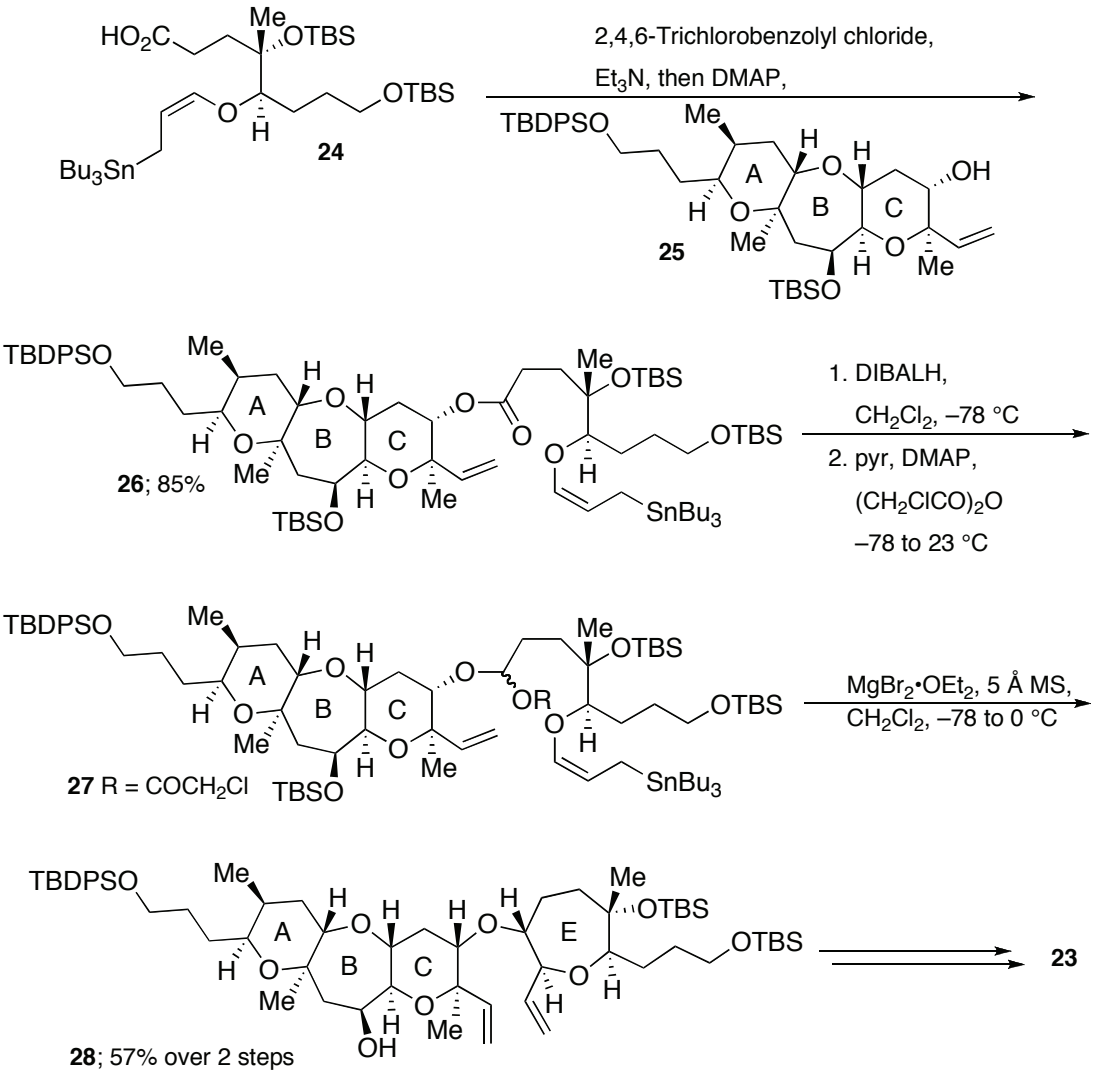


Scheme 2. Kadota's Total Synthesis of Brevenal.

A similar approach was employed in Kadota and co-worker's total synthesis of the nontoxic brevetoxin antagonist brevenal (**23**).[10] As shown in Scheme 2, the 7-membered D ring arose from the reductive

chloroacetylation of ester **20**, followed by treatment of α-acetoxy ether **21** with magnesium bromide etherate and 5 Å molecular sieves. The resulting oxocarbenium ion was then trapped by the allyl stannane to afford the tetracycle **22** in good yield as a single diastereomer (52% from the ester **20**). This cyclization again sets the stage for a ring closing metathesis sequence to afford a pentacycle, which was elaborated to brevenal (**23**).

The authors also reported a second-generation strategy (Scheme 3) where acyclic acid **24** is coupled to ABC alcohol **25**.[10b] This route employs the same reduction/cyclization sequence to forge the E ring in good yield as the single desired diastereomer (57% from the ester **26**) and sets up the closure of the D ring in an analogous fashion.

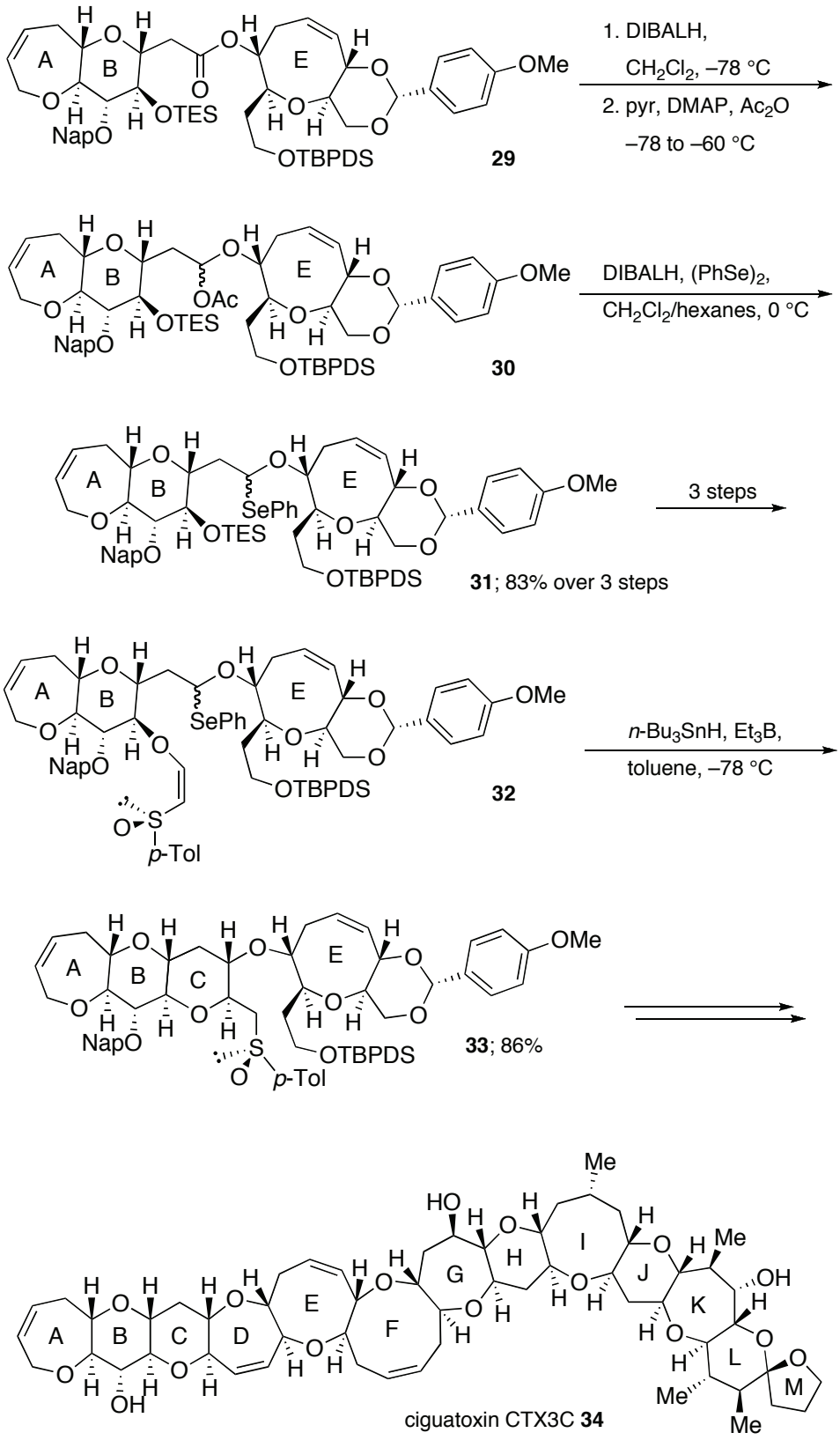


Scheme 3. Kadota's Second Generation Strategy to Brevenal.

Recently, the total synthesis of ciguatoxin CTX3C (**34**) by Yamashita and co-workers employed reductive acetylation to facilitate a radical

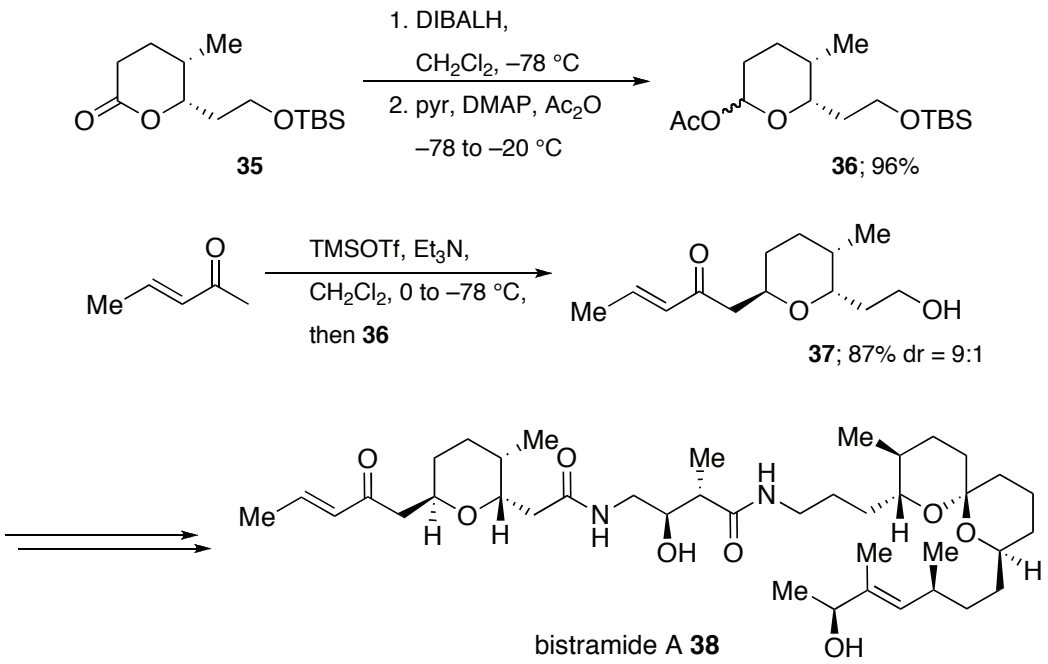
cyclization to give the C ring of tridecacyclic natural product (Scheme 4).[11] The AB acid and E alcohol were subjected to Yamaguchi esterification conditions to afford the ester **29**. Following reductive acetylation, α-acetoxy ether **30** underwent transacetylation in the presence of diisobutylaluminum phenylselenide to afford the α-seleno ether **31** in high yield (83% from the ester). The α-seleno ether **31** was carried through 3 steps before C-ring radical cyclization was initiated by triethylborane and oxygen in the presence of tributyltin hydride to provide sulfoxide **33** in good yield as a single diastereomer (86%). This approach offered increased stereoselectivity over a direct allylation strategy (as in gamberiol). Sulfoxide **33** was then carried forward to afford ciguatoxin CTX3C (**34**).

Reductive acetylation has proven to be a powerful method for the construction of complex cyclic ethers *via* intramolecular allylation. The strategy has played a key role in the preparation of brevetoxin-like ladder polyethers.[12] The method's utility is largely due to the ease with which substrates can be brought together by a Yamaguchi esterification. This protocol allows for a highly convergent and flexible approach to these marine natural products.



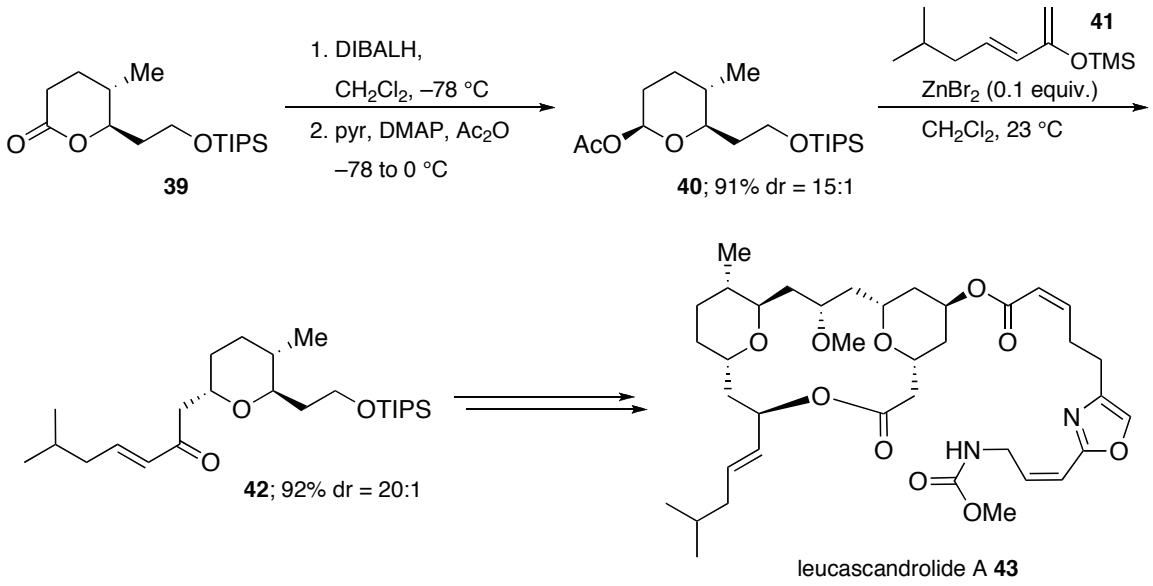
Scheme 4. Yamashita's Total Synthesis of Ciguatoxin CTX3C.

Crimmins and DeBaillie utilized reductive acetylation to install the α,β-unsaturated ketone moiety of the tetrahydropyran fragment of the marine cytotoxin bistramide A (**38**).[13] The synthetic strategy is outlined in Scheme 5. The lactone **35** was reduced with DIBALH followed by trapping with Ac_2O to give the α-acetoxy ether **36** in high yield (87%) and good diastereoselectivity (7:1). Treatment of α-acetoxy ether **36** with (*E*)-3-penten-2-one in the presence of excess TMSOTf led to formation of tetrahydropyran **37**, a key building block for the synthesis of bistramide A (**38**), in high yield (87%) and good diastereoselectivity (9:1).



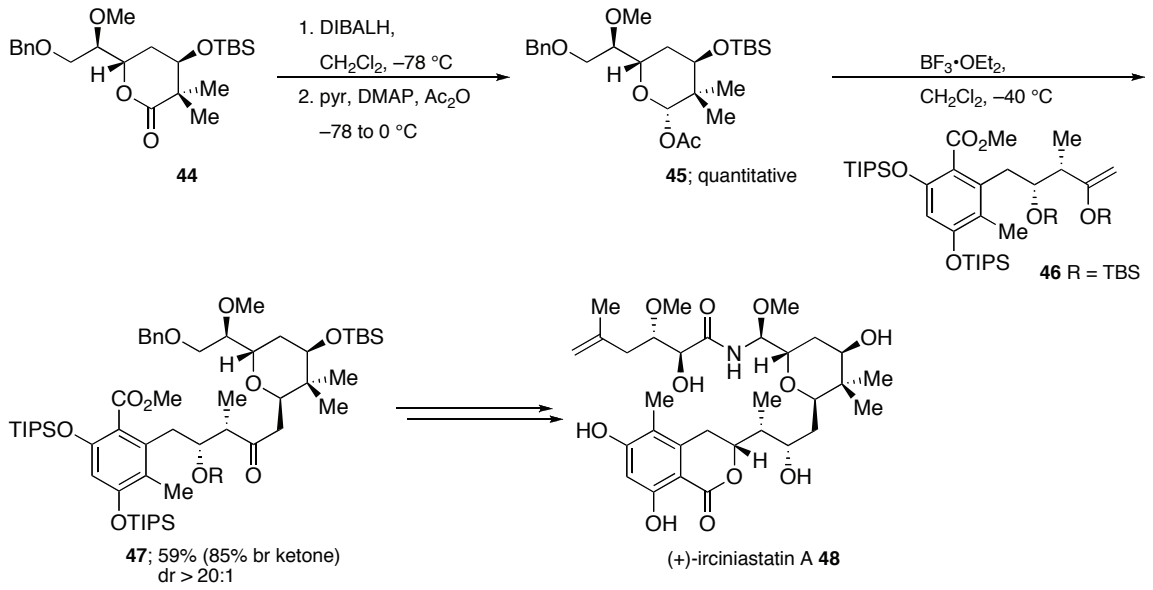
Scheme 5. Crimmins' Total Synthesis of Bistramide A.

Rychnovsky and co-workers used a related strategy to construct the western tetrahydropyran fragment of marine cytotoxin leucascandrolide A (**43**).[14] As shown in Scheme 6, the lactone **39** was reduced with DIBALH followed by trapping with Ac_2O to give the α-acetoxy ether **40** in high yield (91%) and high diastereoselectivity (15:1). Treatment of α-acetoxy ether **40** with silyl enol ether **41** in the presence of catalytic zinc bromide led to formation of tetrahydropyran **42** in high yield (92%) and good diastereoselectivity (20:1). Tetrahydropyran **42** was then further elaborated to leucascandrolide A (**43**).



Scheme 6. Rychnovsky's Total Synthesis of Leuscandrolide A.

The most complex example of such intermolecular couplings comes from Crimmins and co-workers recent synthesis of the cancer cell growth inhibitor (+)-irciniastatin A (**48**).[15] This convergent strategy is outlined in Scheme 7. Reduction of lactone **44** followed by trapping with Ac_2O proceeds to give α-acetoxy ether **45** in quantitative yield. Treatment of the sterically hindered α-acetoxy ether **45** with boron trifluoride etherate followed by a slight excess of the highly functionalized silyl enol ether **46** gave tetrahydropyran **47** in good yield (59%; 85% based on recovered ketone) and high diastereoselectivity (>20:1). Tetrahydropyran **47** was then carried forward to afford (+)-irciniastatin A (**48**).



Scheme 7. Crimmins' Total Synthesis of Irciniastatin A.

Reductive acetylation followed by intermolecular coupling has proven to be a useful strategy for coupling complex fragments in total synthesis.[16] The success of this methodology is largely due to the functional group compatibility of the reduction and mild conditions for oxocarbenium ion formation. Furthermore, the coupling itself often proceeds in high yield and high diastereoselectivity. These features validate this method as a highly convergent process in complex natural product synthesis.

1. Department of Chemistry, 1102 Natural Sciences II, University of California–Irvine, Irvine, CA 92697-2025. Support was provided by the National Institute of General Medicine (GM-43854) and the Vertex Scholar Fellowship (N.S.).

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Professor Rychnovsky earned his B.S. from UC Berkeley in 1981 under the guidance of Paul Bartlett. He obtained his Ph.D. from Columbia University in 1986 with Gilbert Stork. NIH Postdoctoral Fellowships with David Evans at Harvard and Stuart Schreiber at Yale University preceded his academic career at the University of Minnesota in 1988. He was promoted to Associate Professor in 1994, and moved to UC Irvine as a full Professor in 1995. Professor Rychnovsky has received numerous honors including an Arthur C. Cope Scholar and was recently named an ACS Fellow. His research interests include natural product synthesis and the development of new synthetic methods.

Nicholas Sizemore was born in Akron, Ohio in 1981. He obtained a B.S. in Chemistry from Case Western Reserve University under the guidance of Prof. Philip Garner in 2005. He began his career as a medicinal chemist at Sanofi-Aventis in Exploratory and Internal Medicine working with Dr. James Pribish and Dr. Michael Fennie. In 2009, he joined the research group of Prof. Scott Rychnovsky at the University of California, Irvine. His research interests include total synthesis of complex natural products, computational chemistry and synthetic methodology.