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Biosynthetic inspirations: cationic approaches to cyclopropane formation

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1. Introduction

The cyclopropyl group has played and continues to play a prominent role in organic chemistry.[1] Its strained structure, interesting bonding characteristics, and value as an internal mechanistic probe have drawn the attention of the physical organic community. More recently, functionally rich cyclopropanes have been targeted due to their ability to control local conformation and project functionality in three dimensions. The prevalence of cyclopropane containing compounds with biological activity, whether isolated from natural sources or rationally designed pharmaceutical agents, has inspired chemists to find novel and diverse approaches to their synthesis.[2a,b] In fact, natural products often inspire and challenge synthetic chemists to consider mimicking the elegance and efficiency of biosynthesis.[2c] This review will focus on synthetic methods for the construction of cyclopropanes through cationic pathways and their corresponding inspirations from the biosynthesis of cyclopropane-containing natural products.

2. Biosynthesis of oligocyclopropane natural products

Two recently isolated cyclopropane containing natural products contain intriguing contiguous cyclopropane structural units (Fig. 1). FR-900848 is a nucleoside analogue isolated from the fermentation broth *Streptoverticillium fervens*.[3] This interesting compound has shown potent selective activity against filamentous fungi, but is surprisingly inactive against bacteria and non-filamentous fungi. More recently U-106305, a cholesteryl ester transfer protein inhibitor, was isolated from a related microorganism.[4] The presence of a linear sequence of contiguous cyclopropane rings in these compounds inspired many to consider a hypothetical, although unlikely, biosynthetic pathway reminiscent of steroids and the elegant work of W. S. Johnson[5] (Fig. 2). A cascade could begin with the generation of a homoallylic cation, through olefin protonation or an ionization of a precursor polyunsaturated fatty acid, and continues, ultimately generating a contiguous polycyclopropane skeleton (Fig. 2).

However, as a part of their original isolation paper, the UpJohn researchers included results of feeding experiments

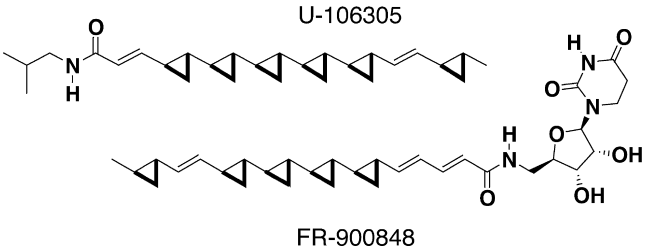

Figure 1. Oligocyclopropane natural products.

Keywords: cyclopropyl; homoallyl; cation.

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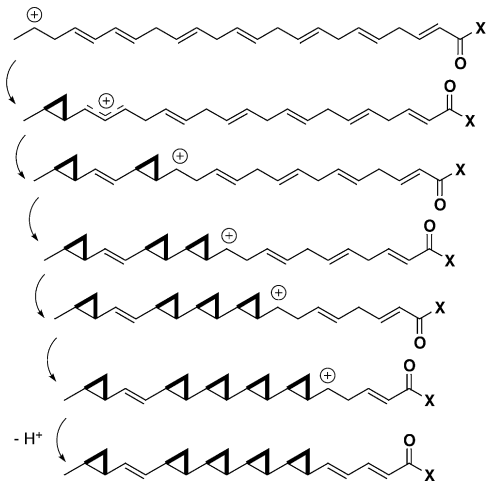
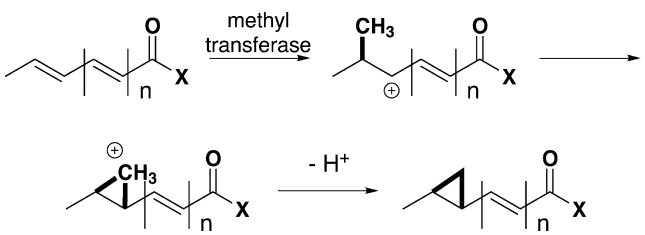


Figure 2. Hypothetical biosynthesis through cationic cascade.



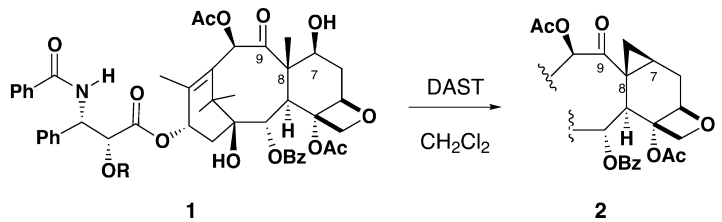
Scheme 1.

which confirmed that the carbon backbone was biosynthetically derived from acetate and a polyketide pathway typical of fatty acid biosynthesis. In addition, the methylene carbon of each of the six cyclopropanes originated from the methyl group of methionine. Consequentially, the authors proposed that a polyunsaturated fatty acid, produced by usual polyketide pathway, was presumably cyclopropanated through the sequential addition of six methylene groups by a separate methyltransferase enzyme. This mechanism has been proposed for the biosynthesis of other bacteria-derived cyclopropane fatty acids and mycolic acids isolated from tuberculosis where cyclopropanations have been observed at the position of isolated olefins of monounsaturated fatty acids.[6] Alternatively, a methyltransferase could be incorporated directly into six of the polyketide synthase (PKS) modules. Methyltransferases have been found in the PKS of several natural products including epothilone.[7] In either case, cyclopropane formation would occur via methylation of an olefin to form an intermediate secondary carbocation as shown in Scheme 1. Ring formation would then occur through cyclization to provide an intermediate protonated cyclopropane. Thus, the transferring methyl group is carbenoid in character, electrophilic in step 1 and nucleophilic in step 2. In the case of FR-900848 and U-106305 the intermediate olefin is conjugated to a C-1 carbonyl which allowed consideration of an alternative mechanism based on methionine sulfur ylide chemistry.[8] In this mechanism deprotonation of the methionine methyl, generating an ylide, would occur prior to conjugate addition and enolate formation.

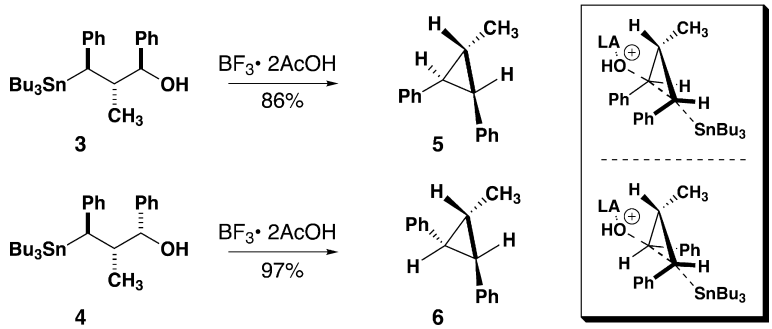
A protonated cyclopropane has been proposed as an intermediate in the formation of analogues of taxol (Scheme 2).[9] Bristol–Myers Squibb researchers, looking to generate a C7-fluoro-analogue, isolated cyclopropane **2** when C2′-protected taxol derivatives **1** were exposed (to diethylamino)sulfur trifluoride (DAST). Presumably, the alternative 1,2-Wagner–Meerwein shift of the C8-methyl was slowed due to the presence of the dissonant C9-carbonyl.

3. Homo-Peterson eliminations

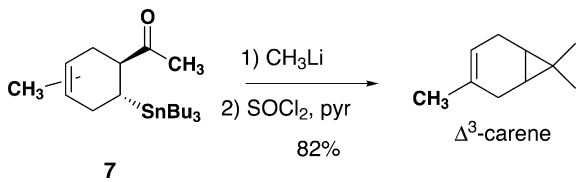
Despite the efficiency of the DAST-induced cyclization in the taxane series, it is unlikely to be the basis for a general method for cyclopropane synthesis. The weak inherent nucleophilicity of a methyl group would allow alternative rearrangement and elimination pathways to be undoubtedly



Scheme 2.



Scheme 3.



Scheme 4.

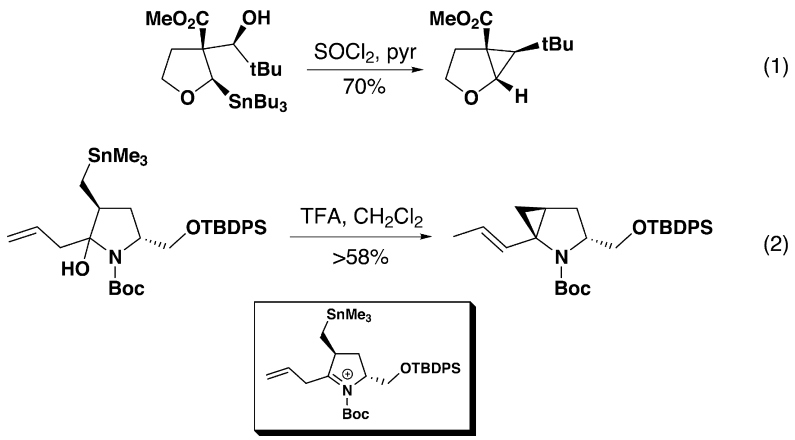
faster in most systems. However, a related process has been successfully developed by replacement of one of the methyl protons with so-called super-proton, a member of the group 14 elements.[10a] The ability of Si and Sn to stabilize γ-carbocation has been recently presented.[10b] Davis and Johnson used conformationally rigid norbornyl systems to investigate the stereoelectronic requirements of cyclopropane formation.[11] A 1000-fold rate acceleration was observed for the stereoisomer which allowed inversion at both reacting centers, often described as a 'W' configuration, (vide infra). Kuivilla determined the kinetic isotope effects to demonstrate that these reactions are concerted, asynchronous processes with direct participation of the C–Sn σ electrons through percaudel homohyperconjugation.[12] A presumed intermediate is the corner-stannylated cyclopropane similar to protonated cyclopropanes proposed in biosynthetic cyclopropane formation.

In the early 1980's Fleming and Urich explored this homohyperconjugation for the stereospecific synthesis of substituted cyclopropanes (Scheme 3).[13] Lewis acid activation of the diastereoisomeric secondary alcohols **3** and **4** provided exclusively a single diastereomeric cyclopropane, **5** and **6** respectively, in high yield. In agreement with the seminal work of Davis and Johnson, the stereospecificity of the ring closure can be attributed to the transition state which proceeds with inversion at both reactive centers, the 'W' configuration as shown.

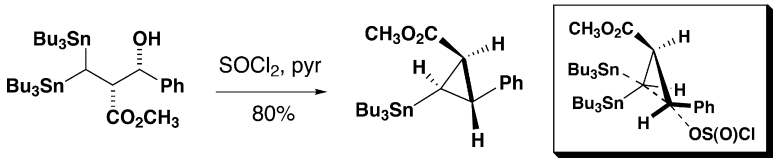
Johnson and Kadow found that they could reliably produce gem-disubstituted cyclopropanes fused to five, six, and seven-membered rings.[14] The activation of the tertiary alcohol with thionyl chloride/pyridine was essential as Fleming had previous noted failure with his BF_3·2AcOH conditions for related cyclizations. Johnson synthesized several natural products using this strategy. As shown in Scheme 4, ketone **7**, efficiently produced via a Diels–Alder cycloaddition between isoprene and a stannyl substituted methyl vinyl ketone, was exposed to methyllithium to provide the corresponding tertiary alcohol. Then treatment with thionyl chloride provided pure Δ^3-carene in 82% yield.

Quayle exploited this 1,3-elimination reaction to prepare 2-oxabicyclo[3.1.0]hexanes (Scheme 5, Eq. (1)).[15] Ring closure proceeded, as expected, through the 'W' transition state originally proposed by Davis. In addition, it was found that optimum activation was dependent on substitution at the alcohol center. More recently, Hanessian reported a highly efficient route to methano-prolines using acid catalyzed destannylative cyclopropanation of an iminium ion intermediate (Eq. (2)).[16]

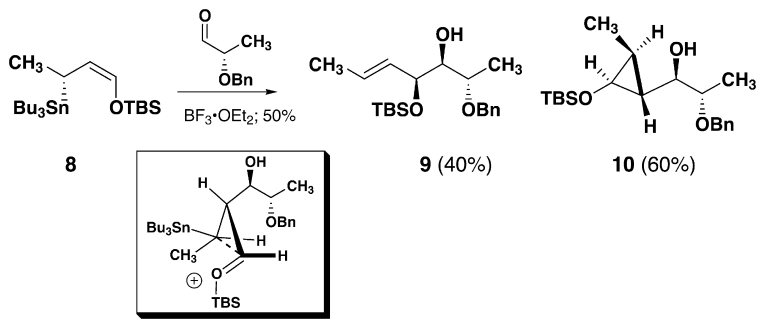
Critical to the synthesis of highly functionalized 1,2,3-trisubsituted cyclopropanes is a stereoselective route to the cyclopropane precursor and a stereospecific cyclization. Mori has accomplished both objectives in the preparation of stannyl-substituted cyclopropanes which can be further modified via Sn–Li exchange chemistry (Scheme 6).[17] Methyl bis(tributylstannyl)propionate was prepared in a single step from readily available methyl propiolate. Reaction between the ester enolate and benzaldehyde provided a mixture of aldol adducts and the ratio was dependent on the reaction conditions. Each diastereomer was efficiently and stereospecifically converted to a corresponding trisubstituted cyclopropane by exposure to thionyl chloride. The stereochemistry of the cyclopropane products were rationalized by a comparison of two possible 'W' transition states and minimizing the 1,3-interactions



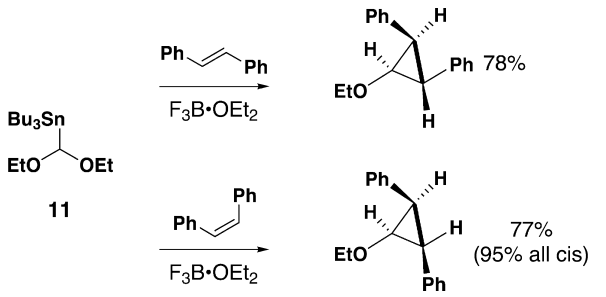
Scheme 5.



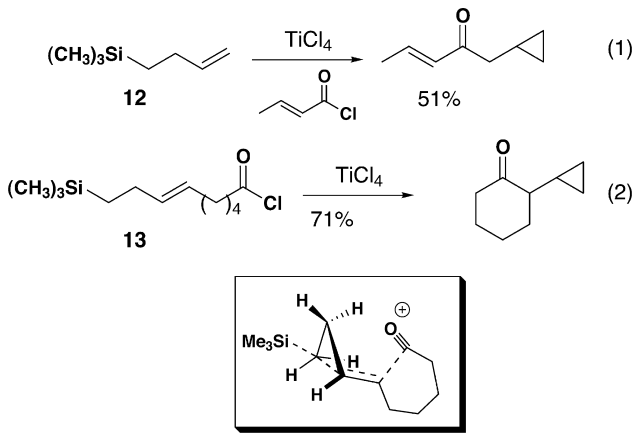
Scheme 6.



Scheme 7.



Scheme 8.



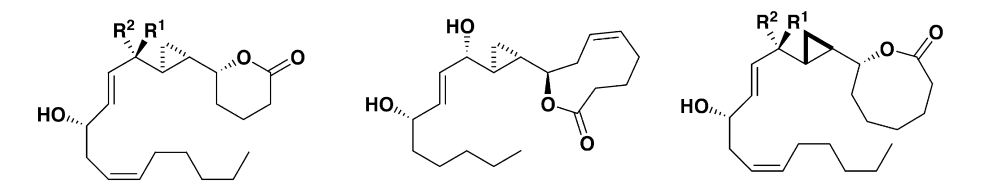
Scheme 9.

between the remaining stannyl group and the phenyl. This should be contrasted with the homoallylic systems discussed later where 1,2-interactions take precedence (vide infra). However, it is important to note that the stereochemistry of the aldol products was not unambiguously assigned.

During the development of their elegant methodology for the preparation of monoprotected 1,2-diols using chiral crotylstannanes **8**, the Marshall group observed the formation of highly functionalized 1,2,3-subsituted cyclopropanes **10** (Scheme 7).[18] The formation of these complex strucures likely proceeded by initial Mukiayama-type aldol between the silyl enol ether and the Lewis acid complexed aldehyde followed by similar 1,3-bond formation on the intermediate oxonium ion. In contrast, to Mori's work it appears that 1,2-interactions, between the methyl and the hydroxypropyl chain, are controlling the orientation of the intermediate oxonium ion and thus the stereochemistry of the product 1,2,3-trisubstituted cyclopropane. Although originally intended to provide *syn*-diol adducts **9** this chemistry has the potential to be optimized into an extremely powerful method for the enantioselective synthesis of highly functionalized cyclopropanes.

Yoshida has exploited the γ-effect of tin to provide an alkene cyclopropanation reaction which provides high *cis*-selectivity.[19] Acetal **11** was used as a precursor to an α-stannyl carbocation under Lewis acid conditions (Scheme 8). Reaction with substituted olefins provided an intermediate γ-stannyl carbocation which closed to form a cyclopropane in good yield. Surprisingly, the selectivity of the reaction greatly favored the formation of *cis*-cyclopropanes which suggested an alternative mechanism. Yoshida suggests that the selectivity can be rationalized by proposing that both carbon–carbon bonds are formed simultaneously related to carbenoid-type chemistry. In fact, starting olefin geometry is retained in the reaction of 1,2-disubstituted alkenes.

There are fewer successful examples of the use of γ-silyl effects for cyclopropane formation due to their lower reactivity.[20] As an extension of their classic allylsilane methodology, Sakurai explored the reactive of the homologous reagent, 3-butenylsilane **12** (Scheme 9).[21] Titanium tetrachloride was found to be the effective activator of acid halides and provided access to cyclopropyl ketones fair to moderate yields (Eq. (1)). Improved yields were observed in



constalactone A R^1 = OH, R^2 = H
constalactone B R^1 = H, R^2 = OH

halicholactone

solandelactone A R^1 = OH, R^2 = H
solandelactone B R^1 = H, R^2 = OH

Figure 3. Oxylipin natural products.

the intramolecular version **13** investigated by Kuwajima (Eq. (2)).[22]

4. Biosynthesis of marine-derived cyclopropyl lactones

Oxylipins are fatty acid metabolites isolated from marine invertebrates and algae. Yamada reported[23] the structure of a lactone and cyclopropane containing eicosanoid, halicholactone, which was isolated from a marine sponge (Fig. 3). The structurally related constanolactones were isolated from the Oregon marine alga *Constantinea simplex* by Gerwick.[24] More recently, Shin isolated and characterized cyclopropane fatty acids, solandelactones, which contained a novel eight-membered lactone.[25]

Gerwick proposed[24b] a pathway for the biosynthesis of the constanolactones through the oxidation and rearrangement of arachidonic acid (Fig. 4). The key intermediate in the biosynthesis of the constanolactones is 12-hydroperoxyicosatetraenoic acid (12-HPETE). Halicholactone and solandelactone are likely formed from related oxidative rearrangements of arachidonic acid and the C22, docosahexenoic acid.

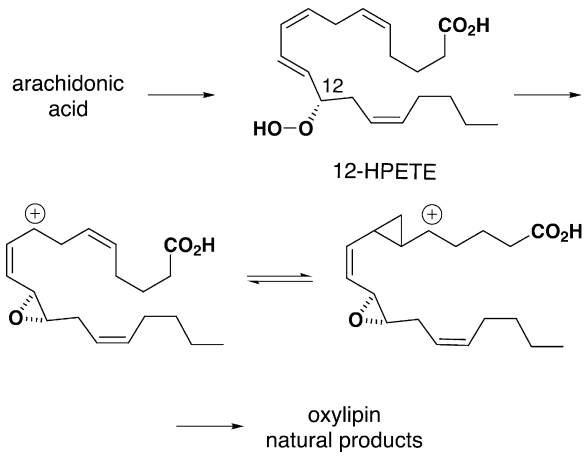


Figure 4. Gerwick's proposed biosynthetic route to oxylipin natural products.

An alternative biosynthetic route was offered by Brash (Fig. 5).[26a,b] This pathway, an extension of Corey's proposed biosynthesis of prostaglandins,[26c] may involve an 8-lipoxygenase and the formation of an allene oxide intermediate. As with all these biosynthetic proposals the key cyclopropane-forming step relies on the well-studied homoallyl-cyclopropyl carbinyl cation equilibrium.[27]

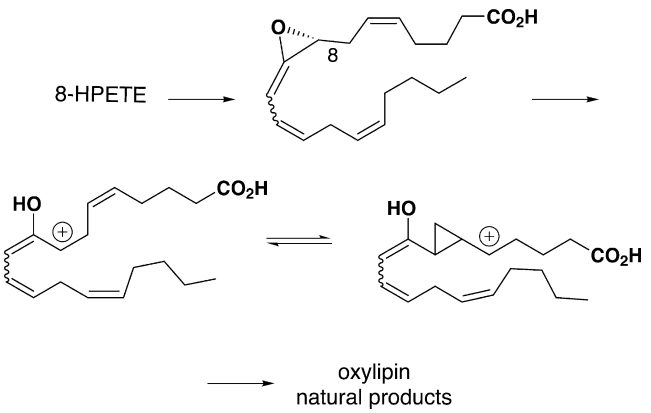
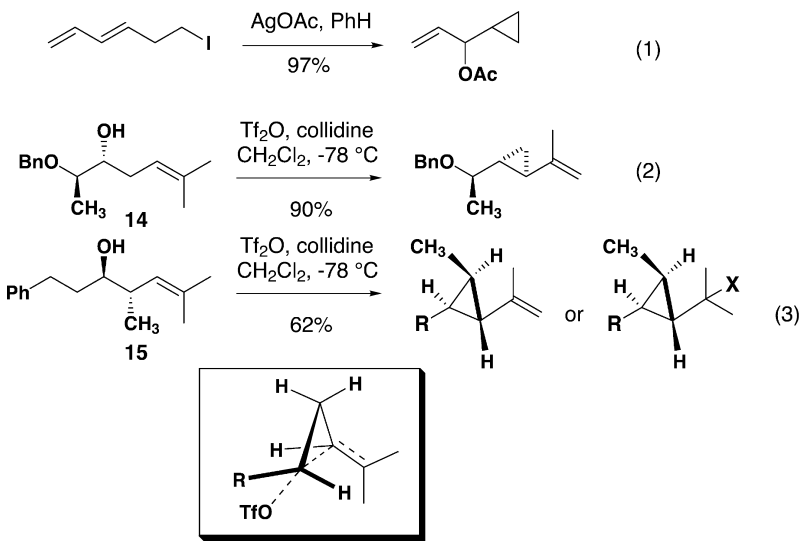


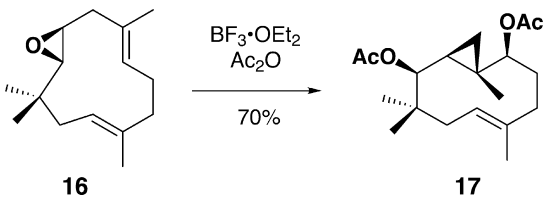
Figure 5. Brash's proposed biosynthetic route to oxylipin natural products.

5. Homoallyl-cyclopropylmethyl carbocation rearrangements

Several groups have exploited the homoallyl-cyclopropylmethyl carbocation rearrangement as a basis for synthetic methodology for the construction of cyclopropanes. In 1984, Previtera, Monaco, and Mangoni reported the synthesis of cyclopropanes from the AgOAc activation of homoallylic iodides (Scheme 10).[28] The reaction was quite efficient as long as the intermediate cyclopropylcarbinyl cation was stabilized by additional substitution or conjugation (Eq. (1)). From a related mechanistic perspective Suzuki utilized homoallylic triflates **14** and **15** which readily converted to their cyclopropylcarbinyl cations and were subsequently trapped with weak nucleophiles or by



Scheme 10.



Scheme 11.

elimination, (Eqs. (2) and (3)).[29] The stereospecific formation of the cyclopropane was rationalized by considering inversion of configuration at the triflate center and a transition state that minimized steric interactions between the olefinic moiety and the substituent R similar to Mori's results.

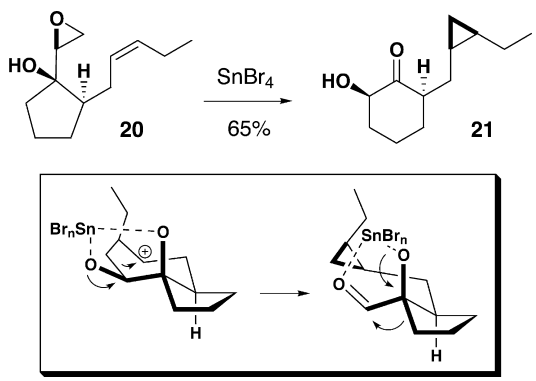
Epoxides have been shown to be efficient initiators for the homoallylic-cyclopropylmethyl cation interconversion. In the example shown in Scheme 11, Matsumoto demonstrated a transannular cyclization of humulene 9,10-epoxide **16** to bicyclohumulenediol **17** in good yield.[30] High selectivity for the formation of the cyclopropane-containing product was attributed to conformational constraints. The authors also proposed that these conformational preferences may contribute to the selectivity observed in sesquiterpene biosynthesis.

In the early 1990's White and Jensen exploited the exchange of an epoxide for a cyclopropane in their biomimetic synthesis of constanolactones A and B. The key step Scheme 12, involved a stannous chloride-induced epoxide fragmentation and trapping of the intermediate cyclopropylcarbinyl cation with a terminal carboxylic acid to provide the cyclopropyl lactone **19**.[31] The starting material **18** was prepared in an enantioselective fashion by a Sharpless asymmetric epoxidation reaction. Although a 1.5:1 mixture of diastereomers was obtained, a single *trans*-cyclopropane was generated in a stereospecific manner through an inversion process.

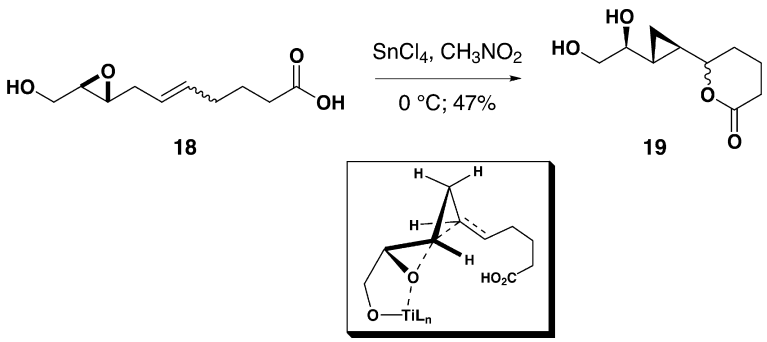
In 2003, Marson and co-workers reported a novel intramolecular methylene transfer from a spiroepoxide to form a *cis*-cyclopropane (Scheme 13).[32] When epoxy alcohol **20** was exposed to Lewis acid conditions, $SnBr_4$ in methylene chloride, cyclopropane **21** was isolated in 65% yield. Although, the mechanism is likely to be a stepwise process through intermediates such as those shown, the accompanying pinacol rearrangement presumably occurs simultaneously with methylene transfer.

Inspired by White's elegant approach to the constanolactones we began to investigate general methodology for the preparation of cyclopropanes which exploited the cation stabilization of the β-silicon effect.[33] A number of potential advantages can be envisioned from the use of the allylsilane moiety. Foremost among these are the increased nucleophilicity of the allylsilane. In addition, the cyclopropane cyclization substrates are easily prepared from readily available chiral starting materials. Our first generation approach proceeded via a three-step silylation/ring-closing metathesis/Si–O cleavage sequence (Scheme 14). The yields for all steps were high even with highly substituted precursors. The key fragmentation reaction can be achieved with HF·pyr to provide the fluorosilanes in quantitative yield. In addition, methyllithium treatment provided high yields of the corresponding trimethylsilanes. Activation of the homoallylic alcohols **24** led to stereospecific and stereoselective formation of a single cyclopropane **25** in good yields for most cases. These initial efforts provided efficient access to 1,2-*trans*-disubstituted, 1,2-*cis*-disubstituted, 1,2,3-trisubstituted vinylcyclopropanes from single precursors. The exclusive formation of a single diastereomer was rationalized through a transition state similar to that reported by Suzuki (vide supra).

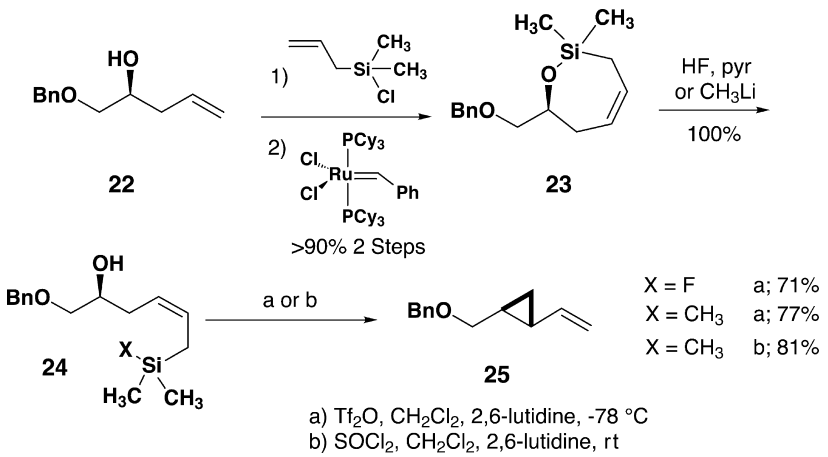
More recently, we disclosed a more efficient approach to the cyclopropane precursors by utilizing an intermolecular metathesis reaction (cross-metathesis) between the same homoallylic alcohol precursors and allyltrimethylsilane.[34] As the results in Table 1 clearly indicate, cross-metathesis between allyltrimethylsilane and homoallylic alcohols **26a–f** efficiently provided the cyclopropane precursors **27a–f** in good yield. Most importantly, activation of the homoallylic alcohols under mild conditions with thionyl



Scheme 13.

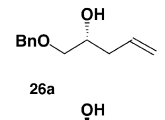
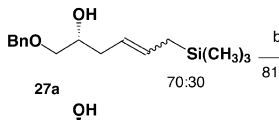
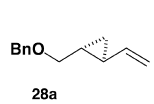
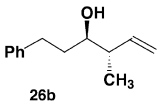
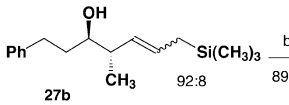
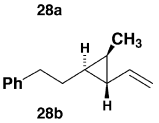
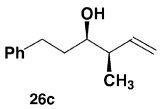
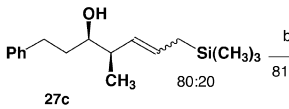
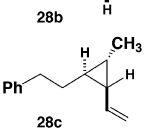
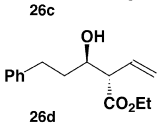
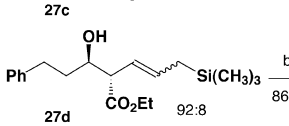
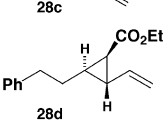
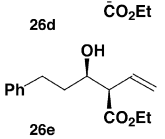
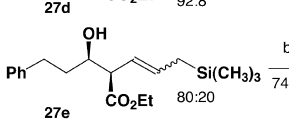
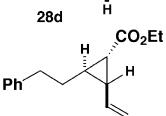
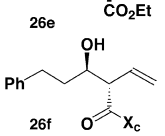
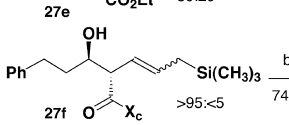
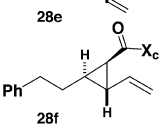


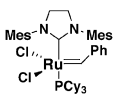
Scheme 12.



Scheme 14.

Table 1. Cross metathesis route to vinylcyclopropanes

homoallylic alcohol	E : Z (ratio)	cyclopropane
 26a	a, 61%	 27a, 70:30	b, 81%	 28a
 26b	a, 86%	 27b, 92:8	b, 89%	 28b
 26c	a, 81%	 27c, 80:20	b, 81%	 28c
 26d	a, 67%	 27d, 92:8	b, 86%	 28d
 26e	a, 81%	 27e, 80:20	b, 74%	 28e
 26f	a, 63%	 27f, >95:<5	b, 74%	 28f

(a)  CH_2Cl_2, reflux; (b) $SOCl_2$, rt.

chloride led to isolation of diastereomerically pure vinylcyclopropanes **28a**–**f**. Although allylsilane geometry had no observable effect on the reaction efficiency, the relative stereochemistry of the starting substrate did control the stereoselectivity of the cyclization.

Based on the fact that these reactions proceed with inversion of stereochemistry two transition states are possible; (1) **A-1** which has a *trans* relationship between C1 and C3, and (2) **A-2** which has a *cis* relationship between C1 and C3 (Fig. 6). Substrate **27a** (R^1=R^2=H) appear to proceed through **A-1** providing exclusively *trans*-vinylcyclopropane. Homoallylic alcohols **27b**,**d**,**f** (R^1=alkyl, R^2=H) also proceed through transition state **A-1**. However, this transition state is disfavored for substrates **27c** and **27e**. In contrast, these substrates prefer to adopt a conformation which minimizes $A_{1,3}$-strain between the C2 and C3 position such as seen in **A-2** (R^1=H, R^2=alkyl). In addition, the longer C1–C3 bond

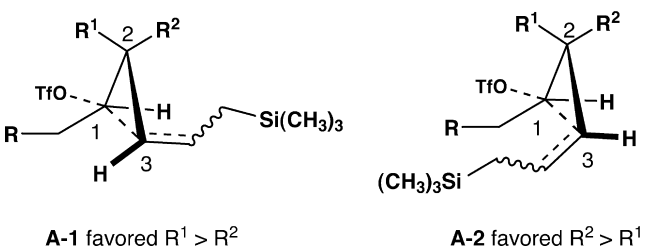
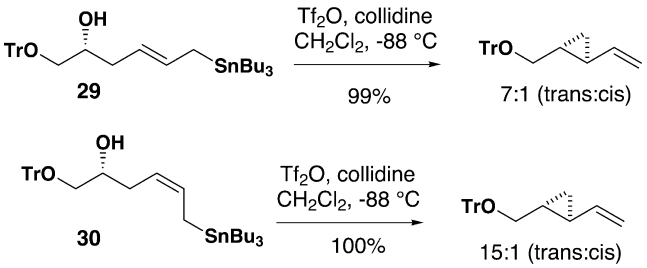
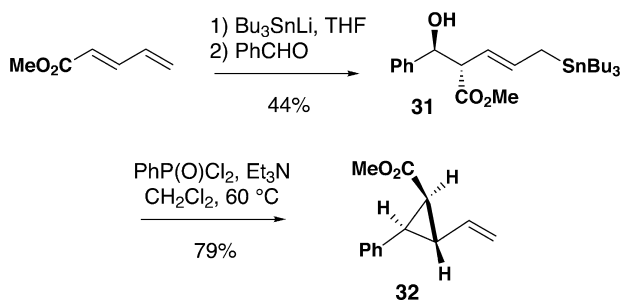


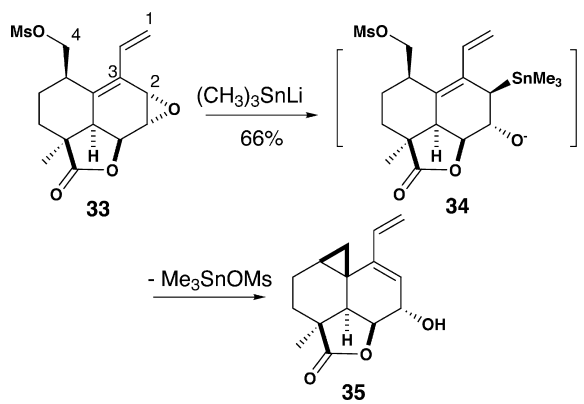
Figure 6. Transition state leading to 1,2,3-trisubstituted cyclopropanes.



Scheme 15.



Scheme 16.



Scheme 17.

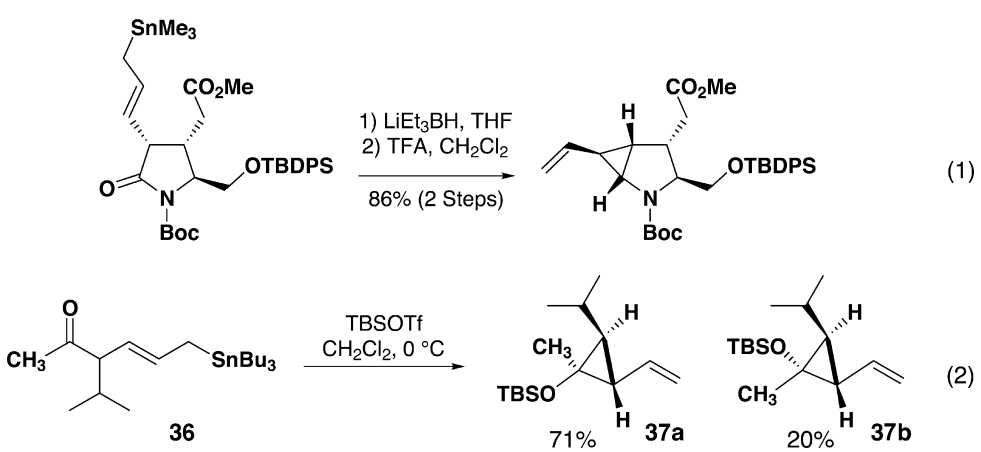
length at the transition state can, presumably, better accommodate a *cis* relationship.

More recently, White and Lincoln explored the stannyl version of this cyclization and uncovered an interesting effect (Scheme 15).[35] The cyclization to form 1,2-disubstituted cyclopropanes proceeded with equal or greater efficiency than the silyl variant. Surprisingly, the cyclopropane product was, however, isolated as a 7:1 *trans*/*cis* mixture from the *E*-allyl stannane **29**. The diastereoselectivity improved to 15:1 when the *Z*-allyl stannane **30** was used as a starting point. Recall that previous work in this area from White, Suzuki, and Taylor observed exclusive formation of *trans*-cyclopropanes. Presumably, the increased nucleophilicity of the allylstannane (10^4> allyltrimethylsilane)[36] leads to less selectivity between competing transition states.

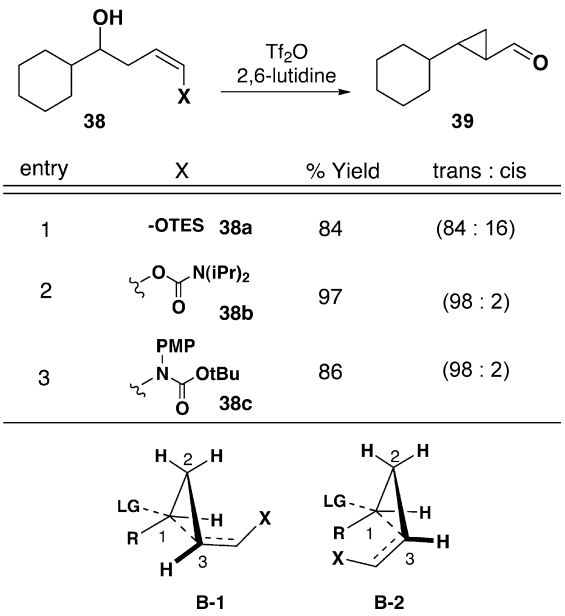
In 1997, Kreif and Provins reported the preparation of 1,2,3-trisubstituted cyclopropanes through a similar allylstannane intermediate.[37] The cyclization substrates were prepared from methyl pentadienoate in tandem conjugate addition/aldol condensation three component coupling. Although the condensation was not stereoselective, the diastereomers could be separated by chromatography. Activation of the intermediate homoallylic alcohol **31** with phosphoryl chloride led to efficient cyclization and isolation of a single trisubstituted cyclopropane **32** in good yield (Scheme 16).

Chu-Moyer and Danishefsky reported an elegant total synthesis of the diterpene, myrocin C, which was highlighted by a remarkable cyclopropanation reaction.[38a] When mesylate **33**, Scheme 17, was exposed to trimethylstannyllithium the cyclopropyl dieniol **35** was isolated in 66% yield. There are numerous potential mechanisms for this novel transformation, which include intermediate stannanyl derivatives with initial C–Sn bond formation at either C1, C2, C3 or C4. In addition, one could propose an electron-transfer mediated sequence which obviates the need for C–Sn bond formation altogether. Particularly attractive, considering the current discussion, is the intermediate allylstannane **34**, through C–Sn bond formation at C2 and subsequent cationic cyclization pathway. The full account of this work included preliminary mechanistic studies but failed to provide strong evidence for one particular intermediate.[38b]

Hanessian and co-workers have previously used the allystannane unit to trap an in situ generated acyliminium ion (Scheme 18, Eq. (1)).[39] The reaction is surprising since one could envision a facile allylic deprotonation and



Scheme 18.

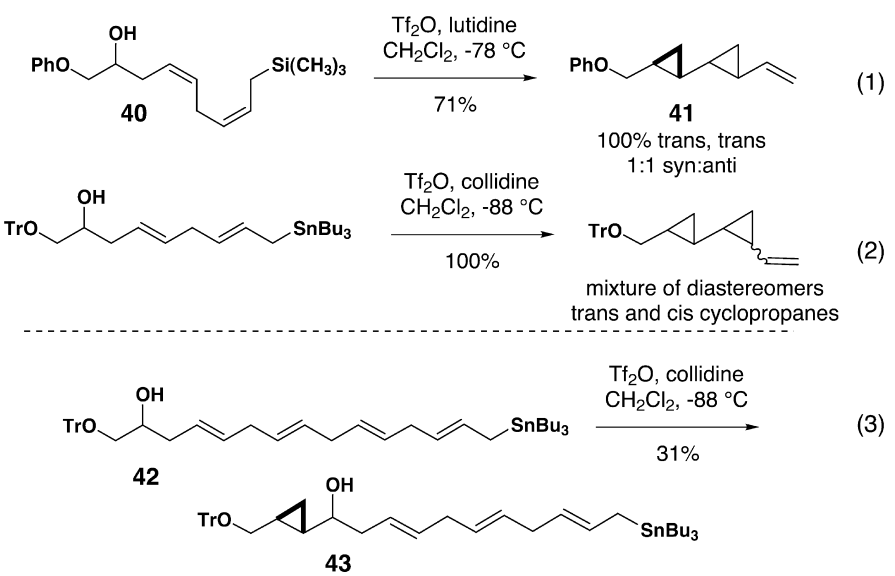


Scheme 19.

elimination to form the diene. The efficient cyclization provided access to conformationally constrained analogues of kainic acid. Keck reported an intramolecular allylstannane-carbonyl condensation to form vinylcyclopropanols (Eq. (2)).[40] Activation of ketone **36** under numerous Lewis acidic conditions yielded only proteo-destannylation products. However, use of *tert*- butyldimethylsilyl triflate led to a high efficient cyclization which selectively formed only two of four possible diastereomeric cyclopropanes **37**. As discussed above, the allylic stereocenter controlled the stereospecificity of the reaction through a minimization of A-strain in the competing transitions states.

More recently, we developed a related process for the homologation of aldehydes to cyclopropylaldehydes in just two simple synthetic operations (Scheme 19). Allyl organometallic reagents were reacted with cyclohexylcarboxaldehydes to provide the enol ether and enamine cyclization precursors **38a–c** in good yields based on the chemistry of Yamamoto **38a**,[41] Hoppe **38b**,[42] and Beak **38c**.[43] Activation of these homoallylic alcohols provided direct access to cyclopropylaldehydes **39** via cyclization to form oxonium ion and iminium ion intermediates which readily hydrolyze upon workup.[44] In contrast to previous work with homoalllic cation closures *cis*-cyclopropanes were observed. Apparently, the increased rate of cyclization led to a decrease in the energy ($\Delta\Delta G$) difference between the two diastereomeric transition states **B-1** and **B-2** (entry 1). However, high selectivity was restored by attenuating the nucleophilicity and sterics of the substrate with the Hoppe and Beak carbamates (entries 2 and 3). This reactivity/selectivity pattern mirrors the allylsilane/allylstannane chemistry discussed previously.

As an extension of our allylsilane mediated cyclopropane methodology we wondered whether it would be possible to use the homoallyl-cyclopropylmethyl cation equilibrium in a tandem fashion to generate oligocyclopropane subunits in a single step. While related to the hypothetical biosynthesis of FR-900848 and U-10635 (Fig. 2) the proposal would test a competition of rates between cyclopropane ring formation and alternative cyclizations and rearrangement pathways. The cyclization substrate, *Z*,*Z*-diene **40**, was prepared in a short sequence of steps and exposed to the triflic anhydride activation conditions (Scheme 20, Eq. (1)).[33b] Remarkably, the bis-cyclopropane **41** was obtained in 71% yield with only minor byproduct formation resulting from elimination. As expected the product was obtained as a 1:1 mixture of *syn* and *anti* diastereomers and, more importantly, no *cis*-cyclopropane isomers were observed. The yield of this tandem bis-cyclization improved dramatically in the stannyl version recently reported by Lincoln and White (Eq. (2)).[35] However, the increased reactivity of the allylstannane neighboring group led to a loss in selectivity and *cis*-substituted cyclopropanes were again observed. It does not appear that olefin geometry plays a significant role in these cationic cascade reactions.[45] In an ambitious attempt to prepare four contiguous cyclopropane subunits in a single step, White and Lincoln also prepared polyene **42**.[35]



Scheme 20.

Exposure of this substrate to their activation conditions resulted in the formation of only a single monocyclopropane product **43**. It appears that trapping of the initially formed cyclopropylcarbinyl cation by a 1,2-disubstituted olefin is not thermodynamically viable. In addition, the high reactivity observed for the stannyl substitution is not felt over the extended skipped polyene system.

6. Conclusions

This focused review has highlighted the synthetic chemist's preparation of cyclopropanes through the control of carbocationic intermediates. The studies presented above demonstrate novel reactivity and intermediates, complex stereochemical issues, and the successful development of general synthetic methods for the preparation of an important class of organic structural units.

Acknowledgements

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Biographical sketch

Richard E. Taylor was born and raised on Smithtown, NY. He attended SUNY Oswego for his undergraduate studies in chemistry having carried out research for Professors Joseph Lefevre and Gus Silveira. The summer months after his junior and senior year were spent at Hamilton College doing research with Professor Hamid Kasmai. Professor Taylor received his PhD from Rensselaer Polytechnic Institute having done thesis research under the direction of the late Art Schultz. From 1992–1995 he was a Merck postdoctoral research fellow at Stanford University where he developed a total synthesis of the anticancer agent taxol with Professor Paul Wender. In July 1995, he joined the faculty of the University of Notre Dame as an Assistant Professor where his group has developed new synthetic methodology and applied this chemistry to the synthesis of biologically active natural products. In 1999, Professor Taylor became a founding member and Principal Investigator of the Walther Cancer Center at the University of Notre Dame. He received the NSF Early Career Award in 1998, an Eli Lilly Grantee Award in 2001 and a Kaneb Teaching Award in 2002. Professor Taylor was promoted to Associate Professor in 2001. Professor Taylor enjoys playing sports such basketball, hockey and golf as well as spending time with his wife, Lynette, and son, Hayden.

F. Conrad Engelhardt was born in Burbank, CA and raised in Lancaster, CA. In 1994 he entered California Polytechnic State University—San Luis Obispo as a double major in Civil/Environmental Engineering. He changed majors after his first year and in 1997, he graduated from Cal Poly (Magna Cum Laude) with a BS in chemistry. Conrad then moved to South Bend, IN and began work on his doctoral thesis at the University of Notre Dame under the direction of Professor Richard E. Taylor. His graduate research focused on the use of homoallylic cations as reactive intermediates for the preparation of cyclopropanes and the use of olefin metathesis chemistry to access these cyclopropane precursors. During his years at Notre Dame, he received multiple teaching awards and fellowships including: the Kaneb Teaching Award (2000), the Rohm and Haas Fellowship (2000), the Jeremiah P. Freeman Teaching Award (2001), and the J. Peter Grace Prize Fellowship (2001). Conrad was also a participant in an industrial internship at Dow Agro Sciences in Indianapolis, IN from September 2001–January 2002. In December 2002, Dr Engelhardt received his PhD from the University of Notre Dame, and promptly moved to Rahway, NJ where he now works as a Senior Process Research Chemist for Merck and Co., Inc.

Michael J. Schmitt was born in Kansas City, MO in 1975. In 1993 he entered Rockhurst College and obtained his BS with honors in Chemistry in 1997. During his undergraduate studies Michael received the ACS Award for Achievement in Organic Chemistry. Michael then moved to South Bend, IN and began work on his doctoral thesis at the University of Notre Dame under the direction of Professor Richard E. Taylor. Michael worked on the stereoselective synthesis of 1,2,3-trisubstituted cyclopropanes using cationic intermediates. During his years at Notre Dame, he received recognition for outstanding teaching and research including: the Jeremiah P. Freeman Teaching Award (1998), the Amoco Research Fellowship (2000) and the J. Peter Grace Prize Fellowship (2002). In December of 2003, Michael Schmitt will receive his PhD from the University of Notre Dame. He is currently employed as a Chemistry Scientist for Tularik, Inc. South San Francisco, CA.