

With compliments of the Author

The Ever-Challenging Quassinoids

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Dedicated to my current and past co-workers.

Abstract: The evolution of a synthetic approach to the challenging targets quassinoids is described.

- 1 Introduction
- 2 The Diels–Alder Reaction as a Key Feature
 - 2.1 Intermolecular Diels–Alder
 - 2.2 Intramolecular Diels–Alder
 - 2.3 Unsuccessful Diels–Alder Cycloadditions
- 3 The Diene-Transmissive Approach to Quassinoids
 - 3.1 Without the C10 Methyl Group
 - 3.2 With the C10 Methyl Group
- 4 A Successful Sequence
- 5 Conclusion and Outlook

Key words: quassinoids, *Simaroubaea*, diene-transmissive Diels–Alder cycloaddition, vinylallenes, S_N2' displacement

1 Introduction

The bitter principles found in the bark and seeds of many shrubs and trees of the sub-tropical genera *Simaroubaea* are known as the quassinoids.¹ The name was derived from the first of these degraded triterpenes for which the structure was elucidated in 1960,² namely quassin, isolated from *quassia amara* in 1937.³ Hundreds of different quassinoids have since been identified.¹ Biosynthetically derived from steroidal intermediates, the quassinoids are triterpenes that have suffered extensive oxidative bio-degradation, which left their carbon framework highly oxygenated. This factor is recognized as the one responsible for the inordinate challenge these natural products have posed to their synthesis.⁴ Difficult their syntheses are indeed. Despite their obvious structural resemblance to steroids, the quassinoids seem incomparably harder to synthesize. For instance, less than twenty different quassinoids have succumbed to the synthetic assaults of only five research groups, worldwide.^{4c–4e,5} Furthermore, over twenty five research groups, including ours, have published an approach to these thorny synthetic targets and have yet to report a completed synthesis.⁶

The synthetic challenge they represent is not the only reason to pursue synthetic efforts towards such complex targets. Quassinoids display a wide range of biological activities and more particularly some are potent anti-

cancer agents.¹ Bruceantin, which failed in phase II of clinical trials,⁷ is attracting attention again as a promising anti-leukemic agent.⁸ In addition, some quassinoids display interesting anti-malarial, anti-tuberculosic, anti-ameobic, and insect anti-feeding properties.⁹

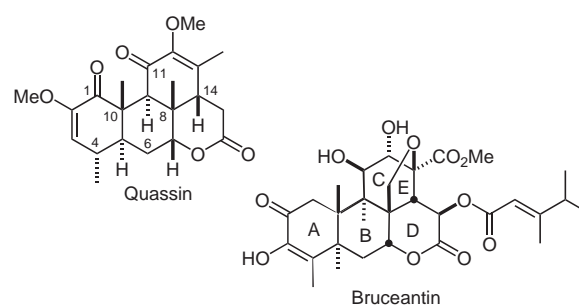


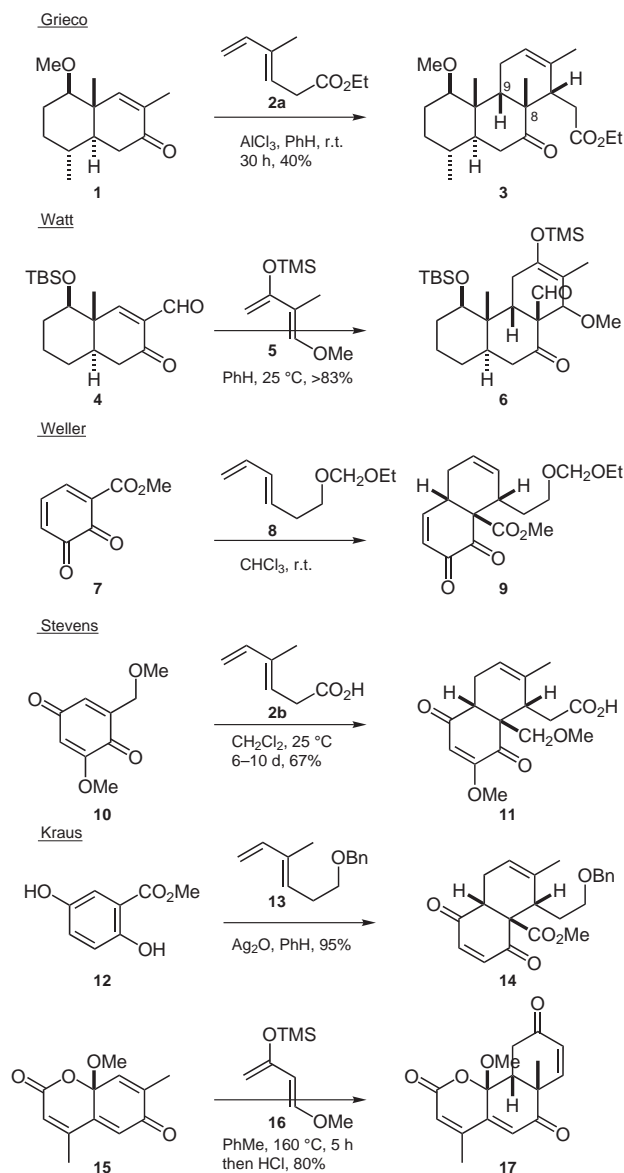
Figure 1 Quassinoids having the typical picrasane carbon skeleton.

2 The Diels–Alder Reaction as a Key Feature

Most quassinoids possess the so-called picrasane carbon skeleton, and either have a tetracyclic or pentacyclic structure (Figure 1). The Diels–Alder cycloaddition being arguably the most powerful reaction to make 6-membered rings, it is not surprising to find such a cycloaddition in many of the synthetic approaches to quassinoids published to date. In fact, with four such 6-membered rings, the common quassinoid framework constitutes a stumping ground for Diels–Alder methodology. Our own strategy to make quassinoids revolves around a sequence of three Diels–Alder cycloadditions. It is thus appropriate to briefly review the synthetic strategies towards the quassinoid framework that used a Diels–Alder cycloaddition as a key reaction.

2.1 Intermolecular Diels–Alder

Quassin was the first member of the quassinoid family to succumb to total synthesis.^{10a} Grieco's group used the Diels–Alder cycloaddition between **1** and **2** to set up the C ring of quassinoids as well as the challenging C8-quaternary center (Scheme 1).^{10b} One downside of the approach is the necessity to epimerize the C9 carbon which has the wrong stereochemistry. However, this is not a particularly difficult stereochemistry to redress since the B–C *trans* ring junction is by far the more stable one. It is an inherent feature to all the approaches that form the C ring via a

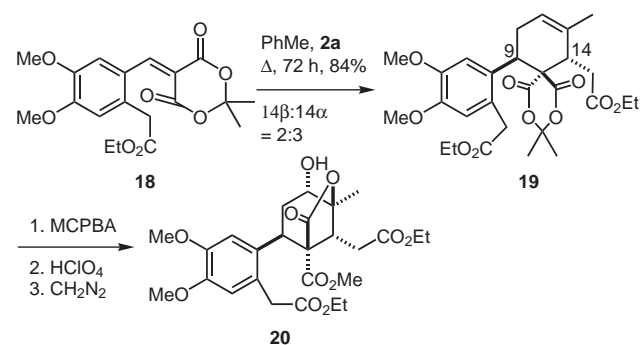


Scheme 1 Intermolecular Diels–Alder approaches to quassinoids where the Diels–Alder reaction forms ring C

Diels–Alder cycloaddition using preformed A–B rings or B ring as dienophile. The Grieco group used their strategy successfully for the synthesis of more than a dozen quassinoids.¹⁰ Watt and co-workers used a very similar cycloaddition between **4** and **5** in their synthesis of (+)-quassin and (+)-picrasine B.^{5d}

Weller's,¹¹ Stevens',¹² and Kraus'^{13a} strategies rest on Diels–Alder reactions of *o*- or *p*-quinones (Scheme 1). Kraus also performed a similar Diels–Alder reaction on quinone ketal **15**.^{13b} Some of these cycloadditions introduce a fair number of oxygenated functional groups in the adduct, which should help decrease the number of subsequent transformations. Convergence is also a strength common to strategies that start with ring B and graft the other atoms on each side of it.

Kraus devised a second intermolecular approach to the quassinoids (Scheme 2).¹⁵ This time, dienophile **18** encompasses ring A but not ring B, which allows them to obtain, as the major product, the adduct with the correct relative stereochemistry at C9 and C14. Epoxidation of the newly formed alkene in **19** and hydrolysis of the epoxide provided a diol. The C13 hydroxyl group of that diol cyclized immediately onto the malonic ester moiety to produce ring E of pentacyclic quassinoids (cf. Figure 1).



Scheme 2 Kraus' intermolecular Diels–Alder using an alkylidene malonate dienophile

Biographical Sketch

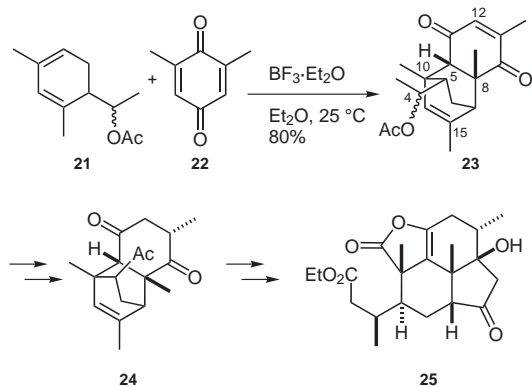


Claude Spino was born in 1961 in Montréal, Canada. He did all his schooling in Montréal, including a BSc in chemistry, which he obtained in 1983. He received his PhD degree in 1988 from the University of British Columbia under the supervision of the late Larry Weiler, working on the total synthesis of polyether antibiotic ionomycin. Then, he moved back to Québec in

the research group of Pierre Deslongchamps at the Université de Sherbrooke where he helped to develop anionic polycyclization reactions. His career as an independent researcher began in 1990 at the University of Victoria where he initiated his work on quassinoids. In 1995, Sherbrooke lured him back, this time as an associate Professor and he was promoted to full professor in

2000. His current research interests are varied and include total synthesis, chiral auxiliary methodology, reaction mechanisms, and isolation of natural products from marine and land organisms. His hobbies are also varied and include music and painting. In sports, ice hockey and rock climbing are two favourites.

Valenta and co-workers performed a face-selective Diels–Alder reaction on cyclohexadiene **21** using 2,6-dimethyl-1,4-benzoquinone (**22**) as dienophile (Scheme 3).¹⁴ Here, ring B was assembled from a preformed ring C. The reaction sets up both C8 and C10 angular methyl groups with the correct stereochemistry. Unfortunately, the stereochemistry at C5 in **23** had to be inverted via an incomplete epimerization. Nonetheless, they later converted **25** to (+)-quassin.^{5b}



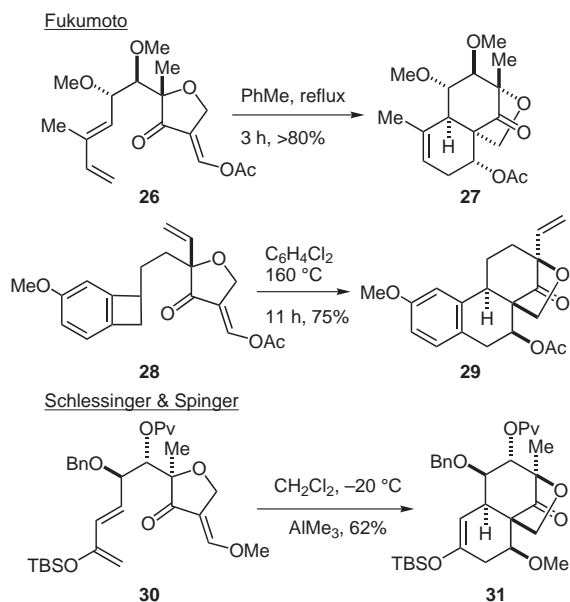
Scheme 3 Valenta's intermolecular Diels–Alder approach to (+)-quassin

2.2 Intramolecular Diels–Alder

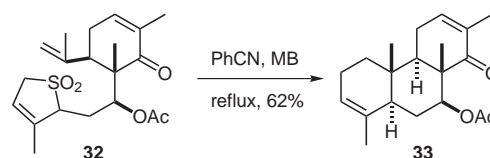
Several synthetic designs towards quassinoids revolved around an intramolecular Diels–Alder reaction. Ring B is always one of the rings formed in these cases. Fukumoto and his co-workers have devised a system where the oxomethanobridge is formed during the Diels–Alder cycloaddition (Scheme 4).^{16a} Unfortunately, the relative stereochemistry at C8 and C9 in **27** was the wrong one and no further report on this issue has appeared since. Earlier, though, the same group reported a similar approach where an *o*-quinodimethane **28** served as diene (Scheme 4).^{16b} Cycloadduct **29** was obtained as a mixture of epimers at C9 but the major diastereomer had the desired stereochemistry. Schlessinger and Springer also reported an advanced intermediate to quassinoids using a very similar system (Scheme 4).¹⁷

Tony Shing and his group from Hong Kong developed a very elegant and efficient synthesis of (+)-quassin from (+)-carvone (Scheme 5).^{4e,18} (+)-Carvone was transformed in four steps to sulfolene **32**, which upon thermolysis extruded SO₂ followed by a stereoselective intramolecular Diels–Alder cycloaddition to give **33**. The latter compound contains 18 of quassin's 20 carbons. Its conversion to (+)-quassin required 24 steps, underscoring the difficulty of introducing the plethora of oxygenated functional groups contained in most quassinoids.

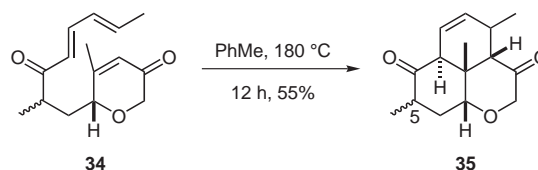
Herscovici published the intramolecular Diels–Alder approach to quassinoids shown in Scheme 6.¹⁹ Ring B and ring C are produced from a preformed ring D. The stereochemistries at C7, C8, C9, and C14 are the correct ones for



Scheme 4 Fukumoto's and Schlessinger's approach



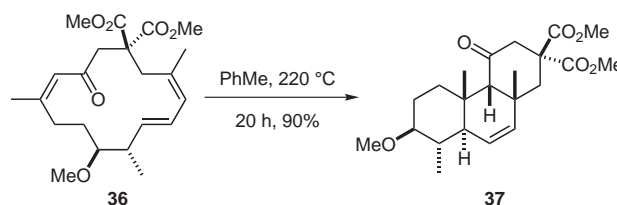
Scheme 5 Shing's synthesis of (+)-quassin based on an intramolecular Diels–Alder



Scheme 6 Herscovici's intramolecular Diels–Alder approach

quassinoids. Compound **35** was obtained as a mixture of C5-epimers.

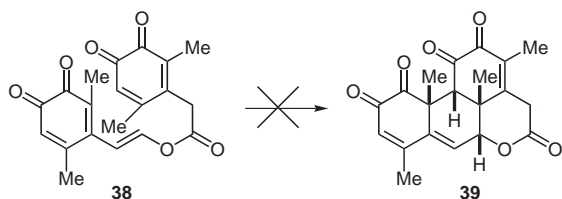
Finally, Deslongchamps, Barriault, and Ouellet have reported an approach to the picrasane skeleton based on the transannular Diels–Alder cycloaddition of **36** (Scheme 7).^{6c} Three rings are formed in one reaction with three of four carbons having the desired stereochemistry.



Scheme 7 Deslongchamps' transannular Diels–Alder approach

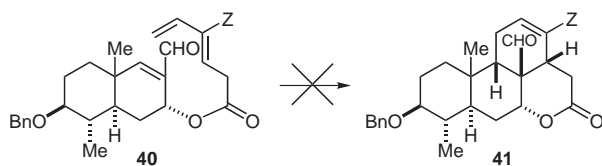
2.3 Unsuccessful Diels–Alder Cycloadditions

Two papers relate unsuccessful strategies based on an intramolecular Diels–Alder cycloaddition. Mandell and co-workers devised a very ingenious, though unsuccessful, Diels–Alder approach towards the quassinoid framework (Scheme 8).²⁰ Diene **38** was prepared from the dimerization of a single intermediate and it contains a highly oxygenated carbon skeleton, just like the quassinoid skeleton. Unfortunately, they were unable to effect this transformation, perhaps because of the high steric demand on both the diene and dienophile. Ring B and ring D would have been formed as well as the two quaternary carbons.



Scheme 8 Mandell's attempt at an intramolecular Diels–Alder cycloaddition with a highly oxygenated reactant

At about the same time they reported their initial intermolecular Diels–Alder strategy^{21a} (cf. Scheme 1), Watt and co-workers published their attempts to effect the intramolecular version of this cycloaddition (Scheme 9).^{21b} Steric effects and conformational restrictions imparted by the ester linkage in **40** were blamed for the failure.



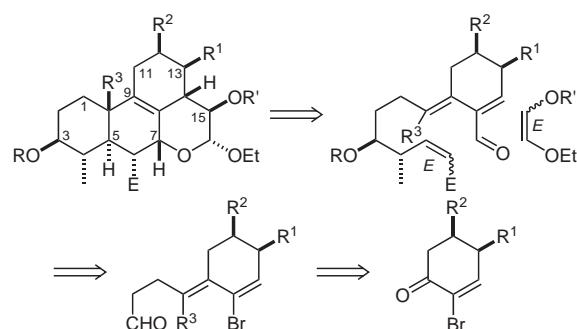
Scheme 9 Watt's attempt at an intramolecular approach to quassinoids

3 The Diene-Transmissive Diels–Alder Approach to Quassinoids

Our own exploration into the realm of quassinoid synthesis began with the premise that we should first establish the complete carbon framework with its stereochemistry in as few steps as possible. In doing so, we would set up only key synthetic handles with which to carry out the unavoidably intricate introduction of all the oxygenated functional groups. Initially, we based our strategy on two tandem Diels–Alder cycloadditions that would form rings A, B, and D. Ultimately, all four 6-membered rings were formed by a Diels–Alder reaction (*vide infra*).

We felt that the retro-synthetic strategy depicted in Scheme 10 allowed for a rapid construction of nearly all the picrasane carbon skeleton (only the carbon at C8 is missing) according to our central premise. Cyclohexenones were considered readily available starting materi-

als obtained from the natural chiral pool and the sequence of two diene-transmissive^{22,23} Diels–Alder cycloadditions (DTDAC) would take care of the stereochemistry of up to seven carbons. We anticipated that the C3 OR group, the C12 and C6 substituents (R^2 and E) should provide enough synthetic lever to accomplish the final elaboration of rings A, B, and C (cf. Figure 1). The final tetrasubstituted endocyclic double bond was a bit of a worry in terms of its reactivity but it seemed nonetheless adequate to set up the C8-substituent, which often comes as a C8–C13 or C8–C11 oxomethano bridge (cf. Figure 1). Little did we know then that the C10 methyl substituent ($R^3 = \text{Me}$ in Scheme 10) would complicate our task but at the same time force us to devise an even more efficient and convergent approach to this carbon skeleton (*vide infra*).



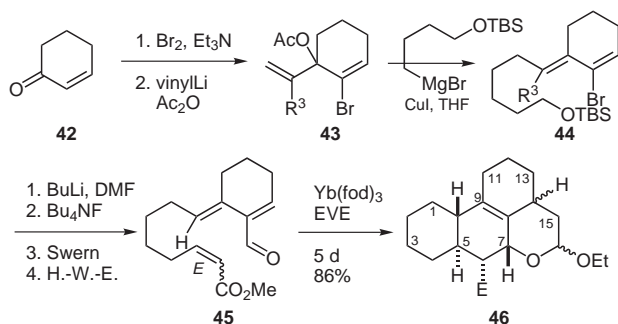
Scheme 10 Synthetic strategy to quassinoids carbon framework utilizing a diene-transmissive Diels–Alder sequence

3.1 Without the C10 Methyl Group

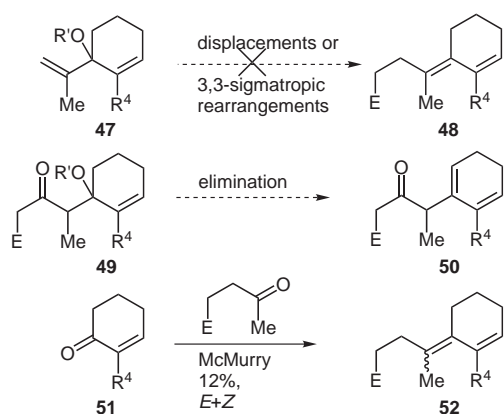
We set out on our trek with the simplest model we could find, starting from cyclohexenone (**42**).²⁴ We built in short order the requisite dienal **45** via a S_N2' displacement of allylic acetate **43** ($R^3 = \text{H}$) by an organocuprate to give **44** (Scheme 11). Anecdotally, this is the reaction that led us to devise an alternative to chiral enolate alkylation based on menthone.²⁵ Note that when R^3 is a methyl group, compound **43** does not undergo this displacement reaction at all.

Stirring **45** in ethylvinyl ether (EVE) in the presence of 10 mol% Yb(III)²⁶ for several days led to a double Diels–Alder cycloaddition sequence to give **46** in good yield. The C5, C7, and C10 carbons had the correct relative orientation but **46** was isolated as two C14 isomers in a 6:1 ratio favoring the α -C14 isomer. This results from a six-fold preference for the cycloaddition taking place on the α -face of the diene. It is notable that the intramolecular cycloaddition occurred at room temperature. In fact, the diene intermediate resulting from the hetero Diels–Alder reaction was never observed during the course of the reaction.

Encouraged by this initial success, we proceeded to examine more closely the stereochemical aspect of each individual cycloadditions, ignoring for the moment the fact that the C10 methyl was escaping all of our attempts to append it to the exocyclic double bond (e.g. in **44**, $R^3 = \text{Me}$). Scheme 12 provides an idea of the efforts we deployed to



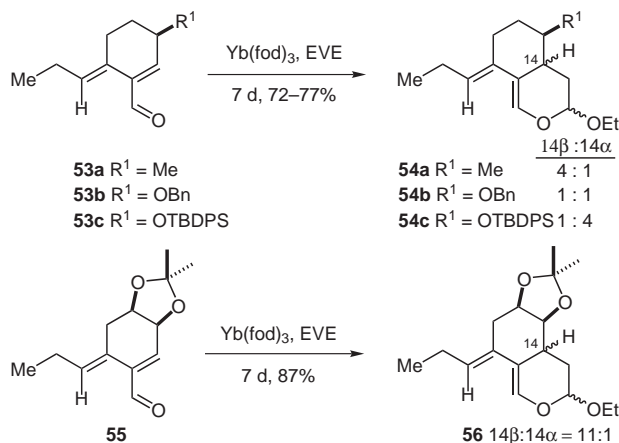
Scheme 11 Proof of principle: the DTDAC strategy toward the carbon framework of quassinoids (H.-W.-E. = Horner–Wadsworth–Emmons)



Scheme 12 Vain efforts to prepare the exocyclic tetrasubstituted alkene

overcome this problem, in vain. Displacement and rearrangement reactions on allylic derivatives **47** did not lead to any product **48** while forcing conditions to affect an elimination reaction on compounds like **49** led to the formation of an endocyclic double bond only (**50**). The best we could achieve was a pathetic yield of **52**, as a mixture of geometric isomers, via a McMurry coupling protocol. We were starting to believe that the steric interaction between the methyl and R^4 group ($R^4 = \text{Br}, \text{CH}_2\text{OR}$ and others) was so severe we may never be able to produce this exocyclic tetrasubstituted double bond.

Meanwhile, the stereochemical issues of the two cycloadditions were brought under control. The substituent at C13 alone exerts a moderate influence over the stereochemistry of the hetero Diels–Alder reaction (Scheme 13, top). However, a second substituent at C12 brings about a sufficient level of stereocontrol (we will show, later on, that perfect stereocontrol is possible in this Diels–Alder reaction with other C12 and C13 substituents). Hence, while a protected alcohol at C13 gave inadequate results (**53b,c** → **54b,c**), isopropylidene **55** underwent the cycloaddition to give a satisfactory ratio of **56(H-β):56(H-α)**.²⁷ Compound **56** was made in eight steps from (–)-quinic acid following the route described in Scheme 11, and it was therefore enantiomerically pure. This led us to believe that (–)-quinic acid could be the ideal starting material for our purpose.



Scheme 13 Stereocontrol in the hetero Diels–Alder cycloaddition

Controlling the stereochemical outcome of the intramolecular Diels–Alder cycloaddition was possible, although the situation was a little more complex than for the hetero Diels–Alder with more than one factor influencing the outcome. The four chair-like transition states (TS) that are competing in this reaction are drawn in Figure 2. The two *exo* TS are disfavored because of the interaction between the C11-ring residue and the C2 methylene group in the chain. Differentiating between the two *endo* TS, we thought, was a matter of introducing substituents around the chain with a defined stereochemistry (exemplified by the C4 methyl group in Figure 2) such that they would occupy a pseudo-equatorial position in the desired *α-endo* TS. However, the predominant formation of the *α*-C14 isomer in **46** (cf. Scheme 2) warned us that ring C and D and their substituents might influence the outcome of this intramolecular cycloaddition.

In actuality, a C4 methyl group was able to cause the preferential formation of the desired *β*-C7, *β*-C10 isomers **58a** (Scheme 14).^{6c} The detrimental effect of the PMB protective group (**58b**) is not well understood. However, the fact

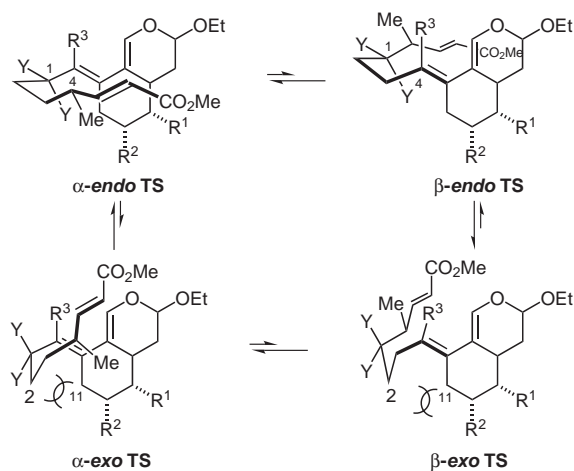
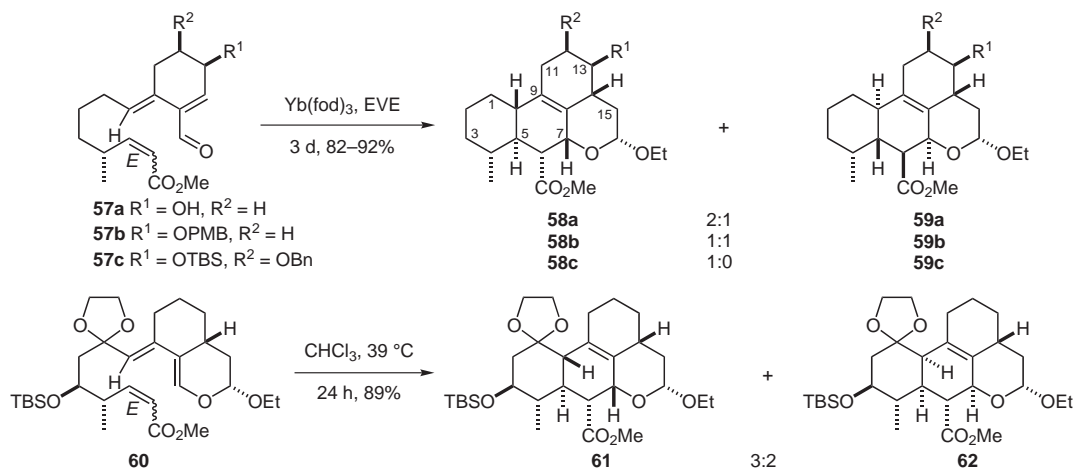


Figure 2 The four chair-like transition states of the intramolecular Diels–Alder cycloaddition



Scheme 14 Control of the stereochemical outcome of the intramolecular Diels–Alder cycloaddition

that tetracyclic compound **58c** was isolated as a single diastereomer was probably the concerted influence of the C4 methyl and the two substituents at C12 and C13. Once, we observed the formation of a tetracyclic compound arising from a β -*exo* TS.²⁷ Compound **62** was formed as the minor component of a mixture and its formation was due to the presence of a dioxolane ring at C1. More precisely, the α -oxygen of that dioxolane ring was responsible for the formation of **62**, being too close to C11 in the desired α -*endo* TS and thus raising its energy (cf. Y in Figure 2). Any α -substituent at C1 is likely to cause this problem. Compound **62** is intriguing in that it exists in two stable conformations that interconvert slowly at room temperature. We were able to freeze out the two conformations at -30 °C and their ¹H NMR signals coalesce above 40 °C.²⁷

3.2 With the C10 Methyl Group

While we seemed well underway to proving this strategy a viable one, the question of the C10 methyl group was becoming urgent. Should we be incapable of building a tetrasubstituted exocyclic double bond (as in **44**, R³ = Me), we would need to devise a way to introduce the C10 methyl group at a later stage. This alternative did not appeal to us because of the extra steps involved, and for the reason that generating a quaternary carbon atom is rarely a particularly easy task. Near our wits end, we realized that only a reaction with a transition state structurally very different than its product (i.e. an early TS where the severe steric interaction would not be present) would stand a chance of alleviating our problem. Fortunately, we found such a reaction – the Diels–Alder cycloaddition! Known to have an early transition state, the [4+2] cycloaddition of vinylallenes²⁸ with various dienophiles should proceed via a transition state free of the severe steric interactions of its product (Figure 3). To prove this concept, we made a few model vinylallenes **63** (only two are shown) and showed that their cycloadducts **64**, having highly strained exocyclic double bonds, could be prepared very easily, even at room temperature in certain cases (Scheme 15). The severe bond strain these double bonds are under is

readily apparent from their 10–22° twist, as we observed by single crystal X-ray diffraction analyses on both of these structures.^{28b} At last, we had access to the long coveted synthetic intermediates having the tetrasubstituted exocyclic double bond.

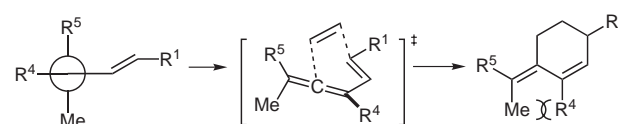
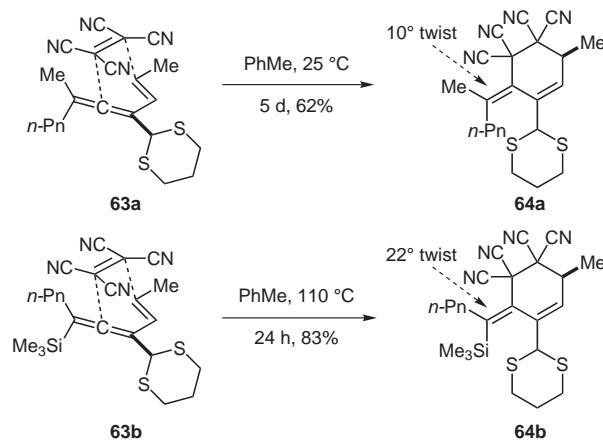
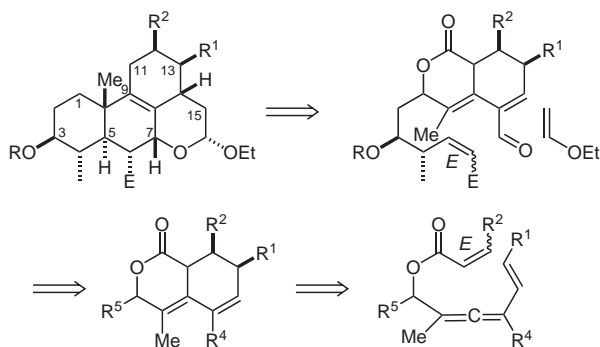


Figure 3 The Diels–Alder cycloaddition of vinylallenes



Scheme 15 Intermolecular Diels–Alder reactions of two vinylallenes leading to products with highly strained exocyclic double bonds

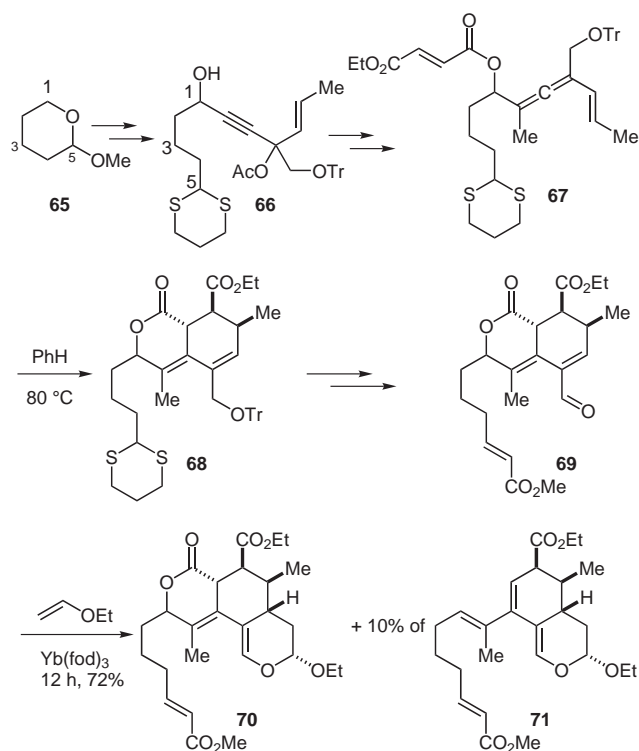
However, the geometry of the exocyclic double bond in the cycloadducts **64** is governed by the relative size of the perpendicular substituents (Me and R⁵ for example, cf. Figure 3). Therefore, in order to obtain the desired geometry for our synthetic plan, the dienophile had to be attached to the larger R⁵ group for same-face delivery. Based on the above results, we devised a new diene-transmissive Diels–Alder strategy, this one involving three [4+2] cycloadditions (Scheme 16).



Scheme 16 Revised diene-transmissive Diels–Alder strategy to construct the quassinoids framework

Implementation of this strategy followed the sequence shown in Scheme 17.^{6c} The high level of stereoselectivity of both Diels–Alder cycloadditions to make **68** and **70** is noteworthy and showed that this new strategy was not only useful because it included the C10 methyl group but also because the control of the stereochemistry was optimal. With **70** in hand, we stood one reaction away from success. It remained that way for nearly three years... Diene **70** would simply not undergo an intramolecular Diels–Alder reaction under a variety of thermal conditions and/or Lewis acid catalysis. Decomposition was observed in most cases but especially when Lewis acids were used.

Ironically, it seemed as though the C10 methyl group we spent so much effort bringing on board was now preventing the intramolecular cycloaddition reaction from taking



Scheme 17 Two of three DTDAC were successful

place at low temperature. For dienes **45**, **57** and **60**, the analogous cycloaddition occurred at room temperature. Was the lactone ring in **70** also preventing the cycloaddition from taking place? Notice that the oxygen at C1 was obviously not helping out as it likely rendered diene **70** sensitive to heat and Lewis acid. The formation of the decarboxylation product **71** (cf. Scheme 17) is indicative of such decomposition pathways that led to many aldehydic products (Figure 4).

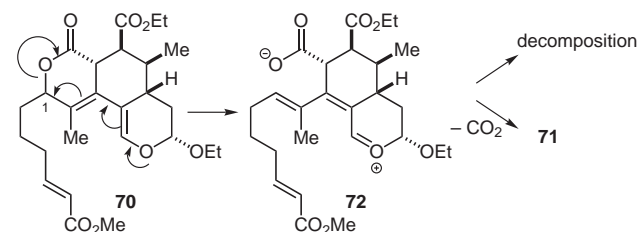
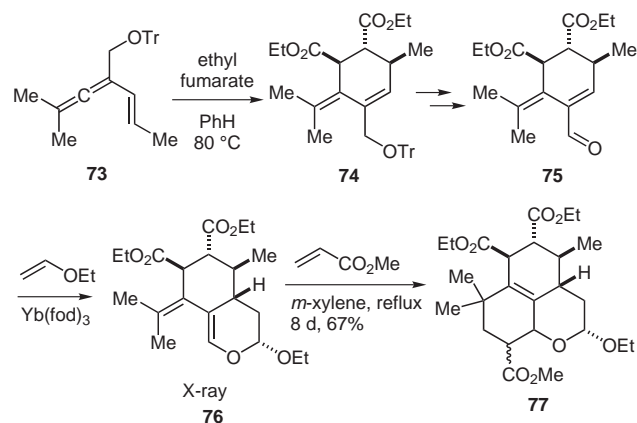


Figure 4 Formation of **71** and decomposition pathway from **72**

Diene **76** would partly answer the above questions in an expedite way. It was synthesized swiftly from propargyl alcohol via **73** and it underwent an intermolecular cycloaddition with methyl acrylate to give **77** (Scheme 18).^{6c} Granted, the reaction conditions were harsh, but the yield was acceptable. Moreover, this reaction is intermolecular and methyl acrylate is not exactly the most reactive of dienophiles. This convinced us that the desired intramolecular Diels–Alder reaction should be possible and, in fact, should proceed under milder conditions. However, the lactone ring and/or perhaps the C1-oxygen would have to be removed, otherwise the molecule would likely decompose under the conditions needed for cycloaddition.



Scheme 18 An all intermolecular demonstration of all three diene-transmissive Diels–Alder cycloadditions

We tried to cleave the lactone ring in **70** and proceed with the cycloaddition. However, we were quickly discouraged and abandoned the idea of messing around with three different ester functionalities. Why not use a linker different from the lactone ring such that we would be able to cleave it selectively? Figure 5 summarizes months of work

aimed at doing just that. It turns out that setting up the new linkers was the easy part. In addition, most linkers allowed for an efficient and stereoselective Diels–Alder cycloaddition. The problem was that very few of the linkers survived the reaction conditions for the subsequent hetero Diels–Alder reaction. In addition, many proved difficult to cleave. Sieburth's diphenylsilyloxy linker²⁹ (**78**, Figure 5) seemed perhaps the most promising but despite our best efforts, we could not elaborate it further into **79** and attempted cleavage (F^- , MeLi, HO^- and others) or Tamao's oxidation of the tether in **78** led to much decomposition. Likewise, compound **80** was formed in reasonable yield but its transformation to **81** was not possible. The ether linkage found in compound **82** is still under investigation as it proved more stable than the others depending of the nature of the R group ($R = CH_2SiMe_3 > CH_2Br > H$). Its transformation to **83** was possible and the overall yield was even very good when $R = CH_2SiMe_3$. Its cleavage, however, remains thus far problematic. Generally, we blame the instability of these molecules on the presence of the C1 oxygen. Evidence came from the numerous aldehydic products that were isolated in each case (cf. Figure 4).

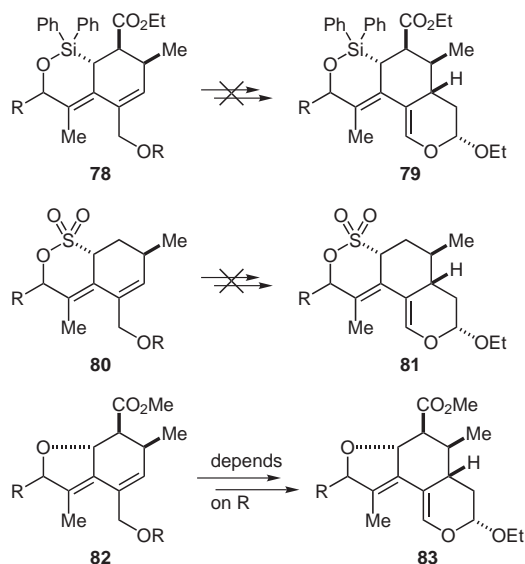


Figure 5 Different linkers for the first Diels–Alder cycloaddition

It was becoming clear that the C1 heteroatom had to go before we could proceed with the strategy. How could we achieve this despite the fact that the very first Diels–Alder cycloaddition in the sequence had to be carried out with a tethered dienophile (cf. **67** → **68**, Scheme 17)? Perhaps, the tether could itself be a part of ring A (Figure 6)? Conceptually, this idea had merit because there would be an economy of atoms (no need to throw away the tethering atoms) and chemical steps. We built compound **84** just for that purpose (Figure 6), but to our great surprise, we could not make it undergo a Diels–Alder cycloaddition under the harshest of conditions! By comparison compound **67** and the precursors to **78** and **82**, underwent cycloaddition at 25–80 °C! This puzzling result underscores the difficul-

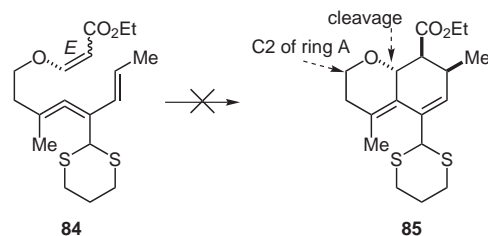
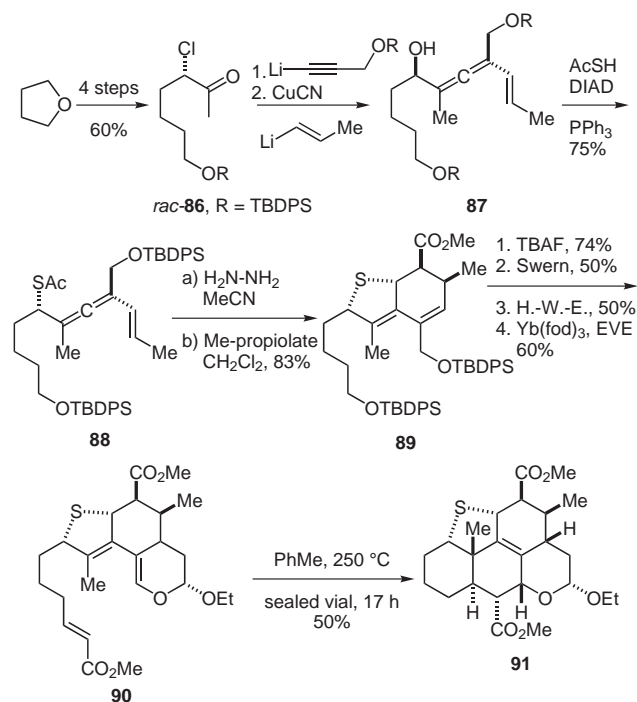


Figure 6 A reluctant cycloadduct precursor

ty of synthetic planning: a seemingly minor modification in the composition (compare **85** with **68** or **82**) of the tether annihilated reactivity toward cycloaddition.

4 A Successful Sequence

Great evils call for great remedies, or so goes the saying. It is only befitting then that we met with success trying for such a drastic solution: a sulfur atom. We planned on using a sulfur atom as tether in a compound similar to **82** (cf. Figure 5, replace O with S in the tether) in order to be able to remove it by reductive desulfurisation. The term drastic applies here because reductive cleavage of this tether would leave no functional group behind for further manipulation. As it turns out, this was not necessary. Vinylallene **87** was prepared from tetrahydrofuran in 7 chemical steps (Scheme 19).³⁰



Scheme 19 Success! (H.-W.-E. = Wadsworth–Emmons)

Of note in that sequence is the 100% stereoselective 'Felkin–Ahn' addition of the anion of the protected propargyl alcohol to α -chloro ketone **86**. We believe we will be able to prepare **86** enantiomerically pure soon. Also of

note is the regioselective Mitsunobu reaction of **87** with thioacetic acid to give the sensitive thioacetate **88**. After much experimentation, we found that hydrazine cleanly cleaved the thiolester. The resulting unstable thiol was not isolated but immediately reacted with methyl propiolate and the adduct underwent an intramolecular Diels–Alder cycloaddition at room temperature to give a single diastereomer of **89**. Its conversion to **90** occurred without incident, and to our delight, compound **90** underwent a stereoselective intramolecular cycloaddition to give **91**. Not only did the C–S bond resist the conditions of the hetero- and intramolecular Diels–Alder cycloadditions but that same bond controlled the stereochemistry of the cycloadduct **91**. A careful NOESY analysis of **91** left no doubt as to its structure. In addition, a single crystal X-ray analysis of the sulfone derivative of **91** confirmed the stereochemistry. Because of the sulfur bridge, only the desired α -endo as well as the β -exo transition states are geometrically attainable (Figure 7). Of these two, the desired α -endo TS is much lower in energy for reasons discussed earlier.

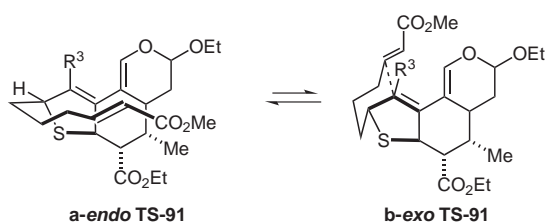


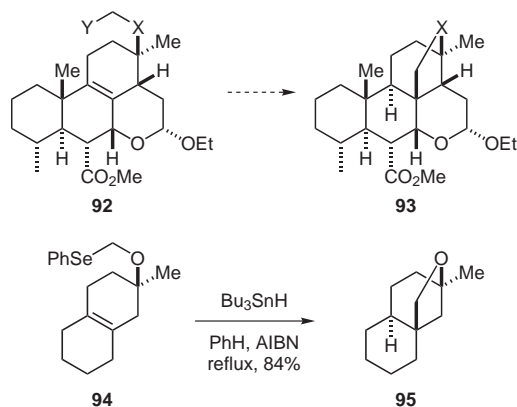
Figure 7 The two attainable chair-like transition states of the intramolecular Diels–Alder cycloaddition of **90**

5 Conclusion and Outlook

Pentacyclic compound **91** was made in only thirteen steps from a very simple molecule (THF). The four rings were constructed with perfect control over all their stereocenters. This, we believe is a significant achievement. The four rings of the quassinoids framework were made from three highly stereoselective Diels–Alder cycloadditions.

We are well aware, however, that many challenges remain before we can complete the synthesis of a natural quassinoid, not least of which is making use of the endocyclic tetrasubstituted double bond found in **91**. One appealing tactic would be to effect a regio- and stereoselective radical cyclization with an appropriate precursor like **92** (Scheme 20). When X is an oxygen, the oxomethano-bridge (cf. Figure 1) would be created. Alternatively, a C8 methyl group would be accessible via reductive desulfurization when X is a sulfur atom.

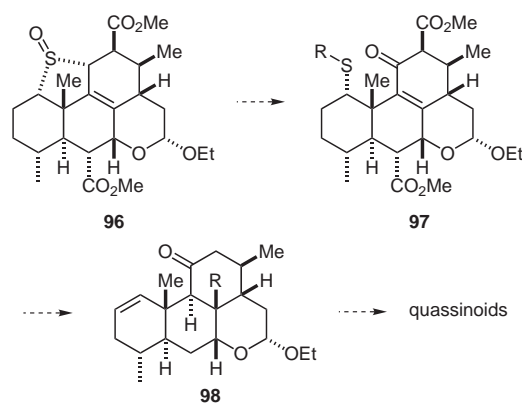
Model studies have been carried out on simple analogues of the B–C ring system (Scheme 20). The yield of cyclization was good and **95** was isolated as a 4:1 mixture of stereoisomers, the major being the desired one. It is likely



Scheme 20 A radical cyclization for the oxomethano-bridge function

that the cyclization to give a pentacyclic system, like the one found in many quassinoids, would be even more stereoselective based on conformational considerations.

Other plans include using the C–S bonds in **91** to introduce the C8 carbon atom (Scheme 21). There are many possibilities and we will not indulge in free speculation as to which is more promising. Nonetheless, nucleophilic addition on an enone, like the one shown in compound **97**, is one option as is cyclopropanation of the enone followed by opening of the cyclopropane under reducing conditions. We are hopeful that the stereochemistry at C8 can be controlled and that ring A and ring C contain sufficient synthetic levers to help us complete the synthesis of a quassinoid in the not too distant future. We have undertaken the task of completing several quassinoids from slightly modified pentacyclic structures like **98**. Perhaps the worse is over in our quest to conquer the ever synthetically challenging quassinoids.



Scheme 21 Outlook on future research

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