Selective Preparation of Complex Polycyclic Molecules from Acyclic Precursors via Radical Mediated- or Transition Metal-Catalyzed Cascade Reactions

Max Malacria

Laboratoire de Chimie Organique de Synthèse, Université Pierre et Marie Curie (Paris VI), URA CNRS 408, Tour 44-54, B.P 229, 4 Place Jussieu, 75252 Paris Cedex 05, France

Received July 10, 1995 (Revised Manuscript Received September 29, 1995)

Contents

Introduction

Synthetic organic chemistry has been strongly influenced over the past 20 years by the explosion of two main areas of research, namely: transition metal-mediated synthetic applications[1] and radical-initiated reactions.[2] Both methodologies allow reactions to proceed under mild conditions, with very high selectivities and exhibit great synthetic performance, but they suffer from major drawbacks mainly associated with problems of toxicity and economical standards.

The development of the "one-pot reaction" technique brings at least partial solutions to these issues: as Trost first claimed, this implies "atom economy",[3] and moreover one can witness the development of very elegant new synthetic combinations,[4] a strategy which is in my opinion the closest expression for chemistry of what is called sometimes: Art in Science.

This survey, which is not meant to be exhaustive, will illustrate the potentiality and growing scientific interest of this field, dealing mainly with recent literature. Prominent work in the field of radical cyclization cascades will be presented, including our own work in this area. A second part will be devoted to the transition metal-catalyzed cascade leading from polyenynes to polycyclic frameworks in a chemo-, regio-, and stereoselective manner.

Max Malacria was born on February 7, 1949, in Marseille (France). He received his Ph.D. degree in 1974 at the University of Aix-Marseille III under the supervision of Professor Marcel Bertrand. From September 1974 to August 1981, he served as an Assistant and Maître Assistant at the University of Lyon I and worked under the supervision of Professor Jacques Goré. From September 1981 to December 1982, he worked as a postdoctoral fellow with Professor K. Peter C. Vollhardt at the University of California Berkeley. In 1983, he returned at the University of Lyon I as a Maître de Conférences. In 1988, he was appointed as a Professor at the University Pierre et Marie Curie (Paris VI). In 1991, he was elected as a member of the Institut Universitaire de France. His current research interests include the development of new selective and efficient approaches to complex polycyclic molecules, transition metal catalyzed reactions and asymmetric synthesis of natural compounds of biological interests.

I. The Radical Cyclization Approach

1. The "One-Ring Template" Strategy

The usefulness of strategies based on radical cyclization cascades has been largely demonstrated in the past 15 years. Among them the contribution from the Curran group[5] in the construction of fused five-membered rings (linear or angular polyquinanes) has been of primary importance as illustrated in this simple and elegant construction of the natural linear triquinane hirsutene **2** as a single stereomer[6] and based on a double 5-*exo*-tin hydride-mediated radical cyclization of iodide **1** (Figure 1).

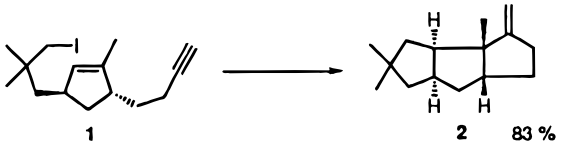


Figure 1.

0009-2665/96/0796-0289$25.00/0

This straightforward approach takes advantage of the easy stereoselective preparation of cyclopentene derivatives. The *trans* geometry of the monocyclic precursor for cyclization here biased the stereochemical outcome of the cyclization, which could proceed to the needed diastereomer.

Other groups have used a similar strategy to provide a stereoselective access to angular triquinanes. Thus, Yadav[7] applied the Stork[8] and Ueno[9] methods of radical cyclization of bromoacetals for the synthesis of the triquinane moiety. When the bromoacetal unit was present on a cyclopentene ring, in an α position relative to the double bond, the derived radical readily cyclized. The stereochemistry of the annelation was governed by the stereochemistry of the carbon−oxygen bond tethering the cyclopentene to the bromoacetal. The resulting carbon-centered radical was *syn* to the side chain, enabling further ring closure to give the oxatriquinane **4** in a 77.5% yield (Figure 2).

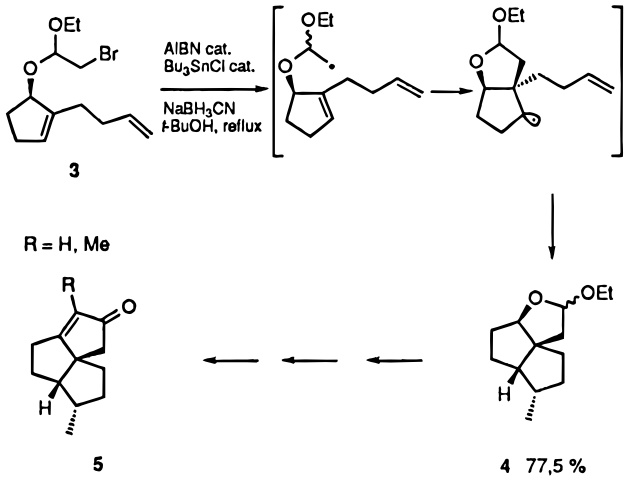


Figure 2.

Another efficient pathway for the stereocontrolled synthesis of functionalized, angularly fused tricyclic carbocycles, starting from easily available 2-formylcycloalkanones has been recently described by Rajagopalan *et al.*[10] Addition of a propargylaluminum sesquibromide solution to ketone **7** gave the needed alcohol as a single diastereomer in 85% yield. The major angularly fused tricyclic system was obtained through a sequence of 5-*exo*-6-*endo*-*trig* radical cyclization (Figure 3). The authors claimed that the preference for the final 6-*endo* mode of cyclization is consistent with a chairlike transition state imposed by the bicyclic structure.

A tandem radical cyclization which proceeds via an addition−elimination mechanism has been applied to the synthesis of norcedrenone, a precursor for the synthesis of (±)-α-cedrene[11] (Figure 4).

Radicals derived from methylenecyclopropane derivatives have been shown to follow a sequence of radical cyclization and fragmentation leading to tricyclic products (Figure 5). In a spectacular example,[12] the vinyl radical obtained from bromide **14** gave a 1:1 mixture of **15** and **16** in a 55% yield.

Finally, Pattenden, using a powerful tandem radical macrocyclization−radical transannulation strategy, was able to propose a radical route to the

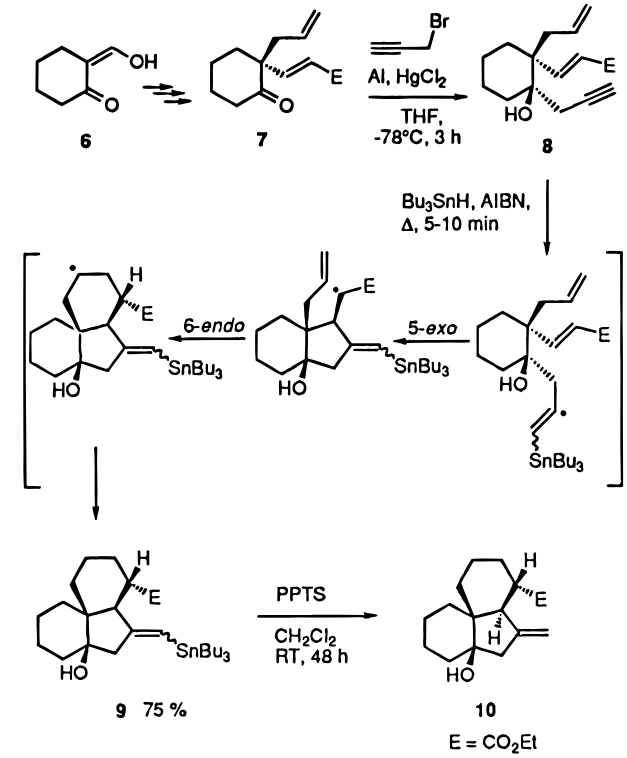


Figure 3.

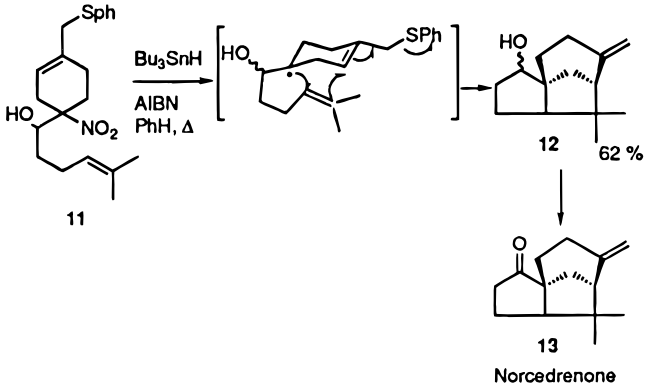


Figure 4.

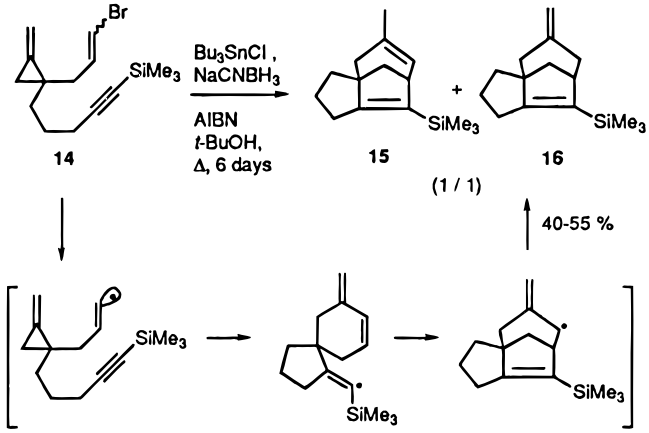


Figure 5.

construction of the tricyclic taxane diterpene skeleton starting from a polyunsaturated precursor bearing the A ring.[13] In this work, the radical precursor model incorporates two conjugated enone moities to impose the unusual radical tandem 12-*endo*-8-*endo* cyclization process. When a solution of the iodide

precursor was heated under reflux in the presence of tributyltin hydride and AIBN, the tandem radical macrocyclization−transannulation sequence produced the taxane ring system as a 3:1 mixture of C-1 epimers in a 25% overall yield (Figure 6).

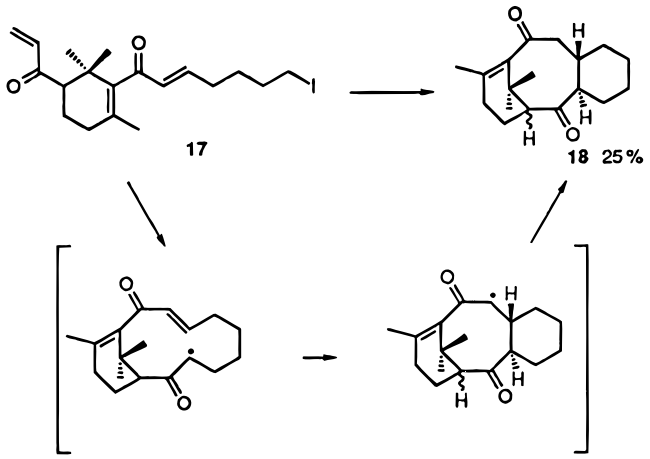


Figure 6.

2. The Acyclic Approach

The presence of a ring on the precursor of the radical cyclization process has been crucial for the success of all the previously mentioned examples. A more elegant and challenging approach consists in a cascade of cyclizations which would deliver chemo-, regio-, and stereoselectively, from a polyunsaturated precursor the targeted polycyclic framework. With this goal in mind, Beckwith in 1985 reported[14] the cyclization of bromo triene **19** that leads to a linear triquinane. Tributylgermanium hydride, a less reactive radical mediator, was used, and they observed the formation, via a triple cyclization sequence, of a mixture of five stereomeric linear triquinanes, beside other isomeric products in a low yield (Figure 7). This pioneering work clearly suggested the potentialities of such a strategy as well as the difficulties of solving the stereochemical problems inherent to this approach.

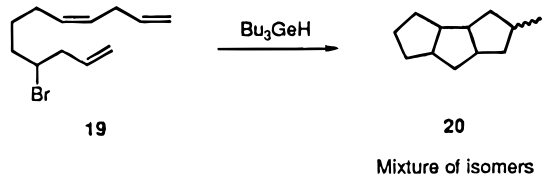


Figure 7.

On the other hand the biomimetic electrophilic polyolefin cyclization has known tremendous development[15] which has recently led to the very interesting achievement of an enantioselective preparation of the steroid skeleton.[16] Comparatively, a radical biomimetic cyclization was not really considered. Although Breslow in 1968 proposed an oxidative free radical cyclization of *trans, trans*-farnesyl acetate with benzoyl peroxide in the presence of Cu(II) as a speculative mechanism for the cyclization of squalene[17] and Julia in a seminal work in 1973 disclosed the radical cyclization of (*E,E*)-13-phenyl-2,6,10-trimethyl-2,6,10-tridecatriene.[18]

It was only after Snider and co-workers achieved intramolecular cyclizations of various unsaturated β-keto esters with Mn(III) and Cu(II), affording an entry to di- and tricyclic systems,[19] that a strategy of radical polyolefin cyclization was investigated. Thus, Zoretic and co-workers have taken advantage of the high performance of the Snider method to prepare stereospecifically a highly functionalized *D*-homo-5α-androstan-3-one, on which seven stereogenic centers have been created in a controlled manner[20] (Figure 8).

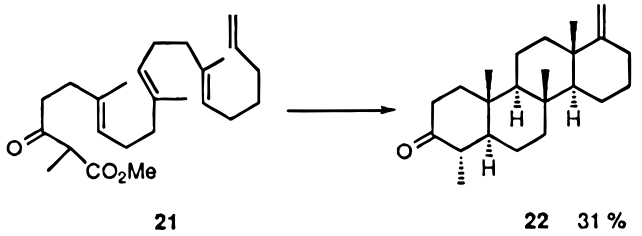


Figure 8.

The authors suggested that the observed stereoselectivity could result from a concerted intramolecular radical cyclization in which the intermediate complexed radical existed in an all-chair conformation. Following the success of this approach, the same group has very recently published a highly selective free-radical cyclization to the synthesis of furanoditerpenes[21] which presents the advantage of stereoselectively introducing in a single step five of the six stereogenic centers present in these marine natural compounds.

Independently, Pattenden and co-workers have shown that free-radical cyclization of polyolefin selenyl esters, in the presence of tributyltin hydride, provided stereospecifically polycycles of linear and angular fused six-membered rings via consecutive 6-*endo-trig* modes of cyclization.[22] For instance the tetraene ester **23**, lacking methyl substitution at the terminal double bond, underwent three consecutive 6-*endo-trig* radical cyclizations, followed by a 5-*exo-trig* closure to deliver the steroid tetracyclic ketone in 51% yield (Figure 9).

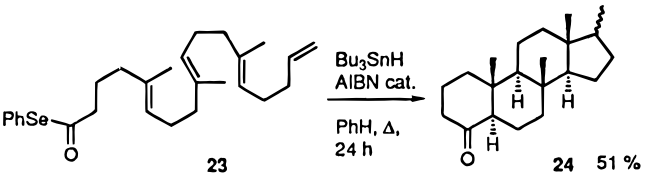


Figure 9.

These interesting results offer immense scope for the efficient construction of a range of substituted linear and angular fused cyclohexanes, including steroid and diterpene systems and should see important synthetic applications in a near future.

A different cascade strategy by the Nottingham group was also examined on the basis of sequential radical macrocyclization. They first confirmed the efficiency of this approach for the preparation of linear 5,6-, 6,6-, and 5,7-fused bicycles[23] from suitable polyolefins and showed that it could lead to an angular 5,7,5-ring fused tricyclic system via a novel sequential 13-*endo-trig* radical macrocyclization fol-

lowed by two consecutive stereoselective 5-*exo-trig* transannulation processes[24] (Figure 10).

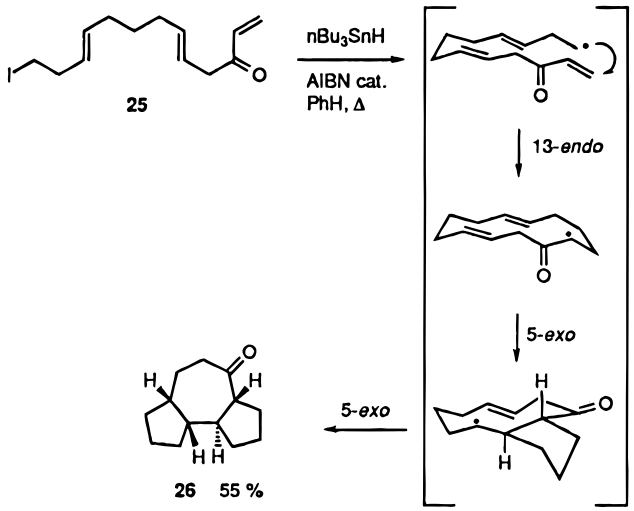


Figure 10.

This strategy, which takes advantage of the easy radical macrocyclization (see above) and then imposes the stereoselectivity of the consecutive transannular cyclization, should see important synthetic applications, even though initial study of the cyclization of (all-*E*)-iodotetraenone **27**, with the aim of building in one step a steroidal skeleton, has failed (Figure 11).

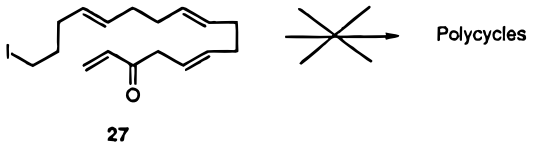


Figure 11.

Finally, at the end of 1994, Saicic and Cekovic reported a regio- and stereoselective synthesis of a linear triquinene from a readily available acyclic precursor under free-radical conditions.[25] In this impressive example, when the thiohydroxamic ester **28** was submitted to the free-radical cyclization conditions, the unsaturated linear triquinane derivative was isolated in 46% yield as an inseparable mixture of two diastereomers in a 2.2:1 ratio (Figure 12).

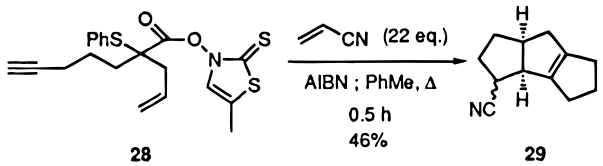


Figure 12.

The initially generated sulfur-stabilized radical regioselectively cyclized following a 5-*exo-dig* fashion, to deliver a vinyl radical which underwent a consecutive 5-*exo-trig* cyclization. The intermediate homoallyl radical is known to give intermolecular addition to acrylonitrile, thus, a subsequent cyclization/β-elimination process furnished the tricyclic compound **29** (Figure 13). This first stereoselective achievement based on tandem cyclizations with the sequential formation of the three rings from an open-chain precursor illustrates the powerful potentialities of this strategy.

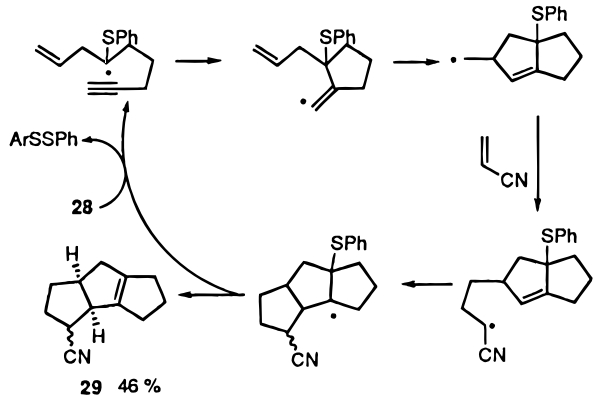


Figure 13.

3. The Propargyl Silyl Ether Approach

A few years ago we started a general program of research aimed at the study of the propargyl analogs,[26] on the basis of the known regio- and stereoselective 5-*exo-trig* cyclization of radicals generated from (bromomethyl)dimethylsilyl allyl ethers first described by Nishiyama[27] and by Stork[28] (Figure 14).

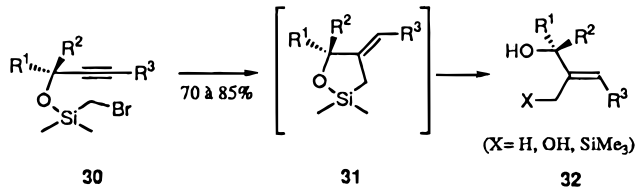


Figure 14.

The radical cyclization of the initially generated α-silyl radical was found to be highly regio-, chemo-, and stereoselective,[29−31] leading after simple *in situ* chemical transformation to di- and trisubstituted functionalized double bonds under very mild conditions. We felt that the intermediate *exo*cyclic vinyl radical involved in this reaction could be trapped intramolecularly by a suitably located unsaturation to afford regioselectively unsaturated five membered carbocycles. This approach proved to be high yielding. Moreover, we were pleased to observe a remarkably total 1,3-asymmetric induction (Figure 15). This diastereoselectivity is really outstanding, since it can involve a stereodifferentiation even between a methyl and a methylene group (R^3 = methyl).

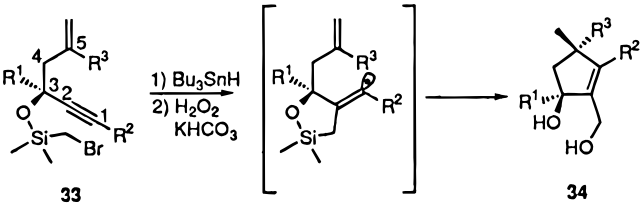


Figure 15.

This high stereoselectivity is consistent with the reaction of the vinyl radical intermediate through the more reactive chairlike conformation *versus* the boatlike approach.

With this interesting result in mind, we were in a position to propose a new strategy for the one-pot preparation of angular as well as linear triquinanes starting from very simple acyclic propargyl silyl ethers. The crucial intermediate is the homoallyl radical (Figure 16); it possesses the structural fea-

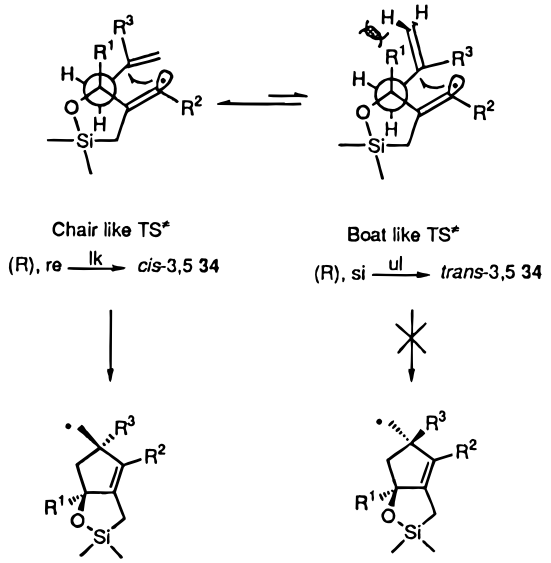


Figure 16.

tures to be a suitable reagent in the Curran [3 + 2] annulation reaction using an electron-deficient olefin[32] and the correct stereochemistry to allow the resulting β-silicon radical which has been stereoselectively formed to be trapped by a suitable radical terminator. If R^2 contains a double bond, an eventual 5-*exo*-*trig* cyclization will offer a new access to highly functionalized angular triquinane skeletons (Figure 17).

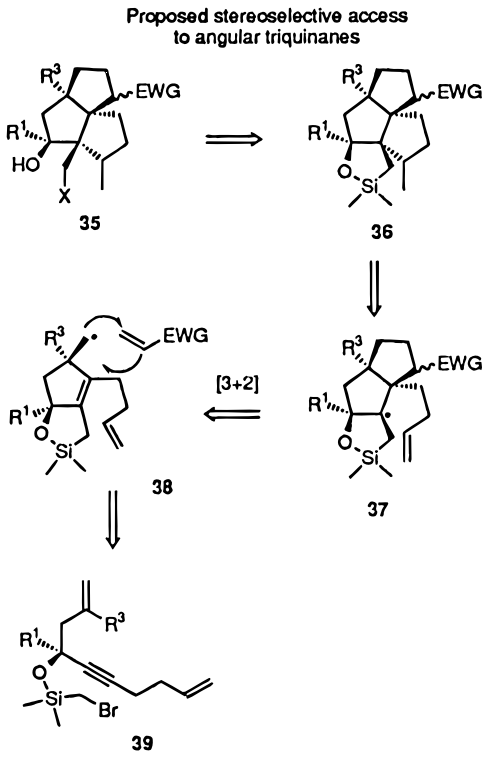


Figure 17.

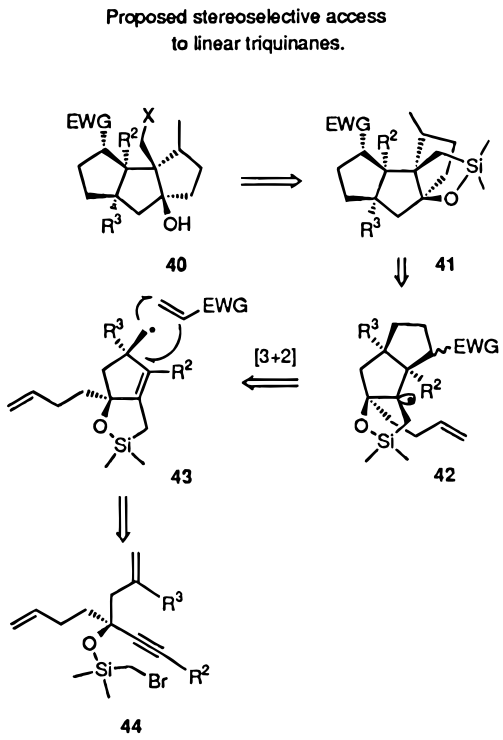


Figure 18.

A similar disconnection, if a suitable radical terminator is located on the appendage R^1, should now lead to the linear triquinane framework (Figure 18).

To check the validity of our strategy, we first studied the behavior of the 4-[(bromomethyl)dimethylsiloxy]-2-methylundec-1-en-5-yne (**45**). A benzene solution (0.01 M) of this propargyl ether was refluxed in the presence of 10 equiv of acrylonitrile and a benzene solution of Ph_3SnH (0.05 M, 1.1 equiv) containing 0.1 equiv of azabis(isobutyronitrile) was slowly added (2×10^{-4} mL/h) by a syringe pump. The mixture was allowed to reflux for five additional hours. The volatile material was removed and the crude mixture subjected to a Tamao oxidation.[33] We were gratified to observe the stereoselective formation of the diquinane **46** in a 51% overall yield[34a] (Figure 19).

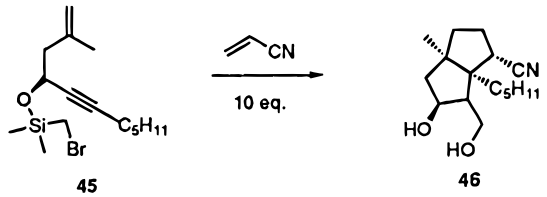


Figure 19.

Four carbon−carbon bonds have been created chemo-, regio-, and stereoselectively in the overall process. Moreover the resulting highly functionalized diquinane possesses two contiguous quaternary centers and exhibit four new stereogenic centers which have been introduced in a complete stereoselective manner. Details of this sequence "*intra*−*intra*−*(tandem-inter)*−*intra*" molecular radical cyclizations are given in Figure 20.

As expected the vinyl radical cyclization was stereoselective. The 1,3-asymmetric induction directed the creation of all additional stereocenters since the

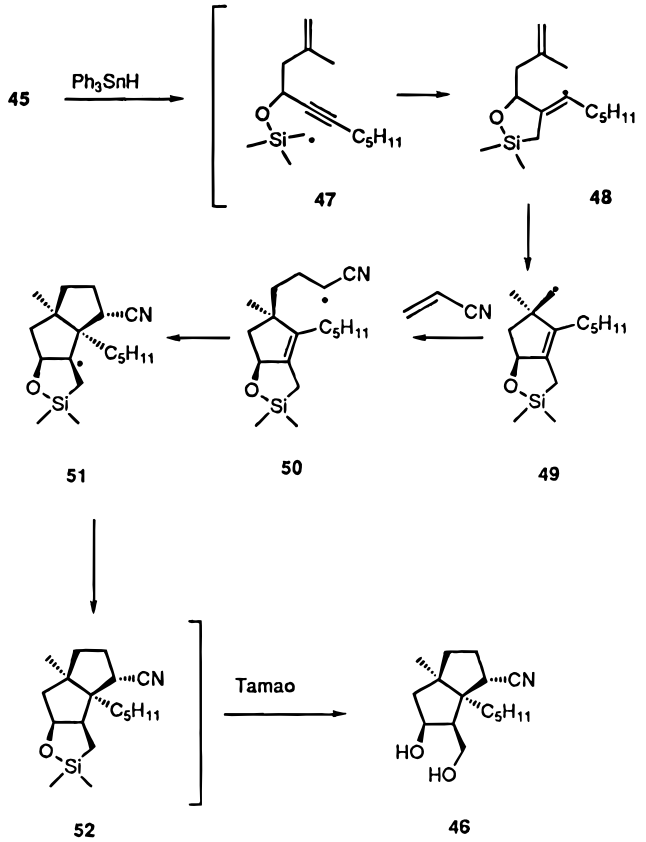


Figure 20.

intermediate heterotriquinane **52** must have a *cis*−*syn*−*cis* configuration, and therefore **50** cyclized with the cyano group on the convex face of the incipient tricyclic skeleton. Finally, a noteworthy feature of the sequence was the reduction of the final radical instead of its further trapping by acrylonitrile, which is probably due to steric hindrance.

Our next task was to apply this strategy to build, in one pot, the angular and linear triquinane frameworks. The syntheses of the needed acyclic precursors **53** and **55** were achieved in only a few steps in very good overall yields.[34b] We first subjected the propargyl ether **53** to the regular conditions of radical cyclization in the presence of 10 equiv of acrylonitrile followed by a Tamao oxidation. Unfortunately this led to a complex mixture of products probably due to the instability of the diol. So, we repeated the cyclization of **53** and treated the crude mixture with 5 equiv of tetrabutylammonium fluoride in dimethylformamide at 70 °C. Under these conditions the highly substituted cyclopentane **54** was isolated as a mixture of stereomers in 50% yield (Figure 21).

This result can be explained by the preference of the initially generated vinyl radical to undergo a 1,5-hydrogen shift[41] involving the activated propargyl position rather than a 5-*exo*-*trig* cyclization. The propargyl radical intermediate thus produced can cyclize via a 5-*exo*-*trig* mode to give the radical **57** which was then trapped by acrylonitrile. A quaternary center at the propargyl position may be necessary in order to avoid this undesired 1,5-hydrogen transfer.

We next turned our attention to the possible access to angular triquinanes, starting in a similar way from **55a** and **55b**. Unfortunately **55a** provided the diol **59a** in 20% yield accompanied by many other unidentified products, whereas **55b** gave a complex mixture (Figure 22).

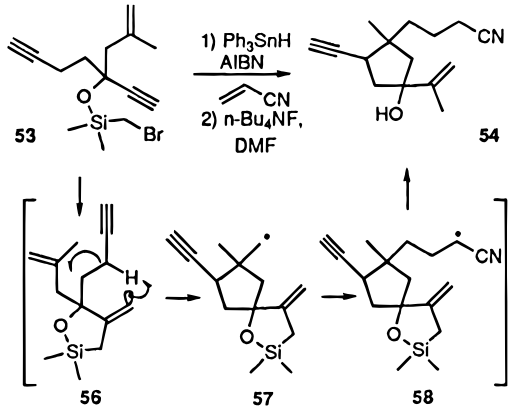


Figure 21.

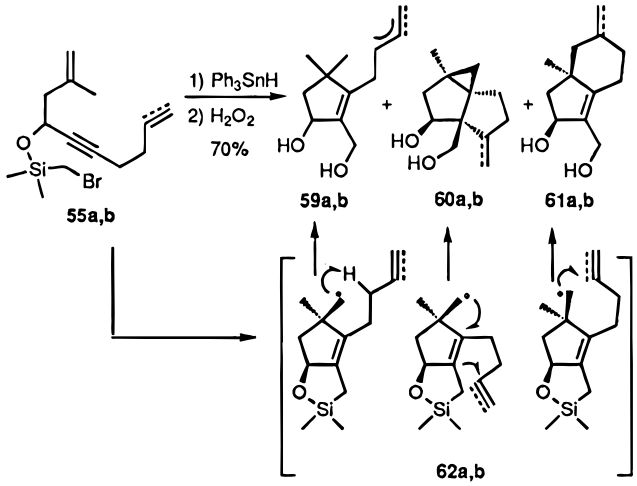


Figure 22.

To clarify this problem the cyclization of **55a** and **55b** was performed in the absence of acrylonitrile in order to verify the compatibility of the unsaturated side chain. Once again, the limiting factor of this approach was a 1,5-hydrogen shift, giving rise to **59a,b** where compound **59a** resulted from a migration of the terminal double bond. This hydrogen translocation is the major pathway (56%) occurring beside two additional processes. First, the homoallyl radical intermediates **62a** and **62b** also underwent a 3-*exo*-*trig* cyclization, and the resulting β-silyl radical was trapped by the unsaturation to furnish cyclopropane derivatives **60a** and **60b** as single diastereomers. To our knowledge, this is the first isolated compound which illustrates the mechanism proposed by Stork[35] and Beckwith[36] for the formation of the rearranged 6-*endo* products via a α-cyclopropyl radicals. In addition, this result suggests that cyclopropane formation from radical cyclization could be a process of synthetic value, as we will discuss later. Finally, the formation of **61a** and **61b** resulted from 6-*exo* cyclization of the homoallyl radical onto the terminal unsaturation. Compound **61b** was isolated as a single stereomer and **61a** was a 1:1 mixture of diastereomers due to the lack of control of the stereoselectivity during the creation of the last stereogenic center. There again, a quaternary center at the propargyl or allyl position seems to be necessary in order to envisage one-step construction of the angular triquinane framework.

Therefore, the required propargyl ether **63** was prepared[37] and subjected to the conditions of radical cyclization followed by a treatment with methyllithium. This led to the selective formation of a functionalized hydrindene framework of great interest[38] as a single stereomer (Figure 23).

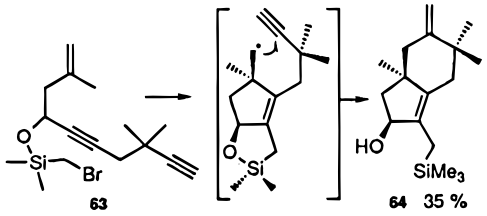


Figure 23.

Two consecutive 5-*exo*-type cyclizations afforded regio- and stereoselective formation of a homoallyl radical which could never be intermolecularly trapped and instead cyclized following a 6-*exo-dig* process. A dramatic Thorpe−Ingold effect of the *gem*-dimethyl group[39] may be involved here. This result seems to preclude this strategy and this kind of synthetic precursor for the one-step preparation of angular triquinanes.

A convenient means to suppress the undesired 1,5-hydrogen migration when a final 6-*exo* process is desired in the cascade process is having an aromatic ring between the internal triple bond and the terminal unsaturation. Indeed, cyclization of bromo ether **65**, via a cascade of radical cyclizations, afforded the tricyclic compound **66** as an inseparable 10:3 mixture of stereomers in 50% yield as the major product of the reaction.[40] The byproduct **67** resulted from a final 7-*endo-trig* mode cyclization, rarely observed but easily explained by the generated stabilized benzylic radical (Figure 24).

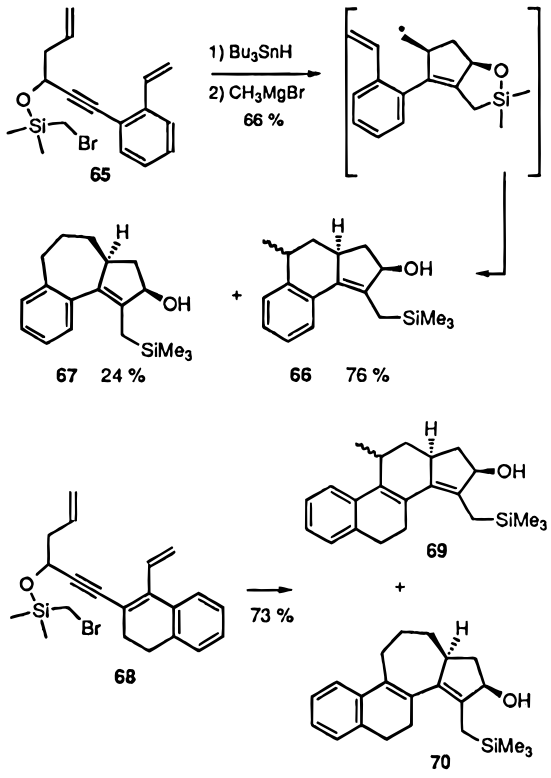


Figure 24.

There again, the total diastereoselective formation of **67** was the result of a chairlike transition state during the cyclization of the vinyl radical and indicated that the mixture of stereomers **66** originates from a lack of stereoselectivity during the 6-*exo-trig* radical process.[34b,37]

The related precursor **68** provided an even more impressive example of the efficiency of this sequence as it affords in 58% isolated yield in a one-pot operation a steroid skeleton with the same level of stereoselectivity as seen previously. Here also, generation of a stabilized allylic radical in the 7-*endo* process may account for the fact that compound **70** was formed in 15% yield. An interesting feature of the homoallyl radical intermediate involved in the cyclization was the total chemoselectivity in favor of the 6-*exo-trig* radical process. Indeed, the reaction proceeded through the most stable rotamer **72** *vs* **71** in which a strong repulsion between the vinyl moiety and the heterocycle was present (Figure 25). Consequently it is not surprising that the 1,5-hydrogen atom transfer did not compete with the cyclization.

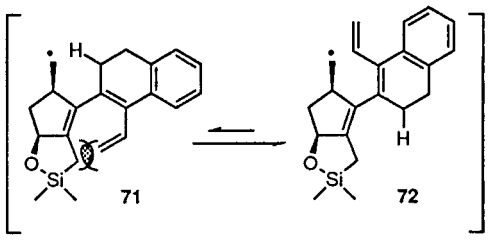


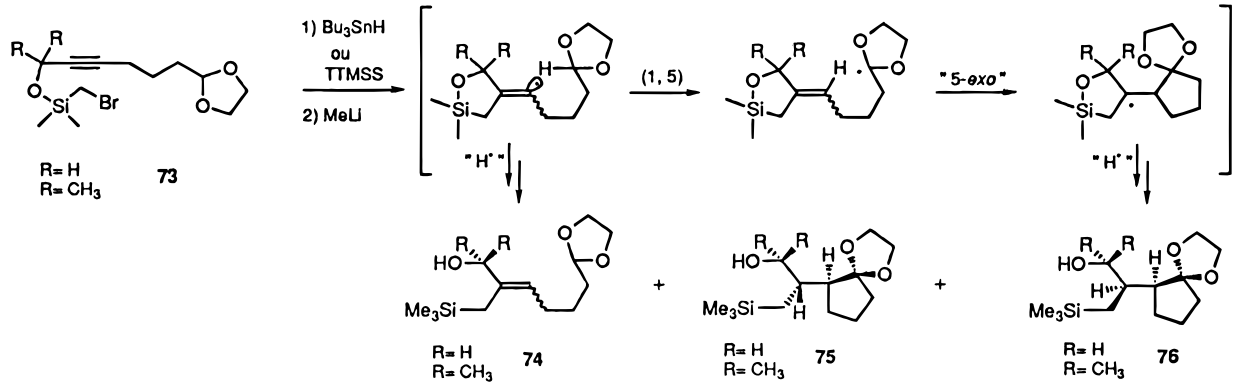
Figure 25.

Following the disappointing results obtained in our strategy to prepare angular triquinane in a one-pot operation, we next turned our attention to the utilization of the characteristics of these failures: 1,5-hydrogen shift and 3-*exo-trig* cyclization in new cascade processes starting from propargyl silyl ethers or even simpler acyclic precursors.

We first demonstrated that simple (bromomethyl)-dimethylsilyl propargyl ethers having a suitably located acetal group led to the transformation of the two sp carbon atoms into new stereogenic centers in a totally stereoselective fashion via a one-pot sequence of radical cyclization, 1,5-hydrogen shift-radical cyclization, and reduction[42] (Figure 26).

The very high diastereoselectivity associated with this synthetic transformation and the ease of working with chiral acetals[43] augurs well for the asymmetric version of this reaction which is under active investigation in our laboratory.

Very recently and more interestingly, we found that when the R substituents in the propargylic position were larger than a methyl group, a totally different behavior of the vinyl radical intermediate occurred. For instance, when R = *i*-Pr, due to the steric hindrance the hydrogen shift from the acetal group is now impossible and even this vinyl radical seems to be reluctant to external reduction. We then observed a new 1,5-hydrogen migration involving the isopropyl group and then the resultant alkyl radical underwent a rather unusual 5-*endo-trig* radical cyclization,[44] the first example of such a process leading to the construction of a highly functionalized cyclopentane derivatives. This new cascade process al-



Entry	R	Hydrogen donor	74 E/Z	74 (%)	75/76	de (%)	75+76 (%)
1	H	Bu_3SnH	50/50	21	30/70	40	71
2	H	TTMSS	50/50	18	20/80	60	69
3	CH_3	Bu_3SnH	0/100	6	90/10	80	92
4	CH_3	TTMSS	-	0	≥99/1	≥98	92

Figure 26.

lowed the formation of four stereogenic centers in a totally stereoselective manner starting from a nonstereogenic acyclic precursor. In addition the heterodiquinane intermediate could be isolated in high yields[45] (Figure 27).

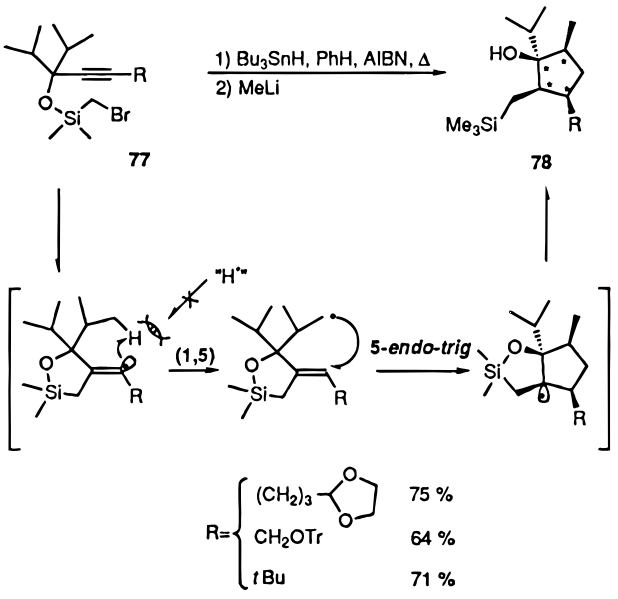


Figure 27.

It is interesting to note that the 5-*endo-trig* process seems to proceed faster than the external reduction under the conditions of the reaction (10^{-2} M concentration of tin hydride).

We have already applied this sequence to the stereoselective synthesis of the diquinane shown in Figure 28.

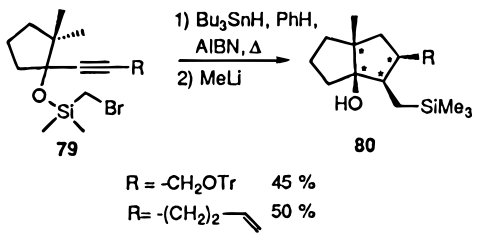


Figure 28.

We are currently investigating the scope and limitations of this process and its application to even more spectacular cascade cyclizations.

Of equal interest would be a strategy starting from very easily accessible acyclic precursors such as **85**. It is well known that cyclopentene could result from thermal vinyl cyclopropane rearrangement.[46] On the other hand, we have already shown that cyclopropanes were accessible albeit in very low yield from 3-*exo-trig* radical cyclization. Thus, our synthetic target was **82** (Figure 29).

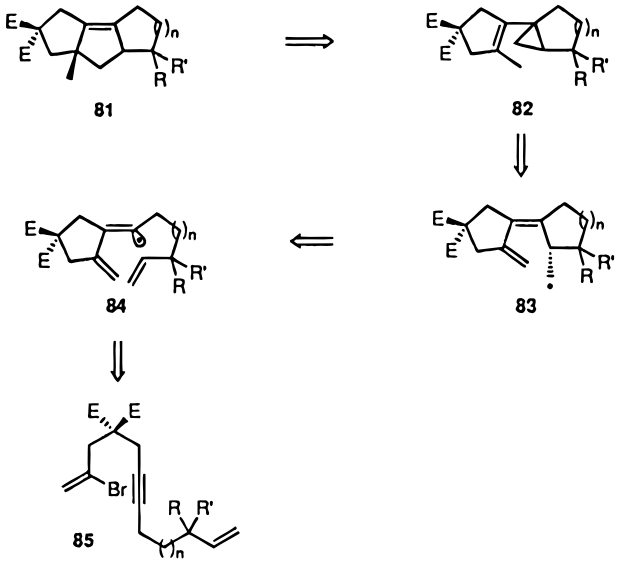


Figure 29.

When acyclic precursor **86**, easily prepared by a convergent synthesis from dimethylmalonate, was treated with tributyltin hydride, an initially favorable 5-(π-*exo*)-*exo-dig* cyclization[47] occurred, which generated a rapidly inverting trisubstituted vinyl radical, reacting only in the *E* configuration[34b] to deliver the homoallylic radical **87**. This intermediate then followed a 3-*exo-trig* mode of cyclization generating the intermediate **88** which exists in two canonical forms. The hydrogen abstraction of the allylic primary radical was faster than the rearrangement[48] or the

reduction of the tertiary α-cyclopropyl radical. Thus, the tricyclic compound **89** was isolated in 48% yield[49] (75% based on recovered starting material). This constitutes a rare example of cyclopropanation in free-radical chemistry.[50−52] The success in the formation of the vinyl cyclopropane derivatives might be the result of the difference in thermodynamic stability of the disubstituted exocyclic double bond compared to the tetrasubstituted endocyclic one. This may account for the fact that no rearranged product was observed (Figure 30).

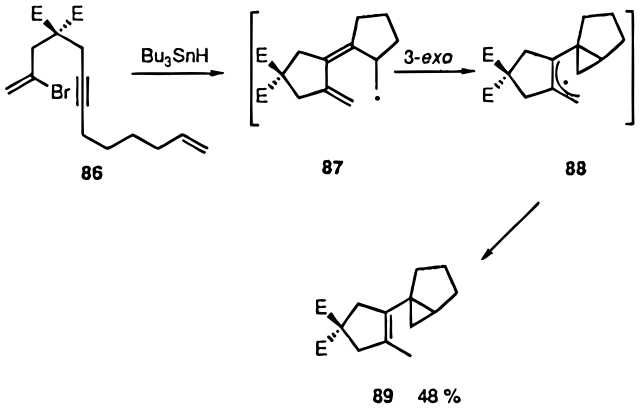


Figure 30.

This sequence was then successfully applied to the homolog precursor **90** and **91** having respectively a carbonyl and an acetal group in the allylic position, in order to avoid an eventual but probable 1,5-hydrogen atom transfer from the trisubstituted vinyl radical[41c,53] (Figure 31). The illustration of the synthetic potentialities of this new approach are under active investigation in our laboratory.

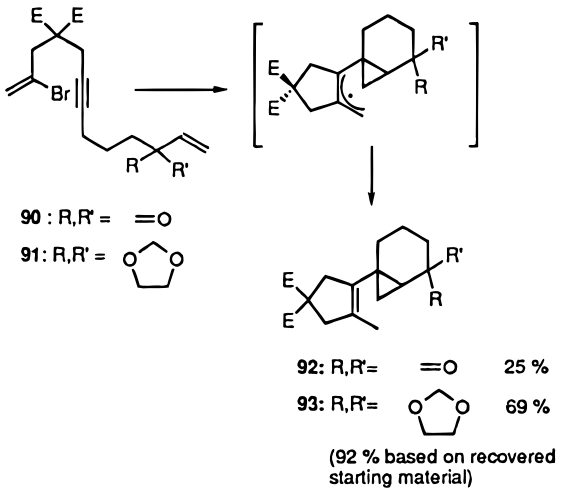


Figure 31.

We next examined the behavior of the same diene intermediate as in the preceding case but where the newly generated vinylic carbon-centered radical (see **94** Figure 32) could not undergo further cyclization and may be involved in a new tandem radical−pericyclic sequence.[54] The study of this novel conceptual advance within the field of free-radical chemistry required the preparation of the trisubstitued vinylic iodide **93** which was efficiently synthesized as a 9:1 inseparable mixture of *Z* and *E* isomers in

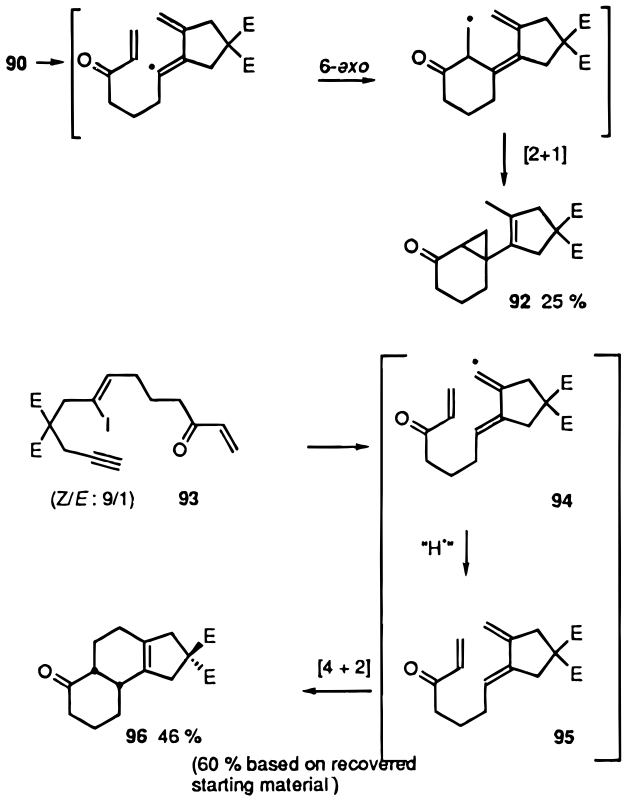


Figure 32.

nine steps from hex-5-ynal in 43% overall yield. It is noteworthy that the stereochemistry of **93** should be without importance. Indeed, σ-vinyl radicals have a very low barrier of inversion[31b,55] and the initial 5-(π-*exo*)-*exo*-*dig* cyclization process should lead mainly to the *E*-trisubstituted exocyclic double bond.[56]

As expected, the initially generated vinyl radical, preferentially cyclized in the *Z* configuration to provide a dienic radical which is subsequently reduced, and then the very reactive diene[57] thus formed reacted in an intramolecular [4 + 2] cycloaddition.[58]

Nevertheless, in that case there was a possibility that the formation of the tricyclic compound was a result of a 10-*endo*/6-*exo* radical macrocyclization−transannulation process[23] although the stereoselectivity was in good agreement with the favored *endo*-like addition[57] according to the Alder rule. In order to prove the utility of this new tandem reaction, we next accomplished the cyclization of **97** (*Z*,*E*/*E*,*E*=6/4), whereas 10-*endo*-*trig* mode cyclization cannot be reasonnably involved (Figure 33).[13,59]

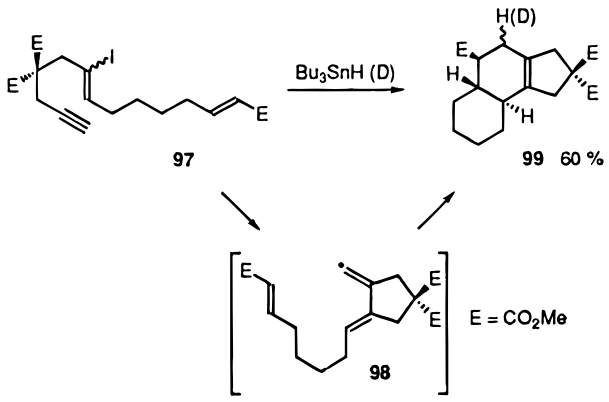


Figure 33.

This finding represents the first tandem radical cyclization−intramolecular Diels−Alder reaction which leads to a stereocontrolled synthesis of 6,6,5-membered tricyclic compounds from an acyclic polyunsaturated substrate in a one-pot sequence.

This new radical−pericyclic sequence may well lead to a general method for the stereocontrolled synthesis of many polycyclic molecules. This, and the above mentioned new cascade processes, are under active investigation in our laboratory. One major development should be the asymmetric version of these reactions that we are investigating using homochiral vinyl sulfoxides as chiral auxiliaries.

II. Transition Metal-Catalyzed Transformation of Acyclic Polyunsaturated Partners into Polycyclic Compounds

Carbon−carbon bond formation as well as functional group transformation are the most important and fundamental processes in modern synthetic organic chemistry. In particular, ring construction by intramolecular carbon−carbon bond formation from polyunsaturated compounds containing double or triple carbon−carbon bonds or allenic partners is very attractive and promising for the synthesis of polycyclic frameworks. The rate accelerations provided by catalysis enhances the synthetic application of reactions that usually require very drastic conditions. A very spectacular example exhibiting such a dramatic effect is the cyclotrimerization of alkynes whose first example was published in 1866 by Berthelot:[60] ethyne was trimerized in harsh conditions to give benzene in 3% yield. To date the transition metal-catalyzed version of this reaction has become one of the most powerful methods for the synthesis of complex polycyclic molecules.[61] On a more general point of view, reductive coupling of unsaturated partners, alkenes, alkynes, allenes etc., catalyzed by low-valent transition metal complexes, would constitute the most promising tool for the construction of polycyclic molecules.[62−65]

However, purely thermal cycloisomerization of polyunsaturated partners is very rare. Recently, K. K. Wang[66] reported a unique example of an original approach to a one step ABCD ring construction of the tetracyclic steroidal core, having an aromatic C ring. On heating, the acyclic enyne precursor **100** underwent a sequence of consecutive intramolecular transformations. In this unique cascade, the intermediate *o*-quinodimethane[67] was generated in a new fashion[68] from a thermally induced Myers cycloaromatization (related to the famous Bergman cycloisomerization of enediyne[69]) reaction of conjugated enyne-allenes. Then, this intermediate underwent a subsequent [4 + 2] cycloaddition reaction to deliver the tetracyclic steroidal skeleton **101** in fair yield (Figure 34). Even if this thermally induced achievement is very promising, it remains unique.

In contrast, during the past three years, several important papers have reviewed the tremendous development of transition metal catalysis in this field.[70−72] However, examples of transition metal complexes catalyzing synthetic transformations which illustrate the efficient and elegant strategy 0 →

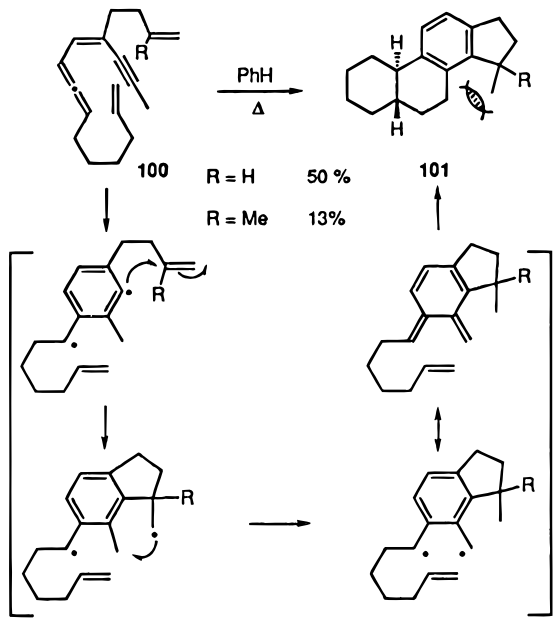


Figure 34.

ABCD in the construction of tetracyclic skeletons remain rare. In this survey, we will shortly describe some of the most prominent contributions devoted to this goal, before disclosing our own work aimed at the discovery of a very fast and selective entry, at will, to the related diterpene families: phyllocladane and kaurane.

1. The Cobalt Route

The first author who demonstrated the efficiency of intramolecular versions of transition metal-catalyzed reductive coupling of polyunsaturated partners was K. P. C. Vollhardt at Berkeley who reported the cobalt-catalyzed cocyclization of diynes with alkynes[62] and in a few cases with alkenes.[73−76] In a selected and illustrative example,[77] the cyclopentadienyldicarbonyl cobalt complex catalyzed the cyclotrimerization of the triyne **102**, the resulting benzocyclobutene underwent in refluxing decane a thermal ring opening to the corresponding orthoquinodimethane which gave a final [4 + 2] thermal cycloaddition to deliver the entire steroid skeleton (Figure 35).

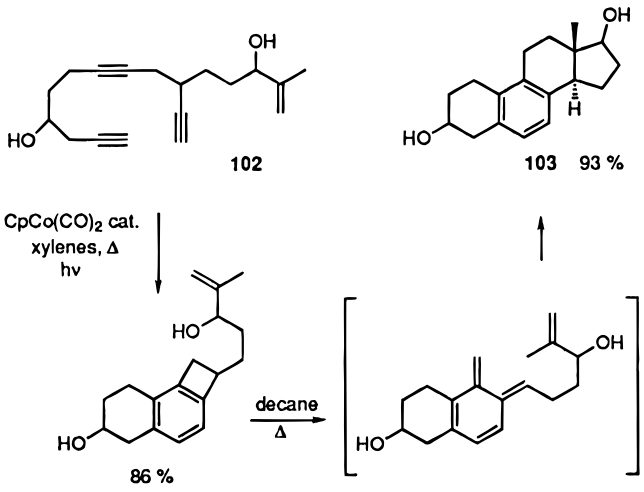


Figure 35.

2. The Palladium-Catalyzed Avenue

The very recent literature shows that palladium catalysts are capable of a wide range of polycyclization processes. Two recent reviews give a complete and up-to-date insight into this field.[71,72] Herein, we just would like to recall the most spectacular and efficient achievement in terms of number of new carbon−carbon bonds and rings being formed.

Negishi and co-workers have shown that vinyl−palladium intermediates generated from the intramolecular addition of a haloalkene to a triple bond could be intramolecularly trapped by alkenes to deliver three or more rings. This sequence has been named by Negishi "zipper" cyclizations.[78] In a very elegant work, he was able to realize a one-step construction of a steroid skeleton[79] (Figure 36).

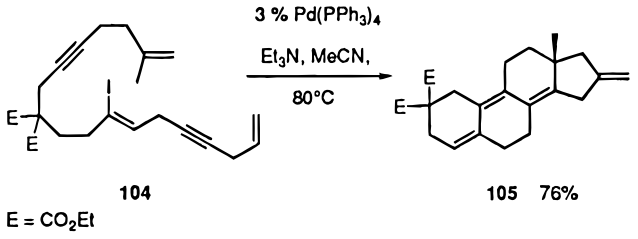


Figure 36.

On the other hand, Trost *et al.* have developed very simple and powerful palladium-catalyzed enyne cyclizations.[80] This cycloisomerization reaction of 1,6-enynes to dimethylene cycloalkanes suppresses the need for vinyl halides. In sharp contrast with the Heck reaction, the initial step is not an oxidative addition of an alkenyl halide into the Pd(0) catalyst but instead, acetic acid is oxidatively added to the catalyst to generate a crucial hydropalladium intermediate, the actual catalyst, which promptly adds to the terminal alkyne in a chemo- and regioselective fashion.[81] A significant number of rings can be created in this cascade process: Trost has shown that using the following heptenyne **106** (Figure 37), the heptaspirane **107** is formed in 77% yield.[82]

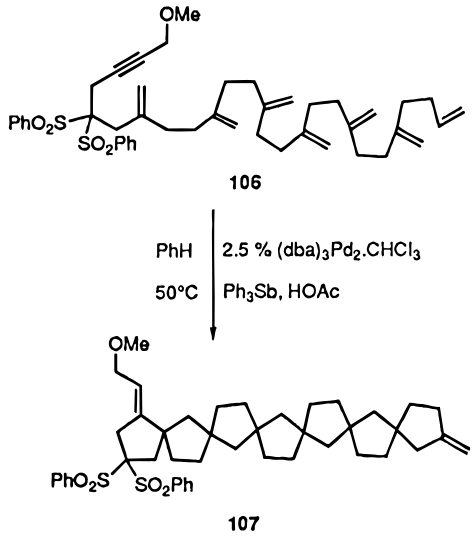


Figure 37.

Conditions have also been found (Figure 38), in order to operate in tandem mode the palladium-catalyzed cycloisomerization of enyne, leading to a 1,3-diene, with an intramolecular Diels−Alder reaction.[83]

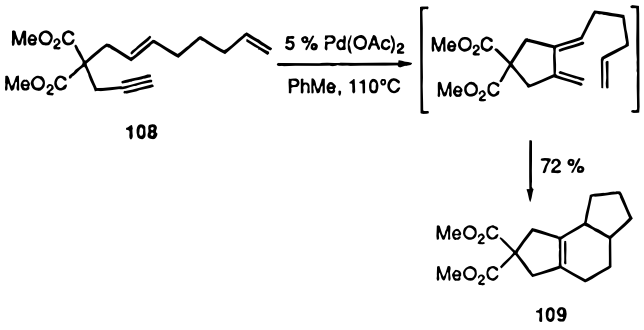


Figure 38.

Moreover, cycloisomerization of enediyne such as **110** allowed an entry to a new reaction cascade: diyne cycloisomerization and subsequent electrocyclization; this process is stereoselective[71] (Figure 39).

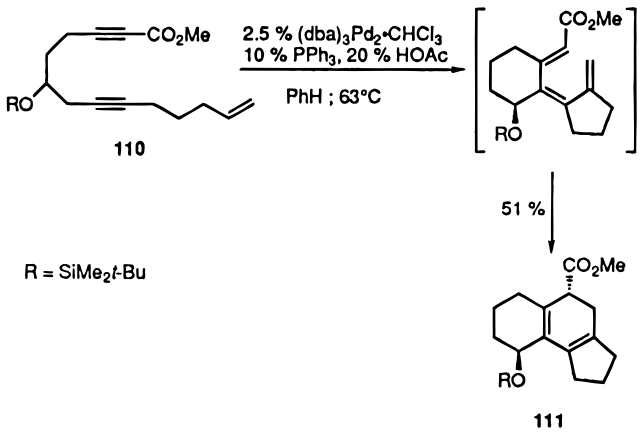


Figure 39.

In an independent work, de Meijere and co-workers[84] realized an ingenious similar cascade for the preparation of enantiomerically pure tricyclic compounds **113** starting from the homochiral 2-bromo dienyne **112** in good yields. In this sequence two consecutive Heck reactions allowed the formation of a triene which underwent a totally stereoselective 6-electrocyclization (Figure 40).

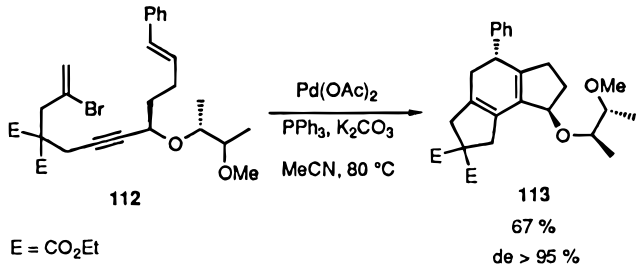


Figure 40.

Briefly, these very few and selected remarkable examples have demonstrated the high potentialities of using transition metal-catalyzed processes, here the Heck reaction in combination with a thermally induced reaction (electrocyclization, Diels−Alder). In these processes an impressive number of new carbon−carbon bonds and rings were created. In the following part of this paper, we will present a method for stereoselective access to diterpene frameworks first

from a sequence of three consecutive cycloaddition reactions which has been simplified to a one-pot process, by the discovery of a new cobalt-catalyzed enetriyne reaction featuring new cascade [ene-like]-[2 + 2 + 2]-[4 + 2] annulations.

3. En Route to a Cobalt-Catalyzed [Ene-like]-[2 + 2 + 2] and [4 + 2] Reactions

Diterpenes belonging to the phyllocladane **114** and kaurane **115** families (Figure 41) are widespread in nature.[85] Some representatives such as steviol, stevioside, hibaol, enmein, cafestol, atractyligenin, etc., display important biological properties[86] and, for example, the ent-kaurane group plays a fundamental role as biosynthetic precursor of the plant growth hormone gibberelins.[87]

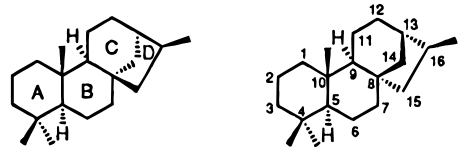


Figure 41.

Inspection of phyllocladane and kaurane molecules reveals the presence of a *trans-anti-trans* perhydrophenanthrene system in **114** and a *trans-anti-cis* one in **115**. The two families differ only in the stereochemistry of the B/C ring junction and they occur naturally in both optical forms. They also have in common with the gibbane-type diterpenes a bridged C/D ring structure which consists of a bicyclo[3.2.1]-octane arrangement.

As a consequence, they have attracted a great deal of interest from synthetic chemists, and many approaches leading to these diterpenoids have been reported.[88] In most cases, the D ring was built in the last stage starting from a tricyclic intermediate. Some notable exceptions are the syntheses of (±)-hibaol by Kametani,[89] gibberelin A_1 by Mander,[90] and (±) cafestol,[91] (±) kaweol,[92] and (±) atractyligenin[93] by Corey. In the latter very elegant achievement, a complete stereoselective cyclization allowing the simultaneous elaboration of rings B and D was developed.

For our purposes, we were interested in the quest for a stereoselective approach to both families using a common synthetic pathway based upon a sequence of three consecutive cycloaddition reactions from a very easily accessible enediyne acyclic precursor. Our strategy, retrosynthetically depicted in Figure 42, featured a combination of very reliable transition metal-catalyzed annelation reactions: Trost palladium-catalyzed [3 + 2] cycloaddition,[94] Vollhardt [2 + 2 + 2] cobalt(I)-mediated cyclotrimerization[62] of bis(trimethylsilyl)ethyne with α,ω-diynes and finally, an intramolecular [4 + 2] cycloaddition reaction of an orthoquinodimethane, which was first investigated by Kametani.[89]

In connection with the fundamental problem of stereochemistry, we have to consider that the *o*-xylylene involved in the [4 + 2] cycloaddition process will react only via the *E* configuration,[67a] indicating that the absolute configuration at C_9 is without

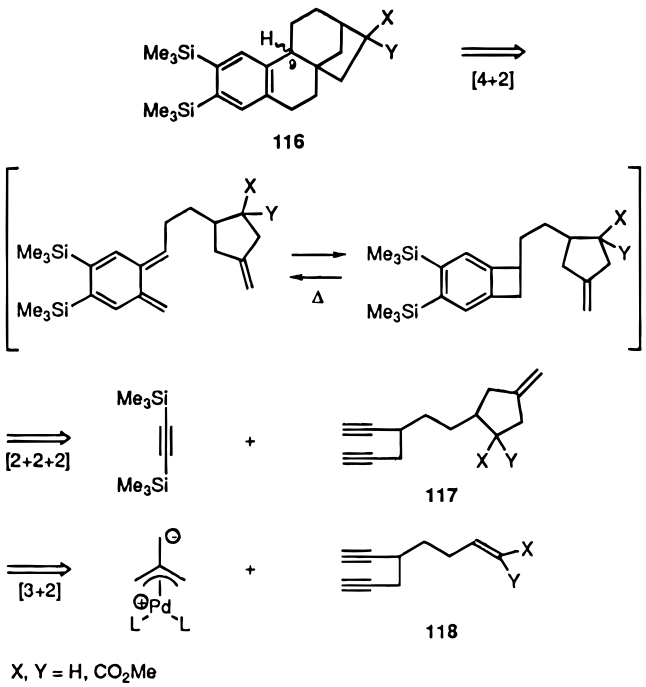


Figure 42.

significance; therefore, the absolute stereochemistry of the final compounds is directly associated with the enantioselective construction of the methylenecyclopentane. Directly related to the initial problem of relative stereochemistry due to the rigidity created by the presence of the cyclopentane moiety in the tether between the orthoquinodimethane and the dienophile is the fact that only two transition states involving the best overlapping are possible. In both cases, there is a "chairlike" arrangement of the carbon chain leading to the ring C (Figure 43). The dienophile can approach either from the bottom (**A**) or from the top (**B**) of the plane defined by the orthoquinodimethane. In **A**, a severe nonbonding interaction between H_1 and R exists; this transition state will deliver the kaurane skeleton. In **B** the nonbonding interaction H_1−R is not present and thus seems to be favored, therefore, providing a new route to phyllocladane skeleton.

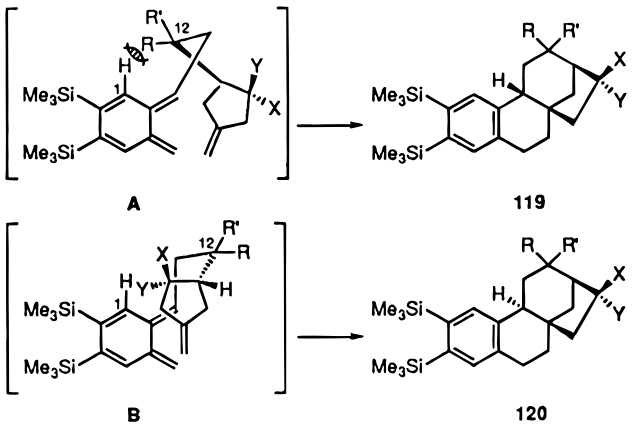
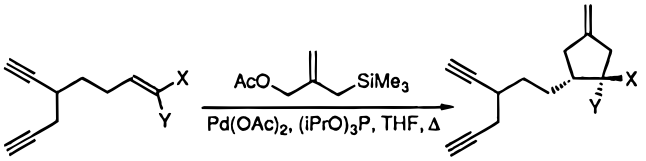


Figure 43.

In order to test our strategy and to gain a better understanding of the factors governing the stereoselectivity of the [4 + 2] cycloaddition process, we first examined the behavior of the acyclic diynes esters

121 and **122** whose preparation was straightforward starting from commercially available 1,5-hexadiyne.[95] The compounds were cyclized through the action of 2 equiv of [2-(acetoxymethyl)-3-allyl]trimethylsilane, 5 mol % of palladium (II) acetate, and 20 mol % of triisopropyl phosphite in refluxing tetrahydrofuran to afford the desired methylenecyclopentane adducts in high yields and in a completely diastereoselective manner for **123** (Figure 44). Moreover using the corresponding homochiral vinyl sulfoxides, we have found conditions to prepare methylenecyclopentanes in good diastereomeric excesses and after a simple chromatographic purification, in good optical purity.[96]



121 : X = CO_2Me; Y = H
122 : X = Y = CO_2Me
123 : X = CO_2Me; Y = H
124 : X = Y = CO_2Me

Figure 44.

Our initial attempts at cobalt(I)-catalyzed [2 + 2 + 2] cycloaddition reactions were conducted according to the regular protocol.[97] Much to our surprise, we obtained a 1:1 mixture of two inseparable benzocyclobutenes in which the double bond had migrated into the endocyclic position (Figure 45). Control experiments showed that no double-bond migration occurred when the enediyne was refluxed in bis-(trimethylsilyl)ethyne (btmse) under irradiation for 24 h in the absence of cobalt catalyst.

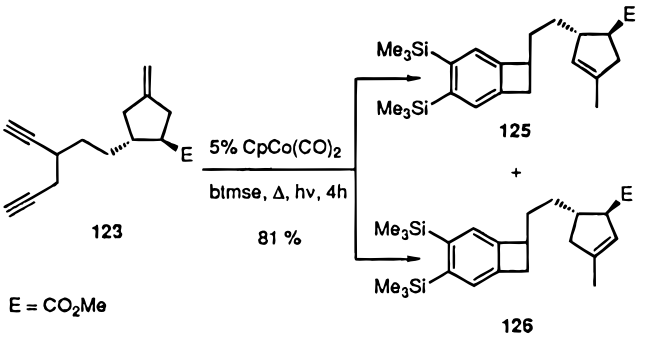
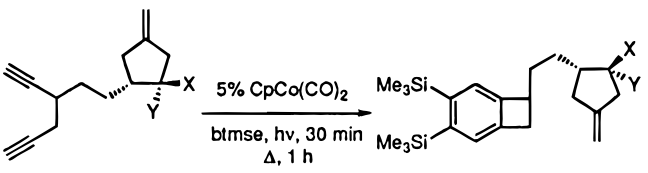


Figure 45.

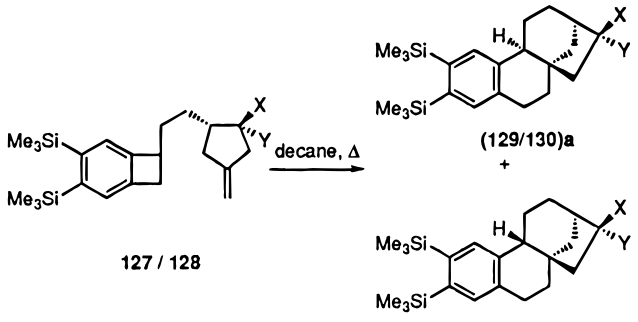
Thus, we anticipated that new cobalt species resulting from the partial decomposition of the catalyst due to a too long reaction time was at the origin of the migration. Gratifyingly, exposure of **123** and **124** to a catalytic amount of $CpCo(CO)_2$ in boiling btmse and irradiation for 30 min furnished the desired benzocyclobutenes in very high yields (Figure 46).



123 or 124
127 : X = CO_2Me ; Y = H ; 81 %
128 : X = Y= CO_2Me ; 85 %

Figure 46.

Thermolysis of these methylenecyclopentene derivatives in refluxing decane completed the preparation of the tetracyclic compounds **129** and **130** in a diastereoselective manner (5:1 and 10:1 respectively). A combination of 2D-NMR and X-ray crystallographic techniques[98] have unambiguously established a *trans* B/C ring junction, for the major stereomer, characteristic of the phyllocladane skeleton (Figure 47).



X = CO_2Me ; Y = H ; 90 % ; 129a/129b = 5/1
X = Y = CO_2Me ; 90 % ; 130a/130b = 10/1

Figure 47.

It is interesting to note that the overall yields of the major stereomer, from commercially available 1,5-hexadiyne, were 40% and 38% respectively for this eight-step sequence.

Undoubtedly, the high diastereoselectivity observed in favor of the phyllocladane formation can be attributed to the severe nonbonding interaction which exists in the transition state **A** (see Figure 43). In order to confirm this effect, we studied the case where an acetal group was present on carbon 12. The presence of this sterically demanding group, as expected, improved the stereoselective access to the phyllocladane family at a 32:1 level. *A contrario* we thought that the presence of a carbonyl substituent would decrease, at least partially, the nonbonding interaction and consequently increase the ratio of kaurane-type framework. That was indeed the case but unfortunately the 58:42 ratio still in favor of the phyllocladane type was useless for further synthetic applications.[99] Nevertheless this sequence of three consecutive cycloaddition reactions allowed the formation of seven carbon−carbon bonds in a highly controlled regio-, chemo-, and stereoselective manner.[100]

Concentrating upon a stereoselective access to the kaurane family, we decided to study the influence of the presence of substituents in the α or α' allylic endocyclic position of the methylenecyclopentane unit (Figure 48).

The situation seems to be clear that in the case of α-disubstitution the steric interaction between E and the orthoquinodimethane moiety will add to the nonbonding interaction already mentioned and we should obtain highly stereoselectively the phyllocladane skeleton. On the other hand, when the substituents are in the α' position, the steric interaction between E and the orthoquinodimethane will exist only in the phyllocladane approach. Thus, a precursor having a carbonyl group on C_{12} should lead stereoselectively to the kaurane family (Figure 48).

The needed methylenecyclopentane precursors were not accessible through Trost methodology, and we

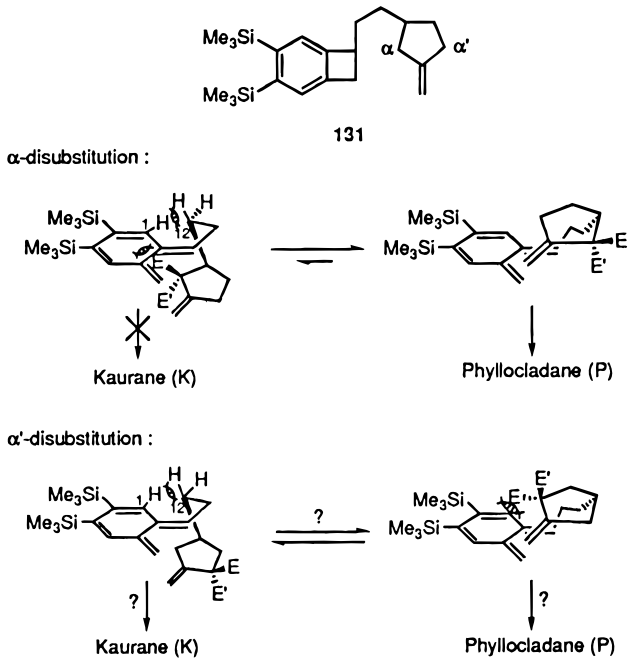


Figure 48.

then decided to reinvestigate the Conia ene reaction[101] (Figure 49).

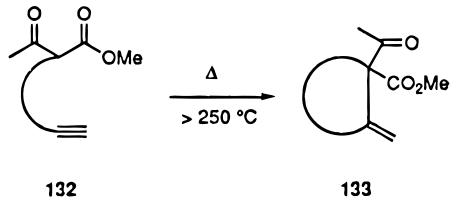


Figure 49.

Considering a [ene-like]-[2 + 2 + 2]-[4 + 2] sequence possible in order to build the diterpene skeletons the needed acyclic precursors are now the simple acyclic triynes **135** and **137** (Figure 50).

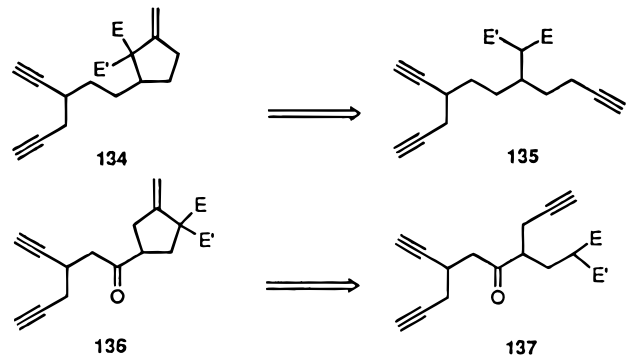


Figure 50.

This new strategy offers the unique opportunity to effect a one-pot process to build the phyllocladane and kaurane skeletons.

Gratifyingly, we found that cyclopentadienyldicarbonylcobalt was a very efficient catalyst for the "Conia-ene reaction". Studies realized on the model compound **138** showed that the corresponding methylenecyclopentane was obtained in 93% yield when submitted to 5 mol % of $CpCo(CO)_2$ in refluxing benzene for 1 h 30 min. In that case, no double-bond migration was observed contrary, to the case in boiling xylenes. This new catalytic reaction could even be carried out in refluxing tetrahydrofuran albeit in lower yield (Figure 51).[102]

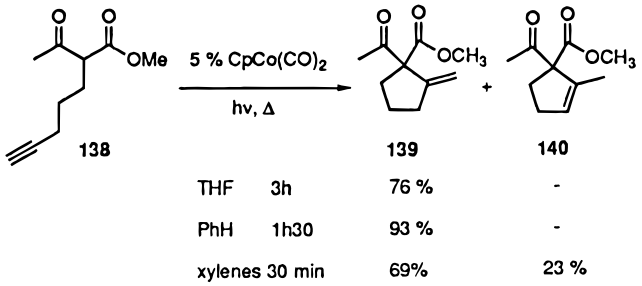


Figure 51.

This new cobalt-catalyzed cycloisomerization of ϵ-acetylenic β-keto ester enhances the synthetic utility of this thermal[103] or Lewis acid[104] promoted reaction.

Interestingly, this reaction turned out to be very chemoselective. In the presence of a catalytic amount of $CpCo(CO)_2$ the β-keto ester **141** furnished the bicyclo[3.2.1]octane derivative in 70% yield, indicating the total chemoselectivity of this cycloisomerization. When the reaction was performed under the cyclotrimerization conditions (btmse as solvent) not even trace amounts of benzocyclobutene adduct was detected showing the total selectivity of this new catalysis: cycloisomerization *versus* [2 + 2 + 2] (Figure 52).

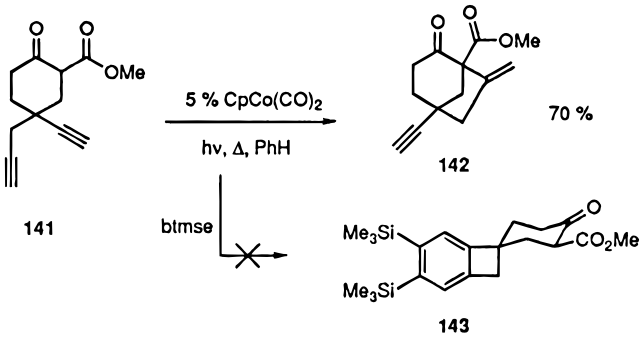


Figure 52.

Moreover, this reaction was found to be highly diastereoselective and could control the relative stereochemistry of two contiguous stereogenic centers (Figure 53).[105]

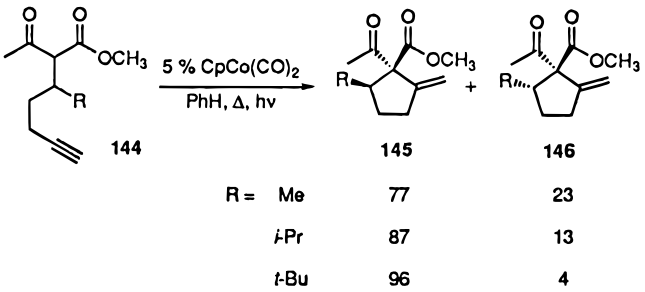


Figure 53.

The observed diastereoselectivities could be reasonably explained by the conformational rigidity of the enol-yne cobalt(I) complex, which is the effective participant in the cyclization as shown in our proposed mechanism (Figure 54). In fact, the process

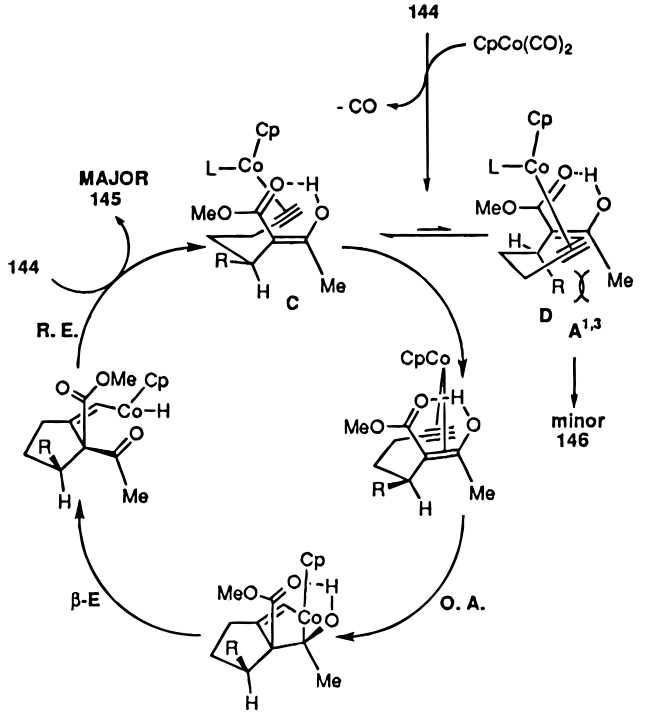


Figure 54.

of the complexation entails the coplanarity of the enolic double bond and the triple bond, thus creating an allylic 1,3-strain between the methyl group and the bulky substituents in β' position (rotamer D).

According to the increasing size of the β' substituents, the complex **C** will be more favored and the diastereomeric excess will increase. The importance of this allylic 1,3-interaction was confirmed by the results observed with the phenyl ketone derivative **148**. In this case, the diastereoselectivity was total (Figure 55).[106]

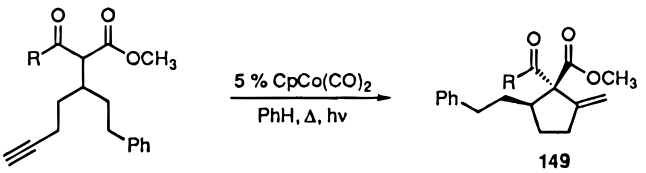


Figure 55.

Since cobalt(I) species catalyze the cycloisomerization of ϵ-acetylenic β-keto esters to form highly functionalized methylenecyclopentanes, we could attempt to combine all operations in a cascade process (Figure 56).

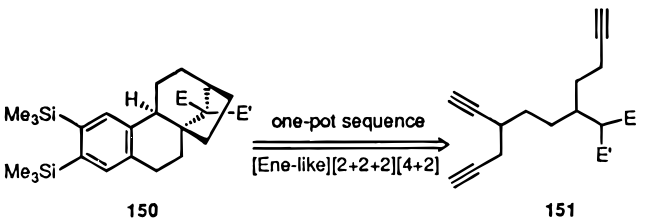
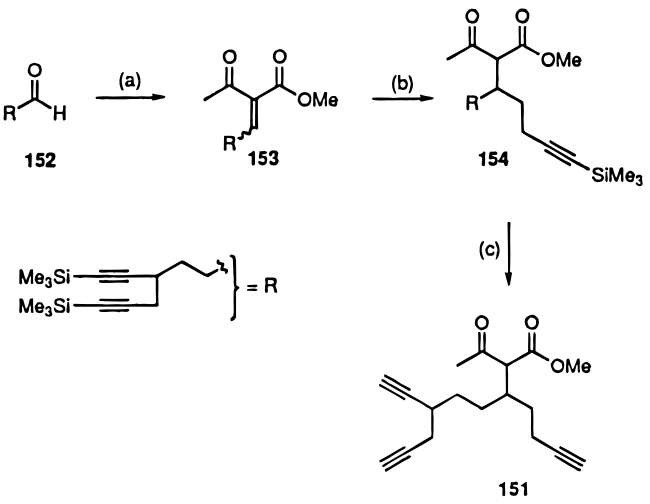


Figure 56.

The needed triyne **151** was efficiently synthesized in three steps from the known aldehyde **152**[100] in 66% overall yield according to Figure 57.



(a) $TiCl_4$, $CH_3COCH_2CO_2Me$, THF, pyridine, 0°C, 75% (b) THF, -78°C, $ClSiMe_3$, CuCN.2LiCl (2 equiv), $Me_3SiC{\equiv}CCH_2CH_2MgCl$, 94% (c)THF, *n*-$Bu_4NF$, 0°C, 94%

Figure 57.

Our initial attempts did not lead to formation of the tetracyclic compounds but gave intractable materials and trace amounts of benzocyclobutenes in which the double bond had migrated in the thermodynamically more stable endocyclic position (Figure 58).

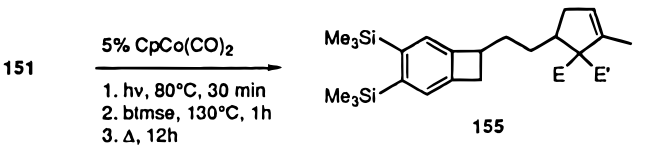
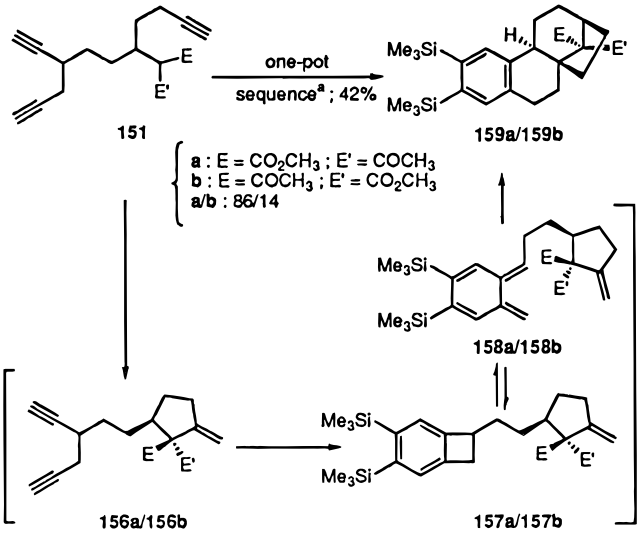


Figure 58.

As mentioned previously, this migration resulted from a partial decomposition of the catalyst due to a too long reaction time. In order to circumvent this migration and to achieve the one-pot sequence, we added a strong donor ligand such as (diphenylphosphino)ethane (dppe) which is able to strongly associate with the cobalt species.[107]

Furthermore, treatment of the triyne **151** with 5 mol % of $CpCo(CO)_2$ under sun lamp irradiation at 80 °C for 8 h produced a diastereomeric mixture of ene adducts. These underwent cycloaddition with bis(trimethylsilyl)ethyne to provide the corresponding benzocyclobutenes (each synthetic individual transformation was evidenced by TLC). Five mole percent of dppe was then added; the reaction mixture was heated in refluxing decane for 12 h; and gratifyingly, we observed the formation of a 86:14 mixture, corresponding to the diastereoselectivity of the initial ene reaction, of tetracyclic compounds in a 42% overall yield. Both stereomers possessed the phyllocladane structure as evidenced by X-ray crystallography (Figure 59).[108]



[a]Reaction conditions: (i) 5% $CpCo(CO)_2$, hv, 80°C, 8 h; (ii) btmse, 136°C, hv 15 min; (iii) 5% dppe, decane, 175°C, 12 h.

Figure 59.

This remarkable one-pot sequence of cascade cyclizations: ene-type, [2 + 2 + 2], [4 + 2] allowed the formation of six carbon−carbon bonds and four rings with a total regio- and chemoselectivity and with a high level of diastereoselectivity from an acyclic precursor bearing three uncontrolled stereogenic centers. Moreover, and as expected, the [4 + 2] cycloaddition reaction was totally stereoselective and delivered only tetracyclic systems having the *trans* B/C ring junction.

At this point, the ultimate goal was to try to achieve a stereoselective access to the kaurane skeleton following an identical strategy. In order to maximize our chances to have the desired inversion of stereoselectivity, we decided to study the case of triyne **160** having a carbonyl group on the tether between the 1,5-hexadiyne unit and the β-keto ester (Figure 60). Unfortunately, the cascade process was unsuccessful in this case due to a competitive participation of the carbonyl group in the cyclization to deliver **161**.

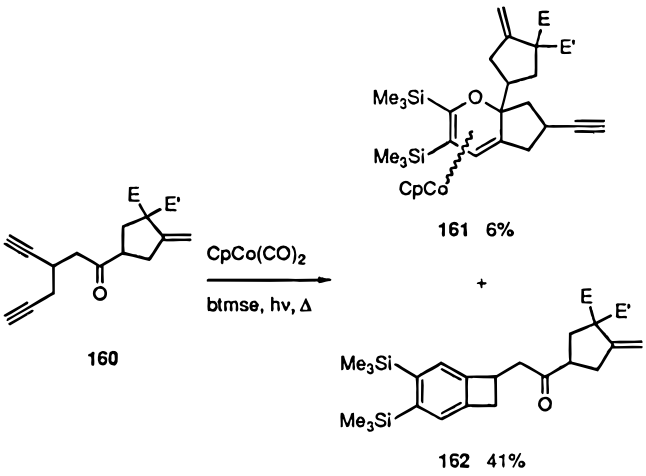
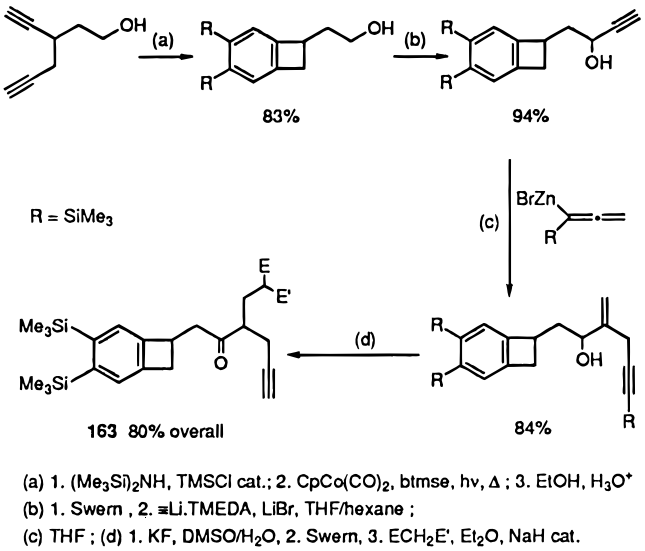


Figure 60.

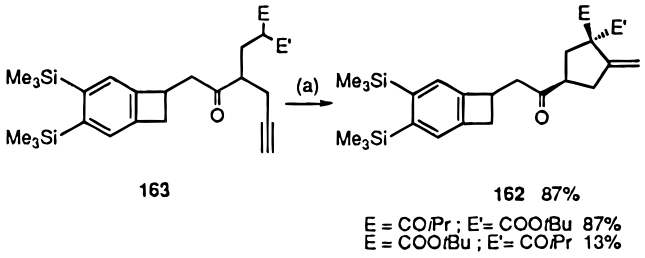
We then decided to prepare the benzocyclobutene **163** following the sequence depicted in Figure 61.



(a) 1. $(Me_3Si)_2NH$, TMSCl cat.; 2. $CpCo(CO)_2$, btmse, hv, Δ ; 3. EtOH, H_3O^+
(b) 1. Swern , 2. ≡Li.TMEDA, LiBr, THF/hexane ;
(c) THF ; (d) 1. KF, DMSO/H_2O, 2. Swern, 3. ECH_2E', Et_2O, NaH cat.

Figure 61.

Having this benzocyclobutene in hand, we could study the synergic influence of an α' substituent on the methylenecyclopentane partner and of the presence of a carbonyl group on the tether. The required methylenecyclopentane was obtained in 87% yield as a 87:13 diastereomeric mixture (Figure 62).



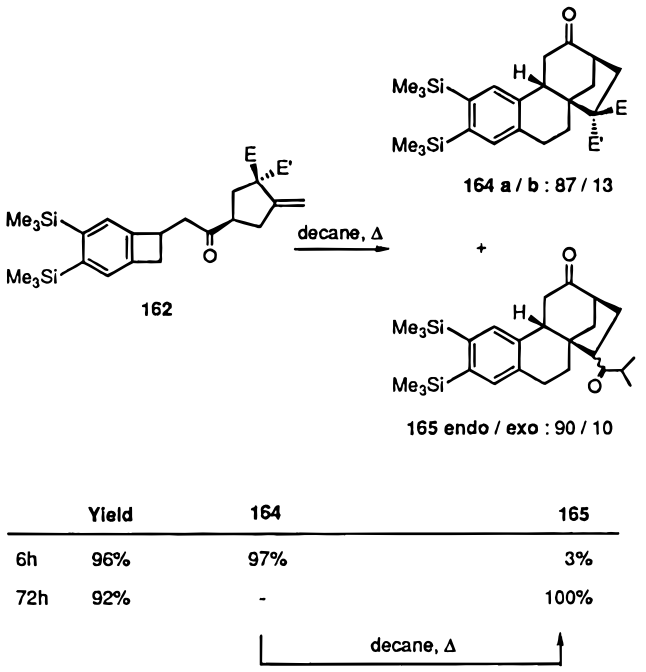
(a) $CpCo(CO)_2$, PhH, hv, Δ, 2h30

Figure 62.

When this compound was heated in refluxing decane for 6 h, a very clean reaction was observed and a mixture of tetracyclic compounds was isolated in a 96% overall yield. A partial thermally initiated decarboxylation occurred. When the reaction mixture was refluxed for 72 h, the decarboxylation was complete and an *endo*−*exo* mixture in a 9:1 ratio of tetracyclic compounds **164** and **165** was isolated (Figure 63). We were pleased to determine that both diastereomers have the *cis* B/C ring junction of the kaurane family.[109]

Finally, we have been able to prepare in a one-pot sequence the tetracyclic system belonging to the phyllocladane skeleton by using a cascade of cyclization reactions: [ene-type], [2 + 2 + 2], [4 + 2]. This concise strategy can be perceived as an illustration of the very high performance of Co(I) catalysis. Moreover, a simple change in the position of the β-keto ester substituent relative to the tether afford a totally stereoselective entry to the related kaurane family. However, in this case a one-pot process has not been achieved yet.

We are currently devoting a great effort in our laboratory to define conditions which will allow a cascade process in the latter case as well as the



	Yield	164	165
6h	96%	97%	3%
72h	92%	-	100%

decane, Δ

Figure 63.

application of this very efficient strategy to the total synthesis of natural products belonging to both families.

Summary and Outlook

In this paper, we have shown the major advancements realized in the growing field of cascade chemistry in order to consecutively form regio-, chemo-, and stereoselectively several new carbon−carbon bonds in a single-step process by using radical-mediated and transition metal-catalyzed reactions. These approaches have already allowed very impressive and economical construction of unnatural and natural polycyclic compounds of very high molecular complexity. However, we feel that most of the cascade strategies presented in this survey are still in their infancy. The initial achievements should stimulate the synthetic community to pursue further works; notably to develop more efficient combinations of reactions which can elegantly solve problems of increasing molecular complexity.

Acknowledgments

The author is grateful for the important efforts of his collaborators: Dr. Corinne Aubert, Dr. Anne-Lise Dhimane, and Dr. Louis Fensterbank in the preparation of this manuscript and to a superb group of talented co-workers who have been identified in the references. The author's own work mentioned in this article was financially supported by the French Ministry of Education, the Centre National de la Recherche Scientifique, and the companies Rhône-Poulenc, Roussel Uclaf, and Glaxo.

References

(1) 1 (a) Davies, S. G. *Organotransition Metal Chemistry: Applications to Organic Synthesis*; Pergamon: Oxford, 1986. (b) McQuillin, F. J.; Parker, D. G.; Stephenson, G. R. *Transition Metal Organometallics for organic synthesis;* Cambridge University Press: Cambridge, 1991.
(2) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (c) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*, Academic Press: London, 1991.
(3) Trost, B. M. *Science* **1991**, *254*, 1471.
(4) (a) Hall, N. *Science* **1994**, *266*, 32. (b) Ho, T. L. *Tandem Reactions in Organic Synthesis*; Wiley-Interscience: New York, 1992. (c) Tietze, L. F.; Beifuss, U. *Angew Chem., Int. Ed. Engl.* **1993**, *32*, 131. (d) Wender, P. A.; Miller, B. L. *Organic Synthesis, Theory and Applications*; Huddlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 27−67.
(5) Curran, D. P. In *Advances in Free Radical Chemistry*; Tanner D. D., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 1, p 121.
(6) (a) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943. (b) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (c) Curran, D. P.; Kuo, S. C. *J. Am. Chem. Soc.* **1986**, *108*, 1106.
(7) Yadav, J. S.; Praveen Kumar, T. K.; Gadgil, V. R. *Tetrahedron Lett.* **1992**, *33*, 3687.
(8) (a) Stork, G.; Mook, R., Jr; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (b) Stork, G. *Selectivity, A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; VCH: Weinheim, 1984; pp 281−298.
(9) (a) Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351. (b) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564.
(10) Janardhanam, S.; Shanmugam, P.; Rajagopalan, K. *J. Org. Chem.* **1993**, *58*, 7782.
(11) (a) Chen, Y.-J.; Chen, C. M.; Lin, W.-Y. *Tetrahedron Lett.* **1993**, *34*, 2961. (b) Chen, Y.-J.; Lin, W.-Y. *Tetrahedron Lett.* **1992**, *33*,-1749.
(12) Santagostino, M.; Kilburn, J. D. *Tetrahedron Lett.* **1994**, *35*, 8863.
(13) Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4843.
(14) Beckwith, A. L. J.; Roberts, D. H.; Schiesser, C. H.; Wallner, A. *Tetrahedron Lett.* **1985**, *26*, 3349.
(15) (a) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890. (b) Stork G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (c) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9.
(16) (a) Johnson, W. S.; Chenera, B.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 493. (b) Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Barlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 497.
(17) Breslow, R.; Olin, S. S.; Groves, J. T. *Tetrahedron Lett.* **1968**, 1837.
(18) Lallemand, J. Y.; Julia, M.; Mansuy, D. *Tetrahedron Lett.* **1973**, 4461.
(19) (a) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759 and references cited therein. (b) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427.
(20) Zoretic, P. A.; Weng, X.; Casper, M. L.; Davis, D. G. *Tetrahedron Lett.* **1991**, *32*, 4819.
(21) (a) Zoretic, P. A.; Shen, Z.; Wang, M.; Ribeiro, A. A. *Tetrahedron Lett.* **1995**, *36*, 2925. (b) Zoretic, P. A.; Zhang, Y.; Ribeiro, A. A. *Tetrahedron Lett.* **1995**, *36*, 2929.
(22) Chen, L.; Gill, G. B.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 2593.
(23) Pattenden, G.; Smithies, A. J.; Walter, D. S. *Tetrahedron Lett.* **1994**, *35*, 2413.
(24) Begley, M. J.; Pattenden, G.; Smithies, A. J.; Walter, D. S. *Tetrahedron Lett.* **1994**, *35*, 2417.
(25) Saicic, R. N.; Cekovic, Z. *Tetrahedron Lett.* **1994**, *35*, 7845.
(26) Magnol, E.; Malacria, M. *Tetrahedron Lett.* **1986**, *27*, 2255.
(27) Nishiyama, N.; Kitajama, T.; Matsumoto, M.; Itoh, K. J. *J. Org. Chem.* **1984**, *49*, 2298.
(28) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500.
(29) (a) Agnel, G.; Malacria, M. *Synthesis* **1989**, 687. (b) Journet, M.; Magnol, E.; Agnel, G.; Malacria, M. *Tetrahedron Lett.* **1990**, *31*, 4445.
(30) Agnel, G; Malacria, M. *Tetrahedron Lett.* **1990**, *31*, 3555.
(31) (a) Journet, M.; Magnol, E.; Smadja, W.; Malacria, M. *Synlett* **1991**, 58. (b) Journet, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 1893.
(32) (a) Curran, D. P.; Van Elburg, P. A. *Tetrahedron Lett.* **1989**, *30*, 2501. (b) Curran, D. P.; Chen, M. H. *J. Am. Chem. Soc.* **1987**, *109*, 6558. (c) Cekovic, Z.; Saicic, R. *Tetrahedron Lett.* **1986**, *27*, 5893.
(33) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1964.
(34) (a) Journet, M.; Smadja, W.; Malacria, M. *Synlett* **1990**, 320. (b) Journet, M.; Malacria, M. *J. Org. Chem.* **1992**, *57*, 3085.
(35) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529.
(36) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525.

(37) Journet, M.; Lacôte, E.; Malacria, M. *J. Chem. Soc., Chem. Commun.* **1994**, 461.
(38) (a) Tietze, L. F.; Subba Roa, P. S. V. *Synlett* **1993**, 291. (b) Mandi, T.; Matsumoto, T.; Kawada, M.; Tsuji, T. *J. Org. Chem.* **1992**, *57*, 1326.
(39) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (b) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305.
(40) Wu, S.; Journet, M.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 8601.
(41) (a) Curran, D. P.; Shen, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 6051. (b) Brown, C. D. S.; Simpkins, N. S.; Clinch, K. *Tetrahedron Lett.* **1993**, *34*, 131. (c) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (d) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377.
(42) Bogen, S.; Journet, M.; Malacria, M. *Synlett* **1994**, 958.
(43) Alexakis, A.; Mangeney P., *Tetrahedron: Asymmetry* **1990**, *1*, 477.
(44) (a) Wilt, J. W.; Manavetz, L. L.; Zawadzki, J. F. *J. Org. Chem.* **1966**, *31*, 3018. (b) Sato, T.; Nakamura, N.; Ikeda, K.; Okado, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2399. (c) Ponaras, A. A.; Zaim, O. *Tetrahedron Lett.* **1993**, *34*, 2879. (d) Goodall, K.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3257. (e) Yao, Q.; Crich, D. *Tetrahedron* **1994**, *50*, 12305. (f) Mendenhall, G. D.; Protasiewicz, J. D.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1994**, *116*, 1718. (g) Clive, D. L. J.; Cantin, M. *J. Chem. Soc., Chem. Commun.* **1995**, 319. (h) Sato, J.; Chono, N.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1115.
(45) Bogen, S.; Malacria, M. To be published.
(46) Hudlicky, T.; Read, J. W. *Rearrangements of vinylcyclopropanes and related systems. In Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 899−970.
(47) Crich, D.; Fortt, S. M. *Tetrahedron Lett.* **1987**, *28*, 2895.
(48) (a) Beckwith, A. L. J.; Ingold, K. U. *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, p 161. (b) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1989**, *54*, 2681. (c) Giese, B.; Heinrich, N.; Horler, H.; Koch, W.; Schwarz, H. *Chem. Ber.* **1986**, *119*, 3528.
(49) Journet, M.; Malacria, M. *J. Org. Chem.* **1994**, *59*, 718−719.
(50) (a) Denis, R. C.; Rancourt, J.; Ghiro, E.; Boutonnet, F.; Gravel, D. *Tetrahedron Lett.* **1993**, *34*, 2091. (b) Denis, R. C.; Gravel, D. *Tetrahedron Lett.* **1994**, *35*, 4531.
(51) Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1992**, *33*, 7307.
(52) Weng, W. W.; Luh, T. Y. *J. Org. Chem.* **1993**, *58*, 5574.
(53) Borthwick, A. D.; Caddick, S.; Parsons, P. J. *Tetrahedron Lett.* **1990**, *31*, 6911.
(54) Journet, M.; Malacria, M. *J. Org. Chem.* **1994**, *59*, 6885.
(55) (a) Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* **1963**, *39*, 2147.(b) Singer, L. A.; Kong, N. P. *J. Am. Chem. Soc.* **1966**, *88*, 5213. (c) Kampmeier, J. A.; Fantazier, R. M. *J. Am. Chem. Soc.* **1966**, *88*, 1959. (d) Curran, D. P.; Kim, D. *Tetrahedron* **1991,** *32*, 6171. (e) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969.
(56) Zahouily, M.; Journet, M.; Malacria, M. *Synlett* **1994**, 366.
(57) (a) Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002. (b) Gras, J. L.; Bertrand, M. *Tetrahedron Lett.* **1979**, 4549. (c) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992.
(58) For reviews see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (c) Roush, W. R. *Intramolecular Diels-Alder Reactions. In Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 513−550.
(59) It has been shown that *endo*-radical processes had to be achieved on α,β-unsaturated ketones for the cyclization of large rings (10−20 membered). (a) Porter, N. A.; Chang, V. H. T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554. (b) Curran, D. P.; Seong, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 9401.
(60) Berthelot, M. *C. R. Acad. Sci.* **1866**, *62*, 905.
(61) Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539.
(62) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.
(63) Shore, N. E. *Chem. Rev.* **1988**, *88*, 1081.
(64) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047.
(65) Negishi, E-i. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S. Ed.; JAI Press: Greenwich, CT, 1989; p 117.
(66) Andemichael, Y. W.; Huang, Y.; Wang, K. K. *J. Org. Chem.* **1993**, *58*, 1651.
(67) (a) Oppolzer, W. *Synthesis* **1978**, 783. (b) Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Proced. Int.* **1991**, *23*, 237−272.
(68) Andemichael, Y. W.; Gu, Y. G.; Wang, K. K. *J. Org. Chem.* **1992**, *57*, 794.
(69) (a) Bharucha, K. N.; Marsh, R. M.; Minto, R. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 3120. (b) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.
(70) Trost, B. M. *Janssen Chim. Acta* **1991**, *9*, 3.
(71) Trost, B. M *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
(72) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2389.
(73) Malacria, M.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 5010.
(74) Dunach, E.; Halterman, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1985**, *107*, 1664.
(75) Johnson, E. P.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 381.
(76) Germanas, J.; Aubert, C.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 4006.
(77) Lecker, S. H.; Nguyen, N. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 857.
(78) Negishi, E-i. *Pure Appl. Chem.* **1992**, *64*, 323.
(79) Zhang, Y.; Wu, G-z.; Agnel, G.; Negishi, E-i. *J. Am. Chem. Soc.* **1990**, *112*, 8590.
(80) (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. (b) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34.
(81) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651.
(82) (a) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 791. (b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491.
(83) Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; Macpherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255.
(84) Meyer, F. E.; De Meijere, A. *Synlett* **1991**, 777.
(85) Nakanishi, K. In *Natural Products Chemistry*; Nakanishi, K., Goto, Y., Ito, S., Natori, S., Nozoe, S., Eds.; Kodansha Ltd.: Tokyo, 1974; Vol. 1, p 242.
(86) Hanson, J. R. *Nat. Prod. Rep.* **1988**, *3*, 211 and references cited therein.
(87) Beale, M. H.; Mc Millian, J. *Nat. Prod. Rep.* **1988**, *3*, 249 and references cited therein.
(88) Goldsmith, D. *The Total Synthesis of Natural Products*; John Wiley: New York, 1992; Vol. 8, pp 101−174.
(89) Kametani, T.; Suzuki, K.; Nemoto, H.; Fukumoto, K. *J. Org. Chem.* **1979**, *44*, 1036.
(90) Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626.
(91) Corey, E. J.; Wess, G.; Xiang, Y. B.; Sing, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717.
(92) Corey, E. J.; Xiang, Y. B. *Tetrahedron Lett.* **1987**, *28*, 5403.
(93) Sing, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187.
(94) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1.
(95) (a) Gotteland, J. P.; Malacria, M. *Tetrahedron Lett.* **1989**, *30*, 2541. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; p 312.
(96) Chaigne, F.; Gotteland, J. P.; Malacria, M. *Tetrahedron Lett.* **1989**, *30*, 1803.
(97) Halterman, R. L.; Nguyen, N. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1985**, *105*, 1379. Exposure of the diyne to refluxing btmse with simultaneous irradiation in presence of catalytic amount of $CpCo(CO)_2$ over 4 h.
(98) Gotteland, J. P.; Malacria, M.; Faure, A. *Acta Crystallogr.* **1990**, *C-46*, 1271.
(99) Gotteland, J. P.; Malacria, M. *Synlett* **1990**, 667.
(100) Aubert, C.; Gotteland, J. P.; Malacria, M. *J. Org. Chem.* **1993**, *58*, 4298.
(101) (a) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1. (b) Mandville, G.; Conia, J. M. *Nouv. J. Chim.* **1981**, *5*, 137. (c) Boaventura, M. A.; Drouin, J. *Bull. Soc. Chim. Fr.* **1987**, 1015.
(102) Stammler, R.; Malacria, M. *Synlett* **1994**, 92.
(103) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476.
(104) Snider, B. B. *Acc. Chem Res.* **1980**, *13*, 426.
(105) Cruciani, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 6677.
(106) Cruciani, P.; Aubert, C.; Malacria, M. To be published.
(107) Butenschön, H.; Kettenbach, R. T.; Krüger, C. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1066.
(108) Cruciani, P.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1995**, *60*, 2664.
(109) Cruciani, P.; Aubert, C.; Malacria, M. To be published.

CR9500186