Approaches Towards The Asymmetric Synthesis Of The Natural Alkaloid Palau'amine

And

Diastereoselective Formation Of 5-Vinyl Cyclopentenes From 1,6-Enynes.

Régis Dolaine

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

Department of Chemistry
McGill University
Montreal, Quebec, Canada
H3A2K6

One day in bloom, the next day scattered,

Life is a delicate flower.

Could you hope for it to last forever ?

To the One who had made sense of it all.

Acknowledgements

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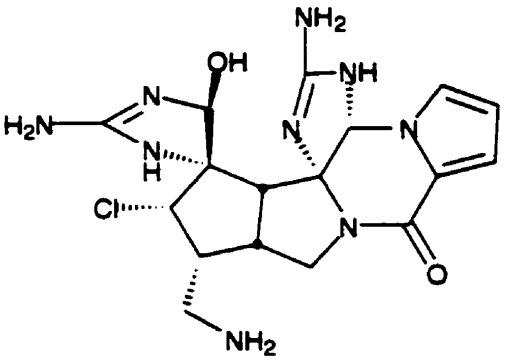
Table of Contents

Part I

Approaches towards the asymmetric synthesis of the natural alkaloid Palau'amine.

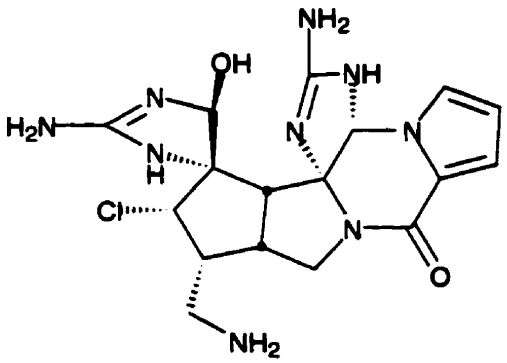
Abstract



Palau'amine

A strategy for the total synthesis of palau'amine is disclosed. The bias of a bicyclic framework is used as a key feature for the enantioselective synthesis of the highly functionalized hexasubstituted cyclopentane core of the molecule. A synthetic approach centering on a tin-catalyzed aldol and a Pauson-Khand reaction is presented. This pathway yielded a penta-substituted cyclopentane ring with four stereocenters positioned and the requisite functionalities to allow for further progress. Installation of the last stereocenter was investigated on a model substrate.

Résumé



Palau'amine

Une stratégie pour la synthèse totale de l'alkaloïde naturel palau'amine est présentée. Le biais d'un système bicyclique est utilisé en tant que clé de la synthèse énantiosélective de cette molécule et de son noyau cyclopentyl hautement fonctionalisé et hexasubstitué. Une approche synthétique centrée sur une réaction aldol catalysée par l'étain ainsi que sur une réaction de Pauson-Khand est présentée. Cette voie a permis la synthèse d'un cyclopentane penta-substitué avec quatre stéréocentres positionnés et comportant les fonctionalités requises pour permettre l'achèvement de la synthèse. L'installation du dernier stéréocentre est étudiée sur un substrat modèle.

INTRODUCTION

1. Immunosuppression

The immunological response remains the main obstacle in the use of transplantation as a therapy for organ failure. Since the first renal transplant performed in 1952, a large amount of research has been carried out, aiming at agents that could render the immune system inert to the graft without harming the non-specific host resistance.

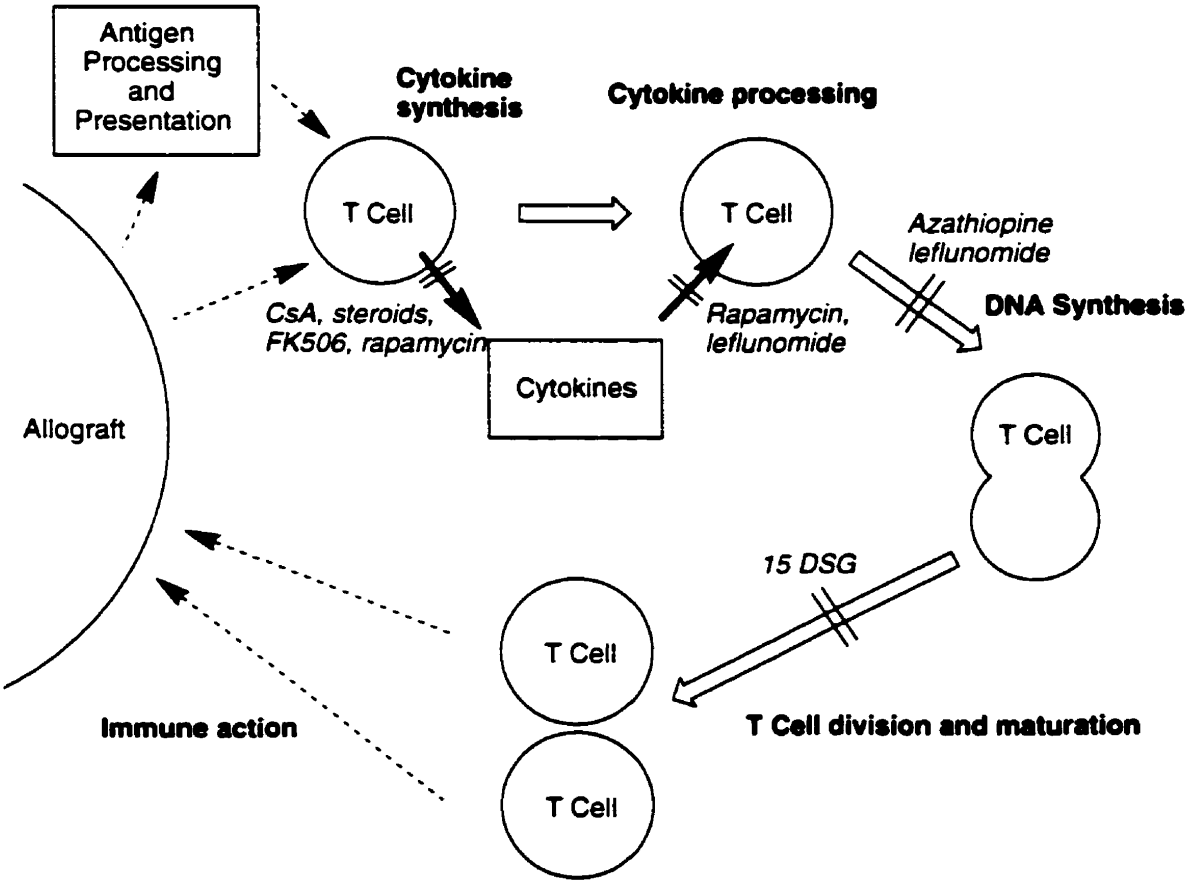
Various approaches were undertaken in four different fields, encompassing the chemical development of new pharmaceutical agents, the biological exploration of the immunological domain, the use of radiology as a physical method, as well as more traditional medical treatments such as surgical therapies. The chemical agents have and still continue to play a dominant role in every day transplant strategies and even in the latest developments where entire limbs are grafted onto patients.

The discovery of drugs such as corticosteroids, cyclosporine A (CsA), azathiopine and FK 506 have each allowed important progress in the transplantation field. Clinical studies are now being carried out on molecules such as rapamycin, 15-deoxyspergualin (15 DSG) and leflunomide. These drugs have different modes of action, unveiling the cell transduction pathway and the mechanism of the immune response.

T cells play a central role in the control of the human immune system of stimuli such as grafts. The pharmacological inhibition of their activation process thus provides an approach for the clinical regulation of the immune system necessary to the success of the transplantation.

Activating an antigen receptor of a T cell triggers a considerable sequence of events mobilizing the entire cell, in a developmental fashion.[1] Over 200 genes are involved in this process and a considerable portion of the genome is suggested to be made transcriptionally active as T lymphocytes go from a dormant state to a fully immunologically operative configuration ready for cell division.[2] Indeed the cell must cope with an acceleration of metabolism and the initiation of the cell cycle which requires that nearly all proteins be doubled before cell division.

Scheme 1 : The immune response and potential sites for its regulation



The T cell will require approximately 2 hours after the first interaction with the allograft to commit to the response, corresponding to a sequence of events that might be classified in four phases (Scheme 1). First of all, the T cell will synthesize cytokines, signaling agents necessary to the coordination of other immunologically involved entities such as B cells, and to the full activation of T cells themselves. At various sub-levels, this step is the direct target of corticosteroids, CsA, FK506 and rapamycin.

Upon co-stimulation by these specific cytokines, the T cell is driven to a proliferation cycle. Rapamycin and leflunomide have been recognized as inhibitors to the T cell processing of the messenger cytokines.

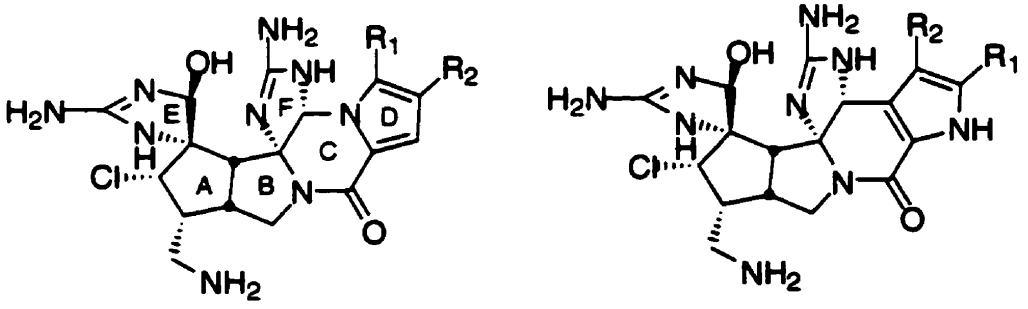
Upon successful signaling, the T cell enters a third phase where nucleotide synthesis is undertaken to provide for the duplication of the DNA material before mitosis. Azathiopine and leflunomide have been shown to prevent the generation of purine and pyrimidine.

In the last stage, T cell division is followed by differentiation and the maturation of the new cells produced, in a process inhibited by 15 DSG. These now active cells, present in great numbers, can attack the allograft. After a pre-programmed duration, the T cell undergoes apoptosis, avoiding a too high concentration that could lead to an auto-immune aggression.[3]

2. Palau'amine discovery and activity

In 1993, the novel alkaloid palau'amine **1** was isolated from the Belau sponge *Stylotella aurentium* by Kinnel *et al.*[4] This off-white amorphous solid of composition $C_{17}H_{23}ClN_9O_2$ (420.1669 MH^+, HRFABMS) was collected a second time in 1998 with its 4-bromo (**2**) and 4,5-dibromo (**3**) derivatives,[5] accompanied by the corresponding three ring D isomers (**4-6**) previously isolated by Kato *et al.*[6] under the name styloguanidine (Scheme 2).

Scheme 2 : Palau'amine and related molecules



Palau'amines

1. $R_1 = R_2 = H$
2. $R_1 = H$; $R_2 = Br$
3. $R_1 = R_2 = Br$

Styloguanidines

4. $R_1 = R_2 = H$
5. $R_1 = H$; $R_2 = Br$
6. $R_1 = R_2 = Br$

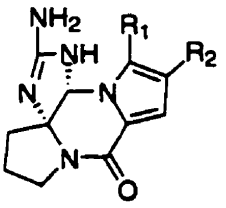
Early on in the discovery process, palau'amine was noticed for its activity in a number of biologically processes. First of all, palau'amine was found to be a more potent antibiotic than the related molecules **2-6**.

An additional feature was its antitumor activity, on the order of 0.3 µM for both P-388 and A-549 cell lines. Even more significant was the activity in the immunosuppression area, with a cytotoxicity assay against murine lymphocytes in the order of 3 µM, and a IC_{50} < 42 nM in the mixed lymphocytes reaction. Compounds **2-6** do not have similar potent activities in any of these assays. In addition, the acute toxicity of **1** in mice has been found to be relatively low (LD_{50} = 13 mg/kg ip). The level of the immunosupressive activity of

palau'amine is similar to those of currently used immunosupressants such as CsA and FK506. These remarkable antifungal, antitumor and immunosuppressive properties led to a patent application[7] by the discovery team as well as to the launch of preclinical studies.

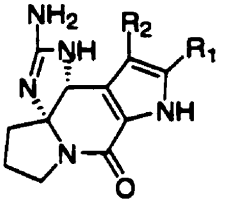
From a structural viewpoint, palau'amine is a hexacyclic ring system, of which five rings are fused to each other (Scheme 2). The last ring E is connected to ring A in a spiro fashion. The system is comprised of the pyrrole ring D, a lactam ring C, a halogen substituted five membered ring A, and two rings containing the guanidine functionality (E and F). The structure and connectivities were partially determined from the comparison with the previously described alkaloids of the phakellins (**7-9**)[8] and isophakellin (**10-11**)[9] families (Scheme 3).

Scheme 3 : Phakellins and isophakellins



Phakellins

7. $R_1 = R_2 = H$
8. $R_1 = H$; $R_2 = Br$
9. $R_1 = R_2 = Br$

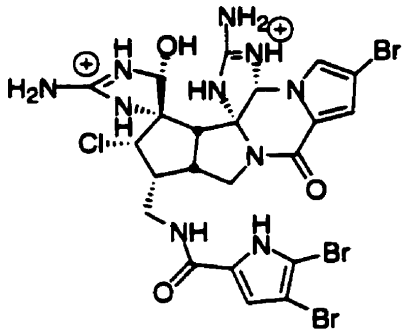


Isophakellins

10. $R_1 = R_2 = H$
11. $R_1 = R_2 = Br$

Enlarging the palau'amine family, Kobayashi *et al.* isolated in 1997, from a *Hymeniacidon* sponge, a novel and related alkaloid, konbu'acidin A (**12**), apparently derived from the N-acylation of compound **2** (Scheme 4).[10]

Scheme 4 : Konbu'acidin A



Konbu'acidin A (12)

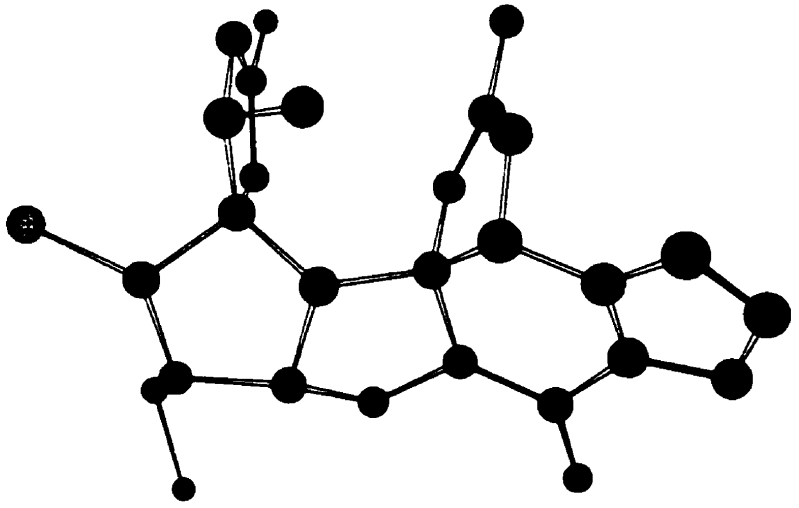
Adding to the structural complexity of alkaloid **1**, an unbroken string of 8 chiral centers is embedded in palau'amine. In particular, the assignment of the mixed aminal stereocenter is ambiguous. The shown configuration for palau'amine was established by Kinnel *et al.*[5] through weak NOE enhancements and in contradiction with their earlier communication[4] and the assignment of Kobayashi for konbu'acidin. From a synthetic viewpoint, the mixed aminal stereocenter as well as both stereocenters at the guanidine ring fusion can be hypothesized as being formed under thermodynamic control.

The absolute stereochemistry of **1** is unknown. The related dibromophakellins have been isolated in one enantiomeric form from *Phakellia flabellata*[8], and in the other enantiomeric form from *Pseudoaxinyssa cantharella*[11]. It is therefore possible that the both enantiomers of palau'amine coexist in nature.

3. The guanidine fork and possible mode of action

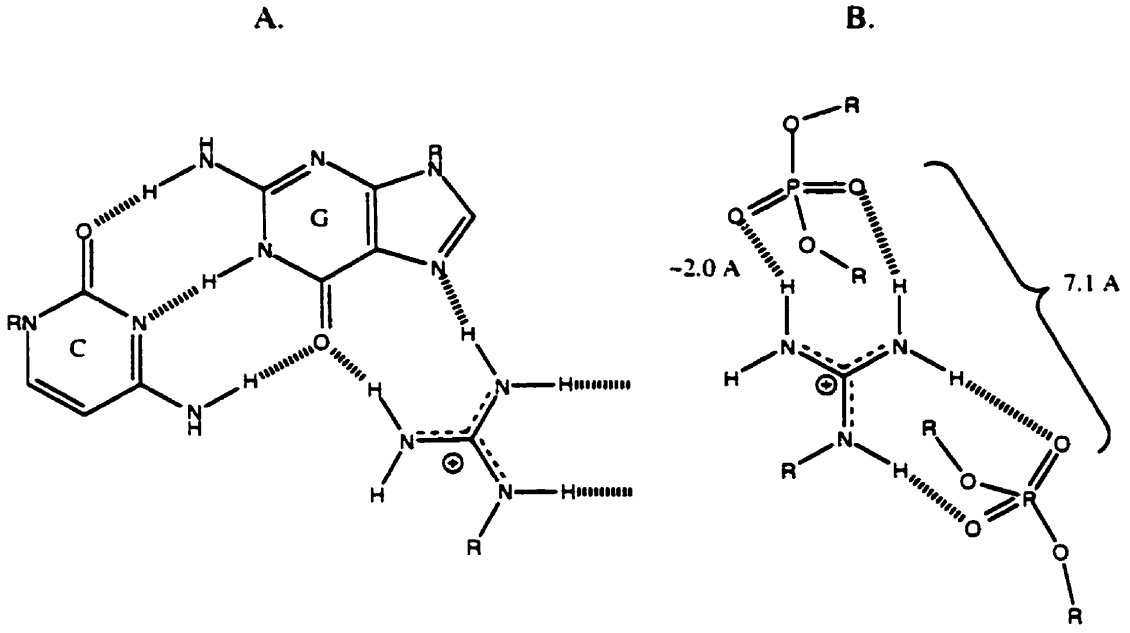
The mode of action of palau'amine remains unknown to this day. However, natural and artificial guanidine bearing compounds have repeatedly shown pronounced biological activities.[12] The two close guanidine functionalities can be hypothesized to play a key role in palau'amine biological activity. As seen in a three-dimensional view obtained on Chem3D (Scheme 5), the two guanidine residues are held rigidly on a tetracyclic scaffold.

Scheme 5 : 3D representation of palau'amine



Guanidine residues have been precedented to interact with DNA and RNA.[13] Interactions between guanidine functions and DNA or RNA can take place through hydrogen bonding with the guanine bases (Scheme 6, A)[14] or through electrostatic interactions with the phosphate backbones (Scheme 6, B)[15].

Scheme 6 : Guanidine interactions with DNA and RNA



Attempts at docking palau'amine onto various strands of DNA on a Macromodel workstation proved unsuccessful. The stringent geometrical characteristics of palau'amine prevented the simultaneous establishment of stabilizing interactions between the two guanidines and the bases and/or the phosphate skeleton.

Nevertheless, palau'amine has the potential for developing interactions with RNA in a specific manner, in the same way a single guanidine residue has been found to recognize a particular RNA strand thanks to the three-dimensional structure of that strand.[14,16]

In an alternate proposal, the activity of palau'amine could lie in its pyrrole moiety. This hypothesis reflects the discrepancies noted between the activities of palau'amine and the lack of any comparable biological activity for compounds **2-6**[5], as well as the lack of cytotoxicity reported for **12**[10]. Similarly, no cytotoxic activity were reported for mono- and di-bromophakellins. Unfortunately, unbrominated phakellin has never been reported and the comparable influence of bromination of the pyrrole ring in the phakellin series could not be evaluated.

4. Synthetic interest

The multiple activities of palau'amine clearly call for an in-depth study of this molecule. First, the total synthesis of palau'amine would provide a definitive proof of structure and stereochemistry. Additionally, attention will be paid to design a synthesis giving access to the related styloguanidine family.

Obtaining significant quantities of palau'amine, and also of relevant intermediates, would allow the study of its activity to be pursued in a greater length. In addition, the investigation of the biological function affected by these compounds would provide novel information on the immunosuppressive process and help the design of novel agents for the control of the specific response to allografts.

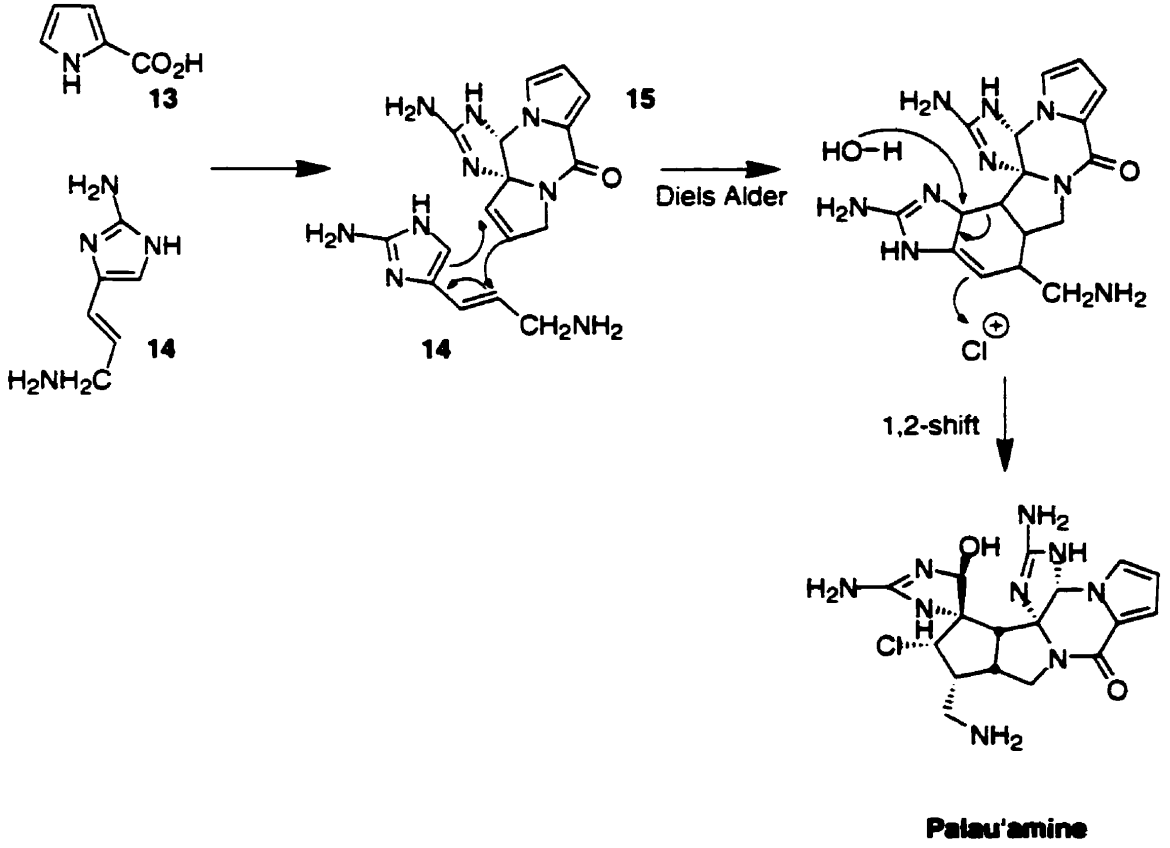
The total synthesis of the molecule itself provides the opportunity to develop our knowledge and chemical applications, as well as discover novel reactions.

The difficulties in the synthesis of palau'amines and styloguanidines reside in the central biscyclopentane system. More specifically, the key of the synthetic work lies in the successful preparation of the cyclopentane ring bearing six substituents, including five on the same face. This challenge is complicated by the density of functionalities and their related stereochemistry required for the installation of the two guanidine moieties.

5. The biosynthetic approach of Romo

Although the biogenesis of palau'amine remains to be elucidated, Kinnel and Scheuer proposed in 1998 a biosynthesis centering on the Diels-Alder reaction between pyrrole-2-carboxylic acid (**13**) and two equivalents of 3-amino-1-(2-aminoimidazolyl)prop-1-ene (AAPE, **14**).[5] Both pyrrole-2-carboxylic acid and AAPE precursors have indeed been identified as common metabolites in sponges, by König[17] and Wright[18] respectively. The dienophile is obtained from the condensation of pyrrole-2-carboxylic acid with the first equivalent of AAPE to provide 11,12-dehydrophakellin (**15**) (Scheme 7).

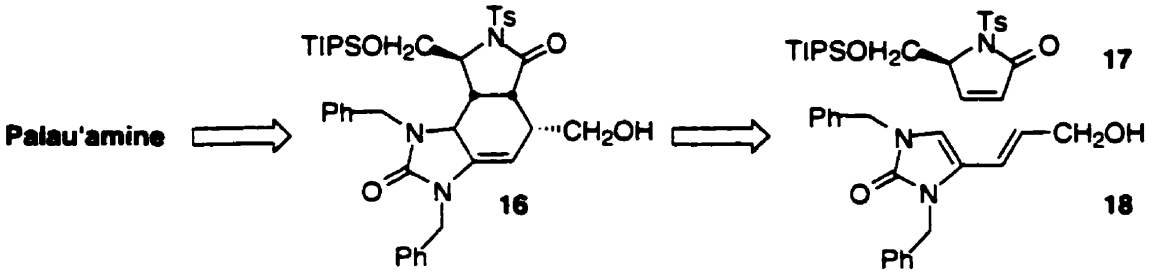
Scheme 7: Biosynthetic analysis



In a second step, a Diels-Alder cycloaddition with the second equivalent of AAPE results in the formation of a substituted cyclohexene ring. A chloroperoxidase is then proposed to trigger the chlorination of the cyclohexene double bond. This event initiates a 1,2-shift and is followed by trapping of the resulting carbocation by water, yielding the fused ring system and the free alcohol functionality of palau'amine.

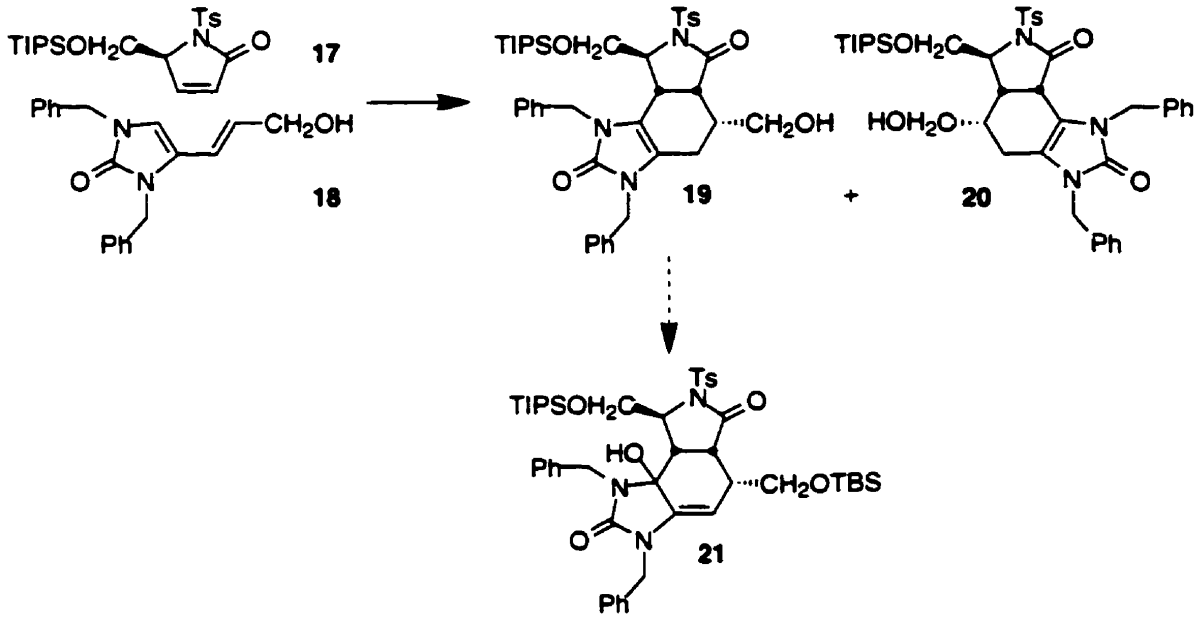
The high convergence of this biosynthetic proposal led Romo to envision the total synthesis of palau'amine from the Cl^+-initiated 1,2-shift in intermediate **16**, which would result from the Diels-Alder reaction of **17** and **18** (Scheme 8).[19]

Scheme 8 : Romo retrosynthetic analysis



The preliminary syntheses of synthons **17** and **18** were successful. However, the subsequent Diels-Alder reaction produced only the isomerized cyclohexenes adducts **19** and **20**. No initial adducts with the double bond located opposite to the 1,3-dihydro-imidazole-2-one ring could be detected. The reaction was improved to a 56% isolated yield of adduct **19**, which results from an endo-cycloaddition with the expected facial and regio-selectivity but followed by double bond migration. Compound **19** was accompanied by the regioisomer **20** obtained in a 14% yield (Scheme 9).

Scheme 9 : Diels-Alder reaction

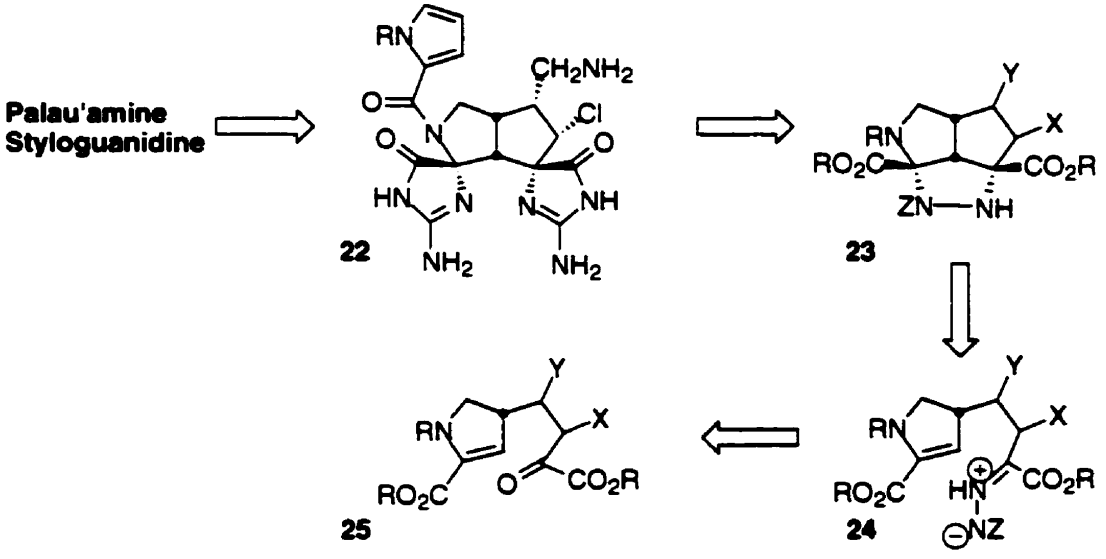


6. Overman approach

In 1997, Overman *et al.* reported a concise strategy for assembling the central *cis*-3-azabicyclo-[3.3.0]octane core of palau'amines and styloguanidines.[20]

Following the disconnection at the pyrrole carboxylic acid and adjustment of oxidation states, Overman envisions intermediate **22** (Scheme 10) as a precursor for palau'amines and styloguanidines. An intramolecular azomethine imine cycloaddition (**24**→**23**) is planned to position the two spiro guanidine rings.

Scheme 10 : Overman retrosynthetic analysis

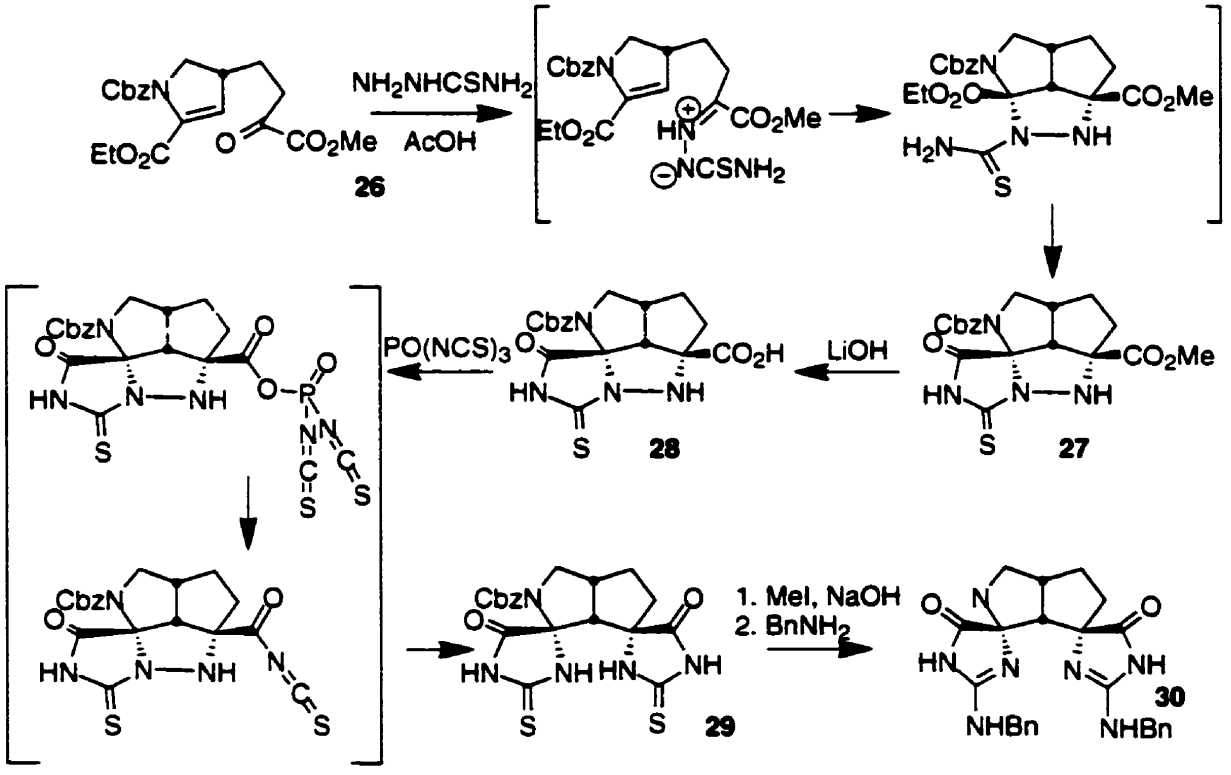


The key azomethine imine cycloaddition was verified on a racemic model substrate, lacking both aminomethyl and chloride substituents eventually required in the synthesis of palau'amine.

Substrate **26**, obtained in 9 steps, was heated in an acetic acid solution in presence of thiosemicarbazide (Scheme 11). The successful cycloaddition provided **27** in excellent yields, while diastereoselectively forming of three new stereocenters. Subsequent hydrolysis

yielded the acid **28**. In a second pivotal step, **28** was treated with excess phosphoryl isothiocyanate which led to the formation of a second thiohydantoin ring and, more unexpectedly, to the reductive cleavage of the N-N bond. These transformations provided **29** in a 72% yield. Reaction of **29** with methyl iodide and subsequent treatment with benzylamine afforded the bis-(acyl guanidine) **30**.

Scheme 11 : Azomethine imine cycloaddition



Although these studies provided a facile access to the spiro-guanidine groups with the proper diastereoselectivity, the application of this model study to the synthesis of palau'amine still requires significant development. Beyond the added difficulties of the asymmetric synthesis of the cycloaddition precursor, the installation of the required aminomethyl and chloride substituents have to be taken into account. The positioning of these elements after the azomethine imine cycloaddition on the concave face of the new system is rendered extremely difficult by the steric environment. If the aminomethyl substituent could be

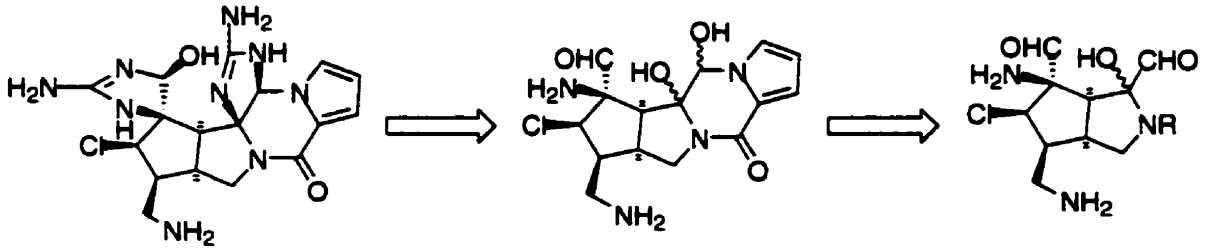
integrated at a previous stage, the chloride substituted center, located α to a ketone, and later an imine, is not likely to resist the sequence of reactions required to finish the synthesis.

7. Retrosynthesis first steps

In addition to its structural complexity, palau'amine's lack of stability makes its synthesis a complex challenge. In fact, this alkaloid has been described by its discoverers as stable in acid but rapidly decomposing when the pH of the medium is maintained above 6.5.[4] More curiously, palau'amine has a pKa as low as 8.5, whereas guanidine containing compounds commonly have a pKa in the order of 13.4. This discrepancy can be hypothesized to originate in a guanidine moiety being forced out of planarity by its ring fusion to the di-azacyclohexane ring. A similar alteration of the pKa has been observed and studied in the related phakellin series.[21]

In view of these stability problems, it appears desirable to minimize the manipulations carried out in presence of the guanidinium residues. Thus, our first retrosynthetic analysis calls for installing the highly sensitive guanidine moieties at the latest stage (Scheme 12). This prospect appears feasible as the stereochemistry at the three aminal positions can be hypothesized as being under thermodynamic equilibrium for both guanidine groups.

Scheme 12 : Retrosynthesis



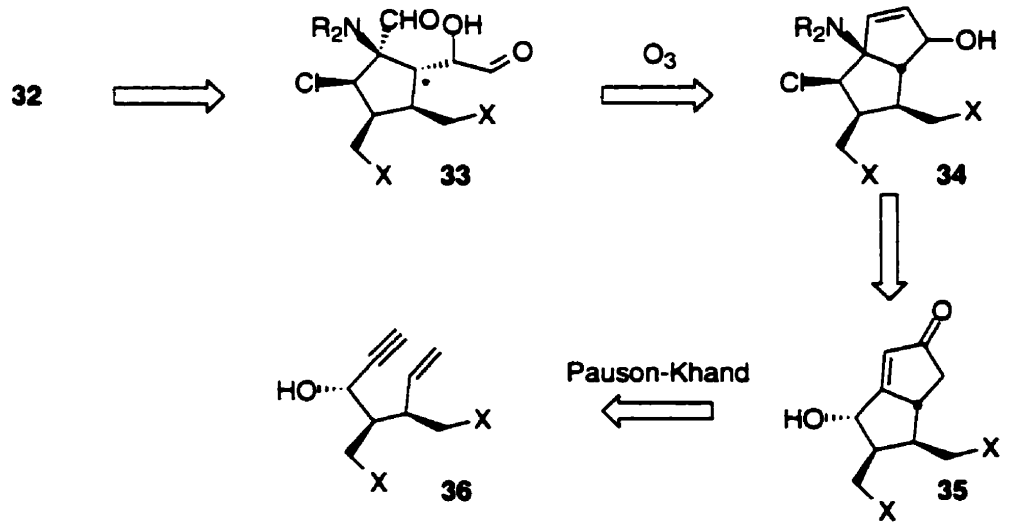
Palau'amine **31** **32**

The spiro guanidine moiety could be formed onto the amine and aldehyde functions with the Miller's reagent ($H_2N(NH=)CSO_3H$).[22] The ring fused guanidine functionality would be placed through the condensation of guanidine on the two mixed aminal groups in the presence of a catalytic amount of acid.[23]

The resulting structure **31** can be further simplified to bicycle **32** by the extrusion of the pyrrole carboxylic acid. Installation of this group would be carried out by condensation of the carboxylic acid onto the cyclic amine and simultaneous formation of the mixed aminal. Late positioning of the pyrrole carboxylic acid is also desirable due to its sensitivity to acidic conditions.

Careful examination of target structure **32** reveals the whole challenge of the total synthesis of palau'amine. More precisely, within **32** lies a hexasubstituted cyclopentane which includes five substituents on the same face.

Scheme 13 : Retrosynthesis



We propose to install the last of these substituents utilizing the stereochemical bias of a bis cyclopentane scaffold (Scheme 13). This strategy will enable us to place the functional groups on the convex face of the bicyclic core. Opening the second ring, and equilibration of the proton at C* will result in cyclopentane system **32**.

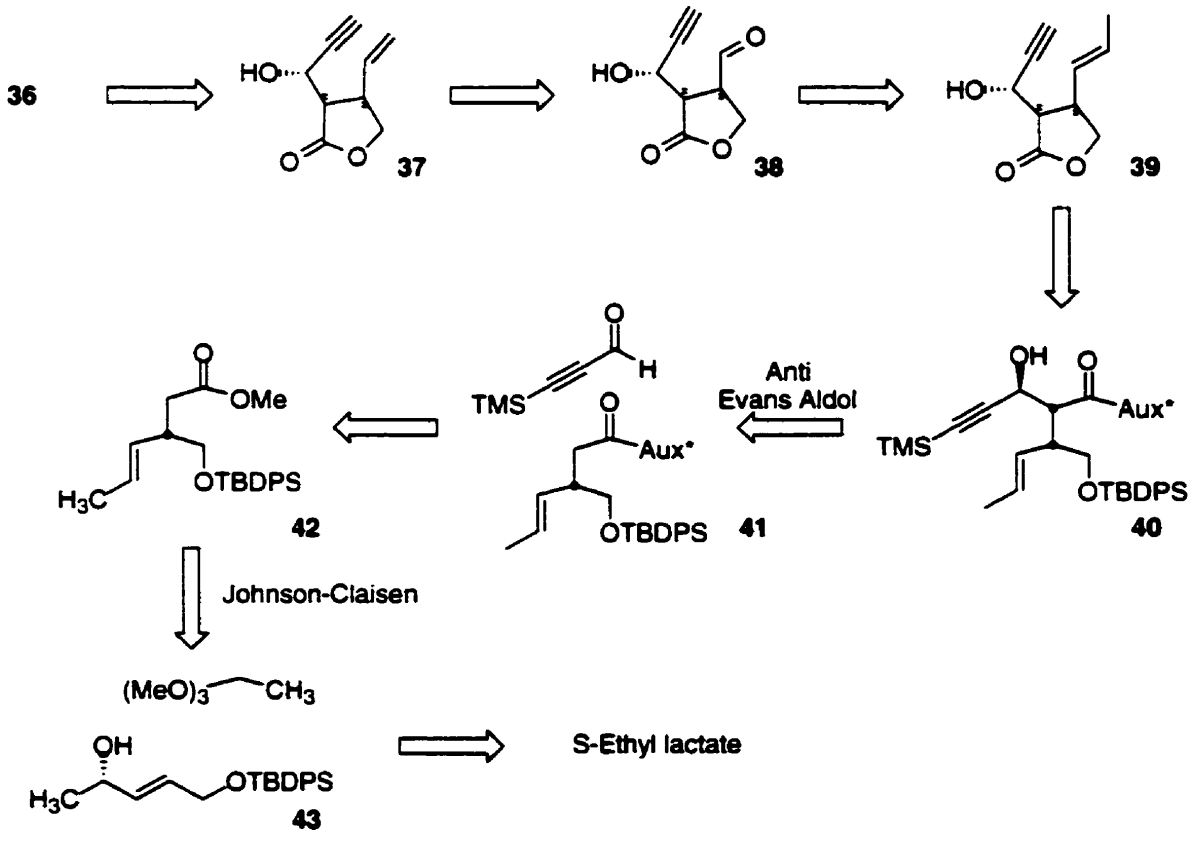
In practice, a system of type **34** would be opened oxidatively, for instance by ozonolysis, to yield the cyclopentane core **33**, which bears a total of six substituents with the required functionalities, four of which being on the same α face. Oxidation of the free

alcohol into a ketone will allow the epimerization required to invert the stereochemistry at the α position of the ketone, leading to a fully α substituted cyclopentane system. This epimerization could be carried out via deprotonation under kinetic control followed by a reprotonation taking place on the least hindered face. With X = NH_2, the epimerization of the ketone will eventually form the bicyclic mixed aminal **32**.

System **34** would be obtained from cyclopentenone **35** in a three-fold procedure including a Rubottom oxidation procedure[24], the reduction of the ketone to an alcohol and an Overman type aza-Claisen rearrangement[25] to position the amino group at the ring fusion.

The cyclopentenone **35** would be provided by an intramolecular Pauson-Khand reaction from the enyne substrate **36**.[26]

Scheme 14 : Retrosynthesis first steps



In order to facilitate the Pauson-Khand reaction, we planned to run this cyclization on a cyclic substrate. This would potentially accelerate the reaction by the physical constraint imposed on the starting material and was also expected to favor the stereoselectivity of the cyclization. Thus lactone **37** presented itself as a desirable target Pauson-Khand substrate.

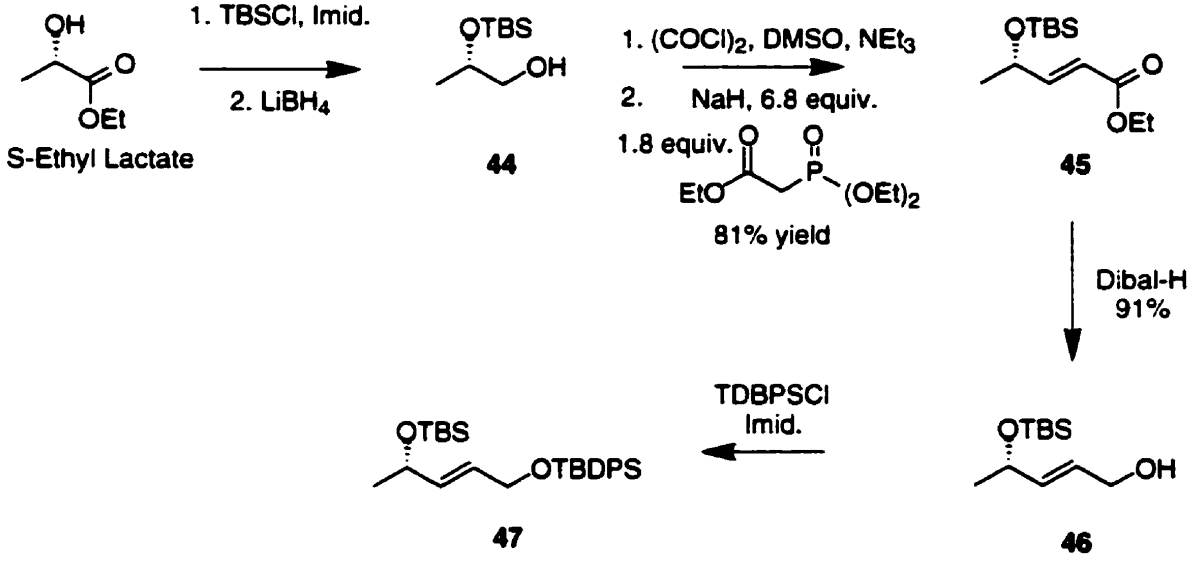
Two of the three stereocenters in compound **37** could be generated through a stereoselective aldol reaction onto substrate **41** (Scheme 14). The third stereocenter would be generated by a Johnson-Claisen reaction onto the chiral pool derivative **43**.

RESULTS AND DISCUSSION

1. Synthesis

The first stereocenter is derived from the commercially available chiral template ethyl (*S*)-(-)-lactate. In a first step, ethyl (*S*)-(-)-lactate is silylated under classical conditions and in quantitative yield (Scheme 15). Subsequent reduction with lithium borohydride afforded alcohol **44** in quantitative yield.[27]

Scheme 15 : Synthesis of compound 47



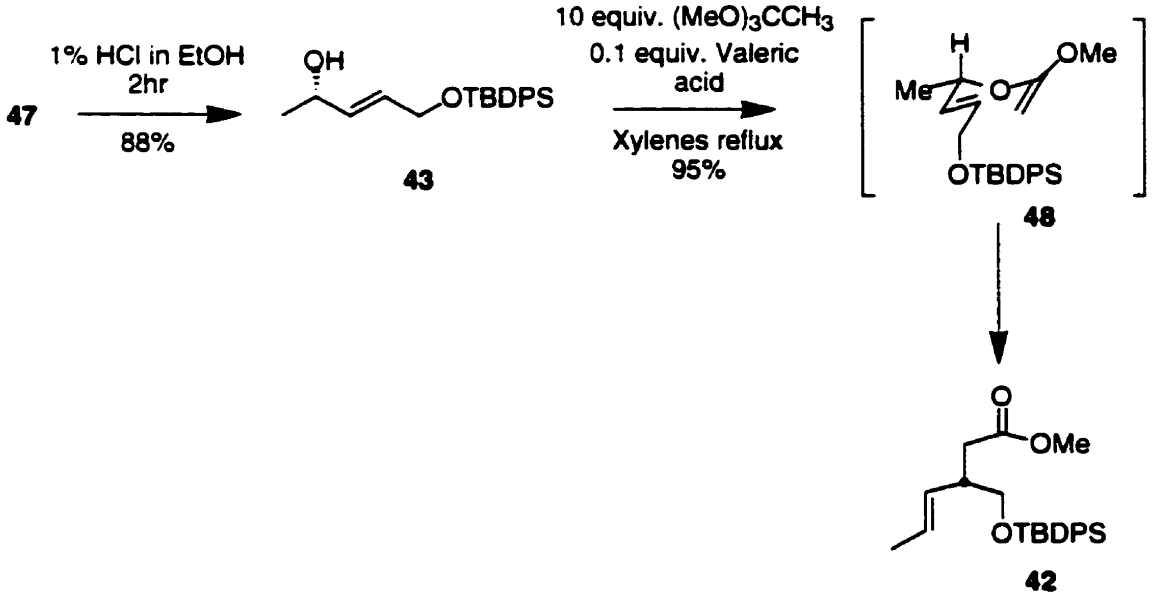
Compound **44** was oxidized by a Swern protocol, and the resulting aldehyde was olefinated *in situ* by the sodium anion of triethyl phosphonoacetate. This one-pot process enabled the synthesis of **45** in 81% isolated yield. The resulting unsaturated ester **45** was reduced chemoselectively by DIBAL-H to the allylic alcohol **46** in 91% isolated yield.

An alternate procedure in which the silylated ethyl (*S*)-(-)-lactate is reduced to the aldehyde by DIBAL-H and olefinated during an independent step is also possible.[28] However, as described by Marshall *et al.*, the volatile intermediate aldehyde would have proved more difficult to isolate.[29] A more direct route involving a one-pot reduction with

DIBAL-H and triethyl phosphonoacetate has been utilized by Takacs *et al.*[30] However, this procedure provides the desired product **46** in a lower yield (60%).

The terminal alcohol function of **46** was protected as a tert-butyl diphenylsilyl ether under usual conditions, providing compound **47** in quantitative yield. The secondary tert-butyl dimethylsilyl ether function of compound **47** is selectively deprotected in presence of a primary tert-butyl diphenylsilyl ether group under acidic conditions, to produce the secondary alcohol **43** in 88% yield (Scheme 16).

Scheme 16 : Synthesis of 42

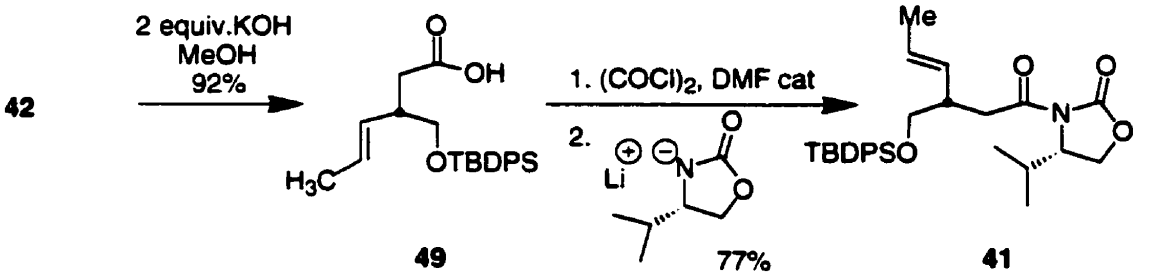


A Johnson-Claisen rearrangement is then undertaken to transfer the chirality of the allylic alcohol **43** to the new tertiary carbon center of **42**. In presence of trimethyl orthoacetate, the mixed orthoester derivative of **43** is formed under acid catalysis.[31] Valeric acid was chosen for this acid catalysis due to its high boiling point. A ketene acetal intermediate **48** resulting from the loss of methanol rearranges *in situ* to the ester **42**, in a 95% isolated yield. This transfer of chirality occurs through a chair-like transition state in

which the methyl substituent of the starting material chiral center places itself in an equatorial position.[32]

The methyl ester **42** is then saponified by KOH in methanol to produce the corresponding acid **49** in an enantiomerically pure form in 92% yield (Scheme 17). The acid functionality thus offered a handle onto which a chiral auxiliary could be introduced to prepare for the key aldol reaction.

Scheme 17 : Synthesis of compound 41



In order to install the chiral oxazolidinone auxiliary, a mixed anhydride was investigated.[33] This intermediate was formed in a preliminary step by the condensation of pivaloyl chloride onto the acid **49**, in presence of triethylamine. The crude mixture obtained was allowed to react with the lithium anion of the (S)-(-)-4-isopropyl-2-oxazolidinone.[34] Unfortunately, approximately one third of the oxazolidinone was found to acylate the pivaloyl portion of the mixed anhydride.

A procedure involving the *in situ* formation of an acyl chloride as activated species was then studied.[35] Thus, the acid **49** was allowed to react with oxalyl chloride in presence of a catalytic amount of dimethylformamide. After concentration, the mixture was added to a solution of the lithium anion of (*S*)-(-)-4-isopropyl-2-oxazolidinone, to produce the desired oxazolidinone **41** in 77% yield (Scheme 17).

Having successfully connected the chiral auxiliary, we further proceeded to the installation of two new stereocenters on compound **41**, via a tin-catalyzed anti-Evans aldol

with the trimethylsilyl protected propargyl aldehyde for electrophile.[36] This latter compound was prepared in two steps from propargyl alcohol.

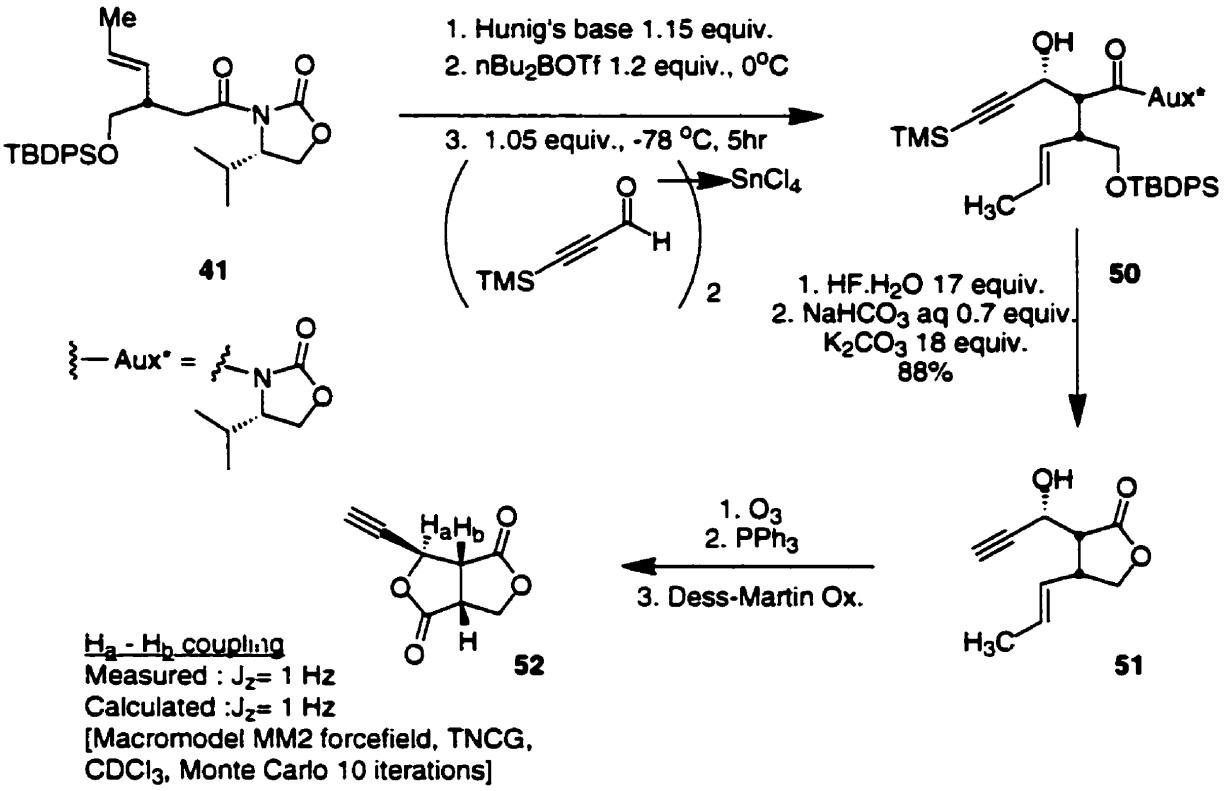
Following the procedure of Heathcock, the boron enolate of **41** was formed using dibutylboron triflate and diisopropylethyl amine, followed by addition of the enolate to a pre-complexed mixture of trimethylsilyl protected propargyl aldehyde and tin-tetrachloride (0.5 equivalent to the aldehyde) to provide a 69% yield of the aldol product **50**.

In order to establish the stereochemistry at the two newly created chiral centers, a series of chemical derivatizations was undertaken (Scheme 18). First, a lactone ring was formed by deprotecting the silyl ether with HF and *in situ* cyclization under basic conditions, yielding compound **51**.[37]

Ozonolyzis of the olefin moiety of **51** and subsequent Dess-Martin oxidation of the resulting crude mixture led to the formation of the bis five membered ring lactone **52**. The formation of the fused lactone demonstrates the *cis*-relationship of the two lactone rings and thus the R configuration of the newly created tertiary carbon stereocenter.

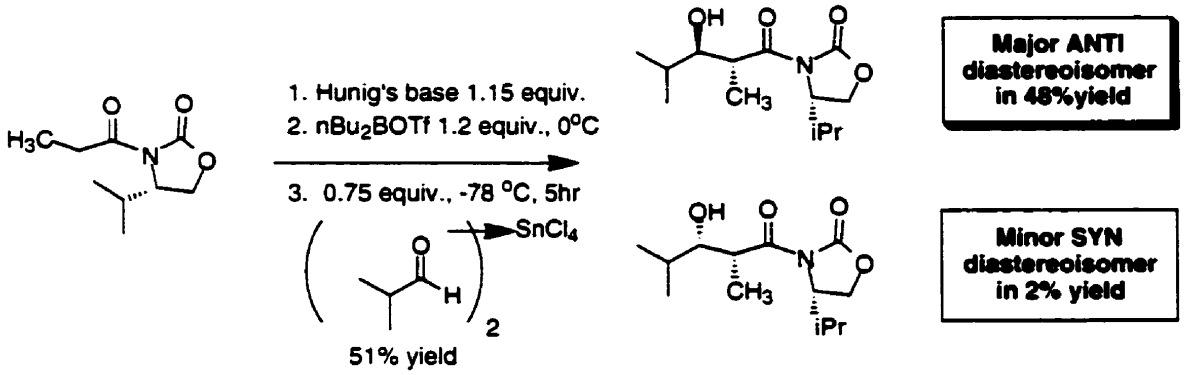
On the same molecule **52**, the coupling between H_a and its vicinal proton was found equal to 1 Hz. The system was modeled on Macromodel software and minimized using MM2 forcefield parameters after a Monte Carlo conformational search. A theoretical coupling constant of 1Hz between H_a and its vicinal proton H_b was then calculated using the conformations found. The epimer was minimized by the same procedure and the corresponding coupling constant was found equal to 7.4 Hz. This modeling experiment clearly indicates the *trans* relationship of these two hydrogens on the bis lactone compound. Hence, the stereochemistry of the aldol product **50** is that of a non-Evans *syn* aldol product, as shown on Scheme 18.

Scheme 18 : Anti-Evans aldol

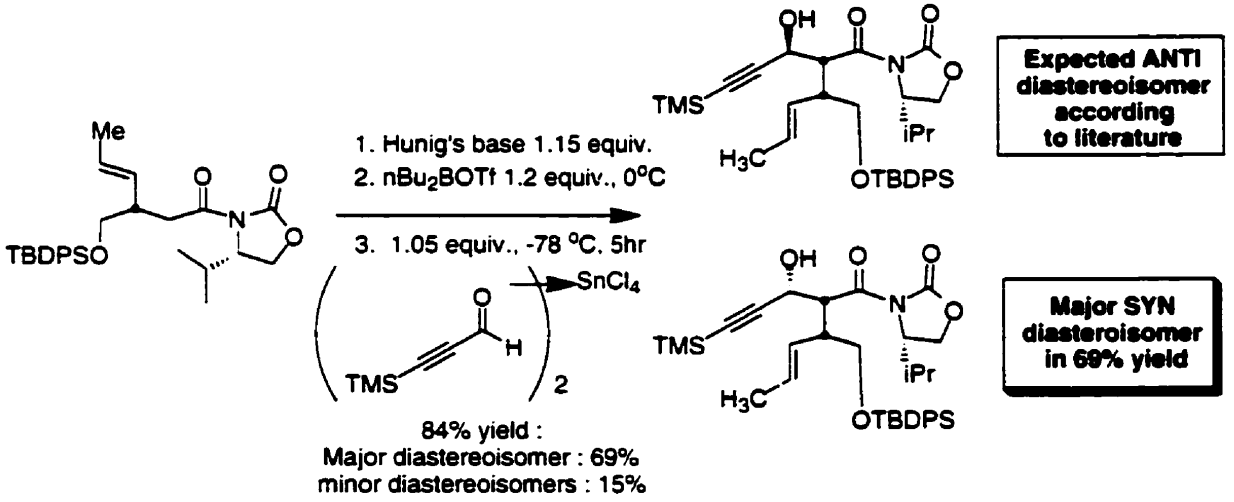


Thus, the unexpected product stereochemistry of **50** contradicts the results of Walker and Heathcock.[36b] In their report, the anti product was obtained in 48% yield along with only 2% of the related non-Evans syn product (Scheme 19).

Scheme 19 : Tin-catalyzed Evans aldol reactions

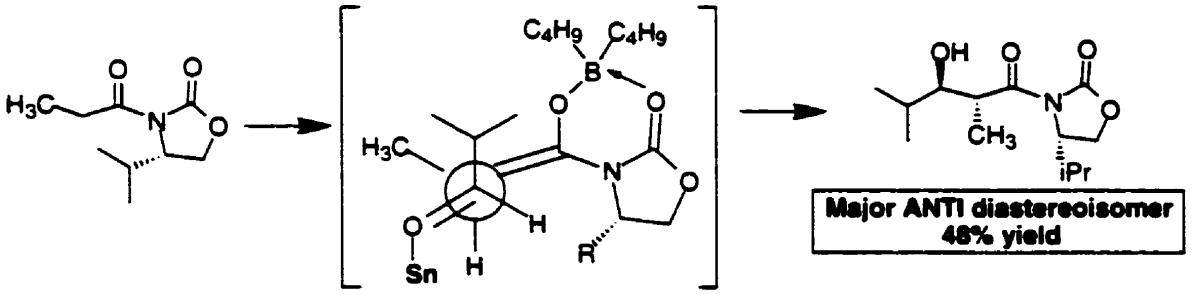


Walker M.A., Heathcock C.H., *J. Org. Chem.* **56**, 5747 (1991)



We propose that the discrepancy observed is linked to the variation of the substituent on the acyl moiety of the substrate. Unfortunately, the attempts at anti-Evans aldol are a rare occurrence in litterature.[38] Heathcock *et al.* propose that, being chelated to two aldehyde molecules, the tin-chloride behaves like a bulky Lewis acid. In this sense, the tin would position itself anti to the incoming Z boron enolate so as to minimize steric interactions with the oxazolidinone moiety (Scheme 20).

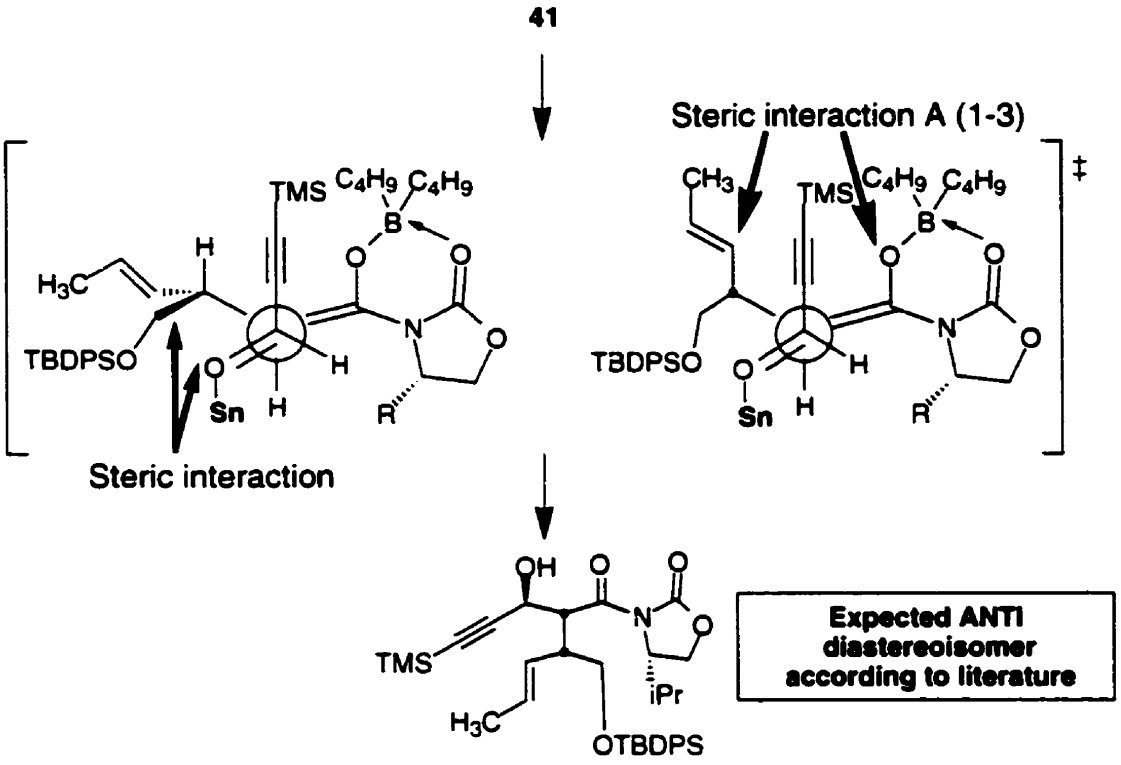
Scheme 20 : Anti Evans aldol transition state



Walker M.A., Heathcock C.H., *J. Org. Chem.* **56**, 5747 (1991)

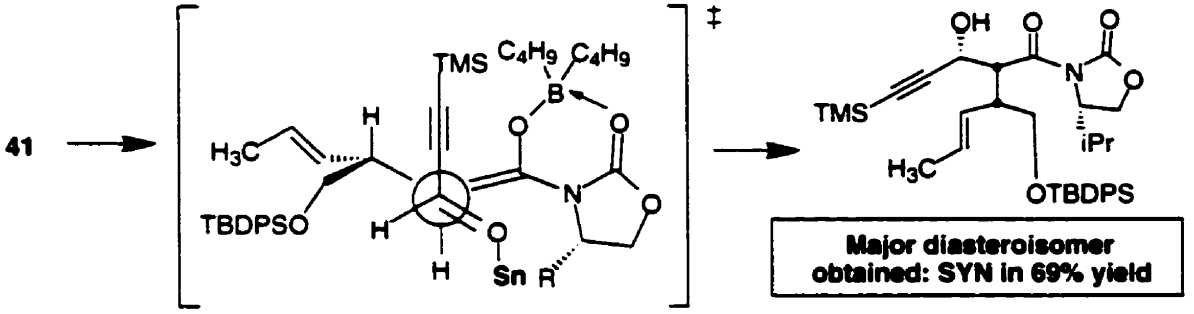
However, with the large substituent on **41**, the expected transition state is thought to be energetically disfavored. As depicted in Scheme 21, a first rotamer presents a large steric between the tin Lewis acid and the -CH_2OTBDPS group of the enolate. A second rotamer, which would minimize the aforementioned interaction, creates in turn a steric A-1,3 interaction between the allyl substituent and oxygen.

Scheme 21 : Expected transition state



We propose that in order to avoid these destabilizing interactions, the Lewis acid is oriented on the oxazolidinone side of the approaching enolate. The opposite face of the aldehyde is then presented for aldol reaction with the boron enolate, resulting in a *S* configuration at the alcohol position (Scheme 22).

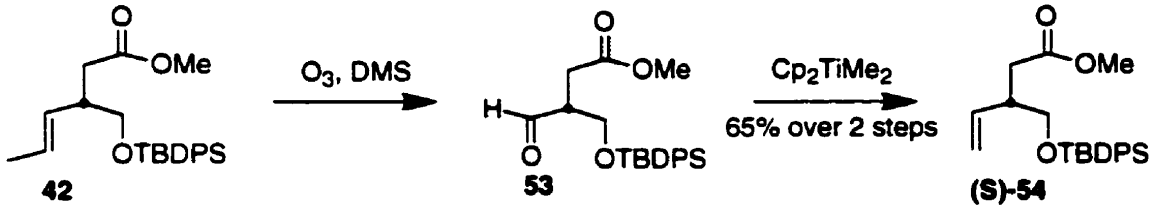
Scheme 22 : Proposed aldol transition state



This result called for a modification of the retrosynthetic analysis, where the chloride would need to be installed with overall retention of configuration from the *S* alcohol, instead of a simpler substitution with inversion from the *R* alcohol. Additionally, the attempts at conducing a normal *syn*-Evans aldol, utilizing *R*-benzyloxazolidinone derivative of **41** proved fruitless, yielding a mixture of epimers at the newly created carbon stereocenter.[34]

The one-carbon shortening of the olefin chain from compound **51** proved to be an elusive task. The required oxidation of the olefin of **51** to the aldehyde and subsequent olefination proved unsuccessful, probably due to the sensitivity to bases of the lactol intermediate. We therefore switched our focus to the possibility of shortening this olefinic chain before the aldol reaction. The alkene group of compound **42** was oxidatively cleaved using a standard ozonolysis procedure, followed by a dimethyl sulfide quench. On the resulting crude aldehyde **53**, a Wittig olefination procedure did not afford the desired product, probably due to the sensitivity of the substrate to basic reagents. However, a procedure using the *in situ* reagent titanocene methylidene was found successful in preparing the desired terminal olefin **54**, in a moderate yield of 65% over two steps (Scheme 23).[39] This procedure proved to be superior to the organozinc reagents (CH_2I_2-Zn-Me_3Al) and (CH_2Br_2-Zn-$TiCl_4$) described by Takai *et al.*[40]

Scheme 23 : Enantioselective synthesis of compound (*S*)-54

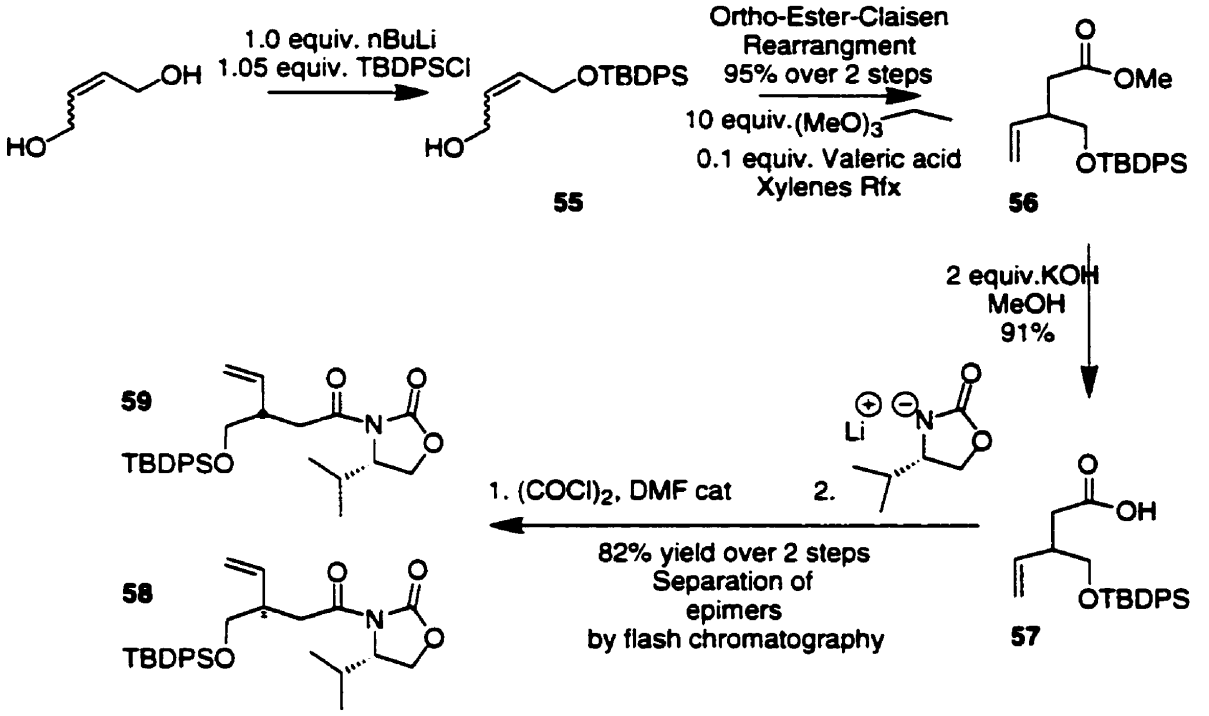


Taking into account the low yield observed in this sequence of steps, the need for a simplification in the retrosynthesis was felt in order to eliminate this carbon chain length alteration. An alternative was conceived aiming in particular at accelerating the synthesis of the palau'amine core. In lieu of preliminary asymmetric synthesis, this modification centers on the racemic synthesis of compound **54** followed by the separation of diastereoisomers formed by derivatization with a chiral compound (Scheme 24).

A monosilylation was carried out on the achiral 1,4-butene-diol, according to the procedures of Roush[41] and Sabol[33]. In a second step, compound **55** is elaborated via a Johnson-Claisen rearrangement to produce the racemate **56** in 95% yield over these two steps.[31] The ester functionality was then saponified in 91% yield. The resulting crude acid **57** was acylated with the lithium anion of the (*S*)-(-)-4-isopropyl-2-oxazolidinone using the acyl chloride protocol developed earlier. The product mixture consisted of the two epimers **58** and **59**, which were separated using silica gel flash chromatography.[34]

In order to identify the desired epimer **59** out of the two epimers isolated, a derivatization of the product **(*S*)-54** was carried out. Under the same conditions as described above, the enantiomerically pure ester **(*S*)-54** was saponified. The resulting acid was then converted to the acyl chloride and acylated with the (*S*)-(-)-4-isopropyl-2-oxazolidinone, yielding **59**.

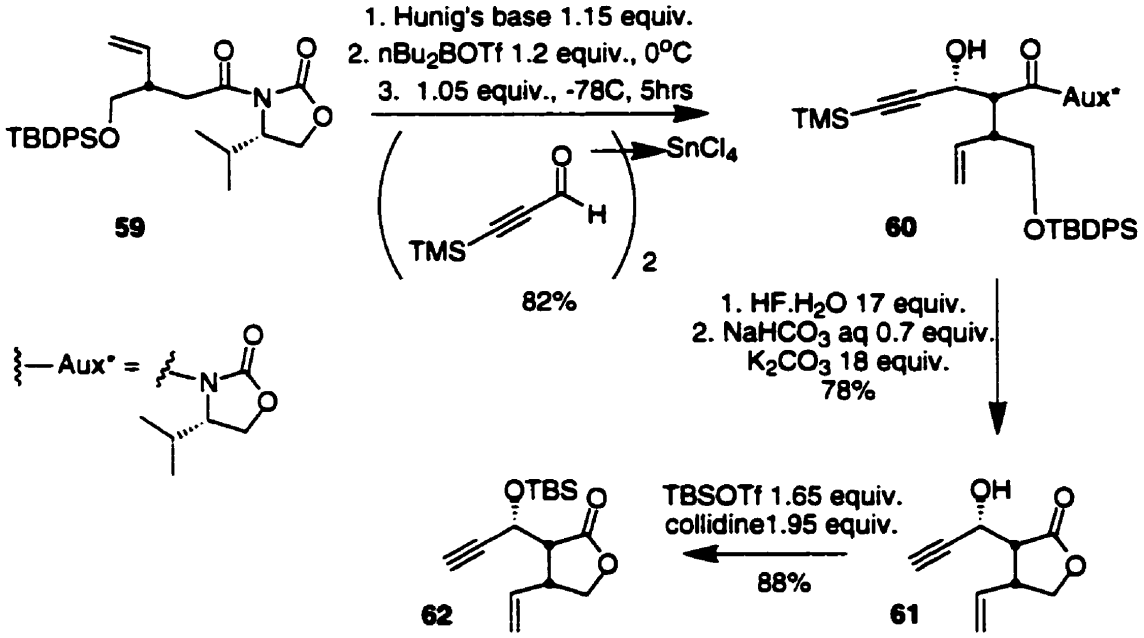
Scheme 24 : Revised synthesis of compound 59



This variation of pathway enabled the synthesis of the aldol substrate from commercially available starting material in a total of four steps, instead of twelve, and an overall yield of 36% of the desired product **59**.

The altered pathway then converges with the key aldol step. The oxazolidinone **59** was then allowed to react with the trimethylsilyl protected propargyl aldehyde, under the standard tin-catalyzed Evans aldol conditions described above. The major product **60** was obtained in 82% yield (Scheme 25).

Scheme 25 : Synthesis of compound 62



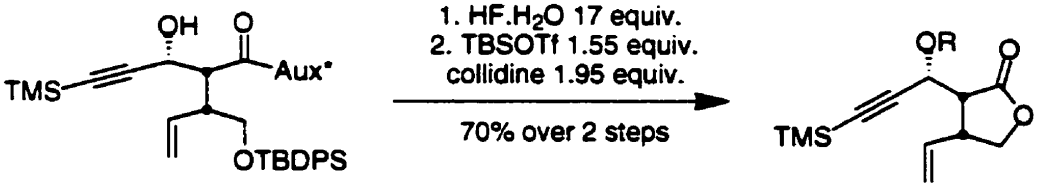
The tert-butyldiphenylsilyl alcohol protecting group of product **60** was removed using aqueous HF in acetonitrile. Addition of $NaHCO_3$ and K_2CO_3 to the reaction mixture quenched the excess hydrofluoric acid, catalyzed the lactonization and the release of the oxazolidinone auxiliary. Furthermore, deprotection of the alkyne terminus occurred in this nucleophilic medium to provide the lactone **61** in a maximum yield of 78%.[37]

However, the duration of this desilylation was found to vary widely. This is probably a consequence of the difficulties to reproduce accurately the reaction conditions, as these transformations occur in a heterogeneous reaction mixture. Unfortunately, extension of the duration of the deprotection also led to the competitive formation of a new product. This by-product results from the epimerization of the lactone in the basic medium at the α position of the carbonyl function, to the *trans* lactone. The possibility of epimerizing this position in the by-product through a deprotonation followed by reprotonation from the least hindered face was tested. Attempts of epimerizing this by-product using lithium diisopropyl amide for the

deprotonation, even in presence of hexamethylphosphoramide, only yielded partial epimerization to the *cis* lactone.

In order to study the following steps in general, and the Pauson-Khand enone formation in particular, a reproducible process was needed to obtain a parent enyne to compound **61**. In addition, a large substituent on the alkyne terminus, such as trimethylsilyl, was reported by Magnus *et al.* to increase the diastereoselectivity of the reaction.[42] It was therefore our interest to keep the trimethylsilyl group in place until after the Pauson-Khand reaction, where alternate procedures for its cleavage would be investigated. Thus, after the removal of the tert-butyldiphenylsilyl moiety from product **60** with HF, the reaction was quenched and worked up immediately, to prevent the deprotection of the alkyne terminus from occurring. This variation of procedure provided the enyne **63** in 93% yield (Scheme 26).

Scheme 26 : Synthesis of enyne 64



60
Aux* = (S)-isopropyl oxazolidinone

63 R=H
64 R=TBS

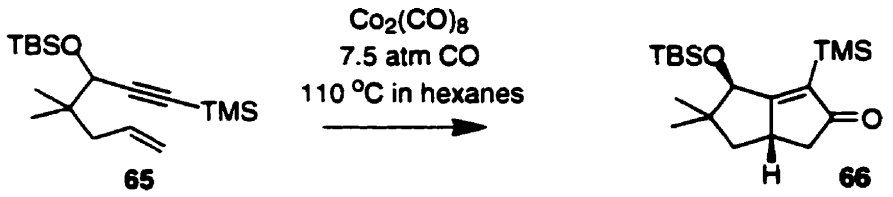
The following key step aims at completing the carbon backbone of the central cyclopentane in palau'amine. Hence, the Pauson-Khand reaction has for objective the formation of a cyclopentenone ring of the tricyclic core **35**. During this process, a new stereocenter is formed which will provide the bias of the scaffold designed for the introduction of the last substituents. Since its discovery[43] in 1973, a range of both stoichiometric[44] and catalytic[45] conditions has been developed to ensure the successful outcome of this three component process.

The Pauson-Khand reaction has been reported to give lower yields for substrates with a free alcohol functionalities at the propargylic position.[25c] To remedy this situation, a tert-butyldimethylsilyl group was chosen for the protection role. The relative bulkiness of a tert-butyldimethylsilyl ether group, as compared to a methyl substituent for instance, has been reported to enhance the diastereoselectivity of the cyclopentenone formation.[46] To install this protection on the alcohol **61**, the classic procedure, using tert-butyldimethylsilyl chloride in dimethylformamide in presence of imidazole, returned only starting material. The low reactivity of the substrate was successfully compensated by a procedure using tert-butyldimethylsilyl triflate with lutidine as a base. The enyne **62** was thus obtained in 88% yield (Scheme 25). Similarly, the protection method using tert-butyldiphenylsilyl triflate was effected onto **63**, giving **64** in a 75% yield (Scheme 26).

Various Pauson-Khand procedures chosen for their practicality were studied on both compounds **62** and **64**. First of all, following Krafft's procedure, these enynes were complexed by $Co_2(CO)_8$ and *in situ* thermolyzed, but did not provide the desired cyclopentenones.[47] Similarly, the activation by N-methyl morpholine N-oxide of the cobalt alkyne complexes, as described by Schreiber or Jeong *et al.* also proved unsuccessful.[48]

Advantage was taken of the model substrate **65**, which was functionally similar to **64** and had been used by Magnus to study the diastereoselectivity of the Pauson-Khand procedure.[46b] When the reaction was conducted at 110°C under 7.5 atmospheres of carbon monoxide using 1.2 equivalent of $Co_2(CO)_8$, the cyclopentenone **66** was formed in a stoichiometric process in a 79% yield (Scheme 27). The epimer of **66** at the ring junction was isolated in a 3% yield. In the course of this research, we improved this transformation by using catalytic amounts of $Co_2(CO)_8$. In addition to the greater practicality obtained by this modification, product **66** was isolated in an almost identical yield. A more in-depth study of the reactivity of enyne **65** complexed with $Co_2(CO)_8$ led to the discovery and development of a novel cyclization reaction which is described in Part II of this thesis.[49]

Scheme 27 : Pauson-Khand reaction of enyne 65

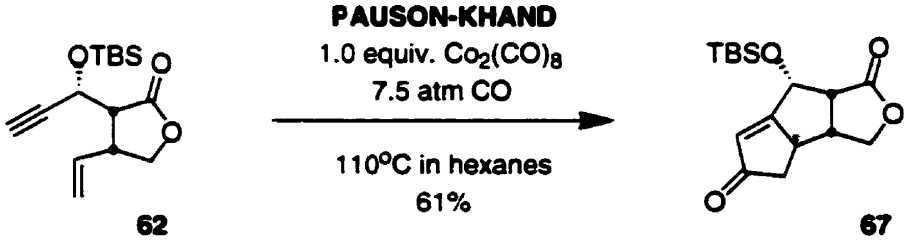


65 66

Equivalents of $Co_2(CO)_8$	Yield of **66**
1.0	79%
0.1	78%

Following the stoichiometric procedure optimized for the synthesis of **66**, the enyne **62** was complexed with $Co_2(CO)_8$ and placed under 7.5 atm of carbon monoxide. Heating this complex to 110°C provided the desired cyclopentenone **67** in 61% isolated yield (Scheme 28).

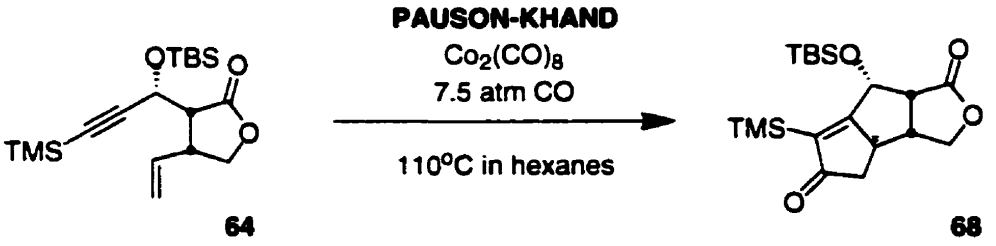
Scheme 28 : Synthesis of cyclopentenone 67



62 67

Following this experiment, a similar process was effected with the trimethylsilyl protected enyne **64**. The procedure was successful in giving the tricyclic enone **68** in 77% yield (Scheme 29). In both cases, minor compounds were detected in the crude mixture although not isolated.

Scheme 29 : Synthesis of cyclopentenone 68



64 68

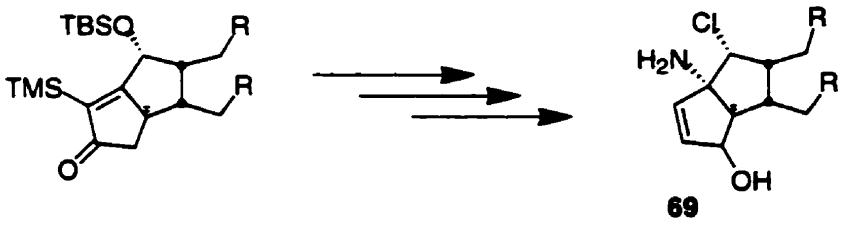
Equivalents of $Co_2(CO)_8$	Yield of **68**
1.0	77%
0.1	91%

In order to obtain a cleaner crude product as well as to simplify the work up, the Pauson-Khand procedure was attempted using catalytic amounts of dicobalt octacarbonyl. This procedure enabled the synthesis of the Pauson-Khand adduct **68** in a 91% yield. No minor products were detectable in the ^{1}H NMR spectrum of the crude mixture.

The stereocenters of **66** and **68** created during the Pauson-Khand reaction were assigned according to the work of Magnus on the diastereoselectivity of this procedure.[46b]

The carbon skeleton of the central five membered ring of palau'amine being established, the focus of the work shifted to the elaboration of the final substituent pattern. From the tricyclic product **68**, a nitrogen group must be introduced at the ring fusion, *cis* to the hydrogen, and a hydroxyl substituent has to be introduced α to the ketone functionality. Moreover, the trimethylsilyl group of **68** is to be cleaved and the tert-butyldimethylsilyl ether substituted for a chlorine atom with overall retention, to provide with target structure **69** (Scheme 30).

Scheme 30 : Target structure 69

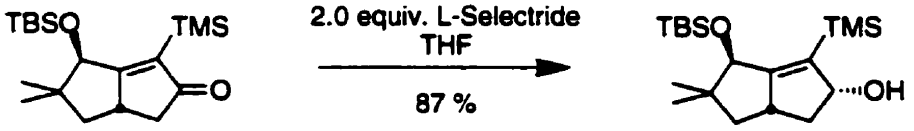


In order to facilitate this study, we chose to investigate the required succession of reactions on a model substrate. Racemic compound **66**, as detailed above, bears all the functionality we plan to modify on structure **68** and in an identical arrangement. Furthermore, bicycle **66** is easily obtainable in two steps and in an overall yield close to 75% from commercially available materials.

Preliminarily, a strategy was chosen for the introduction of the nitrogen bearing group. An Overman rearrangement was proposed to allow for simultaneously solving the nitrogen group addition and the migration of the double bond, as in structure **69**. Towards this goal, the enone **66** was reduced to the corresponding allylic alcohol with L-Selectride. The crystalline product **70** was obtained in 87% yield and ^{1}H NMR analysis indicated a single epimer at the alcohol stereocenter (Scheme 31). Attempts to convert this product to the trichloroacetimidate with trichloroacetonitrile proved unsatisfactory with base such as DBU[50], sodium hydride[51], n-butyl lithium or sodium hexamethyldisilazane. Indeed, the analysis of the ^{1}H NMR coupling of **70**, through the molecular modeling of the two possible epimers, revealed that the product **70** was of the *S* configuration at the newly formed stereocenter. This study of the coupling between the proton geminal to the alcohol function and its vicinal counterparts was carried out by modeling compound **70** on Macromodel software. When the alcohol function is located on the exo face of the system, couplings of 5.4 Hz and 1.4 Hz are calculated, whereas values of 9.4 Hz and 7.6 Hz are indicated for the endo epimer. The latter coupling constants are found to be in accordance with the experimental data (8.6 Hz for both couplings). It became apparent that an additional

inversion at the alcohol center was then necessary for the Overman rearrangement to proceed.

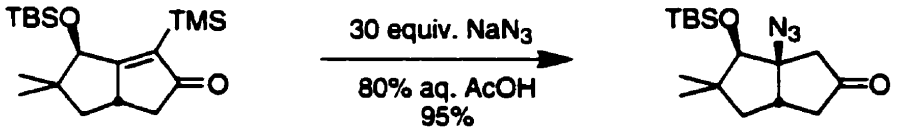
Scheme 31 : Synthesis of alcohol 70



66 **70**

A more attractive solution was to use the enone as the substrate for a Michael addition of a nitrogen nucleophile. This strategy has been precedented by Wengel *et al.* who have taken advantage of the excellent nucleophilicity of the azide group.[52] Model compound **66** was thus placed in presence of a large excess of hydrazoic acid formed *in situ* from sodium azide and the aqueous acetic acid used as solvent (Scheme 32).

Scheme 32 : Michael addition of azido group on compound 66



66 **71**

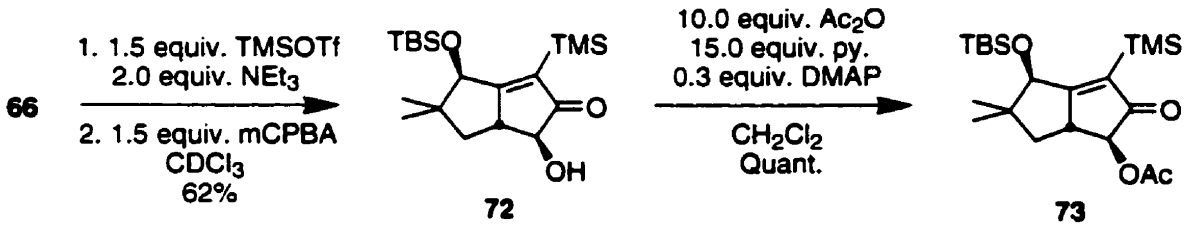
The NMR analysis of the product provided clear evidence for the effectiveness of the Michael addition. In addition, the IR spectrum showed absorptions at 2104 cm^{-1} and 1252 cm^{-1}, corresponding to regions characterictic of the asymmetric ([2250-2080] cm^{-1}) and symmetric ([1350-1180] cm^{-1}) stretches for an azido substituent, respectively.[53] Not unexpectedly, the trimethylsilyl group of the substrate was also cleaved in this reaction. In fact, exposure to acidic medium has been precedented by Utimoto *et al.* as an easy method to

cleave such vinylic silane groups.[54] Altogether, this reaction, albeit of long duration (72 hours), proves to be a potent process for simultaneous introduction of the nitrogen bearing group and trimethylsilyl group cleavage. However, the removal of this latter group is made at the loss of the differentiation between the two carbons vicinal to the ketone functionality in **71**, thereby demonstrating the need for a previous introduction of the required hydroxyl moiety.

In this aim, the Rubottom procedure was attempted on enone **66**.[24] It is noteworthy that the formation of the intermediate trimethylsilyl enol ether failed when lithium diisopropyl amide was used with trimethylsilyl chloride, or 2,4,6 collidine along with trimethylsilyl triflate. However, when trimethylsilyl triflate was used in conjunction with triethylamine, formation of the trimethylsilyl enol ether could be observed by thin layer chromatography. After removal of the excess of triflate reagent and base by concentration under vacuum, the silyl enol ether intermediate was oxidized with *meta*-chloroperbenzoic acid. An acidic quench provided the desired α-hydroxy ketone functionality. Compound **72** was obtained in a moderate 62% yield. Again, no epimer was detected by NMR analysis. Although the total synthesis strategy later require the oxidation of this alcohol to the ketone, the presence of a single epimer simplifies greatly the analysis of the following reactions.

A protection scheme for the new hydroxy functionality of **72** was required. For this model study, it was thought that a methyl group would be of sufficient sophistication. In fact, this transformation proved interesting in itself as the efforts to position such a methyl protective group highlighted the particular reactivity of compound **72**. All attempts at methylation were frustrated, including techniques such as methyl iodide in presence of sodium hydride[55], methyl sulfate with potassium hydroxide[56], Meerwein's reagent or methyl triflate with di-tert-butylpyridine[57]. Other protection schemes, for instance benzylation with benzyl bromide and sodium hydride[58] or allylation with allyl trichloroacetimidate and triflic acid[59], also proved unsuccessful. Finally, we resorted to the installation of an acetate ester to protect the hydroxy group. The most conventional method, involving acetic anhydride, pyridine and dimethylaminopyridine as catalyst, provided the desired ester **73** in a quantitative yield (Scheme 33).[60]

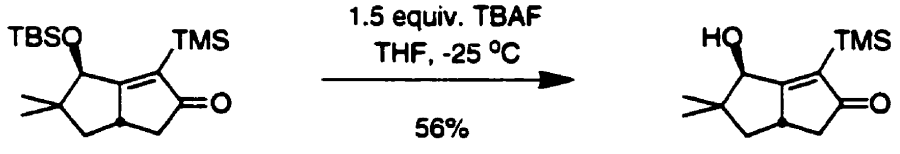
Scheme 33 : Synthesis of compound 73



On substrate **73** was attempted the previously described azide introduction and trimethylsilyl group cleavage. According to ^{1}H NMR analysis of the crude material, the reaction progresses extremely slowly. After a total of ten days of reaction, the removal of the trimethylsilyl moiety was complete, and a total of three compounds were present. In any case, the introduction of the azido group onto **73** was found to be impractical.

The removal of the *tert*-butyldimethylsilyl group of **73** was then studied in the hypothesis that the steric environment due to this large ether moiety hinders the Michael addition of the azido group. Unfortunately, procedures including aqueous HF[61], HCl[62] or *tert*-butyl ammonium fluoride[63] reagents all ultimately failed to provide the free alcohol in a satisfactory manner.

Scheme 34 : Deprotection of *tert*-butyldimethylsilyl ether 66

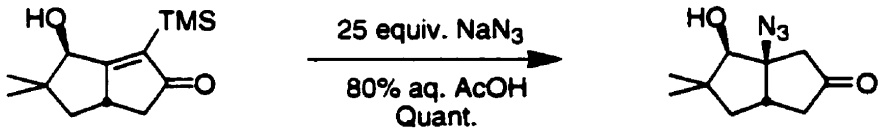


Therefore, our focus was shifted to the *tert*-butyldimethylsilyl ether group of **66** and transformations at this position of the bicyclic framework. The difficulties encountered previously for the cleavage of this group from **73** resurfaced when considering this

deprotection from the simpler substrate **66**. After optimization, a procedure relying on the *tert*-butyl ammonium fluoride was found to provide the best yields of free alcohol **74** at 56% (Scheme 34). This reaction was carried out in at -25 °C as no progress was recorded when cooling the medium to -78 °C. In contrast, warming the reaction up to 0 °C ultimately led to an uncharacterizable mixture of products.

The study of the reactivity of substrate **74** to the previously discussed Michael addition of an azido group evidenced the effects of the *tert*-butyldimethylsilyl ether group of **66** or **73** (Scheme 35). Indeed, compound **75** was obtained in quantitative yields after a reaction period of only 12 hours, instead of 72 hours for compound **71**.

Scheme 35: Michael addition of azido group on compound 74

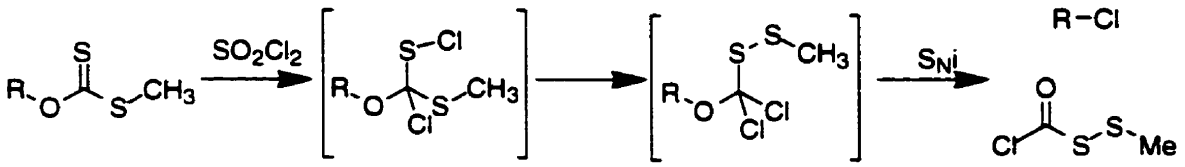


74 **75**

The positioning of the chlorine substituent with overall retention from the free hydroxyl group was undertaken from the model substrate **74**. A first protocol centered on the use of thionyl chloride which, according to Lewis *et al.*, acylates at the free hydroxyl before undergoing elimination of SO_2 and substitution via a four membered transition state.[64] Applied to the free alcohol substrate **74**, this procedure only gave an uncharacterizable mixture of products.

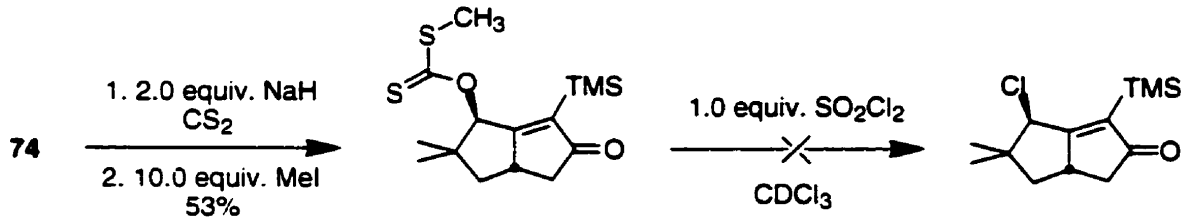
An alternate and milder protocol involved the formation of the xanthate followed by treatment with sulfuryl chloride. This technique has been used for the substitution of chlorine with retention in a number of hindered substrates, such as isomenthyl alcohol or 2-adamantanol.[65] The mechanism appears to include the break down of the intermediate disulfanyl via an ion pair process to yield the product arising from a front-side S_Ni attack mode (Scheme 36).[66]

Scheme 36 : Degradation of a xanthate into a chloride with sulfuryl chloride.



In the case of substrate **74**, the xanthate intermediate was formed under the classic conditions described by Ireland (Scheme 37).[67] This compound **76**, however, showed poor stability upon concentration. Treatment of this product with sulfuryl chloride was ultimately found to be unsuccessful.

Scheme 37 : Attempt at chlorine substitution on xanthate 76

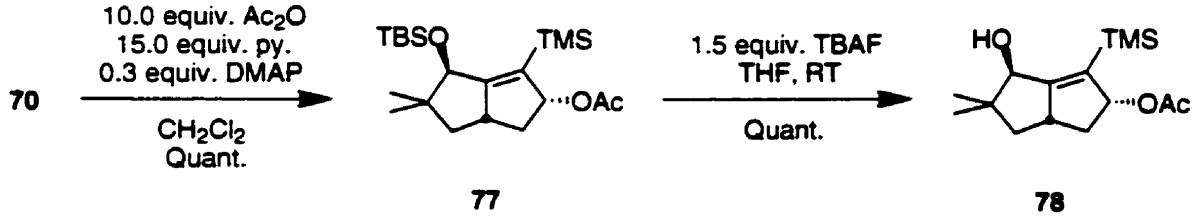


76

Altogether, the poor reactivities of the alcohol **74** and its derivative **76** were hypothesized to be due to the enone functionality of these substrates. Further efforts were therefore directed at the study of the substitution pattern on a related protected allylic alcohol, which was in turn obtained from the reduction of **66**. For the protection of alcohol **70**, an acetyl group was chosen taking account of its simplicity and ease of formation as well as its orthogonality with common silyl ether group cleaving techniques. Ester **77** was actually obtained in a quantitative yield. The *tert*-butyldimethylsilyl moiety of substrate **77** was then removed with tetrabutyl ammonium fluoride at room temperature, providing **78**. This transformation was also carried out in a quantitative yield (Scheme 38). It is interesting to

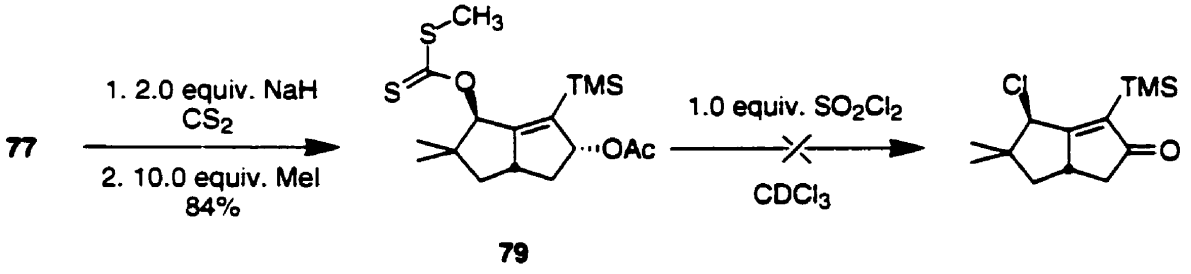
notice the difference of reactivity of **78** and **66** with this fluoride reagent, highlighting the chemical sensitivity of otherwise apparently simple structures.

Scheme 38 : Synthesis of ester 78



Unfortunately, attempts at substituting the hydroxyl group of **78** for a chloride via the xanthate intermediate **79** as proposed for **76** proved fruitless (Scheme 39).

Scheme 39: Attempt at chlorine substitution on xanthate 79

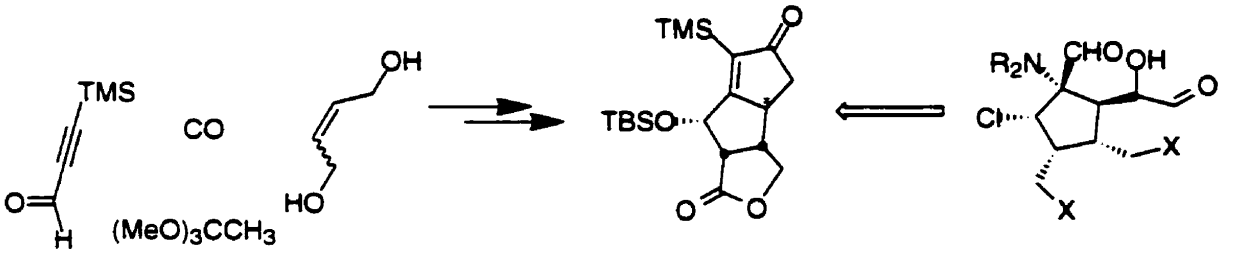


The reactivity of compound **78** was then studied in order to assess the viability of a double inversion method. The starting material **78** proved unreactive to a Mitsunobu procedure using diisopropyl azodicarboxylate, benzoic acid and triphenylphosphine.[68] Compound **78** was also found unreactive under the protocol developed by Barret *et al.*, employing the Vilsmeier Haack reagent formed *in situ* for activation of the alcohol for substitution with silver benzoate.[69]

Finally, direct chlorine introduction, with inversion from the alcohol **78**, was tried. A reaction carried out according to the procedure described by Appel *et al.* and centering on the use of triphenylphosphine and carbon tetrachloride in acetonitrile did not yield the desired chloride product. In a last attempt and following a protocol presented by Collington et al., *in situ* activation of alcohol **78** by mesylation and in presence of lithium chloride and collidine only provided with starting material.[70]

2. Conclusion

Through this work, an approach towards the total synthesis of palau'amine was designed with a focus at the central hexasubstituted cyclopentane ring. An enantiomerically pure core of this alkaloid has been synthesized via an Evans aldol type reaction and a Pauson-Khand cyclization reaction. Ultimately, the pathway to this tricyclic molecule was shortened and optimized by the use of an achiral starting material and a subsequent separation of diastereoisomers.



This work has also shown particularities of tin-catalyzed Evans aldols, and enabled the discovery of a new cobalt reactivity, as detailed in Part II.

The study of the final functionalization of the tricyclic core was undertaken onto a bicyclic model. Introduction of the desired nitrogen or alkoxy substituents was carried out, although the chlorine insertion remains a central difficulty on this model.

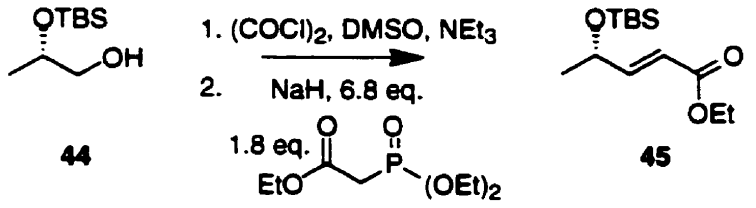
CONTRIBUTIONS TO KNOWLEDGE

During this total synthesis work, a number of advancements were made:

1. An alternate retrosynthetic analysis of palau'amine was designed.
2. A tricyclic core of this alkaloid was synthesized in an enantioselective fashion via a short and practical pathway.
3. During the course of this synthesis, the influence of a chiral substituent on a tin-catalyzed Anti-Evans aldol was observed and analyzed.
4. The study of a cobalt mediated key step led to the discovery of a new reaction.

EXPERIMENTAL

Ethyl (*S*)-4-((dimethylethyl)-dimethylsilyloxy)-2-pentenoate 45:



44 45

To a solution of oxalyl chloride (5.23 mL, 60.0 mmol, 2.00 equiv.) in dichloromethane (100 mL) at -78 °C was added a solution of dimethyl sulfoxide (5.35 mL, 75.0 mmol, 2.50 equiv.) in dichloromethane (5 mL). After 15 minutes, a solution of (*S*)-2-((dimethylethyl)-dimethylsilyloxy)-propanol **44** (5.70 g, 30.0 mmol, 1.00 equiv.) in dichloromethane (20 mL) was added, leading to the formation of a white suspension. After 40 minutes, triethylamine (20.90 mL, 150.0 mmol, 5.00 equiv.) was added to the reaction mixture which was then slowly warmed up to 0 °C. After stirring for 3 hours, NaH (6.00 g, 60%, 150.0 mmol, 5.00 equiv.) and THF (50 mL) were added. To this reaction mixture was then added a solution of triethylphosphonoacetate (7.14 mL, 36.0 mmol, 1.20 equiv.) and NaH (1.44 g, 60%, 36.0 mmol, 1.20 equiv.) in THF (80 mL) previously stirred at 0 °C for 20 minutes. After 1.5 hour, the reaction mixture was allowed to warm up to room temperature. After 2 hours, a solution of triethylphosphonoacetate (3.57 mL, 18.0 mmol, 0.60 equiv.) and NaH (720 mg, 60%, 18.0 mmol, 0.60 equiv.) in THF (40 mL) previously stirred at 0 °C for 20 minutes was added to the reaction mixture. After stirring for 13 hours, the reaction was quenched by cannulating the mixture onto a saturated aqueous solution of ammonium chloride (500 mL) at 0 °C. The resulting mixture was extracted with three portions of ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford ethyl (*S*)-4-((dimethylethyl)-dimethyl-silyloxy)-2-pentenoate **45** as a colorless oil (6.28 g, 24.3 mmol, 81%).

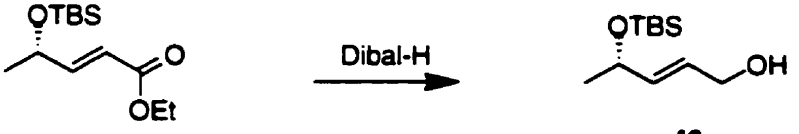
^{1}H NMR ($CDCl_3$, 270 MHz):

δ 6.93 (dd, 1H, J = 15.5 Hz, 4.2 Hz), 5.99 (dd, 1H, J = 15.5 Hz, 1.7 Hz), 4.45 (m, 1H), 4.19 (q, 2H, J = 6.4 Hz), 1.31 (d, 3H, J = 7.2 Hz), 1.27 (t, 3H, J = 6.4 Hz), 0.91(s, 9H), 0.06 (s, 6H);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 166.7 151.8, 119.2, 67.8, 59.7, 25.8, 23.6, 18.4, 14.2, -4.8.

(*S*)-4-((dimethylethyl)-dimethylsilyloxy)-2-pentenol 46:



45 **46**

To a solution of ethyl (*S*)-4-((dimethylethyl)-dimethylsilyloxy)-2-pentenoate **45** (6.28 g, 24.3 mmol, 1.00 equiv.) in toluene (60 mL) at -78 °C was added Dibal-H (40.50 mL, 1.5 M in toluene, 60.75 mmol, 2.50 equiv.). After stirring for 1 hour, the reaction mixture was warmed up to -10 °C. After stirring for another 1.5 hours, the reaction was quenched by the addition of Rachelle's salt (244 mL, 0.5 M in water, 121.50 mmol, 5.00 equiv.) and toluene (30 mL). The resulting mixture was stirred overnight and then extracted with four portions of ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (20% ethyl acetate in hexanes as eluent) to afford (*S*)-4-((dimethylethyl)-dimethylsilyloxy)-2-pentenol **46** as a colorless oil (4.78 g, 22.06 mmol, 91%).

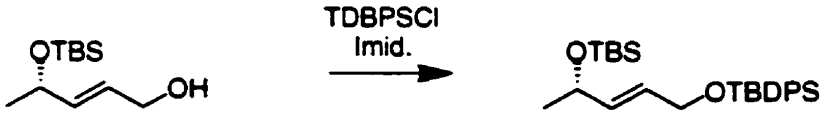
^{1}H NMR ($CDCl_3$, 270 MHz):

δ 5.74 (m, 2H), 4.34 (m, 1H), 4.13 (d, 2H, J = 3.9 Hz), 1.21 (d, 3H, J = 6.2 Hz), 0.91 (s, 9H), 0.06 (s, 6H);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 136.6, 127.5, 68.6, 63.2, 25.9, 24.4, 18.2, -4.5, -4.7.

(*S*)-4-((dimethylethyl)-dimethylsilyloxy)-((dimethylethyl)-diphenylsilyloxy)-2-pentene 47:



46 **47**

To a solution of (*S*)-4-((dimethylethyl)-dimethylsilyloxy)-2-pentenol **46** (3.93 g, 18.43 mmol, 1.00 equiv.) in DMF (50 mL) at 0°C was added imidazole (1.85 g, 27.20 mmol, 1.50 equiv.) and (dimethyl ethyl) diphenyl silylchloride (5.66 mL, 21.76 mmol, 1.2 equiv.). After stirring overnight, the reaction was quenched by pouring onto water. The resulting mixture was extracted with two portions of diethyl ether. The combined organic layers were washed with three portions of water and one portion of saturated aqueous ammonium chloride solution, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (20% ethyl acetate in hexanes as eluent) to afford (*S*)-4-((dimethylethyl)-dimethylsilyloxy)-((dimethylethyl) diphenylsilyloxy)-2-pentene **47** as a colorless oil (8.37 g, 18.40 mmol, quantitative).

^{1}H NMR ($CDCl_3$, 270 MHz):

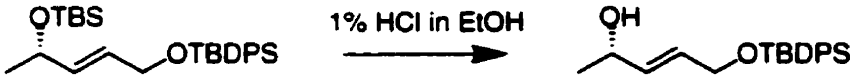
δ 7.69 (m, 4H), 7.38 (m, 6H), 5.70 (m, 2H), 4.32 (m, 1H), 4.18 (d, 2H, J = 4.2 Hz), 1.20 (d, 3H, J = 6.2 Hz), 1.06 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 135.6, 134.2, 133.7, 129.8, 128.8, 127.5, 68.5, 63.2, 26.2, 24.3, 23.3, 19.3, 18.2, -4.3, -4.6.

Anal. calcd for $C_{27}H_{42}O_2Si_2$: C 71.31%, H 9.31%; found C 71.58%, H 9.18%.

(*S*)- ((dimethylethyl)-diphenylsilyloxy)-2-penten-4-ol 43:



47 **43**

(*S*)-4-((dimethylethyl)-dimethylsilyloxy)-((dimethylethyl)-diphenylsilyloxy)-2-pentene **47** (12.37 g, 34.20 mmol, 1.00 equiv.) was added to a 1% w/w HCl/water (97 g) solution at 0 °C. After stirring for 2.2 hours, the reaction was quenched by adding saturated aqueous sodium carbonate solution till the pH of the mixture equaled 7. The ethanol was removed under vacuum and the resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by filtration on silica gel to afford (*S*)-4-((dimethylethyl)-diphenylsilyloxy)-2-penten-4-ol **43** as a colorless oil (10.35 g, 30.25 mmol, 88%).

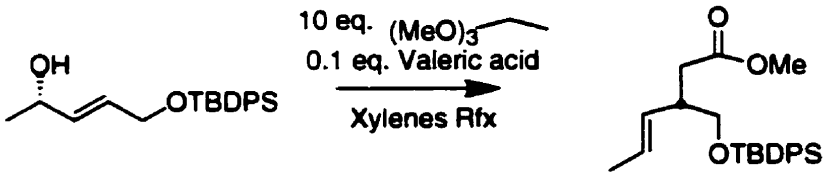
^{1}H NMR ($CDCl_3$, 270 MHz):

δ 7.65 (m, 4H), 7.40 (m, 6H), 5.74 (m, 2H), 4.32 (m, 1H), 4.20 (d, 2H, J = 4.7 Hz), 1.38 (d, 1H, J = 4.8 Hz), 1.24 (d, 3H, J = 6.4 Hz), 1.06 (s, 9H);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 135.6, 134.1, 133.8, 129.8, 128.9, 127.7, 68.4, 63.9, 26.9, 23.3, 19.3.

Compound 42:



43 **42**

To a solution of (*S*)-4-((dimethylethyl)-diphenylsilyloxy)-2-penten-4-ol **43** (3.90 g, 17.55 mmol, 1.00 equiv.) in xylenes (100 mL) at room temperature was added trimethyl orthoacetate (22.34 mL, 175.54 mmol, 10.00 equiv.) and valeric acid (190 µl, 1.76 mmol, 0.10 equiv.). The mixture was then brought to reflux. After stirring overnight, the reaction was quenched with saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with one portion of ethyl acetate. After saturation with sodium chloride, the aqueous phase was extracted with three portions of ethyl acetate. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to afford compound **42** as a colorless oil (4.64 g, 16.67 mmol, 95%).

^{1}H NMR ($CDCl_3$, 270 MHz):

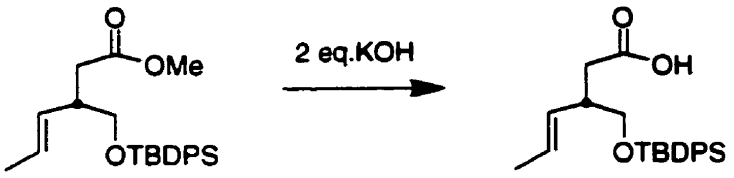
δ 7.68 (m, 4H), 7.41 (m, 6H), 5.52 (dt, 1H, *J* = 7.2 Hz, 14.8 Hz), 5.35 (dd, 1H, *J* = 14.8 Hz, 7.4 Hz), 3.68 (m, 1H), 3.66 (s, 3H), 3.55 (m, 1H), 2.79 (m, 1H), 2.73 (d, 1H, *J* = 14.8 Hz), 2.35 (dd, 1H, *J* = 14.8 Hz, 8.4 Hz), 1.65 (d, 3H, *J* = 7.2 Hz), 1.09 (s, 9H);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 173.1, 135.5, 133.5, 130.4, 129.6, 127.6, 126.9, 66.7,51.3, 41.7, 36.4, 26.8, 19.2, 18.0.

Anal. calcd for $C_{24}H_{32}O_3Si$: C 72.68%, H 8.13%; found C 72.57%, H 8.25%.

Compound 49:



42 **49**

To a solution of compound **42** (6.46 g, 16.37 mmol, 1.00 equiv.) in methanol (75 mL) at room temperature was added KOH (1.84 g, 32.70 mmol, 2.00 equiv.). The mixture was then brought to 45 °C. After stirring for 48 hours, the reaction mixture was cooled down to room temperature and concentrated. The reaction was quenched with saturated aqueous ammonium chloride solution. The resulting mixture was extracted with three portions of dichloromethane. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum to afford compound **49** as a colorless oil (5.77 g, 15.09 mmol, 92%).

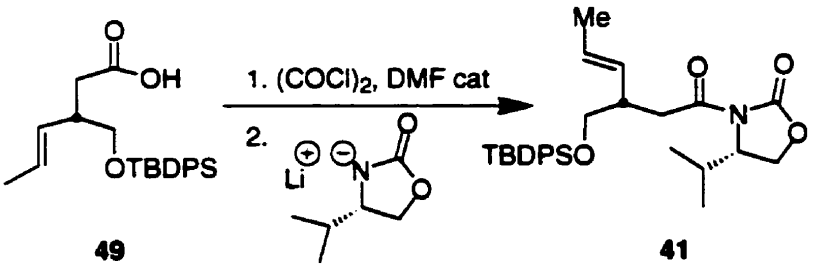
^{1}H NMR ($CDCl_3$, 270 MHz):

δ 7.67 (m, 4H), 7.41 (m, 6H), 5.52 (m, 1H), 5.35 (m, 1H), 3.65 (m, 1H), 3.52 (m, 1H), 2.75 (m, 2H), 2.36 (d, 1H, J = 14.8 Hz), 2.35 (m, 1H.), 1.65 (d, 3H, J = 5.9 Hz), 1.07 (s, 9H);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 179.2, 135.6, 133.2, 130.4, 129.6, 127.6, 126.8, 66.8, 41.4, 36.6, 26.8, 19.2, 18.0.

Compound 41:



To a solution of **49** (1.08 g, 2.82 mmol, 1.00 equiv.) in dichloromethane (20 mL) at room temperature was added oxalyl chloride (374 µl, 4.23 mmol, 1.50 equiv.) and DMF (11 µl, 0.14 mmol, 0.05 equiv.). After stirring for 2 hours, the mixture was concentrated under vacuum. A solution of the residue in THF (10 mL) was added to a mixture of (*S*)-(-)-4-isopropyl-2-oxazolidinone (401 mg, 3.10 mmol, 1.10 equiv.) and butyl lithium (1.17 mL, 2.635M in hexanes, 3.10 mmol, 1.10 equiv.) in THF (20 mL) previously stirred for 30 minutes at -78 °C. After stirring at this temperature for 3 hours, the reaction was quenched with saturated aqueous ammonium chloride solution. The resulting mixture was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to afford compound **41** (1.06 g, 2.16 mmol, 77%) in crystalline form.

^{1}H NMR ($CDCl_3$, 270 MHz):

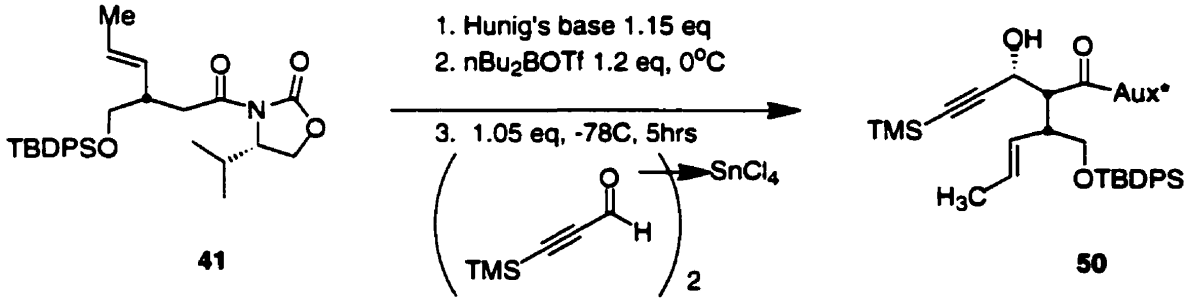
δ 7.65 (m, 4H), 7.37 (m, 6H), 5.47 (dq, 1H, *J* = 15.3 Hz, 6.2 Hz), 5.30 (dd, 1H, *J* = 15.3 Hz, 8.2 Hz), 4.40 (m, 1H), 4.19 (m, 2H), 3.59 (m, 2H), 3.23 (dd, 1H, *J* = 13.7 Hz, 4.7 Hz), 2.98 (dd, 1H, *J* = 13.7 Hz, 7.2 Hz), 2.85 (br s, 1H), 2.30 (m, 1H), 1.61 (d, 3H, *J* = 6.2 Hz), 1.03 (s, 9H), 0.89 (d, 3H, *J* = 6.8 Hz), 0.84 (d, 3H, *J* = 6.8 Hz);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 172.3, 154.0, 135.6, 133.7, 130.9, 129.5, 127.6, 127.1, 67.0, 63.2, 58.4, 41.5, 37.4, 28.4, 26.8, 19.3, 18.0, 14.6.

Anal. calcd for $C_{29}H_{39}NO_4Si$: C 70.55%, H 7.96%, N 2.84%; found C 70.45%, H 7.67%, N 2.70%.

Compound 50:



To a solution of compound **41** (1.06 g, 2.15 mmol, 1.00 equiv.) in dichloromethane (9 mL) at 0 °C were added successively diisopropylethylamine (430 µl, 2.47 mmol, 1.15 equiv.) and dibutylboron triflate (1.56 mL, 1.651 M in hexanes, 2.58 mmol, 1.20 equiv.). After stirring for 2.5 hours, the solution was cooled down to -78 °C. To this reaction mixture was added a solution of trimethylsilyl propargyl aldehyde (675 µl, 4.52 mmol, 2.10 equiv.) and tin tetrachloride (264 µl, 2.26 mmol, 1.05 equiv.) in dichloromethane (9 mL) previously stirred for 5 minutes at -78 °C. After stirring at this temperature for 5 hours, the reaction was quenched by the addition of a solution of H_2O_2 (2 mL, 30% in water) and methanol (8 mL) and brought to 0 °C. After stirring for 30 minutes, the resulting mixture was extracted with three portions of dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution and brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to afford compound **50** (0.92 g, 1.48 mmol, 69%) in crystalline form.

^{1}H NMR ($CDCl_3$, 270 MHz):

δ 7.62 (m, 4H), 7.39 (m, 6H), 5.54 (m, 2H), 4.83 (t, 1H, J = 6.5 Hz), 4.52 (m, 1H), 4.12 (m, 1H), 4.02 (m, 1H), 3.73 (m, 2H), 3.12 (d, 1H, J = 6.4 Hz), 2.91 (m, 1H), 2.33 (m, 1H), 1.61

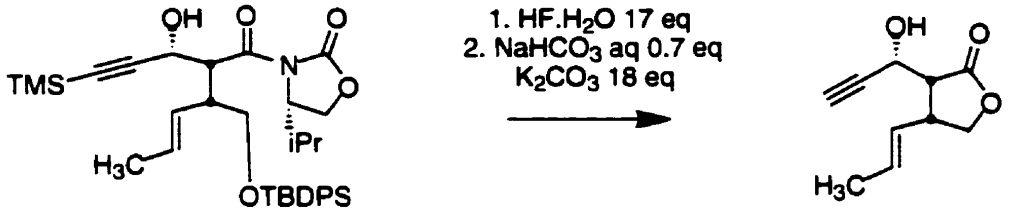
(d, 3H, J = 4.7 Hz), 1.05 (s, 9H), 0.89 (d, 6H, J = 6.5 Hz), 0.15 (s, 9H);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 171.6, 154.1, 135.6, 133.6, 130.4, 129.7, 129.1, 127.7, 104.4, 91.4, 65.9, 63.7, 63.4, 58.8, 50.0, 45.8, 28.9, 26.9, 19.3, 17.9, 15.1, -0.2.

Anal. calcd for $C_{35}H_{49}NO_5Si_2$: C 67.81%, H 7.97%, N 2.26%; found C 67.96%, H 8.11%, N 2.16%.

Compound 51:



50 **51**

To a solution of compound **50** (1.70 g, 2.74 mmol, 1.00 equiv.) in acetonitrile (150 mL) at room temperature was added aqueous HF (1.70 mL, 48% w/w HF/H_2O, 46.60 mmol, 17.00 equiv.). After 3 hours, the reaction mixture was treated with saturated aqueous sodium bicarbonate solution (2.50 mL, 0.9 M in H_2O, 1.92 mmol, 0.70 equiv.) and potassium carbonate (3.68 g, 49.30 mmol, 18.00 equiv.). After stirring overnight, the reaction was quenched by the addition of water (100 mL) and diethyl ether (100 mL). The resulting mixture was extracted with two portions of diethyl ether. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (30% ethyl acetate in hexanes as eluent) to afford compound **51** as a colorless oil (0.43 g, 2.41 mmol, 88%).

^{1}H NMR ($CDCl_3$, 270 MHz):

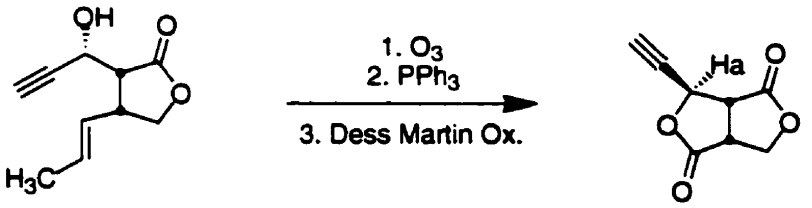
δ 5.67 (m, 2H), 4.60 (m, 1H), 4.36 (t, 1H, J = 7.9Hz), 4.20 (dd, 1H, J = 7.9 Hz, 8.9Hz), 3.39

(m, 1H), 2.96 (m, 2H), 2.57 (d, 1H, J = 2.0 Hz), 1.71 (d, 1H, J = 4.9 Hz);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 176.4, 130.9, 125.4, 82.3, 75.3, 72.2, 60.5, 50.0, 41.3, 17.7.

Compound 52:



51 **52**

Through a solution of compound **51** (51.4 mg, 0.29 mmol, 1.00 equiv.) and indicator Sudan III (0.5 mg) in dichloromethane (20 mL) at - 78 °C was bubbled a stream of ozone until the red color faded. Triphenylphosphine (112.0 mg, 0.43 mmol, 1.50 equiv.) was added to the reaction mixture which was then warmed up to room temperature. After stirring 10 minutes, the solution was concentrated under vacuum. The residue was dissolved in dichloromethane (5 mL). This solution was treated with Dess-Martin periodinane (212.5 mg, 0.50 mmol, 1.70 equiv.) at room temperature. After 9 hours, the reaction was diluted with diethyl ether and quenched by the addition of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulphate solution. The resulting mixture was extracted with four portions of diethyl ether. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (50% ethyl acetate in hexanes as eluent) to afford compound **52** as a colorless oil (23.0 mg, 0.14 mmol, 47%).

^{1}H NMR ($CDCl_3$, 270 MHz):

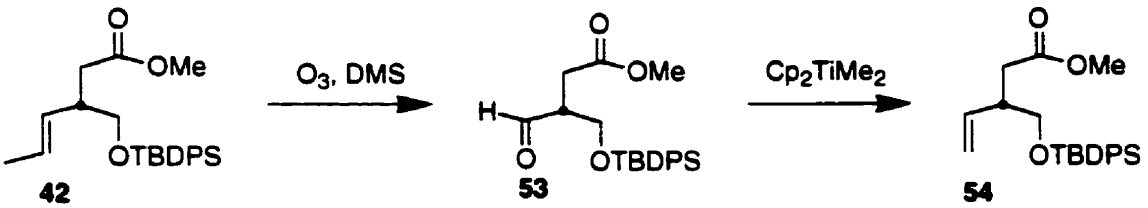
δ 5.41 (d, 1H, J = 1.3 Hz), 4.71 (d, 1H, J = 9.6Hz), 4.55 (dd, 1H, J = 9.6 Hz, 6.4 Hz), 3.62 (m, 2H), 2.75 (s, 1H);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 174.3, 173.2, 78.1, 77.6, 69.5, 68.9. 47.4, 40.2.

Anal. calcd for $C_8H_6O_4$: C 57.84%. H 3.64%; found C 57.71%. H 3.52%.

Compound (*S*)-54:



Through a solution of compound **42** (210.0 mg, 0.53 mmol, 1.00 equiv.) and indicator Sudan III (0.5 mg) in dichloromethane (20 mL) at - 78 °C was bubbled a stream of ozone until the red color faded. Dimethylsulfide (117.0 µl, 1.59 mmol, 3.00 equiv.) was added to the reaction mixture which was then warmed up to room temperature. After stirring overnight, the solution was concentrated under vacuum. The residue was dissolved in toluene (5 mL). This solution was treated with dimethyl titanocene (133.0 mg, 0.64 mmol, 1.20 equiv.) at room temperature before being brought to 60 °C and stirred overnight in the absence of light. The reaction was then cooled down to room temperature and diluted with diethyl ether. The resulting mixture was filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford compound (*S*)-**54** as a colorless oil (131.8 mg, 0.35 mmol, 65%).

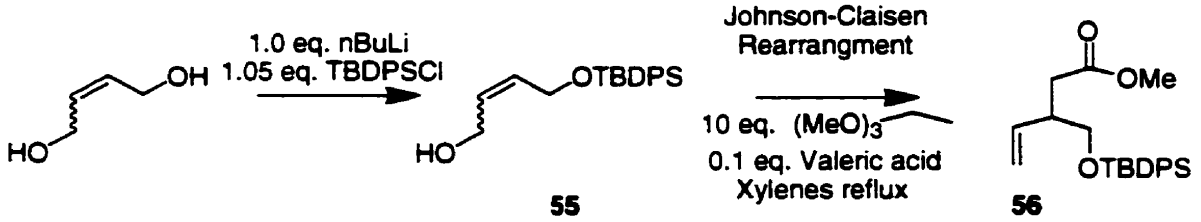
^1H NMR ($CDCl_3$, 270 MHz):

δ 7.63 (m, 4H), 7.38 (m, 6H), 5.70 (m, 1H), 5.05 (d, 1H, J = 19.1Hz), 5.01 (d, 1H, J = 6.8 Hz), 3.61 (m, 4H), 3.54 (m, 1H), 2.71 (m, 1H), 2.66 (dd, 1H, J = 5.7 Hz, 15.1 Hz), 2.35 (dd, 1H, J = 4.75 Hz, 15.1 Hz), 1.03 (s, 9H);

^{13}C NMR ($CDCl_3$, 100.61 MHz):

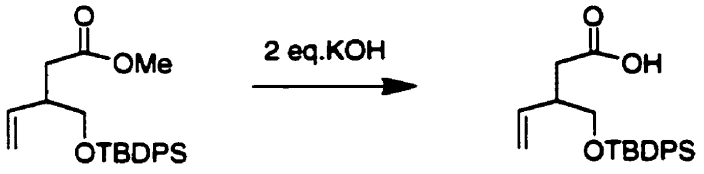
δ 174.0, 135.6, 133.5, 132.4, 129.5, 127.7, 129.9, 67.8, 51.4, 41.5, 37.4. 26.6, 18.1.

Compound 56 (racemate):



To a solution of 1,4-butene diol (500 mg, 5.67 mmol, 1.00 equiv.) in THF (20 mL) at -78 °C was added a 2.65 M solution of butyl lithium in hexanes (2.15 mL, 5.67 mmol, 1.00 equiv.). After stirring for 20 minutes, tert-butyldiphenylsilyl chloride (1.55 mL, 5.96 mmol, 1.05 equiv.) was added to the reaction mixture. After 5 minutes, the reaction was allowed to warm up to 0 °C. After stirring for 1 hour, the reaction was quenched with saturated aqueous ammonium chloride solution. The resulting mixture was extracted with two portions of ethyl acetate. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum. To a solution of the residue in xylenes (50 mL) at room temperature was added trimethyl orthoacetate (2.17 mL, 17.01 mmol, 3.50 equiv.) and valeric acid (31 µl, 0.28 mmol, 0.05 equiv.). The mixture was then brought to reflux. After stirring for 5 hours, the reaction was cooled down to room temperature and quenched with saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with one portion of ethyl acetate. After saturation with NaCl, the aqueous phase was extracted with three portions of ethyl acetate. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford racemate **56** as a colorless oil (1.98 g, 5.37 mmol, 95%).

Compound 57:



56 **57**

To a solution of compound **56** (1.98 g, 5.37 mmol, 1.00 equiv.) in methanol (25 mL) at room temperature was added KOH (527 mg, 9.40 mmol, 1.75 equiv.). The mixture was then brought to 50 °C. After stirring for 48 hours, the reaction mixture was cooled down to room temperature and concentrated. The reaction was quenched with saturated aqueous ammonium chloride solution. The resulting mixture was extracted with three portions of dichloromethane. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum to afford compound **57** as a colorless oil (1.80 g, 4.89 mmol, 91%).

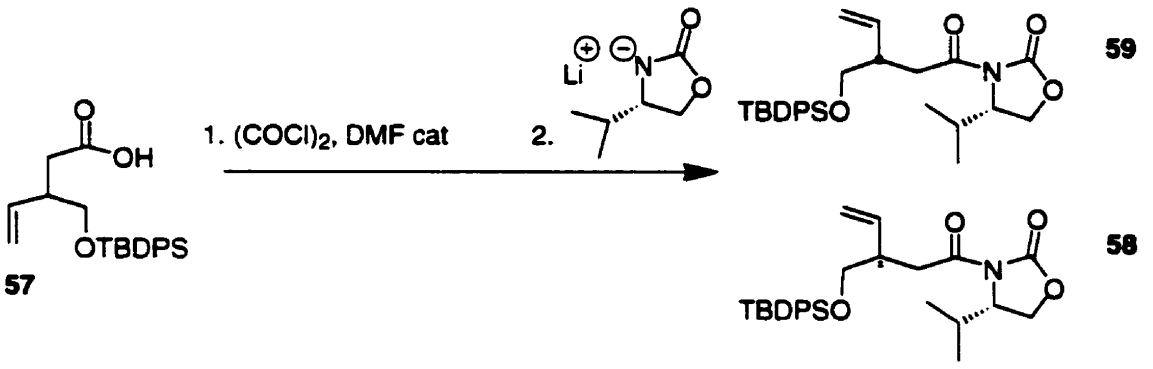
^{1}H NMR ($CDCl_3$, 270 MHz):

δ 7.59 (dd, 4H, J =1.9Hz, 6.4 Hz), 7.30 (m, 6H), 5.68 (m, 1H), 5.00 (d, 1H, J = 17.2 Hz), 4.92 (d, 1H, J = 10.6 Hz), 3.53 (s, 1H), 3.45 (d, 2H, J = 5.7 Hz), 2.64 (m, 1H), 2.40, (dd, 1H, J = 3.6 Hz, 15.3 Hz), 2.12 (dd, 1H, J = 11.4 Hz, 15.3 Hz), 0.98 (s, 9H);

^{13}C NMR ($CDCl_3$, 100.61 MHz):

δ 180.5, 135.7, 134.9, 133.7, 129.6, 127.7, 115.6, 67.1, 60.4, 43.2, 26.8, 19.3.

Compounds 58 and 59:



To a solution of compound **57** (15.61 g, 42.37 mmol, 1.00 equiv.) in dichloromethane (100 mL) at room temperature was added oxalyl chloride (5.61 mL, 63.56 mmol, 1.50 equiv.) and DMF (165 µl, 2.10 mmol, 0.05 equiv.). After stirring for 2 hours, the mixture was concentrated under vacuum. To a solution of the residue in THF (150 mL) was cannulated a mixture of (*S*)-(-)-4-isopropyl-2-oxazolidinone (5.63 g, 43.64 mmol, 1.03 equiv.) and butyl lithium (15.95 mL, 2.71M in hexanes, 43.22 mmol, 1.02 equiv.) in THF (100 mL) previously stirred for 25 minutes at -78 °C. After stirring at this temperature overnight, the reaction was quenched with saturated aqueous ammonium chloride solution. The resulting mixture was extracted with three portions of ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to afford compound **58** (7.30 g, 15.22 mmol, 72%) and **59** (8.35 g, 17.40 mmol, 82%) in crystalline form.

Compound 58:

^{1}H NMR ($CDCl_3$, 270 MHz):

δ 7.65 (m, 4H), 7.39 (m, 6H), 5.81 (m, 1H), 5.09 (d, 1H, J = 14.5 Hz), 5.05 (d, 1H, J = 9.1 Hz), 4.37 (m, 1H), 4.15 (m, 2H), 3.66 (m, 2H), 3.19 (m, 2H), 2.95 (m, 1H), 2.31 (m, 1H), 1.05 (s, 9H), 0.87 (d, 3H, J = 6.9 Hz), 0.83 (d, 3H, J = 6.9 Hz);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 172.3, 154.1, 137.4, 135.6, 133.3, 129.2, 127.8, 119.1, 66.7, 63.4, 58.8, 41.9, 38.0, 28.6, 26.2, 19.3, 18.8, 14.5.

Compound 59:

^{1}H NMR ($CDCl_3$, 270 MHz):

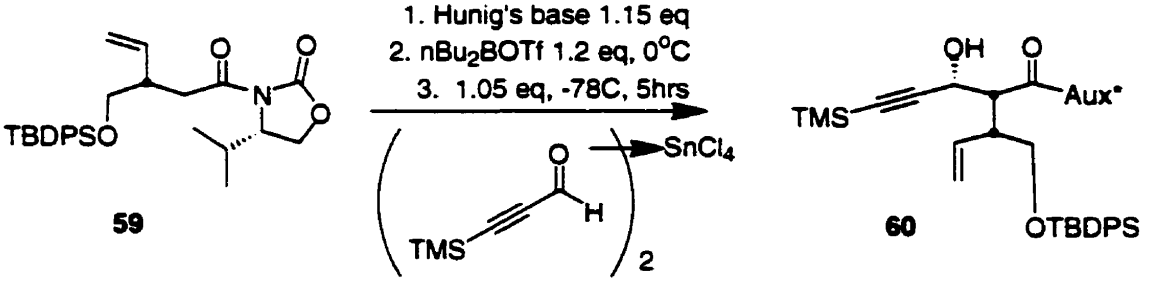
δ 7.65 (m, 4H), 7.39 (m, 6H), 5.78 (m, 1H), 5.08 (d, 1H, J = 16.5 Hz), 5.05 (d, 1H, J = 8.7 Hz), 4.40 (m, 1H), 4.18 (m, 2H), 3.66 (m, 2H), 3.24 (A of ABX, 1H, J = 16.2 Hz, 2.7 Hz), 3.07 (B of ABX, 1H, J = 16.2 Hz, 8.1 Hz), 2.82 (m, 1H), 2.31 (m, 1H), 1.05 (s, 9H), 0.88 (d, 3H, J = 6.9 Hz), 0.83 (d, 3H, J = 6.9 Hz);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 172.1, 154.1, 137.5, 135.6, 133.5, 129.6, 127.7, 118.9, 66.9, 63.4, 58.7, 42.2, 38.0, 28.7, 26.9, 19.3, 17.9, 14.5.

Anal. calcd for $C_{28}H_{37}NO_4Si$: C 70.11%, H 7.77%, N 2.92%; found C 69.96%, H 7.83%, N 2.97%.

Compound 60:



To a solution of compound **59** (7.93 g, 16.53 mmol, 1.00 equiv.) in dichloromethane (60 ml) at 0 °C were added successively diisopropylethylamine (3.45 mL, 19.01 mmol, 1.15 equiv.) and dibutylboron triflate (6.41 mL, 3.097 M in hexanes, 19.84 mmol, 1.20 equiv.).

After stirring for 3.8 hours, the solution was cooled down to -78 °C. To this reaction mixture was added a solution of trimethylsilyl propargyl aldehyde (5.19 mL, 34.72 mmol, 2.10 equiv.) and tin tetrachloride (2.03 mL, 17.36 mmol, 1.05 equiv.) in dichloromethane (80 mL) previously stirred for 5 minutes at -78 °C. After stirring at this temperature for 7.5 hours, the reaction was quenched by the addition of a solution of H_2O_2 (22 mL, 30% in water) and methanol (90 mL) and brought slowly to room temperature. After stirring for 1 hour, the resulting mixture was extracted with three portions of dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution and brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to afford compound **60** as white crystals (8.18 g, 13.51 mmol, 82%).

^{1}H NMR ($CDCl_3$, 270 MHz):

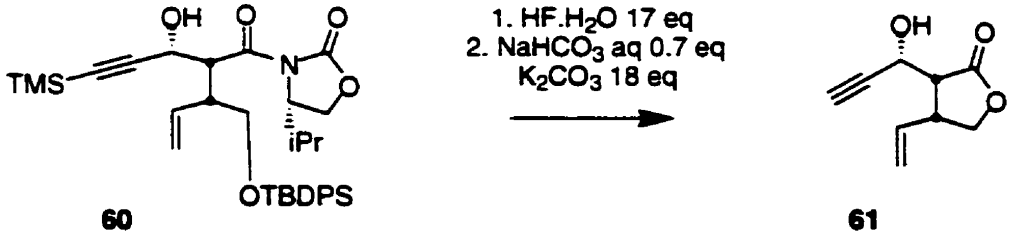
δ 7.61 (m, 4H), 7.37 (m, 6H), 5.99 (dt, 1H, J = 9.9 Hz, 17.1 Hz), 5.09 (m, 2H), 4.82 (m, 1H), 4.57 (t, 1H, J = 6.91 Hz), 4.32 (m, 1H), 4.11 (m, 2H), 3.77 (m, 2H), 2.96 (m, 1H), 2.35 (m, 1H), 1.04 (s, 9H), 0.87 (d, 6H, J = 6.9 Hz), 0.14 (s, 9H);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 171.4, 154.2, 137.4, 135.6, 133.3, 129.7, 127.7, 118.4, 103.7 91.6, 65.3, 63.5, 63.3, 58.7, 49.8, 46.7, 28.7, 26.9, 19.3, 17.9, 15.0, -0.2.

Anal. calcd for $C_{34}H_{47}NO_5Si_2$: C 67.40%, H 7.82%, N 2.31%; found C 67.17%, H 7.87%, N 2.22%.

Compound 61:

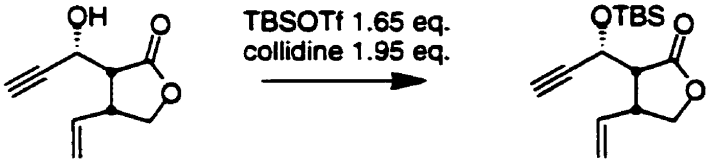


60 **61**

To a solution of compound **60** (2.14 g, 3.54 mmol, 1.00 equiv.) in acetonitrile (140 mL) at room temperature was added aqueous HF (2.18 mL, 48% w/w HF/H_2O, 60.13 mmol, 17.00 equiv.). After 3 hours, the reaction mixture was treated with saturated aqueous sodium bicarbonate solution (2.75 mL, 0.9 M in H_2O, 2.48 mmol, 0.70 equiv.) and potassium carbonate (8.81 g, 63.72 mmol, 18.00 equiv.). After stirring overnight, the reaction was quenched by the addition of water (100 mL) and diethyl ether (100 mL). The resulting mixture was extracted with two portions of diethyl ether. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (30% ethyl acetate in hexanes as eluent) to afford compound **61** as a colorless oil (0.46 g, 2.76 mmol, 78%).

^{1}H NMR ($CDCl_3$, 270 MHz):
δ 6.04 (dt, 1H, J = 17.0 Hz, 9.4 Hz), 5.27 (d, 1H, J = 17.0 Hz), 5.25 (d, 1H, J = 9.4 Hz), 4.64 (m, 1H), 4.38 (t, 1H, J = 7.9 Hz), 4.24 (d, 1H, J = 7.9 Hz), 3.43 (p, 1H, J = 7.9 Hz), 3.04 (d, 1H, J = 8.6), 2.98 (dd, 1H, J = 9.6 Hz, 4.2 Hz), 2.57 (d, 1H, J = 2.2 Hz);
^{13}C NMR ($CDCl_3$, 67.94 MHz):
δ 176.5, 132.5, 119.9, 81.9, 75.5, 71.8, 60.1, 49.5, 42.0

Compound 62:



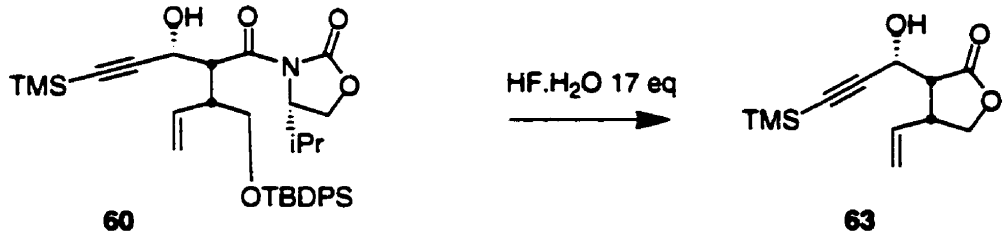
61 **62**

To a solution of lactone **61** (97.5 mg, 0.59 mmol, 1.00 equiv.) in dichloromethane (5 mL) at 0 °C were added successively collidine (101 µl, 0.76 mmol, 1.30 equiv.) and *tert*-

butyldimethylsilyl triflate (148 µl, 0.65 mmol, 1.10 equiv.). After stirring for 30 minutes, the reaction mixture was allowed to warm to room temperature. After 3 hours, collidine (50 µl, 0.38 mmol, 0.65 equiv.) and tert-butyldimethylsilyl triflate (74 µl, 0.32 mmol, 0.55 equiv.) were added successively to the reaction mixture. The reaction was quenched with saturated aqueous ammonium chloride solution. The resulting mixture was extracted with three portions of ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford compound **62** as a colorless oil (145.0 mg, 0.52 mmol, 88%).

^{1}H NMR ($CDCl_3$, 270 MHz):
δ 6.27 (dt, 1H, *J* = 17.3 Hz, 9.6 Hz), 5.20 (d, 1H, *J* = 17.3 Hz), 5.16 (d, 1H, *J* = 9.6 Hz), 4.96 (m, 1H), 4.31 (t, 1H, *J* = 8.7 Hz), 4.10 (d, 1H, *J* = 8.7 Hz), 3.38 (p, 1H, *J* = 8.7 Hz), 2.77 (dd, 1H, *J* = 9.6 Hz, 2.5 Hz), 2.47 (d, 1H, *J* = 2.5 Hz), 0.87 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H);
^{13}C NMR (CDCl3, 100.62 MHz):
δ 177.0, 133.2, 119.5, 82.3, 74.8, 71.7, 61.5, 48.6, 42.9, 25.6, 18.2, -4.5, -5.1.

Compound 63:



60 **63**

To a solution of compound **60** (1.21 g, 2.00 mmol, 1.00 equiv.) in acetonitrile (140 mL) at room temperature was added aqueous HF (1.23 mL, 48% w/w HF/H_2O, 33.95 mmol, 17.00 equiv.). After 3 hours, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with two portions of

diethyl ether. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (30% ethyl acetate in hexanes as eluent) to afford compound **63** as a colorless oil (0.44 g, 1.86 mmol, 93%).

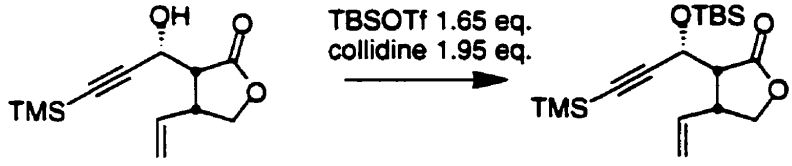
1H NMR (CDCl3, 270 MHz):
δ 6.03 (dt, 1H, J = 17.0 Hz, 8.6 Hz), 5.24 (d, 1H, J = 17.0 Hz), 5.21 (d, 1H, J = 8.6 Hz), 4.60 (m, 1H), 4.35 (t, 1H, J = 5.5 Hz), 4.20 (d, 1H, J = 8.1 Hz), 3.40 (m, 1H), 3.07 (m, 1H), 2.94 (m, 1H), 0.13 (s, 9H);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 176.6, 132.6, 119.7, 103.4, 92.2, 71.7, 63.6, 49.6, 42.1, -0.5.

Anal. calcd for $C_{12}H_{18}O_3Si$: C 60.47%, H 7.61%; found C 60.37%, H 7.50%.

Compound 64:



63 **64**

To a solution of lactone **63** (91.6 mg, 0.45 mmol, 1.00 equiv.) in dichloromethane (5 mL) at 0 °C were added successively collidine (78 µl, 0.59 mmol, 1.30 equiv.) and *tert*-butyldimethylsilyl triflate (115 µl, 0.50 mmol, 1.10 equiv.). After stirring for 30 minutes, the reaction mixture was allowed to warm to room temperature. After 3 hours, collidine (39 µl, 0.30 mmol, 0.65 equiv.) and tert-butyldimethylsilyl triflate (58 µl, 0.25 mmol, 0.55 equiv.) were added successively to the reaction mixture. The reaction was quenched with saturated aqueous ammonium chloride solution. The resulting mixture was extracted with three portions of ethyl acetate. The combined organic layers were washed with brine, dried with

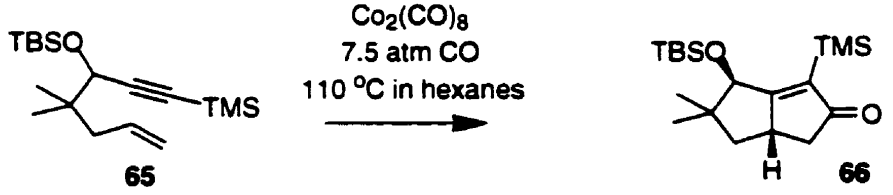
sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford compound **64** as white crystals (107.7 mg, 0.34 mmol, 75%).

^{1}H NMR ($CDCl_3$, 270 MHz):

δ 6.27 (dt, 1H, *J* = 16.8 Hz, 9.4 Hz), 5.21 (d, 1H, *J* = 16.8 Hz), 5.12 (d, 1H, *J* = 9.4 Hz), 4.93(d, 1H, *J* = 2.5 Hz), 4.29 (t, 1H, *J* = 8.4 Hz), 4.10 (d, 1H, *J* = 8.7 Hz), 3.38 (p, 1H, *J* = 9.3 Hz), 2.77 (dd, 1H, *J* = 9.6, 2.5 Hz), 0.86 (s, 9H), 0.86 (s, 9H), 0.15 (s, 6H), 0.13 (s, 9H);

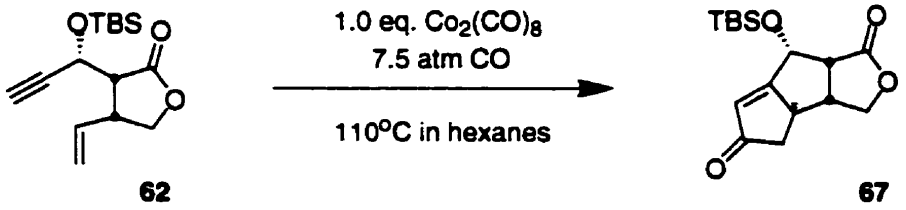
13C NMR ($CDCl_3$, 100.62 MHz):
δ 177.2, 133.9, 118.3, 104.6, 92.4, 72.6, 63.5, 50.1, 43.4, 25.8, 18.2, -0.3, -4.6, -5.3.

Compound 66, catalytic process:



To a solution of compound **65** (48.7 mg, 0.15 mmol, 1.00 equiv.) in hexanes (5 mL) at room temperature was added $Co_2(CO)_8$ (5.1 mg, 0.02 mmol, 0.10 equiv.). The system was purged twice by successively bringing under 7.5 atm of carbon monoxide and releasing the pressure. After ultimately placing the system under 7.5 atm of carbon monoxide, the reaction mixture was brought to 110 °C. After 24 hours, the reaction mixture was allowed to cool down to room temperature, after which the pressure was released. The mixture was filtered through Celite and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford compound **66** as a colorless oil (41.3 mg, 0.12 mmol, 78%).

Compound 67:



62 **67**

To a solution of lactone **62** (45.0 mg, 0.16 mmol, 1.00 equiv.) in hexanes (5 mL) at room temperature was added $Co_2(CO)_8$ (55.2 mg, 0.16 mmol, 1.00 equiv.). The system was purged twice by successively bringing under 7.5 atm of carbon monoxide and releasing the pressure. After ultimately placing the system under 7.5 atm of carbon monoxide, the reaction mixture was brought to 110 °C. After 24 hours, the reaction mixture was allowed to cool down to room temperature, after which the pressure was released. The reaction mixture was concentrated and the residue dissolved in a mixture of water (1 mL) and acetone (9 mL). The reaction was quenched by treating with ceric ammonium nitrate (440.0 mg, 0.80 mmol, 5.00 equiv.) and stirred until the resulting mixture had become a clear solution. The mixture was concentrated under vacuum and extracted with three portions of ethyl acetate. The organic layers were combined, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (50% ethyl acetate in hexanes as eluent) to afford compound **67** as a colorless oil (30.1 mg, 0.10 mmol, 61%).

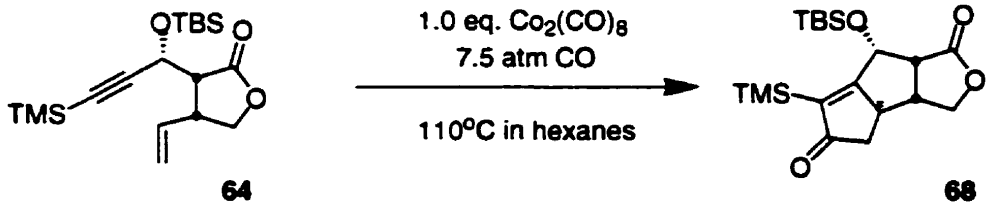
1H NMR (CDCl3, 270 MHz):

δ 5.92 (d, 1H, 2.0 Hz), 5.03 (d, 1H, J = 4.9 Hz), 4.6$_6$ (t, 1H, J = 9.3 Hz), 4.19 (dd, 1H, J = 9.3 Hz, 6.7 Hz), 3.34 (br s, 1H), 3.24 (dd, 1H, J = 4.9 Hz, 10.9 Hz), 2.85 (dd, 1H, J = 18.0 Hz, 7.2 Hz), 2.79 (m, 1H), 2.19 (dd, 1H, J = 18.0 Hz, 3.5 Hz), 0.85 (s, 9H), 0.14 (s, 3H), 0.06 (s, 3H);

13C NMR (CDCl3, 67.94 MHz):

δ 208.7, 183.8, 173.5, 123.8, 74.5, 69.2, 52.9, 47.8, 43.4, 42.9, 25.5, 17.9, -4.8, -5.3.

Compound 68, stoichiometric process:



64 **68**

To a solution of lactone **64** (52.3 mg, 0.17 mmol, 1.00 equiv.) in hexanes (5 mL) at room temperature was added $Co_2(CO)_8$ (56.5 mg, 0.17 mmol, 1.00 equiv.). The system was purged twice by successively bringing under 7.5 atm of carbon monoxide and releasing the pressure. After ultimately placing the system under 7.5 atm of carbon monoxide, the reaction mixture was brought to 110 °C. After 24 hours, the reaction mixture was allowed to cool down to room temperature, after which the pressure was released. The reaction mixture was concentrated and the residue dissolved in a mixture of water (1 mL) and acetone (9mL). The reaction was quenched by treating with ceric ammonium nitrate (453.0 mg, 0.83 mmol, 5.00 equiv.) and stirred until the resulting mixture had become a clear solution. The mixture was concentrated under vacuum and extracted with three portions of ethyl acetate. The organic layers were combined, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (15% ethyl acetate in hexanes as eluent) to afford compound **68** as a colorless oil (45.0 mg, 0.13 mmol, 61%).

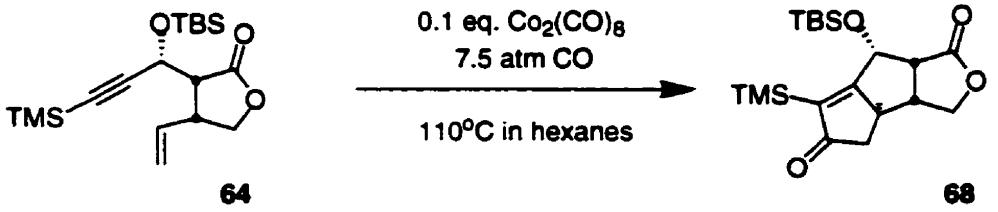
^{1}H NMR ($CDCl_3$, 270 MHz):

δ 5.15 (d, 1H, J = 4.5 Hz), 4.72 (t, 1H, J = 9.1 Hz), 4.20 (d, 1H, J = 9.1 Hz), 3.32 (m, 1H), 3.13 (dd, 1H, J = 4.5 Hz, 10.9 Hz), 2.82 (dd, 1H, J = 17.9 Hz, 7.4 Hz), 2.75 (m, 1H), 2.15 (dd, 1H, J = 17.9 Hz, 3.7 Hz), 0.87 (s, 9H), 0.22 (s, 9H), 0.15 (s, 3H), 0.05 (s, 3H);

^{13}C NMR ($CDCl_3$, 67.94 MHz):

δ 198.7, 182.4, 140.7, 115.5, 76.3, 68.4, 52.9, 46.5, 44.2, 41.8, 25.4, 18.0, -0.1, -4.6, -5.3.

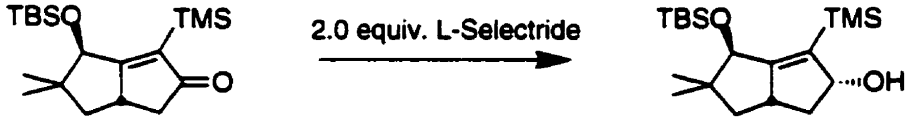
Compound 68, catalytic process:



64 68

To a solution of lactone **64** (34.1 mg, 0.11 mmol, 1.00 equiv.) in hexanes (5 mL) at room temperature was added $Co_2(CO)_8$ (4.2 mg, 0.01 mmol, 0.10 equiv.). The system was purged twice by successively bringing under 7.5 atm of carbon monoxide and releasing the pressure. After ultimately placing the system under 7.5 atm of carbon monoxide, the reaction mixture was brought to 110 °C. After 24 hours, the reaction mixture was allowed to cool down to room temperature, after which the pressure was released. The mixture was filtered through Celite and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (15% ethyl acetate in hexanes as eluent) to afford compound **68** as a colorless oil (33.5 mg, 0.10 mmol, 91%).

Compound 70:



66 70

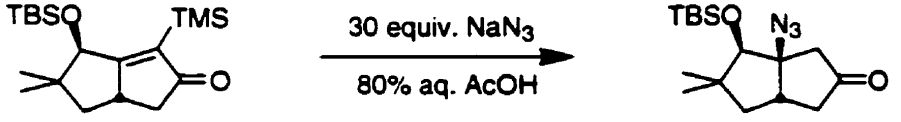
To a solution of compound **66** (1.50 g, 4.25 mmol, 1.00 equiv.) in THF (50 mL) at -78 °C was added L-Selectride (8.50 mL, 1.0 M in THF, 8.50 mmol, 2.00 equiv.). After stirring for 2.25 hours, the reaction was allowed to warm to room temperature. After 6 hours, the reaction was quenched with 1.0 M aqueous sodium hydroxide solution (42.0 mL) and 30% aqueous hydroperoxide solution (3.7 mL). The resulting mixture was stirred for 3 hours

and extracted with three portions of ethyl acetate. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford compound **70** as a colorless oil (1.30 g, 3.68 mmol, 87%).

^{1}H NMR ($CDCl_3$, 270 MHz):
δ 5.00 (q, 1H, J = 8.6 Hz), 3.91 (s, 1H), 3.05 (m, 1H), 2.72 (m, 1H), 1.85 (t, 1H, J = 11.5 Hz), 1.33 (d, 1H, J = 8.6 Hz), 1.11 (dt, 1H, J = 11.8 Hz, 8.6 Hz), 1.05 (s, 3H), 1.00 (dd, 1H, J = 3.9 Hz, 11.5 Hz), 0.85 (s, 9H), 0.82 (s, 3H), 0.21 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H);
^{13}C NMR ($CDCl_3$, 67.94 MHz):
δ 165.4, 137.2, 86.4, 78.3, 47.9, 46.3, 44.4, 42.4, 28.8, 26.0, 24.2, 18.6, 0.5, -3.8, -4.2

Anal. calcd for $C_{19}H_{38}O_2Si_2$: C 64.34%, H 10.80%, found C 63.98%, H 10.92%.

Compound 71:



66 **71**

To a solution of compound **66** (52.2 mg, 0.15 mmol, 1.00 equiv.) in 80% acetic acid (5 mL) and triethylamine (0.5 mL) at room temperature was added sodium azide (289 mg, 4.40 mmol, 30.00 equiv.). After stirring for 72 hours, the reaction mixture was diluted with ethyl acetate and water. The resulting mixture was extracted with two portions of ethyl acetate. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to afford compound **71** as a colorless oil (46.0 mg, 0.14 mmol, 95%).

IR (thin film) : 2104 cm^{-1}, 1252 cm^{-1}.

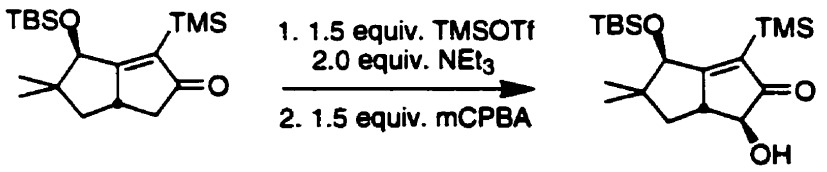
^1H NMR ($CDCl_3$, 400 MHz):

δ 3.62 (s, 1H), 2.68 (m, 2H), 2.55 (d, 1H J = 18.6 Hz), 2.37 (d, 1H J = 18.6 Hz), 2.11 (d, 1H J = 16.0 Hz), 1.87 (dd, 1H, J = 7.8 Hz, 13.3 Hz), 1.10 (m, 1H), 1.02 (s, 6H), 0.96 (s, 9H), 0.11 (s, 3H). 0.08 (s, 3H);

^{13}C NMR ($CDCl_3$, 100.61 MHz):

δ 215.4, 88.9, 73.8, 50.2, 43.7, 43.6, 42.5, 41.8, 28.5, 25.8, 18.1, -4.0, -4.9

Compound 72:



66 **72**

To a solution of compound **66** (2.14 g, 6.07 mmol, 1.00 equiv.) in dichloromethane (20 mL) at 0 °C were added successively triethylamine (1.69 mL, 12.14 mmol, 2.00 equiv.) and trimethylsilyl triflate (1.65 mL, 9.10 mmol, 1.50 equiv.). After stirring for 1.5 hours, the reaction mixture was concentrated under vacuum. To the residue dissolved in dichloromethane (40 mL) at 0 °C was added mCPBA (1.59 g, 92%, 8.50mmol, 1.40 equiv.). After stirring for 30 minutes, the mixture was allowed to warm to room temperature. After 3 hours, the reaction was quenched with saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with two portions of dichloromethane. The combined organic layers were concentrated under vacuum. The residue was dissolved in THF (20 mL) and 1.0 M aqueous hydrochloric acid (10 mL) at room temperature. After stirring overnight, the reaction mixture was extracted with two portions of dichoromethane, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford compound **72** as a colorless oil (1.40 g, 3.80 mmol, 62%).

^{1}H NMR ($CDCl_3$, 300 MHz):

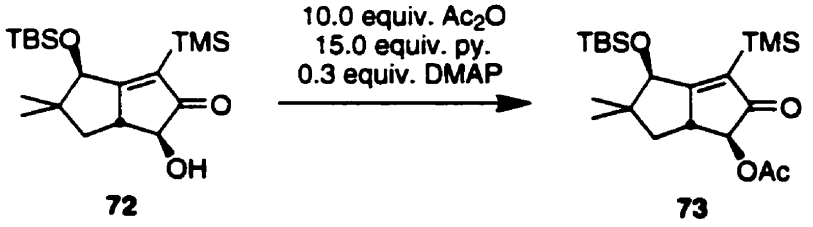
δ 4.16 (s, 1H), 4.09 (d, 1H, J = 6.5 Hz), 3.48 (dt, 1H, J = 11.8 Hz, 6.5 Hz), 1.71 (d, 1H, J = 12.8 Hz), 1.61 (dd, 1H, J = 12.8 Hz, 11.8 Hz), 1.16 (s, 3H), 0.89 (m, 11H), 0.76 (s, 3H), 0.23 (s, 9H), 0.13 (s, 3H). 0.03 (s, 3H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 195.0, 154.6, 132.4, 77.9, 72.4, 46.4, 43.2, 32.5, 27.4, 25.7, 24.0, 18.2, -0.9, -4.1, -4.7.

Anal. calcd for $C_{19}H_{36}O_3Si_2$: C 61.90%, H 9.84%; found C 61.53%, H 9.63%.

Compound 73:



72 **73**

To a solution of alcohol **72** (200 mg, 0.54 mmol, 1.00 equiv.) in dichloromethane (20 mL) at room temperature were added successively dimethylaminopyridine (13.0 mg, 0.10 mmol, 0.20 equiv.), pyridine (654 µl, 8.10 mmol, 15.00 equiv.) and acetic anhydride (515 µl, 5.40 mmol, 10.00 equiv.). After stirring for 11 hours, the reaction was quenched with saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with two portions of dichloromethane. The combined organic layers were washed with saturated aqueous ammonium chloride solution, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford compound **73** as a colorless oil (221.9 mg, 0.54 mmol, quantitative).

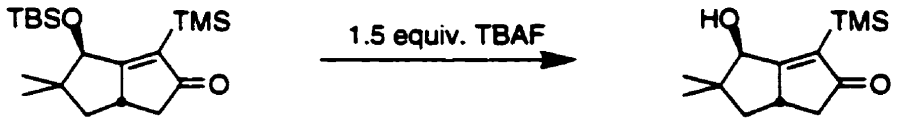
^{1}H NMR ($CDCl_3$, 300 MHz):

δ 5.09 (d, 1H, J = 6.5 Hz), 4.18 (s, 1H), 3.63 (dt, 1H, J = 12.3 Hz, 6.5 Hz), 2.10 (s, 3H), 1.73 (t, 1H, J = 12.3 Hz), 1.14 (s, 3H), 1.05 (dd, 1H, J = 6.5 Hz, 12.3 Hz), 0.89 (s, 9H), 0.76 (s, 3H), 0.24 (s, 9H), 0.12 (s, 3H). 0.02 (s, 3H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 210.0, 194.0, 170.3, 134.0, 77.8, 74.2, 45.5, 43.3, 34.3, 27.6, 25.7, 23.9, 20.7, 18.2, -1.0, -4.1, -4.7.

Compound 74:



66 **74**

To a solution of compound **66** (1.07 g, 2.85 mmol, 1.00 equiv.) in THF (35 mL) at -78 °C was added tetrabutylammonium fluoride (4.28 mL, 1.0M in THF, 4.28 mmol, 1.50 equiv.). After stirring for 3 hours, the reaction was brought to -25 °C. After 6 hours, the reaction was quenched with saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with two portions of dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution and brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to afford compound **74** as a colorless oil (382.0 mg, 1.60 mmol, 56%).

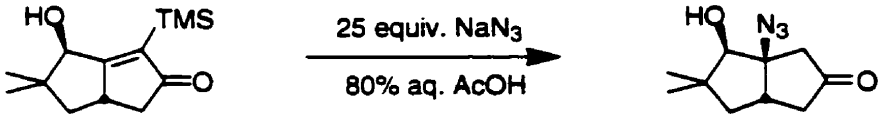
^{1}H NMR ($CDCl_3$, 270 MHz):

δ 4.26 (s, 1H), 3.31 (m, 1H), 2.65 (dd, 1H J = 6.7 Hz, 17.6 Hz), 2.01 (m, 2H), 1.70 (br s, 1H), 1.16 (s, 3H), 1.09 (dd, 1H, J = 8.6 Hz, 12.6 Hz), 0.94 (s, 3H), 0.22 (s, 9H);

^{13}C NMR ($CDCl_3$, 100.61 MHz):

δ 195.1, 139.5, 111.0, 46.3, 44.9, 44.3, 44.1, 30.3, 23.8, 15.2, 0.

Compound 75:



74 **75**

To a solution of compound **74** (330.0 mg, 1.38 mmol, 1.00 equiv.) in 80% acetic acid (20 mL) and triethylamine (2 mL) at room temperature was added sodium azide (2.25 g, 35.00 mmol, 25.00 equiv.). After stirring for 12 hours, the reaction mixture was diluted with ethyl acetate and water. The resulting mixture was extracted with two portions of ethyl acetate. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (15% ethyl acetate in hexanes as eluent) to afford compound **75** as a colorless oil (287.7 mg, 1.38 mmol, quantitative).

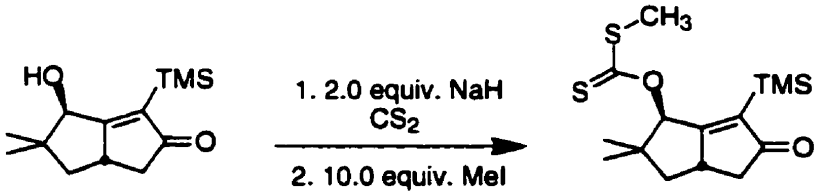
^{1}H NMR ($CDCl_3$, 400 MHz):

δ 3.51 (d, 1H, J = 9.0 Hz), 2.70 (m, 4H), 2.10 (m, 2H), 2.00 (dd, 1H J = 7.9 Hz, 13.4 Hz), 1.11 (dd, 1H, J = 9.3 Hz, 13.4 Hz), 1.08 (s, 3H), 1.02 (s, 3H);

^{13}C NMR ($CDCl_3$, 100.61 MHz):

δ 217.3, 87.7, 74.1, 48.9, 44.8, 44.3, 42.6, 42.1, 28.4, 20.7.

Compound 76:



74 **76**

To a solution of compound **74** (51.1 mg, 0.21 mmol, 1.00 equiv.) in dimethylsulfide (5 mL) at 0 °C was added sodium hydride (17.0 mg, 60%, 0.43 mmol, 2.00 equiv.). The mixture was then brought to room temperature. After stirring for 3.5 hours, methyl iodide (133 µl, 2.14 mmol, 10.00 equiv.) was added to the reaction mixture. After stirring overnight, the reaction was quenched with water. The resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (8% ethyl acetate in hexanes as eluent) to afford compound **76** as a colorless oil (37.1 mg, 0.11 mmol, 53%).

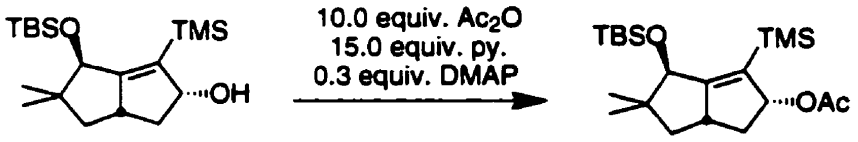
^{1}H NMR ($CDCl_3$, 400 MHz):

δ 6.29 (s, 1H), 3.33 (m, 1H), 2.68 (dd, 1H *J* = 7.0 Hz, 18.0 Hz), 2.58 (s, 3H), 2.08 (m, 2H), 1.14 (m, 7H), 0.22 (s, 9H);

^{13}C NMR ($CDCl_3$, 100.61 MHz):

δ 216.3, 189.1, 142.0, 86.9, 46.4, 45.7, 45.6, 44.6, 30.7, 25.0, 20.5, 0.

Compound 77:



70 **77**

To a solution of alcohol **70** (400 mg, 1.13 mmol, 1.00 equiv.) in dichloromethane (20 mL) at room temperature were added successively dimethylaminopyridine (28.0 mg, 0.23 mmol, 0.20 equiv.), pyridine (1.40 mL, 16.95 mmol, 15.00 equiv.) and acetic anhydride (1.07 mL, 11.30 mmol, 10.00 equiv.). After stirring for 2.5 hours, the reaction was quenched with saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with two portions of dichloromethane. The combined organic layers were washed with saturated aqueous ammonium chloride solution, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford compound **77** as a colorless oil (443.0 mg, 1.12 mmol, quantitative).

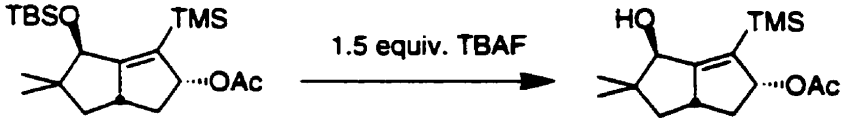
^{1}H NMR ($CDCl_3$, 400 MHz):

δ 5.95 (t, 1H, J = 7.1 Hz), 3.93 (s, 1H), 3.10 (m, 1H), 2.80 (dt, 1H, J = 7.1 Hz, 12.3 Hz), 2.04 (s, 3H), 1.86 (t, 1H, J = 12.3Hz), 1.18 (m, 1H), 1.05 (s, 3H), 1.00 (, dd, 1H, J = 4.6 Hz, 12.3 Hz), 0.85 (s, 9H), 0.82 (s, 3H), 0.14 (s, 9H), 0.06, (s, 3H), -0.03 (s, 1H);

^{13}C NMR ($CDCl_3$, 100.61 MHz):

δ 170.7, 166.7, 132.7, 87.7, 46.7, 44.6, 44.0, 42.3, 28.7, 26.0, 24.2, 21.6, 18.6, 0.2, -3.8, -4.2.

Compound 78:



76 **78**

To a solution of tert-butyldimethylsilyl ether **76** (403 mg, 1.02 mmol, 1.00 equiv.) in THF (30 mL) at -78 °C was added tetrabutyl ammonium fluoride (1.52 mL, 1.0 M solution in THF, 1.52 mmol, 1.52 equiv.). The reaction mixture was then allowed to warm slowly to room temperature. After stirring overnight, the reaction was quenched with saturated aqueous ammonium chloride solution. The resulting mixture was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (15% ethyl acetate in hexanes as eluent) to afford compound **78** as white crystals (285.9 mg, 1.01 mmol, quantitative).

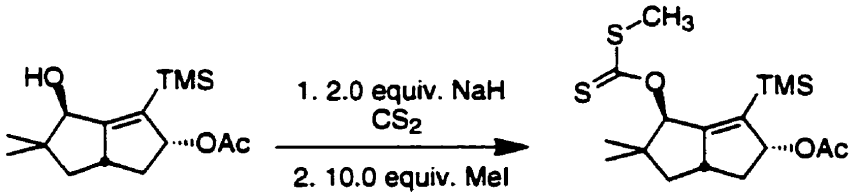
^{1}H NMR ($CDCl_3$, 400 MHz):

δ 5.95 (t, 1H, J = 6.2 Hz), 4.01 (s, 1H), 3.12 (m, 1H), 2.78 (dt, 1H, J = 6.2 Hz, 12.1 Hz), 2.02 (s, 3H), 1.86 (dd, 1H, J = 12.9 Hz, 10.6 Hz), 1.68 (br s, 1H), 1.21 (m, 1H), 1.09 (m, 4H), 0.92 (s, 3H), 0.14 (s, 9H);

^{13}C NMR ($CDCl_3$, 100.61 MHz):

δ 170.4, 165.9, 135.8, 87.5, 47.0, 44.9, 43.6, 42.8, 29.4, 25.6, 22.9, 21.3, -0.4.

Compound 79:



77 **79**

To a solution of compound **77** (26.8 mg, 0.09 mmol, 1.00 equiv.) in dimethylsulfide (5 mL) at room temperature was added sodium hydride (8.0 mg, 60%, 0.19 mmol, 2.00 equiv.). After stirring for 3.5 hours, methyl iodide (58 µl, 0.94 mmol, 10.00 equiv.) was added to the reaction mixture. After stirring overnight, the reaction was quenched with water. The resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (8% ethyl acetate in hexanes as eluent) to afford compound **79** as a colorless oil (28.7 mg, 0.08 mmol, 84%).

^{1}H NMR ($CDCl_3$, 400 MHz):

δ 6.24 (s, 1H), 6.02 (t, 1H, J = 7.2Hz), 3.18 (m, 1H), 2.84 (m, 1H), 2.55 (s, 3H), 2.04 (s, 3H), 1.91 (dd, 1H J = 9.9 Hz, 12.9Hz), 1.23 (m, 2H), 1.14 (s, 3H), 1.05 (s, 3H), 0.13 (s, 9H);

^{13}C NMR ($CDCl_3$, 100.61 MHz):

δ 170.2, 161.2, 140.0, 88.2, 87.1, 48.4, 47.6, 45.8, 43.2, 30.2, 24.5, 21.2, 19.7, 0.

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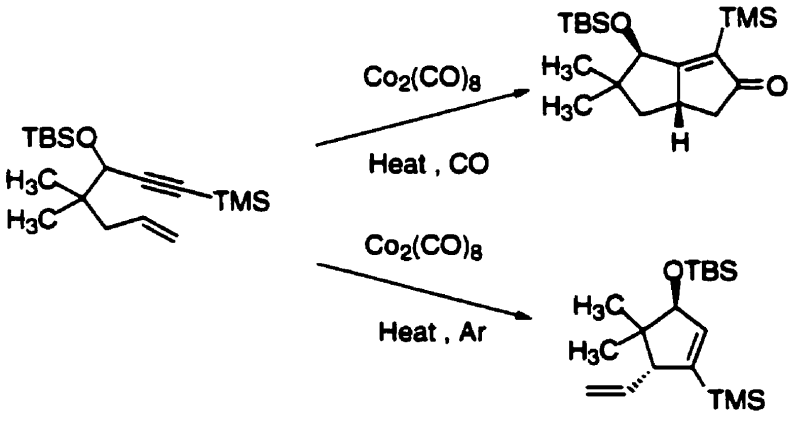
Part II

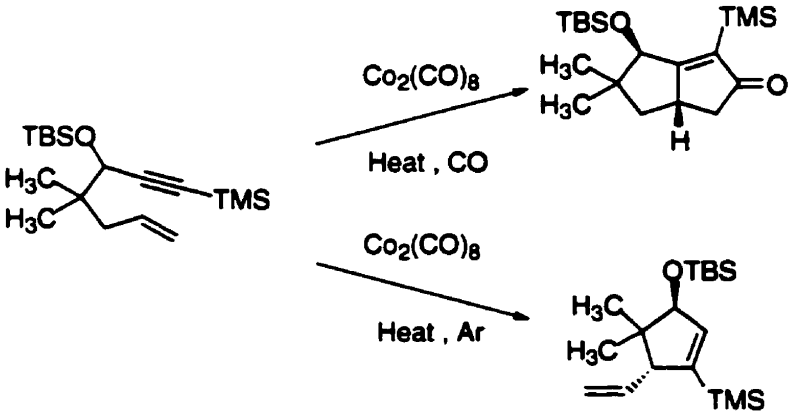
Diastereoselective formation of 5-vinyl cyclopentenes from 1,6-enynes: Cobalt mediated C-H allylic activation and 5-endo-dig cyclization.

Abstract



A novel intramolecular cyclization reaction mediated by dicobalt octacarbonyl ($Co_2(CO)_8$), is reported. Thermolysis under an argon atmosphere transforms the cobalt complex of 1-trimethylsilyl-6-hepten-1-ynes into 1-trimethylsilyl-5-vinylcyclopentenes in good yield and in a highly diastereoselective manner. The reaction is proposed to proceed via an allylic C-H insertion and a formal 5-endo-dig cyclization. The limitations of the substrate as well as the reaction parameters will be discussed.

Résumé



Une nouvelle réaction de cyclisation intramoléculaire effectuée par le dicobalt octacarbonyle ($Co_2(CO)_8$) est décrite. La thermolyse sous une atmosphère inerte d'argon transforme les complexes de di-cobalt de 1-triméthylsilyl-6-hepten-1-ynes en 1-triméthylsilyl-5-vinylcyclopentenes avec de hauts rendements ainsi que d'excellentes diastéréosélectivités. Un mécanisme reposant sur une insertion allylique C-H et une cyclisation formelle 5-endo dig est proposé. Les limitations du substrat de même que les paramètres de cette réaction sont discutés.

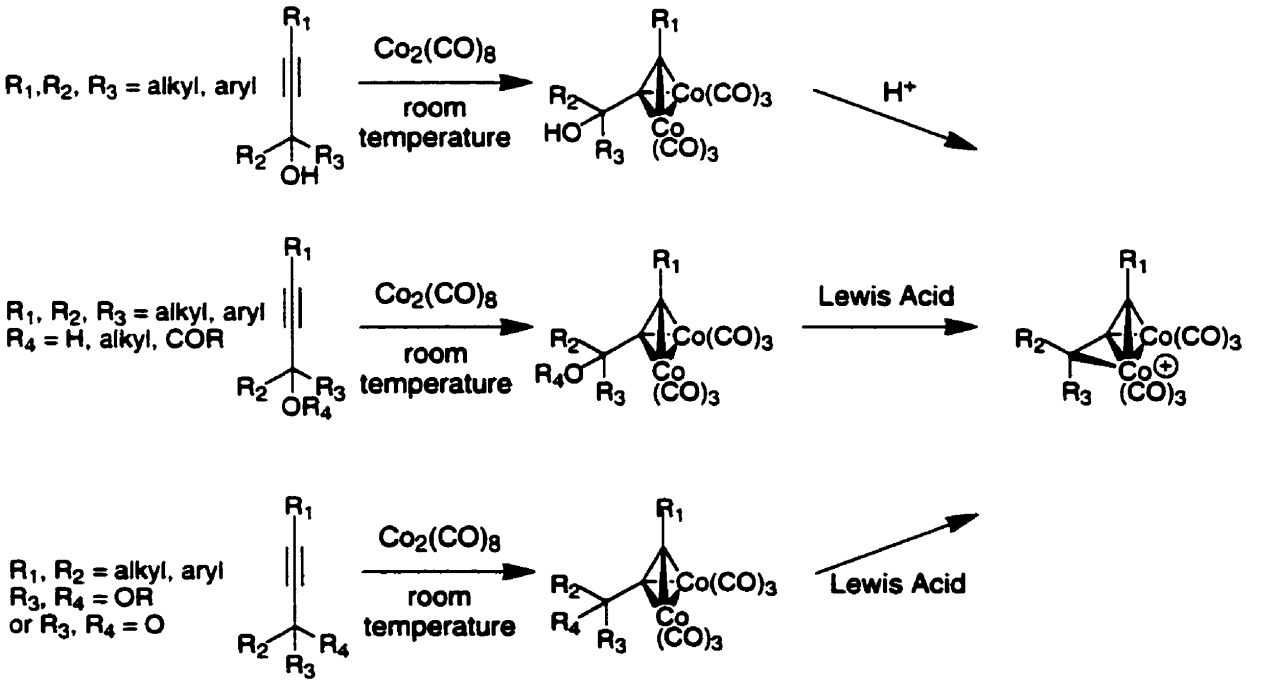
INTRODUCTION

1. The chemistry of cobalt-alkyne complexes

The utility of cobalt-alkyne complexes has been demonstrated on numerous occasions in organic synthesis. These readily accessible compounds have been employed to facilitate substitutions at propargylic sites[1], to protect alkynes, to affect their linearity so as to allow for macrocyclization and for the formation of carbocycles through cycloadditions with alkenes and alkynes.[2]

The cobalt-alkyne complexes have elicited great interest as precursors to stabilized propargylic cations allowing for SN_1 reactions at the propargylic sites.[3]

Scheme 1 : Generation of $Co_2(CO)_6$-stabilized propargylic cations

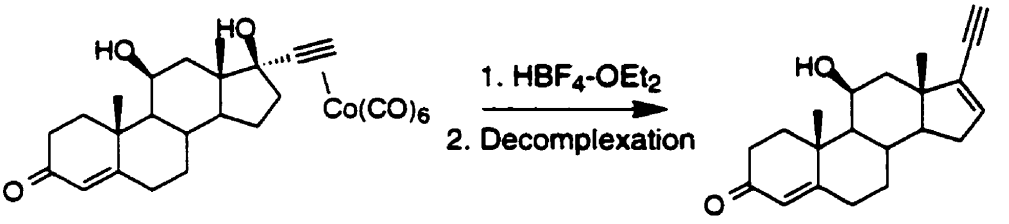


Cobalt-alkyne complexes can be easily prepared in gram quantities by adding dicobalt octacarbonyl ($Co_2(CO)_8$) to a solution of alkyne in an apolar solvent, usually toluene or hexanes. In most cases, such complexes are air-stable and can be purified by column

chromatography on silica gel. Procedures allowing for the decomplexation of the alkyne by oxidants such as Fe^{3+}, Ce^{4+}, I_2 or trimethylamine N-oxide are also well precedented.[4]

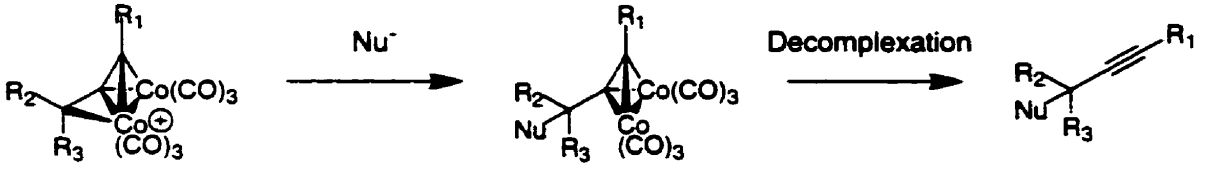
The corresponding transition metal stabilized propargylic cations are obtained by placing the cobalt-alkyne complexes in presence of a Brönsted or a Lewis acid (Scheme 1). The loss of the β-proton of these cationic species was utilized by Turuta to provide a precursor of 16a, 17a epoxycorticosterone (Scheme 2).[5]

Scheme 2 : Dehydration procedure



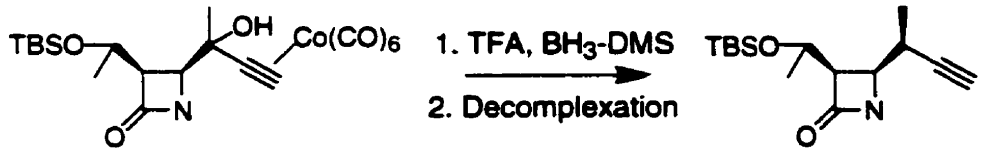
These stabilized propargylic cations found their main synthetic uses as electrophilic propargyl synthons, which are reactive towards a wide range of nucleophiles in a process known as the Nicholas reaction (Scheme 3). The cationic cobalt-alkyne complexes show regioselectivity for reaction at propargylic position, adding to their synthetic interest.

Scheme 3 : Nicholas reaction



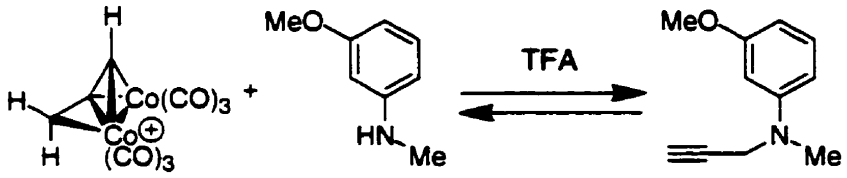
Intercepting the stabilized propargylic cations by hydrides such as $NaBH_4$ or borane-dimethyl sulfide results in net reduction at the propargylic position (Scheme 4).

Scheme 4 : Reduction[6]



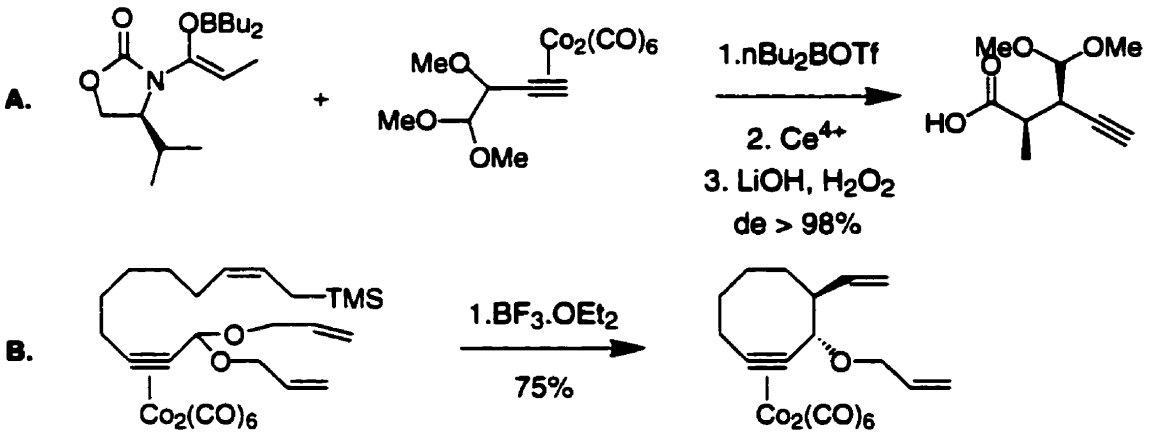
Alternatively, the propargylic cation can be attacked by oxygen or nitrogen nucleophiles (Scheme 3, Nu^- = HO^-, RO^-, R_2NH and RNH_2 respectively). With this methodology, Magnus introduced the propargylic moiety as an amino protective group (Scheme 5)[7].

Scheme 5 : Amine alkylation



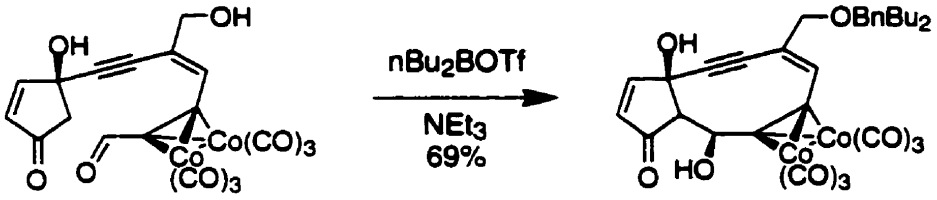
Carbon centered nucleophiles are well tolerated and add to the interest of the Nicholas reaction. A highly stereoselective propargylation was reported by Jacobi expanding the potential of chiral boron enolates (Scheme 6A).[8] Allyl silanes nucleophiles also afford high yields of substituted propargylic products (Scheme 6B).[9]

Scheme 6 : Carbon nucleophiles



In studies of models of neocarzinostatin, Magnus used the angle between the alkynic substituents, resulting from the complexation to $Co_2(CO)_6$, to facilitate the cyclization to a strained 9-membered ring via an aldol reaction (Scheme 7).[10]

Scheme 7 : Neocarzinostatin studies



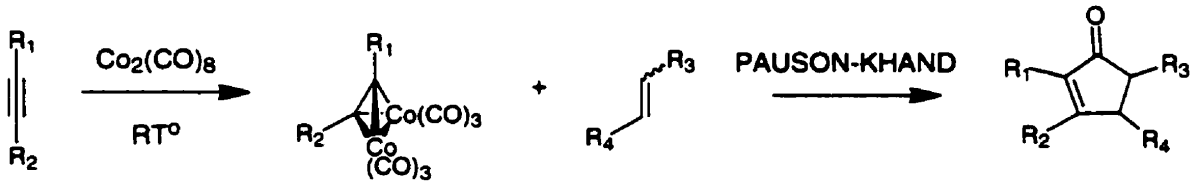
The Nicholas reaction benefits from the easy access to propargyl cations and constitutes a main reaction class of cobalt-alkyne complexes. It also exemplifies the stabilization and electrophilicity of propargyl cations complexed by $Co_2(CO)_6$. Upon the choice of appropriate synthons, the Nicholas reaction offers a fast entry into substrates for intramolecular Pauson-Khand reactions (vide infra).

2. The Pauson Khand reaction

In addition to the Nicholas reaction, cobalt-alkyne complexes have been utilized to provide a direct entry to cyclopentenones.[2a-b] This process, known as the Pauson Khand reaction, involves the reaction of dicobalt hexacarbonyl-alkyne complexes with alkenes to form cyclopentenones.[11]

The cyclopentenone results from a formal [2+2+1] cycloaddition between three components: the alkyne π bond, the alkene π bond and carbon monoxide (Scheme 8).

Scheme 8 : Pauson Khand reaction

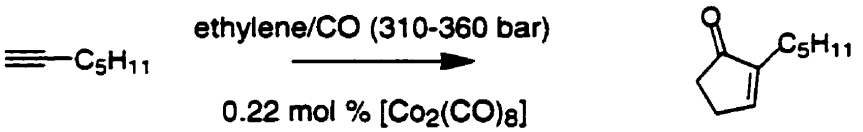


Various conditions have been found to effectively promote the Pauson-Khand reaction. The original procedure relied on the thermolysis of a cobalt-alkyne complex in presence of an alkene.[12] The additive N-methyl morpholine oxide, which oxidizes carbon monoxide ligands to CO_2 and thus freeing cobalt coordination sites for the alkene, enables the reaction to proceed in higher yields and at room temperature.[12b,13] Phosphine oxides have also been used to enhance the reaction, probably by exchanging with CO to provide a cobalt complex with more labile ligands.[14] A similar mode of action is proposed for other efficient additives such as acetonitrile or DMSO.[15] Passing oxygen on the substrate adsorbed on silica gel have also been shown by Smit and Caple to improve the reaction outcome.[16] More recently, the use of primary amines as co-solvents was reported to give an increase in reaction rates.[17]

One of the most common protocols employed today involves thermolysis of the cobalt-alkyne complex under a CO atmosphere in an apolar solvent.[18] Importantly, this

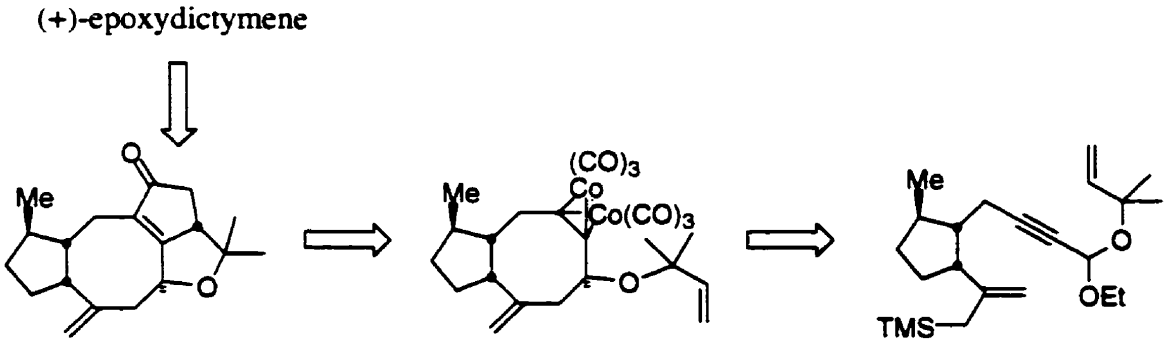
procedure has been shown to allow for catalysis, albeit in a limited number of cases. The catalytic potential of this reaction is actually hampered by the formation of inactive clusters such as $Co_4(CO)_{12}$.[19] This problem was circumvented by the use of modified cobalt catalysts such as $[Co_2(CO)_8/P(OPh)_3]$, [(indenyl)Co(cod)] or $[Co(acac)_2/NaBH_4]$ under CO pressure.[2b] Another strategy using the photolytic activation of $Co_2(CO)_8$, leading the loss of a CO ligand, was developped by Livinghouse *et al.* and permits the catalyzed cyclopentenone formation to proceed at 50 °C and under 1 atm of CO.[20] More detailed studies showed that harsher conditions (dichloromethane, 150 °C, 10 atm CO) can turn inactive species such as $Co_4(CO)_{12}$ into reactive catalysts.[21] Thermolysis at high temperature combined with a high pressure of CO have been efficiently used in syntheses of natural molecules as shown by Rastentrauch *et al.* (Scheme 9)[22] and our own studies towards Palau'amine[23].

Scheme 9 : Catalytic Pauson-Khand reaction[22]



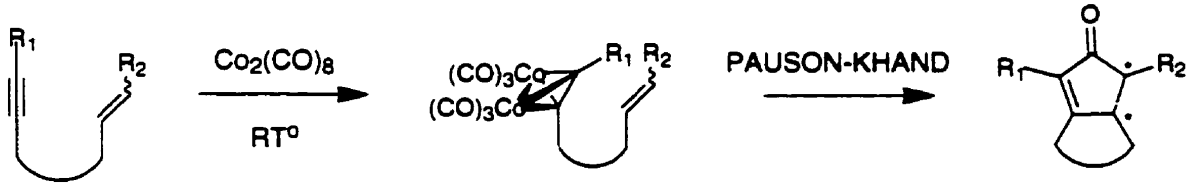
The utility of the Pauson Khand reaction has been demonstrated in a number of total syntheses.[24] The synthesis of (+)-epoxidictymene by Schreiber *et al.* is a showcase for the potential of the combination of the Pauson-Khand process with the Nicholas reaction (Scheme 10).[25]

Scheme 10 : (+)-epoxidictymene retrosynthesis



In particular, the intramolecular variant (Scheme 11) is very useful for the formation of bicyclic structures and is often highly diastereoselective.[26]

Scheme 11 : Intramolecular Pauson-Khand

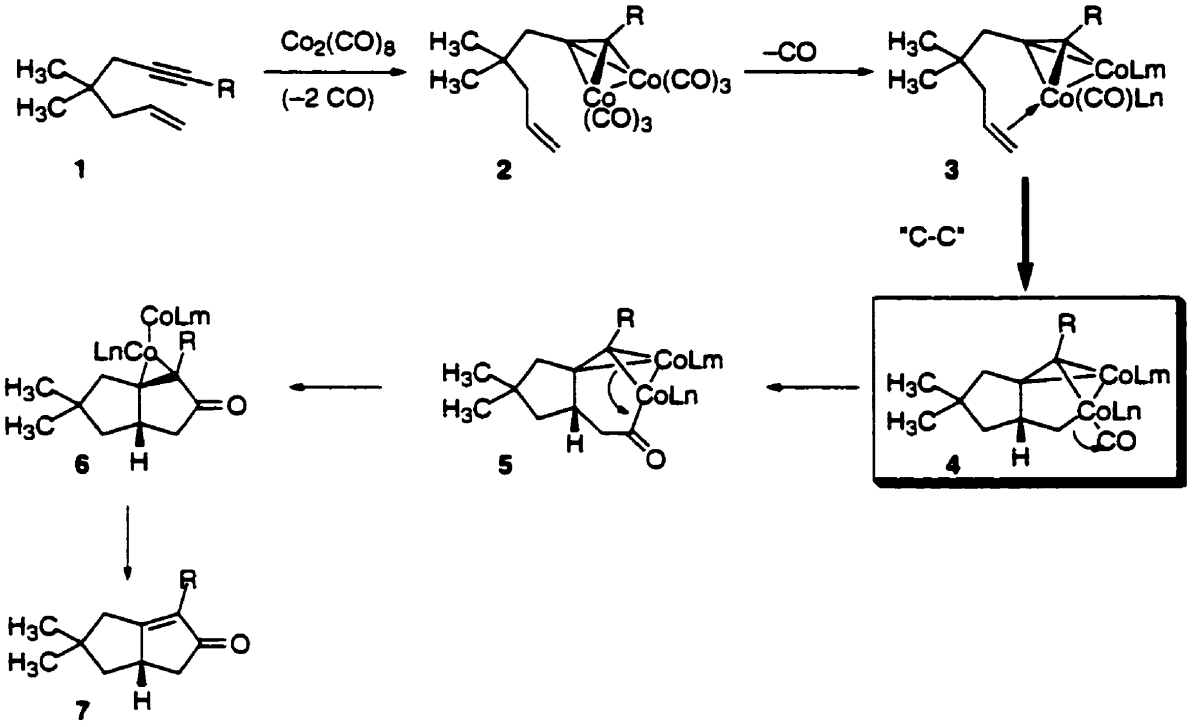


Olefins linked to alkynic moieties by a 3 or 4 atom linker are amenable to the Pauson-Khand process, which will provide bicyclo-[3.3.0]oct-1-en-3-ones and [3.4.0]non-1-en-3-ones, respectively. Oxygen or nitrogen containing linkers are also compatible with the reaction conditions.

The effects of substitution have been studied for the hept-1-en-6-yne series. The Thorpe-Ingold effect, generated by *gem*-alkyl substituted linkers at C4 or by heteroatoms at position 4, reduces the importance of competitive intermolecular processes, leading to cleaner reactions and a subsequent yield increase.[27] However, substitution at C4 does not result in highly diastereoselective reactions.[26c] Nevertheless, substitution at C5 or C3 greatly

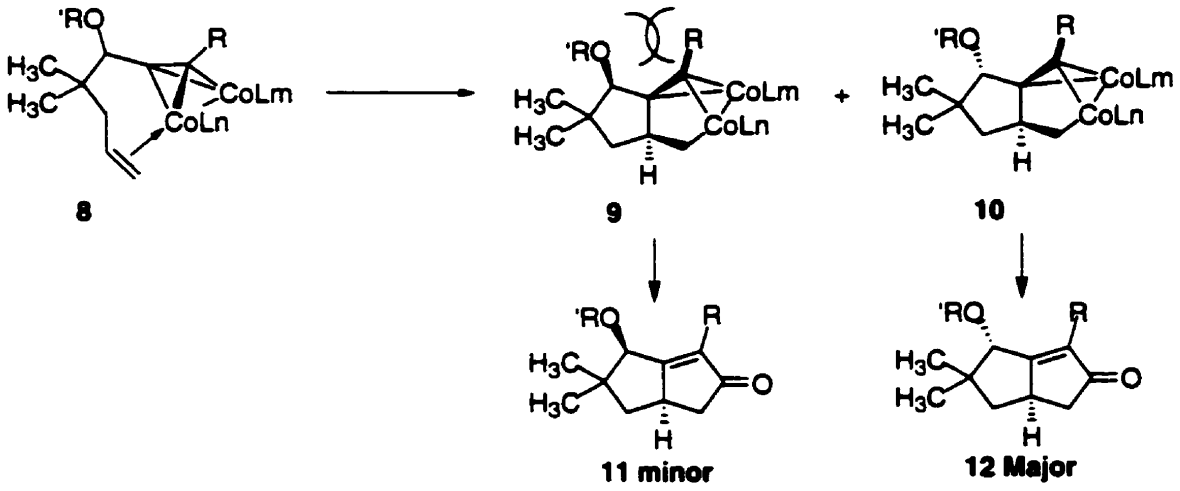
influences the stereochemical outcome. A mechanistic proposal was put forth by Magnus to explain these results (Scheme 12).[26a-b]

Scheme 12 : Pauson-Khand mechanism



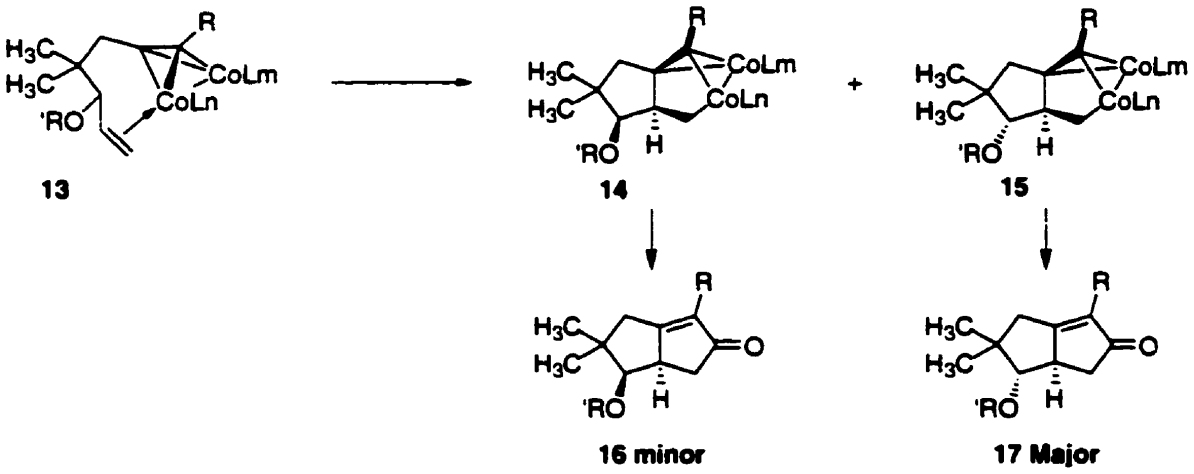
Isolable complex **2** is obtained from enyne **1** after exposure to $Co_2(CO)_8$ at room temperature. Under thermolysis, this system is proposed to degrade to complex **3**, which results from the loss of a CO ligand and coordination of the alkene moiety of the substrate. Evidence for complexes of type **3** resulting from initial ligand loss has been gathered by Krafft *et al.* in related systems.[28] Formation of a carbon-carbon bond resulting from the insertion of the alkene into the internal carbon-cobalt bond in **3** lead to metallocycle **4**. The newly formed five membered rings are *cis* fused, providing the stereochemical relationship between the new carbon stereocenter and the cobalt atoms. The five membered metallocycle is subject to insertion of a CO ligand to give the acyl-cobalt complex **5**. Elimination of the cobalt atom provides complex **6** and further decomplexation yields in the Pauson-Khand product **7**.

Scheme 13 : Substitution at C5



Magnus proposed that substitution at C3 and C5 results in high level of diastereoselectivities, through minimization of the sterics interactions in the intermediate metallocycles.[26a-b] In the case of C5 substitution (Scheme 13), insertion of the alkene moiety into the internal C-Co bond can lead to the two metallocycles **9** and **10**. Intermediate **9** is disfavored due to a 1,3 pseudo diaxial interaction on the concave face of the bicyclic framework. The thermodynamic ratio between **9** and **10** is reflected in the Pauson-Khand product mixture (OR' = OTBS, R = TMS : **12/11** = 26:1).

Scheme 14 : Substitution at C3

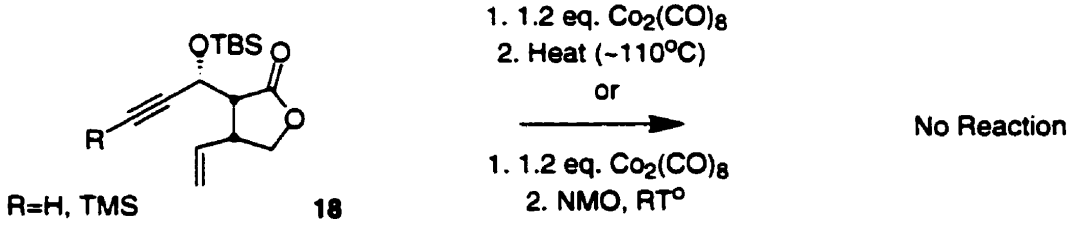


A similar rationale is suggested to explain the influence of substitution at C3 (Scheme 14). Intermediate **14** is destabilized by a 1,4-diaxial interaction between OR' and R, and by a *cis* relationship between OR' and the metallocycle. For OR' = OMOM and R = TMS, only the Pauson-Khand product of type **17** was isolated.

3. Application of the Pauson Khand reaction to Palau'amine core and model substrates

During our progress towards the total synthesis of Palau'amine, various conditions for the Pauson-Khand process were studied on molecule **18** (Scheme 15).[29] In particular, an attempt at thermolysing enyne **18** under an argon atmosphere after in-situ complexation of $Co_2(CO)_8$ failed to provide the desired cyclopentenone derivative.[12] Similarly, activation by N-methyl morpholine oxide proved unsuccessful.[12b,13]

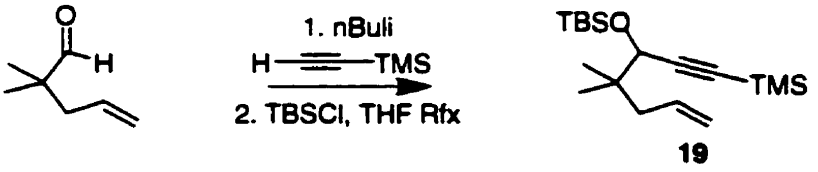
Scheme 15 : Pauson-Khand processes towards Palau'amine



From a practical viewpoint, these two methods for Pauson-Khand cyclopentenone synthesis do not require a high-pressure apparatus nor a carbon monoxide atmosphere. The importance of this technical attractiveness called for a more detailed study on a related model substrate.

The simple substrate 4,4-dimethyl-5-((dimethylethyl)dimethylsilyloxy)-7-trimethylsilyl-1-hepten-6-yne **19** possesses an array of functionalities similar to that of Palau'amine precursor **18,** namely a terminal olefin, a trimethyl silyl protected alkyne moiety and a tert-butyl dimethyl silyl protected alcohol group at an equivalent position on the carbon skeleton. In addition, this substrate can be easily prepared from commercially available 2,2-dimethyl-4-pentenal (Scheme 16).[26c] Alternatively, 2,2-dimethyl-4-pentenal can be obtained from the Claisen rearrangement of isobutanal and allyl alcohol.[30] More importantly, the detailed study by Magnus *et al.* of the Pauson-Khand reaction of enyne **19**, via thermolysis of the related cobalt complex under carbon monoxide pressure, made this molecule a clear choice for a model substrate.[26a-c]

Scheme 16 : Preparation of 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-7-trimethylsilyl-1-hepten-6-yne

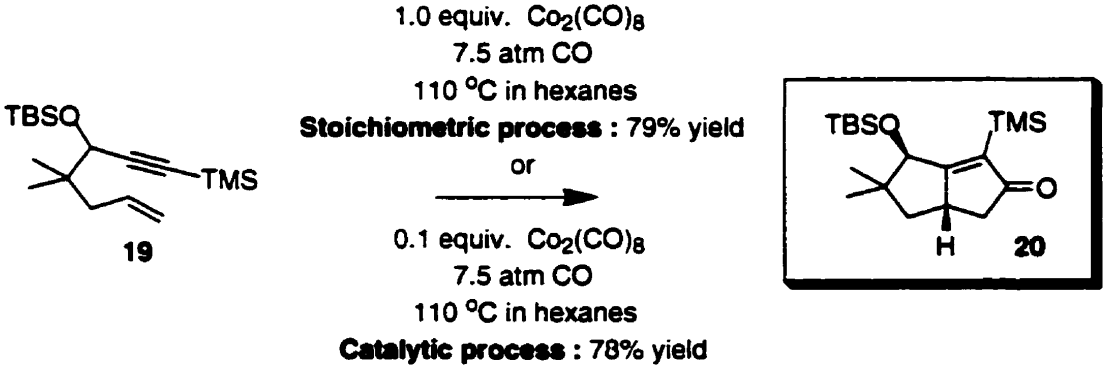


19

According to Magnus' stoichiometric procedure, the cyclopentenone **20** can be obtained from **19** in a 79% yield, along with the related diastereoisomer (3% yield) (Scheme 17).

Indeed, we have been able to improve this reaction by using a catalytic Pauson-Khand process. When the reaction is carried out using only 0.1 equivalent of $Co_2(CO)_8$ **20** is isolated in 78 % yield (Scheme 17). Its diastereoisomer could not be detected by ^1H NMR analysis of the crude material.

Scheme 17 : Pauson-Khand reaction of enyne 19

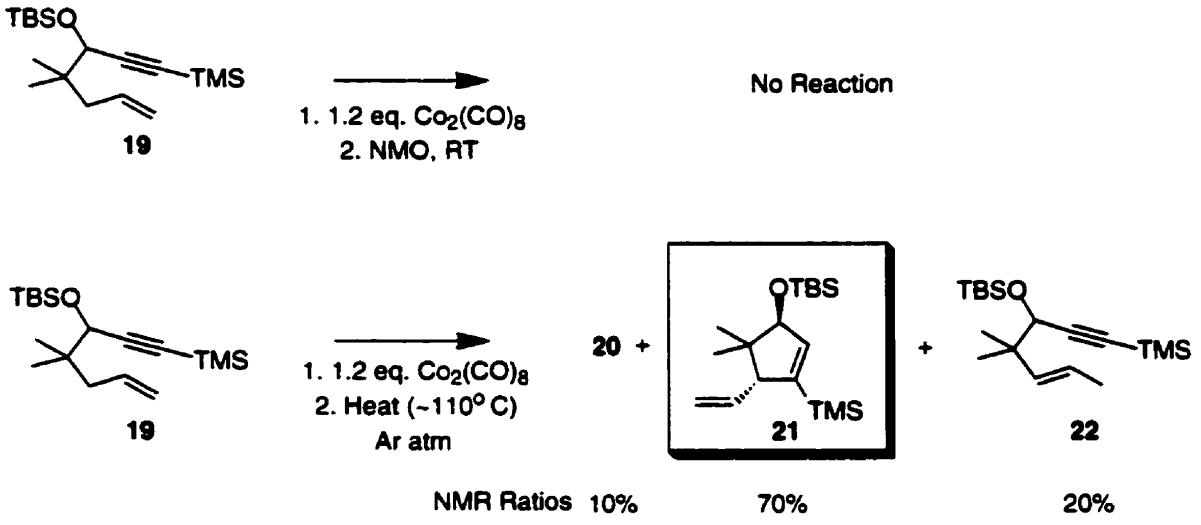


19 **20**

In order to avoid the requirement of a CO chamber, alternative methods were examined. N-Methyl morpholine oxide activation at room temperature of the cobalt complex

of **19** formed *in situ* did not give the expected Pauson-Khand product **20**. In fact, the cobalt complex of **19** proved unreactive under these conditions (Scheme 18).

Scheme 18 : Reactivity of substrate 19



More interestingly, it was found that the thermolysis of the cobalt complex of **19** in an argon atmosphere did not result in the formation of Pauson-Khand cyclopentenone **20** as the major product. In fact, a novel carbocyclic compound **21** was obtained in a 70% ^{1}H NMR ratio. The following discussion reports the characterization of this compound as well as a mechanistic proposal for this transformation and the development of this novel reaction.

RESULTS AND DISCUSSION

1. Reaction discovery and characterization of the reaction products

As described by Magnus,[26a-c] enyne **19** readily forms a cobalt complex upon exposure to $Co_2(CO)_8$ in toluene and subsequent thermolysis of this intermediate in a CO atmosphere results in clean transformation to the cyclopentenone **20**. We have found that if the reaction is conducted instead in an argon atmosphere, the typical substrate **19** gives raise to a mixture including the cyclized product (3R*, 5S*) 4,4-dimethyl-5-ethenyl-3-((dimethylethyl) dimethylsilyloxy)-1-trimethylsilyl cyclopentene (**21**) in a 70% ^{1}H NMR ratio, and isolated as a single stereoisomer. It is accompanied by the isomerized olefin trans 4,4-dimethyl-5-((dimethylethyl)-dimethylsilyloxy)-7-trimethylsilyl-2-hepten-6-yne (**22**) in a 20% ^{1}H NMR ratio as well as a small amount of the Pauson-Khand product **20** (10% ^{1}H NMR ratio).

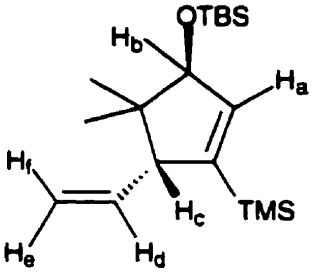
Separation of **21** from **22**, obtained after complete degradation of the cobalt species of the reaction mixture with ceric ammonium nitrate, proved difficult. The similar polarity and molecular weights made separation by chromatography or distillation impractical.

However, the analysis of the functional variations between these two products shows the silylated alkynic terminus as a potential site for differentiation by a subsequent reaction. Such trimethylsilyl groups have been demonstrated to be sensitive to nucleophilic conditions. In practice, we have been able to selectively degrade compound **22** with potassium carbonate in methanol. This procedure allowed product **21** to be isolated and fully characterized by common techniques. The structure of **21** is fully supported by ^{1}H, ^{13}C, COSY, HMQC and HMBC NMR experiments. Compound **22** could not be isolated from the reaction mixture and its degradation by potassium carbonate in methanol yielded a too volatile product for identification.

The ^{1}H NMR spectrum (Figure 1) clearly identifies two internal olefinic protons at δ 5.85 ppm and δ 5.54 ppm, as well as two terminal alkenic protons at δ 4.99 ppm and δ 4.96 ppm. The coupling pattern of the δ 5.54 ppm (doublet of triplet), δ 4.99 ppm (doublet of doublet) and δ 4.96 ppm (doublet of doublet) protons is consistent with a monosubstituted olefin. A pattern of two singlets at δ 0.90 ppm and δ 0.06 ppm, accounting for fifteen

protons each indicates that the gem-dimethyl, tert-butyl dimethyl silyl and trimethyl silyl groups of the starting material are also present in the product **21**.

Figure 1 : ^{1}H NMR analysis of compound 21



21

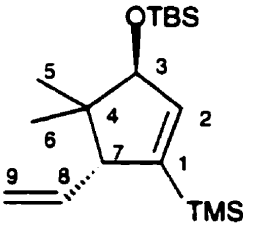
Proton	^{1}H NMR shift (ppm)	Coupling constants (Hz)
H_a	δ = 5.85	-
H_b	δ = 4.39	-
H_c	δ = 2.93	J_{Hc-Hd} = 10.0
H_d	δ = 5.54	J_{Hc-Hd} = 10.0
		J_{Hd-He} = 10.0
		J_{Hd-Hf} = 17.0
H_e	δ = 4.99	J_{Hd-He} = 10.0
		J_{He-Hf} = 1.7
H_f	δ = 4.96	J_{Hd-Hf} = 17.0
		J_{He-Hf} = 1.7

The COSY spectrum shows a spin system encompassing the three olefinic protons described above (δ 5.54 ppm, δ 4.99 ppm, δ 4.96 ppm), as well as a proton showing as a doublet at δ 2.93 ppm. None of the other protons is shown to be involved in any coupling.

The analysis of the ^{13}C NMR spectrum (Figure 2) provides evidences for four olefinic carbons at δ 148.3 ppm, δ 144.0 ppm, δ 139.7 ppm and δ 115.5 ppm. The presence of the tert-butyl dimethyl silyl ether is also verified by the characteristic pattern of peaks at δ 26.1

ppm ($OSiMe_2C(\mathbf{Me})_3$), δ 18.5 ppm($OSiMe_2C(Me)_3$), δ -4.2 ppm and δ -4.6 ppm ($OSi\mathbf{Me}_2C(Me)_3$). In addition, the occurrence of an allylic silyl ether is indicated by a peak at δ 85.4 ppm (**C**HOTBS). The gem-dimethyl substitution is also verified by two peaks at δ 23.5 ppm and δ 23.2 ppm. Finally, a peak at δ -1.1 ppm is consistent with a trimethyl silyl group.

Figure 2 : ^{13}C NMR analysis of compound 21

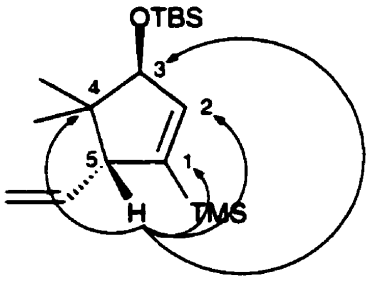


21

Carbon	^{13}C NMR shift (ppm)
C_1	δ = 148.3
C_2	δ = 144.0
C_3	δ = 85.4
C_4	δ = 23.5
C_5	δ = 23.5
C_6	δ = 23.2
C_7	δ = 63.7
C_8	δ = 139.7
C_9	δ = 115.5

The HMQC spectrum confirms the assignment of proton peaks by delineating geminal C-H relationship present in **21**.

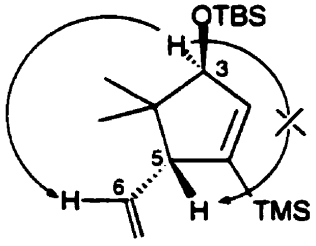
Figure 3 : HMBC experiment



21

Beyond the functional group identification, the key for the structure determination is given by an HMBC analysis (Figure 3). In particular, this long range C-H coupling study reveals correlations between the H5 proton and the C1, C2, C3 and C4 carbons, providing clear evidence for the C1-C5 σ bond formation during a formal 5-endo-dig cyclization of enyne **19**.

Figure 4 : NOE correlation



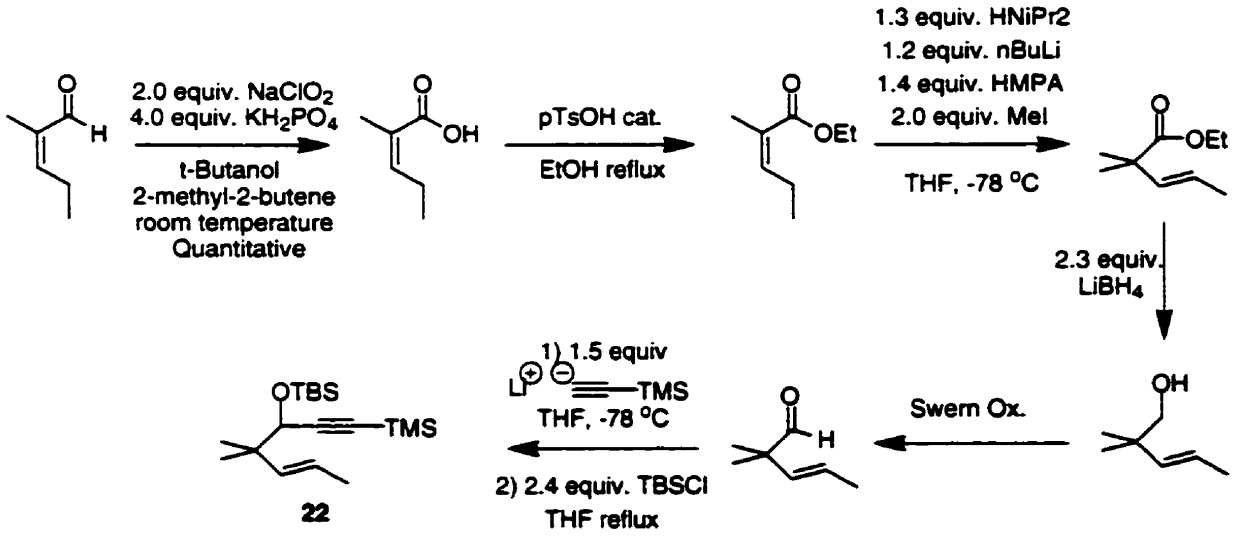
21

Importantly, only a single cyclopentene diastereomer of **21** is produced. The (3R*, 5S*) trans stereochemistry of this product was assigned by observation of an NOE from H3 to H6. This pattern was further substantiated by the lack of an NOE between H3 and H5 (Figure 4).

A final verification of the identity of compound **21** was carried out by high resolution mass spectrometric analysis which measured the exact mass ($M-H^+$) of **21** to be consistent with the mass calculated for the molecular formula $C_{18}H_{36}OSi_2-H^+$ ($M-H^+$ 323.2225 (calculated for $C_{18}H_{36}OSi_2-H^+$ 323.2227)).

The structure of the minor isomerized enyne **22** could be confirmed by independent synthesis from 2-methyl-2-pentenal (Scheme 19). This commercially available material was oxidized to the corresponding acid by sodium chlorite in a system buffered by monobasic potassium phosphate. The subsequent esterification was carried out in methanol and catalyzed by para-toluene sulfonic acid. Under the conditions developed by Herrman *et al.*, the ester was deprotonated by LDA in a THF in presence of HMPA and alkylated with methyl iodide to provide the ethyl trans 2,2-dimethyl-3-pentenoate ester as a single isomer.[31] It is interesting to note that the omission of HMPA in this procedure results in the clean 1,4 addition of diisopropylamine onto the unsaturated ester.

Scheme 19 : Synthesis of trans 4,4-dimethyl-5-((dimethylethyl)-dimethylsilyloxy)-7-trimethylsilyl-2-hepten-6-yne (22)



Reduction to the aldehyde was achieved in two steps by first reducing the ester to the alcohol followed by oxidation to the desired aldehyde according to the Swern procedure. In a

one-pot procedure, this aldehyde was alkylated by lithium TMS acetylene prepared *in situ* and the resulting alcohol protected by a TBS group.

This independent synthesis confirmed the *trans* alkene pattern of compound **22**, identified by a $J = 16$ Hz coupling constant between the olefinic protons.

2. Influence of the reaction conditions over cyclopentene formation

A. Stoichiometry and duration

With the goal of increasing the amount of **21** formed in the reaction relative to the other products **20** and **22** as well as to reach an understanding of the key parameters of the reaction producing **21**, variations of the stoichiometry and duration of the reaction were studied (Table 1).

Increasing the duration of the thermolysis step from 12 to 36 hours did not affect the product ratio (entry 1 vs. entry 2). Indeed, the thermal Pauson-Khand protocols, using apolar solvents such as hexanes, call generally for thermolysis durations shorter than 12 hours, attesting to the instability of the alkyne cobalt complexes under these conditions. In addition, after a 12-hour thermolysis under an argon atmosphere, a cobalt (0) mirror coating was found to cover the reaction flask and the original black reacting solution evolved into a suspension of cobalt particles. These phenomenona are also commonly observed in thermal Pauson-Khand procedures.

Table 1 : Stoichiometry and duration parameters

Entry	Solvent	Temp °C	$Co_2(CO)_8$ equiv.	Time H	Ratio **21:22:20**
1	PhMe	110	1.2	12	70:20:10
2	PhMe	110	1.2	36	70:20:10
3	PhMe	110	2.0	12	70:20:10
4	PhMe	110	0.9	12	50:20:10[a]

[a]Ratio reflects 20% recovered starting material.

When the reaction was conducted with a slight deficit of cobalt octacarbonyl, the ratio of products was essentially unchanged. This observation indicated that olefin isomerization was not a result of the slight excess of reagent used in the normal procedure (entry 4).

Likewise, use of a large excess of $Co_2(CO)_8$ also resulted in no significant change in product ratio. In particular, a relative increase in **21** over **22** was not observed (entry 3). These results also indicate that the isomerization to **22** is not an intermediate in the formation of **21**, but rather a side-product.

These stoichiometric alterations of the procedure clearly rule out any role of uncomplexed $Co_2(CO)_8$ in the formation of **21** and **22**. The mechanisms accounting for the synthesis of these two products are therefore the result of a thermal degradation in the absence of a CO atmosphere of the intermediate cobalt alkyne complex, in a unimolecular fashion in cobalt.

B. Solvent influence

The reactivity of organometallic complexes can potentially be altered by a change of solvents. More specifically, polarity changes may affect the electronic properties of the complexes while the nature itself of these species can be modified directly by chelation of the solvent onto the metal.

A study of the solvent effects was thus performed, targeting the product ratio obtained through the cobalt mediated rearrangement. Solvents of different polarities and chelation abilities were tried while maintaining the reaction temperature in the same range [101 °C - 115 °C] and other parameters such as duration and stoichiometry identical (Table 2).

Switching from toluene to 2-pentanone rendered inoperative both the Pauson-Khand pathway to the enone **20** and the cyclopentene formation to **21** (entry 1 vs. entry 5). The only product formed was the isomerized olefin **22**, albeit in 50 % conversion from **19**.

Table 2 : Solvent alterations

Entry	Solvent	Temp °C	$Co_2(CO)_8$ equiv.	Time h	Ratio **21:22:20**
1	PhMe	110	1.2	12	70:20:10
5	2-Pentanone	101	1.2	12	0:50:0[b]
6	nPrCN	115	1.2	12	0:0:100
7	DMF	110	1.2	12	NR

[b]Ratio reflects 50% recovered starting material.

Using butyronitrile as solvent yielded the Pauson-Khand derived enone **20** as the only product (entry 6). In fact, Hoye and Suriano have previously shown that acetonitrile can be a useful promoter of the Pauson-Khand reaction.[15b] This activation is proposed to be the result of solvent exchanging for CO ligands, yielding a more reactive complex towards alkene insertion.

Dimethyl formamide is also ineffective in producing the desired cylopentene product **21** (entry 7). Instantaneous degradation of cobalt octacarbonyl by CO displacement is observed upon addition of $Co_2(CO)_8$ into the DMF solution, as attested by intense bubbling. The resulting cobalt species are found to be inert under the usual reaction conditions and only starting material is detected after 12 hours at 110 °C.

In conclusion, the use of more polar or more strongly chelating solvents than toluene did modify the reaction pathway but did not provide an improvement regarding the synthesis of cyclopentene **21**.

C. Reaction temperatures

Taking into account the results of the precedent study indicating the importance of an apolar and non-chelating solvent, the temperature required for thermolysis leading to the cyclopentene formation was analyzed (Table 3).

Table 3 : Temperature variations

Entry	Solvent	Temp °C	$Co_2(CO)_8$ equiv.	Time h	Ratio **21:22:20**
1	PhMe	110	1.2	12	70:20:10
8	PhH	80	1.2	12	NR
9	p-xylene	135	1.2	12	65:20:15

This parameter was investigated by performing the reaction in solvents of similar polarities to the solvent of reference, toluene (entry 1). The cobalt complex formation in benzene and the subsequent thermolysis, carried out by bringing the mixture to reflux, were not effective in reproducing the desired rearrangement (entry 8). In fact, only starting material was detected after the usual cobalt oxidation by ceric ammonium nitrate.

A solvent of higher boiling point was then tried in this string of reactions. A run with para-xylene yielded a mixture of the products **20**, **21** and **22** in a manner similar to reaction in toluene (entry 9 vs. entry 1). However, the use of a higher temperature was not successful in providing an improved ratio of **21** over the milder conditions of entry 1.

These alterations over the rearrangement procedure evidenced a temperature threshold in the formation of the cyclopentene **21**, but also indicated that similar ratio of products would be obtained above this threshold. Overall, the studies focusing on the polarity, chelating characteristics and thermolysis abilities of solvents indicated that toluene is the best medium for the cobalt mediated cyclopentene formation.

D. Process optimization and representative experimental procedure

Although the modifications reported above were helpful in the understanding of this novel cyclopentene formation, no improvement of the reaction outcome was obtained.

In particular, the formation of the Pauson-Khand product was observed in a reproducible manner, although the thermolysis was carried out under an argon atmosphere. Under the mechanism proposed for the cobalt mediated cyclopentenone formation under thermal conditions, a total of three CO ligands are displaced from the cobalt complex into the reaction mixture to form the first intermediate metallocycle. Based on the fact that saturation of the reaction mixture with the help of carbon monoxide pressure is instrumental in the Pauson-Khand reaction, we hypothesized that the CO released from the cobalt complexes could favor the Pauson-Khand mechanism and lead to the formation by-product **20**.

Table 4 : Optimization of conditions for carbocyclization of enyne 19

Entry	Solvent	Temp °C	$Co_2(CO)_8$ equiv.	Time h	Ratio **21:22:20**
1	PhMe	110	1.2	12	70:20:10
10[c]	PhMe	110	1.2	12	75:25:0

[c]Conducted with constant bubbling of argon through the reaction medium.

With the objective of lowering the proportion of **20**, an experimental set-up was designed so as to allow for the constant degassing of the reaction mixture by bubbling argon through the medium via a fine glass tubing. In agreement with our hypothesis, the formation of the Pauson-Khand product **20** was completely inhibited by bubbling argon through the reaction mixture (Table 4, entry 10). The overall yield of cyclopentene **21** was also improved by the active removal of CO from the medium, while the ratio cyclopentene **21** versus isomerized olefin **22** is unchanged. Using this optimized protocol, the cyclopentene **21** could

be isolated in 70% yield after chemical derivatization of the co-product **22**. This protocol was used for all the cyclopentene formation reactions described hereafter.

3. Mechanistic proposal

A. Mechanistic evidence

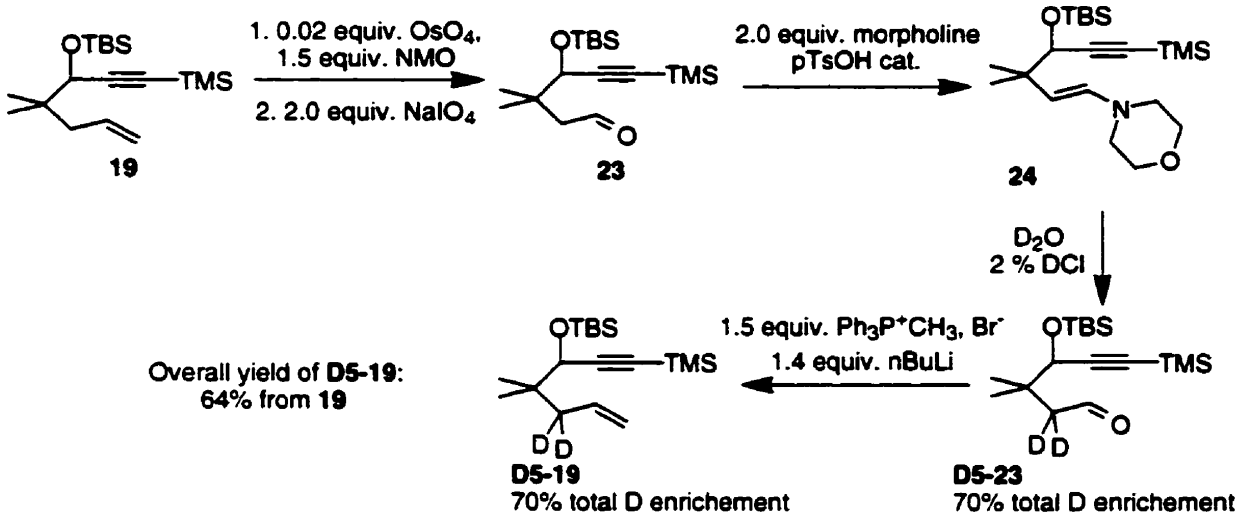
Additional experiments were undertaken in order to provide supplementary mechanistic evidence for the formation of the cyclopentene **21** and isomerized olefin **22**.

First of all, an experiment was designed aiming at elucidating the origin of the hydrogen atom at the C3 position of the cyclopentene. More specifically, the possibility that this hydrogen results from an atom transfer from the C5 position of the starting material was investigated by a labeling experiment.

In practice, deuterium enrichment was most practically obtained at the position C5 of the enyne starting material by the hydrolysis in D_2O of the morpholine derived enamine intermediate **24** (Scheme 20), in the presence of 2 % DCl. A 70 % overall enrichment of **D5-23** in deuterium at C5 was observed by ^1H NMR. A Wittig reaction with methyl triphenylphosphinium iodide was carried out on the resulting deuterated aldehyde **D5-23**, leading to the corresponding enyne **D5-19** deuterated at C5 in good overall yield and with an identical level of enrichment.

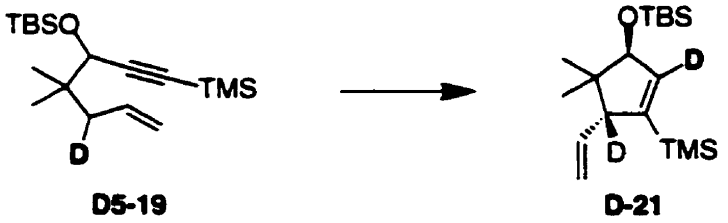
It is noteworthy that other strategies based on the deuterium incorporation at the aldehyde **23** stage, by exchange with MeOD under basic or acidic conditions, or by quenching the corresponding enolate with electrophilic deuterium sources, proved completely unsuccessful. The dimethyl hydrazone **25** derived from aldehyde **23** also could not be deuterated under various conditions, including exchange with MeOD under acidic conditions, or deprotonation with n-BuLi or t-BuLi.

Scheme 20 : Deuterium incorporation at C5 of enyne 19



Submission of **D5-19** to the standard reaction conditions described above, led to a mixture containing the cyclopentene **D-21**, for which ^{1}H NMR analysis revealed an total enrichement in deuterium in the order of 70 % at positions C2 and C5 of the cyclopentene (Scheme 21). This result is a clear evidence for overall hydrogen migration from the C5 position of the substrate to the C2 position of the cyclopentene. In particular, it excludes the participation of the solvent in this process.

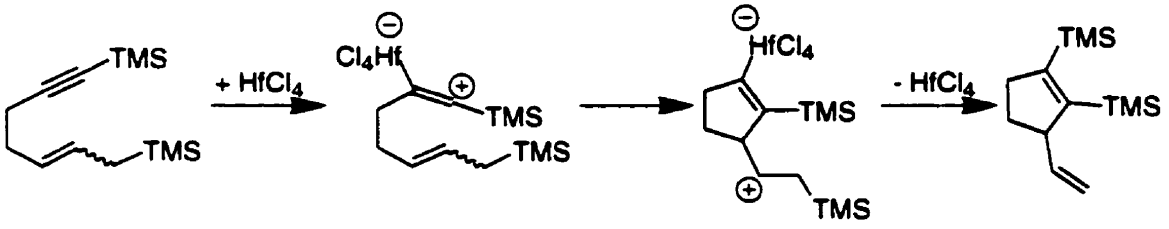
Scheme 21 : Cobalt mediated cyclopentene formation from D5-19



A related cyclopentene formation has been reported by Yamamoto *et al.*, wherein 7-trimethylsilyl-5-hepten-1-ynes undergo 5-endo-dig cyclizations under the influence of

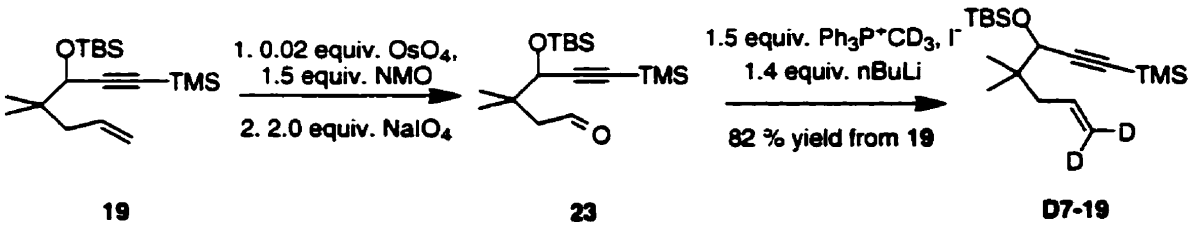
halfnium(IV) chloride (Scheme 22).[32] This cyclization process is terminated by the migration of the allylic trimethylsilyl group, yielding a 5-vinyl substituted cyclopentene with a structure similar to that of **21**.

Scheme 22 : $HfCl_4$ catalyzed *endo-dig* carbocyclization of an alkyne



However, this process appears to be mechanistically different to the cobalt mediated cyclopentenone formation. Indeed, the study of the stoichoimetry of the reaction in $Co_2(CO)_8$ hinted that olefin isomerization to **22** is not an intermediate step in the formation of **21**. In order to confirm this indication, a second experiment based on deuterium labeling was designed. The terminally deuterated enyne **D7-19** was prepared by the Wittig reaction of d_3-methyl triphenylphosphinium iodide on the aldehyde **23** in an overall yield of 82 % from **19** (Scheme 23). The deuterium enrichment of **D7-19** at C7 was evaluated by ^1H NMR at 90 %.

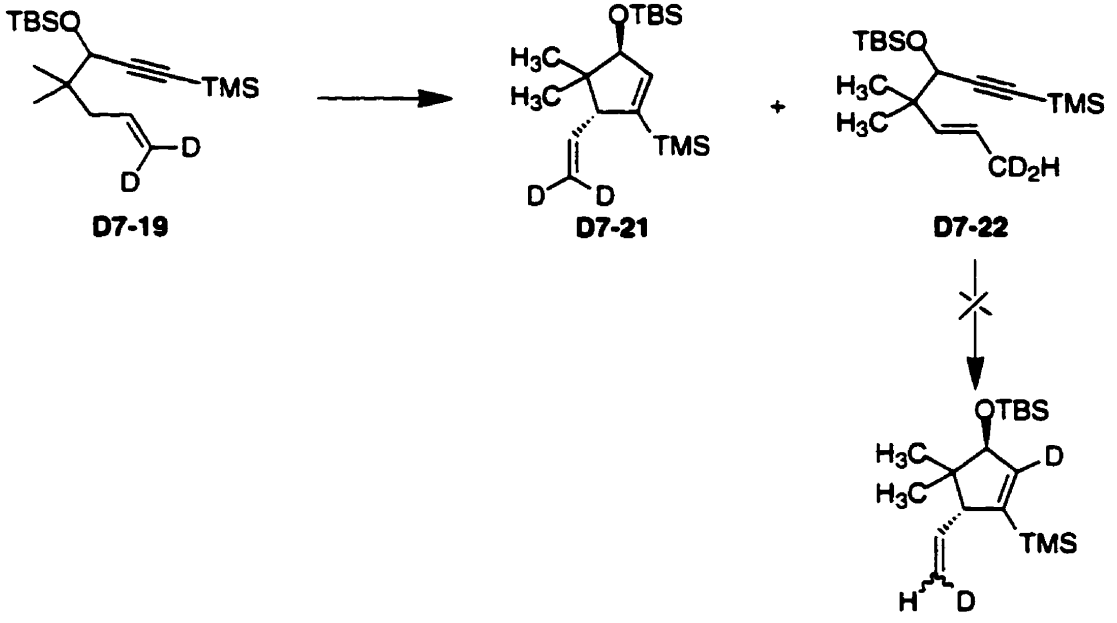
Scheme 23 : Deuterium incorporation at C7 of enyne 19



When compound **D7-19** was subjected to the same standard reaction conditions, no migration of the deuterium label was observed in the resulting mixture, in either the

cyclopentene or the isomerized olefin products (Scheme 24). As determined by ^{1}H NMR, compounds **D7-21** and **D7-22** showed an enrichment level of 90 % in deuterium at the terminal position, similar to that of starting material **D7-19**. Additionally, the ratio of the integration values for the hydrogens at position C2 and C3 in **D7-21** was found nearly identical to that observed for **21** itself (0.97:1 vs. 0.96:1, respectively).

Scheme 24 : Cobalt mediated cyclopentene formation and olefin isomerization from D7-19

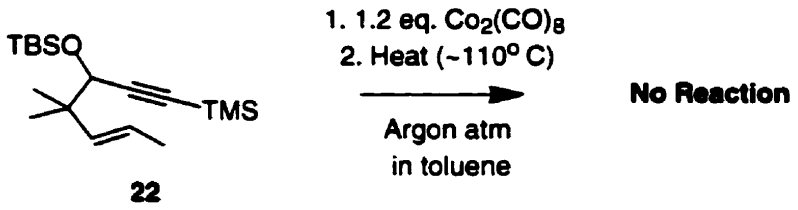


We have previously demonstrated that the hydrogen at C2 in the cyclopentene product has been shown to result from an overall migration from the C5 position of the substrate. If the olefin isomerization process were a preliminary step towards the cyclopentene formation, the necessary allylic abstraction from C7 of **D7-22** would have led to partial incorporation of deuterium at C2 in the cyclopentene product, and an integration ratio in the order of 0.68:1.

A final proof that the isomerized olefin **22** is a by-product of cyclopentene **21** formation was obtained by submitting the independently synthesized **22** (Scheme 19) to the

standard reaction conditions. In this experiment, **22** was recovered completely unchanged (Scheme 25).

Scheme 25 : Lack of reactivity of isomerized olefin 22



22

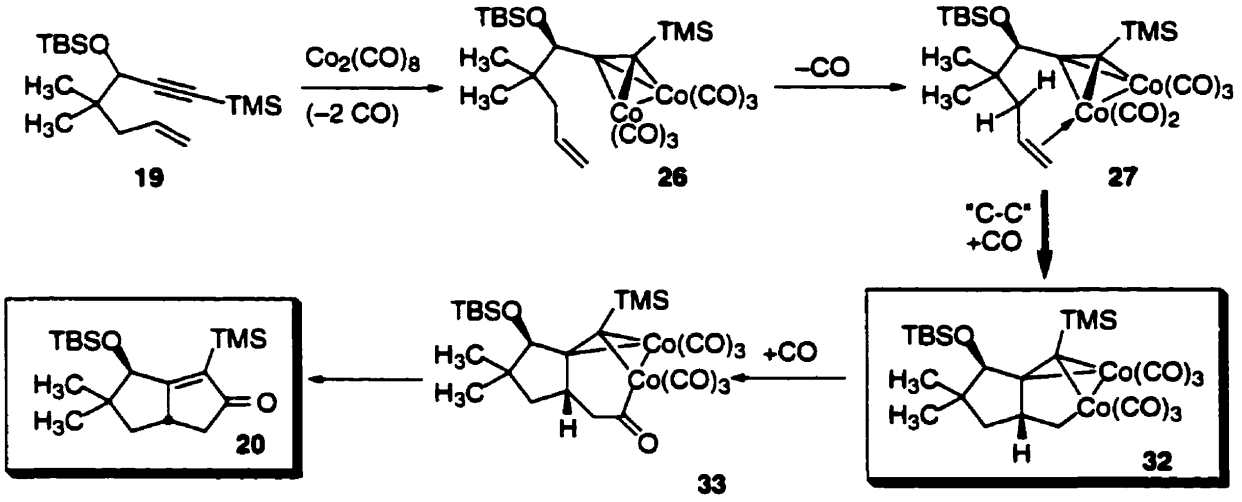
B. Mechanisms

The results obtained from the investigation of the reaction parameters, more specifically the insight provided by the study of the stoichiometry in $Co_2(CO)_8$ and of the influence of released CO in the reaction mixture, have led us to propose the following mechanism to account for the formation of both cyclopentene **21** and isomerized olefin **22**. The proposed mechanism is in agreement with the observations made in the deuterium labeling experiments.

The above experimental results were found consistent with the allylic C-H bond cleavage of the cobalt complex of **19** under thermolysis. A subsequent diverging point would lead to a reductive elimination providing **22** for one part, and on the other part to a C-C bond formation followed ultimately by reductive elimination to **21**, in an overall C5-C2 hydrogen migration and formal 5-endo-dig cyclization. Furthermore, these data are inconsistent with a mechanism by which the alkene first isomerizes to the internal olefin **22** prior to cyclopentene ring formation.

We propose that the first mechanistic steps in the synthesis of both **21** and **22** mirror those previously invoked for the Pauson-Khand reaction (Scheme 26 and 27).[26a-b,33] Thus, in presence of $Co_2(CO)_8$, the enyne substrate **19** forms a cobalt complex (**26**) at room temperature, causing the release of two CO ligands. Heating induces loss of an additional CO ligand. This ligand is replaced on the cobalt valency shell by coordination of the alkene (complex **27**). As with the Pauson-Khand reaction, it has not been possible to detect any intermediates other than the initial cobalt complex **26**, although evidence for the initial ligand loss exists.[28]

Scheme 26 : Pauson-Khand mechanism

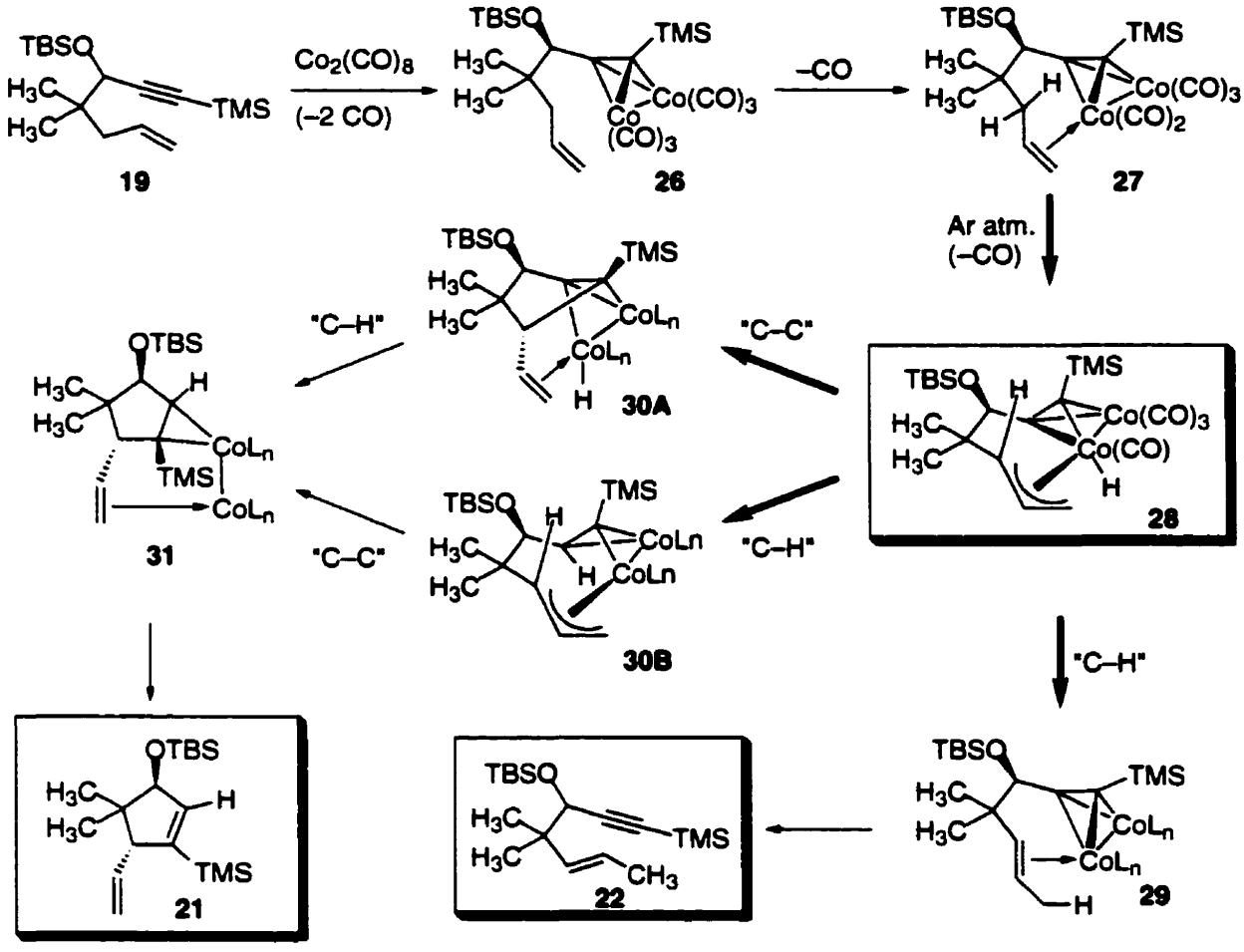


In the normal Pauson-Khand process, migratory insertion in **27** leads to metallocycle **32**, creating a carbon-carbon bond, and subsequent CO insertion (**33**) followed by reductive elimination give rise to the cyclopentenone product **20** (Scheme 26).

We propose that this migratory insertion process (**27**→**32**) is driven by recomplexation of a CO ligand and that in the absence of a CO atmosphere, a competing allylic C-H oxidative addition occurs forming the η^3-allylcobalt hydride **28** (Scheme 27).

The alternative of η^1-allylcobalt hydride complexes to compound **28** is refuted, as the subsequent intermediate towards product **22** would then necessarily include a trans double bond within a seven membered metallocycle.

Scheme 27 : Proposed mechanism



Complex **28** can reductively eliminate between the cobalt hydride and the terminal allylic carbon to form a C-H bond (complex **29**). Decomplexation of complex **29** yields the isomerized alkene **22** in an overall alkene isomerization process.

Alternatively, complex **28** can undergo reductive elimination between the positions C5 and C1 of the starting material to form a C-C σ bond (complex **30A**). A subsequent reductive elimination between the cobalt hydride and the C2 position of the substrate leads to the formation of a C-H bond, giving rise to **31**. Another possibility resides in the formation of **30B** by reductive elimination between the cobalt hydride and the C2 position of the substrate.

In this case, reductive elimination between the positions C5 and C1 of the starting material to form a C-C σ bond follows to provide **31**. The complex **31** yields the cyclopentene **21** after decomplexation. This process can be identified as a formal 5-endo-dig cyclization from enyne **19**.

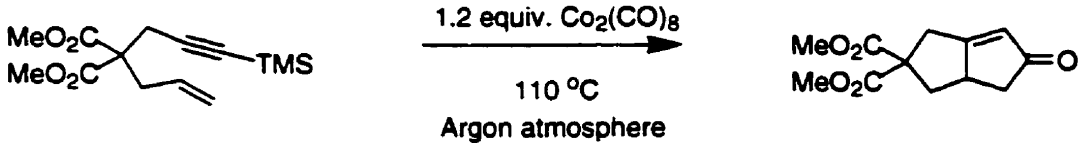
The lack of reactivity observed for 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-7-trimethylsilyl-2-hepten-6-yne (**22**) can be compared to the general unreactivity of hex-1-en-5-ynes towards the Pauson-Khand reaction. These enynes, which would form four-membered rings upon intramolecular addition, instead undergo alkyne trimerization.[34] Although the thermodynamically unfavored insertion of the double bond to yield cyclobutene fused metallocycles could be a key factor in this latter case, the stereoelectronic difficulties to overcome for the preliminary intramolecular chelation of the olefin to the cobalt alkyne complex would provide a common explanation to these two phenomena.

C. The role of CO

The notion that a CO atmosphere is required for driving the migratory insertion process (**27→32**) under thermal conditions is at present limited to this particular class of substrates, as there are cases where the Pauson-Khand pathway occurs in the absence of such a CO atmosphere (vide infra).

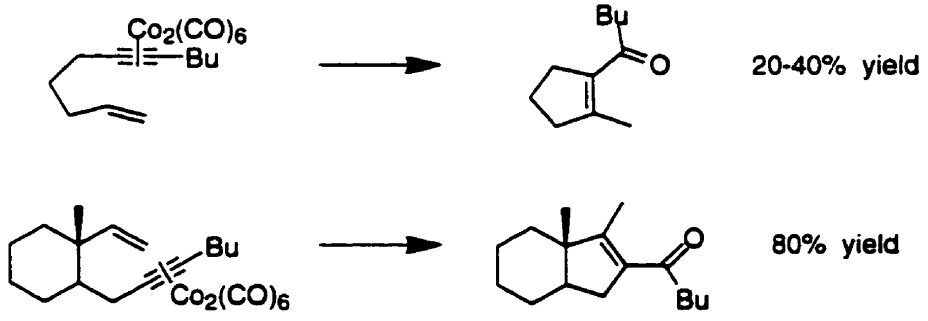
Various steps in the mechanistic proposals for the Pauson-Khand reaction or towards compounds **21** and **22** necessarily generate a vacant coordination site (**28→29**, **28→30A**, **28→30B**, **27→28**, **27→32**, **32→33**). However, it is important to notice that these processes do not specifically require extraneous CO to fulfill the electronic requirements of both cobalt atoms. The valence shells of these metal centers could be filled by invoking the bridging of CO ligands, by the formation of multiple cobalt-cobalt bonds or by a combination thereof. Nevertheless, to our knowledge, no successful thermal Pauson-Khand reaction procedure involving the constant removal of the CO released has been reported, except when either the solvent or the substrate itself bore potentially coordinating heteroatoms (Scheme 28).[35]

Scheme 28 :



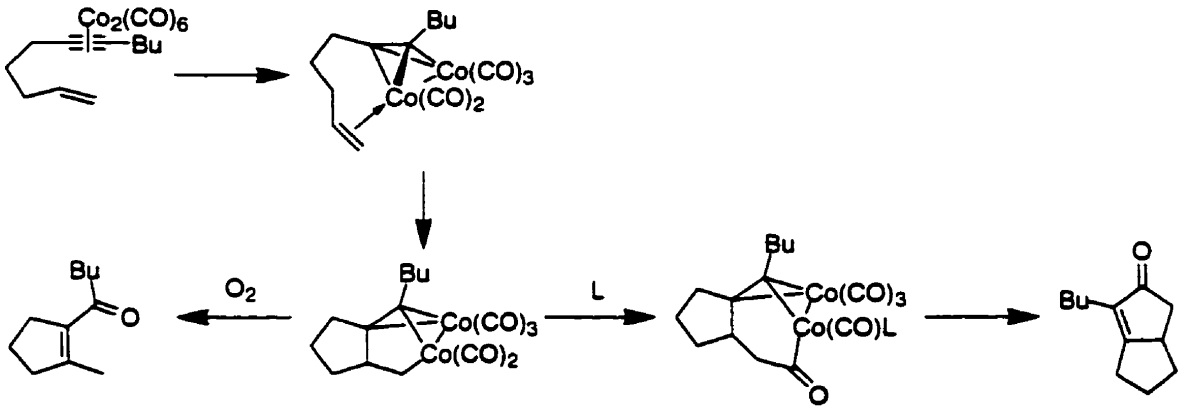
The importance of the atmosphere in which cobalt rearrangements occur has been stressed previously by the work of Krafft *et al.*[36] In this research effort, Pauson-Khand reactions of various enynes were found to be interrupted by oxidation by adventitious oxygen from the air, yielding novel enones (Scheme 29).

Scheme 29 : Interrupted Pauson-Khand reactions



This process is proposed by the authors to rely on the inhibition by molecular oxygen of the CO insertion on the intermediate metallocycle (Scheme30). Although this phenomenon appears to be mechanistically different from the cobalt mediated formation of cyclopentenes under study, it provides an example of a reaction competing with the Pauson-Khand process. In particular, the key factor in this competition is an atmosphere borne reagent, oxygen, hinting that the thermal Pauson-Khand reaction for the substrates reported does require the recomplexation by extraneous CO to proceed.

Scheme 30 : Mechanistic proposal for the Pauson-Khand interruption



The thermolysis of the cobalt complex of enyne **19** has been shown to provide **20** as the major product when using a CO atmosphere and as the minor product in the case of an argon atmosphere. Complete removal of CO from the reaction inhibits completely the formation of **20** (vide infra). More specifically, the structures of products **21** and **22** show that the divergence with the Pauson-Khand mechanism occurs before the formation of metallocycle **32**. Additionally, the ratio **21**:**22** is independent of the CO levels in the reaction medium. These results show evidence that for this class of substrate, extraneous CO is necessary for the thermal Pauson-Khand reaction to proceed and that metal-metal bond formation or bridging CO ligands do not account exclusively for filling the vacant coordination sites of the cobalt atoms during this process. The coordination with extraneous CO is thus demonstrated to be the driving factor towards the formation of **32**.

D. η^3-allylcobalt hydride species

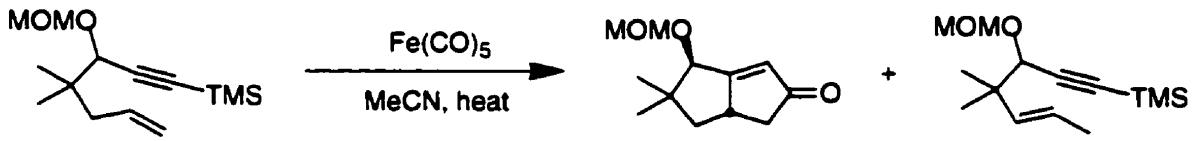
A strength of the mechanistic hypothesis presented above is to propose a common divergence from the Pauson-Khand pathway, to yield both compounds **21** and **22**.

The shared intermediate η^3-allylcobalt hydride **28** is postulated to undergo four possible transformations :

1. Reductive elimination between the hydride and the internal allylic carbon to **27**;
2. Reductive elimination between the hydride and the terminal allylic carbon to **29**;
3. Reductive elimination between the positions C5 and C1 of the starting material, to **30A**;
4. Reductive elimination between the hydride and the position C5 of the starting material, to **30B**.

The existence of η^3-allylmetal hydride species has been previously suggested in a related iron pentacarbonyl mediated Pauson-Khand process to explain for the isomerization of the alkene moiety of the enyne substrate (Scheme 31).[37]

Scheme 31 : Iron pentacarbonyl mediated Pauson-Khand and isomerization processes

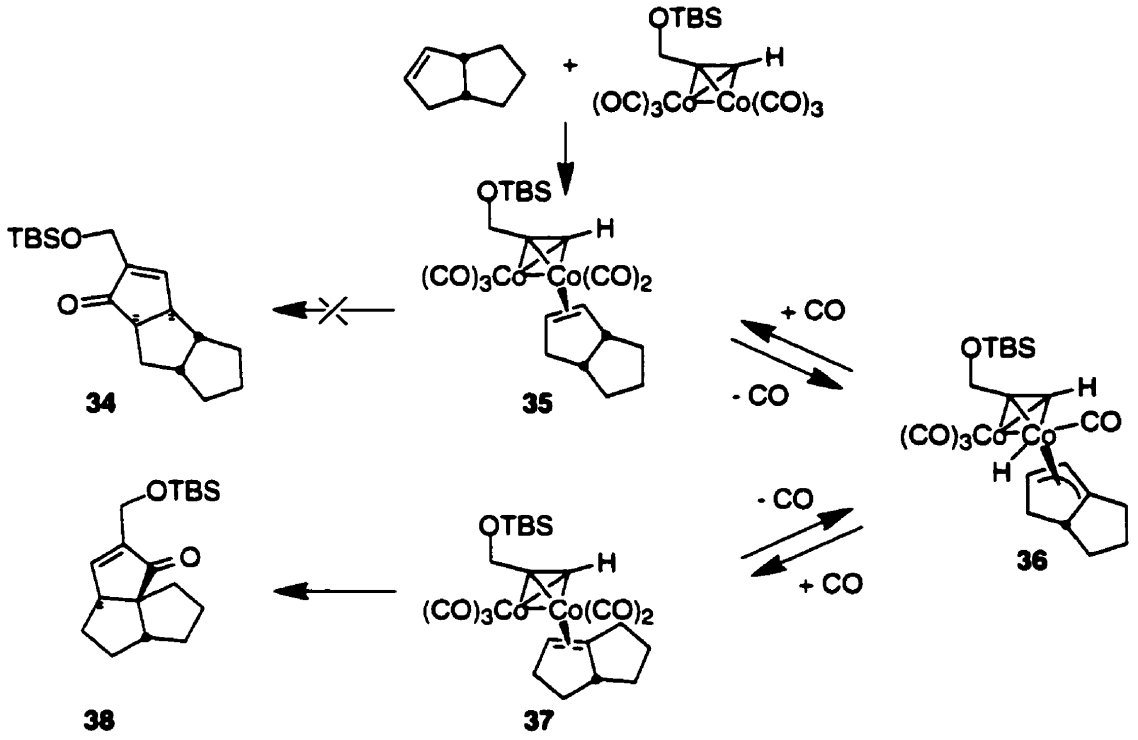


The formation of η^3-allylcobalt hydride complexes has been found to have few precedents in the literature. Such intermediates were postulated in a potential mechanism for the isomerization of bicyclo[3.3.0]oct-2-enes to bicyclo[3.3.0]oct-1-enes during intermolecular Pauson-Khand reactions (Scheme 32).[38]

In this example, the thermolysis of the cobalt alkyne complex **35** in a CO atmosphere led to the synthesis of the cyclopentenone **38** instead of providing the expected isomer **34**. The mechanism proposed by Serratosa *et al.* hypothesizes the existence of an intermediate η^3-allylcobalt hydride **36**, giving rise to complex **37** after reductive elimination between the hydride and the least hindered allylic carbon. Compound **38** was typically obtained in 10 to 18 % yields at temperatures ranging between 80 and 134 °C. At higher temperatures (e.g. 220 °C), no cyclopentenone **38** was produced, although a number of other products were isolated, including the corresponding cyclopentanone and compounds in which the silyloxy moiety

had been lost through a reduction process. These latter results support the hypothesis of the intermediacy of a cobalt hydride complex.

Scheme 32 : η^3-allylcobalt hydride in Pauson-Khand reaction



In order to explain the unexpected formation of **38**, it is suggested that, following an established trend, the greater strain of the olefin moiety in complex **37** enhances its reactivity towards the Pauson-Khand process.[2a] This factor would override the increased steric hindrance of the tri-substituted olefin as well as the thermodynamically unfavored isomerization of the double bond to the ring junction. The presence of a tertiary allylic C-H increases the feasibility of the proposed pathway by facilitating the formation of the η^3-allylcobalt hydride complex. This proposal is in agreement with the Curtin-Hammett principle, as applied to the competitive Pauson-Khand reactions of the two alkenes **35** and **37** in equilibrium through the formation of the η^3-allylcobalt hydride intermediate **36**.

In a similar series of substrates, Pauson *et al.* have reported a similar cyclopentenone formation preceded by alkene isomerization albeit in low yields (Scheme 33).[39] This overall transformation is consistent with the above propositions of Serratosa *et al.*.

Scheme 33 : Olefin isomerization and cyclopentenone formation

In these two examples, carried out in presence of carbon monoxide, the intermediate η^3-allylcobalt hydride complex reportedly only led to the isomerization of the olefin moiety. No product resulting from a C-C σ bond formation between the alkynic ligand and either of the terminal allylic positions of this intermediate was isolated.

The lack of reactivity of the bicyclo[3.3.0]oct-2-enes towards the Pauson-Khand reaction is probably the factor allowing for the η^3-allylcobalt hydride complex to compete. The presence of CO and the higher reactivity of the isomerized bicyclo-octenes ultimately lead to the related cyclopentenone in poor yields.

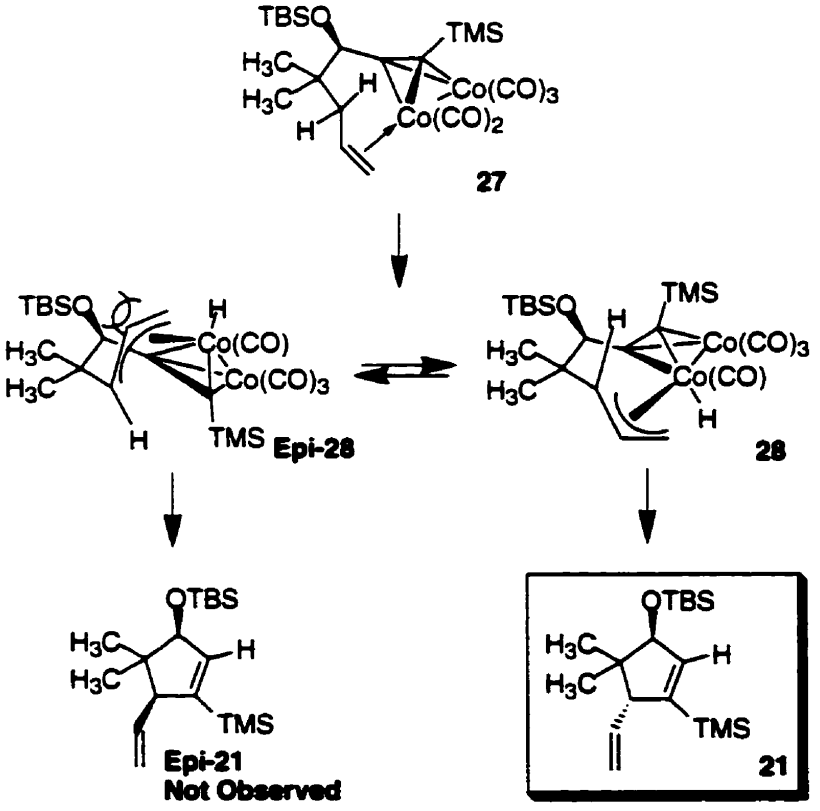
The precedents reported in the literature lead credence to the proposed η^3-allylcobalt hydride intermediate such as **28** upon the thermolysis of cobalt enyne complexes. For particular classes of reactants, these intermediates are hypothesized to form in competition with metallocycles of type **32**, when the thermal Pauson-Khand reaction is inhibited by poor substrate reactivity, or by the lack of extraneous CO. The partition of the η^3-allylcobalt hydride complex between C-H and C-C bond formation, giving respectively compounds type **26** and **27**, is proposed to be function of the stereoelectronic effects imparted by the enyne ligand onto the cobalt complex.

E. Diastereoselectivity issues

If the proposed mechanism is correct, the trans diastereoselectivity observed in the cyclopentene formation is defined during the C-H allylic activation step (**27→28**). The facial selectivity for the formation of the η^3-allylcobalt species is proposed to result from the minimization of non-bonded interactions between the ring substituent at C5 and the tert-butyldimethylsilyloxy group at C3.

The C-H allylic activation of compound **24** can potentially lead to the two η^3-allylcobalt species **28** and **Epi-28** (Scheme 34). These intermediates present a ring structure resulting from the chelation of cobalt to the allyl group. While formation of **28** provides ultimately the observed product **21**, **Epi-28** is the precursor of **Epi-21** via the C-C σ bond formation between C1 and C5.

Scheme 34: Steric interactions



In the case of **Epi-28** , strong steric interactions will develop during the necessary substituent positioning for the σ bond formation between the allyl and tert-butyldimethylsilyloxy groups present on the same face of the ring structure. In the intermediate **28**, the allyl and tert-butyldimethylsilyloxy groups are located on different faces of this ring structure. The difference in energy of **Epi-28** and **28** is proposed to result in the formation of cyclopentene **21** as a single diastereomer, to the exclusion of **Epi-21**.

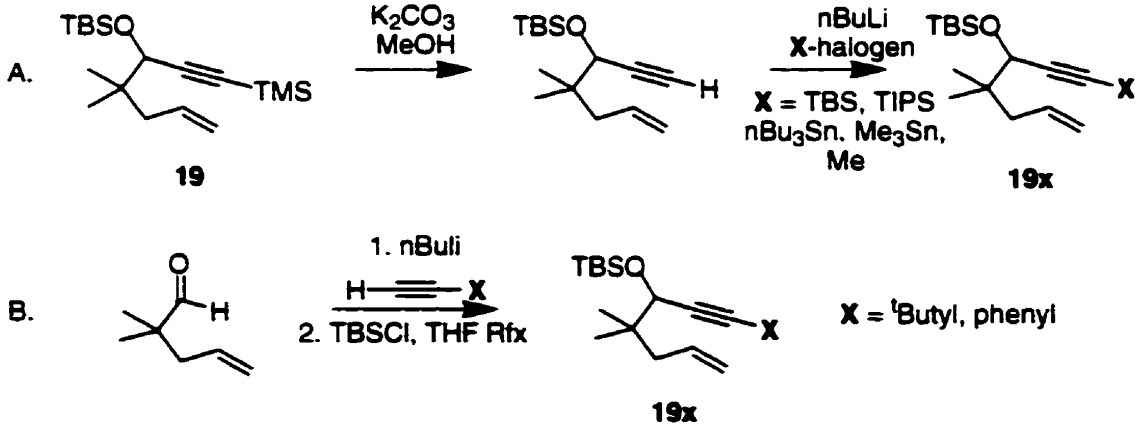
4. Influence of the functionalization of the substrate

A. Substitution at the alkynic terminus

The next step in the understanding and development of the cobalt mediated cyclopentene formation centered on the study of the substitution pattern at the alkynic terminus.

These alternative substitutions were introduced in a straightforward manner by two complementary pathways. A first possibility consists in first deprotecting the substrate **19** at the alkynic terminus, using nucleophilic conditions such as potassium carbonate in methanol. The intermediate 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-1-hepten-6-yne obtained could then be deprotonated and allowed to react with various electrophiles (Scheme 35A). This technique was suitable for the preparation of methyl, trialkylsilyl, -stannyl, and -germyl substitutions.

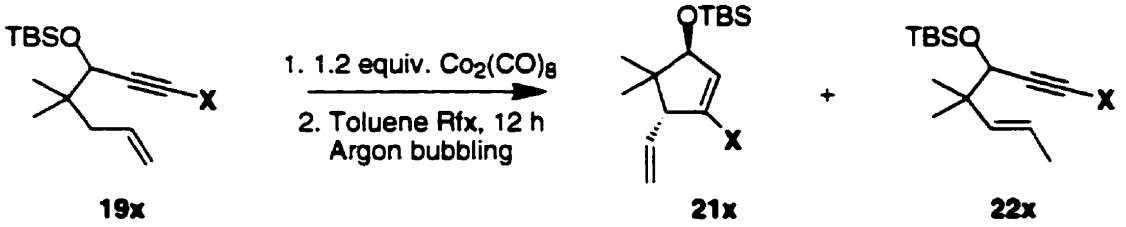
Scheme 35 : Introduction of alternate substitution at C1



However, another route was necessary to obtain substitution patterns for which related electrophiles were not amenable to the alkylation reaction. A direct pathway

centering on the alkylation of a suitably mono-substituted alkyne onto 2,2-dimethyl-4-pentenal was then preferred (Scheme 35B). This alternative procedure allowed the access to ^{t}butyl and phenyl terminated alkynic substrates.

Table 5 : Alkynic substitution and cyclopentene formation



19x **21x** **22x**

Entry	X	Product Ratio[1] **19:21:22**	Isolated Yield of **21**
a	Me_3Si	0:75:25	70%
b	Me	-	-
c	^{t}Bu	-	-
d	Ph	-	-
e	Me_3Ge	0:80:20	72%
f	nBu_3Sn	–	-
g	Me_3Sn	–	-
h	t-$BuMe_2Si$	75:15:10	–
i	iPr_3Si	100:0:0	-

1. Determined by ^{1}H NMR.

This series of substrates was submitted to the optimized reaction conditions to investigate the scope of the rearrangement (Table 5). Internal aliphatic alkynes (X = CH_3, ^{t}Bu) gave complex mixtures of products inconsistent with the desired cyclopentene (entry b, c). A similar observation was also made for the phenyl substituted enyne (entry d).

However, selecting another substituent in the same column of the periodic table as silicon (IVB), so as to keep an electronic environment similar to that of trimethylsilyl, was found to be fruitful. The trimethylgermyl derivative **19e** underwent clean reaction and an improved ratio of cyclopentene to isomerized olefin was realized. Cyclopentene **21e** was isolated in a 72% yield. The corresponding trimethyl alkynyltin substrate **19f** proved to be too unstable to the reaction conditions and gave only decomposition products. An attempt at improving stability by using the tributylalkynyltin substrate **19g** was unsuccessful.

Interestingly, an increase in steric bulk of the silyl group is detrimental to the efficiency of the reaction. With the tert-butyldimethylsilyl alkyne **19h**, the cobalt rearrangement is hampered, as only 25% of the starting material is consumed during the reaction. The ^{1}H NMR data were consistent with the formation of both **21h** and **22h**, in a 1.5:1 ratio. In addition, the incorporation of an even larger TIPS substituent at the terminal alkynic position gives a completely unreactive substrate to the standard conditions (entry i).

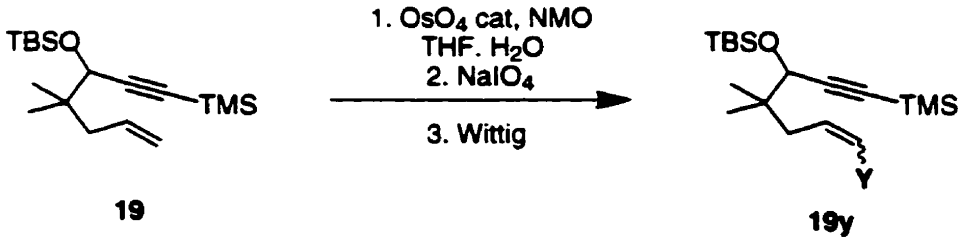
Overall, a comparison between the respective influence on the reactivity of X= ^{t}Bu, TMS and $GeMe_3$ hints that a key factor in the promotion of the cyclopentene formation is the relative electron density of the cobalt complex, itself induced by the electronic environment created by the alkyne ligand. In the Pauson-Khand process, it has been noticed that alkynes substituted by electron withdrawing groups do not undergo the cycloaddition.[2a] For a very similar electronic setting, the cobalt mediated rearrangement is also sensitive to the steric demands of the alkynic substituent.

Nevertheless, the stringent limitations imposed on the alkynic substituent for the formation of cyclopentene **21** in good yield does not restrict the general utility of the reaction. In a general context, it has been demonstrated that vinyl silanes can be efficiently desilylated to provide simple olefins[40], or substituted for iodine, yielding vinyl iodides[41]. In turn, this latter class of compounds has been utilized as substrates for palladium catalyzed carbon-carbon bond formation with organostannanes[42] or organoboranes[43]. Such two step transformation eventually would result in the overall substitution of the silyl substituent for an alkyl group.

B. Substitution at the olefinic terminus

In addition to the variations at the terminal alkyne position, we also studied the introduction of various functional groups at the alkene terminus of the substrate and their reactivity in the cobalt mediated cyclopentene rearrangement.

Scheme 36 : Introduction of alternate substitution at C7



19 **19y**

The alternate substitution patterns at C7 were introduced by first oxidizing enyne **19** by osmium tetroxide in a catalytic process. The product was eventually oxidized to the aldehyde by sodium periodate. This oxidation was followed by Wittig or Horner-Emmons-Wadsworth reactions on the crude aldehyde to provide enynes type **19y** (Scheme 36) in good overall yields. These substrates **19y** were then submitted to the optimized reaction conditions to verify the generality of the rearrangement (Table 6).

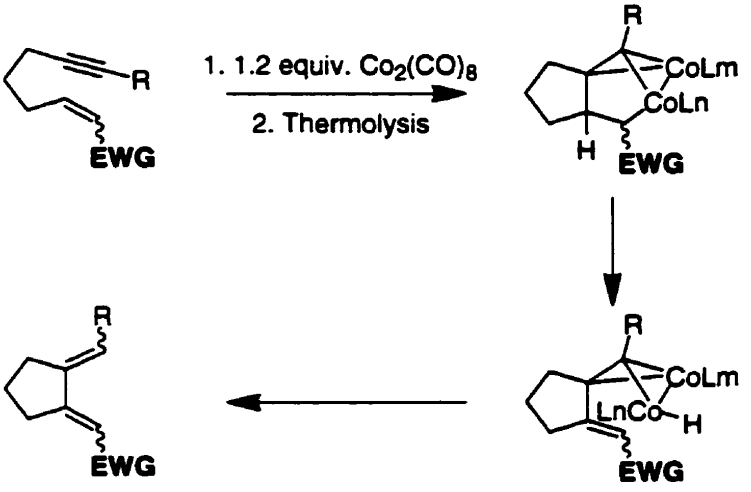
In particular, the α,β-unsaturated ester **19j** was obtained exclusively as the *trans* isomer by a Horner-Emmons-Wadsworth reaction with triethyl phosphonoacetate. Under the above standard reaction conditions, substrate **19j** afforded exclusively cyclopentene **21j** and recovered starting material, with a 58% conversion to cyclized product (Table 6, entry j). No evidence of alkene migration was detected by ^1H NMR analysis. For this particular run, it was also noted that the thermolysis after a 12 hour duration yielded a colorless suspension of black particles accompanied with a cobalt(0) mirror coating the reaction vessel. This observation clearly indicates the complete decomplexation of the cobalt complex to provide unreactive cobalt species. For this particular substrate **19j**, the decomplexation process is found to be competitive over the irreversible formation of complex type **29** (Scheme 27).

This competition might be increased by the lower reactivity of the double bond, due to its conjugation with the ester function.

In order to increase the yield of the reaction, the process was reiterated twice. This procedure involved the removal of the solids from the reaction medium by simple filtration, addition of fresh cobalt and thermolysis. The overall conversion was thus increased to 95% according the ^{1}H NMR analysis. The product **21j** was isolated as a single diastereoisomer by silica gel flash chromatography in 92% yield. An attempt at streamlining this reaction by doing three successive additions, each of 1.2 equivalent of $Co_2(CO)_8$, without any intermediate filtration led to a lower conversion and the appearance of other uncharacterized products. A similar result was observed when using a single iteration with an increase of the amount of $Co_2(CO)_8$ to six equivalents.

It is noteworthy that unsaturated esters such as **19j** are known to react in an anomalous fashion under the Pauson-Khand reaction conditions (Scheme 37).[44] In competition with CO insertion, the metallocyclic intermediate is proposed to undergo elimination of the β-hydrogen and subsequent elimination to the 1,3 diene. However, such dienes were not detected in the series of experiments using substrate **19j**, attesting for the absence of metallocyle in this reaction.

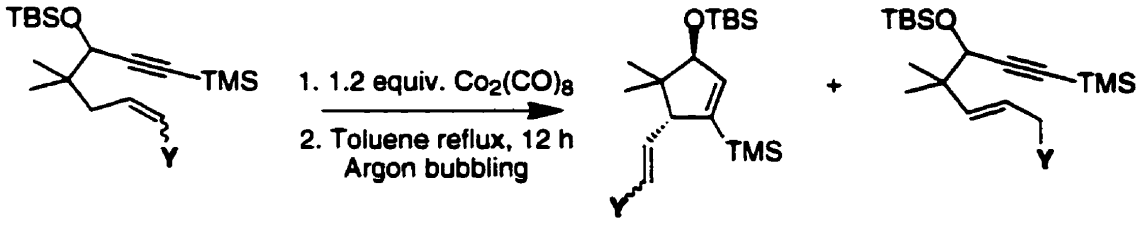
Scheme 37 : Anomalous reactivity of alkenes bearing an electron withdrawing group under Pauson-Khand conditions



The related protected allylic alcohol **19k** was obtained in two steps from the parent ester **19j** by reduction with Dibal-H, followed by protection with 'butyldimethylsilyl chloride in presence of imidazole. In contrast with **19j**, silyloxymethyl substituted **19k** underwent cyclization to form cyclopentene **21k** in a 71% isolated yield with no starting material recovered (Table 6, entry k). Several minor products were present in the crude mixture and a pattern consistent with a 'butyl dimethyl silyl enol ether was detected by ^{1}H NMR for one of them. Unfortunately, this product proved difficult to isolate and could not be fully characterized.

The reactivity of **19k** confirms that the steric environment of the alkene moiety is not a serious limitation. In addition, it also shows that the lower reactivity of **19j** is most likely due to electronic rather than steric factors.

Table 6 : Alkenic substitution and cyclopentene formation



19y 21y 22y

Entry	Y	Cis:Trans Ratio	Product Ratio[1] **19:21:22**	Isolated Yield of **21**
a	H	-	0:75:25	70%
j,	CO_2Et	0:100	42:58:0	-
1rst iteration				
j,	CO_2Et	0:100	5:95:0	92%
3rd iteration				
k	CH_2OTBS	0:100	0:74:0[2]	71%
l	Ph	33:66	30:70:0	50%[3]

1. Determined by 1H NMR. 2. Several unidentified minor products were observed in this reaction. 3. Mixture of isomers.

Finally, a third type of substitution, namely the styryl derivative, was investigated. Compound **19l** was obtained in the 33:66 mixture of cis:trans isomers from a Wittig reaction with benzyltriphenyl phosphonium chloride. Using the standard cyclopentene formation conditions, a 70% conversion was noted from ^{1}H NMR analysis. Purification by silica gel flash chromatography afforded a mixture of isomers in a 50% yield (Table 6, entry l).

This series of substrates clearly shows that the cobalt mediated formation of cyclopentenes is compatible with a range of olefin substitutions. The presence of an electron withdrawing group or an increase in steric bulk of the olefinic substituent has not hampered the reaction. These variations in substitution pattern enable the synthesis of complex cyclopentenes in good yield.

5. Proposals for future work

A first area for improving the understanding of the reaction potential is highlighted by the results obtained in the processing of styril derivative **19l**. In this particular run, the ratio of conversion is found to be remarkably close to the cis:trans ratio itself. It would then be of great interest to study the effect of the olefin isomerization on the cyclization process. In this objective, the **19l** cis:trans ratio could be altered significantly by synthesizing this substrate using a salt free protocol. The products obtained from the submission to the standard conditions of this altered mixture would provide a definitive element in the comprehension of this factor.

In addition, the extension of this technology by modification of the chain linking the olefinic and alkynic reactive moieties has been undertaken. Undergraduate student W. Felzmann is studying the possibility of a one-carbon extension of the linker, in an attempt towards the synthesis of 1-trimethylsilyl 6-vinyl cyclohexenes.

The synthesis of heterocycles through this novel cobalt mediated formal 5-endo dig cyclization is the focus of graduate student A. Ajamian's research. This project includes the replacement of the *gem*-dimethyl group by heteroatoms such as oxygen or nitrogen on the enyne substrate and the optimization of the cyclization conditions.

Another level for the development of this reaction resides in the potential for enantioselectivity of the process. High enantioselectivity have been reported in Pauson-Khand reactions through the generation of a chiral cobalt core.[45] In particular, the use of chiral phosphine Glyphos as a co-ligand was reported by Kerr *et al.*.[46] After verification of the reactivity of 1-trimethylsilyl-6-heptene under the standard conditions for cyclopentene formation, the utility of this chiral co-ligand could be extended on this substrate for this latter reaction. On substrate **19**, Glyphos could as well provide a key for enantioselective kinetic resolution.

Chiral auxiliaries attached either to the alkene[47] or the alkyne[48] have been used in asymetric Pauson-Khand reactions. These latter methods have been assessed in the total syntheses of brefeldin A[49] and β-cuparenone[50]. Although the possibilities for substitution at

the alkyne position were found to be restricted, these general concepts could be adapted to the cyclopentene formation under consideration. More specifically, a methodology developed by Carretero *et al.* relies on the substitution at the alkene by a 'butylsulfinyl group for inducing enantioselectivity in Pauson-Khand reactions.[51] Taking into account the possibility of functionalization at the alkene terminus for the cyclopentene formation, this technique could be assayed in this novel reaction for the simple 1-trimethylsilyl 6- heptene substrate. Again it could also be valuable in the kinetic resolution of propargylic substituted substrates such as **19**.

6. Conclusion

In conclusion, we have discovered that a variation in the Pauson-Khand protocol can produce novel and highly functionalized cyclopentenes through dicobalt octacarbonyl mediation.

In agreement with labelling experiments, we have proposed a mechanism involving a C-H allylic activation to form a η^3-allylcobalt hydride complex, subsequently yielding a formal 5-endo-dig cyclization of the 1,6-enyne substrates.

The experimental conditions have been developed, so as to allow for the synthesis of single diastereoisomers of highly functionalized compounds in good to excellent yields.

The reaction is tolerant of ester and silyl ether groups. Although the reaction appears to be limited to trimethylsilyl and trimethylgermyl alkynes, it should be possible to transform the vinyl silanes and germanes into other functional groups.

Further studies in this area will include the extension of this methodology to cyclic ethers and amines as well as a delineation of the factors which induce different substrates to follow either the Pauson-Khand or cyclopentene-forming pathways.

CONTRIBUTIONS TO KNOWLEDGE

During this methodology work, a number of advances were made:

1. A new reaction was uncovered and the products characterized.
2. A mechanism consistent with the product outcome and the stereochemistry was proposed and substantiated by labelling experiments and the study of the reaction stoichiometry.
3. The compatibility of different substitution patterns for the reaction substrates was investigated.

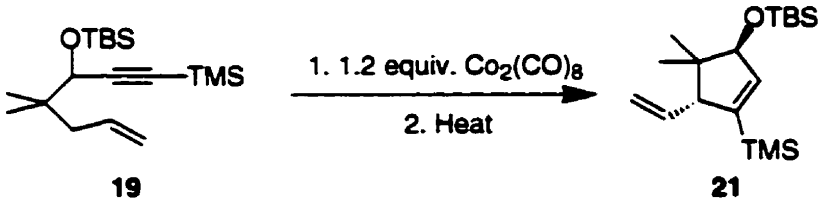
EXPERIMENTAL

Representative procedure for the diastereoselective formation of 5-vinyl cyclopentenes from 1,6-enynes

According to the study of the reaction parameters, a representative experimental procedure can be drawn as follows:

In a round bottom flask fitted with a condenser, a magnetic spin-bar and a glass tube which permits constant bubbling of argon through the reaction medium, $Co_2(CO)_8$ (632 mg, 1.85 mmol, 1.20 equiv) is added to a solution of the enyne **19** (500 mg, 1.54 mmol, 1.00 equiv) in anhydrous toluene (40 mL). After stirring at 21 °C for 2 hours, the black solution is heated at reflux for 12 hours, during which time a suspension forms and a cobalt (0) mirror coating is observed on the sides of the flask. After cooling to 21 °C, the black suspension is concentrated and the products are separated using chemical derivatization and flash chromatography techniques.

(3R*, 5S*)-4,4-dimethyl-5-ethenyl-3-((dimethylethyl)-dimethylsilyloxy)-1-trimethylsilyl cyclopentene 21:



19 **21**

In a round bottom flask fitted with a condenser, a magnetic spin-bar and a glass tube which permits constant bubbling of argon through the reaction medium, $Co_2(CO)_8$ (632 mg, 1.85 mmol, 1.20 equiv) was added to a solution of 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-7-trimethylsilyl-1-hepten-6-yne **19** (500 mg, 1.54 mmol, 1.00 equiv) in anhydrous toluene (40 mL). After stirring at 21 °C for 2 hours, the black solution was heated at reflux

for 12 hours, during which time a suspension forms and a cobalt (0) mirror coating is observed on the sides of the flask. After cooling to 21 °C, the black suspension was concentrated under vacuum and the residue was diluted with a mixture of acetone (20 ml) and distilled water (4 ml) and treated with ceric(VI) ammonium nitrate (4.18 g, 7.7 mmol, 5.00 equiv). After stirring for 2 hours, the solution was concentrated to remove acetone, and the aqueous residue was poured on to a pad of Celite and rinsed with several portions of dichloromethane. The filtrate is concentrated and the residue is dissolved in methanol (5 ml) and treated with potassium hydroxide (100 mg, 1.78 mmol, 1.15 equiv). After stirring for 2 hours, the solution is concentrated and diluted with saturated ammonium chloride solution. The resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. The product was purified by flash chromatography on silica gel (100% hexanes as eluent) to afford compound **21** as a colorless oil (350 mg, 1.08 mmol, 70%).

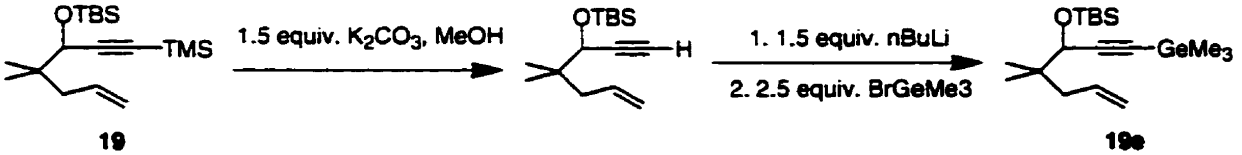
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.85 (s, 1H), 5.54 (dt, 1H, J = 17.0, 10.0 Hz), 4.99 (dd, 1H, J = 17.0, 1.7 Hz), 4.96 (dd, 1H, J = 10.0, 1.7 Hz), 4.39 (s, 1H), 2.93 (d, 1H, J = 10.0 Hz), 0.90 (s, 15H), 0.06 (s, 15H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 148.3, 144.0, 139.7, 115.5, 85.4, 63.7, 47.5, 26.1, 23.5, 23.2, 18.5, −1.1, −4.2, −4.6;

HRMS exact mass M-H$^+$ 323.2225 (calcd for $C_{18}H_{36}OSi_2$-H$^+$ 323.2227).

4,4-dimethyl-5-((dimethyl-ethyl)-dimethylsilyloxy)-7-trimethylgermyl-1-hepten-6-yne 1b:



19 **19e**

To a solution of 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-7-trimethylsilyl-1-hepten-6-yne **19** (1.015 g, 3.13 mmol, 1.00 equiv) in methanol (5 mL) was added potassium carbonate (650 mg, 4.69 mmol, 1.5 equiv). After stirring for 24 hours, the solution was concentrated and saturated ammonium chloride solution was added. The resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give the intermediate 4,4-dimethyl-5-((dimethylethyl)-dimethylsilyloxy)-1-hepten-6-yne. Due to the volatility of this material, it was used immediately in subsequent transformations.

To a solution of 4,4-dimethyl-5-((dimethylethyl)-dimethylsilyloxy)-1-hepten-6-yne in THF (20 mL) at –78 °C was added a 2.55 M solution of n-BuLi in hexanes (1.73 mL, 4.69 mmol, 1.50 equiv). After 15 minutes, trimethyl germyl bromide (1.0 g, 7.8 mmol, 2.50 equiv) was added. The mixture was allowed to warm slowly to room temperature and stirred at that temperature for 2 hours. The reaction was diluted with saturated ammonium chloride solution and the resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (100% dichloromethane as eluent) to afford 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-7-trimethylgermyl-1-hepten-6-yne **19e** as a colorless oil (1.082 g, 2.93 mmol, 94%).

^{1}H NMR ($CDCl_3$, 300 MHz):

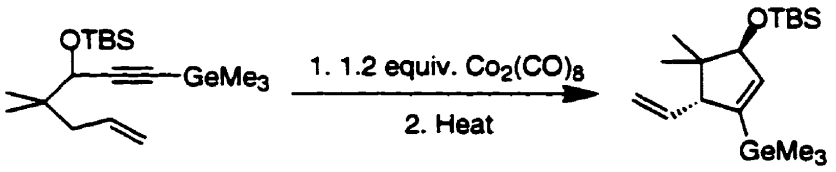
δ 5.82 (m, 1H), 5.05 (m, 1H), 5.00 (m, 1H), 4.00 (s, 1H), 2.96 (d, 1H, J = 7.6 Hz), 0.91 (s, 15H), 0.33 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 135.5, 117.0, 105.0, 89.9, 71.0, 42.6, 39.0, 25.8, 22.7, 22.5, 18.3, –0.4, –4.2, –5.1;

HRMS exact mass M-H$^+$ 369.1668 (calcd for $C_{18}H_{36}GeOSi$-H$^+$ 369.1669).

(3R*,5S*)-4,4-dimethyl-5-ethenyl-3-((dimethylethyl)-dimethylsilyloxy)-1-trimethylgermyl cyclopentene 21e:



19e **21e**

In a round bottom flask fitted with a condenser, a magnetic spin-bar and a glass tube which permits constant bubbling of argon through the reaction medium, $Co_2(CO)_8$ (135 mg, 0.40 mmol, 1.20 equiv) was added to a solution of the 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-7-trimethylgermyl-1-hepten-6-yne **19e** (122 mg, 0.33 mmol, 1.00 equiv) in anhydrous toluene (10 mL). After stirring at 21 °C for 2 hours, the black solution was heated at reflux for 12 hours, during which time a suspension forms and a cobalt (0) mirror coating is observed on the sides of the flask. After cooling to 21 °C, the black suspension was concentrated under vacuum and the residue was diluted with a mixture of acetone (5 ml) and distilled water (1 ml) and treated with ceric (VI) ammonium nitrate (905 mg, 1.65 mmol, 5.00 equiv). After stirring for 2 hours, the solution was concentrated to remove acetone, and the aqueous residue was poured on to a pad of Celite and rinsed with several portions of dichloromethane. The resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. The product was purified by flash chromatography on silica gel (100% hexanes as eluent) to afford (3R*, 5S*)-4,4-dimethyl-5-ethenyl-3-((dimethylethyl)-dimethylsilyloxy)-1-trimethylgermyl cyclopentene **21e** as a colorless oil (88 mg, 0.24 mmol, 72%).

^{1}H NMR ($CDCl_3$, 400 MHz):

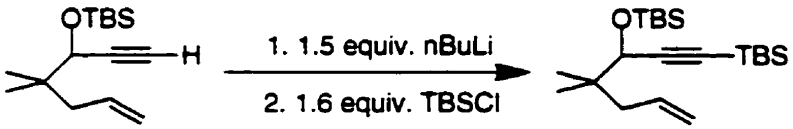
δ 5.76 (t, 1H, J = 1.5 Hz), 5.54 (dt, 1H, J = 17.2, 9.8 Hz), 5.00 (m, 1H), 4.96 (m, 1H), 4.37 (t, 1H, J = 1.5 Hz), 2.96 (d, 1H, J = 10 Hz), 0.90 (s, 15H), 0.32 (s, 3H), 0.18 (s, 9H), 0.06 (s, 6H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 149.7, 141.0, 139.1, 115.5, 85.0, 63.8, 47.0, 25.9, 23.5, 23.1, 18.3, –1.8, –4.4, –4.8;

HRMS exact mass M-H^+ 369.1668 (calcd for $C_{18}H_{36}GeOSi$-H^+ 369.1669).

4,4-dimethyl-5-((dimethylethyl)-dimethylsilyloxy)-7-(dimethylethyl)-dimethylsilyl-1-hepten-6-yne 19h:



19h

To a solution of crude intermediate 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-1-hepten-6-yne (239.4 mg, 0.95 mmol, 1.00 equiv) in THF (20 ml) at -78 °C was added a 2.55 M solution of nBuLi in hexanes (0.557 ml, 1.42 mmol, 1.50 equiv). After 15 minutes, t-butyl dimethyl silyl chloride (230 mg, 1.52 mmol, 1.60 equiv) was added. The mixture was allowed to warm up slowly to room temperature and stirred at that temperature for 12 hours. The reaction was diluted with saturated ammonium chloride solution and the resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (100% hexanes as eluent) to afford 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-7-(dimethyl ethyl) dimethylsilyl-1-hepten-6-yne **19h** as a colorless oil (338 mg, 0.92 mmol, 97%).

^1H NMR ($CDCl_3$, 400 MHz):

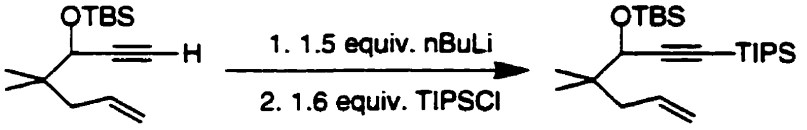
δ 5.82 (m, 1H), 5.04 (bs, 1H), 5.00 (m, 1H), 4.00 (s, 1H), 2.11 (dd, 2H, J = 4.3, 7.8 Hz), 0.92 (s, 24H), 0.33 (s, 9H), 0.14 (s, 3H), 0.09 (s, 9H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 135.3, 117.1, 107.0, 88.1, 70.9, 42.6, 39.1, 26.1, 25.8, 22.7, 22.6, 18.2, 16.5, –4.3, –4.7, –5. 2;

HRMS exact mass M+H$^+$ 367.2851 (calcd for $C_{21}H_{42}OSi_2$ +H$^+$ 367.2853).

4,4-dimethyl-5-((dimethylethyl)-dimethylsilyloxy)-7-tri-isopropylsilyl-1-hepten-6-yne 19i:



19i

To a solution of crude intermediate 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-1-hepten-6-yne (208.6 mg, 0.83 mmol, 1.00 equiv) in THF (15 ml) at -78 °C was added a 2.55 M solution of nBuLi in hexanes (0.486 ml, 1.24 mmol, 1.50 equiv). After 15 minutes, tri-isopropyl silyl chloride (0.285 ml, 1.33 mmol, 1.60 equiv) was added. The mixture was allowed to warm up slowly to room temperature and stirred at that temperature for 12 hours. The reaction was diluted with saturated ammonium chloride solution and the resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (100% hexanes as eluent) to afford 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-7-tri-isopropylsilyl-1-hepten-6-yne **19i** as a colorless oil (335 mg, 0.82 mmol, 99%).

^1H NMR ($CDCl_3$, 400 MHz):

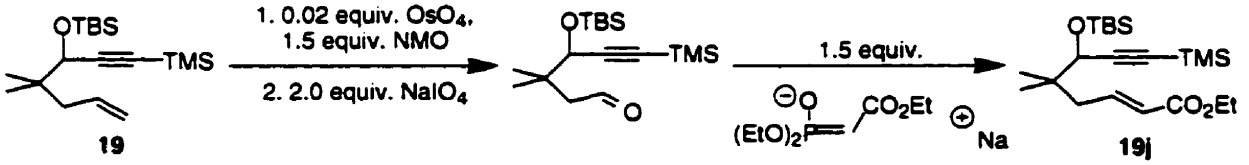
δ 5.82 (m, 1H), 5.04 (s, 1H), 5.00 (m, 1H), 4.03 (s, 1H), 2.13 (dd, 2H, J = 0.8, 7.5 Hz), 1.08 (s, 3H), 1.07 (bs, 15H), 1.03 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 135.6, 117.3, 108.3, 86.0, 71.2, 42.8, 39.5, 26.0, 22.9, 22.8, 22.6, 19.1, 18.8, 18.4, 11.2, –4.1, –5.0;

HRMS exact mass M-H$^+$ 407.3165 (calcd for $C_{24}H_{48}OSi_2$ -H$^+$ 407.3166).

Compound 19j:



Compound **19** (2.33 ml, 7.19 mmol, 1.00 equiv.) was dissolved in a mixture of THF (20ml) and water (5ml) and treated with N-methyl morpholine *N*-oxyde (2.23 ml, 10.79 mmol, 1.50 equiv.) and osmium tetroxide (2.00 ml of a 0.072 M solution in benzene, 0.14 mmol, 0.02 equiv.) at room temperature. After 4.5 hours, the mixture was diluted with distilled water (5 ml) and sodium periodate (3.075 g, 14.38 mmol, 2.00 equiv.) was added. The reaction mixture was stirred for 12 hours and then diluted with saturated ammonium chloride solution. The resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were dried with sodium sulfate and the solution was filtered through a small pad of silica gel and rinsed with several portions of diethyl ether. The solution was concentrated under vacuum to afford the intermediate aldehyde 3,3-dimethyl-4-((dimethylethyl)-dimethylsilyloxy)-6-trimethylsilyl-6-hexyn-1-al which was used immediately without further purification.

Triethyl phosphonoacetate (1.44 ml, 9.18 mmol, 1.50 equiv) was added to sodium hydride (367 mg, 9.18 mmol, 1.50 equiv) suspended in THF (20 ml) at 0 °C. To this mixture, a solution of 3,3-dimethyl-4-((dimethylethyl)-dimethyl-silyloxy)-6-trimethylsilyl-6-hexyn-1-al (2.0 g, 6.12 mmol, 1.00 equiv) in THF (10 ml) was cannulated after 20 minutes. The resulting solution was allowed to warm up slowly to room temperature and stirred at that temperature for 5 hours. The reaction was diluted with saturated ammonium chloride solution and the resulting mixture was with three portions of diethyl ether. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (2% ethyl acetate in hexanes as eluent) to afford **19j** as a colorless oil (1.62 g, 4.07 mmol, 67%).

^{1}H NMR ($CDCl_3$, 400 MHz):

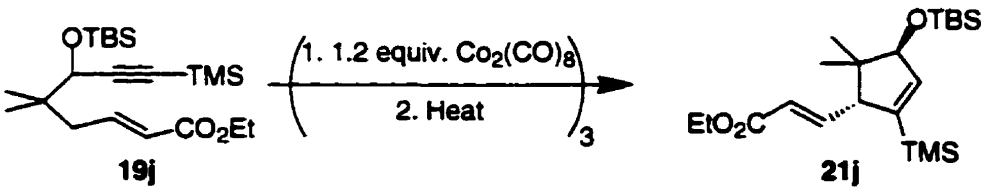
δ 6.99 (dt, 1H, J = 7.9, 15.8 Hz), 5.82 (d, 1H, J = 15.8 Hz), 4.18 (q, 2H, J = 7.0 Hz), 3.99 (s, 1H), 2.25 (m, 2H), 1.28 (t, 3H, J = 7.0Hz), 0.97 (s, 3H), 0.95 (s, 1H), 0.89 (s, 9H), 0.15 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 188.0, 166.7, 146.7, 123.8, 105.9, 76.8, 71.3, 60.3, 41.0, 39.9, 29.9, 26.0, 23.2, 23.21, 18.5, 14.5, 0.01, −4.1, −5.0;

HRMS exact mass M-H$^+$ 395.2439 (calcd for $C_{21}H_{40}O_3Si_2$ -H$^+$ 395.2438).

Compound 21j:



In a round bottom flask fitted with a condenser, a magnetic spin-bar and a glass tube which permits constant bubbling of argon through the reaction medium, $Co_2(CO)_8$ (515 mg, 1.51 mmol, 1.20 equiv) was added to a solution of the enyne **19** (500 mg, 1.26 mmol, 1.00 equiv) in anhydrous toluene (30 mL). After stirring at 21 °C for 2 hours, the black solution was heated at reflux for 12 hours, during which time a colorless suspension forms and a cobalt (0) mirror coating is observed on the sides of the flask. After cooling to 21 °C, the suspension was poured on to a pad of Celite and rinsed with several portions of dichloromethane. The filtrate is concentrated under vacuum. Two additional iterations of this process were carried out on this residue. The crude product was then purified by flash chromatography on silica gel (2% ethyl acetate in hexanes as eluent) to afford compound **21j** as a colorless oil (477 mg, 1.16 mmol, 92%).

^{1}H NMR ($CDCl_3$, 300 MHz):

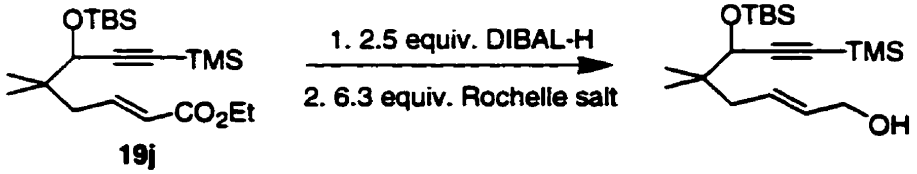
δ 6.69 (dd, 1H, J = 10.8, 15.6 Hz), 5.92 (s, 1H), 5.77 (d, 1H, J = 15.6 Hz), 4.44 (s, 1H), 4.60 (q, 2H, J = 6.9 Hz), 3.04 (d, 1H, J = 10.8 Hz), 1.27 (t, 3H, J = 6.9 Hz), 0.92 (s, 3H), 0.91 (s, 3H), 0.88 (s, 9H), 0.18 (s, 9H), 0.05 (s, 6H), 0.03 (s, 9H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 186.7, 150.3, 145.7, 121.8, 85.2, 61.8, 60.4, 49.0, 26.1, 23.4, 23.3, 18.5, −1.2, −4.2, −4.6;

HRMS exact mass M-H$^+$ 395.2439 (calcd for $C_{21}H_{40}O_3Si_2$ -H$^+$ 395.2438).

5,5-dimethyl-6-((dimethylethyl)-dimethylsilyloxy)-8-trimethylsilyl-2-octen-7-yne 1-ol 19l:



19j

To a solution of **19j** (595 mg, 1.43 mmol, 1.00 equiv) in 25 ml toluene at -78 °C was added dropwise a 1.55 M solution of DIBAL-H in toluene (2.39 ml, 3.58 mmol, 2.50 equiv). The reaction was brought to -10 °C. After 2 hours, the solution was allowed to warm up slowly to room temperature and stirred at that temperature for 3 hours. The reaction was diluted with 18 ml 0.5 M aqueous Rochelle's salt solution (18.0 ml, 9.0 mmol, 6.30 equiv) and stirred overnight. The mixture was extracted with four portions of ethyl acetate. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to afford 5,5-dimethyl-6-((dimethylethyl)-dimethylsilyloxy)-8-trimethylsilyl-2-octen-7-yne-1-ol as a colorless oil (505 mg, 1.42 mmol, quantitative).

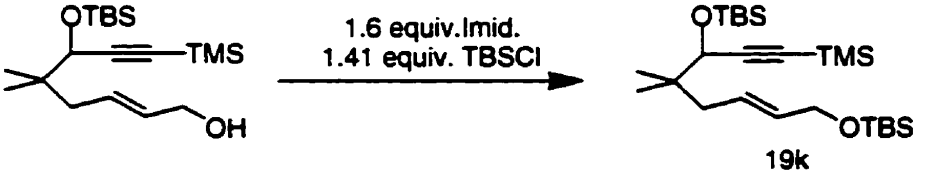
^{1}H NMR ($CDCl_3$, 400 MHz):

δ 5.68 (m, 2H), 4.10 (d, 2H, J = 5.1 Hz), 3.99 (s, 1H), 2.09 (t, 2H, J = 9.2 Hz), 1.42 (bs, 1H), 0.91 (s, 3H), 0.89 (s, 12H), 0.15 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 131.9, 129.8, 106.4, 90.3, 71.1, 64.0, 41.0, 39.3, 26.0, 22.9, 22.7, 18.4, –0.1, –4.2, –5.0.

Compound 19k:



19k

To a solution of 5,5-dimethyl-6-((dimethylethyl)-dimethylsilyloxy)-8-trimethylsilyl-2-octen-7-yne-1-ol (505 mg, 1.42 mmol, 1.00 equiv) and imidazole (156 mg, 2.29 mmol, 1.6 equiv) in N,N' dimethyl formamide (20 ml) at room temperature was added t-butyl dimethyl silyl chloride (302 mg, 2.0 mmol, 1.41 equiv). After 12 hours, the reaction was diluted with

distilled water and the resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were washed with three portions of distilled water, dried with sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (1% ethyl acetate in hexanes as eluent) to afford **19k** as a colorless oil (663 mg, 1.41 mmol, quantitative).

^{1}H NMR ($CDCl_3$, 400 MHz):

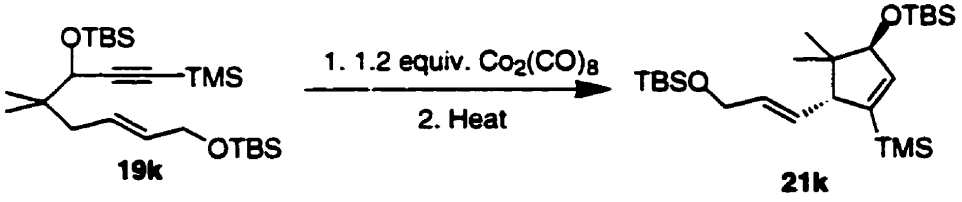
δ 5.63 (m, 1H), 5.57 (m, 1H), 4.13 (dd, 2H, J = 1.2, 5.1 Hz), 3.99 (s, 1H), 2.07 (dd, 2H, J = 4.3, 7.0 Hz), 0.91 (s, 12H), 0.89 (s, 12H), 0.15 (s, 9H), 0.14 (s, 6H), 0.07 (s, 6H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 132.0, 127.4, 106.4, 90.0, 70.9, 64.0, 40.9, 39.5, 26.0, 25.8, 22.7, 22.6, 18.5, 18.3, –0.1, –3.6, –4.3, –5.1;

HRMS exact mass M-^{t}butyl$^+$ 411.2572 (calcd for $C_{21}H_{40}O_3Si_2$ -^{t}butyl$^+$ 411.2571).

Compound 21k:



In a round bottom flask fitted with a condenser, a magnetic spin-bar and a glass tube which permits constant bubbling of argon through the reaction medium, $Co_2(CO)_8$ (410 mg, 1.20 mmol, 1.20 equiv) was added to a solution of enyne **19k** (469 mg, 1.00 mmol, 1.00 equiv) in anhydrous toluene (25 mL). After stirring at 21 °C for 2 hours, the black solution was heated at reflux for 12 hours, during which time a colorless suspension forms and a cobalt(0) mirror coating is observed on the sides of the flask. After cooling to 21 °C, the

suspension was poured on to a pad of Celite and rinsed with several portions of dichloromethane. The filtrate is concentrated under vacuum. To a THF solution (15 ml) of the residue was added 1 M HCl aqueous solution (5 ml). After stirring for 3 hours, the resulting solution was diluted with saturated $NaHCO_3$ aqueous solution. The resulting mixture was extracted with three portions of dichloromethane. The combined organic phases were dried with sodium sulfate, filtered and concentrated under vacuum. The crude product was then purified by flash chromatography on silica gel (1% ethyl acetate in hexanes as eluent) to afford compound **21k** as a colorless oil (333 mg, 0.71 mmol, 71%).

^{1}H NMR ($CDCl_3$, 300 MHz):

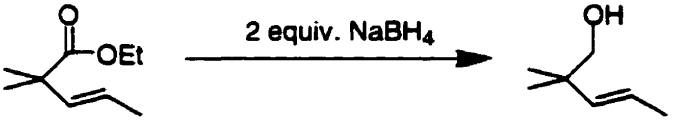
δ 5.85 (s, 1H), 5.45 (m, 2H), 4.39 (s, 1H), 4.12 (d, 2H, J = 5.3 Hz), 2.95 (d, 1H, J = 10.0 Hz), 0.90 (s, 24H), 0.15 (s, 9H), 0.06 (s, 12H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 148.3, 143.5, 131.2, 130.3, 84.9, 63.7, 61.8, 47.4, 26.0, 25.9, 25.8, 23.3, 23.0, 18.3, 18.2, 0.4, −1.3, −4.4, −4.0, −5.1, −5.2;

HRMS exact mass M-H$^+$ 467.3196 (calcd for $C_{25}H_{52}O_2Si_3$ -H$^+$ 467.3197).

***trans*-2,2-dimethyl-3-pentenol:**



To a solution of ethyl *trans*-2,2-dimethyl-3-pentenoate[52] (1.010 g, 7.05 mmol, 1.00 equiv) in diethyl ether (25 ml) at 0 °C was added $NaBH_4$ (353 mg, 16.20 mmol, 2.30 equiv) and the mixture was warmed up slowly to room temperature. After stirring for 5 hours, the solution was brought to 0 °C and quenched with saturated ammonium chloride solution. The

resulting mixture was extracted three times with diethyl ether and the organic layers were combined and dried with sodium sulfate. The crude product was purified by flash chromatography on silica gel (1% ethyl acetate in hexanes as eluent) to afford *trans* 2,2-dimethyl 3-pentenol as a colorless oil (620 mg, 5.43 mmol, 77%).

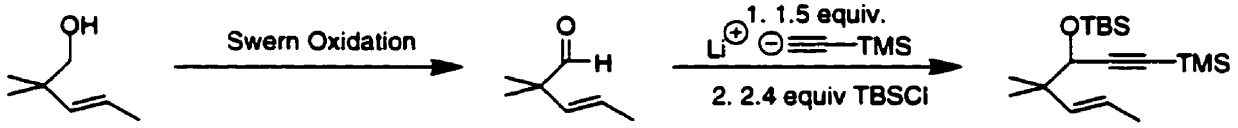
^{1}H NMR ($CDCl_3$, 300 MHz):

δ 5.47 ppm (dq, 1H, J = 5.8, 15.8 Hz), 5.36 (d, 1H, J = 15.8 Hz), 3.29 (d, 1H, J = 6.4 Hz), 1.70 (d, 3H, J = 5.8 Hz), 1.33 (t, 1H, 6.4 Hz), 0.99 (s, 6H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 138.9, 123.4, 72.4, 39.3, 33.2, 23.0, 22.6.

4,4-dimethyl-5-((dimethylethyl)-dimethylsilyloxy)-7-trimethylsilyl-2-hepten-6-yne 22:



22

A solution of dimethyl sulfoxide (358 µl, 5.00 mmol, 2.50 equiv) in dichloromethane (500 µl) was cannulated to a solution of oxalyl chloride (350 µl, 4.00 mmol, 2.00 equiv) in dichloromethane (20 ml) at -78 °C. After 30 minutes, a solution of trans-2,2-dimethyl-3-pentenol (228 mg, 2.00 mmol, 1.00 equiv) in dichloromethane (2 ml) was then cannulated to this mixture. The subsequent white suspension was stirred for 1 hour before dropwise addition of triethylamine (1.40 ml, 10.00 mmol, 5.00 equiv). The mixture was allowed to warm up slowly to 21 °C and stirred at that temperature for 4 hours. The solution was diluted with saturated ammonium chloride solution and the resulting mixture was extracted with three portions of diethyl ether. The combined organic layers were dried with sodium sulfate, filtered through a small pad of silica gel and concentrated under vacuum to afford the

intermediate trans 2,2-dimethyl 3-pentenal[53] as a colorless oil which was used immediately without further purification.

To a solution of diisopropylamine (420 µl, 3.00 mmol, 1.50 equiv) in THF (30ml) at -78 °C was added dropwise a 2.65 M solution of n-BuLi in hexanes (1.06 ml, 2.80 mmol, 1.40 equiv). After 10 minutes, (trimethylsilyl)acetylene (424 µl, 3.00 mmol, 1.50 equiv) was added to the solution. After 30 minutes, to the resulting mixture was cannulated a solution of the intermediate trans 2,2-dimethyl 3-pentenal in THF (5ml) at -78 °C. The resulting mixture was allowed to warm up slowly to 21 °C and stirred at that temperature for 3 hours. tbutyldimethylsilyl chloride (724 mg, 4.80 mmol, 2.40 equiv) was added. After 30 minutes, the subsequent solution was warmed to reflux. After 12 hours, the reaction was cooled to 21 °C and diluted with saturated ammonium chloride solution. The resulting mixture was extracted with three portions of ethyl acetate. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum.

The crude product was then purified by distillation under reduced pressure (120 °C, 8 mm Hg) to afford 4,4-dimethyl-5-((dimethyl ethyl) dimethyl silyloxy)-7-trimethylsilyl-2-hepten-6-yne **22** (160 mg, 0.49 mmol, 25%)

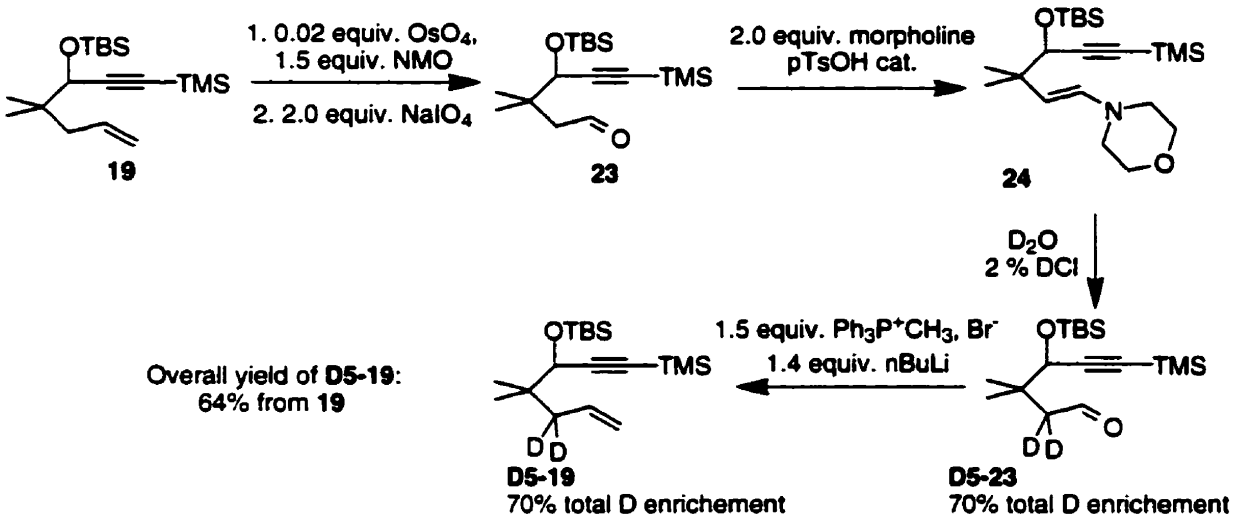
^{1}H NMR ($CDCl_3$, 300 MHz):

δ 5.51 (d, 1H, *J* = 16.6Hz), 5.43 (dq, 1H, *J* = 16.6, 6.0 Hz), 3.95 (s, 1H), 1.67 (dd, 3H, *J* = 6.0, 1.5 Hz), 1.02 (s, 6H), 0.90 (s, 9H), 0.15 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H);

^{13}C NMR ($CDCl_3$, 75.45 MHz):

δ 137.7, 122.6, 106.5, 89.5, 71.4, 41.3, 25.8, 23.1, 22.7, 18.2, -0.2, -4.5, -5.2.

Compound D5-19 :



The intermediate aldehyde 3,3-dimethyl-4-((dimethylethyl)-dimethylsilyloxy)-6-trimethylsilyl-6-hexyn-1-al **23** (469 mg, 1.44 mmol, 1.00 equiv) was dissolved in toluene (10 ml). To this mixture were added morpholine (1.25 ml, 14.40 mmol, 10.0 equiv) and para-toluenesulfonic acid (15 mg, 0.07 mmol, 0.05 equiv). The reaction mixture was then brought to reflux. After stirring for 24 hours, the reaction mixture was cooled to room temperature and quenched with saturated ammonium chloride solution. The resulting mixture was extracted with three portions of ethyl acetate. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum.

The crude compound obtained was diluted in THF (15 ml). To this solution was added a 2% DCl in D_2O solution (1 ml). The mixture was brought to reflux. After stirring overnight, the mixture was cooled down and quenched with saturated ammonium chloride solution. The resulting mixture was extracted with three portions of ethyl acetate. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum.

Methyl triphenylphosphinium bromide (644 mg, 1.80 mmol, 1.50 equiv) was dissolved in THF (10 ml) at -78 °C. To this mixture was added a solution of nBuLi in hexanes (660 µl, 1.68 mmol, 1.40 equiv). After stirring for one hour, this mixture was

brought to 0 °C and a solution of the previous crude compound (394 mg, 1.20 mmol, 1.00 equiv) in THF (15 ml) at 0 °C was added. The mixture was slowly brought to room temperature. After stirring overnight, the mixture was quenched with saturated ammonium chloride solution. The resulting mixture was extracted with three portions of ethyl acetate. The combined organic layers were dried with sodium sulfate, filtered and concentrated under vacuum.

The material obtained **D5-19** (298 mg, 64% from **19**) was found to have NMR data consistent with **19**, at the exception of the integration for the allylic methene which integrates for 0.6 H instead of 2 H for **19**.

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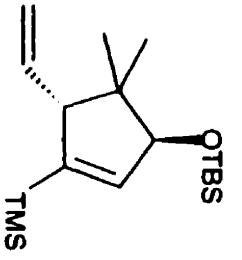
ANNEXES

Std parameters for H1 PFG-ID probe

INDEX	FREQUENCY(Hz)	FREQUENCY(ppm)	HEIGHT
1	2925.014	5.852	206.0
2	2787.558	5.577	37.1
3	2777.540	5.557	76.9
4	2770.712	5.543	69.1
5	2767.782	5.537	48.9
6	2760.702	5.523	88.0
7	2750.692	5.503	46.9
8	2501.661	5.005	127.7
9	2486.524	4.975	206.4
10	2484.815	4.971	228.0
11	2476.758	4.955	121.3
12	2475.049	4.952	107.1
13	2194.767	4.391	225.6
14	1469.158	2.939	116.0
15	1459.148	2.919	115.3
16	627.824	1.256	27.0
17	511.365	1.023	28.5
18	475.475	0.951	26.8
19	462.047	0.924	42.6
20	449.596	0.899	4211.9
21	430.552	0.861	31.6
22	386.117	0.772	27.0
23	29.173	0.058	1427.3
24	25.755	0.052	3160.2
25	12.326	0.025	33.9
26	11.838	0.024	33.3
27	11.350	0.023	32.5

181



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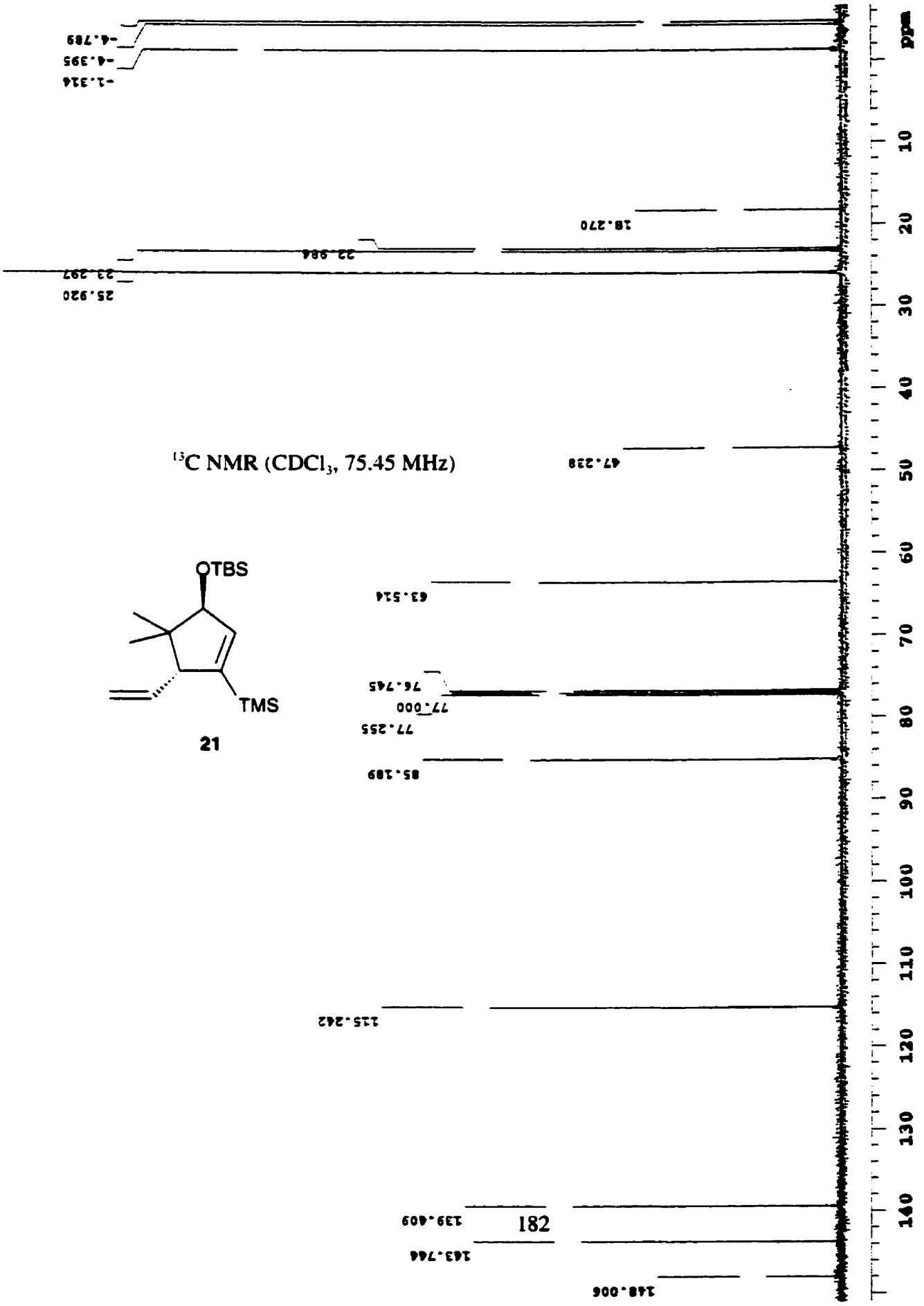
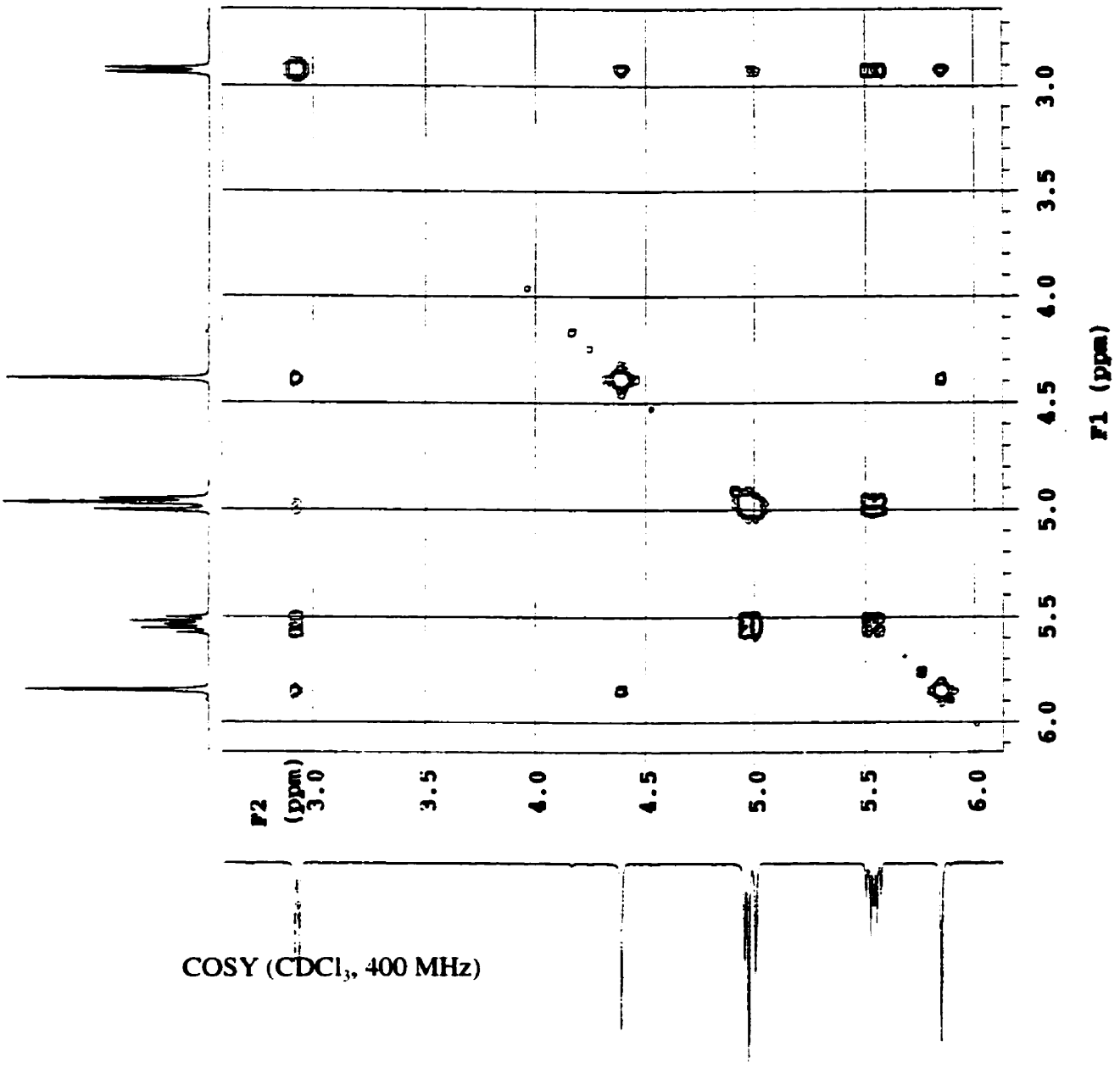
^{1}H NMR ($CDCl_3$, 400 MHz)

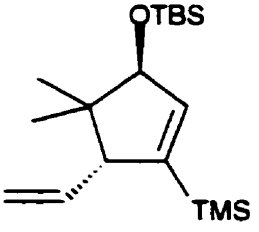


^{13}C NMR ($CDCl_3$, 75.45 MHz)

21



COSY ($CDCl_3$, 400 MHz)



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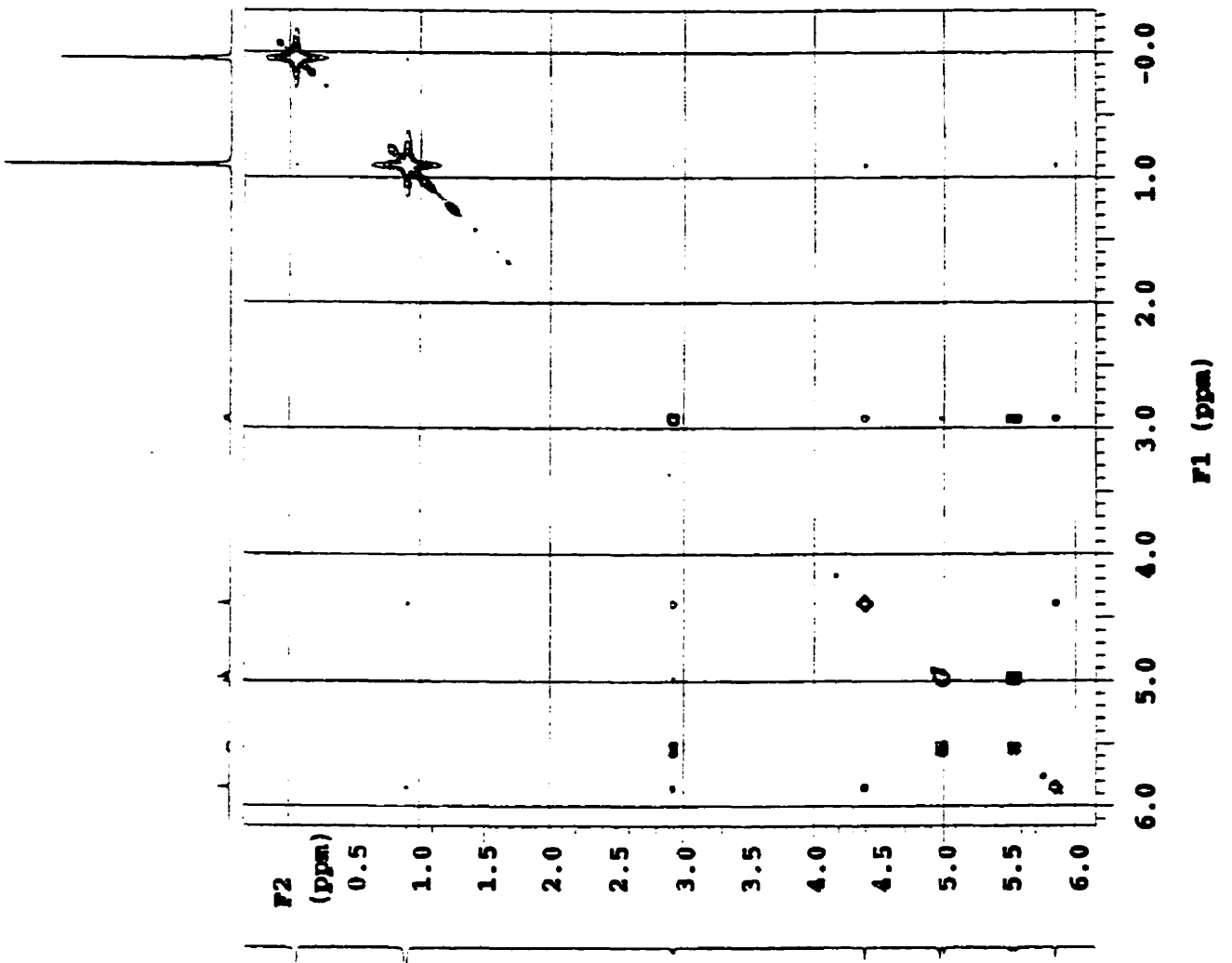
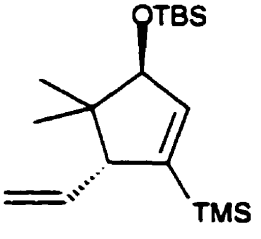
Std parameters for H1 PFG-ID probe



COSY ($CDCl_3$, 400 MHz)

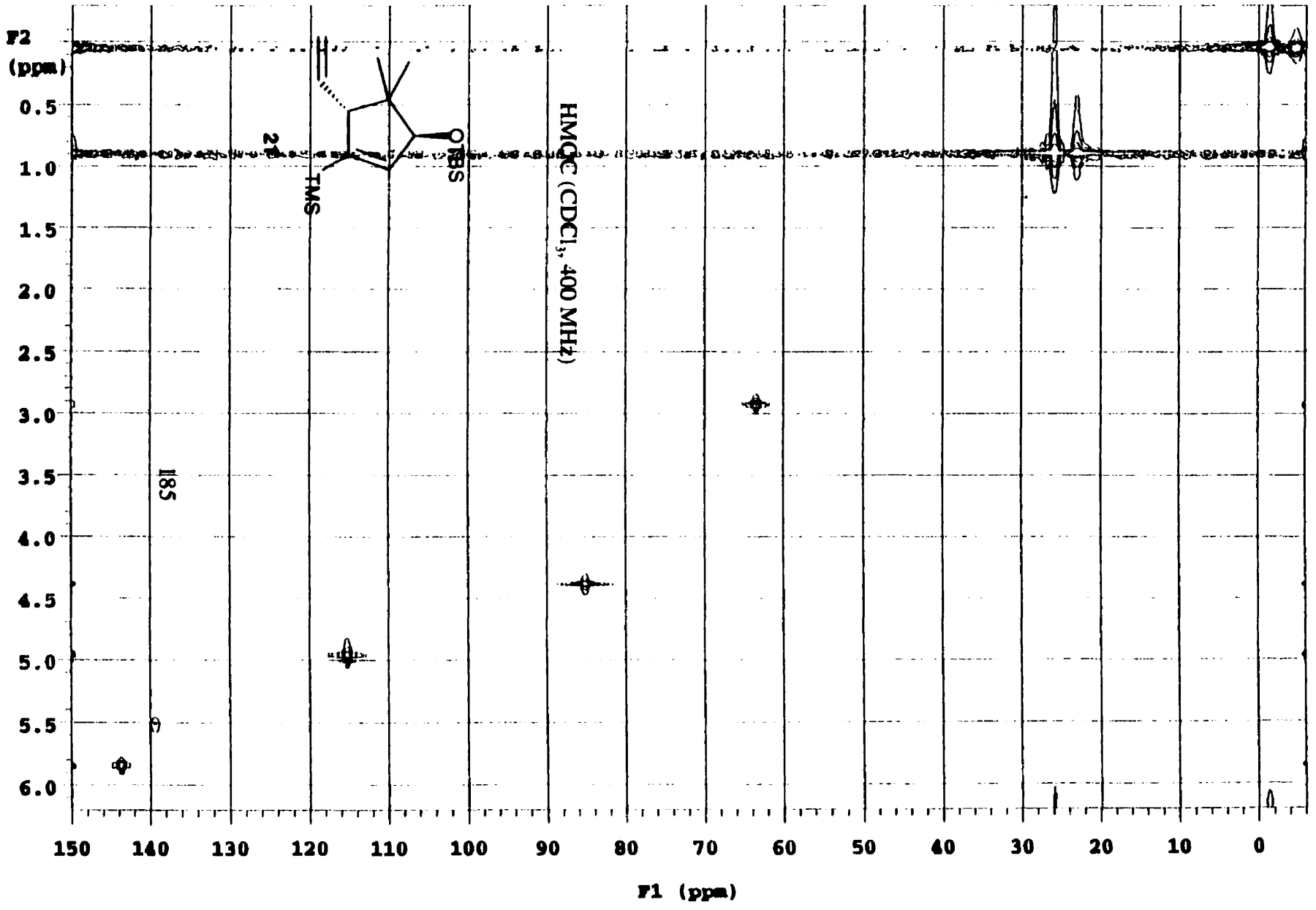


21

Std parameters for H1 PFG-1D probe

hmqc

Std parameters for H1 PFG-ID probe



General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian XL300, XL400, Unity 500 or a Jeol Eclipse 270 spectrometer. The ^{1}H NMR spectra were referenced with respect to the residual signals of deuterated chloroform (δ = 7.24 ppm). Data for the ^{1}H NMR spectra are reported as follows: chemical shift, multiplicity, integration and coupling constants. The ^{13}C NMR spectra were referenced with respect to the signals of deuterated chloroform (δ = 77.0 ppm). Chemical shifts are always given in the δ scale in parts per million (ppm). The multiplicities were given according to the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), br s (broad singlet).

IR spectra were recorded on Nicolet Avatar FT-IR ESP spectrometer and using a film of the compound placed on a KBr pellet.

Before use, diethyl ether was distilled from sodium benzophenone ketyl. Tetrahydofuran was distilled from potassium benzophenone ketyl. Hexanes, dichloromethane, toluene, triethylamine, diisopropylamine and acetonitrile were distilled from calcium hydride. Anhydrous DMF was purchased from Aldrich Chemical Company Inc. in Sure Seal™ bottles and used with no further drying.

Tin tetrachloride was used freshly distilled under vacuum. Dibutylboron triflate solutions in hexanes were prepared from distilled hexanes and dibutylboron triflate freshly synthesized and distilled neat. All other compounds were purchased from Aldrich Chemical Company Inc. and used without further purification.

All reactions were carried out in flame-dried glassware and under an argon atmosphere, unless otherwise specified.

Thin layer chromatography was performed using silica gel glass plates (250 μm). Flash chromatography was performed using Silicycle silica gel (230-400 mesh) and the eluent specified.