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Abbreviations

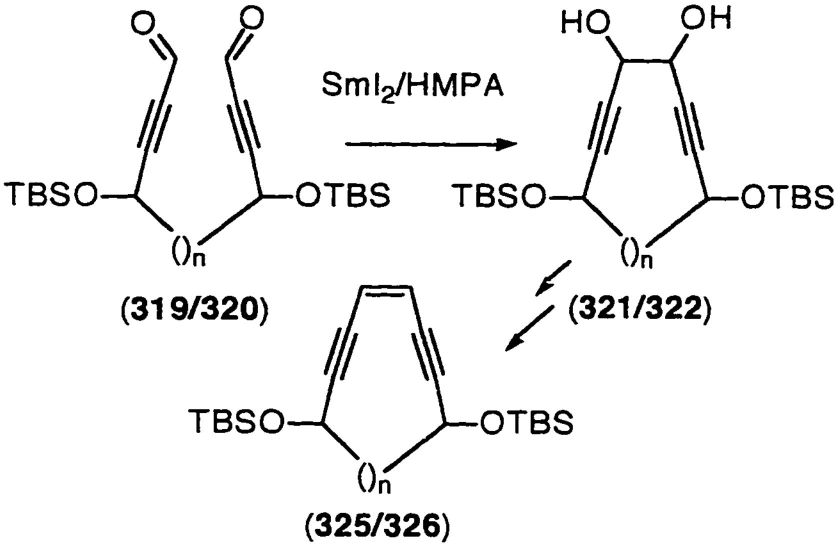
Ac	acetyl
Bu	butyl
Bz	benzoyl
CAN	cerium ammonium nitrate
CHD	1,4-cyclohexadiene
CSA	camphorsulphonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCCI	dicycohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethylazodicarboxylate
DMAP	4-dimethylaminopyridine
E	electrophile
EG	ethylene glycol
Et	ethyl
HMPA	hexamethylphosphoric triamide
imid	imidazole
Ipc$_2$BCl	diisopinocampheylboron chloride
iPr	isopropyl
KHMDS	potassium hexamethyldisilazane
LA	Lewis acid
LDA	lithium diisopropylamine
LHMDS	lithium hexamethyldisilazane
LiTMP	N-lithium-2,2,5,5-tetramethylpiperidine
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MEM	methoxyethoxymethyl
MOM	methoxymethyl
MsCl	mesyl chloride
MTCl	*p*-methoxytrityl chloride
n	normal
Nu	nucleophile
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PhthCl	phtaloyldichloride
PMB	*para*-methoxybenzyl
PPTS	piridinium toluenesulfonate
Py	pyridine
t	tertiary

TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEBA	triethylbenzylammonium chloride
Tf	triflouromethanesulfonyl
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TMSOTf	trimethylsilyl triflate
TSA	*para*-toluenesulfonic acid

ABSTRACT

The thesis investigates synthetic routes to enediynes, a class of compounds of widespread interest due to their unusual molecular structure, potent antitumor activity and interesting mode of action.

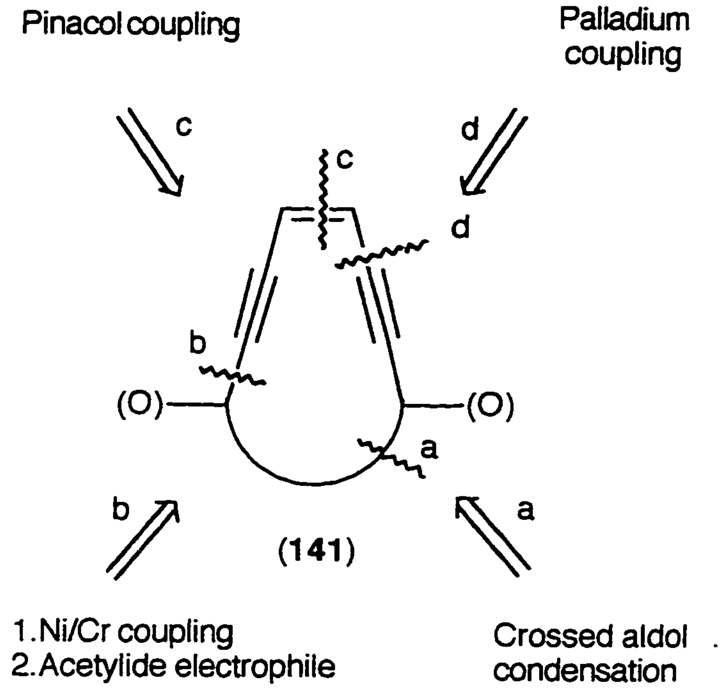
The preparation of eleven and twelve membered ring enediynes bearing oxy substituents in both propargylic positions is described *via* a novel intramolecular samarium diiodide coupling reaction of α,β-unsaturated acetylenic aldehydes.



(319/320) **(321/322)** **(325/326)**

Enediynes synthesis via intramolecular pinacol coupling approach

Other synthetic strategies based on various cyclization reactions (crossed aldol condensation, acetylide electrophile reaction, silicon directed electrophilic substitution and low valent palladium coupling) were examined.



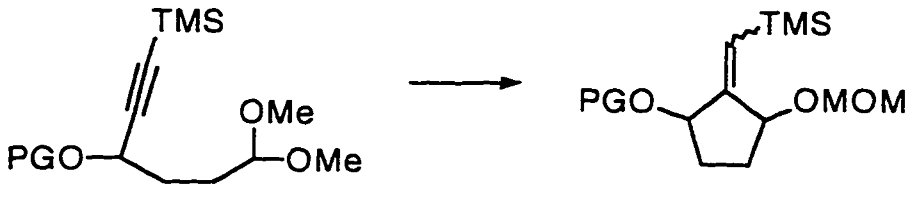
(141)

Investigated Synthetic Routes to Enediynes

A new *anti*-Brook rearrangement of acetophenone enol ethers was discovered that allows regiospecific migration of the silicon from oxygen to the *ortho* position of the aromatic ring. The enolate generated in the process allows tandem electrophilic reactions to be carried out at the carbon α to the carbonyl.

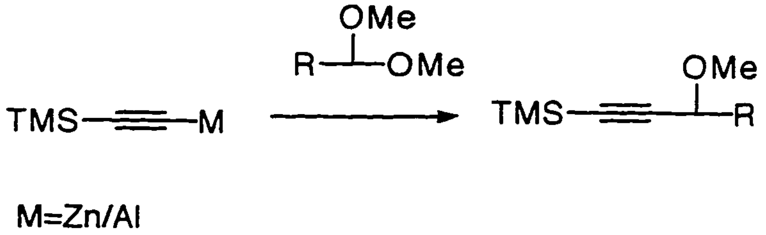
Tandem anti-Brook rearrangement-alkylation reaction

It was found that titanium tetrachloride induced the rearrangement of TMS acetylene derivatives providing an interesting entry to unsaturated exocyclic cyclopentanes.



Cyclopentane synthesis

The reaction of silyl substituted zinc/aluminum acetylides with ketals yields the corresponding propargylic ethers in a single step.



Zn/Al TMS-acetylide reaction with ketals

These findings provided useful solutions to the synthesis of the target compounds and hold promise for further utilization in the field of enediyne chemistry.

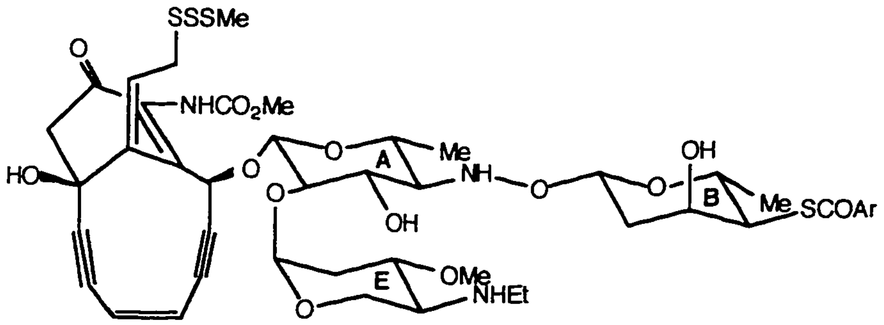
CONTENTS

1. Introduction

1.1 Enediynes. Structure Activity Relationship

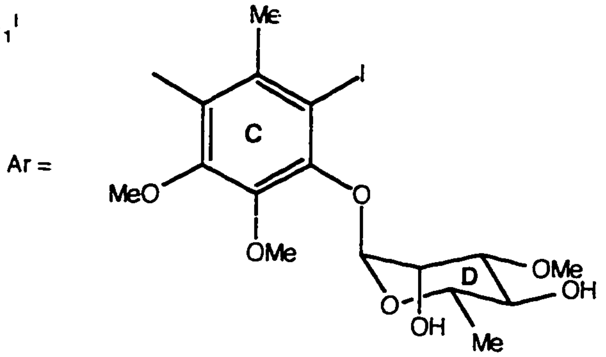
Over the past ten years, considerable effort has been dedicated by the scientific community to the elucidation of the structure activity relationship displayed by the novel enediyne antibiotics. Shortly after their isolation, the enediynes received international attention in chemical, biological and medical research due to their unusual molecular structure, potent antitumor activity and interesting mode of action.

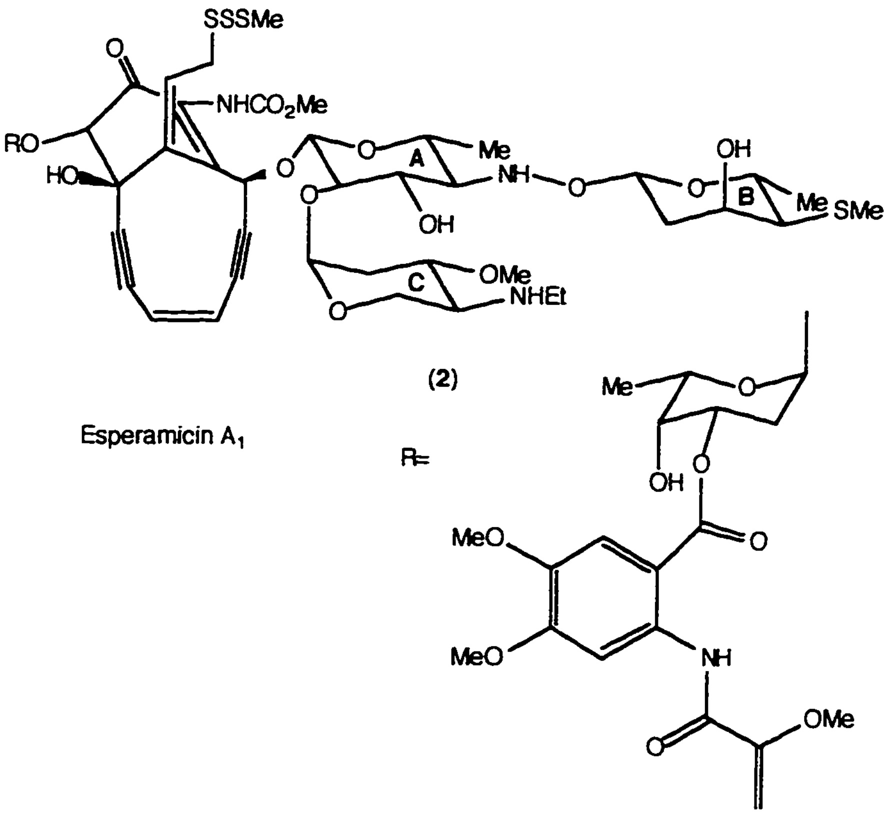
Calicheamicin γ_1^I(1)[1], esperamicin-A$_1$ (2)[2] and dynemicin-A (3)[3], are representative members of this class of biologically active compounds isolated from various bacterial cultures (Figure 1).



(1)

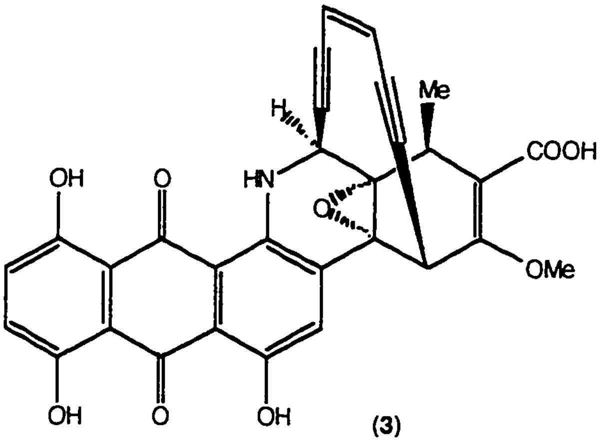
Calicheamicin γ_1^I





(2)

Esperamicin A_1



(3)

Dynemicin A

Figure 1.

It is easy to recognize that these molecules share a certain structural similarity through the presence of a common 3-ene-1,5-diyne fragment attached to a variable molecular *platform*. The endiyne moiety had been previously shown by Robert Bergman to undergo facile electrocyclization^4 through a *para*-phenylene diradical intermediate (Figure 2). The rearrangement of the parent deuterated 3-en-1,5-diyne (4) proceeded at 156°C with a rate constant of $10^{-4}s^{-1}$ and had an estimated enthalpy of reaction ΔH^{o}=32 kcal/mole.

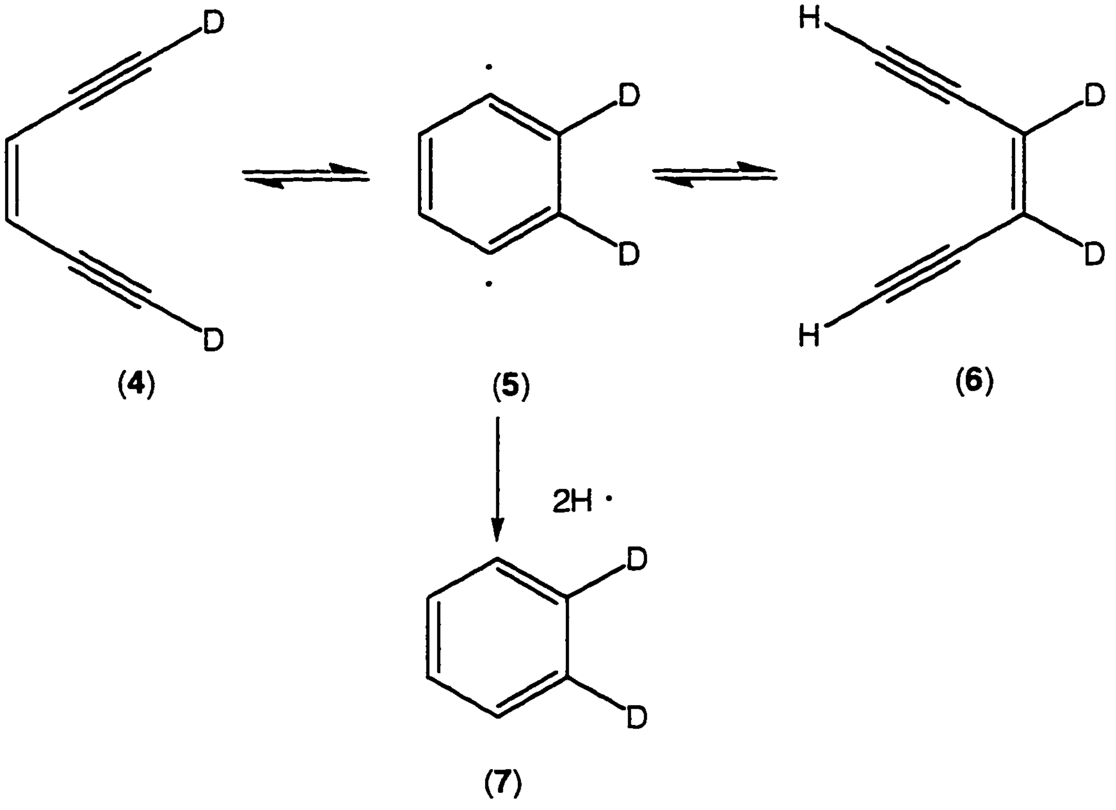


Figure 2.

Inspired by Bergman's seminal work, a similar mechanism of action has been proposed for enediynes, featuring a high energy diradical intermediate that is able to abstract two hydrogen atoms from the DNA 5'-deoxyribosyl sugar backbone ultimately resulting in site selective nucleic acid cleavage and cell death[5].

The site selectivity and/or potency of the DNA cleavage is ensured by the sugar moiety in calicheamicin γ_1^{I}(1)[5a,b] and esperamicin-A_1 (2)[5i,j] or by the anthraquinone part in dynemicin-A (3)[5k,l]. It has been shown that removal of this fragment leads to a decrease in the DNA cleavage potency and/or a dramatic reduction in the site specificity of the attack.

These molecules and related compounds exhibit one of the most powerful *in-vivo* and *in-vitro* antitumor activities known to date[6]. How do the microorganisms manage to handle these extremely toxic enediynes without endangering first their own existence?

Examination of the natural compounds and related experimental work provided convincing evidence that these molecules follow a bioreductive pathway leading to the active form responsible for the triggering of the Bergman cyclization.

In the case of calicheamicin $\gamma_1{}^I$(1) and esperamicin-A_1 (2) the trisulfide function is attacked by a nucleophile at the central sulfur atom (Figure 3) to release a highly nucleophilic thiolate (8) that is

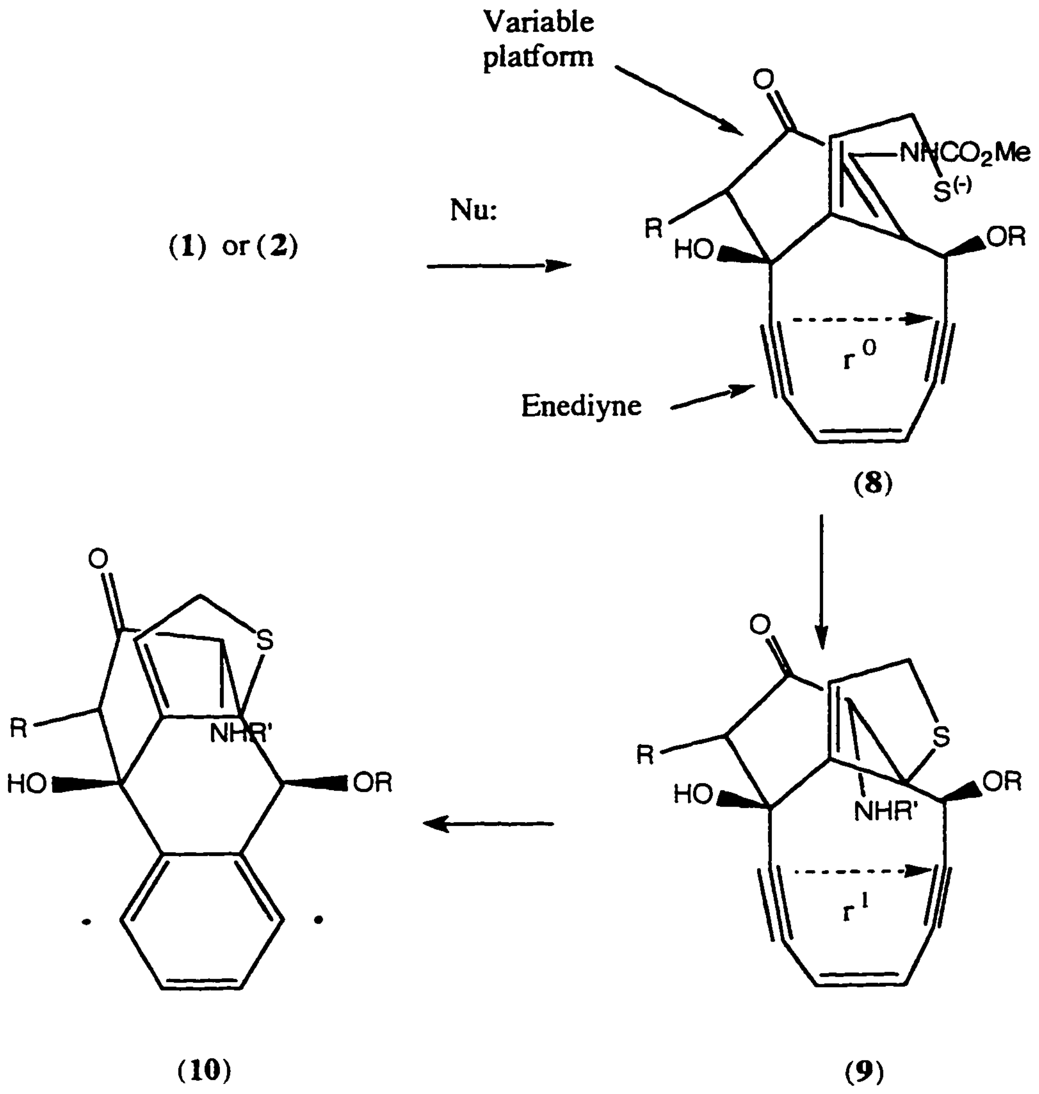
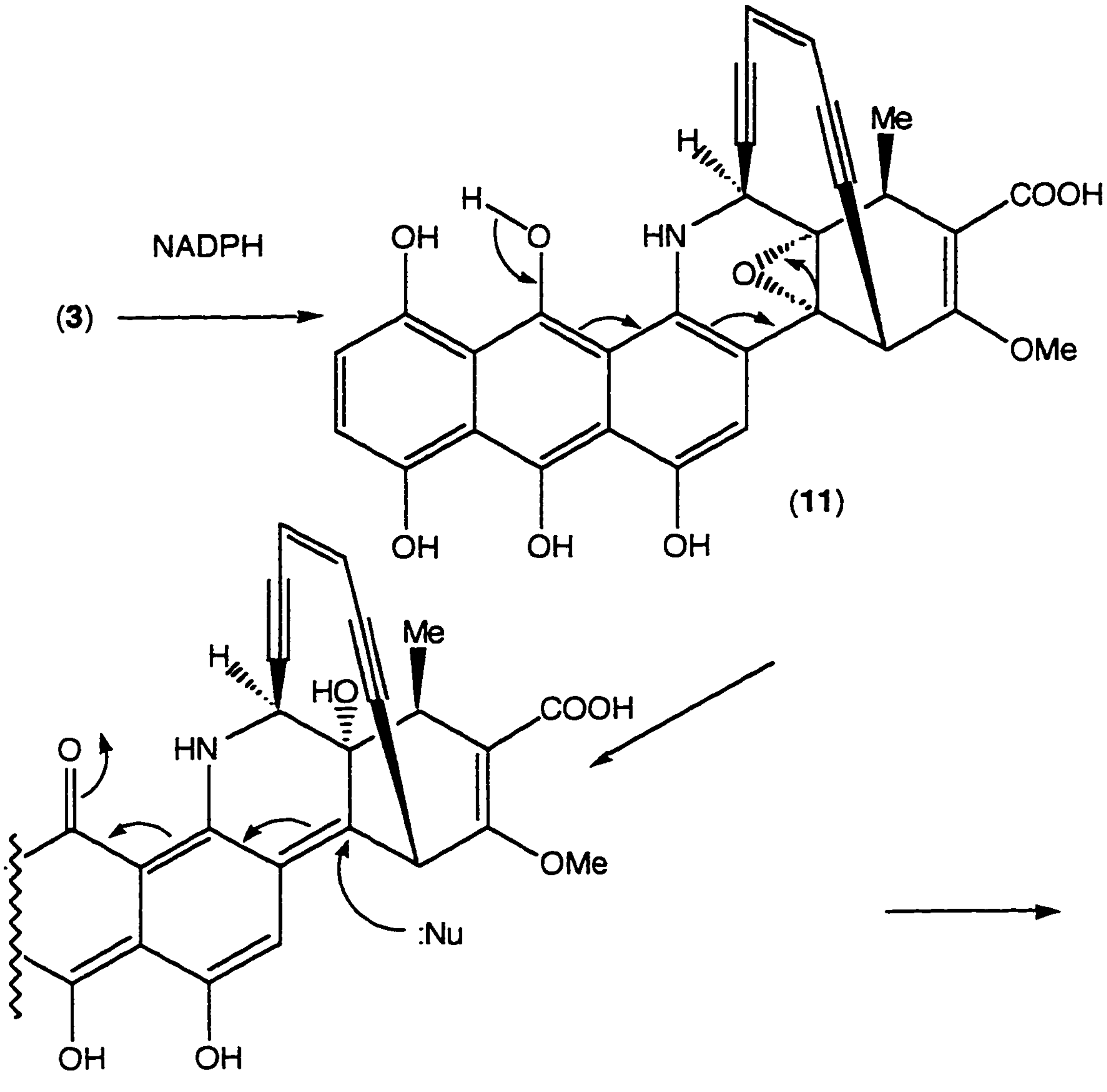


Figure 3.

ideally placed[7] for an intramolecular 5-*exo*-trig Michael addition onto the neighboring reactive bridgehead double bond. The whole sequence of events ultimately results in an overall conformational change of the ***platform*** leading to a thermodynamically and kinetically[8] favorable situation whereby the enediyne moiety collapses to the DNA cleaving *para*-phenylene diradical (10) even at 37°C

Dynemicin A (3) has a similar triggering mechanism[9] which is controlled by the epoxide functionality (Figure 4). Bioreduction will generate the semiquinone form (12) which can undergo a conjugated



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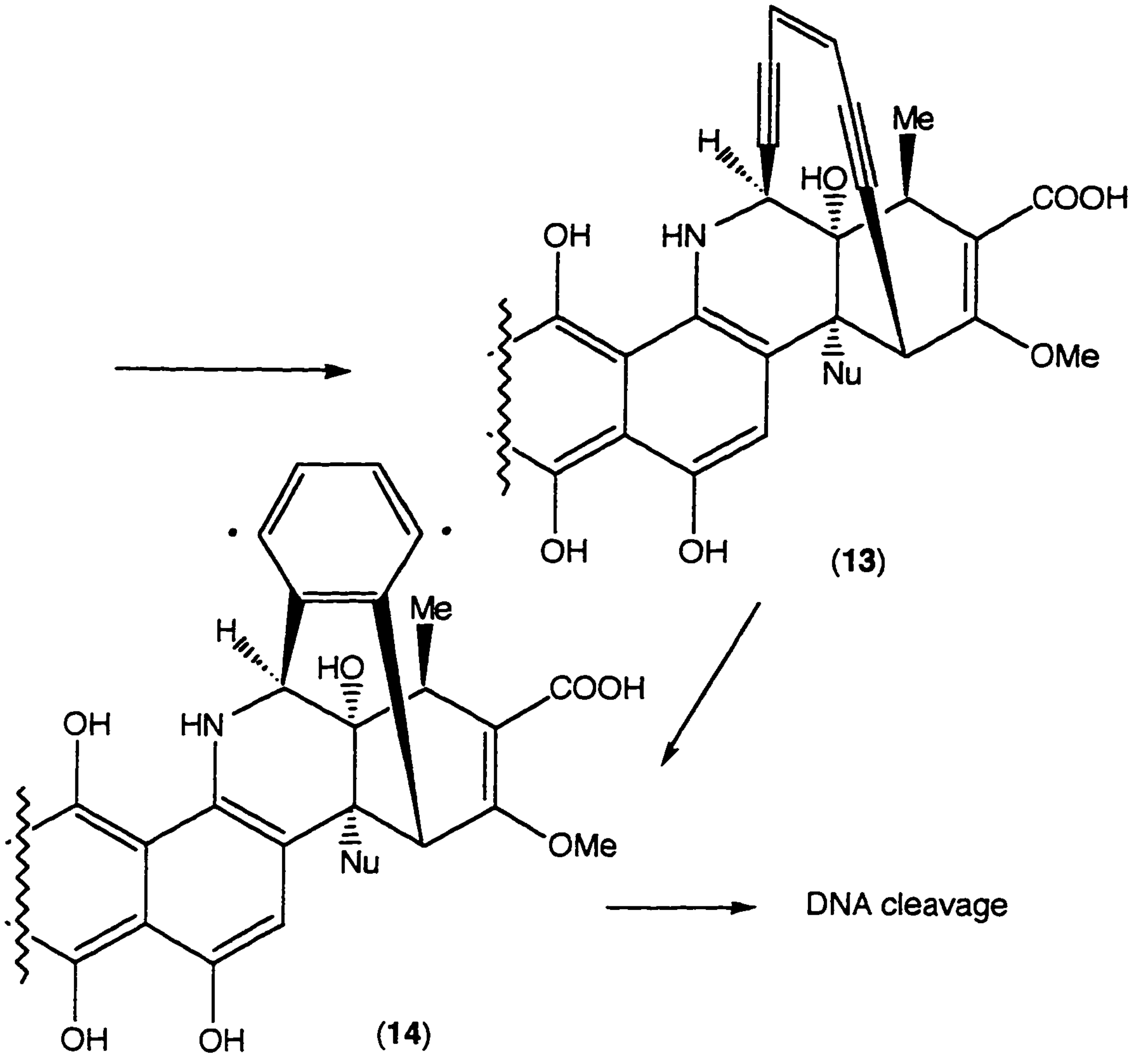
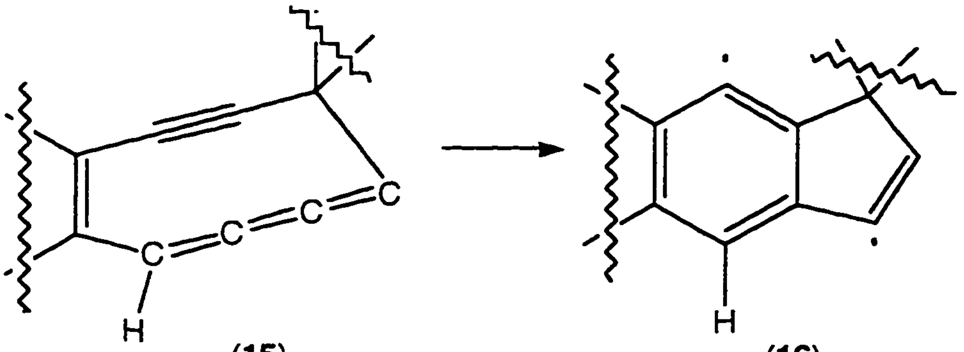


Figure 4.

addition upon intermolecular attack of a suitable nucleophile. The overall result is again a decrease of the distance between the terminal acetylenic carbons leading to Bergman cyclization and generation of a *para*-phenylene diradical (14).

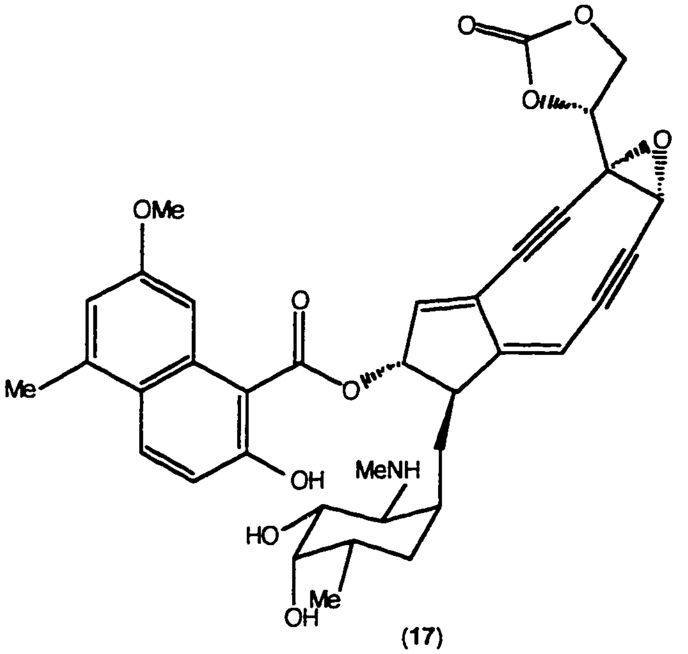
This mode of action has been related by Andrew Meyers to the previously known DNA cleaving neocarzinostatin chromophore (17) whose action is also based on the generation of a reactive σ diyl radical[10] as shown in Figure 5.



(15) (16)

Figure 5.

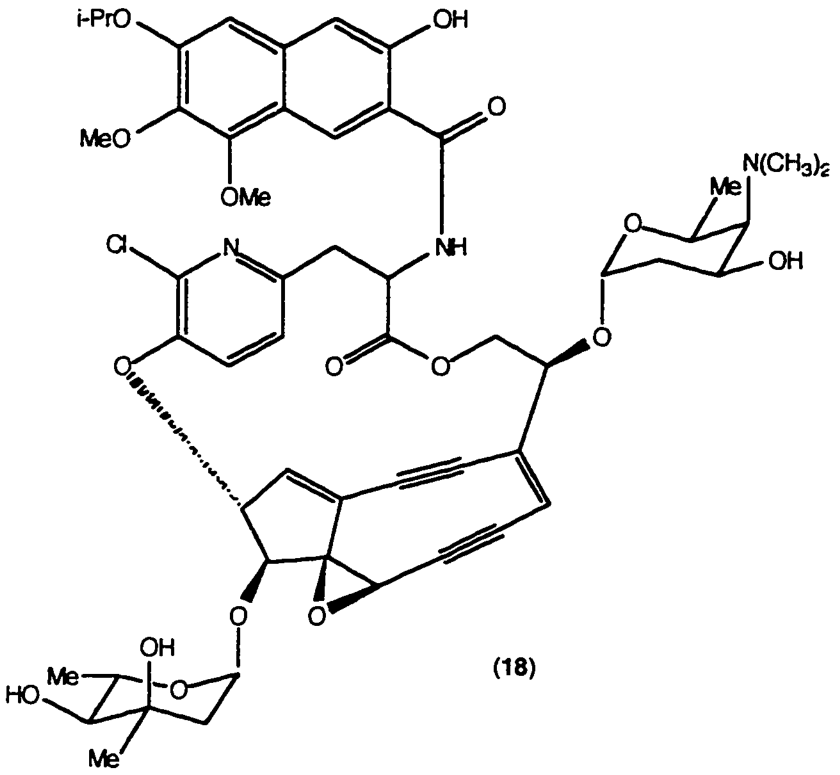
The diyl radical (16) is the reactive species involved in the DNA



(17)

Figure 6a

cleaving properties of recently discovered antibiotics like neocarzinostatin (17)[11] (Figure 6a) kedarcidin (18)[12] (Figure 6b) and C-1027[13] chromophores. Thus a unifying theme emerges wherein the unmasking or activation of a cyclic strained cumulene drug leads to the formation of a diyl radical that in turn functions as a DNA cleaving agent leading to the cell death.



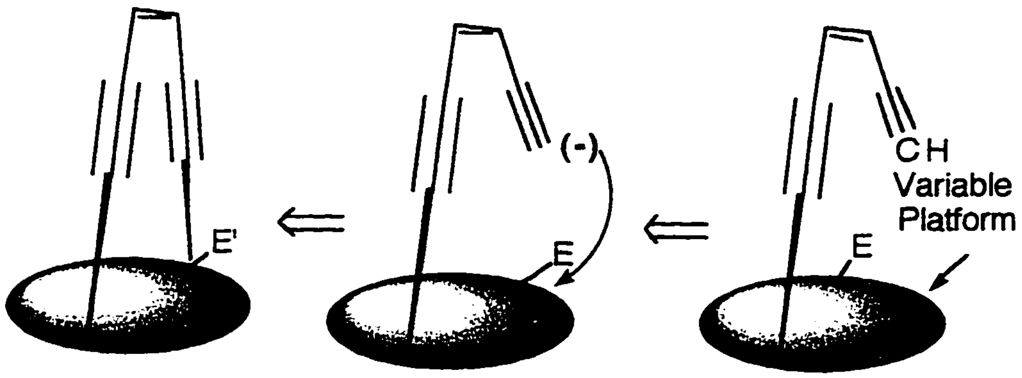
(18)

Figure 6b.

The multidisciplinary approach to the discovery of this new class of antitumor agents has continuously revealed new insights into the mode of action displayed by these molecules. Organic synthesis, physical organic and computational chemistry have all contributed in advancing hypothesis, designing molecular targets and finally delineating the factors that hopefully will inspire the scientific community to work out a new generation of anti cancer drugs. The complexity associated with this task is bewildering and goes beyond the purpose of this introductory chapter. The interested reader is referred to excellent books and reviews[14] that have been published recently describing both the biological and chemical aspects of this huge subject. We chose to focus on the crucial synthesis of the enediyne moiety with the emphasis placed on the key annulation step leading to the 1,5-diyn-3-ene containing cycle. This will be relevant for our reported research results and for the understanding of the current synthetic methodology in this field.

1.2 Intramolecular Acetylide-Electrophile Cyclization

In the most popular synthetic approach the strained enediyne system (C) (Figure 7) is accessed via a highly reactive acetylide anion (B) which adds intramolecularly to an electrophilic center (usually an aldehyde) conveniently situated on the *platform*.



Strained cyclic enediyne (**C**)

High Energy Acetylide (**B**)

Low Energy Acyclic Enediyne (**A**)

Figure 7.

The overall energetic evolution along the reaction coordinate is schematically suggested in Figure 8. One can observe that this type of approach relies on the generation of a highly reactive intermediate

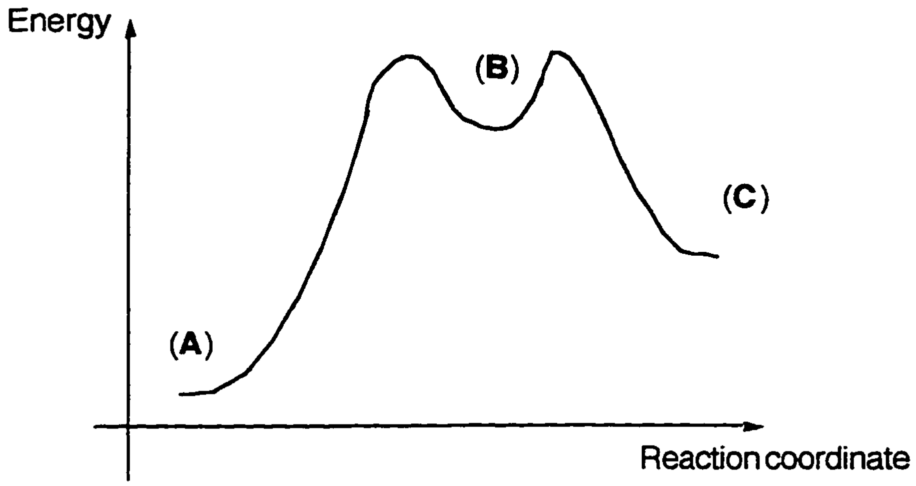


Figure 8.

(B) which will forcibly tolerate little functionality on the variable platform and allow funneling of the acetylide through other competitive counterproductive pathways[15].

Therefore it is not surprising that utilization of this method in

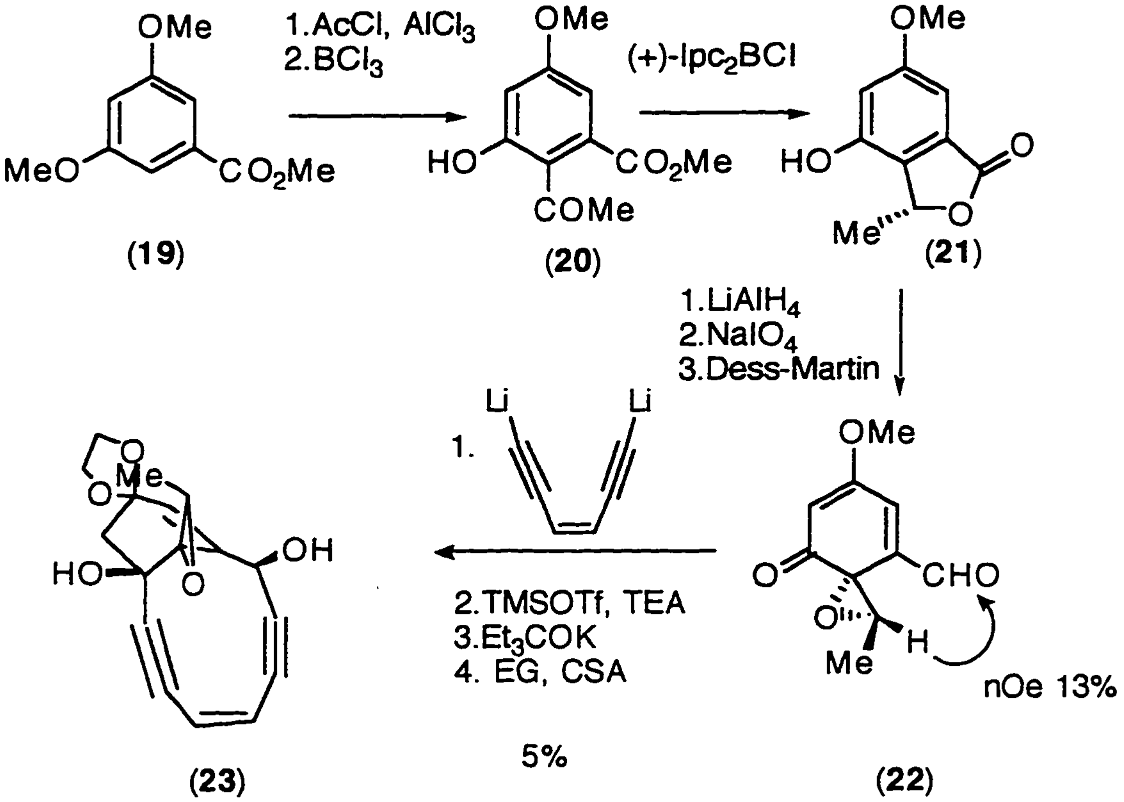


Figure 9.

the cyclization step has met in many cases with only limited success. Figure 9 illustrates this by reproducing Danishefsky's pioneering approach to the synthesis of the descarbamoyl aglycone component of (-)-calichemicinone[16].

Regioselective acylation of (19) followed by deprotection of the phenolic hydroxyl provided ketone (20) which in turn was stereoselectively reduced to generate the lactone (21). Generation of the lactol with lithium aluminum hydride followed by stereospecific Becker-Adler and finally Dess-Martin oxidation provided the pivotal spiroepoxide (22). An nOe enhancement (13%) between the epoxymethine and aldehydo protons defined the stereochemistry as shown. The spiroepoxide successfully controlled the stereochemistry in the annulation step however the low chemical yield (5%) rendered this approach impractical for the descarbamoyl series. The same paper reports the complete failure of the cyclization step in the attempted enantiospecific synthesis of the caliceamicinone series. Eventually, enzymatic kinetic resolution of the racemic product (which was obtained in better yield in the demethyl epoxide series-

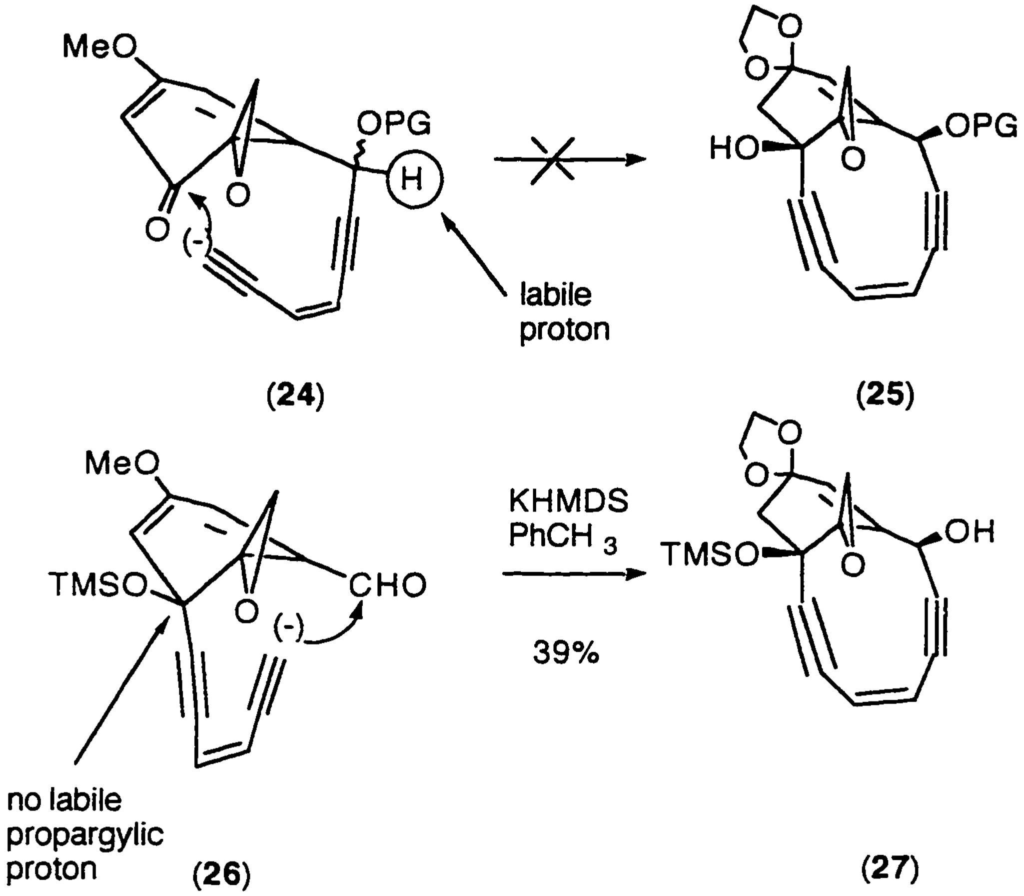


Figure 10.

vide infra) led to enantiomerically pure precursors of calicheamicinone[17].

Many other alternatives for the cyclization step[18] were explored in the racemic synthesis of caliceamicinone (e.g. 24 to 25) however the best result was obtained by reversing the order of the addition of the dianion to the *platform*, saving the aldehyde electrophile for the problematic cyclization step[19] (Figure 10). Product (27) marks the first reported synthesis of the "core structure of an enediyne drug"[14a]. In the process, the lability of the protons in the propargylic position was recognized as an irreducible contradiction to the high basicity of the required acetylide electrophile. Based on these early results the synthesis of the aglycon portion of descarbamoyl caliciamicin and caliceamicin itself have been successfully completed[20].

Another outstanding contribution coming from Danishefsky's laboratories was the total synthesis of dynemicin A (1)[21] (Figure 11).

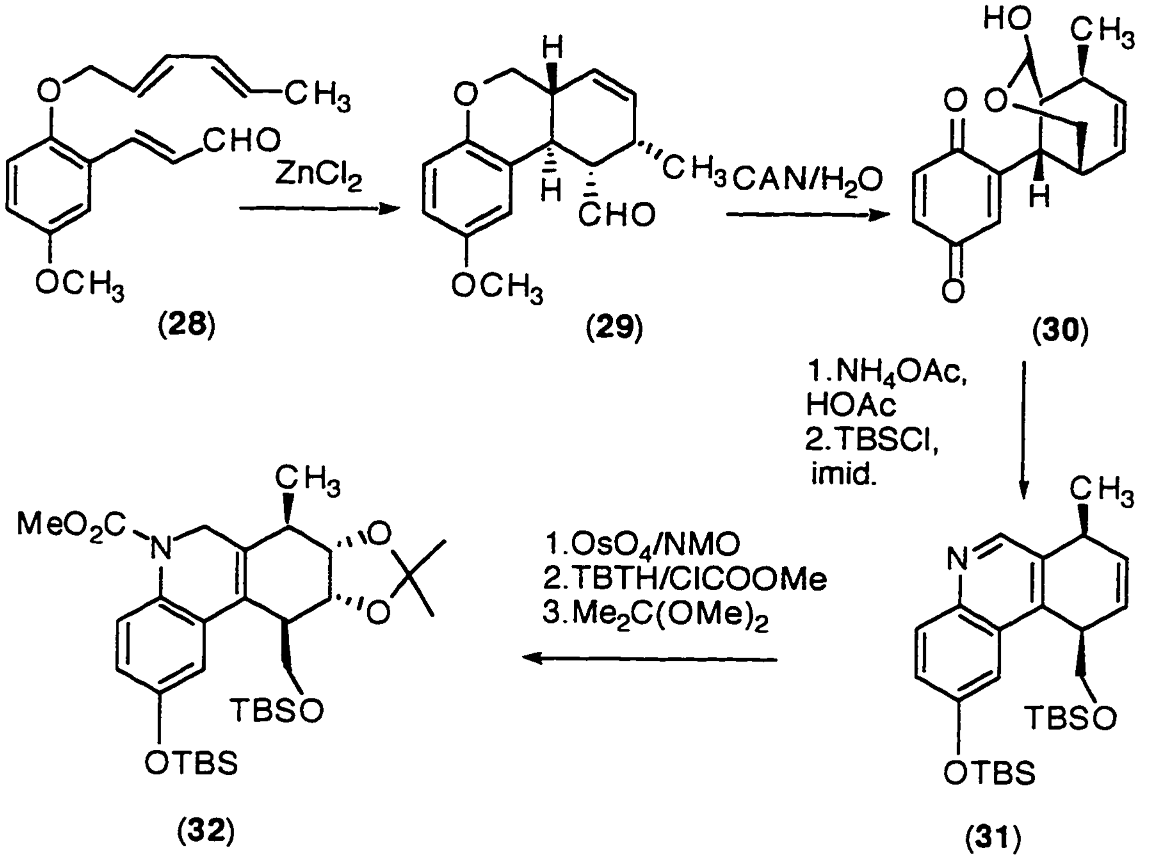


Figure 11.

After an efficient elaboration of the Diels-Alder precursor (28), Lewis acid catalyzed [4+2] cycloaddition generated *via* an intramolecular *endo* transition state, compound (29) as the major adduct. Treatment with cerium ammonium nitrate effected simultaneous oxidation of the aromatic ring and protection of the aldehyde as a hemiacetal (30). Ammonolysis with ammonium acetate and silylation of the two hydroxy groups provided the pivotal quinolinic structure (31). Facially selective dihydroxylation with osmium tetroxide/NMO followed by reductive carbamoylation of the imine double bond and protection of the diol as an acetonide resulted in the successful synthesis of the intermediate (32). After a sequence of protections and deprotections the authors report the construction of the enediyne fragment itself through a Corey-Fuchs aldehyde to acetylene homologation followed by a palladium catalyzed Stevens-Castro coupling with *cis*-trimethylsilylchloroenyne that ultimately led to the cyclization precursors (33) and (35) (Figure12).

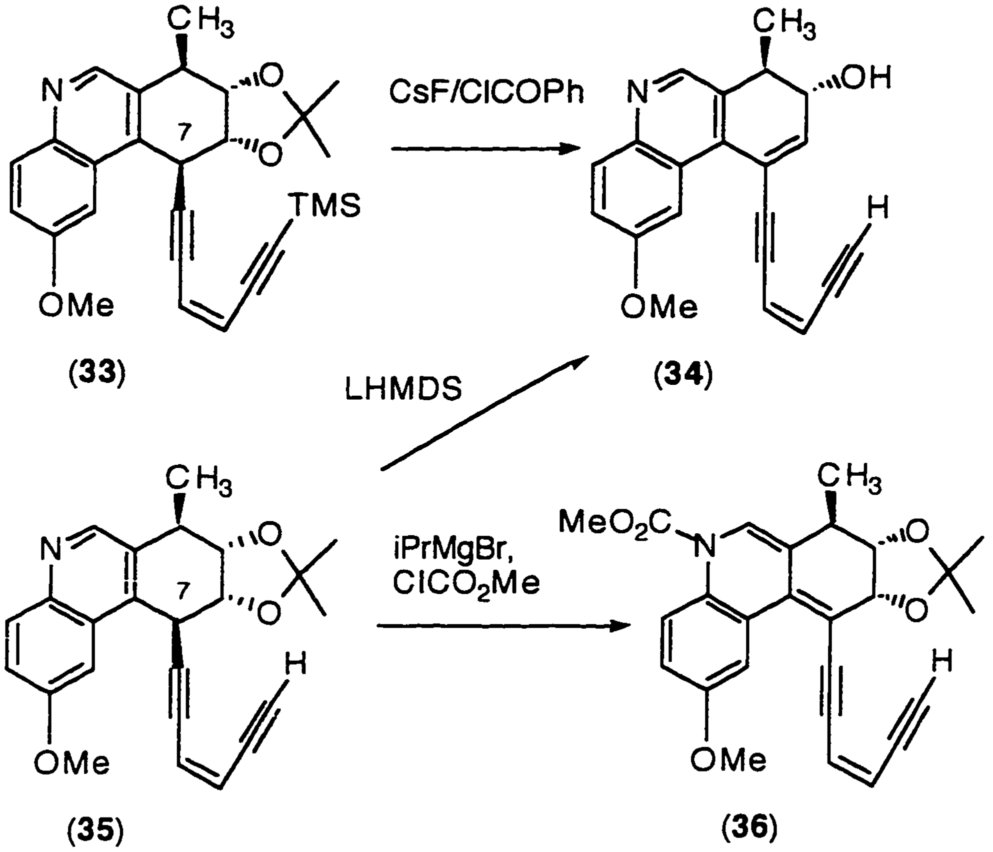


Figure 12.

Unfortunately, treatment of various cyclization precursors under basic conditions (in order to generate the required acetylide intermediate) resulted in a series of unexpected elimination reactions instead of intramolecular cyclization[14a,22]. Once again the acidity of the propargylic proton next to the enediyne system was found to open the door to competitive reaction pathways which ultimately led to the redirection of this synthesis from a totally new perspective which will be discussed in the context of subchapter "1.6.Intramolecular Coupling Strategies".

Nicolau's synthesis of (-)-calicheamicinone[23] relies in the enediyne cyclization step on the same acetylide-electrophile approach displaying at the same time a profound originality in the elaboration of the highly functionalized *platform* moiety (Figure 13).

Stereoselective allylborination of the racemic lactol (37) led to intermediate (38) which is amenable to the oxime (39). Oxidation to nitrile oxide generates, *via* an intramolecular [3+2] cycloaddition, the enantiomerically pure dihydrooxazole (40). This intermediate contains both the required nitrogen for the C-10 carbamoyl group and the oxygen leading to C-8 hydroxyl in calicheamicinone.

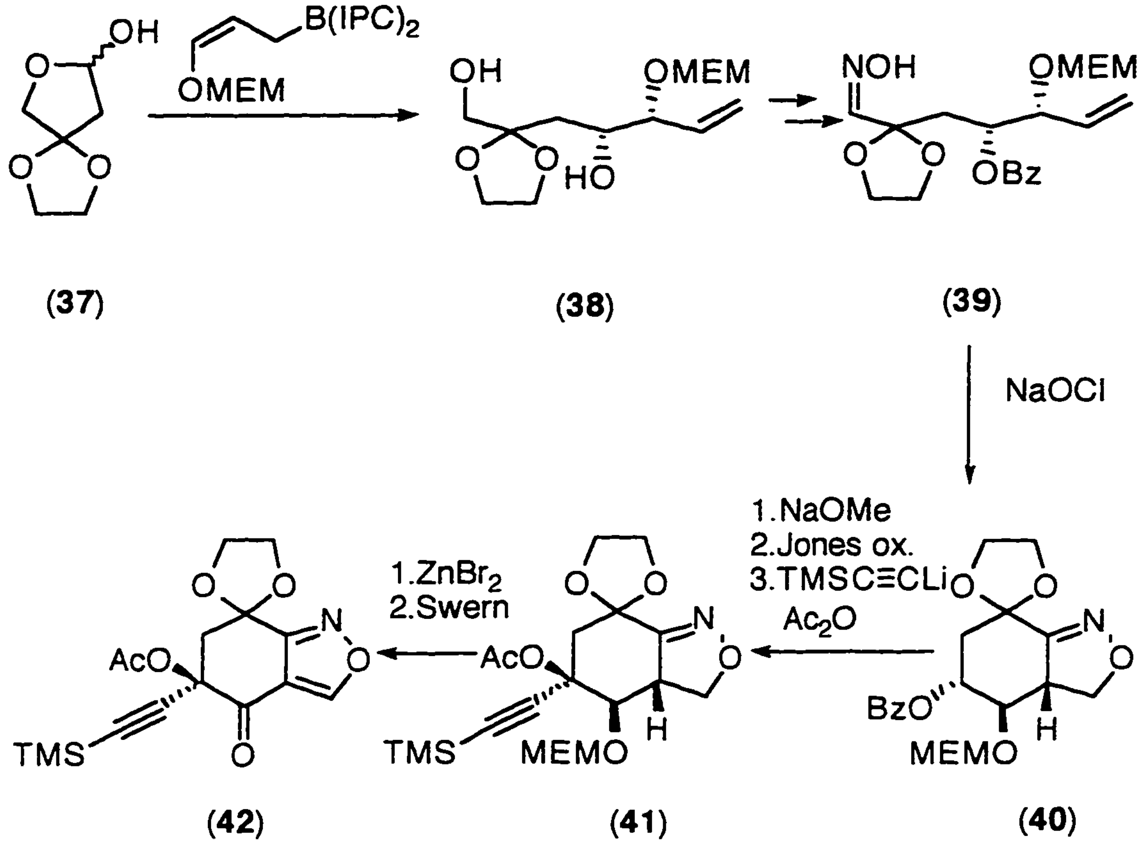


Figure 13.

Further elaboration of the dihydrooxazole (40) led to the oxazole (42) which was finally developed *via* Pd(0) chemistry to the enediyne containing intermediate (43) (Figure 14). At this point the oxazole fragment has served its purpose and the nitrogen oxygen bond was cleaved with molybdenum hexacarbonyl to unveil the precursor for the acetylide electrophile cyclization (44). Treatment with potassium hexamethyldisilazide in toluene at -90°C provided a 9:1 mixture of the alcohol (45) and the desired lactone (46) in 44% combined yield. The wrong stereochemistry of the major product was subsequently corrected through an intramolecular nucleophilic displacement of the alcohol by the neighboring carboxylate and the enantioselective synthesis successfully completed.

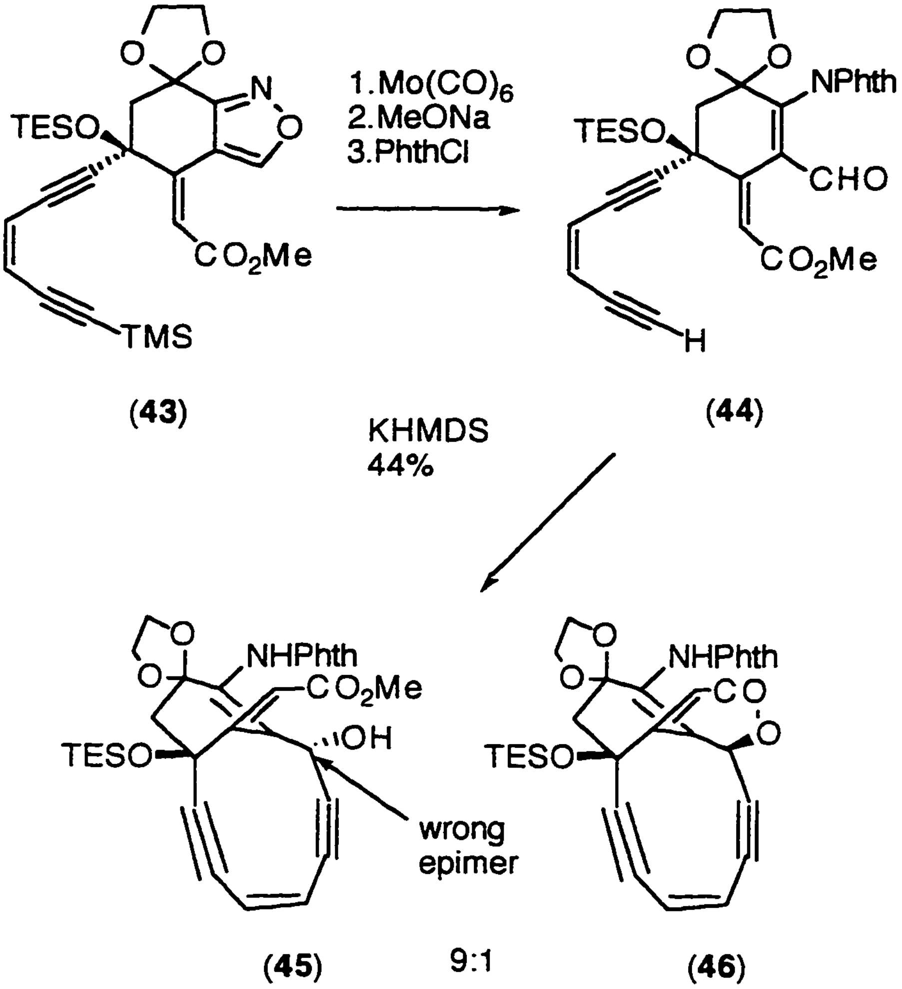


Figure 14.

Nicolau has also achieved a milestone contribution in the rational design of new dynemicin A analogs. Starting from basic chemical principals and following the assumed mode of action of the natural compound Nicolau designed in a systematic way simpler molecules with selective and potent anticancer activity[14c].

The general structure shown in Figure 15 embodies the considered molecular factors controlling the reactivity of these systems: (i) The epoxide moiety should "lock" the enediyne core preventing it from undergoing a Bergman cycloaromatization. (ii) Engaging the lone pair of electrons on the nitrogen with an electron withdrawing group should ensure stability of the epoxide, while liberation of the free amine should allow electrons to flow towards the epoxide and trigger the radical generation; therefore this position could serve as the point of attachment for an initiator (R^1). (iii) Position R^2 could in principle serve as a second conceivable source of electrons for the epoxide opening. (iv) R^3, sterically and electronically neutral substituent that should be the logical choice for tethering DNA delivery systems or solubility increasing moieties. (v) R^4 should also influence both the triggering mechanism and the reactivity of the enediyne itself. (vi) Position R^5 could be occupied by deactivators such as benzene or naphthalene and serve therefore as modulators of the reactivity towards Bergman cyclization.

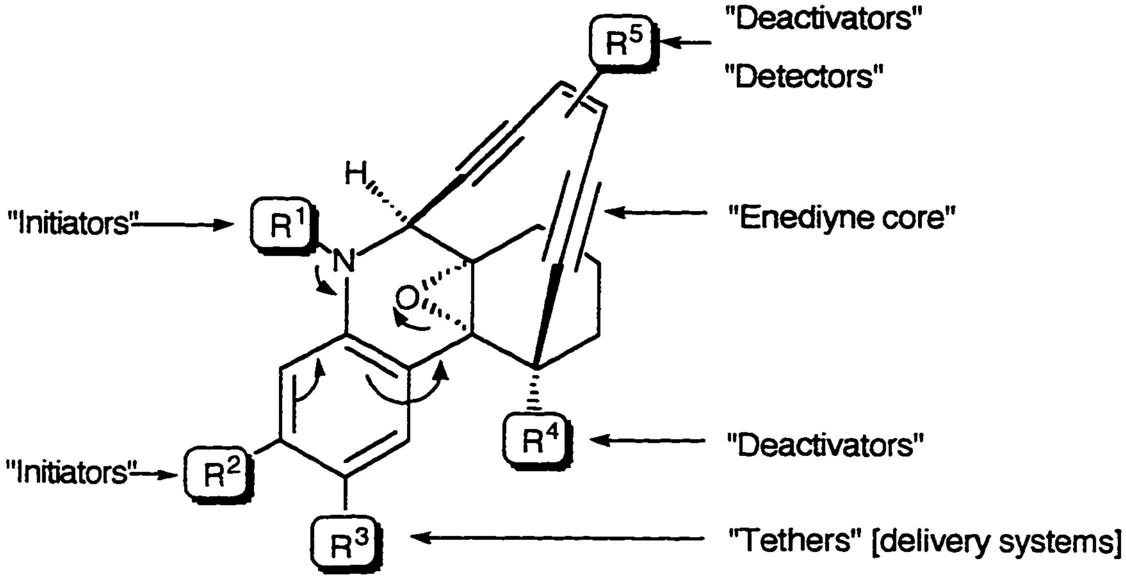


Figure 15

Starting from these general considerations two main triggering scenarios were submitted to experimental scrutiny (Figure 16). In the first one a base should abstract the most acidic proton of the molecule (47) to generate the corresponding sulphone stabilized carbanion. This in turn releases a negative charge flow over the conjugated covalent system towards the oxirane electron sink. In the second alternative the oxirane benzylic C-O bond will activate the ester for nucleophilic attack through the π aromatic system (51). Ultimately a homo-Michael type addition will lead in both scenarios to an inward compression of the enediyne system (49) followed by spontaneous Bergman cyclization and generation of the lethal *para*-phenylene diradical (50).

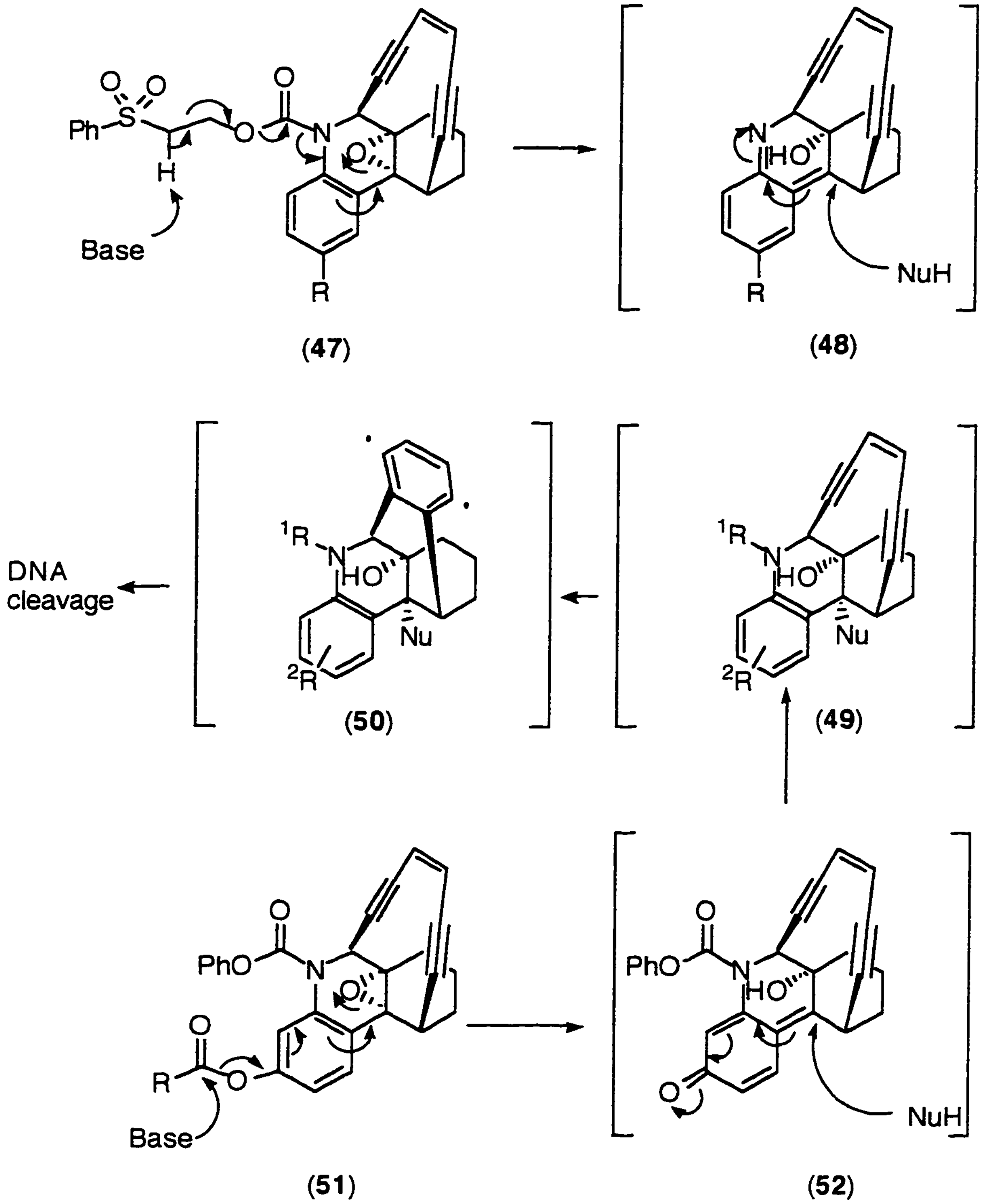


Figure 16.

The practical realization of this project[24] started from readily

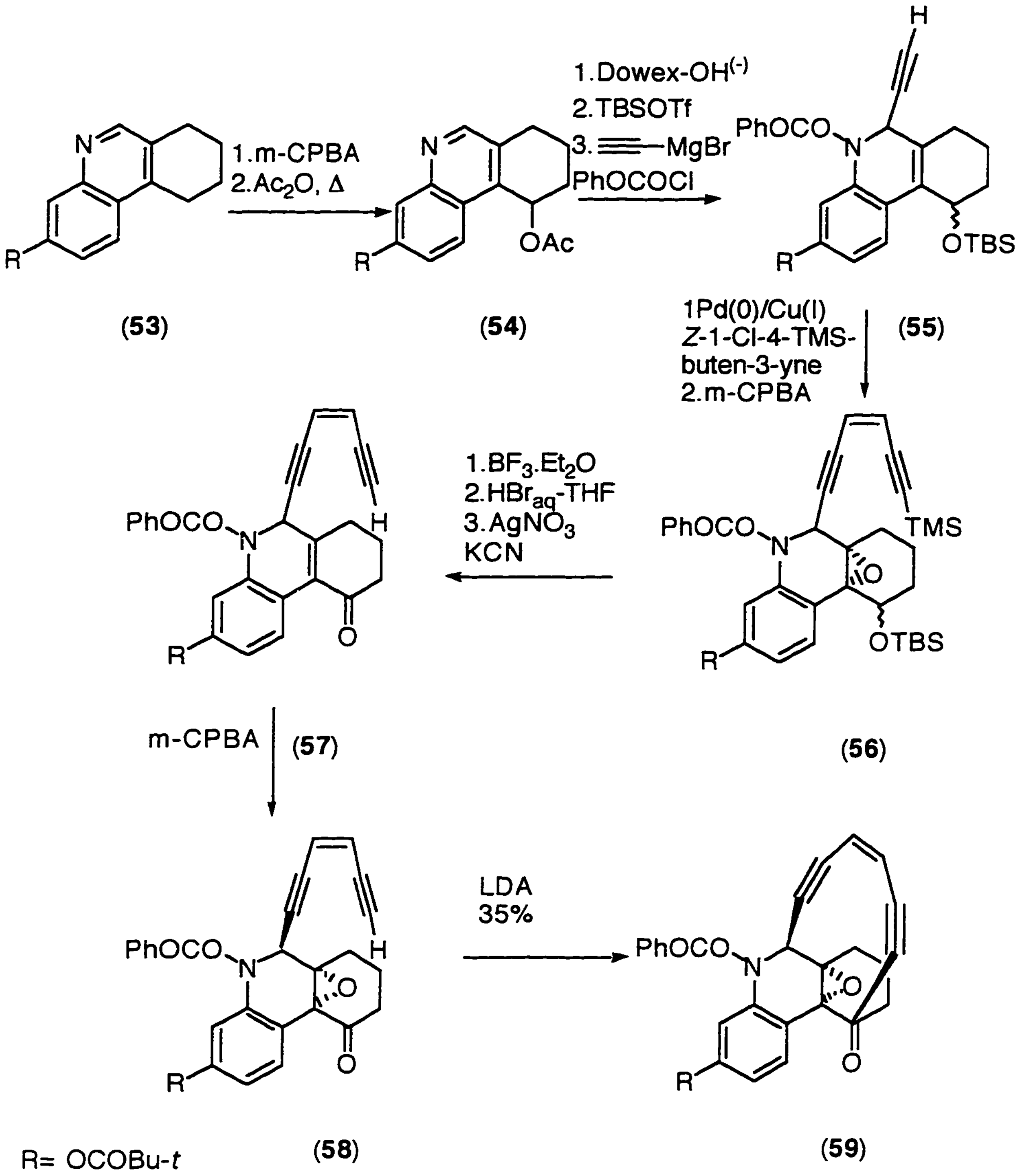
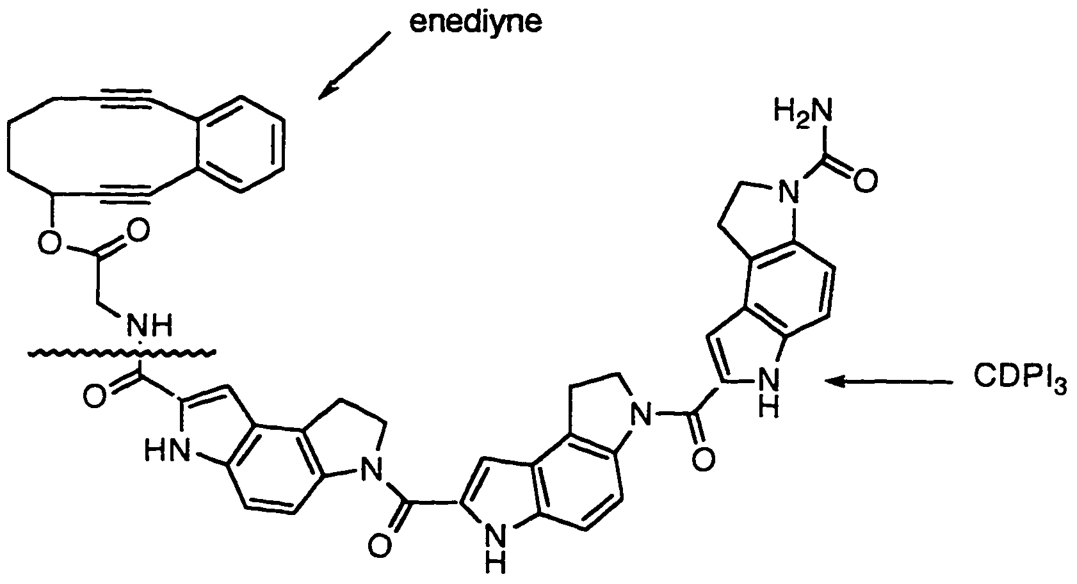


Figure 17.

available quinoline derivatives (53) (Figure 17). N-oxide rearrangement in acetic anhydride followed by an Yamaguchi addition allowed rapid access to the enediyne precursor (55).

Stephens-Castro reaction with *cis*-chlorotrimethylsilylenyne and further manipulation led to the cyclization precursor (58). The acetylide finally added intramolecularly on the ketone electrophile to generate the dynemicin A analogue (59) in 35% yield.

Due to the abundance of the starting quinolines this approach proved to be quite general and afforded a variety of analogs that displayed excellent *in vivo* and *in vitro* selective antitumor activity.



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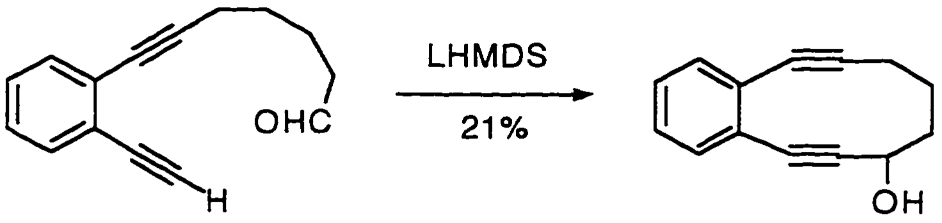


(61) **(62)**

Figure 18.

An interesting contribution to the understanding of the enediyne-minor groove DNA binding agent conjugates was presented by Bogger who reported the synthesis and DNA cleaving properties for structure (60)[25]. The key 10 membered ring cyclization was achieved in 21% optimized yield upon tretment with LHMDS. Use of many other bases did not improve the yield or failed altogether (Figure 18).

The enediyne (62) displayed a reasonable rate of cyclization at 40°C (7.5x10^{-5}min^{-1}) and DNA cleaving properties at 2x10^{-5}M while its conjugate (60) was effective at concentrations as low as 4x10^{-9}M thus validating the effect of the appended minor groove DNA binding agent.

In a conceptually related approach Wender[26] and Isobe[27] developed independently the cesium fluoride promoted cyclization of trimethylsilyl protected enediynes onto carbonylic electrophilic partners. Their approach avoids the additional desilylation step and the use of strong base to generate an alkynylide.

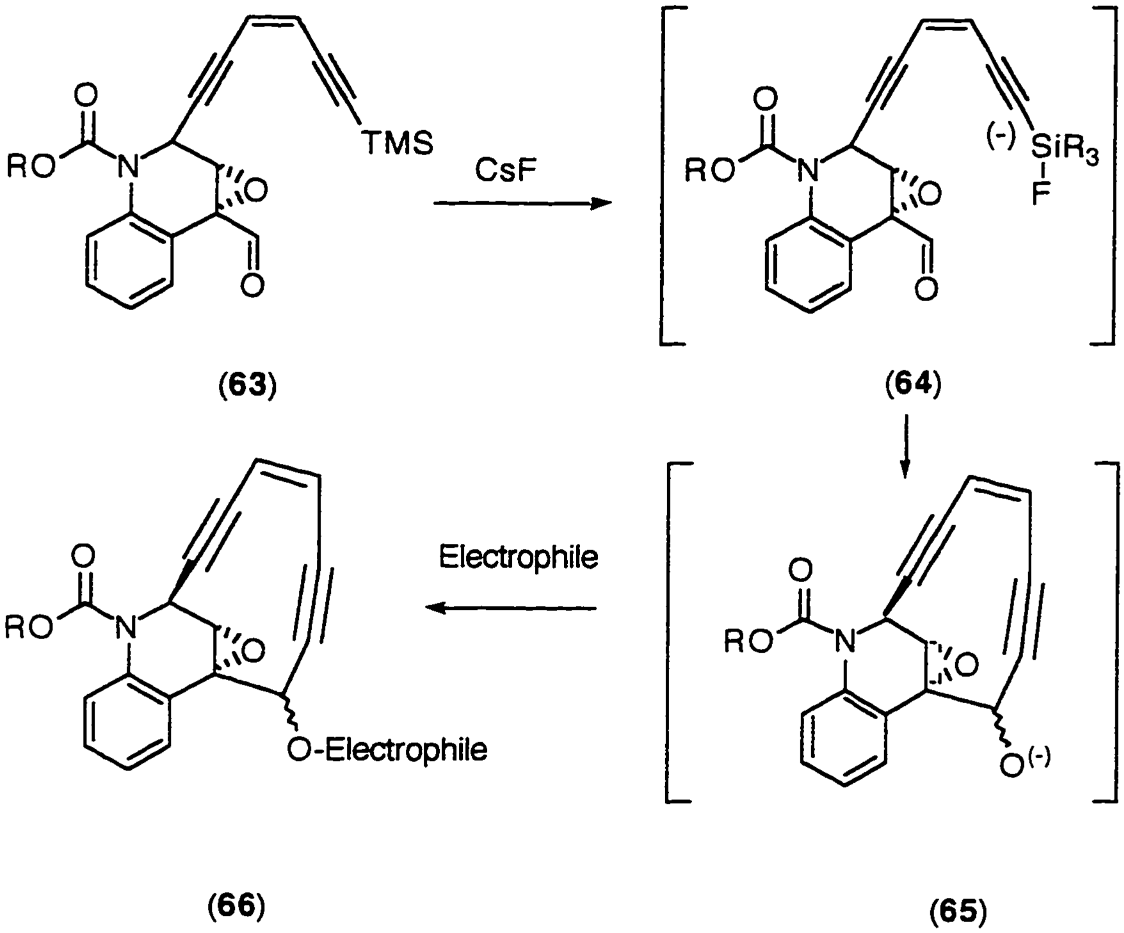


Figure 19.

For example Wender reported an useful method (Figure 19) for the cyclization of more sensitive substrates such as (63) whereby the deprotection of the trimetylsilyl protecting group, cyclization step and the trapping of the generated alkoxy anion by an electrophile can be performed in one pot. Thus generation of the enediyne core (*via* a presumed silicate intermediate (64) rather than an acetylide anion!) and attachment of spacers or DNA recognizing elements would be greatly facilitated. In practice the electrophilc trapping method provided good yields (40 to 80%) of the desired cyclized products.

Isobe's method (CsF, 18-crown-6,CH3CN/THF) led to the generation of a simple bicyclo[7.3.1] enediyne system in up to 40% optimized chemical yield.

1.3 The Ring Contraction Approach

Pioneering efforts in developing synthetic strategies to the natural products focused on methodologies for the construction of the enediyne system and evaluation of the factors governing the

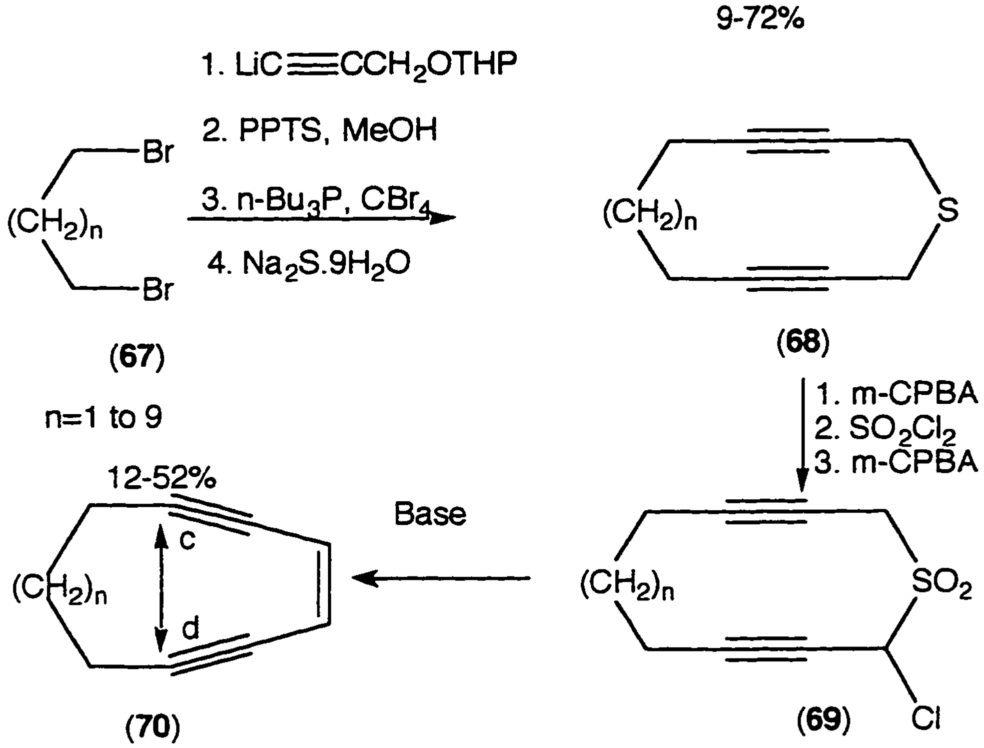


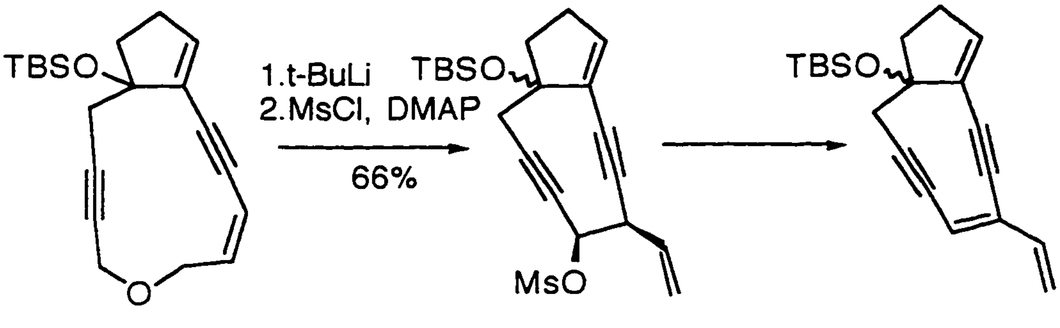
Figure 20.

cycloaromatization in simpler systems. In order to determine the influence of the ring size on the Bergman cyclization rate Nicolau[28] has synthesized a series of monocyclic enediynes in which the problem of effecting direct ring closure to the strained enediyne is avoided by the use of a Ramberg-Bäcklund rearrangement (Figure 20).

Double nucleophilic displacement of the α,ω-dibromide (67) by the lithium acetylide of tetrahydropyranyl protected propargyl alcohol, followed by alcohol deprotection and displacement led to a dibromoderivative which was cyclized with sodium sulphide to the corresponding thiacyclodiyne (68) in 9 to 72% yield. The chemical yields in the cyclization step dropped spectacularly with the increasing ring strain. The precursor for the ring contraction (69) was synthesized through a sequence of standard operations and submitted to basic conditions to effect the cheletropic rearrangement in 12% for the case of the highly strained 10 membered enediyne (70).

The study of this series of compounds revealed a correlation of the distance between terminal acetylenic carbons (r_{cd}) (Figure 20) with the propensity of the enediyne system to undergo Bergman cyclization. It was proposed as a rule of thumb that enediynes with the r_{cd} distance smaller than 3.2-3.3 Å will likely cyclize spontaneously at room temperature. While this rule holds for simple monocyclic systems it has been shown for polyciclic systems that one has to take into account the overall strain energy related to each particular case (*vide infra*).

Another approach this time based on a [2,3] Wittig ring contraction was developed by Takahashi[29] in his synthetic efforts towards neocarzinostatin (Figure 21). Treatment of key compound (71) with t-butyllithium at -100°C followed by mesylation of the alcohol resulted in the formation of the nine membered ring (72) in good yield which subsequently underwent elimination to the enediyne system (73).



(71) (72) (73)

Figure 21.

In France, Grierson[30] has developed a conceptually related synthesis on a model for the calicheamicyn/esperamicin core, *via* a similar [2,3]-Wittig rearrangement (Figure 22). The thirteen membered oxatridecadiyne (75) could be synthesized in high yield by an intramolecular nucleophilic displacement of the corresponding primary allylic bromide (74) upon treatment of the hydroxy group with sodium hydride in wet THF. Unfortunately this success is somewhat offset by the relatively low yield in the [2,3]-Wittig rearrangement step. The resulting D-labeled enediyne (77) underwent spontaneous Bergman cyclization at room temperature in the presence of 1,4-cyclohexadiene to result in the monodeuteration of the aromatic ring as a consequence of the fast intramolecular 1,5 deuterium transfer from the benzylic position to the proximal phenyl radical. The less efficient intermolecular hydrogen transfer from the cyclohexadiene occurs exclusively in the *para* (distal) position.

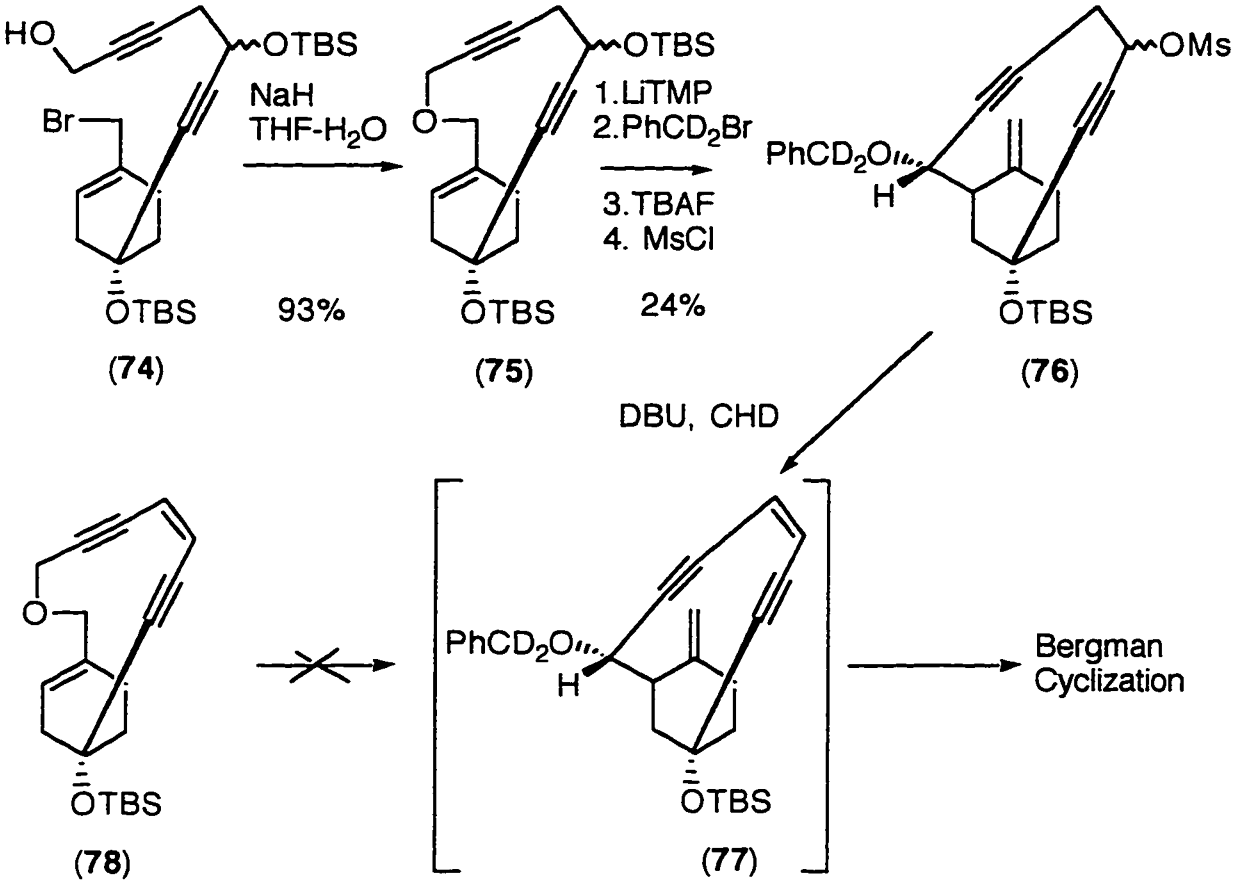


Figure 22.

The Wittig rearrangement was unsuccessful when the precursor (78) had the enediyne moiety in place.

1.4 The Diels Alder Route

A highly original synthesis of the bicyclic core of the esperamicin/caliceamicin class of antitumor agents was achieved by Schreiber[31] based on a very interesting consideration of plausible biogenetic origins of systems such as those found in neocarzinostatin (NCS) chromophore (17) or esperamicin (2).

NCS chromophore could be obtained from (79) by a series of transformations (Figure 23) that include a 12 π electrocyclization (80) followed by proton transfer, isomerization and transannular cyclization to the NCS related skeleton (81). The esperamicin/caliceamicin class requires an additional carbon at the acetylene terminus of (79) in order to provide the vinyl allene (82) which can undergo Diels-Alder reaction to esperamicin skeleton (83). Thus NCS chromophore and esperamicin families seem to be related not only through their mechanism of action but also through their biosynthetic roots (Figure 23).

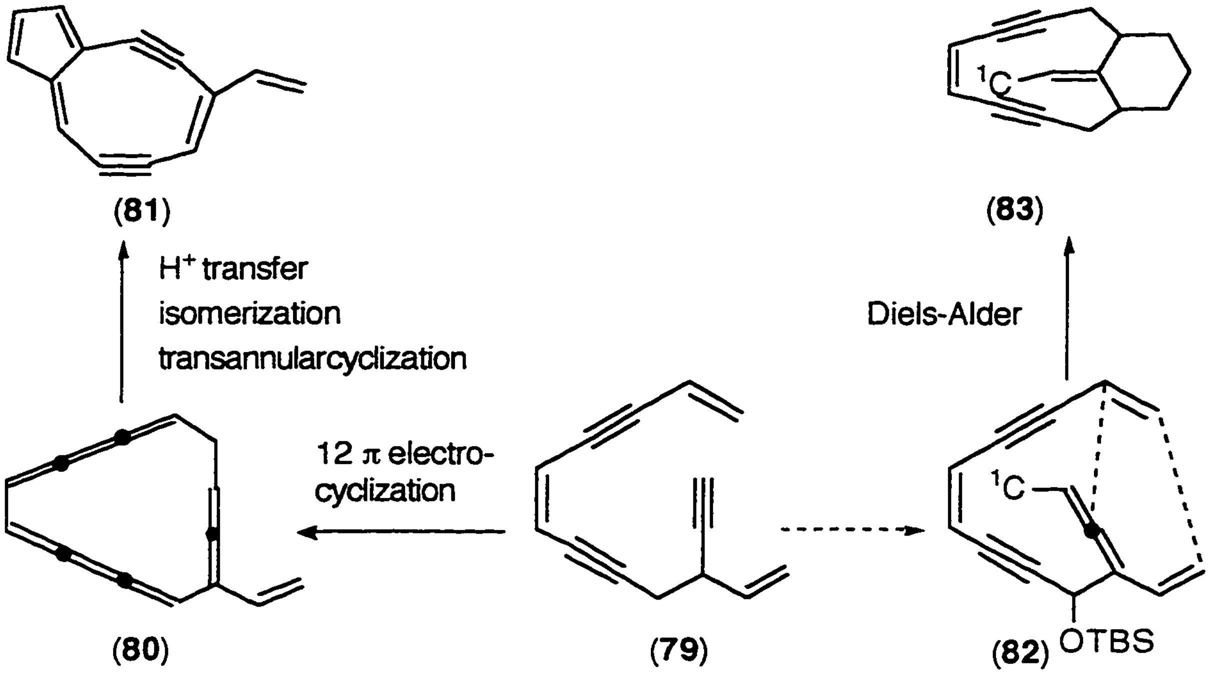


Figure 23.

The cycloaddition precursor (84) (Figure 24) was expected to react due to geometrical constrains imposed by the enediyne tether in an *exo* manner. Stereoelectronic effects should favor conformer (84) over the alternative (86) (Figure 25) as starting points for the corresponding transition states. This rationale led initially to the

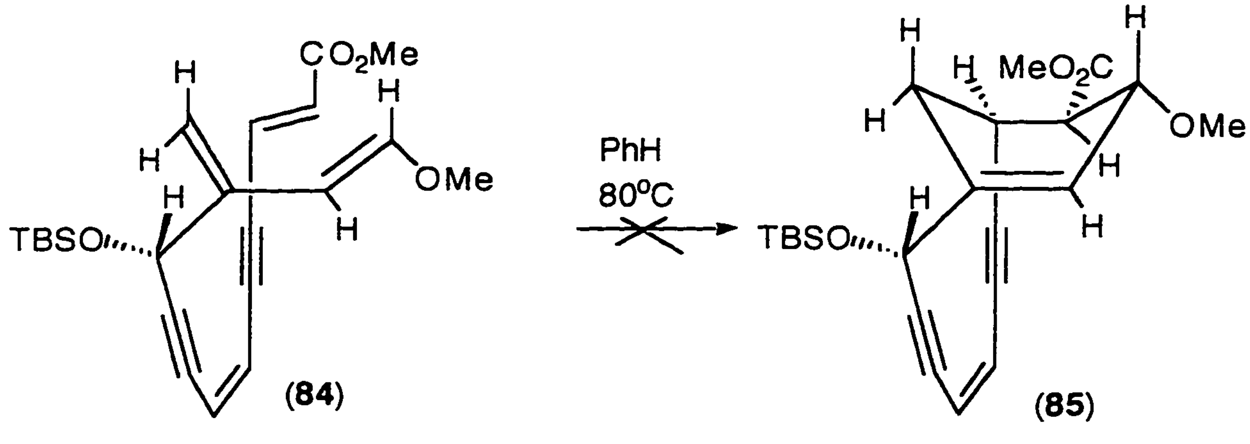


Figure 24.

incorrect assignment of cycloadduct (85) as reaction product which was subsequently corrected to structure (87).

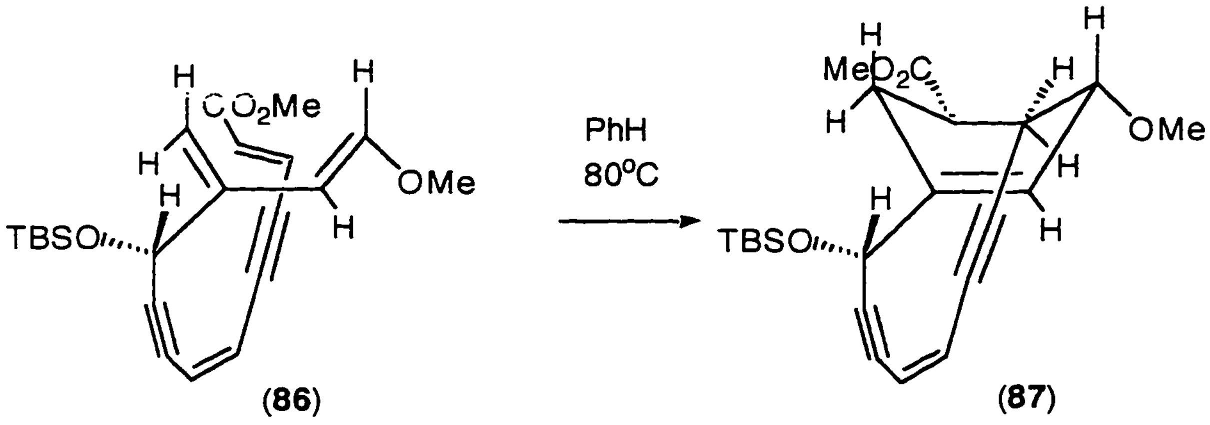


Figure 25

Capitalizing on the finding that the bicyclic core with the enediyne in place is stable to the thermal conditions required by the Diels-Alder reaction, the original approach was modified using the less reactive ethylene carbonate dienophile (88) (Figure 26). The initial cycloadduct (89) was then further developed into intermediate (90) which could rearrange under Lewis acid conditions to an acyloin intermediate (91) that tautomerizes stereoselectively to the pseudoequatorial hydroxy substituted cyclohexene platform of the

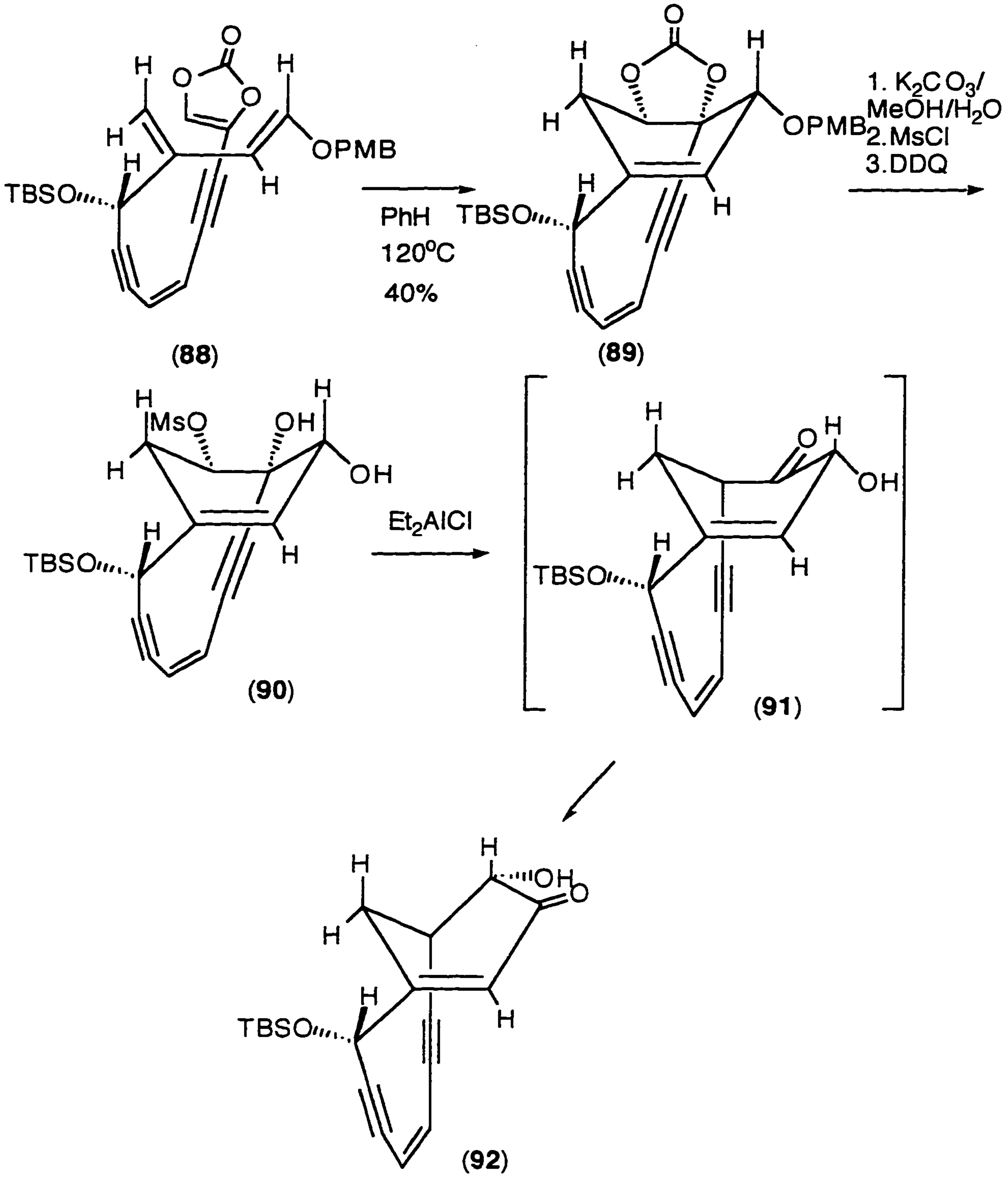


Figure 26.

desired esperamycin/caliceamicin aglycone analog (92).

1.5 Intramolecular Nicholas Reaction

Another highly original contribution to the elaboration of the byciclo[7.3.1] enediyne system was reported by Magnus[32] who realized the potential of the dicobaltohexacarbonyl acetylene complexes to circumvent the high energy transition states leading to the strained 10 membered ring cycle. This hypothesis was based on

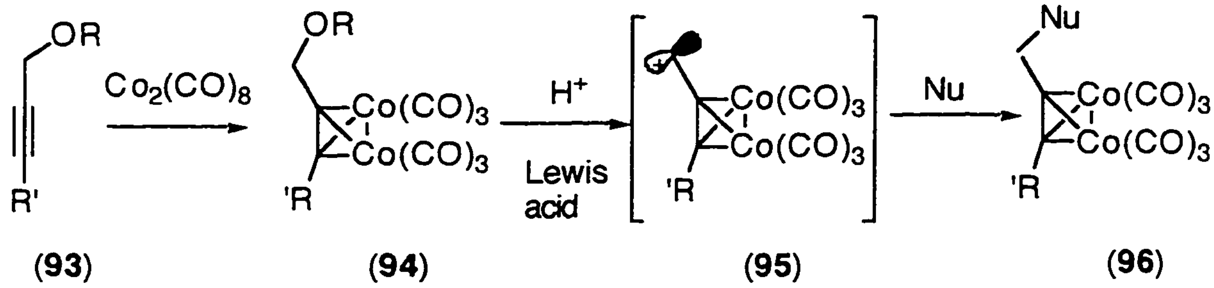


Figure 27.

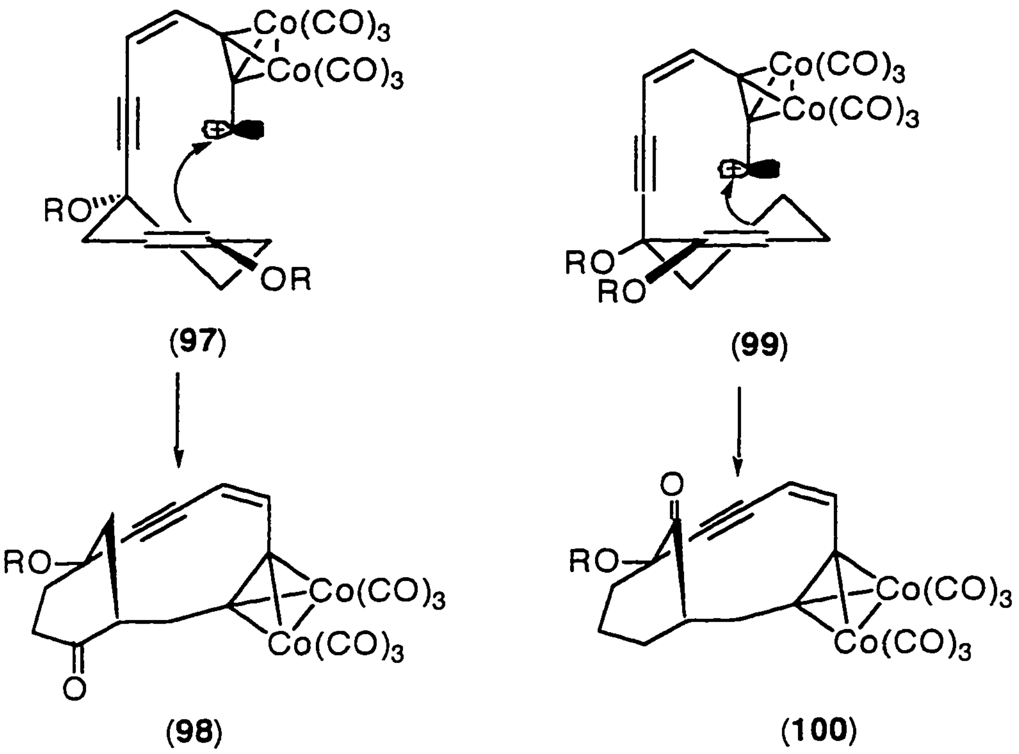


Figure 28.

the previously known property of these complexes to bend the normally linear acetylene ligand from 180° to approximately 145° (Figure 27). On the other hand the acetylene dicobalto complexes are notoriously efficient in stabilizing carbocations in the propargylic position which are known to effect synthetically useful reactions with electron rich reaction partners (Nicholas reaction)[33].

An essential prerequisite for this approach was the successful intramolecular axial attack of the carbocation (97/99) onto the electron rich π system of the appropriately positioned enol ethers to generate (98/100) respectively (Figure 28).

In the event the cyclization occurred upon treatment of the TBS enol ether with titanium tetrachloride in the presence of DABCO, a base that does not allow the hydride transfer to the propargyl carbocation due Bredt's rule violation. Decomplexation with NMMO unmasked the enediyne system which underwent spontaneous Bergman cyclization in the case of (98) while (100) provided a stable crystalline compound. The transannular distance between the terminal sp carbons of both enediynes is practically the same. Consequently, it was proved experimentally that in the case of the bicyclic systems the locking/unlocking switch is controlled by a favorable conformational modification of the entire molecule and not by the transannular distance between the terminal sp carbons of the hex-3-ene-1,5-diyne system.

1.6 Intramolecular Coupling Strategies

The high basicity of lithium, potassium or magnesium acetylides can be avoided by taking advantage of the chromium (II) chloride capability to reduce alkynyl iodides and generate nucleophilic alkynylchromium compounds that can selectively add onto aldehydes in the presence of ketones. The intramolecular variant of the Nozaki-Kishi reaction[34] was used by Beau in the synthesis of the monocyclic enediyne (103)[35a]. This compound was the first monocyclic enediyne having a hydroxy group in the propargylic position, a mimic of the hydroxy group found in the natural enediynes.(Figure 29).

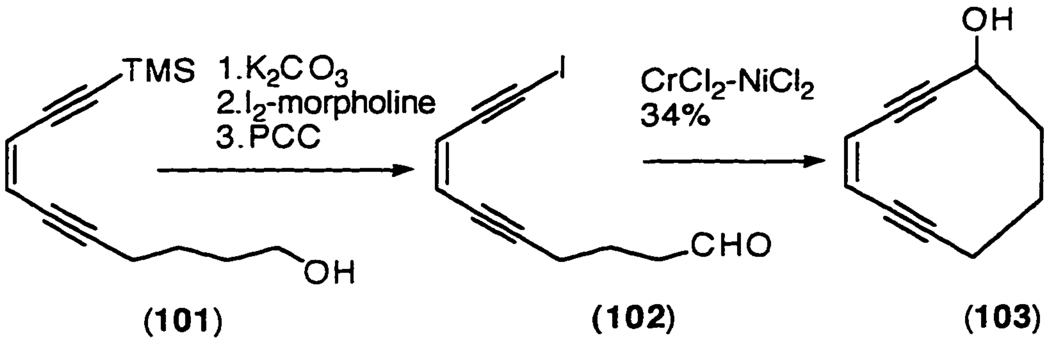


Figure 29

An interesting contribution regarding the synthesis of a sugar based enediyne (109) was achieved by Maier[35b] (Figure 30) and uses in the crucial cyclization step the Nozaki-Kishi type of coupling.

Protection of the known epoxide (104) followed by regioselective ring opening of the strained oxirane afforded ketone (105) which was further developed to the iodoaldehyde (108). Intramolecular chromium-nickel coupling resulted in bicyclic enediyne (109) which upon heating in refluxing benzene in the presence of cyclohexadiene yielded the corresponding Bergman

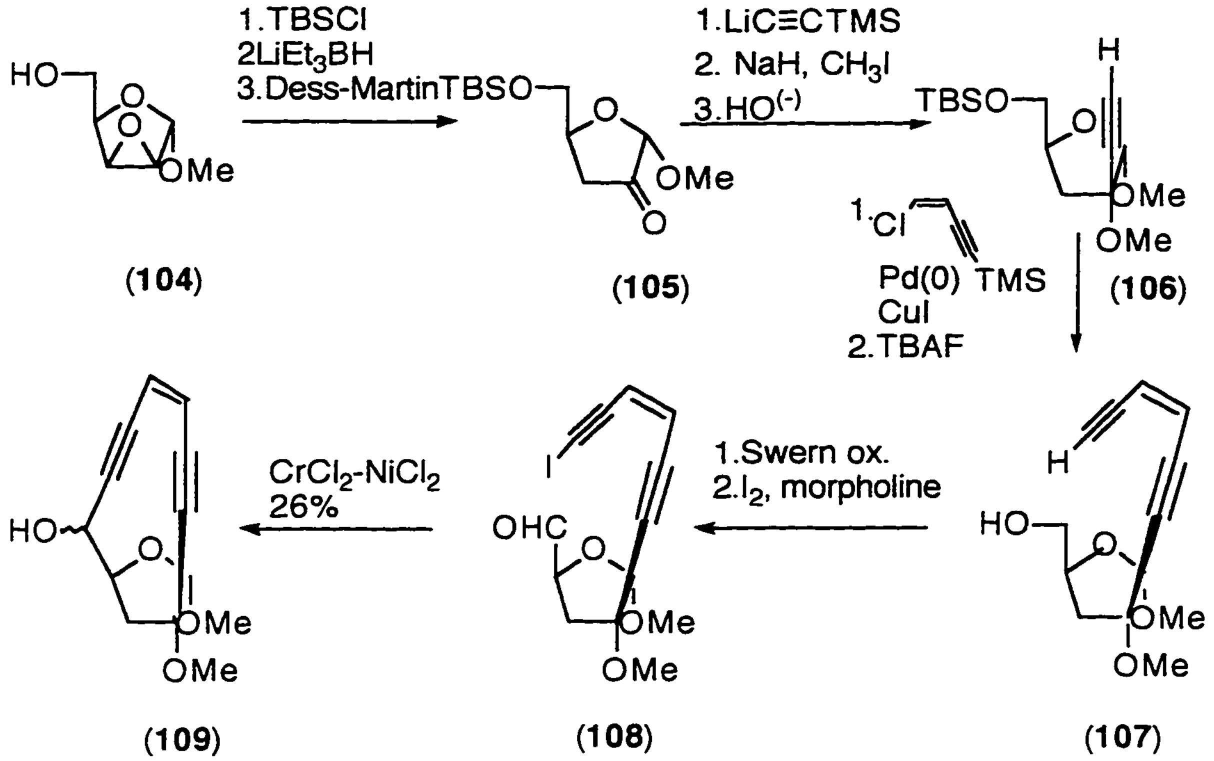


Figure 30.

cycloadduct in 26%.

Fallis group also reported the successful use of Nozaki-Kishi cyclization in the synthesis of Taxamycin-12[35c] (Figure 31), a hybrid bycylic molecule consisting of the A ring in Taxol and a twelve membered ring enediyne (111). The bicyclic enediyne could serve as an interesting starting point for the synthesis of a series of new constructs that might display interesting biological properties. On the other hand, Bergman cyclization of Taxamycin-12 could offer a new way for the synthesis of Taxol benzenoid analogs.

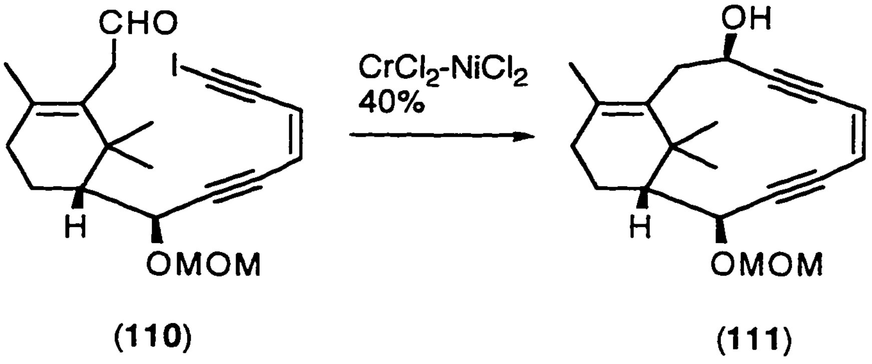
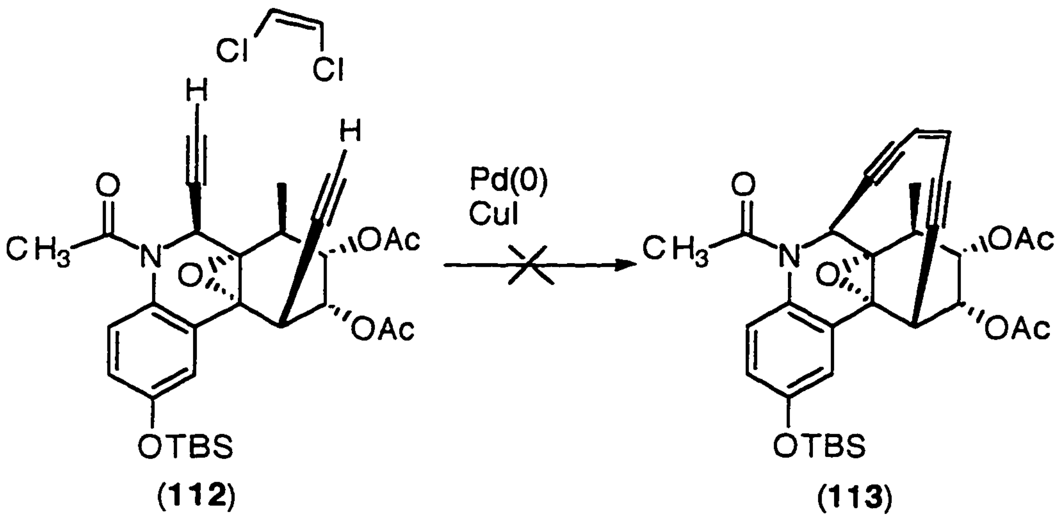
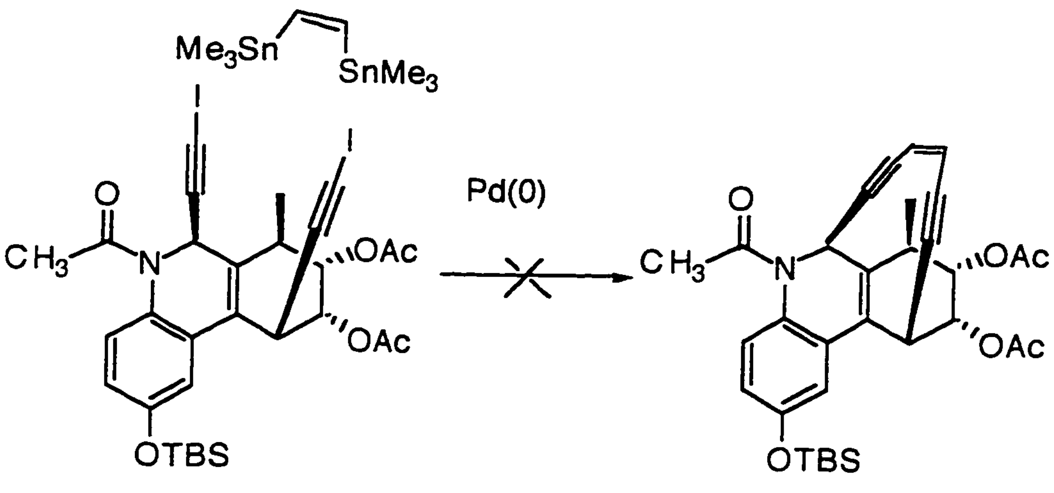


Figure 31.

Another conceivable way to build the enediyne system is the intramolecular palladium (0) catalyzed coupling of a terminal acetylene with an active ethylene derivative. This approach has been used by Danishefsky in his total synthesis of dynemicin A[36].



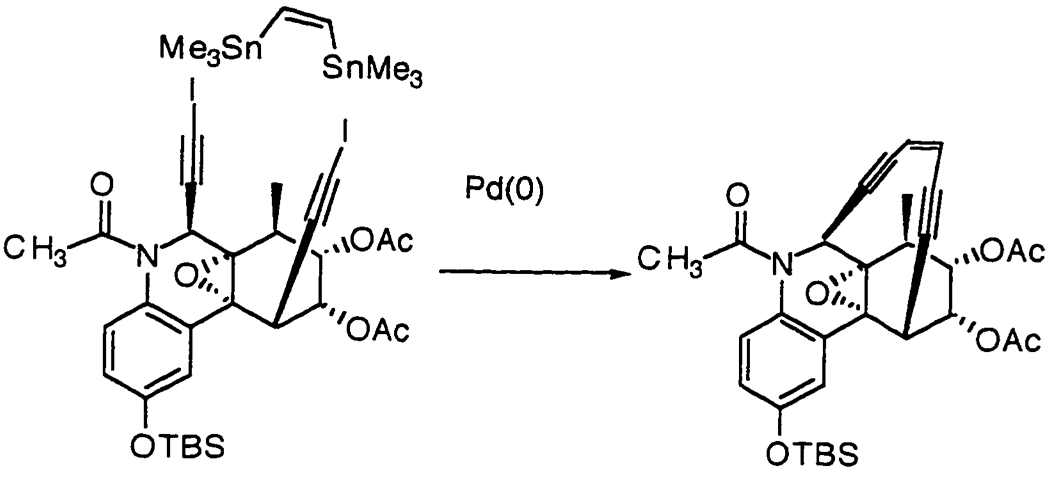


(114)

(115)

Figure 32.

Attempts to effect the cyclization of the enediyne moiety under conventional Stevens-Castro conditions were unsuccessful (112 to 113) while Stille coupling on the bis-iodo intermediate (114) also failed (Figure 32). It was hoped however that the presence of the C8-C9 epoxido linkage would serve to bring the two ethynyl functions closer together and to facilitate the projected cyclization. In the event treatment of compound (116) with the 1,2-bistrimethylstannyl ethylene in the presence of tetrakis(triphenylphosphine)palladium (0) gave rise to the epoxy enediyne (117) in 78% yield (Figure 33). This was the first



(116)

(117)

Figure 33.

successful construction of a 10 membered cyclic enediyne array through Pd(0) coupling and represented conceptually a very useful contribution to the synthetic methodology of the field. However, the different behavior of three very closely related cases reflects the subtle factors that control the Pd(0) catalyzed cyclization throughout the mechanistic sequence and shows that anticipation of the reaction outcome in this approach could be quite challenging.

In the same trend, Schinzer and Kabbara[37] completed the first synthesis of a 11 membered bicyclic enediyne (Figure 34).

The tricarbonyl iron hexafluorophosphate (118) reacted with bis(trimethylsilylacetylene)dilithiocyanocuprate to provide the η^4-irontricarbonyl (119) which was further deprotected to enone (120). Regio and stereoselective Sakurai reaction followed by acid catalyzed transketalization of the ketone afforded the pivotal intermediate (121). Finally the intramolecular Stephens-Castro reaction

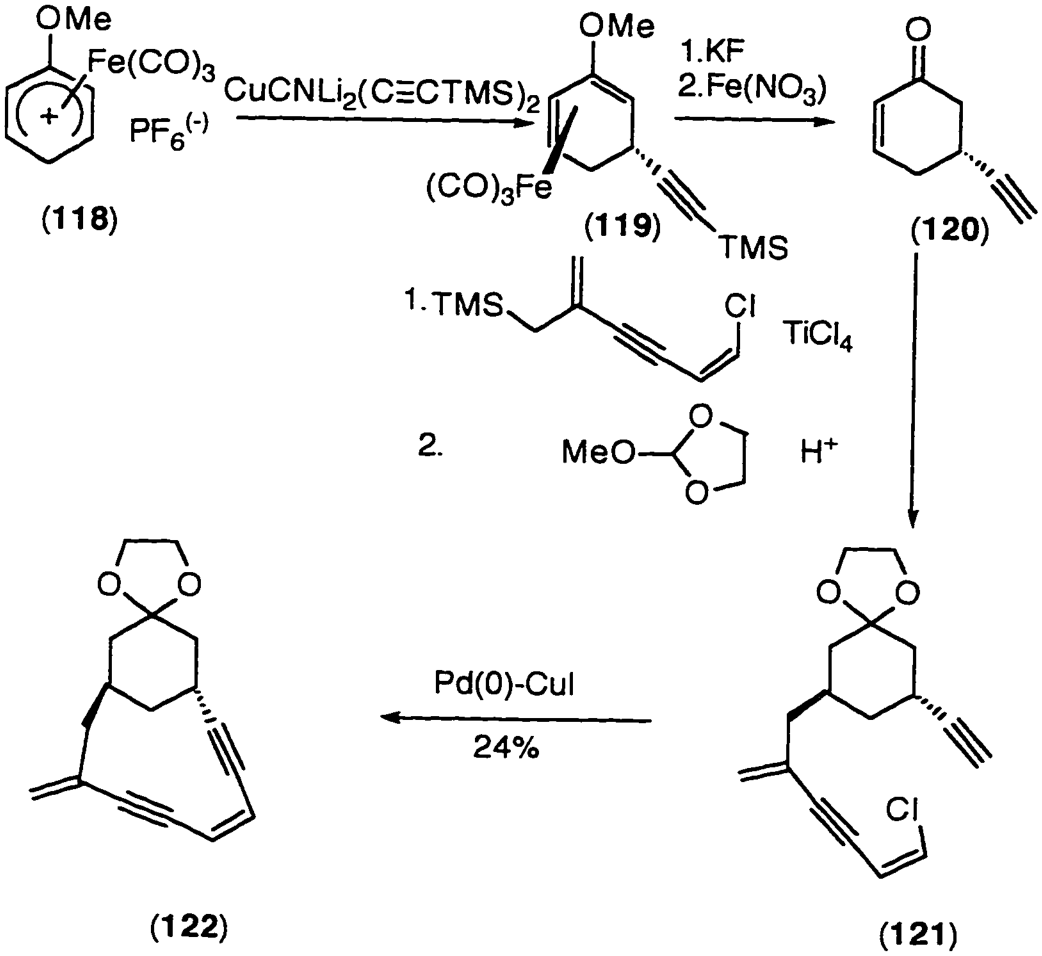


Figure 34.

accomplished the difficult ring closure to give the strained bicyclic target (122).

Two other unique reports in the literature used the intramolecular pinacol coupling *en route* to enediyne systems synthesis.

Thus in a joint project carried out by Nicolau and Bergman[38a], the ten membered ring enediyne (124) was accessed through a SmI_2 pinacol coupling of the dialdehyde (123). The presence of the *gem*-dimethyl group in the propargylic positions was essential for the successful coupling to occur (Figure 35). Further oxidation of the diol led to the vicinal dicarbonyl compound (124) which was expected to accommodate the keto groups in an orthogonal conformation thus preventing the Bergman cyclization. UV irradiation did not lead to the generation of the desired tetraradical (125) but rather to other hydroperoxidic by-products.

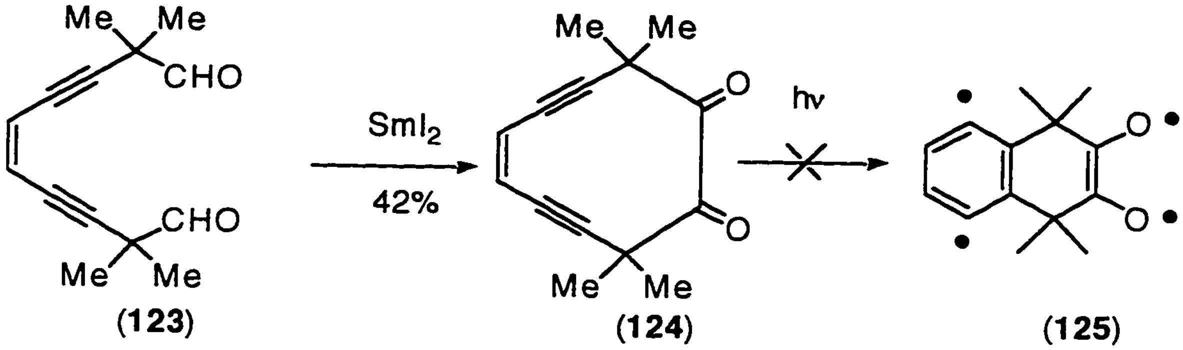


Figure 35.

Myers[38b] envisaged by analogy with dynemicin A (Figure 36) that bioreduction of anthraquinone (128) would result in the formation of the desired enediyne (129). The formation of the central double bond is facilitated in this example by the aromaticity of the furane ring. To test this triggering mechanism the authors reported the successful intramolecular pinacol coupling of the dialdehyde (126) using $VCl_3.3THF/Zn$ (Pedersen reagent). The resulting diol was oxidized to the keto alcohol (127) which was further developed to the ester (128). Enzymatic reduction provided the enediyne (129) which underwent Bergman cycloaromatization in cyclohexadiene at 37°C

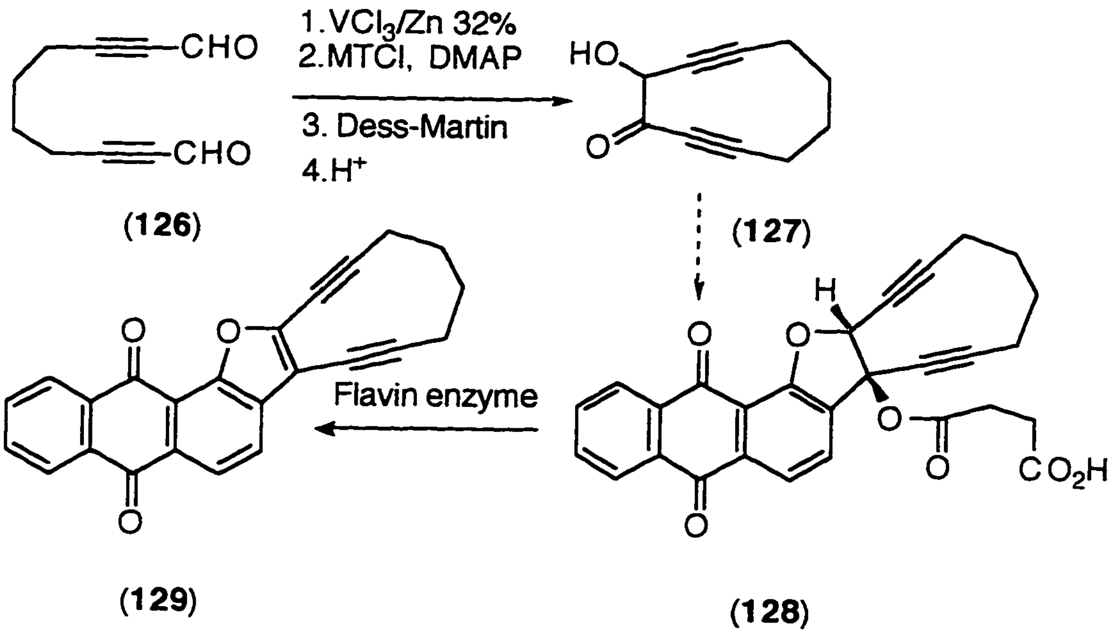


Figure 36.

1.7 Enediynes *via* Nucleophilic Displacement

A last widely used approach to enediyne synthesis is the intramolecular displacement of a leaving group by an internal nucleophile. For example this method was used in the synthesis of oxa[39] and thia[40] heterocyclic enediyne analogs such as those shown in Figure 37.

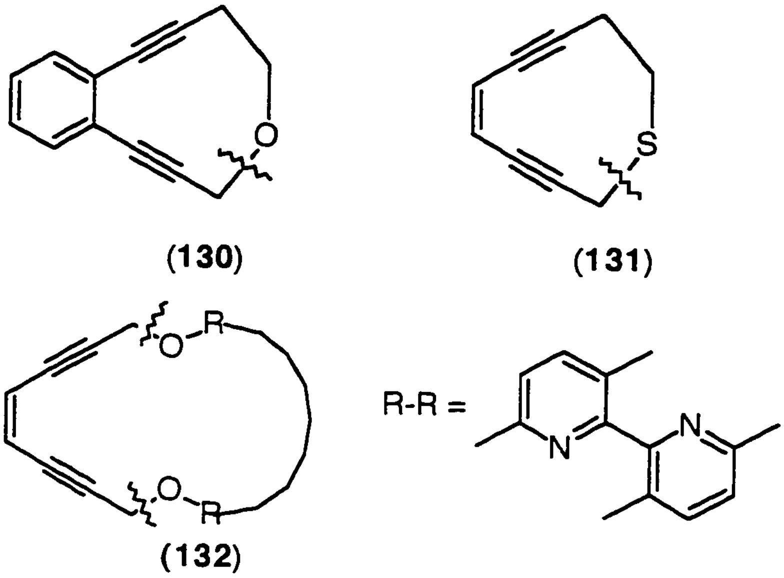
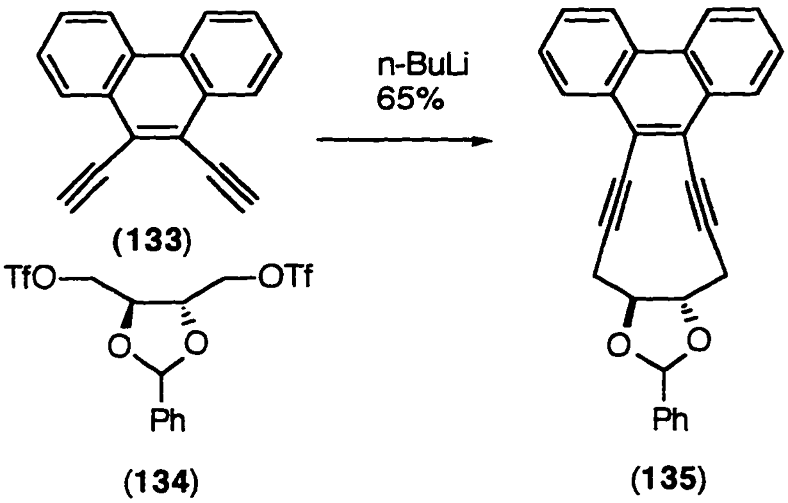


Figure 37.

Synthesis of various carbacycles[41] are also known and usually it is an acetylide anion to perform the nucleophilic substitution on a primary substituted derivative as illustrated below with a recent example of photoactive DNA cleaving agent (Figure 38).



(133) (134) (135)

Figure 38.

1.8 Concluding Remarks

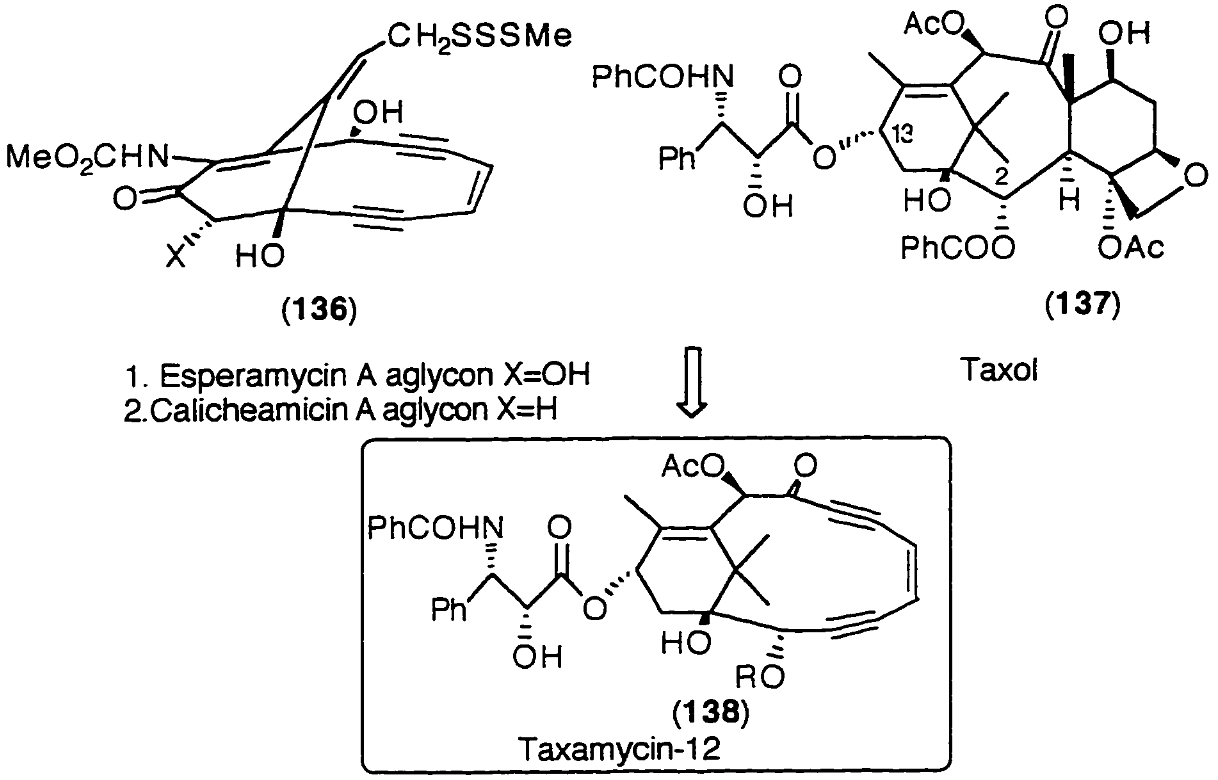
The continuous efforts directed to the development of new synthetic strategies and procedures towards cyclic enediynes allowed the in depth understanding of the mechanism of action as well as structure activity relationship of this class of emerging drug candidates.

It is unfortunate however that so far none of the reported solutions were truly general. This is due on one hand to the required high energy of the ionic intermediates implied by the transformation of the acyclic precursors to the highly strained cyclic enediynes which is reflected by the low yields in the crucial cyclization step and/or toleration of little functionality. On the other hand coupling strategies based on organometallic reactions proved so far highly inconsistent at best. The development of milder, more general methods for the cyclization to enediynes systems is therefore a stringent and permanent need for the development of this field.

2. Results and Discussions

2.1 Preamble

The enediynes antitumor agents have generated widespread interest due to their novel mechanism of DNA cleavage and the synthetic challenge presented by these new chemical entities. The common characteristic of this family is the presence of the 3-en-1,5-diyne moiety as shown in **Figure 39** for calicheamicinone and esperamycin aglycone (136) which can undergo a Bergman cycloaromatization to a paraphenylene diradical capable of cleaving DNA. An equally potent antitumor agent is taxol (137) whose C_{13} side chain and C_2 benzoate are required for binding. Consequently a new family of potentially active compounds can be envisaged whereby the defining elements of the two families of molecules are preserved resulting into a new hybrid structure called taxamycin (138).



(136)

(137)

1. Esperamycin A aglycon X=OH
2. Calicheamicin A aglycon X=H

Taxol

(138)
Taxamycin-12

Figure 39

Taxamycin-12 ring system and lower homologues (where the number represents the size of the smallest enediyne containing cycle) hold promise for the rapid construction of various aromatic taxanes (**Figure 40**, pathway a) while the smaller ring derivatives may possess interesting therapeutic potential provided the appropriate side chain and suitable functionality to trigger cycloaromatization are present (**Figure 40**, pathway b). Moreover, the paraphenylene diradical intermediate could add intramolecularly to appropriate radical acceptors tethered by the hydroxyl functions vicinal to the enediyne system adding functionality at these sites (**Figure 40**, pathway a). This would constitute a functionalization of aromatic ring under neutral conditions.

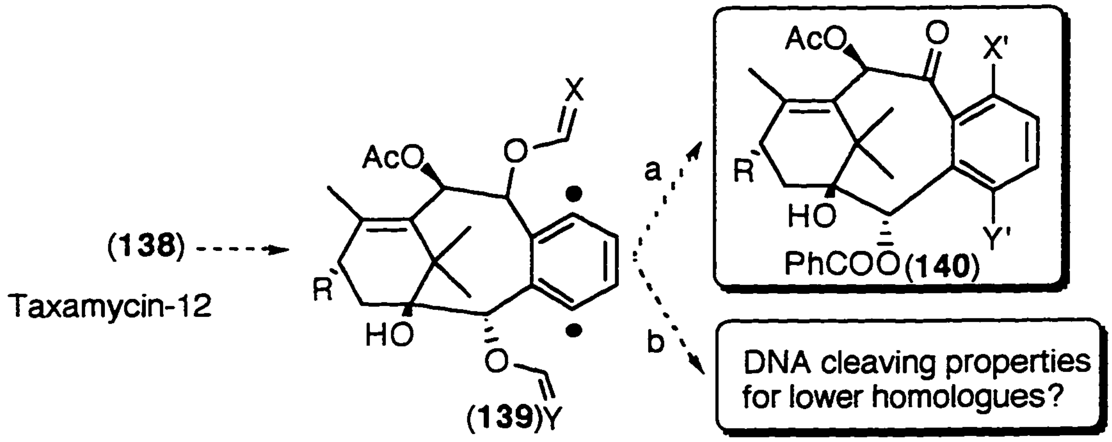
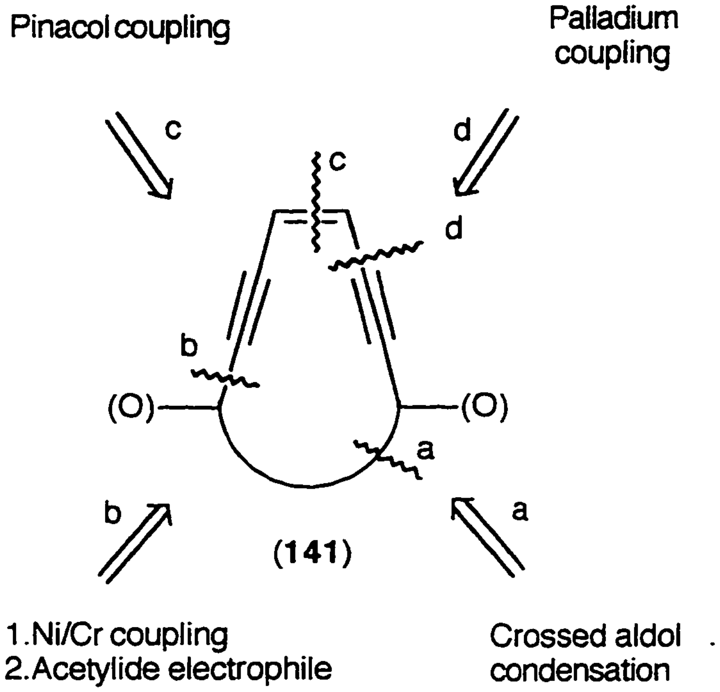


Figure 40

In order to test these hypothesis we set out to synthesize model systems for twelve, eleven and ten membered enediynes. The presence of the oxy substituents in both propargylic positions of the envisaged enediyne analogues was considered important since this would mimic the functionality found in the natural products. At the same time, based on earlier findings on substituent effects in propargylic positions to the enediyne moiety (*vide infra*) we anticipated that the bisoxy tethers would render these novel systems more prone to undergo Bergman cyclization and thus were hopeful that the models themselves might display antitumor properties. Indeed, while this work was under progress Semmelhack[25b] showed that similar enediyne structures conjugated with a DNA binding agent display an *in-vitro* activity comparable to that of calicheamicin γ_1^I. Finally, since there was no precedent for the synthesis of bisoxysubstituted monocyclic enediynes in the propargylic position and given the mixed results displayed by the available synthetic methods we anticipated the challenge of developing new and milder cyclization conditions in order to access these systems.

2.2 Envisaged Retrosynthetic Disconnections for Monocyclic α,α'-Bisoxyenediyne

The retrosynthetic analysis of a simplified monocyclic enediyne, bisoxy substituted in the propargylic position, suggests several possibilities (Figure 41).



(141)

Figure 41

At the outset of our research few of these disconnections had been examined experimentally and with the exception of pathway b very little data was available in the literature.

The crossed aldol condensation (disconnection a), traditionally a widespread cyclization method for the synthesis of rings of various sizes, including 10, 11 and 12 membered ring has not been applied to the synthesis of enediynes.

The Nozaki-Kishi intramolecular reaction (disconnection b) has been applied with partial success to the synthesis of a few structurally related systems while the acetylide-electrophile approach also suffered from low yields in the cyclization step. Given its generality we initially rated this approach as the safest way to access the target systems.

The pinacol coupling approach (disconnection c) and the palladium (0) coupling route (disconnection d) were considered as the most desirable, given the mildness of the reaction conditions, but the least predictable in cyclization results due to the subtle mechanistic aspects implied by these reactions.

The following discussion is structured in four subchapters each dedicated to one of the four routes highlighted above.

2.3 Enediyne Synthesis *via* Intramolecular Crossed Aldol Condensation

2.3A Retrosynthesis

Directly related to our interest in Taxamycin analogs, we focused initially on model compounds containing 11 and 12 membered ring enediynes.

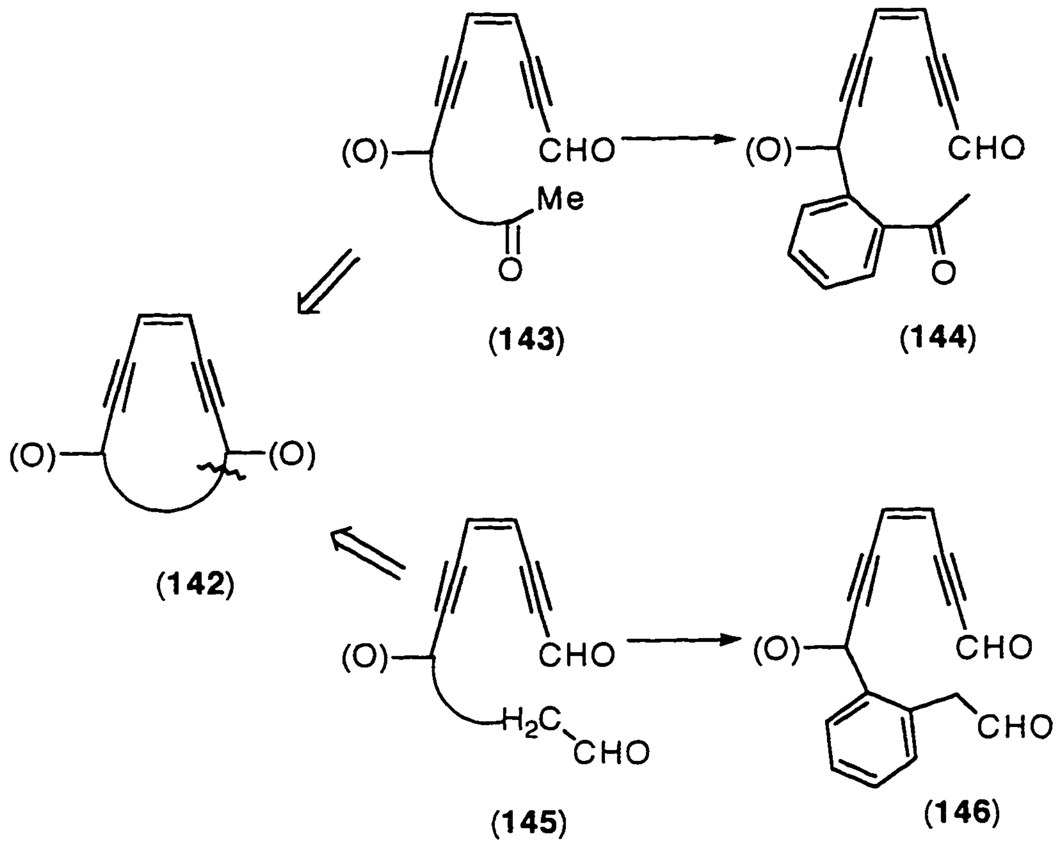


Figure 42

Retrosynthetic analysis of simplified enediyne (142) led to structures (143) and (145) as possible candidates for an intramolecular crossed aldol reaction leading to 12 and 11 membered rings respectively (Figure 42). In particular, inspection of molecular

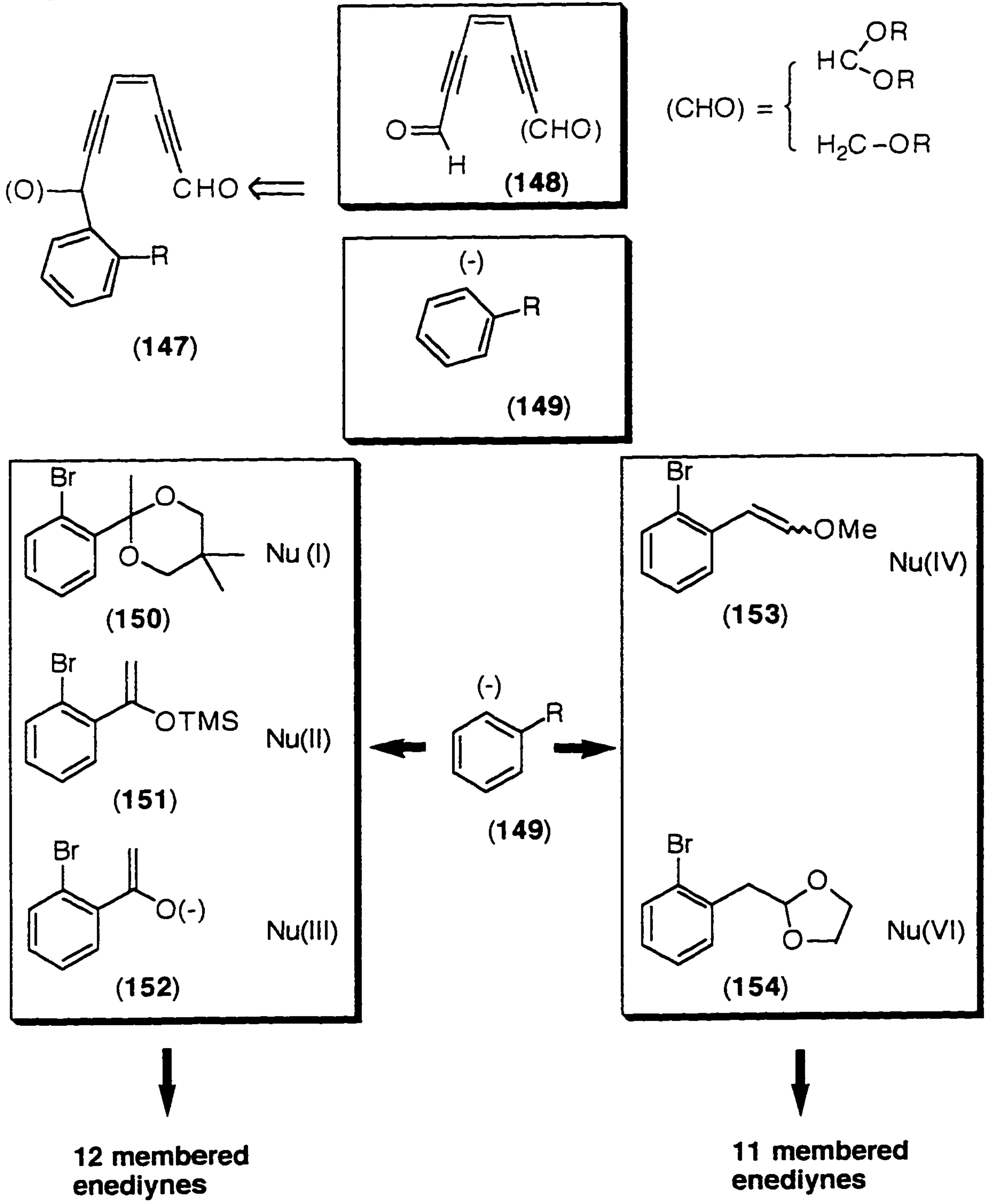


Figure 43

models as well as computer simulations (see Appendix 2) predicted structures (144) and (146) as strong candidates for cyclization precursors. These targets display a reasonable distance between the reactive centers while the use of the aromatic tether keeps the system flat, reducing the number of degrees of freedom and entropically favoring the intramolecular aldol condensation.

Moreover, the two conceivable dicarbonyl compounds could share a common synthetic route as shown in **Figure 43**, reducing the problem to a nucleophilic addition of a phenyl anion (**149**) to a common form of the monoaldehyde (**148**).

An α,ω-silyl substituted enediyne carbaldehyde had been previously reported as marginally unstable[31a]. It was not initially clear to us to what extent the oxy substitution (CH_2- OR) at the other propargylic position of the enediyne (**148**) would influence the stability of this pivotal common species. On the other hand, masking of the enediyne carbaldehyde as an acetal was an attractive alternative since one could anticipate the possibility of a simultaneous unmasking of the two carbonyl partners and an intramolecular crossed aldol reaction under mild acidic conditions. As a matter of fact all the chemical synthons for the phenyl anion (**149**) were specifically designed both in the 11 membered and the 12 membered series to respond to relatively mild acidic conditions and allow this type of one step double deprotection- aldol cyclization reaction.

With these goals in mind we set out to test our ideas by synthesizing first 12 membered ring enediynes which were directly related to the Taxamycin-12 project.

2.3B 12-Membered Ring Enediynes

2.3B.1 Nucleophile I-Nu (I)

Inspired by previous reports on enediyne synthesis we successfully assembled (**Figure 44**) the alcohol (**157**) using Stevens-Castro reaction[42]. Upon oxidation of the alcohol under a variety of conditions we have obtained various yields of unstable aldehyde (**158**) which was characterized as a crude product.

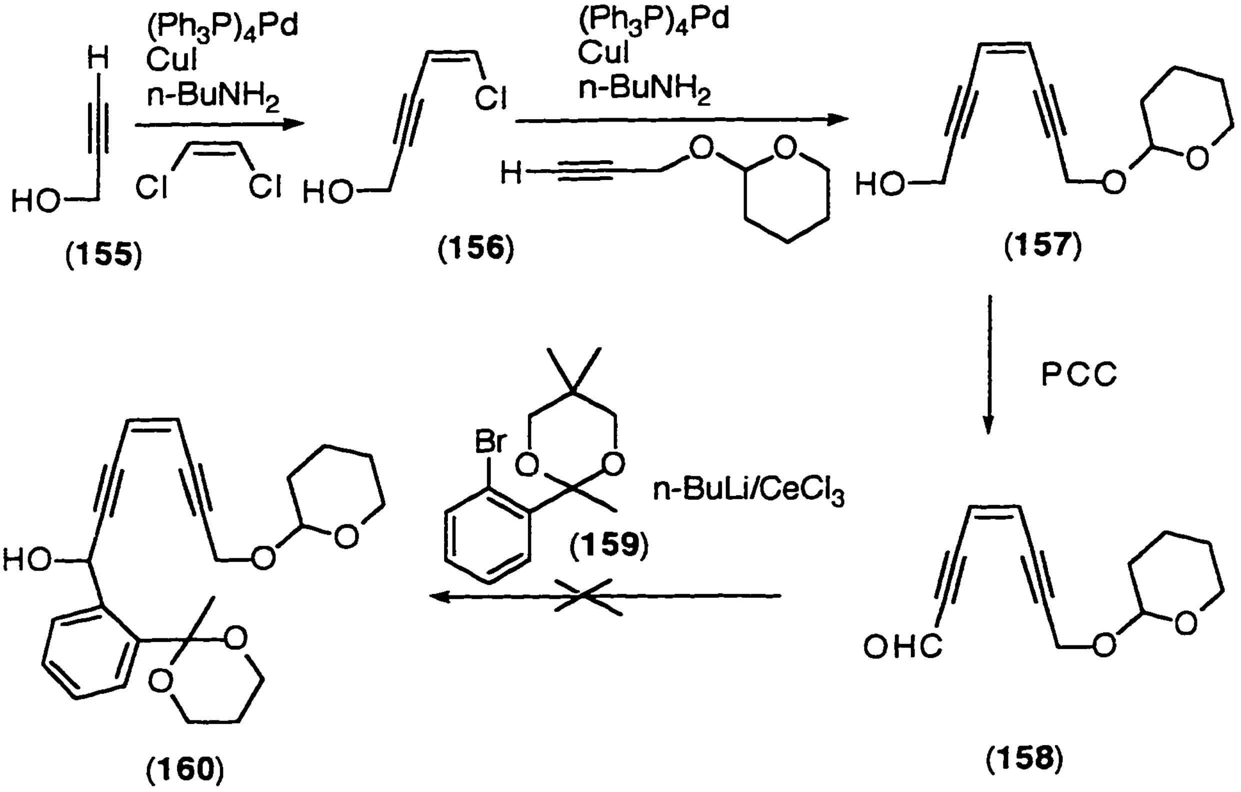
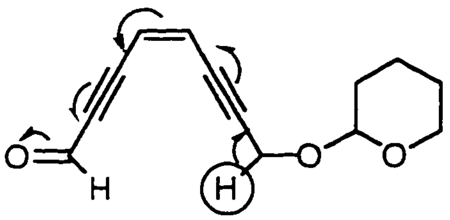


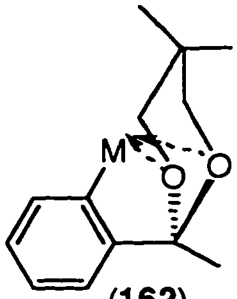
Figure 44

	Oxidation Yields for Alcohol (157)
Dess-Martin	0%
Swern	0%
MnO_2	30-50%
PCC	40-60%

The attempted addition of the lithium anion derived from halogen-metal exchange of *o*-bromoacetophenone ketal (150, Nu I), afforded only recovered debromo derivative and none of the desired product (160). Transmetallation to the organocerium species gave the same result while the organomagnesian provided no improvement. The instability of the aldehyde associated with the lack of response to nucleophilic addition made this route impractical. We felt however that aldehyde (158) offered us a good opportunity to test whether the acidity of the propargylic proton (conceivably enhanced by the conjugative effect of the aldehyde over the enediyne system) was the cause of the poor substrate electrophilicity. Alternatively, intramolecular chelation might reduce the nucleophilicity of the phenyl anion (Figure 45).



(161)
increased
proton acidity



(162)
metal chelation
hypothesis

Figure 45

In the event we reacted aldehyde (158) with the lithium carbanion derived from bromobenzene to obtain the addition product (163) in 86% yield as a mixture of diastereoisomers (Figure 46).

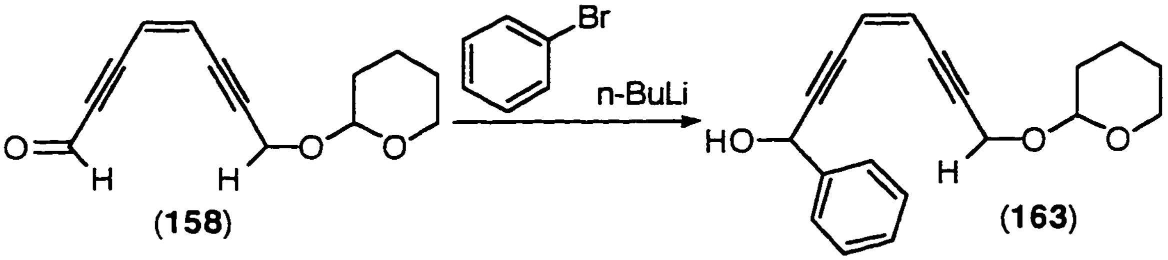


Figure 46

In conclusion although this route did not provide a cyclization precursor it taught us valuable information. (i) It seemed that oxy substitution in the propargylic position rendered enediyne carbaldehydes less stable than the previously reported congener[31a]. (This initial assumption was later supported by the TBS protected homologue (166) whose oxidation product could not be isolated (Figure 47).(ii) The increased acidity of the proton in the propargylic position of the common enediyne carbaldehyde is unlikely to cause any problems in the nucleophilic addition step.
(iii) The possibility of intramolecular chelation should be avoided in the design of different nucleophilic partners.

2.3B.2 Nucleophile II-Nu (II)

Armed with this empirical knowledge, we proceeded on a similar pathway to the synthesis of a new aldehyde (168). This proved to be indeed reasonably stable and therefore used for the rest of the experiments (Figure 47).

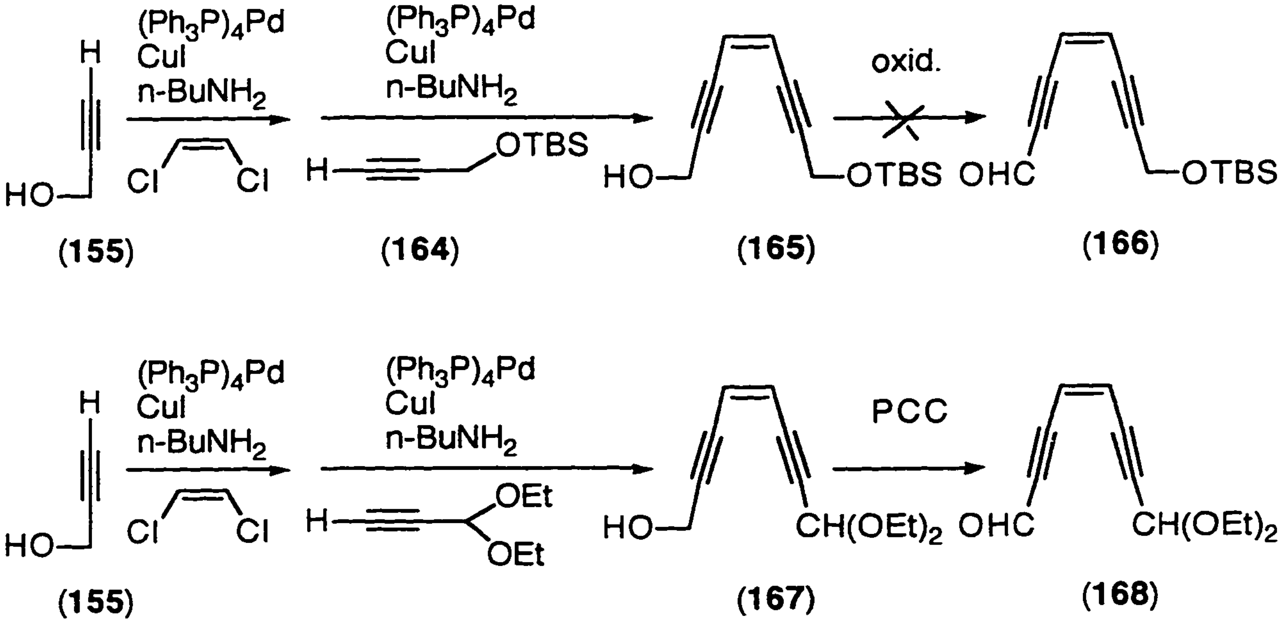


Figure 47

Compound (151, Nu(II)) was chosen as nucleophilic partner, given the reduced chelating properties of the silyl ethers.

The addition of (151) onto the aldehyde procedeed this time in good yield resulting in the unexpected rearranged product (169).

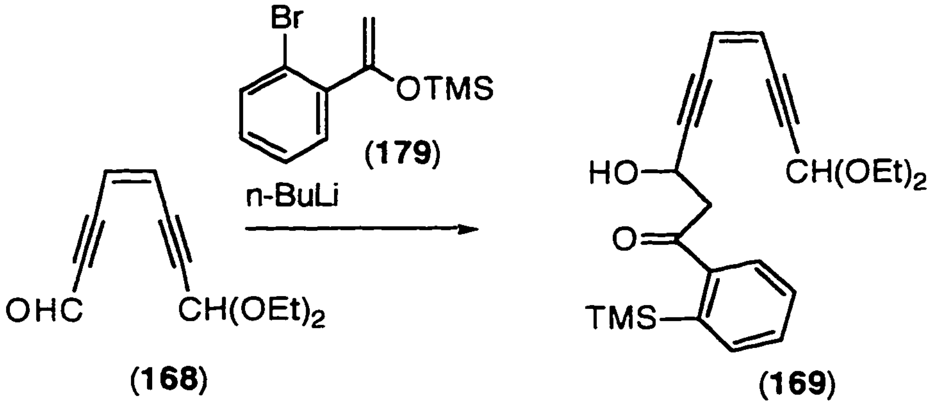


Figure 48

This result is consistent with an anti-Brook rearrangement possibly occurring through transition state (170). The reaction ultimately leads to the formation of the lithium enolate which adds efficiently onto the enediyne carbaldehydealdehyde (Figure 49).

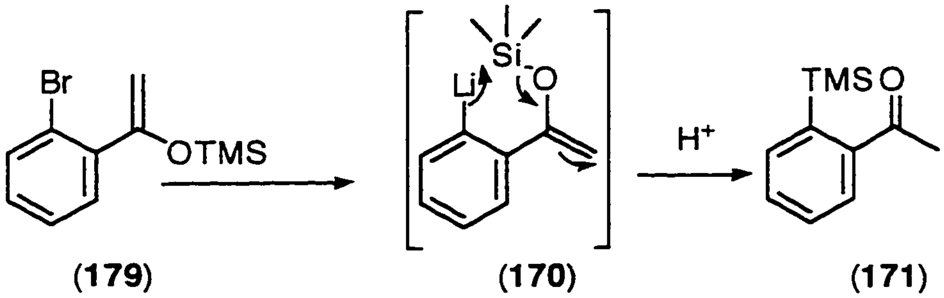


Figure 49

We tried to turn this unexpected result to our advantage by attempting an intramolecular silicon directed electrophilic substitution[43] (Figure 50 Pathway a). Unfortunately this reaction led to the loss of the starting material under a variety of experimental conditions. We have reasoned that the presence of the carbonyl group next to the aromatic nucleus had a detrimental effect

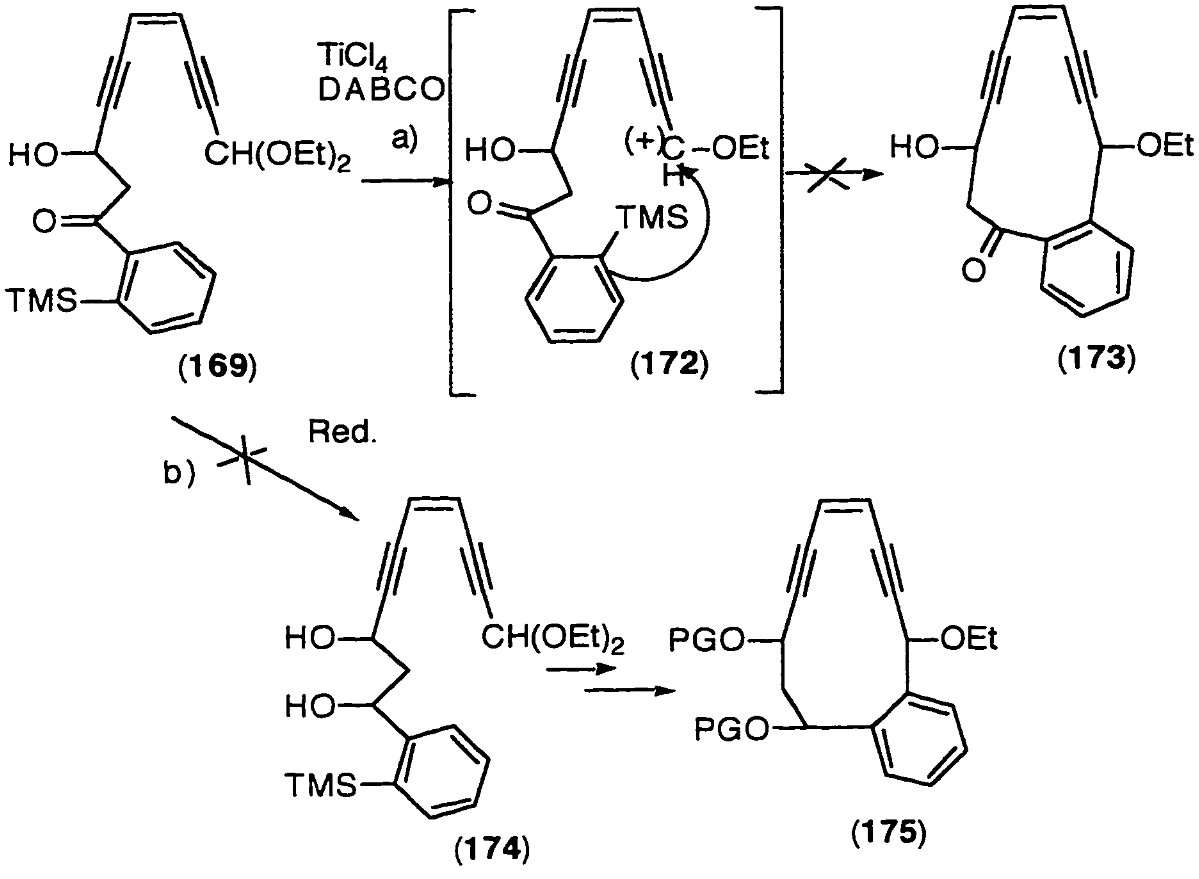
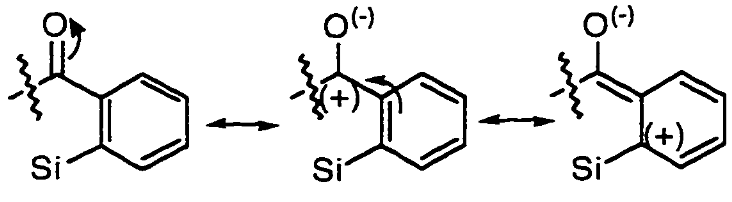


Figure 50

on the intramolecular electrophilic attack and decide therefore to reduce this ketone to the corresponding benzylic alcohol and then effect the silicon directed cyclization (Figure 50 Pathway b). Unfortunately the reduction of the ketone proved to be unachievable under the usual reductive conditions.

Intrigued by the lack of response to reductive conditions of ketone (169) we have performed a computer energy minimization and discovered an unexpected lowest energy conformation whereby two of the methyls of the trimethylsilyl group from the *ortho* position were blocking both faces of the carbonyl group (Appendix 2). On the other hand, thinking in terms of resonance structures, it is well known the electronic destabilizing effect[44] of silicon for positive charges in the α (178) and γ (177) positions thus reducing the electrophilicity of the carbonyl group (Figure 51).



(176) (177) (178)

(+) γ to the Si (+) α to the Si

Figure 51

In order to check experimentally this unfavorable local stereoelectronic effect caused by the trimethylsilyl group we have synthesized the crossed aldol condensation products of benzaldehyde with *o*-bromo-O-trimethylsilyl acetophenone enol ether (179) and acetophenone (182) respectively (Figure 52). While trimethylsilyl substituted ketoalcohol (180) displayed a total lack of reactivity to a variety of reducing agents, the structurely related aldol product (183), lacking the trimethylsilyl group, was smoothly reduced diastereoselectively[45] to the coresponding diol whose *syn* stereorelationship was firmly established by the diagnostic 10 ppm shift difference in the ^{13}C spectrum of its acetonide (184) among the axial methyl and equatorial methyl signals as well as the typical chemical shift of the quaternary carbon in the acetonide[46].

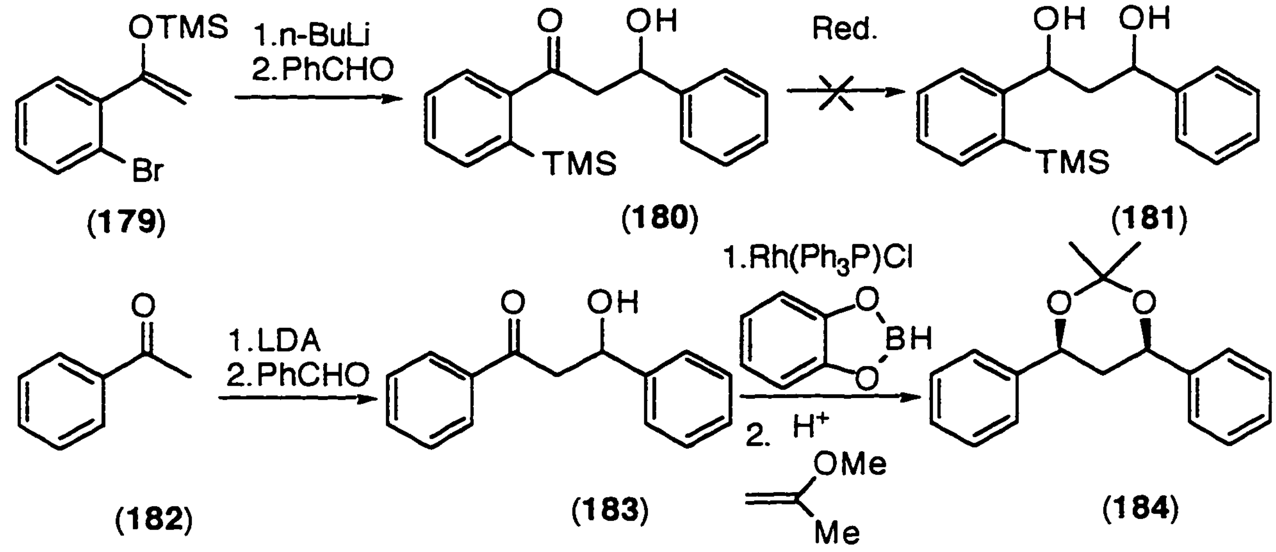


Figure 52

Clearly, difficulties associated with this reductive approach prevented us from reaching the cyclization stage as planned. We felt however that another way to reduce the electron deactivating effect of the carbonyl group next to the aromatic system would be to create an extended conjugated system by dehydration of the ketoalcohol (169) to the corresponding enone (185) as shown in Figure 53. Based on the results given by computer simulations we hoped to effect the dehydration stereoselectively to access the *trans* geometrical isomer since the *cis* isomer did not seem adequate for the desired cyclization step (Appendix 3). To our satisfaction, treatment of the β-ketoalcohol under Mitsunobu conditions gave the desired *trans* isomer (185) in good yield. The attemted cyclization under acidic conditions[32] however failed and led only to the destruction of the starting material.

Two days later, upon a routine verification of the elimination product (185) we observed the development of a new family of new signals in the ^1H NMR spectrum These were initially ascribed to the tendency of the product to isomerize about the enone double bound from *trans* to *cis*. A closer study of the case revealed however that we were actually observing an *s-cis* (185) to *s-trans* (186) isomerization about the C-C sigma bond. Although we were not able to separate the two conformers by column chromatography and characterize them separately this behavior pointed to an unexpected rigidity of the molecular structure. This unpredicted conformational

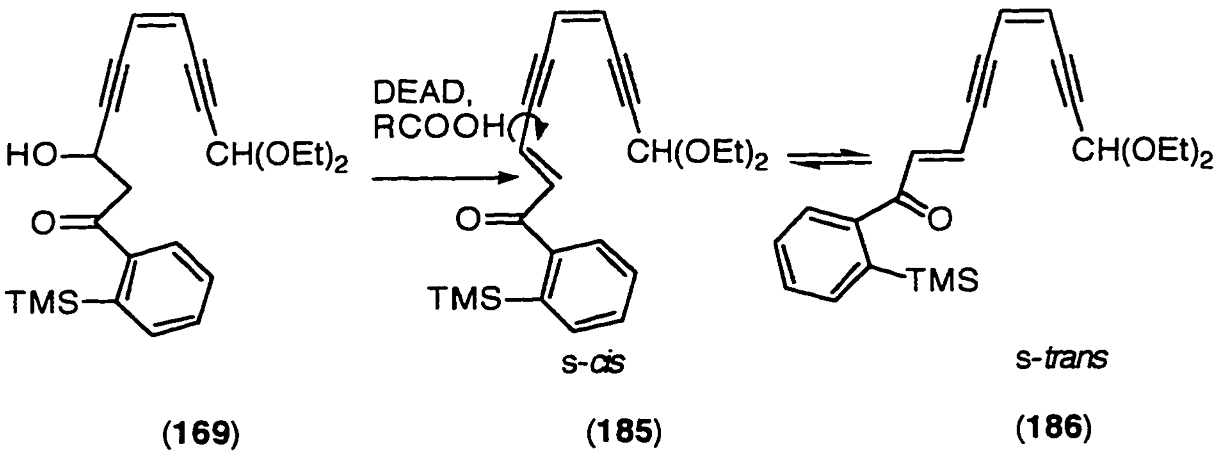


Figure 53

equilibration provided us with a golden opportunity to explore the intramolecular distance between the ketal site and the aromatic ring by an nOe study. Irradiation of the sharp signal of the ketal proton caused no nOe enhancement for either of the two conformers. This

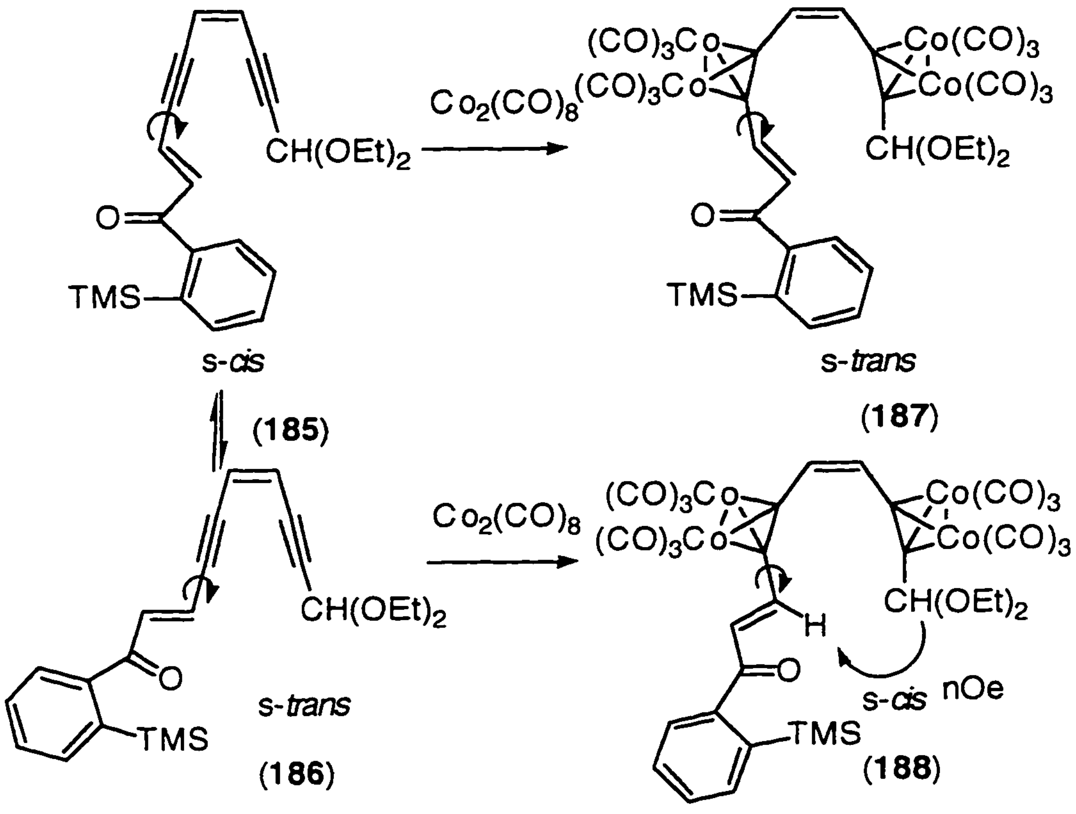
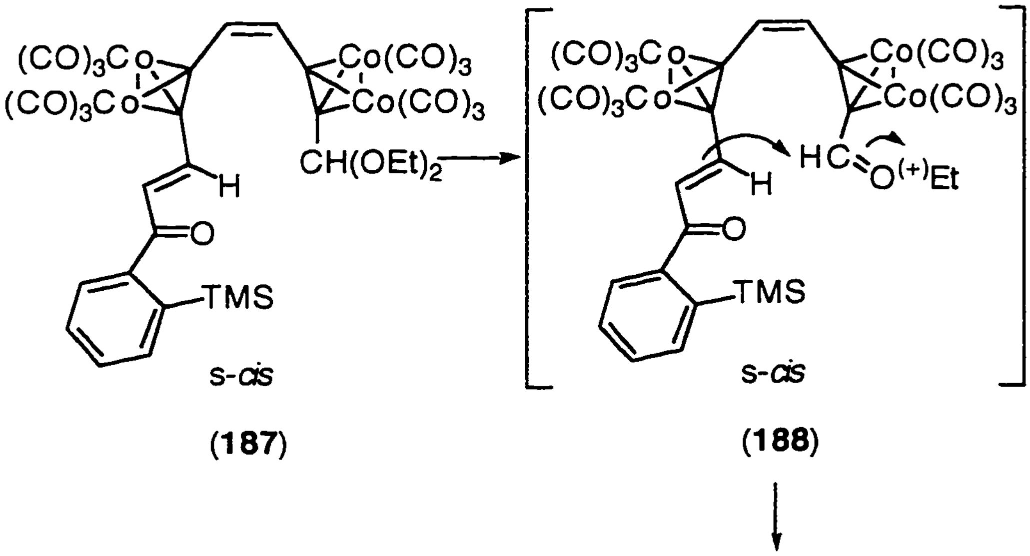


Figure 54

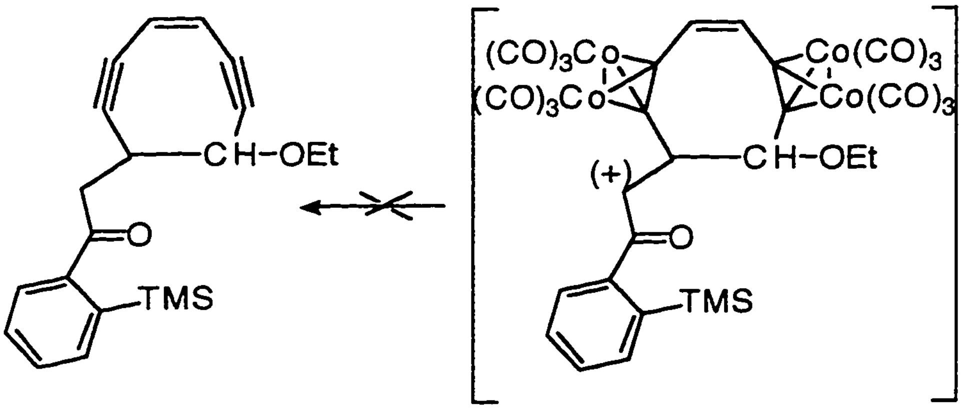
enabled us to conclude that the enediyne preferred in solution a conformation that was not advantageous for our cyclization purposes.

In an attempt to bring the reaction sites closer to one another we treated the mixture of conformers with dicobaltooctacarbonyl (Figure 54) and isolated the tetracobalto complexes (187) and (188) which did not equilibrate in time. As expected from previous literature precedent[47] these cobalto complexes were separable by HPLC and we were able this time to detect an nOe (11%) between the ketal proton and the proton in the β position of the enone (188). This was indicative of the potential offered by the tetracobalto enediyne complexes to access ten and even nine membered ring enediynes and as a matter of fact this was later confirmed by a report coming from a different laboratory[48].

From our point of view however, the detection of this nOe signal meant that the projected Nicholas cyclization will most probably occur with the attack of the initial carbocation onto the electron poor enone double bond (Figure 55) instead of the desired silicon *ipso* substitution on the aromatic ring to produce the highly strained 8 membered enediyne (190) after deprotection of the triple bonds. This reaction goes through a high energy carbocation intermediate (189), α to a carbonyl group, thus we expected that the cyclization step would fail which was eventually confirmed experimentally.



(187) **(188)**



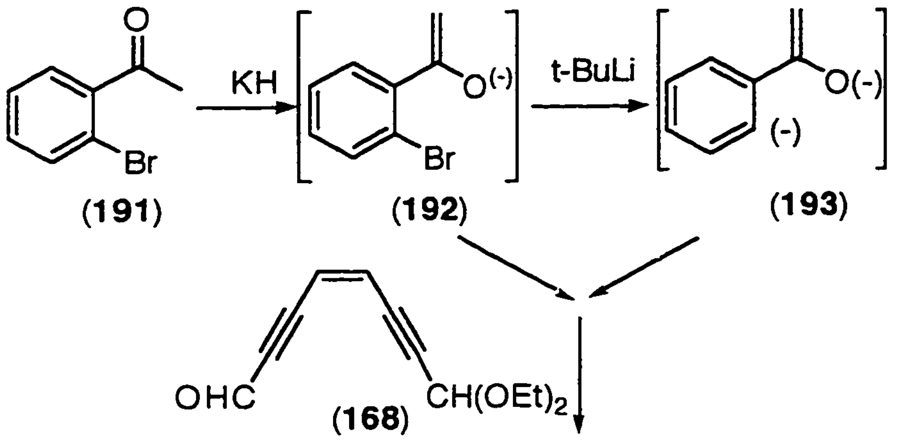
(190) **(189)**

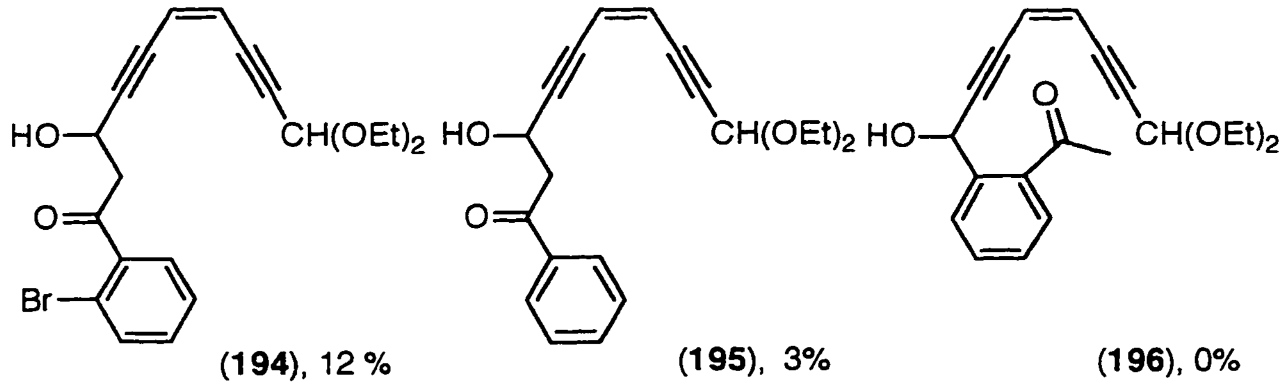
Figure 55

2.3B.3 Nucleophile III-Nu (III)

In a last attempt to access a monocyclic 12 membered ring enediyne we decided to investigate a third possible approach which featured the addition of the dianion (193) onto the aldehyde (168) as shown in Figure 56. The more reactive phenyl anion should ensure the chemoselective reactivity at this site rather than at the softer, less reactive enolate anion alternative. Unfortunately the metal halogen exchange on the enolate (192) did not occur quantitatively even when we treated (192) with tert-butyllithium for six hours at - 78°C temperature and the only isolated product in low yield was the bromoderivative (194) as well as a minuscule quantity of aldol addition product (195) whose structure was tentatively assigned from its proton NMR spectrum.

At this point we decided to turn our attention to the elaboration of an 11 membered ring monocyclic enediyne.



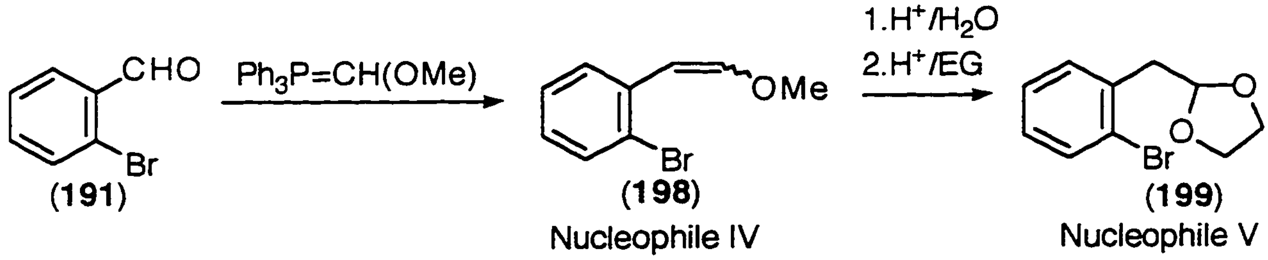


(194), 12 % **(195)**, 3% **(196)**, 0%

Figure 56

2.3C 11-Membered Ring Enediynes

Figure 57 details the synthesis of the nucleophilic partners required for the generation of the 11 membered ring monocyclic enediynes. Commercially available *o*-bromobenzaldehyde (197) was transformed to a 1:1 *cis* to *trans* mixture of *o*-bromophenylmethoxystyrene (198). This in turn was hydrolyzed under acidic conditions to *o*-bromophenylacetaldehyde that ultimately provided the *ketal* (199) in *quasi* quantitative yield.



(191)

(198)
Nucleophile IV

(199)
Nucleophile V

Figure 57

The excellent response to deprotection under relatively mild acidic conditions of Nu (IV) suggested the simultaneous unmasking of the two aldehydes groups for the intramolecular aldol to the desired cyclic enediyne should occur efficiently.

In the event the addition of Nu (IV) onto aldehyde (168) proceeded satisfactorily to provide a 1:1 mixture of *cis:trans* mixture of the corresponding addition product (200/201). Treatment of compounds (200/201) under the same acidic conditions that had accomplished the deprotection of (198, Nu IV) caused immediate decomposition of the molecule so we decided to esterify the alcohol as a cinnamate. (The cynamyl moiety was introduced with the purpose to serve as an intramolecular radical acceptor for the anticipated Bergman cyclization.). Unfortunately the cinnamate (202/203) was also unstable to a range of acidic conditions (Figure 59) used in several cycliztion attempts. ^{1}H-NMR monitoring of the

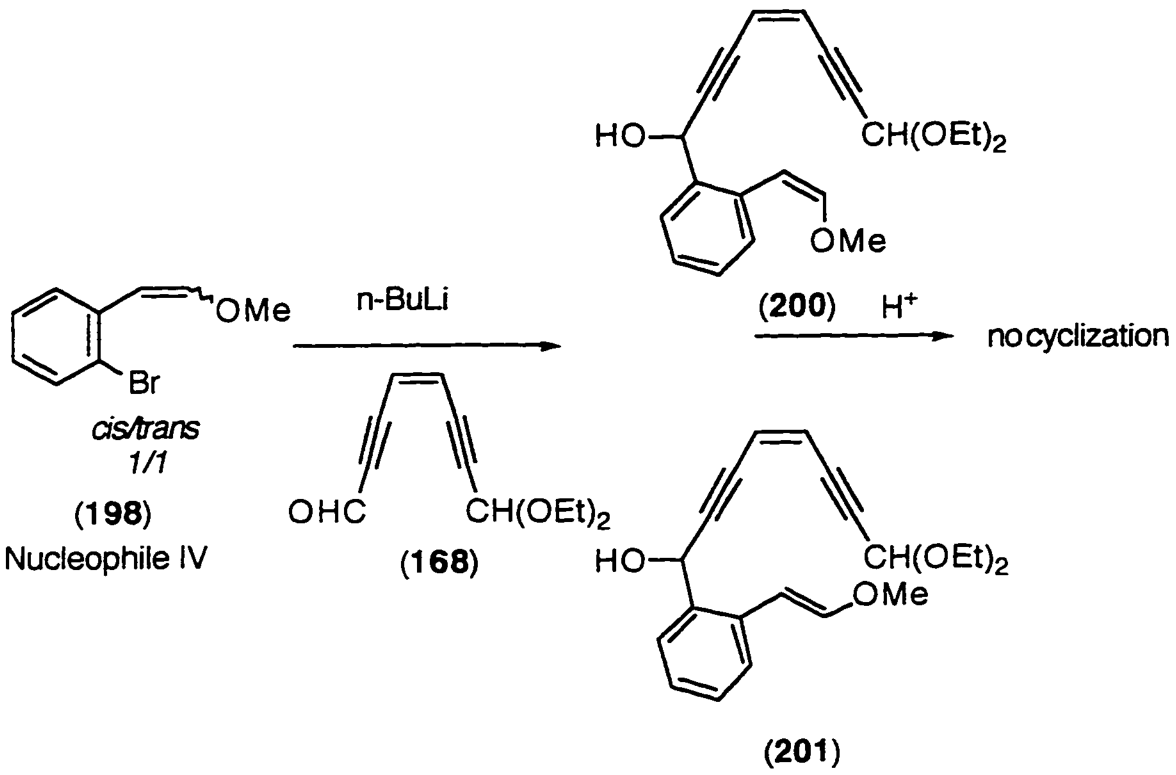


Figure 58

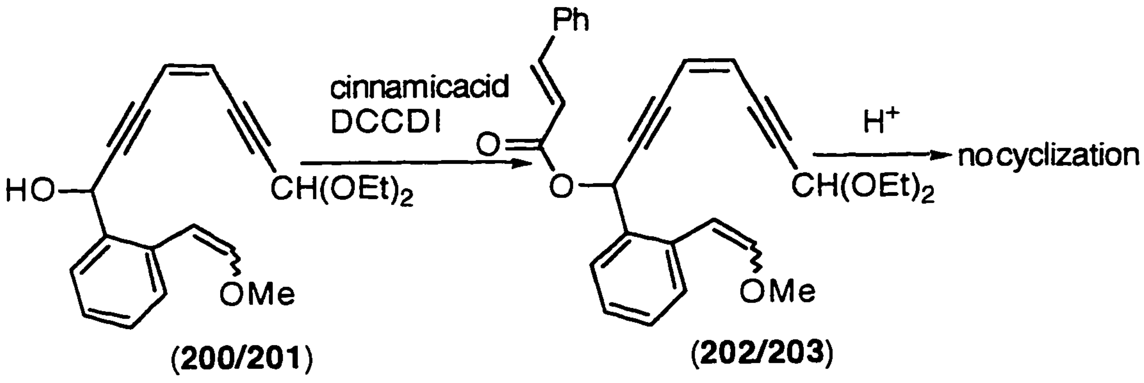


Figure 59

hydrolysis reaction revealed that the ketal signal disappeared very fast to generate the enediyne carbaldehyde which was most likely unstable under the cyclization conditions.

A final attempt was made with o-bromoacetaldehyde ethylene acetal (199, Nucleophile V) as outlined in Figure 60. Unfortunately the addition compound (204) displayed a similar behavior in the cyclization step leading to its complete destruction under a variety of acidic conditions.

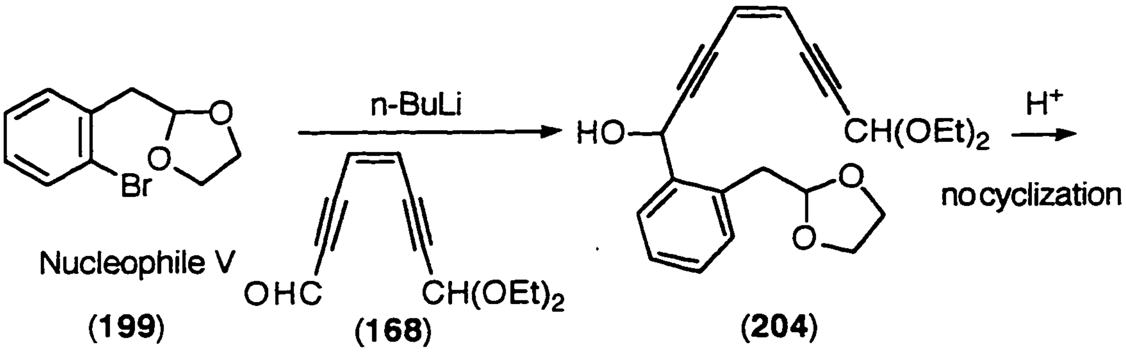


Figure 60

2.3D Conclusions to the Aldol Cyclization Approach

The most important conclusion we have drawn from this study is that heterosubstituents situated in the α,α' propargylic positions will communicate across the enediyne system to a considerable extent. Thus, it seems that oxy substituted enediyne carbaldehydes enjoy very limited stability as proven by the series of compounds (158), (166), while the α'-gembisoxysubstituted systems (acetal function) are easier to handle as chemical intermediates (168).

This limited stability hypothesis is reinforced by our observations regarding the mildly acidic hydrolysis conditions necessary for the deprotection of α'-oxy-α-ketals (200/201), (202/203) and (204) which resulted in unstable enediyne carbaldehydes and failure of the aldol cyclization.

Secondly, the successful synthesis and characterization of the conformationally locked teracobaltocomplexes (187) and (188) allowed us to obtain valuable information suggesting that highly strained 9 and even 8 membered ring enediynes could be available through this approach. While our attempt to synthesize the first 8 membered ring enediyne was unsuccessful, recent reports coming from other laboratories fully confirmed our early hypothesis in the case of the 9 membered ring enediynes[48].

Finally, a new interesting anti-Brook rearrangement has been found that allows regiospecific migration of the silicon from a trimethylsilyl acetophenone enol ether to the *ortho* position of the aromatic ring. The enolate generated in the process allows tandem aldol type reaction to be carried out at the carbon α to the carbonyl. Interestingly enough, these ketones were found to be efficiently protected by the neighboring trimethylsilyl group towards a wide range of reductive conditions. The rich chemistry related to the silyl substituted aromatic systems should allow further development of numerous synthetic applications of this reaction.

2.4 Enediyne Synthesis *via* Acetylide-Electrophile Cyclization

> *"Happily many other groups were now practicing this chemistry* [acetylide-electrophile closures] *in the enediyne field. In fact, with the notable exception of Schreiber approach to dynemicin .... every route was utilizing, in one form or another, an acetylide electrophile bond connection for fashioning the cyclic enediyne."*
>
> *Samuel Danishefsky*
> *J. Org. Chem., Vol. 61, 33, 1996*

2.4A Retrosynthesis

The acetylide-electrophile approach to the synthesis of enediyne systems was introduced by Danishefsky in his early work related to the synthesis of calicheamicinone[49]. It has been used since then as the "work horse" of the synthetic methodology leading to a wide range of enediynes that led to a better understanding of their mechanism of action. Consequently, this approach has become probably the soundest route to the generation of these systems.

We have already touched in the introductory chapter theoretical aspects related to this subject, and showed why competitive reactions in the cyclization step are likely to decrease the yield. From a practical perspective, we envisaged that a monocyclic bisoxysubstituted enediyne of generic type (205) (Figure 61), could be obtained through an acetylide-electrophile cyclization of an intermediate (206), which in turn might arise through a second similar disconnection from a dialdehyde synthetic equivalent (207) and the required enediyne (208).

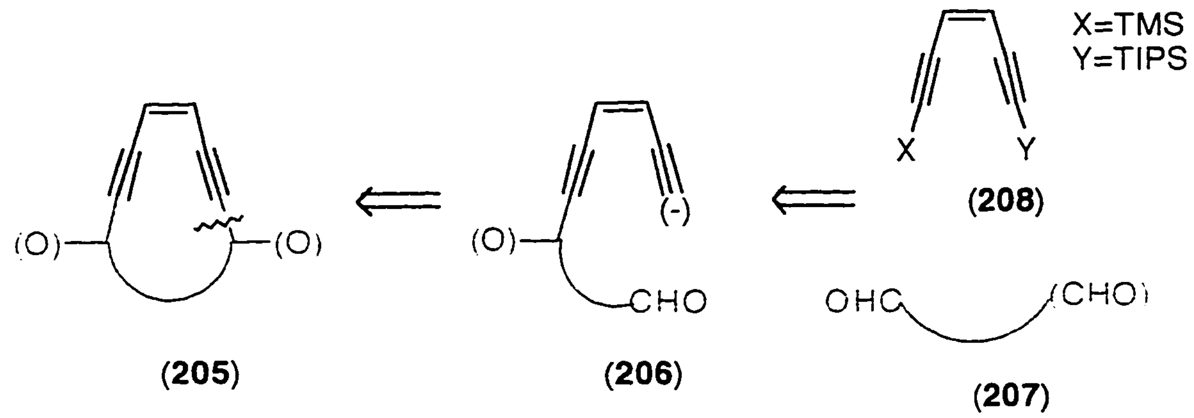


Figure 61

This approach also takes advantage of the versatile substituted enediyne building block (208) (X=TIPS and Y=TMS) which had been developed in our laboratory in connection to the Taxamycin-12 project[35c].

Based on these considerations we decided to investigate the possibility of accessing bisoxysubstituted enediynes (205) following the synthetic route highlighted in Figure 61.

2.4B Synthesis of the 12 and 11 Membered Ring Cyclization Precursors

Ozonolysis of cyclohexene (209) following Schreiber's procedure[50] provided a convenient route to the adipic dialdehyde synthon (211) as shown in Figure 62.

On the other hand, Pd(0)-based coupling of *cis*-dichloroethylene with the required silyl substituted acetylene derivatives (212) and (214) afforded the unsymmetrical TIPS-TMS substituted enediyne (215). The trimethylsilyl group could be removed selectively under mild basic conditions[51] to generate intermediate (216).

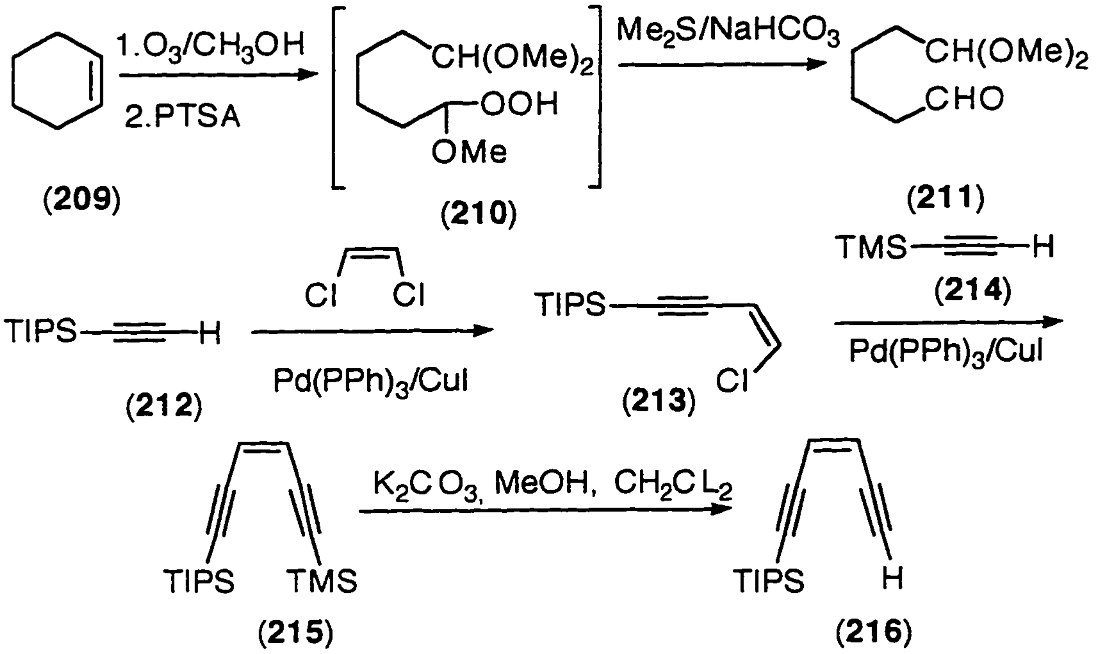


Figure 62

The corresponding lithium acetylide afforded the alcohol (217) in low yield (10%), while metal exchange with cerium trichloride did not spectacularly improve the overall outcome of the reaction (48%). Protection of the alcohol as its methyl ether (218) followed by unmasking of the aldehyde group afforded the cyclization precursor (219).

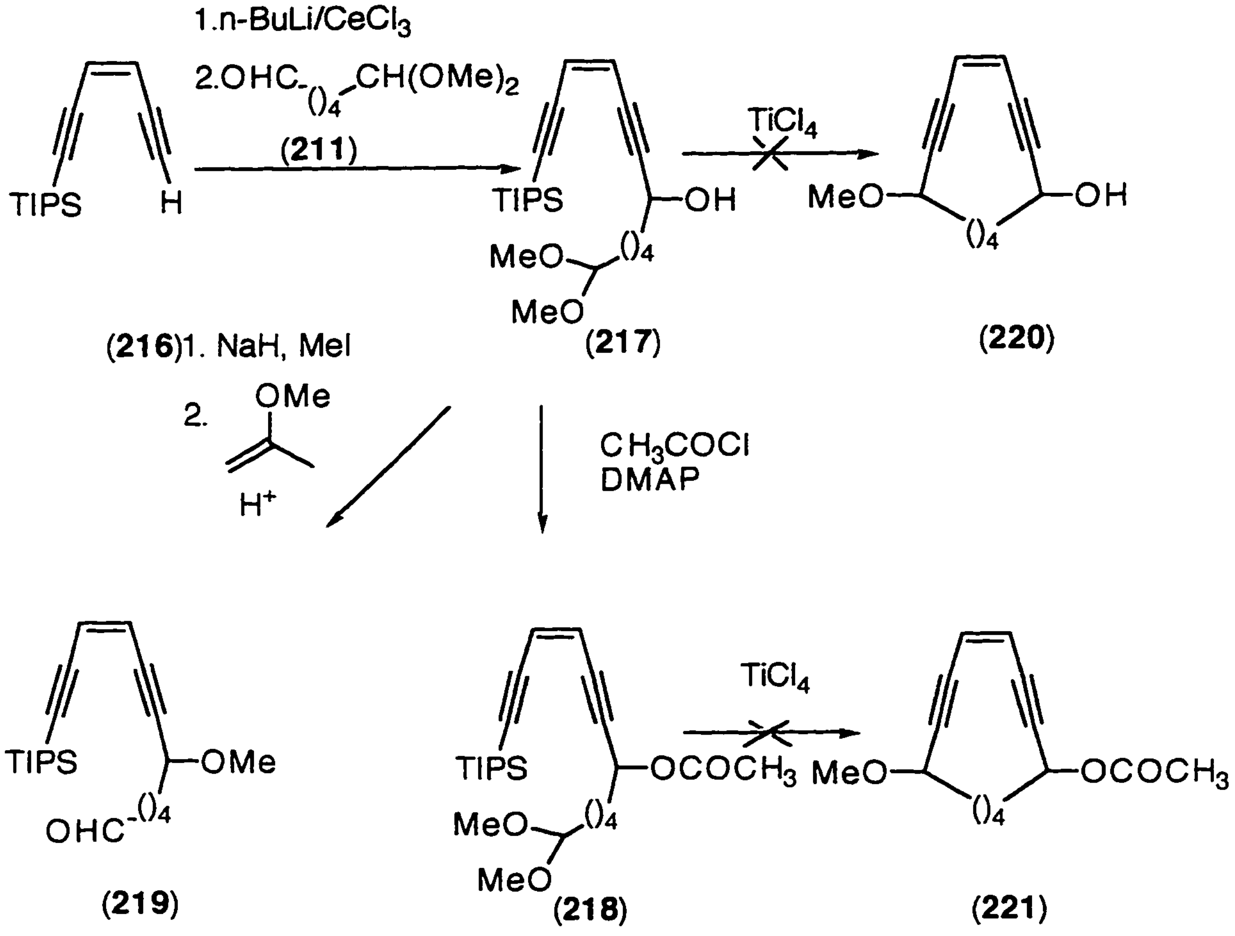
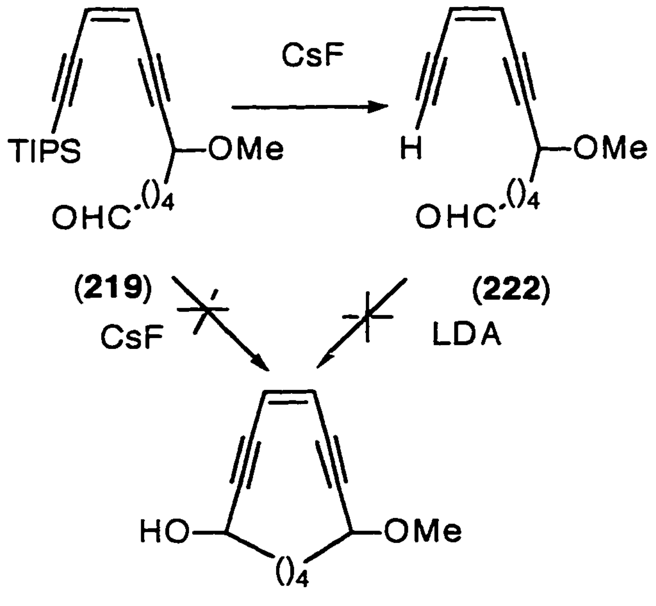


Figure 63

The attempted cesium fluoride mediated tandem desilation-condensation reaction[26] yielded instead of the expected cyclized product (220) only deprotected enediyne (222) (Figure 64). Treatment of this compound with various metal amides did not lead to a successful acetylide-electrophile ring closure to compound (220) as shown in Figure 64. Alternatively, ketal based ring closure of intermediates (217) and (218) under Lewis acid conditions resulted in the loss of starting material only.



(220)

Figure 64

As stated before, the addition of the acetylide anion derived from the enediyne (216) to the ketal-aldehyde (211) occurred in low yield under a variety of conditions. A quenching experiment with deuterated methanol revealed an increase of the M^+ ion in the mass spectrum of enediyne (216) by one atomic mass unit. Intrigued by this result we initially addressed the question whether the poor yield is related to the particular aldehyde substrate (211) or is it an intrinsic problem of the enediyne acetylide nucleophile (216)? Consequently we replaced first the initial aldehyde with a new electrophilic partner (224) to check if the abnormal behavior is substrate related. The adopted synthetic route is outlined in Figure 65.

Oxacyclohex-2-ene (209) was reacted under acid catalysis with excess ethylene glycol (10 equivalents) in DMF to provide monoprotected glycol (223) as the major product along with some diprotected derivative. Pahrikh-Doering oxidation[52] of the alcohol (223) led to the corresponding aldehyde (224) which reacted with the acetylide derived from enediyne (216) to yield the desired addition product (225) in only 41% yield. The reaction yield was thus comparable with the one obtained in the previous case (217) thus pointing to a reduced nucleophilicity of the enediyne acetylides.

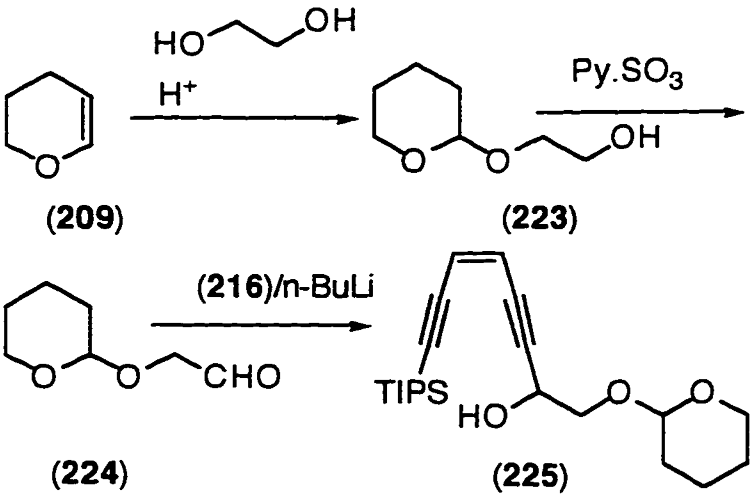
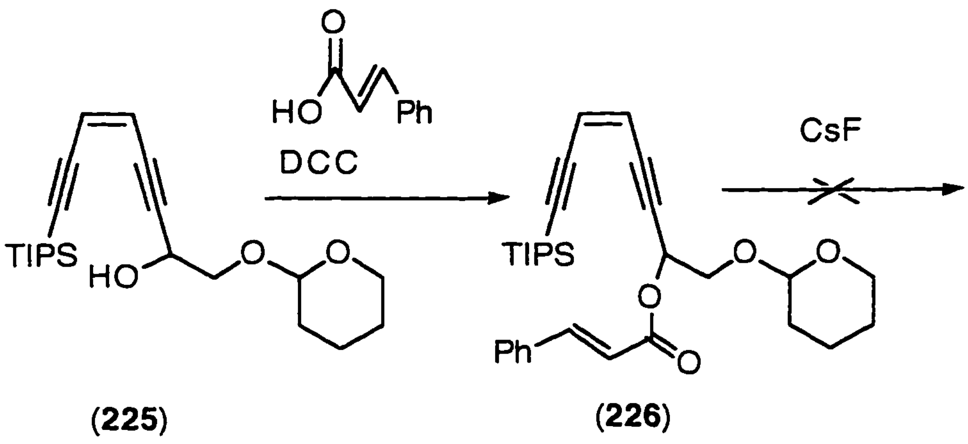
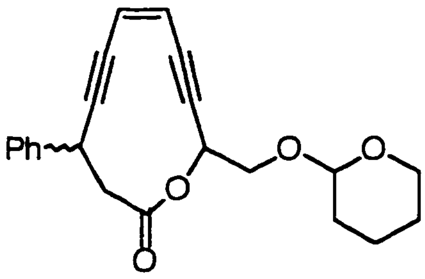


Figure 65

Inspection of the literature revealed other related examples where one had to use acetylide anions in up to ten equivalents excess[53] which was obviously unacceptable in our case since the enediyne moiety was the most valuable reagent. We decided therefore that this problem has a broader synthetic significance and undertook a study in this respect. The results of our work in this field are presented in section 2.4E at the end of this chapter.

The addition product (225) was conceived as a turning point for two cyclization scenarios highlighted below. After initial protection of the alcohol as its cinnamate an attempt to perform a CsF induced intramolecular Michael addition to 11 membered enediyne (227) led to the loss of the starting material (Figure 66).





(227)

Figure 66

Alternatively, the ester (226) was selectively deprotected under mild acid conditions to the primary alcohol (228). It was envisaged that oxidation to the key intermediate (228) followed by a

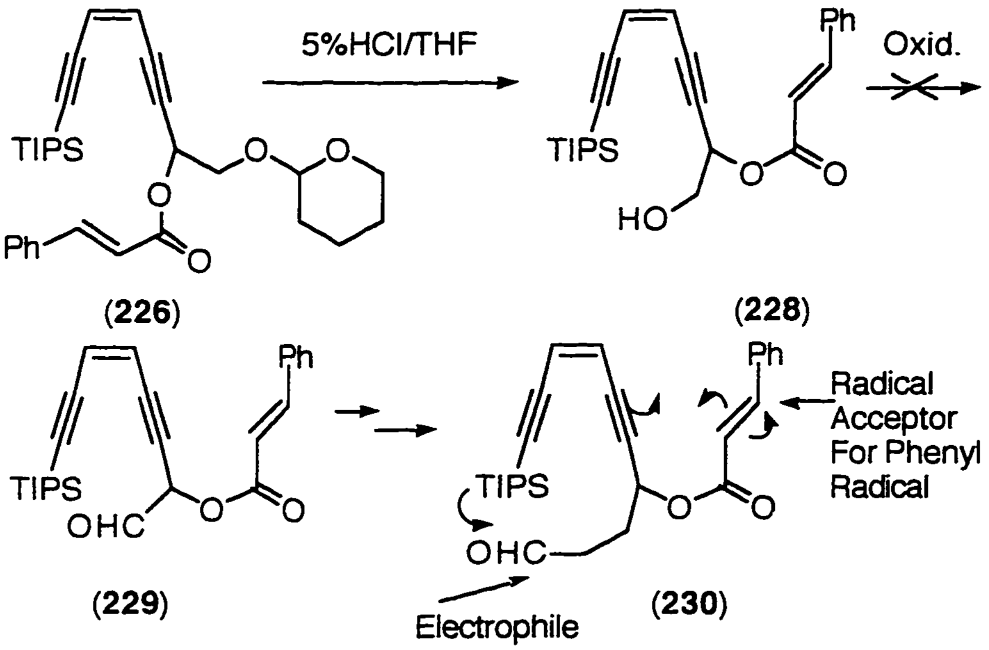


Figure 7

classic two carbon homologation[54] should lead to the cyclization precursor (230). This intermediate has the added bonus of having an intramolecular radical acceptor already in place. Unfortunately, we could not isolate any aldehyde (229) under Swern oxidation conditions and therefore the project was abandoned at this point.

2.4C Synthesis of the 10 Membered Ring Cyclization Precursor

The synthesis of 11 and 12 membered ring monocyclic enediyne in the acetylide-electrophile approach failed in spite a variety of versatile cyclization precursors that have been accessed successfully. We have decided therefor to direct our attention to the synthesis of a 10 membered ring enediyne through a new reaction route whereby the TIPS protecting group was replaced by the less bulky, more reactive TMS group (Figure 68).

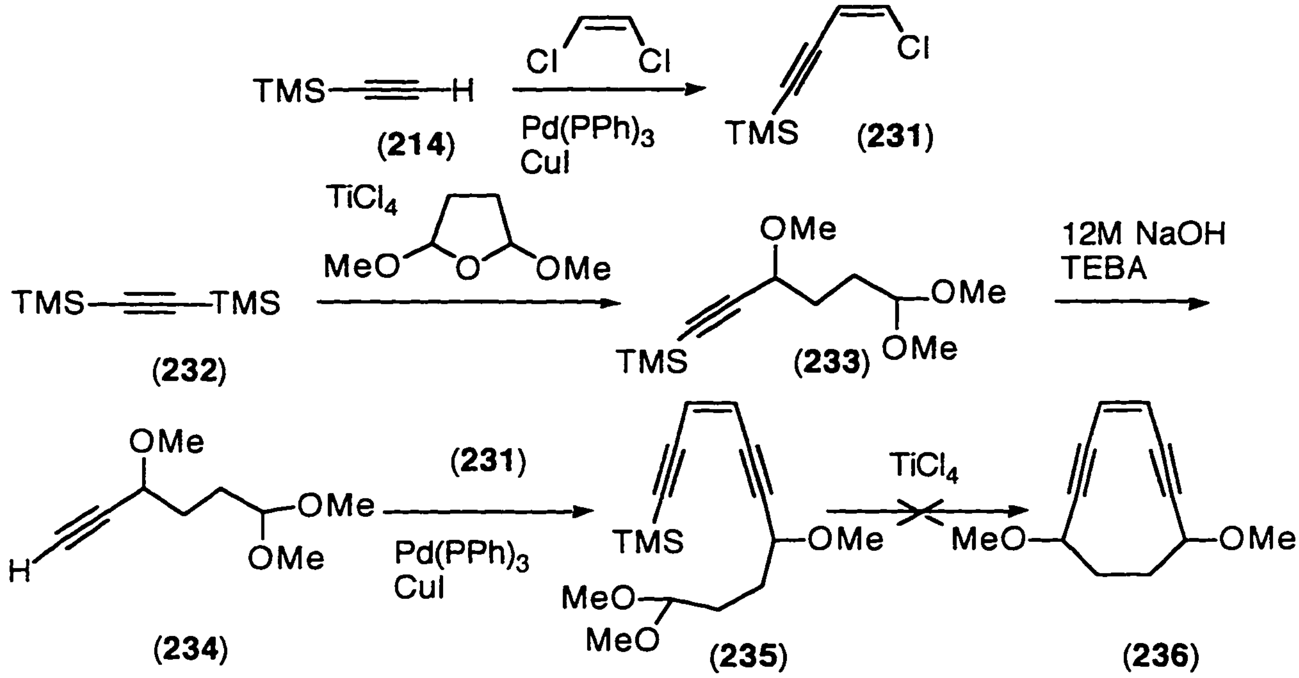


Figure 68

Thus trimethylsilylacetylene (214) was coupled under palladium (0) catalysis with *cis*-dichloroethylene to yield intermediate (231) which in turn could be further developed under the same conditions to the key compound (235). The coupling partner (234) for the second palladium catalyzed step was obtained from bistrimethylsilylacetylene (232) through an efficient sequence of reactions which will be discussed in more depth in Section 2.6E. An attempt to effect the intramolecular Lewis acid[58f] mediated cyclization of ketal (235) to the monocyclic enediyne (236) failed.

Deprotection of the ketal (235) yielded the cyclization precursor (237) which was treated with CsF in the presence of acetic anhydride[26,27]. Again the cyclization to (238) failed to occur returning instead only the deprotected product (239). Treatment of this compound with various bases did not result in the isolation of the corresponding cyclized alcohol (241). An attempt to obtain the iodoacetylene precursor (240) for the Nozaki-Kishi cyclization also failed (Figure 69).

Reasoning that the presence of the aldehyde group might interfere in the synthesis of the iodoacetylene we have reconsidered the order of the reaction sequence as shown in Figure 70. Thus the ketal-enediyne (235) was first desilylated to compound (242) which in turn provided the iodoketal (243). Unmasking of the aldehyde

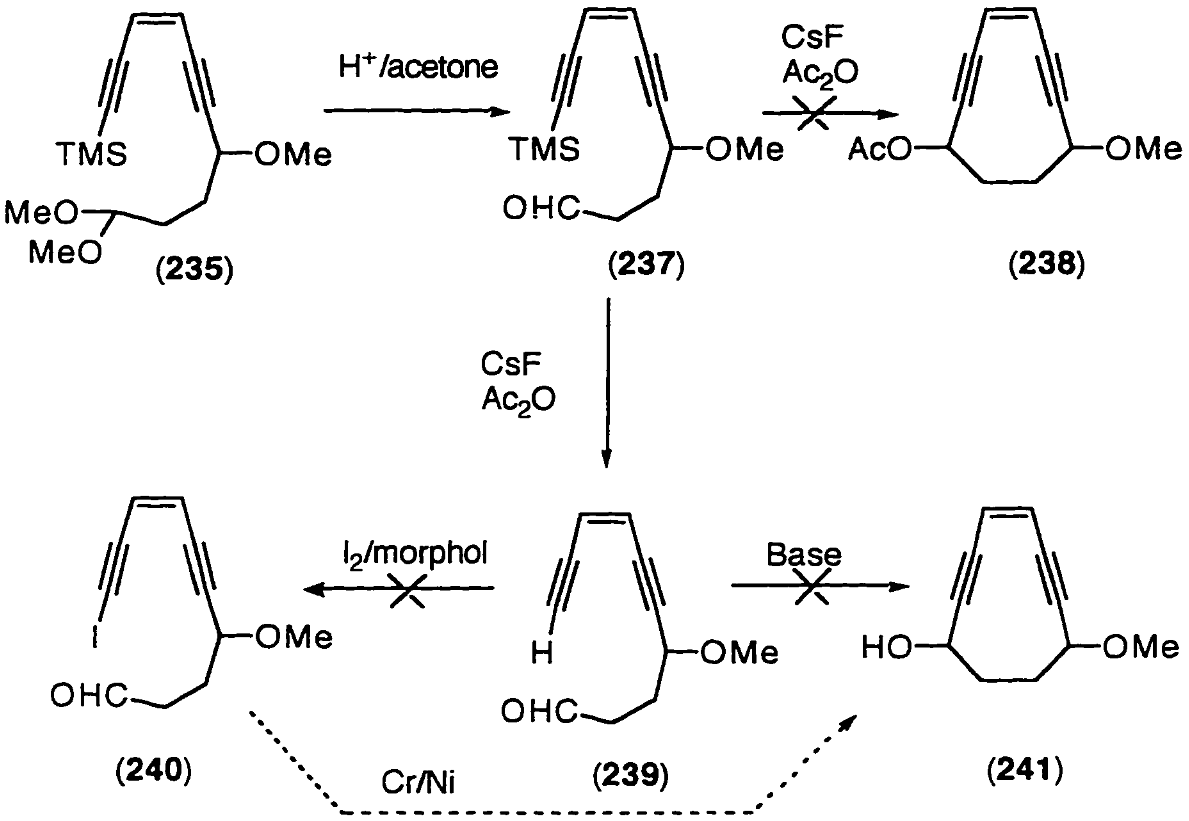


Figure 69

however failed to provide the cyclization precursor (240) thus preventing us to try the ring closure under Nozaki-Kishi cyclization conditions.

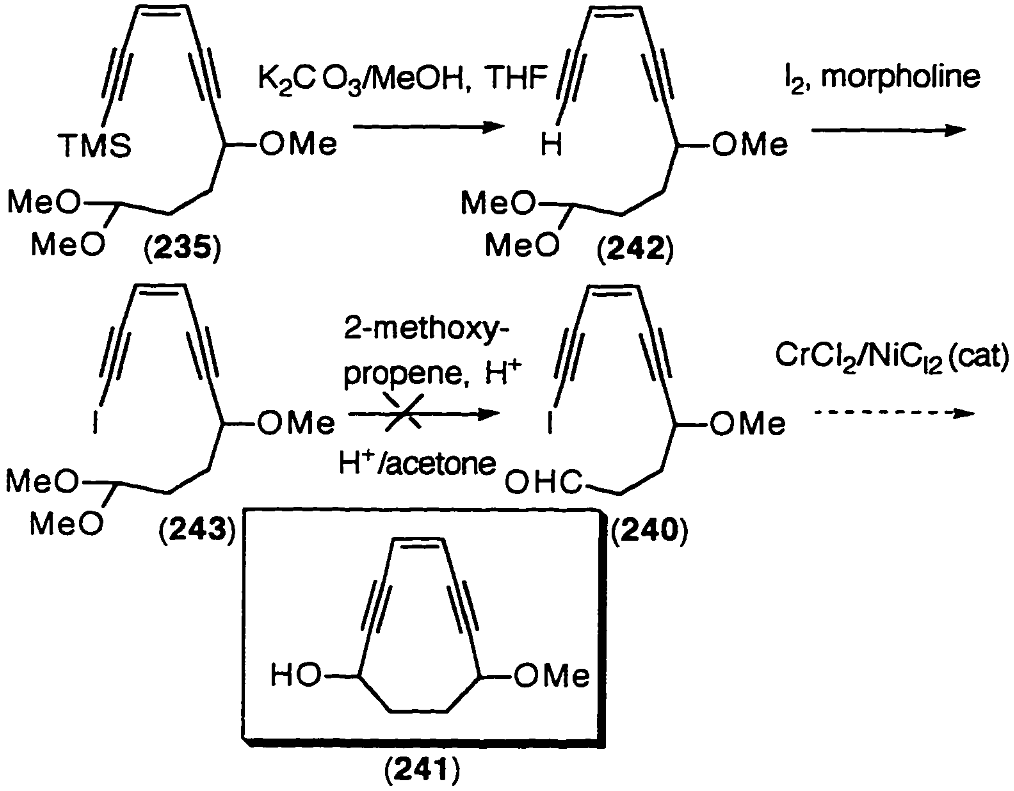


Figure 10

2.4D New Synthetic Methodology for Oxy Substituted Acetylenes in the Propargylic Position

The addition of acetylides to aldehydes is one of the most significant approach to the generation of propargylic alcohols, a class of compounds with numerous applications in organic chemistry^{55a}. The basic nature of these reagents and the requirement of strong bases such as alkylmetals and metal amides for their generation can often induce undesirable side reactions. In order to overcome these problems a continuous search for improved synthetic methods resulted in the development of new B^{55b}, Al^{55c}, Ce^{53}, V^{55d}, Mn^{55e} and Sn^{53f} acetylides that add successfully to carbonyl compounds.

In the context of the synthesis of new enediyne compounds (*Vide supra*) we found that acetylide anions derived from 1,5-hexadiyn-3-ene did not add in satisfactory yields to enolizable aldehydes according to any of the previously reported literature procedures. The best results were obtained by generating the cerium acetylide which provided the addition products in moderate yields.

Besides the basicity of the nucleophile we felt that the required use of an excess acetylide in all these procedures is unacceptable in this case due to the high synthetic value of the enediyne moiety.

We have investigated therefore the possibility of achieving this transformation by reacting acetylides of highly oxophilic metal counterion (Zn and Al in particular) with various acetals. Based on a series of analogies and literature precedents[53, 56] we hoped that the aluminum will coordinate one of the acetal oxygens (Figure 71) to yield an *ate* complex (246) which in turn will be attacked by the oxygen stabilized carbonium anion (247) to deliver the oxy substituted derivative in the propargylic position (250). Alternatively, direct activation of the ketal through Lewis acid complexation followed by nucleophilic displacement is conceivable.

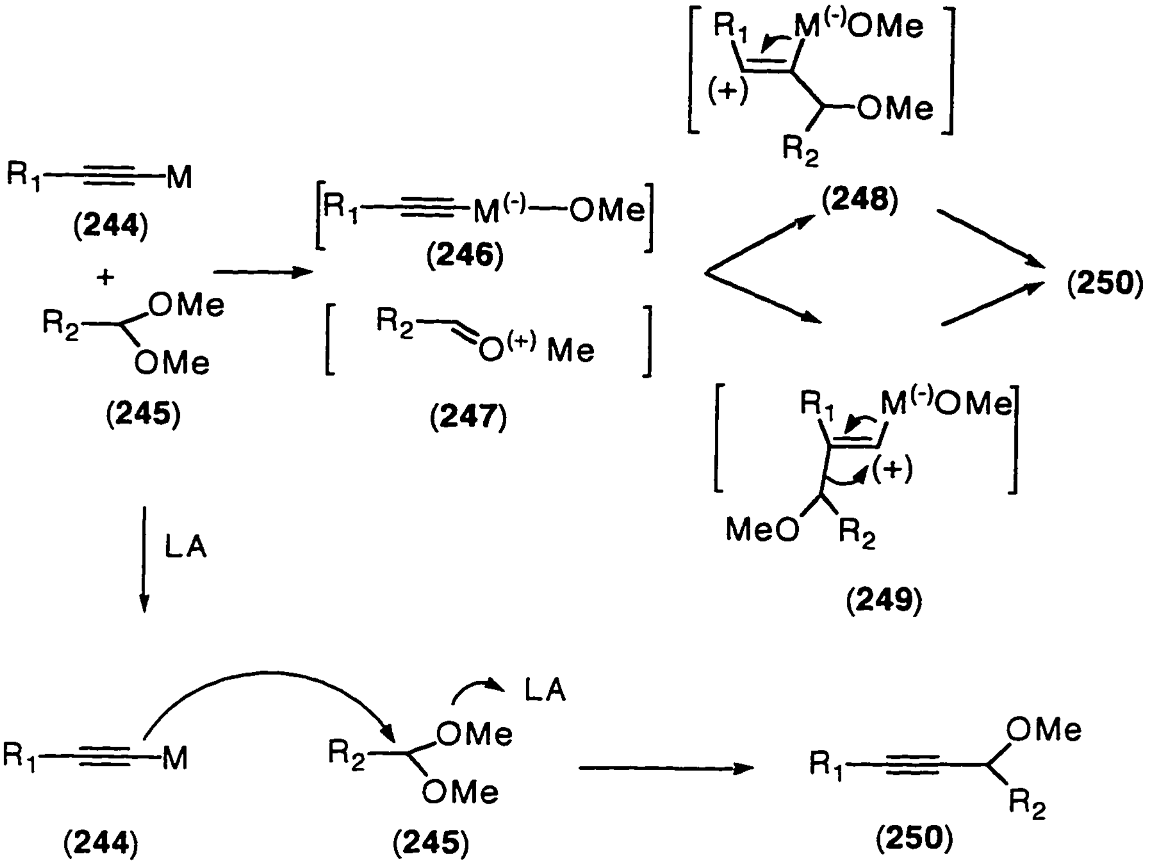


Figure 71

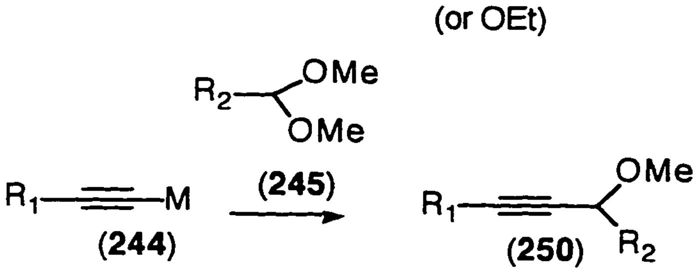
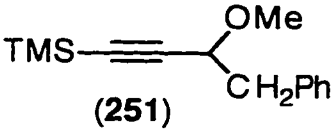
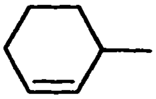
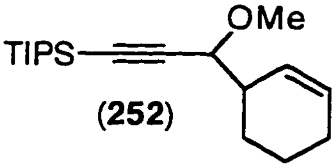
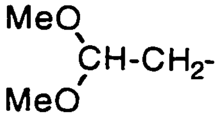
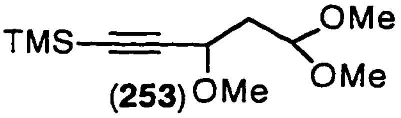
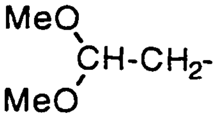
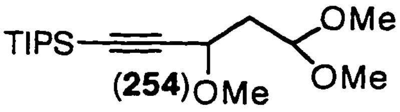
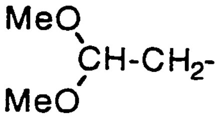
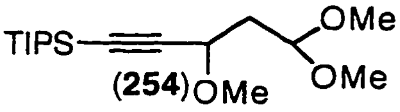
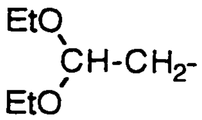
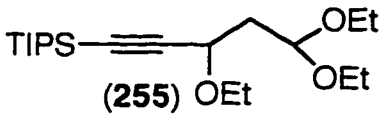
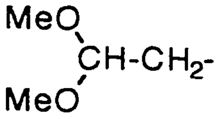
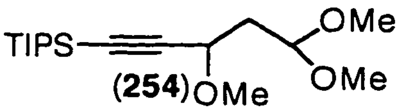


Table 1

R1	R2	Reaction Conditions	Product	Yield %
TMS	PhCH2	A	 (251)	81
TIPS		A	 (252)	53
TMS	 $\mathrm{(MeO)_2CH\text{-}CH_2\text{-}}$	A	 (253)	23
TIPS	 $\mathrm{(MeO)_2CH\text{-}CH_2\text{-}}$	A	 (254)	18
TIPS	 $\mathrm{(MeO)_2CH\text{-}CH_2\text{-}}$	B	 (254)	37
TIPS	 $\mathrm{(EtO)_2CH\text{-}CH_2\text{-}}$	B	 (255)	27
TIPS	 $\mathrm{(MeO)_2CH\text{-}CH_2\text{-}}$	C	 (254)	33

Since our needs required a silyl substituted enediyne system we explored the behavior of TMS and TIPS acetylides in reaction with acetals derived from extremely enolizable aldehydes as shown in the Table 1.

In the event we have found that silyl substituted acetylides undergo a clean reaction with a variety of ketals in low to satisfactory yields. It is noteworthy that these acetylides are poor nucleophiles[53e] and the reported direct reaction of lithium and magnesium acetylides yielded the addition product in poor yield[53b]. Moreover, all of the previously known methods used an excess acetylide varying anywhere between 2 to 15 equivalents [53b, 53c] while method A and B uses one equivalent only. Finally the reaction provides direct access to the protected alcohol ensuring a more convergent approach to the synthetic target.

In method A one equivalent of silyl substituted acetylene is treated in ether with one equivalent of n-butyllithium at 0°C and then one equivalent of $ZnCl_2$ ether solution is added to generate the corresponding zinc acetylide. Simple addition of the acetal does not yield any reaction. However borontrifluoride activation of the acetal results in the formation of the oxy substituted coupling compound.

Malondialdehyde tetramethyl acetal was found as a particularly sensitive substrate to the reaction conditions and was chosen therefore as an worst case event in the subsequent experiments.

In method B one equivalent of silyl substituted acetylene is treated in hexanes with one equivalent of n-buytl lithium at 0°C and then one equivalent of $AlCl_3$ is added. After 30 minutes the solvent is stripped off under a stream of nitrogen and replaced by mehtylene chloride. Finally the tetraacetal is added and the reaction is monitored by TLC to completion.

Method C is identical with method B with the exception that 2 equivalents of acetylene are used for one equivalent of $AlCl_3$.

Although we did not undertake any mechanistic investigations we feel that the two reactions are fundamentally different. Most likely methods B and C, based on the use of aluminum metal, follows the anticipated reaction pathway presented in Figure 71. In the $ZnCl_2/BF_3$ reaction probably the zinc acetylide reacts with the intermediate carbocation generated upon addition of boron trifluoride etherate to the acetal solution.

2.4E Conclusions to the Acetylide-Electrophile Approach

We have successfully achieved the synthesis of five cyclization precursors for 12 (219, 222), 11 membered (226) and 10 memebered ring enediynes (237, 239). The acetylide-electrophile approach did not provide a satisfactory solution to the synthesis of the target bisoxysubstituted enediynes. Alternatively, cyclization reactions of ketals 217, 218 and 235, based on the silicon directed electrophilic substitution, also failed.

In the event, it was found that silicon substituted acetylides can react directly with acetals to yield the corresponding protected propargylic alcohols.

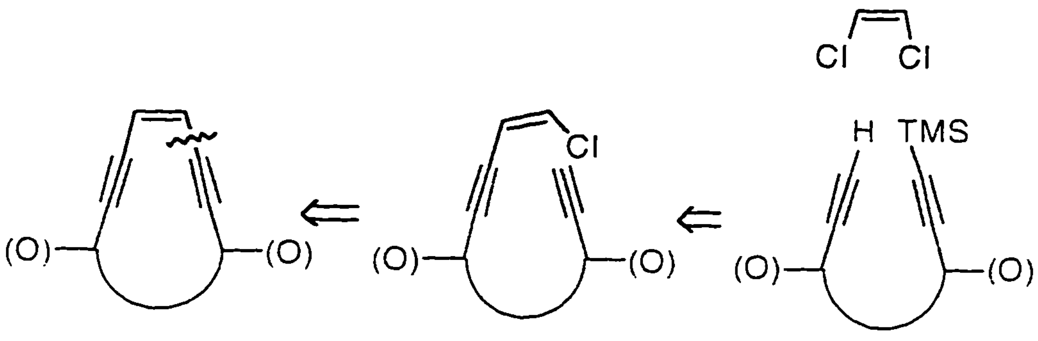
2.5 Enediyne Synthesis *via* Intramolecular Palladium (0) Coupling

2.5A Retrosynthesis

One of the most fascinating and rapidly developing domains of modern chemistry is undoubtedly organometallic chemistry. A corpus of interdisciplinary knowledge combining classical organic and inorganic chemistry as well as new inspiring insights gained from the mode of action of various living systems has resulted in this exciting new field.

Within organometallic chemistry, lower valence palladium complexes have already acquired the status of unquestionable stardom due to the very mild conditions required for a variety of unique reactions. Stephens-Castro reaction[42] or Stille type coupling[57a,b] have already become part of basic tools used by organic chemists around the world in a wide variety of applications.

We were therefore surprised that the obviously interesting disconnection showed in Figure 73 had not been given careful consideration at the time when we addressed this problem.



(258) **(259)** **(260)**

Figure 73

Thus, the generic monocyclic enediyne (258) could in principle be accessed by using an intramolecular palladium (0) catalyzed coupling on structure (259) which in turn could stem from *cis*-dichloroethylene and diyne (260).

Before commencing, there were several aspects that had to be carefully addressed in order to assess the chances of success in the crucial cyclization step. Palladium catalyzed annulations have been widely reported in the literature, but we felt that this particular case is different in the sense that the intramolecular coupling has to provide a direct pathway from the unstrained and extremely flexible structure (259) to the strained cyclic enediyne (258). This might be a tremendous challenge on thermodynamic grounds.

The general mechanism of the palladium catalyzed coupling[57] is given in Figure 74. The low valent palladium will insert oxidatively into vinyl carbon-halogen bond to generate intermediate (262) which in turn has to generate metallacycle (263). This subsequently collapses via a reductive elimination pathway to the envisaged target (258).

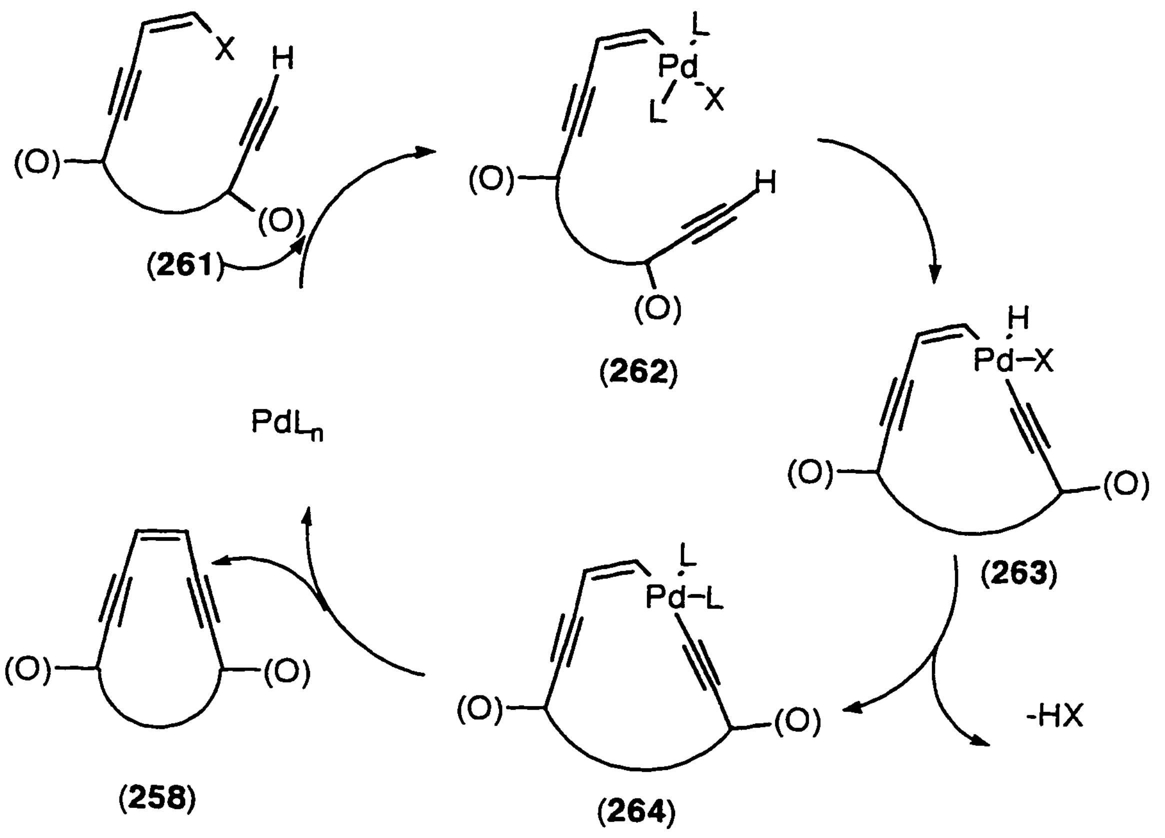


Figure 74

We directed our attention to the pivotal metallacycle (263). The literature survey has yielded no reliable data on the nature of this type of intermediate which as yet has not been either isolated or characterized to the best of our knowledge. However admitting that the metallacycle (263) is involved in this reaction pathway, it should contain the ligands around the palladium atom in a square planar orientation and either fluxionality or ligand dissociation might allow either the *cis* configuration shown in Figure 74 or the *trans* orientation of the ligands. Molecular models show that the *cis* orientation will actually lower the tension of the metallacycle and it is likely to be preferred as a reasonable intermediate on the reaction pathway. It was our belief that if this intermediate could be reached the subsequent mechanistic events which are practically irreversible should lead to the molecular target.

These theoretical considerations looked more promising when we identified one isolated precedent in the literature[37] which was prevously presented in the introductory part of this thesis.

2.5B Synthesis of Cyclization Precursors for the 12 and 11 Membered Ring Enediynes

In order to access the required cyclization precursors we conceived an efficient route that possessed the added benefit of

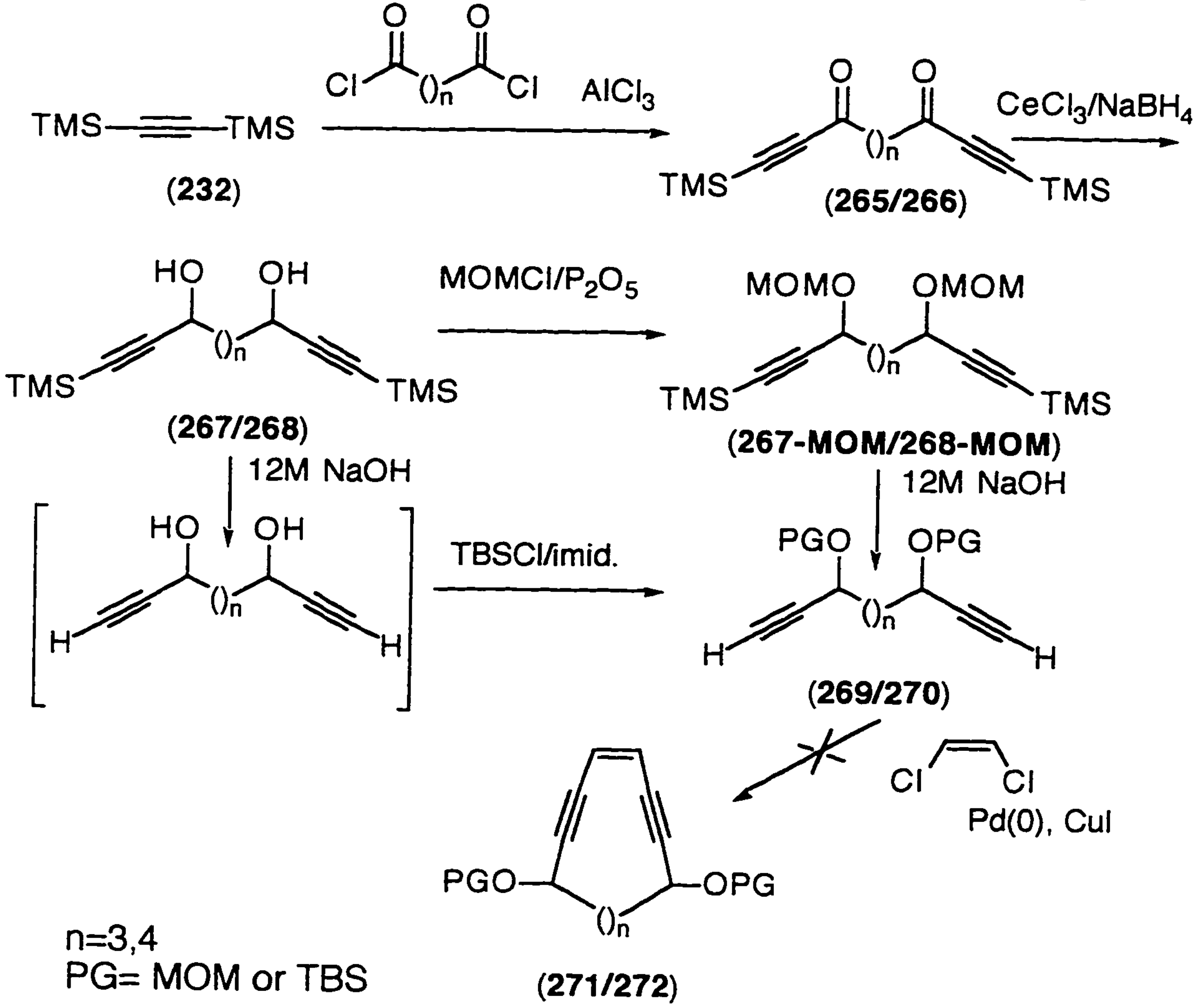


Figure 75

allowing us to test both the palladium cyclization approach and the samarium diiodide coupling, which will be discussed in the next chapter.

Bistrimethylsilylacetylene (232) was acylated with adipoyl dichloride or glutaryl dichloride under Lewis acid conditions[58] to generate the diynones (265/266) in high yield (Figure 75). Luche reduction[58] followed by deprotection of the terminal acetylene under phase transfer catalysis[59] led rapidly to intermediates (267/268). Protection of the diol occurred smoothly providing the corresponding MOM and TBS protected diynes (269/270). It was hoped that the use of protecting groups of different polarities would increase the chances of attaining a favorable conformation for the cyclization event. At this point we were already in the position to try a Sonogashira type cyclization[60] with *cis*-dichloroethylene (using the injection pump technique in order to encourage the intramolecular reaction) however only polymerization products could be observed in the crude NMR in all cases.

Finally, we pursued the idea of an intramolecular cyclization which should be entropically favored in comparison with the intermolecular case. Treatment of the diynes (269/270) with one

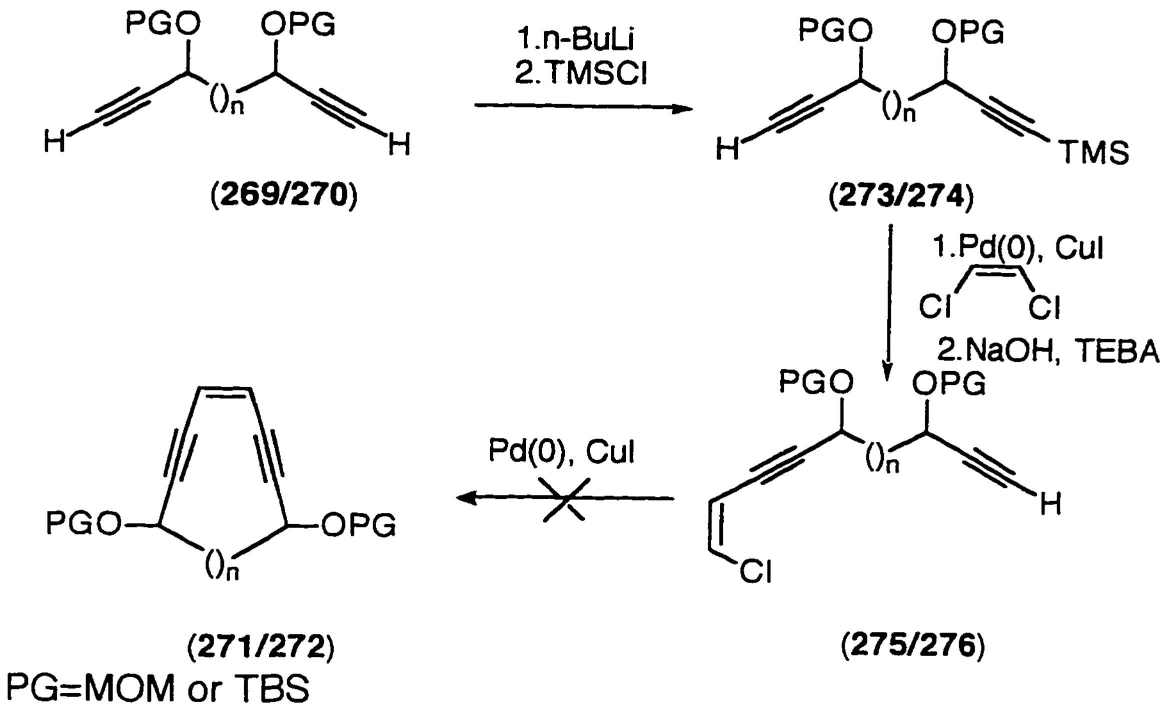


Figure 76

equivqlent of n-butyllithium, allowing equilibration and quenching with TMSCl led to a mixture of bistrimethylsilyl intermediates and the desired monoprotected diynes (273/274) as the major product. Stephens-Castro coupling with *cis*-dichloroethylene followed by selective deprotection of the TMS group resulted in the desired cyclization precursors (275/276) (Figure 76).

Unfortunately none of the intramolecular cyclization attempts led to the desired product. Only polymerized material, resulted from the competitive intermolecular pathway was isolated even when we used high dilution technique combined with injection pump addition of the precursors. The mass balance of the reactions was very good (more than 90%) and the proton NMR of the crude revealed clean coupling and no unexpected impurities, thus we concluded that the intramolecular palladium coupling approach failed because of unreasonably strained metallacyclic intermediates (263) as discussed in the beginning of this chapter. Obviously, according to our initial assumptions, the ten membered ring synthesis would have to go through an even higher energy species and therefor we have not further pursued this hypothesis experimentally.

Similar attempts briefly reported by Nicolau's[28d] and Beau's[35a] groups were unsuccessful. It is worth mentioning here that one year after we have carried out this work Danishefsky reported his successful approach to Dynemicin A which was based on a similar coupling philosophy. In his case, the Sonogashira type coupling also failed (as shown in the introductory chapter) however the Stille type coupling worked marvelously affording the cyclized product in nearly 80% yield[36] starting from a rigid polycyclic structure that brings the reactive sites within optimum distance.

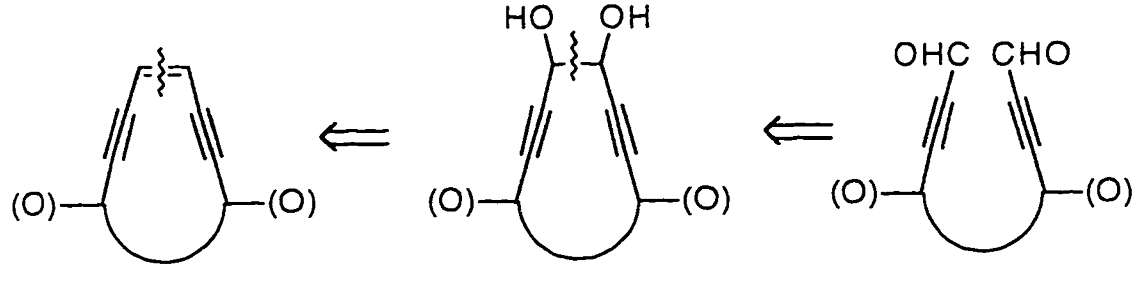
2.6 Enediyne Synthesis *via* Intramolecular Samarium Diiodide Pinacol Coupling

2.6A Retrosynthesis

The reductive coupling of carbonyl compounds to give pinacols is an important group of carbon-carbon bond forming reactions, that proceeds with a variety of one or two electron reducing agents. Metals reported to effect this transformation[61] include Mg (0)[62] and low valent Ti[63], Nb[64] Sn[65], Sm[66], V[67], Zn[68] and Zr[69]. Intramolecular pinacol coupling reactions succeeded in performing difficult ring annulations such as the generation of the 8 membered B ring in Nicolau's total synthesis of Taxol[70]. This is explained mechanistically by the propensity of the reducing metal to chelate intramoleculary the two carbonyl partners and bring them within reaction distance[71]. Thus both the entropy and enthalpy of activation to achieve the required transition state is reduced.

On the other hand vicinal diols are classical synthons for carbon carbon double bond and there is a solid body of literature that describes this chemical transformation[72].

Keeping in mind the difficulties encountered by us in generating the monocyclic enediyne systems through other reaction pathways which had the central double bond already in place we reasoned that the pinacol approach highlighted in Figure 77 might provide a stepwise route to the highly strained target system. The diol intermediate (278) should allow more flexibility serving therefore as a stepping stone en route to the required enediyne.



(277) **(278)** **(279)**

Figure 77

The literature survey did not provide relevant information for the pinacol coupling of α,β-unsaturated acetylenic aldehydes or ketones with one notable exception already presented in the introductory chapter[38b]. In that case the required dialdehyde lacked the oxy substituents in the propargylic positions, which were essential for our program. Nevertheless, it established an encouraging precedent that determined us to proceed experimentally.

2.6B.Model Compounds Synthesis

We reasoned that diol (282) could serve as a model intermediate that could provide valuable information about the viability of the pinacol coupling itself as well as the subsequent double bond generation (Figure 78).

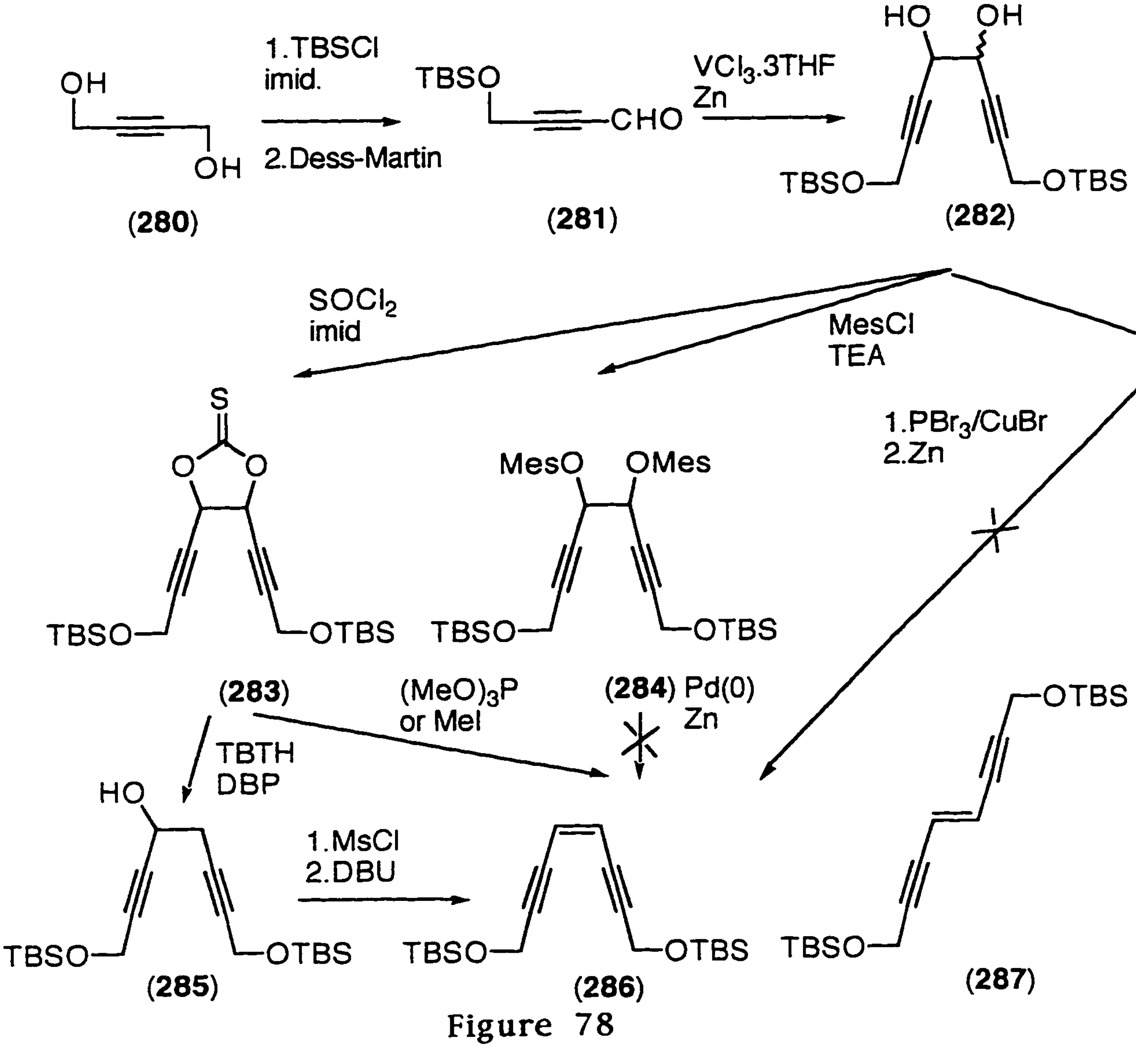


Figure 78

Commercially available 1,4-propynediol (280) was monoprotected with TBSCl and oxidized to the corresponding aldehyde (281). In a series of experiments presented in Table 2 the only pinacol coupling procedure that has been found to work on these acetylenic systems was indeed the one reported by Myers[38b] using the recently developed Pederson reagent[67]. Other attempts to generate the central double bond of the enediynes (286/287) directly[63e] from the aldehyde also failed.

Pinacol or McMurray Coupling	Isolated Product	*cis/trans*
$VCl_3.3THF$/Zn (Pederson reag.)[67]	74%	2/1
SmI_2[66]	-no product	
$TiCl_3$[63g]	-returned starting material	
$TiCl_4$/Zn[63i]	-no product	
$TiCl_4$/Mg(Hg)[63c]	-no product	
$CpTiCl_3/LiAlH_4$[63c]	-no product	
$TiCl_3/LiAlH_4$[63d,e]	-no product	
$TiCl_3$/Zn-Cu[63f]	-no product	

Table 2

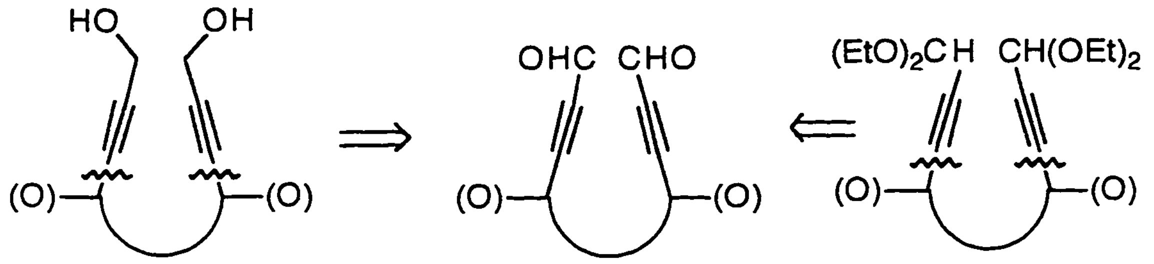
Direct transformation of the diol (282) to enediyne (286/287) using PBr_3-CuBr/Zn[72l] failed while palladium catalyzed elimination on the vicinal mesylate (284)[72h] returned starting material only.

The diastereomeric diols (282) were further transformed into the corresponding 2:1 mixture of *cis* and *trans* thionocarbonates (283) isolable by HPLC. Corey-Winter elimination[72c,d] finally yielded stereospecifically the corresponding 2:1 mixture of *Z* (286) and *E* (287) enediynes.

The diastereoselectivity of the pinacol coupling was of concern since formation of the *trans* thionocarbonate could be counterproductive for the generation of the *cis* double bond required by the envisaged cyclic system. It was important therefore before proceeding any further to find other elimination conditions that would not depend on the stereochemical outcome of the pinacol coupling. Thus, in an alternative approach the thionocarbonate led to the required enediyne upon treatment with MeI following a procedure originally developed by Vedejs[72n]. The mechanism of this reaction implies the discrete formation of a vicinal iodo substituted methylthionocarbonate which should lead to the unmasking of the *cis* double bond regardless of the initial stereorelationship. Alternatively, radical chemistry conditions[72g] can yield the monoalcohol (285) which can ultimately lead to the enediyne system through derivatization and elimination as established by literature related precedent[30].

2.6C.Synthesis of the 12 and 11 membered Ring Enediynes

Encouraged by these preliminary results we started to work on a synthetic pathway to the required cyclization precursors (279) for the intramolecular pinacol coupling approach. Conceivable synthetic equivalents for the generic dialdehyde (279) are shown in Figure 79.



(278) (279) (288)

Figure 79

Aiming initially at the 12 membered ring series we tried to acylate various trimethlsilyl substituted acetylenic compounds with commercially available adipoyl dichloride (Figure 80).

Thus, propargyl alcohol (289) was treated with n-BuLi and TMSCl to yield bis-TMS protected intermediate (290) which was submitted to acylating conditions to result in the diester (291) instead of desired diketone (292). Resubmiting the ester (291) to the reaction conditions revealed that the product (291) is stable in the presence of Lewis acids. Since the mass balance of the acylation reaction was poor we envisaged that the desired product may have been formed preferentially but due to its *lack of stability* could not be isolated. In another approach the propionaldehyde diethyl acetal was deprotonated with n-BuLi to afford the corresponding trimethylsilyl propionaldehyde diethyl acetal. Subsequent treatment

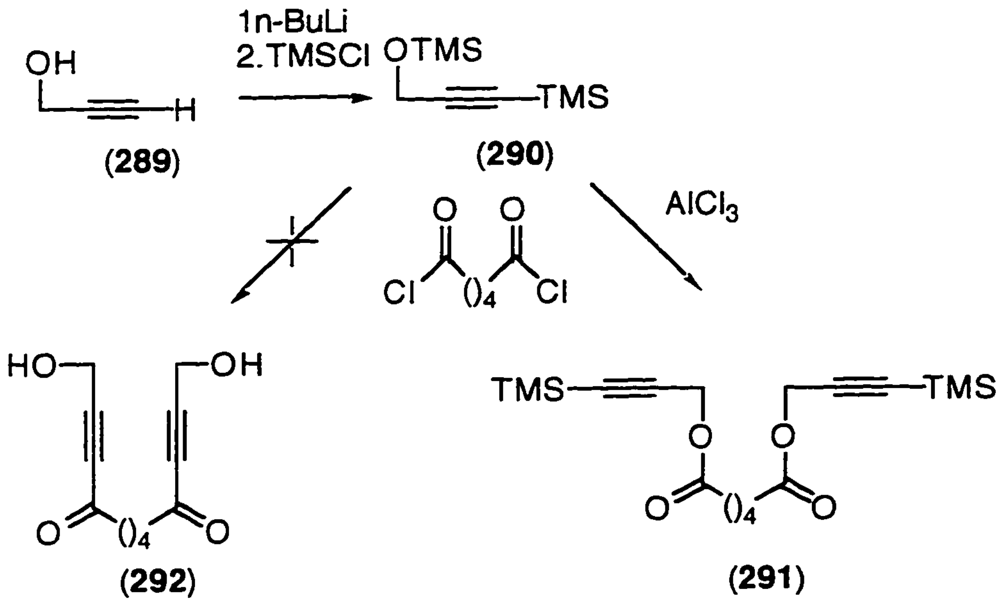
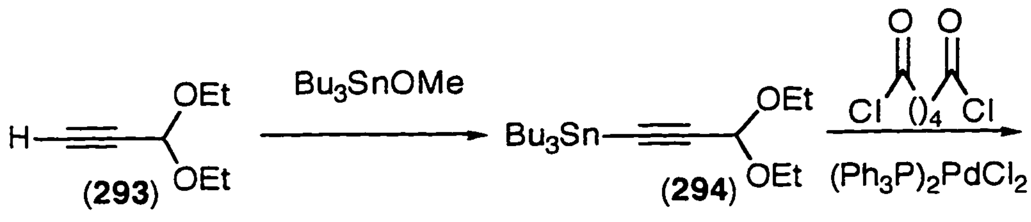


Figure 80

under the same acylating conditions led to the loss of the starting material only.

In order to avoid the harsh reaction conditions implied by the presence of Lewis acids, propargyl aldehyde diethyl acetal (293) was heated with tributyltin methoxide or deprotonated with base and then quenched with tributyltin chloride to obtain tributylstannyl propionaldehyde diethyl acetal (294)[57c]. Its coupling reaction with adipoyl dichloride (Figure 81) in the presence of bistriphenylphosphine palladium dichloride could be followed by NMR since the ketal proton in the starting stannane shifts from 5.21 to 5.38 ppm in the product ketone (295). After one hour no more starting material was present by NMR, so the reaction was worked up and yielded the highly unstable diketone (295) which could not be isolated and characterized. Direct reduction of the crude material under Luche conditions[58] did not provide diol (296) either.



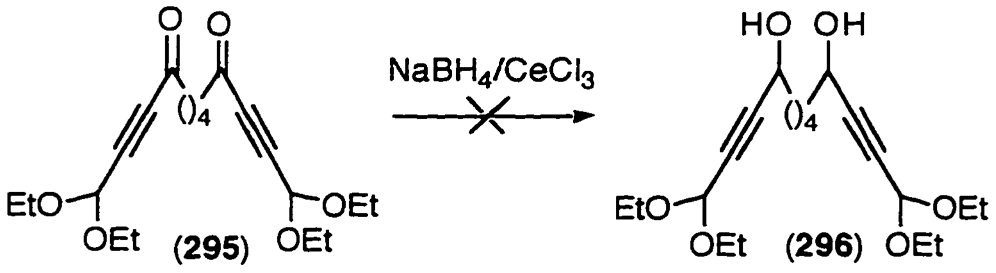


Figure 81

The elusive oxy substituted ynones could finally be isolated when we followed the reaction route highlighted in Figure 82. Propargyl alcohol (289) was protected as its TBS derivative and sequentially treated with n-butyllithium and tributyltin chloride. The resulting stannane (297) was submitted to the previously developed palladium coupling conditions to yield desired diketone (298). Since the diketone was barely stable enough to allow iso;ation and characterization by ^{1}H and ^{13}C NMR we attempted to reduce it immediately to the corresponding diol (299) under a variety of conditions (Luche[58], DIBALH, binaphtoxyethoxyaluminum hydride[nm]), however (299) could not be isolated successfully.

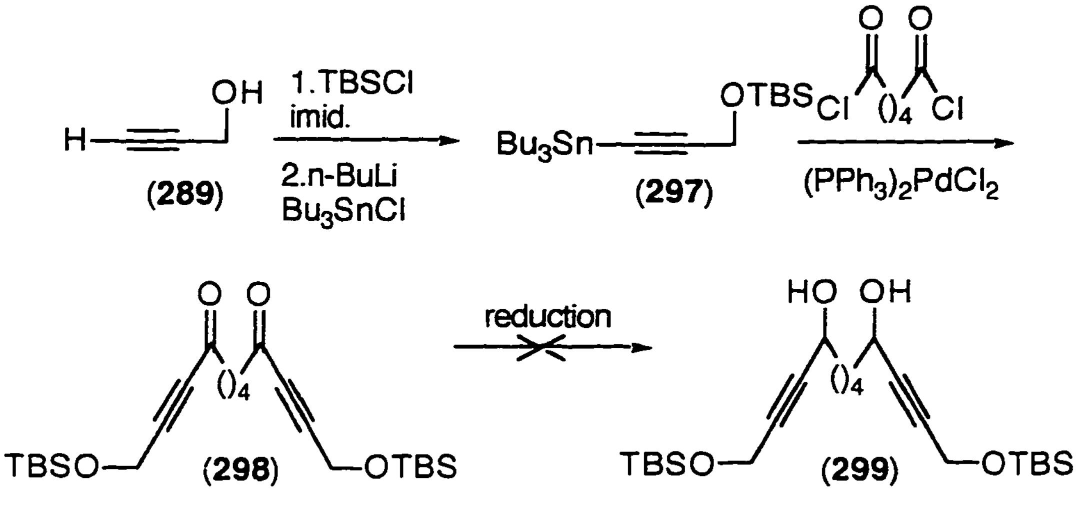


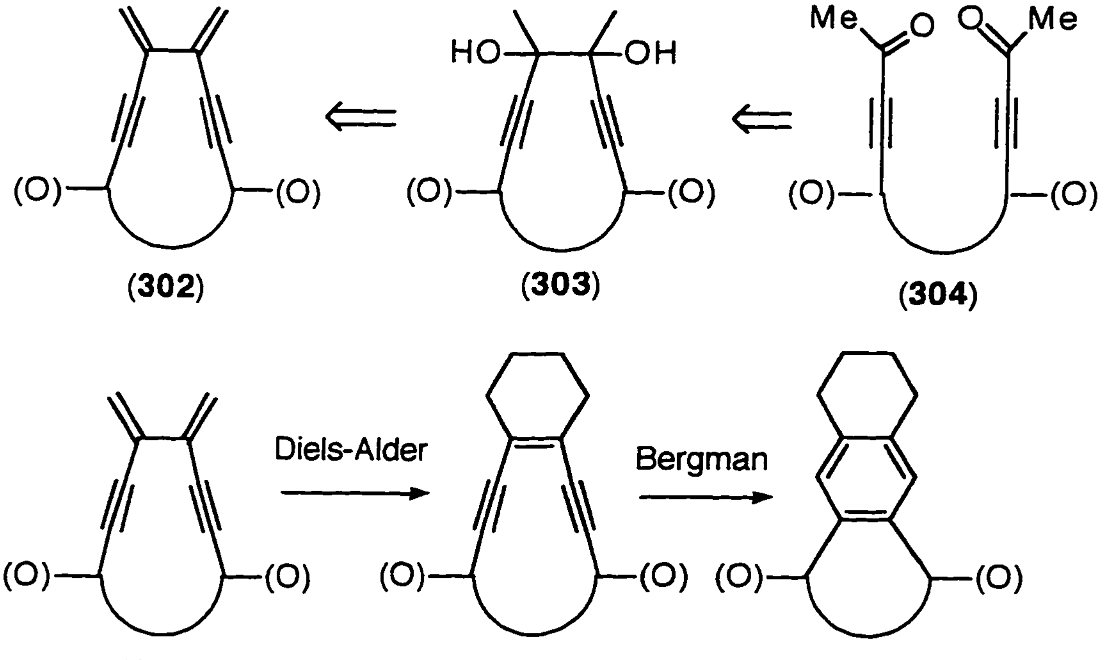
Figure 82

Given the lack of stability of the "primary" γ-oxy ynones (300) we decided to investigate if "secondary" γ-oxy ynones (301) could better serve our synthetic purposes (Figure 83).

(300) Primary oxyynone **(301)** Secondary oxyynone

Figure 83

In this context we based our envisaged cyclization step on an intramolecular pinacol cyclization carried out on the diketone precursor (304) and not a dialdehyde as initially planned (Figure 84). Provided this approach worked, the pinacol product (303) might serve as a precursor for the diene (302) which in turn would open the door to an unprecedented tandem Diels-Alder-Bergman reaction (305) and (306).



(302) **(303)** **(304)**

(302) **(305)** **(306)**

Figure 84

In order to reach the diketone cyclization precursor (304) we followed the reaction scheme shown in Figure 85. Acylation of bistrimethylsilylacetylene (232) followed by Luche reduction and protection of the diol with MOMCl led to intermediate (308) which in turn was deprotected under phase transfer catalysis to the diacetylene (309). This compound was further elaborated to the bisstannyl intermediate (310) which was coupled under palladium catalysis to the required diketone (311). The silicon directed

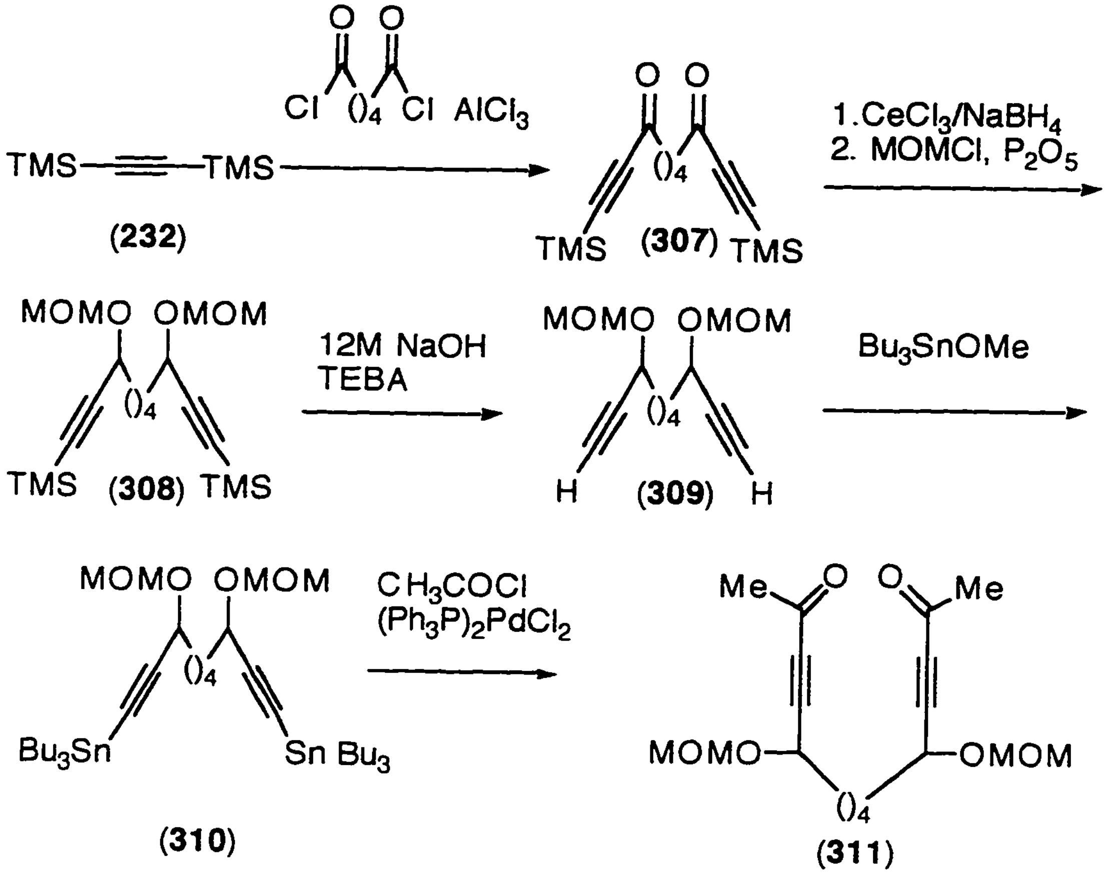


Figure 85

acetylation of the intermediate (308) failed to provide a one step approach to the diketone (311).

In the event pinacol coupling of the diketone failed under all the conditions previously tried on the acyclic model compounds. This secondary oxyynone (311) revealed however improved stability in comparison to the previously synthesized primary oxyynones. On the other hand, it is well known that the aldehydes enjoy considerably higher reactivity in pinacol coupling reactions[66]. We have redirected therefore our efforts to the synthesis of a dialdehyde cyclization precursor this time taking advantage of the newly developed reaction sequence.

The synthesis of the cyclization precursor for the 12 membered ring enediynes followed a common route to the bisacetylene (309) (*vide supra*). Treatment of compound (309) with n-butyllithium (Figure 86) followed by trapping of the diacetylide by dimethylformamide (or paraformaldehyde followed by oxidation) afforded the target dialdehyde (312) in poor chemical yield. Formation of a dark brown precipitate upon treatment with alkyllithium suggested that the acetylide dianion might precipitate out of the solution at low temperature. Switching the solvent from ether to THF, THP or DME or addition of HMPA or NMP to the THF solution did not improve the yield of the addition. Submitting the dialdehyde (312) to Pederson pinacol coupling conditions provided however the desired diol (314) in 28 % chemical yield.

Encouraged by this initial result we required larger quantities of precursor dialdehyde in order to test the pinacol coupling against a variety of reagents and conditions. In order to do this we reasoned that the solubility of the acetylide dianion derived from (309) should improve if the diol protective group is changed from MOM to the less polar TBS.

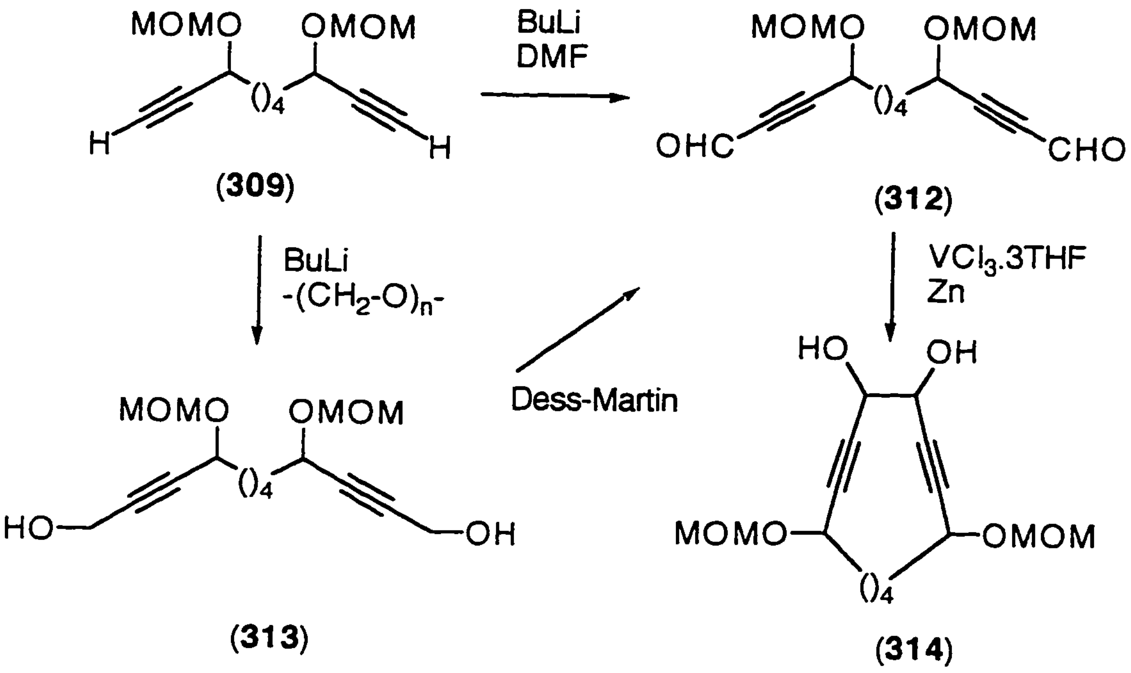


Figure 86

This rationale proved correct and finally led us to an efficient chemical route that also streamlined the acquisition of the required homologues for the 11 membered ring series as shown in Figure 87. Interestingly enough, the direct DMF homologation of precursors (317/318) occurred again in low chemical yield even when a large excess of reagent was present, presumably due to an unfavorable equilibrium of the acetylide addition. Fortunately, trapping of the acetylide with paraformaldehyde followed by Dess-Martin oxidation provided the target compound in more than 70% combined yield for the two steps.

With dialdehydes (319/320) in hand we undertook a screening test with most usual pinacol coupling procedures and even tackled briefly the possibility of an intramolecular McMurray reaction to generate the central double bond directly. The results of our investigation, carried out on the 12 membered ring cycle, are summarized in Table 3. It turned out that only two procedures have actually produced the desired pinacol, namely the one based on Pedersen reagent[67] and a second one, originally developed by Kagan[66], using samarium diiodide. This was rather surprising in view of the negative result obtained with samarium diiodide in the intermolecular study. Moreover, the yield in the samarium reaction was reasonably good and encouraged us to try various other alternatives in order to improve it. Finally, we have found that addition of excess HMPA can considerably increase the efficiency of the reaction up to 80% yield range both in the 11 and 12 membered ring enediynes case as shown in Figure 88. Treatment of pinacols

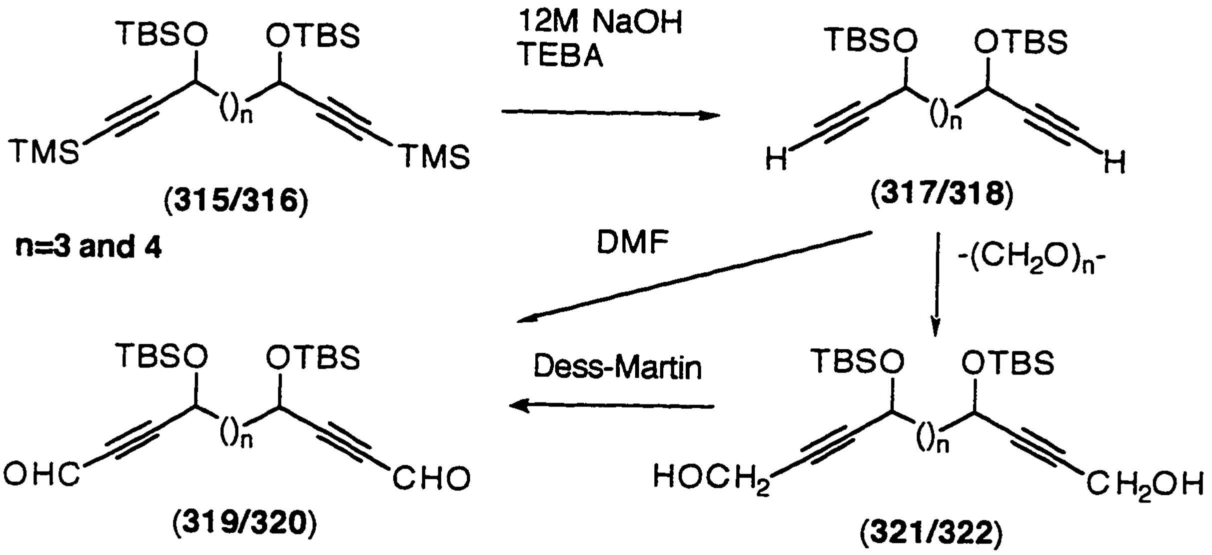


Figure 87

Pinacol Procedure	Yield
VCl3.3THF/Zn[67]	-no product (11 membered)

$VCl_3.3THF/Zn$	35 (12 membered)
SmI_2[66]	21 (11 membered)
SmI_2	52 (12 membered)
$SmI_2/HMPA$	70-80 (11 membered)
$SmI_2/HMPA$	70-80 (12 membered)
$TiCl_3/K$[63d]	-no product
$TiCl_4/Zn$[63i]	-no product
$TiCl_4/Mg(Hg)$[63c]	-no product
$CpTiCl_3/LiAlH_4$[63c]	-no product
$TiCl_3/LiAlH_4$[63d,e]	-no product
$TiCl_3/Zn\text{-}Cu$[63f]	-no product

Table 3

(321'/322') with thiophosgene/imidazole allowed synthesis of thionocarbonates (323/324) which in turn yielded the target 11 and 12 membered ring endiynes (325/326) through a Corey-Winter elimination. Both in the 11 and 12 membered ring series, the pinacol

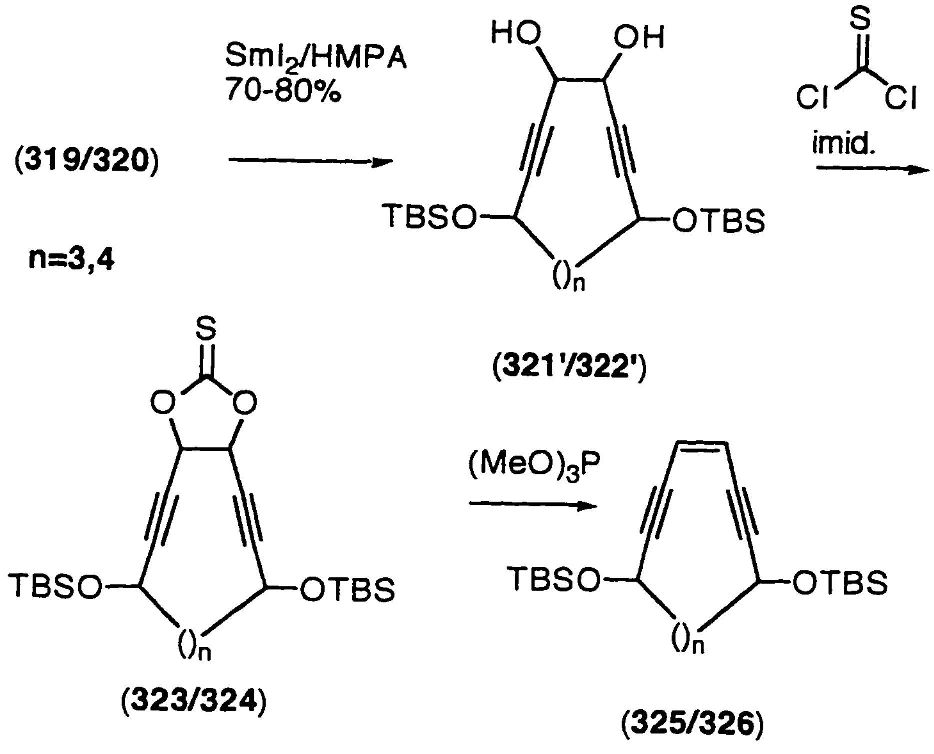


Figure 88

coupling was not diastereoselective affording a 1:1 mixture of *cis* and *trans* diols as determined by HPLC chromatogram of the corresponding thionocarbonates.

The generation of the double bond required a careful temperature study since the standard conditions (refluxing trimethylphosphite) afforded the 12 membered ring enediyne in only 22% (Table 4). We have found that the reaction can occur with trimethylphosphite at temperatures as low as 45°C to yield the corresponding enediyne in up to 75%. Even lower temperatures were accessible when we used more electron rich phosphines[25b] however at the expense of lower yields in isolated product. In the case of diazaphospholidines we have carried out the reactions in neat reagent and in solution (ether, THF).

Corey Elimination for the 12 Membered Enediynes

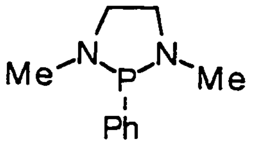
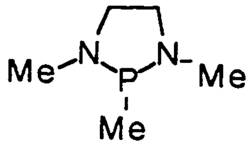
Phosphine	Temperature	Yield
$(MeO)_3P$ (neat)		22
	80	45
	60	59
	50	66
	45	71-75
	35	no product at 24 hrs
	25	21 (neat)
	0	no reaction
	25	0
	0	0
	-20	0

Table 4

The accessibility of the 12 membered ring enediynes at temperatures at least 80°C degrees lower than the usual Corey-Winter elimination procedure is relevant for the reduced activation energy required by this elimination. The wide range in reaction yields with the temperature indicates the availability of competitive reaction pathways at higher temperatures or with more reactive phosphines.

A totally different behavior was displayed by the 11 membered ring enediyne(325). The best found conditions to effect elimination were in trimethylphosphite at 55°C but the product was isolated in only 9% yield. At 40°C only starting material was recovered after 3 days while temperatures higher then seventy degrees afforded no product at all. Other alternative procedures that failed to lead us to the enediyne are summarized in Table 5.

Corey Elimination for the 11 Membered Enediynes

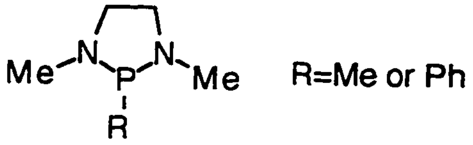
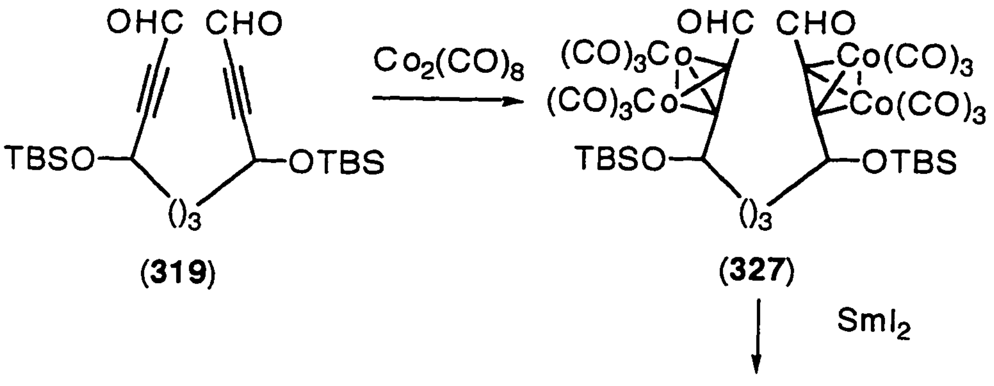
Procedure	Yield
$(MeO)_3P$, 55°C	9
iPrI or MeI	0
 R=Me or Ph	0
thermolysis	2
MeI/I_2	0

Table 5

This unexpected difference stems most likely from the increased strain present in the 11 membered ring as opposed to the 12 membered ring. Obviously the transition state leading to elimination will be higher in energy allowing the competitive decomposition pathways to become preponderant even at low temperatures.

We have decided next to try to complex the triple bonds of the 11 membered system with dicobaltooctacarbonyl in order to lower the strain and try subsequently the Corey-Winter elimination and decomplexation of the enediyne. At the same time, we wanted to examine the compatibility required by the intramolecular pinacol step with the presence of the acetylene cobalt complexes.



(319)

(327)

(328)

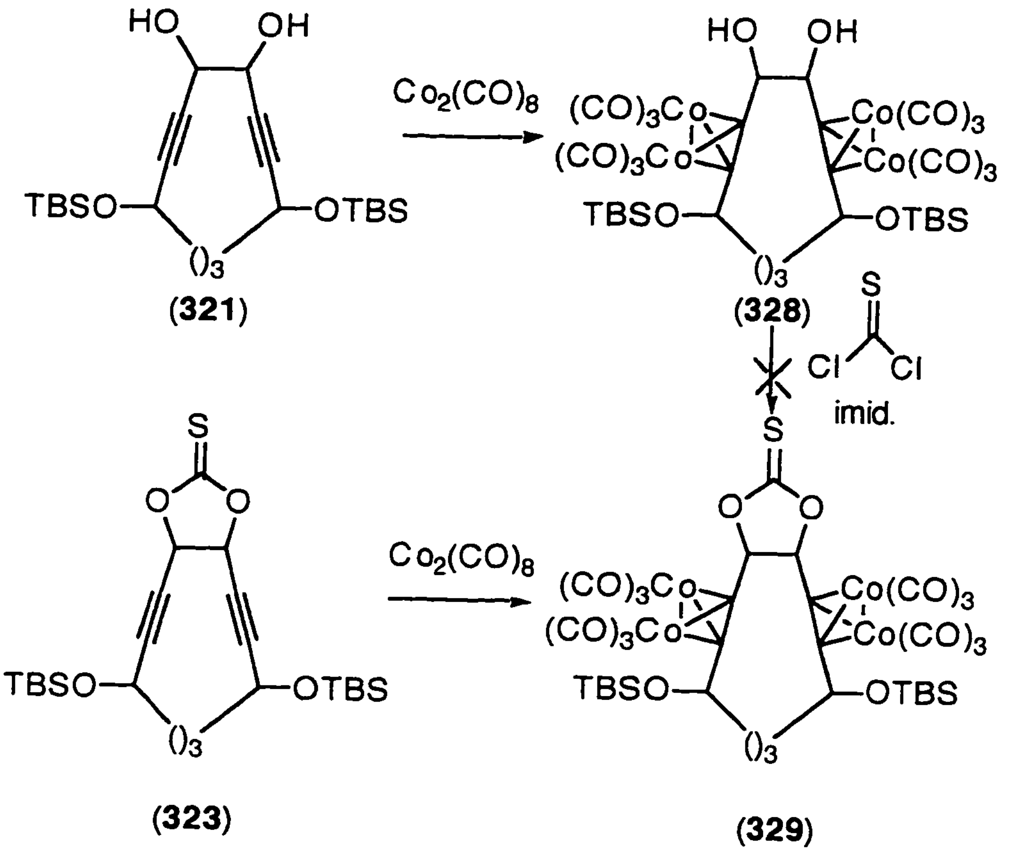


Figure 89

Dialdehyde (319) reacted with dicobaltooctacarbonyl to generate tetracobaltocomplex (327) which was further submitted to samarium pinacol cyclization to yield to our satisfaction the diol (328). This complex has been characterized by NMR and IR and gave the expected molecular mass and decomposition pattern (12 CO losses) by FAB, however did not yield satisfactory elemental analysis rezults. We have secured its structure by synthesis of the same complex this time starting from the diol (321) and comparison of the NMR and FAB spectral data. Further attempt to obtain the thionocarbonate (329) from the diol under usual conditions returned starting material only presumably due to excedingly high steric hindrance with the vicinal complexed triple bonds. Finally, direct complexation of the thionocarbonate (323) afforded the required enediyne precursor (329).

Unfortunately, various trials to generate the double bond from intermediate (329) under Corey-Winter elimination conditions led to the loss of the starting material. Most likely cobalt decomplexation reaction occurred first, unmasking the 11 membered ring thionocarbonate which was subsequently destroyed (*vide supra*).

Both the twelve and the eleven membered enediynes (325/326) were the first reported bioxysubstituted monocyclic enediynes and based on precedent observations we were hopeful that the presence of a second oxygen substituent in the propargylic position would cause a decrease for the Bergman cyclization temperature. In the event, a benzene solution of each compound was heated in a sealed tube up to 150°C in the presence of cyclohexadiene for up to two hours to return unchanged starting material only with good mass balance.

This disappointing result rendered the implementation of the original project aiming at the synthesis of taxol analogs via taxamycins-11 and taxamycin-12 route, doubtful. It also offered a negative response to the effect of a second oxysubstituent in the propargylic position of the monocyclic enediynes.

We decided therefore to attempt simultaneous deprotection of the hydroxy groups in order to access an enyne allene that should have a lower activation energy to a Myers type electrocyclization. To our surprise TBS deprotection under basic conditions (TBAF), acidic (HCl/THF, CF_3COOH) or even very mildly acidic ($PdCl_2(PhCN)_2$) conditions lead to loss of starting material. These negative results are summarized in Figure 90.

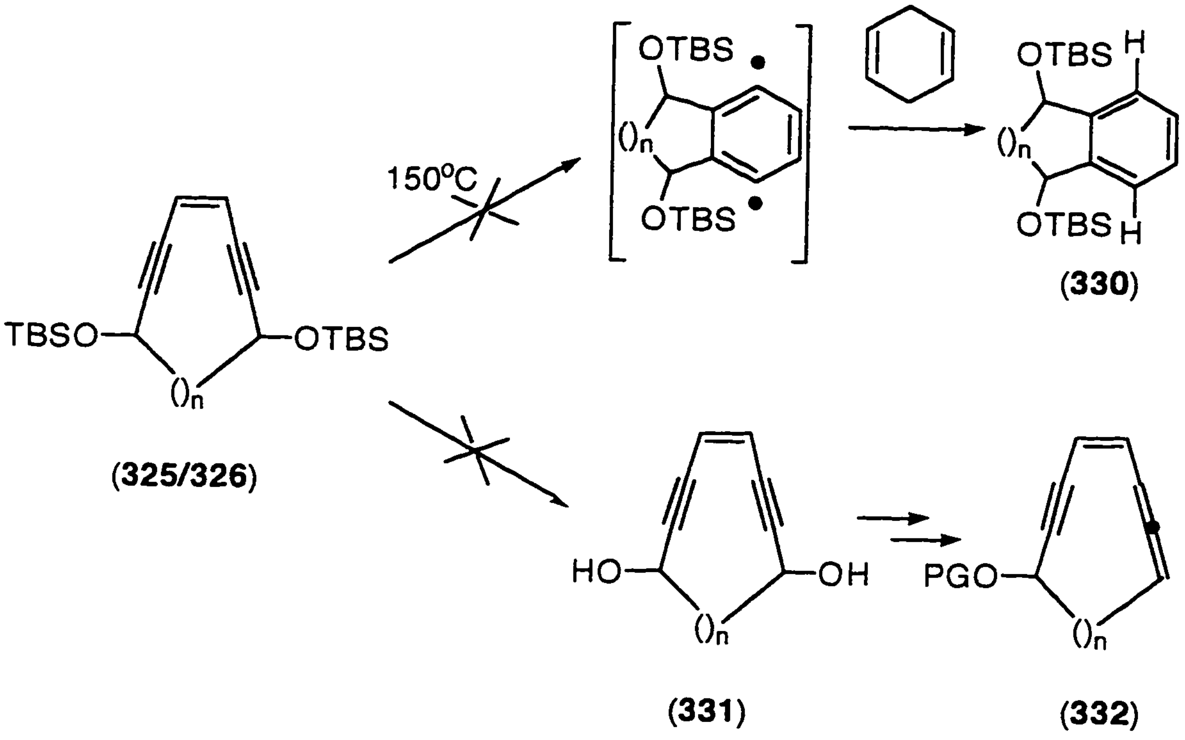


Figure 90

At this point the 12 and 11 membered ring monocyclic enediynes project came to a dead end since it became obvious that none of these system is easily amenable to Bergmann or Myers electrocyclization.

2.6D.Synthesis of the 10 Membered Ring Enediyne

In a logical continuation of our project we started to work on the synthesis of a monocyclic ten membered ring enediyne. We wanted to find out if from a synthetic stand point the pinacol approach was a viable route to this interesting class of compounds.

Double acylation of bistrimethylsilylacetylene with succinyl dichloride did not provide the diketone (333) in satisfactory yields so we tried to access this symmetrical intermediate through a dimerization reaction as shown in Figure 91. Most likely the presence of the triple bond had interfered with the copper, iron and silver metals required by this type of reaction since no desired product could be isolated.

In another approach the addition of the trimethysilylacetylide anion on the bis-Weinreb amide derived from succinic acid had also failed to produce the target dione (333).

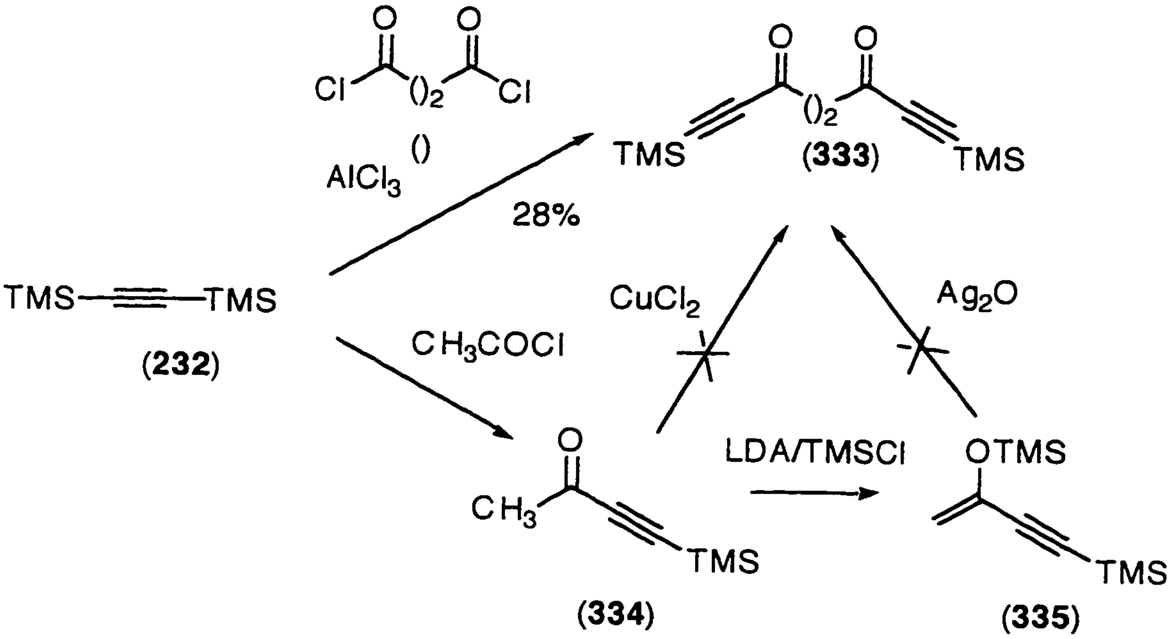


Figure 91

In the event we found that direct alkylation of bis-TMS acetylene occurs smoothly under Lewis Acid conditions if we use 1,5-dimethoxyfurane as an electrophilic partner (Figure 92) to yield intermediate (336). This reaction is an extension of the previously reported alkylation of acetylenes by ketals under Lewis acid conditions^{58a}. Therefore we attempted the reaction of ketal (336) with bistrimethylsilylacetylene to obtain the desired symmetrical diyne (337) however a totally unexpected rearranged product (344) was isolated in high chemical yield.

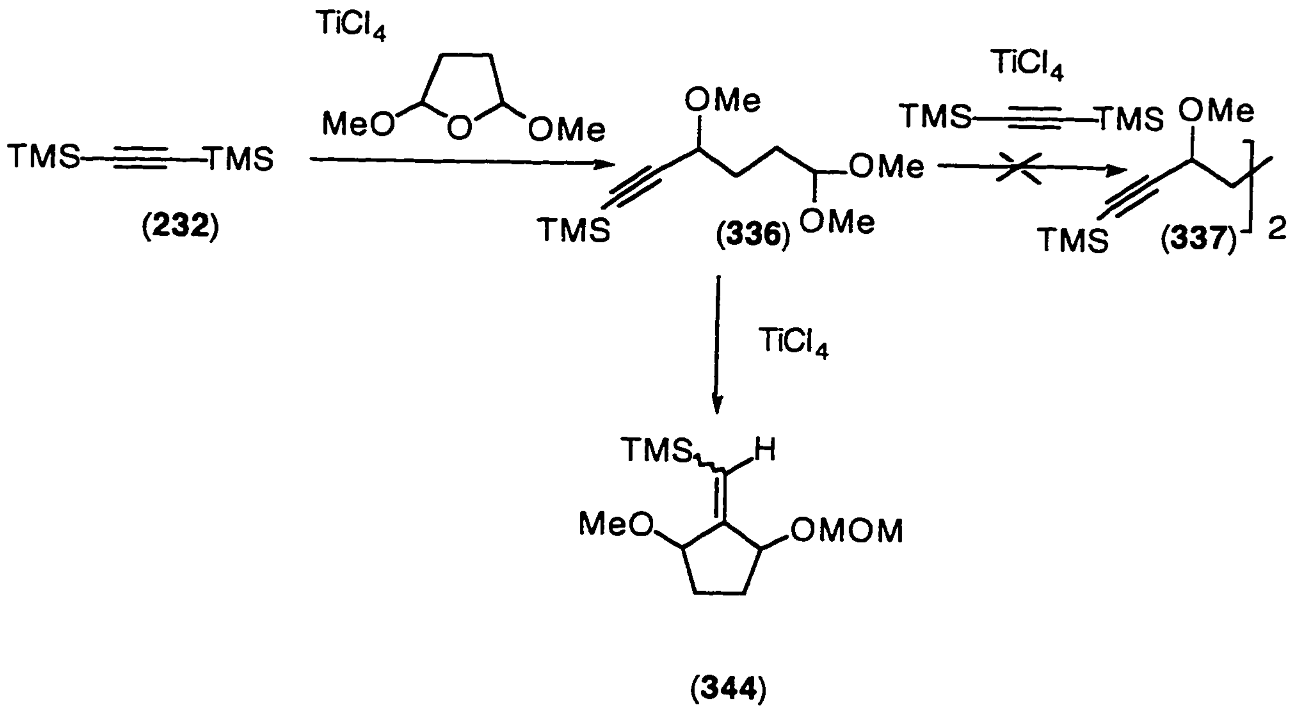


Figure 92

The outcome of the reaction can be explained by the mechanism proposed in Figure 93. Initial formation of the oxonium ion (339) was followed by an intramolecular electrophilic addition onto the triple bond in an 1,5-*exo* rather than 1,6-*endo*^{58n} manner.The high energy vinyl carbocation (342) will relax through an 1,4-hydride abstraction to generate the low energy oxonium ion (343) that will react in turn with the metanol added during the work up of reaction to give product (344). Alternatively, oxonium ion (339) could add in a 1,6-*endo* manner to generate vinyl carbocation (340) stabilized by a silicon β-effect which evolves into lower

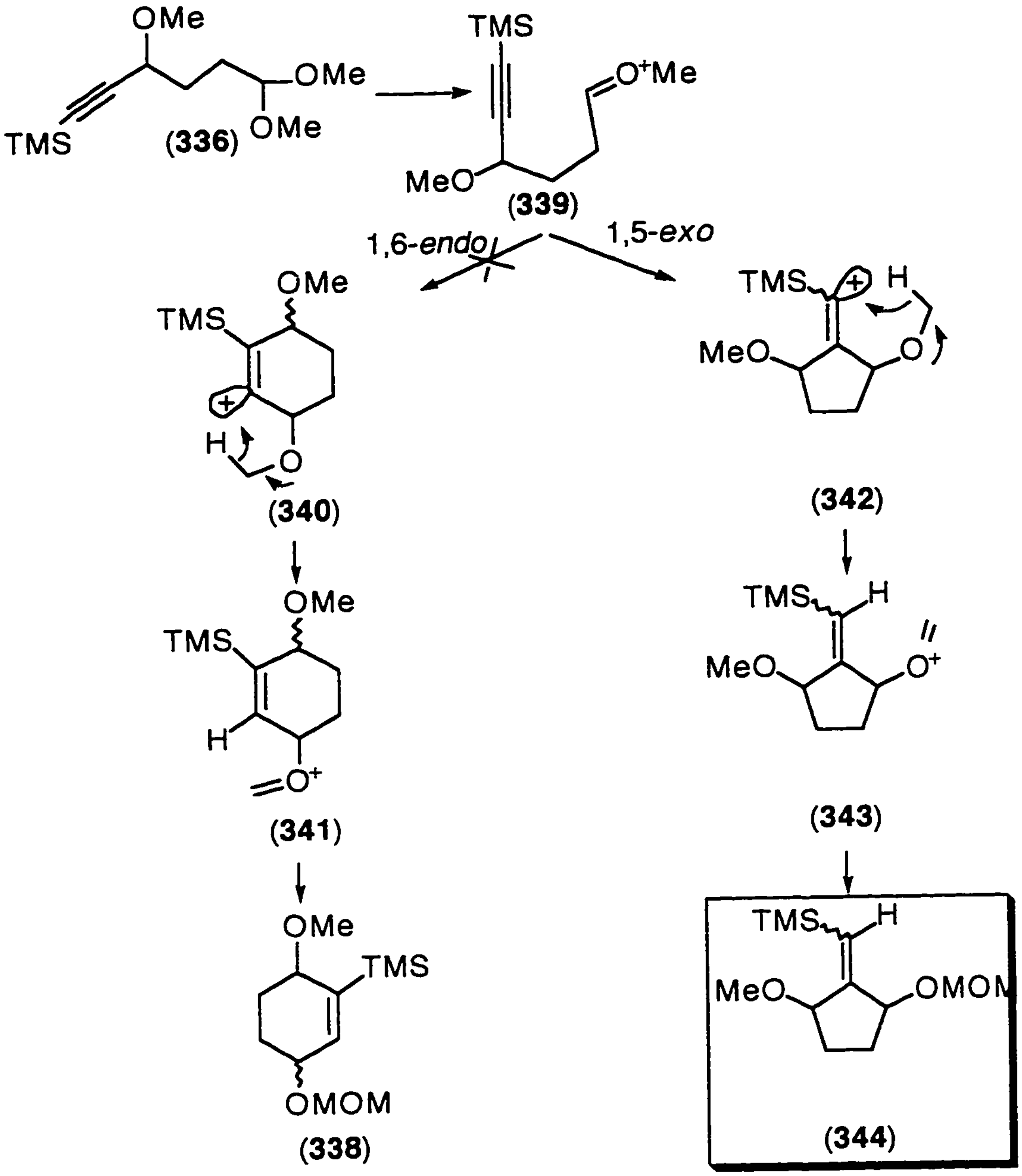


Figure 93

energy oxonium ion (341) through a 1,5-hydride transfer. Ultimately, this reacts with methanol during work up to generate the MOM protected derivative (338). The correct structure of the rearranged product (344) was based on the diagnostic ^{13}C NMR chemical shift of the quaternary carbon found at 158.26 ppm, typical for an exocyclic double bond[580].

This unexpected turn of events forced us to go back to the alkylation of bis-TMS acetylene and change the quenching reagent from methanol to water (Figure 94). This allowed us to gain access to the aldehyde (345) which gave upon addition of the TMS acetylide and protection of the alcohol with TBSCl the intermediate (346). Chemoselective TMS double deprotection followed by homologation with paraformaldehyde as shown previously in the higher homologues series provided the required diol (348) as well as some undesired hemiacetal (349) that could not be removed by column chromatography or HPLC. Direct oxidation of the mixture yielded the cyclization precursor (350) and some formate derivative (351), as determined from the ^{1}H NMR spectrum of the mixture. Again, an attempt to separate the undesired ester by HPLC failed. We reasoned that the ester function should be inert to the samarium diiodide coupling conditions and submitted therefore the mixture to the intramolecular cyclization with the hope that we will be able to purify the cyclic pinacol. Unfortunately the results of the cyclization were inconclusive so we went back to the troublesome homologation step and performed it this time with DMF instead of paraformaldehyde (Figure 95) to access directly the pure

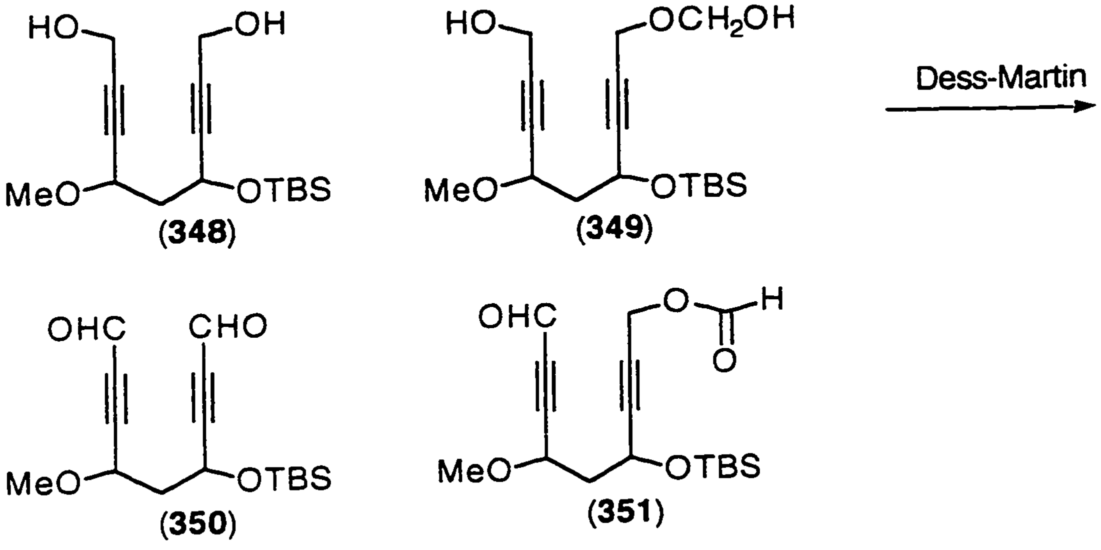


Figure 94

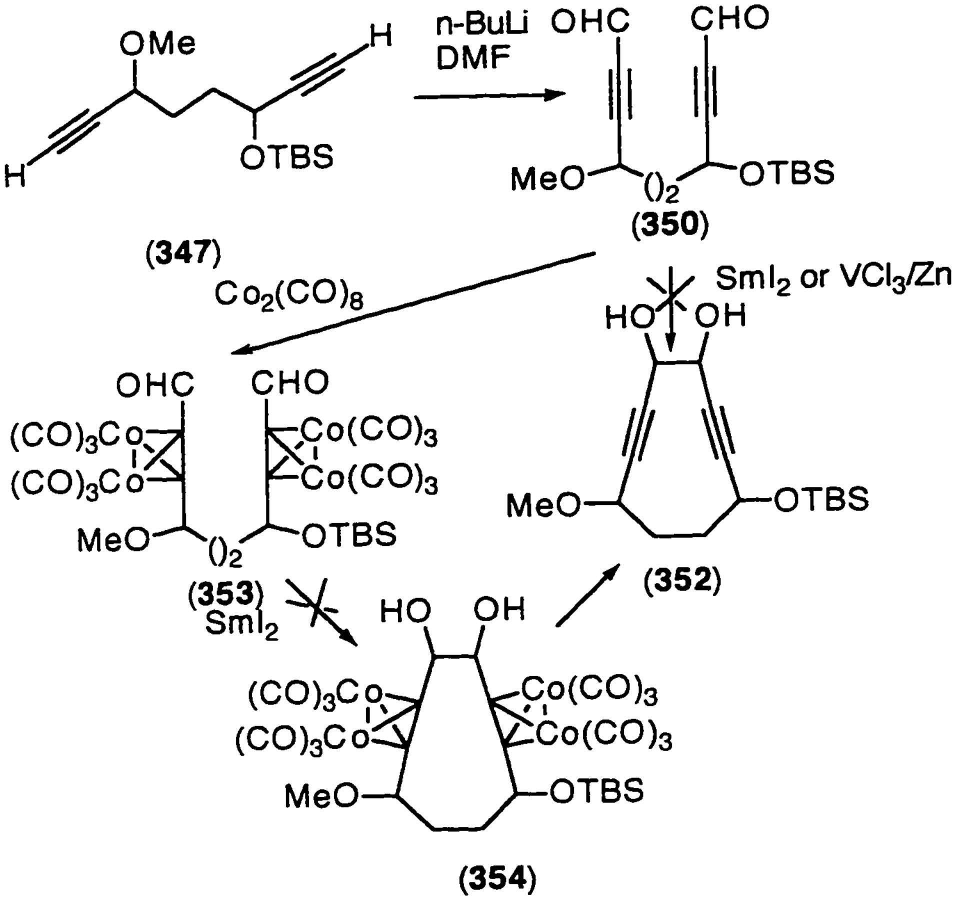


Figure 95

dialdehyde (350). Neither the samarium diiodide cyclization nor the Pederson reagent provided however the expected 10 membered pinacol coupling product (352). The dialdehyde (350) was subsequently complexed with dicobaltooctacarbonyl to provide the tetracobaltocomplex (353). The attempted cyclization on this intermediate failed to provide any cyclization product (354).

Appendix 1. DNA Strand Cleavage Mechanism[73]

DNA strand cleavage is mainly initiated by C(5') hydrogen atom abstraction (Figure 96). Minor DNA cleavage pathways include C(4') and C(1') hydrogen abstraction as shown in Figure 97 and 98 respectively.

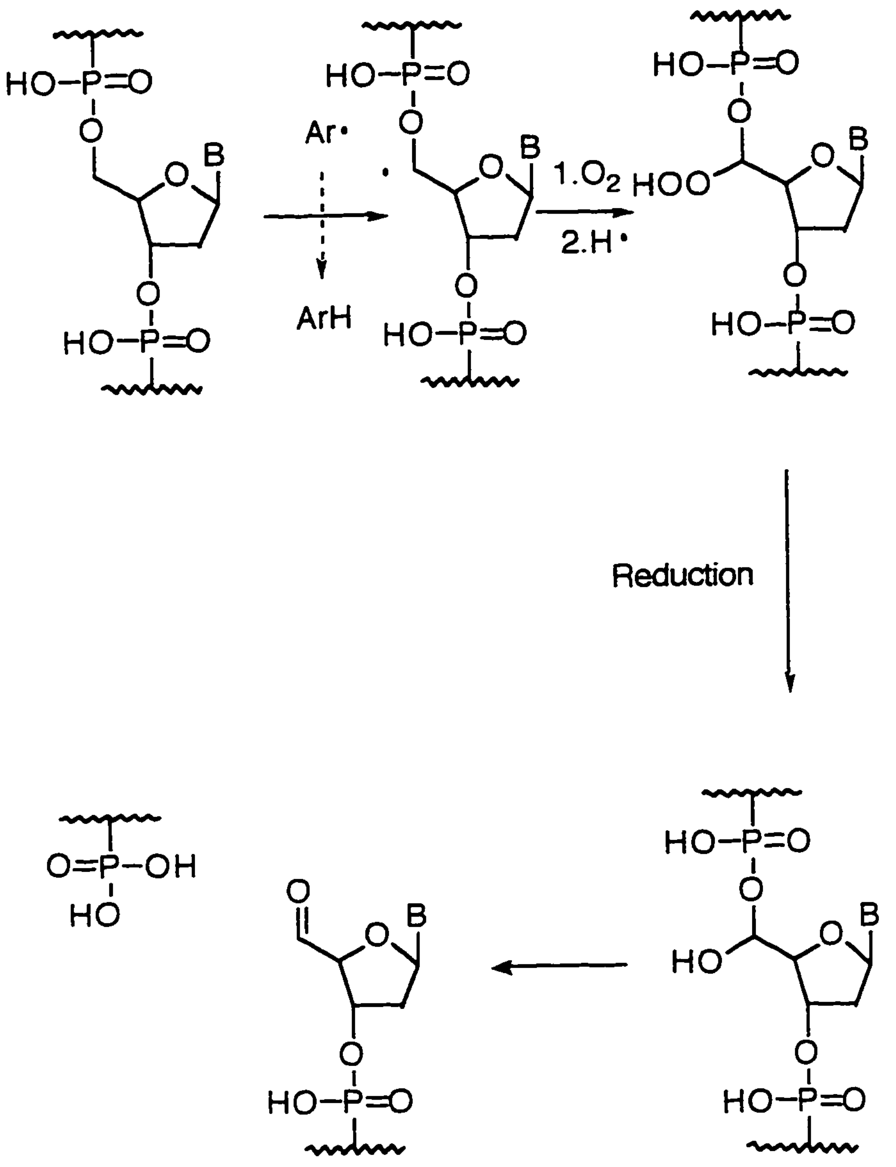


Figure 96

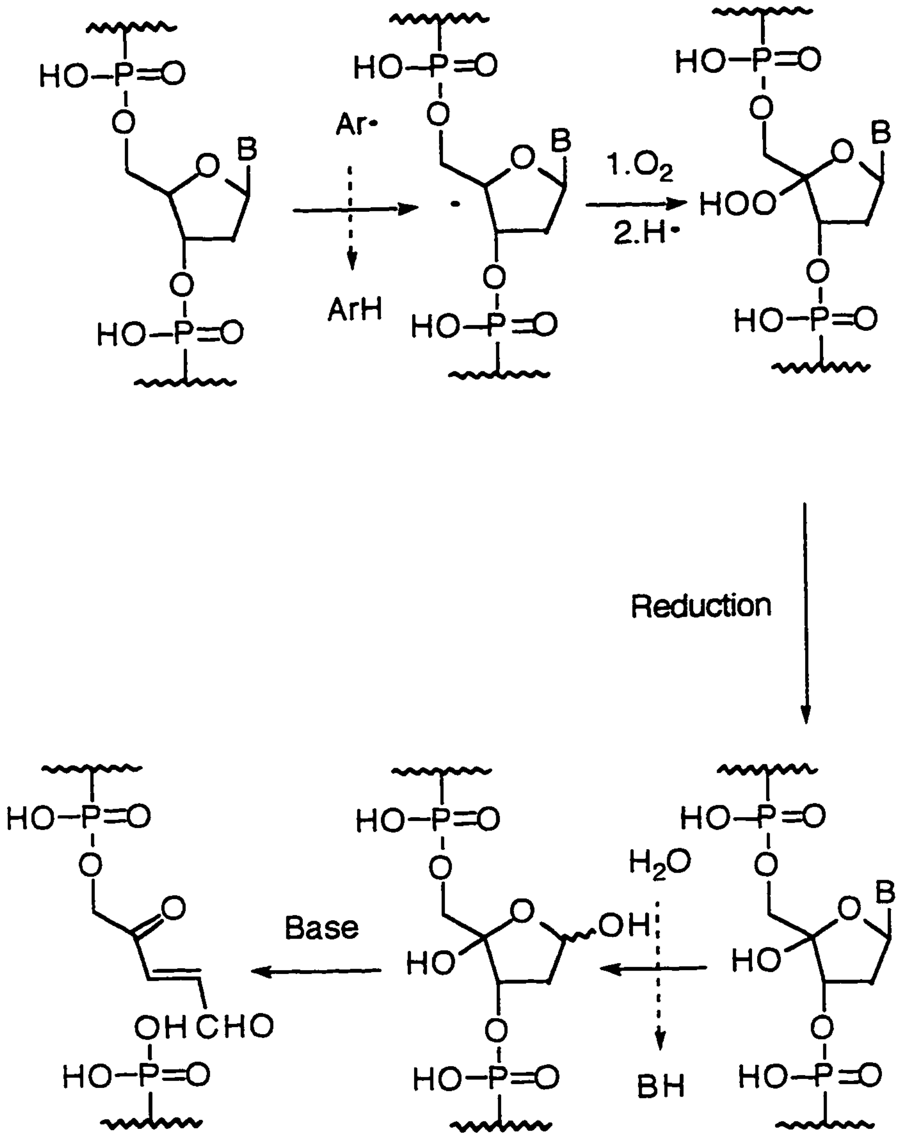


Figure 97

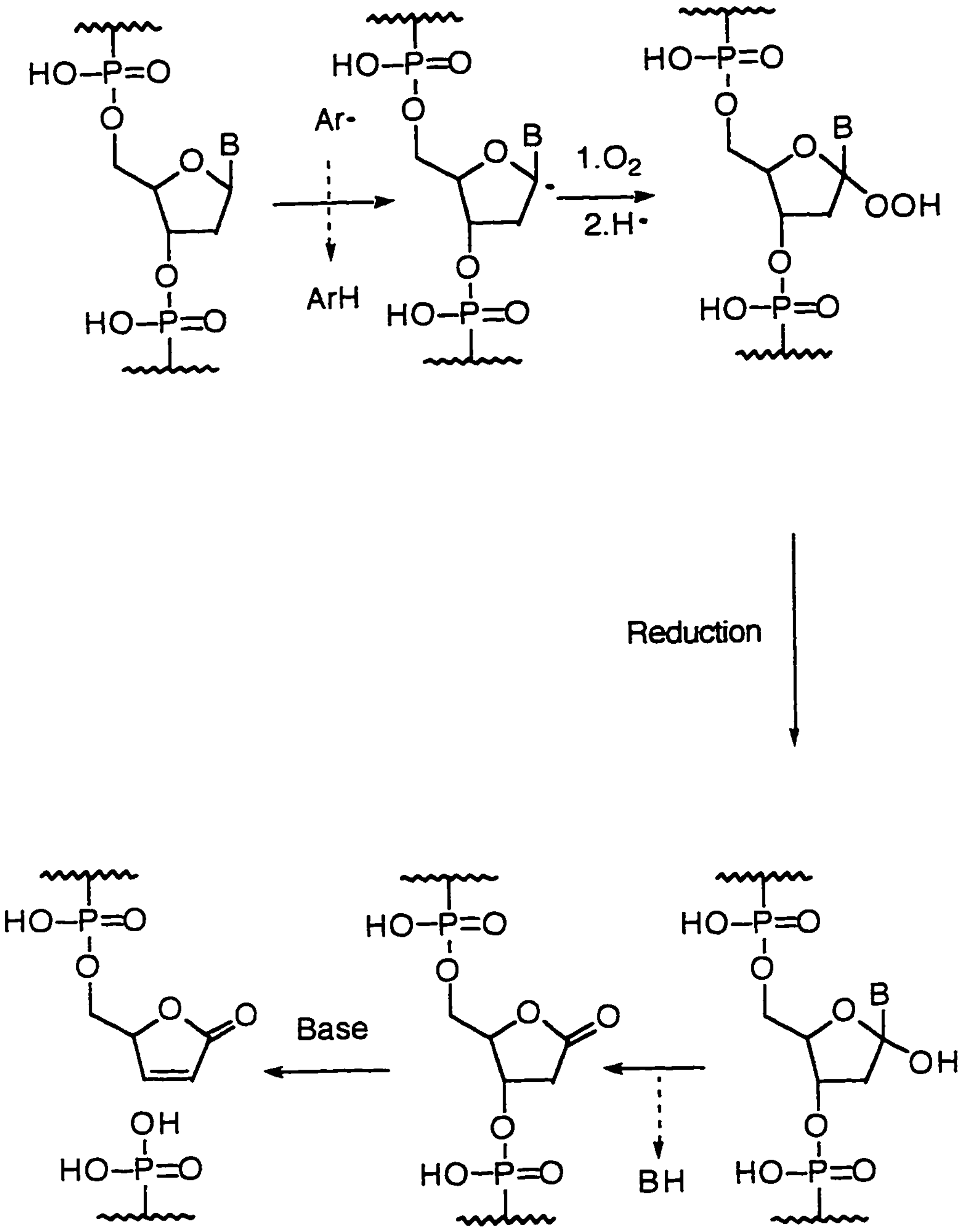


Figure 98

The following calculations represent molecular mechanics energy minimization performed on a Power Mac 8100/100 using CAChe software Version 3.7.

Appendix 2. Favorable Conformers for Intramolecular Crossed Aldol Condensation

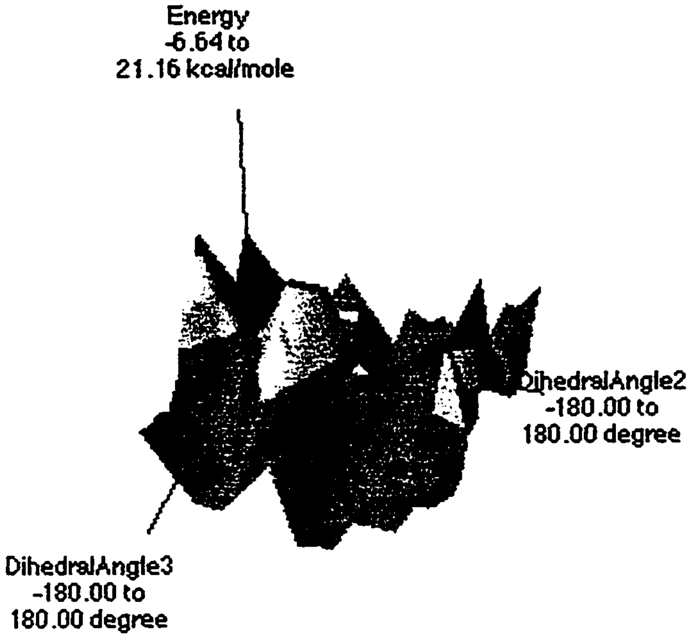


Figure 99

Figure 99 represents an energy map of various conformers generated by the stepwise variation of the 2 dihedral search angles marked with letter "s" in Figure 100.

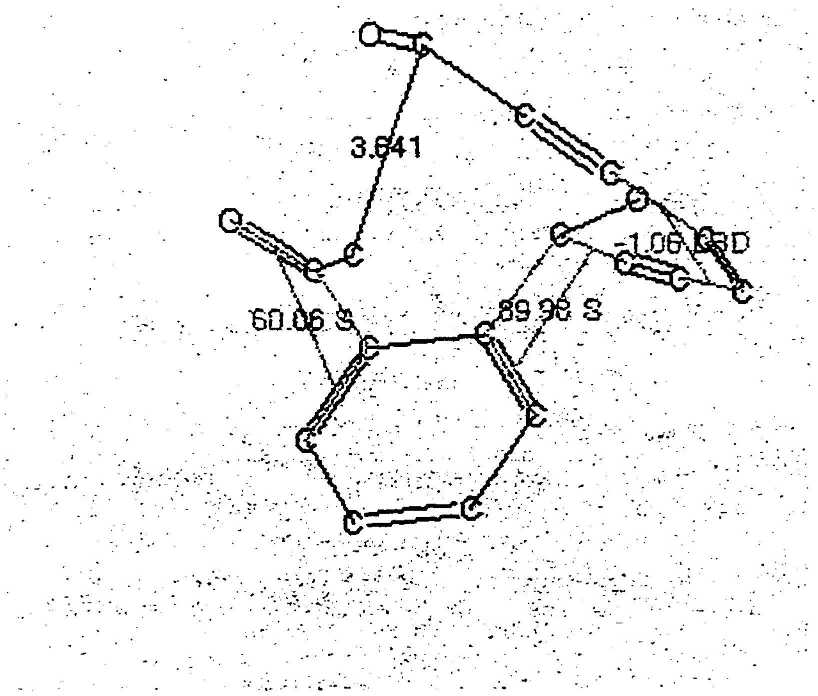


Figure 100

The low energy conformer showed in Figure 100 corresponds to the black ball pointer in Figure 99 and is one of many possible candidates for cyclization. The distance between the reactive centers is 3.6Å. Note the favorable orientation of the orbitals as the enol attacks the aldehydo group.

Appendix 3. Model for Stereoselective Dehydration of β-Hydroxyketone (169)

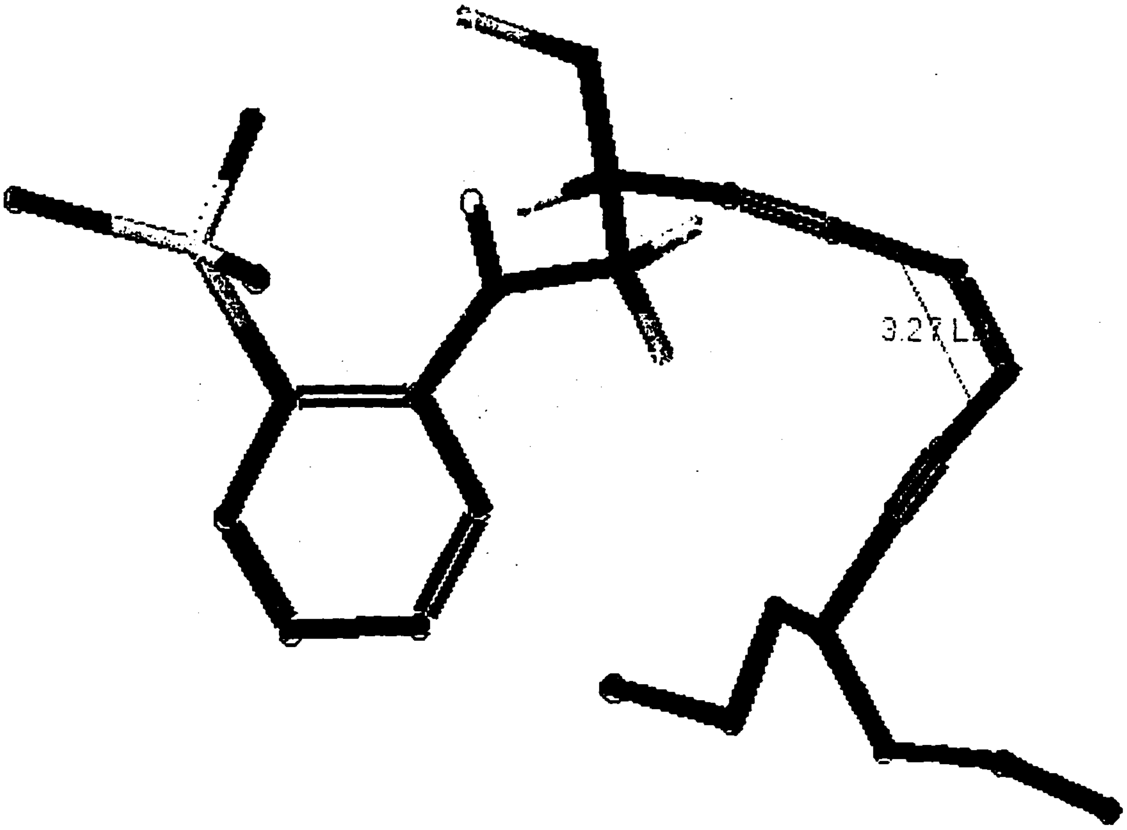


Figure 101

Figure 101 represents the lowest energy conformer for β-Hydroxyketone (169). If the elimination occurs by a concerted mechanism then the desired *trans*-stereoisomer would be formed preferentially.

4. Experimental

4.1 General Experimental

Infrared spectra (IR) were obtained either as a thin film on sodium chloride or chloroform solutions in potassium bromide cells. All IR spectra were recorded on a BOMEM Michelson 100 Fourier transform spectrometer (FTIR).

All nuclear magnetic resonance (NMR) spectra were obtained from deuterochloroform solutions unless otherwise noted. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 200 MHz on a Varian Gemini spectrometer, or at 500 MHz on a Brucker WM 500 relative to an internal lock on the $CDCl_3$ signal (δ 7.25 ppm) of deterochloroform. All chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane (δ scale). The multiplicity, coupling constants and number of protons are indicated in parenthesis.

Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 200 MHz on a Varian Gemini spectrometer, or 300 MHz on a Varian XL-300 or at 500 MHz on a Brucker WM 500 relative to an internal lock on the $CDCl_3$ signal (δ 77.0 ppm) of deterochloroform. All chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane (δ scale)

Gas chromatography-mass spectroscopy (GC-MS) determinations were performed on a Hewlett Packard 5890 Series II chromatograph equipped with a 25 m polysiloxane coated glass capillary column connected to a Hewlett Packard 5971A mass selective detector.

Low resolution mass spectroscopy (MS) using either electron impact (EI), or chemical ionization (CI) mode was performed on a V.G. Micromass 7070 HS mass spectrometer with an electron beam energy of 70 eV.

High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-IIA mass spectrometer with an electron beam energy of 70 eV.

Microanalyses were performed at M-H-WLaboratories, Phoenix, Arizona or by the in-house elemental analysis services at the University of Ottawa.

Analytical thin layer chromatography (TLC) was performed on commercial aluminum-backed silicagel plates (E.Merck, type 5554). Visualization was accomplished with ultraviolet light, iodine vapor, and/or heating the plate after immersion in either 5% solution of ammonium molybdate in 10% aqueous H_2SO_4 (W/V) or a 2.5% solution of *p*-anisaldehyde in ethanol containing 3% H_2SO_4. Flash column chromatography were performed with E.Merck Silica Gel 60 (70-230 or 230-400 mesh) Radial chromatography was performed on a Harrison Research Chromatotron model 7924T using silicagel (Merck Silica Gel 60, PF_{254} containing gypsum) plates of 1,2, or 4 mm thickness and 10-11 cm radius.

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Distillation temperatures are uncorrected.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry nitrogen in flame or oven dried glassware equipped with a magnetic stirring bar and rubber septa. Standard inert atmosphere techniques were used in handling all air and/or moisture-sensitive compounds.

4.2 Solvents and Reagents

Petroleum ether refers to a hydrocarbon mixture with a boiling range 30-60°C. Ether refers to diethyl ether (Et_2O). Tetrahydrofurane (THF) and diethyl ether were freshly distilled from potassium- and sodium-benzophenone ketyls, respectively. Dichloromethane (CH_2Cl_2), benzene and toluene were freshly distilled from CaH_2.

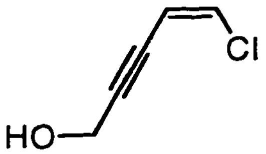
Methanol (MeOH), hexamethylphosphoramide (HMPA), triehtyl amine (Et_3N), acetonitrile (CH_3CN) and diisopropyl amine (*i*-Pr_2NH) were distilled from CaH_2 and stored over 4Å molecular sieves.

Cerium trichloride was prepared by measuring the corespondent quantity of cerium trichloride heptahydrate and heating it up slowly to 140°C over three hours under vacuum and stirring followed by maintenance of this temperature overnight. Next day the solution was cooled to room temperature under nitrogen and then suspended in tetrahydrofurane under vigorous stirring until a white slurry was formed. Finally the slurry was treated with *tert*-butyllithium until an orange color persisted.

Lithium diisopropylamide (LDA) was prepared by addition of a solution of *n*-butyllithium in hexanes (1.05 eq.) to a cooled solution (-78°C) of dry diisopropylamine in freshly distilled THF. The resulting colorless or slightly yellow solution was stirred at 0°C for 15 minutes before use.

4.3 Experimental procedures

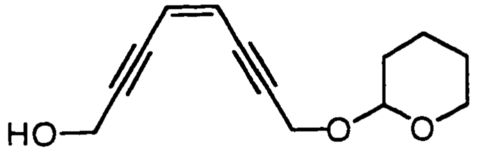
(*Z*)-5-Chloro-4-penten-2-yn-1-ol



156

Tetrakis(triphenylphosphine)palladium (0.3 g, 0.26 mmol) was weighed in a round bottom flask in a nitrogen bag followed by direct rapid addition of copper iodide (0.2 g, 1.04 mmol) under a stream of nitrogen. An ether solution (10 mL) containing propargyl alcohol (0.43 ml, 7.43 mmol), *cis* - dichloroethylene (0.61 ml, 8.17 mmol) and *n*-butylamine (2.93 ml, 29.7 mmol) was prepared in a separate flask and added via canula over the catalyst. The reaction was allowed to stir overnight, then filtered through Celite®, concentrated and purified by column chromatography (ether/petroleum ether=1/1) to afford 0.67 g (5.8 mmol) of pure enyne in 78%.^{1}H NMR (200 MHz, $CDCl_3$) δ 6.35 (dd, ^{6}J=0.57Hz, ^{3}J = 7.48Hz, 1H), 5.86 (dt, ^{5}J=2.0Hz, ^{3}J = 7.49Hz, 1H), 4.4 (dd, ^{6}J=0.59Hz, ^{5}J= 1.99Hz, 2H), 2.8 (bs, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 51.2, 79.2, 95.5, 111.5, 128.6; IR (NaCl, neat) 3316, 2901, 1601, 1384; MS 118 (M^+, 11.8), 116 (M^+, 35.7), 81 (M-Cl, 100); HRMS (EI): calcd. for C_5H_5OCl 116.0029, found 116.0071.

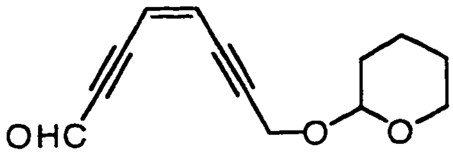
(*Z*)-8-[(2-Oxacyclohexyl)oxy]-4-en-2,6-octadiyn-1-ol



157

Tetrakis(triphenylphosphine)palladium (0.15 g, 0.13 mmol) were weighed in a round bottom flask in a nitrogen bag followed by rapid addition of copper iodide (0.1 g, 0.52 mmol) under a stream of nitrogen. An ether solution (10 ml) containing enyne alcohol (156) (0.31 g, 2.6 mmol), THP protected propargyl alcohol (0.4 ml, 2.86 mmol) and *n*-butylamine (1.2 ml, 10.4 mmol) was prepared in a separate flask and added via canula over the catalyst. The reaction was allowed to stir overnight, then filtered through Celite®, concentrated and purified by column chromatography (ether/petroleum ether=1/1) to afford 0.43 g (2.28 mmol) of pure endiyne in 88%. ^{1}H NMR (200 MHz, CDCl3) δ 5.85 (dd, ^{5}J =1.4Hz, ^{3}J = 10.8Hz, 1H), 5.81 (d, ^{5}J =1.4Hz, ^{3}J = 10.8Hz, 1H), 5.0 (m,1H), 4.43 (d, ^{5}J =1.4Hz, 2H),4.4 (d, ^{5}J =1.4Hz, 2H), 3.7 (m, 2H), 3.0 (bs, 1H), 1.4-1.9 (m, 6H); ^{13}C NMR (200 MHz, CDCl3) δ 18.5, 25.3, 29.9, 51.3, 54.5, 61.5, 82.6, 83.6, 92.4, 95.6, 95.7, 119.5, 120.0; IR (NaCl, neat) 3383, 2912, 2854, 2247, 1442, 1352, 1264; MS 220 (M+, 0.8), 85 (100); HRMS (EI): calcd. for $C_{13}H_{16}O_3$ 220.1099 found 220.1090.

(*Z*)-8-[(2-Oxacyclohexyl)oxy]-4-en-2,6-octadiyn-1-al



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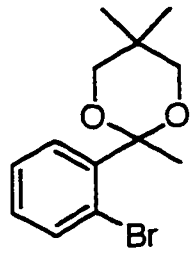
The alcohol (157) (0.38 g, 1.73 mmol) was dissolved in 2 mL methylene chloride and added quickly to a suspension of pyridinium chlorochromate (1.11 g, 5.2 mmol), sodium acetate (0.25 g) and 0.25 g molecular sieves 4Å in the same solvent (7 mL). The reaction was stopped after two hours with anhydrous ether (50 mL) and filtered through a short Fluorisil column. The solid residue remaining in the flask was washed with ether (3 portions of 10 mL) and also passed through the column. The combined organic phase was concentrated to afford pure unstable aldehyde in 41 to 58% yield which was characterized as a crude. ^{1}H NMR (200 MHz, CDCl3) δ 9.3 (d, ^{5}J =1.0Hz, 1H), 6.15 (dt ^{5}J =2Hz, ^{3}J =10.9Hz, 1H), 5.94 (d, ^{3}J =10.8 Hz, 1H), 4.8 (m, 1H), 4.41 (d, ^{5}J =2.0 Hz, 2H), 3.8 (m, 1H), 3.5 (m, 1H), 1.3-1.8 (m, 6H); ^{13}C NMR (200 MHz, CDCl3) δ 18.8, 25.2, 25.3, 30.0, 30.3, 54.4, 61.9, 82.3, 90.8, 93.5, 96.6, 97.2, 116.3, 126.1, 176.3; IR (NaCl, neat) 3047, 2942, 2862, 2175, 1662, 1444 (unstable compound).

2-(*o*-Bromophenyl)-2,5,5-trimethyl-1,3-dioxacyclohexane



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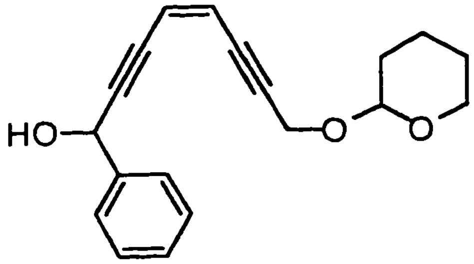
p-toluenesulphonic acid monohydrate (0.15 g, 0.78 mmol) , *o*-bromoacetophenone (1.48 g, 7.4 mmol) and 2,2-dimethyl-1,3-propanediol 3.86 g (37 mmol) were dissolved in benzene (175 mL) and refluxed for 6 hours using a Dean-Stark trap to remove the water. The benzene solution was subsequently extracted with sodium bicarbonate solution then with brine and finally concentrated to yield 1.98 g (6.95 mmol) of pure ketal in 94%.^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61 (dd, ^4J =1.32Hz, ^3J =7.8Hz, 1H), 7.56 (dd, ^4J =1.83Hz, ^3J =7.9Hz, 1H), 7.2-7.35 (m, 1H), 7.11-7.16 (m, 1H), 3.41 ^2J=10.7Hz, 2H), 3.35 ^2J=10.7Hz, 2H), 1.6 (s, 3H), 1.3 (s, 3H), 0.6 (s, 3H); ^{13}C NMR (200 MHz,$CDCl_3$) δ 21.9, 22.9, 29.1, 29.7, 71.5, 71.6, 100.3, 112.2, 120.8, 127.5, 128.3, 129.3, 130.3, 135.6, 138.3; IR (NaCl, neat) 3088, 3035, 2942, 2864, 1563; MS 285 (M+H$^+$, 0.08), 271 (M-Me$^+$, 100), 269 (M-Me$^+$, 100); HRMS (EI): calcd. for $C_{12}H_{14}BrO_2$ 269.0178, found 269.0184.

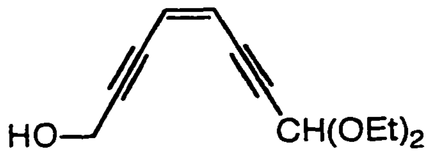
(*Z*)-8-[(2-Oxacyclohexyl)oxy]-1-phenyl-4-en-2,6-octadiyn-1-ol



163

Cerium trichloride heptahydrate (0.32 g, 0.86 mmol) was stirred in a round bottom flask at 140°C under vacuum (2 Torr) for 3 hours, cooled to room temperature and then suspended in tetrahydrofurane (3 mL) until a white slurry formed (2 hours under vigorous stirring). Meanwhile, bromobenzene (0.087 mL, 0.83 mmol) was dissolved in tetrahydrofurane (2 mL), cooled to - 78°C and treated dropwise with *n*-butyllithium in hexanes (0.35 mL, 0.86 mmol, 2.5M solution). The solution was transferred via canula after approximately 45 minutes over the cerium trichloride slurry that had been previously cooled to - 78°C. The color turned immediately lemon yellow and the metal exchange accomplished in one hour at the same temperature. Finally, the aldehyde (158) (0.093 g (0.43 mmol) in tetrahydrofurane (1 mL) was added dropwise over the organocerium solution and the reaction was monitored by TLC. After one hour, the reaction was quenched with ammonium chloride solution, partitioned between ether and brine, dried on anhydrous magnesium sulfate and concentrated down to 0.111 g (0.37 mmol) of product which was pure by ^{1}H-NMR spectroscopy. Yield 86%. An analytical sample was prepared by chromatography on Fluorisil (ether/petroleumroleum ether=1/3).^{1}H NMR (200 MHz, $CDCl_3$) δ 7.6 (m,2H), 7.3 (m,3H), 5.9 (m, 2H), 5.6 (m, 1H), 5.05 (m, 1H), 4.4 (m,2H), 3.6 (m, 3H), 1.3-1.9 (m, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 18.3, 18.4, 25.2, 29.6, 29.8, 54.5, 61.4, 64.7, 64.8, 83.6, 83.8, 92.6, 92.7, 95.4, 95.6, 96.9, 120.0, 120.2, 126.7, 128.2, 128.5, 128.6, 140.4, 140.5; IR (NaCl, neat) 3377, 3044, 2945, 2864, 1493, 1450; MS 296 (M^+, 0.9), 295 (M^+-H, 2.8), 73 (100); HRMS (EI): calcd. for $C_{19}H_{20}O_3$ 296.1412, found 296.1405.

(*Z*)-8-Hydroxy-4-en-2,6-octadiyn-1-al diethyl acetal

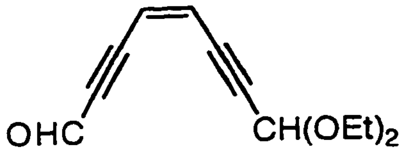


167

Tetrakis(triphenylphosphine)palladium (0.05 g, 0.043 mmol) and copper iodide (0.033 g, 0.17 mmol) were suspended in ether (1 mL) and a solution containing the enyne alcohol (156) (0.1 g, 0.85 mmol), *n*-butylamine 0.34 mL (3.4 mmol) in ether (1 mL) was injected over the catalyst. An ether solution (3 mL) containing propargyl aldehyde diethyl acetal (0.182 mL, 1.27 mmol) was subsequently injected over 16 hours using a syringe pump then the reaction mixture was filtered through Celite®, concentrated and purified by column chromatography on silicagel (ether/petroleum ether=1/2) solution to afford pure endiyne (0.14 g, 0.69 mmol) in 81%.^{1}H NMR (200 MHz, $CDCl_3$) δ 5.84 (dt, ^{5}J =1.5Hz, 1H), 5.82 (dd, ^{5}J

=1.1Hz, 1H), 5.39 (d, ^{5}J =1.1Hz, 1H), 4.4 (bs, 1H), 3.7 (m, 4H), 2.3 (bs, 1H), 1.2 (t, ^{3}J=7Hz, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 14.9, 51.2, 61.0, 82.3, 82.4, 91.4, 91.5, 96.0111.5, 118.5, 120.8, 128.5; IR (NaCl, neat) 3385, 2948, 2212, 1381, 1072; MS 208 (M^+, 0.8), 179 (M^+-Et, 24), 117 (100); HRMS (EI): calcd. for $C_{12}H_{16}O_3$ 208.1099 found 208.1104.

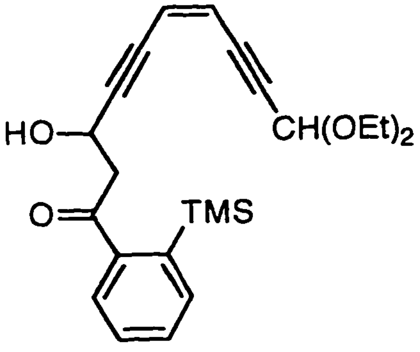
(*Z*)-3-Ene-1,5-hexadiyn-1,5-dicarbaldehyde diethyl acetal



168

The alcohol (167) (0.045 g, 0.21mmol) was dissolved in methylene chloride (0.5 mL) and added quickly to a suspension of pyridinium chlorochromate (0.18 g, 0.86 mmol), sodium acetate (0.1 g) and molecular sieves 4Å (0.1 g) in the same solvent (2 mL). The reaction was stopped after one hour by adding anhydrous ether (10 mL) and filtered through a short Fluorisil column. The solid residue remaining in the flask was washed with ether (3 x 3 mL) and also passed through the column. The combined organic phase was concentrated to afford pure unstable aldehyde (0.027 g, 0.12 mmol) in 61%.^{1}H NMR (200 MHz, $CDCl_3$) δ 9.3 (d, ^{5}J =0.9Hz, 1H), 6.17 (dd, ^{5}J =1.5Hz, ^{3}J=11Hz, 1H), 6.02 (dd, ^{5}J=1.5Hz, ^{3}J =11 Hz, 1H), 5,4 (d, 1H), 3.6 (m, 4H), 11.2 (t, ^{3}J=7.1Hz, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.0, 61.2, 81.2, 90.4, 91.5, 95.3, 117.8, 125.3, 176.1; IR (NaCl, neat) 2976, 2953, 2854, 2176, 1661, 1077; MS 205 (M^+-H, 01), 177 (M-Et^+, 16), 161 (100); HRMS (EI): calcd. for $C_{10}H_9O_3$ 177.0552, found 177.0569 (unstable compound).

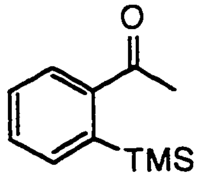
(*Z*)-10-Oxo-10-o-trimethylsilyl-8-hydroxy-4-decen-2,6-diyn-1-al diethyl acetal



169

Anhydrous cerium trichloride (0.41 g,1.72 mmol) was stirred in a round bottom flask at 140°C under vacuum (2 Torr) for 3 hours, cooled to room temperature and then suspended in tetrahydrofurane (6 mL) until a white slurry formed (2 hours under vigorous stirring). Meanwhile *o*-bromoacetophenone trimethylsilyl enol ether (0.47 g mL, 1.72 mmol) was dissolved in tetrahydrofurane (4 mL), cooled to - 78°C and treated dropwise with *n*-butyllithium in hexanes (0.69 mL, 1.76 mmol, 2.5M solution). The solution was transferred via canula after approximately 45 minutes over the cerium trichloride slurry that had been previously cooled to - 78°C. The color turned immediately lemon yellow and the metal exchange accomplished in one hour at the same temperature. Finally, the aldehyde (168) (0.25 g, 0.1.2 mmol in 1 mL tetrahydrofurane) was added dropwise over the organocerium solution and the reaction was monitored by TLC. After one hour, the reaction was quenched with ammonium chloride solution, partitioned between ether and brine, dried on anhydrous magnesium sulfate, concentrated and purified by column chromatography on Fluorisil (ether/petroleum ether=1/2)to afford 0.34 g of pure unexpected aldol condensation product in 72%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.8 (dd, ^{3}J = 8.8Hz, ^{4}J = 1.6Hz, 1H), 7.6 (m, 1H), 7.4 (m, 2H), 5.8 (bs, 2H), 5.3 (d, ^{5}J=0.9Hz), 5.1 (m, 1H), 3.3-3.7 (m, 7H), 1.1 (t, ^{3}J=7Hz, 6H), 0.2 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 0.1, 14.9, 46.2, 58.9, 60.8, 81.782.1, 91.4, 91.6, 97.4, 111.2, 118.7, 120.5, 128.6, 128.7, 129.0, 131.7, 135.8, 142.0, 200.3; IR (NaCl, neat) 3403, 3030, 2982, 1683, 1585, 1344; Anal. Calcd. for $C_{23}H_{30}O_4Si$: C, 69.35; H 7.53 . Found: C 69.16, ; H 7.46.

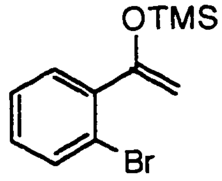
o-Trimethylsilylacetophenone



171

Trimethylsilyl *o*-bromoacetophenone enol ether (0.270 g, 1 mmol) was dissolved in tetrahydrofurane (5 mL), cooled to - 78°C and treated dropwise with *n*-butyllithium in hexanes (1 mL, 1 M solution). The solution was quenched after 15 minutes with methanol and then partitioned between ether and water. The organic phase was dried on anhydrous magnesium sulfate filtered through a pad of silicagel and concentrated to afford 0.176 g (0.91 mmol) of product which was pure by NMR spectroscopy. An analytical sample was prepared by column chromatography (ether/petroleum ether=1/9) eluent. Chemical yield 91%.^{1}H NMR (200 MHz, $CDCl_3$) δ 7.87 (m, 1H), 7.72 (m, 1H), 7.6 (m, 2H), 2.6 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 0.3, 27.3, 128.8, 129.6, 131.6, 135.9, 142.0, 142.4, 200.2; IR (NaCl, neat) 3056, 2950. 1685, 1562, 1428, 1358, 1256; MS 192 (0.1), 191 (0.6), 177(100); HRMS (EI): calcd. for $C_{10}H_{13}OSi$ 177.0735 found 177.0728.

o-Bromoacetophenone trimethylsilylenol ether

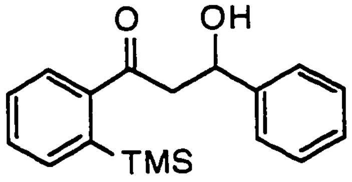


179

o-bromoacetophenone (1.6 mL, 12 mmol), chlorotrimethylsilane (1.9 mL, 15 mmol) and triethylamine (4.18 mL, 30 mmol) were dissolved in dimethylformamide (15 mL) and heated at 75^{o}C for 19 hours, then cooled to room temperature, diluted with 10 mL pentane and extracted successively with ice cold sodium bicarbonate solution, 1M hydrochloric acid, then sodium bicarbonate and brine. The organic phase was dried on anhydrous magnesium sulfate, concentrated and columned on Fluorisil with (ether/petroleum ether=3/97)to afford 1.8 g (6.65 mmol) pure enolate in 55%.^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54 (dd, ^4J=1.4Hz, ^3J

=7.8Hz, 1H), 7.38(dd, ^4J=1.8Hz, ^3J=7.6Hz, 1H), 7.2 (m, 1H), 7.1 (m, 1H), 4.554 and 4.552 (^5J = 0.6Hz, ^2J =1.4 Hz, 2H), 0.2 (s, 9H) ;^{13}C NMR (200 MHz, $CDCl_3$) δ 0.1, 96.0, 112.3, 121.6, 127.0, 129.3, 130.6, 133.2, 140.0, 155.9; IR (NaCl, neat) 3098, 3061, 2960, 1627, 15088, 1467, 1428, 1311; MS 272 (M^+, 8), 270 (M^+, 8), 257 (M-Me^+, 34), 255 (M-Me^+, 34), 191 (M-Br, 100); HRMS (EI): calcd. for C11H15BrOSi 270.0076, found 270.0045.

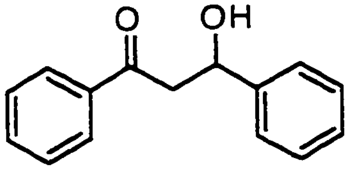
o-Trimethylsilylphenyl 2-phenyl-2-hydroxyethyl ketone



180

Trimethylsilyl *o*-bromoacetophenone enol ether (0.8 g, 2.9 mmol) was dissolved in tetrahydrofurane (8 mL), cooled to - 78°C and treated with n-butyllithium in hexanes (1.18 mL, 2.95 mmol, 2.5M solution). After 30 minutes, benzaldehyde (0.31 mL, 0.3 mmol) was added and the reaction was quenched after a half of an hour with ammonium chloride solution, extracted with sodium bicarbonate solution and brine, dried on anhydrous magnesium sulfate, filtered and concentrated under vacuum. Column chromatography on silica gel (ether/petroleum ether=1/5) afforded pure condensation product (0.65 g, 2.18 mmol) in 74% yield.^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (dd, ^3J= 7.5Hz, ^4J= 1.4Hz, 1H), 7.76 (dd, ^3J= 7.7Hz, ^4J= 1.4Hz, 1H), 7.42 (m, 7H), 5.4 (m, 1H), 3.61 (d, 1H), 3.39 (d, 1H), 3.36 (s, 1H), 0.3 (s, (H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 0.3, 47.8, 70.2125.7, 127.6, 128.5, 128.8, 129.2, 131.9, 136.1, 142.1, 142.2142.9, 202.4; IR (NaCl, neat) 3436, 3059, 3030, 2942, 1678, 1561, 1452, 1406, 1251; MS 280 (MW-18), 265 (100), 235; Anal. Calcd. for $C_{18}H_{22}O_2Si$: C 72.438; H 7.429 . Found: C 72.12, ; H 7.33.

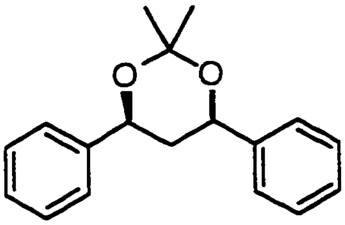
Phenyl 2-phenyl-2-hydroxyethyl ketone



183

Diisopropylamine (0.22 mL, 1.56 mmol) was dissolved in tetrahydrofurane (4.4 mL), cooled to 0°C and treated with a solution of *n*-butyllithium (0.64 mL, 1.56 mmol, 2.5M). After 10 minutes, acetophenone (0.19 mL, 1.58 mmol) was added dropwise and stirred for a quarter of an hour followed by the dropwise addition of benzaldehyde (0.165 mL, 1.56 mmol). The reaction was quenched after 30 minutes with sodium bicarbonate solution, extracted with brine, dried on anhydrous magnesium sulfate, concentrated and columned on silicagel (ether/petroleum ether=4/1)to afford 0.24 g (1.06 mmol) product in 67% yield.^{1}H NMR (200 MHz, CDCl3) δ 7.93 (dd, ^4J=1.4 Hz, ^3J=7.1 Hz, 2H)7.4 (m, 8H), 5.3 (m, 1H), 3.74 (d, ^3J = 2.4 Hz, 1H), 3.36 (d. 1H), 3.33 (s, 1H); ^{13}C NMR (200 MHz, CDCl3) δ 47.3, 69.9, 125.6, 127.6, 128.0, 128.4, 128.5, 133.5, 136.4, 142.9, 199.9; IR (NaCl, neat) 3453, 3061, 3030, 2911, 1677, 1597, 1449, 1210.

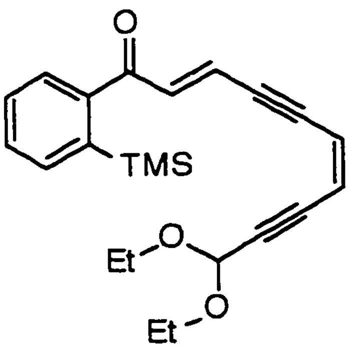
cis-4,6-Diphenyl-2,2-dimethyl-1,3-dioxacyclohexane



184

Ketoalcohol (183) (0.1g, 0.44 mmol) and tris(triphenylphosphine)rhodium chloride (0.02 g) were dissolved in tetrahydrofurane (8.5 mL) and cooled to -10°C. The solution was then treated dropwise with catechol borane (0.27 mL, 2.2 mmol) and allowed the reaction to warm up to 0°C in 4 hours. The reaction was quenched with methanol (4.2 mL) and saturated solution of sodium potassium tartrate (4.2 mL), allowed to stir overnight then partitioned between ethyl acetate and sodium bicarbonate solution. The organic phase was dried on anhydrous magnesium sulfate and concentrated down to 0.114 g crude which was pure diol by ^{1}H-NMR. The crude was taken in a solution of dimethylformamide (2 mL) containing 2-methoxypropene (0.3 mL, 3.2 mmol) and a catalytic amount of p-toluenesulphonic acid and allowed to stir overnight. Finally the reaction mixture was partitioned between ether and sodium bicarbonate saturated solution, then the organic phase was extracted with brine, dried on anhydrous magnesium sulfate, filtered and purified by column chromatography on silicagel (ether/petroleum ether=1/3) to afford diastereoselectively *syn* acetonide (0.098 g, 0.36 mmol) in 83% yield for two steps. 1H NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 10H), 5.06 (dd, ^3J = 2.75Hz, ^3J = 11.5 Hz, 2H), 2.0 and 1.94 (2t, ^3J=2.75Hz, 1H), 1.79 and 1.78 (2t, ^3J=11.5 Hz, 1H), 1.67, 1.60 and 1.53 (3s, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 19.8, 30.4, 41.3, 71.7, 76.4, 99.6, 125.9, 127.6, 128.5, 142.0; IR (NaCl, neat) ; MS 268 (M^+, 0.2), 253 ($M\text{-}Me^+$, 29.7), 193 (29.7), 149 (17.9), 104 (100); HRMS (EI): calcd. for $C_{18}H_{20}O_2$ 268.1463, found 268.1446.

(4*Z*, 8*E*)-10-*o*-Trimethylsilylphenyl-10-oxo-4,8-decadien-2,6-diyn-1-al diethylacetal



185

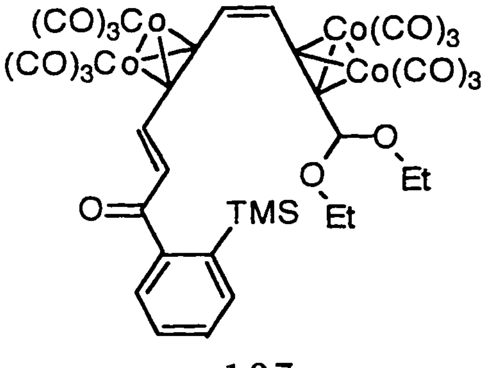
The starting alcohol (169) (0.189 g, 0.45 mmol), triphenylphosphine (3 g, 1.27 mmol) and *trans*-cinnamic acid (0.17 g, 1.17 mmol) were dissolved in tetrahydrofurane (5 mL) and then treated dropwise with a solution of diethylazodicarboxylate (DEAD) (0.2 g, 1.17 mmol) in the same solvent (1 mL). After approximately 1 hour the solvent was removed under vacuum and the residue taken in methylene chloride (10 mL), then briefly extracted with sodium bicarbonate and finally with brine. The organic phase was dried on anhydrous magnesium sulfate, filtered and purified on a silicagel column (ether/petroleum ether=1/3) to provide the product (0.16 g, 0.42 mmol) in 94% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.7 (m, 2H), 7.5

(m, 2H), 7.2 (AB, d, ^3J= 15.7Hz, 1H), 6.89 (dd, ^3J=15.7Hz, ^5J=2.2Hz, 1H), 6.06 (dd, ^3J =10.9Hz, ^5J =2.2Hz, 1H), 5.97 (dd, ^3J =10.9Hz, ^5J =1.2Hz, 1H), 5.45 (d, ^5J = 1.2Hz, 1H), 3.7 (m, 4H), 1.21 (t, ^3J=7Hz, 6H), 0.27 (s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 0.2, 15.1,61.0, 82.1, 91.6, 93.4, 94.9, 96.0, 120.3, 120.7, 124.8, 128.43, 128.48, 131.0, 136.0, 136.4, 142.0, 142.2, 192.9 ; IR (NaCl, neat) 3053, 2976, 2892, 2177, 1659, 1582; MS 380 (0.1), 379 (0.2), 365 (100), 335 (19), 273 (23); HRMS (EI): calcd. for $C_{22}H_{25}O_3Si$ 365.1573, found 365.1576.

7-*s cis*-{(2,3-η^2)-(6,7-η^2)-[(4*Z*, 8*E*)-10-*o*-Trimethylsilylphenyl-10-oxo-4,8-decadien-2,6-diyn-1-al]bishexacarbonyldicobalt} diethyl acetal (188)

7-*s trans*-{(2,3-η^2)-(6,7-η^2)-[(4*Z*, 8*E*)-10-*o*-Trimethylsilylphenyl-10-oxo-4,8-decadien-2,6-diyn-1-al]bishexacarbonyldicobalt} diethyl acetal (187)

{(2,3-η^2)-[(4*Z*, 8*E*)-10-*o*-Trimethylsilylphenyl-10-oxo-4,8-decadien-2,6-diyn-1-al]hexacarbonyldicobalt} diethyl acetal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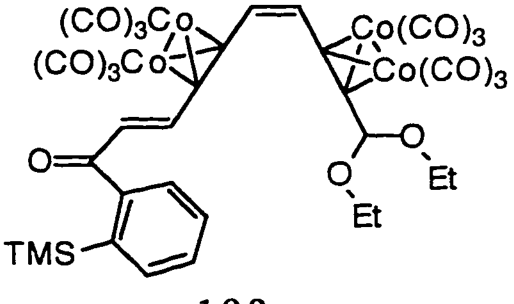
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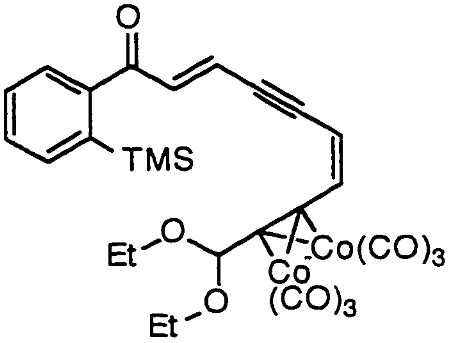
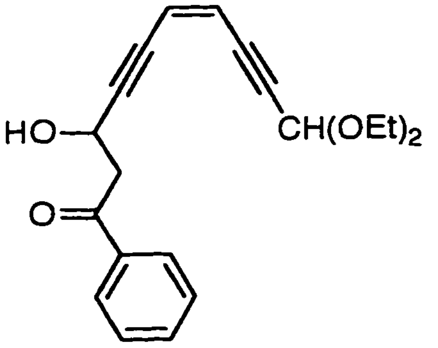

189

$Co_2(CO)_8$ (0.18 g, 0.47 mmol) was dissolved in 5 mL hexane, cooled to -23°C, treated with a solution of enediyne (185/186, an *s-cis* and *s-trans* mixture) (0.1 g, 0.26 mmol) in hexanes (5 mL) and allowed to warm up at room temperature. After one hour the reaction mixture was concentrated and purified on a silicagel column using the dry loading technique (ether/petroleum ether=1/9) to obtain three fractions. The first fraction was the *s-cis* tetracobalto complex (1 8 8)and weighed 0.154 g. The second fraction was *s-trans* tetracobalto complex (1 8 7) and weighed 0.105 g. The last fraction was the dicobalto complex (1 8 9) and weighed 0.056 g. The overall yield in desired teracobalto complex was 51%.*s-cis* isomer (1 8 8).^{1}H NMR (200 MHz, $CDCl_3$) δ 8.29 (AB, d, ^{3}J=14.5Hz, 1H), 7.73 (m, 2H), 7.47 (m, 2H), 7.1 (AB, d, ^{3}J = 14.5Hz, 1H), 6.59 and 6.48 (d, ^{3}J=11.9Hz, 2H), 5.74 (s, 1H), 3.7 (m,4H), 1.19 (t, ^{3}J=7.1 Hz, 6H), 0.3 (bs, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 0.3, 63.5, 81.3, 87.1, 87.5, 98.1, 101.1, 126.1, 127.8, 128.1, 128.5, 128.7, 131.0, 136.1, 142.0, 144.0, 144.2, 192.8, 198-199 m; IR (NaCl, neat) 2920. 2852, 2036, 1858, 1640, 1574; MS-FAB 783.9 (MW-6CO), 755.9 (MW-7CO), 727.9 (MW-8CO), 699.9 (MW-9CO), 671.9 (MW-10CO), 643.9 (MW-11 CO), 615.9 (MW-12CO); *s-trans* isomer (1 8 7).^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (AB, d, ^{3}J=14.7Hz, 1H), 7.7 (m, 2H), 7.5 (m, 2H), 7.17 (AB, d, ^{3}J =14.7Hz, 1H), 7.13 (bs, 2H), 5.56 (s, 1H), 3.7 (m, 4H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 1.0, 14.6, 62.3, 85.7, 86.7, 91.5, 94.6, 101.6, 127.7, 128.03, 128.06, 128.2, 129.0, 130.5, 131.0, 132.8, 135.6, 144.4, 192.4, 197.8 m ; IR (NaCl, neat) 2960, 2940, 2035, 1606, 1286; MS-EI 952 (MW), 924 (MW-CO), 896 (MW-2CO), 868 (MW-3CO), 840 (MW-4CO), 812 (MW-5CO), 784 (MW-6CO), , 755.9 (MW-7CO), 728 (MW-8CO), 700 (MW-9CO), 672 (MW-10CO), 644 (MW-11 CO), 616 (MW-12CO); (1 8 9).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, ^{3}J =6.8Hz, 1H), 7.65 (d, ^{3}J =7.7Hz, 1H), 7.48 (m,1H), 7.42 (m, 1H), 7.16 (d, ^{3}J=15.7Hz, 1H), 6.99 (d, ^{3}J=10.8Hz, 1H), 6.91 (d,d, ^{3}J = 15.7Hz, ^{5}J= 2.6Hz, 1H), 6.06 (dd, ^{3}J = 10.8Hz, ^{5}J= 2.6Hz, 1H), 5.6 (s, 1H), 3.8 (m, 2H), 3.6 (m, 2H), 1.2 (m, 6H), 0.3 (s, 9H); IR (NaCl, neat) 2960, 2940. 2171, 2058, 2028, 1660, 1586.

(*Z*)-10-Phenyl-10-oxo-8-hydroxy-4-decen-2,6-diyn-1-al diethyl acetal (195)

(*Z*)-10-(*o*-Bromophenyl)-10-oxo-8-hydroxy-4-decen-2,6-diyn-1-al diethyl acetal (194)



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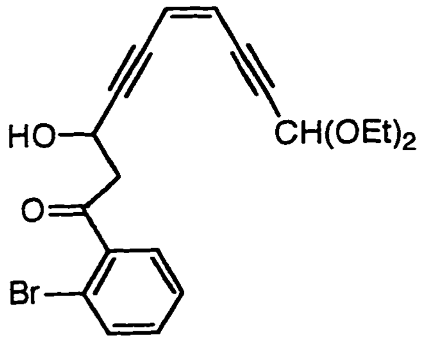
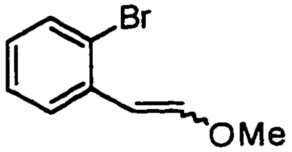


194

Anhydrous cerium trichloride (0.69 g, 2.8 mmol) was stirred in a round bottom flask at 140°C under vacuum (2 Torr) for 3 hours, cooled to room temperature and then suspended in tetrahydrofurane (7 mL) until a white slurry formed (2 hours under vigorous stirring). Meanwhile *o*-bromoacetophenone (0.19 mL, 1.4 mmol) was added over a -10°C precooled suspension of potassium hydride (0.056 g, 1.4 mmol) in tetrahydrofurane and allowed one hour at this temperature and another hour at 0°C for the formation of the potassium enolate. The reaction mixture was subsequently cooled to - 78°C and treated dropwise with *n*-butyllithium in hexanes (0.56 mL, 1.4 mmol, 2.5M solution). The solution was transferred via canula after approximately other 45 minutes over the cerium trichloride slurry that had been previously cooled to - 78°C. The solution turned immediately lemon yellow and was allowed to exchange for one hour at the same temperature. Finally, the aldehyde (0.165 g, 0.8 mmol in 1 mL tetrahydrofurane) was added dropwise over the organocerium solution and the reaction was monitored by TLC. After one hour, the reaction was quenched with ammonium chloride solution, partitioned between ether and brine, dried on anhydrous magnesium sulfate concentrated and purified by column chromatography on silicagel (ether/petroleum ether=3/7). The aldol condensaton product (195) 0.011 g (0.028 mmol) was isolated in 3.6% yield along with bromoderivative (194) (0.03 g, 0.09 mmol, 12%) as well as starting 2'-bromoacetophenone. (195) (0.048 g, 0.24 mmol). ^{1}H NMR (200 MHz,CDCl$_3$) δ 7.3 (m, 5H), 5.8 (m, 2H), 5.4 (m, 1H), 5.1 (m, 1H), 3.6 (m, 7H), 1.2 (m, 6H); (194)^{1}H NMR (200 MHz, CDCl$_3$) δ 7.96 (dd, ^4J =1.5Hz, ^3J =8.5Hz, 1H), 7.6 (dd, ^4J =1.8Hz, ^3J =7.3Hz, 1H), 7.2-7.5 (m, 2H), 5.8 (bs, 2H)5.4 (bs, 1H), 5.1 (m, 1H), 3.5 (m, 6H), 3.1 (d, ^3J =3.5Hz, 1H), 1.2 (m, 6H); ^{13}C NMR (200 MHz, CDCl$_3$) δ 14.9, 45.4, 49.3, 58.9, 60.9, 82.1, 91.5, 91.7, 92.9, 96.9, 97.2, 119.0, 120.5,121.9, 128.1128.0, 128.6, 128.9, 132.0, 133.7, 140.4, 201.5.

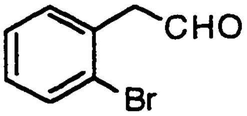
trans-1-*o*-Bromophenyl-2-methoxyethene
cis-1-*o*-Bromophenyl-2-methoxyethene



198

Potassium metal (1.8 g, 46 mmol) was dissolved in dry *tert*-butanol (57 mL) over 3 hours to provide a 0.8M solution of fresh potassium t-butoxide in *tert*-butanol. In a separate flask, *o*-bromobenzaldehyde (3.5 mL, 29.7 mmol) was added to a solution of mehtoxymethyltriphenylphosphonium chloride (13.9 g, 40.6 mmol) in *tert*-butanol (52.8 mL) and treated dropwise with previously prepared *tert*-butoxide solution (41 mL). The reaction was left overnight and then most of the *tert*-butanol distilled under vacuum. The remaining *tert*-butanol was distilled azeotropically with benzene. The remaining benzene solution was cooled and filtered through a plug of silicagel to afford after vacuum concentration 6.3 g (29.7 mmol) of a 1:1 mixture of *trans* /*cis* mixture of desired pure product in quantitative yield. Alternatively the reaction can be worked up by evaporating most of the *tert*-butanol under vacuum followed by addition of hexanes, filtration of the triphenylphosphinoxide, extraction with ammonium chloride solution, drying over anhydrous magnesium sulfate, filtration, concentration and purification on a silicagel column (ether/petroleum ether=2/98) to afford the product in 91% yield. 1H NMR (200 MHz, CDCl$_3$) δ 7.5 (d, ^3J=8Hz, 2H), 7.1-7.4 (m, 4H), 7.05 (m, 2H), 6.97 (d, ^3J=12.9 Hz, 1H), 6.24 (d, ^3J =7.2 Hz, 1H), 6.1 (d, ^3J=12.9Hz, 1H), 5.61 (d, ^3J=7.2 Hz, 1H), 3.76 (s, 3H), 3.73 (s,3H); ^{13}C NMR (200 MHz, CDCl$_3$) δ 56.4, 60.7, 103.7, 104.2, 122.6, 122.8, 125.531, 127.0, 128.4, 130.2, 132.4, 132.8, 135.0, 136.2, 149.1, 150.4; IR (NaCl, neat) 3059, 3012, 2941, 2830, 1642, 1466, 1237, 1098; MS 214 (M^+, 97), 212 (M^+, 100), ; HRMS (EI): calcd. for C_9H_9BrO 211.9837, found 211.9842.

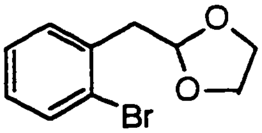
o-Bromophenylacetaldehyde



198'

o-bromo-2-methoxystyrene (0.214 g, 1 mmol) was dissolved in tetrahydrofurane (2 mL), cooled to -20°C, treated dropwise with 5 drops of concentrated hydrochloric acid and monitored by GC-MS. The reaction was done in 2 hours and stopped by addition of cooled ether (10 mL) followed by dropwise treatment with iced sodium bicarbonate solution until neutral pH was reached. The organic layer was subsequently extracted with brine, dried on anhydrous magnesium sulfate, filtered and concentrated to provide pure *o*-bromophenylacetaldehyde (0.191 g, 0.955 mmol) in 95.5% yield. 1H NMR (200 MHz, CDCl$_3$) δ 9.73 (t, ^3J =1.8Hz, 1H), 7.6 (dd, ^4J= 1.25 Hz, ^3J= 7.9Hz, 1H), 7.1-7.3 (m, 3H), 3.8 (d, ^3J=1.8 Hz, 2H); ^{13}C NMR (200 MHz,CDCl$_3$) δ 50.5, 125.0, 128.5, 129.3, 131.8, 133.4, 137.2, 198.2; IR (NaCl, neat) 3060, 2927, 2725, 1724, 1567, 1472; MS 200 (M$^+$, 14), 198 (M$^+$,14), 171 (M-CHO$^+$, 86), 169 (M-CHO$^+$, 87), 119 (100); HRMS (EI): calcd. for C$_8$H$_7$OBr 199.9637, found 199.9641.

o-Bromophenylacetaldehyde ethylene acetal



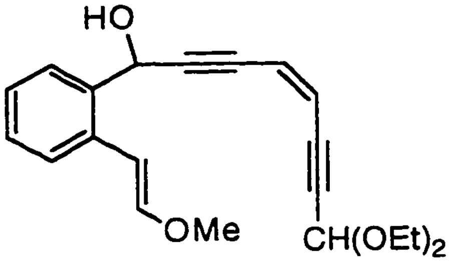
199

Aldehyde 198 (1.6 g, 8 mmol) and ethylene glycol (1.34 mL, 24 mmol) were dissolved in benzene (200 mL) and para-toluenesulphonic acid (0.16 g) was added. The solution was refluxed overnight with a Dean-Stark trap, then cooled and extracted with saturated sodium bicarbonate solution and the organic phase was finally dried on anhydrous magnesium sulphate and purified by column chromatography (ether/petroleum ether=3/97) to afford the pure product (1.27 g, 5.22 mmol) in 65.3% yield.^{1}H NMR (200 MHz, CDCl$_3$) δ 3.05 (d, ^3J=5 Hz, 2H), 3.7-3.9 (m, 4H), 5.1 (t, ^3J=5 Hz, 1H), 7.0 (ddd, $^3J1$ and $^3J2$ approx. 7.5 Hz, ^4J =1.9 Hz,1H), 7.15 (ddd, $^3J1$ and $^3J2$ approx. 7.5 Hz, ^4J =1.3 Hz, 1H), 7.25 (dd, ^3J =7.6 Hz, ^2J =1.9 Hz, 1H), 7.45 (dd, ^3J=7.9 Hz,^4J=1.3 Hz, 1 H); ^{13}C NMR (200 MHz, CDCl$_3$) δ

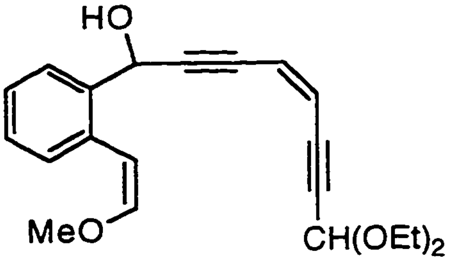
41.2, 65.6, 103.9, 125.6, 128,129, 132.5, 133.3, 136.5; IR (NaCl, neat) 2953, 2882, 1473.5, 1437.8, 1398.9, 1129.7, 1033.8, 989, 753.8; Anal. Calcd. for $C_{10}H_{11}BrO_2$: C, 49.58; H, 4.30. Found: C, 49.67; H, 4.54.

(*Z*)-8-[*o*-[(*E*)-2-Methoxyvinyl]phenyl]-8-hydroxy-4-octen-2,6-diyn-1-al diethyl acetal (200)

(*Z*)-8-[*o*-[(*Z*)-2-Methoxyvinyl]phenyl]-8-hydroxy-4-octen-2,6-diyn-1-al diethyl acetal (201)



200



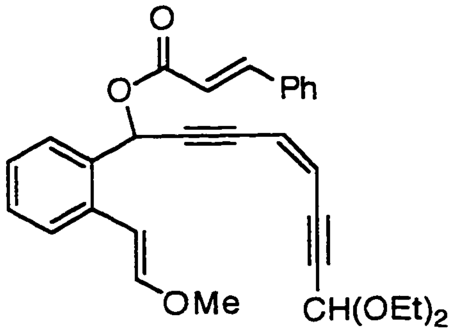
201

Cerium trichloride heptahydrate (0.52 g, 1.4 mmol) was stirred in a round bottom flask at 140°C under vacuum (2 Torr) for 3 hours, cooled to room temperature and then suspended in tetrahydrofurane (3 mL) until a white slurry formed (2 hours under vigorous stirring). Meanwhile bromoderivative (198, as an 1/1 mixture of *cis* and *trans* geometrical isomers) (0.25 g, 1.2 mmol) was dissolved in tetrahydrofurane (5 mL), cooled to - 78°C and treated dropwise with *n*-butyllithium in hexanes (1.4 mL, 2.4 mmol, 1.7 M) solution and allowed 6 hours for the metal halogen exchange. The solution was transferred via canula over the cerium trichloride slurry that had been previously cooled to - 78°C. The solution turned immediately lemon yellow and was allowed to exchange for one hour at the same temperature. Finally, the freshly prepared aldehyde (168) (0.2 g, 0.1 mmol in 1 mL tetrahydrofurane) was added dropwise over the organocerium solution and the reaction was monitored by TLC. After one hour, the reaction was quenched with deuterium oxide , partitioned between ether and brine, dried on anhydrous magnesium sulfate and purified by chromatography on silicagel (ether/petroleum ether=1/2) as eluent to afford desired alcohol (0.2 g, 0.56 mmol) in 56% yield as well as debrominated excess nucleophile (0.52 g, 0.4 mmol) with deuterium incorporated in the aromatic ring. (200-*trans*) ^{1}HNMR (500 MHz,$CDCl_3$) δ 7.68 (dd, ^4J

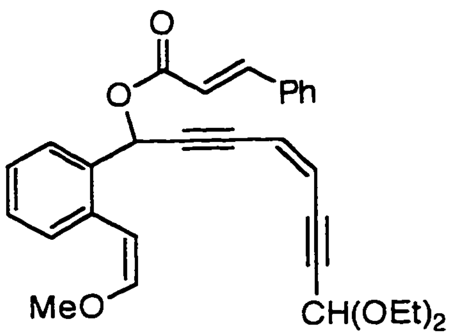
=1.8Hz, ^{3}J=7.2Hz, 1H), 7.1-7.3 (m, 3H), 6.87 (d, ^{3}J=12.8Hz, 1H), 6.19 (d, ^{3}J=12.8Hz, 1H), 5.93 (dd, ^{5}J=1.8Hz, ^{3}J=10.8 Hz, 1H), 5.87 (dd, ^{5}J =1.4 Hz, ^{3}J=10.8 Hz, 1H), 5.7 (s, 1H), 5.38 (d, ^{5}J=1.4 Hz, 1H), 3.5-3.8 (m, 4H), 3.7 (s, 3H), 2.8 (bs, 1H), 1.2 (m, 6H), ; ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.0, 56.4, 60.9, 61.0, 63.0, 82.4, 83.9, 91.6, 91.8, 97.1, 101.6, 119.1, 120.8, 126.3, 127.2, 128.6, 134.8, 136.2, 150.5; IR (NaCl, neat) 3412, 2954, 2848, 1643; Anal. Calcd. for $C_{21}H_{24}O_4$,: C 74.12; H 7.05. Found: C 74.52, ; H 7.43 (201-*cis*)^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, ^{4}J =1.35Hz, ^{3}J=7.7Hz, 1H), 7.69 (dd, ^{4}J =1.5Hz, ^{3}J=7.7Hz, 1H), 7.25 (dd, ^{4}J =1.5Hz, ^{3}J=7.7Hz, 1H), 7.19(dd, ^{4}J =1.36Hz, ^{3}J=7.7Hz, 1H), 6.2 (d, ^{3}J=7.16Hz, 1H), 6.19 (d, ^{3}J=12.8Hz, 1H), 5.93 (dd, ^{5}J =1.8Hz, ^{3}J=10.8 Hz, 1H), 5.85 (dd, ^{5}J=1.5 Hz, ^{3}J=10.8 Hz, 1H), 5.8(s, 1H), 5.6 (d, ^{3}J=7.15Hz, 1H), 5.38 (d, ^{5}J=1.47 Hz, 1H), 3.5-3.8 (m, 4H), 3.7 (s, 3H), 2.8 (bs, 1H), 1.2 (m, 6H), ; ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.6, 61.2, 61.6, 61.7, 63.7, 83.1, 84.3, 92.2, 92.4, 97.9, 102.2, 119.6, 121.6, 127.0, 127.7, 128.8, 130.4, 134.0, 137.0, 149.2; IR (NaCl, neat) 3412, 2954, 2848, 1643; Anal. Calcd. for $C_{21}H_{24}O_4$,: C 74.12; H 7.05. Found: C 74.52, ; H 7.43.

(*Z*)-8-[*o*-[(*E*)-2-Methoxyvinyl]phenyl]-8-(*trans*-cinnamoyloxy)--4-octen-2,6-diyn-1-al diethylacetal (202)

(*Z*)-8-[*o*-[(*Z*)-2-Methoxyvinyl]phenyl]-8-(*trans*-cinnamoyloxy)-4-octen-2,6-diyn-1-al diethylacetal (203)



202

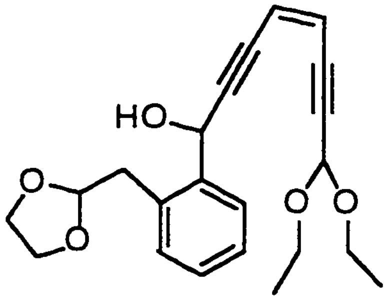


203

Method A. *trans*-cinnamic acid (0.058 g, 0.38 mmol) , N,N'-dicyclohexylcarbodiimide (0.086 g, 0.42 mmol), enediyne alcohol (200/201) (0.130 g, 0.38 mmol) and 4-(N-pyrolidyl)pyridine (0.005 g) were dissolved in methylene chloride (1 mL) and stirred for 1.5 hours under an inert atmosphere. After the reaction was done (TLC monitoring) methylene chloride (10 mL) were added and the precipitated dicyclohexyl urea removed by filtration. The filtrate was washed with brine , 5% acetic acid, sodium bicarbonate solution and brine again, dried on anhydrous magnesium sulfate and concentrated down to 0.145 g crude product which showed complete consumption of the starting alcohol. The product was purified by column chromatography (ether/petroleum ether=1/2) mixture to afford desired product (0.058 g, 0.12 mmol) as a 1:1 mixture of cis/trans stereoisomers along with starting alcohol (0.052 g, 0.15 mmol) (We assume that the alcohol was regenerated by hydrolysis of the ester on the column). Yield 54% (based on recovered alcohol).

Method B. In another experiment a solution of triphenylphosphine (0.059 g, 0.22 mmol) and alcohol (200/201) (0.05 g, 0.14 mmol) in ether (0.5 mL) was added dropwise to a solution of diethylazodicarboxylate (0.035 mL, 0.22 mmol) and *trans*- cinnamic acid (0.033 g, 0.22 mmol) solution in the same solvent (1 mL). After 1 hour the TLC showed no more starting material. The crude was purified on a silicagel column (ether/petroleum ether=1/3) to isolate the corresponding *cis* and *trans* geometrical isomers (0.025 g, 0.053 mmol) in a 1:1 ratio and starting alcohol (0.014 g, 0.04 mmol). Yield 53% based on recovered alcohol. (202-*trans*) ^1H NMR (200 MHz, $CDCl_3$) δ 7.7 (d, ^3J =16.1Hz, 1H), 7.2-7.5 (m, 9H), 6.88 (d, ^3J=12.7Hz, 1H), 6.44 (d, ^3J=16.0 Hz, 1H), 6.06 (d, ^3J=12.7 Hz, 1H), 5.92 (bs, 3H), 5.38 (s, 1H), 3.5-3.8 (m, 4H), 3.7 (s, 3H), 1.2 (m, 6H), ; ^{13}C NMR (200 MHz,$CDCl_3$) δ 15.1, 56.3, 61.0, 64.1, 82.1, 84.2, 91.6, 92.1, 93.4, 101.2, 117.3, 119.7, 120.2, 126.1, 126.3, 128.1, 128.5, 128.6, 128.9, 129.3, 130.5, 133.0, 134.2, 135.4, 145.9, 151.2, 166.2; IR (NaCl, neat) 3060, 2975, 2932, 2880, 1715, 1636, 1450, 1330 ; Anal. Calcd. for $C_{30}H_{30}O_5$,: C 76.57; H 6.42 . Found: C 76.01 ; H 6.29 (203-*cis*) ^1H NMR (200 MHz, $CDCl_3$) δ 7.85 (d, ^3J =9.0Hz, 1H), 7.77 (d, ^3J =6.5Hz, 1H), 7.7(d, ^3J =16.1Hz, 1H), 7.5 (m, 2H), 7.2 (m, 5H), 6.92 (d, ^5J =1.3Hz, 1H), 6.43 (d, ^3J=16.1Hz, 1H), 6.21 (d, ^3J=7.14 Hz, 1H), 5.9 (m, 2H), 5.45 (d, ^3J=7.14Hz, 1H), 5.38 (s, 1H), 3.5-3.7 (m, 4H), 3.7 (s, 3H), 1.2 (m, 6H), ; ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.0, 61.0, 64.1, 82.2, 84.0, 91.7, 93.7, 101.2, 117.5, 119.5, 120.4, 126.4, 128.1, 128.2, 128.6, 128.8, 128.9, 129.9, 130.4, 132.9, 134.0, 134.3, 145.7, 148.9, 165.6, ; IR (NaCl, neat) 2975, 2929, 1714, 1637 ; Anal. Calcd. for $C_{30}H_{30}O_5$,: C 76.57; H 6.42 . Found: C 76.01 ; H 6.29.

(*Z*)-8-[o-(2,5-Dioxacyclopentylmethyl)phenyl]-8-hydroxy-4-en-2,6-octadiyn-1-al diethyl acetal

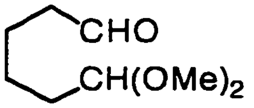


MW=370

204

Bromoderivative (199) (0.29 g, 1.2 mmol) was dissolved in tetrahydrofurane (5 mL) and treated at - 78°C with tert-butyllithium (1.42 mL, 2.4 mmol, 1.7 M solution in hexanes) allowing 5 hours for the metal halogen exchange. Subsequently the reddish solution was transferred via canula over 1.4 mmol cerium trichloride (prepared as described above) and allowed one hour for the metal exchange to take place at - 78°C. Aldehyde (168) (0.250 g) dissolved in tetrahydrofurane (2 mL) was added dropwise to the yellow cerium acetylide solution and after 30 minutes the reaction was quenched with sodium bicarbonate aqueous solution and allowed to warm up to room temperature. The solution was partitioned between ether/aqueous sodium bicarbonate then the organic phase was extracted with brine, dried on anhydrous magnesium sulfate filtered and purified by column chromatography (ether/petroleum ether=1/9 up tp pure ether to afford pure alcohol (0.105 g, 0.28 mmol) in 29% yield. ^{1}H NMR (200 MHz, CDCl3) δ 7-7.22 (m, 4H), 5.82 (d, ^5J=1.4 Hz, 1H), 5.74 (s, 1H), 5.7-5.8 (m,1H), 5.3 (s, 1H), 5.0 (t, ^3J=4.3 Hz, 1H), 3.4-3.9 (m, 8H), 3.15 (^3J=4.3 Hz, ^2J=12 Hz, 2H), 1.0-1.2 (m, 6H); ^{13}C NMR (200 MHz, CDCl3) δ 15.6, 37.4, 61.5, 61.6, 63.7, 65.6, 83.0, 84.0,92.3, 97.7, 104.9, 119.5, 121.5,125.7,126.4,128.0, 129.1,132.3, 140.0; IR (NaCl, neat) 3413, 2921, 1644.4, 1449, 1360.2; Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.35; H, 7.02. Found: C, 71.37; H, 7.15.

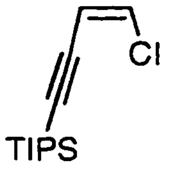
Adipic dialdehyde dimetyl acetal



211

Cyclohexene (1.5 mL, 14.6 mmol) was dissolved in 35 mL methylene chloride and 7 mL methanol, cooled to -78 °C and ozonized for two hours. The reaction mixture was purged with nitrogen then treated with 0.2 g of p-toluene sulphonic acid and allowed to stir for 1.5 hours at room temperature. At this point 1.5 g sodium bicarbonate was added and after other quarter of an hour the reaction was cooled to -30°C and treated with dimethyl sulfide overnight. The suspension was filtered through a frite and the solvent removed under vacuum at room temperature. The product was purified by column chromatography on silicagel using 1% triethyl amine in 30% ether in (ether/petroleum ether=/) to afford 1.9 g (11.9 mmol) pure material in 81% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.6 (t, ^3J = 1.7Hz, 1H), 4.2 (t, ^3J= 5.5Hz, 1H), 3.2 (s, 6H), 2.3 (dt, $^3J_1$ = 1.7Hz, $^3J_2$ = 7.2Hz, 2H), 1.5 (m, 4H), 1.3 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 21.7, 23.9, 32.1, 43.6, 52.5, 104.1, 202.1; IR (NaCl, neat) 2940, 2860, 2720, 1727, 1453, 1378, 1083; MS 159.1 (M-H$^+$, 1), 129 (M-OMe$^+$, 5), 75 (100); HRMS (EI): calcd. for $C_8H_{15}O_3$ 159.1021, found 159.1031. (Lit. ref. 50)

(*Z*)-Chloro-4-triisopropylsilyl-1-buten-3-yne

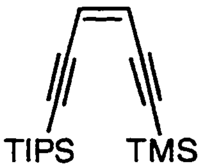


213

Copper (I) iodide (0.61 g, 3 mmol) was added to a stirred mixture of triisopropylsilylacetylene (10.98 g, 108 mmol), 1.2-*cis*-dichloroethylene (10.63 mL, 210 mmol), tetrakis(triphenylphosphine)palladium (0) (3.76 g, 3 mmol) and *n*-butylamine (21 mL, 216 mmol) in ether (500 mL). The reaction was stirred for 15 hours at room temperature, then filtered through a plug of Celite®, washed thoroughly with ether, concentrated and purified by column chromatography (petroleum ether) to yield 21.7 g of pure product

(83%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.37 (d, *J*=7.4 Hz, 1H), 5.88 (d, *J*=7.4 Hz, 1H), 1.08 (s, 18H), 1.06 (s, 3H); ^{13}C NMR δ 129.2, 112.3, 100.7, 100.1, 18.6, 11.2; IR (NaCl, neat, cm^{-1}) 2945, 2154, 1463, 882, 671; HRMS calcd for $C_{13}H_{23}SiCl$ (M^+): 242.1257 found 242.1285. (Lit. ref. 35c)

(Z)-1-Triisopropylsilyl-6-trimethylsilyl-3-hexen-1,5-diyne

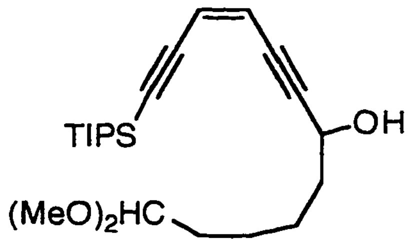


215

Method A. Copper (I) iodide (0.19 g, 1 mmol) was added to a stirred mixture of trimethylsilylsilylacetylene (1.7 ml, 12 mmol), chloroenyne (214) (2.45 g, 10 mmol), tetra-kis(triphenylphosphine)-palladium (0) (0.58 g, 0.5 mmol) and *n*-butylamine (2 ml, 20 mmol) in ether (20 mL). The reaction was stirred for 15 hours at room temperature, then filtered through a plug of Celite®, washed thoroughly with ether, concentrated and purified by column chromatography (petroleum ether) to yield the pure product (2.4 g, 7.8 mmol) in 78% yield.

Method B. A suspension of *tetrakis*-(triphenylphosphine)-palladium (0) (1.16 g,1 mmol), copper iodide (0.38 g, 2 mmol), *cis*-dichloroethylene (3 mL, 40 mmol), butylamine (4 mL, 40 mmol) in benzene (40 mL) was treated (by syringe pump technique) with triisopropylsilyl acetylene (4.5 mL, 20 mmol) over 4 hours and then allowed to react overnight. The solvent was evaporated under vacuum and piperidine (50 mL) were added to the crude followed by *bis*-(benzonitrile)palladium dichloride (0.39 g, 1 mmol) and trimethylsilylacetylene (3.4 mL, 24 mmol). The reaction was quenched next day with saturated ammonium chloride solution and partitioned between ether and water. The organic phase was dried on anhydrous magnesium sulfate filtered and concentrated to crude product which was purified by column chromatography on silicagel to afford pure enediyne (4.2 g, 13.8 mmol) in 69% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ ; ^{13}C NMR (200 MHz, $CDCl_3$) δ ; IR (NaCl, neat) ; MS 304 (M^+, 6), 261 (M^+-iPr, 98), 219 (100), 191 (58), 177 (98). (Lit. ref. 35c)

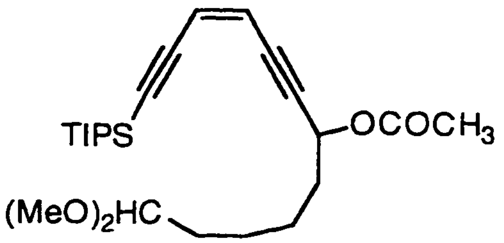
(Z)-12-Triisopropylsilyl-6-hydroxy-9-dodecen-7,11-diyn-1-al dimethyl acetal



217

Commercial anhydrous cerium trichloride (Aldrich) (0.1885 g, 0.76 mmol) was suspended in tetrahydrofurane (3 mL) until a white slurry formed (2 hours under vigorous stirring). Meanwhile, triisopropylsilyl protected enediyne (0.15 g, 0.63 mmol) were dissolved in tetrahydrofurane (2 mL), cooled to - 78°C and treated dropwise with *n*-butyllithium in hexanes (1.26 mL, 0.63 mmol, 0.5 M solution). The solution was transferred via canula after approximately 45 minutes over the cerium trichloride slurry that had been previously cooled to - 78°C. The solution was allowed to exchange metal for one hour at the same temperature. Finally, the aldehyde (211) (0.16 g, 1 mmol in 2 mL tetrahydrofurane) was added dropwise over the organocerium solution and the reaction was monitored by TLC. After one hour, the reaction was quenched with ammonium chloride solution, partitioned between ether and brine, dried on anhydrous magnesium sulfate and purified by column chromatography (ethyl acetate/petroleum ether=1/2.5) to afford the product (0.12 g, 0.3 mmol) in 48% yield and recovered enediyne (0.048 g, 0.2 mmol) .^{1}H NMR (200 MHz,$CDCl_3$) δ 5.8 (s, 2H), 4.5 (t, ^3J =6.4Hz, 1H), 4.3 (t, ^3J=5.6Hz, 1H), 3.3 (s, 6H), 1.1 (s, 21H); ^{13}C NMR (200 MHz,$CDCl_3$) δ 11.4, 18.5, 25.2, 25.9, 33.0, 38.2, 53.6, 63.2, 83.1, 96.8, 99.5, 104.6, 120.3, 120.7; IR (NaCl, neat) ; MS 392 (M^+, 0.3), 361 (M-OMe^+, 1.3), 317 (16), 285 (14), 75 (100); HRMS (EI): calcd. for $C_{23}H_{40}O_3Si$ 392.2746, found 392.2754.

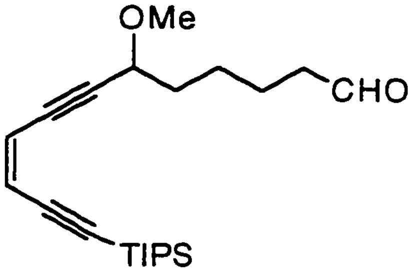
(*Z*)-12-Triisopropylsilyl-6-acetoxy-9-dodecen-7,11-diyn-1-al dimethyl acetal



218

Alcohol (217) (0.4 g, 1 mmol) triethylamine (0.56 mL, 4 mmol) and a catalytic amount of DMAP were dissolved in tetrahydrofurane (5 mL) treated dropwise with acetyl chloride (0.14 mL, 2 mmol) and allowed to react overnight. The reaction was partitioned between 1M HCl and ether and then extracted with brine, concentrated and purified by column chromatography (10% ether/petroleum.ether) to yield the desired product (0.24 g, 0.55 mmol) in 55% chemical yield.^{1}H NMR (200 MHz, $CDCl_3$) δ 5.83 (s, 2H), 5.55 (t, 1H), 4.36 (t, 1H), 3.26 (s, 6H), 2.05 (s, 3H), 0.8-1.8 (m, 8H), 1.1 (s, 21H); ^{13}C NMR (200 MHz,$CDCl_3$) δ 11.4, 18.5, 21.4, 25.2, 25.8, 33.1, 38.2, 53.7, 66.1, 83.3, 96.7, 99.5, 104.9, 120.4, 120.7, 170.2.

(*Z*)-12-Triisopropylsilyl-6-methoxy-9-dodecen-7,11-diyn-1-al

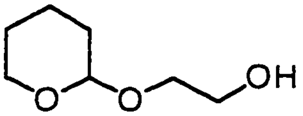


219

Method A. Adipaldehyde dimethylacetal (0.125 g, 0.78 mmol) an (*Z*)-1-triisopropylsilyl-6-trimethylsilyl-3-hexene-1,5-diyne (0.95 g, 3.12 mmol) were dissolved in methylene chloride (16 mL) and treated at - 78°C with titanium chloride (1.1 mL, 1.1 mmol, 1M solution in methylene chloride). After 20 minutes, the reaction was quenched with methanol (1 mL) and the reaction mixture was allowed to warm up to room temperature, taken in methylene chloride (100 mL) and extracted thrice with 1M hydrochloric acid

solution followed by rinsing with water, sodium bicarbonate and water again. After column chromatography (ether/petroleum ether=1/4) we recovered starting enediyne (0.39 g, 1.28 mmol) and isolated the desired product (0.068 g, 0.18 mmol) in 23% yield.
Method B. Alcohol (217) (0.04g, 0.1mmol) was dissolved in tetrahydrofurane (1 mL), added dropwise to a sodium hydride (0.024 g, 1mmol) suspension in the same solvent (1 mL) and allowed to react for a half of an hour. The reaction mixture was then treated with MeI (0.120 mL, 2 mmol) and was quenched the next day with saturated sodium bicarbonate. The resulting solution was partitioned between water and ether and then extracted with brine, concentrated and submitted directly to deprotection in 2-methoxyethene in the presence of a catalytic amount of *para*-toluenesulphonic acid. The reaction was purified by column chromatography (ether/petroleum ether=1/9) to yield the desired product (0.022 g, 0.055 mmol) in 55% chemical yield. ^{1}H NMR (200 MHz,CDCl3) δ 9.7 (t, ^3J =1.7Hz, 1H), 5.8 (s, 2H), 4.1 (m, 1H), 2.4 (m, 2H), 1.3-1.8 (m, 6H), 1.1 (bs, 21H); ^{13}C NMR (200 MHz, CDCl3) δ 11.2, 18.6, 21.8, 24.8, 35.3, 43.7, 56.6, 71.4, 83.4, 95.7, 99.6, 103.6, 119.5, 120.0, 202.4; IR (NaCl, neat) 2950, 2825, 1725.4; MS 317 (M-iPr+, 100); HRMS (EI): calcd. for $C_{19}H_{29}O_2Si$ 317.1936, found 317.1926.

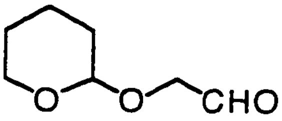
2-(2-Tetrahydropyranyloxy)ethanol



223

Ethylene glycol (4 mL, 70 mmol) and dihydropyrane (0.6 mL, 6.3 mmol) were dissolved in a minimal quantity of dimethylformamide to ensure homogeneity (1.6 mL) and *para*-toluenesulphonic acid (0.05 g) was added. The reaction mixture was allowed to stir overnight and then partitioned between ethyl acetate and saturated sodium bicarbonate solution, back extracted with ethyl acetate and the combined organic phase reextracted with brine, dried on anhydrous magnesium sulfate, filtered and columned on neutral alumina to give the pure product (0.43 g, 3 mmol) in 47% yield. ^{1}H NMR (200 MHz, CDCl3) δ 4.38 (m,1H), 3.2-3.8 (m, 6H), 3.08 (bs, 1H), 1.3-1.7 (m, 6H); ^{13}C NMR (200 MHz, CDCl3) δ 20.4, 25.8, 31.2, 62.52, 63.53, 70.9, 100.4 ; IR (NaCl, neat) 3406, 2922, 1449; Anal. Calcd. for $C_7H_{14}O_3$: C, 57.53; H, 9.59. Found: C, 57.39; H, 9.77.

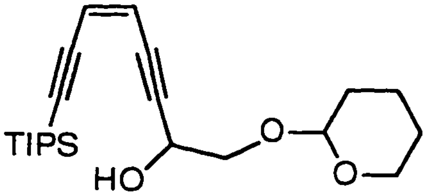
2-Oxacycloxyloxyacetaldehyde



224

Pyridinium sulphur trioxide (0.972 g, 6.21 mmol) was dissolved in dimethylsulphoxide (10 mL) and treated dropwise with a DMSO solution (3.6 mL) of alcohol (223) (0.3 g, 2 mmol) and triethylamine (2.3 mL, 16 mmol). The reaction mixture was partitioned after one hour between water and ethyl acetate. The aqueous layer was back extracted three times with ethyl acetate and the combined organic phase was washed with brine, dried over anhydrous magnesium sulfate concentrated and purified by column chromatography (ethyl acetate/petroleum ether 1/8) to yield the desired pure compound (0.2 g, 1.38 mol) in 69% yield. ^{1}H NMR (200 MHz,CDCl3) δ 9.6 (bs, 1H), 4.5 (m, 1H), 4.1 (m, 2H), 3.3-3.8 (m, 2H), 1.3-1.9 (m, 6H); ^{13}C NMR (200 MHz, CDCl3) δ 19.2, 25.1, 30.2, 62.6, 72.9, 99.4, 200.1; IR (NaCl, neat) 2940, 28880, 1735; Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.38. Found: C, 58.33; H, 8.07.

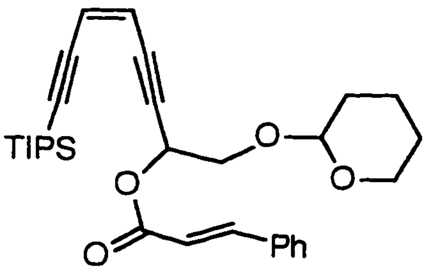
(*Z*)-1-(2'-oxacyclohexyl)oxy-8-triisopropylsilyl-5-octen-3,7-diyn-2-ol



225

TIPS protected enediyne (216) (0.146 g, 0.63 mmol) was dissolved in tetrahydrofurane (2 mL) and treated at - 78°C with n-butyllithium (0.25 mL, 0.63 mmol, 2.5 M solution in hexanes). The aldehyde (224) (0.043 g, 0.3 mmol) was dissolved in tetrahydrofurane (1 mL) and added dropwise to the lithium acetylide solution. The reaction was allowed to slowly warm up to 0°C and quenched with deuterated water. (The GC-MS showed incorporation of deuterium in the enediyne) The reaction mixture was partitioned between 10% ammonium chloride solution and ethyl acetate, then the organic phase was extracted with brine , dried on anhydrous magnesium sulfate and finally the crude was purified by flash chromatography (ethyl acetate/hexanes=1/5) to provide deuterated enediyne (0.080 g, 0.34 mmol) and the pure product (0.046 g, 0.12 mmol) in 41% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 5.8 (m, 2H), 4.7 (m, 1H), 4.6 and 4.5 (2m, 1H), 3.8-4.0 (m, 2H), 3.6-3.75 (m, 1H), 3.4-3.6 (m, 1H), 3.0 (bs, 1H), 1.4-1.9 (m, 6H), 1.1 (m,21H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 11.2, 18.5, 19.6, 19.9, 25.1, 25.2, 30.5, 30.7, 62.5, 62.6, 62.9, 63.4, 72.4, 73.2, 82.8, 82.9, 94.3, 94.6, 99.71, 99.72, 100.20, 100.23, 103.6, 119.52, 119.55, 120.32, 120.37; IR (NaCl, neat) 3401, 2945, 2880, 1460, 1387.

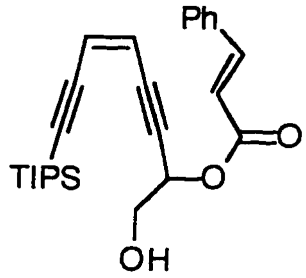
(*Z*)-1-(2-oxacyclohexyl)oxy-2-cinnamoyloxy-8-triisopropylsilyl-5-octen-3,7-diyne



226

trans-cinnamic acid (1.0 g, 6 mmol) was dissolved in benzene (10 mL), treated dropwise with oxalyl chloride (0.8 mL, 9 mmol) and allowed one hour to react. The reaction mixture was concentrated and the crude was dissolved in methylene chloride (5 mL) and added over a solution of alcohol (225) (0.38 g, 1 mol) in methylene chloride/pyrridine 1/1 (10 mL) at 0°C. The reaction was allowed to warm up slowly to room temperature and the next day partitioned between ether and water. The acidity of the water phase was adjusted to pH=2 with 10% HCl and subsequently the ether phase was extracted with sodium bicarbonate, brine and finally dried on anhydrous magnesium sulfate. Purification on a silicagel column (ether/petroleum ether=1/5.5) gave the pure ester (0.403 g, 0,8 mol) in 80% yield. ^1H NMR (200 MHz, $CDCl_3$) δ 7.6(d, ^3J=16Hz, 1H), 7.35-7.5 (m,2H), 7.2-7.35 (m, 3H), 6.3 (d, ^3J=16Hz, 1H), 5.7-5.9 (m, 3H), 4.6 (m, 1H), 3.6-4.0 (m, 3H), 3.4 (m, 1H), 1.3-1.8 (m, 6H), 1.0 (s, 21H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 11.0, 14.0, 18.4, 18.5, 22.5, 25.2, 30.1, 31.5, 61.7, 62.8, 64.0, 64.7, 68.7, 83.4, 91.2, 97.5, 99.1, 100.0, 103.3, 117.3, 119.0, 120.8, 120.9, 127.9, 128.8, 130.3, 134.1, 145.4, 165.5; IR (NaCl, neat) 2942, 2865, 1722, 1637, 1458.

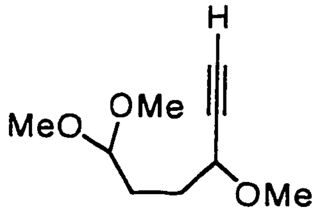
(*Z*)-2-Cinnamoyloxy-8-triisopropylsilyl-5-octen-3,7-diyn-1-ol



228

Ketal (226) (0.38 g, 0.75 mmol) was dissolved in tetrahydrofurane (18 mL) and treated with 5% HCl (2 mL). The reaction was allowed to stir overnight to afford pure desired product (0.24 g, 0.57 mmol). Yield=76%. An analytical sample was purified by flash chromatography.^{1}H NMR (200 MHz, CDCl$_3$) δ 7.6 (d, ^3J=16Hz, 1H), 7.4 (m, 2H), 7.25 (m, 3H), 6.35 (d, ^3J=16Hz, 1H), 5.75 (bs, 2H), 5.68 (m, 1H), 3,6 (bs, 1H), 3.75 (d, 2H), 0.95 (s, 21 H);^{13}C NMR (200 MHz, CDCl$_3$) δ 11.2, 18.5, 58.4, 63.9, 83.3, 91.4, 100.1, 103.4, 117.35, 119.20, 120.9, 127.8, 128.8, 130.4, 134.15, 145.3, 165.3.

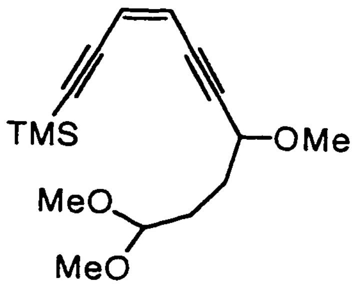
4-Methoxy-5-hexyn-1-al dimethyl acetal



234

2,5-Dimethoxyfurane (0.990 mL, 7.5 mmol) and *bis*-trimehtylsilylacetylene (1.68 mL, mmol) were dissolved in mehtylene chloride (30 mL), cooled at - 78°C and treated with titanium tetrachloride (11.25 mL 1M solution in methylene chloride. After 30 minutes the reaction was quenched with excess methanol and allowed to warm up at room temperature, then extracted with 10% hydrochloric acid solution, and brine, dried on anhydrous magnesium sulfate to get 1.85 g crude product. This crude was dissolved in acetonitrile (10 mL) TEBA (0.35 mmol) was added and the solution was treted with a 12 M sodium hydroxide solution under vigorous stirring at 0°C for 45 minutes. The reaction was quenched by the addition of 1/1 mixture water and ether (60 ml), then the organic phase was further extracted with water and brine, dried on anhydrous magnesium sulfate and finally purified by column chromatography (ether/petroleum ether 1/19) to get the pure compound (0.7 g) in 54% overall yield for the two steps. ^{1}H NMR (200 MHz,CDCl3) δ 4.3 (m, 1H), 3.9 (m, 1H), 3.3 (s, 3H), 3.2 (s, 6H), 2.4 (d, ^4J =2.0Hz, 1H), 1.7 (m, 4H); ^{13}C NMR (200 MHz, CDCl3) δ 27.9, 30.4, 52.6, 56.3, 70.5, 73.9, 82.2, 104.0; IR (NaCl, neat) 3273, 2935, 2828, 2109, 1453, 1092; MS-EI 172 (0.03), 171 (0.3), 141 (2.2), 109 (24.7), 75 (100); HRMS (EI): calcd for $C_8H_{13}O_2$, found 141.09344.

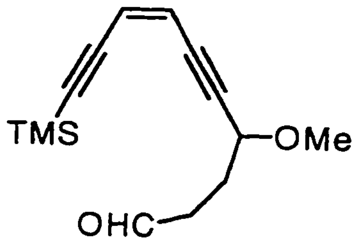
(*Z*)-4-Methoxy-10-trimethylsilyl-7-decen-5,9-diyn-1-al dimethyl acetal



235

Trimethylsilylacetylene (3 mL, 21 mmol), *cis*-dichloroethylene (3 mL, 42 mmol) and n-butylamine (10 mL, 100 mmol) were dissolved in ether (50 mL). Tetrakis(triphenylphosphine)palladium (1.16 g, 1 mmol) and copper iodide (0.4 g, 2.2 mmol) were added and the reaction was stirred under inert atmosphere overnight. The reaction mixture was concentrated and the crude taken in petroleum ether, filtered through a plug of Celite®, concentrated again and columned on silicagel (ether/petroleum ether=1/9) to afford the pure enyne (2.0 g, mmol) in 57% yield (GC-MS). The alkyne (234) (0.172 g, 1 mmol), eneyne (231) (0.16 g, 1 mmol) and n-butylamine (1 mL, 10 mmol) were dissolved in ether (10 mL). Tetrakis(triphenylphosphine)palladium (0.05 g, 0.05 mmol) and copper iodide (0.04 g, 0.21 mmol) were added to the reaction mixture and allowed to stir overnight. After concentration of the reaction mixture the crude was taken in ether and filtered through a plug of Celite® then concentrated and columned on silicagel (ether/petroleum ether=1/4) to obtain the pure enediyne (0.120 g (0.40 mmol)) in 40% yield. ^{1}H NMR (200 MHz,CDCl3) δ 5.8 (m, 2H), 4.4 (m, 1H), 4.1 (m, 1H), 3.4 (s, 3H), 3.3 (s, 6H), 1.7 (m, 4H), 0.1 (s, 9H);^{13}C NMR (200 MHz,$CDCl_3$) δ -0.3, 28.0, 30.4, 30.5, 52.6, 56.5, 71.2, 83.3, 95.8, 101.8, 102.9, 104.1, 119.8, 110.0; IR (NaCl, neat) 2954, 2858, 2827, 2145, 1453, 1251, 1093; MS-EI 293 (0.04), 279 (0.17), 263 (5.22), 191 (26.8), 159 (17.2), 89 (27.3), 75 (100); HRMS (EI): calcd for $C_{15}H_{23}O_2Si$ 263.1467, found 263.1467.

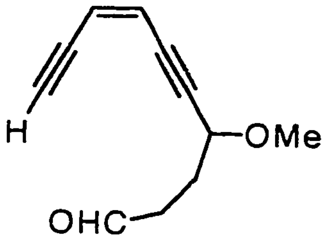
(*Z*)-4-Methoxy-10-trimethylsilyl-7-decen-5,9-diyn-1-al



237

Dimethylacetal (235) (0.080 g, 0.27 mmol) was dissolved in dry acetone (3 mL) and treated with a catalytic amount of *para*-toluenesulphonic acid. The next day the reaction mixture was partitioned between chloroform and water, dried, and purified by column chromatography (ether/petroleum ether=1/9) to yield the pure aldehyde (0.042 g, 0.17 mmol) in 63% yield.^{1}H NMR (200 MHz, $CDCl_3$) δ 9.8 (bs, 1H), 5.8 (s, 2H), 4.2 (t, 1H), 3.4 (s, 3H), 2.6 (t, 2H), 2.1 (m, 2H), 0.18 (s, 9H);^{13}C NMR (200 MHz, $CDCl_3$) δ -0.2, 28.1, 39.5, 56.6, 70.4, 83.8, 94.9, 101.7, 103.1, 119.6, 120.2, 201.5; IR (NaCl, neat) 2950.5, 2825, 2144, 1725, 1446, 1390, 1251, 1098; MS-EI 248 (0.9), 220 (1.2), 191 (11.5)159.0 (10.9), 115.1 (11.8)84.0 (100); HRMS (EI): calcd for $C_{14}H_{20}O_2Si$, 248.1232, found 248. 1219.

(*Z*)-4-Methoxy-7-decen-5,9-diyn-1-al

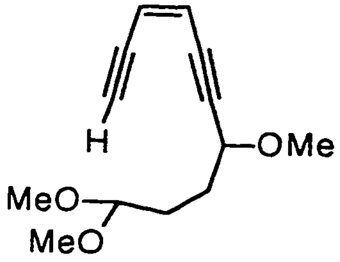


239

Starting enediyne (237) (0.11 g, 0.44 mmol) and acetic anhydride (0.084 mL, 0.88 mmol) were dissolved in acetonitrile (2 mL) cesium fluoride (0.23 g, 1.54 mmol) and sodium bicarbonate

(0.037 g) was added and the reaction was stirred under nitrogen for three hours when no more starting material was present by TLC. The reaction mixture was filtered through silicagel, concentrated and purified by column chromatography (ether/petroleum ether=1/7) to afford the pure pure deprotected endiyne (0.069 g, 0.39 mmol) in 89%. Special Precautions Required: i) CsF was dried by heating under vacuum for two hours at 100 deg. ii) acetonitrile was dried by refluxing with calcium hydride and distillation. iii) acetic anhydride was dried by refluxing with quinoline and distillation. ^1H NMR (200 MHz,$CDCl_3$) δ 9.8 (bs, 1H), 5.9 (d, ^3J= 11 Hz, 1H), 5.75(d, ^3J= 11 Hz, 1H), 4.1 (m, 1H), 3.4 (s, 3H), 2.6 (t, 2H), 2.1 (m, 2H), 1.8 (s, 1H);^{13}C NMR (200 MHz, $CDCl_3$) δ 28.4, 39.3, 56.4, 71.1, 80.3, 82.6, 84.9, 95.7 118.5, 121.4, 201.2; IR (NaCl, neat) 3275, 2938, 2825, 1724, 1097.

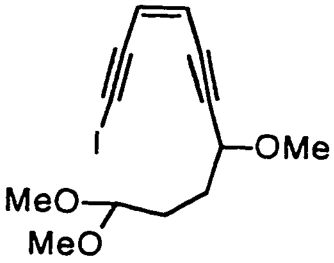
(*Z*)-4-Methoxy-7-decen-5,9-diyn-1-al dimethyl acetal



242

Starting TMS protected enediyne (235) (1.4 g, 4.7 mmol) were dissolved in THF (4 mL) and added over a solution of potassium carbonate (1 g) in THF (10 mL) and of methanol (28 mL). The solution was allowed to stir under nitrogen for 2.5 hours and then partitioned between ether and water. The organic phase was dried on anhydrous magnesium sulfate and after usual work up was purified by column chromatography (ether/petroleum ether=1/4).. The desired product (242) was isolated in 87%.^1H NMR (200 MHz, $CDCl_3$) δ 5.9 (dd, ^3J= 11 Hz, ^5J= 0.75 Hz, 1H), 5.75(dd, ^3J= 11 Hz, ^5J = 2.2 Hz, 1H), 4.3 (m, 1H), 4.1 (m, 1H), 3.4 (s, 3H), 3.2 (s, 6H), 1.7 (m, 5H);^{13}C NMR (200 MHz, $CDCl_3$) δ 27.9, 30.3, 52.5, 56.3, 71.1, 80.5, 82.8, 84.8, 95.3, 103.9, 118.8, 121.0; IR (NaCl, neat) 3271, 2937, 2828, 1453, 1387, 1336,; MS-EI 191 (4.6), 161 (3.9), 159 (13.8),128 (20), 75 (100); HRMS (EI): calcd for $C_{13}H_{18}O_3$ 191.1072, found 191.1061.

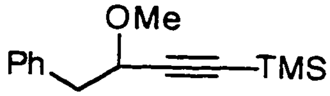
(*Z*)-4-Methoxy-10-iodo-7-decen-5,9-diyn-1-al dimethyl acetal



243

Starting enediyne (242) (0.176 g, 0.8 mmol) was dissolved in benzene (12 mL) and morpholine (1 mL) solution containing iodine (1.0 g). The solution was heated at 45°C for 45 minutes, then concentrated on the rotavapor and purified by column chromatography (ether/petroleum ether=1/4) to obtain the pure product (0.270 g, 0.77 mmol) in 97% yield. ^1H NMR (200 MHz, $CDCl_3$) δ 5.9 (d, ^3J= 10.8 Hz, 1H), 5.75 (dd, ^3J= 10.8 Hz, ^5J= 1.5 Hz, 1H), 4.3 (m, 1H), 4.1 (m, 1H), 3.4 (s, 3H), 3.2 (s, 6H), 1.7 (m, 4H);^{13}C NMR (200 MHz,$CDCl_3$) δ 15.3, 27.9, 30.4, 52.6, 56.4, 71.1, 83.0, 91.4, 95.9, 103.9, 119.8, 121.4; IR (NaCl, neat) 3045, 2935, 2827, 2152, 1572, 1452, 1387, 1335, 1191, 1089; MS-EI 317 (2.4), 245 (27), 75.1 (100); HRMS (EI): calcd for $C_{12}H_{14}O_2I$ 317.0040, found 317.0027.

1-Trimethylsilyl-4-phenyl-3-methoxy-1-butyne

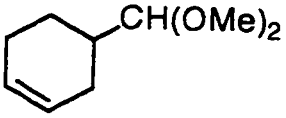


251

Trimethysilylacetylene (0.7 mL, 5 mmol) was dissolved in ether (12.5 mL), treated with *n*-butyllithium (2.25 mL, 5.6 mmol, 2.5 M solution of in hexanes) at 0°C and after a quarter of an hour zinc dichloride (5.5 mL, 5.5 mmol, 1M solutionin ether) was added and allowed thirty minutes for the metal exchange. Subsequently, phenylacetaldehyde dimethylacetal (0.9 g, 5.4 mmol) was added and immediately treated with boron trifluoride etherate (0.93 mL, 6.2 mmol). The reaction can be monitored by TLC or GC-MS. The reaction was quenched with methanol after 4 hours and then extracted thoroughly with sodium bicarbonate and brine, dried on anhydrous magnesium sulfate, filtered and concentrated down to pure product

(0.96 g, 4.1 mmol) in 81% yield.^{1}H NMR (200 MHz, CDCl$_3$) δ 7.2 (m, 5H), 4.1 (t, ^{3}J =6.7Hz, 1H), 3.4 (s, 3H), 3.0 (m, 2H), 0.1 (s, 9H); ^{13}C NMR (200 MHz, CDCl$_3$) δ -0.1, 42.0, 56.5, 72.6, 91.5, 103.8, 126.5, 128.1, 128.2, 129.4, 129.7, 137.2; IR (NaCl, neat) 3061, 3028, 2954, 2865, 2169, 1694, 1601; MS 232 (M$^+$, 0.6), 217 (M-Me$^+$, 16), 141 (100); HRMS (EI): calcd. for $C_{13}H_{17}OSi$ 217.1048, found 217.1038.

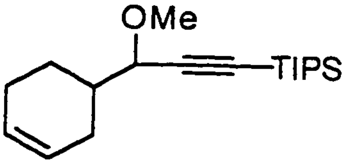
3-Cyclohexenylcarbaldehyde dimethyl acetal



252'

Cerium trichloride heptahydrate (7.45 g, 20 mmol) was dissolved in methanol (500 mL) and then trimethylorthoformate (20.16 mL, 175 mmol) along with 3-cyclohexene carboxaldehyde (1.17 mL, 10 mmol) were added and stirred overnight. The solvent was removed under vacuum and the crude partitioned between ether and water. The organic phase was dried on anhydrous magnesium sulfate, filtered and concentrated down to NMR pure product (1.1 g) in 70% yield.^{1}H NMR (200 MHz, CDCl$_3$) δ 5.6 (m, 2H), 4.06 (d, ^{3}J=6.9Hz, 1H), 3.3 (d, 6H), 1.6-2.1 (m, 6H), 1.2 (m, 1H); ^{13}C NMR (200 MHz,CDCl$_3$) δ 23.8, 24.5, 26.7, 35.9, 53.2, 53.4, 107.7, 125.9, 126.9; IR (NaCl, neat) 3022, 2917, 1730, 1652, 1448; MS 155 (M-H$^+$, 0.4), 125 (M-OMe$^+$, 12), 75 (100); HRMS (EI): calcd. for $C_8H_{13}O$ 125.0966, found 125.0979.

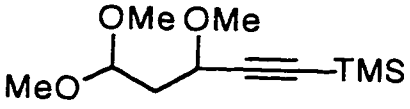
1-Triisopropylsilyl-3-mehtoxy-3-(3'-cyclohexenyl)-1-propyne



252

Triisopropylsilylacetylene (0.393 mL, 1.75 mmol) was dissolved in ether (4 mL), cooled to 0°C and treated successively with *n*-butyllithium (0.77 mL, 1.9 mmol, 2.5M solution in hexanes) and zinc dichloride (1.9 mL, 1.9 mmol, 1M solution in ether) allowing 30 minutes for metal exchange. Finally 3-cyclohexene carboxaldehyde dimethylacetal (0.3 g, 1.92 mmol) was added followed by borontrifluoride etherate (0.24 mL, 1.92 mmol). The reaction was quenched after 4 hours with methanol, thoroughly extracted with sodium bicarbonate and brine, dried on anhydrous magnesium sulfate and purified by column chromatography(ether/petroleum ether=1/20) to afford the pure product (0.29 g, 0.94 mmol) in 54% yield.^{1}H NMR (200 MHz, CDCl$_3$) δ 5.6 (bs, 2H), 3.84 and 3.82 (2d, *J* =4.0Hz, *J* =4.4Hz, 1H), 3.4 (s, 3H), 1.8-2.2 (7H)1.1 (bs, 21H); ^{13}C NMR (200 MHz, CDCl$_3$) δ 11.2, 18.6, 22.7, 24.4, 24.8, 24.9, 27.2, 27.6, 38.7, 56.5, 75.8, 76.0, 87.4, 105.2, 105.3, 125.9, 126.1, 126.8, 127.0; IR (NaCl, neat) 3023, 2946, 2858, 2165, 1457, ; MS 305 (M-H$^+$, 0.3), 291 (M-Me$^+$, 12), 263 (M-iPr$^+$, 23), 75 (100); HRMS (EI): calcd. for C$_{18}$H$_{31}$OSi 291.2144, found 291.2178.

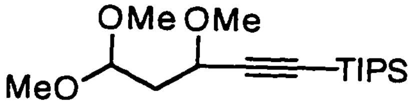
5-Trimethylsilyl-3-methoxy-4-pentyn-1-al dimethyl acetal



253

Trimethylsilylacetylene (0.331 mL, 2.3 mmol) was dissolved in ether (4 mL), cooled to 0°C and treated successively with *n*-butyllithium (1.012 mL, 2.5 mmol, 2.5M solution of in hexanes) and zinc dichloride (2.5 mL, 2.5 mmol, 1M solution in ether) allowing 30 minutes for metal exchange. Finally, malondialdehyde tetramethylacetal (0.46 g, 2.5 mmol) was added followed by borontrifluoride etherate (0.31 mL, 2.5 mmol). The reaction was quenched after 16 hours with methanol, thoroughly extracted with sodium bicarbonate and brine, dried on anhydrous magnesium sulfate and purified by column chromatography (ether/petroleum ether=1/4) to afford the pure product (0.128 g, 0.4 mmol) in 23% yield.^{1}H NMR (200 MHz, CDCl$_3$) δ 4.54 (t, ^3J =5.9Hz, 1H), 4.0 (t, ^3J =6.4Hz, 1H), 3.4 (s, 3H), 3.3 (s, 6H), 1.8-2.1 (m, 2H), 0.1 (s, 9H), ; ^{13}C NMR (200 MHz, CDCl$_3$) δ -0.1, 38.7, 52.9, 53.3, 56.3, 68.1, 90.9, 101.6, 103.7; IR (NaCl, neat) 2940, 2828, 2170, 1455, 1380; MS 215(M-Me$^+$, 0.6), 200 (M-2Me$^+$, 1), 199 (M-OMe$^+$, 3), 141 (19), 75 (100); HRMS (EI): calcd. for C$_{10}$H$_{19}$O$_3$Si 215.1103, found 215.1115.

5-Triisopropylsilyl-3-methoxy-4-pentyn-1-al dimethyl acetal



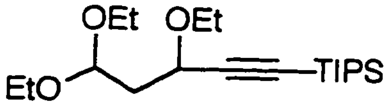
254

Method A. Triisopropylsilylacetylene (0.515 mL, 2.3 mmol) was dissolved in ether (4 mL), cooled to 0°C and treated successively with *n*-butyllithium (1.012 mL, 2.5 mmol, 2.5M solution in hexanes) and zinc dichloride (2.5 mL, 2.5 mmol, 1M solution in ether) allowing 30 minutes for metal exchange. Finally, malondialdehyde tetramethylacetal (0.46g, 2.5 mmol) was added followed by borontrifluoride etherate (0.31 mL, 2.5 mmol). The reaction was quenched after 16 hours with methanol. thoroughly extracted with sodium bicarbonate and brine, dried on anhydrous magnesium sulfate and purified by column chromatography (ether/petroleum ether=1/5) to afford the pure product (0.128 g, 0.4 mmol) in 18% yield.

Method B. Triisopropyl acetylene (0.9 mL, 4 mmol) were dissolved in hexane (8 mL), cooled to 0°C and treated with n-butyllithium (1.78 mL, 4.4 mmol, 2.5 M solution in hexanes). After 15 minutes, the solution was transferred via canula over aluminum trichloride (0.49 g, 3.7 mmol) stirred for another half of an hour and then the solvent was stripped off under a stream of nitrogen and replaced with methylene dichloride (10 mL). Malondialdehyde tetramethylacetal (0.6 mL, 3.6 mmol) was added and the reaction was allowed to stir for 16 hours at 0°C. The reaction was quenched with deuterium oxide and then partitioned between ether and potassium sodium tartrate solution. The organic phase was extracted repeatedly until it became clear, then dried on anhydrous magnesium sulfate, concentrated and purified by column chromatography to yield the desired product (0.4 g, 1.3 mmol) in 37% yield.

Method C. Triisopropyl acetylene (0.26 mL, 1.2 mmol) were dissolved in hexane (2 mL), cooled to 0°C and treated with n-butyllithium (0.47 mL, 4.4 mmol, 2.5 M solution in hexanes). After 15 minutes, the solution was transferred via canula over aluminum trichloride (0.072 g, 0.54 mmol) stirred for another half of an hour and then the solvent was stripped off under a stream of nitrogen and replaced with methylene dichloride (3 mL). Malondialdehyde tetramethylacetal (0.09 mL, 0.54 mmol) was added and the reaction was allowed to stir for 16 hours at 0°C and then 24 hours at room temperature. The reaction was quenched with deuterium oxide and then partitioned between ether and potassium sodium tartrate solution. The organic phase was extracted repeatedly until it became clear, then dried on anhydrous magnesium sulfate, concentrated and purified by column chromatography to yield the desired product (0.06 g, 0.18 mmol, 33%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.6 (t, ^{3}J=5.9Hz, 1H), 4.0 (t, ^{3}J=6.7Hz, 1H), 3.4 (s, 3H), 3.3 (s, 6H), 1.7-2.1 (m, 2H), 1.0 (s, 21H), ; ^{13}C NMR (200 MHz, $CDCl_3$) δ 11.1, 18.5, 39.1, 53.1, 53.6, 56.2, 68.2, 87.1, 102.0, 105.7; IR (NaCl, neat) 2908, 2167, 1731, 1457, 1378, 1071 ; MS 283($M-OMe^+$, 1.9), 271 ($M-iPr^+$, 16), 213 (92), 105 (100); HRMS (EI): calcd. for $C_{14}H_{27}O_3Si$ 271.1729, found 271.1718.

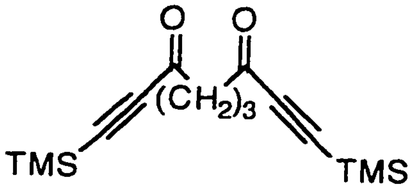
5-Triisopropylsilyl-3-ethoxy-4-pentyn-1-al diethyl acetal



255

Triisopropylsilylacetylene (0.194 mL, 0.86 mmol) was dissolved in hexanes (2 mL), cooled to 0°C , treated with *n*-butyllithium (0.38 mL, 0.94 mmol, 2.5 M solution in hexanes) and transferred via canula over aluminum trichloride (0.115 g, 0.86 mmol) allowing 30 minutes for metal exchange. The solvent was striped off by purging the flask with nitrogen and methylene chloride (10 mL) were added. Finally malonaldehyde tetraethylacetal (0.21 mL, 0.86 mmol) was injected and the reaction was brought to room temperature and maintained for 2.5 hours (can be monitored by TLC). The reaction was partitioned between hexanes and potassium sodium tartrate solution and the organic phase repeatedly extracted until a clear phase was obtained that was subsequently dried on anhydrous magnesium sulfate and purified by column chromatography (ether/petroleum ether=1/9) to afford the pure product (0.063 g, 0.17 mmol) in 27% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.7 (t, ^{3}J=5.9Hz, 1H), 4.1(t, ^{3}J=6.5Hz, 1H), 3.4 (m, 6H), 1.7-2.1 (m, 2H), 1.2 (t, ^{3}J=7Hz, 9H), 1.0 (s, 21H), ; ^{13}C NMR (200 MHz, $CDCl_3$) δ 11.1, 15.1, 15.3, 18.6, 40.3, 61.5, 62.1, 64.0, 66.5, 100.3, 106.6; IR (NaCl, neat) 2913, 2166, 1458, 1367, 1078; MS 313 ($M-iPr^+$, 19), 241 (100); HRMS (EI): calcd. for $C_{17}H_{33}O_3Si$ 313.2199, found 313.2204.

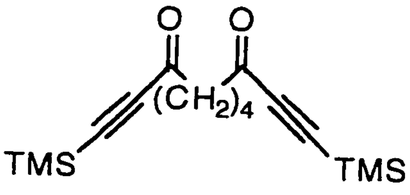
3,7-Dioxo-1,9-ditrimethylsilyl-1,8-nonadiyne



265

A solution of glutaryl chloride (2.94 mL, 23 mmol) and *bis*-trimethylsilylacetylene (10.39 mL, 46 mmol) in carbon disulfide (10 mL) was injected via syringe pump (30 minutes) over a vigorously stirred suspension of aluminum trichloride (6.14 g, 46 mmol) in 50 mL of the same solvent at 0°C. After the addition was complete we allowed other 30 minutes and then the brown suspension was poured over crushed ice in a large glass beaker. The organic phase was further extracted several times with 10% hydrochloric acid then with brine and dried on anhydrous magnesium sulfate, filtered and concentrated down to a crude product (4.4 g, 14.95 mmol) which was pure by NMR. Chemical yield 66%. An anlytical sample was prepared by flash chromatography. 1H NMR (200 MHz, $CDCl_3$) δ 2.5 (t, *J* = 7.1Hz, 4H), 1.8 (qv, *J* = 7.1Hz, 2H), 0.08(s, 18H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -0.08, 17.6, 43.8, 43.9, 98.14, 101.7, 186.5; IR (NaCl) 2919, 2900.8, 2150.2, 1677.3, 1253. 1108, 860.9; MS 277.1 (16.2), 167.1 (18.6), 125 (100), 97 (41.1), 73 (59); HRMS (EI): calcd for $C_{14}H_{21}O_2Si_2$ 277.1080, found 277.1091; Anal. Calcd. for $C_{15}H_{24}O_2Si_2$: C, 61.58; H, 8.26. Found: C, 61.42; H, 8.25.

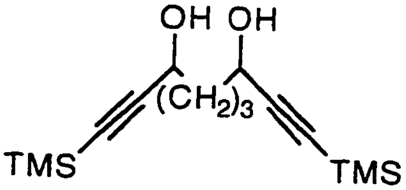
3,8-Dioxo-1,10-ditrimethylsilyl-1,9-decadiyne



266

A solution of adipoyl chloride (3.36 mL, 23 mmol) and *bis*-trimethylsilylacetylene (10.39 mL, 46 mmol) in carbon disulfide (10 mL) was injected via syringe pump (30 minutes) over a vigorously stirred suspension of aluminum trichloride (6.14 g, 46 mmol) in 50 mL of the same solvent at 0°C. After the addition was complete we allowed other 30 minutes and then the brown suspension was poured over crushed ice in a large glass beaker. The organic phase was further extracted several times with 10% hydrochloric acid then with brine and dried on anhydrous magnesium sulfate, filtered and concentrated down to a slightly yellow product (6.3 g, 20.7 mmol) which was pure by NMR. Chemical yield 90%. An anlytical sample was prepared by flash chromatography. 1H NMR (200 MHz, $CDCl_3$) δ 2.44 (m, 4H), 1.55 (m, 4H), 0.1 (s, 18H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -0.8, 22.9, 44.7, 97.8, 101.8, 187; IR (NaCl) 2943, 2150, 2092, 1676, 1407, 1357, 1252, 1109, 1045, 859, 762; MS 291 (13), 263 (2.6), 193(2.4), 173 (4.2), 155(8.7), 140 (15.7), 125 (93.7), 97 (41,6), 73 (100); HRMS (EI): calcd for $C_{15}H_{23}O_2Si_2$ 291.1236, found 291.1219.

1,9-Ditrimethylsilyl-1,8-nonadiyn-3,7-diol

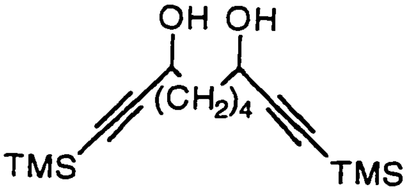


267

A solution of glutaryl chloride (2.94 mL, 23 mmol) and *bis*-trimethylsilylacetylene (10.39 mL, 46 mmol) in carbon disulfide (10 mL) was injected via syringe pump (30 minutes) over a vigorously stirred suspension of aluminum trichloride (6.14 g, 46 mmol) in 50 mL of the same solvent at 0°C. 30 minutes after the addition was completed the brown suspension was poured over crushed ice in a large glass beaker. The organic phase was further extracted several times with 10% hydrochloric acid then with brine and dried on anhydrous magnesium sulfate, filtered and concentrated down to a slightly yellow crude (4.4 g, 14.95 mmol) which was pure by NMR. The crude diketone was dissolved in methanol (500 mL) and cerium trichloride heptahydrate (51 g, 138 mmol) was added over and stirred for ten minutes. The solution was cooled to 0°C and sodium borohydride (6.96 g, 184 mmol) was added portionwise and the reaction was monitored by TLC and quenched with 10% hydrochloric acid. The aqueous/methanolic phase was first concentrated under vacuum, then throughly extracted with ethyl acetate and finally the organic phase was extracted with brine, then dried with anhydrous magnesium sulfate, filtered and concentrated down to crude product (3.9 g, 13.11 mmol) which was pure by NMR. An analytical sample was prepared by column chromatography (ether/petroleum ether=1/2). Overall yield for two steps 57%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.26 (m, 2H), 2.5 (bs, 2H), 1.4-1.7 (m, 6H), 0.02 (s, 18H); ^{13}C

NMR (200 MHz, $CDCl_3$) δ -0.1, 20.7, 37.0, 62.4, 89.22, 106.8; IR (NaCl) 3359, 2943, 2172, 1397, 1326, 1251.

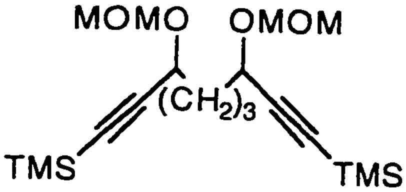
1,10-Ditrimethylsilyl-1,9-decadiyn-3,8-diol



268

A solution of adipoyl chloride (3.36 mL, 23 mmol) and *bis*-trimethylsilylacetylene (10.39 mL, 46 mmol) in carbon disulfide (10 mL) was injected via syringe pump (30 minutes) over a vigorously stirred suspension of aluminum trichloride (6.14 g, 46 mmol) in 50 mL of the same solvent at 0°C. After the addition was complete we allowed other 30 minutes and then the brown suspension was poured over crushed ice in a large glass beaker. The organic phase was further extracted several times with 10% hydrochloric acid then with brine and dried on anhydrous magnesium sulfate, filtered and concentrated down to a slightly yellow product (6.3 g, 20.7 mmol) which was pure by NMR. The crude diketone was dissolved in methanol (500 mL) and cerium trichloride heptahydrate (51 g, 138 mmol) was added over and stirred for ten minutes. The solution was cooled to 0°C and sodium borohydride (6.96 g, 184 mmol) was added portionwise and the reaction was monitored by TLC and quenched with 10% hydrochloric acid. The aqueous/methanolic phase was first concentrated under vacuum, then thoroughly extracted with ethyl acetate and finally the organic phase was extracted with brine, then dried with anhydrous magnesium sulfate, filtered and concentrated down to a crude product (6.2 g, 20.2 mmol) which was again pure by NMR. An analytical sample was prepared by column chromatography (ether/petroleum ether=1/2). Overall yield for two steps 88%. ^1H NMR (200 MHz, $CDCl_3$) δ 4.23 (t, J = 6.4 Hz, 2H), 2.1 (bs, 2H), 1.55 (m, 4H), 1.37 (m, 4H), 0.04 (s, 18H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -0.12, 24.7, 37.4, 62.6, 89.3, 106.8; IR (NaCl) 3350, 2919, 2171, 1411, 1251, 1036, 855.

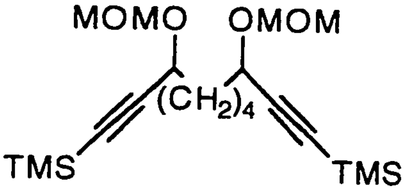
3,7-Di(methoxymethyloxy)-1,9-ditrimethylsilyl-1,8-nonadiyne



267-MOM

Diol (267) (0.8 g, 2.7 mmol) was dissolved in chloroform (60 mL) and dimethoxymethane (60 mL) and treated overnight with phosphorous pentoxide (15 g) under vigorous stirring. The reaction mixture was cautiously pored over an iced cold solution of sodium bicarbonate and the remaining oil in the flask was treated (caution!) with bicarbonate solution The aqueous phase was extracted several times with ether and then the organic phase was rinsed with brine and dried on magnesium sulfate and concentrated down to pure protected diol (0.91 g, 2.42 mmol) in 90% yield. An analytical sample was prepared by column chromatography on silicagel using a 25% ether in petroleum ether eluent. ^{1}H NMR (200 MHz, $CDCl_3$) δ4.8 and 4.45 (AB, *J* = 6.7 Hz, 4H), 4.2 (m , 2H), 3.2 (s, 6H), 1.4-1.7 (m, 6H), 0.03 (s, 18H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -0.1, 21.2, 35.2, 55.5, 65.7, 90.22, 94.0, 104.1; IR (NaCl) 2936, 2822, 2170, 1455, 1340, 1251; MS 337 (6.3), 275 (15.2), 238.9 (66.8), 141 (100); Anal. Calcd. for $C_{19}H_{36}O_4Si_2$: C, 59.32; H 9.43, . Found: C, 59.46; H, 9.28.

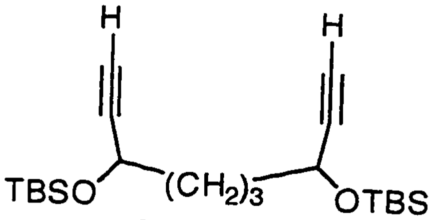
3,8-Di(methoxymethyloxy)-1,10-ditrimethylsilyl-1,9-decadiyne



268-MOM

Diol (268) (2.2 g, 7 mmol) was dissolved in chloroform (140 mL) and dimethoxymethane (140 mL) and treated overnight with phosphorous pentoxide (35 g) under vigorous stirring. The reaction mixture was cautiously pored over an iced cold solution of sodium bicarbonate and the remaining oil in the flask was treated (caution!) with bicarbonate solution The aqueous phase was extracted several times with ether and then the organic phase was rinsed with brine and dried on magnesium sulfate and concentrated down to pure protected diol (2.7 g, 7 mmol) in 99% yield. An analytical sample was prepared by column chromatography (ether/petroleum ether=1/2).^{1}H NMR (200 MHz, $CDCl_3$) δ4.8 and 4.5 (AB, J = 6.7 Hz, 4H), 4.2 (t, J = 6.4 Hz, 2H), 3.2 (s, 6H), 1.5-1.7 (m, 4H), 1.3-1.5 (m, 4H), 0.03 (s, 18H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -0.1, 25.0, 35.5, 55.6, 65.9, 90.2, 94.0, 104.2; IR (NaCl) 2932, 2822, 2170.4, 1457, 1338, 1250; MS 353 (4.2), 323 (41.9), 219 (100); Anal. Calcd. for $C_{20}H_{38}O_4Si_2$: C, 60.25; H, 9.60. Found: C, 60.36; H, 9.78.

3,7-Di(*t*-Butyldimethylsilyloxy)-1,9-ditrimethylsilyl-1,8-nonadiyne

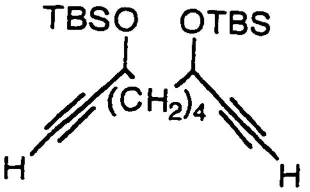


269-TBS

Sodium hydroxide solution (12 M, 36% W/W, d=1.39 g/mL, 24 mL, 288 mmol) was added dropwise over an ice cold solution of 1,9-ditrimethylsilyl-1,8-decadiyn-3,7-diol (267) (8.27 g, 28.3 mmol) and benzyltriethylammonium chloride (0.3 g) in 25 mL acetonitrile under vigorous stirring. 30 minutes after the addition was completed the reaction mixture was diluted with ether and partitioned between ether and water. The organic phase was reextracted with brine, dried on anhydrous magnesium sulfate filtered and concentrated down to a crude product (4 g, 26.7 mmol) which was pure by NMR. The crude diol (4 g, 26.7 mmol) and imidazole (9.5 g, 140.4 mmole) were dissolved in tetrahydrofurane (20 mL). In a separate flask, tert-butyldimethylsilylchloride (9.75 g, 65 mmol) was dissolved in tetrahydrofurane (20 mL) and then added to the first solution. After stirring overnight the reaction mixture was partitioned between petroleum ether and 1M hydrochloric acid solution and the organic phase was extracted with aqueous saturated solution of sodium bicarbonate and brine. After drying over anhydrous magnesium sulfate the solution was filtered and concentrated down to a crude product (9.1 g, 23.9 mmol) which was practically pure by TLC and spectroscopic methods. Yield 90%. An anlytical sample was prepared by flash chromatography.^{1}H NMR (200 MHz, $CDCl_3$) δ 4.3 (m, 2H), 2.3 (d, ^4J= 2.1Hz, 2H), 1.4-1.8 6H), 0.9 (s, 18H), 0.09 (d, 12H);^{13}C NMR

(200 MHz, $CDCl_3$) δ -5.0, -4.5, 18.1, 21.0, 25.8, 38.2, 62.6, 72.1, 85.5; IR (NaCl) 3303, 2910, 1467; MS 380 (0.05), 323 (17.4), 147 (79.6), 73 (100); HRMS (EI): calcd for $C_{17}H_{31}O_2Si_2$ 323.1862, found 323.1858.

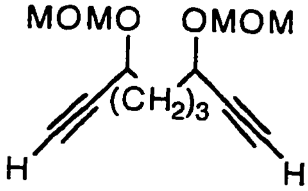
3,8-Di(*t*-Butyldimethylsilyloxy)-1,10-ditrimethylsilyl-1,9-decadiyne



270-TBS

Sodium hydroxide solution (12 M, 36% W/W, d=1.39 g/mL, 24 mL, 288 mmol) were added dropwise over an ice cold solution of 1,10-ditrimethylsilyl-1,9-decadiyn-3,8-diol (268) (4.8 g, 15.5 mmol) and benzyltriethylammonium chloride (0.3 g) in acetonitrile (25 mL) under vigorous stirring. 30 minutes after the addition was completed the reaction mixture was diluted with ether and partitioned between ether and water. The organic phase was reextracted with brine, dried on anhydrous magnesium sulfate filtered and concentrated down to a crude product (2.5 g, 15 .5 mmol) which was pure by NMR. The diol was submitted directly to *tert*-butyldimethylsilyl protection, by dissolving the crude in dimethylformamide (16 mL) together with imidazole (5.8 g, 85 mmol) and then treating the mixture with *tert*-butyldimethylsilylchloride (5.8 g, 40 mmol) in dimethyformamide. (16 mL). The reaction mixture was partitioned upon completion between water and hexanes, then the organic phase was thoroughly extracted with brine and finally dried on anhydrous magnesium sulfate, filtered and concentrated to afford a crude product (5.8 g, 14.7 mmol) which was pure by NMR. An analytical sample was prepared by column chromatography (ether/petroleum ether=1/30). Overall yield for two steps 95%. ^1H NMR (200 MHz, $CDCl_3$) δ 4.23 (dt, ^1J = 6 Hz, ^2J = 2 Hz, 2H), 2.26 (d, ^2J=2 Hz, 2H), 1.6 (m, 4H), 1.3 (m, 4H), 0.8 (s, 18 H), 0.0 (2s, 12 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -5.1, -4.5, 18.2, 24.7, 25.7, 38.5, 62.6, 71.9, 85.6; IR (NaCl) 3307, 2943, 2859, 1467, 1361, 1254, 1081, 841, 779; MS 337 (11), 263 (7.5), 243 (8.1), 189 (12.2), 169 (11.3), 147 (100), 131 (14.6), 91 (14.3), 73 (83); HRMS (EI): calcd for $C_{18}H_{33}O_2Si_2$ 337.2019, found 337.2052; Anal. Calcd. for $C_{22}H_{42}O_2Si_2$: C, 66.94; H, 10.72. Found: C, 66.79; H, 10.84.

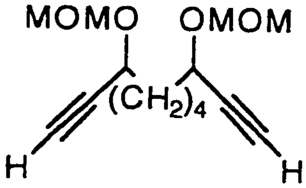
3,7-Di(methoxymethyloxy)-1,8-nonadiyne



269-MOM

Starting silylated compound (267-MOM) (0.87 g, 2.3 mmol) were dissolved in acetonitrile (1.5 mL) and triethylbenzylammonium chloride (0.02 g) were added before cooling to 0°C. The solution was treated under stirring with aqueous sodium hydroxide (12 M, 1.5 mL) and allowed to react for 30 minutes. The reaction was quenched with ether and partitioned between ether and water, extracted with brine, dried on magnesium sulfate filtered and concentrated to afford pure product (0.52 g, 2.18 mmol) in 95 % yield. An analytic sample was prepared by column chromatography (ether/petroleum ether=1/3). ^{1}H NMR (200 MHz, CDCl$_3$) δ4.79 and 4.45 (AB, *J* = 6.8 Hz, 4H), 4.2 (m , 2H), 3.2 (s, 6H), 2.3 (d, *J* = 2 Hz), 1.4-1.7 (m, 6H); ^{13}C NMR (200 MHz, CDCl$_3$) δ 20.9, 35.1, 55.6, 65.0, 73.6, 82.3, 94.0; IR (NaCl) 3279, 2926, 1455.9, 1341.1; MS 240.9 (2.7), 179 (52), 147 (86), 119 (100); Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.97; H 8.38; Found: C, 65.1; H 8.27.

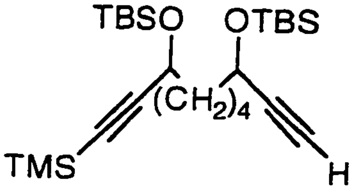
3,8-Di(methoxymethyloxy)-1,9-decadiyne



270-MOM

Starting silylated compound (268-MOM) (2.6 g, 6.6 mmol) was dissolved in acetonitrile (6 mL) and triethylbenzylammonium chloride (0.05 g) were added before cooling to 0°C. The solution was treated under stirring with aqueous sodium hydroxide (12 M solution, 6 mL) and allowed to react for 30 minutes. The reaction was quenched with ether and partitioned between ether and water, extracted with brine, dried on magnesium sulfate filtered and concentrated to afford the pure product (1.6 g, 6.3 mmol) in 96 % yield. An analytic sample was prepared by column chromatography (ether/petroleum ether=1/3). ^{1}H NMR (200 MHz, $CDCl_3$) δ4.8 and 4.45 (AB, ^2J = 6.8 Hz, 4H), 4.2 (dt, ^3J = 6 Hz, ^4J =2 Hz, 2H), 3.2 (s, 6H), 2.3 (d, J = 2 Hz), 1.5-1.7 (m, 4H), 1.3-1.5 (m, 4H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 24.8, 35.4, 55.6, 65.1, 73.5, 82.4, 94.0; IR (NaCl) 3278.6, 2924.4, 2112.01456.9; MS 193 (21), 167 (100) 161 (55.8) 133 (65.4); Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.14; H, 8.71. Found: C, 66.64; H, 8.98.

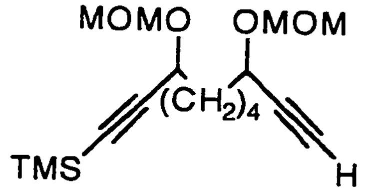
3,8-Di(*t*-Butyldimethylsilyloxy)-1-trimethylsilyl-1,9-decadiyne



273

Diyne (270-TBS) (0.788 g, 2 mmol) was dissolved in ether(8 mL) and treated with n-butyllithium (0.84 mL, 2.1 mmol, 2.5 M solution in hexanes) at - 78°C and allowed to stir for 30 minutes. Trimethyl-silylchloride (0.31 mL, 2.2 mmol) was added dropwise and the reaction mixture was allowed to warm up to ambient temperature and stirred for other two hours under inert atmosphere. The reaction was quenched with crushed ice, water was added and the layers were separated in a funnel. The aqueus layer was reextracted with pentane then the combined organic extracts were rinsed with water, brine, dried on magnesium sulfate, filtered and concentrated under vacuum. The crude product was columned with 1% ether in petroleum ether to get the monosilylated product (273) (0.45 g, 1 mmol) and bis TMS protected acetylene (0.25 g, 0.45 mmol). Chemical yield 50%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.2 (m, 2H), 2.25 (d, ^2J = 2 Hz, 1H), 1.55 (m, 4H), 1.35 (m, 4H), 0.8 (s, 18H), 0-0.1 (3s, 21H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -5.0, -4.5, -0.1, 18.23,18.28, 24.7, 24.9, 25.8, 38.4, 62.6, 63.2, 71.9, 85.7, 88.3, 107.8; IR (NaCl) 3310, 2943, 2858, 2171, 1731, , 1467, 1360, 1253, 1092, 842, 778; MS 409 (4), 337 (8.7), 319 (2.8), 277 (7.1), 205 (12.2), 169 (10.5), 147 (89.7), 133 (14.3), 83 (25), 73 (100); HRMS (EI): calcd for $C_{21}H_{41}O_2Si_3$, found 409.24161; Anal. Calcd. for $C_{25}H_{50}O_2Si_3$: C, 64.30; H, 10.79. Found: C, 64.25; H, 10.84.

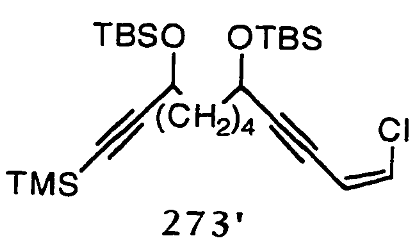
3,8-Di(methoxymethyloxy)-1-trimethylsilyl-1,9-decadiyne



274

Starting diyne (270-MOM) (1 g, 3.9 mmol) was dissolved in ether (10 mL), cooled to - 78°C and treated with n-butyllithium (1.8 mL, 3.9 mmol, 2.2 M solution in hexanes) for 30 minutes. The lithium acetylide solution was subsequently treated with trimethylsilyl chloride (0.5 mL, 3.9 mmol) and then allowed to stirr at room temperature for two hours. The rection mixture was partitioned between ether and iced water then the organic phase extracted with brine, dried on magnesium sulphate and purified by column chromatography (ether/petroleum ether=1/20) to obtain the desired product (0.45 g, 1.53 mmol) and *bis* -silylated byproduct (0.09 g, 0.25 mmol). The yield for monosilylated product was 39%.^{1}H NMR (200 MHz,$CDCl_3$) δ4.79 and 4.45 (AB, ^{2}J = 6.8 Hz, 2H), 4.79 and 4.43 (AB, ^{2}J = 6.8 Hz, 2H), 4.2 (m, 2H), 3.23 and 3.22 (2s, 6H), 2.3 (d, J = 1.9 Hz, 1H), 1.5-1.7 (m, 4H), 1.3-1.5 (m, 4H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -0.17, 24.8, 35.4, 55.5, 65.1, 73.5, 82.4, 90.2, 94.0, 104.2; IR (NaCl) 3283.9, 2924,5, 2169.9, 1457.9, 1339.8; MS 193 (21), 167 (100) 161 (55.8) 133 (65.4); Anal. Calcd. for $C_{17}H_{30}O_4Si$: C, 62.53; H 9.26. Found: C 62.38, ; H 9.27.

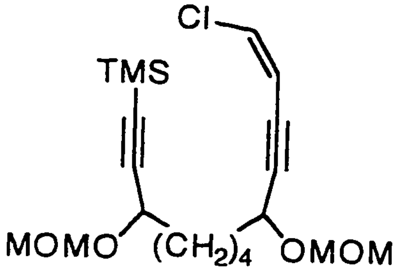
(*Z*)-1-Chloro-5,10-di(*t*-butyldimethylsilyloxy)-12-trimethylsilyl-1-dodecen-3,11-diyne



273'

Starting (273) (0.7 g, 1.56 mmol), *cis*-dichloroethylene (0.130 mL, 1.7 mmol) and butylamine (0.62 mL, 6.28 mmol) were dissolved in 5 mL ether and injected over *tetrakis*(triphenylphosphine)-palladium (0) (0.09 g, 0.78 mmol) and CuI (0.06 g, 0.31 mmol). The reaction mixture was partitioned upon completion between ether and ammonium chloride saturated solution and the organic phase rinsed with brine, dried on magnesium sulfate and purified by column chromatography (ether/hexanes=1/30) to afford 0.45 g (0.8 mmol) product in 51% yield.^{1}H NMR (200 MHz, CDCl$_3$) δ 6.24 (d, ^{1}J=7.45Hz, 1H), 5.76 (dd, ^{1}J= 7.45 Hz, ^{2}J= 1.7 Hz, 1H), 4.4 (m, 1H), 4.2 (m, 1H), 1.5-1.7 (m, 4H), 1.3-1.5 (m, 4H), 0.8 (s, 18H), 0.0-0.1 (3s, 21H); ^{13}C NMR (200 MHz, CDCl$_3$) δ -5.0, -4.5, -0.1, 18.3, 24.8, 24.9, 25.8, 38.4, 63.2, 63.3, 78.0, 88.4, 99.5, 107.9, 111.8, 128.2; IR (NaCl) 2944.15, 2858.45, 2171,52, 1590.7, 1466.8, 1360.8, 1338.8, 1253.33, 1071.6, 842, 777.7; Anal. Calcd. for $C_{27}H_{51}ClO_2Si_3$: C, 61.48; H, 9.74.Found: C, 61.55; H, 9.55.

(*Z*)-1-Chloro-5,10-di(methoxymethyloxy)-12-trimethylsilyl-1-dodecen-3,11-diyne

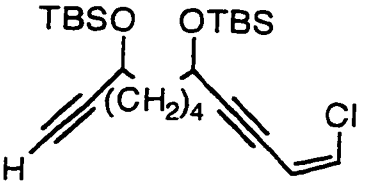


274'

Starting (274) (0.35 g, 1.07 mmol) was dissolved in benzene (1.5 mL) and then sequentially n-butylamine (0.3 mL, 2.96 mmol), and *cis*-dichloroethylene (0.085 mL, 1.12 mmol) were added. This solution was injected in one portion over a pre-weighed mixture of tetrakis(triphenylphosphine)palladium (0.085 g, 0.074 mmol) and copper iodide (0.056 g, 0.29 mmol) and allowed to stir overnight. The reaction was quenched with ammonium chloride and partitioned between ether and 1M HCl, then rinsed with brine and dried on anhydrous magnesium sulfate. Usual operations and purification by column chromatography (ether/petroleum ether=1/9) to get the pure product (0.135 g, 0.35 mmol) in 35% yield. Reaction was repeated on 0.68 g and product was isolated in 38 % yield.^{1}H NMR (200 MHz, CDCl$_3$) δ 6.3 (d, ^{3}J=7.45 Hz, 1H), 5.76 (dd, ^{3}J=7.45 Hz, ^{5}J=1.6 Hz, 1H), 4.8-4.9 and 4.4-4.5 (2 AB, $^{2}J_1$ =6.8 Hz, $^{2}J_2$ =6.77 Hz, 4H), 4.38 (t, ^{3}J = 6.3 Hz, ^{5}J=1.6 Hz, 1H), 4.2 (t, ^{3}J = 6.2 Hz, 1H), 3.26 and 3.24 (2s, 6H), 1.5-1.8 (m, 4H), 1.3-1.5 (m, 4H), 0.03 (s, 9H); ^{13}C NMR (200 MHz, CDCl$_3$) δ -0.2, 24.9, 35.37, 35.43, 55.55, 55.62, 65.8, 79.4, 90.2, 94.0, 96.2, 104.2, 111.5, 128.8; IR (NaCl) 2924, 2169.7, 1456.3, 1338.2;

Anal. Calcd. for $C_{17}H_{30}O_4Si$: C, 58.99; H 8.02, . Found: C 59.12, ; H 8.08.

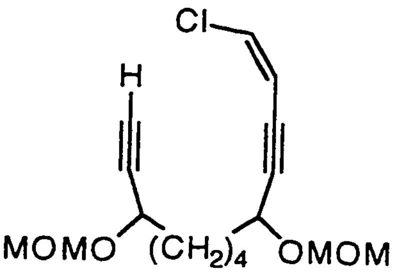
(*Z*)-1-Chloro-5,10-di(*t*-butyldimethylsilyloxy)-1-dodecen-3,11-diyne



275

Starting material (273') (0.394 g, 0.75 mmol) and triethylbenzylammonium chloride (TEBA) (0.008 g, 0.035 mmol) were dissolved in acetonitrile (1 mL), cooled to 0°C and treated with sodium hydroxide (1 mL 12 M solution, 36% w/w) under vigorous stirring. Ether was added after 20 minutes and the reaction mixture was partitioned between water and ether, then thoroughly extracted with brine, dried on magnesium sulfate, filtered and purified on a silicagel column with 1% ether in petroleum ether. to afford the desired product (0.3 g, 0.67 mmol) in 95% yield. ^1H NMR (200 MHz, $CDCl_3$) δ 6.25 (d, $^1J = 7.5$Hz, 1H), 5.77 (dd, $^1J = 7.5$ Hz, $^2J = 1.7$ Hz, 1H), 4.4 (m, 1H), 4.2 (m, 1H), 2.26 (d, $^2J = 2$ Hz, 1H), 1.5-1.7 (m, 4H), 1.3-1.5 (m, 4H), 0.8 (s, 18H), 0.0-0.1 (2s, 12H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -5.0, -4.6, -4.5, 18.2, 24.7, 24.8, 25.8, 38.1, 38.4, 62.6, 63.3, 78.6, 71.9, 85.6, 99.4, 111.8, 128.1; IR (NaCl) 3306.9, 2942.2, 2858, 1466.9, 1389, 1254, 1087, 840, 778; Anal. Calcd. for $C_{24}H_{43}ClO_2Si_2$: C, 63.32; H, 9.52. Found: C, 63.53; H, 9.23.

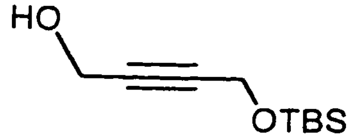
(*Z*)-1-Chloro-5,10-di(methoxymethyloxy)-1-dodecen-3,11-diyne



276

Silylated compound (274) (0.1 g, 0.26 mmol) and triehylbenzylammonium chloride (TEBACl) (0.002 g) were dissolved in acetonitrile (0.5 mL) cooled in an iced water bath. and treated dropwise with sodium hydroxide (0.5 mL, 12M solution). The reaction was allowed to stir for 20 minutes quenched with ether, extracted with water and brine dried on anhydrous magnesium sulfate and concentrated down to NMR pure product (0.075 g, 0.24 mmol) of in 92% yield. ^{1}H NMR (200 MHz, CDCl$_3$) δ 6.25 (d, ^3J=7.4 Hz, 1H), 5.75 (dd, ^3J = 7.4 Hz, ^5J=1.4 Hz, 1H), 4.8-4.9 and 4.4-4.5 (2 AB, $^2J_1$ =6.78 Hz, $^2J_2$ =6.72Hz, 4H), 4.4 (dt, ^3J = 6.3 Hz, ^5J=1.4 Hz, 1H), 4.18 (dt, ^3J = 6.2 Hz, ^4J=1.5 Hz,1H), 3.26 and 3.25 (2s, 6H), 2.3 (d, ^4J = 1.45 Hz, 1H), 1.55-1.8 (m, 4H), 1.3-1.55 (m, 4H); ^{13}C NMR (200 MHz,CDCl$_3$) δ 24.72, 24.76, 35.2, 35.33, 55.62, 55.68, 65.4, 72.3, 78.8, 85.1, 98.8, 111.4,128.6; IR (NaCl) 3308, 2941.2, 1466.7, 1339.3.

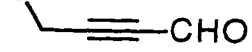
4-*t*-Butyldimethylsilyloxy-2-butyn-1-Ol



280'

1,4-butynediole (12.9 g, 150 mmol) was dissolved in DMF (12 mL) and then cooled to - 50°C. TBSCl (15 g, 100 mmol) and imidazole (14 g, 200 mmol) was dissolved in DMF (30 mL) and added dropwise over the diol solution with the syringe pump . After other two hrs. ether was added and the organic phase was extracted with 10% HCl and then brine, dried on anhydrous magnesium sulfate and concentrated down to 17.6 g crude mixture of monoprotected and diprotected diol. Column chromatography (ether/petroleum ether=1/4) provided the desired product (12g, 60 mmol) in 60% as well as bis-protected diol (4.3g, 13.7 mmol). 1H NMR (200 MHz, CDCl$_3$) δ 4.3 (m, 2H), 4.26 (m, 2H), 2.2 (bs, 1H), 0.9 (m, 9H), 0.06 (m 6H);^{13}C NMR (200 MHz, CDCl$_3$) δ; IR (NaCl) 3353, 2954, 2856, 1463.7, 1257, ; MS 185 (0.5), 167 (0.7), 125 (28.3), 75 (100).

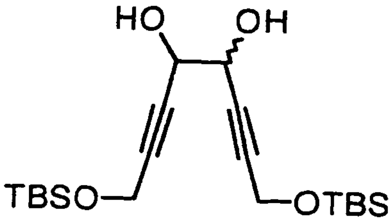
4-*t*-Butyldimethylsilyloxy-2-butynal



281

Monoprotected diol (280') (0.1 g, 0.5 mmol) were dissolved in methylene chloride (3 mL) and treated with Dess-Martin reagent (0.25 g 0.6 mmol) for 10 min. After subsequent addition of ether, concentration and addition of another portion of ether followed by thorough extraction with sodium thiosulfate/sodium bicarbonate 1/1 solution, the solution was dried with anhydrous magnesium sulfate, filtered and then purified by column chromatography (ether/petroleum ether=1/3) to obtain the pure aldehyde (0.095 g, 0.47 mmol) in 96% yield. 1H NMR (200 MHz, $CDCl_3$) δ 9.2 (s,1H), 4.5 (s, 2H), 0.9 (s, 9H), 0.1 (s, 6H);^{13}C NMR (200 MHz, $CDCl_3$) δ -5.3, 18.2, 25.6, 51.5, 84.2, 94.8, 176.3; IR (NaCl) 2942, 2858, 2188, 1674, 1467; MS 198 (0.2), 183 (4.5), 141 (43), 111 (100); HRMS (EI): calcd for $C_6H_9O_2Si$, 141.0372 found 141.0387.

1,8-di(*t*-Butyldimethylsilyloxy)-2,6-octadiyn-4,5-diol

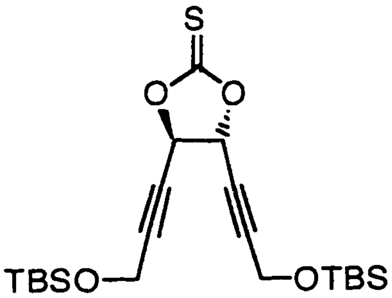


282

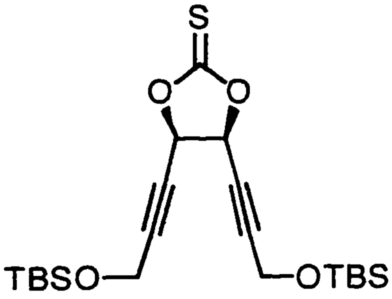
Vanadium trichloride.3THF complex (12.62 g, 33.75 mmol) and purified zinc dust (1.4 g, 21.4 mmol) were suspended in methylene chloride (300 mL) and stirred vigorously for 20 min, when the initial brown color changed to dark green. Aldehyde (281) (6 g, 30 mmol) was dissolved in 50 mL methylene chloride then added quickly over the low valent vanadium solution and the color changed to dark brown. After 3 hrs the reaction was quenched and shaken with 10% sodium tartrate until two almost clear phases separated in the separatory funnel. The aqueous layer was back extracted three times with methylene chloride and finally the combined organic phase was dried on anhydrous magnesium sulfate, filtered through approx. 20 g silicagel, then washed with methylene chloride. The silicagel was then washed with ether to collect separately the NMR pure desired diol (4.2 g) in 71%-74% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.4-4.5 (m, 2H), 4.3 (m, 4H), 2.2-2.4 (bs, 2H), 0.8 (s, 18H), 0.1 (s, 12H);^{13}C NMR (200 MHz, $CDCl_3$) δ -5.1, 18.3, 25.8, 51.7, 65.9, 66.2, 81.3, 85.7; IR (NaCl) 3571, 2942, 2859, 2468, 2375, 1257.6, 1333, 1078.

trans-4,5-di(3'-*t*-Butyldimethylsilyloxypropynyl)-2-thiono-1,3-dioxolane (283-*trans*)

cis-4,5-di(3'-*t*-Butyldimethylsilyloxypropynyl)-2-thiono-1,3-dioxolane



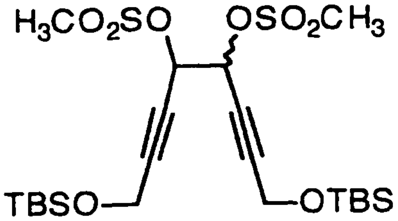
283-*trans*



283-*cis*

Starting diol (282) (0.24 g, 0.600 mmol) and DMAP (0.175 g, 1.43 mmol) were dissolved in methylene chloride (4 mL) cooled to 0°C and treated dropwise with thiophosgene (0.55 mL, 0.72 mmol). After 1 hr., 0.5 g silicagel was added to the reaction mixture, the solvent was evaporated and the crude was purified by column chromatography (ether/petroleum ether=1/9) using the dry loading procedure, to isolate 0.057 g of 283-*trans* (more polar) and 0.113 g. of 283-*cis* (less polar) in 65% overall yield. 283-*trans* ^1H NMR (200 MHz, $CDCl_3$) δ 5.3 (m, 2H), 4.3 (m, 4H), 0.9 (s, 18H), 0.1 (s, 12H);^{13}C NMR (200 MHz, $CDCl_3$) δ -5.2, 18.2, 25.7, 51.4, 71.4, 75.6, 90.8, 188.9; IR (NaCl) 2942, 2858, 1467, 1366, 1154; MS 383 (2.6), 147.1 (18.8), 73.1 (100); HRMS (EI): calcd for $C_{17}H_{27}O_4SSi_2$, 383.11854 found 383.11568; H 283-*cis* ^1H NMR (200 MHz, $CDCl_3$) δ 5.5 (m, 2H), 4.4 (m, 4H), 0.9 (s, 18H), 0.1 (s, 12H);^{13}C NMR (200 MHz, $CDCl_3$) δ -5.2, 18.2, 25.7, 51.4, 70.2, 73.9, 74.2, 92.4, 189.0; IR (NaCl) 2948, 2862, 1467, 1351, 1150; MS 383 (1.6), 323 (7.7), 147 (25), 73 (100); HRMS (EI): calcd for $C_{17}H_{27}O_4SSi_2$ 383.1185 found 383.1157.

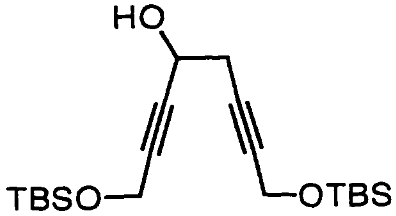
1,8-di(*t*-Butyldimethylsilyloxy)-4,5-dimethanesulphonyloxy-2,6 octadiyne



284

Starting diol (282) (0.560 g, 1.4 mmol) was dissolved in methylene chloride (50 mL) and cooled to - 78°C. The addition of triethylamine (0.78 mL, 5.6 mmol, 2 eq.) was followed by dropwise addition of methanesulphonyl chloride (0.49 mL, 6.4 mmol, 2.3 eq.) and the reaction mixture was allowed to warm up to 0°C and kept at this temperature for other 2 hrs. The reaction was quenched and extracted with 10% aqueous HCl, water, dried on anhydrous magnesium sulfate and finally columned on silica gel with 25% ether to obtain a 2:1 diastereomeric mixture of pure bis-mesylate (0.560 g) in 72% yield. ^{1}H NMR (200 MHz, CDCl3) δ 5.4 and 5.3 (2s, 2H), 4.4 (s, 4H), 3.1 (s, 6H), 0.9 (s, 18H), 0.1 (s, 12H);^{13}C NMR (200 MHz, CDCl3) δ -5.2, 18.2, 25.7, 39.4, 39.5, 51.5, 70.5, 70.6, 75.2, 90.0, 90.2; IR (NaCl) 2952, 2858, 2243, 1467, 1361; MS - CI 497 (1.3), 459 (100); MS-FAB 555 (0.1), 497(0.2), 459 (1.5), 73.1 (100).

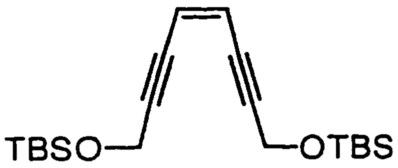
1,8-di(*t*-Butyldimethylsilyloxy)-2,6-octadiyn-4-ol

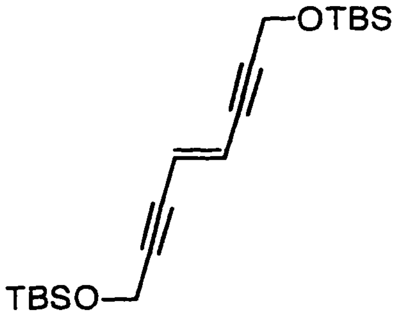


285

Starting thionocarbonate (0.11 g, 0.25 mmol) was dissolved in toluene (20 mL) deoxygenated by bubbling nitrogen through for 10 minutes and brought to the refluxing temperature. Dibenzoyl peroxide (0.005 g) and tributyltin hydride were dissolved in toluene (10 mL) and injected by syringe pump in one hour over the thionocarbonate solution. The refluxing was continued for one hour and then the solution was allowed to cool down, concentrated and purified by column chromatography (ether/petroleum ether=1/4) to get 0.028 g product in 29% chemical yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.5 (m, 1H), 4.3 (m, 4p), 2.6 (m, 2p), 1.3 (bs, 1H), 0.9 (s, 18H), 0.1 (s, 12H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -5.1, 18.28, 25.73, 25.81, 28.78, 51.66, 51.87, 60.93, 79.93, 81.96, 84.01, 84.09; IR (NaCl) 3401, 2941, 2858, 1823, 1467, 1368, 1256; MS-EI 382 (M^{+}), 367 (M^{+}-Me), 325 (M^{+}-*t*-Bu); HRMS (EI): calcd for $C_{16}H_{29}O_3Si_2$ 325.1655, found 325.1660.

cis-1,8-di(*t*-Butyldimethylsilyloxy)-4-octen-2,6-diyne
(286-*cis*)
trans-1,8-di(*t*-Butyldimethylsilyloxy)-4-octen-2,6-diyne
(287-*trans*)





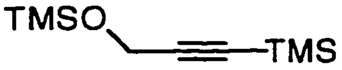
286-*cis* 287-*trans*

Method A. Starting thionocarbonate (283) (100 mg, 0.22 mmol, approx. 2/1 mixture of cis and trans) was dissolved in 5 mL trimethyl phosphite under an inert nitrogen atmosphere and warmed to 45°C in a round bottom flask. After 2 days the solution was pored over ether (25 mL) and vigorously shaken for 10 -15 minutes in a separatory funnel with saturated sodium bicarbonate solution then extracted with brine. The organic layer was then dried on anhydrous magnesium sulfate, filtered and concentrated to a crude product that was purified by column chromatography (ether/petroleum ether=1/9) to give a 2/1 mixture of desired *cis* and *trans* enediynes (0.054 g) in 68% yield.

Method B. Starting alcohol (285) (0.028 g, 0.073 mmol) was dissolved in methylene chloride (1 mL) and cooled to - 78°C. The solution was treated with triethylamine (0.021 mL, 0.15 mmol) then with mesyl chloride (0.013 mL, 0.17 mmol) and allowed to warm up to 0°C where it was kept for two hours. The reaction was quenched and extracted with 10% aqueous HCl, water, sodium bicarbonate saturated solution and brine and dried on anhydrous magnesium sulfate. Concentration of the solution yielded a crude product (0.026

g) that was taken in methylene chloride (2 mL) solution of DBU (0.152 g, 1 mmol). The reaction mixture was extracted after 24 hours with 1 M HCl, and purified after usual work up by flash chromatography to yield a 1/1 mixture (GC-MS) of *cis* and *trans* enediynes (0.015 g) in 56% over two steps. 1H NMR (200 MHz,CDCl$_3$) δ 5.96 (s, 2H), 5.8 (s, 2H), 4.47 (s, 4H), 4.42 (s, 4H), 0.9 (s), 0.1 (s);^{13}C NMR (200 MHz, CDCl$_3$) δ -5.1, 18.3, 25.8, 52.2, 81.96, 82.91, 93.21, 95.4, 119.089, 120.675; IR (NaCl) ; MS 364 (0.1), 349 (0.4), 307 (33.9), 147 (89.6), 103 (80.9), 73 (100); HRMS (EI): calcd for $C_{16}H_{27}O_2Si_2$ 307.1549, found 307.1542.

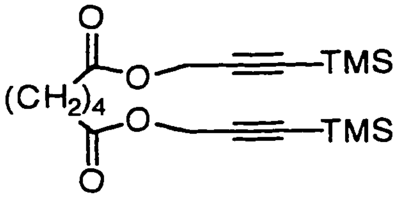
3-Trimethylsilyloxy-1-trimethylsilylpropyne



290

Propargyl alcohol (5.8 mL, 100 mmol) was dissolved in tetrahydrofurane (400 mL), cooled to - 78°C and treated with n-butyllithium (88 mL, 220 mmol, 2.5 M solution in hexanes). After a quarter of an hour the reaction mixture was treated with trimethylsilylchloride (34 mL, 240 mmol) and allowed to warm up to room temperature when it was allowed to stir for other three hours then filtered, concentrated under water pump vacuum then redissolved in petroleum ether and filtered through Celite®. The product was then distilled under water pump vacuum at 63-68°C to afford the product (19.5 g, 97.5 mmol) in 97.5% yield.^{1}H NMR (200 MHz,CDCl$_3$) δ 4.17 (s, 2H), 0.06, 0.05 (2s, 18H); ^{13}C NMR (200 MHz, CDCl$_3$) δ -0.25, 51.6, 89.8, 104.1; IR (NaCl) 2941.1, 2177.6, 1411, 1364.4; MS 199 (0.7), 185.1 46.9), 155.1 (100), ; HRMS (EI): calcd for $C_8H_{17}OSi_2$ 185.0818, found 185.0793.

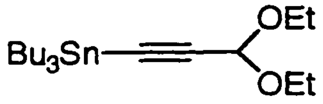
Di-3-trimehtylsilyl-2-propynyl adipate



291

Silylated propargyl alcohol (290) (6.2 g, 31 mmol) and adipoyl chloride (1.95 mL, 13.3 mmol) were dissolved in carbon disulfide (13 mL) and added by injection pump over a suspension of aluminum trichloride (3.9 g, 29 mmol) in 26 mL of the same solvent at 0°C. After the complete addition of the reactants the reaction mixture was allowed to stir for 45 minutes and quenched the reaction with iced 1M hydrochloric acid in an attempt to perform the deprotection of the silylated alcohol in one pot. After one hour, ether was added and the organic phase was extracted with water, sodium bicarbonate solution and brine, dried on anhydrous magnesium sulfate and finally filtered, concentrated to a crude crude which was distilled on a Kugelrohr to afford 2.4 g (6.6 mmol) of unexpected ester (291) in 49% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.6 (s, 4H), 2.3 (m, 4H), 1.6 (m, 4H), 0.07 (s, 18H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -0.4, 24.1, 33.5, 52.6, 92.0, 99.0, 172.3; IR (NaCl) 2946.3, 2185.8, 1743.8; Anal. Calcd. for $C_{18}H_{30}O_4Si_2$: C, 58.97; H 8.24,. Found: C, 58.73; H, 8.21.

3-Tributyltinpropiolaldehyde diethyl acetal



294

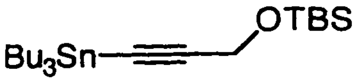
Propiolaldehydediethyl acetal (4.3 mL, 30 mmol) was dissolved in tetrahydrofurane (25 mL) and treated at 0°C with n-butyllithium (18.75 mL, 30 mmol, 1.6 M solution in hexanes). After 30 minutes chlorotributyltin (8.5 mL, 30 mmol) were added dropwise and the reaction was stirred overnight at room temperature. The cloudy white suspension was diluted dichloromethane, extracted with water and dried over anhydrous magnesium .sulfate. The solvent was removed under vacuum and the residue was distilled under 4 mm vacuum at 162-165°C to afford the product (9.3 g, 22.3 mmol) in 74% yield. 1H NMR (200 MHz, $CDCl_3$) δ 5.2 (s, 1H), 3.5-3.8 (m, 4H), 0.7-1.7 (m, 27H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 11.0, 13.6, 15.0, 26.3, 26.9, 28.8, 60.6, 89.4, 91.3, 104.5; IR (NaCl) 2914.4, 1458.4, 1337.5; MS 417.15 (0.2), 361 (6.2), 317 (100).

t-Butyldimethylsilyloxypropyne

289'

Propargyl alcohol (2.8 g, 50 mmol), *tert*butyldimehtylsilyl chloride (9.05 g, 60 mmol) and imidazole (8.5 g, 125 mmol) were dissolved in dimethylformamide (6 mL) and magnetically stirred for 17 hours at room temperature under nitrogen. The mixture was then diluted with pentane (40 mL) and washed thrice with portions of 20 mL water. The pentane layer was dried over anhydrous magnesium sulfate and concentrated. Distillation of the crude under water aspirator at 45-48°C gave the pure product (7.2 g, 42.35 mmol) in 85 % yield. ^{1}H NMR (200 MHz, CDCl3) δ 4.28 (d, 2.4 Hz, 2H), 2.36 (d, 2.4 Hz), 0.9 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (200 MHz, CDCl3) δ -5.2, 18.3, 25.6, 25.7, 51.5, 72.8, 82.4; IR (NaCl) 3299.3, 2913.2, 1466.4, 1098. (Lit. ref. 57c)

3-*t*-Butyldimethylsilyloxy-1-tributyltinpropyne

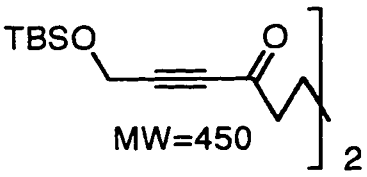


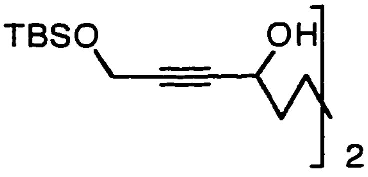
297

Silylated propargyl alcohol (289') (7.65 g, 35 mmol) was dissolved in tetrahydrofurane (25 mL) and treated at 0°C with n-butyllithium (22.2 mL, 35 mol, 1.6M solution in hexanes). After 30 minutes, chlorotributyltin (10 mL, 35 mmol) was added dropwise and the reaction was stirred overnight at room temperature. The cloudy white suspension was diluted with dichloromethane, extracted with water and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue was distilled to afford the product (10.5 g) in 70% at 2 Torr, 162°C. ^{1}H NMR (200 MHz, CDCl3) δ 4.3 (s, 2H), 1.4-1.6 (m, 6H), 1.2-1.4 (m, 6H), 0.8-1.0 (m, 15H), 0.1 (s, 6H); ^{13}C NMR (200 MHz, CDCl3) δ -5.3, 10.9, 13.7, 18.3, 25.8, 27.0, 28.8, 52.5, 87.9, 108.9; IR (NaCl) 2938, 2855, 1462, 1365. (Lit. ref. 57c)

1,12-Di(*t*-butyldimethylsilyloxy)-4,9-dioxo-2,10-diyne (298)

1,12-Di(*t*-butyldimethylsilyloxy)-2,10-diyn-4,9-diol (299)



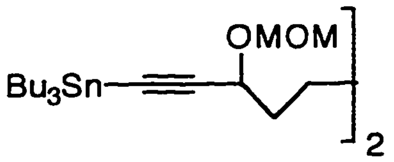


298 299

Benzyl-*tris*-(triphenylphosphine)palladium catalyst (0.1 g), stannane (297) (2.125g, 5 mmol) and adipoyl dichloride (0.362 mL, 2.5 mmol) were dissolved in chloroform (30 ml) and refluxed gently for 1 hour under argon. The reaction mixture was cooled down to room temperature, diluted with ether (60 mL) and vigorously stirred with a solution of potassium fluoride (5 g in 5 mL water) for 5 minutes to give a crude (1.1 g) which, according to proton and carbon NMR ,was almost pure diketone (298). Due to the instability of the compound to usual purification procedures the crude was submitted directly to various reduction procedures (Luche, DIBAL) to afford the impure diol (299) in low yield (less than 5%). Both products were purified on HPLC for analytical purposes , but only diketone 64 was satisfactorily characterized. Note that(*bis*-(triphenyphosphine)-palladiumdichloride also works very well as catalyst for this reaction. (298)^{1}H NMR (200 MHz, CDCl3) δ 4.4(s, 4H), 2.5 (m, 4H), 1.6 (m, 4H), 0.9 (s, 18H), 0.1 (s, 12H); ^{13}C NMR (200 MHz, CDCl3) δ -5.3, 18.2, 22.9, 25.7, 44.8, 51.4, 83.6, 90.5, 186.7; IR (NaCl) 2943, 2857, 2215, 1678.7, 1463.8, 1366.5; Anal. Calcd. for C24H42O4Si2: C, 63.95; H 9.39. Found: C 64.04; H 9.40. (299)^{1}H NMR (200 MHz, CDCl3) δ 4.3-4.4 (m, 2H), 4.35 (d, ^{5}J = 1.6 Hz, 2H), 2.0-2.2 (bs, 2H), 1.5-1.8 (m, 4H), 1.2-1.5 (m, 4H), 0.9 (s, 18H), 0.08 (s, 12H); ^{13}C NMR (200 MHz,CDCl3) δ -5.2, 4.7, 18.3, 24.8, 25.8, 37.5, 51.7, 62.2, 83.4, 85.7.

For compounds 307, 308 and 309 please see 266, 268-MOM and 270-MOM respectively.

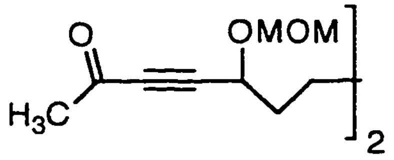
3,8-Di(methoxymethyloxy)-1,10-tributyltin-1,9-decadiyne



310

Diyne (309) (2.6 g, 10.2 mmol) was refluxed with tributylmehtoxytin (6.4 mL, 22 mmol) at 110°C for three hours and then chromatographed (ether/petroleum ether=1/8) to get the pure product (4.4 g, 5.28 mmol) in 52% yield. 1H NMR (200 MHz, $CDCl_3$) δ 4.97 and 4.56 (AB, ^2J=6.6Hz, 4H), 4.29 (t, ^3J = 5.9Hz, 2H), 3.3 (s, 6H), 0.8-1.9 (62H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 11.0, 13.7, 25.2, 26.9, 28.8, 36.0, 55.5, 66.1, 88.3, 93.8, 108.6; IR (NaCl) 2908.8, 1458.9, 1338.7.

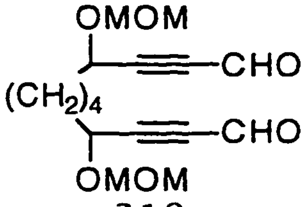
5,10-Di(methoxymethyloxy)-2,13-dioxo-3,11-tetradecadiyne



311

Stannane (310) (1 g, 1.2 mmol) was dissolved in chloroform (5 mL) and the benzyl-*tris*-(triphenylphosphine)palladium catalyst (0.05 g, 0.06 mmol) was added. Acetyl chloride (0.170 mL, 2.3 mmol) was injected and the solution was refluxed at 65ºC for 1 hour (reaction time established by NMR monitoring), cooled to room temperature and diluted with ether followed by vigorous stirring with aqueous potassium fluoride solution for thirty minutes. The ether layer was decanted and the fluoride treatment was repeated when considerably less tributyltin fluoride precipitates which allows easy filtration through a pad of Celite®. The etheral phase was extracted with brine, dried on anhydrous magnesium sulfate, filtered, concentrated down to a crude which was taken in ethyl acetate to cause further precipitation of the tributyltin fluoride. After filtration through Celite® concentration and chromatography (ether/petroleum ether=1/4) the pure acylated product (0.11 g, 0,37 mmol) were obtained in 27% yield.^1H NMR (200 MHz, $CDCl_3$) δ 4.87 and 4.60 (AB, ^2J= 6.95Hz, 4H), 4.46 (t, ^3J= 6.4 Hz, 2H), 3.4 (s, 6H), 2.3 (s, 6H), 1.7-1.9 (m, 4H), 1.5-1.7 (m, 4H);^{13}C NMR (200 MHz, CDCl$_3$) δ 24.8, 32.7, 34.7, 55.8, 65.1, 84.7, 89.9, 94.5, 184.0; IR (NaCl) 2915.98, 2212, 1680.5, 1440, 1357; Anal. Calcd. for $C_{18}H_{26}O_6$: C, 63.91; H 7.69,. Found: C 63.95, ; H 7.57.

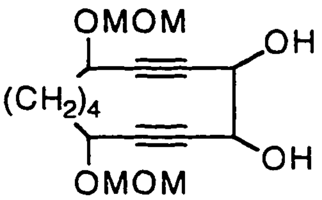
4,9-Di(methoxymethyloxy)-2,10-diyn-1,12-dodecadial



312

Starting diyne (309) (0.1 g, 0.4 mmol) and 2,2'-bipyridyl indicator (0.005 g) were dissolved in 5 mL tetrahydrofurane, cooled to - 78°C and treated dropwise with n-butyllithium (0.5 mmol, 1.6 M) until the solution remained pink. Dry DMF (0.6 mL, 8 mmol) was added dropwise and the reaction was stirred for six hours at the same temperature. The reaction was quenched with ammonium chloride and then partitioned between water and ether. The organic phase was extracted with brine , dried on anhydrous magnesium sulfate and after usual operations chromatographed (ether/petroleum ether=1/3) to get the corresponding monoaldehyde (0.14 mg, 0.05 mmol) in 12% yield and the desired dialdehyde (312) (0.021 g, 0.0065 mmol) in16% yield. Repeated on a 0.65 g scale the yield increased to 22% yield.^{1}H NMR (200 MHz, CDCl$_3$) δ 9.1 (bs, 2H), 4.72 and 4.51 (AB, ^2J= 6.95, 4H), 4.4 (t, ^3J = 6.4 Hz, 2H), 3.3 (s, 6H), 1.6-1.8 (m, 4H), 1.3-1.5 (m, 4H); ^{13}C NMR (200 MHz, CDCl$_3$) δ 24.7, 34.6, 35.2, 55.9, 65.2, 84.6, 94.67, 94.75, 176.3; IR (NaCl) 2908, 1669.2; MS 220 (22), 205 (92.1), 45 (100).

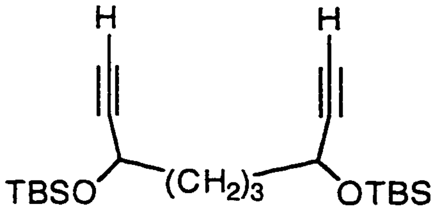
5,10-Di(methoxymethyloxy)-3,11-cyclododecadiyn-1,2-diol



314

A THF solution of samarium diiodide (20 mL, 2 mmol, 0.1M) was injected in a flask which had been previously flamed and cooled under a stream of nitrogen three times. In a separate flask, dried in the same manner, dialdehyde (312) (0.15 g, 0.8 mmol) was dissolved in tetrahydrofurane (10 mL) and then degassed by three freeze - vacuum- thaw cycles. This solution was added dropwise by syringe over the samarium diiodide at room temperature and after other five minutes the reaction was quenched with 1 M hydrochloric acid aqueous solution and the color turned from deep blue to yellow. After addition of ether (50 mL), the organic phase was separated and extracted with 1 M sodium thiosulfate solution and brine then dried on anhydrous magnesium sulfate and column on silicagel with ether to afford the pure diol (0.072 g, 0.23 mmol) in 28 % yield.^1H NMR (200 MHz, $CDCl_3$) δ 4.79(AB, ^2J = 6.8 Hz, 2H), 4.76(AB, ^2J = 6.8 Hz, 2H), 4.4 (m, 4H), 3.3 (s, 6H), 3.2 (b, 2H, exchanges with D_2O), 1.6-2 (m, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 23.6, 23.9, 33.3, 33.5, 55.6, 65.5, 65.8, 65.9, 67.0, 67.1, 83.8, 83.9, 85.5, 85.7, 94.2; IR (NaCl) 3376.7, 2911.3, 1449.6, 1344.6; for $C_{16}H_{24}O_6$: C, 61.52; H 7.74, . Found: C 61.01; H 7.98.

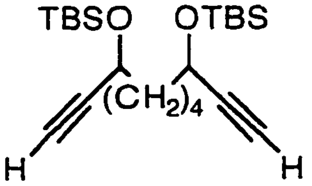
3,7-Di(*t*-Butyldimethylsilyloxy)-1,9-ditrimethylsilyl-1,8-nonadiyne



317

A solution of glutaryl chloride (6 mL, 46 mmol) and *bis*-trimethylsilylacetylene (20.8 mL, 92 mmol) in carbon disulfide (20 mL) was injected via syringe pump (30 minutes) over a vigorously stirred suspension of aluminum trichloride (12.28 g, 92 mmol) in 100 mL of the same solvent at 0°C. 30 minutes after the addition was completed the brown suspension was poured over crushed ice in a large glass beaker. The organic phase was further extracted several times with 10% hydrochloric acid then with brine and dried on anhydrous magnesium sulfate, filtered and concentrated down to a crude (8.9 g, 30 mmol) which was pure by NMR. The crude diketone was dissolved in methanol (750 mL), cerium trichloride heptahydrate (102 g, 280 mmol) was added to the solution and the suspension was stirred for ten minutes. The solution was cooled to 0°C and sodium borohydride (14 g, 370 mmol) was added portionwise and the reaction was monitored by TLC and quenched with 10% hydrochloric acid. The aqueous/methanolic phase was first concentrated under vacuum, then thoroughly extracted with ethyl acetate and finally the organic phase was extracted with brine, then dried with anhydrous magnesium sulfate, filtered and concentrated down to a crude (7.8 g, 26.2 mmol) product which was practically pure by NMR. The crude was dissolved in DMF (8 mL) and added dropwise to a solution of TBSCl (4 g, 26.3 mmol) and imidazole (4.4 g, 65.5 mmol) in DMF (10 mL). The reaction was allowed to stir for 4 hours, then partitioned between petroleum ether and 10% HCl. The organic phase was repeatedly extracted with brine, dried on anhydrous magnesium sulfate, and filtered through a plug of silicagel to yield 13.8 g of crude. This was dissolved in acetonitrile, (20 mL), triethylbenzylammonium chloride (0.160 g, 0.7 mmol) was added as phase transfer catalyst, the reaction mixture was cooled to 0°C and treated dropwise with sodium hydroxide (20 mL 12 M solution). After the addition was completed the reaction was allowed to stir vigorously for 20 minutes and partitioned between petroleum ether and water. The organic phase was repeatedly extracted with water and finally with brine, then dried on anhydrous magnesium sulfate, concentrated and purified by flash chromatography to yield the pure compound (11.8 g) in 52% overall yield. over four steps. The spectral data of the compound were similar to those reported earlier for 269-TBS.

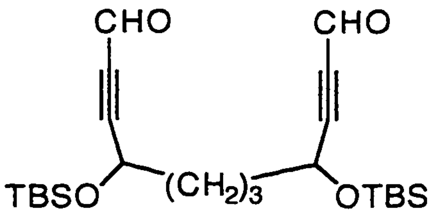
3,8-Di(*t*-Butyldimethylsilyloxy)-1,10-ditrimethylsilyl-1,9-decadiyne



318

A solution of adipoyl chloride (6.7 mL, 46 mmol) and *bis*-trimethylsilylacetylene (20.8 mL, 92 mmol) in carbon disulfide (20 mL) was injected via syringe pump (30 minutes) over a vigorously stirred suspension of aluminum trichloride (12.4 g, 92 mmol) in 100 mL of the same solvent at 0°C. After the addition was complete we allowed other 30 minutes and then the brown suspension was poured over crushed ice in a large glass beaker.. The organic phase was further extracted several times with 10% hydrochloric acid then with brine and dried on anhydrous magnesium sulfate, filtered and concentrated down to a slightly yellow product (12.6 g, 41.4 mmol) which was pure by NMR. The crude diketone was dissolved in methanol (750 mL) and cerium trichloride heptahydrate (102 g, 280 mmol) was added over and stirred for ten minutes. The solution was cooled to 0°C and sodium borohydride (14 g, 370 mmol) was added portionwise and the reaction was monitored by TLC and quenched with 10% hydrochloric acid. The aqueous/methanolic phase was first concentrated under vacuum, then thoroughly extracted with ethyl acetate and finally the organic phase was extracted with brine, then dried with anhydrous magnesium sulfate, filtered and concentrated down to a crude product (12.4 g, 40.4 mmol) which was practically pure by NMR. The crude was dissolved in DMF (8 mL) and added dropwise to a solution of TBSCl (6.1 g, 40.6 mmol) and imidazole (6.9 g, 101 mmol) in DMF (15 mL). The reaction was allowed to stir for 4 hours, then partitioned between petroleum ether and 10% HCl. The organic phase was repeatedly extracted with brine, dried with anhydrous magnesium sulfate, and filtered through a plug of silicagel to yield 38.4 g of crude. This was dissolved in acetonitrile, (30 mL) triethylbenzylammonium chloride (0.250 g, 1 mmol) was added as phase transfer catalyst, the reaction mixture was cooled to 0°C and treated dropwise with sodium hydroxide (30 mL 12 M solution). After the addition was completed the reaction was allowed to stir vigorously for other 20 minutes and was partitioned between petroleum ether and water. The organic phase was repeatedly extracted with water and finally with brine, then dried on anhydrous magnesium sulfate, concentrated and purified by flash chromatography to yield 16.8 g of pure compound in 71 % overall yield. The spectral data of the compound were similar to those reported earlier for 270-TBS.

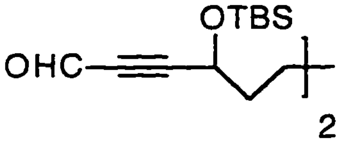
4,8-Di(*t*-butyldimethylsilyloxy)-2,9-diyn-1,11-undecadial



319

Starting diol (321) (1.8 g, 4 mmol) was dissolved in methylene chloride (200 mL) and then Dess-Martin reagent (3.7 g, 8.8 mmol) was added in one portion. After 15 minutes the reaction was quenched by adding ether (200 mL) then concentrated to 10-20 mL and taken in ether (300 mL). The etheral suspension was stirred vigorously with 300 mL of a 1:1 mixture of 1 M sodium thiosulphate and 1 M sodium bicarbonate aqueous solution until two clear phases separate and the organic phase was extracted with brine. All aqueous washings were back extracted with ether. The organic phase was then dried on anhydrous magnesium sulfate concentrated and chromatographed (ether/petroleum ether=1/20) to yield the pure product (1.5 g, 3.5 mmol) in 87% yield.^{1}H NMR (200 MHz, $CDCl_3$) δ 9.2 (s, 2 H), 4.5 (t, ^3J = 6.1Hz, 2 H), 1.5-1.7 (m, 6H), 0.8 (s, 18 H), 0.07 (d, 12 H);^{13}C NMR (200 MHz,$CDCl_3$) δ -5.2, -4.7, 18.0, 20.6, 25.6, 37.1, 62.4, 83.6, 97.2, 176.4; IR (NaCl) 2943, 2858, 2215, 1671, 1467; MS-CI $(M-1)^+$, 421; MS-EI 421, 407, 379.

4,9-Di(*t*-butyldimethylsilyloxy)-2,10-diyn-1,12-dodecadial



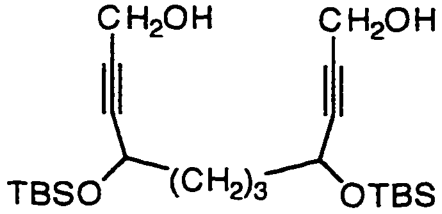
320

Method A. Starting diol (322) (2.3 g, 5 mmol) was dissolved in methylene chloride (250 mL) and then Dess-Martin reagent (4.6 g, 11 mmol) were added in one portion. After 15 minutes the reaction is quenched by adding ether (200 mL) then concentrated down to 10-20 mL and taken in 300 mL ether. The etheral suspension was stirred vigorously with 300 mL of a 1:1 mixture of 1 M sodium thiosulfate and 1 M sodium bicarbonate aqueous solution until two clear phases separate and the organic phase was extracted with brine. All aqueous washings were back extracted with ether. The organic phase was then dried on anhydrous magnesium sulfate concentrated and chromatographed (ether/petroleum ether=1/20) to yield 2.1 g (4.65 mmol) in 93% yield.

Method B. Starting diyne (318) (0.4 g, 1 mmol) was dissolved in dry tetrahydrofurane (12.5 mL), cooled to - 78°C and treated dropwise with n-butyllithium (1.25 mL, 2 mmol, 1.6 M solution in hexanes). After 15 minutes dry dimethylformamide (1.2 mL, 16.4 mmol) was added and the reaction was allowed 7 hours at low temperature. The reaction was quenched with ammonium chloride solution at low temperature and after usual operations chromatographed (ether/petroleum ether=1/20) to afford the pure dialdehyde (0.19 g, 0.42 mmol) in 42% as well as monoaldehyde byproduct (0.073 g, 0.17 mmol) in 17% yield.^{1}H NMR (200 MHz, $CDCl_3$) δ 9.2 (s, 2H), 4.5 (t, ^3J = 6.4 Hz, 2H), 1.6-1.8 (m, 4H), 1.3-1.5 (m, 4H), 0.9 (s, 9H), 0.09 (d, ^4J =6 Hz, 6H);^{13}C NMR (200 MHz, $CDCl_3$)

δ -5.2, -4.7, 18.1, 24.5, 25.6, 37.5, 62.583.5, 97.5, 176.5; IR (NaCl) 2909, 2215, 1671.6, 1467, 1388.

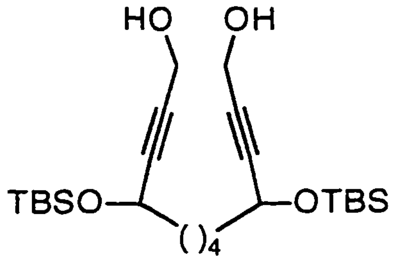
4,8-Di(*t*-butyldimethylsilyloxy)-2,9-diyn-1,11-undecadiol



321

Starting diyne (317) (5.5 g, 14.5 mmol) was dissolved in tetrahydrofurane (100 mL), cooled to - 78°C and treated dropwise with n-butyllithium (13 mL, 33 mmol, 2.5 M solution in hexanes). After 15 minutes paraformaldehyde (4.3 g, 145 mmol) (previously dried under water aspirator vacuum for two hours at 80°C) was added quickly and the reaction mixture was allowed to slowly warm up overnight to room temperature when it was quenched with saturated ammonium chloride solution. Partition between ether/brine followed by drying on anhydrous magnesium sulfate, filtration, concentration and column chromathography (ether/petroleum ether=1/5) mixture afforded the pure diol (321) (5.2 g, 11.8 mmol) in 82% yield. 1H NMR (200 MHz, $CDCl_3$) δ 4.3 (m, 2H), 4.2 (s, 4H), 2.7-2.9 (bs, 2H), 1.5-1.8 (m, 6H), 0.8 (s, 18H), 0.06 (d, 6H);^{13}C NMR (200 MHz, $CDCl_3$) δ -5.0, -4.5, 18.1, 20.7, 20.9, 25.7, 38.0, 50.8, 62.9, 82.5, 86.9; IR (NaCl) 3344, 2942, 2858, 1466; MS 422.8 (M^+-H_2O, 2.5), 382.9 (M^+-tBu, 1.7), 364.9 (4.1), 291 (100).

4,9-Di(*t*-butyldimethylsilyloxy)-2,10-diyn-1,12-dodecadiol

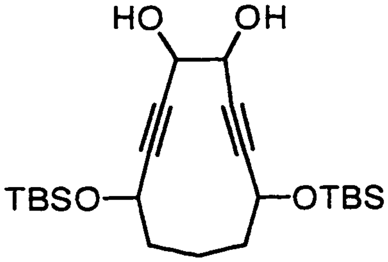


MW=454

322

Starting diyne (318) (1.8 g, 4.5 mmol) was dissolved in tetrathydrofurane (50 mL) and cooled to - 78°C. Treatment with *n*-butyllithium (3.7 mL, 9.25 mmol, 2.5 M solution in hexanes) followed by addition of excess dry paraformaldehyde (10 equivalents) and stirring of the reaction mixture for 6 hours at the same temperature indicated complete consumption of the starting material by TLC. The reaction was quenched with ammmonium chloride, allowed to slowly warm up to room temperature, extracted with water and brine, dried on anhydrous magnesium sulfate and chromatographed (ether/petroleum ether=1/2) to yield the desired product (1.7 g, 3.8 mmol) in 84% yield and some monoalcohol byproduct (0.095 g, 0.225 mmol) in 5% yield. 1H NMR (200 MHz, CDCl3) δ 4.25-4.4 (m, 2H), 4.2 (s, 4H), 2.3-2.5 (bs, 2H), 1.5-1.7 (m, 4H), 1.3-1.5 (m, 4H), 0.8 (s, 18H), 0.07 (d, 6H);^{13}C NMR (200 MHz, CDCl3) δ -5.0, -4.5, 18.2, 24.7, 25.8, 38.4, 50.9, 62.8, , 82.2, 87.3; IR (NaCl) 3355, 2909, 1468.9.

5,9-Di(*t*-butyldimethylsilyloxy)-3,10-cycloundecadiyn-1,2-diol

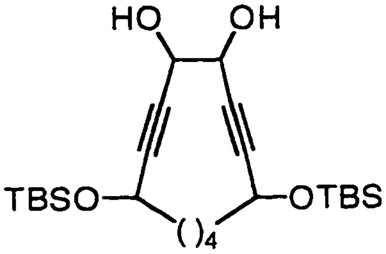


321'

Method A. Dialdehyde (319) (0.1 g, 0.22 mmol) was dissolved in tetrahydrofurane (3 mL) under nitrogen and frozen in liquid nitrogen. Subsequently the two neck flask was vacuumed down to 2 torr , isolated from the pump and allowed to warm up till the solid melted. The freeze-thaw cycle was repeated thrice. In a separate flask, flame dried and cooled under a flow of nitrogen, of dry HMPA was added (1 mL), diluted with tetrahydrofurane (4 mL) and degassed by the same freeze-thaw procedure. Samarium diiodide (8.8 mL, 0.88 mmol, 0.1M solution in tetrahydrofurane was then added over the HMPA solution to give a dark purple solution which was cooled down to - 78°C. Subsequently the degassed dialdehyde solution was injected by syringe pump over one hour and the reaction was quenched with 1 M hydrochloric acid solution and partitioned between ether and sodium thiosulfate solution . The organic phase was extracted with brine dried over anhydrous magnesium sulfate and chromatographed (ether/petroleum ether=1/2.5) to yield 0.081 g (0.18 mmol) of diol in 84% yield.

Method B. Starting dialdehyde (319) (0.12 g, 0.27 mmol) was dissolved in tetrahydrofurane (3 mL) and degassed carefully by freeze-pump-thaw technique. The solution was transferred via canula over samarium diiodide (6 mL, 0.6 mmol, 0.1M solution in tetrahydrofurane. The reaction was quenched with 1 M aqueous hydrochloric acid solution, when the color turned from deep blue to yellow. Further purification with 1 M sodium thiosulfate extraction followed by usual operations and column chromatography (ether/petroleum ether=1/1) mixture afforded the pure diol (0.026 g (0.057 mmol) in 21% yield.^{1}H NMR (200 MHz, $CDCl_3$) δ 4.3-4.5 (bs, 4H), 2.7-2.9 (bs, 1H), 2.5-2.7 (bs, 1H), 1.5-2.0 (m, 6H), 0.8 (s, 18H), 0.08 (d. 12H);^{13}C NMR (200 MHz, $CDCl_3$) δ -5.0, -4.9, -4.6, -4.3, 18.2, 19.7, 20.1, 25.8, 37.0, 63.4, 63.5, 68.0, 68.1, 82.8, 89.6; IR (NaCl) 3363, 2910, 1466; Anal. Calcd. for $C_{23}H_{42}O_4Si_2$: C, 62.96; H 9.64. Found: C 63.32; H 9.75.

5,10-Di(*t*-butyldimethylsilyloxy)-3,11-cyclododecadiyn-1,2-diol

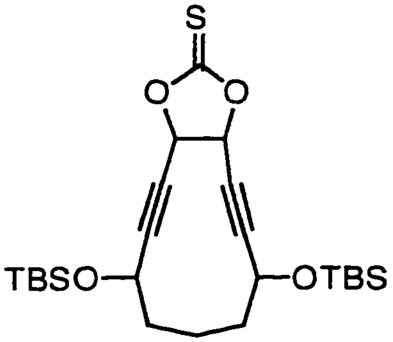


322'

Method A. Dialdehyde (319) (0.1 g, 0.22 mmol) was dissolved in tetrahydrofurane (3 mL) under nitrogen and frozen in liquid nitrogen. Subsequently the two neck flask was vacuumed down to 2 torr , isolated from the pump and allowed to warm up till the solid melted. The freeze-thaw cycle was repeated thrice. In a separate flask, flame dried and cooled under a flow of nitrogen, dry HMPA (1 mL) was added, diluted with tetrahydrofurane (4 mL) and degassed by the same freeze-thaw procedure. Samarium diiodide (8.8 mL, 0.88 mmol, 0.1M solution of in tetrahydrofurane) was then added over the HMPA solution to give a dark purple solution which was cooled down to - 78°C. Subsequently the degassed dialdehyde solution was injected by syringe pump over one hour and the reaction was quenched with 1 M hydrochloric acid solution and partitioned between ether and sodium thiosulfate solution. The organic phase was extracted with brine dried over anhydrous magnesium sulfate

and chromatographed (ether/petroleum ether=1/1) to yield the diol (0.074 g, 0.16 mmol) in 74% yield.
Method B. Starting dialdehyde (320) (0.12 g, 0.27 mmol) were dissolved in tetrahydrofurane (3 mL) and degassed carefully by freeze-pump-thaw technique. The solution was transferred via canula over samarium diiodide (6 mL, 0.6 mmol, solution in tetrahydrofurane. The reaction was quenched with 1 M aqueous hydrochloric acid solution, when the color turned from deep blue to yellow. Further purification with 1 M sodium thiosulfate extraction followed by usual operations and column chromatography (ether/petroleum ether=1/1) mixture afforded 0.064 g (0.14 mmol) pure diol in 52% yield.
Method C. Vanadium trichloride tris(tetrahydrofurane) complex (0.144 g, 0.38 mmol) and zinc (0.014 g, 0.21 mmol) was suspended in methylene chloride and stirred for 15 minutes to allow the formation of the reducing agent which is signaled by a dark green color of the solution. A dialdehyde (320) (0.05 g, 0.11 mmol) solution in methylene chloride (1 mL) , was added dropwise and allowed three hours for the reaction to go to completion. After quenching with sodium tartrate 10% w/v (the mixture should be shaken vigorously) and back extraction with dichloromethane, the combined organic phases were washed with saturated sodium bicarbonate and dried on anhydrous magnesium sulfate. The crude was chromatographed on a silicagel column (ether/petroleum ether=1/2) to isolate after concentration the pure product (0.018 g, 0.038 mmol) in 35% yield.^{1}H NMR (200 MHz, $CDCl_3$) δ 4.4-4.7 (m, 4H), 2.5-2.8 (m, 2H), 1.6-1.9 (m, 8H), .95 (bs, 18H), 0.15 (bs, 12 H);^{13}C NMR (200 MHz, $CDCl_3$) δ -5.0, -4.9, -4.5, 18.21, 23.1, 23.3, 23.6 23.7, 25.8, 36.3, 36.4, 36.7, 62.7, 62.8, 63.04, 63.2, 67.1, 67.2, 81.7, 81.8, 89.0, 89.1; IR (NaCl) 3373, 2942, 2858, 1254, 1075.7, 842.2; Anal. Calcd. for $C_{24}H_{44}O_4Si_2$: C, 63.66; H 9.79. Found: C 63.80; H 9.81.

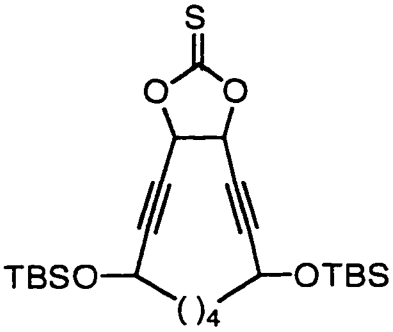
Bicyclo[9,3,0]-3,8-di(*t*-butyldimethylsilyloxy)-13-thiono-12,14-dioxa-2,9-tetradecadiyne



323

Starting diol (321') (0.1 g, 0.22 mmol) and DMAP (0.064 g, 0.53 mmol) were dissolved in methylene chloride (2 mL), cooled to -10°C and treated dropwise with thiophosgene (0.02mL, 0.26 mmol). The reaction was done in 30 minutes and quenched with 0.4 g silicagel, concentrated and chromatographed (ether/petroleum ether=1/20) mixture to get the pure product (0.074 g, 0.14 mmol) in 66% yield.^{1}H NMR (200 MHz, CDCl$_3$) δ 5.39 (^3J=11.3, ^5J=2.24, 1H), 5.31-5.36 (m, 2H), 5.26 (^3J=11.3, ^5J=1.3, 1H), 1.6-2.0 (m, 6H), 0.9 (d, 18H), 0.07 (d, 12 H);^{13}C NMR (200 MHz, CDCl$_3$) δ -5.1, -5.0, -4.8, -4.7, 18.1, 18.6, 18.9, 19.2, 25.7, 38.4, 38.6, 38.9, 63.3, 63.5, 75.0, 75.1, 75.9, 76.0, 100.0, 100.2, 189.3; IR (NaCl) 2910, 2222, 1842, 1465; MS 423, (9.4), 363.2 (3.5), 231 (13.5), 147 (25.9), 73 (100); HRMS (EI): calcd for $C_{20}H_{31}O_4Si_2S$ 423.1498, found 423.1472.

Bicyclo[10,3,0]-3,10-di(*t*-butyldimethylsilyloxy)-14-thiono-13,15-dioxa-2,10-tetradecadiyne

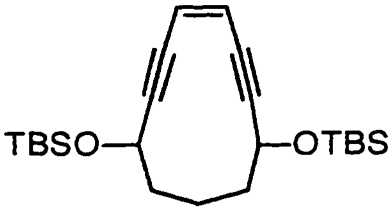


324

Starting diol (322') (0.170 g, 0.37 mmol) and 4-dimethylaminopyridine (0.110 g, 0.88 mmol) were dissolved in mehtylenchloride (2 mL) and cooled to 0°C. Thionophosgene (0.034

mL, 0.44 mmol) was subsequently added dropwise and after 30 minutes the reaction was quenched with silcagel, concentrated and chromatographed (ether/petroleum ether=1/20) by using the dry loading technique to afford the product (0.129 g, 0.2 mmol) in 71%.^{1}H NMR (500 MHz, CDCl$_3$) δ 5.2-5.4 (2H) (5.35 (dd, ^3J =11.4Hz, ^5J =2.4Hz, 1H), 5.29 (bs, 2H), 5.24 (dd, ^3J =11.4Hz, ^5J =1.1Hz, 1H), 4.5 (m, 1H), 4.4 (m, 1H), 1.4-1.8 (m, 8H), 0.87 (bs, 18 H), 0.09 and 0.07(s, 12H ;^{13}C NMR (500 MHz, CDCl$_3$) δ -5.1, -4.7, 18.1, 23.7, 23.8, 23.9, 24.2, 25.7, 25.8, 37.0, 37.4, 37.6, 62.6, 62.7, 62.9, 63.0, 74.0, 74.1, 74.3, 74.5, 75.5, 75.6, 97.9, 98.0, 189.5; IR (NaCl) 2911, 2234, 1843, 1465,6; MS 437 (4.5), 73 (100); HRMS (EI): calcd for $C_{21}H_{33}O_4Si_2S$ 437.1655, found 437.1622.

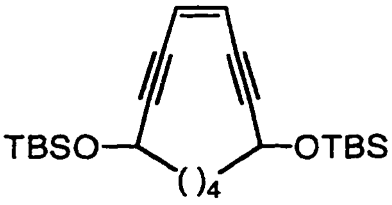
7,11-Di(*t*-butyldimethylsilyloxy)-3-en-1,5-cycloundecadiyne



325

Thionocarbonate (323) (0.120 g, 0.25 mmol) was heated in trimethylphosphite at 55°C for 3 days (when starting material disappears). The reaction mixture was concentrated and the residue was partitioned between petroleum ether/sodium bicarbonate saturated aqueous solution. The organic phase was dried on anhydrous magnesium sulfate filtered, concentrated and chromatographed (ether/petroleum ether=1/20) to afford the pure enediyne (0.009 g, 0.022 mmol) in 9%. ^{1}H NMR (200 MHz, CDCl$_3$) δ 5.8 (s, 2H), 4.6-4.8 (m, 2H), 1.6-1.9 (m, 6H), 0.8 (s, 18H), 0.1 (s, 12H);^{13}C NMR (200 MHz, CDCl$_3$) δ -5.0, -4.6, 18.4, 20.1, 25.8, 37.2, 63.4, 82.1, 98.2, 120.3;IR (NaCl) 2950, 2850, 1468, 1339; MS 347.1 (12.6), 271 (7.9), 215 (25), 141 (41), 73 (100); HRMS (EI): calcd for $C_{19}H_{31}O_2Si_2$, 347.1862, found 347.1858.

7,12-Di(*t*-butyldimethylsilyloxy)-3-en-1,5-cyclododecadiyne

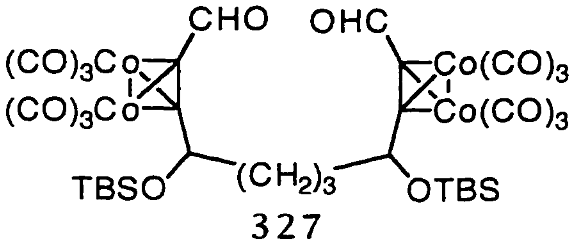


326

Method A. Thionocarbonate (324) (1 g, 2 mmol) was dissolved in trimethylphosphite (20 mL) and heated to 45°C for 24 hours. The reaction mixture was concentrated and the residue was partitioned between petroleum ether/sodium bicarbonate saturated aqueous solution. The organic phase was dried on anhydrous magnesium sulfate filtered, concentrated and chromatographed (ether/petroleum ether=1/20) to afford the pure enediyne (0.62 g. 1.48 mmol) in 75% yield.

Method B. N,N-dimethyl-P-phenyl-1,3-diaza-2-phospholidine (0.12 mL) was injected over thionocarbonate (324) (0.095 g) at room temperature. The reaction was stopped after 1.5 hours , worked up according to the literature reference[25b] and chromatographed as above to yield the product (0.016 g, 0.04 mmol) in 21 % yield. The identity of the product was established by proton NMR and GC-MS by comparison with a sample obtained through the trimethylphosphite route. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8 (s, 2H), 4.6 (m, 2H), 1.6-1.9 (m, 8H), 0.9 (s, 18 H), 0.08 and 0.1 (2s, 12H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -4.9, -4.5, 18.3, 23.8, 24.3, 25.8, 36.7, 36.8, 63.6, 64.0, 82.9, 98.5, 98.7, 120.6; IR (NaCl) 2810, 2234, 1468, 1337; MS 361 (12.6), 229 (28), 155 (30.6), 73 (100); HRMS (EI): calcd for $C_{20}H_{33}O_2Si_2$ 361.2019, found 361.2038.

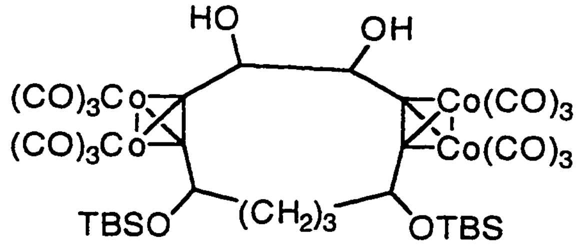
(2,3-η^2)-(9,10-η^2)-[4,8-Di(*t*-butyldimethylsilyloxy)-2,9-diyn-1,11-undecadial]bishexacarbonydicobalt



327

Dialdehyde (319) (130 mg, 0.3 mmol) was dissolved in hexanes (5 mL) and a solution of dicobaltooctacarbonyl (210 mg, 0.65 mmol) in 5 mL of the same solvent was added over at -23°C. The reaction mixture was then stirred for one hour at room temperature, concentrated and chromatographed (ether/petroleum ether=1/20) . to provide the pure product (0.167 g, 0.16 mmol) in 55% yield.^{1}H NMR (500 MHz, $CDCl_3$) δ 10.2 (s, 2H), 4.8 (m, 2H), 1.4-1.8 (m, 6H), 0.9 (s, 18H), 0.06-0.08 (3s, 12H);^{13}C NMR (500MHz, $CDCl_3$) δ -4.6, -4.4, -4.2, -4.1. 18.0, 22.2, 22.3, 25.8, 40.6, 40.7, 72.3, 87.0, 87.1, 103.1, 190.0, 190.1, 198.1; IR (NaCl) 2945, 2859, 2100, 1667, 15705; MS-FAB 895.9 (MW-4CO), 867.9 (MW-5CO), 840.9 (MW-6CO), 811.9 (MW-7CO), 783.9 (MW-8CO), 755.9 (MW-9CO), 727.9 (MW-10CO), 699.9 (MW-11CO), 671.9 (MW-12CO).

(3,4-η^2)-(10,11-η^2)-[5,9-Di(*t*-butyldimethylsilyloxy)-3,10-cycloundecadiyn-1,2-diol]bishexacarbonydicobalt



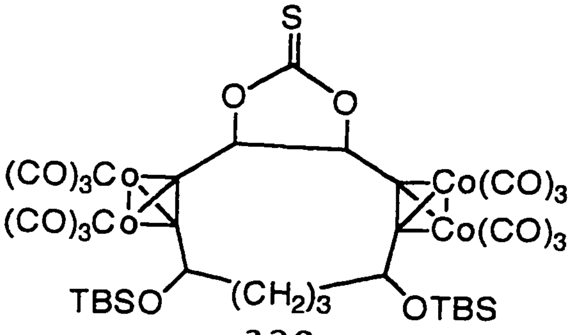
328

Method A. Starting dialdehyde (327) (0.1 g, 0.1 mmol) was dissolved in THF (2 mL) under inert atmosphere and the solution was degassed through three freeze-pump-thaw cycles using liquid nitrogen as cooling agent. Subsequently it was transferred dropwise via canula over samarium diiodide (3 mL, 0.3 mmol, 0.1 M solution in tetrahydrofurane). After the addition was complete the reaction was cooled to 0°C and quenched with ice cold 1M aqueous hydrochloric acid solution and extracted with 1M aqueous sodium thiosulfate then brine and dried on anhydrous magnesium sulfate. The crude was purified by column chromatography (ether/petroleum ether=1/25) to yield the product (0.045 g, 0.045 mmol) in 45% yield.

Method B. Diol (321) (0.1 g, 0.22 mmol) was dissolved in hexanes (5 mL) and a solution of dicobaltooctacarbonyl (0.142 g, 0.44 mmol) in 5 mL of the same solvent was added over at -23°C. The reaction mixture was then stirred for one hour at room temperature, concentrated and chromatographed (ether/petroleum ether=1/25) to provide the product (0.110 g, 0.11 mmol) in 50% yield.^{1}H NMR (500 MHz, $CDCl_3$) δ 4.7-5.0 (m, 4H), 2.7-3.1 (3d, 2H), 1.8-2.0 (m, 4H), 1.5-1.7 (m, 2H), 0.9 (s, 18H), 0.1(d, 6H);^{13}C NMR (500MHz, $CDCl_3$) δ -4.7,

-4.5, 18.2, 19.8, 37.8, 73.8, 75.6, 97.6, 99.4, 199.5; IR (NaCl) 3490, 2943, 2860, 2000-2100, 1467; MS-FAB 1010 (MW, 0.1), 982 (MW-CO, 0.5), 954 (MW-2CO, 0.2), 926 (MW-3CO, 0.8), 898 (MW-4CO, 4.3), 870 (MW-5CO, 7.2), 842 (MW-6CO, 10.7), 814 (MW-7CO, 4.7), 786 (MW-8CO, 11.0), 758 (MW-9CO, 3.2), 730 (MW-10 CO, 2.6), 702 (MW-11CO, 3.4), 674 (MW-12CO, 2.9), 307.1 (36.2), 154.1 (100).

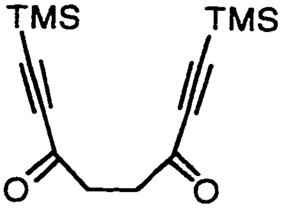
(2,3-η^2)-(9,10-η^2)-[Bicyclo[9,3,0]-3,8-di(*t*-butyldimethylsilyloxy)-13-thiono-12,14-dioxa-2,9-tetradecadiyne]bishexacarbonydicobalt



329

Thionocarbonate (323) (0.075 g, 0.15 mmol) was dissolved in hexanes (5 mL) and added over a solution of dicobaltooctacarbonyl (0.11 g, 0. 33 mmol) in hexanes (5 mL) at - 23°C. The reaction was kept at room temperature for one hour then concentrated and purified by flash chromatography (ether/petroleum ether=1/20) to afford the product (0.145 g) in 92% yield. ^{1}H NMR (200 MHz, CDCl$_3$) δ 5.3-5.8 (m, 2H), 4.7-5.1 (m, 2H), 1.6-2.0 (m, 4H), 1.2-1.5 (m, 2H), 0.9 (bs, 18H), 0.1 (bs, 12H); ^{13}C NMR (200 MHz, CDCl$_3$) δ -4.7, -4.6, -4.5, -4.4, 18.0, 19.7, 25.7, 25.8, 37.4, 39.4, 72.5, 72.7, 72.9, 87.5, 87.7, 100.5, 100.7, 188.9, 198.3 (m); IR (NaCl) 2944.8, 2860.5, 2038; MS-FAB 1052 (M$^+$).

1,8-Di(trimethylsilyl)-3,6-dioxo-1,7-octadiyne

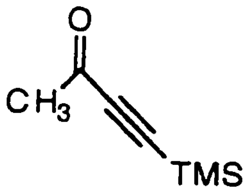


333

Method A. Bis-trimethylsilylacetylene (2.5 mL, 11.2 mmol) and succinic anhydride (0.42 mL, 3.8 mmol) were dissolved in methylene chloride (18 mL), cooled to - 78°C and aluminum trichloride (1 g, 7.6 mmol) was quickly added in one portion. The reaction mixture was allowed to warm up to 0°C at a rate of approximately one degree/minute and then pored over crushed ice (20 g). The aqueous phase was extracted with ether and the organic phase was back extracted with 1 M hydrochloric acid and brine to yield the pure product (0.36 g) after usual operations and column chromatography (ether/ petroleum ether=1/8) in 28 to 34% yield.

Method B. Tributyltintrimethysilylacetylene (8.2 g, 1.2 mmol) was dissolved in chloroform (40 mL, previously passed through neutral alumina) and succinyl dichloride (1.1 mL, 10 mmol) was injected. The reception mixture was purged with nitrogen, bis(triphenylphosphine)benzylpalladium dichloride catalyst (400 mg) was added followed by mild refluxing in chloroform for one hour and a half. Usual potassium fluoride work up for tin (five minutes reaction time only, to avoid simultaneous deprotection of the TMS group) followed by a final purification by column chromatography (ether/petroleum ether=1/20) afforded the desired diketone (1.16 g) in 42% yield. ^{1}H NMR (200 MHz, CDCl3) δ 2.8 (s, 4H), 0.1 (s, 18H);^{13}C NMR (200 MHz, CDCl3) δ -1.0, 38.3, 98.4, 101.2, 184.4; IR (NaCl) 2963, 2907, 2152, 1680; MS 178 (0.9), 163 (36.7), 125 (100); HRMS (EI): calcd for $C_{13}H_{19}O_2Si_2$ 263.0924, found 263.0927.

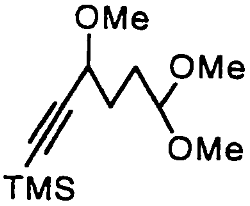
Methyl trimethylsilylethynyl ketone



334

Aluminum chloride (39.26 g, 294 mmol) was suspended in methylene chloride (300 mL), cooled to 0°C under mechanical stirring and treated with a solution of bis-(trimethylsilylacetylene) (66.66 mL, 294 mmol) and acetyl chloride (21 mL, 294 mmol) in methylene chloride (100 mL). After approximately three hours the reaction mixture was pored onto crushed ice and extracted repeatedly with 10% hydrochloric acid. After extraction with petroleum ether and usual manipulation the crude (which was pure by NMR) was distilled under water pump vacuum at 63-65°C to give an oily liquid (39 g) in 95% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.3 (s, 3H), 0.2 (s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -0.9, 32.4, 97.3, 102.3, 184.4; IR (NaCl) 2964, 2152, 1683, 1419, 1537.8; MS 139.9 (0.3)125.0 (100).

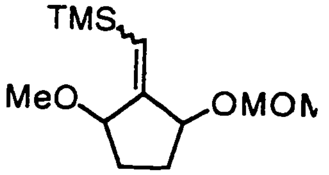
4-Methoxy-6-trimethylsilyl-5-hexynal dimethylacetal



336

Starting 2,5-dimethoxytetrahyrofurane (0.330 mL, 2.5 mmol) were dissolved in methylene chloride (10 mL) together with bis-(trimehtylsilyl)acetylene (0.56 mL, 2.5 mmol, 1 eq.), then cooled down to - 78°C, and treated with titanium tetrachloride (0.375mL, 1M solution in methylene chloride). After 30 min. the reaction was quenched with excess methanol, allowed to warm up at room temperature and extracted with 10% HCl aqueous solution, water and dried on anhydrous magnesium sulfate. After filtration, the organic phase was concentrated and chromatographed (ether/petroleum ether 1/4) to afford the product (0.310 g) in 51%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.3-4.4 (m, 1H), 3.9-4.0 (m, 1H), 3.3 (s, 3H), 3.2 (s. 6H), 1.6-1.8 (m, 4H), 0.1 (s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -0.1. 27.9, 30.4, 52.5, 56.3, 71.1, 90.6, 104.0, ; IR (NaCl) 2950, 2856, 2169, 1727, 1453, 1250; MS 244 (0.1), 229 (0.3), 198(3.6), 182 (5.4), 154 (12.7), 141 (20.2), 75(100); MS-FAB 555 (0.1), 497(0.2), 459 (1.5), 73.1 (100); HRMS (EI): calcd for $C_{11}H_{21}O_3Si$ 229.1260, found 229.1250.

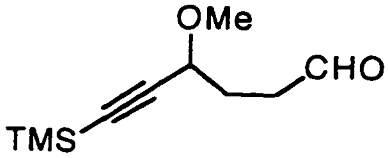
1-Methoxy-2-(2-trimethylsilylmethylen)-3-methoxymethyloxycyclopentane



344

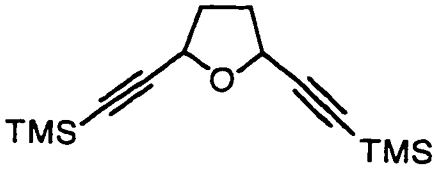
Starting ketal (336) (0.110 g, 0.45 mmol) was dissolved in methylene chloride (10 mL) together with bis-(trimehtylsilyl)-acetylene (0.3 mL, 1.3 mmol, 1.3 eq.), then cooled down to - 78°C, and treated with titanium tetrachloride (0.7 mL, 1M solution in methylene chloride). After 30 min. the reaction was quenched with excess methanol, allowed to warm up at room temperature and extracted with 10% HCl aqueous solution, water and dried on anhydrous magnesium sulfate. After filtration, the organic phase was concentrated and purified by (ether/petroleum ether=1/6) to afford the product (0.091 g, 0.37 mmol) in 82% yield.^1H NMR (200 MHz, $CDCl_3$) δ 5,9 (bs, 1H), 4.71 and 4.64 (AB, *J* = 6.5HZ, 2H), 4.1-4.2 (m, 1H), 4.0-4.1 (m,1H), 3.3 (s, 3H), 3.2 (s, 3H), 1.6-1.9 (m, 4H), 0.9 (s, 9H);^{13}C NMR (200 MHz, $CDCl_3$) δ -0.4, 27.5, 29.4, 55.2, 55.3, 79.57, 79.63, 94.6, 130.4, 158.3 ; IR (NaCl) 2952, 2820, 1727, 1637, 1452, 1355, 1247, 1149; MS 229 (0.5), 199 (7.1), 182 (14.3), 167 (24.9), 89 (100); MS-FAB 555 (0.1), 497(0.2), 459 (1.5), 73.1 (100); HRMS (EI): calcd for $C_{11}H_{21}O_3Si$ 229.1260, found 229.1252.

4-Methoxy-6-trimethylsilyl-5-hexynal



345

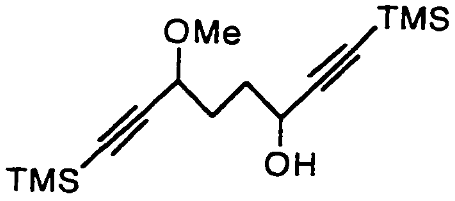
2,5-Di(2'-trimethylsilylethynyl)tetrahydrofurane



345'

A methylene chloride solution (3 mL) of dimethoxy-tetrahydrofurane (0.132 g, 1 mmol) and bis-trimethylsilylacetylene (0.68 g, 4 mmol) was treated with titanium tetrachloride (3 mL solution, 1M solution in methylene chloride at - 78°C and quenched with 10% HCl aqueous solution upon completion of the reaction. After extraction with 10% HCl solution and brine, the organic extract was concentrated and purified by column chromathography (ether/petroleum ether =1/20) to yield (345') (0.1 g, 0.38 mmol) and desired aldehyde (345) (0.09 g, 0.45 mmol) in 45% yield. 345.^{1}H NMR (200 MHz,$CDCl_3$) δ 9.7 (bs, 1H), 3.97 (t, *J* = 6.1 Hz, 1H), 3.3 (s, 3H), 2.6 (m, 2H), 2.0 (m, *J* = 6.1, 2H), 0.1 (s, 9H);^{13}C NMR (200 MHz,$CDCl_3$) δ -0.2, 28.0, 39.5, 56.4, 70.3, 91.5, 103.2, 201.7; IR (NaCl) 2952, 2850, 2726, 2251, 2171, 1724; MS 198 (0.2), 170 (6.0), 154 (34.2), 141 (100); HRMS (EI): calcd for $C_{10}H_{17}O_2Si$ 197.0998, found 197.0999. 345'.^{1}H NMR (200 MHz, $CDCl_3$) δ 4.5 (m, 2H). 2.1 (m, 4H), 0.1 (s, 18H);^{13}C NMR (200 MHz,$CDCl_3$) δ -0.2, 33.2, 68.9, 89.6, 104.7; IR (NaCl) 2961, 2900, 2247, 2174, 1452, 1338; MS 264 (1.6), 263 (2.1), 249 (2.6), 236 (28.7), 221 (17), 123 (50.5), 73 (100); HRMS (EI): calcd for $C_{14}H_{24}OSi_2$ 264.1366, found 264.1340.

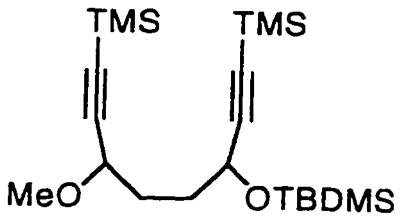
1,8-Di(trimethylsilyl)-6-methoxy-1,7-octadiyn-3-ol



345'

Trimethylsilylacetylene (0.5 g, 5 mmol) was dissolved in THF (10 mL) and treated with *n*-butyllithium (2 mL, 5 mmol, 2.5 M solution in hexanes) at - 78°C. After 15 min the lithium acetylide solution was treated with a THF solution (2 mL) of aldehyde (345) (0.2 g, 1 mmol) and allowed to warm up slowly to room temperature to obtain after usual work up and column chromatography (ether/petroleum ether=1/5) the desired alcohol (0.168 g, 0.54 mmol) in 54% yield.^{1}H NMR (200 MHz, $CDCl_3$) δ 4.35 (bs, 1H), 3.95 (m, !H), 3.3 (s, 3H), 2.7 (m, 1H), 1.8 (m, 4H), 0.12 (s, 9H), 0.11 (s, 9H);^{13}C NMR (200 MHz,$CDCl_3$) δ -0.1, 30.9, 31.1, 33.2, 33.5, 56.2, 62.1, 62.2, 71.0, 71.1, 89.2, 90.9, 103.7, 103.8, 106.5, 106.6; IR (NaCl) 3396, 2950, 2852, 2248, 2170, 1251; MS 281 (0.8), 266 (1.1), 206 (9.8), 167 (24), 141 (100); HRMS (EI): calcd for $C_{14}H_{25}O_2Si_2$ 281.1393, found 281.1402.

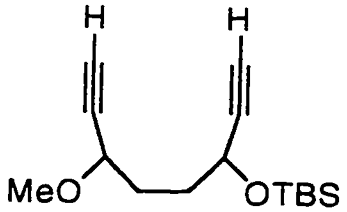
1,8-Di(trimethylsilyl)-6-methoxy-3-*t*-butyldimethylsilyloxy-1,7-octadiyne



346

TBSCl (0.066 g, 0.44 mmol) and imidazole (0.062 g, 0.92 mmol) was dissolved in approximately 5 mL methylene chloride and subsequently treated with alcohol (345') (0.120 g, 0.40 mmol) dissolved in 5 mL of the same solvent. After the completion of the reaction the organic phase was extracted with 10% HCl aqueous solution, and columned with 5% (ether/petroleum ether=/) to obtain 0.160 g (0.39 mmol) of desired product (yield 98%).^{1}H NMR (200 MHz,CDCl$_3$) δ 4.35 (bs, 1H), 3.95 (m, 1H), 3.36 (s, 3H), 1.8 (m, 4H), 0.9 (s, 9H), 0.1 (4s, 24H);^{13}C NMR (200 MHz, CDCl$_3$) δ -5.0, -4.5, -0.2, -0.1, 18.3, 25.8, 31.1, 34.0, 56.3, 63.0, 71.2, 71.3, 88.7, 90.7, 104.3, 107.3; IR (NaCl) 2954, 2851, 2170, 1464.2, 1334, 1068; MS 410 (0.08), 380 (0.3), 353 (1.8), 321 (3.9), 249 (20.3), 155 (17.9), , 73 (100); HRMS (EI): calcd for $C_{17}H_{33}O_2Si_3$ 353.17882, found 353.17914.

6-Methoxy-3-*t*-butyldimethylsilyloxy-1,7-octadiyne

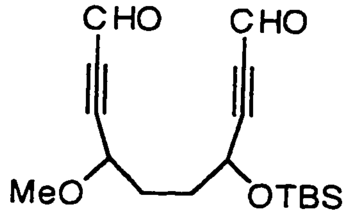


347

Starting TMS protected dialkyne (346) (21 g, 50 mmol) were dissolved in 100 mL acetonitrile and then triethylbenzylammonium chloride (3.5 mmol, 0.8 g) were added as a phase transfer catalyst. The solution was cooled to 0°C and treated with 100 mL of 12 M sodium hydroxide solution under vigorous stirring. 10 minutes after the addition was complete the reaction was quenched by adding 300 mL ether and 200 mL water. The etheral phase was further extracted several times with water and finally with brine. Usual work up associated with column chromatography (5%

(ether/petroleum ether=/)) on silicagel provided 7g of pure desired product plus another 7g of desired product and TBS deprotected side product in a 1.5/1 ratio. This fraction was resubmitted to column chromatography with 2% (ether/petroleum ether=/) to provide other 3.2 g of pure product in 77% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.4 (m, 1H), 4.0 (m, 1H), 3.4 (s, 3H), 2.42 (d, ^4J = 1.9Hz, 1H), 2.36 (d, ^4J = 2.1Hz, 1H), 1.8 (m, 4H), 0.9 (s, 9H), 0.1 and 0.08 (2s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -5.1, -4.6, 18.2, 25.7, 30.9, 30.1, 33.9, 34.0, 56.4, 62.3, 70.6, 72.3, 74.0, 82.3, 85.0; IR (NaCl) 3287, 2951, 2858, 2112, 1460.2, 1338, 1091; MS 266 (0.04), 265 (0.5), 209 (5.4), 143 (19.7), 89 (100); HRMS (EI): calcd for $C_{11}H_{17}O_2Si$ 209.09977, found 209.10035.

7-Methoxy-4-*t*-butyldimethylsilyloxy-2,8-decadiyn-1,10-dial



350

Method A. Starting diyne (347) (0.18 g, 0.68 mmol) was dissolved in tetrahydrofurane (10 mL), cooled in an dry ice-acetone bath and treated with n-butyllithium (0.68 mL, 1.7 mmol, 2.5 M solution in hexanes). After 15 minutes dry dimethyl-formamide (1 mL, 13.6 mmol) was added and the reaction was allowed to stir for 6 hours at low temperature. The reaction was quenched with 10% hydrochloric acid solution and partitioned between ether and 10 % hydrochloric acid solution, then the organic phase was extracted with brine and dried on anhydrous magnesium sulfate. After filtration and concentration followed by purification through flash chromatography (ether/petroleum ether=1/6) the dialdehyde was obtained in only 23 % yield (0.050 g, 0.16 mmol) and most of the starting enediyne was recovered. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.1 (m, 2H), 4.6 (bs, 1H), 4.2 (bs, 1H), 3.4 (s, 3H), 1.9 (bs, 4H), 0.9 (s, 9H), 0.05 (d, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ -5.2, -4.7, 18.1, 25.6, 30.1, 33.0, 57.1, 62.2, 70.5, 83.7, 85.2, 94.1, 96.6, 176.3, 176.4 ; IR (NaCl) 2954, 2858, 2216, 1672, 1465. 1338, 1255, 1101; MS-EI 322 (0.01), 321 (0.03), 293 (0.5), 265 (1.7), 237 (29.6), 89 (100); HRMS (EI): calcd for $C_{13}H_{17}O_4Si$ 265.0896, found 265.0886.

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6. Claims to Original Research

1. A novel intramolecular SmI_2 pinacol coupling reaction of α,β-unsaturated acetylenic aldehydes was developed. This reaction provided an useful solution to the synthesis of monocyclic enediynes bearing heterosubstituents on both propargylic sites. A structurally related compound has recently displayed calicheamicin level activity.

2. New 11 and 12 membered monocyclic enediynes bearing oxy substituents on *both* propargylic positions were prepared.

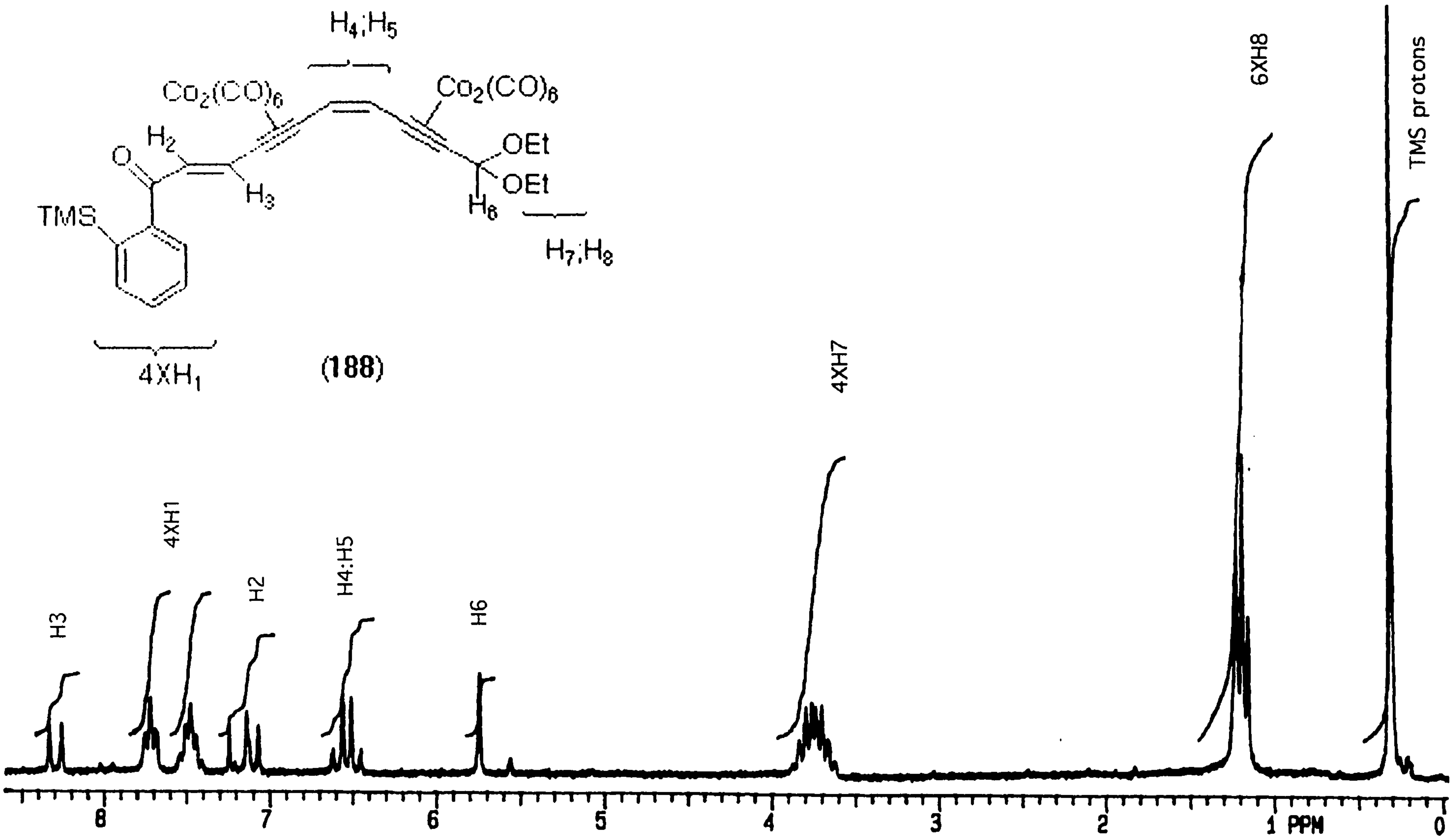
3. A novel anti-Brook rearrangement was discovered that allows regiospecific migration of the silicon from oxygen to the *ortho* position of the aromatic ring. The enolate generated in the process allows tandem electrophilic reactions to be carried out at the carbon α to the carbonyl.

4. The trimethylsilyl group in the *ortho* position suppressed the reactivity of the ketone towards usual reducing agents.

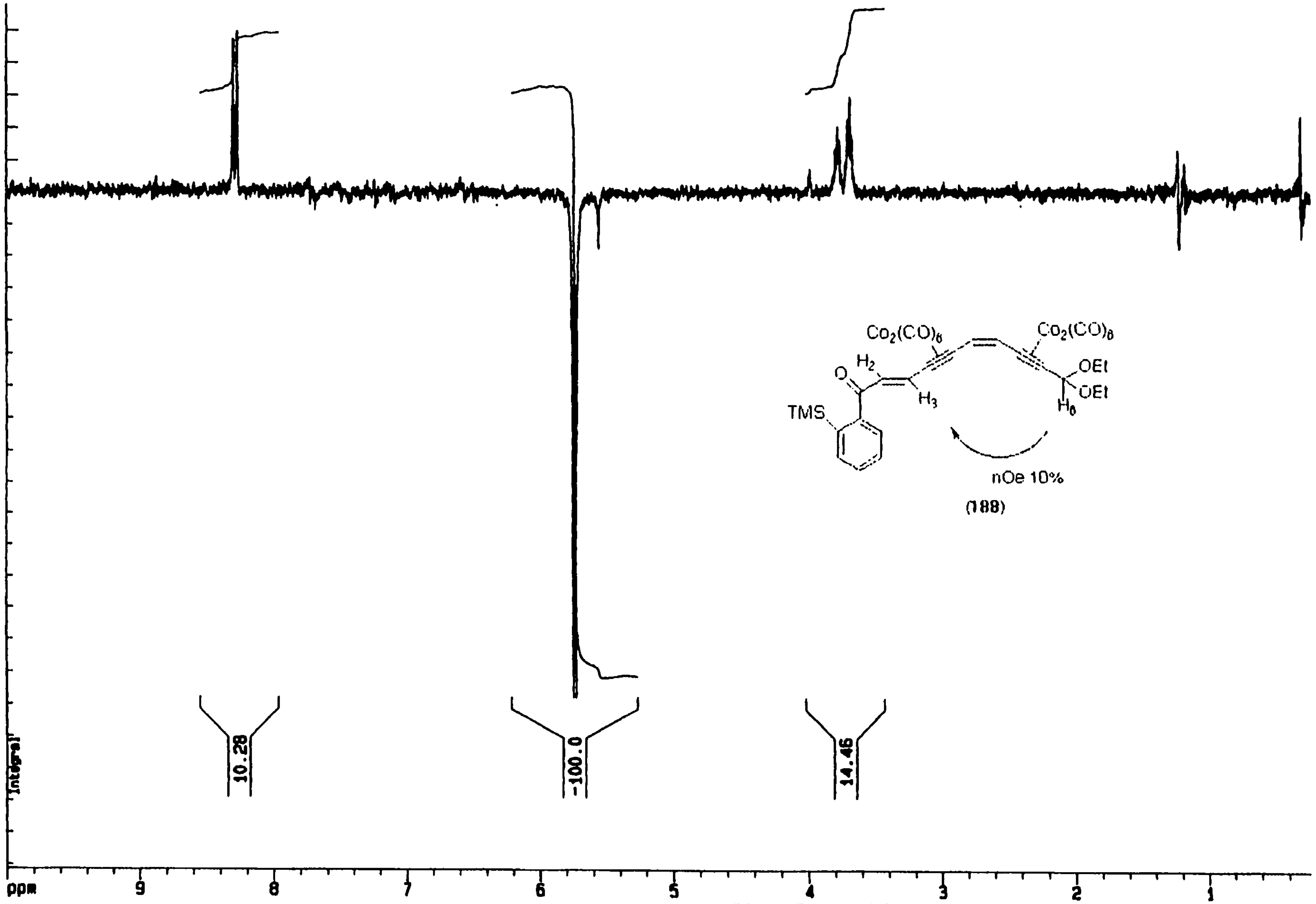
5. Titanium tetrachloride induced rearrangement of trimethylsilyl acetylene derivatives providing an interesting entry to trimethylsilylmethylene cyclopentanes.

6. Zinc/aluminum mediated condensation of acetals with silyl acetylenes afforded propargylic ethers in a single step.

7. Relevant Spectra

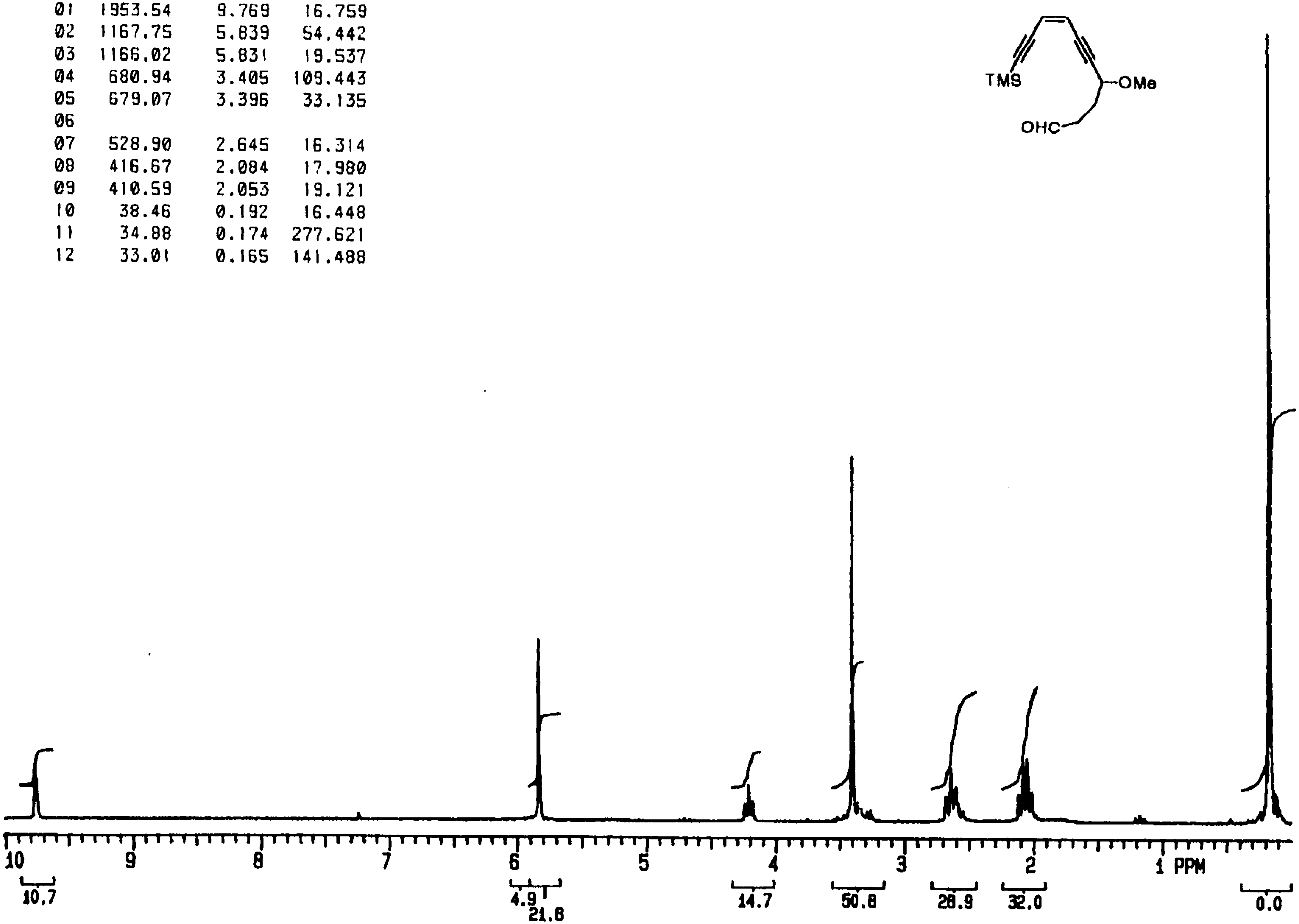


Proton NMR of compound (188).



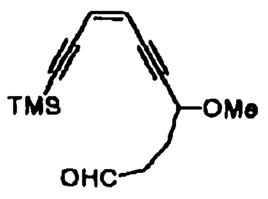
nOe effect for (188)

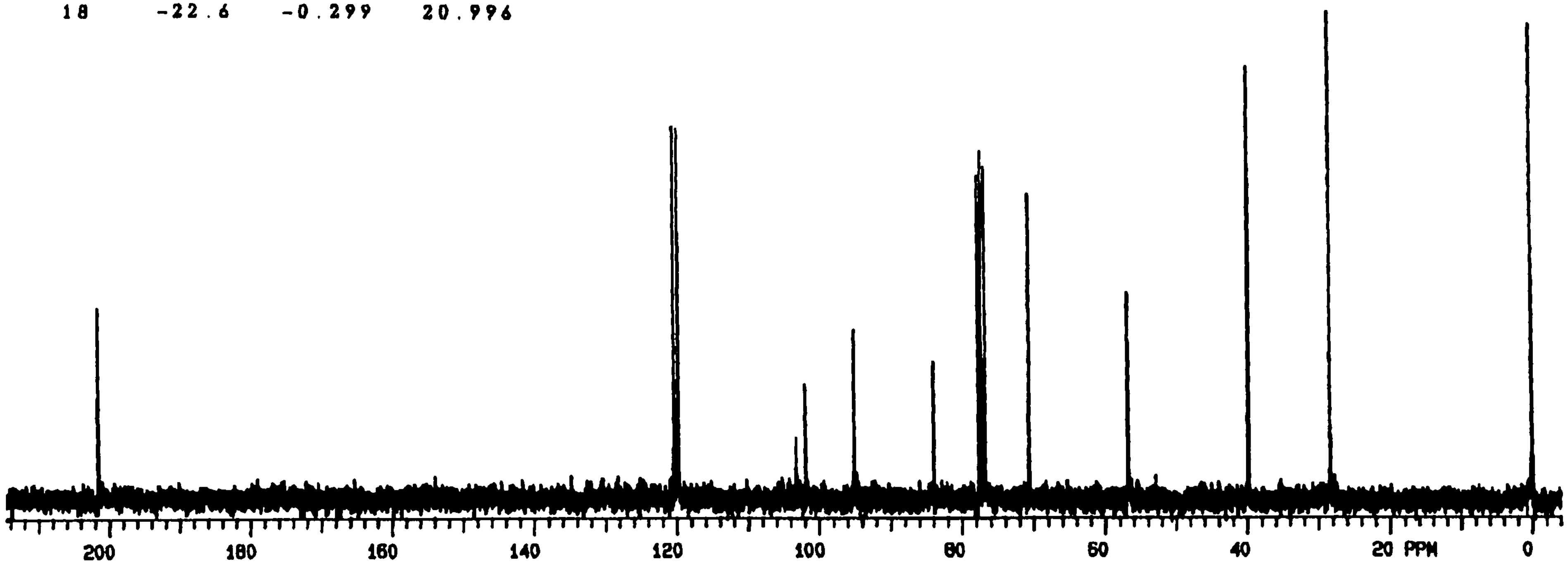
```
SPEC  AL LINES FOR TH=   12.69
  RFL=  1881.2  RFP=  1447.8

INDEX  FREQ      PPM    INTENSITY
 01  1953.54    9.769    16.759
 02  1167.75    5.839    54.442
 03  1166.02    5.831    19.537
 04   680.94    3.405   109.443
 05   679.07    3.396    33.135
 06
 07   528.90    2.645    16.314
 08   416.67    2.084    17.980
 09   410.59    2.053    19.121
 10    38.46    0.192    16.448
 11    34.88    0.174   277.621
 12    33.01    0.165   141.488
```



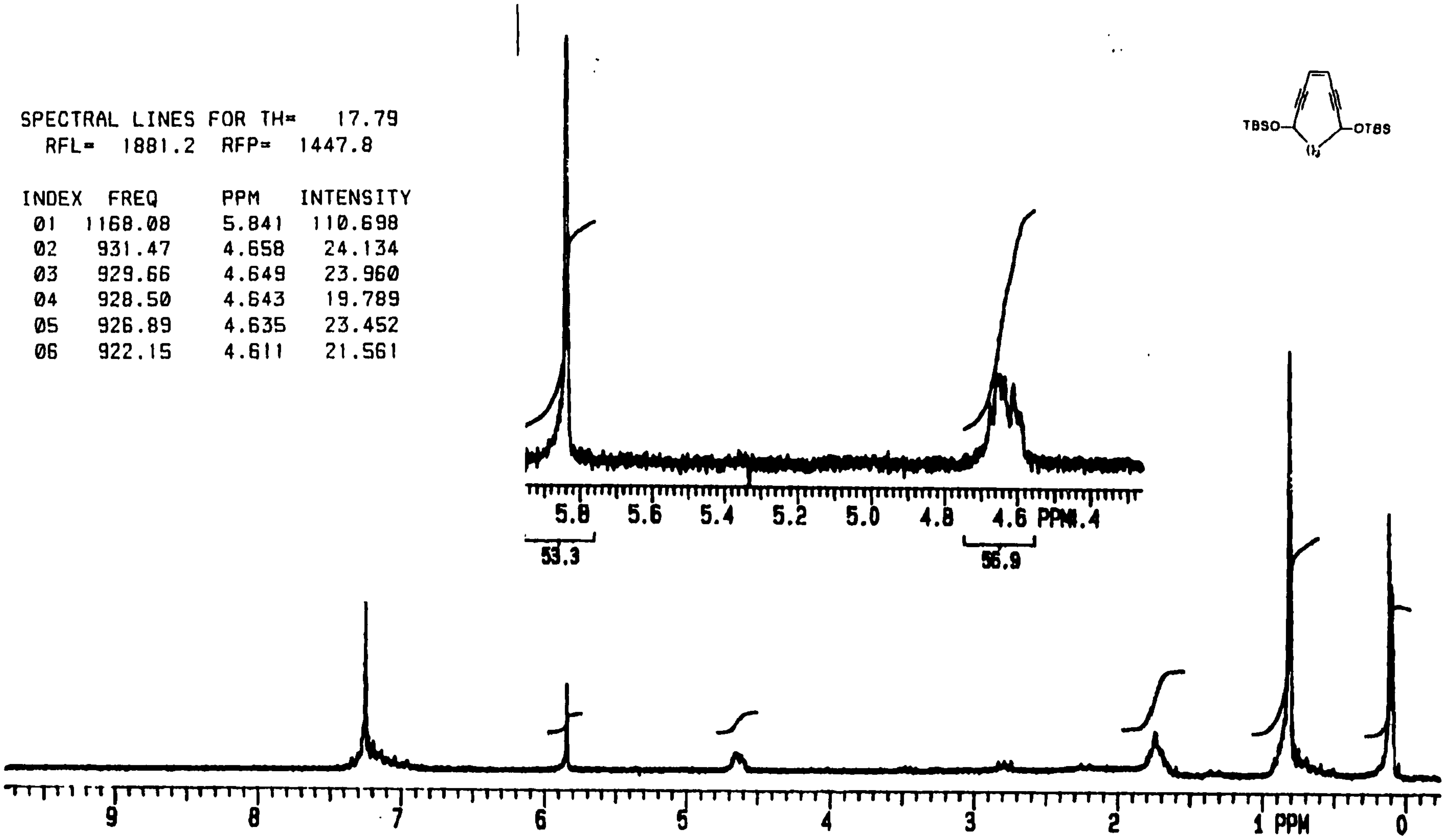
Proton Spectrum for (237)

```
VARIAN XL-300
SPECTRAL LINES FOR TH=    13.39
  RFL=  6131.2  RFP=  5808.0

INDEX   FREQ      PPM     INTENSITY
 01   15200.7   201.523    47.852
 02    9069.6   120.240    93.706
 03    9023.2   119.626    92.794
 04    7777.4   103.109    15.909
 05    7673.4   101.730    28.188
 06    7160.7    94.933    42.252
 07    6321.6    83.809    33.588
 08    5841.0    77.437    80.775
 09    5809.0    77.013    86.189
 10    5777.0    76.589    85.655
 11    5313.8    70.448    78.086
 12    4268.8    56.594    50.902
 13    2986.6    39.595   106.552
 14    2980.9    39.519    23.240
 15    2119.6    28.101   123.949
 16    2112.7    28.009    20.239
 17     -17.2    -0.228   119.159
 18     -22.6    -0.299    20.996
```





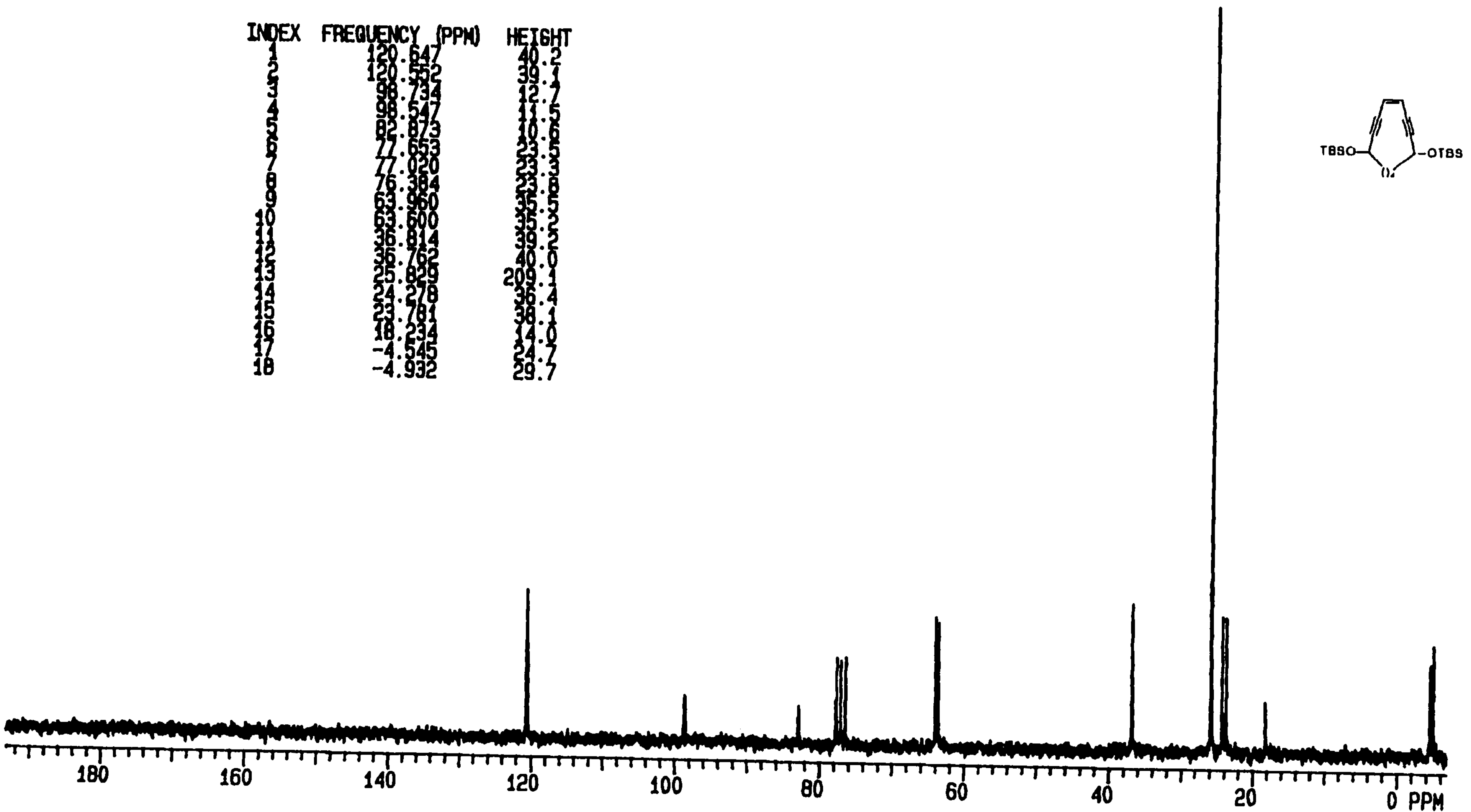
Carbon Spectrum for (237)



```
SPECTRAL LINES FOR TH=    17.79
  RFL=  1881.2  RFP=  1447.8

INDEX  FREQ      PPM    INTENSITY
 01   1168.08    5.841   110.698
 02    931.47    4.658    24.134
 03    929.66    4.649    23.960
 04    928.50    4.643    19.789
 05    926.89    4.635    23.452
 06    922.15    4.611    21.561
```

Proton Spectrum for (325)

INDEX	FREQUENCY (PPM)	HEIGHT
1	120.647	40.2
2	120.552	39.1
3	98.734	12.7
4	98.547	11.5
5	82.873	10.6
6	77.653	23.5
7	77.020	23.3
8	76.384	23.8
9	63.960	35.5
10	63.600	35.2
11	36.814	39.2
12	36.762	40.0
13	25.829	209.1
14	24.278	36.4
15	23.781	38.1
16	18.234	14.0
17	-4.545	24.7
18	-4.932	29.7



Carbon Spectrum for (326)