Universidad de Oviedo

Departamento de Química Orgánica e Inorgánica

Programa de Doctorado

"Síntesis y Reactividad Química"

Cationic Carbocyclisation Reactions of Alkynols and Enynes for the Synthesis of Cyclic Alkenyl Halides and Triflates

Tesis doctoral

Pedro Alonso Figaredo

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RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis	
Español: Reacciones de Carbociclación Catiónica de Alquinoles y Eninos para la Síntesis de Halogenuros y Triflatos de Alquenilo Cíclicos	Inglés: Cationic Carbocyclisation Reactions of Alkynols and Enynes for the Synthesis of Cyclic Alkenyl Halides and Triflates
2.- Autor	
Nombre: PEDRO ALONSO FIGAREDO	DNI/Pasaporte/NIE:
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RESUMEN (en español)

La reactividad de 1,5-alquinoles y 1,5-eninos en el contexto de reacciones de carbociclación catiónica promovidas por ácidos de Brønsted y Lewis ha sido estudiada y consecuentemente se ha encontrado un comportamiento de los citados sistemas sin precedentes en la bibliografía. En términos generales, el uso de un triple enlace terminal como nucleófilo en carbociclaciones cationicas resultó en ciclaciones *6-endo-dig* dando lugar a procesos altamente estereoselectivos en lo que se refiere a la estereoquímica de la olefina resultante.

En el capítulo 1 de esta tesis, se describe la síntesis de halogenuros de ciclohexenilo. Como hecho destacable de esta transformación, el halogenuro se incorpora a la molécula final a través de un proceso de abstracción de halógeno al disolvente. De este modo, la síntesis de cloruros, bromuros o yoduros de ciclohexenilo se ha llevado a cabo simplemente cambiando el disolvente de la reacción.

Además, esta metodología ha sido aplicada en la síntesis de triflatos de ciclohexenilo. En este caso, el empleo de un disolvente no nucleofílico fue clave para permitir que la captura del catión vinilo intermedio por parte de un anión triflato. Esto resulto en la síntesis estereoselectiva de triflatos de ciclohexenilo a través de una operación sintética muy eficiente. Los resultados obtenidos en este estudio figuran en la parte A del capítulo 2 de esta tesis doctoral.

En la parte B del capítulo 2, se describe una nueva transformación para acceder a esqueletos de ciclohexanona a través de una carbociclación catiónica catalizada por ácido tetrafluorobórico. En este caso, el empleo de 1,1,1,3,3,3-hexafluoro-2-propanol como disolvente de la reacción permitió la obtención de los productos deseados de reacción empleando cantidades subestequiométricas de ácido tetrafluorobórico.

Finalmente, la metodología desarrollada ha sido aplicada en las ciclaciones biomiméticas de diferentes polieninos. Los excelentes resultados obtenidos en las ciclaciones de alquinoles fueron también observados en este caso. De hecho, en el capítulo 2 se ha demostrado que estos procesos de carbociclación en cascada permiten la construcción eficiente del esqueleto de multitud de productos naturales y se ha demostrado la compatibilidad de nuestra metodología en la síntesis de diferentes moléculas de interés.

RESUMEN (en Inglés)

The reactivity of unsubstituted 1,5-alkynols and 1,5-enynes towards cationic carbocyclisation reactions upon acid activation has been studied and new interesting behaviours of these systems have been found. In general terms, the use of a terminal triple bond as the nucleophile in cationic carbocyclisations resulted in exclusive *6-endo-dig* type of cyclisations, leading to a highly stereoselective processes regarding the stereochemistry of the resulting alkene moiety.

In chapter 1, the synthesis of cyclohexenyl halides is described. Noteworthy, the halide is incorporated through halide abstraction of the solvent. Therefore, the synthesis of cyclohexenyl chlorides, bromides or iodides is performed in a straightforward manner by simply changing the solvent of the reaction.

Besides, cyclic alkenyl triflate derivatives have been easily synthesised by this method as well. In this case, use of a non-nucleophilic solvent was key to enable the capture of the key cationic intermediate of the carbocyclisation by the triflate ion. This resulted in the stereoselective synthesis of cyclic alkenyl triflates by means of a highly efficient synthetic operation. The results obtained in this study are gathered in part A of chapter 2.

In part B of chapter 2, a new process for the synthesis of cyclohexanones by means of a catalytic carbocyclisation of alkynols is described. In this case, use of 1,1,1,3,3,3-hexafluoroisopropanol as the solvent of the reaction was key in order to achieve catalytic turnover of the acid employed to promote the transformation.

Finally, all of the above-mentioned reactions have also been applied to cascade transformations of a series of polyenynes. The virtues regarding the efficiency of our methodology were also encountered in the polycyclisations explored. In fact, as demonstrated in chapter 2, this polyenyne carbocyclisations are of wide applicability in the synthesis of natural products. It has been demonstrated that they represent useful tools for the selective synthesis of valuable intermediates that can be manipulated in a straightforward manner for the installation of different functionalities.

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Abreviations

Ac	acetyl
acac	acetylacetonate
aq	aqueous
Bn	benzyl
Bu	butyl
DCE	1,2-dichloroethane
Et	ethyl
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
HMDS	hexamethyldisilazane
HOTf	trifluoromethanesulfonic acid
LBA	Lewis acid-assited activation of Brønsted acid
LHMDS	Lithium hexamethyldisilazane
Me	methyl
Ms	mesyl (methanesulfonyl)
NTf_2	bis(trifluoromethane)sulfonimide
Nu	nucleophile
Ph	phenyl
$PhCH_3$	toluene
PPh_3	triphenylphosphine
Pr	propyl
p-TsOH	*para*-toluenesulfonic acid
T	temperature
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroetan-1-ol
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl

Table of contents

General Introduction

I.1 Introduction

Deep into the 21st Century, it is still unquestionable that the most complex organic architectures have been produced by natural organisms. Nature makes use of the most selective and efficient catalysts (enzymes) to perform the most outstanding transformations that exist in the Synthetic Chemistry arena. For the moment, synthetic chemists generally stand at the stage of mimicry, trying to identify the minimal functional unit to build our own catalysts by making use of a far greater number of available substances than Nature (e.g., transition metal catalysts, strong Brønsted acids) and an adaptive environment (solvents, temperature range).[1]

In this regard, many natural products have some type of cyclic structures in its skeleton. This has motivated a quest for cyclisation reactions since the early beginnings of synthetic chemistry. Yet today, the development of processes that allow efficient construction of cyclic structures through the creation of carbon-carbon or carbon-heteroatom bonds is an area of great interest, especially when some stereocontrol is exerted on the transformation. This thesis falls within the scope of the above commented reaction and therefore represents a contribution to the topic. Thus, before disclosing the results of our investigation, some general considerations about cationic cyclisations and an overview of recent applications of this reaction in the synthesis of target structures will be presented.[2]

[1] R. A. Yoder, J. N. Johnston, *Chem*. *Rev*. **2005**, *47*, 4730-4756.
[2] C. Thebtaranonth, Y. Thebtaranonth, *Cyclization Reactions CRC Press*, Boca Raton, **1994**.

I.2 Cyclisation Reactions: A Definition

Cyclisation reactions can be defined as transformations where a linear substrate is converted into a cyclic structure. This general definition also allows the recognition of different subgroups, depending on the type of species involved in the mechanism of the reaction. Thus, cationic, anionic, radical and metal complex intermediates, either stable or transient, are probably the four main types of species involved in cyclisation reactions. A simplistic scheme of the abovementioned types of cyclisations is depicted in **Figure I.1**.

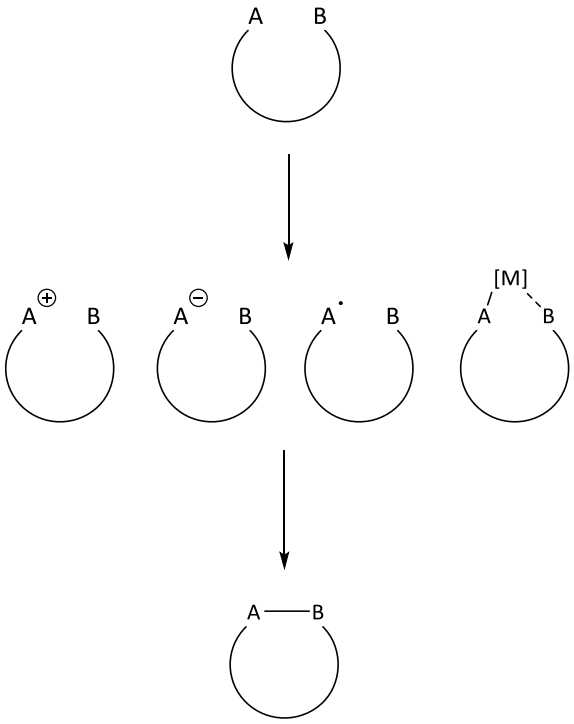


***Figure I.1**. Four main types of cyclisation reactions.*

The work gathered in this thesis is related to the study of cationic cyclisations. Therefore, a more detailed definition of this type of transformations, as well as a description of the chemical entities that participate in such processes, will be done in the next section.

I.3 Cationic Cyclisations

Cationic cyclisations are a particular type of cyclisations where cationic species are involved in the process, as defined in the previous section. Nevertheless, in order to understand the different stages of a typical cationic cyclisation reaction and therefore classify them in a comprehensive manner, some other concepts must be defined.

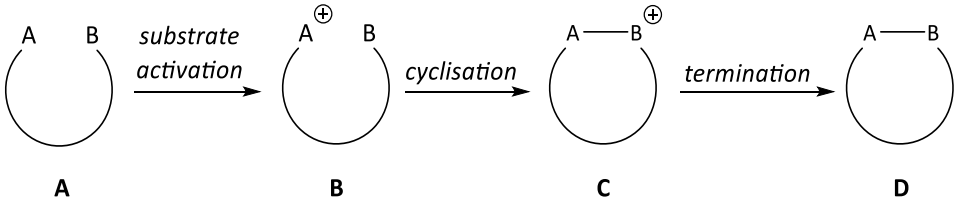


***Figure I.2**. Schematic representation of cationic cyclisations.*

In **Figure I.2**, a simplistic scheme of cationic cyclisations is presented. Accepting the previous definition, the first step of all cationic cyclisations involves the initial transformation of a neutral substrate **A** into a cationic intermediate **B**. This operation is called *substrate activation*. Next, this cationic intermediate is intramolecularly trapped by a nucleophile in a *cyclisation* step, in which the skeleton of the final product is built. Finally, the *termination* phase involves the stabilisation of cationic intermediate **C** to yield final product **D**, that is neutral in charge.

Moreover, cationic cyclisations usually involve the creation of a C-C bond in the *cyclisation* step. Given the frequency and the relevance of these transformations, these processes are known as cationic carbocyclisations. Herein, exclusive reference to cationic carbocyclisations will be done.

I.4 Cationic Carbocyclisations: An Overview

The sort of species actively involved in a cationic carbocyclisation reaction will determine to a great extent the nature of the transformation. Thus, for a better understanding of the steps that comprise cationic carbocyclisations, a classification will next be done:

I.4.1 Cationic Species Involved

As previously shown in **Figure I.2**, the initial step of a carbocyclisation reaction involves the formation of a cation. Thus, different type of cationic species might be implicated in this initial step of the carbocyclisation. On the one hand, carbenium ions stabilised by the lone pair of heteroatoms can be formed. This gives rise to the formation of oxonium, iminium or thionium species depending on the heteroatom that stabilises the cation. These cationic species are commonly known as *heteroatom-stabilised carbenium ions*. However, on the other hand, in many occasions the initial cationic species are not stabilised by the lone pair of any heteroatom. This last type of intermediates are described as *non-stabilised carbenium ions*. All of these species are depicted in **Figure I.3**:

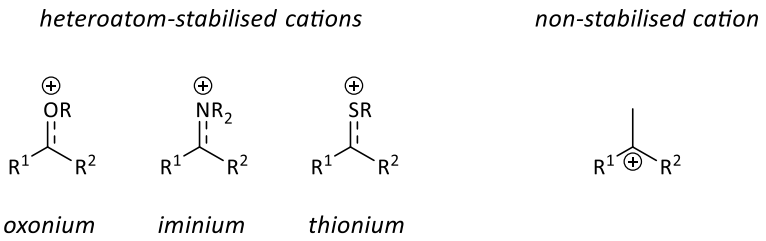
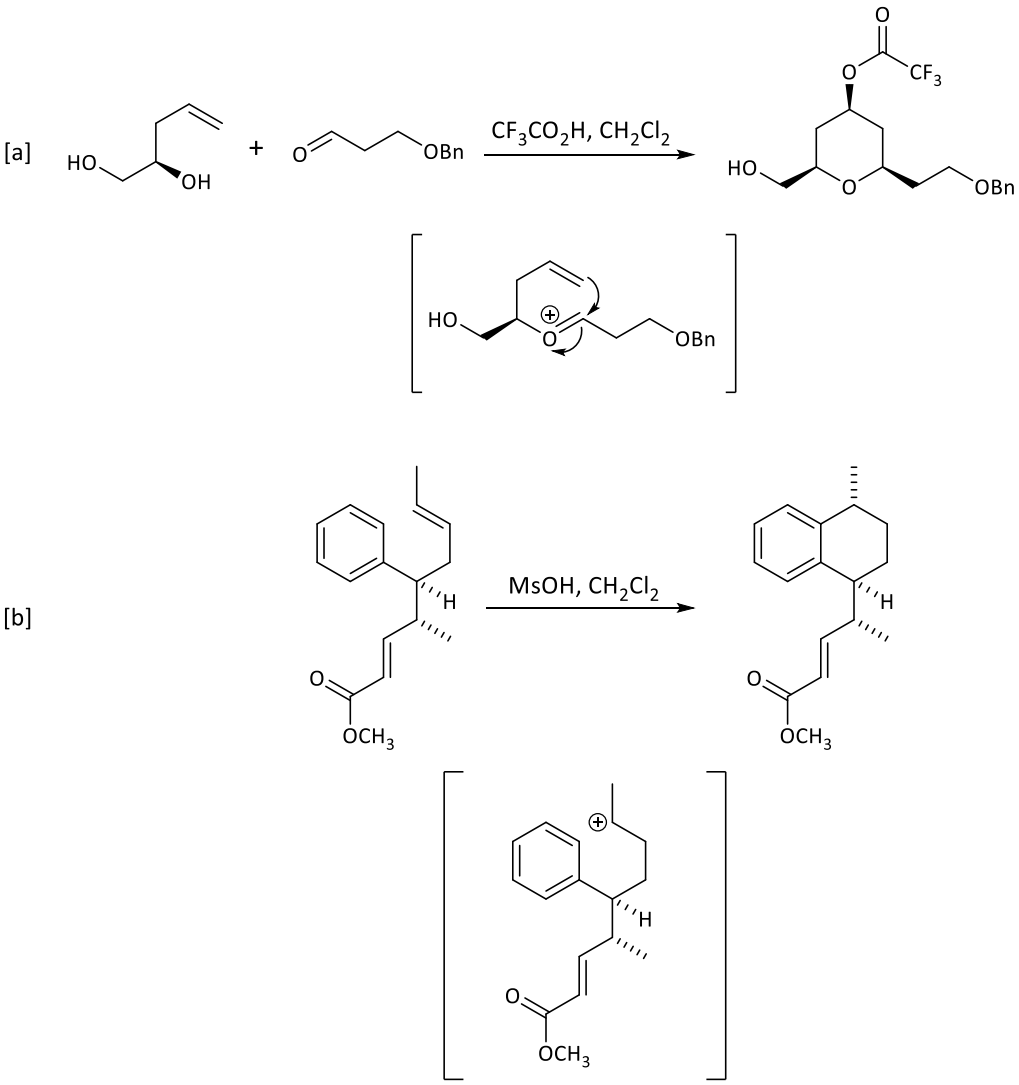


***Figure I.3**. Different species involved in cationic carbocyclisations*

Cationic carbocyclisations involving the initial formation of heteroatom-stabilised cations are commonly considered separately from those involving the formation of non-stabilised carbenium ions. Besides, higher stereocontrol has tipically been exerted on those transformations involving stabilised species. As a result of this, carbocyclisation reactions involving non-stabilised cations have received less attention.

In **Scheme I.1**, two examples of cationic carbocyclisations of heteroatom-stabilised cations and non-stabilised cations are presented.



***Scheme I.1**. Examples of cationic carbocyclisations involving heteroatom-stabilised carbenium ions [a] and non-stabilised carbenium ions [b].*

Prins cyclisations are typical cationic cyclisations where cationic species stabilised by heteroatom are initially formed (**Scheme I.1**, eq. [a]).[3] Besides, as shown in eq. [b] in **Scheme I.1**, alkenes are prone to suffer protonation under acidic conditions to form a

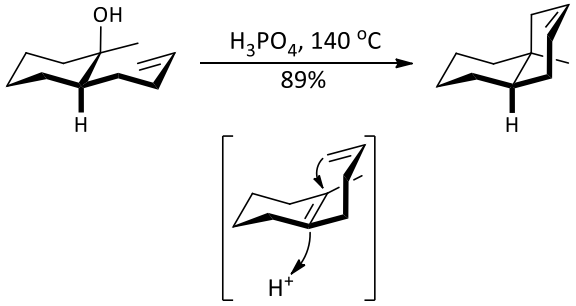
[3] G. Sabitha, M. N. Prasad, K. Shankaraiah, N. M. Reddy, J. S. Jadav, *Synthesis* **2010**, 3891-3898.

non-stabilised cation that might be intramolecularly trapped by a nucleophile, in this case, an arene.[4]

As far as this introduction is concerned, a particular emphasis will be done in reviewing the reactivity of non-stabilised carbenium ions, since they are intimately related to the experimental work gathered in this thesis. Next, some theoretical considerations concerning the reactivity of non-stabilised carbenium ions will be presented.

I.4.2. Non-Stabilised Carbenium Ions: Theoretical Considerations.

The 1,5-diene cationic cyclisation was among the first type of cationic carbocyclisations to be studied and recognised, so theoretical considerations were built upon this transformation as well. In the context of cyclohexannulations, Linstead and coworkers were the first to study diastereoselection, as early as 1936.[5] The authors observed the formation of a *cis*-decalin when submitting the tertiary alcohol shown in **Scheme I.2** to Brønsted acid cyclisation conditions (either H_2SO_4, HOAc, Ac_2O, 25 °C or H_3PO_4, 140 °C).



***Scheme I.2**. Linstead's stereoselective cis-decalin formation.*

It is important to remark that Linstead always observed the formation of the depicted *cis*-fused decaline regardless of the regioisomer taken as starting material. This finding was used by Stork to hypothesise that a tetrasubstituted olefin could be an intermediate of the reaction, to later suffer protonation and diastereoselective cyclisation (as shown in **Scheme I.2**).

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[4] C. A. Incerti-Pradillos, M. A. Kabeshov, P. S. O'Hora, S. A. Shipilovskikh, A. E. Rubstov, V. A. Drobkova, S. Y. Balandina, A. V. Malkov, *Chem*. *Eur*. *J*. **2016**, *22*, 14390-14396.

[5] a) D. C. Hibbit, R. P. Linstead, *J. Chem*. *Soc*. **1936**, 476-478; b) R. P. Linstead, A. B. L. Wang, J. H. Williams, K. D. Errington, *J. Chem*. Soc. **1937**, 1136-1140; c) R. P. Linstead, A. F. Millidge, A. L. Walpole, *J. Chem*. *Soc*. **1937**, 1140-1145.

This initial work by Linstead inspired perhaps one of the most remarkable contributions to the field of cationic cyclisations. The groups of Stork and Eschenmoser independently hypothesised about the antiparallel addition of a carbenium ion and a nucleophile to an alkene as the mechanism operating in 1,5-diene cationic cyclisations.[6]

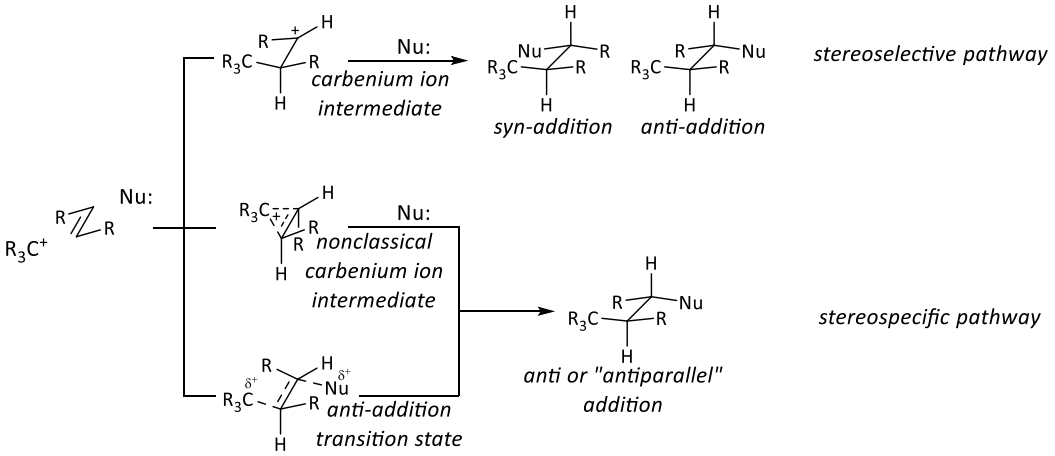
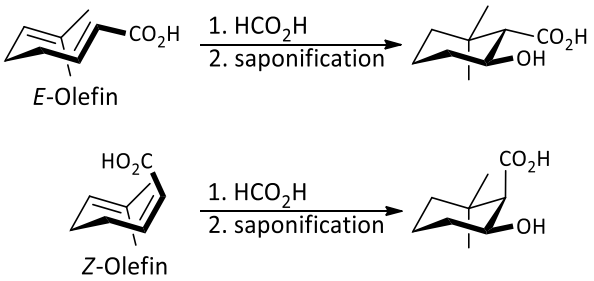


***Figure I.4**. Mechanistic possibilities and stereochemical outcomes of carbenium ion additions to olefins.*

Their proposal of two plausible mechanisms for this transformation explained whether a polyolefin cyclisation occurs in a stereoselective (as the best case scenario when discrete carbenium ions are involved in the process) or a stereospecific way (through a concerted antiparallel addition) (**Figure I.4**).

The definitive experimental support for the cyclisation of 1,5-dienes through antiparallel addition came in 1954 thanks to complementing experiments done by Schinz and Eschenmoser (**Scheme I.3**).[7]



[6] a) G. Stork, A. Burgstahler, *J. Am. Chem. Soc.* **1955**, *77*, 5068-5077; b) A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta* **1955**, *38*, 1890-1904.

[7] G. Gamboni, H. Schinz, A. Eschenmoser, *Helv. Chim. Acta* **1954**, *37*, 964-971

***Scheme I.3**. Schinz-Eschenmoser evidence for anti-carbenium ion addition to olefin.*

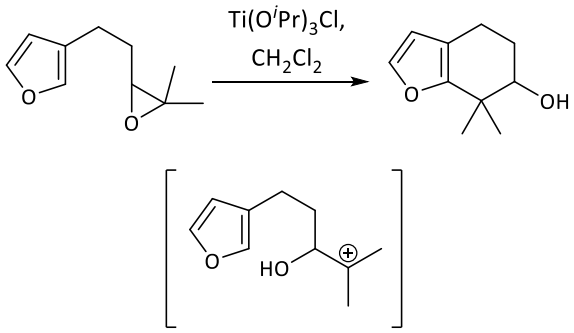
They observed that each of the two geometric isomers of norgeranic acid produced a single diastereoisomer in each case, after cyclisation in formic acid and saponification of the formate ester obtained. This behavior led the authors to almost exclude the intermediacy of carbenium ions and rather propose a charlike folding intermediate to finally dispose the carboxylic acid moiety either in equatorial or in axial position.

The importance of these early studies should not be underestimated, since by the middle of the 20th century, Stork and Eschenmoser had not only developed the theory under cationic polyene cyclisations, but they also provided evidence of the existence of the antiparallel addition above disclosed. Thus, back in the 1950s, a basis for the diastereoselective cyclisation of prochiral polyene substrates had already been set.

Continuing with a revision of the processes where non-stabilised carbocations are involved, in the next section, the most typical modes of formation of these cationic species will be discussed.

I.4.3. Non-Stabilised Carbenium Ions: Initiating Groups

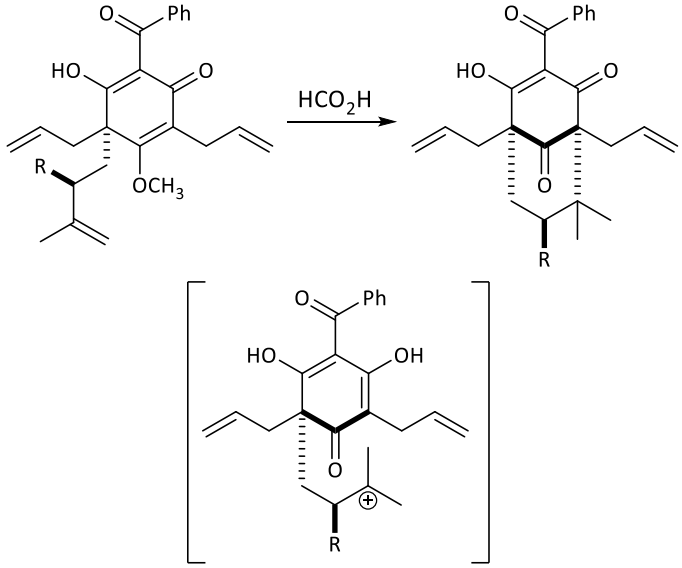
The initial step of a carbocyclisation reaction is the formation of a cation. A wide variety of different strategies can be found in the literature to generate non-stabilised cations. Among them, probably the most frequently used in the context of carbocyclisation reactions are: cationic opening of epoxides, addition of proton to an olefin and protonation of alcohols and subsequent dehydration (other oxygenated functionalities might fall into this category as well). An example of each case is shown in **Scheme I.4**, **I.5** and **I.6**: [8]



[8] a) S. P. Tanis, P. M. Herrinton, *J. Org. Chem.* **1983**, *48*, 4572-4580; b) J. H. Boyce, J. A. Porco Jr. *Angew. Chem. Int. Ed.* **2014**, *53*, 7832-7837; c) Z. Li, H. Su, W. Yu, X. Li, H. Cheng, M. Liu, X. Pang, X. Zou, *Org. Biomol. Chem.* **2016**, *14*, 277-287.

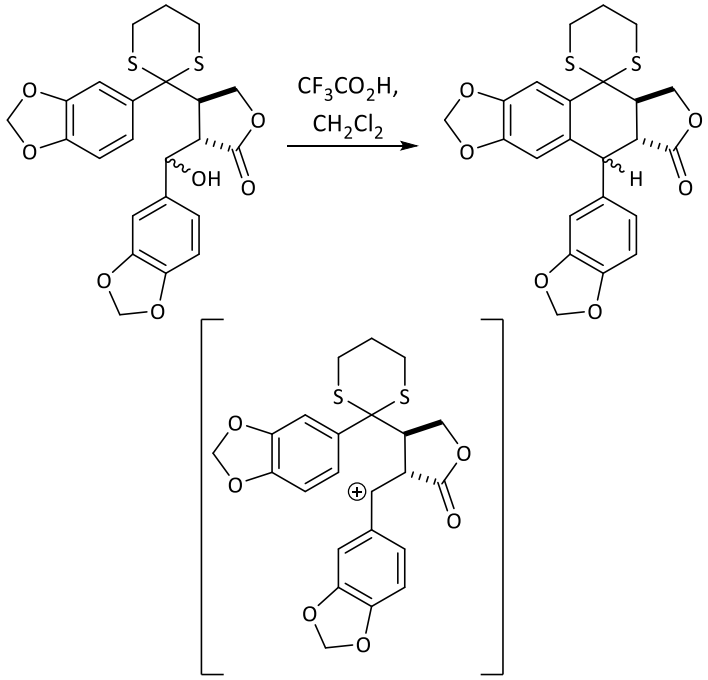
***Scheme I.4**. Cationic carbocyclisation promoted by the activation of an epoxide.*

Epoxides have been widely used as easily activable functional groups to trigger cationic carbocyclisations. Tipically, they are activated by means of a Lewis acid, as shown in **Scheme I.4**. In this example, the initially formed cation is trapped by a furan through a Friedel-Crafts-type intramolecular process. On the other hand, alkenes normally give way to the formation of non-stabilised carbocation by treatment with a protic acid. In the particular case shown in **Scheme I.5**, the treatment of the starting material with formic acid leads to the selective protonation of one of the alkenes to generate the most stable tertiary cation. This cation is trapped by the enol to form the final bicyclic product.



***Scheme I.5**. Cationic carbocyclisation promoted by the protonation of an alkene.*

Similarly, dehydration of alcohols promoted by Lewis or Brønsted acid is a very common way of initiating cationic carbocyclisations. As depicted in **Scheme I.6**, treatment of a benzylic alcohol with trifluoroacetic acid leads to the formation of the corresponding benzylic cation that is intramolecularly trapped by an aromatic ring through a Friedel-Crafts-type reaction.



***Scheme I.6**. Cationic carbocyclisation promoted by the protonation of an alcohol.*

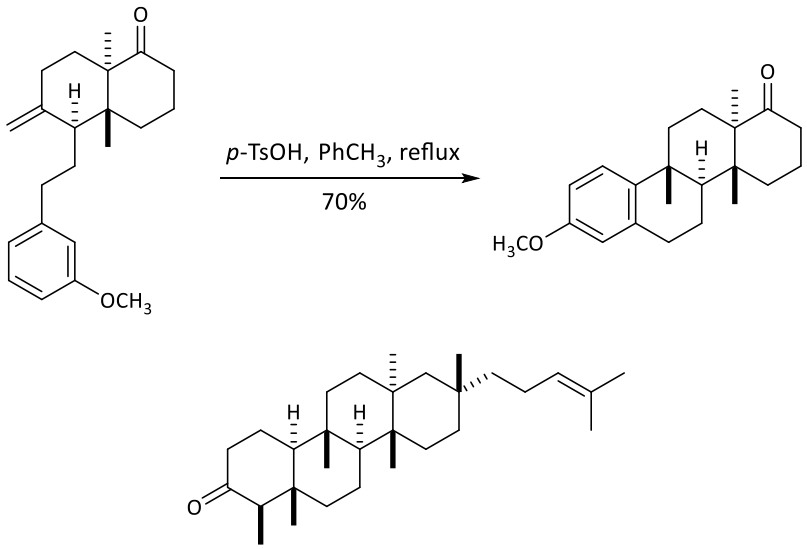
The outcome of the carbocyclisation will depend to a great extent on the intramolecular nucleophile that is to react with the carbenium ions formed, thus defining structure of the final product. This will be studied in the next section.

I.4.4 Terminating Groups in Cationic Carbocyclisations

The chemical identity of the nucleophile that traps a carbocation and the concomitant stabilisation of the subsequent carbenium ion are 2 steps of the mechanism of cationic carbocyclisations that are intimately related (see **Scheme I.3**). In this regard, in the following sections a brief discusion of Brønsted and Lewis acid promoted cationic cyclisations will be done, with special emphasis on the formation of non-stabilised cationic species and grouped by the terminating group of the transformation.

I.4.4.1 Cationic Carbocyclisations Terminated by Arenes

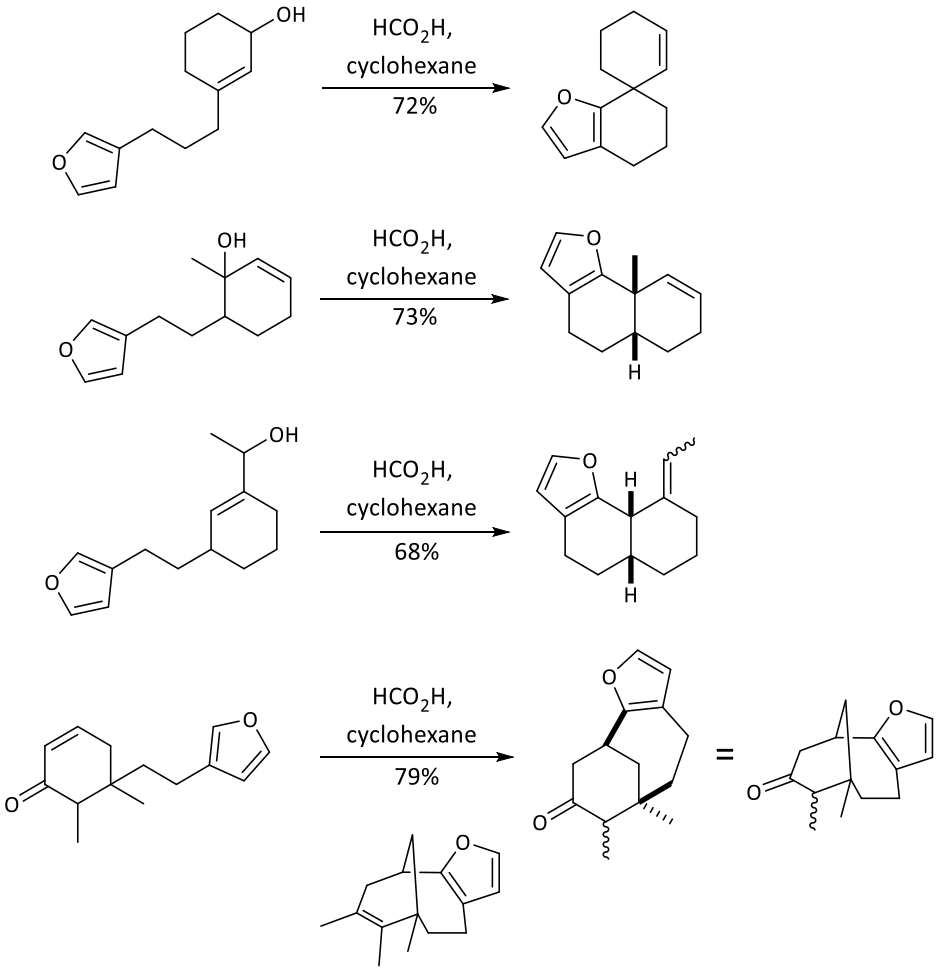
Few years after the pioneering works discussed in section **I.3** many authors recognised the potential of Fridel-Crafts type reactions as a useful termination mode in cationic cyclisations. The methodology proved to be very useful in the synthesis of 6-member ring cycles, present in the skeleton of plethora of organic compounds. In fact, application of this transformation in the context of natural product synthesis was already explored in the 1970s. For example, R. E. Ireland and coworkers used this strategy in 1975 to synthesise the key tetracyclic intermediate in the total synthesis of *(±)*-shionone depicted in **Scheme I.7**.[9]



Scheme I.7*. Ireland's studies for the synthesis of (±)-shionone.*

[9] R. E. Ireland, M. I. Dawson, C. J. Kowalski, C. A. Lipinski, D. R. Marshall, J. W. Tilley, J. Bordner, B. L. Trust, *J. Org. Chem*. **1975**, *40*, 973-990.

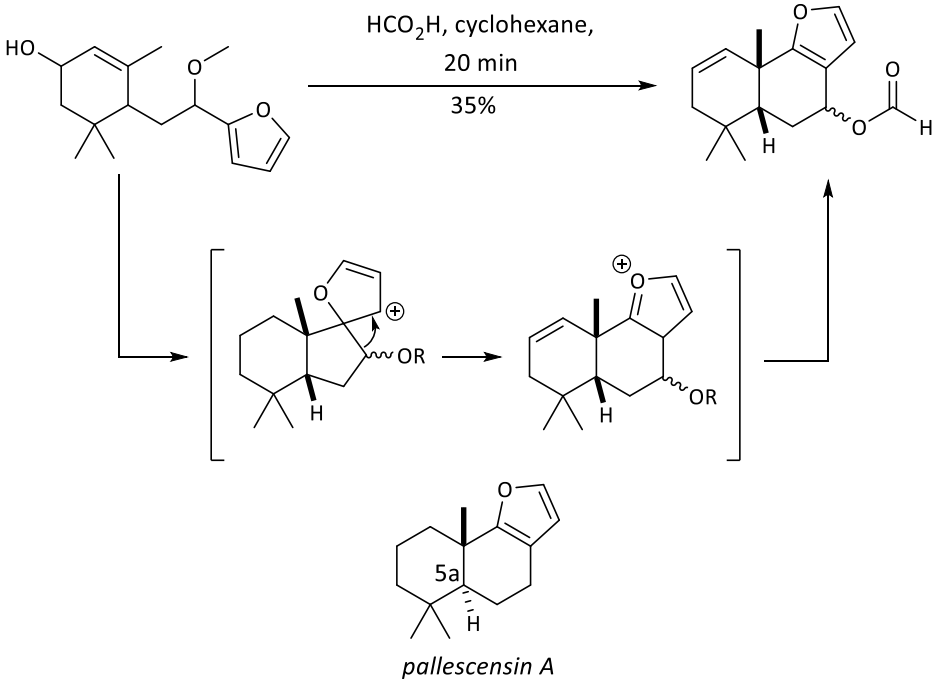
With this work, Ireland and coworkers demonstrated that arenes are good terminators for cationic cyclisation reactions. If electron rich arenes are prone to undergo Friedel-Crafts intramolecular reactions, then the use of electron rich heteroarenes should also be fruitful for this purpose. This hypothesis was tested by the team of S. P. Tanis as part of their studies towards the synthesis of *(±)*-nakafuran 9 in 1985.[10] They demonstrated the feasibility of the transformation in a series of substrates, synthesising a variety of furan-containing cyclised products (**Scheme I.8**):



Scheme I.8*. Tanis' studies on the cyclisation of furan-containing substrates.*

[10] S. P. Tanis, P. M. Herrinton, *J. Org. Chem*. **1985**, *50*, 3988-3996.

Given the structural diversity in the compounds synthesised by S. P. Tanis and coworkers through cationic cyclisation of furan containing substrates, the versatility of this protocol would later draw the attention of other synthetic chemists. Thus, in 1995, S. Blechert and coworkers designed a synthesis of meroterpenoid pallescensin A based on this strategy.[11,12] As shown in **Scheme I.9**, Blechert's group made use of the conditions optimised by S. P. Tanis and collaborators to construct the skeleton of the target molecule.



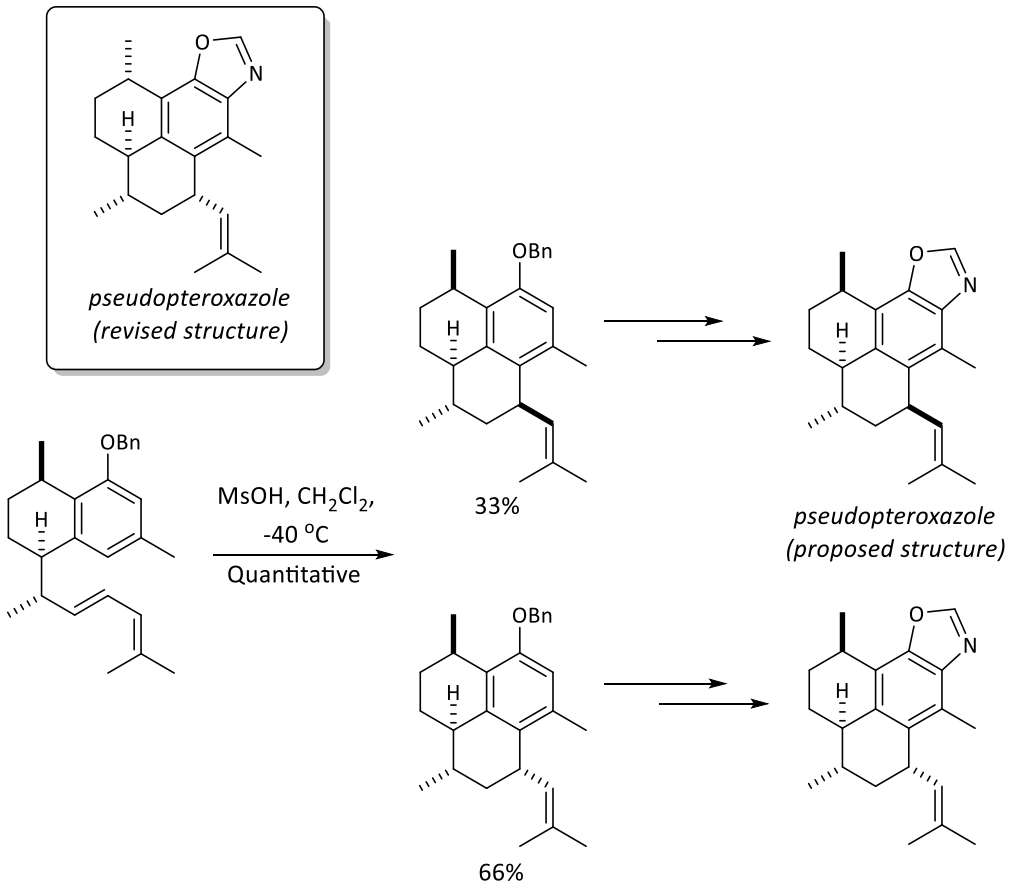
***Scheme I.9**. Blechert's key step on route to (±)-pallescensin A.*

The regioselectivity of the cyclisation was proposed to be the same as observed by S. P. Tanis. Thus, nucleophilic attack of C2 of the furan to the initially formed allylic cation was proposed prior to a Wagner-Meerwein rearrangement to yield the formate ester depicted in **Scheme I.9**. It should also be noted that the methoxy functionality suffered solvolysis during the transformation. Nevertheless, it should be noted that fusion of the decalin skeleton is not the same as in pallescensin A. Consequently, the 5a position had to be epimerised to synthesise the target molecule.

Another remarkable application of cationic cyclisations in the context of natural product synthesis came in 2001 by the group of E. J. Corey.[13] The authors revised the

[11] Meroterpenoids are natural products produced from polyketide and terpenoid precursors.
[12] U. Lange, S. Blechert, *Synthesis* **1995**, 1142-1146.
[13] T. W. Johnson, E. J. Corey, *J. Am. Chem. Soc.* **2001**, *123*, 4475-4479.

stereochemistry of diterpenoid pseudopteroxazole by synthesising the proposed structure at the time. One of the cyclohexane rings of the proposed structure was constructed by means of a cationic cyclisation catalysed by methanesulfonic acid (**Scheme I.10**).

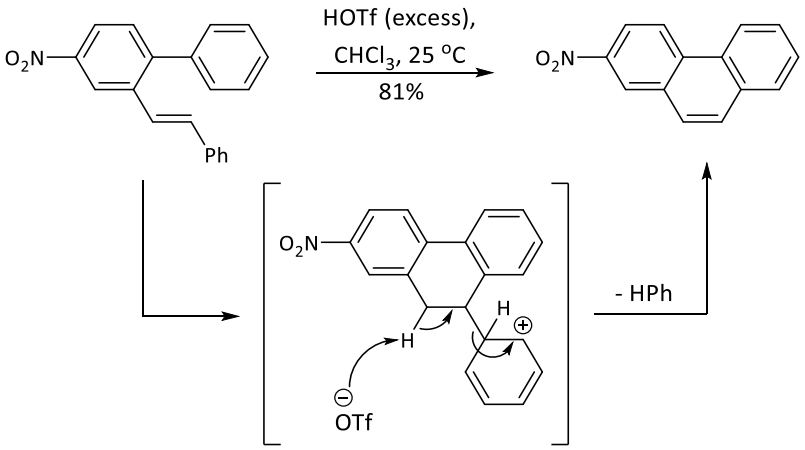


***Scheme I.10**. Divergent synthesis of proposed structures of pseudopteroxazole.*

The authors used the poor diastereoselectivity of the transformation to execute a divergent approach to the two isomers of pseudopteroxazole depicted above and confirm that neither of them would match with the real structure of the target molecule.

Given the polycyclic core of pseudopteroxazole, a fundamental question arises concerning the feasibility of cationic cyclisation reactions as a method to synthesise polycyclic aromatic compounds. The group of D. A. Klumpp became interested in the

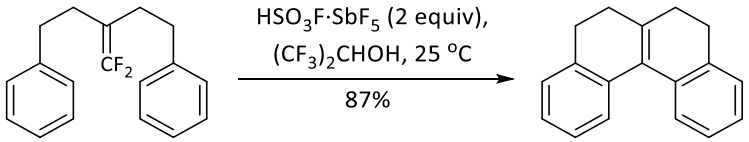
synthesis of these structures and in 2009 developed a protocol for this purpose (**Scheme I.11)**.[14]



Scheme I.11*. Klumpp's synthesis of polycyclic aromatic compounds.*

The authors described a cationic carbocyclisation reaction where an alkene was activated with excess of trifluoromethanesulfonic acid with subsequent Friedel-Crafts-type reaction to trap the formed carbenium ion. Formation of the highly conjugated products observed happened by means of loss of benzene. Thus, protonation at the *ipso* positon of the phenyl substituent yielded the cationic intermediate depicted in **Scheme I.11**, that evolved by loss of benzene and aromatisation of the system.

Some years later, the group of J. Ichikawa demonstrated that similar transformations are possible without the aromatization step, that represents a thermodynamic sink.[15] Interestingly, a series of compounds were synthesised to demonstrate the feasibility of the reaction.



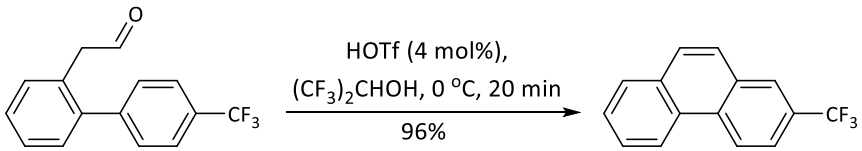
Scheme I.12*. Ichikawa's cationic cyclisation of difluoroalkenes.*

This transformation is based on the activation of difluoroalkenes by a combination of a Brønsted and a Lewis acid. The choice of the difluoroalkene moiety was key to

[14] A. Li, D. J. DeSchepper, D. A. Klumpp, *Tetrahedron Lett*. **2009**, *50*, 1924-1927.
[15] K. Fuchibe, H. Jyono, M. Fujiwara, T. Kudo, M. Yokota, J. Ichikawa, *Chem*. *Eur*. *J*. **2011**, *17*, 12175-12185.

perform the transformation, since fluorine atoms stabilise the transient cationic species. Moreover, the consecutive loss of the two fluorine atoms present in the starting material enable the formation of the second ring and the alkene observed in the final product. The authors described as well a practical protocol to oxidise the obtained tetrasubstited olefins into the corresponding polycyclic aromatic compounds in near quantitative yields.

However, a much more practical approach has been recently published again by the group of Ichikawa.[16] In this occasion, phenanthrene or anthracene derivatives are accessed in one single step from biaryl-2-ylacetaldehydes.



***Scheme I.13**. Ichikawa's cationic cyclisation of biaryl-2-ylacetaldehydes.*

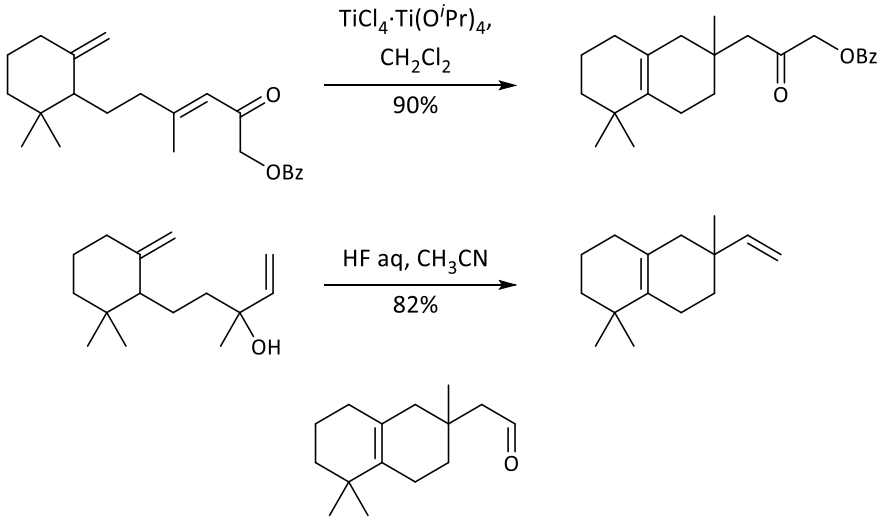
Remarkably, 4 mol% of trifluoromethanesulfonic acid was proved enough to promote the transformation in only 20 min. Combination of $(CF_3)_2CHOH$ as solvent and triflic acid as catalyst was crucial to obtain a series of compounds in near quantitative yields while making use of much milder reaction conditions compared to previous examples.

I.4.4.2 Cationic Carbocyclisations Terminated by Alkenes

One of the most reliable strategies concerning acid activation of 1,6-diene substrates has consisted of considering *α,β*-unsaturated carbonyl systems. Noteworthy, activation of these type of systems often enabled the synthesis of highly functionalised compounds with interesting structural features.

The following selected examples are representative of this statement. The group of T. A. Engler published in 1996 an extensive study on cationic cyclisation reactions for the synthesis of acanthodoral, nanaimoal and other derivatives.[17]

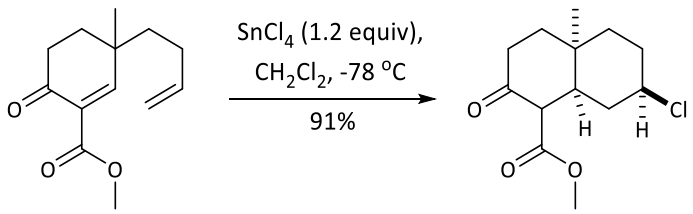
[16] T. Fujita, I. Takahashi, M. Hayashi, J. Wang, K. Fuchibe, J. Ichikawa, *Eur*. *J*. *Org*. *Chem*. **2017**, 262-265.
[17] T. A. Engler, M. H. Ali, F. Takusagawa, *J*. *Org*. *Chem*. **1996**, *61*, 8456-8463.



***Scheme I.14**. Engler's cationic cyclisation studies.*

In this case, the skeleton of nanaimoal was accesed following two different approaches by activating two different initiating groups. As shown, either an *α,β*-unsaturated ketone or an allylic alcohol performed well under cationic cyclisation conditions (**Scheme I.14**).

Perhaps a contemporaneous study made by the group of H.-J. Liu is of higher synthetic interest. The authors described a practical way to access 2-decalone skeletons exerting a high degree of stereocontrol in the cyclisation.[18]



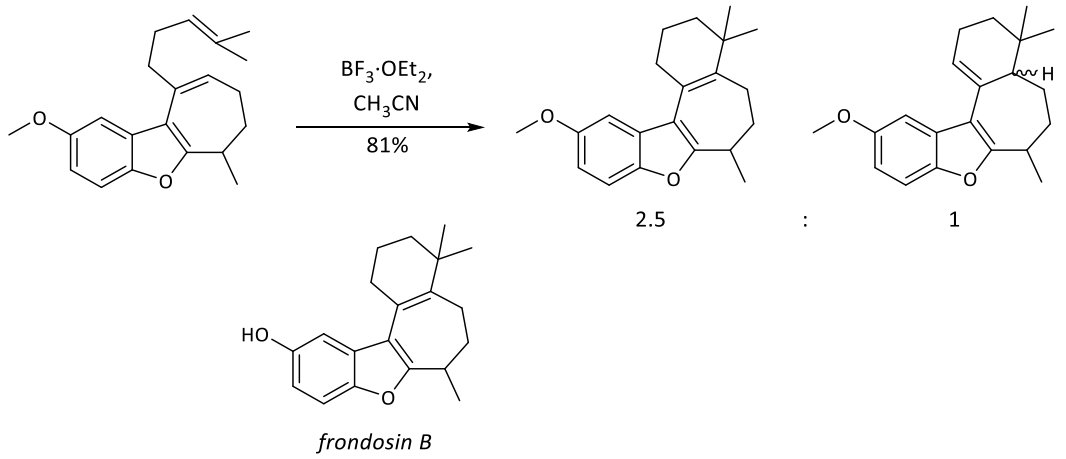
***Scheme I.15**. 2-decalone synthesis by a cationic cyclisation reaction.*

Remarkably, the decalone formation took place with total stereocontrol concerning the ring fusion. Besides, a chlorine atom is abstracted from $SnCl_4$ leading to the formation of a highly functionalised decalone.

[18] H.-J. Liu, D. Sun, K.-S. Shia, *Tetetrahedron Lett*. **1996**, 8073-8076.

On the other hand, 1,5-dienes have demonstrated great utility since the very first studies on cationic cyclisation in the 1950s. Indeed, in the last decades some examples can be found in the literature where this type of transformations is used in the total synthesis of different natural compounds. The following selected examples illustrate de utility of 1,5-diene cationic cyclisation in the synthesis of molecules with different structural features.

S. J. Danishefsky and coworkers completed the synthesis of frondosin B in 2000, applying a cationic cyclisation reaction to construct a cyclohexene ring in late stages of the synthetic sequence (**Scheme I.15**).[19]

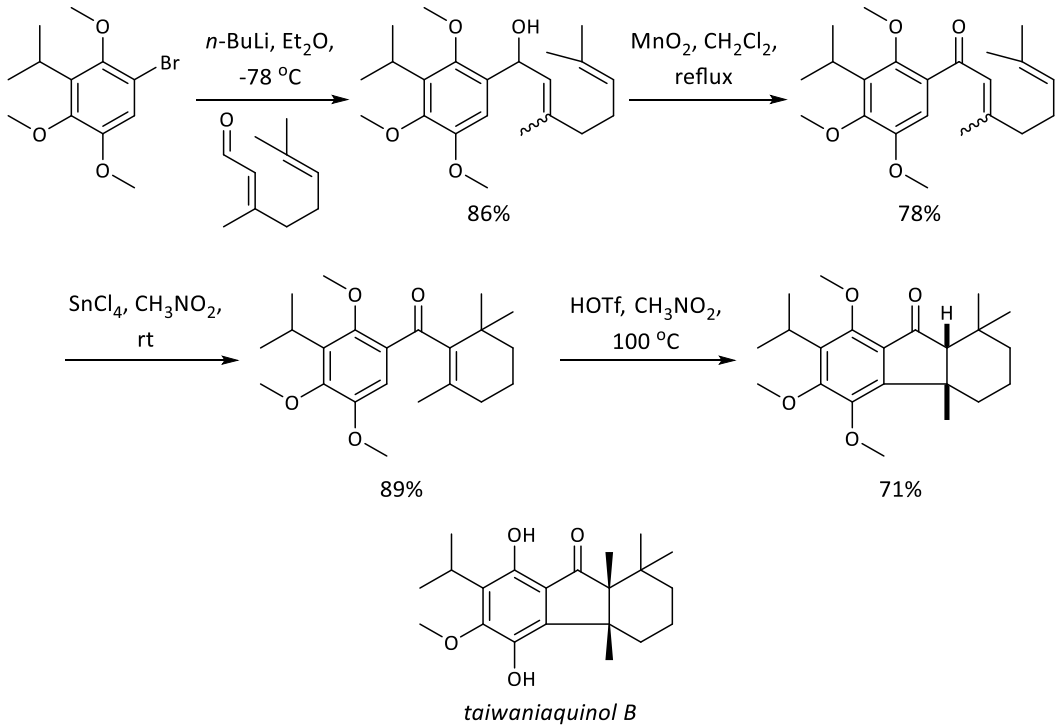


***Scheme I.16**. Danishefsky's cationic cyclisation for the synthesis of frondosin B.*

The cyclisation depicted in **Scheme I.16** promoted by $BF_3{\cdot}OEt_2$ enabled the synthesis of the cyclohexene ring of frondosin B. However, a mixture of isomers was obtained that could not be separated.

A more efficient transformation was developed by the group of P. Chiu in 2008 as part of their formal synthesis of *(±)*-taiwaniaquinol B.[20] The authors concluded that their approach was very practical to synthesise derivatives of the target molecule. The complete synthetic sequence is depicted in **Scheme I.17**.

[19] M. Inoue, M. W. Carson, A. J. Frontier, S. J. Danishefsky, *J. Am. Chem. Soc.* **2001**, *123*, 1878-1889.
[20] S. Li, P. Chiu, *Tetrahedron Lett.* **2008**, 1741-1744.

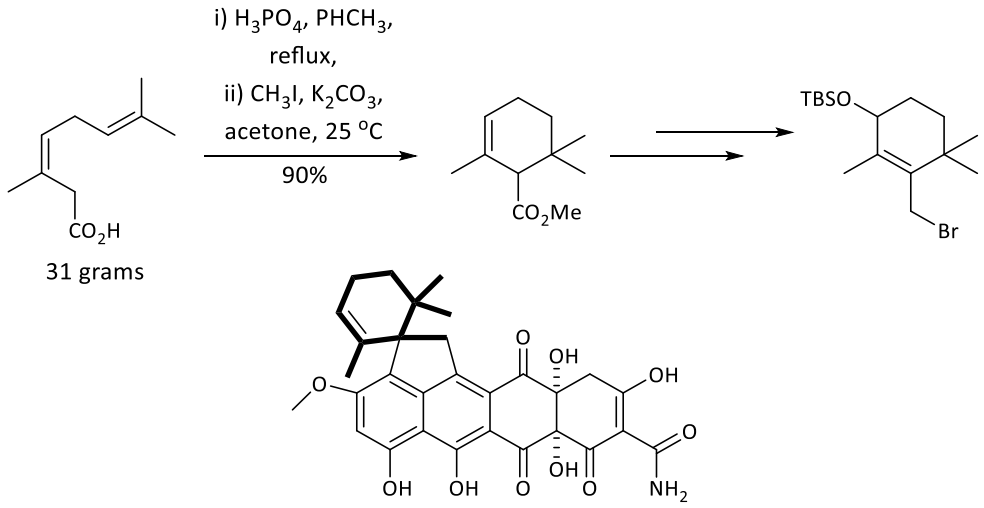


***Scheme I.17**. Formal synthesis of taiwaniaquinol B.*

The tricyclic core of taiwaniaquinol B is built in the last two steps of the sequence, by means of a cationic cyclisation promoted by $SnCl_4$ that delivers the cyclohexane ring. Subsequently, a Nazarov cyclisation was used to construct the cyclopentenone moiety.

Finally, the group of K. C. Nicolau demonstrated in 2014 that cationic cyclisation reactions are also useful tools in convergent synthetic sequences.[21] In this work, geranic acid is cyclised in multigram scale in the first stage of the synthesis of *(±)*-viridicatumtoxin B.

[21] K. C. Nicolau, C. R. H. Hale, C. Nilewski, H. A. Ioannidou, A. ElMarrouni, L. G. Nilewski, K. Beabout, T. T. Wang, Y. Shamoo, *J. Am. Chem. Soc.* **2014**, *136*, 12137-12160.



viridicatumtoxin B

***Scheme I.18**. Nicolau's cyclisation of geranic acid in the synthesis of viridicatumtoxin B.*

Noteworthy, the authors described a protocol where 31 grams of geranic acid are cyclised to cyclogeranic acid in quantitative yield. This transformation was the first step of a short synthetic sequence to construct the scaffold depicted in **Scheme I.18**.

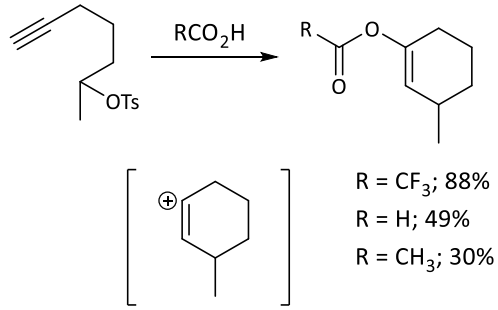
1,5-Dienes have been extensively used as building blocks in cationc cyclisations for the construction of cyclohexane structures but also for the synthesis of polycycles through tandem cationic cyclisations or polycyclisations. In the next section, some of the most transcendent transformations found in the literature will be highlighted.

I.4.4.3 Cationic Carbocyclisations Terminated by Alkynes

In this section, some of the most remarkable contributions in the context of cationic cyclisation reactions terminated by alkynes will be reviewed. This type of transformations is underdeveloped compared to those revised in sections **I.4.4.1** and **I.4.4.2**. Thus, many of the selected examples for the following revision involve the initial formation of heteroatom stabilised carbenium ions due to the lack of examples involving non-stabilised species.

Yet, the first example of alkyne terminated cationic cyclisation appeared in the literature as early as 1969.[22] The group of Kamat described the solvolysis of tosylates to obtain interesting cyclised vinyl esters (**Scheme I.19**).

[22] P. E. Peterson, R. J. Kamat, *J. Am. Chem. Soc.* **1969**, 4521-4527.



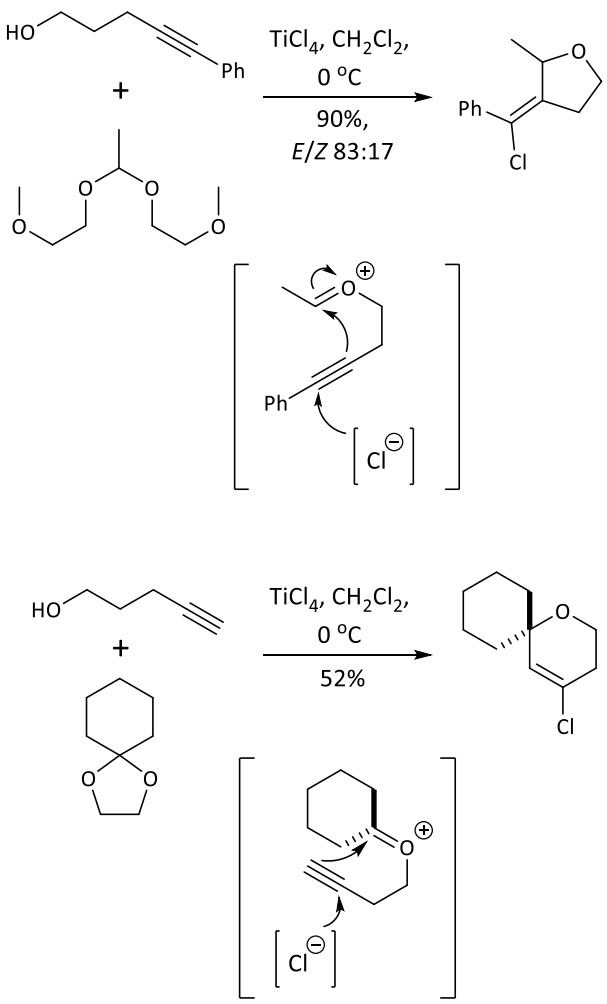
***Scheme I.19**. Solvolysis of tosylates studied by Kamat.*

The cited vinyl esters were obtained through the solvolysis reaction of the tosylate depicted in **Scheme I.19**. The carboxylic acid used as solvent is able to promote the cyclisation and trap the subsequent alkenyl cation formed *in-situ*. The authors observed high reactivity of the substrates in trifluoroacetic acid, but lower yields were obtained when weaker carboxylic acids were employed. Despite this early discovery and the synthetic potential of the transformation, cationic cyclisations involving non-stabilised carbenium species and alkynes as terminating groups remained underdeveloped, since no more examples can be found in the literature.

On the contrary, great efforts have been devoted to the study of related reactions involving the initial formation of oxonium cations. In fact, the first cascade process of transacetalisation-cationic cycisation was described already in 1989 by David W. Thompson.[23] In this work, two compounds are synthesised by means of a catonic cyclisation terminated by a triple bond. This examples are shown in **Scheme I.20**.

Notably, combination of $TiCl_4$ and CH_2Cl_2 afforded chlorinated compounds. Nucleophilic attack of the alkyne moiety on the oxonium cation is followed by halide abstraction either from the solvent or the Lewis acid. Also, some differences between internal and terminal acetylenes were observed in the outcome of the reaction. *5-exo* mode of cyclisation was observed exclusively in the case of substituted substrates, leading to a mixture of stereoisomers. However, treatment of terminal alkynol in the same reaction conditions enabled the synthesis of a cyclohexenyl chloride as single product of the reaction, albeit in lower yield.

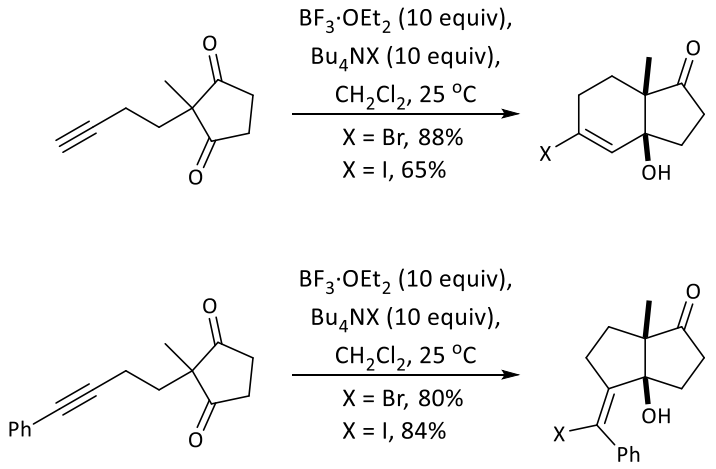
[23] N. A. Nikolic, E. Gonda, C. P. D. Longford, N. T. Lane, D. W. Thompson, *J. Org. Chem*. **1989**, *54*, 2748-2751.



***Scheme I.20**. Pioneering tandem processes developed by Thompson.*

This concept was later be by different research groups in variety of substrates. For instance, D. P. Curran and coworkers envisioned that a similar reaction should take place when submitting alkynylcyclopentane-1,3-diones to acid conditions.[24] Furthermore, an interesting study on the effect of different additives was done and the synthesis of interesting halogenated cyclised products was described (**Scheme I.21**).

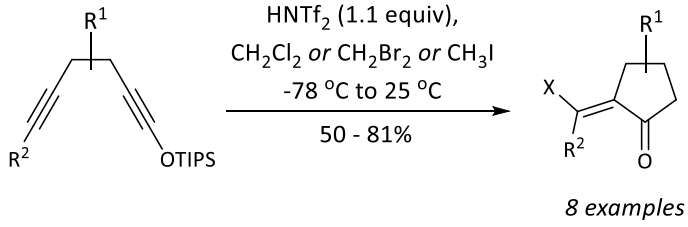
[24] A. Balog, S. J. Geib, D. P. Curran, *J. Org. Chem*. **1995**, *60*, 345-352.



***Scheme I.21**. Cationic cyclisations of alkynylcyclopentane-1,3-diones.*

D. P. Curran and collaborators demonstrated in this work that the halogen introduced in the product of the reaction can be different from that of the solvent or the Lewis acid. In this regard, addition of a source of halide afforded excellent results for the synthesis of brominated or iodinated cyclised products. Nevertheless, considerable excess of reagents had to be used in order to activate the diketones and avoid the formation of other halogenated derivatives.

In this regard, a much more convenient approach towards halogen-containing cyclopentenones was developed by Kozmin and coworkers in 2005.[25] As depicted in **Scheme I.22**, *5-exo* mode of cyclisation was exclusively observed when internal alkynes were used as terminating agents.



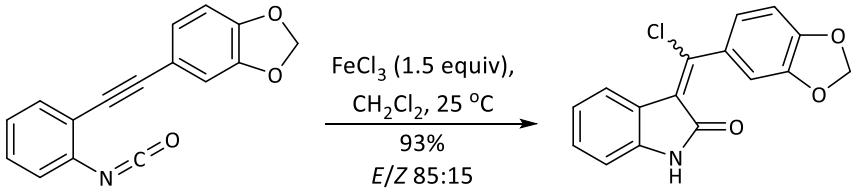
***Scheme I.22**. Kozmin's synthesis of (E)-halocyclopentenones.*

The bulky triisopropylsiloxy functionality proved useful in this study to direct the stereochemistry of the double bond. Besides, 1.1 equivalents of $HNTf_2$ was enough to trigger the transformation at low temperatures, resulting in milder reaction conditions in

[25] J. Sun, S. A. Kozmin, *J. A*m. *Chem*. *Soc*. **2005**, *127*, 13512-13513.

comparison to earlier studies described in this section. However, the siloxyalkyne functionality has not attracted much attention to synthetic chemists for the moment, so there is a considerable lack of protocols to access to this particular functionality. Consequently, the study developed by S. A. Kozmin's group was narrow in scope since only 8 examples out of 5 different substrates were described.

A similar reaction was described in 2009 by the group of C. Meyer and J. Cossy.[26] They envisioned that activation of isocyanates under acidic conditions would enable *5-exo* cyclisation of substrates bearing substitution at the acetylene moiety, with subsequent halide abstraction. Indeed, they synthesised a series of cyclised derivatives, as depicted in **Scheme I.23**.



14 examples

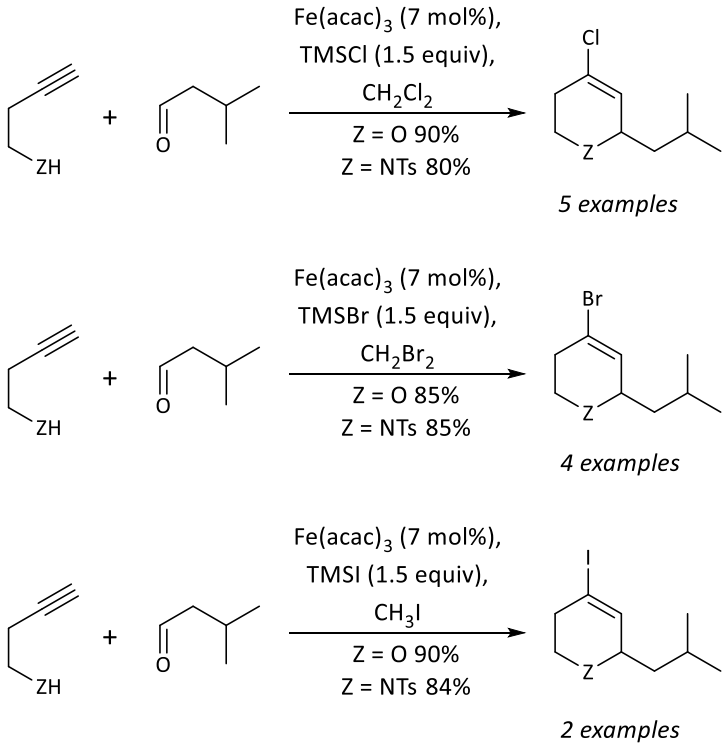
***Scheme I.23**. Cationic cylisation of isocyanates.*

A comparison between the methodology developed by S. A. Kozmin's group and that highlighted in **Scheme I.23** reveals a significantly broader scope for the latter one, albeit lower stereocontrol is exerted. All products were obtained as a mixture of geometric isomers with preference towards *E* configuration. The absence of a bulky group in the isocyanate unlike in the case of Kozmin's study would explain the lack of stereo discrimination. This problematic behavior might be the reason of the underdevelopement of similar process, since generally mixtures of double bond isomers are obtained. In this context, the works of Curran (**Scheme I.21**) and Kozmin (**Scheme I.22**) constitute the only examples where total stereocontrol is exerted in *5-exo* cationic cyclisations of internal acetylenes.

On the contrary, more studies have explored the potential utility of terminal triple bonds as terminating agents in cationic cyclisations. Unlike the case of substituted acetylenes, total stereocontrol of the double bond is exerted with ease. A nice example is represented by the works of J. I. Padrón and V. S. Martín. In 2003 they developed a Prins-type reaction promoted by stoichiometric amounts of Iron (III) salts.[27] Some years later,

[26] G. Cantagrel, B. Carné-Carnavalet, C. Meyer, J. Cossy, *Org*. *Lett*. **2009**, *19*, 4262-4265.
[27] P. O. Miranda, D. D. Díaz, J. I. Padrón, J. Bermejo, V. S. Martín, *Org*. *Lett*. **2003**, *5*, 1979-1982.

they would describe a catalytic version of this transformation. This work is highlighted in **Scheme I.24**.[28]

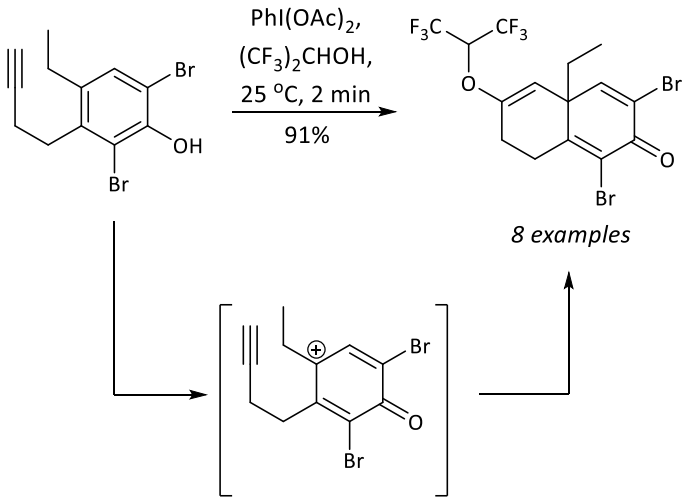


***Scheme I.24**. Prins-type process developed by Padrón and Martín.*

The catalytic cycle was designed by paying the toll of introducing a source of halide in stoichiometric amounts. Consequently, the halogen present in trimethylsilyl salts and the solvent had to be matched in order to avoid the formation of cross halogenation byproducts. Notably, the choice of Iron acetylacetonate (acac), a non-hygroscopic source of Iron (III), as catalyst for the transformation afforded excellent results.

Finally, another remarkable example is the innovative approach developed by S. Canesi and coworkers based on the cationic cyclisation of phenol containing substrates.[29] This transformation involved the oxidative activation of a phenolic ring, that rendered cationic species that are subsequently trapped by a terminal alkyne, as depicted in **Scheme I.25**.

[28] P. O. Miranda, R. M. Carballo, V. S. Martín, J. I. Padrón, *Org*. *Lett*. **2009**, *2*, 357-360.
[29] a) M. – A. Beaulieu, K. C. Guérard, G. Maertens, C. Sabot, S. Canesi, *J*. *Org*. *Chem*. **2011**, *76*, 9460-9471; b) S. Desjardins, J. – C. Andrez, S. Canesi, *Org*. *Lett*. **2011**, *13*, 3406-3409.



***Scheme I.25**. Oxidative cyclisation of phenols.*

The system showed a somewhat suprising tendency to cyclise exclusively through *para*-position of the phenolic ring. Final stabilisation of the *sp* carbenium species formed after nucleophilic attack of the alkyne was achieved after trapping by the solvent. This interesting transformation was nevertheless limited by the fact that bromine atoms in *ortho* position significantly improved the yield and stereoselectivity of the transformation therefore implicating a loss of generality.

I.5. Polyene or Biomimetic Carbocyclisations

I.5.1 Polyene Cationic Carbocyclisations: A Definition

Cationic polycyclisations or tandem cyclisations are defined as transformations initiated by the formation of a cation and where several bonds are formed in a single synthetic operation. Polycyclic structures are created through this type of reactions. These highly efficient processes are of significant interest, since they represent useful tools to generate molecular complexity from simple substrates (**Figure I.5**).

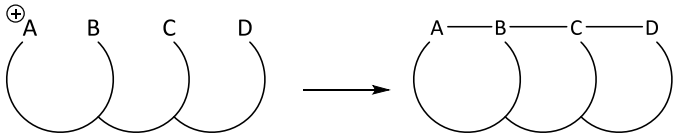
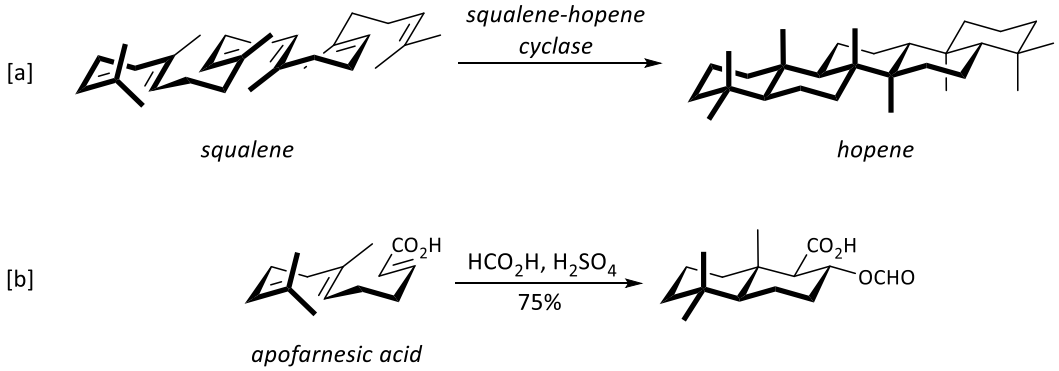


***Figure I.5**. Schematic representation of cationic polycyclisations.*

The term *biomimetic* cyclisation also refers to this type of operations, particularly when a 1,5-polyene is transformed into a polycyclic structure, in analogy to the biosynthesis of steroids from isoprenoid subunits.



***Scheme I.26**. Biosynthesis of Hopene in bacteria and polycyclisation of apofarnesic acid.*

For instance, the squalene-hopene cyclase, present in bacteria, catalyses the cyclisation of squalene, a 1,5-polyene, into hopene, a polycyclic compound (**Scheme I.26**, eq. [a]). In analogy to this biosynthetic approach, the *biomimetic* cyclisation of apofarnesic acid under acidic conditions affords a decalin skeleton in good yield as described by A. Eschenmoser and coworkers (**Scheme I.26**, eq. [b]).[30]

[30] a) P. A. Stadler, A. Nechvatal, A J. Frey, A. Eschenmoser, *Helv*. *Chim*. *Acta* **1957**, *40*, 1373-1409; b) P. A. Stadler, A. Eschenmoser, H. Schinz, G. Stork, *Helv*. *Chim*. *Acta* **1957**, *40*, 2191-2198.

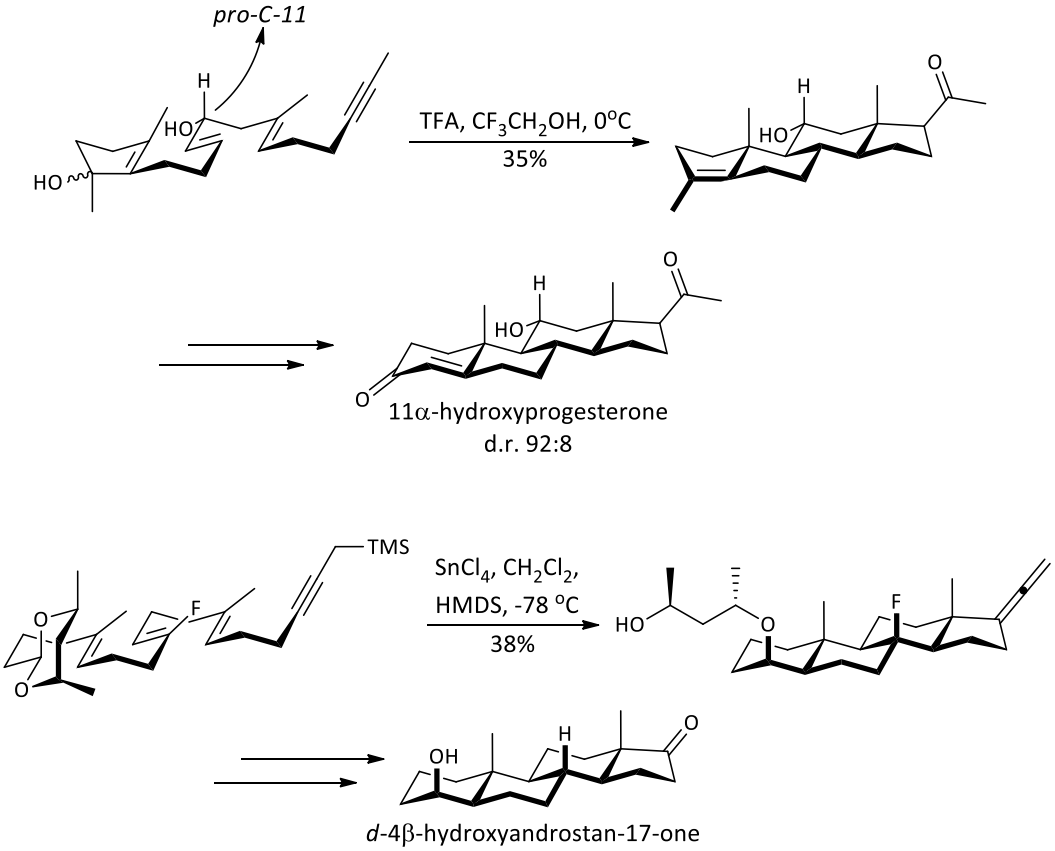
I.5.2 Polyene Cationic Carbocyclisations: An Overview

Perhaps one of the most prolific authors in the field was W. S. Johnson. He became interested in the total synthesis of steroidal natural products in chiral nonracemic form, so he developed two techniques that led to enantioenrichment during the polyene cyclisation. First, his group designed a polyolefin backbone possessing a chiral center in 1977. The cyclisation of the cited substrate led diastereoselectively to a tetracyclic intermediate in the synthesis of 11α-hydroxyprogesterone (**Scheme I.27**).[31]

Second, W. S. Johnson and collaborators also developed the use of chiral acetals as initiators for polyene cyclisation reactions in 1993, in his route to the synthesis of *d*-4β-hydroxyandrostan-17-one (**Scheme I.27**).[32]

[31] W. S. Johnson, R. S. Brinkmeyer, V. M. Kapoor, T. M. Yarnell, *J. Am. Chem. Soc.* **1977**, *99*, 8341-8343.

[32] W. S. Johnson, V. R. Fletcher, B. Chenera, W. R. Bartlett, F. S. Tham, R. K. Kullnig, *J. Am. Chem. Soc.* **1993**, *115*, 497-504.



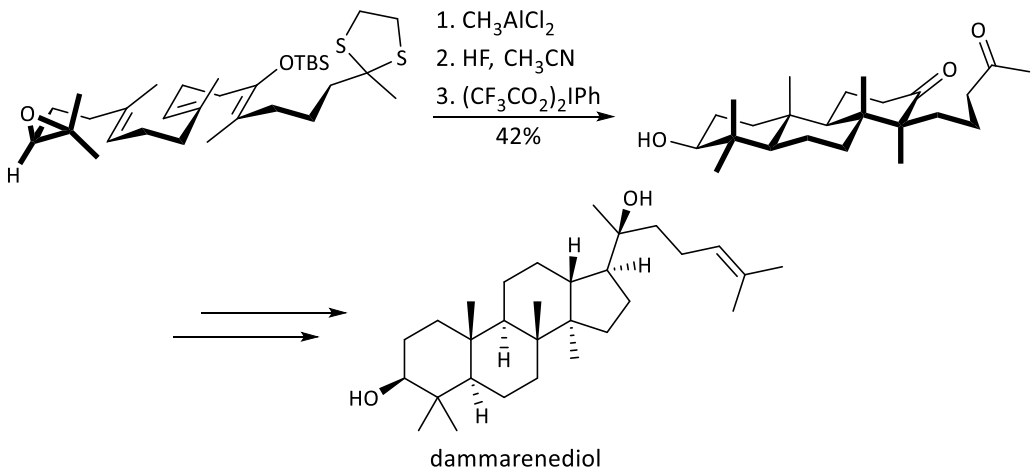
***Scheme I.27**. W. S. Johnson's synthesis of 11α-hydroxyprogesterone through an asymmetric polyene cyclisation and cascade cyclisation of a chiral acetal on the synthesis of d-4β-hydroxyandrostan-17-one.*

At this point, it should be noted a common point in Johnson's strategies above highlighted. He exploited the utility of an internal triple bond as a tool to construct the D ring of steroid skeletons through a final 5-*exo* cyclisation.

In 1982, E. E. van Tamelen and coworkers pioneered the use of epoxides as activating functional groups to trigger cascade cyclisations of polyenes, though in racemic form.[33] It was the group of E. J. Corey who made use of that strategy to produce enantioenriched polycyclic structures in 1996.[34] In his route to dammarenediol, Corey performed the construction of the A, B and C rings of the skeleton by means of polyene cyclisation of a chiral epoxide promoted by $MeAlCl_2$. After desilylation and thioacetal hydrolysis, the tricyclic diketone depicted in **Scheme I.27** was obtained. Then, in a

[33] E. E. van Tamelen, T. M. Leiden, *J. Am. Chem. Soc.* **1982**, *104*, 2061-2062.
[34] E. J. Corey, L. S. Lin, *J. Am. Chem. Soc.* **1996**, *118*, 8765-8766.

different approach to the one designed by Johnson, he accessed the D ring of dammarenediol by means of an aldol reaction in later steps.

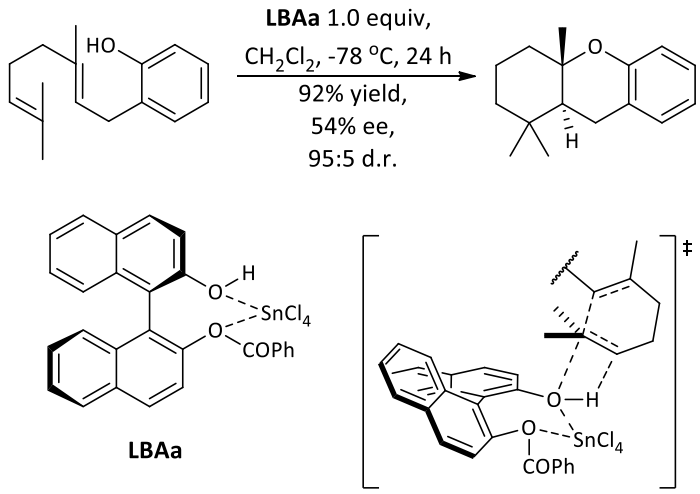


***Scheme I.28**. Key step in Corey's total synthesis of dammarenediol.*

This approach proved to be very useful and versatile, since Corey applied a similar strategy in 1997 and 1998 to the total syntheses of different natural products.[35] It is also worth mentioning the approach designed by the group of L. E. Overman for the synthesis of adociasulfate 1 in 1998 exploiting a similar idea.[36]

Despite all the advances made in asymmetric polyene cyclisations through diastereoselective transformations of chiral nonracemic substrates, it was not until 1999 that H. Yamamoto and collaborators reported the first enantioselective cascade reaction of prochiral substrates.[37] This proton-initiated biomimetic cyclisation was based on the principle of Lewis acid-assisted activation of Brønsted acids (LBA), wherein a Lewis acid increases Brønsted acid reactivity through coordination. These complexes were initially evaluated as promoters for the cyclisation of a series of linear polyene substrates containing phenolic terminating groups (**Scheme I.29**).

[35] a) E. J. Corey, G. Luo, L. S. Lin, *J. Am. Chem. Soc.* **1997**, *119*, 9927-9928; b) E. J. Corey, G. Luo, L. S. Lin, *Angew. Chem. Int. Ed.* **1998**, *37*, 1126-1128.
[36] M. Bogenstäter, A. Limberg, L. E. Overman, A. L. Tomasi, *J. Am. Chem. Soc.* **1999**, *121*, 12206-12207.
[37] K. Ishihara, S. Nakamura, H. Yamamoto, *J. Am. Chem. Soc.* **1999**, *121*, 4906-4907.



***Scheme I.29**. Yamamoto's first enantioselective cyclisation using LBAs as promoters.*

The authors proposed that during the protonation step (see TS in **Scheme I.29**), the developing partial positive charge at the initiating site is electronically stabilized by an n-π* interaction between an oxygen lone pair and the LUMO of the olefin. It should be noted that despite no protons are incorporated to the substrate in the overall process, stoichiometric amounts of LBA are necessary to achieve good results.

Careful tuning of the Brønsted acid scaffold gave birth to the second-generation of LBA developed by H. Yamamoto and coworkers.[38] Having identified these LBAs as suitable acids to trigger polyene cyclisations, the group of H. Yamamoto also used them in the context of natural product synthesis. Thus, they demonstrated that this methodology was useful to synthesise *(-)*-Ambrox®, *(-)*-chromazonarol and *(+)*-ferruginol.[37,39]

Finally, the group of E. J. Corey made as well some modifications of H. Yamamoto's first generation LBA.[40] They chose a more sterically demanding Lewis Acid, $SbCl_5$, and a more electron-deficient *o,o'*-dichlorinated BINOL derivative scaffold. Overall, this resulted in tighter coordination within the promoter and increased Brønsted acidity.

[38] K. Kumazawa, K. Ishihara, H. Yamamoto, *Org*. *Lett*. **2004**, *6*, 2551-2554.
[39] a) K. Ishihara, H. Ishibashi, H. Yamamoto, *J*. *Am*. *Chem*. *Soc*. **2001**, *123*, 1505-1506; b) H. Ishibashi, K. Ishihara, H. Yamamoto, *J*. *Am*. *Chem*. *Soc*. **2004**, *126*, 11122-11123.
[40] K. Surendra, E. J. Corey, *J*. *Am*. *Chem*. *Soc*. **2012**, *134*, 11992-11994.

So far, this background section collects some of the most relevant examples found in the literature regarding cationic cyclisations. It was intended to highlight the potential of these processes as efficient synthetic tools. Particular emphasis has been made on describing the reactivity of enynes in the context of cationic cyclisations.

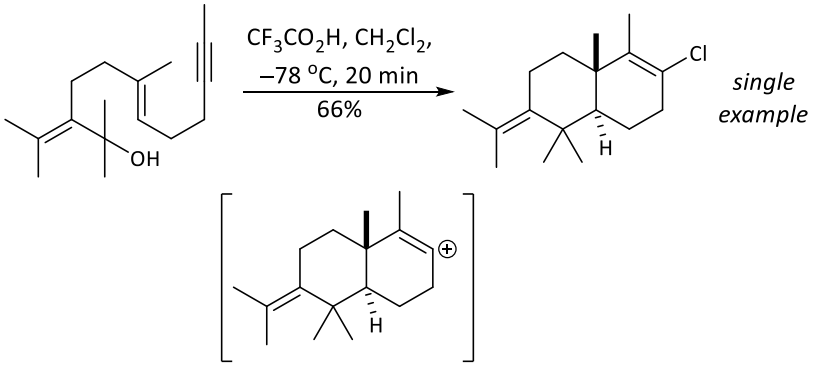
In this regard, the main objective of our investigation was to study new cationic carbocyclisations where a terminal alkyne acted as the terminating agent.

This dissertation gathers the most relevant results obtained during our studies, organised in two different chapters. In the first chapter a new methodological study towards the synthesis of cyclohexenyl halides structures is described. In the second chapter a new reaction for the synthesis of cyclohexenyl triflates is presented. Additionally, two synthetic applications are disclosed. Besides, the utility of 1,5-enynes and 5-hexyn-1ol derivatives to access to cyclohexanones is described in the second chapter.

Chapter 1

1.1 Introduction and Objectives

In previous sections, different carbocyclisation reactions have been reviewed in order to stress the applicability of this type of processes in organic synthesis. An inspiring contribution by W. S. Johnson and coworkers that was not highlighted in the General Introduction is depicted in **Scheme 1.1**.[41] The authors observed that the tertiary allylic alcohol shown underwent a cationic carbocyclisation upon treatment with trifluoroacetic acid to yield a *trans*-decalin derivative with complete diastereoselection.[42]

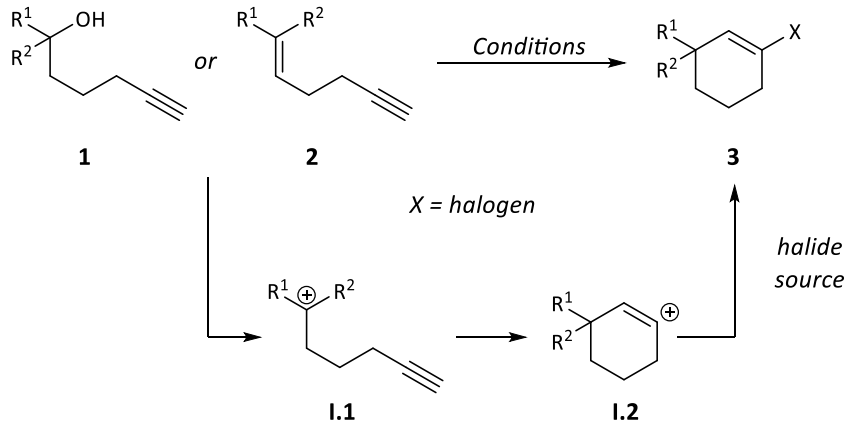


***Scheme 1.1**. Johnson's decalin synthesis involving a triple bond as a terminating agent.*

Interestingly, an alkenyl chloride was formed in this reaction as a result of trapping the alkenyl cation intermediate by a chloride coming from the solvent of the reaction (dichloromethane). In spite of the remarkable features of this transformation, this useful strategy to access to cyclohexenyl halide skeletons has remained essentially unexploited since the publication of this single example depicted in **Scheme 1.1**. Moreover, the role of alkynes as terminating agents in cationic carbocyclisations remains underdeveloped. It should also be noted that, apart from the example above mentioned, carbocyclisation reactions with alkynes as terminating groups implying an initial non-stabilised cation have not been reported.

With all this in mind, our objective was to develop new carbocyclisation reactions promoted by Lewis or Brønsted acids and using acetylenes as terminating functionalities to synthesise different halogen-containing molecules.

[41] W. S. Johnson, M. B. Gravestock, R. J. Parry, D. A. Okorie, *J. Am. Chem. Soc.* **1972**, *94*, 8604-8605.
[42] The *sp*-cation is invoked in this case only for a better understanding of the reaction mechanism, though probably it is not an actual intermediate of the reaction.

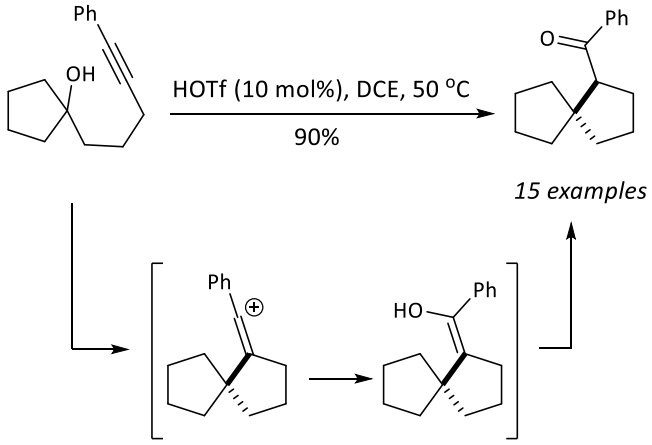


***Scheme 1.2**. Our initial approach.*

At this point, we envisioned that treatment of 5-hexyn-1-ol derivatives **1** or enynes **2** with stoichiometric amounts of a protic acid should lead to cationic intermediate **I.1** through a dehydration or an alkene protonation respectively. Intramolecular trapping of this cation by the triple bond would render the cyclic alkenyl cation intermediate **I.2**, that, in the presence of a halide source should lead to the final cyclic alkenyl halide **3**.[43] Surprisingly, this simple process to synthesise cyclic alkenyl halides had not been exploited before our studies in the area.

However, at the beginning of our investigation we were also aware of a work by the group of Y. Yamamoto reported in 2009 about the synthesis of cyclopentyl ketones from alkynol derivatives similar to **1** (**Scheme 1.3**).[44] These alkynols react upon treatment with a strong Brønsted acid through loss of a molecule of water. After addition of the alkyne to the initially formed cation, the resulting alkenyl cation intermediate is captured by the molecule of water previously released. This leads to the formation of an enol that tautomerizes to the final product.

[43] The sp^2 and *sp*-cation are invoked in this case only for a better understanding of the reaction mechanism, though they may not be actual intermediates of the reaction.
[44] T. Jin, M. Himuro, Y. Yamamoto, *Angew*. *Chem*. *Int*. *Ed*. **2009**, *48*, 5893-5896.



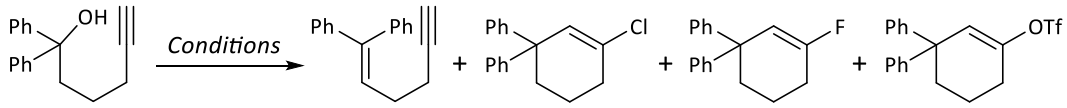
***Scheme 1.3**. Catalytic spirocyclisation developed by Y. Yamamoto.*

This work suggests that in our proposal, a molecule of water could compete with the halogen source to trap the key cationic species, evidencing that our plan was far from trivial. Yet, we reasoned that fine tunning of the reaction conditions should pave the way for the specific reactivity we were searching. It is also important to note that both Johnson's and Yamamoto's works made use of internal alkynes, while our initial proposal was the use of terminal alkynes. The results of our investigation on this challenging goal are presented in the next sections.

1.2 Synthesis of Cyclohexenyl Chlorides

1.2.1 Optimisation and preliminary results

In order to evaluate the viability of the proposal, alkynol **1a** was chosen as model substrate and different conditions were tested to optimise the process. All possible products of the reaction are depicted in the scheme of **Table 1.1**.



1a **2a** **3a** **3aF** **6a**

entry	solvent [M]	acid (x equiv)	T (°C)	time (h)	**2a** (%)	**3a** (%)	**3aF** (%)
[a]1	CH_2Cl_2 [0.1]	HOTf (1)	25	0.5	48	20	-
2	CH_2Cl_2 [0.1]	$HBF_4{\cdot}OEt_2$ (1)	25	0.5	53	25	8
3	CH_2Cl_2 [0.05]	$HBF_4{\cdot}OEt_2$ (1)	25	0.5	65	25	n. d.
4	CH_2Cl_2 [0.05]	$HBF_4{\cdot}OEt_2$ (1)	25	8	50	42	n. d.
5	**CH_2Cl_2 [0.05]**	**$HBF_4{\cdot}OEt_2$ (1)**	**25**	**16**	**n. d.**	**92**	**n. d.**
6	CH_2Cl_2 [0.05]	$HBF_4{\cdot}OEt_2$ (1)	60	8	8	65	n. d.
7	CH_2Cl_2 [0.05]	$HBF_4{\cdot}OEt_2$ (1)	60	10	n. d.	73	n. d.
8	CH_2Cl_2 [0.05]	$HBF_4{\cdot}OEt_2$ (0.2)	25	16	78	17	n. d.
9	hexane [0.1]	$AlCl_3$ (1)	25	16	48	35	-
10	CH_2Cl_2 [0.1]	$AlCl_3$ (1)	25	16	n. d.	84	-
11	hexane [0.1]	TMSCl + MeOH (1)	25	16	78	n. d.	-
12	CH_2Cl_2 [0.1]	TMSCl + MeOH (1)	25	16	75	n. d.	-

***Table 1.1**. Optimisation studies for the synthesis of **3a**. Yields determined by NMR analysis of the crude. n. d. = not detected. [a]4% of alkenyl triflate **6a** was also observed.*

For the initial experiment we selected conditions similar to those previously used by Y. Yamamoto in his work devoted to the synthesis of cycloalkyl ketones (**Scheme 1.3**). It is important to remark that our proposal required the use of a chlorinated solvent that, considering Johnson's work (see **Scheme 1.1**), could act as a source of chloride. Thus, although the formation of ketone derivatives could be expected, we thought that the synthesis of cyclohexenyl chlorides would be feasible. On the other hand, we envisioned that the use of terminal alkynes instead of internal ones could direct the reaction through the formation of 6-member ring products instead of 5-member ring ones. With all this in mind, alkynol **1a** was treated with 1 equivalent of trifluoromethanesulfonic acid (HOTf) in dichloromethane at room temperature. In this initial experiment gathered in entry 1, our desired cyclic alkenyl chloride **3a** was obtained in 20% yield after only 30 min of reaction. Along with this compound we also observed the formation of enyne **2a** (48% yield, formed

by dehydration of alkynol **1a**) and cyclohexenyl triflate **6a** (4% yield). Surprisingly, formation of ketone derivatives was not observed. Although formation of triflate **6a** raised our attention (see Chapter 2 of this thesis), at this point we wanted to avoid its formation. As this product comes from the trapping of the alkenyl cation intermediate **I.2** (see **Scheme 1.2**), by a triflate anion (coming from triflic acid), the obvious way to avoid its formation is the use of a different acid to promote the reaction.

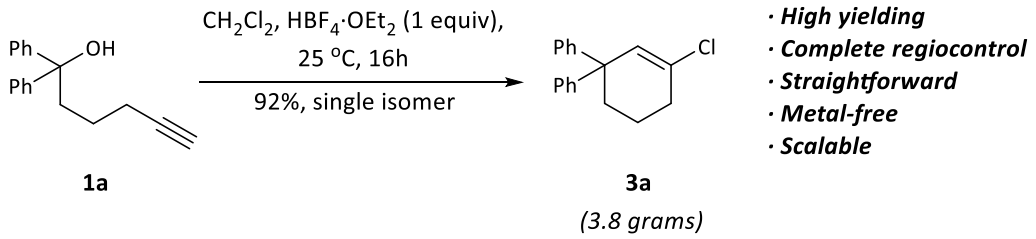
Thus, in a subsequent experiment we tried the reaction with tetrafluoboric acid ($HBF_4{\cdot}OEt_2$) instead of triflic acid (**Table 1.1**, entry 2). As shown, under these conditions we observed that the formation of the desired alkenyl chloride **3a** occurred with a slightly higher yield (25% yield). However, we also observed the formation of other products. More precisely, the byproducts formed in this case were enyne **2a** and fluoride **3aF**, the latter formed due to the trapping of alkenyl cation **I.2** by a fluoride coming from the tetrafluoroborate anion. This fluorinated byproduct was no longer observed when the reaction was carried out under more diluted conditions (entry 3).

By extending the reaction time from 0.5 h to 16 h (entries 3-5) we observed that the amount of enyne **2a** decreased and the yield of our desired chloride **3a** increased (92% yield, entry 5). This observation suggests that enyne **2a** is an intermediate of the reaction that is slowly transformed into the desired final product **3a**. Also, increasing the temperature allowed to achieve full conversion in 10 h, albeit with lower yields (entries 5-7). As expected, employing catalytic amounts of acid led to the formation of sub-stoichiometric amounts of product **3a**, while dehydration product **2a** was formed in high yield (entry 8).

Some experiments were done in order to check the feasibility of the process in non-halogenated solvents. Our idea was to find an acid capable of triggering the cyclisation and that, at the same time, it could act as a source of chloride. For this purpose, Lewis acid $AlCl_3$ seemed ideal and control experiments performed with this acid demonstrated that product **3a** was formed in hexane (entry 9). However, the yields obtained were lower than those observed with tetrafluoroboric acid, even when dichloromethane was used as solvent (entry 10). Moreover, other combinations of Lewis or Brønsted acids carried out in order to avoid the use of halogenated solvents as the halogen source were not effective (entries 11, 12).

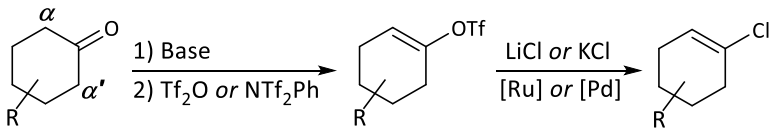
Therefore, after this optimisation study, the best conditions found to perform the desired transformation were those highlighted in entry 5 in **Table 1.1**, that imply the use of CH_2Cl_2 as the solvent, 1 equivalent of tetrafluoroboric acid to promote the cyclisation and 25 ^oC as the reaction temeprature. No other additives are required in order to promote the transformation of alkynol **1a** into cyclic alkenyl chloride **3a**. The reaction takes place in very high yield and with complete stereocontrol regarding the

stereochemistry of the double bond. Moreover, the process is operationally very simple, the starting material is easily available and the process can be performed at gram-scale. Indeed, 3.8 grams of **3a** were synthesised in one single batch.



***Scheme 1.4**. Optimised synthesis of **3a**.*

At this point, a comparison between our new method and conventional approaches to synthesise cyclic alkenyl halides should be done in order to stress the importance of this result. One of the most reliable strategies to access to this type of structures has been recently developed in the groups of S. L. Buchwald and T. Hayashi and is depicted in **Scheme 1.5**.[45] Tipically, alkenyl chlorides and bromides are accessed through a transition metal (namely Pd or Ru) catalysed reaction of alkenyl triflates. These triflates have been traditionally prepared by means of a reliable protocol developed more than 40 years ago by J. E. McMurry and W. J. Scott, that consists of the enolisation of a ketone and trapping of the subsequently formed enolate with a triflating reagent.

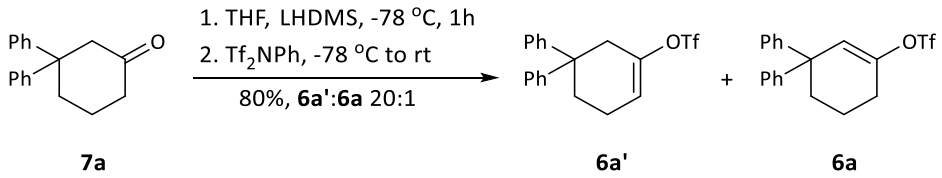


***Scheme 1.5**. Conventional approach to alkenyl chlorides.*

The main problem of this methodology is the differentiation of *α* and *α'* positions of the ketone under basic conditions, a classilcal problem in organic chemistry. The outcome of this initial enolisation will determine the stereochemistry of the final alkene moiety. Indeed, the regiochemical control achieved with our methodology was not observed when the conventional methodology was applied. For comparative reasons we

[45] a) J. E. McMurry, W. J. Scott, *Tetrahedron Lett*. **1983**, *24*, 979-982. b) E. Shirakawa, Y. Imazaki, T. Hayashi, *Chem*. *Commun*. **2009**, *34*, 5088-5090. c) X. Shen, A. M. Hyde, S. L. Buchwald, *J. Am*. *Chem*. *Soc*. **2010**, *132*, 14076-14078. d) Y. Imazaki, E. Shirakawa, R. Ueno, T. Hayashi, *J. Am*. *Chem*. *Soc*. **2012**, *134*, 14760-14763.

attempted the synthesis of triflate **6a** from cyclohexanone **7a** following the traditional McMurry method. Noteworthy, we observed the formation of a mixture of the two expected regioisomers **6a** and **6a'** with the alkenyl triflate **6a** being the minor regioisomer (**6a**:**6a'** ratio = 1:20), as shown in **Scheme 1.6**:



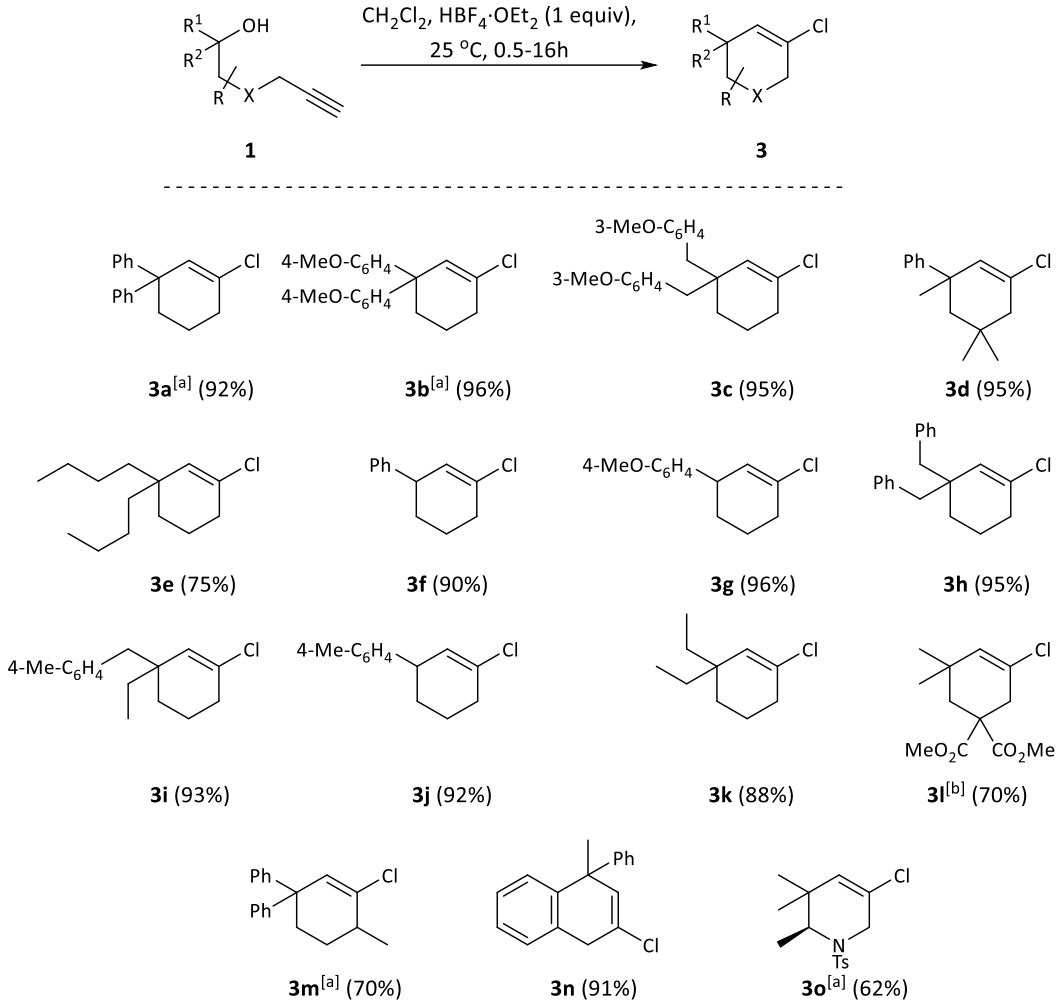
***Scheme 1.6**. Failed attempt for the synthesis of **6a** through conventional methodology.*

This experiment shows how *β*-substitution hampers the enolisation of *α* position of ketones in certain cases, thus favouring the enolisation of easily accessible *α'* position. In this regard, considering our result highlighted in **Scheme 1.4**, our methodology would challenge and complement existing protocols to synthesise cyclic alkenyl chlorides. To test the robustness of our method in this context, the scope of the reaction was next studied.

1.2.2 Scope of the Reaction

Once the optimal conditions were set up, the scope of the process was examined by probing changes in starting materials. These conditions could be applied successfully to a variety of alkynols **1** and enynes **2**. Thus, a series of cyclohexenyl chloride derivatives were easily obtained. These results are shown in **Scheme 1.7**.

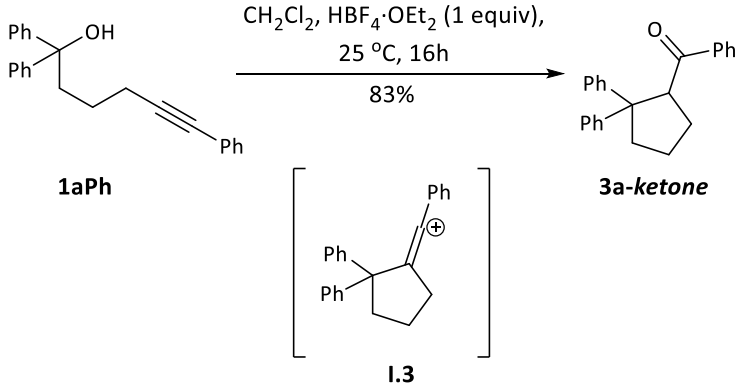
The reaction allowed a wide range of substitution with yields ranging from 62% to 96%. Besides, no isomerisation of the double bond was observed, since all products were obtained as single regioisomers, thus making the process reliable and predictable. Alkyl and aryl substituents were well tolerated at the R^1 and R^2 positions (e.g. see **3a**, **3e**, **3h**). Remarkably, tertiary (R^1 and $R^2 \neq H$) and secondary ($R^2 = H$) substrates performed equally well, since high yields were obtained in very short reaction times (0.5h). It should be noted though that those alkynols substituted with aromatic groups at the R^1 and R^2 positions (**1a**, **1b** and **1m**) required longer reaction times (16h) to be converted into the corresponding products **3**. This is a consequence of the formation of highly conjugated enynes **2a,b,m**, that require longer time to be converted to the desired cyclohexenyl chlorides **3**. Also, this methodology could be applied to the synthesis of dihydronaphthalenes (see **3n** in **Scheme 1.7**). Finally, the methodology is compatible with the presence of heteroatoms (see examples **3l** and **3o**) and therefore with the synthesis of heterocycles.



***Scheme 1.7**. Scope explored for the synthesis of cyclohexenyl chlorides. Ts = p-toluenesulfonyl. [a]Reaction time: 16 h for substrates **3a**, **3b** and **3m**, 4 h for substrates **3l** and **3o** and 0.5 h for the rest of the substrates. [b]Synthesised from corresponding enyne **2l**.*

On the other hand, the reaction was limited to the synthesis of six-membered ring derivatives, since 4-pentyn-1-ol and 6-heptyn-1-ol derivatives failed to be converted into the corresponding five and seven-membered ring products. Instead, the corresponding enynes **2** were recovered but they could not be further transformed into the desired cyclic products. Besides, *6-endo* type cyclisations were exclusively observed when using alkynols **1** containing terminal alkynes (**Scheme 1.7**). When alkynols decorated with substituted triple bonds were used, products derived from *5-exo* cyclisations were observed with subsequent capture of the *sp* cation by water. More precisely, when alkynol **1aPh** was

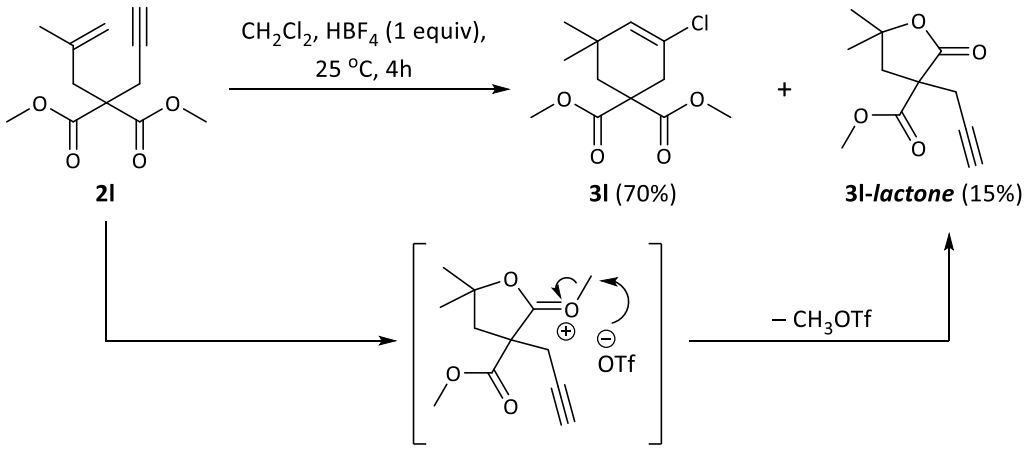
treated with 1 equivalent of tetrafluoroboric acid in dichloromethane, the exclusive formation of **3a-*ketone*** was observed in 84% yield. This result is depicted in **Scheme 1.8**.



***Scheme 1.8**. 5-exo cyclisation typical of substituted alkynols.*

This product is formed through intermediate **I.3**, generated by a *5-exo* cyclisation. Interestingly, this intermediate is trapped by the water formed in the initial dehydration process, but not by a chloride coming from the solvent. This is in contrast with our observations with terminal alkynes but is in agreement with previous results developed by Y. Yamamoto (**Scheme 1.3**). In conclusion, when internal alkynes are used, not only the cyclisation mode is different, but also the generation of alkenyl chlorides seems to be restricted and formation of cyclopentylketones derivatives is favoured.

Besides, competitive trapping of the initial cation by other nucleophiles present in some particular starting materials was also observed. For example, when enyne **2l** was treated with 1 equivalent of tetrafluoroboric acid, cyclohexenyl chloride **3l** was obtained in 70% yield, but competitive trapping of the sp^2 carbenium ion by the ester functionality was also observed. Consequently, **3l-*lactone*** was also isolated with 15% yield (**Scheme 1.9**).



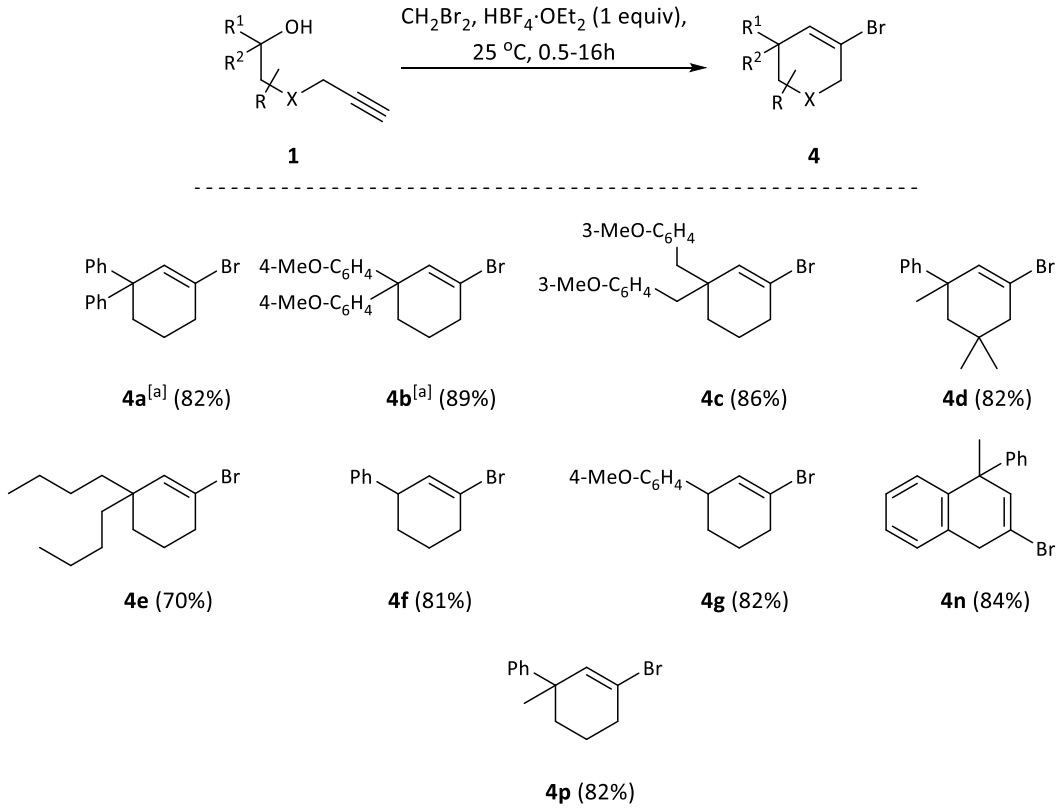
***Scheme 1.9**. Particular behaviour of enyne **2l**.*

The formation of this byproduct could be explained by the initial trapping of the sp^2 carbenium ion by the ester functionality, leading to the cationic intermediate depicted in **Scheme 1.9**. This intermediate would evolve through loss of CH_3OTf as depicted above, to finally yield compound **3l-*lactone***.

1.3 Synthesis of Cyclohexenyl Bromides and Iodides

1.3.1 Synthesis of Cyclohexenyl Bromides

Once conditions for the synthesis of cyclohexenyl chlorides had been found and the scope of the transformation studied, an extension of the study to access other halogenated derivatives was next explored. Considering that in the previously commented reaction the halogenated solvent (dichloromethane) is the source of halide (chloride), we just tried the reaction with other halogenated solvents. In this context, we were delighted to observe that alkynol derivatives **1** could be efficiently transformed into the cyclic alkenyl bromides **4** when dibromomethane was used as solvent of the reaction (**Scheme 1.10**). As shown, a variety of bromide derivatives were easily obtained in high yields and without isomerisation of the bromoalkene moiety. In analogy to the synthesis of the chlorinated derivatives, the reaction time (0.5 to 16h) had to be optimised for every substrate tested. Hence, alkynols **1a** and **1b** substituted with aromatic groups at the R^1 and R^2 positions required longer reaction times (16 h) to be converted into the corresponding products **4a** and **4b**. Again, this is due to the formation of enynes **2a** and **2b**, that showed slower reactivity towards the formation of **4a** and **4b** when compared to the rest of the substrates in **Scheme 1.10**. Nevertheless, the reactivity of secondary (R^2 = H) substrates is still remarkable regarding the short reaction times (0.5h) required for substrates **4f** and **4g** in **Scheme 1.10**.



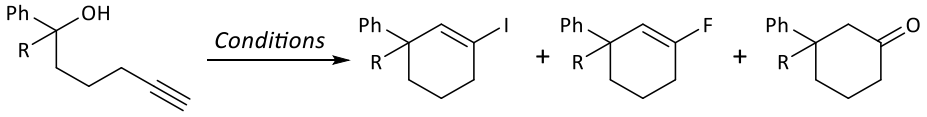
***Scheme 1.10**. Scope studied for the synthesis of cyclohexenyl bromides. [a]Reaction time: 16 h for substrates **4a** and **4b** and 0.5h for the rest of the substrates.*

Moreover, as discussed in the previous section, terminal alkynes showed a remarkable tendency to cyclise exclusively through a *6-endo* manner, making the reaction very predictable in terms of ring closure stereochemistry.

Finally, it should also be noted that other potential products of these reactions such as the corresponding cyclic alkenyl fluorides similar to **3aF** (see **Table 1.1**) were not observed under these reaction conditions. Moreover, the formation of cyclohexanones was never detected, which is in good agreement with the results obtained for the synthesis of cyclohexenyl chlorides.

1.3.2 Synthesis of Cyclohexenyl Iodides

Our next objective was the synthesis of the corresponding cyclic alkenyl iodides. This task proved to be more challenging than we had anticipated. Considering our previous results, the obvious way to synthesise the desired cyclic alkenyl iodides was the use of an appropriate iodinated solvent that could act as a source of iodide. In this regard, it should be noted that only iodomethane seems to be a suitable option considering its low boiling point (bp = 41 °C). Other small iodoalkanes such as diiodomethane would be difficult to remove due to its relatively high boiling point (bp = 181 °C). With all this in mind, we began the study of the synthesis of cyclochexenyl iodides, by treating alkynol **1p** with tetrafluoroboric acid in iodomethane at room temperature for 30 min (**Table 1.2**).



1p (R = CH_3) **5p** (R = CH_3) **5pF** (R = CH_3) **7p** (R = CH_3)

1a (R = Ph) **5a** (R = Ph) **5aF** (R = Ph) **7a** (R = Ph)

entry	alkynol	solvent [M]	acid (x equiv)	T (°C)	time (h)	**5p** (%)	**5pF** (%)	**7p** (%)
1	**1p**	CH_3I [0.1]	$HBF_4{\cdot}OEt_2$ (1)	25	0.5	15	50	10
2	**1p**	CH_3I [0.1]	AlI_3 (1)	25	0.5	50[a]	n. d.	n. d.
3	**1p**	**CH_3I [0.1]**	**AlI_3 (1)**	**-60**	**0.5**	**70**	**n. d.**	**n. d.**
4	**1a**	**CH_3I [0.1]**	**AlI_3 (1)**	**25**	**16**	**85**	**n. d.**	**n. d.**

Table 1.2 *Optimisation study for the synthesis of **5p**. Yields determined by NMR analysis of the crude. n. d. = not detected. [a] Obtained as a 5:1 mixture of isomers.*

When alkynol **1p** was submitted to these reaction conditions (entry 1), cyclohexenyl iodide **5p** was obtained in 15% yield. Along with this product, cyclohexenyl fluoride **5pF** (50% yield) and cyclohexanone **7p** (10% yield) were also formed. At this point, it should be noted that the formation of cyclohexanone **7p** would be explained by the trapping of cationic species **I.2** (see **Scheme 1.2**) by water coming from alkynol **1p**. This interesting result will receive more attention in chapter 2 of this thesis.

In order to avoid the formation of the fluorinated by-product **3aF** we considered the option of using AlI_3 instead of HBF_4 as promoter of the cationic cyclisation. Thus, when alkynol **1p** was treated with 1 equivalent of AlI_3 in iodomethane as solvent during 30 min at room temperature, cyclohexenyl iodide was formed in 50% yield as a 5:1 mixture of isomers, due to isomerisation of the double bond (entry 2). Noteworthy, no other

byproducts were observed in this experiment. By lowering the temperature to –60 °C, this process was not observed and **5p** was obtained in 70% yield as a single isomer.

In the case of alkynol **1a**, the reaction was run at room temperature for 16 h in the presence of 1 equivalent of AlI_3. Under these conditions, cyclohexenyl iodide **5a** was obtained in 85% yield as a single isomer (entry 4).

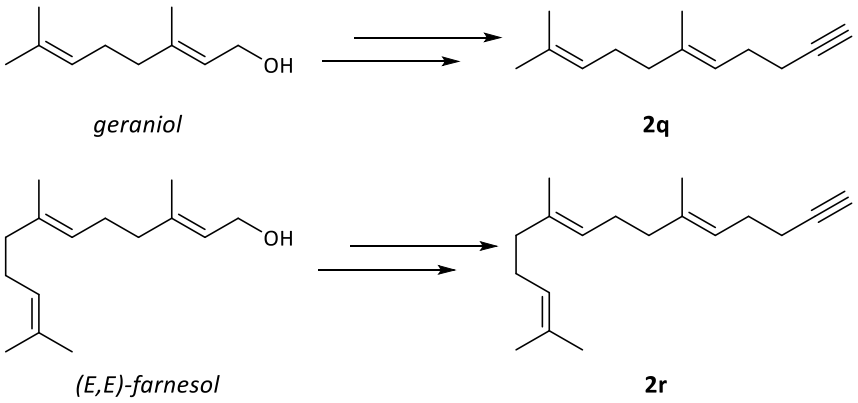
Only cyclohexenyl iodides **5a** and **5p** could be obtained in high yields and as single isomers. Other alkynols **1** or enynes **2** tested under the reaction conditions above described were obtained as a mixture of isomers even with short reaction times (0.5 h) and at low temperatures (-60 °C).

Having developed a new methodology for the synthesis of cyclohexenyl halides and studied the scope on simple substrates, the next objective was to perform some biomimetic polycyclisations on terpene derived substrates. These results are gathered in the next section.

1.4 Biomimetic Carbocyclisations: Synthesis of Polycyclic Halides

After the study summarized in the previous sections on the synthesis of cyclic alkenyl halides from simple alkynol or enyne derivatives, we envisioned that our methodology could be applicable to the synthesis of polycyclic compounds by means of biomimetic cyclisations of linear terpene-derived substrates.

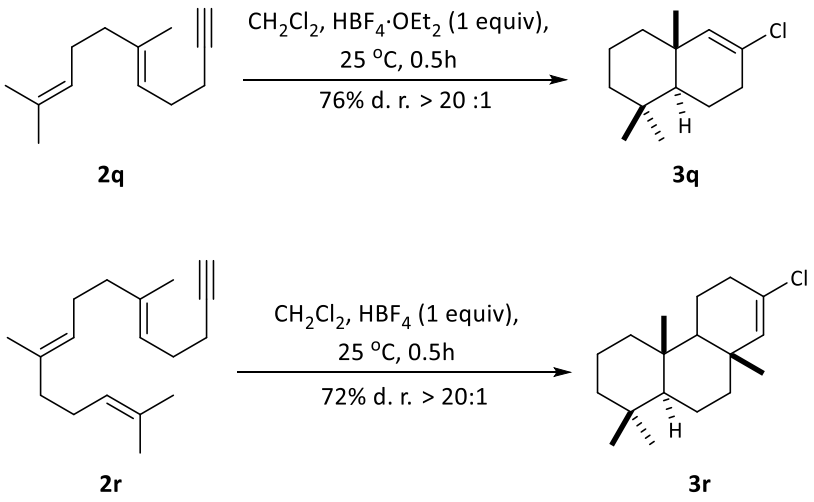
To get appropriate substrates to try these biomimetic cyclisation reactions, commercially available geraniol and *(E,E)*-farnesol were easily manipulated following known procedures as shown in **Scheme 1.11** to synthesise key enynes **2q** and **2r**.[46]



***Scheme 1.11**. Synthesis of polyenynes **2q** and **2r** from geraniol and (E,E)-farnesol.*

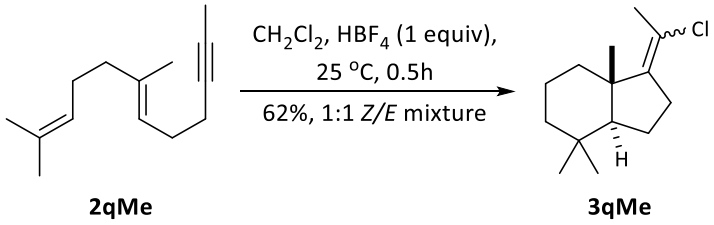
When substrates **2q,r** were reacted with 1 equivalent of tetrafluoroboric acid in dichloromethane at room temperature during 30 minutes, the clean formation of the corresponding bicyclic (**3q**) and tricyclic (**3r**) alkenyl chlorides was observed. Moreover, these products were isolated in high yield and basically as single diastereoisomers, as depicted in **Scheme 1.12**.

[46] The protocol for the installation of the alkyne moiety can be found in: a) J. L. Paz, J. A. R. J. Rodriges, *J. Braz. Chem. Soc.* **2003**, *14*, 975-981; b) V. Domingo, L. Lorenzo, J. F. Quilez del Moral, A. F. Barrero, *Org. Biomol. Chem.* **2013**, *11*, 559-562.



***Scheme 1.12**. Polyene biomimetic cyclisations developed for the synthesis of alkenyl chlorides.*

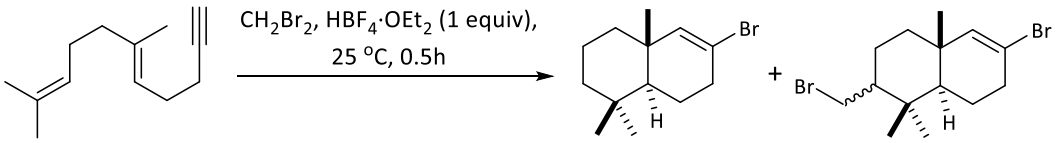
An interesting result was obtained from dienyne **2qMe** containing in its structure an internal alkyne and easily available from **2q** (**Scheme 1.13**). Thus, when **2qMe** was subjected to the same cyclisation conditions than those previously used for substrates **2q**,**r**, instead of the expected decaline derivative, we observed the formation of alkenyl chloride **3qMe** in 62% yield as a 1:1 mixture of *Z/E* isomers. This result is in agreement with our observations (see **Scheme 1.7**), since the use of internal alkynes normally leads to products resulting from a final *5-exo* type cyclisation. On the contrary, W. S. Johnson had observed a different behavior when activating a similar substrate at low temperatures, as shown in **Scheme 1.1**.



***Scheme 1.13**. Exo-cyclisation of substituted enynes.*

On the other hand, treatment of dienyne **2q** under general conditions for the synthesis of cyclohexenyl bromides afforded a mixture of the expected compound **4q** in a relatively low 56% yield and compound **4qMeBr** in 10% yield. Remarkably, the simple

addition of 2-methyl-2-butene (5 equiv) avoided the formation of **4qMeBr** and allowed the isolation of desired **4q** in 70% yield (see **Scheme 1.14**).



2q

	4q	**4qMeBr**
without additives	56%, d.r. > 20:1	10%, d.r. 1:1
with 5 equiv of 2-methyl-2-butene	70%, d.r. > 20:1	n. d.

***Scheme 1.14**. Biomimetic cyclisations for the synthesis of **4q**.*

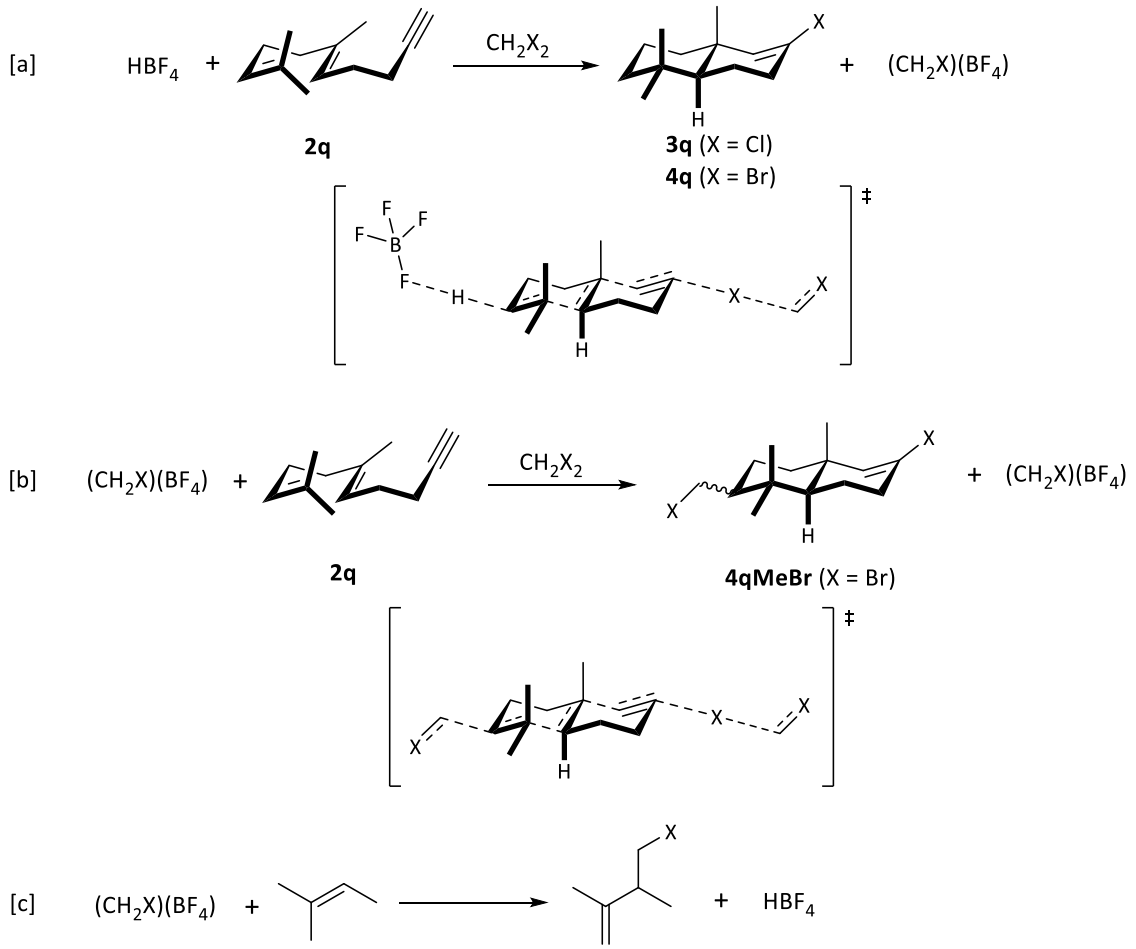
Finally, it should be noted that these biomimetic cyclisation reactions can be performed at large scale without problems. In this sense, 7.8 g of product **4q** was synthesised in one batch, without observing significant changes in yield or diastereoselectivity. Moreover, the compounds obtained through the biomimetic cyclisations here presented possess very interesting structural skeletons that are ubiquitous in many organic architectures, including a wide variety of natural products. In this context, the reaction of synthesis of **4q** from dienyne **2q** has been strategically used to develop a new method for the divergent synthesis of both enantiomers of 9-*epi*-Ambrox.[47]

In the next section, a brief discussion on the mechanism of the transformation will be done.

[47] a) Raquel Fontaneda López, PhD Thesis currently in preparation. b) R. Fontaneda, P. Alonso, F. J. Fañanás, F. Rodríguez, *Org*. *Lett*. **2016**, *18*, 4626-4629.

1.5 Some Mechanistic Considerations

The observations gathered in the last part of section **1.4** set some experimental basis on the mechanism operating in the halide abstraction process. Also, the diastereoselectivity of polyenyne cyclisations described in this chapter can be explained through a charlike folding of enynes **2q** and **2r** and antiparallel addition of carbenium ions and nucleophiles to olefins. In this regard, a mechanistic proposal is depicted in **Scheme 1.15**.



***Scheme 1.15**. Mechanistic proposal for the synthesis of **3q** and **4q**.*

A plausible transition state for the transformation of **2q** into **3q**/**4q** is depicted in equation [a] of **Scheme 1.15**. As shown, a chairlike folding of dienyne **2q** would explain the relative configuration of the substituents in product **3q**/**4q**. A concerted activation-cyclisation-termination process with charge delocalisation is proposed in agreement to

similar transition states proposed in the literature. Besides, formation of $(CH_2X)(BF_4)$ would lead to a variety of possible continuations. To explain the formation of product **4qMeBr**, dienyne **2q** would react with CH_2X^+ and a molecule of dibromomethane to generate another equivalent of CH_2X^+ (equation [b]). As shown in **Scheme 1.14**, our strategy to avoid the formation of the undesired by-product **4qMeBr** consisted in the addition of 2-methyl-2-butene as additive. Under these conditions, we think that the initially formed $(CH_2X)(BF_4)$ may react preferentially with this additive as shown in equation [c] of **Scheme 1.15**.

1.6 Summary

Summarising, three new reactions have been developed where different alkynols **1** or enynes **2** are activated by a Brønsted or Lewis acid to promote cationic carbocyclisations. As a novelty, terminal triple bonds have been used as terminating agents of the cyclisations, finding stabilisation through a halide abstraction from the solvent of the reaction. Thus, by simply making the appropriate choice of solvent, different cyclohexenyl halides **3**, **4** or **5** can be easily sinthesised in high yields. Remarkably, the use of terminal alkynes as intramolecular nucleophiles led exclusively to a *6-endo* type of cyclisation, since all compounds were obtained as single isomers.

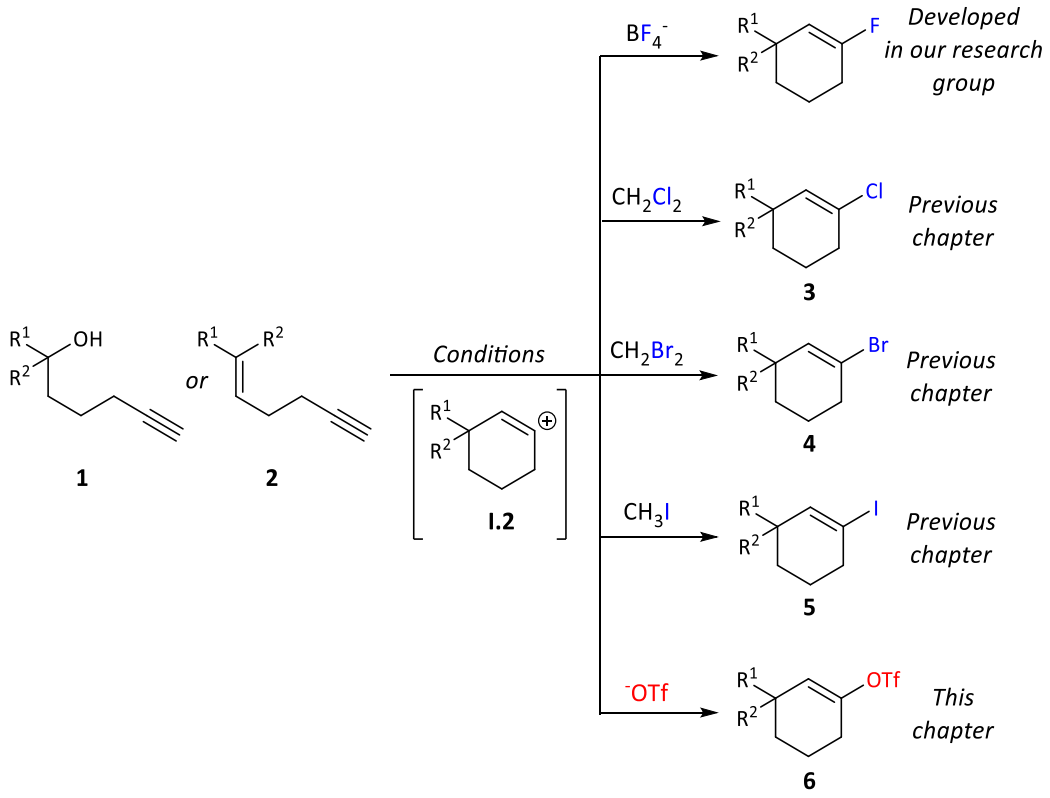
Moreover, the new conditions found for the above commented transformation were also extended to more complex substrates, enabling the development of some pioneering biomimetic cyclisations. Therefore, the virtues of this reaction allowed the synthesis of some interesting structures with huge potential in natural product synthesis.

Chapter 2

PART A

2.1 Introduction and Objectives

In the previous chapter, a new methodology for the synthesis of cyclohexenyl halides has been described. All these reactions imply the treatment of an alkynol or enyne derivative with tetrafluoroboric acid (HBF_4) to generate a cation that is intramolecularly trapped by the alkyne to generate a vinyl cation. Depending on the conditions, this cation can be trapped by a fluoride coming from the tetrafluoroborate (BF_4^-) anion or by a halogen (Cl, Br, I) coming from the solvent of the reaction.[48] In this context, we wondered if other products different from alkenyl halides could be obtained following the same strategy but using other protic acids different from HBF_4.

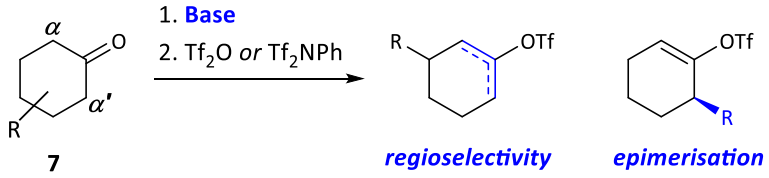


***Scheme 2.1**. Our proposal for the synthesis of cyclohexenyl triflates.*

[48] Our cationic carbocyclisation methodology for the synthesis of cyclic alkenyl fluorides is described in: a) Pilar Pardo Llamas, PhD Thesis, **2015**; b) P. Alonso, P. Pardo, F. J. Fañanás, F. Rodríguez, *Chem. Commun.* **2014**, *50*, 14364-14366.

More precisely, we thought that the treatment of alkynols **1** or enynes **2** with trifluoromethanesulfonic acid (HOTf) should induce the proton-promoted cyclisation of these starting materials to deliver the alkenyl cation **I.2** that in the absence of any other nucleophile could be trapped by the triflate anion to finally get interesting cyclic alkenyl triflates **6** (**Scheme 2.1**).

It is important to remark at this point that the most reliable strategy to access alkenyl triflates is the protocol developed by McMurry and Scott already disclosed in the previous chapter.[45a] This process involves the enolisation of a cyclic ketone **7** by treatment with a base (usually lithium amides), followed by trapping of the enolate with a triflating agent such as triflic anhydride or *N*,*N*-bis(trifluoromethanesulfonyl)aniline (**Scheme 2.2**). A limitation of this methology is the challenging distinction of α and α' positions of **7** when both positions are prone to enolisation. As a result of this, controlling the regioselectivity of the overall transformation is not trivial. Furthermore, the presence of a chiral center in α-position often results in a loss of optical purity due to undesired enolisation.



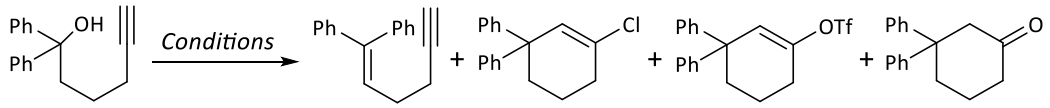
Scheme 2.2 *Problems often encountered with conventional synthesis of alkenyl triflates.*

It should be noted at this point that the feasibility of our proposal is far from trivial considering the existing studies reported by Y. Yamamoto and highlighted in chapter 1.[44] Y. Yamamoto developed a carbocyclisation methodology where alkenyl cation species similar to **I.2** were trapped by a molecule of water coming from the triflic acid-promoted initial dehydration of alkynols (see **Scheme 1.2** in section **1.1**). In this regard, this result reported by Y. Yamamoto suggest that water may outcompete triflate ions as nucleophiles. Nevertheless, in spite of the high tendency of this kind of systems to cyclise under acidic activation to yield cyclic ketones, we thought that if we succeeded with the porposed reaction, the methodology could challenge and complement McMurry's protocol to get cyclic alkenyl triflates. Therefore, we tested our hypothesis and the results are presented in the following sections.

2.2 Synthesis of Cyclohexenyl Triflates

2.2.1 Preliminary results

Initial experiments were performed with the model substrate **1a**. These results are gathered in **Table 2.1**:



1a **2a** **3a** **6a** **7a**

entry	solvent [M]	acid (x equiv)	T (°C)	time (h)	**2a** (%)	**3a** (%)	**6a** (%)	**7a** (%)
1	CH_2Cl_2 [0.1]	HOTf (1)	25	15	n. d.	72	10	n. d.
2	CH_3CN [0.1]	HOTf (1)	25	15	25	-	-	63
3	hexane [0.1]	HOTf (1)	25	8	43	-	49	n. d.
4	**hexane [0.1]**	**HOTf (1)**	**25**	**15**	**n. d.**	-	**98**	n. d.
5	hexane [0.1]	HOTf (1)	50	8	n. d.	-	82	n. d.
6	C_6F_6 [0.1]	HOTf (1)	25	15	n. d.	-	93	n. d.

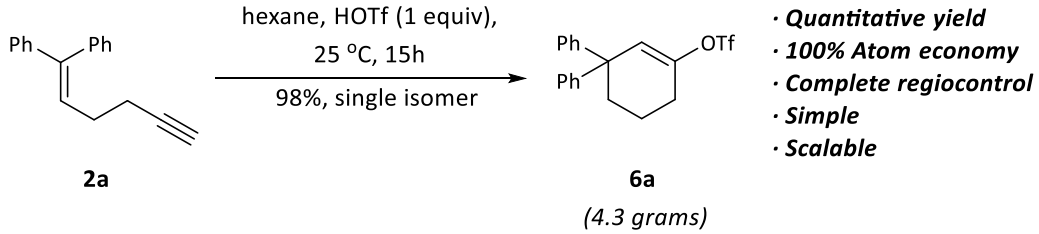
***Table 2.1**. Optimisation study for the synthesis of alkenyl triflate **6a**. Yields determined by NMR analysis of the crude. n. d. = not detected.*

Our confidence about the viability of our proposal to get alkenyl triflates came from our initial studies on the synthesis of alkenyl chlorides summarized in the previous chapter of this thesis. More precisely, when we were developing and optimising the reaction conditions (see Table **1.1** in section **1.2**) we observed that the treatment of alkynol **1a** with 1 equivalent of trifluoromethanesulfonic acid in dichloromethane afforded product **6a** in 4% yield after only 30 minutes of reaction at room temperature. When the same experiment was carried out with longer reaction times (15h, see entry 1 in **Table 2.1**) enyne **2a** was no longer detected and cyclic alkenyl triflate was obtained in 10% yield, bein alkenyl chloride **3a** the major product of the reaction. At this point, a screening of solvents seemed imperative, and therefore different solvents were tested. For example, when acetonitrile was used as solvent (entry 2 **Table 2.1**), enyne **2a** was formed in 25% yield, cyclic alkenyl chloride **3a** was not detected and a new compound identified as cyclohexanone **7a** was obtained in 63% yield (more attention will be paid to this experiment in part **B** of this chapter). Nevertheless, desired alkenyl triflate **6a** was not detected in acetonitrile.

As it will be discussed in detail in part B of this chapter, ketone **7a** is former through the reaction of cation **I.2**. (see **Scheme 1.2** in chapter 1) with a molecule of water

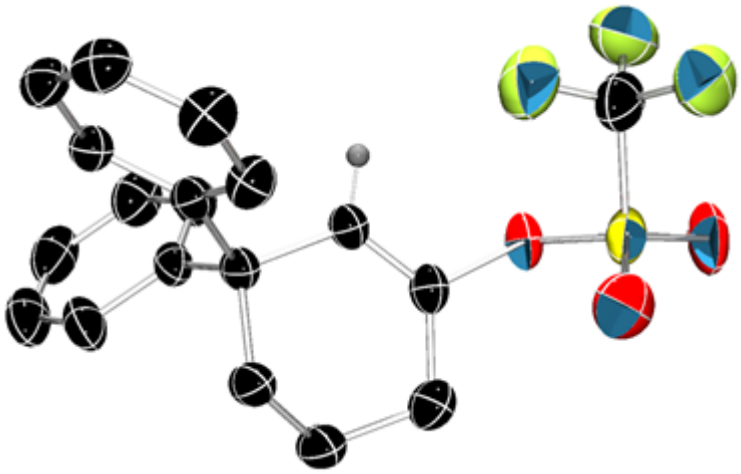
(formed in the initial dehydration step). Thus, our goal was to suppress the hydration of alkenyl cation **I.2**. In this sense, solvents in which the *in situ* formed water was as insoluble as possible would be ideal (*e. g.* alkanes). In fact, we found that alkynol **1a** reacted with one equivalent of HOTf in hexane at room temperature to give the desired triflate **6a** in 49% yield after 8 hours of reaction (entry 3 of **Table 2.1**). Along with this compound enyne **2a** was also isolated in 43% yield. To achieve complete consumption of enyne **2a**, the reaction time had to be extended to 15h. In this case, quantitative formation of **6a** was observed (entry 4). Increasing the temperature of the reaction to 50 °C resulted in complete conversion of the starting alkynol **1a** into the desired triflate **6a** in just 8 hours (entry 5). However, the yield of isolated product (82%) was slightly lower than in the case of the reaction performed at room temperature for 15h (entry 4). Finally, the use of hexafluorobenzene as solvent was suitable for the transformation, since 93% yield of compound **6a** was obtained after 15 hours of reaction at room temperature (entry 6).

Once we had demonstrated the viability of the transformation of alkynols **1** into cyclic alkenyl triflates **6**, we also attempted the synthesis of these products from enynes. In this regard, enyne derivative **2a** was reacted with one equivalent of triflic acid (HOTf) in hexane as solvent at room temperature for 15 hours. This operation afforded triflate **6a** in basically quantitative yield, since all reactants are converted into a unique final product, no by-products are formed and no additional catalysts or promoters are required for the transformation (100% atom economy). Moreover, the starting material is easily available, the final product does not require purification and the reaction is easy to scale up, since 4.3 grams of **6a** were synthesised in one single batch without problems. Finally, it should be noted that alkenyl triflate **6a** was obtained as a single regioisomer and isomerisation of the double bond was not observed.



2a **6a**

(4.3 grams)



***Scheme 2.3**. Our preliminary result. ORTEP representation of alkenyl triflate **6a**.*

At this point, the reader is reminded that this regiochemical control could not be achieved by following conventional methodologies. Indeed, when we attempted the synthesis of triflate **6a** from cyclohexanone **7a** following traditional protocols, we observed the formation of a mixture of the two expected regioisomers **6a** and **6a'** with the alkenyl triflate **6a** being the minor regioisomer (**6a**:**6a'** ratio = 1:20), as shown in **Scheme 1.6** in chapter 1. In this regard, this experiment shows how our new method to get cyclic alkenyl triflates can challenge and complement conventional strategies.

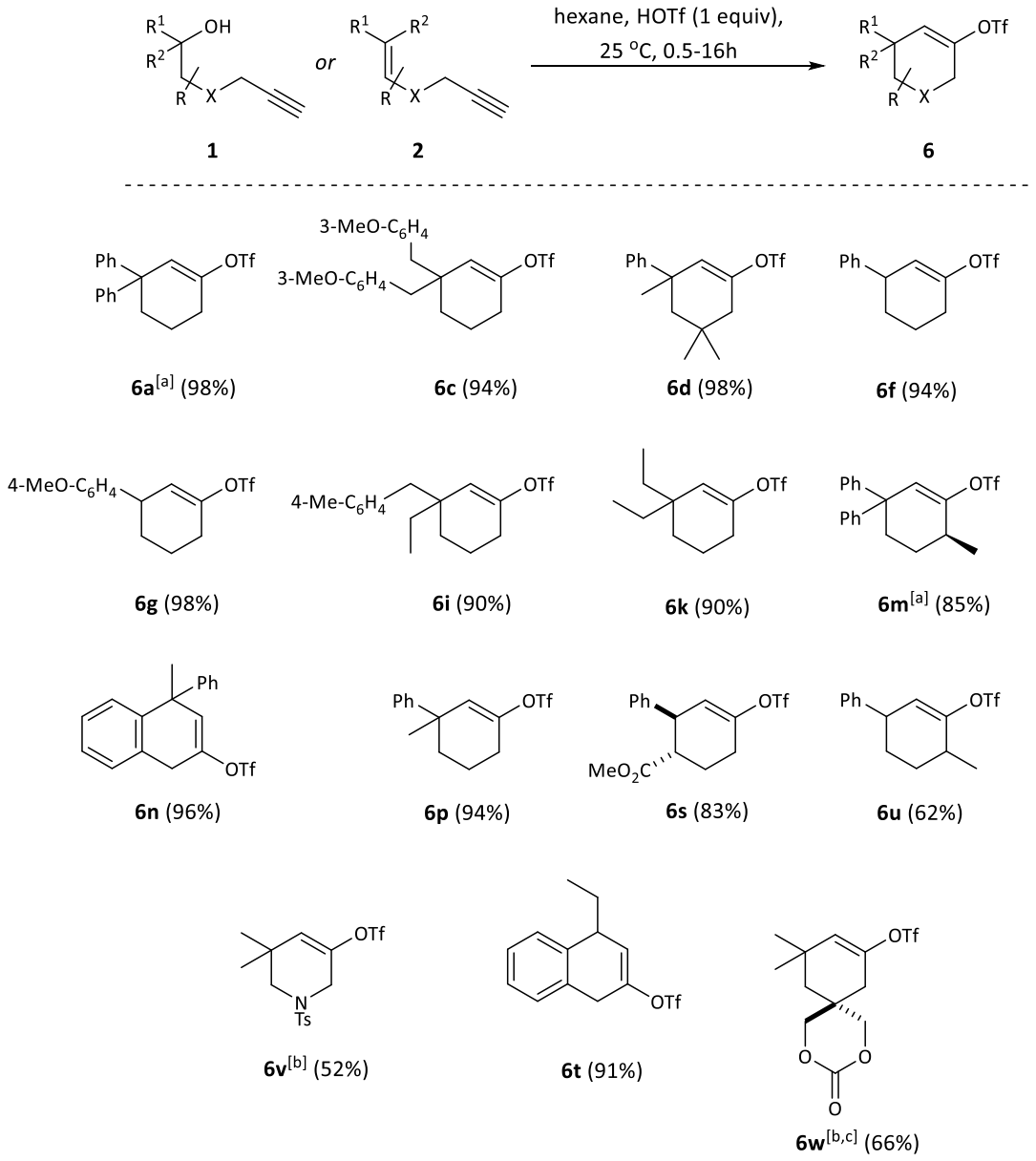
2.2.2 Scope of the Reaction

The scope of the cationic cyclisation reaction was surveyed by synthesising a series of cyclic alkenyl triflates **6**. The optimal conditions described in the previous sections were applied to a series of alkynols **1** and enynes **2**. These results are gathered in **Scheme 2.4**.

Optimal conditions could be successfully applied to the synthesis of a series of cyclic alkenyl triflates in good to excellent yields (52 – 98%) as shown in **Scheme 2.4**. Generally, cyclic alkenyl triflates **6** were synthesised from corresponding alkynols **1**. Besides, as previously demonstrated in the synthesis of **6a** from alkynol **1a** (**Table 2.1**, entry 4) or enyne **2a** (**Scheme 2.3**), no difference in terms of yield were observed when the reactions were performed from enynes **2**. Moreover, most of the products were obtained as single isomers.

Also, different substitution patterns were well tolerated, including tertiary (R^1, R^2 ≠ H, see **6a**) and secondary alcohols (R^2 = H, see **6f**). Following the general tendency described in the previous chapter, those substrates substituted with aromatic groups at

the R^1 and R^2 positions needed longer reaction times to be converted into the desired triflates (**6a,m**) (see footnote in **Scheme 2.4**).



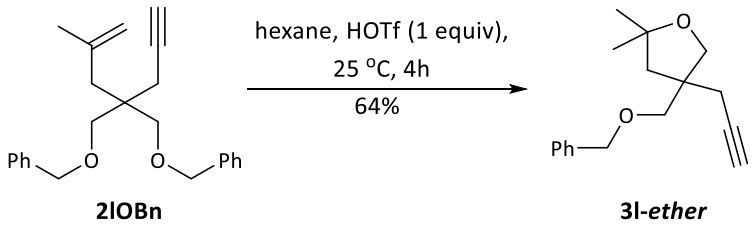
***Scheme 2.4**. Scope studied for the synthesis of cyclic alkenyl triflates. Ts = p-toulenesulfonyl. OTf = trifluoromethanesulfonate. [a][b]Reaction times 16 h for substrates **6a** and **3m**, 2 h for substrates **6v** and **6w** and 0.5 h for the rest of the substrates.*

*[c]Substrate **6w** was isolated as a 3:1 mixture of regioisomers. All products were synthesised from corresponding alkynols **1** except for **6v** and **6w**.*

Moreover, the method could be applied to the synthesis of the nitrogenated heterocycle **6v** (52% yield) and dihydronaphthalenes **6n** and **6t** in excellent yields.

Regarding the limitations, it should be noted that the reaction showed preference for a *6-endo* type of cyclisation only when terminal alkynes where used as terminating agents. Also, formation of corresponding enynes **2** was observed when 4-pentyn-1-ol or 6-hexyn-1-ol derivatives were tested under reaction conditions.

Also, oxygenated functionalities are well tolerated as long as they cannot compete with the acetylene as a nucleophile, either because they are not in an appropppriate position to trap the carbenium ion (see **6s**) or because they are being blocked by a suitable protecting group. Therefore, enyne **2w** possessing a carbonate functionality led to the formation of **6w** in good yield (66%), but benzyl ether **2lOBn** failed to be converted into the expected cyclic alkenyl triflate. Instead, product **3l-*ether*** was isolated in 64% yield, as shown below in **Scheme 2.5**:

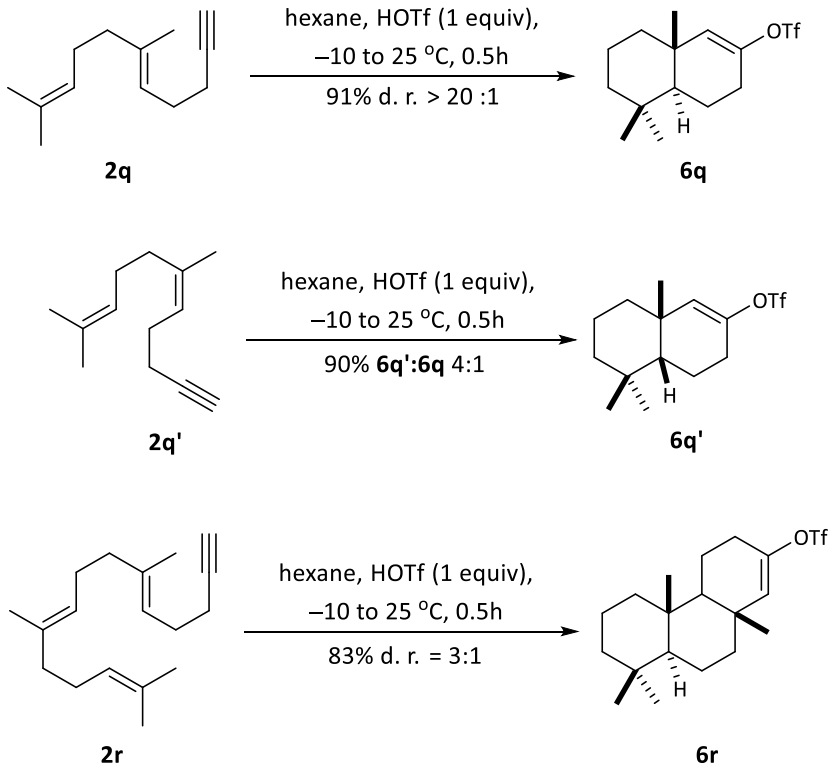


2lOBn **3l-*ether***

***Scheme 2.5**. Reactivity of benzyl ethers under optimised conditions.*

2.3 Biomimetic Carbocyclisations: Synthesis of Polycyclic Alkenyl Triflates

Considering the positive results obtained in our previous studies on biomimetic cyclisation reactions of polyenyne derivatives for the synthesis of polycyclic alkenyl halides (see section **1.4**), we thought that interesting triflates could also be obtained following a similar strategy. Therefore, enynes **2q**,**q'**,**r** were synthesised respectively from geraniol, nerol and (*E*,*E*)-farnesol as shown in **Scheme 1.11** and were tested under the optimal conditions. It should be noted that for a better control of the stereochemistry of the cascade cyclisations, addition of trifluoromethanesulfonic acid was done portionwise at –10 °C and the reaction was subsequently stirred at room temperature for 30 minutes. The results obtained are depicted in **Scheme 2.6**.



***Scheme 2.6**. Biomimetic cyclisations performed with polyenyne substrates.*

Thus, geraniol-derived dienyne **2q** was cleanly transformed into decalin **6q** in 91% yield. Remakably, compound **6q** was obtained as a single diastereoisomer. On the other hand, compound **6q'** was obtained in excellent yield (90%) as a 4:1 mixture of diastereoisomers from nerol-derived dienyne **2q'**. Finally, we also achieved the more

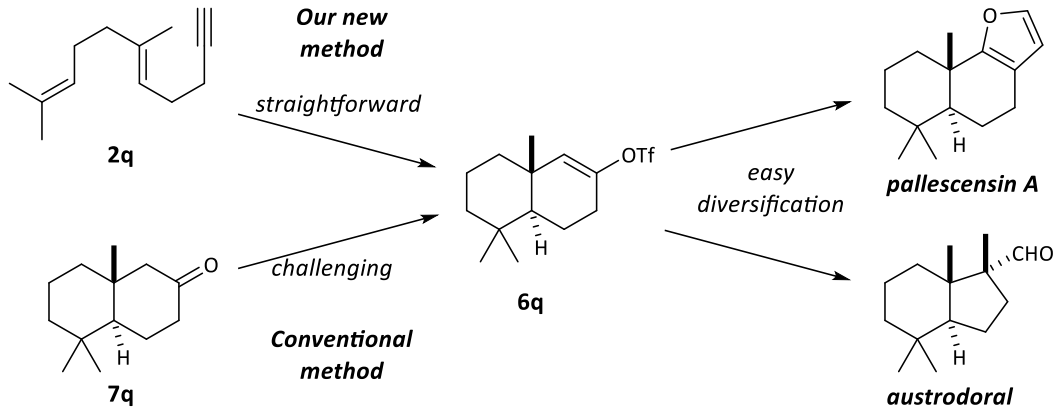
challenging transformation of trienyne **2r** derived from farnesol. To our delight, tricyclic triflate **6r** was synthesised in 83% yield as shown in **Scheme 2.6**.

At this point, the high atom economy of these transformations should be noted, since no additives were needed and the mass of products **6q,q',r** is the sum of the mass of the corresponding enyne **2q,q',r** and trifluoromethanesulfonic acid (HOTf). It is also important to remark that these reactions can be performed at gram-scale. In fact, product **6q** was easily synthesised in multigram scale (4.1 grams) in one single batch.

To the best of our knowledge there are no precedents in the literature about cationic biomimetic cylisation reactions applied to the synthesis of alkenyl triflates. Considering the interesting structural features of these compounds, we thought that they could be used for the synthesis of some products of interest. Hence, in the next section, some natural product syntheses are described, in which the core of the target molecule is built by means of a biomimetic cationic polycyclisation reaction.

2.4 Total Synthesis of *(±)*-Pallescensin A and *(±)*-Austrodoral

To demonstrate the potential applicability of our methodology in the total synthesis of natural products, we selected pallescensin A and austrodoral as synthetic targets. In this sense, we thought that these two natural products could be obtained from the common intermediate **6q**. As previously mentioned, this alkenyl triflate **6q** is easily available at multigram scale from geraniol-derived dienyne **2q** following our cationic biomimetic cyclisation reaction with trifluoromethanesulfonic acid (see **Scheme 2.6**).

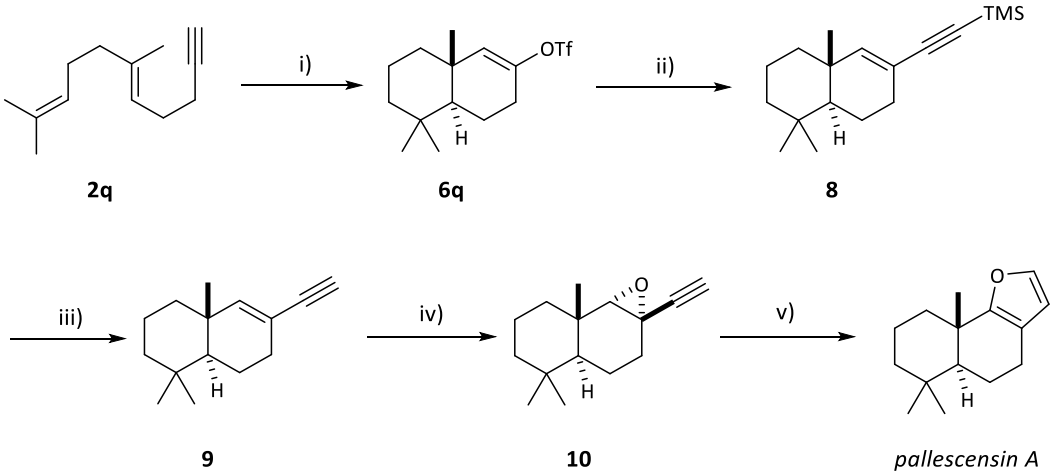


***Scheme 2.7**. Our divergent synthethic approach.*

At this point, it should be noted that the selective synthesis of **6q** from ketone **7q** following McMurry's method would be a difficult task because formation of the undesired regioisomer (unselective enolization) would be favoured. On the contrary, selective synthesis of **6q** at multigram scale from dienyne **2q** is straightforward, as shown in **Scheme 2.7**.

Thus, our synthesis of pallescensin A from dienyne **2q** (available from cheap geraniol in 70% yield) is depicted in **Scheme 2.8**. More precisely, treatment of dienyne **2q** with trifluoromethanesulfonic acid (1 equiv) in hexane yields **6q**. The crude obtained in the triflic acid promoted carbocyclisation is submitted to a Sonogashira-like coupling with trimethylsilylacetylene. A simple filtration with a plug of silica gel is enough to obtain enyne **8** in analytically pure form. Crude enyne **8** is refluxed in MeOH in the presence of potassium fluoride to remove the TMS-group and obtain terminal acetylene **9** that was used in the following step without purification. Selective epoxidation of enyne **9** with *m*-chloroperoxybenzoic acid, led to oxirane **10**. Finally, pallescensin A was obtained through a modification of Pale's protocol to synthesise furans from propargylic oxiranes by gold-

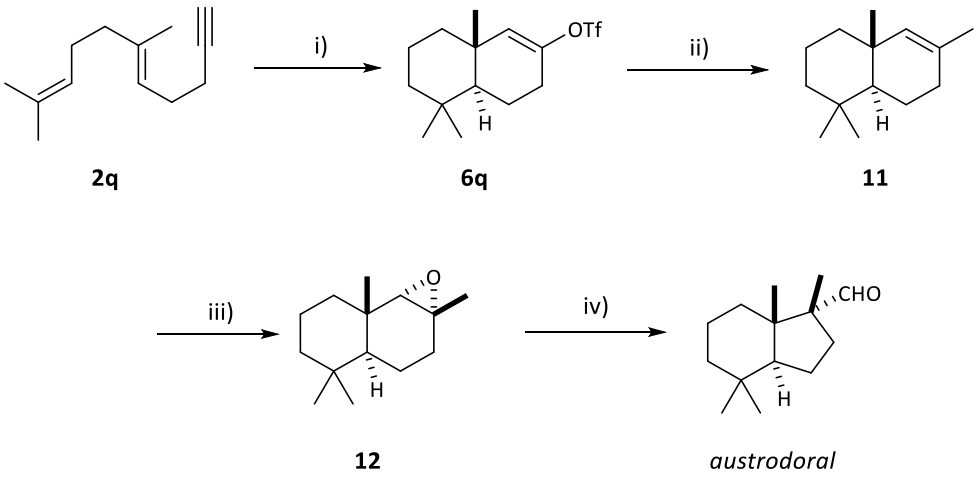
catalysis (**Scheme 2.8**).[49] More precisely, treatment of crude oxirane **10** with catalytic amounts of methanol (20 mol%), chloro(triphenylphosphine)gold (I) (5 mol%) and silver trifluoromethanesulfonate (5 mol%) in dichloromethane, at room temperature over 12 hours led to the construction of the furan moiety in good yield. Remarkably, pallescensin A (1.1 grams) was synthesised in 40% global yield from dienyne **2q** with just one final chromatographic purification.



***Scheme 2.8**. Synthesis of pallescensin A from dienyne **2q**. Reagents and conditions: i) hexane, HOTf (1 equiv), -10 to 25 °C, 0.5h. ii) diethyl ether, trimethylsilylacetylene (1 equiv), [Pd(PPh$_3$)$_2$Cl$_2$] (5 mol%), CuI (10 mol%), Et$_2$NH (5 equiv), 25 °C, 3h. iii) MeOH, KF (1.3 equiv), reflux, 15h. iv) CH$_2$Cl$_2$, m-CPBA (1.3 equiv), 25 °C, 2h. v) CH$_2$Cl$_2$, MeOH (20 mol%), [Au(PPh$_3$)Cl] (5 mol%), AgOTf (5 mol%), 25 °C, 12h.*

For the synthesis of austrodoral, crude alkenyl triflate **6q** obtained from dienyne **2q** in the same way than previously commented in the synthesis of pallescensin A, was methylated by means of an iron catalysed cross coupling reaction developed by Fürstner and coworkers, employing methylmagnesium bromide as coupling partner.[50] Thus, trisubstituted alkene **11** was obtained and used in the next step after a simple filtration through a plug of silica. Alkene **11** was treated with *m*-chloroperoxybenzoic acid to obtain epoxide **12** as a single diastereoisomer. Again, this epoxide was used in the next step without further purification. Finally, a BF_3-catalysed Meinwald rearrangement of **12** afforded austrodoral, as a single isomer (**Scheme 2.9**). It should be noted that only one final chromatographic purification was necessary to isolate austrodoral (1.2 grams), in 50% yield from dienyne **2q**.

[49] A. Blanc, K. Tenbrick, J.-M. Weibel, P. Pale, *J. Org. Chem.* **2009**, *74*, 5342-5348.
[50] B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943-3949.



***Scheme 2.9**. Synthesis of austrodoral from dienyne **2q**. Reagents and conditions: i) hexane, HOTf (1 equiv), -10 to 25 °C, 0.5h. ii) THF, N-methylpyrrolidinone, CH_3MgBr (3 equiv), $[Fe(acac)_3]$ (5 mol%), 25 °C, 12h. iii) CH_2Cl_2, m-CPBA (1.3 equiv), 25 °C, 2h. iv) CH_2Cl_2, $BF_3{\cdot}OEt_2$ (5 mol%), 25 °C, 0.5h.*

Summarising, austrodoral and pallescensin A were easily synthesised from geraniol in a few steps, in multigram scale and with only one chromatographic purification for each natural product. These syntheses demonstrate the utility of alkenyl triflates obtained by our biomimetic cationic cyclisations reactions in the context of synthesis of natural products.

PART B

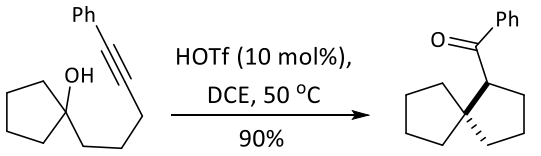
2.5 Introduction and Objectives

Continuing with our quest to extend our carbocyclisation methodology to the synthesis of interesting compounds, we turned our attention to the reaction described in 2009 by Yoshinori Yamamoto previously shown in chapter 1 of this thesis.[44] In this work, Yamamoto and coworkers described a cationic cyclisation of alkynols substituted at the alkyne by an aryl group. Treatment of these substrates with catalytic amounts of trifluoromethanesulfonic acid led to the formation of cyclopentyl ketones.

Surprisingly, in this work there are not examples of reactions performed with terminal alkynes. In our previous studies on the synthesis of cyclic alkenyl halides and triflates we had observed a marked difference between the reactivity terminal alkynes and that of internal ones. More precisely, we have observed that the cationic cyclisation with terminal alkynes always occurred through the terminal carbon of the triple bond. In this way, when 5-hexyn-1-ol derivatives containing a terminal alkyne were used as starting materials we always observed the formation of six-membered cyclic alkenyl halides (or triflates). These products are formed through a formal 6-*endo* cyclisation process. However, when we used 5-hexyn-1-ol derivatives containing an internal alkyne, we observed the formation of 5-membered cyclic products derived from the cyclisation through the internal carbon of the alkyne (5-*exo* cyclisation). In this regard, we wondered whether it would be possible to design a catalytic system that triggered the transformation of terminal alkynols and enynes into cyclohexanones. This reaction would complement that reaction developed by Y. Yamamoto for the synthesis of cyclopentyl ketones.

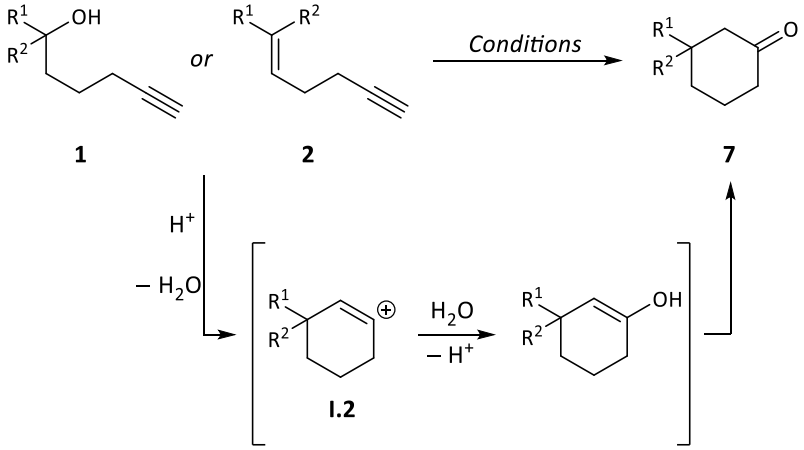
This initial idea is depicted in **Scheme 2.10**. Our proposal would imply to find conditions to avoid the trapping of cationic intermediate **I.2** by any nucleophile different from water. Nevertheless, this apparently simple task represents a synthetic challenge of significant magnitude, given the prominent tendency of halogenated solvents and triflate or tetrafluoroborate ions to trap intermediate **I.2**.

Yamamoto's work:



15 examples

Our proposal:



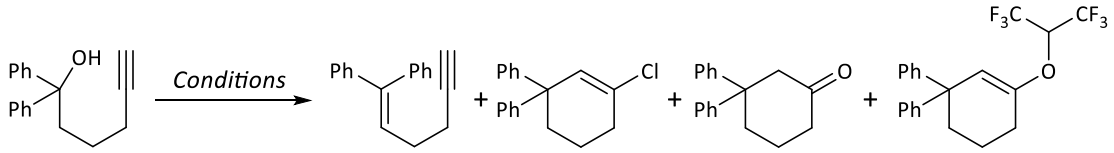
***Scheme 2.10**. Our proposal for the synthesis of cyclohexanones.*

In the next section, the optimisation study done to find the appropriate conditions for the transformation above commented will be disclosed.

2.6 Synthesis of Cyclohexanones

2.6.1 Optimisation Study

In order to evaluate the viability of the proposal, alkynol **1a** was chosen as model substrate and different conditions were tested to optimise the process (**Table 2.2**).



1a **2a** **3a** **7a** **13a**

entry	Solvent [M]	acid (x equiv)	T (°C)	time (h)	**2a** (%)	**3a** (%)	**7a** (%)	**13a** (%)
[a]1	CH_2Cl_2 [0.1]	HOTf (1)	25	15	n. d.	72	n. d.	-
2	CH_3CN [0.1]	HOTf (1)	25	20	19	-	60	-
3	CH_3CN [0.1]	$HBF_4{\cdot}OEt_2$ (1)	25	20	36	-	57	-
4	CH_3CN [0.1]	$HBF_4{\cdot}OEt_2$ (1)	25	48	20	-	72	-
5	CH_3CN [0.1]	$HBF_4{\cdot}OEt_2$ (1.3)	25	16	25	-	58	-
6	CH_3CN [0.1]	$HBF_4{\cdot}OEt_2$ (1)	80	15	16	-	73	-
[b]7	CH_3CN [0.1]	$HBF_4{\cdot}OEt_2$ (1)	80	15	53	-	34	-
8	CH_3CN [0.1]	$HBF_4{\cdot}OEt_2$ (1)	80	24	12	-	78	-
9	TFE [0.1]	$HBF_4{\cdot}OEt_2$ (1)	25	4	n. d.	-	80	-
10	HFIP [0.1]	$HBF_4{\cdot}OEt_2$ (1)	25	0.33	n. d.	-	80	n. d.
11	TFE [0.1]	$HBF_4{\cdot}OEt_2$ (0.2)	25	0.5	22	-	72	-
12	HFIP [0.1]	$HBF_4{\cdot}OEt_2$ (0.2)	25	0.5	n. d.	-	85	n. d.
13	**HFIP [0.1]**	**$HBF_4{\cdot}OEt_2$ (0.05)**	**25**	**0.5**	**n. d.**	**-**	**92**	**n. d.**
14	HFIP [0.1]	$Ca(NTf_2)_2$ (0.05)	25	15	n. d.	-	n. d.	75
15	HFIP [0.1]	$Ca(NTf_2)(PF_6)$ (0.05)	25	0.5	n. d.	-	86	n. d.

***Table 2.2**. Optimisation studies for the synthesis of **7a**. [a]10% of alkenyl triflate **6a** was also obtained. [b]1 equivalent of water was added. Yields determined by NMR analysis of the crude. n. d. = not detected. HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol. TFE = 2,2,2-trifluoroethan-1-ol.*

The initial conditions tested are similar to those reported by Y. Yamamoto for the synthesis of cyclopentyl ketones. Thus, alkynol **1a** was reacted with one equivalent of trifluoromethanesulfonic acid (HOTf) in dichloromethane as solvent at room temperature for 15 hours (**Table 2.2** entry 1). Under these conditions, we observed the formation of cyclohexenyl chloride **3a** in 72% yield along with corresponding alkenyl triflate **6a**. Formation of these two products is easily explained by the mechanisms commented in

previous sections of this thesis. From this initial experiment we concluded that those conditions used by Y. Yamamoto to synthesise cyclopentyl ketone were not appropriate in our case with the use of alkynols **1** decorated with terminal alkynes. Also, considering this initial experiment where the solvent (dichloromethane) acted as source of chloride to trap intermediate **I.2** (see **Scheme 1.2**), it seems obvious that a change of solvent was required to synthesised the desired cyclohexanones **7**.

Interestingly, employment of acetonitrile as solvent allowed the synthesis of ketone **7a** when alkynol **1a** was treated with 1 equivalent of trifluoromethanesulfonic acid at room temperature for 20 hours (entry 2). However, under these conditions we also isolated enyne **2a** in 19% yield. It should also be noted that the analysis of the crude of this reaction showed that other unidentified products were also formed. In order to avoid the formation these by-products, the reaction was tried with other acids. More precisely, when we performed the reaction with $HBF_4{\cdot}OEt_2$ instead of HOTf under similar conditions in acetonitrile as solvent (entry 3), we observed the formation of ketone **7a** in basically the same yield than before (57%). This reaction was much cleaner than the previous reaction with HOTf and the only by-product observed was enyne **2a** (36% yield). Longer reaction times (entry 4), the use of an excess of acid (entry 5), increasing the temperature (entries 6 and 8) or addition of 1 equivalent of water (entry 7), did not lead to a substantial improvement in terms of efficiency.

Nevertheless, a dramatic change in reactivity was observed when the solvent was changed from acetonitrile to 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) or 2,2,2-trifluoroethan-1-ol (TFE) (entries 9 and 10). In these cases, we observed the complete consumption of alkynol **1a** and enyne **2a** in 4 hours in the case of TFE or 20 minutes in the case of HFIP. These results strongly called for a catalytic turnover study of the reaction.

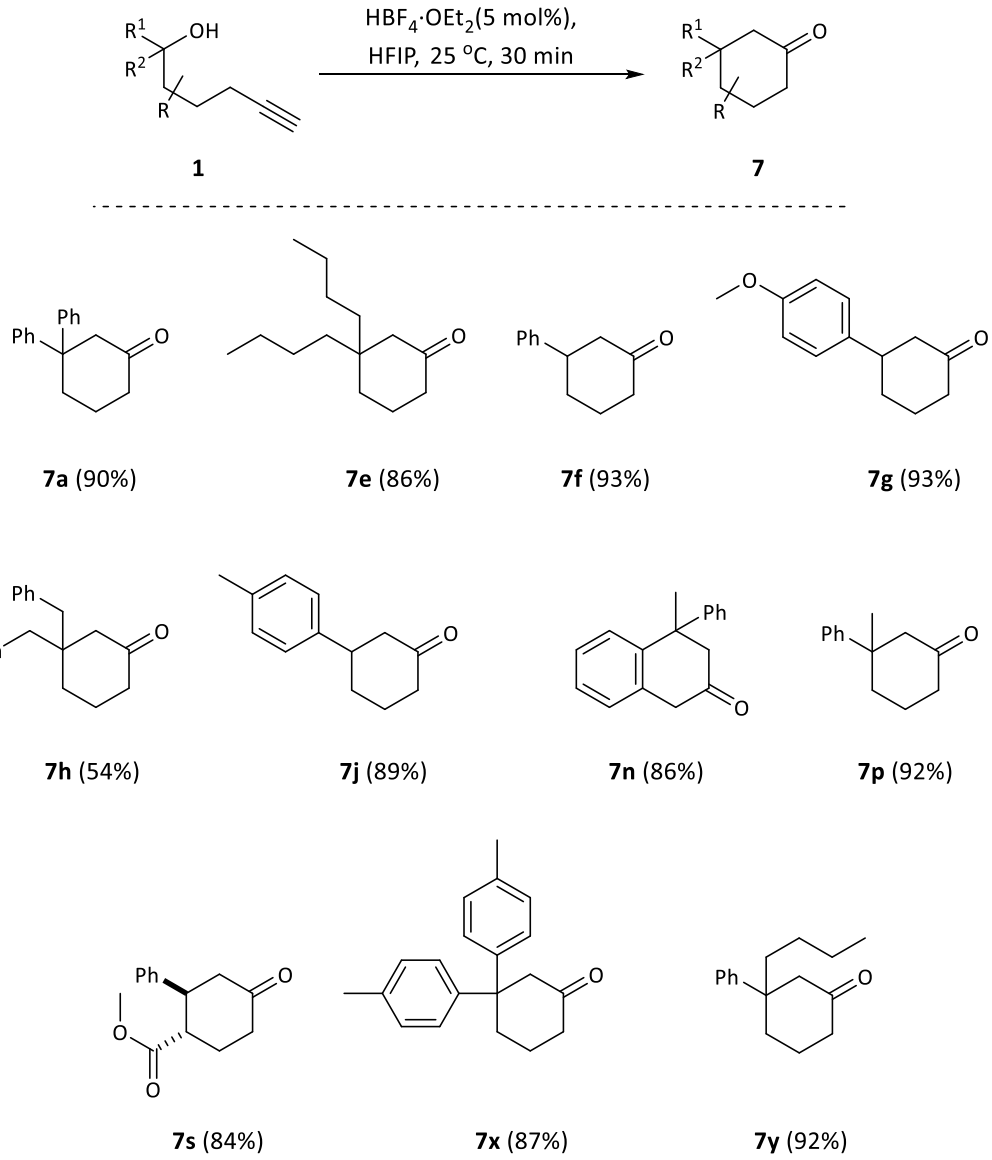
In this regard, treatment of alkynol **1a** with substoichiometric amounts of tetrafluoroboric acid afforded high yields for ketone **7a**. However, only when HFIP was used as solvent complete conversion of enyne **2a** was observed (entries 11 and 12). Notably, the yield of product **7a** increased from 80% to 85% when catalytic amounts of acid were used in HFIP (entries 10 and 12). Lowering the catalyst loading to 5 mol% enabled the synthesis of **7a** in basically quantitative yield in only 30 min of reaction at room temperature (entry 13).

Finally, other Lewis acids were tested to check whether the outstanding reactivity shown in HFIP was observed with different catalysts than tetrafluoroboric acid. Noteworthy, Calcium salts performed very well as promoters of the cationic cyclisation of alkynol **1a** (entries 14 and 15). Indeed, a subtle change in the counterion of Calcium salts afforded either ketone **7a** or enol ether **13a** (that comes from the trapping of intermediate **I.2** depicted in **Scheme 2.10** by the solvent of the reaction) in high yields. Anyway, a

slightly higher yield was obtained when using tetrafluoroboric acid instead of $Ca(NTf_2)(PF_6)$. Consequently, those conditions highlighted in entry 13 were taken as optimal to promote the transformation.

2.6.2 Reaction Scope

Having found optimal conditions for the catalytic carbocyclisation of 5-hexyn-1-ols to cyclohexanones, we next explored the scope of the transformation by testing a variety of substrates. These results are gathered in **Scheme 2.11**.



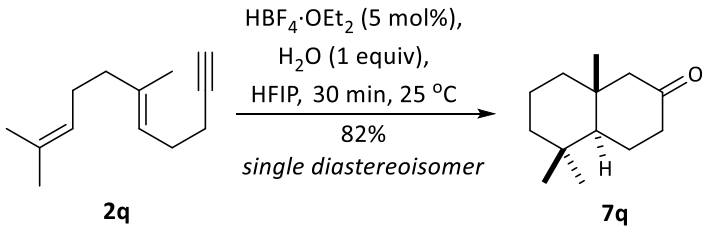
***Scheme 2.11**. Scope studied for the HBF_4 catalysed synthesis of compounds **7**.*

The catalytic protocol for the synthesis of cyclohexanones proved general since it allowed the synthesis of a variety of compounds with different substitution patterns. Remarkably, the mild acidic conditions triggered high reactivity in all cases, since complete conversions were observed in all cases after stirring for 30 min at room temperature. Moreover, high yields were obtained regardless of the employment of tertiary ($R^2 \neq H$) or secondary ($R^2 = H$) alkynols (e.g. see compounds **7a** and **7f**).

Despite of this outstanding reactivity, complete stereocontrol in the cyclisation was observed in all cases, since only products derived from *6-endo* ring closure were observed. Internal alkynes, however, followed the trend described in previous sections to yield cyclopentyl ketones, which is in good agreement with the results reported by Y. Yamamoto. In addition, certain functionalities that are sensitive to acidic conditions were perfectly compatible with the reaction conditions as demonstrated in the synthesis of cyclohexanone **7s**.

2.7 Catalytic Biomimetic Carbocyclisations: Synthesis of Polycyclic Ketones

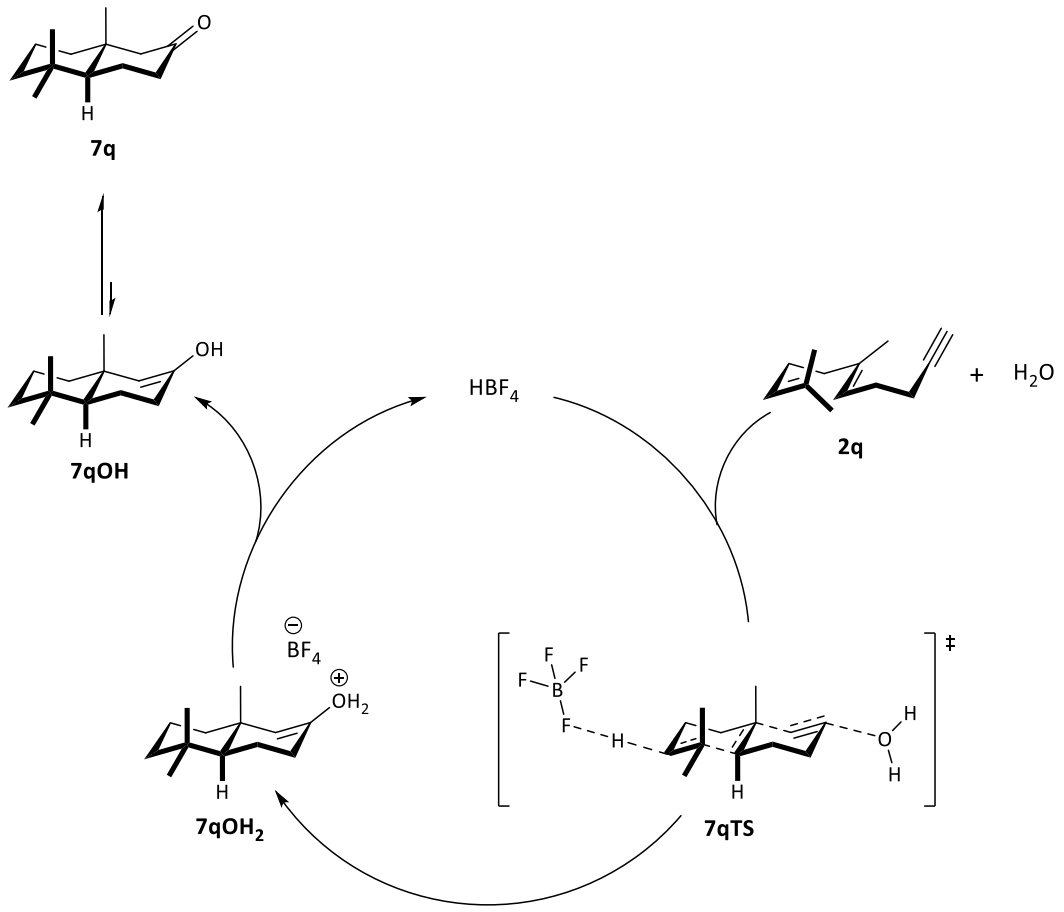
Next, we tried to extent the scope of the above commented synthesis of cyclohexanones to related biomimetic polycyclisations. It should be noted that in contrast to the cyclisation of alkynols where a molecule of water is delivered, the cyclisation of dienynes such as **2q** (**Scheme 2.12**) would require the addition of one equivalent of water, to be transformed into the desired ketone **7**.



***Scheme 2.12**. Biomimetic catalytic cyclisations of dienyne **2q** for the synthesis of **7q**.*

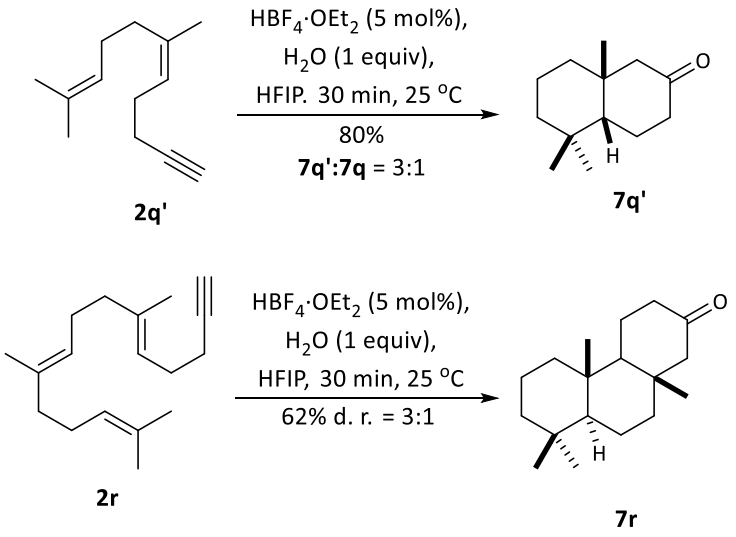
In this context, when geraniol-derived dienyne **2q** was treated with 5 mol% of tetrafluoroboric acid and 1 equivalent of water in HFIP at room temperature for 30 min, cyclohexanone **7q** was obtained as a single diastereoisomer in an excellent 82% yield. Interestingly, this reaction could be performed at large scale. In fact, the yield and diastereoselectivity of the process did not change when the transformation was performed at multigram-scale, synthesising 1.5 grams of **7q** in one single batch. For a better understanding of the formation of bycyclic ketone **7q** and subsequently all ketones shown in this section, a plausible mechanism is shown in **Scheme 2.13**.

An interaction between a molecule of HBF_4, dienyne **2q** and H_2O is proposed as the first step of the mechanism. The stereochemistry of compound **7q** can be explained through a charlike folding of dienyne **2q**, that suffers antiparallel addition through transition state **7qTS**, where concerted activation of olefin by HBF_4 and nucleophilic attack of a molecule of water is mandatory in order to propose a delocalisation of positive charge all over the system. This transition state leads to the formation of cationic intermediate **7qOH$_2$**. This intermediate would evolve through proton loss to yield enol **7qOH** and HBF_4 that would enter another catalytic cycle. Finally, enol **7qOH** undergoes ketoenolic tautomerisation to final product **7q** (see **Scheme 2.13**).



***Scheme 2.13**. Plausible mechanism for the formation of **7q**.*

Next, we tried the biomimetic cationic cyclisation with other polyenynes (**Scheme 2.14**). For example, nerol-derived dienyne **2q'** was reacted under identical to those previously used for geraniol-derived **2q** and as expected, decalone **7q'** was obtained in high yield (80%) as a 3:1 mixture of diastereoisomers (**7q':7q** ratio 3:1). Similarly, the more challenging substrate (*E,*E)-farnesol-derived trienyne **2r** was also smoothly transformed into the tricyclic ketone **7r** under the same reaction conditions. In this case, **7r** was obtained in 62% yield as a 3:1 mixture of diastereoisomers. These results are depicted in **Scheme 2.14**.



***Scheme 2.14**. Catalytic cationic carbocyclisations of **2q'** and **2r** into ketones **7q'** and **7r**.*

2.8 Summary

In part A of this chapter, a new triflic acid promoted carbocyclisation to synthesise cyclic alkenyl triflates has been developed. This new transformation was proved useful to access to a small library of compounds. Remarkably, the high yields generally obtained as well as the discrimination to produce most of the products as single isomers demonstrate the efficiency of this reaction. These good initial results were also found when this protocol was applied to polyene substrates. In this case, a cascade process was triggered by triflic acid, promoting the formation of several C-C bonds. The unique features of these polycyclic compounds make them very interesting synthetic intermediates in the synthesis of natural products, as exemplified in the total synthesis of pallescensin A and austrodoral.

Moreover, analising the results of this chapter, the synthetic utility of the protocol described should be remarked. Our methodology overcomes some of the difficulties encountered by conventional protocols in which synthetic chemists have trust for more than 30 years. Nevertheless, discrimination between α and α' positions in the enolisation of ketones is a classic problem in organic chemistry. In this regard, the results gathered in this chapter represent a humble contribution to the field.

In part B, a new tetrafluoroboric acid catalysed cationic carbocyclisation to synthesise cycliclohexanone skeletons has been developed. This methodology was successfully applied to a variety of alkynols to study the scope of the transformation, thus enabling the synthesis of a library of compounds. Exclusive *6-endo* cyclisation was observed when terminal triple bonds were used as nucleophiles in the cyclisation as opposed to those results published by Y. Yamamoto with internal alkynes. Noteworthy, a series of biomimetic cyclisations are also described, were the addition of one equivalent of water is key to achieve catalytic turnover. In this context, results gathered in section **3.4** represent a rare example of a polyene cationic cyclisation promoted by catalytic amounts of a Brønsted acid.

Finally, a plausible catalytic cycle is proposed to account for the formation of cyclohexanone derivatives **7**. The high diastereoselectivity observed for product **7q** could be explained through a charlike folding of corresponding polyenynes that lead to the final products observed through a concerted transition state with charge delocalisation.

Conclusions

The reactivity of unsubstituted 1,5-alkynols and 1,5-enynes towards cationic carbocyclisation reactions upon acid activation has been studied and new interesting behaviours of these systems have been found. In general terms, the use of a terminal triple bond as the nucleophile in cationic carbocyclisations resulted in exclusive *6-endo-dig* type of cyclisations, leading to a highly stereoselective processes regarding the stereochemistry of the resulting alkene moiety.

In chapter 1, the synthesis of cyclohexenyl halides is described. Noteworthy, the halide is incorporated through halide abstraction of the solvent. Therefore, the synthesis of cyclohexenyl chlorides, bromides or iodides is performed in a straightforward manner by simply changing the solvent of the reaction.

Besides, cyclic alkenyl triflate derivatives have been easily synthesised by this method as well. In this case, use of a non-nucleophilic solvent was key to enable the capture of the key cationic intermediate of the carbocyclisation by the triflate ion. This resulted in the stereoselective synthesis of cyclic alkenyl triflates by means of a highly efficient synthetic operation. The results obtained in this study are gathered in part A of chapter 2.

In part B of chapter 2, a new process for the synthesis of cyclohexanones by means of a catalytic carbocyclisation of alkynols is described. In this case, use of 1,1,1,3,3,3-hexafluoroisopropanol as the solvent of the reaction was key in order to achieve catalytic turnover of the acid employed to promote the transformation.

Finally, all of the above-mentioned reactions have also been applied to cascade transformations of a series of polyenynes. The virtues regarding the efficiency of our methodology were also encountered in the polycyclisations explored. In fact, as demonstrated in chapter 2, this polyenyne carbocyclisations are of wide applicability in the synthesis of natural products. It has been demonstrated that they represent useful tools for the selective synthesis of valuable intermediates that can be manipulated in a straightforward manner for the installation of different functionalities.

Conclusiones

La reactividad de 1,5-alquinoles y 1,5-eninos en el contexto de reacciones de carbociclación catiónica promovidas por ácidos de Brønsted y Lewis ha sido estudiada y consecuentemente se ha encontrado un comportamiento de los citados sistemas sin precedentes en la bibliografía. En términos generales, el uso de un triple enlace terminal como nucleófilo en carbociclaciones cationicas resultó en ciclaciones *6-endo-dig* dando lugar a procesos altamente estereoselectivos en lo que se refiere a la estereoquímica de la olefina resultante.

En el capítulo 1 de esta tesis, se describe la síntesis de halogenuros de ciclohexenilo. Como hecho destacable de esta transformación, el halogenuro se incorpora a la molécula final a través de un proceso de abstracción de halógeno al disolvente. De este modo, la síntesis de cloruros, bromuros o yoduros de ciclohexenilo se ha llevado a cabo simplemente cambiando el disolvente de la reacción.

Además, esta metodología ha sido aplicada en la síntesis de triflatos de ciclohexenilo. En este caso, el empleo de un disolvente no nucleofílico fue clave para permitir que la captura del catión vinilo intermedio por parte de un anión triflato. Esto resulto en la síntesis estereoselectiva de triflates de ciclohexenilo a través de una operación sintética muy eficiente. Los resultados obtenidos en este estudio figuran en la parte A del capítulo 2 de esta tesis doctoral.

En la parte B del capítulo 2, se describe una nueva transformación para acceder a esqueletos de ciclohexanona a través de una carbociclación catiónica catalizada por ácido tetrafluorobórico. En este caso, el empleo de 1,1,1,3,3,3-hexafluoro-2-propanol como disolvente de la reacción permitió la obtención de los productos deseados de reacción empleando cantidades subestequiométricas de ácido tetrafluorobórico.

Finalmente, la metodología desarrollada ha sido aplicada en las ciclaciones biomiméticas de diferentes polieninos. Los excelentes resultados obtenidos en las ciclaciones de alquinoles fueron también observados en este caso. De hecho, en el capítulo 2 se ha demostrado que estos procesos de carbociclación en cascada permiten la construcción eficiente del esqueleto de multitud de productos naturales y se ha demostrado la compatibilidad de nuestra metodología en la síntesis de diferentes moléculas de interés.

Experimental Section

1. General Features

Manipulation of organometallic compounds or any moisture or air sensitive chemicals was carried out under inert atmosphere of argon (99.999%) by using Schlenk techniques. All glassware used was previously dried and evacuated.

For those reactions carried out at low temperatures, cooling mixtures of liquid nitrogen and acetone or 2-propanol were used. For those reactions that required low temperatures during long periods of time, acetone or 2-propanol baths were refrigerated by immersion of a cooling probe of a JULABO® F70 immersion cooler.

For those reactions performed at high temperatures, mineral oil or silicone baths were heated with a temperature probe and stirred with a magnetic stirrer.

2. Solvents

All solvents used for those reactions carried out under inert atmosphere were dried with appropriated dehydration agents as specified below:

Diethyl ether, toluene, acetonitrile, *N*,*N*-dimethylformamide and hexane were dried using the Puresolv® solvent purification system before use.

Tetrahydrofuran, 1,4-dioxane and methanol were dried by refluxing over sodium and subsequently distilled and stored under inert atmosphere.

Dichloromethane and 1,2-dichloroethane were dried by refluxing over calcium hydride and subsequently distilled and stored under inert atmosphere.

3. Purchased Chemicals

Unless otherwise stated, all purchased chemicals were used as received from corresponding commercial source.

4. Chromatographic Techniques

Chromatographic purification of products was carried out employing silica gel (230-240 mesh, Aldrich) as the stationary phase.

Thin layer chromatography (TLC) was performed using silica gel plates with F254 indicator applied on an aluminium base. The plates were developed by exposure to UV light (λ = 254 nm), iodo or to colorant solutions of vanillin, potassium permanganate or Ce and Mo and heat.

5. Analytical Techniques

5.1 Nuclear Magnetic Resonance (NMR) Spectroscopy

Spectrometers DPX-300, AV-300 and AV-400 were used for ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR experiments. The values for chemical shifts (δ) are shown in parts-per-million (ppm) and are referenced to the appropriate residual solvent peaks for ^{1}H-NMR experiments and to the chemical shifts of corresponding deuterated solvents for the ^{13}C-NMR experiments. The values for coupling constants (*J*) are shown in hertzs (Hz) in all cases. The abbreviations used to describe multiplicity of the signals are as follows: (s) = singlet, (d) = doublet, (t) = triplet, (q) = quatriplet, (br) = broad, (dd) = doublet of doublets, (dt) = doublet of triplets, (ddd) = doublet of doublets, (m) = multiplet, (app) = apparent.

5.2 High Resolution Mass Spectrometry (HRMS)

Experiments of high resolution mass spectroscopy were performed in a Micromass AutoSpec (University of Burgos) and Electronic Impact fragmentation methods (EI) have been employed.

5.3 Melting Points

Melting points have been measured in a Gallenkamp device and have not been corrected.

5.4 Optical Rotation

Optical rotations were measured using a 2 mL cell with a 1 dm path length on an Autopol IV Rudolph Research Analytical polarimeter at 589 nm. They are reported as [α]TD (concentration in grams/mL solvent).

5.5 High-Performance Liquid Chromatography

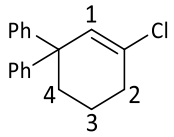
For the High-Performance Liquid Chromatography, Waters 2695 Alliance instrument provided with a V-UV detector was used.

Chapter 1

Synthesis of compounds 3

To a solution of the corresponding alkynol **1** or enyne **2** (0.3 mmol) in dry dichloromethane (5 mL), tetrafluoroboric acid diethyl ether complex (0.3 mmol, 41 µL, 1 equivalent) was dropwise added. The reaction was then gently stirred for the stated time. After this time, the mixture was diluted with ethyl acetate (5 mL) and quenched with potassium carbonate (50 mg). The mixture was filtered and volatile components were removed under reduced pressure. The crude was purified by flash chromatography to obtain pure cyclohexenyl chlorides **3**.

5'-chloro-3',4'-dihydro-2'H-1,1':1',1''-terphenyl (3a)



Colourless oil.

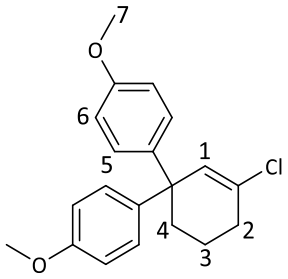
R_f 0.36 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.40 - 7.23 (m, 10H, Ar-H), 6.35 (t, *J* = 1.4 Hz, 1H, H_1), 2.46 (td, *J* = 6.4, 1.4 Hz, 2H, H_2), 2.39 - 2.30 (m, 2H, H_4), 1.82 – 1.76 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 147.9, 133.0, 131.7, 128.1, 127.6, 126.0, 50.3, 34.9, 32.7, 20.0.

HRMS calculated for $C_{18}H_{17}Cl$ $[M]^+$ 268.1019, found 268.1017.

5'-chloro-4,4''-dimethoxy-3',4'-dihydro-2'H-1,1':1',1''-terphenyl (3b)



Colourless oil.

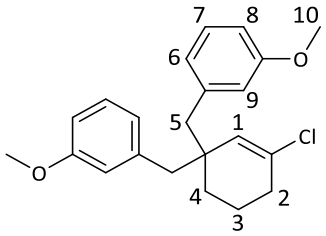
R_f 0.37 (hexane:ethyl acetate, 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.16 (d, *J* = 9.0 Hz, 4H, H_5), 6.86 (d, *J* = 9.0 Hz, 4H, H_6), 6.24 (t, *J* = 1.7 Hz, 1H, H_1), 3.83 (s, 6H, H_7), 2.41 (td, *J* = 6.3, 1.7 Hz, 2H, H_2), 2.29 – 2.22 (m, 2H, H_4), 1.78 – 1.68 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.6, 140.2, 132.6, 132.1, 128.6, 113.4, 55.1, 49.1, 35.2, 32.7, 20.0.

HRMS calculated for $C_{20}H_{21}ClO_2$ $[M]^+$ 328.1230, found 328.1236.

3,3'-[(3-chlorocyclohex-2-ene-1,1-diyl)bis(methylene)]bis(methoxybenzene) (3c)



Colourless oil.

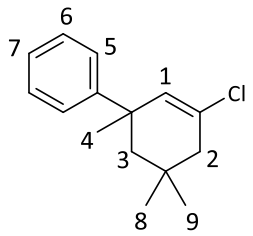
R_f 0.37 (hexane:ethyl acetate, 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.21 (t, *J* = 7.9 Hz, 2H, H_7), 6.80 (ddd, *J* = 7.9, 2.4, 1.0 Hz, 2H, H_8), 6.74 (ddd, *J* = 7.9, 1.6, 1.0 Hz, 2H, H_{16}), 6.69 (dd, J = 2.4, 1.6 Hz, 2H, H_9), 5.70 (t, *J* = 1.6 Hz, 1H, H_1), 3.81 (s, 6H, H_{10}), 2.74 (d, *J* = 13.1 Hz, 2H, H_{5a}) 2.66 (d, *J* = 13.1 Hz, 2H, H_{5b}), 2.08 (td, *J* = 6.2, 1.6, Hz, 2H, H_2), 1.65 – 1.54 (m, 2H, H_4), 1.48 – 1.42 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.1, 139.5, 132.0, 131.7, 128.7, 123.1, 116.0, 111.7, 55.1, 47.0, 42.3, 32.2, 29.9, 19.9.

HRMS calculated for $C_{22}H_{25}ClO_2$ $[M]^+$ 356.1546, found 356.1537.

5-chloro-1,3,3-trimethyl-1,2,3,4-tetrahydro-1,1'-biphenyl (3d)



Colourless oil.

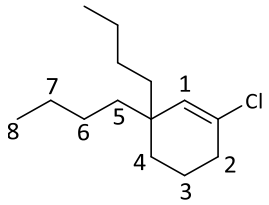
R_f 0.42 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.38 – 7.27 (m, 4H, H_5, H_6), 7.19 (tt, *J* = 6.9, 1.6 Hz, 1H, H_7), 6.08 (br s, 1H, H_1), 2.24 (dd, *J* = 17.3, 1.9 Hz, 1H, H_{2a}), 2.10 (dd, *J* = 17.3, 1.3 Hz, 1H, H_{2b}), 2.00 (d, *J* = 13.7 Hz, 1H, H_{3a}), 1.62 (d, *J* = 13.7 Hz, 1H, H_{3b}), 1.39 (s, 3H, H_4), 1.03 (s, 3H, H_9), 0.60 (s, 3H, H_8).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 149.4, 131.0, 130.4, 128.0, 125.9, 125.7, 49.9, 46.5, 41.9, 32.7, 32.5, 31.2, 27.9.

HRMS calculated for $C_{15}H_{19}Cl$ $[M]^+$ 234.1175, found 234.1170.

3,3-dibutyl-1-chlorocyclohex-1-ene (3e)



Colourless oil.

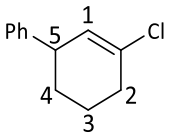
R_f 0.80 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.82 (t, *J* = 1.6 Hz, 1H, H_1), 2.35 (td, *J* = 6.3, 1.6 Hz, 2H, H_2), 1.80 – 1.63 (m, 2H, H_4), 1.47 – 1.37 (m, 2H, H_3), 1.37 – 1.09 (m, 12H, H_5, H_6, H_7), 0.89 (t, *J* = 6.9 Hz, 6H, H_8).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 137.6, 121.5, 41.0, 39.2, 35.4, 31.3, 26.1, 23.7, 21.2, 14.3.

HRMS calculated for $C_{14}H_{25}Cl$ $[M]^+$ 228.1645, found 228.1647.

5-chloro-1,2,3,4-tetrahydro-1,1'-biphenyl (3f)



Colourless oil.

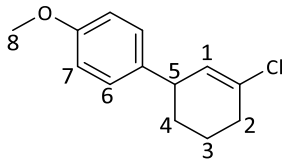
R_f 0.53 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.40 – 7.17 (m, 5H, Ar-H), 5.95 – 5.87 (m, 1H, H_1), 3.58 – 3.48 (m, 1H, H_5), 2.60 – 1.96 (m, 6H, H_2, H_3, H_4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 144.9, 133.4, 128.4, 127.5, 127.4, 126.4, 43.0, 32.6, 31.3, 22.0.

HRMS calculated for $C_{12}H_{13}Cl$ $[M]^+$ 192.0706, found 192.0703.

5-chloro-4'-methoxy-1,2,3,4-tetrahydro-1,1'-biphenyl (3g)



Colourless oil.

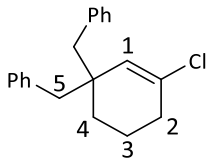
R_f 0.35 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.15 (d, *J* = 8.6 Hz, 2H, H_6), 6.89 (d, *J* = 8.6 Hz, 2H, H_7), 5.93 – 5.86 (m, 1H, H_1), 3.83 (s, 3H, H_8), 3.52 – 3.42 (m, 1H, H_5), 2.52 – 2.30 (m, 2H, H_2,), 2.05 – 1.68 (m, 3H, H_3, H_{4a}), 1.58 – 1.42 (m, 1H, H_{4b}).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 158.1, 137.1, 133.1, 128.5, 127.7, 113.7, 55.2, 42.1, 32.6, 31.3, 22.0.

HRMS calculated for $C_{13}H_{15}ClO$ $[M]^+$ 222.0811, found 222.0805.

[(3-chlorocyclohex-2-ene-1,1-diyl)bis(methylene)]dibenzene (3h)



Colourless oil.

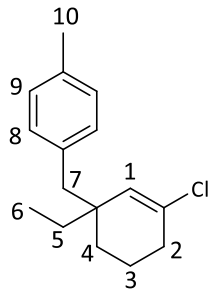
R_f 0.37 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.35 – 7.13 (m, 10H, Ar-H), 5.71 (t, *J* = 1.6 Hz, 1H, H_1) 2.77 (d, *J* = 13.2 Hz, 2H, H_{5a}), 2.70 (d, *J* = 13.2 Hz, 2H, H_{5b}), 2.08 (td, *J* = 6.2, 1.6 Hz, 2H, H_2), 1.68 – 1.55 (m, 2H, H_4), 1.50 – 1.43 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 137.9, 132.0, 131.6, 130.6, 127.8, 126.1, 46.8, 42.2, 32.2, 29.8, 19.8.

HRMS calculated for $C_{20}H_{21}Cl$ $[M]^+$ 296.1332, found 296.1329.

1-[(3-chloro-1-ethylcyclohex-2-en-1-yl)methyl]-4-methylbenzene (3i)



Colourless oil.

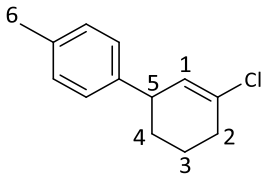
R_f 0.39 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.14 (d, *J* = 7.9 Hz, 2H, H_9), 7.07 (d, *J* = 7.9 Hz, 2H, H_8), 5.59 (t, *J* = 1.6 Hz, 1H, H_1) 2.68 (d, *J* = 13.2 Hz, 1H, H_{7a}), 2.63 (d, *J* = 13.2 Hz, 1H, H_{7b}), 2.38 (s, 3H, H_{10}), 2.31 – 2.24 (m, 2H, H_2), 1.77 (quintuplet, *J* = 6.2 Hz, 2H, H_3), 1.50 – 1.42 (m, 2H, H_4), 1.39 (q, *J* = 7.5 Hz, 2H, H_5), 0.93 (t, *J* = 7.5 Hz, 3H, H_6).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 135.4, 134.9, 132.2, 131.4, 130.3, 128.4, 44.7, 40.9, 32.6, 31.4, 30.2, 20.9, 20.0, 8.3.

HRMS calculated for $C_8H_{12}Cl$ $[M-105]^+$ 143.0628, found 143.0631.

5-chloro-4'-methyl-1,2,3,4-tetrahydro-1,1'-biphenyl (3j)



Colourless oil.

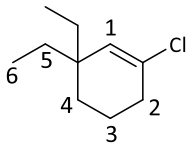
R_f 0.44 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.21 – 7.11 (m, 4H, Ar-H), 5.92 (td, *J* = 3.0, 1.5 Hz, 1H, H_1) 3.56 – 3.48 (m, 1H, H_5), 2.58 – 2.40 (m, 2H, H_2), 2.40 (s, 3H, H_6), 2.09 – 1.70 (m, 3H, H_3, H_{4a}), 1.57 (dddd, *J* = 13.0, 10.3, 8.1, 3.0, 1H, H_{4b}).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 141.9, 135.9, 133.2, 129.0, 127.4, 126.6, 42.6, 32.6, 31.3, 22.1, 20.9.

HRMS calculated for $C_{13}H_{15}Cl$ $[M-35]^+$ 171.1174, found 171.1172.

1-chloro-3,3-diethylcyclohex-1-ene (3k)



Colourless oil.

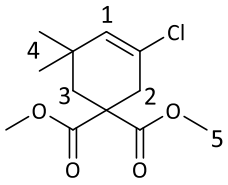
R_f 0.78 (hexane).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 5.62 (t, *J* = 1.6 Hz, 1H, H_1), 2.25 (td, *J* = 6.3, 1.6 Hz, 2H, H_2), 1.74 (quintuplet, *J* = 6.3 Hz, 2H, H_3), 1.45 – 1.28 (m, 6H, H_4, H_5), 0.83 (t, *J* = 7.5 Hz, 6H, H_6).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 132.5, 131.1, 39.6, 32.8, 30.9, 30.3, 20.1, 8.0.

HRMS calculated for $C_8H_{12}Cl$ $[M-29]^+$ 143.0628, found 143.0628.

Dimethyl 3-chloro-5,5-dimethylcyclohex-3-ene-1,1-dicarboxylate (3l)



Colourless oil.

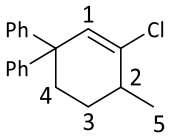
R_f 0.36 (hexane:ethyl acetate 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 5.58 (t, *J* = 1.5 Hz, 1H, H_1), 3.71 (s, 6H, H_5), 2.73 (d, *J* = 1.5 Hz, 2H, H_2), 2.09 (br s, 2H, H_3), 0.97 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 171.4, 133.1, 127.0, 53.6, 52.9, 40.0, 36.9, 33.7, 29.9.

HRMS calculated for $C_{12}H_{17}ClO_4$ $[M]^+$ 260.0815, found 260.0811.

5'-chloro-4'-methyl-3',4'-dihydro-2'H-1,1':1',1''-terphenyl (3m)



Colourless oil.

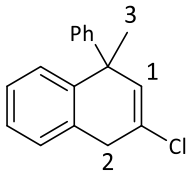
R_f 0.12 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.36 – 7.19 (m, 10H, Ar-H), 6.27 (br s, 1H, H_1) 2.49 (sextuplet, *J* = 6.7 Hz, 1H, H_2), 2.35 – 2.29 (m, 2H, H_4), 1.97 – 1.86 (m, 1H, H_{3a}), 1.54 – 1.41 (m, 1H, H_{3b}), 1.24 (d, *J* = 7.4 Hz, 3H, H_5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.0, 138.5, 131.8, 128.1, 127.6, 126.0, 50.8, 35.9, 32.9, 28.1, 19.1.

HRMS calculated for $C_{19}H_{19}Cl$ $[M]^+$ 282.1175, found 282.1170.

3-chloro-1-methyl-1-phenyl-1,4-dihydronaphthalene (3n)



Colourless oil.

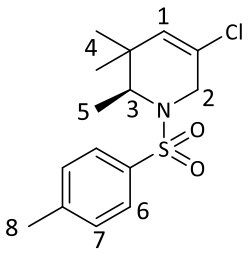
R_f 0.37 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.34 – 6.94 (m, 9H, Ar-H), 5.90 (t, *J* = 1.7 Hz, 1H, H_1), 3.82 (d, *J* = 1.7 Hz, 2H, H_2), 1.83 (s, 3H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.1, 141.4, 132.4, 131.7, 128.5, 128.2, 127.7, 127.2, 127.1, 126.8, 126.2, 126.1, 46.5, 36.6, 29.6.

HRMS calculated for $C_{17}H_{15}Cl$ $[M]^+$ 254.0862, found 254.0858.

(*S*)-5-chloro-2,3,3-trimethyl-1-tosyl-1,2,3,6-tetrahydropyridine (3o)



Colourless oil.

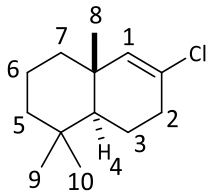
R_f 0.32 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.71 (d, *J* = 7.8 Hz, 2H, H_6), 7.31 (d, *J* = 7.8 Hz, 2H, H_7), 5.56 (br s, 1H, H_1), 4.07 (d, *J* = 16.4 Hz, 1H, H_{2a}), 3.83 (q, *J* = 6.6 Hz, 1H, H_3), 3.45 (d, *J* = 16.4 Hz, 1H, H_{2b}), 2.43 (s, 3H, H_8), 1.15 (s, 3H, H_{4a}), 0.96 (s, 3H, H_{4b}), 0.83 (d, *J* = 6.7 Hz, 3H, H_5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 143.5, 136.8, 131.5, 130.0, 127.1, 124.2, 56.0, 44.4, 38.8, 28.8, 24.9, 21.5, 12.3.

HRMS calculated for $C_{15}H_{20}ClNO_2S$ $[M+Na]^+$ 336.0796, found 336.0795.

(4a*S,8a*S**)-7-chloro-4,4,8a-trimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene (3q)**



Colourless oil.

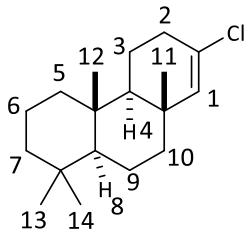
R_f 0.82 (hexane).

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm) = 5.54 (t, *J* = 1.6 Hz, 1H, H_1), 2.35 (ddd, *J* = 8.9, 4.2, 1.6 Hz, 2H, H_2), 1.85 – 1.78 (m, 1H, H_{3a}), 1.70 – 1.41 (m, 5H, H_{3b}, H_5, H_7), 1.28 – 1.14 (m, 3H, H_4, H_6), 1.01 (s, 3H, H_8), 0.93 (s, 3H, H_9), 0.86 (s, 3H, H_{10}).

^{13}C-RMN ($CDCl_3$, 75 MHz) δ (ppm) = 137.7, 129.9, 50.3, 41.9, 39.4, 37.3, 35.6, 34.5, 32.9, 21.2, 21.1, 20.0, 18.8.

HRMS calculated for $C_{13}H_{21}Cl$ $[M]^+$ 212.1332, found 212.1331.

(4a*S,4b*R**,8a*R**,10a*S**)-7-chloro-1,1,4a,8a-tetramethyl-1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydrophenanthrene (3r)**



Colourless oil.

R_f 0.91 (hexane).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) = 5.48 (t, *J* = 1.7 Hz, H_1), 2.38 – 2.26 (m, 2H, H_2), 1.90 – 0.85 (m, 14H, H_3, H_4, H_5, H_6, H_7, H_8, H_9, H_{10}), 0.96 (s, 3H, H_{11}), 0.84, 0.82, 0.81 (3s, 9H, H_{12}, H_{13}, H_{14}).

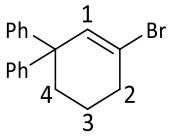
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) = 137.8, 129.5, 56.9, 54.6, 42.3, 42.3, 42.0, 41.4, 39.2, 38.8, 34.3, 33.2, 33.2, 22.2, 21.1, 18.9, 18.1, 16.0.

HRMS calculated for $C_{18}H_{29}Cl$ $[M]^+$ 280.1958, found 280.1967.

Synthesis of compounds 4

To a solution of the corresponding alkynol **1** or enyne **2** (0.3 mmol) in dibromomethane (5 mL), tetrafluoroboric acid diethyl ether complex (0.3 mmol, 41 µL, 1 equivalent) was dropwise added. The reaction was then gently stirred for the stated time. After this time, the mixture was diluted with ethyl acetate (5 mL) and quenched with potassium carbonate (50 mg). The mixture was filtered and volatile components were removed under reduced pressure. The crude was purified by flash chromatography to obtain pure cyclohexenyl chlorides **4**.

5'-bromo-3',4'-dihydro-2'H-1,1':1',1''-terphenyl (4a)



Colourless oil.

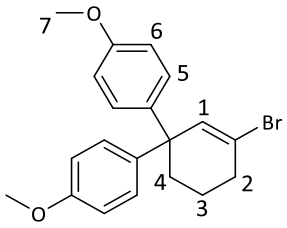
R_f 0.36 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.37 – 7.20 (m, 10H, Ar-H), 6.53 (br s, 1H, H_1), 2.46 (td, *J* = 6.3, 1.3 Hz, 2H, H_2), 2.38 – 2.31 (m, 2H, H_4), 1.80 – 1.68 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 147.7, 135.7, 128.1, 127.6, 126.1, 123.5, 51.6, 35.1, 34.7, 20.8.

HRMS calculated for $C_{18}H_{17}Br$ $[M]^+$ 312.0514, found 312.0521.

5'-bromo-4,4''-dimethoxy-3',4'-dihydro-2'H-1,1':1',1''-terphenyl (4b)



Colourless oil.

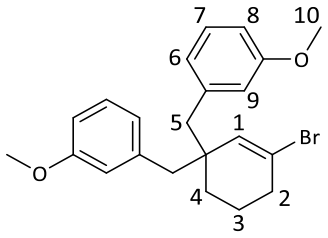
R_f 0.25 (hexane:ethyl acetate, 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.14 (d, *J* = 9.7 Hz, 4H, H_5), 6.82 (d, *J* = 9.7 Hz, 4H, H_6), 6.39 (t, *J* = 1.8 Hz, 1H, H_1), 3.53 (s, 6H, H_7), 2.13 (td, *J* = 6.9, 1.8 Hz, 2H, H_2), 1.87 – 1.82 (m, 2H, H_4), 1.72 – 1.69 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 157.7, 140.1, 136.2, 128.7, 123.1, 113.4, 55.2, 50.4, 35.2, 35.1, 20.9.

HRMS calculated for $C_{20}H_{21}BrO_2$ $[M]^+$ 372.0725, found 372.0733.

3,3'-[(3-bromocyclohex-2-ene-1,1-diyl)bis(methylene)]bis(methoxybenzene) (4c)



Colourless oil.

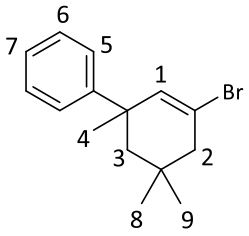
R_f 0.28 (hexane:ethyl acetate 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.21 (t, *J* = 7.9 Hz, 2H, H_7), 6.80 (ddd, *J* = 7.9, 2.4, 1.0 Hz, 2H, H_8), 6.74 (ddd, *J* = 7.9, 1.6, 1.0 Hz, 2H, H_{16}), 6.69 (dd, J = 2.4, 1.6 Hz, 2H, H_9), 5.70 (t, *J* = 1.6 Hz, 1H, H_1), 3.81 (s, 6H, H_{10}), 2.72 (d, *J* = 13.2 Hz, 2H, H_{5a}) 2.65 (d, *J* = 13.2 Hz, 2H, H_{5b}), 2.20 (td, *J* = 6.3, 1.6, Hz, 2H, H_2), 1.63 – 1.43 (m, 4H, H_3, H_4), 1.48 – 1.42 (m, 2H, H_3).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 159.1, 139.4, 136.0, 128.7, 123.1, 122.4, 115.9, 111.9, 55.1, 46.9, 43.6, 34.5.

HRMS calculated for $C_{22}H_{25}ClO_2$ $[M]^+$ 400.1038, found 400.1034.

5-bromo-1,3,3-trimethyl-1,2,3,4-tetrahydro-1,1'-biphenyl (4d)



Colourless oil.

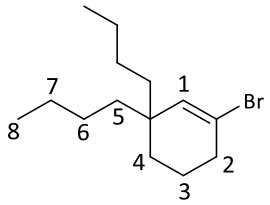
R_f 0.37 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.39 – 7.27 (m, 4H, H_5, H_6), 7.19 (tt, *J* = 7.0. 1.6 Hz, 1H, H_7), 6.33 – 6.30 (m, 1H, H_1), 2.37 (dd, *J* = 17.4, 2.0 Hz, 1H, H_{2a}), 2.25 (dd, *J* = 17.4, 1.4 Hz, 1H, H_{2b}), 2.02 (d, *J* = 13.8 Hz, 1H, H_{3a}), 1.64 (d, *J* = 13.7 Hz, 1H, H_{3b}), 1.40 (s, 3H, H_4), 1.03 (s, 3H, H_9), 0.62 (s, 3H, H_8).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 149.2, 134.6, 128.0, 125.8, 125.7, 121.4, 49.7, 48.8, 43.2, 33.3, 32.3, 31.1, 28.0.

HRMS calculated for $C_{15}H_{19}Br$ $[M]^+$ 278.0670, found 268.0666.

1-bromo-3,3-dibutylcyclohex-1-ene (4e)



Colourless oil.

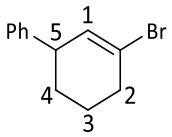
R_f 0.83 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.82 (t, *J* = 1.6 Hz, 1H, H_1), 2.35 (td, *J* = 6.3, 1.6 Hz, 2H), 1.74 – 1.66 (m, 2H, H_4), 1.45 – 1.37 (m, 2H, H_3), 1.37 – 1.09 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 137.6, 121.5, 41.0, 39.2, 35.4, 31.3, 26.1, 23.7, 21.2, 14.3.

HRMS calculated for $C_{14}H_{25}Br$ $[M]^+$ 272.1140, found 272.1132.

5-bromo-1,2,3,4-tetrahydro-1,1'-biphenyl (4f)



Colourless oil.

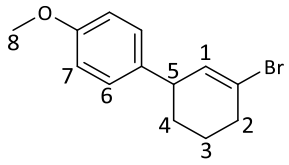
R_f 0.40 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.41 – 7.21 (m, 5H, Ar-H), 6.17 (br s, 1H, H_1), 3.53 (ddt, *J* = 11.2, 5.8, 3.0, 1H, H_5), 2.62 – 2.51 (m, 2H, H_2), 2.14 – 1.72 (m, 3H, H_4, H_{3a}), 1.65 – 1.59 (m, 1H, H_{3b}).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 144.7, 131.7, 128.4, 127.5, 126.4, 123.7, 44.3, 35.0, 31.0, 22.9.

HRMS calculated for $C_{12}H_{13}$ $[M - 79]^+$ 157.1017, found 157.1012.

5-bromo-4'-methoxy-1,2,3,4-tetrahydro-1,1'-biphenyl (4g)



Colourless oil.

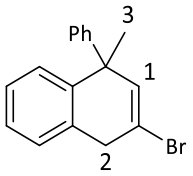
R_f 0.28 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.15 (d, *J* = 8.6 Hz, 2H, H_6), 6.89 (d, *J* = 8.6 Hz, 2H, H_7), 6.13 (br s, 1H, H_1), 3.83 (s, 3H, H_8), 3.50 – 3.41 (m, 1H, H_5), 2.63 – 2.44 (m, 2H, H_2,), 2.08 – 1.96 (m, 1H, H_{4a}), 1.92 – 1.69 (m, 2H, H_{4b}, H_{3a}), 1.63 – 1.50 (m, 1H, H_{3b}).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 158.2, 136.8, 132.0, 128.5, 123.5, 113.8, 55.2, 43.4, 35.0, 31.1, 22.8.

HRMS calculated for $C_{13}H_{15}BrO$ $[M]^+$ 266.0306, found 266.0304.

3-bromo-1-methyl-1-phenyl-1,4-dihydronaphthalene (4n)



Colourless oil.

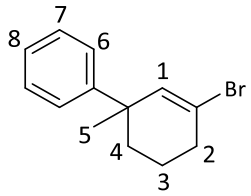
R_f 0.26 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.35 – 6.91 (m, 9H, Ar-H), 6.10 (t, *J* = 1.8 Hz, 1H, H_1), 3.91 (d, *J* = 1.8 Hz, 2H, H_2), 1.80 (s, 3H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 147.8, 141.1, 136.4, 132.1, 128.8, 128.2, 127.5, 127.2, 126.8, 126.2, 126.1, 117.0, 47.4, 38.7, 28.8.

HRMS calculated for $C_{17}H_{15}Cl$ $[M]^+$ 298.0357, found 298.0359.

5-bromo-1-methyl-1,2,3,4-tetrahydro-1,1'-biphenyl (4p)



Colourless oil.

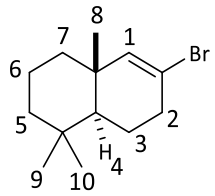
R_f 0.36 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.37 – 7.30 (m, 4H, H_6, H_7), 7.25 – 7.18 (m, 1H, H_8), 6.13 (br s, 1H, H_1), 2.51 – 2.45 (m, 2H, H_2), 1.96 – 1.86 (m, 1H, H_{4a}), 1.74 – 1.63 (m, 2H, H_{4b}, H_{3a}), 1.63 – 1.52 (m, 1H, H_{3b}), 1.44 (s, 3H, H_5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.3, 136.6, 128.3, 126.5, 126.2, 122.9, 43.3, 37.7, 35.3, 29.0, 21.2.

HRMS calculated for $C_{14}H_{25}Br$ $[M]^+$ 250.0357, found 250.0361.

(4a*S,8a*S**)-7-bromo-4,4,8a-trimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene (4q)**



Colourless oil.

R_f 0.82 (hexane).

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm) = 5.71 (t, *J* = 1.4 Hz, 1H, H_1), 2.51 – 2.42 (m, 2H, H_2), 1.80 – 1.65 (m, 1H, H_{3a}), 1.64 – 1.52 (m, 1H, H_{6a}), 1.51 – 1.39 (m, 3H, H_{7a}, H_{6b}, H_{5a}), 1.30 – 1.10 (m, 4H, H_{7b}, H_{5b}, H_4, H_{3b}), 1.00 (s, 3H, H_8), 0.89, 0.82 (2s, 6H, H_9, H_{10}).

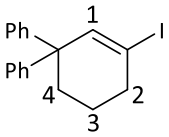
^{13}C-RMN ($CDCl_3$, 75 MHz) δ (ppm) = 142.0, 120.7, 50.3, 42.1, 39.4, 39.0, 37.1, 33.1, 33.0, 21.4, 21.2, 21.2, 19.0.

HRMS calculated for $C_{13}H_{22}Br$ $[M+H]^+$ 257.0899, found 257.0866.

Synthesis of compounds 5

To a solution of the corresponding alkynol **1** or enyne **2** (0.3 mmol) in iodomethane (3 mL), aluminium iodide (0.3 mmol, 122 mg, 1 equivalent) was portionwise added. The reaction was then gently stirred for the stated time. After this time, the mixture was diluted with ethyl acetate (5 mL) and quenched with a saturated aqueous solution of sodium bicarbonate (10 mL). The aqueous layer was extracted with ethyl acetate. The organic combined organic layers were dried over sodium sulfate and filtered. The volatile components were removed under reduced pressure. The crude was purified by flash chromatography to obtain pure cyclohexenyl iodides **5**.

5'-iodo-3',4'-dihydro-2'H-1,1':1',1''-terphenyl (5a)



Colourless oil.

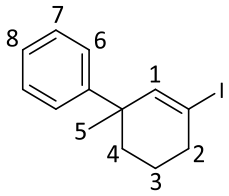
R_f 0.32 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.50 – 7.09 (m, 10H, Ar-H), 6.81 (br s, 1H, H_1), 2.63 (td, *J* = 6.3, 1.8 Hz, 2H, H_2), 2.47 – 2.32 (m, 2H, H_4), 1.79 – 1.61 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 147.8, 144.1, 128.3, 127.9, 126.3, 98.4, 53.1, 39.5, 34.6, 21.9.

HRMS calculated for $C_{18}H_{17}I$ $[M]^+$ 360.0375, found 360.0379.

5-iodo-1-methyl-1,2,3,4-tetrahydro-1,1'-biphenyl (5p)



Colourless oil.

R_f 0.31 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.36 – 7.31 (m, 4H, H_6, H_7), 7.25 – 7.17 (m, 1H, H_8), 6.42 (br s, 1H, H_1), 2.60 – 2.50 (m, 2H, H_2), 1.94 (ddd, *J* = 13.0, 6.8, 3.1 Hz, 1H, H_{4a}), 1.77 – 1.45 (m, 3H, H_{4b}, H_3), 1.41 (s, 3H, H_5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.2, 145.0, 128.3, 126.5, 126.2, 97.5, 44.6, 39.5, 37.4, 28.7, 22.1.

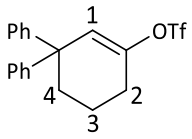
HRMS calculated for $C_{13}H_{15}I$ $[M]^+$ 298.0218, found 298.0212.

Chapter 2 – part A

Synthesis of compounds 6

To a solution of the corresponding alkynol **1**, or enyne **2** (0.3 mmol) in dry hexane (3 mL) trifluoromethanesulfonic acid (0.3 mmol, 27 µL, 1 equivalent) was dropwise added. The reaction was then gently stirred at room temperature for the stated time. After this time the mixture was diluted with ethyl acetate (5 mL) and quenched with potassium carbonate (50 mg). The mixture was filtered and the volatile components were removed under reduced pressure. The crude was purified by flash chromatography on silica gel to give pure cyclohexenyl triflates **6**.

3',4'-dihydro-2'H-(1,1':1',1''-terphenyl)-5'-yl trifluoromethanesulfonate (6a)



White solid.

R_f 0.60 (hexane).

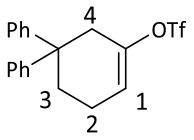
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.42 – 7.13 (m, 10H, Ar-H), 6.26 (br s, 1H, H_1), 2.45 (td, *J* = 6.3, 1.3 Hz, 2H, H_2), 2.36 – 2.27 (m, 2H, H_4), 1.88 – 1.72 (m, 2H, H_3).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 149.5, 146.8, 132.1, 131.0, 130.0, 126.2, 118.5 (q, *J*= 320.1 Hz), 35.1, 30.9 27.6, 19.2.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.0.

HRMS calculated for $C_{19}H_{17}F_3O_3S$ $[M]^+$ 382.0845, found 382.0859.

5',6'-dihydro-2'H-(1,1':1',1''-terphenyl)-3'-yl trifluoromethanesulfonate (6a')



White solid.

R_f 0.60 (hexane).

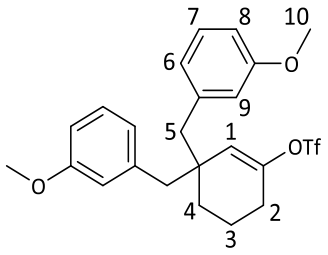
Isolated as a 20:1 mixture of **6a':6a**. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.64 – 7.20 (m, 10H, Ar-H**, 6a'**), 7.42 – 7.13 (m, 10H, Ar-H, **6a**), 6.26 (br s, 1H, H_1, **6a**), 5.82 – 5.75 (m, 1H, H_1, **6a'**), 2.98 – 2.95 (m, 2H, H_4, **6a'**), 2.45 (td, *J* = 6.3, 1.3 Hz, 2H, H_2, **6a**), 2.40 (t, *J* = 5.9 Hz, 2H, H_3, **6a'**), 2.36 – 2.27 (m, 2H, H_4, **6a**), 2.02 – 1.94 (m, 2H, H_2, **6a'**), 1.88 – 1.72 (m, 2H, H_3, **6a**).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 147.5 (**6a'**), 146.7 (**6a'**), 132.1 (**6a**), 131.0 (**6a**), 130.0 (**6a**), 128.4 (**6a'**), 126.7 (**6a'**), 126.4 (**6a'**), 126.2 (**6a**) 119.4 (q, *J* = 324.3 Hz; **6a'**), 118.9 (**6a'**), 118.5 (q, *J* = 320.1 Hz; **6a**), 46.8 (**6a'**), 39.7 (**6a'**), 32.0 (**6a'**), 21.5 (**6a'**).

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -70.7 (**6a'**), -74.0 (**6a**).

HRMS calculated for $C_{19}H_{17}F_3O_3S$ $[M]^+$ 382.0845, found 382.0853.

3,3-bis(3-methoxybenzyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (6c)



Colourless oil.

R_f 0.25 (hexane:ethyl acetate 10:1).

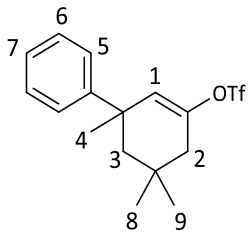
H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.23 (t, *J* = 7.9 Hz, 2H, H_9), 6.75 (d, *J* = 7.9 Hz, 2H, H_8), 6.82 (d, *J* = 7.9 Hz, 2H, H_6), 6.69 (s, 2H, H_9), 5.62 (s, 1H, H_1), 3.84 (s, 6H, H_{10}), 2.76 (q, *J* = 13.2 Hz, 4H, H_5), 2.13 (t, *J* = 6.3 Hz, 2H, H_2), 1.71 – 1.50 (m, 4H, H_3, H_4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.3, 148.9, 138.7, 128.9, 125.3, 123.1, 118.4 (q, *J* = 323.2 Hz), 116.4, 111.8, 55.1, 47.1, 41.2, 30.4, 27.0, 19.0.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.5.

HRMS calculated for $C_{23}H_{25}F_3O_3S$ $[M]^+$ 470.1369 found 470.1377.

1,5,5-trimethyl-1,4,5,6-tetrahydro-(1,1'-biphenyl)-3-yl trifluoromethanesulfonate (6d)



Colourless oil.

R_f 0.17 (hexane).

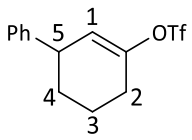
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.35 – 7.17 (m, 5H, Ar-H), 6.30 (br s, 1H, H_1), 2.26 (dd, *J* = 17.0, 1.7 Hz, 1H, H_{2a}), 2.11 (dd, *J* = 17.0, 1.0 Hz, 1H, H_{2b}), 2.01 (dd, *J* = 13.9, 1.0 Hz, 1H, H_{3a}), 1.65 (d, *J* = 13.9 Hz, 1H, H_{3b}), 1.45 (s, 3H, H_4), 1.06 (s, 3H, H_6), 0.66 (s, 3H, H_5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.5, 148.2, 128.3, 126.1, 125.7, 124.6, 118.5 (q, *J* = 319.5 Hz), 50.1, 41.2, 40.9, 32.6, 32.1, 30.8, 27.9.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.0.

HRMS calculated for $C_{16}H_{19}F_3O_3S$ $[M]^+$ 348.1002, found 348.1006.

1,4,5,6-tetrahydro-(1,1'-biphenyl)-3-yl trifluoromethanesulfonate (6f)



Yellow oil.

R_f 0.40 (hexane).

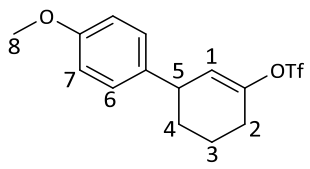
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.41 – 7.20 (m, 5H, Ar-H), 5.93 – 5.86 (m, 1H, H_1), 3.70 – 3.60 (m, 1H, H_5), 2.52 – 2.40 (m, 2H, H_2), 2.12 – 1.71 (m, 3H, H_3, H_{4a}), 1.63 – 1.51 (m, 1H, H_{4b}).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 150.3, 148.4, 144.1, 128.6, 126.6, 121.4, 118.5 (q, *J* = 320.2 Hz), 40.9, 31.4, 27.6, 21.1.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.2.

HRMS calculated for $C_{13}H_{13}F_3O_3S$ $[M]^+$ 306.0532, found 306.0534.

4'-methoxy-1,4,5,6-tetrahydro-(1,1'-biphenyl)-3-yl trifluoromethanesulfonate (6g)



Colourless oil.

R_f 0.28 (hexane:ethyl acetate 30:1).

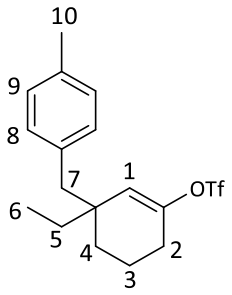
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.12 (d, *J* = 8.9 Hz, 2H, H_6), 6.89 (d, *J* = 8.9 Hz, 2H, H_7), 6.21 – 5.98 (m, 1H, H_1), 3.81 (s, 3H, H_8), 3.61 – 3.54 (m, 1H, H_5), 2.52 – 2.31 (m, 2H, H_2), 2.05 – 1.90 (m, 2H, H_{3a}, H_{4a}), 1.83 – 1.72 (m, 1H, H_{3b}), 1.57 – 1.47 (m, 1H, H_{4b}).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 158.4, 150.2, 135.8, 121.8, 120.1, 118.5 (q, *J* = 320.2 Hz), 113.9, 55.2, 40.4, 31.3, 27.5, 20.9.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.2.

HRMS calculated for $C_{14}H_{15}F_3O_4S$ $[M]^+$ 336.0638, found 336.0643.

3-ethyl-3-(4-methylbenzyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (6i)



Colourless oil.

R_f 0.32 (hexane).

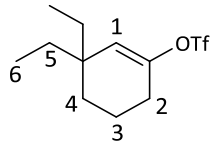
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm)= 7.12 (d, *J* = 7.9 Hz, 2H, H_8), 7.03 (d, *J* = 7.9 Hz, 2H, H_9), 5.48 (t, *J* = 1.5 Hz, 1H, H_1), 2.70 (d, *J* = 13.3 Hz, 1H, H_{7a}), 2.64 (d, *J* = 13.3 Hz, 1H, H_{7b}), 2.36 (s, 3H, H_{10}), 2.31 – 2.25 (m, 2H, H_2), 1.86 – 1.70 (m, 2H, H_3), 1.50 – 1.45 (m, 2H, H_4), 1.44 – 1.38 (m, 2H, H_5), 0.92 (t, *J* = 7.5 Hz, 3H, H_6).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 148.4, 135.9, 134.3, 130.4, 128.7, 126.0, 118.5 (q, *J* = 320.2 Hz), 44.9, 40.1, 31.5, 30.2, 27.5, 21.0, 19.2, 8.2.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.1.

HRMS calculated for $C_{17}H_{21}F_3O_3S$ $[M]^+$ 362.1158, found 362.1163.

3,3-diethylcyclohex-1-en-1-yl trifluoromethanesulfonate (6k)



Colourless oil.

R_f 0.51 (hexane).

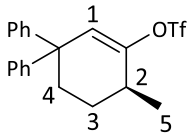
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.55 (t, *J* = 1.4 Hz, 1H, H_1), 2.30 (td, *J* = 6.3, 1.4 Hz, 2H, H_2), 1.82 – 1.77 (m, 1H, H_3), 1.47 – 1.38 (m, 6H, H_4, H_5), 0.86 (t, *J* = 7.5 Hz, 6H, H_6).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 148.7, 126.1, 118.5 (q, *J* = 320.2 Hz), 38.8, 31.0, 30.0, 27.5, 19.3, 7.9.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.0.

HRMS calculated for $C_{11}H_{17}F_3O_3S$ $[M]^+$ 286.0845, found 286.0849.

(*S*)-4'-methyl-3',4'-dihydro-2'H-(1,1':1',1''-terphenyl)-5'-yl trifluoromethanesulfonate (6m)



Colourless oil.

R_f 0.27 (hexane:ethyl acetate 50:1).

^{1}H-NMR (400 MHz, C_6D_6) δ (ppm) = 7.24 – 6.95 (m, 10H, Ar-H), 6.21 (d, *J* = 1.6 Hz, 1H, H_1), 2.37 – 2.27 (m, 1H, H_2), 2.04 (ddd, *J* = 13.5, 8.4, 2.6 Hz, 1H, H_{4a}), 1.87 (ddd, *J* = 13.5, 9.8, 2.7 Hz, 1H, H_{4b}), 1.46 (dddd, *J* = 10.9, 8.4, 6.2, 2.7 Hz, 1H, H_{3a}), 1.07 (app tdd, *J* = 10.5, 6.9, 2.6 Hz, 1H, H_{3b}), 0.86 (d, *J* = 7.0 Hz, 3H, H_5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 153.4, 147.1, 146.6, 129.4, 128.47, 128.4, 127.7, 127.5, 126.5, 126.5, 126.0, 118.5 (q, *J* = 319.9 Hz), 49.9, 33.5, 32.5, 28.0, 17.5.

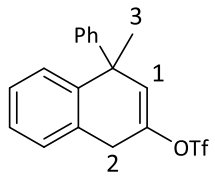
^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.3.

HRMS calculated for $C_{20}H_{19}F_3O_3S$ $[M]^+$ 396.1002, found 396.1002.

$[\alpha]^{16}_D$= -197° (*c* 0.1, DCM).

The enantiomeric ratio was determined by HPLC in comparison with the racemate. [Daicel CHIRALPAK ODH, 250 x 4.6 mm, hexane, 0.5 mL/min, 196.6 nm, t_R (major)= 27.2 min, t_R (minor)= 35.6 min].

4-methyl-4-phenyl-1,4-dihydronaphthalen-2-yl trifluoromethanesulfonate (6n)



Yellow oil.

R_f 0.17 (hexane:ethyl acetate 30:1).

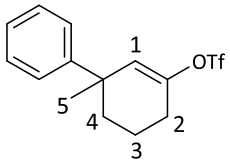
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.38 – 6.93 (m, 9H, Ar-H), 5.87 (t, *J* = 1.6Hz, 1H, H_1), 3.90 (d, *J* = 1.6 Hz, 2H, H_2), 1.88 (s, 3H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 147.0, 144.7, 140.8, 129.8, 128.5, 128.4, 128.2, 127.3, 127.1, 126.6, 126.4, 126.2, 118.2 (q, *J* = 320.5 Hz), 45.9, 31.7, 28.9.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.2.

HRMS calculated for $C_{18}H_{15}F_3O_3S$ $[M]^+$ 368.0689, found 368.0699.

1-methyl-1,4,5,6-tetrahydro-(1,1'-biphenyl)-3-yl trifluoromethanesulfonate (6p)



Colourless oil.

R_f 0.36 (hexane).

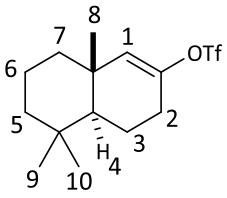
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.35 – 7.17 (m, 5H, Ar-H), 5.81 (t, *J* = 1.7 Hz, 1H, H_1), 2.38 – 2.31 (m, 2H, H_2), 1.80 – 1.54 (m, 4H, H_3, H_4), 1.46 (s, 3H, H_5).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 149.4, 147.3, 128.3, 126.3, 126.2, 126.1, 118,5 (q, *J* = 320.2 Hz), 40.8, 37.8, 28.6, 27.5, 19.3.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.0.

HRMS calculated for $C_{14}H_{15}F_3O_3S$ $[M]^+$ 320.0689 found 320.0702.

(4a*S,8a*S**)-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl trifluoromethanesulfonate (6q)**



Colourless oil.

R_f 0.41 (hexane).

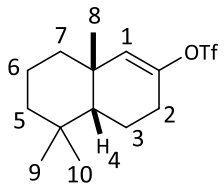
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.48 (t, *J* = 1.5 Hz, 1H, H_1), 2,43 – 2.36 (m, 2H, H_2), 1.95 – 1.84 (m, 1H, H_{3a}), 1.72 – 1.43 (m, 5H, H_{3b}, H_{5a}, H_6, H_{7a}), 1.37 – 1.13 (m, 3H, H_4, H_{5b}, H_{7b}), 1.08 (s, 3H, H_9), 0.94 (s, 3H, H_{10}), 0.86 (s, 3H, H_8).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 147.8, 130.9, 118.5 (q, *J* = 320.3 Hz), 50.2, 41.7, 39.1, 35.9, 32.9, 32.9, 29.0, 21.3, 21.2, 19.0, 18.7.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.3.

HRMS calculated for $C_{14}H_{21}F_3O_3S$ $[M]^+$ 326.1158, found 326.1165.

(4a*R,8a*S**)-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl trifluoromethanesulfonate (6q')**



Colourless oil.

R_f 0.41 (hexane).

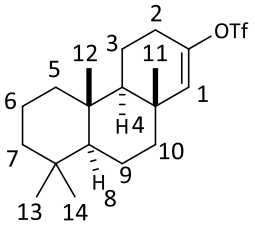
Isolated as a 4:1 mixture of **6q'**: **6q**. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.51 (t, *J* = 1.5 Hz, 1H, H_1, **6q'**), 5.48 (t, *J* = 1.5 Hz, 1H, H_1, **6q**) 2,43 – 2.20 (m, 3H, **6q**, **6q'**), 2.16 – 2.03 (m, 1H, **6q**, **6q'**), 1.99 – 1.84 (m, 1H, **6q**, **6q'**), 1.69 – 1.16 (m, 8H, $H_{4,}$ H_{5b}, H_{7b}, **6q**, **6q'**), 1.16 (s, 3H, H_9, **6q'**), 1.08 (s, 3H, H_9, **6q**), 1.04 (m, 3H, H_{10}, **6q'**), 0.99 (s, 3H, H_9, **6q'**) 0.94 (s, 3H, H_{10}, **6q**), 0.86 (s, 3H, H_8, **6q**).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.9 (**6q'**), 147.8 (**6q**), 130.9 (**6q**), 129.3 (**6q'**), 119.0 (q, *J* = 320.3 Hz, **6q'**), 50.2 (**6q**), 47.8 (**6q'**), 41.7 (**6q**), 40.8 (**6q'**), 39.7 (**6q'**), 39.1 (**6q**), 37.0 (**6q'**), 36.3 (**6q**), 34.3 (**6q'**), 32.9 (**6q**), 32.9 (**6q**), 32.6 (**6q'**), 32.3 (**6q'**), 29.0 (**6q**), 26.7 (**6q'**), 26.4 (**6q'**), 21.3 (**6q**), 21.2 (**6q**), 20.8 (**6q'**), 19.8 (**6q'**), 19.0 (**6q**), 18.7 (**6q**).

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -71.4, -74.3.

HRMS calculated for $C_{14}H_{21}F_3O_3S$ $[M]^+$ 326.1158, found 326.1149.

(4b*S,8a*S**,10a*R**)-4b,8,8,10a-tetramethyl-3,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydrophenanthren-2-yl trifluoromethanesulfonate (6r)**



Colourless oil.

R_f 0.67 (hexane).

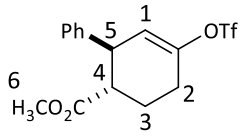
Isolated as a 3:1 mixture of diastereoisomers. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 5.43 (t, *J* = 1.4 Hz, 1H, H_1), 2,40 – 2.32 (m, 2H, H_{10}), 1.80 – 0.80 (m, 26H, H_2, H_3, H_4, H_5, H_6, H_7, H_8, H_9, H_{11}, H_{12}, H_{13}, H_{14}).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 147.6, 130.8, 118.5 (q, *J* = 320.3 Hz), 56.7, 54.6, 47.9, 42.0, 40.3, 39.5, 37.1, 36.2, 33.2, 28.9, 22.4, 21.3, 18.4, 17.9, 16.2.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.2.

HRMS calculated for $C_{19}H_{29}$ $[M-148]^+$ 245.2269, found 245.2275.

methyl (1*S,2*S**)-5-{[(trifluoromethyl)sulfonyl]oxy}-1,2,3,4-tetrahydro-(1,1'-biphenyl)-2-carboxylate (6s)**



Colourless oil.

R_f 0.63 (hexane:ethyl acetate 5:1).

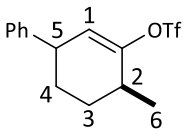
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.37 – 7.17 (m, 5H, Ar-H), 5.81 (dt, *J* = 3.1, 1.6 Hz, 1H, H_1), 4.04 – 3.98 (m, 1H, H_5), 3.62 (s, 3H, H_6), 2.66 – 2.43 (m, 3H, H_2, H_4), 2.17 – 2.00 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 173.9, 148.8, 141.4, 128.8, 127.8, 127.4, 120.8, 118.5 (q, *J* = 320.3 Hz), 51.9, 47.1, 43.2, 26.5, 24.8.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -76.3.

HRMS calculated for $C_{14}H_{15}F_3O_3S$ $[M]^+$ 364.0592, found 364.0593.

4-methyl-1,4,5,6-tetrahydro-(1,1'-biphenyl)-3-yl trifluoromethanesulfonate (6u)



Yellow oil.

R_f 0.40 (hexane:ethyl acetate 20:1).

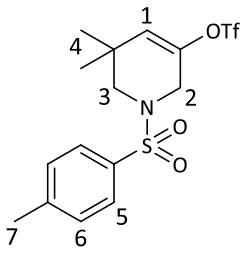
Isolated as a 2:1 mixture of diastereoisomers. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.53 – 7.06 (m, 5H, Ar-H), 5.86 (br s, 1H, H_{1minor}), 5.83 (br s, 1H, H_{1major}), 3.69 – 3.51 (m, 1H, $H_{5majorminor}$), 2.73 – 2.55 (m, 1H, H_{2major}), 2.52 – 2.32 (m, 1H, H_{2minor}), 2.12 – 1.41 (m, 4H, $H_{3majorminor}$, $H_{4majorminor}$) 1.26 (d, *J* = 7.0 Hz, 3H, H_{6minor}), 1.22 (d, *J* = 6.9 Hz, 1H, H_{6major}).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.6, 152.1, 148.7, 147.6, 128.7, 128.7 (d, *J* = 3.3 Hz), 127.6 (d, *J* = 4.6 Hz), 127.5, 126.8, 121.7, 121.2 (d, *J* = 108.3 Hz), 42.0, 41.5 (d, *J* = 56.0 Hz), 32.7, 32.1, 30.7 (d, *J* = 6.8 Hz), 29.0, 28.0, (d, *J* = 115.6), 21.2, 17.9, 17.8.

^{19}F-NMR (282 MHz, $CDCl_3$) δ = -74.1, -75.1.

HRMS calculated for $C_{14}H_{15}F_3O_3S$ $[M]^+$ 320.0694, found 320.0689.

5,5-dimethyl-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl trifluoromethanesulfonate (6v)



Colourless oil.

R_f 0.27 (hexane:ethyl acetate 10:1).

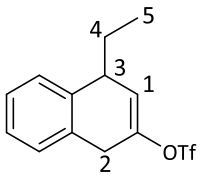
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.69 (d, *J* = 8.3 Hz, 2H, H_5), 7.38 (d, *J* = 8.3 Hz, 2H, H_6), 5.67 (t, *J* = 1.8 Hz, 1H, H_1), 3.68 (d, *J* = 1.8 Hz, 2H, H_2), 2.47 (s, 2H, H_3), 2.47 (s, 3H, H_7), 1,16 (s, 6H, H_4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 144.3, 141.7, 130.0, 127.6, 127.1, 118.3 (q, *J* = 321.6), 54.2, 45.2, 34.2, 26.2, 21.6.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -73.3.

HRMS calculated for $C_{15}H_{18}F_3NO_5S$ $[M]^+$ 413.0573, found 413.0581.

4-ethyl-1,4-dihydronaphthalen-2-yl trifluoromethanesulfonate (6t)



Yellow oil.

R_f 0.38 (hexane).

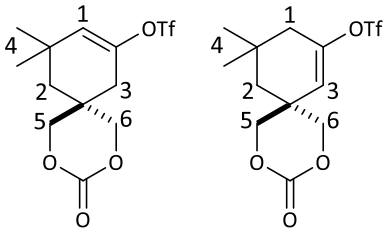
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.28 – 7.14 (m, 4H, Ar-H), 5.96 (dd, *J* = 5.2, 2.5 Hz, 1H, H_1), 3.90 – 3.52 (m, 3H, H_2, H_3), 1.90 – 1.79 (m, 2H, H_4), 0.82 (t, *J* = 7.5 Hz, 3H, H_5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 146.6, 135.5, 131.6, 128.2, 127.6, 127.0, 126.4, 119.7, 118.5 (q, *J* = 320.3 Hz), 40.9, 31.9, 30.4, 9.3.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -74.2.

HRMS calculated for $C_{13}H_{13}F_3O_3S$ $[M]^+$ 306.0532, found 306.0539.

10,10-dimethyl-3-oxo-2,4-dioxaspiro[5.5]undec-8-en-8-yl trifluoromethanesulfonate (6w)



A **B**

Colourless oil.

R_f 0.15 (hexane:ethyl acetate 2:1).

Isolated as a 3:1 mixture of isomers, being **A** major isomer. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 5.68 (s, 1H, H_{1A}), 5.54 (s, 1H, H_{3B}), 4.23 (m, 4H, H_{5A} H_{6A}), 4.10 (m, 4H, H_{5B} H_{6B}), 2.42 (s, 2H, H_{3A}), 2.17 (s, 2H, H_{3B}), 1.52 (s, 2H, H_{2A}), 1.47 (s, 2H, H_{2B}), 1.13 (s, 6H, H_{4A}), 1.09 (s, 6H, H_{4B}).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 147.6, 145.9, 145.2, 143.4, 128.0, 127.3, 118.4 (q, *J* = 320.4 Hz), 75.2, 39.6, 39.2, 33.3, 32.6, 32.5, 32.2, 31.7, 31.0, 30.6.

^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -73.5, -73.7.

HRMS calculated for $C_{12}H_{15}F_3O_6S$ $[M]^+$ 354.0541, found 354.0547.

Procedure for the synthesis of pallescensin A from 6q

Diethylamine (7.17 mL, 69.3 mmol, 5 equiv.), ethynyltrimethylsilane (2.15 mL, 15.25 mmol, 1.1 equiv.), copper iodide (263 mg, 10 mol%) and bis(triphenylphosphine)palladium(II) dichloride (486 mg, 5 mol %) were added in this order at room temperature to a solution of (4a*S**,8a*S**)-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl trifluoromethanesulfonate **6q** (4.07 g; 12.5 mmol) in dry diethyl ether (70 mL). The resulting mixture was stirred at room temperature for 3 h under an argon atmosphere. After this time, 40 mL of a saturated aqueous solution of ammonium chloride were added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2x). The organic extracts were dried over anhydrous sodium sulfate and the volatile components were removed under reduced pressure. The resulting residue was dissolved in 10 mL of hexane and filtered through a short plug of silica gel. Trimethyl{[(4a*S**,8a*R**)-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl]ethynyl}silane **8** (3.42 g) was obtained as a colourless oil that was used in the next step without further purification.

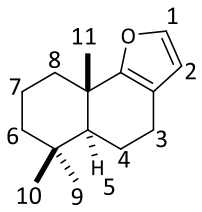
Potassium fluoride (848 mg, 15 mmol, 1.3 equiv.) was added to a solution of trimethyl{[(4a*S**,8a*R**)-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl]ethynyl}silane **8** (3.42 g) in dry methanol (11 mL) and the mixture was refluxed for 12 h. After this time, 15 mL of water were added and methanol was removed under reduced pressure. Then, 15 mL of diethyl ether were added to the aqueous residue. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2x). The organic extracts were dried over anhydrous sodium sulphate and the volatile components were removed under reduced pressure. (4a*S**,8a*R**)-7-Ethynyl-4,4,8a-trimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene **9** (2.25 g; 11,1 mmol) was obtained as a colourless oil that was used in the next step without further purification.

3-Chloroperbenzoic acid (3.87 g, 22.4 mmol, 2 equiv.) was added portionwise to a solution of (4a*S**,8a*R**)-7-ethynyl-4,4,8a-trimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene **9** (2.25 g) in dry dichloromethane (70 mL). The resulting mixture was stirred for 2 h at room temperature. After this time, the reaction was quenched with 20 mL of an aqueous 2 M sodium hydroxide solution. The organic phase was separated

and the aqueous phase was extracted with dichloromethane (2x). The organic extracts were dried over anhydrous sodium sulfate and the volatile components were removed under reduced pressure. Thus, (3a*S**,7a*S**)-1a-ethynyl-4,4,7a-trimethyldecahydronaphtho[1,2-*b*]oxirane **10** (2.23 g; 10.2 mmol) was obtained as a colourless oil that was used in the next step without further purification.

Methanol (84 µL, 20 mol%), chloro(triphenylphosphine)gold(I) (240 mg, 5 mol%) and silver trifluoromethanesulfonate (137 mg, 5 mol%) were added to a solution of (3a*S**,7a*S**)-1a-ethynyl-4,4,7a-trimethyldecahydronaphtho[1,2-b]oxirane **10** (2.23 g, 10.2 mmol) in dry dichloromethane (30 mL). The resulting mixture was stirred at room temperature for 12 h under an argon atmosphere. After this time, volatile components were carefully removed and the residue was purified by flash chromatography on silica gel using hexane as eluent to yield pallescensin A (1.1 g; 5.05 mmol) as colourless oil.

pallescensin A



Colourless liquid.

R_f 0.7 (hexane).

^{1}H-NMR (300 MHz, CD_2Cl_2) δ (ppm) = 7.21 (d, *J* = 1.8Hz, 1H, H_1), 6.14 (d, *J* = 1.8 Hz, 1H, H_2), 2.56 – 2.31 (m, 2H, H_3), 2.19 – 2.08 (m, 1H, H_{7a}), 1.92 – 1.13 (m, 7H, H_4, H_6, H_{7a}, H_8), 1.22 (s, 3H, H_{11}), 0.96 (s, 3H, H_9), 0.93 (s, 3H, H_{10}).

^{13}C-NMR (75 MHz, CD_2Cl_2) δ (ppm) = 159.8, 140.0, 113.7, 110.1, 52.3, 41.9, 36.5, 35.5, 33.4, 33.0, 22.7, 21.4, 21.3, 19.5, 18.6.

HRMS calculated for $C_{15}H_{22}O$ $[M]^+$ 218.1671, found 218.1675.

Procedure for the synthesis of austrodoral from 6q

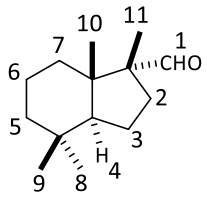
4. Procedure for the synthesis of austrodoral from dienyne 6q

A solution of methylmagnesium bromide (3M in Et_2O, 11.5 mL, 3 equiv.) was rapidly added at room temperature to a THF (150 mL) solution of (4a*S**,8a*S**)-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl trifluoromethanesulfonate **6q** (3.75 g, 11.5 mmol) containing iron(III) acetylacetonate (180 mg, 5 mol%) and dry methylpyrrolidone (10 mL). This caused an immediate colour change from orange-red to brown/black. The mixture was stirred for 12 h at room temperature and then quenched with a saturated aqueous solution of ammonium chloride (100 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3x). The organic extracts were dried over anhydrous sodium sulfate and the volatile components were removed under reduced pressure. Then, the residue was dissolved in hexane (20 mL) and filtered through a short pad of silica gel. (4a*S**,8a*R**)-4,4,7,8a-tetramethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene **11** (1.54 g; 7.9 mmol) was obtained as a colourless liquid and used in the next step without further purification.

3-Chloroperbenzoic acid (2.76 g, 16 mmol, 2 equiv.) was added portionwise to a solution of (4a*S**,8a*R**)-4,4,7,8a-tetramethyl-1,2,3,4,4a,5,6,8a-octahydronaphtalene **11** (1.54 g) in dry dichloromethane (50 mL) at room temperature. The resulting mixture was stirred for 2 h and then quenched with 10 mL of an aqueous 2 M solution of sodium hydroxide. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3x). The organic extracts were dried over anhydrous sodium sulfate and the volatile components were removed under reduced pressure. (1a*R**,3a*S**,7a*S**,7b*S**)-1a,4,4,7a-tetramethyldecahydronaphtho[1,2-b]oxirane **12** (1.52 g; 7.3 mmol) was obtained as a colourless liquid and used in the next step without further purification.

Boron trifluoride THF complex (40 µL, 5 mol %) was added to a solution of (1a*R**,3a*S**,7a*S**,7b*S**)-1a,4,4,7a-tetramethyldecahydronaphtho[1,2-*b*]oxirane **12** (1.52 g) in dry dichloromethane (35 mL) at room temperature. The mixture was stirred for 30 min and then the volatile components were removed under reduced pressure. The residue was purified by flash chromatography on basic aluminium oxide using hexane as eluent. Pure austrodoral (1.2 g, 5.76 mmol) was thus obtained as colourless oil.

austrodoral



Colourless liquid.

R_f 0.7 (hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.69 (s, 1H, H_1), 2.22 – 2.11 (m, 1H, H_4), 1.76 – 0.76 (m, 10H, H_2, H_3, H_5, H_6, H_7), 1.05 (s, 3H, H-Me), 0.89, (s, 3H, H-Me), 0.88, (s, 3H, H-Me), 0.86, (s, 3H, H-Me).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 208.5, 58.7, 55.1, 47.0, 41.5, 34.0, 33.6, 33.5, 28.9, 21.8, 21.8, 20.0, 16.9, 16.3.

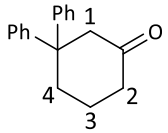
HRMS calculated for $C_{14}H_{24}O$ $[M]^+$ 208.1827, found 208.1832.

Chapter 2 – part B

Synthesis of compounds 7

To a solution of the corresponding alkynol **1**, or enyne **2** (0.3 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (3 mL) tetrafluoroboric acid, diethyl ether complex (0.015 mmol, 2 µL, 0.05 equivalents) was dropwise added (in the case of enynes **2**, water (0.3 mmol, 5.4 µL, 1 equivalent) was added prior to tetrafluoroboric acid). The reaction was then gently stirred at room temperature for the stated time. After this time the mixture was diluted with diethyl ether (5 mL) and quenched with sodium acetate (25 mg). The mixture was filtered and the volatile components were removed under reduced pressure. The crude was purified by flash chromatography on silica gel to give pure cyclohexanones **7**.

3,3-diphenylcyclohexan-1-one (7a)



Colourless oil.

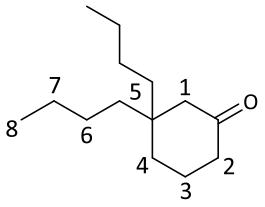
R_f 0.30 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.36 – 7.16 (m, 10H, Ar-H), 2.99 (s, 2H, H_1), 2.65 – 2.57 (m, 2H, H_2), 2.38 (t, *J* = 6.7 Hz, 2H, H_4), 1.77 – 1.65 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 210.7, 147.3, 128.5, 127.0, 126.3, 53.7, 50.4, 40.8, 35.7, 21.1.

HRMS calculated for $C_{18}H_{18}NaO$ $[M+Na]^+$ 273.1250, found 273.1248.

3,3-dibutylcyclohexan-1-one (7e)



Colourless oil.

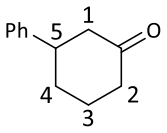
R_f 0.37 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.28 (t, *J* = 6.7 Hz, 2H, H_2), 2.16 (s, 2H, H_1), 1.90 – 1.78 (m, 2H, H_3), 1.62 – 1.55 (m, 2H, H_4), 1.34 – 1.08 (m, 12H, H_5, H_6, H_7), 0.90 (t, *J* = 7.0 Hz, 3H, H_8).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 212.8, 52.3, 41.1, 40.8, 36.9, 33.8, 25.1, 23.4, 21.7, 14.1.

HRMS calculated for $C_{14}H_{26}NaO$ $[M+Na]^+$ 233.1876, found 233.1876.

3-phenylcyclohexan-1-one (7f)



Colourless oil.

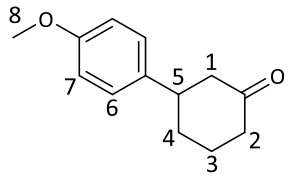
R_f 0.31 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.40 – 7.21 (m, 5H, Ar-H), 3.11 – 2.96 (m, 1H, H_5), 2.68 – 2.33 (m, 4H, H_1, H_2), 2.22 – 2.06 (m, 2H, H_4), 1.96 – 1.71 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 211.0, 144.3, 128.7, 126.7, 126.6, 49.0, 44.8, 41.2, 32.8, 25.5.

HRMS calculated for $C_{12}H_{14}NaO$ $[M+Na]^+$ 197.0937, found 197.0934.

3-(4-methoxyphenyl)cyclohexan-1-one (7g)



Colourless oil.

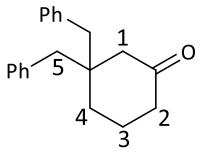
R_f 0.23 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.16 (d, *J* = 8.5 Hz, 2H, H_6), 6.89 (d, *J* = 8.5 Hz, 2H, H_7), 3.81 (s, 3H), 3.04 – 2.93 (m, 1H, H_5), 2.64 – 2.31 (m, 4H, H_1, H_2), 2.21 – 2.03 (m, 2H, H_4), 1.91 – 1.68 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 211.2, 158.3, 136.6, 127.5, 114.0, 55.3, 49.2, 44.0, 41.2, 33.0, 25.5.

HRMS calculated for $C_{13}H_{16}NaO_2$ $[M+Na]^+$ 227.1043, found 227.1039.

3,3-dibenzylcyclohexan-1-one (7h)



Colourless oil.

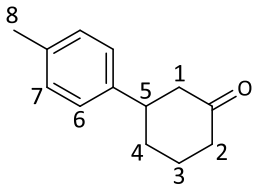
R_f 0.37 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.37 – 7.10 (m, 10H, Ar-H), 2.70 (d, *J* = 13.4 Hz, 2H, H_{5a}), 2.57 (d, *J* = 13.4 Hz, 2H, H_{5b}), 2.26 – 2.17 (m, 4H, H_1, H_2), 2.11 – 1.98 (m, 2H, H_4), 1.70 – 1.61 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 212.9, 137.3, 131.1, 128.0, 126.4, 49.3, 44.8, 43.4, 40.5, 31.9, 21.7.

HRMS calculated for $C_{20}H_{22}NaO$ $[M+Na]^+$ 301.1563, found 301.1562.

3-(p-tolyl)cyclohexan-1-one (7j)



Colourless oil.

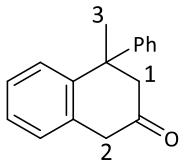
R_f 0.35 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.20 – 7.11 (m, 4H, Ar-H), 3.07 – 2.94 (m, 1H, H_5), 2.65 – 2.37 (m, 4H, H_1, H_2), 2.36 (s, 3H, H_8), 2.21 – 2.05 (m, 2H, H_4), 1.93 – 1.70 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 211.2, 141.4, 136.3, 129.3, 126.4, 49.1, 44.4, 41.2, 32.9, 25.6, 21.0.

HRMS calculated for $C_{13}H_{16}NaO$ $[M+Na]^+$ 211.1093, found 211.1093.

4-methyl-4-phenyl-3,4-dihydronaphthalen-2(1H)-one (7n)



Colourless oil.

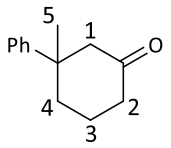
R_f 0.30 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.56 – 7.05 (m, 9H, Ar-H), 3.48 (d, *J* = 20.5 Hz, 1H, H_{2a}), 3.33 – 3.23 (m, 2H, H_{1a}, H_{2b}), 2.66 (d, *J* = 16.7 Hz, 1H, H_{1b}), 1.75 (s, 3H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 209.5, 145.8, 143.6, 133.4, 128.8, 128.6, 127.3, 127.0, 126.5, 126.3, 126.0, 52.5, 44.9, 44.2, 29.6.

HRMS calculated for $C_{17}H_{16}NaO$ $[M+Na]^+$ 259.1093, found 259.1092.

3-methyl-3-phenylcyclohexan-1-one (7p)



Colourless oil.

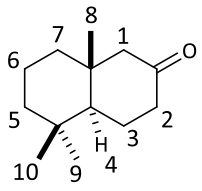
R_f 0.27 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.37 – 7.18 (m, 5H, H-Ar), 2.91 (d, *J* = 14.2 Hz, 1H, H_{1a}), 2.46 (d, *J* = 14.2 Hz, 1H, H_{1b}), 2.34 (t, *J* = 6.8 Hz, 2H, H_2), 2.21 (dddd, *J* = 8.0, 5.6, 3.7, 1.5 Hz, 1H, H_{4a}), 2.00 – 1.82 (m, 2H, H_{4b}, H_{3a}), 1.77 – 1.61 (m, 1H, H_{3b}), 1.35 (s, 3H, H_5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 211.5, 147.4, 128.5, 126.2, 125.6, 53.1, 42.8, 40.8, 37.4, 29.8, 22.0.

HRMS calculated for $C_{13}H_{16}NaO$ $[M+Na]^+$ 211.1093, found 211.1092.

(4a*S,8a*R**)-5,5,8a-trimethyloctahydronaphthalen-2-(1H)-one (7q)**



White solid.

Melting point: 128 – 130 ^{0}C.

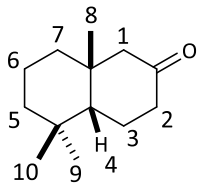
R_f 0.43 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.48 – 2.38 (m, 1H, H_4), 2.29 (td, *J* = 13.6, 7.2 Hz, 1H, H_{2a}), 2.15 (d, *J* = 13.2 Hz, 1H, H_{1a}), 2.07 – 1.95 (m, 2H, H_{1b}, H_{2b}), 1.76 – 1.19 (m, 8H, H_3, H_5, H_6, H_7), 0.97, 0.90, 0.86 (3s, 3H, H-Me).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 211.8, 59.6, 52.1, 42.3, 42.0, 42.0, 38.4, 33.3, 33.2, 23.1, 21.4, 19.4, 18.8.

HRMS calculated for $C_{13}H_{22}NaO$ $[M+Na]^+$ 217.1563, found 217.1563.

(4a*R,8a*R**)-5,5,8a-trimethyloctahydronaphthalen-2-(1H)-one (7q')**



Colourless oil.

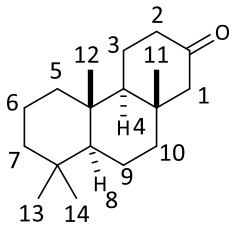
R_f 0.43 (hexane:ethyl acetate 10:1).

Isolated as a 3:1 mixture of **7q'**:**7q**. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.72 (d, *J* = 14.5 Hz, 1H, **7q'**H_{1a}), 2.50 – 1.95 (m, 6H, **7q**H_1, **7q**H_2, **7q**H_4, **7q'**H_2, **7q'**H_4), 1.86 (ddd, *J* = 14.5, 1.4, 1.4 Hz, 1H, H_{1b}), 1.73 – 1.20 (m, 11H, **7q7q'**H_3, **7q7q'**H_5, **7q7q'**H_6, **7q7q'**H_7), 1.12 (s, 3H, **7q'**), 1.04 (s, 3H, **7q'**), 0.98 (s, 3H, **7q'**), 0.97 (s, 1H, **7q**), 0.90 (s, 1H, **7q**), 0.86 (s, 1H, **7q**).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 213.9, 211.8, 59.6, 52.1, 50.5, 47.9, 42.3, 42.0, 42.0, 41.8, 40.3, 38.9, 38.4, 34.5, 33.3, 31.4.

HRMS calculated for $C_{13}H_{22}NaO$ $[M+Na]^+$ 217.1563, found 217.1561.

(4a*S,4b*S**,8a*S**,10a*S**)-4b,8,8,10a-tetramethyldodecahydrophenanthren-2-(1H)-one (7r)**



White solid

Melting point: 123 – 125 °C.

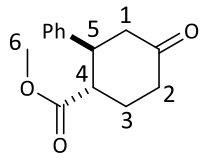
R_f 0.27 (hexane:ethyl acetate 10:1).

Isolated as a 3:1 mixture of diastereoisomers. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.43 – 2.33 (m, 1H), 2.32 – 2.10 (m, 2H), 2.03 – 0.75 (m, 15H), 0.89 (s, 3H), 0.88 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 212.9 (***diast minor***), 212.0 (***diast major***), 60.0 (***diast major***), 57.5 (***diast minor***), 57.1 (***diast major***), 56.8 (***diast major***), 54.8 (***diast minor***), 47.1 (***diast minor***), 43.3 (***diast major***), 42.7 (***diast minor***), 42.2 (***diast major***), 41.7 (***diast major***), 41.5 (***diast minor***), 40.9 (***diast minor***), 40.2 (***diast major***), 39.2 (***diast major***), 38.5 (***diast minor***), 38.4 (***diast minor***), 37.8 (***diast major***), 34.7 (***diast minor***), 33.6 (***diast major***), 33.5 (***diast major***), 32.1 (***diast minor***), 25.8 (***diast minor***), 25.6 (***diast minor***), 22.2 (***diast major***), 21.9 (***diast minor***), 21.7 (***diast major***), 20.6 (***diast major***), 19.8 (***diast minor***), 19.0 (***diast minor***), 18.7 (***diast major***), 18.7 (***diast major***), 16.0 (***diast major***).

HRMS calculated for $C_{18}H_{30}NaO$ $[M+Na]^+$ 285.2189, found 285.2189.

methyl (1*S,2*S**)-4-oxo-2-phenylcyclohexane-1-carboxylate (7s)**



Colourless oil.

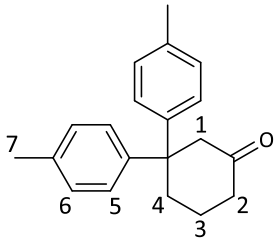
R_f 0.23 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.41 – 7.15 (m, 5H, Ar-H), 3.48 (s, 3H, H_6), 3.32 (td, *J* = 10.9, 6.2 Hz, 1H, H_5), 3.02 (td, *J* = 10.9, 3.5 Hz, 1H), 2.70 – 2.41 (m, 4H, H_1, H_2), 2.39 – 2.25 (m, 1H, H_{3a}), 2.14 – 1.95 (m, 1H, H_{3b}).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 208.7, 174.0, 141.6, 128.8, 127.2, 126.7, 51.7, 48.6, 47.6, 46.5, 39.8, 28.5.

HRMS calculated for $C_{14}H_{16}NaO_3$ $[M+Na]^+$ 255.0992, found 255.0987.

3,3-di-p-tolylcyclohexan-1-one (7x)



Colourless oil.

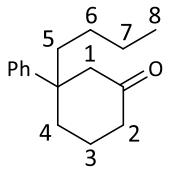
R_f 0.23 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.19 – 7.04 (m, 8H, Ar-H), 2.95 (s, 2H, H_1), 2.56 (dd, *J* = 7.0, 4.6 Hz, 2H, H_2), 2.36 (t, *J* = 6.7 Hz, 2H, H_4), 2.32 (s, 3H, H_7), 1.75 – 1.67 (m, 2H, H_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 210.9, 144.5, 135.7, 129.2, 126.8, 53.8, 49.8, 40.8, 35.8, 21.2, 20.9.

HRMS calculated for $C_{20}H_{22}NaO$ $[M+Na]^+$ 301.1563, found 301.1561.

3-butyl-3-phenylcyclohexan-1-one (7y)



Colourless oil.

R_f 0.23 (hexane:ethyl acetate 10:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.37 – 7.17 (m, 5H, Ar-H), 2.93 (d, *J* = 14.3 Hz, 1H, H_{1a}), 2.46 (d, *J* = 14.3 Hz, 1H, H_{1b}), 2.41 – 2.13 (m, 3H, H_2, H_{4a}), 2.01 (ddd, *J* = 13.6, 9.9, 3.5 Hz, 1H, H_{5a}), 1.93 – 1.51 (m, 4H, H_3, H_{4b}, H_{5b}), 1.30 – 0.83 (m, 4H, H_6, H_7), 0.79 (t, *J* = 7.2 Hz, 3H, H_8).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 211.5, 145.3, 128.4, 126.3, 126.0, 51.1, 46.1, 42.9, 41.0, 36.5, 25.6, 23.1, 21.5, 13.9.

HRMS calculated for $C_{16}H_{22}NaO$ $[M+Na]^+$ 253.1563, found 253.1562.