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Synthesis and Applications of Cyclohexenyl Halides Obtained by a Cationic Carbocyclization Reaction

Pedro Alonso,[a] Pilar Pardo,[a] Raquel Fontaneda,[a] Francisco J. Fañanás,*[a] and Félix Rodríguez*[a]

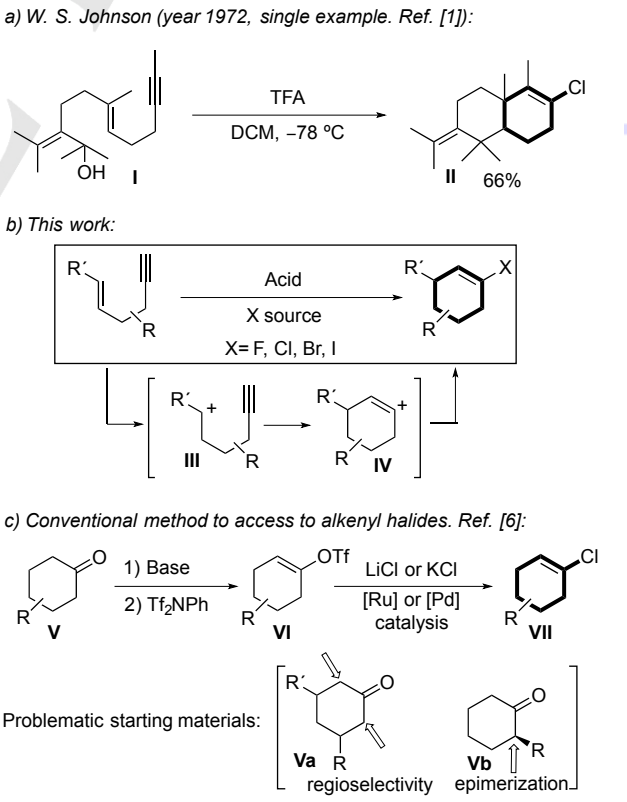
Dedication ((optional))

Abstract: The synthesis of cyclic alkenyl halides (mainly fluorides, chlorides and bromides) from alkynol or enyne derivatives through an acid mediated cationic cyclization reaction is disclosed. This high-yielding, scalable and technically very simple method complements and challenges conventional methodologies. This study includes the development of biomimetic cationic cyclization reactions of polyenyne derivatives to give interesting halogen-containing polycyclic compounds. The application of this reaction in the key step of the synthesis of two terpenes, austrodoral and pallescensin A, and a potent odorant, 9-epi-Ambrox, demonstrates the potential of the cationic cyclization process here presented.

Introduction

In the year 1972 W. S. Johnson and co-workers published a work where they reported the transformation of dienynol **I** into the chlorodiene **II** by treatment of the starting material with an excess of trifluoroacetic acid in dichloromethane at low temperature (Scheme 1a).[1] Although this is a remarkable transformation, probably because just a single example is reported,[2] this work seems to have passed somewhat unnoticed by the synthetic organic community through the years.[3] However, we believed that this initial finding by Johnson and co-workers could be further exploited for the development of a general method for the synthesis of cyclic alkenyl halides (Scheme 1b). Thus, we thought that the treatment of a simple enyne derivative with an acid (H^+) should lead to the formation of a cation **III** that should be trapped by the alkyne to form the new alkenyl cation **IV**. The final reaction of this intermediate with a halide should deliver the desired alkenyl halides. It should be noted that alkenyl halides are versatile reagents widely used in metal-promoted cross-coupling reactions. Moreover, they may act as alkenyl electrophiles or alternatively they can be easily transformed into alkenyl nucleophiles by treatment with magnesium or lithium. Although alkenyl halides can be prepared by several methods, including elimination of hydrogen halides from dihaloalkanes or hydrometalation of alkynes followed by halogenolysis, one of the most reliable strategies to access cyclic alkenyl halides is the transformation of a ketone **V** into an alkenyl triflate **VI** by the protocol developed by McMurry,[4] followed by stannylation and halogenolysis.[5] Alternatively, some recent methods have appeared for the direct conversion of alkenyl triflate **VI** into the corresponding halide through metal catalysed reactions (Scheme 1c).[6] In any case, this sequence suffers from some important drawbacks. Thus, the control of the regiochemistry of the enolization reaction when both α- and α´-positions are similar (ketone **Va**) is difficult or almost impossible in some cases. Also, the basic conditions required in that initial step usually lead to racemization problems with ketones possessing an stereogenic centre at α-position (ketone **Vb**). In principle, all these shortcomings seem that could be surpassed if our proposed reaction were successful. Considering the interest of fluorine-containing molecules, the possibility of applying the proposed method to synthesize cyclohexenyl fluorides seems particularly appealing.

With all this in mind, we initiated an investigation with the aim of developing a cationic carbocyclization reaction for the synthesis of cyclic alkenyl halides.[7] Herein we present our results.



Scheme 1. Johnson's work, our proposal and conventional method for the synthesis of alkenyl halides.

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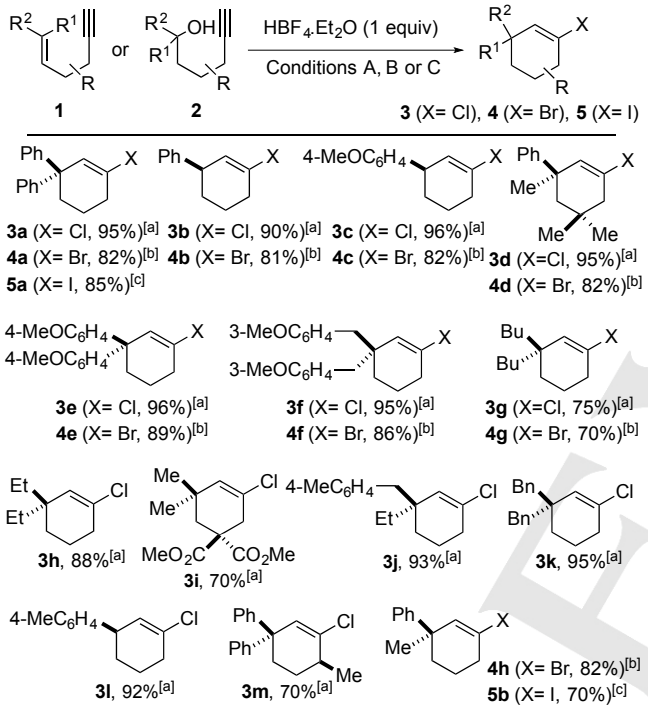
Results and Discussion

We started our investigation by checking if the single experiment reported by Johnson in the context of polyene cyclization reactions could be extended to the synthesis of simpler cyclohexyl chlorides. After some experimentation, we found that enyne derivatives **1** were completely transformed into the desired cyclohexenyl chlorides **3** when reacted with one equivalent of tetrafluoroboric acid ($HBF_4.Et_2O$) in dichloromethane as solvent at room temperature (Scheme 2; Conditions A).[8] Under these conditions, compounds **3** were isolated in very high yield in most cases.



Scheme 2. Cyclohexenyl chlorides (**3**), bromides (**4**) and iodides (**5**) through an acid mediated cationic cyclization. [a] Conditions A: $HBF_4{\cdot}Et_2O$ (1 equiv), CH_2Cl_2, RT. [b] Conditions B: $HBF_4{\cdot}Et_2O$ (1 equiv), dibromomethane, RT. [c] Conditions C: AlI_3 (1 equiv; instead of $HBF_4{\cdot}Et_2O$), iodomethane, RT.

Considering that the proposed intermediates **III** (see Scheme 1) could also be formed from alcohols **2** by a dehydration reaction in the presence of an acid, we tried the reactions not only with enynes **1** but also with alcohols **2**. Similar results in terms of chemical yield were observed independently on the starting material. The reaction of synthesis of cyclic alkenyl chlorides **3** from alcohols **2** is particularly remarkable because we did not observe the formation of the corresponding ketone derivatives coming from the capture of alkenyl cation **IV** by the water formed in the reaction as reported by Yamamoto and co-workers for similar processes.[3k] Another interesting issue of these reactions was the complete selectivity of the process when terminal alkynes were used. Thus, the addition of the alkyne to the cation **III** exclusively occurs through the terminal carbon of the alkyne to give six-membered rings. This is also in contrast with the results observed by Yamamoto and co-workers for internal alkynes.[3k] Thus, these authors reported not only the formation of ketone derivatives, as previously noted, but also the exclusive formation of five-membered rings coming from the addition of the internal carbon of the alkyne to the cationic intermediate similar to **III**.[9]

It seems that this reaction is limited to the synthesis of cyclohexenyl chlorides because we were not able to extend the method to the synthesis of other cycloalkenyl chlorides when using starting materials similar to **1** or **2** with a shorter or longer alkyl chain.

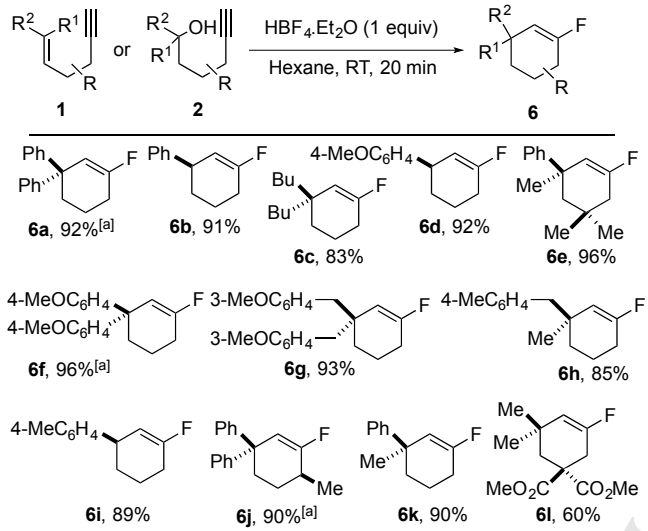
At this point, it should be remarked that the synthesis of compounds **3** would be very difficult through the conventional method shown in Scheme 1 because a selective enolization of the starting ketone would be almost impossible.

It should be noted that in these reactions the chlorine atom incorporated to the final product **3** comes from the solvent of the reaction, dichloromethane, which acts not only as solvent but also as a source of chloride. Interestingly, a simple solvent change from dichloromethane to dibromomethane allowed the synthesis of the corresponding cyclohexenyl bromides **4** in high yield (Scheme 2; Conditions B). After the successful synthesis of cyclic alkenyl chlorides and bromides we tried the synthesis of the corresponding iodides. The use of an iodinated solvent such as iodomethane, a potential source of iodide, led to the formation of the desired cyclohexenyl iodides **5** from alcohols **2** in low yield (< 20%). However, the change of the acid promoter from $HBF_4.Et_2O$ to aluminium iodide (AlI_3) in combination with iodomethane as solvent allowed access to the final products **5a,b** in moderate yield (Scheme 2; Conditions C).

Once we had demonstrated the feasibility of our method for the synthesis of cyclohexenyl chlorides, bromides and iodides we faced a more challenging goal, the synthesis of the corresponding fluorides.[10] In the above described method for the synthesis of cyclohexenyl halides, the halide is delivered by the solvent. However, due to the strength of the carbon-fluorine bond, the use of fluorinated solvents as potential fluoride sources did not seem an option. Though, we were aware about the possibility of the tetrafluoroborate anion to act as a source of fluoride in the absence of other nucleophiles.[11] Thus, we speculated that our desired cationic cyclization reaction to give alkenyl fluorides could be possible if the reaction was performed in the presence of tetrafluoroboric acid but in the absence of any other potential nucleophile (solvents that could act as source of nucleophiles or any external nucleophile). Under these circumstances, tetrafluoroboric acid would act not only as promoter (source of proton) but also as source of fluoride.[12]

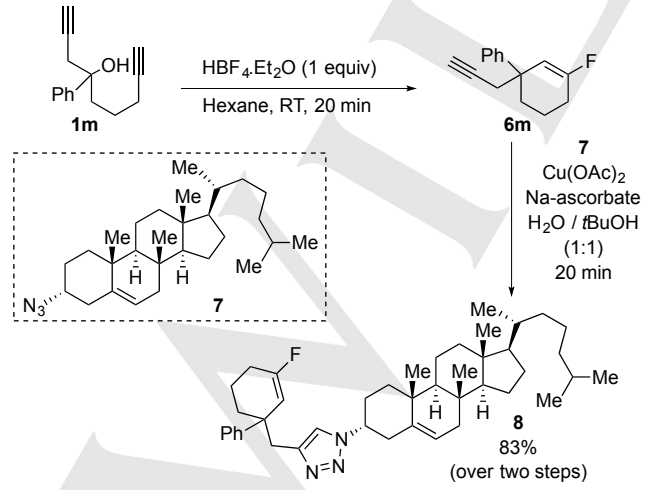
To test our hypothesis, a series of experiments were performed by reacting enyne derivatives **1** or alkynols **2** with one equivalent of tetrafluoroboric acid ($HBF_4.Et_2O$) in a variety of solvents. Obviously, conventional chlorinated solvents were not appropriate to get the desired cyclohexenyl fluorides because formation of the corresponding chlorinated products **3** was favoured. When alcoholic solvents were used, formation of ketones, probably coming from a hydrolysis of the initially generated enol ethers, was observed. A mixture of several

products was observed when benzene, toluene or acetonitrile were used. No reaction was perceived with other typical solvents such as diethyl ether, tetrahydrofuran, ethyl acetate or acetone. Finally, we found that formation of the desired cyclohexenyl fluorides **6** was efficient if hexane was used as solvent (Scheme 3). In most cases, the reactions were also successful when performed in hexafluorobenzene.



Scheme 3. Cyclohexenyl fluorides **6** through an acid mediated cationic cyclization. [a] 8 hours were required for completion of the reaction.

In the context of fluorination reactions, it should be noted that the reaction here described is fast, it does not require the use of any peculiar reagent or solvent, it is a metal-free reaction, it proceeds at room temperature in very high yield and it is amenable to gram-scale synthesis. As a demonstration of the potential of this reaction, we synthesized gram quantities of the cyclohexenyl fluoride **6m** from diyne derivative **1m** in high yield in just 20 minutes (Scheme 4).

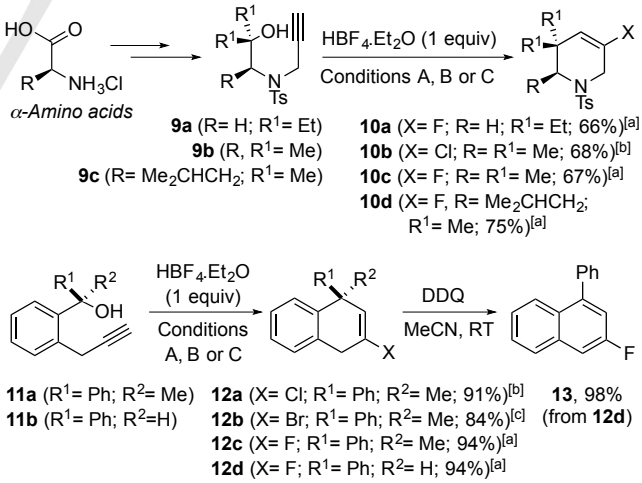


Scheme 4. Synthesis of the fluorine-labelled cholesterol derivative **8**.

Interestingly, this reaction is the result of a cyclization involving just one of the alkynes. No competitive reaction of the other alkyne in the cyclization process was noticed. However, the pendant alkyne moiety in **6l** allows further modification. For example, a conventional azide-alkyne cycloaddition reaction with cholesterol-derived azide **7** was performed (Scheme 4). Thus, compound **8** was isolated in high yield after 20 minutes. Interestingly, the short reaction time and efficiency of the sequence to get the fluorine-labelled compound **8** are in the range of those required for the synthesis of ^{18}F-labelled radiotracers for Positron Emission Tomography (PET) imaging. The potential application of the fluorination reaction here presented in this context seems an attractive field for future investigations.

Application of the cationic cyclization reaction in the synthesis of heterocycles and naphthalene derivatives

In an attempt to show some of the potential of our method in the context of synthesis of cyclic alkenyl halides, we have used this reaction to obtain some potentially useful compounds. In this context, we thought that α-amino acids were ideal templates for the synthesis of interesting halogen-containing heterocyclic derivatives through our strategy. Thus, by conventional organic chemistry reactions, α-amino acids such as glycine, alanine and leucine were easily transformed into alkynol derivatives **9** (Scheme 5). Further cyclization of these compounds under appropriate conditions afforded the halogen-containing tetrahydropyridine derivatives **10** in high yield. Along with being interesting structural motifs in organic synthesis, these tetrahydropyridine derivatives are important molecules in the context of medicinal chemistry.[13]



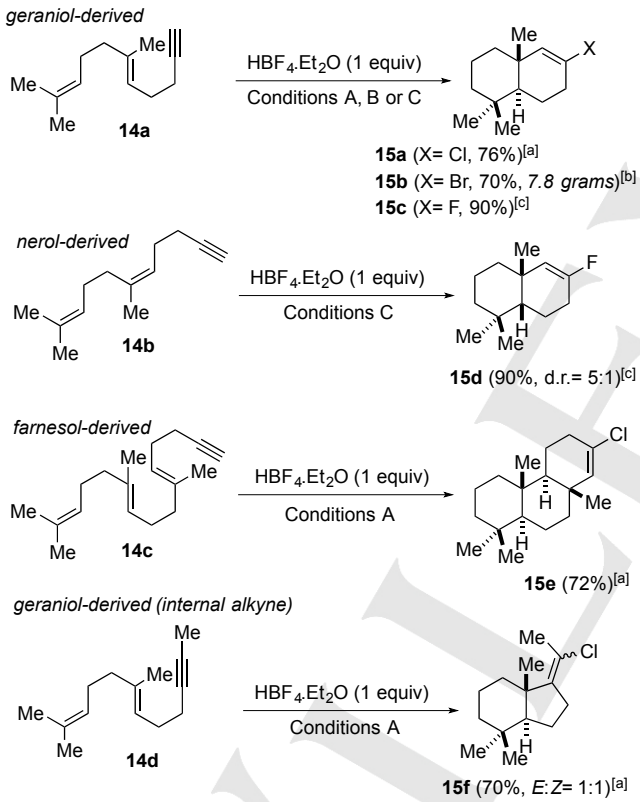
Scheme 5. Synthesis of halogenated tetrahydropyridines **10** and halogenated naphthalene derivatives **12** and **13**. [a] Conditions A: $HBF_4{\cdot}Et_2O$ (1 equiv), hexane, 50 ºC for **10** or RT for **12**. [b] Conditions B: $HBF_4{\cdot}Et_2O$ (1 equiv), dichloromethane, reflux for **10** or RT for **12**. [c] Conditions C: $HBF_4{\cdot}Et_2O$ (1 equiv), dibromomethane, RT.

Our cationic cyclization reaction is also an appropriate tool for the synthesis of interesting halonaphthalene derivatives, which

are also interesting molecules in several fields.[14] For example, easily available alkynol derivatives **11** were transformed into halogenated dihydronaphthalenes **12** under the optimized reaction conditions previously found (Scheme 5). The possibility of transforming these compounds into naphthalene derivatives was demonstrated by the reaction of **12d** with the oxidizing agent DDQ to get fluoronaphthalene **13**.

Biomimetic cyclizations and synthesis of terpenes

We have also extended the above commented reactions to some biomimetic polyenyne cyclizations (Scheme 6). Thus, when geraniol- or nerol-derived dienynes **14a,b** and farnesol-derived trienyne **14c** were reacted under appropriate conditions, the corresponding halogenated bi- and tricyclic meroterpenes **15a-e** were obtained in high yield. Interestingly, the geraniol-derived dienyne **14d** containing an internal alkyne did not produce the expected octahydronaphthalene derivative and instead, the indane derivative **15f** was isolated in high yield as mixture of isomers (*E*:*Z*= 1:1).

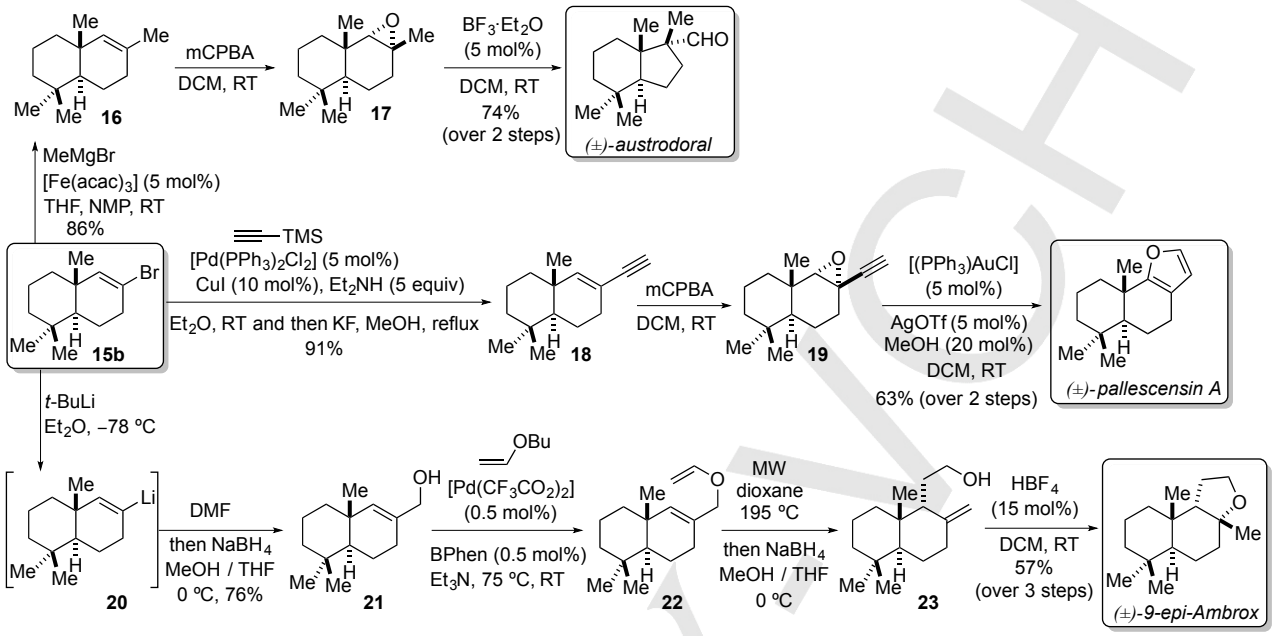


Scheme 6. Cyclizations of polyenynes **14**. [a] Conditions A: $HBF_4{\cdot}Et_2O$ (1 equiv), dichloromethane, RT. [b] Conditions B: $HBF_4{\cdot}Et_2O$ (1 equiv), dibromomethane, RT. [c] Conditions C: $HBF_4{\cdot}Et_2O$ (1 equiv), hexane, RT.

Some of these polycyclic halogen-containing products could be further elaborated to easily synthesize some natural products. More precisely, the bromine-containing derivatives are particularly attractive because of the wide synthetic possibilities that the carbon-bromine bond offers. As an illustration, we have used bicyclic bromide **15b** as a common intermediate for the synthesis of terpenes austrodoral[15] and pallescensin A,[16] and the amber odorant 9-*epi*-Ambrox (Scheme 7). At this point, it should be noted that the biomimetic cyclization reactions above mentioned can be performed on a gram scale. Thus, 7.8 g of **15b** could be easily prepared as a single diastereoisomer in one batch (Scheme 6). Terpene austrodoral was easily available from this intermediate though an initial iron-catalysed cross-coupling reaction with methylmagnesium bromide that delivers the alkene **16** in 86% yield (Scheme 7).[17] This coupling process worked as efficiently as the reaction performed from the corresponding alkenyl triflate.[7] Following our previously devised strategy,[7] which implies a selective epoxidation of the alkene in **16** to give **17** followed by a BF_3-catalyzed ring contraction reaction, the natural product austrodoral could be straightforwardly synthesized. Terpene pallescensin A was also available from **15b** through an initial different cross-coupling reaction. In this case, a Sonogashira-type reaction led to the enyne derivative **18** (91% yield), which assured a formal synthesis of the natural product (Scheme 7).[7] In fact, selective epoxidation of the alkene delivered epoxide **19** that under gold-catalyzed conditions could be transformed into the furan-containing natural product pallescensin A. As shown, the initial steps in these syntheses of austrodoral and pallescensin A are two different metal-catalysed cross-coupling reactions. However, the rich reactivity of the carbon-bromine bond in **15b** offers the opportunity for other type of reactions. This is a clear advantage over the similar triflate derivatives we had previously accessed following an alternative method.[7] For example, the synthesis of organolithium compound **20** from **15b** through a bromine-lithium exchange is straightforward (Scheme 7). Treatment of this intermediate with *N*,*N*-dimethylformamide (DMF) followed by treatment with sodium borohydride ($NaBH_4$) led to the alcohol **21** in 76% yield. This alcohol could be easily transformed into the enol ether **22** that evolves to the new alcohol **23** through a Claisen rearrangement followed by reduction of the so-formed aldehyde. A simple acid-catalysed cyclization reaction led to the amber odorant 9-*epi*-Ambrox.[18]

Conclusions

In summary, the cationic cyclization reaction of enyne or alkynol derivatives mediated by tetrafluoroboric acid has shown to be an efficient method to synthesize cyclic alkenyl halides (mainly, fluorides, chlorides and bromides). This reaction, inspired by a single result reported in the early 1970's, complements and challenges conventional methodologies. A remarkable feature of the method here described is the complete regiocontrol in the formation of the haloalkene. The concept behind these halocyclization reactions has been extended to the development of biomimetic cyclizations of polyenyne derivatives to get interesting halogen-containing polycyclic compounds. The utility of these biomimetic halocyclization processes has been demonstrated by the easy transformation of one of the obtained bromine-containing decalins into two different terpenes, austrodoral and pallescesin, and a recognized odorant, 9-epi-Ambrox. Finally, we anticipate the potential of the reaction here described in the synthesis of carbo- and heterocyclic pharmaceuticals and tracers.



Scheme 7. Synthesis of austrodoral, pallescensin A and 9-*epi*-Ambrox from a common starting material

Experimental Section

General procedure for the synthesis of cyclohexenyl chlorides 3, 10, 12, or 15. Tetrafluoroboric acid diethyl ether complex (41 µL, 0.3 mmol) was dropwise added to a solution of the corresponding enyne **1**, or alkynol **2**, **9** or **11**, or dienyne **14a**,**b**, or trienyne **14c** (0.3 mmol) in dry dichloromethane (5 mL) and under argon atmosphere. The reaction was then gently stirred at room temperature for 30 min (12 h for alkynols **2a**, **2e**, **2m** and **9**). 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. In most cases, the corresponding cyclohexenyl chlorides **3**, **10**, **12**, or **15** thus obtained did not need further purification. However, if necessary, the crude was purified by flash column chromatography on silica gel.

General procedure for the synthesis of cyclohexenyl bromides 4 or 12. Tetrafluoroboric acid diethyl ether complex (41 µL, 0.3 mmol) was dropwise added to a solution of the corresponding enyne **1**, or alkynol **2**, or **11** (0.3 mmol) in dry dibromomethane (5 mL) and under argon atmosphere. The reaction was then gently stirred at room temperature for 30 min (12 h for alkynols **2a**, **2e** and **2m**). 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. In most cases, the corresponding cyclohexenyl bromides **4** or **12** thus obtained did not need further purification. However, if necessary, the crude was purified by flash column chromatography on silica gel.

General procedure for the synthesis of cyclohexenyl iodides 5a,b. Aluminium iodide (122 mg, 0.3 mmol) was portionwise added to a solution of the corresponding alkynol **2** (0.3 mmol) in iodomethane (3 mL) and under argon atmosphere. The reaction was then gently stirred at room temperature for 30 min (12 h for alkynol **2a**). 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 organic layer was separated and the aqueous one was extracted with ethyl acetate (2x). The combined organic phase was dried with anhydrous sodium sulphate and filtered. The volatile components were removed under reduced pressure. The crude was purified by flash chromatography on silica gel to give pure cyclohexenyl iodides **5.**

General procedure for the synthesis of cyclohexenyl fluorides 6, 10, 12 or 15. Tetrafluoroboric acid diethyl ether complex (41 µL, 0.3 mmol) was dropwise added to a solution of the corresponding enyne **1**, or alkynol **2**, **9** or **11**, or dienyne **14a,b** (0.3 mmol) in dry hexane (5 mL) and under argon atmosphere. The reaction was then gently stirred at room temperature for 30 min (12 h for alkynols **2a**, **2e**, **2m** and **9**). 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. In most cases, the corresponding cyclohexenyl fluorides **6, 10, 12** or **15** thus obtained did not need further purification. However, if necessary, the crude was purified by flash column chromatography on silica gel.

Gram-scale synthesis of decalin 15b. Tetrafluoroboric acid diethyl ether complex (4.32 mL, 31.76 mmol, 1 equiv) was dropwise added with a syringe pump (1 mL/h) to a solution of dienyne **1** (5.6 g, 31.76 mmol) and 2-methyl-2-butene (16.8 mL, 158.8 mmol, 5 equiv) in dibromomethane (320 mL). Then, the reaction was stirred at room temperature for 1h. After this time, solid potassium carbonate (1.84 g) was added and the suspension was stirred for 10 minutes. The mixture

was filtered and the volatile components were removed under reduced pressure to give the alkenyl bromide **15b**. The crude was used in the next step without further purification.

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Keywords: alkenyl halides • cyclization • halogens • synthesis design • synthetic methods

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[8] The reaction of alkynol **2a** (1,1-diphenyl-5-hexyn-1-ol) in hexane (or dichloromethane) with water-free hydrogen chloride (solution in diethyl ether) led to the formation of the corresponding enyne derivative **1a** (1,1-diphenyl-1-hexen-5-yne) through a dehydration reaction but we did not observe the evolution of this compound to the desired cyclization product **3a**.

[9] As expected considering Yamamoto's work (reference [3k]) when a reaction was performed with an alkynol similar to **2** but containing an internal alkyne (1,1,6-triphenyl-5-hexyn-1-ol) we observed the formation of the corresponding cyclopentyl ketone derivative [(2,2-diphenylcyclopentyl)(phenyl)methanone]. We also performed an experiment with the related enyne derivative 1,1,6-triphenyl-1-hexen-5-yne, and in this case, we observed the formation of a complex mixture of unidentified products.

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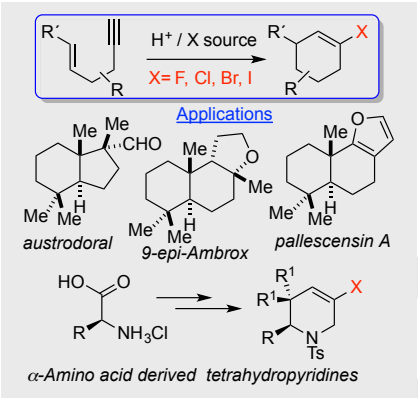
FULL PAPER

Cyclic alkenyl halides are easily available through a cationic cyclization process. Interesting alkenyl fluorides, chlorides, bromides and iodides are accessible. Related biomimetic polycyclization reactions allows the synthesis of interesting polycyclic core skeletons that may be used in the context of natural product synthesis.



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