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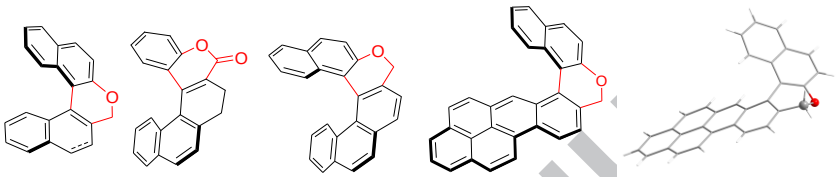

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Synthesis of partially hydrogenated oxa[5] and oxa[6]helicenes from β-chlorovinylaldehydes

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ABSTRACT

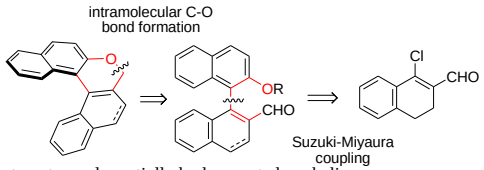
Synthesis of partially hydrogenated oxa[5]helicenes is described starting from easily available β-chlorovinylaldehydes. The short sequence involved a Suzuki-Miyaura type coupling between β-chlorovinylaldehydes and arylboronic acids bearing *ortho*-methoxy groups. The presence of both the formyl and the methoxy groups allowed after reduction and demethylation respectively, the construction of the central dehydropyran ring. The molecular structure of the extended benzopyrene-based oxa[5]helicenes has been fully determined in solution and in the solid state. The strategy could be extended to oxa[6]helicene. Atroposelective Suzuki-Miyaura couplings were the key steps of the non racemic preparation of oxa[5]helicenes. Ee observed are in good agreement with the theoretically calculated racemisation barriers.

1. Introduction

Aromatic molecules that adopt non planar, twisted or helical topologies have fascinated the scientific community for more than one century. Over hundred years of helicene chemistry until their most recent applications in different domains such as material sciences or catalysis has been recently and extensively reviewed by Gingras.[1-3] The presence of heteroatoms or metallic centers at both the inner and the outer helix usually induces structural modifications and specific properties.[4-7] Among this class of appealing architectures, partially hydrogenated helicenes that incorporate heteroatoms within a six membered ring remains by far understudied. Metal-promoted [2+2+2] cycloisomerisation of aromatic triynes,[8] cascade hydroarylation/cycloisomerisation of diynes[9] or base-catalyzed ring transformation of variously substituted chromenes account for the more relevant and elegant accesses to such architectures even in their nonracemic issues.[10] Construction of the pyran ring embed into the [5]helicenes core may also be obtained through photoracemization of transient binaphthyl quinone methodes[11] or intramolecular nucleophilic substitution at 2,2'-disubstituted fluorobinaphthyls.[12] Although, versatile the latter strategies seem strictly restricted to binaphthyl motifs.

We have been recently involved in the preparation of β-chlorovinylaldehydes. Such fragments, easily available from methylketones, revealed especially valuable as starting material for the construction of various heterocycles.[13-16] β-Chlorovinylaldehydes arising from fused cycloalkanones advantageously combine a benzyl/vinyl chloride atom, a vinyl carboxaldehyde moiety, a flexible ethylene fragment to a fused aromatic part which thus can be considered as appealing precursors of partially hydrogenated oxahelicenes.

As shown below, we anticipated that the helicene motif could be obtained through a short sequence starting from β-chlorovinylaldehydes (scheme 1).



Scheme 1. Strategy towards partially hydrogenated oxahelicenes

The formation of the pyran heterocycle would be obtained through intramolecular C-O bond formation in the last step after reduction of the carboxaldehyde function and deprotection of the methylether. The second aromatic fragment can be installed through a Suzuki-Miyaura coupling reaction. One of the further advantage of our strategy is the use of commercially available fused cycloalkanones such as tetralone, phenanthrone and benzopyrenone as starting materials.

Thus we first focused on the preparation of β-chlorovinylaldehydes derived from tetralone, dihydrophenanthrenone and dihydrobenzopyrenone. β-Chlorovinylaldehydes **1**[17] and **2**[18] were prepared from the parent cycloalkanone and Vilsmeier-Haack

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reagent according to previous reports (figure 1). The new β-chlorovinylaldehydes **3** was obtained in a comfortable 85% yield.

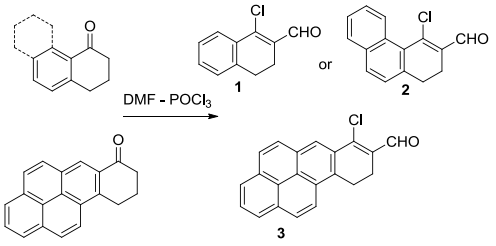
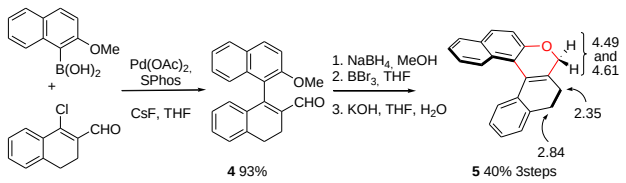


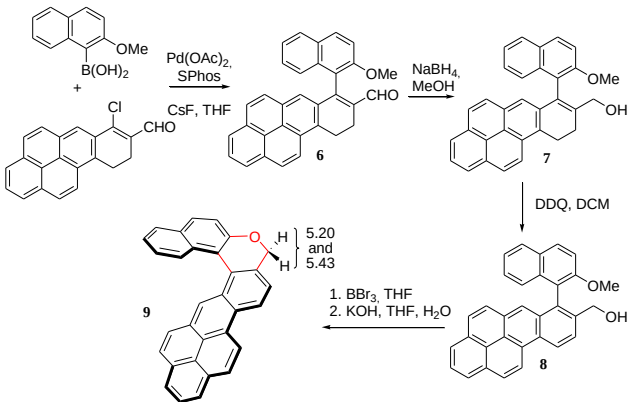
Figure 1. Preparation of starting β-chlorovinylaldehydes **1**-**3**.

The next step was to install the 2-methoxynaphthyl group at β-chlorovinylaldehyde **1** and further to build up the pyran ring in order to validate the overall strategy towards the [5]oxahelicene architecture. Gratifyingly, Suzuki-Miyaura[17-18] reaction, using $Pd(OAc)_2$/SPhos as a catalytic system led to the corresponding binaphthyl **4** in a 93 % yield. The synthesis of the [5]-oxahelicene **5** was realized as shown in scheme 2. Reduction of the carboxaldehyde function using sodium borohydride was followed by deprotection of the methoxy ether with BBr_3 and further cyclisation under KOH-H_2O/THF at room temperature for 18h. The latter sequence could be realized without purification of the intermediates after noting the disappearence of the starting materials by TLC. [5]Oxahelicene **5** was obtained in an overall 37% yield (four steps) and exhibits the expected characteristic ^{1}H NMR signals at δ = (2.35, 2.84) and (4.49, 4.61) ppm that account for ethylene and geminal protons of both contiguous partially hydrogenated rings respectively.



Scheme 2. Synthesis of oxa[5]dihydrohelicene **5**.

The same strategy was then extended to β-chlorovinylaldehyde **3**. Similarly coupling reaction afforded the biaryl core **6** in a high 80% yield. Reduction of the carboxaldehyde moiety was successfully achieved under classical conditions affording the methylalcohol **7** in a 85% yield (scheme 3). Unfortunately, attempts to cleave the methyl group failed whatever the deprotection method used.[19] We finally decided to aromatize the benzopyrene unit. The use of 1eq. of DDQ in DCM at room temperature cleanly afforded the less flexible aromatic structure **8** in nearly quantitative yield. Gratifyingly, the [5]oxahelicene **9** was then obtained in an overall 55% yield after BBr_3 induced deprotection and cyclization of the corresponding diol under basic conditions. Interestingly, the presence of characteristic benzylic proton NMR signals that resonate at 5.20 and 5.43 ppm are consistent with compound **9**.



Scheme 3. Access to extended oxa[5]dihydrohelicene **9**.

Single crystal X-ray diffraction analysis confirmed the helical structure of oxahelicene **9** (figure 2). Interestingly, the methylene fragment and the oxygen atom of the pyran ring lie on both sides of a median plane. As shown below, the crystalline lattice is formed by an arrangement of two (*M*)-9 and two (*P*)-9 units in the plane (ab). Along the c-axis, each of these four molecules forms a columnar arrangement resulting from well-defined intermolecular π-π interactions (3.52 Å) between adjacent planar benzopyrene units .

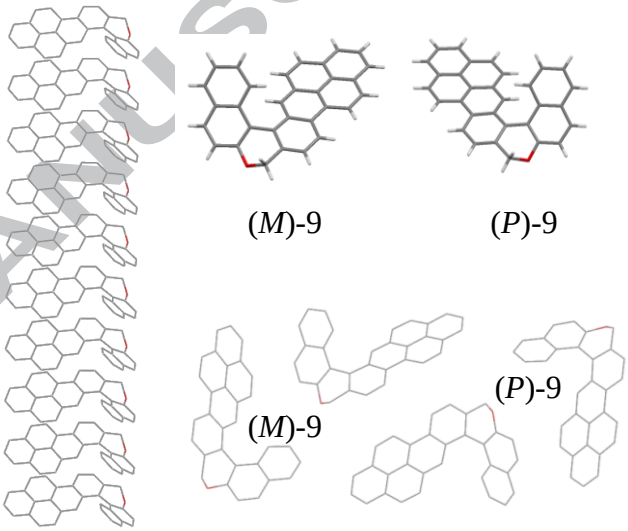
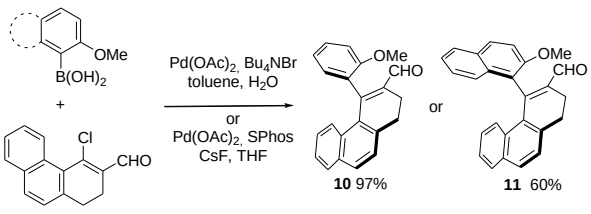


Figure 2. Molecular architecture of oxa[5]helicene **9** (CCDC 935941).

We next focused on the preparation of oxahelicenes from β-chlorovinylaldehyde **2**.



Scheme 4. Suzuki-Miyaura coupling from β-chlorovinylaldehyde **2**

In this context coupling reaction of **2** with 2-methoxyphenyl- and naphthylboronic acid afforded carboxaldehydes **10** and **11** in 97 and 60% yields respectively (scheme 4). Noteworthy, the installation of the naphthyl fragment required the use of Pd(OAc)2/SPhos CATALYTIC combination to ensure conversion of the starting chloride without production of large amounts of side products.

Disappointingly, application of a similar sequence to obtain the corresponding [5]oxahelicene from **10** failed (scheme 5). We were unable to remove the methyl ether in order to generate the free phenol required for the nucleophilic intromecular construction of the pyran ring. Neither at the carboxaldehyde nor at the hydroxymethyl stages the use of various methods such as

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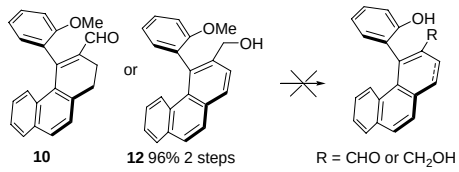
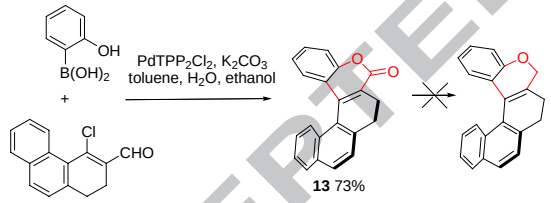


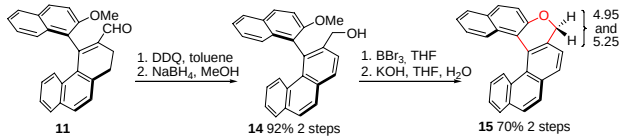
Scheme 5. Deprotection attempts of compounds **10** and **12**.

A reasonable alternative was next envisioned involving the formation of a [5]helicene-like lactone intermediate. Coupling reaction between -chlorovinylaldehyde **2** and 2-hydroxybenzeneboronic acid did not afford the expected corresponding hydroxy carboxaldehyde target but directly afforded the novel [5]helicene-like lactone **13**. Unfortunately reduction of the lactone by LAH followed by intramolecular cylization either under aqueous KOH or APTS conditions did not allow us to identify or isolate the expected oxa[5]helicene (scheme 6).



Scheme 6. Synthesis of [5]helicene-like lactone **13**.

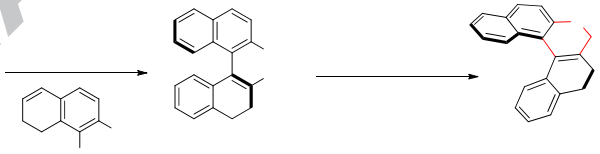
We next moved towards the preparation of oxa[6]helicene (scheme 7). Taking into account potential methylether cleavage problems as aforementioned, we decided to first aromatize compound **11** by addition of DDQ in refluxing toluene and reduce the carboxaldehyde moiety into the expected methylalcohol **14**. The latter was cleanly obtained in an overall 92% yield. Using a sequence involving BBr_3-induced deprotection followed by KOH-mediated pyran ring formation gave the expected oxa[6]helicene **15** in 70% yield for two steps.



Scheme 7. Preparation of oxa[6]helicene **15**.

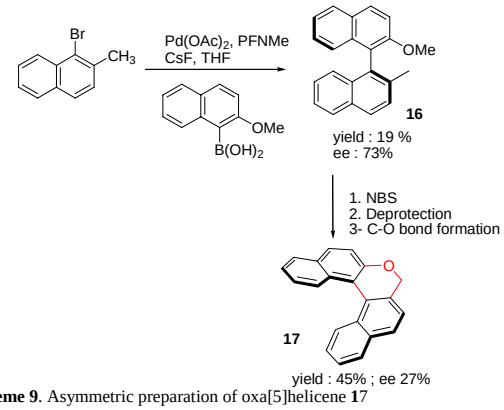
Again, characteristic signals resonating at 4.95 and 5.20 account for the geminal protons of the pyran ring. Deprotection and further formation of the pyran ring under basic conditions allowed us to prepare the oxa[6]helicene **15** in 90% yield for two steps.

Our strategy is based on a sequence that involves a Suzuki-Miyaura coupling as the key step. An asymmetric issue would imply an atroposelective coupling from -chlorovinylaldehydes and further steps under non-demanding reaction conditions in order to preserve potential benefits from a non racemic Suzuki-Miyaura coupling. Taking into account recent advances in this area[20] a major hurdle to overcome would be to find a coupling catalytic system able to ensure the non racemic C-C bond formation compatible with sterically hindered vinylaldehyde and *ortho*-substituted boronic acids. If non racemic monosubstituted binaphthyl-like compounds represent the most examined targets using various catalytic systems including phosphane-based or pyridine-based catalysts,[20, 21] the asymmetric preparation of 2,2'-disubstituted binaphthyls is still challenging. The presence of ethylene fragment at the -chlorovinylaldehyde **1** core may generate additional flexibility and thus be beneficial to the coupling reaction. In this context, we choose the $Pd(OAc)_2$/ (*R*, S_p)-[1-(2-diphenylphosphino-ferrocenyl)ethyl]-dimethylamine (PFNMe) reported by Espinet[22] as the catalytic system. As shown below the use of Espinet's catalytic combination revealed efficient, compound **4** being obtained in a satisfying 58% yield and 51% ee. Unfortunately, repetition of the aforementioned reduction-deprotection-cyclisation sequence led to the racemic oxa[5]helicene **5**.



Scheme 8. Asymmetric Suzuki coupling and further cyclization into oxa[5]helicene **5**.

If the increase of flexibility induced by the presence of an ethylene fragment at the vinylaldehyde substrate seemed to be beneficial to a successful first step, it might plausibly be detrimental to a conversion of axial to helical chirality during the construction of the helicene motif. Thus moving from the flexible vinylaldehyde **1** to the more rigid and fully aromatic binaphthyl analogue might afford an acceptable compromise.[22]



Scheme 9. Asymmetric preparation of oxa[5]helicene **17**

In fact the known compound **16** was obtained in 19% yield and 73 % ee, close to literature results[23] and in good agreement with an increased rigidification of the substrate and thus a higher atroposelectivity of the coupling reaction (scheme 9). The further

radical bromination-deprotection-C-O bond forming reaction accounted for the preparation of oxa[5]helicene **17**.[24] Under such non demanding conditions, the latter oxahelicene could be obtained in an overall 45% yield and in an appealing 27% ee. However, a decrease of the ee was observed in solution at room temperature, giving rise to the racemic mixture within a few days evidencing a low racemization barrier. Indeed, these experimental results were confirmed by DFT calculations.[25] The racemization barrier of **17** was calculated to 105 kJ/mol instead of 73 kJ/mol for the more flexible **5**, corresponding to a 10^{13} faster interconvertion at room temperature.

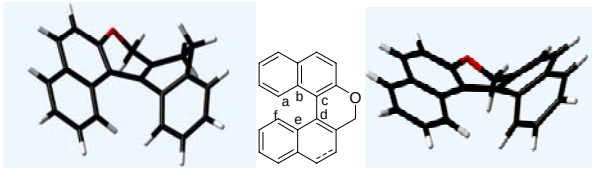


Figure 3. Racemization transition state for oxa[5]helicenes **5** (left) and **17** (right) at B3LYP/6-31+G(d,p) 298.15K and 1 atm (gas phase).

As depicted in Figure 3, racemization transition states exhibit twisted envelop shapes. Dihedral angles $_{abcd}$ and $_{cdef}$ are of -21° and +66° respectively for TS-**5** and -24° and +47° for TS-**17**, evidencing that the presence of an ethylene fragment in **5** generates a more flexible TS and renders racemization possible at room temperature.

In conclusion, unprecedented partially hydrogenated oxa[5] and [6]helicenes are both available from common intermediate -chlorovinylaldehydes. Their preparation requires a starting material bearing a very essential CHO group. Furthermore, they are easily accessible from a short step methodology that involves a Suzuki-Miyaura coupling, reduction of carboxaldehyde moiety and intramolecular C-O bond formation. Our approach even allows the access on more sophisticated structures such as helicene **9** that necessitated the preparation of the novel -chlorovinylaldehyde **3**.

We are well focused on asymmetric synthesis of oxa[5]helicene using atroposelective Suzuki-Miyaura coupling. Unfortunately, the joint presence of two partially hydrogenated rings appeared to be detrimental to the conversion of axial to helical chirality. These experimental observations were also confirmed by quantum chemical calculations of racemisation barriers.

Acknowledgments

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Supplementary Material

Experimental procedures, characterization data including ^{1}H and ^{13}C NMR spectra of new compounds as well as Chiral HPLC ee determination, racemization barriers in the form of GAUSSIAN archive.

Graphical Abstract

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