Organic synthesis can be a form of art, and sometimes chemists are artists who pursue the synthesis of a molecule not because of its use but for its aesthetic beauty. One such molecule is $\eta$-1,2,3,4,5,6-hexafluorocyclohexane, with its symmetry, structural simplicity, and the presence of one fluorine atom bound to each carbon atom. Cyclohexanes form a central structural motif in organic chemistry but until recently this fascinating cyclohexane existed only on paper and in chemists’ dreams as a curiosity. Although theoretical studies have been carried out on the various isomers of this compound, a convincing synthesis of $\eta$-1,2,3,4,5,6-hexafluorocyclohexane remained elusive. Recently, however, the research group of Professor David O’Hagan at the University of St Andrews (UK) have reported the first unambiguous synthesis of an isomer of this cyclohexane.

One of the goals of Professor O’Hagan’s research has been to explore the consequences of placing C-F bonds adjacent to each other on carbon frameworks. Professor O’Hagan commented, “The synthesis of these molecules has proven challenging, however this is rewarded by their analysis by X-ray crystallography and NMR, which allows us to explore their structures and conformation in significant detail.” He continued, “We started with acyclic chains but were always attracted by the prospect of preparing a cyclohexane with a fluorine atom on each carbon, thus we set out to synthesise at least one stereoisomer of $\eta$-1,2,3,4,5,6-hexafluorocyclohexane.” Representatives of the chloro- and bromo family of such compounds have been known for many years. In 1825 Michael Faraday of London prepared hexachlorocyclohexane as a mixture of stereoisomers, in a photochemical (sunlight) reaction on chlorine and benzene. In 1835 Eilhard Mitcherlich of Berlin generated hexabromocyclohexane in 1835, again as a mixture of stereoisomers. This reaction used synthetic benzene produced from benzoic acid. Faraday’s hexachlorocyclohexane was subsequently developed by ICI who introduced it as a global insecticide (Lindane) in 1942. However Lindane was subsequently withdrawn due to its persistence in the ecosphere. Despite the early preparations of the bromo and choro analogues, $\eta$-1,2,3,4,5,6-hexafluorocyclohexane has remained rather obscure. The only claim of a preparatory report in the literature came from the Birmingham team of Colin Tatlow and Paul Coe, 1969 who suggested that a hexafluorocyclohexane had been formed from the reaction of benzene with CoF$_3$, although their characterisation was tentative and a synthesis was unconfirmed (see the original paper for references).

“In our approach we revisited a procedure from 1980 by Arnold Zweig et al, who reacted benzene with silver (II) fluoride to produce fluorobenzene,” said Professor O’Hagan. “Two stereoisomers of 3,4,5,6-tetrafluorocyclohexene were produced as minor side products of this reaction, and these minors became the starting point for synthesising a single stereoisomer of the hexafluorocyclohexane.”
Alastair Durie, a final year Ph.D student, repeated the reaction although purification was unsuccessful due to the volatile nature of the products. Therefore the crude product was treated with potassium permanganate, to give the tetrafluorocyclohexadiol as a mixture of isomers. These were cyclised with sulfuryl chloride to give the corresponding cyclic sulfates, from which a single stereoisomer was purified and the stereochemistry was established by Prof. Alexandra Slawin using X-ray diffraction analysis. The cyclic sulfate was then ring opened using Et₃N.3HF at 120°C to give the free pentafluoroalcohol and again the relative stereochemistry was established by X-ray diffraction analysis. The installation of the final fluorine was successfully achieved by treatment of the pentafluoroalcohol using Deoxofluor™ at 115°C.

Fig. 1. X-Ray image of η-1,2,3,4,5,6-hexafluorocyclohexane

“The isomer produced was the η-hexafluorocyclohexane, and somewhat unexpectedly this compound was a crystalline solid,” explained Professor O’Hagan. The relative stereochemistry and solid-state conformation were shown by the X-ray structure analysis (Fig. 1). “The molecule seems to be particularly polar because of the 1,3-diaxial C-F bonds on the cyclohexane framework,” said Professor O’Hagan. The room temperature ¹⁹F NMR of this compound was unusual and uninteresting, as it showed...
only three signals, two sharp and one very broad. However, when Dr. Tomas Lebl cooled the sample down to -80°C, the spectrum resolved into 6 sharp signals as all the fluorines have a unique environment in the chair conformation, and ring interconversion is slowed down. The 1,3-diaxial fluorines show a large through space 19F-19F coupling constant in the NMR, consistent with the close proximity of these atoms across the top of the ring. “This study resulted in the first unambiguous synthesis of a 1,2,3,4,5,6-hexafluorocyclohexane stereoisomer, and adds to the synthesis of the hexachlorocyclohexanes and hexabromocyclohexanes from Faraday and Mitcherlich respectively,” said Professor O’Hagan. “Our challenge now is to develop methods to make this and related compounds in quantities where their properties and applications can be explored and developed.”

We are very grateful to the HRMS service at Swansea for providing accurate masses of key intermediates in this synthesis.

From left to right: Prof Alexandra Slawin, Alastair Durie, Dr Tomas Lebl, Prof David O’Hagan