Isostrychnine Synthesis Mediated by Hypervalent Iodine Reagent

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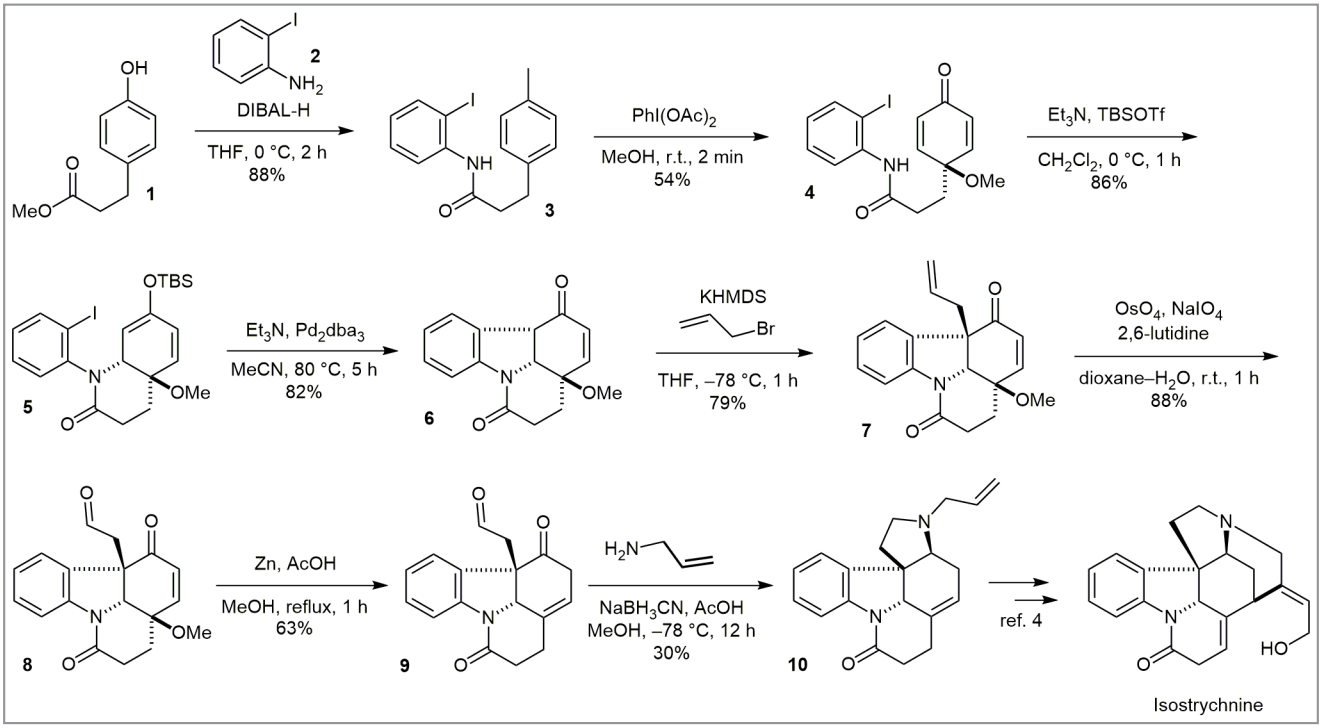
Strychnine is one of the best known compounds in the world, not only by the scientific community but also by the general population, probably due to its remarkable heptacyclic structure and its poisonous effect. Strychnine was isolated in 1818 by Pelletier and Caventou from *Strychnos ignatii* Bergius[1] and its structure was elucidated by Woodward and Brehm in 1948. At this time, *for its molecular size*, strychnine was considered as *the most complex substance known*, as mentioned by Robinson. The first total synthesis of strychnine, reported by Woodward and co-workers in 1954,[2] is considered to be the first complex total synthesis achieved in organic chemistry. A new era in total synthesis had started, in which strychnine has played an important role. Indeed, during the past decades, it has been revealed to be a wonderful source of inspiration for chemists, as illustrated by Overman,[3] and has led to numerous advances in organic chemistry.

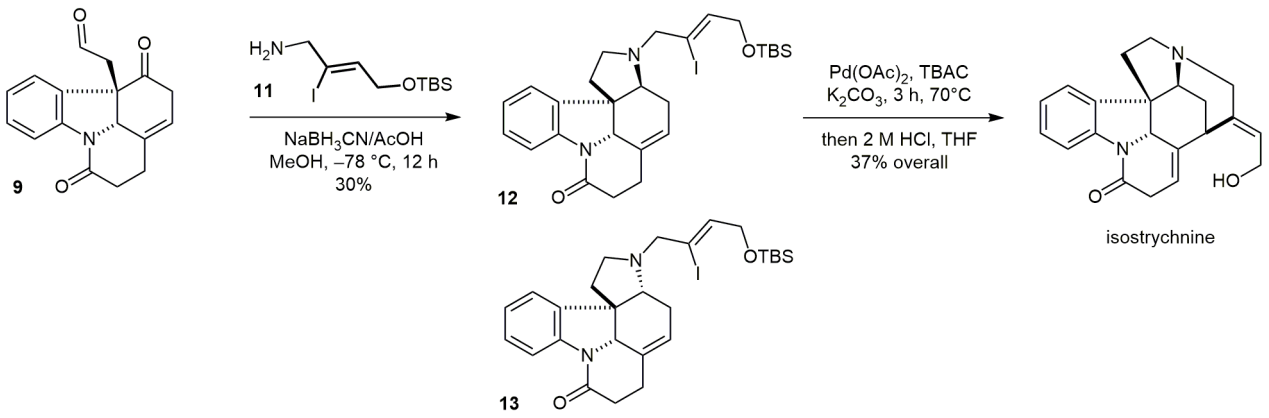
When the group of Professor Sylvain Canesi at the Université du Québec à Montréal (Canada) started their project, there were already around twenty syntheses of strychnine reported in the literature. Professor Canesi said: "However, our interest in developing new and rapid strategies involving hypervalent iodine reagents for the synthesis of complex natural products led us to rise to the challenge. We thus decided to focus on the synthesis of isostrychnine, the natural opened isomer of strychnine. Moreover, in order for it to stand out from the other syntheses, we envisaged basing our strategy on a dearomatization of a phenol mediated by a hypervalent iodine reagent."

He continued: "We first focused on the racemic synthesis of the tetracyclic core of the molecule. We were pleased to note that our strategy was efficient since we faced no real issues yet. We managed to produce aldehyde **9** in only a few weeks, and after optimization, less than two weeks were necessary to prepare a substantial amount of **10**, a known precursor of strychnine that was described in the synthesis of Bodwell and Li (Scheme 1).[4]"

Professor Canesi and co-workers were interested in using a double amination strategy to produce a more advanced pre-



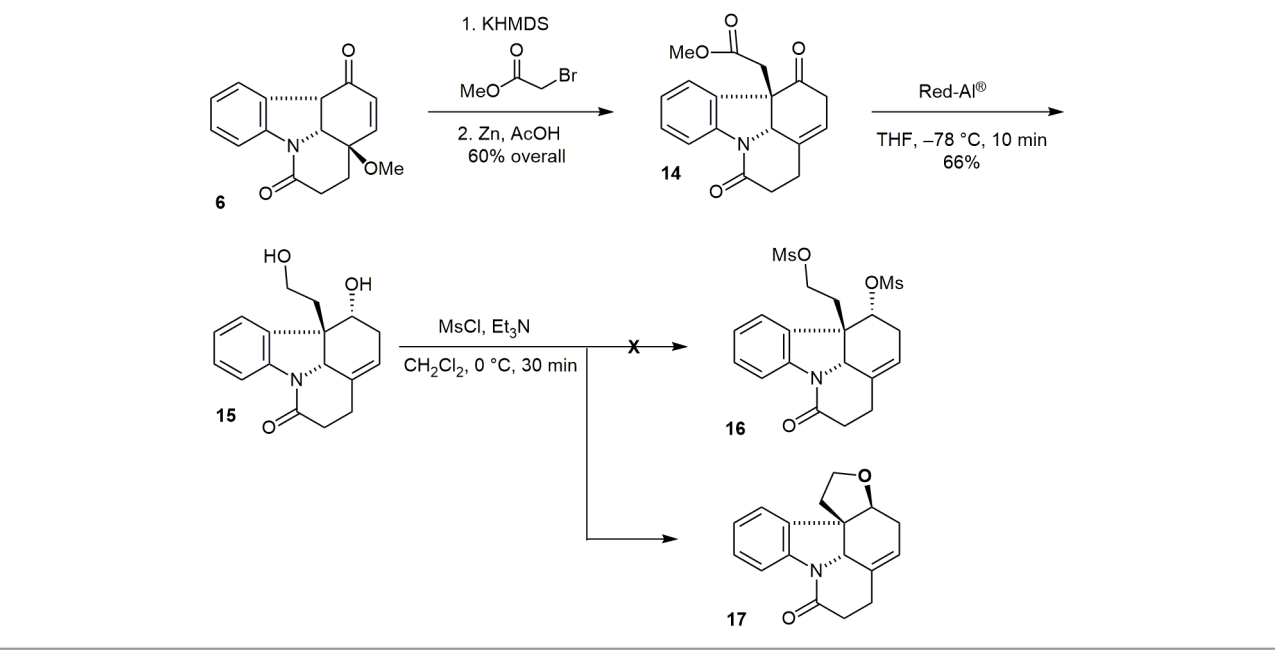
Scheme 1



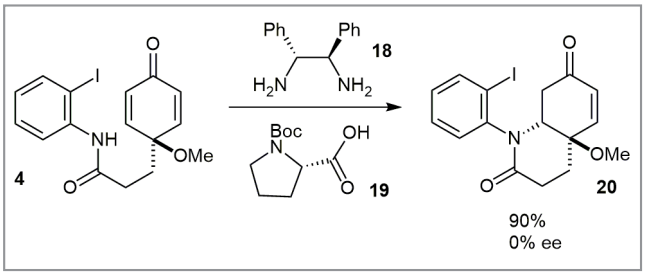
Scheme 2

cursor with an elaborated amine. "However, when we moved to the formation of the new cycloamine **12**, at this point we were very surprised to note that the double reductive amination strategy delivered a considerable amount of the *trans*-diastereoisomer **13**, probably due to the new steric hindrance of our substituted allylamine," explained Professor Canesi (Scheme 2). He continued: "We thus tried to modify the conditions to improve this selectivity. We first tried to decrease or increase the temperature of the reaction, without any success. We also tried to perform the reaction in other solvents. We finally tried to use other sources of acids or hydrides, again without real improvement."

In order to investigate an alternative approach, the group envisaged forming the cycloamine by a double nucleophilic substitution and thus synthesized the diols **15** by alkylation of compound **6** with methyl bromoacetate, followed by a reduction with zinc in acetic acid to produce compound **14**, which was further transformed into diol **15**. Diol **15** was then



Scheme 3



Scheme 4

activated by treatment with MsCl in the presence of Et_3N. "However, we noticed that only the cycloether **17** was formed," said Professor Canesi. This result implied that the β-hydroxy compound **15** was obtained instead of the α-hydroxy during the reduction process. Professor Canesi continued: "In order to avoid the presence of oxygen atoms, we tried to convert them into bromine atoms using Appel conditions, but it resulted again in the formation of the cycloether **17** (Scheme 3). We also tried to invert the stereoselectivity of the reduction by using other hydrides, without any success."

Professor Canesi explained: "Therefore, we considered that even if the formation of compound **12** was accompanied by an important ratio of its undesired diastereoisomer, the rapid elaboration of the polysubstituted main core **9** was a good compromise to conclude a rapid synthesis in only nine steps." He concluded: "We have also tried to develop an asymmetric pathway from prochiral dienone **4** (Scheme 4). Indeed, if we were able to control the selectivity during the 1,4-addition, the synthesis would become asymmetric. We tried several processes[5] including a treatment with diamine[6] **18** but unfortunately no selectivity was observed for the formation of **20**."

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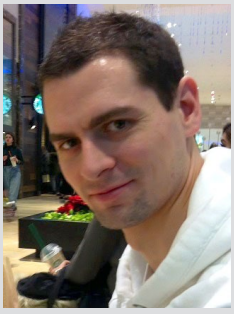
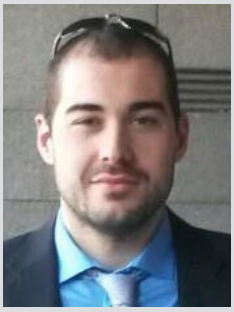


Dr. G. Jacquemot

Guillaume Jacquemot was born in 1986 in Münsingen (Germany). He obtained an engineering diploma in chemistry at ECPM in Strasbourg (France) along with a Master's degree at the University of Strasbourg (France) in 2010. He joined the group of Professor Sylvain Canesi at the Université du Québec à Montréal (Canada) in 2011 and worked on the development of new oxidative methodologies using hypervalent iodine reagents and their application in total synthesis. He obtained his Ph.D. in 2014 and is currently working as a research scientist at Intellisyn R&D (Montreal, Canada).



G. Maertens

Gaëtan Maertens (Rouen, France, 1989) obtained an M.Sc. in organic chemistry and an advanced degree in chemistry from the Institut National des Sciences Appliquées de Rouen (France) in 2012. He is currently a Ph.D. candidate under the supervision of Professor Sylvain Canesi at the Université du Québec à Montréal (Canada). His research interests center on the asymmetric total synthesis of natural diterpenes and alkaloids.

Prof. S. Canesi

Sylvain Canesi (Ajaccio, Corsica, France, 1977) obtained an advanced degree in chemistry from the Ecole Supérieure de Chimie, Physique et Electronique de Lyon (France), and went on to become a graduate student in the group of Professor Marco A. Ciufolini, obtaining his Ph.D. in 2004. After postdoctoral studies in the group of Professor Pierre Deslongchamps at the University of Sherbrooke (Canada), he accepted a faculty position at the Université du Québec à Montréal (Canada). He is interested in the development of new methodologies and their application to the total synthesis of natural products.