Enantioselective Organocatalytic Michael/Aldol Sequence: Anticancer Natural Product (+)-*trans*-Dihydrolycoricidine

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The group of Professor James McNulty at McMaster University in Hamilton (Ontario, Canada) has recently reported a short, asymmetric total synthesis of the anticancer amaryllidaceae alkaloid (+)-*trans*-dihydronarciclasine (**3**). "The amaryllidaceae plant family, which includes well-known species such as daffodils, jonquils and snowdrops, has been of medicinal interest for millennia," explained Professor McNulty. "Extracts of narcissus and pancratium were employed by ancient Greek (Theophrastus) and Roman (Pliny) physicians in the treatment of skin cancers and other ailments. The modern-era isolation of alkaloids from amaryllidaceae plants began in the mid-19th century with the structure of bases such as lycorine being firmly established by the late 1950s," he added. Interest in the lycorane class of amaryllidaceae natural products increased with the discovery of new members demonstrating potent nanomolar anticancer activity, notably narciclasine (**1**) (G. Ceriotti *Nature* **1967**, *213*, 595), pancratistatin (**2**) (G. R. Pettit et al. *Chem. Commun.* **1984**, 1693; *J. Nat. Prod.* **1984**, *47*, 1018) and *trans*-dihydrolycoricidine (**3**) (G. R. Pettit et al. *J. Nat. Prod.* **1993**, *56*, 1682). Interest in the isolation, structure, biosynthesis, total synthesis and biological evaluation of amaryllidaceae constituents continues unabated (Z. Jin *Nat. Prod. Rep.* **2013**, *30*, 849).

Professor McNulty has been investigating various aspects of the chemistry of these constituents for the last 18 years. "I was conducting bioassay-guided isolation on unrelated marine-sponge-derived natural product extracts as a postdoctoral fellow in Bob Pettit's group at ASU," explained

Figure 2 *Zephyranthes grandiflora (Amarillidaceae) in full bloom, source of pancratistatin and other alkaloids (from the author's collection)*

Professor McNulty. "Two of my colleagues, Drs. Brian Orr and Noleen Melody, were preparing synthetic derivatives of pancratistatin (**1**) and the anticancer activity of some of them was quite astonishing." According to Professor McNulty, of equal surprise was the fact that nothing was known regarding the mechanism of action of these anticancer agents, meaning that a novel biological target might be involved. "Analysis using the COMPARE algorithm demonstrated no correlation of activity of these compounds with any known class of anticancer agent! As an Assistant Professor, this was one of the

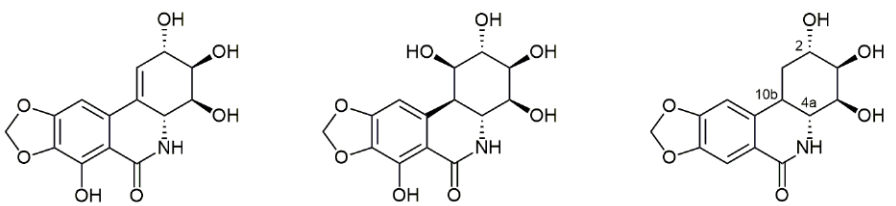

Figure 1

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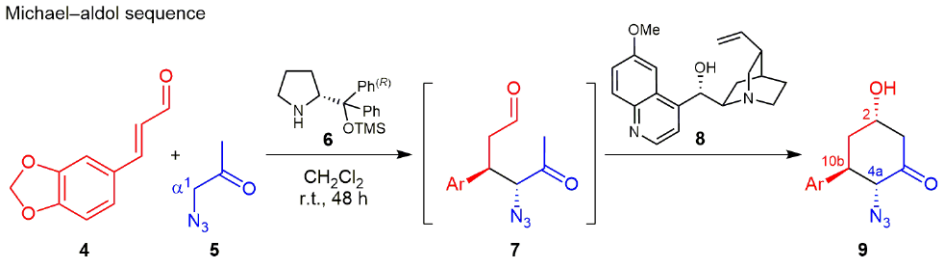
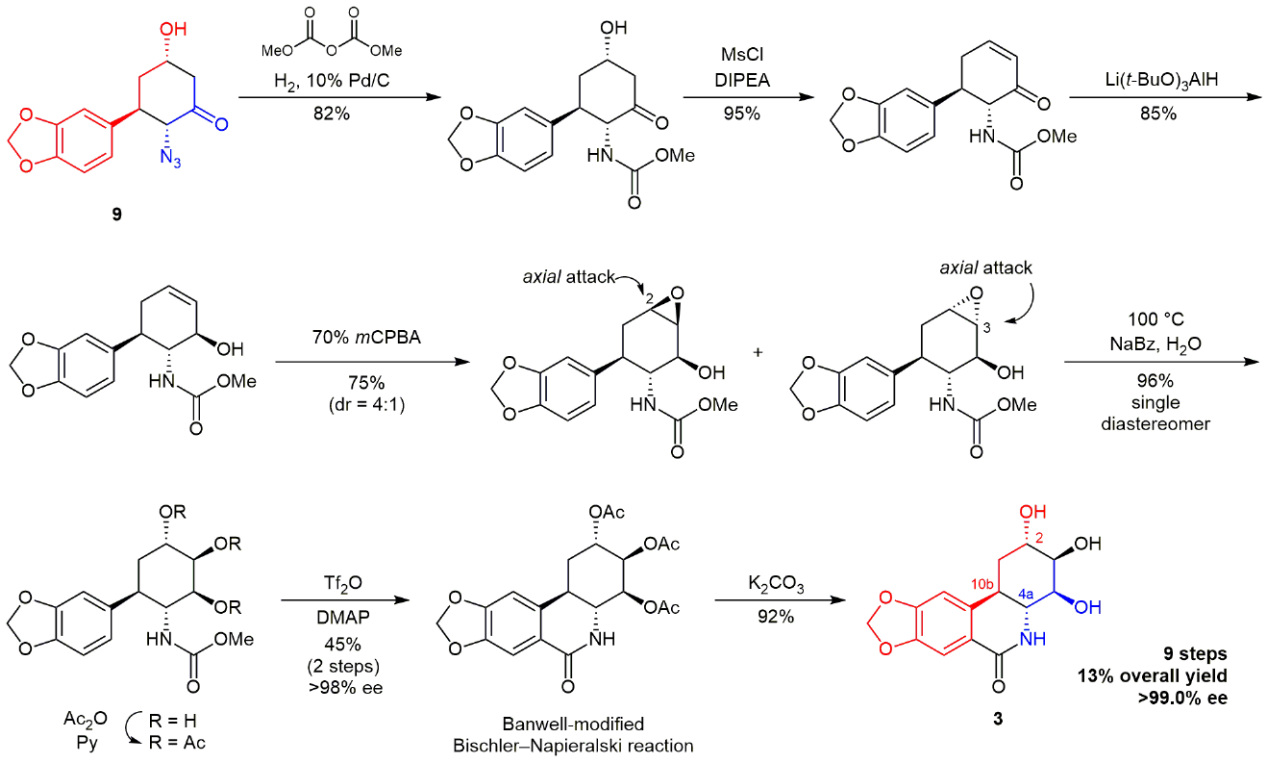


Scheme 1

first projects we got off the ground," continued Professor McNulty. To date, the group has prepared the core lycorane structure employing four totally different synthetic strategies as well as the synthesis of fully functionalized *seco*-analogues. Through extensive synthetic and biological evaluations, the minimum anticancer pharmacophore in the lycorane series was determined to be that contained within *trans*-dihydrolycoricidine (**3**) (T. Hudlicky et al. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2911; J. McNulty et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5315). Further deletions or stereochemical modifications to **3** result in compounds with significantly reduced, or no, anticancer activity, conferring a privileged standing on natural product **3** as a target for total synthesis.

The total asymmetric synthesis of *trans*-dihydrolycoricidine (**3**) was achieved in only nine chemical steps from azidoacetone (**5**) and the methylenedioxy-substituted cinnamaldehyde **4** shown in Scheme 1. While a few examples of organocatalytic [3+3] Michael–aldol sequences have been reported, some of which utilize a doubly activated methylene to control regioselectivity, no prior report on the use of an



Scheme 2

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α-nitrogen-substituted ketone existed in the literature. The authors' current view on the mechanism of the stepwise cycloaddition reaction is that it proceeds via iminium ion activation. "We were delighted to find that azidoacetone reacts exclusively at the azidomethylene (α^1), adding to the iminium ion generated from the alkenal and chiral secondary amine **6**," said Professor McNulty. "The subsequent intramolecular aldol reaction is not spontaneous and requires addition of a second tertiary base, such as quinidine (**8**). The absolute stereochemistry of the process is controlled only by the chiral prolinol silyl ether catalyst to give the major stereoisomer shown (**9**)."

With the key cyclohexane ring in place, the target was prepared in eight further steps as outlined in Scheme 2.

"The synthesis of the polyhydroxy-containing lycorane core structure has been a lucrative proving ground for the development of synthetic methodology and a fantastic training ground for students in synthetic organic chemistry over the years," explained Professor McNulty. "In addition to issues of regio- and stereocontrol, there are several pitfalls and opportunities for elimination reactions and aromatization of the polyhydroxyl ring that need to be successfully navigated." In addition to completion of the synthesis of **3**, Professor McNulty noted that the general methodology outlined in Scheme 1 opens up an asymmetric entry to aminocyclitols in general, which are an important subclass of natural and non-natural compounds of wide-ranging therapeutic potential. "The methodology allows construction of the natural product **3** *and* many structural analogues including epimeric and deoxy derivatives. We have been able to explore the biological activity of these compounds and uncover new insights into the pharmacophore as well as target and mechanism of action, studies that will be reported in the near future," concluded Professor McNulty.

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About the authors

Prof. J. McNulty

James McNulty was born in Glasgow, Scotland (UK). He received B.Sc., M.Sc. and Ph.D. degrees at the University of Toronto (Canada) with Professor Ian Still (1993). He subsequently completed postdoctoral work at the University of Geneva (Switzerland) under the guidance of Professor Charles Jefford and at Arizona State University in Tempe, Arizona (USA) under the guidance of Professor Bob Pettit. He began his independent career at Brock University (Canada), moving to McMaster University (Canada) in 2003 where he is now Full Professor. His research focuses on methodology development in olefination chemistry, late-transition-metal and organocatalysis, as well as applications in various areas of total synthesis and chemical biology.

Dr. C. Zepeda-Velazquez

Carlos Zepeda-Velazquez completed his B.Sc. degree in pharmaceutical chemistry from La Salle University (USA) and his M.Sc. in organic chemistry from National Autonomous University of Mexico in 2003 and 2006, respectively. Subsequently, he worked as a process chemist at Signa, S.A de C.V. (Mexico) where he focused on the development and manufacture of chemical reagents that are used as raw materials in the pharmaceutical industry. For his doctoral studies he moved to Canada in 2009 and joined the group of Professor McNulty at McMaster University, where he developed an enantioselective synthesis of *trans*-dihydrolycoricidine. Currently he is undertaking postdoctoral studies at the Ontario Institute of Cancer Research (Canada) under the supervision of Dr. Rima Al-Awar, contributing to the design, synthesis and evaluation of novel anti-tumor agents.

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