Nitro-polyols via Pyridine-Promoted C=C Cleavage of 2-Nitroglycals. Application to the Synthesis of (–)-Hyacinthacine A1

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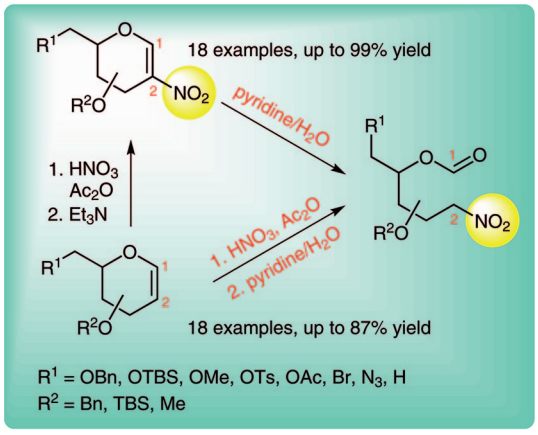
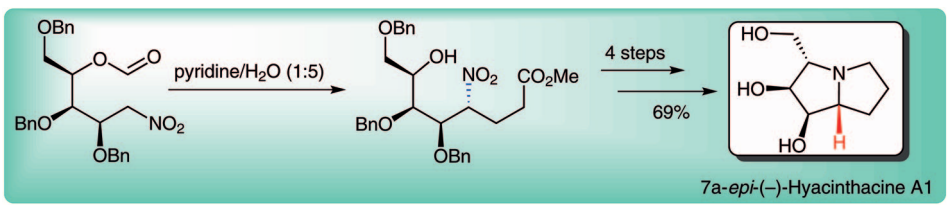
Iminosugars, which are widely represented among natural products, possess many important biological activities, such as glycosidase inhibition, immune modulatory and chaperoning activity. However, only relatively few iminosugars are available for pharmaceutical evaluation due to difficulties connected with their separation and synthesis. Recently, Professor Xin-Shan Ye from Peking University (P. R. of China) and co-workers developed a new and convenient method for achieving the synthesis of nitro-polyols and further explored their applications in the synthesis of iminosugars.

Professor Ye's group has studied in detail iminosugars as immunosuppressive agents or promising drugs for treating Gaucher's disease by exploiting their capacity to act as molecular chaperones. Professor Ye said: "We have always tried to find efficient ways to synthesize various kinds of iminosugars. Carbohydrates are ideal starting materials due to their easy accessibility. What's more, carbohydrates are considered a 'chiral pool' by organic chemists." Glycals are important building blocks in synthetic carbohydrate chemistry and many 'chiral synthons' can be obtained via the scission of the carbon–carbon double bond in glycals. However, this conversion always took place under harsh conditions. "So, we introduced a nitro group at the C-2 position of glycals to make the cleavage of the double bond easier, leading to nitro-sugar derivatives," explained Professor Ye, continuing: "The chain-type nitro-polyol derivatives obtained are versatile intermediates, and have the potential to provide a synthetic entry to monocyclic and bicyclic iminosugars by means of Henry, Michael and various cycloaddition reactions, and the nitro group can be reduced to the amino group as well."

According to Professor Ye, only a handful of methods for the preparation of nitro-polyol derivatives are described; therefore, new synthetic methods are needed. "We use a Michael-type water addition–retro-Henry-type reaction to break the double bond in 2-nitroglycals," said Professor Ye. "This is a novel, mild and efficient method for the synthesis of nitro-polyol derivatives." After optimization of the reaction conditions, the authors found that the quantitative conversion could be accomplished at room temperature for 24 hours with pyridine as both solvent and base, and water was essential for the transformation to be efficient. "To our delight, we found that nitration of glucal and scission of the carbon–carbon double bond could be conducted in a sequential manner without significantly reduced yield," said postgraduate student Shengbiao Tang, the first author of this paper, "and we also expanded this method to a series of glycoforms with different protecting groups."



Scheme 1



Scheme 2

To verify the capacity and scope of this method, the authors applied one of the obtained nitro-polyol derivatives to the synthesis of 7a-*epi*-(–)-hyacinthacine A1, which is a bicyclic polyhydroxylated pyrrolidine compound. The nitro-polyol underwent a good stereoselective Michael addition reaction at first and was then transformed to 7a-*epi*-(–)-hyacinthacine A1 in 69% yield over four steps.

"In summary, a new and convenient transformation method for the synthesis of nitro-polyols via a pyridine-promoted scission of the carbon–carbon double bond in 2-nitroglycals has been developed. Moreover, a concise and asymmetric total synthesis of (–)-hyacinthacine A1 and 7a-*epi*-(–)-hyacinthacine A1 was achieved in four steps from the Michael addition products of one obtained nitro-polyol intermediate in high overall yield," said Professor Ye, concluding: "Thus, this protocol may be widely used in the preparation of nitro-sugar intermediates of iminosugars and other bioactive natural or non-natural products."

About the authors

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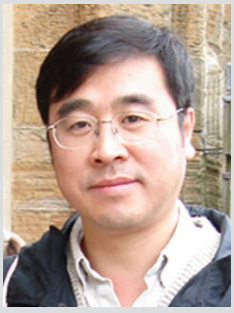
Xin-Shan Ye obtained his B.S. (1985) and M.S. (1988) degrees from Wuhan University (P. R. of China) before becoming a lecturer at Huazhong Agricultural University (P. R. of China) from 1988–1993. He obtained his Ph.D. (1996) from The Chinese University of Hong Kong (P. R. of China) in the lab of Professor Henry N. C. Wong. From 1996–2000, he was a research associate at The Scripps Research Institute (USA) under the direction of Professor Chi-Huey Wong. He has been a full professor at Peking University (Beijing, P. R. of China) since 2000. His research interests include the development of new methodologies or strategies for the assembly of oligosaccharides, the synthesis and evaluation of biologically important oligosaccharides such as tumor-associated carbohydrate antigens, and the design, synthesis and evaluation of carbohydrate-processing enzyme inhibitors as well as discovery of new carbohydrate-based drugs.



Prof. S. Jiang

Shende Jiang was born in 1963 and raised in the rural area of Shandong peninsula (P. R. of China). He obtained his B.S. degree in chemistry in 1983 at Liaocheng Normal College (P. R. of China) and his M.S. degree in medicinal chemistry at Shandong Medical University (now part of Shandong University, P. R. of China) in 1986. He received his Ph.D. at the University of Teesside (formerly Teesside Polytechnic, UK) in 1996. In early 1996, he moved with Gurdial Singh to the University of Sunderland (formerly Sunderland Polytechnic, UK) and remained there for six years as a postdoctoral research fellow. He returned to China in 2004 and is currently a professor in medicinal chemistry at Tianjin University (P. R. of China).

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S. Tang

Shengbiao Tang was born in Hunan Province (P. R. of China) in 1987. He received his B.S. degree from South-Central University for Nationalities (Wuhan, P. R. of China) in 2011 and then became a graduate student under the supervision of Professor Shende Jiang at Tianjin University (P. R. of China). Since August 2013, he has been a Ph.D. student and an exchange student in Professor Xin-Shan Ye's lab at Peking University (P. R. of China). His main research interest is the development of synthetic methodology from glycals.

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