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

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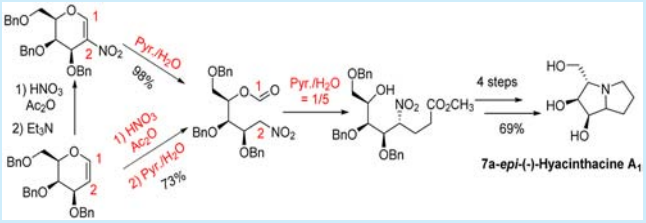
Supporting Information

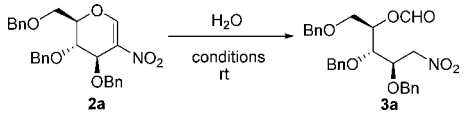
ABSTRACT: A mild and convenient transformation for the synthesis of nitro-polyols is described. The nitro-polyol derivatives were prepared either from 2-nitroglycals via a pyridine-promoted scission of the carbon−carbon double bond or from glycals via a sequential nitration−scission procedure. The generated nitro-polyols could undergo a stereoselective Michael addition reaction. The utility of the addition products was exemplified by the concise synthesis of (−)-hyacinthacine A1 and 7a-*epi*-(−)-hyacinthacine A1.



The abundance of carbohydrates in Nature makes them an ideal chemical feedstock.[1] Especially, the employment of carbohydrates as "chiral pool" starting materials has drawn considerable attention from organic chemists.[2] Among them, nitro-sugars and their derivatives are versatile intermediates in organic synthesis, especially for carbon−carbon bond formation by means of the Henry, Michael and various cycloaddition reactions, as well as for the transformation of the nitro group to the amino group.[3] In addition, nitro-sugars decorate many natural products including aromatic and reduced polyketides as well as oligosaccharides.[4] These nitro-sugar-related compounds show many important biological activities such as antibiotic and antitumor activity.[5] However, only a handful of methods for the preparation of nitro-sugars and their derivatives are known.[3d,6] New transformations for the synthesis of nitro-sugar derivatives are still needed.

As part of our continuing studies on the synthesis and biological evaluation of iminosugar derivatives,[7] we have been attempting to develop new transformations for the synthesis of nitro-sugar derivatives and further explore their applications in the synthesis of iminosugars. Glycals are a class of readily available building blocks in synthetic carbohydrate chemistry.[3g] Many "chiral synthons" have been obtained via the scission of the carbon−carbon double bond in glycals.[8] Nevertheless, harsh reaction conditions are always employed for the conversion. Therefore, we imagined that the introduction of a nitro group at the C-2 position of glycals could make the cleavage of the double bond easier and lead to nitro-sugar derivatives being formed. Herein, we report a novel, mild, and efficient transformation for the synthesis of nitro-polyols via a Michael-type water addition- retro-Henry-type breakage of the double bond in 2-nitroglycals, and we show some applications

Table 1. Optimization of the Transformation of 2-Nitroglucal 2a to Nitro-polyol 3a[a]



entry	solvent	base	yield (%)[b]
1	THF	KO^{t}Bu	0
2	THF	NaOH	0
3	THF	K_2CO_3	0
4	THF	Et_3N	0
5	THF	DMAP	16
6	THF	pyridine	14
7	THF	dtbpy	28
8	CH_3CN	dtbpy	19
9	acetone	dtbpy	27
10	DMF	dtbpy	74
11	pyridine	dtbpy	99
12	pyridine	–	99

[a]All reactions were carried out with **2a** (0.24 mmol), base (3 equiv), H_2O (0.4 mL), and solvent (2 mL) at room temperature for 24 h. [b]Isolated yield. DMAP = 4-dimethylaminopyridine. dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

Scheme 1. Sequential Protocol for the Cleavage Reaction of D-Glucal 1a

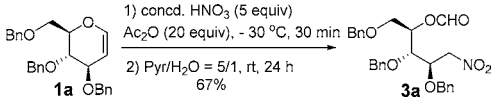


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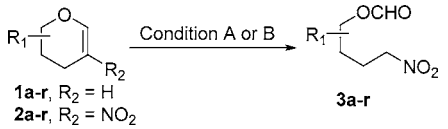
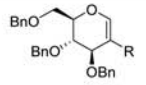
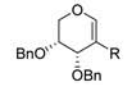
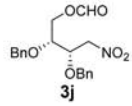
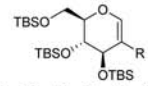
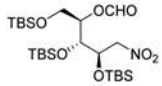
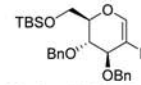
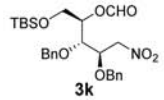
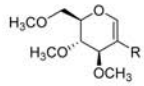
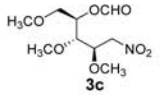
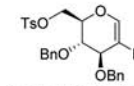
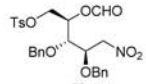
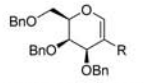
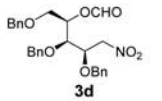
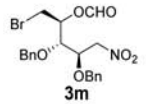
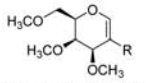
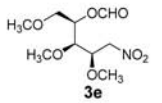
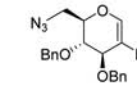
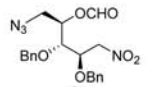
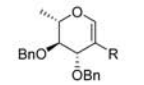
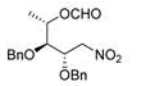
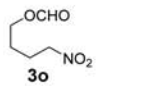
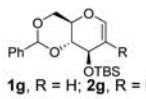
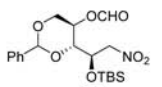
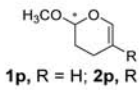
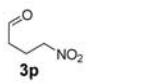
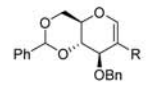
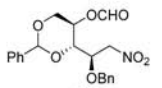
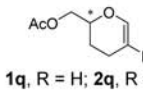
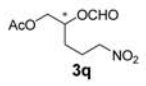
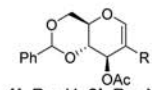
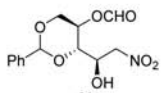
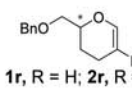
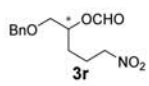
Table 2. Scope of Glycals and 2-Nitroglycals



entry	substrate	product	yield from 1(%)[b,c]	yield from 2(%)[a,c]	entry	substrate	product	yield from 1(%)[b,c]	yield from 2(%)[a,c]
1	 **1a**, R = H; **2a**, R = NO_2	**3a**	67	99	10	 **1j**, R = H; **2j**, R = NO_2	 **3j**	65	96
2	 **1b**, R = H; **2b**, R = NO_2	 **3b**	45	92	11	 **1k**, R = H; **2k**, R = NO_2	 **3k**	87	98
3	 **1c**, R = H; **2c**, R = NO_2	 **3c**	80	97	12	 **1l**, R = H; **2l**, R = NO_2	 **3l**	81	93
4	 **1d**, R = H; **2d**, R = NO_2	 **3d**	73	98	13	 **1m**, R = H; **2m**, R = NO_2	 **3m**	82	97
5	 **1e**, R = H; **2e**, R = NO_2	 **3e**	78	94	14	 **1n**, R = H; **2n**, R = NO_2	 **3n**	84	95
6	 **1f**, R = H; **2f**, R = NO_2	 **3f**	72	95	15	 **1o**, R = H; **2o**, R = NO_2	 **3o**	56	88
7	 **1g**, R = H; **2g**, R = NO_2	 **3g**	73	89	16	 **1p**, R = H; **2p**, R = NO_2	 **3p**	85	94
8	 **1h**, R = H; **2h**, R = NO_2	 **3h**	80	94	17	 **1q**, R = H; **2q**, R = NO_2	 **3q**	60	95
9	 **1i**, R = H; **2i**, R = NO_2	 **3i**	56	75	18	 **1r**, R = H; **2r**, R = NO_2	 **3r**	65	96

[a]Condition A: nitroglycal (0.24 mmol), pyridine (2 mL), H_2O (0.4 mL), room temperature for 24 h. [b]Condition B: glycal (0.24 mmol), concd. HNO_3 (1.2 mmol), Ac_2O (4.8 mmol); then pyridine (2 mL), H_2O (0.4 mL), room temperature for 24 h. [c]Isolated yield.

of this reaction in the synthesis of bicyclic polyhydroxylated pyrrolidine compounds.

To test the reaction, 2-nitro-glucal **2a** was employed as the starting material in the initial experiments and variations were made to either the solvent or the base (Table 1). The quantitative conversion to **3a** was achieved at room temperature within 24 h using pyridine as both the solvent and base (entry 12). Other bases such as KO^{t}Bu, NaOH, K_2CO_3, and Et_3N were found to be ineffective (entries 1−7, Table S1 in Supporting Information). It was found that 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) was also effective when using DMF or pyridine as the solvent (entries 10−11, Table 1). Water was essential for the transformation to be efficient (Table S1). So, the optimized reaction conditions are 2-nitroglycal (0.24 mmol), H_2O (0.4 mL), and pyridine (2.0 mL), at room temperature for 24 h.

Having verified the feasibility of cleavage of the double bond in 2-nitroglucal **2a**, and with the optimized conditions in hand, we further imagined the nitration of glucal and scission of the carbon−carbon double bond could be realized in a sequential manner. Thus, glucal **1a** was treated under the standard nitration conditions. The nitration product was generated within 30 min. Indeed, after the addition of pyridine−water (5/1, v/v) to the reaction mixture, compound **3a** was obtained in 67% yield (Scheme 1; see Supporting Information for the detailed procedure). Therefore, compound **3a** was prepared either from 2-nitroglucal **2a** or from glucal **1a** via the sequential protocol with high efficiency.

Next, the scope of glycals and 2-nitroglycals in this reaction was examined. As shown in Table 2, benzylated/^{t}butyldimethylsilylated/methylated/benzylidenated 2-nitroglucals, or 2-nitroglucals with tosyl, bromo, or azido substituents, could be used

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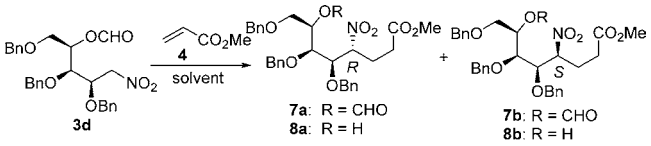
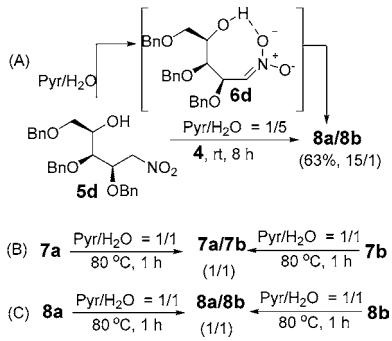
Table 3. Michael Addition Reaction of 3d with Methyl Acrylate[a]



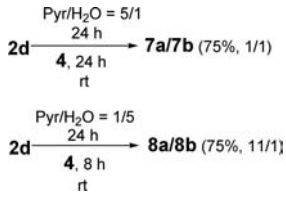
entry	solvent (v_{Pyr}/v_{H_2O})	time (h)	yield (%)[b] 7a:8a:7b:8b	4*R*:4*S*
1	1:0	72	0	–
2	5:1	36	37:0:37:0	1:1
3	3:1	24	38:0:37:0	1:1
4	2:1	24	30:15:30:0	1.5:1
5	1:1	12	20:35:11:4	4:1
6	1:2	8	0:57:0:12	4.8:1
7	1:5	8	0:67:0:5.3	13:1

[a]All reactions were carried out with **3d** (0.24 mmol), methyl acrylate (**4**) (1.20 mmol), mixed solvent of pyridine–H_2O (6 mL), room temperature. [b]Isolated yield.

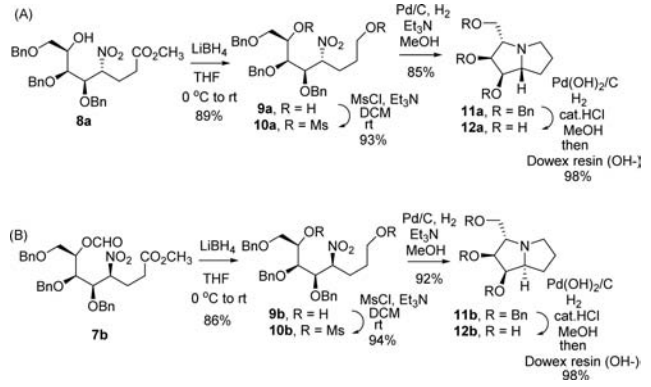
Scheme 2. Control Experiments



Scheme 3. One-Pot Scission-Michael Addition Reaction



Scheme 4. Synthesis of 7a-*epi*-(−)-Hyacinthacine A_1 and (−)-Hyacinthacine A_1



for the reaction and gave the ring-opening nitrosugar derivatives in good to excellent yields (entries 1–3, 7–9, and 11–14). The cleavage reaction of 2-nitrogalactal/2-nitrorhamnal/2-nitroarabinal/5-nitro-3,4-dideoxy-glucal proceeded smoothly as well under the same conditions (entries 4–6, 10, and 15–18), leading to the desired products in high yields. Although the cleavage reaction of the nitroglycal **2i** with an acetyl protective group took place in satisfactory yield, the acetyl group was absent in the product due to deacetylation that resulted from the influence of the neighboring nitro group (entry 9). Furthermore, the nitrosugar derivatives **3a–3r** were also prepared directly from glycals **1a–1r** via sequential nitration and breakage of the carbon–carbon double bond in a "one-pot" protocol. Except for glycals with acid-sensitive functionalities such as silyl and benzylidene groups (entries 2, 7–9), most glycals underwent this reaction smoothly in moderate to good yields.

To further demonstrate the utility of this transformation for organic synthesis, the Michael addition reaction of the nitrosugar derivative **3d** with methyl acrylate (**4**) in pyridine–water was performed (Table 3). To our delight, the reaction proceeded smoothly in satisfactory yields. It was found that water could accelerate the reaction and is essential for this transformation. Notably, the ratio of the octanoate products (**7a**, **7b**, **8a**, and **8b**) and diastereoselectivity changed with alteration in the ratio of pyridine/H_2O (entries 2–6). A decrease of the ratio of pyridine/H_2O to 1/5 resulted in the formation of products **8a** and **8b** along with a significant improvement in diastereoselectivity (**8a**/**8b** = 13/1, entry 7). It was noticed that the deformylated product **8** increased with the decrease of pyridine. Thus, under the condition of pyridine/H_2O (1/5), a total deformylation of **3d** may occur.

To account for the high diastereoselectivity of the Michael addition reaction, we propose an intermediate **6d** where there is an eight-membered-ring intramolecular hydrogen bond, in which the *si*-face of the carbon–nitrogen double bond is effectively shielded, as depicted in Scheme 2A. To verify this assumption, the deformylated compound **5d** was subjected to the mixed solvent (pyridine/H_2O, 1/5). Indeed, compound **8a** was obtained with high diastereoselectivity (**8a**/**8b** = 15/1, 63% yield). In addition, it was found that **7a** and **7b** can transform into each other and an equilibrium can be reached eventually in the solvent of pyridine/H_2O (Scheme 2B and Table S3). The equilibrium between **8a** and **8b** was observed as well (Scheme 2C and Table S3). Next, we conducted the scission-Michael addition reaction in a one-pot manner, and similar diastereoselectivity was obtained (Scheme 3).

Iminosugars have many important biological activities. Hyacinthacine A_1 was isolated from the bulbs of *Muscari armeniacum* in about 0.0005% yield and was confirmed to be an effective inhibitor of rat intestinal lactase (IC_{50} value of 4.4 μM).[9] Thus, the synthesis of these pyrrolidine alkaloids and their analogues from simple and readily accessible chemicals is of importance.[10] Therefore, with compounds **7b** and **8a** in hand, the synthesis of (−)-hyacinthacine A_1 and 7a-*epi*-(−)-hyacinthacine A_1 was attempted. As shown in Scheme 4, the reduction of compound **8a** gave alcohol **9a** in 89% yield. Then the alcohol **9a** was mesylated to produce compound **10a** in 93% yield. Compound **10a** was treated with H_2 (4 atm), Pd/C, and Et_3N to smoothly generate the bicyclic compound **11a** in 85% yield. The debenzylation of **11a** via hydrogenolysis afforded the target compound 7a-*epi*-(−)-hyacinthacine A_1 (**12a**) (69% overall yield, four steps from **8a**) (Scheme 4A). In the same way, (−)-hyacinthacine A_1 (**12b**) was successfully prepared from **7b** in 73% overall yield (Scheme 4B).

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In conclusion, a new and convenient transformation for the synthesis of nitro-polyols via either a pyridine-promoted scission of the carbon−carbon double bond in 2-nitroglycals or a successive nitration-scission reaction of glycals in a "one-pot" protocol has been disclosed. One of the formed 4-*O*-formyl-nitro-polyol derivatives underwent a unique and stereoselective Michael addition reaction. Moreover, a concise and asymmetric total synthesis of (−)-hyacinthacine A_1 and 7a-*epi*-(−)-hyacinthacine A_1 was achieved in four steps from the Michael addition products in high overall yield. Thus, the disclosed protocol may find wide application in the preparation of nitro-sugar intermediates and hold the potential to allow the synthesis of iminosugars and other bioactive natural or non-natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03607.

Detailed experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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