J|A|C|S COMMUNICATIONS

Published on Web 05/28/2009

Concise Synthesis of Iminocyclitols via Petasis-Type Aminocyclization

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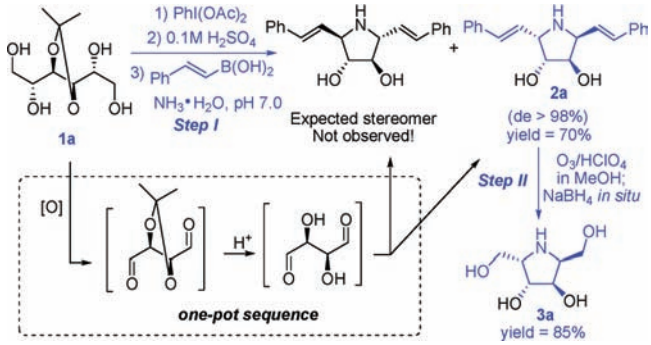
Iminocyclitols are metabolically inert carbohydrates mimicking the oxocarbenium ion-like transition state of carbohydrate-processing enzymes.[1] Many iminocyclitols exhibit strong binding to glycosidases and glycotransferases. Accordingly they have been intensively evaluated for antivirial, anticancer, and antidiabetic properties.[2] Some of them have already achieved market success, such as Miglitol for treatment of noninsulin-dependent diabetes. Further biopharmaceutical studies on iminocyclitols are warranted. However, a significant challenge that remains to be overcome is the demand for a cost-effective method to make iminocyclitols.[3] Currently most iminocyclitol syntheses involve the introduction of an amino function in the sugar skeleton, followed by aminocyclization to generate the piperidine or pyrrolidine ring through reductive amination. These syntheses often require lengthy protection/deprotection steps and are tedious and low-yielding. An additional problem often encountered is the low diastereoselectivity in reductive amination.

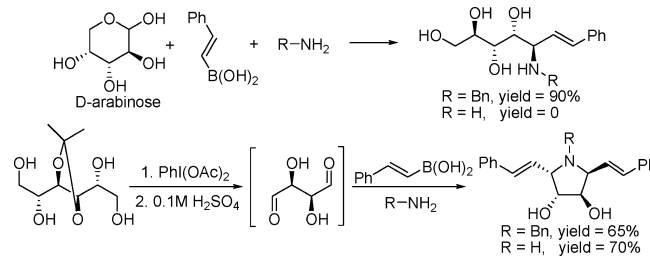
Here we report a novel, concise approach to iminocyclitols that exploits an unprecedented synthetic strategy to build piperidine and pyrrolidine rings with high stereocontrol via Petasis-type three-component condensation. The advantage of the Petasis boronic acid-Mannich reaction[4] is that chiral compounds can be efficiently produced in a single process with minimum protecting group manipulation. Accessibility of the reagents and the mild reaction conditions also make the method extremely practical. Previously we developed a three-step route to sialic acids and analogues by using the Petasis reaction.[5] We now demonstrate for the first time that the Petasis reaction can be used to synthesize several types of biologically important iminocyclitols.

Scheme 1



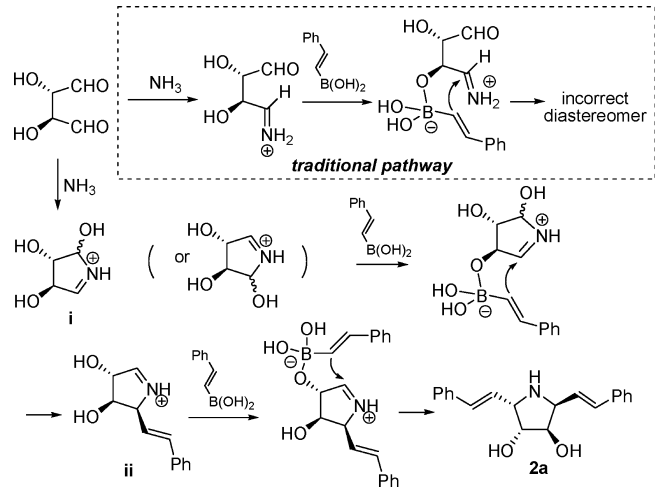
As a representative example, the new synthesis is detailed in Scheme 1 for the preparation of iminocyclitol **3a**. The starting material is a polyhydroxyl dialdehyde that was readily prepared from the corresponding commercially available monosaccharide, i.e., 3,4-*O*-isopropylidene-D-mannitol (**1a**). To avoid the use of toxic Pb-containing reagents, it was found that $PhI(OAc)_2$ could quantitatively oxidize **1a** to a dialdehyde at room temperature. Addition of 0.1 M H_2SO_4 to the reaction mixture removed the acetone protecting group. Subsequently NH_3 and styrylboronic acid were added to the aqueous reaction mixture, resulting in two Petasis-type condensations. The final product of the above one-pot reaction sequence was compound **2a** (de >98%) in 70% isolated yield from **1a**.

Scheme 2



Some unusual observations are worth noting for the above Petasis-type condensation. First, according to the previous studies on Petasis-type condensation,[4] compound **3a** is not the "expected" diastereomer (note: the "expected" product was not observed even in trace amount in our experiment). Second, the condensation in Scheme 1 surprisingly presents the first example for the use of ammonia in Petasis boronic acid-Mannich condensation. In fact, our experiments with D-arabinose clearly show that although benzylamine can readily condense with this saccharide, ammonia cannot do so (Scheme 2). On the other hand, both benzylamine and ammonia can condense with the dialdehyde generated *in situ* from 3,4-*O*-isopropylidene-D-mannitol.

Scheme 3



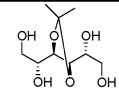
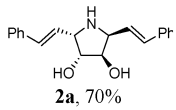
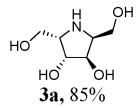
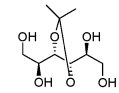
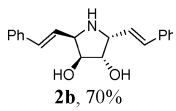
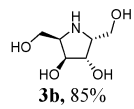
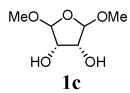
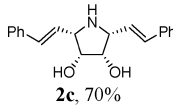
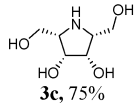
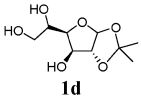
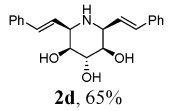
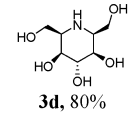
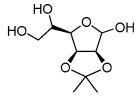
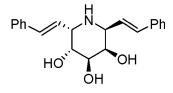
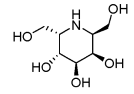
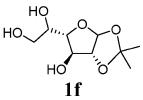
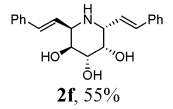
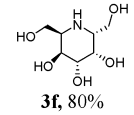
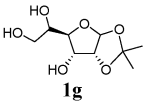
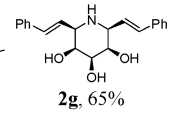
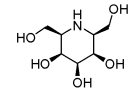
To interpret the observations we suggest that the above reaction proceed *via* a cyclic intermediate. As shown in Scheme 3, it is

10.1021/ja901656e CCC: $40.75

proposed that the dialdehyde intermediate may form a five-membered imininum ion **i**. Reversible coordination of styrylboronic acid with an OH group promotes *cis*-addition of the vinyl group to the C=N double bond. This step produces a new five-membered iminium ion **ii** that may undergo *cis*-vinylation producing compound **2a**. The mechanism explains that the *cis*, but not the *trans*, product is observed in the condensation. The favored formation of a five-membered ring also explains that NH_3 (which does not form stable imines with aldehydes) may participate in this particular reaction.

Ozonolysis of **2a** should yield **3a** in theory (Scheme 1). However, from the standard ozonolysis/reduction procedure only some unidentified byproducts were obtained. It was hypothesized that the free amino group in **2a** interfered with ozonolysis. To test this speculation, **2a** was protected with $(Boc)_2O$ and the corresponding carbamate was subjected to ozonolysis and $NaBH_4$ reduction. After TFA treatment, compound **3a** was obtained successfully in 60% yield. To improve the synthesis a proton was used to protect the amino group in **2a**. After examinations with a number of acids, it was found that by adding $HClO_4$ to the MeOH solution of **2a** ozonolysis occurred and the product was reduced with $NaBH_4$ to **3a** in 85% yield.

Table 1. Two-Step Synthesis of Iminocyclitols

Entry	Starting material	Product of step 1	Product of step 2	Overall yield
1	 **1a**	 **2a**, 70%	 **3a,** 85%	60%
2	 **1b**	 **2b**, 70%	 **3b,** 85%	60%
3	 **1c**	 **2c**, 70%	 **3c,** 75%	52%
4	 **1d**	 **2d**, 65%	 **3d,** 80%	52%
5	 **1e**	 **2e**, 60%	 **3e,** 75%	45%
6	 **1f**	 **2f**, 55%	 **3f,** 80%	44%
7	 **1g**	 **2g**, 65%	 **3g,** 85%	55%

At this point the synthesis of **3a** was accomplished from a readily available starting material (i.e., **1a**) in only two steps. Both steps were readily carried out under mild conditions. The overall yield is 60% (Table 1, entry 1), and the synthesis can be easily scaled up. Previously **3a** was synthesized from PMP-protected ethyl 4-hydroxybut-2-enoate in eight steps with an overall yield of 8%.[6] By using the same procedure, the enantiomer of **3a** (i.e., **3b**) was synthesized from 3,4-*O*-isopropylidene-L-mannitol (entry 2). As a strong inhibitor of α-fucosidase, **3b** was recently synthesized in seven steps from tri-*O*-benzyl-D-glucal with an overall yield of 38%.[7] Furthermore, from readily available *cis*-3,4-dihydroxy-2,5-dimethoxy tetrahydrofuran, a dialdehyde was generated by using 0.1 M H_2SO_4 and condensed with NH_3. Ozonolysis/reduction of the intermediate produced **3c** with an overall yield of 52%. As a strong inhibitor of α-galactosidase,[8] **3c** was previously synthesized chemoenzymatically from dihydroxyacetone phosphate and 2-azido-3-hydroxypropanal in three steps by using fructose-1-phosphate aldolase.[8]

The above synthetic route can also be used to prepare six-membered iminocyclitols (entries 4−7). The starting materials for the syntheses were 1,2 or 2,3-*O*-isopropylidene-protected D-glucose, D-mannose,[9] D-galactose,[10] and D-allose, which are either commercially available or readily synthesized. The same one-pot reaction sequence of $PhI(OAc)_2$ oxidation, H_2SO_4 deprotection, and Petasis condensation provided the bis-vinylated intermediates, which were ozonolyzed to iminocyclitols **3d**−**3g**[11,12] with an overall yield of *ca.* 50%.

In summary, a two-step method has been developed to synthesize several biologically important iminocyclitols in *ca.* 44−60% yields by using Petasis-type condensation. The method is very general and operationally simple, affording a series of iminocyclitols from easily available sugar derivatives. Unexpected diastereoselectivities are observed, suggesting that the condensation may proceed through a five- or six-membered cyclic iminium ion intermediate.

Acknowledgment. We thank the National Institutes of Health for the financial support.

Supporting Information Available: Experimental details and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA901656E