A New Catch-and-release Purification Method Using a Levulinyl Group as a Tag and Its Application to Oligosaccharide Synthesis

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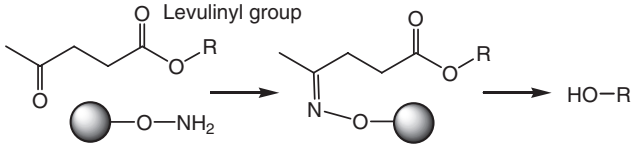
Products possessing a levulinyl group were selectively isolated from reaction mixtures using a new resin-capture method and a polymer-supported aminooxy group. Successive treatment with NaOH in MeOH readily liberated purified products from the resins. Applications of this method to oligosaccharide syntheses are described.

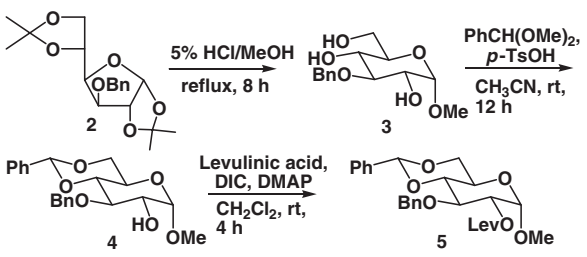
In organic synthesis, isolation of products is often a tiresome and time-consuming procedure. Therefore, various techniques such as polymer-supported synthesis have been developed for high throughput synthesis.[1–7] Catch-and-release purification based on chemospecific interactions between two functional groups is a promising method in the phase tag strategy; the tagged intermediate can be isolated from the reaction mixture by specific interactions. Various strategies for synthesis of oligosaccharide have also been developed and reported.[8–13] In the present study, we develop a new catch-and-release purification method using a levulinyl group as a tag (Scheme 1).

Although the levulinyl group is stable under acidic conditions, it is readily removed by a reaction with hydrazine (NH_2NH_2). Hence, we speculated that compounds containing a levulinyl group would be trapped by aminooxy (NH_2O–) resins based on imination between carbonyl group and aminooxy function.[14–16]

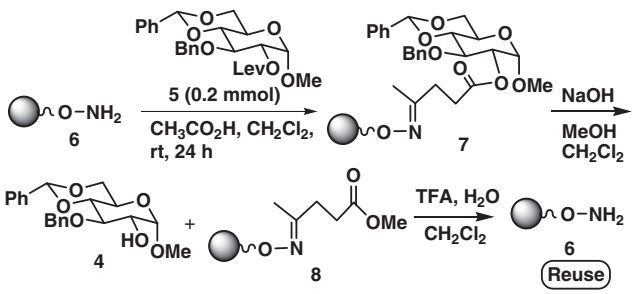
Scheme 2 depicts the synthesis of the monosaccharide possessing a levulinyl group. Compound **2** was prepared from glucose according to a well-known method.[17–19] Ring opening and then reclosing by the Fischer glycosidation in the presence of MeOH and HCl afforded methyl 3-*O*-benzyl-glucoside **3**. Compound **3** was treated with benzaldehyde dimethylacetal and *p*-toluenesulfonic acid to give 4,6-benzylidene compound **4**. The levulinyl (Lev) group was introduced to the 2-position by levulinic acid and DIC to give compound **5**.



Scheme 1.



Scheme 2.



Scheme 3.

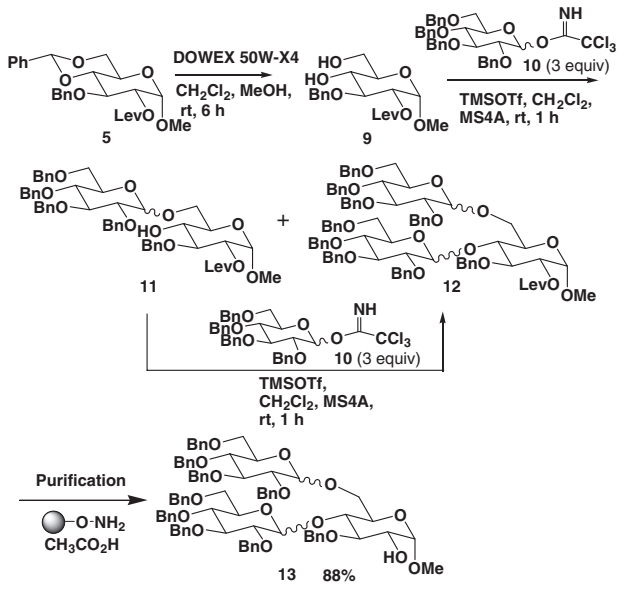
Table 1. Catch-and-release purification using 2-*O*-levulinyl-monosaccharide **5**

Entry	Solid-support	Function group on resin/mmol	Binding of **5**[a] /mmol	Yield[a] /%
1	–NH_2 (3.0 g)	4.5	0	0
2	–NH-NH_2 (3.0 g)	7.5	0	0
3	–O—NH_2 (3.0 g)	7.5	0.20	100

[a]Calculated from amount of monosaccharide **4** obtained from resin after treatment with NaOH in MeOH.

After completing the synthesis, we examined the catch-and-release of resins using 2-*O*-levulinyl-monosaccharide **5** (Scheme 3, Table 1). The resins were added to a solution of **5** in dichloromethane, and the mixture was shaken at room temperature for 24 h. Then remaining **5** was removed by simply rinsing with CH_2Cl_2. Then solid-supported monosaccharide **7** was treated with NaOH in CH_2Cl_2 and MeOH to release monosaccharide **4**. Pure **4** was obtained after excess NaOH was removed by an ion-exchange resin and a short silica-gel column. The aminomethylated polystyrene did not show absorbability (Entry 1). Although *p*-toluenesulfonyl hydrazide polystyrene resin has been used as a scavenger resin for aldehydes,[20] it did not trap **5** (Entry 2). On the other hand, the aminooxy resin[21] efficiently captured compound **5** under acidic conditions (Entry 3). Acetic acid was more effective as an acid catalyst for oxime formation than trifluoroacetic acid because imination proceeds at pH 4 (In the case of TFA as acid catalyst, yield was 88%). The resin could be reused after washing with 10% TFA in MeOH/CH_2Cl_2 and then MeOH/CH_2Cl_2 (Scheme 3).[22]

This new catch-and-release procedure was then applied to oligosaccharide syntheses. As shown in Scheme 4, 3 equiv of glycosyl donor **10** was allowed to react with 1 equiv of glyco-



Scheme 4.

syl acceptor **9** using TMSOTf as an activator in the presence of molecular sieves 4A. Generally, the glycosylation reaction affords a 1-hydroxy sugar as a by-product via the hydrolysis of the glycosyl donor. Because 1-hydroxy sugar has a latent aldehyde function, it might be captured by the aminooxy resin.[23] Fortunately, in our case, the aminooxy resin did not catch the 1-hydroxy sugar formed by the hydrolysis of donor **10**. Because glycosylation gave a mixture of disaccharide **11** and trisaccharide **12**, glycosylation was repeated. The reaction mixture was then neutralized with K_2CO_3 and subsequently filtered. Aminooxy–polystyrene resin was added to the filtrate to catch levulinyl trisaccharide **12** onto the resin. The reagents and by-products without the levulinyl moiety were removed by simply rinsing with CH_2Cl_2 to yield the solid-supported trisaccharide, which was then treated with NaOH in MeOH/CH_2Cl_2. Excess NaOH was removed by ion-exchange resin Dowex 50W-X4. Pure delevulinylated trisaccharide of **13** was obtained in 88% yield.[24]

In conclusion, a new catch-and-release purification using a levulinyl group as a tag was demonstrated to be simple and very effective. Because a new free hydroxy function is generated through this purification procedure, this method can be regarded as a combination of purification and deprotection. Hence, this method offers a new approach to purify compounds in organic synthesis, especially in the field of combinatorial synthesis.

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20 PS resin (100–200 mesh, CA. 2.5 mmol/g) is commercially available from Sigma-Aldrich as a scavenger resin for carbonyl compounds like as aldehydes.
21 Aminooxy resin (Hydroxylamine Wang resin, 100–200 mesh, 1.5–2.5 mmol/g Novabiochem) is commercially available from Novabiochem.
22 Procedure for chemical fishing of the levulinylated saccharide **5**. Aminooxy–PS resin (3.0 g, 7.5 mmol) was added to a solution of dichloromethane of levulinylated monosaccharide **5** (94 mg, 0.20 mmol) and acetic acid (0.1 mL, 1.7 mmol), and stirred at rt. After 24 h, the resin was filtered, washed with dichloromethane twice, and suspended in 6 mL of dichloromethane. Then 2 mL of 1 M NaOH in MeOH solution was added, and the mixture was shaken at rt. for 3 h, and filtered. Ion-exchange resin Dowex 50W-X4 (ca. 200 mg) was added to the filtrate, which was filtered again. The solution was concentrated in vacuo. The residue was dissolved in dichloromethane and charged on a short silica gel column ($1 \times 2\,cm^2$). After flushing the column with 5 mL of dichloromethane, the product was eluted with $CHCl_3$/MeOH 9:1, and the solvent was removed in vacuo to give delevulinylated monosaccharide **4** (74 mg, 0.20 mmol, quant) as a colorless solid.
23 The 1-hydroxysugars were not captured under the present conditions, though free 1-hydroxy sugars were selectively captured by aminooxy resins for glycomics: Y. Miura, S. Nishimura, *Trends Glycosci. Glycotechnol.* **2008**, *20*, 17, and references therein.
24 Procedure of chemical fishing of mixture of methyl 4,6-bis-*O*-(2,3,4-tri-*O*-benzyl-D-glucopyranosyl)-2-*O*-levulinyl-3-*O*-benzyl-β-D-glucopyranoside (**13**). After a mixture of levulinyl-methyl-glycoside **9** (0.19 g, 0.50 mmol), glycosyl donor **10** (1.03 g, 1.50 mmol), TMSOTf (0.03 g, 0.15 mmol), and molecular sieves 4A (ca. 500 mg) in 2 mL of dichloromethane was stirred on ice bath, the mixture was stirred at rt. for 3 h. Then K_2CO_3 was added to neutralize the solution, which was then filtered. The same reagents for glycosylation were added to the filtrate on an ice bath and stirred for 3 h. After 3 h, K_2CO_3 was added, and then the solution filtered. Aminooxy–PS resin (3.0 g, 7.5 mmol) and acetic acid (0.1 mL, 1.7 mmol) were added to the filtrate, and the mixture was stirred at rt. for 24 h, and then filtered. The resin was washed with dichloromethane twice, and subsequently suspended in 6 mL of dichloromethane. Then 2 mL of 1 M NaOH in MeOH solution was added, and the mixture was shaken at rt. for 3 h, and filtered. Ion exchange resin Dowex 50W-X4 (ca. 200 mg) was added to the filtrate, which was filtered again. The solution was concentrated in vacuo. The residue was dissolved in dichloromethane and charged on a short silica gel column ($1 \times 2\,cm^2$). After flushing the column with 5 mL of dichloromethane, the product was eluted with $CHCl_3$/MeOH 9:1, and the solvent was removed in vacuo to give delevulinylated trisaccharide **13** (0.29 g, 0.44 mmol, 88% yield) as a colorless solid; ESI-MS m/z: Calcd for $[(M + Na)^+]$ 1341.6, found 1341.6.

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