

## INDIUM-MEDIATED STEREOSPECIFIC GLYCOSYLATION OF ALCOHOLS

Bimal K. Banik,\* Susanta Samajdar, Indrani Banik, Oliwia Zegrocka, and Frederick F. Becker

The University of Texas, M. D. Anderson Cancer Center, Department of Molecular Pathology, Box 89, 1515 Holcolombe Blvd., Houston, TX 77030, USA

**Abstract** – Indium has been shown to be effective in the stereospecific glycosylation of various alcohols with bromosugars.

The glycosylation of alcohols is an attractive area of research because of the biological activities of *O*-glycosides.<sup>1</sup> Therefore, methods to develop effective glycosylation are in demand.<sup>2</sup> Glycosyl fluoride method,<sup>3a</sup> thioglycoside<sup>1</sup> method and Ferrier rearrangement<sup>3b</sup> are most widely used processes for this purpose. Several Lewis acids<sup>4</sup> and acidic-support<sup>5</sup> have been utilized to accomplish this transformation. The main shortcomings of these processes are the non-stereoselectivity of the reaction and, as a result, mixtures of  $\alpha$  and  $\beta$ -glycosides are generally formed in varying proportions. Attempts have been made to improve the stereoselectivity of the process and some successful realization of this goal has been reported.<sup>6</sup> Recently, Lewis acid-mediated synthesis of  $\beta$ -glycosides using relatively unstable glycosyl phosphates as donors has been demonstrated.<sup>7</sup> These reagents can be prepared as a mixture of isomers in a three-steps of which the first step is the oxidation of glycol by dimethyldioxirane.<sup>8</sup> The other effective trichloroacetamidate method in some cases produces a mixture of isomers.<sup>9</sup> Some of these methods have proven effective, however, they still have limitations: lengthy synthesis of the donor or the acceptor, the use of toxic activators and exotic unstable activating agents. Therefore, development of new, easily accessible, non-toxic and environmentally friendly activators is highly desirable.

Recently, we have demonstrated Reformatsky-type of reaction mediated by indium for the synthesis of 3-unsubstituted  $\beta$ -lactams.<sup>10</sup> The formation of  $\beta$ -lactam by the reaction of ethyl bromoacetate and imines in the presence of indium is of considerable interests. This reaction indicates that indium metal in the presence of bromo compound can react with imino functional group instead of producing the dimeric product of the halides or the imines. This principle has also been shown by the facile addition reaction to the carbonyl group.<sup>11</sup> Therefore, we hypothesize that the combination of indium and bromo derivative can be used for the nucleophilic displacement reaction with the alcohols. Our exploration of this premise

resulted in a convenient method for the stereoselective synthesis of  $\beta$ -glycosides by the reaction of alcohols and  $\alpha$ -D-bromoglucose derivatives. We believe this is the first stereoselective method for glycosylation of alcohols mediated by indium.<sup>12</sup> The other organometallics like zinc, samarium diiodide and titanium reagents produced the glycols when treated with **1**.<sup>13</sup>

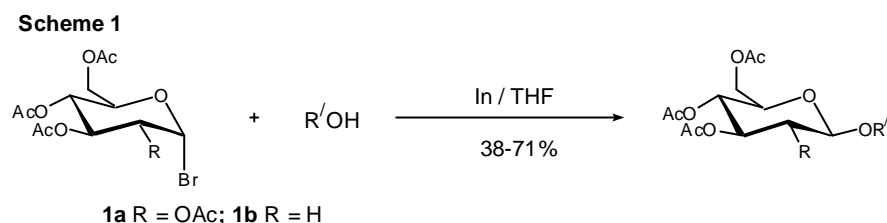
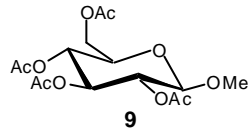
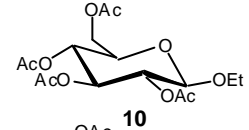

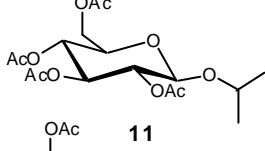
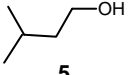
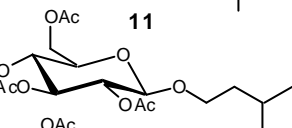
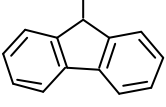
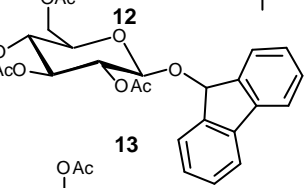
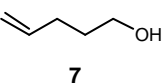
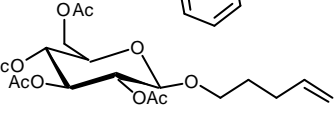
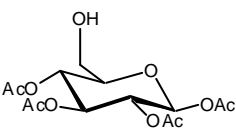
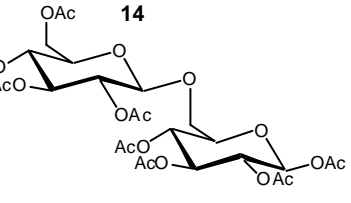


Table 1: Indium-mediated glycosylation of alcohols by 2,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl bromide .

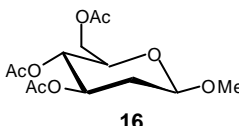
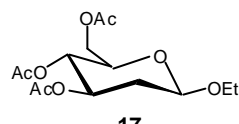

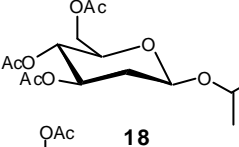
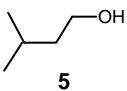

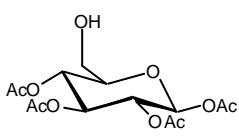
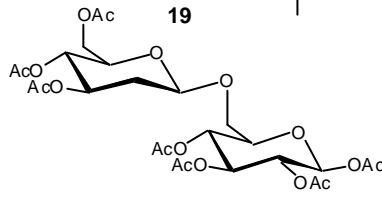
Entry	Alcohol	Sugar	Glycoside	Time (h)	yield (%)
1	MeOH <b>2</b>	<b>1a</b>	 <b>9</b>	10	47
2	EtOH <b>3</b>	<b>1a</b>	 <b>10</b>	9	45
3	 <b>4</b>	<b>1a</b>	 <b>11</b>	12	44
4	 <b>5</b>	<b>1a</b>	 <b>12</b>	11	40
5	 <b>6</b>	<b>1a</b>	 <b>13</b>	10	43
6	 <b>7</b>	<b>1a</b>	 <b>14</b>	8	38
7	 <b>8</b>	<b>1a</b>	 <b>15</b>	14	40

Reaction of methanol (**2**), ethanol (**3**), isopropanol (**4**), 3-methylbutanol (**5**), 9-fluorenol (**6**) and pentenol (**7**)<sup>14</sup> with 2,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl bromide (**1a**) in the presence of indium powder under reflux temperature using THF as the solvent produced the glycosides (**9** to **14**) respectively in 38-47% yield along with some uncharacterized products (20%). The anomeric stereochemistry in these glycosides was determined as  $\beta$  from the coupling constant of the anomeric

hydrogen (7.5-10 Hz) (**Scheme 1**). Using this method, a disaccharide (**15**) was prepared from the alcohol (**8**) in 40% yield (Table 1).

In order to increase the scope and yield, this reaction was then performed with sugar (**1b**) in which the acetoxy group at C-2 is absent with alcohols (**2-5**) [Table 2, Entries 1-4, compounds (**16-19**)] and (**8**) [(Table 2, Entry 5, compound (**20**)]. The yield and time of the reaction with (**1b**) was dramatically improved compared to (**1a**).

Table 2: Indium-mediated glycosylation of alcohols by 2-deoxy-3,4,6-tri-O-acetyl- $\alpha$ -D-glucopyranosyl bromide .

Entry	Alcohol	Sugar	Glycoside	Time (h)	yield (%)
1	MeOH <b>2</b>	<b>1b</b>	 <b>16</b>	2	70
2	EtOH <b>3</b>	<b>1b</b>	 <b>17</b>	1.5	69
3	 <b>4</b>	<b>1b</b>	 <b>18</b>	2.5	66
4	 <b>5</b>	<b>1b</b>	 <b>19</b>	2	71
5	 <b>8</b>	<b>1b</b>	 <b>20</b>	3	65

The exclusive formation of the  $\beta$ -glycoside deserves some special comments. Unlike the Lewis acid mediated glycosyl phosphate and triflate methods, we can exclude the formation of anomeric triflate or onium ion, as our method produces only  $\beta$ -glycosides without any acid promoter with sugar (**1b**) where there is no functionality present at C-2. Therefore, the question of participation of the C-2 functionality in promoting the formation of  $\beta$ -glycosides does not arise by the indium-mediated method. We found that the presence of indium is necessary in the formation of the  $\beta$ -glycosides. This can be explained by a  $S_N2$  type of reaction of the alcohols with the bromosugars. However the role of indium in promoting the formation of the  $\beta$ -glycosides with 2-acetoxy and 2-deoxy bromosugar is not properly understood.

In general, this method is effective for the stereospecific glycosylation of primary alcohol, secondary alcohol, unsaturated alcohol and benzylic alcohol (Table 1, Entries 1 to 7). The good yield of the glycosides (Table 2, Entries 1-5) with the sugar (**1b**) is encouraging. In addition disaccharides (Table 1, Entry 7 and Table 2, Entry 5) can also be prepared without degradation.

In conclusion, we have demonstrated for the first time a general stereospecific glycosylation of alcohols by indium.<sup>15</sup>

## ACKNOWLEDGEMENTS

We gratefully acknowledge the funding support received for this research project from the Golden Family Fund for cancer research and NIH Cancer Center Support Grant, 5-P30-CA16672-25, in particular the shared resources of the Pharmacology and Analytic Center Facility.

## REFERENCES AND NOTES

1. For a review on *O*-glycosylation, see: K. Toshima and K. Tatsuta, *Chem. Rev.*, 1993, **93**, 1503.
2. For example, see: (a) H. Paulsen, *Angew Chem.*, 1982, **94**, 184. (b) R. R. Schmidt, *Angew Chem.*, 1986, **98**, 213.
3. (a) For a recent review, see: K. Toshima, *Carbohydr. Res.*, 2000, **327**, 15. (b) R. Ferrier, *J. Adv. Carbohydr. Chem. Biochem.*, 1969, 199.
4. (a) G. Descotes and J. C. Martin, *Carbohydr. Res.*, 1979, **68**, 33. (b) P. Bhate, D. Horton and W. Priebe, *Carbohydr. Res.*, 1985, **144**, 331 and references cited therein.
5. For an example, see: K. Toshima, T. Ishizuka, G. Matsuo, and M. Nakata, *Synlett*, 1995, 306.
6. For some recent examples towards  $\alpha$ -anomer, see: (a) M. Bols, *J. Chem. Soc., Chem. Commun.*, 1992, 913. (b) B. K. Banik, M. S. Manhas, and A. K. Bose, *J. Org. Chem.*, 1994, **59**, 4714. For some recent examples towards  $\beta$ -anomer, see: (a) W. Roush and C. E. Bennett, *J. Am. Chem. Soc.*, 1999, **121**, 3541. (b) B. Yu and Z. Yang, *Tetrahedron Lett.*, 2000, **41**, 2961.
7. O. J. Plante, R. B. Andrade, and P. H. Seeberger, *Org. Lett.*, 1999, **1**, 211.
8. R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, 1985, **50**, 2847.
9. R. R. Schmidt and W. Kinzy, *Adv. Carbohydr. Chem. Biochem.*, 1994, **50**, 21.
10. B. K. Banik, A. Ghatak, and F. F. Becker, *J. Chem. Soc. Perkin Trans. 1*, 2000, 2179.
11. C. J. Li and T. H. Chan, *Tetrahedron*, 1999, **55**, 11149.
12. A glycosylation reaction utilizing indium salt as a promoter has been published recently, see: B. S. Babu and K. K. Balasubramanian, *Tetrahedron Lett.*, 2000, **41**, 1271.
13. For example, see: C. L. Cavallaro and J. Schwartz, *J. Org. Chem.*, 1995, **60**, 7055 and references cited therein.
14. For an elegant application of *n*-pentenyl glucosides, see: T. Buskas, E. Soderberg, P. Konradsson, and B. Fraser-Reid, *J. Org. Chem.*, 2000, **65**, 958.
15. General procedure for glycosylation of alcohols: A mixture of the alcohol (1 mmol), glycosyl bromide (1.5 mmol), indium powder (2 mmol) and THF (15 mL) were refluxed (for a period specified in the Tables). The solvent was then evaporated in vacuo and directly subjected to flash chromatography using silica gel (230-400 mesh) (30% ethyl acetate-70% hexane as eluent) to afford the pure  $\beta$ -glycosides.