Tetrahedron 69 (2013) 2608–2612

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# One pot conversion of carbohydrates alcohol into chloride via benzotriazole sulfonate

Chandra S. Azad, Anil K. Saxena *

*Division of Medicinal and Process Chemistry Division, Central Drug Research Institute (CDRI), CSIR, Chattar Manzil Palace, MG Road, Lucknow 226001, Uttar Pradesh, India*

ARTICLE INFO

*Article history:*
Received 8 November 2012
Received in revised form 8 January 2013
Accepted 15 January 2013
Available online 24 January 2013

Dedicated to Professor Richard R. Schmidt on the occasion of his 78th birthday.

*Keywords:*
Deoxyhalogeno-carbohydrate
Bezotriazole-1-sulfonate
Alcohols to chloride
Appel reaction

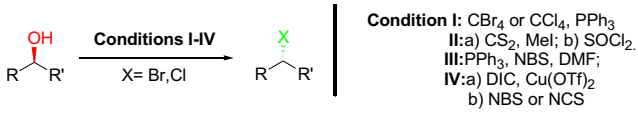
ABSTRACT

A one pot method for chloro-dehydroxylation of carbohydrates alcohol including sterically and electrically hindered ones in excellent yield was developed. The benzotriazole-1-sulfonate proposed to play a crucial role in the reaction medium, which undergoes substitution by chloride ion in the reaction medium to give only desired chloride derivative without the formation of side product. The optimized methodology can be used in the synthesis of number of biologically active compounds or chiral synthones.



## 1. Introduction

Deoxyhalogeno-carbohydrates are of key importance to carbohydrate and medicinal chemists as they are used as potent artificial sweeteners,[1] male antifertility agents,[2] hepatocyte cellular glycosaminoglycan inhibitors[3] and major scaffolds in antibiotics.[4] Recently halogenated carbohydrates have been shown to be a part of pharmacophores.[5] The 2-deoxy-D-glucose known for its medicinal utility,[6] can be easily synthesized from the corresponding 2-halo derivatives of glucose via free radical elimination.[7] In general, the conversion of alcohol functionality of carbohydrate into halide involves first the conversion of alcohol into nucleofugal group e.g., mesylate, tosylate, triflate and imidazylate etc., followed by its substitution with an appropriate nucleophile.[8] In general mesylates and tosylates are considered as good leaving groups but not in the field of the carbohydrate chemistry because their substitution involves drastic reaction conditions, such as heating at 130 °C for 80 h in DMF and that too provide nominal amount of the desired product.[9] Though the replacement of mesylates and tosylates by triflates, substantially extended the scope of reactivity[10] of these sulfonic esters towards nucleophilic substitution reaction, but the major limitations of some triflate esters are their inadequate self life, high cost and cumbersome application in large scale synthesis. Appel reaction, a milestone in this direction where triphenylphosphine ($PPh_3$) and carbon tetrachloride or bromide are used in the conversion of alcohols into halides (**I**, Scheme 1).[11] The major disadvantage associated with the Appel reaction is the formation of triphenylphosphine oxide and its removal from the reaction mixture. Further attempts have been made by different research groups, which include (**II**) conversion of alcohol into chloride with the retention of configuration treating its xanthates with thionyl chloride,[12] (**III**) conversion of alcohols into halide with the aid of the Vilsmeier-type reagent ($PPh_3$, *N*-bromosuccinimide and DMF)[13] and (**IV**) conversion of hydroxyl into halides by treating its *O*-alkyl isoureas derivatives with *N*-halosuccinimide (Scheme 1).[14]




**Scheme 1.** Various protocol for simple conversion of alcohol to halide (Br or Cl).

All these methods involve harsh reaction conditions and expensive reagents. Furthermore, the formation of halides from nucleofugal groups leads in the formation of unsaturated products due to competitive elimination reaction. Therefore, investigations

* Corresponding author. Tel.: +91 522 2612411 8x4268, +91 522 2624273; fax: +91 522 2623405/2623938; e-mail addresses: anilsak@gmail.com, ak_saxena@cdri.nic.in (A.K. Saxena).

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http://dx.doi.org/10.1016/j.tet.2013.01.044

were made to find a new, simple, cost effective and one pot method for the synthesis of deoxy-halogenated carbohydrate.

We describe herein one pot conversion of sterically and electronically hindered alcohol of carbohydrates to their respective chlorides via benzotriazole sulfonate (Btz), which was designed on the basis of imidazole-1-sulfonate (Imz, Fig. 1). The Imz is known for its cost effectiveness and good nucleofugal properties.[15] Unlike Imz, which is used after isolation and purification from the reaction mixture, the Btz synthesized from sulfuryl chloride and 1,2,3-benzotriazole (BtH) was used as such without isolation (in situ) for converting the alcohol of carbohydrates to their respective chloride derivative (**1b**–**7b**, Fig. 2). The in situ generated Btz possibly fragments into BtH and $SO_3$, may be due to the remote activation of carbon bearing –OH group by the benzotriazolium salt ($BtH^+Cl^-$) during the reaction, which leads to the displacement of nucleofuge (sulfonic ester). This has been exemplified in the conversion of carbohydrates alcohol (carb-OH) to their corresponding chloride in excellent yield. These chlorides may be useful synthons for the synthesis of bioactive molecules.

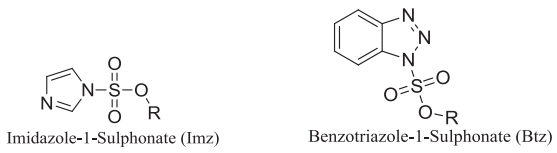
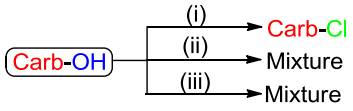



**Fig. 1.** Schematic representation of Imz and Btz.




**Scheme 2.** (i) First approach: $SO_2Cl_2$, BtH, DMF, –40 °C. (ii) Second approach: NaH, DMF, $BtSO_2Bt$, –40 °C. (iii) Third approach: (a) $NH(SiMe_3)_2$, Py; (b) $Bu_4NF$, DCM, $BtSO_2Bt$.

In the first approach the isolated product was the chloride derivative of the corresponding carb-OH instead of the expected Btz, while in the second and third approach a complex nonseperable mixture was obtained. Thus the unusual formation of chloride derivative in 88–96% yield with complete inversion of configuration in the first approach is only possible through Btz. Although, Btz was not isolated from the reaction mixture, but its formation can be explained on the basis of the product obtained. In order to identify the role of BtH, the reaction was performed between carb-OH (**1a**) and sulfuryl chloride without BtH under the similar reaction conditions *viz.* temperature –40 °C, time 24 h to yield the chloride derivative (**2b**) in less than 10% yield with retention of configuration. This reaction may involve the chlorosulfonate ester, which might have been substituted by the chloride ion through $S_Ni$ Mechanism (Scheme 3). However the formation of the product in presence of BtH suggests that Btz is formed in the reaction and gets substituted by the chloride ion due to its high nucleofugal property to give an excellent yield of the chloride derivatives **1b**–**7b**. These derivatives were characterized by the state of art techniques like

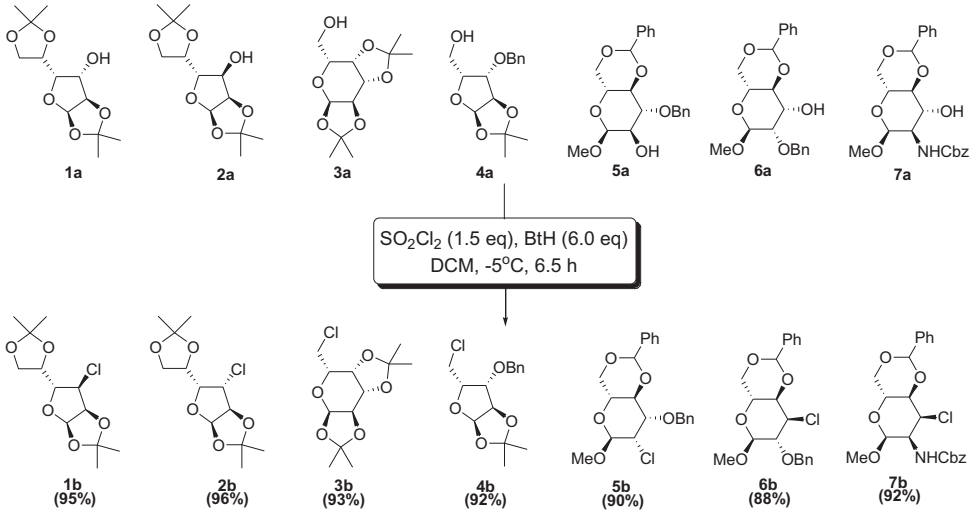
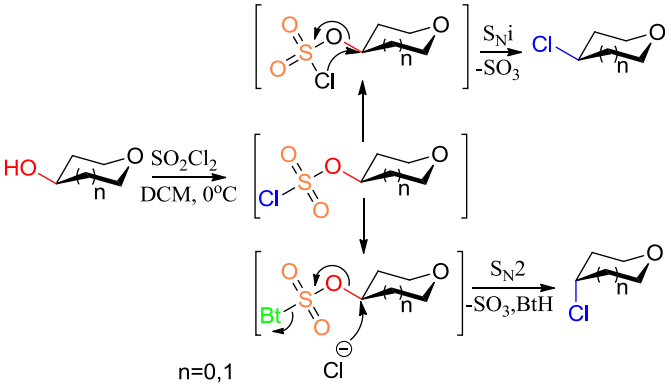



**Fig. 2.** One pot conversion of alcohols into chlorides.

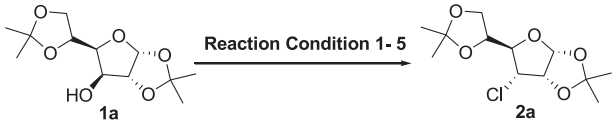
In view of several successful attempts in increasing the stability and reactivity of benzotriazole derived reagents over the corresponding imidazole derivatives,[16] possibly due to the increase in their electron withdrawing nature as compared to corresponding imidazole derivatives, the Btz analogue of Imz was synthesized. Three approaches were adopted for the synthesis of Btz. In the first approach the carb-OH was reacted with sulfuryl chloride at –40 °C in DMF in the presence of BtH. In the second approach, the carb-OH was converted to its sodium salt with NaH at 0 °C, which was reacted with $BtSO_2Bt$ at –40 °C. The $BtSO_2Bt$ was prepared by the action of sulfuryl chloride with 1-(trimethylsilyl)-benzotriazole according to the reported procedure.[17] In the third approach, carb-OH was converted into its silyl ether with the HMDS in pyridine. The silyl ether was then reacted with $BtSO_2Bt$ in presence of $Bu_4NF$ under reflux (Scheme 2).




**Scheme 3.** Plausible reaction mechanism.

NMR, IR, Mass and elemental analysis. The isolation of Btz by the second and third approach was not successful and complex non separable mixture was formed in both cases. The results obtained in the present methodology are better than the earlier reported methods, which are summarized in Table 1.

**Table 1**
Preparation of chlorides from alcohols of carbohydrates moiety (**1a**)




**1a** **2a**

| Entry | Reaction conditions | Yield | Ref. |
|---|---|---|---|
| 1. | (i) $Tf_2O$, Py, DCM (ii) $But_4NCl$, $C_6H_6$, Δ, 12 h | 22% | 19 |
| 2. | (i) $Tf_2O$, Py, DCM (ii).$Bu_4NCl$, $NaHCO_3$, $C_6H_6$, Δ, 18 h | 62% | 19 |
| 3. | (i) Imidazole, NCS, $PPh_3$, $C_6H_5Cl$, Δ, 3 h | 54% | 13 |
| 4. | (i) $PPh_3$,DEAD,4-$MeC_6H_4SO_2Cl$ (ii) Toluene, Δ,5 h | 5% | 24 |
| 5. | $SO_2Cl_2$, BtH, DMF, −40 °C | 95% | [a] |

[a] The present methodology.

In order to widen the scope of the novel methodology, the studies were extended to optimize the reaction conditions and its applicability to different sterically and electronically hindered carb-OH. Hence the reactions were performed using different solvents at different temperatures and time. The best results were obtained with the DCM as solvent at temperature range −5 °C to −0 °C for 6.5 h. Thus the conditions for the first approach were optimized in terms of temperature, time and solvent to give the desired chloride derivative in excellent yield. Based on these results, we hypothesized the mechanism of our reaction as shown in Scheme 3. When the reaction was performed without BtH there was the retention of configuration in **1a**, while in the presence of BtH the reaction yielded the completely inverted product, the plausible pathways adopted in the reaction might be $S_Ni$ and $S_N2$, respectively (Scheme 3).

The formation of **1b** in excellent yield through Btz as compared to triflate (Table 1) may be explained in two ways, first may be due to the poor approach of nucleophile because of dipolar interaction (electronically hindrance)[18] and second because of the formation of unsaturated side products.[19] Further the more facile formation of **2b** than **1b** may be due the lesser steric and electronic hindrance at C-3 of **2a** than **1a**. The conversion of primary alcoholic group of **3b** directly into its chloride has been reported by the Samuelsson et al. in excellent yield but the method involved the use of triphenylphosphine dichloride, which gives triphenylphosphine oxide as a side product, which is difficult to be removed from the reaction at the time of workup and involves the separate reagent preparation.[20] The present one pot methodology provides **3b** in excellent yield with easy workup, and without any separate preparation of reagent. The same is true in case of xylose derivative **4b**. The substitution by chloride at C2 position of **5a** to give **5b** has been reported in poor yield because of torsional, electrostatic and steric strain in the transition state.[21,22] Whereas in our case the formation of **5b** from **5a** in 90% yield is the first report and may be utilized in the synthesis of potent bioactive 2-deoxy-D-glucose by its reduction with tributyltin hydride ($Bu_3SnH$). Similarly nucleophilic substitution at C3 of **6a** and **7a** to give **6b** and **7b**, respectively has also been reported difficult due to the steric hindrance of axial anomeric substitutent.[18] In the case of **7a** it has also led to formation of oxazolidine as side product instead of the desired product (**7b**) by the involvement of *N*-carbamate.[23] However in our presented methodology the synthesis of **7b** is better both in terms of yield and without the formation of side product oxazolidine. The **6b** and **7b** can easily be utilized in the synthesis of 3-deoxy derivative by its reduction with $Bu_3SnH$ in refluxing toluene in the presence of 2-2′-azoisobutyronitrile (AIBN).[7]

## 2. Conclusion

In conclusion, we have developed one pot conversion for the sterically and electronically hindered alcohol of carbohydrates into their corresponding chloride derivatives in excellent yield by the cost effective hitherto unknown in situ generated reagent (Btz), which plays an important role in the formation of desired product via $S_N2$ type reaction. The present methodology may be considered complementary to the Appel reaction, which involves the formation of side product (triphenylphosphine oxide). Application of this reagent system allows for conversion of carb-OH into chlorides under mild reaction conditions, including short reaction time and devoid of side products.

## 3. Experimental

### 3.1. General method

Reagent grade solvents were used for the extraction and flash chromatography. All the reagents and chemicals were purchased from Sigma–Aldrich Chemical Co., Lancaster and were used directly without further purification. The progress of reactions was checked by analytical thin-layer chromatography (TLC, Merck silica gel 60F-254 plates). The plates were visualized first with UV illumination followed by charring with 10% $H_2SO_4$ in $CH_3OH$. Flash column chromatography was performed using silica gel (230–400 mesh). The solvent compositions reported for all chromatographic separations are on a volume/volume (v/v) basis. $^1H$ NMR spectra were recorded at either 200 or 300 MHz and are reported in parts per million (ppm) on the $\delta$ scale relative to tetramethylsilane as an internal standard.$^{13}C$ NMR spectra were recorded at either 50 or 75 MHz and are reported in parts per million (ppm) on the $\delta$ scale relative to $CDCl_3$ ($\delta$ 77.00). Mass spectra were obtained using JEOL SX-102 (ESI) instrument. Melting points were determined on a Mel Temp II melting point apparatus and are uncorrected.

### 3.2. General procedure

*First approach*: Freshly distilled sulfuryl chloride (1.5 mmol) was added to the stirred solution of carbohydrate (1 mmol) in DCM (10 ml) in an RB flask under nitrogen atmosphere at −5°–0 °C using NaCl ice bath. The stirring was continued for 40 min at 0 °C and benzotriazole (6.0 mmol) in DCM (10 ml) was added. The reaction mixture was stirred at room temperature for 6.5 h and precipitated salt was filtered. The filtrate was washed with water (3×50 ml) and the organic layer was then washed with saturated solution of $Na_2CO_3$ to remove excess of benzotriazole. The combined organic extract was dried over $Na_2SO_4$, and filtered. The filtrate was dried under vacuum to give chloro derivative.

*Second approach*: NaH 60% (1.5 mmol) was taken in 50 ml RB flask and freshly distilled DMF (5 ml) was added under nitrogen atmosphere followed by the addition of alcohol (1 mmol). The mixture was stirred continuously for about 45 min and cooled to −40 °C. *N*,*N*′-sulfuryldibezotriazole ($BtSO_2Bt$) (1.5 mmol) in 5 ml of DMF was added and stirred for 45 min at −40 °C, red coloration was observed in the reaction mixture. 25 ml cold water was added in the reaction mixture and then extracted with the DCM. The

combined organic layer repeatedly washed with water to remove DMF, then dried over $Na_2SO_4$ and dried under vacuum to dryness.

*Third approach*: Alcohol (1.5 mmol) was taken in 50 ml RB flask and 5 ml pyridine, 1 ml hexamethyldisilazane and 0.5 ml of trimethylsilyl chloride (TMSCl) is added consecutively, and stirred for 45 min at room temperature followed by the evaporation to the dryness. The residue so left was dissolved in 10 ml of dichloromethane and 2.5 ml of tetrabutyl ammonium fluoride (TBAF) in THF (1 M) and $BtSO_2Bt$ (1.5 mmol) added consecutively. The reaction mixture was refluxed under nitrogen atmosphere for about 5 h and then diluted with DCM, washed with water, dried over $Na_2SO_4$ and evaporated under vacuum to dryness.

*3.2.1. 3-Chloro(R)-3-deoxy-1,2:5,6-di-O-isoproplylidene-α-D-allofuranose (**1b**).* The crude product obtained from 1 g **1a** using first approach was purified using column chromatography (5% EtOAc/hexane) to give the title compound (1.01 g, 95%) as off white solid; mp 53–54 °C (from hexane); $[\alpha]_D^{20\ °C}$ +42 (*c* 0.5, $CHCl_3$); IR ($\nu_{max}$, Neat, $cm^{-1}$): 1435, 1373, 1150, 740; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 6.01 (d, *J*=3.6 Hz, 1H), 5.42–5.21 (m, 1H), 4.92 (d, *J*=3.7 Hz, 1H), 4.40–4.20 (m, 2H), 4.16 (m, 1H), 4.10–3.93 (m, 1H), 1.47–1.24 (m, 12H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 113.03, 107.52, 101.05, 81.27, 79.93, 72.90, 69.23 63.93, 27.43, 26.61, 25.43, 24.94; Anal. Calcd for $C_{12}H_{19}ClO_5$ (278.09): C, 51.71; H, 6.87%, Found: C, 51.63; H, 5.79. ES-MS ($M+H^+$) 279.1 *m*/*z*.

*3.2.2. 3-Chloro(S)-3-deoxy-1,2:5,6-di-O-isoproplylidene-α-D-allofuranose (**2b**).* The crude product obtained from 1 g **2a** using first approach was purified using column chromatography (5% EtOAc/hexane) to give the title compound (1.01 g, 96%) as off white solid; mp 63–64 °C (from hexane); $[\alpha]_D^{20\ °C}$ −39 (*c* 0.5, $CHCl_3$); IR ($\nu_{max}$, Neat, $cm^{-1}$): 1432, 1369, 1148, 739; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.99 (d, *J*=3.7 Hz, 1H), 4.95–5.01 (m, 1H), 4.46–4.40 (m, 3H), 4.40–4.38 (m, 1H), 4.24–4.20 (m, 1H), 1.79–1.57 (m, 12H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 113.01, 107.53, 105.57, 81.26, 79.93, 72.88, 69.23, 63.93, 27.42, 26.59, 25.14, 24.94; Anal. Calcd for $C_{12}H_{19}ClO_5$ (278.09): C, 51.71; H, 6.87%, Found: C, 51.64; H, 5.76. ES-MS ($M+H^+$) 279.1 *m*/*z*.

*3.2.3. 6-Chloro-6-deoxy-1,2:3,4-di-O-isopropylidine-α-galactopyranose (**3b**).* The crude product obtained from 1.0 g **3a** using first approach was purified using column chromatography (5% EtOAc/hexane) to give the title compound (1.0 g, 93%) as off white solid; mp 43–44 °C (from hexane); $[\alpha]_D^{20\ °C}$ −58 (*c* 0.5, $CHCl_3$); IR ($\nu_{max}$, Neat, $cm^{-1}$): 1440, 1370, 1120, 735; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.55 (d, *J*=5.0 Hz, 1H), 4.72–4.52 (m, 3H), 4.37 (dd, *J*=5.0, 2.6 Hz, 1H), 4.32–4.12 (m, 2H), 1.54 (s, 3H), 1.47 (s, 3H), 1.35 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 101.58, 108.29, 100.47, 75.48, 75.21, 73.28, 69.82, 68.48, 44.04, 27.49, 27.26, 26.08, 25.94; Elemental Anal. for $C_{12}H_{19}ClO_5$ (278.09) Calcd C, 51.71; H, 6.87%, Found: C, 51.65; H, 5.69. ES-MS ($M+H^+$) 279.1 *m*/*z*.

*3.2.4. 1,2-O-Isopropylidene-3-O-benzyl-5-deoxy-5-iodo-α-D-xylofuranose (**4b**).* The crude product obtained from 1.0 g **4a** using first approach was purified using column chromatography (15% EtOAc/hexane) to give the title compound (0.97 g, 92%) as off white solid; mp 73–74 °C (from hexane); $[\alpha]_D^{20\ °C}$ −39 (*c* 0.5, $CHCl_3$); IR ($\nu_{max}$, Neat, $cm^{-1}$): 1430, 1363, 1114, 890, 732; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.45–7.12 (m, 5H), 5.58 (1H), 4.75–4.55 (m, 3H), 4.28 (m, 1H), 3.78, (1H), 3.55–3.72 (m, 2H), 1.48 (3H), 1.31 (3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 137.56, 128.30, 127.80, 127.74, 111.9, 81.75, 80.16, 79.32, 71.36, 39.60, 26.34, 25.81; Elemental. Anal. for $C_{15}H_{19}ClO_4$ (298.10) Calcd C, 60.30; H, 6.41%, Found: C, 59.98; H, 6.31. ES-MS ($M+H^+$) 299.1 *m*/*z*.

*3.2.5. Methyl 3-O-benzyl-4,6-O-benzylidene-2-chloro-2-deoxy-α-D-mannopyranoside (**5b**).* The crude product obtained from 0.5 g **5a** using first approach is purified using column chromatography (5–10% EtOAc/hexane) to give the title compound (0.470 g, 90%) as an oil; $[\alpha]_D^{20\ °C}$ +4.2 (*c* 0.3, $CHCl_3$); IR ($\nu_{max}$, Neat, $cm^{-1}$): 1590, 1465, 1360, 1250, 785; $^1H$ NMR (300 MHz, $CDCl_3$) : $\delta_H$ 7.58–6.97 (m, 10H), 5.69 (s, 1H), 5.02 (d, *J*=11.9 Hz, 1H), 4.90 (d, *J*=12.1 Hz, 1H), 4.79 (s, 1H), 4.45 (d, *J*=10.3 Hz, 1H), 4.34 (d, *J*=8.0 Hz, 2H), 4.08–3.74 (m, 3H), 3.39 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 138.91, 138.03, 129.24, 128.48, 128.30, 128.18, 127.51, 126.02, 102.08, 95.90, 79.14, 75.77, 73.72, 67.01, 60.80, 59.57, 55.32; Anal. Calcd for $C_{21}H_{23}ClO_5$ (390.12): 64.53; H, 5.93%, Found: C, 64.47; H, 5.2.79. ES-MS ($M+H^+$) 391.1 *m*/*z*.

*3.2.6. Methyl 3-O-benzyl-4,6-O-benzylidene-3-chloro-3-deoxy-α-D-altroside (**6b**).* The crude product obtained from 1.0 g **6a** using first approach was purified using column chromatography (15% EtOAc/hexane) to give the title compound (0.92 g, 88%) as off white solid; mp 83–84 °C (from hexane); $[\alpha]_D^{20\ °C}$ +188 (*c* 0.5, $CHCl_3$); IR ($\nu_{max}$, Neat, $cm^{-1}$): 1465, 1397, 1210, 715; $^1H$ NMR (300 MHz, $CDCl_3$) :7.8–7.1 (m, 10H), 5.77 (s, 1H), 4.95–4.84 (m, 2H), 4.65 (m, 1H), 4.43 (m, 1H), 4.22 (m, 1H), 3.8–4.18 (m, 4H), 3.40 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 137.17, 136.83, 129.04, 128.57, 128.18, 127.79, 126.37, 101.86, 98.86, 77.87, 76.32, 73.58, 67.85, 66.33, 63.22, 55.08; Elemental Anal. for $C_{21}H_{23}ClO_5$ (390.12) Calcd C, 64.53; H, 5.93%, Found: C, 64.21; H, 5.84. ES-MS ($M+H^+$) 391.1 *m*/*z*.

*3.2.7. Methyl 4,6-O-benzylidene-2-benzyloxycarbonylamino-2,3-dideoxy-3-ioso-α-D-allopyranoside (**7b**).* The crude product obtained from 0.5 g of **7a** using first approach was purified using column chromatography (30% EtOAc/hexane) to give the title compound (0.480 g, 92%) as an off white solid; mp 99–102 °C (from ethanol); $[\alpha]_D^{20\ °C}$ −19.5 (*c* 0.7, $CHCl_3$); IR ($\nu_{max}$, Neat, $cm^{-1}$):1585, 1456, 1345, 950, 815, 785; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.58–7.42 (m, 2H), 7.26 (d, *J*=23.4 Hz, 8H), 5.77 (s, 1H), 5.06 (d, *J*=14.3 Hz, 3H), 4.81 (s, 1H), 4.52–4.17 (m, 1H), 4.17–3.85 (m, 1H), 3.36 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 155.96, 136.74, 129.06, 128.68, 128.20, 128.04, 126.37, 103.87, 101.99, 76.62, 68.92, 67.42, 66.95, 60.60, 57.78, 55.29; Anal. Calcd for $C_{22}H_{24}ClNO_6$ (433.88): C, 60.90; H, 5.58; N, 3.23%. Found: C, 60.53; H, 5.18; N, 3.14. ES-MS ($M+H^+$) 434.9 *m*/*z*.

## Acknowledgements

C.S.A. is thankful to CSIR, New Delhi for the award of SRF and acknowledges, A.S. Kushwaha, Mr. Zahid Ali for their technical support. The authors also acknowledge SAIF-CDRI for providing spectral and analytical data. The CDRI communication number allotted to this manuscript is 8391.

## Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.01.044.

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