Nucleophilic Substitutions on Multipin™ Systems Linked with a Traceless Linker

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Abstract: The displacement of polymer-supported glucose **7** at the 6-position by azide, iodide, and acetate was achieved through a 4-hydroxybenzenesulfonate-linked Multipin^{TM} system giving the corresponding glucose derivatives **8** in excellent yields. Macrocyclization of polymer-supported cyanohydrin ether **13** by displacement of the traceless sulfonate linker provided the cyclic compound **14** in moderate yield but in pure form.

Solid-phase synthesis is gaining prominence in organic chemistry.[1] The choice of linker that connects substrates onto polymers occupies an important place in designing a synthetic plan for small molecule library preparation. The linker must provide stability in all reactions in the synthesis and should be easily cleavable from the solid-support under mild conditions ideally in each step to confirm its accomplishment. There are many linkers that are available in the solid phase synthesis and several traceless linkers on resins have been reported.[2-8] We are interested in a traceless linker that can be displaced with various nucleophiles introducing new functionalities instead of original one (Figure 1). We considered that 4-hydroxybenzenesulfonate is an attractive linker, because a phenol can be used for attaching the linker to a polymer and a sulfonate can be used for a leaving group in nucleophilic reactions.[7,8] We have reported that the hydroformylation of 1,1-disubstituted alkene linked with this sulfonate linker to Multipin^{TM} systems proceeds effectively preparing the corresponding aldehyde.[9] Herein, we wish to report an efficient substitution of polymer-supported mono-saccharide and a new cyclization method of polymer-supported cyanohydrin ether by displacement of the traceless sulfonate linker on Multipin^{TM} systems.

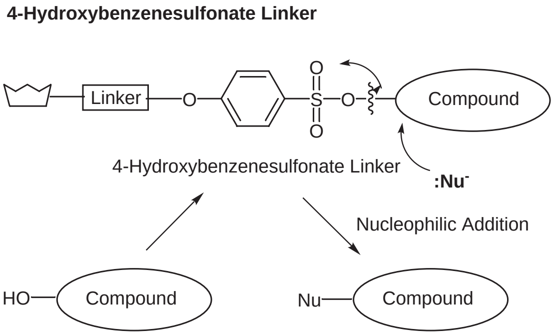
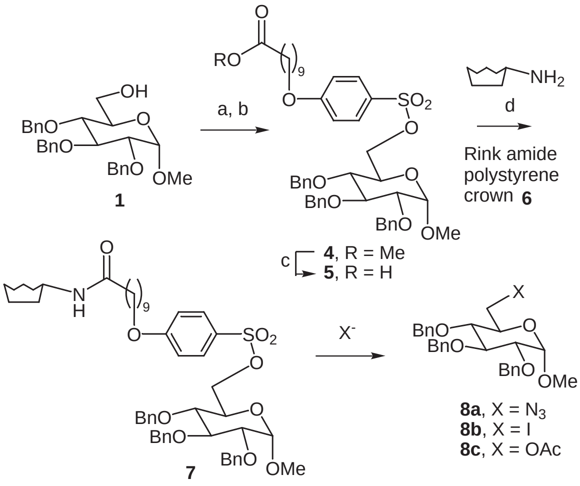


Figure 1

Treatment of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**1**)[10] with 4-hydroxybenzenesulfonyl chloride (**2**)[11] was followed by Mitsunobu reaction[12] with methyl 10-hydroxydecanoate (**3**) leading to methyl ester **4**, which was hydrolyzed with LiOH giving acid **5** in 51% overall yield. Acid **5** was attached to Rink amine[13] polystyrene crowns **6**[14,15] in the presence of 1,3-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) in DMF at 25 °C to provide mono-saccharide-supported crowns **7** linked with the traceless sulfonate linker at the 6-position of a glucose.[16]

Nucleophilic displacement of the mono-saccharide-supported crowns **7** was examined with azide, iodide, and acetate ions, respectively.[7] The results are shown in Table 1. Azidation of **7** with sodium azide smoothly proceeded in DMF at either 60 °C or 80 °C in 12 h providing azide **8a** in pure form (>95%) (Entries 1 and 2).[17] Iodination of **7** with sodium iodide also efficiently provided iodide **8b** in DMF at 80 °C in 24 h (Entry 6), while lower temperature and shorter reaction time gave low conversions of the reaction (Entries 3-5). The reaction does not effectively take place in 2-butanone, which is a good solvent in solution phase (60 °C, 18 h, 80%) and also reported reaction on resins[7] (Entries 7 and 8). The purity of the obtained **8b** was >95% analyzed by HPLC. Entry 9 and 10 show the displacement by an acetate ion. When the crowns **7** were treated with sodium acetate in the presence of crown ether in DMF at 80 °C, the reaction was not complete in 24 h (Entries 9 and 10). However, cesium acetate instead of sodium acetate was used according to Nakata's procedure,[18] the reaction was complete within 6 h to give pure **8c** (Entries 11 and 12). It is demonstrated that nucleophilic additions for polymer-supported mono-saccharide by azide, iodide, and acetate ions were optimized on crowns giving 6-substituted glucose derivatives. This method could be used for various functionalized saccharides and is important from the point of view of preparing an oligosaccharide library.



Reagents and Conditions: (a) HO-(*p*)C_6H_4-SO_2Cl (**2**), Py, $CHCl_3$; (b) $MeO_2C(CH_2)_9$-OH (**3**), PPh_3, DEAD, NEt_3, THF; (c) LiOH, dioxane-H_2O (51% in 3 steps); (d) DIC, HOBt, DMF, 24 h.

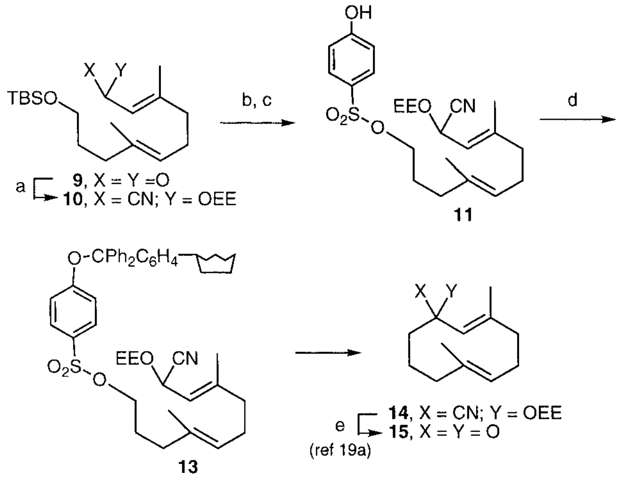
Scheme 1

Since intramolecular alkylation of cyanohydrin ethers is useful for the formation of small-, medium-, and large-membered ring ketones,[19] the reaction on solid phase must be attractive in preparing a library of cyclic ketones if it works using the sulfonate traceless linker.[20] Cyanohydrin ether **10** was prepared from 10-(*t*-butyldimethylsilyloxy)-3,7-dimethyldeca-2,6-dienal (**9**)[19a] in three steps. Deprotection of TBS group, followed by sulfonylation with 4-hydroxybenzensulfonyl chloride (**2**) gave **11** in 46% overall yield. The phenol **11** was loaded on trityl linked crowns **12**[21] to provide sulfonate-supported crowns **13** in 50% yield, which was determined by acid cleavage (10% TFA in CH_2Cl_2, 1 h) of **13** from the trityl-crown. The intramolecular alkylation of **13** in the presence of base was carried out and the results are shown in Table 2.

Table 1

Entry	Nucleophile[a]	Solvent	T / °C	Time / h	Conversion[b] %	Purity[c] %
1	NaN_3	DMF	60	12	>95	>95
2			80	12	>95	>95
3	NaI	DMF	60	12	67	>95
4			60	24	72	>95
5			80	12	88	>95
6			80	24	>95	>95
7		2-butanone	60	12	46	>95
8			60	24	75	>95
9	NaOAc	DMF	80	6	61	>95
10			80	24	71	>95
11	CsOAc		80	12	>95	>95
12			80	6	>95	>95

a NaN_3 0.1 M; NaI 0.1 M; NaOAc or CsOAc 0.1 M, 18-Crown-6 0.02 M. *b* See ref 17. *c* HPLC purity of **8** determined by refractive index after a simple work-up.



(a) TMSCN, DC-18-crown-6·KCN; 1M HCl , THF; ethyl vinyl ether, *p*-TsOH, CH_2Cl_2; (b) TBAF·xH_2O, THF; (c) HO-(p)C_6H_4-SO_2Cl (**2**), Py, $CHCl_3$, 46% in 5 steps; (d) *i*-Pr_2EtN, $C_6H_4CPh_2$-Cl (**12**) , 24 h, 48%; (e) H^+; OH^-.

Scheme 2

Treatment of crowns **13** with lithium hexamethyldisilazide as a base,[22] the desired cyclization proceeded in THF providing **14** in 20-24% yields (Entries 1 and 2). The isolated yield was increased up to 46% when the reactions were carried out in refluxing dioxane (Entries 3-5).[23] A mixed solvent (toluene : dioxane = 1 : 3) did not affect the yield (Entries 6 and 7). The reaction did not proceed in the presence of non-soluble base, such as NaH and KH (Entries 8 and 9). Although the yield is moderate, it should be noted that the product obtained is enough pure after a simple work-up procedure. We have already reported that **14** is easily converted to cyclic ketone **15**.[19a]

In conclusion, we have demonstrated a 4-hydroxybenzenesulfonate linker is a useful traceless linker linked with crowns in various substituted reactions. Displacement of mono-saccharide by azide, iodide, and acetate ions gave 6-functionalized sugar derivatives. Intramolecular cyanohydrin alkylation on the Multipin$^{\text{TM}}$ system also provides a cyclic ketone isolated in pure form.

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Table 2

Entry	Base (Conce / M)	Solvents	T / °C	Time / h	Yield[a] / %
1	LHMDS (0.1)	THF	reflux	18	20
2	(0.05)	THF	reflux	18	24
3	(0.05)	dioxane	reflux	6	23
4	(0.05)	dioxane	reflux	12	25
5	(0.05)	dioxane	reflux	24	46
6	(0.05)	toluene / dioxane = 1 : 3	80	12	20
7	(0.05)	toluene / dioxane = 1 : 3	reflux	12	37
8	NaH (0.1)	toluene / dioxane = 1 : 3	80	12	0_b
9	KH (0.1)	toluene / dioxane = 1 : 3	80	12	0_b

a Determined by HPLC with peak area (refractive index) of **14** obtained by a simple work-up comparing with that an authetic sample in a certain concetration; See ref 23. *b* Starting material was recovered after acid cleavage.

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(14) Rink amine crowns were prepared from Fmoc-NH-Rink-Polystyrene crowns by treatment with 20% piperidine in DMF for 20 min before use. Batch no. 491-13, Loading = 2.0 μmol per crown, Chiron Technologies Pty. Ltd., 11 Duerdin St., Clayton, Victoria 3168, Australia.

(15) The Multipin$^{\text{TM}}$ system has been successfully used in the synthesis of a chemical library. See, Valerio, R. M.; Bray, A. M.; Maeji, N. J. *Int. J. Peptide Protein Res.* **1994**, *44*, 158. Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11580. Valerio, R. M.; Bray, A. M.; Patsiouras, H. *Tetrahedron Lett.* **1996**, *37*, 3019.

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(16) Complete conversion was detected by a color test (negative result) with a solution of trinitrobenzenesulfonic acid in DMF : DIEA = 10 : 1 in a few minutes.

(17) After the reaction, the crowns were washed several times and treated under acid cleavage conditions to observe whether the starting material is recovered. The conversion was determined by HPLC with integration of peak area (UV, 260 nm) of the recovered material comparing with that of an authentic sample in a certain concentration.

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(21) Trityl chloride crowns were prepared from trityl alcohol crowns with acetyl chloride before use. $HOC(Ph)_2C_6H_4CONHCH_2$-Polystyrene, Batch no. 799-19, Loading = 9.3 μmol per crown. See ref 9.

(22) The intramolecular alkylation of trityl protected derivative of **11** in solution phase (LiHMDS, THF, 60 °C) gave the desired 10-membered ring compound **14** in 76% yield.

(23) After the reaction, the crowns were washed several times and treated with 10% TFA in CH_2Cl_2 for 20 min. None of the starting material was observed in HPLC analyses except Entries 8 and 9.