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A practical and scalable process to selectively monofunctionalize water-soluble α,ω-diols

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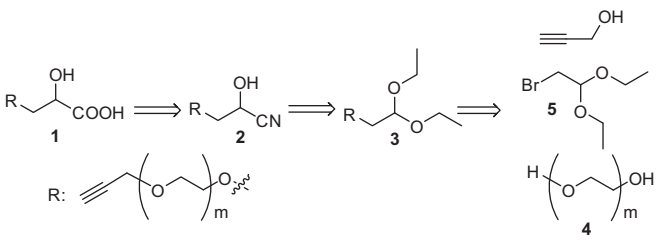
ABSTRACT

A practical protocol for rapid and scalable synthesis of monofunctionalized α,ω-diols using a simple and inexpensive THP ether protection/deprotection strategy was described. Use of inexpensive DHP source and ease to remove excess water-soluble α,ω-diols and THP ether after deprotection render the process scale-friendly without need of column chromatographic separation. The application of present method was also illustrated in the preparation of heterobifunctional diols and well-defined extended oligo (ethylene glycol).

Introduction

Water-soluble α,ω-diol is an important family of synthons in organic synthesis and material science. A crucial step in application of those α,ω-diols is to differentiate the reactivity of two chemically equivalent terminal hydroxyl groups for selective monofunctionalization.[1] A stoichiometric amount of water-soluble α,ω-diols relative to the functional/protective reagents usually generates a mixture of unreacted, monofunctionalized and bis-functionalized α,ω-diols in a statistical distribution of 1:2:1.[2] To favor the formation of monofunctionalized α,ω-diols selectively, a large excess of starting α,ω-diols is usually utilized compared to the functional/protective reagents.[1d–f,3] Use of catalysts or additives, such as strongly acidic ion exchange resins,[4] polymer supports,[5] and cesium base,[6] in stoichiometric feeding of α,ω-diols and the functional/protective reagents is required for selective monofunctionalization. However, these methods all produced a mixture of monofunctionalized and bis-functionalized α,ω-diols. In addition, these methods all required employing column chromatography to separate target monofunctionalized products for further elaboration, which is costly and time-consuming. Silver(I) oxide mediated selective monotosylation and monoalkylation of diols under mild condition were reported to be a great protocol with excellent functional group tolerance in the presence of a catalytic amount of potassium iodide.[7] However, it requires using a large amount of expensive and freshly prepared silver(I) oxide (1.5 equiv). Column chromatography was also required to separate the desired products. All these reported methods failed to deliver a practical and scalable process for the synthesis of monofunctionalized α,ω-diols.

In our endeavor to prepare clickable polylactide biomaterials, it is crucial to establish a library of α-hydroxy acids (**1**) bearing oligo(ethylene glycol) (OEG) spacer between terminal alkyne and α-hydroxy acid moiety. And we envisioned that a practical and scalable process to monofunctionalize OEGs (**4**, a family of water-soluble α,ω-diols) is highly desirable to scale up the synthesis of desired α-hydroxy acids **1** (Scheme 1). Herein, we report a practical and scalable method for monofunctionalization of water-soluble α,ω-diols using a simple and inexpensive THP-protection/deprotection strategy. The synthesis proceeded in high yields of readily purified products without need of column chromatography.



Scheme 1. Retrosynthetic analysis of α-hydroxy acids (**1**).

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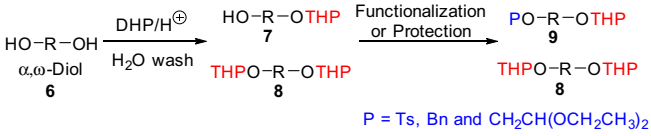
Table 1
Differentiation and functionalization of α,ω-diols (**6**)



Entry	Diol (**6**)	Ratio (**7**:**8**)[a]	Products (**8**+**9**)[b]	Yield[c] (**8**+**9**) (%)
1	$HO(CH_2CH_2O)_4H$ (**6a**)	**7a**:**8a**8:1	$TsO(CH_2CH_2O)_4THP$ (**9a**)	97.0
2			$BnO(CH_2CH_2O)_4THP$ (**9b**)	92.8
3			$(CH_3CH_2O)_2CHCH_2O(CH_2CH_2O)_4THP$(**9c**)	92.1
4	$HO(CH_2)_4OH$ (**6b**)	**7b**:**8b**10:1	$TsO(CH_2)_4OTHP$ (**9d**)	85.0
5			$(CH_3CH_2O)_2CHCH_2O(CH_2)_4OTHP$ (**9e**)	84.1
6	$HO(CH_2)_6OH$ (**6c**)	**7c**:**8c**9:1	$TsO(CH_2)_6OTHP$ (**9f**)	86.7
7			$(CH_3CH_2O)_2CHCH_2O(CH_2)_6OTHP$ (**9g**)	83.5

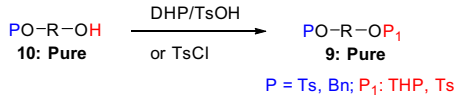
[a] Calculated from ^1H NMR.
[b] Tosylation was conducted in a mixture of aqueous KOH solution and THF. Alkylation was completed in THF in the presence of NaH.
[c] Isolated yield of the mixture.

Results and discussion

Two chemically equivalent hydroxyl groups of water-soluble α,ω-diols (**6a–c**, Table 1) were differentiated with dihydropyran (DHP) using a ~5-fold excess of **6** in THF or CH_2Cl_2 in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH). A mixture of **7** and **8** with mono-THP protected **7** as major product was obtained. This mixture of **7** and **8** was used directly in the next step without purification. Due to their high polar nature and high solubility in water, excess of α,ω-diols was simply removed by washing a CH_2Cl_2 solution of **7** and **8** with water and saturated aqueous NaCl solution. THP is demonstrated to be an efficient alcohol protecting group due to its excellent stability towards neutral and basic conditions. This would allow for incorporating suitable functional groups (**P**) to mono-THP protected **7** under neutral or basic condition in our synthesis. The mixture of **7** and **8** was then tosylated with tosyl chloride (Table 1, entries 1, 4 and 6) or alkylated upon reaction with benzyl bromide (Table 1, entry 2) or bromoacetaldehyde diethyl acetal (**5**, Scheme 1; Table 1, entries 3, 5 and 7) to quantitatively provide bifunctional diols (**9a–g**). The bis-THP protected α,ω-diols (**8**) were carried over to the next step without separation (Table 1).

When a mixture of **8** and **9** was subjected to acidic conditions, analytically pure monofunctionalized diols (**10a–g**, Table 2) including tosylates, benzylate and diethyl acetals were obtained after removal of THP protecting groups. The complete cleavage of THP ethers was accomplished via transacetalization reaction between THP ethers and methanol or ethanol solvent in the presence of a catalytic amount of TsOH.[8] To avoid potential impurities from methanolysis of diethyl acetal,[9] it is important to note that ethanol was used solely as acetal exchange solvent in the deprotection of

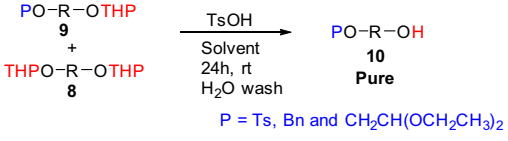
Table 3
THP protection/tosylation of pure monofunctional diols (**10**)



Entry	Substrate (**10**)[a]	Product[b]	Yield[c] (%)
1	$TsO(CH_2CH_2O)_4H$ (**10a**)	$TsO(CH_2CH_2O)_4THP$ (**9a**)	98.3
2	$BnO(CH_2CH_2O)_4H$ (**10b**)	$BnO(CH_2CH_2O)_4THP$ (**9b**)	94.0
3	$TsO(CH_2)_4OH$ (**10d**)	$TsO(CH_2)_4OTHP$ (**9d**)	91.1
4	$TsO(CH_2)_6OH$ (**10f**)	$TsO(CH_2)_6OTHP$ (**9f**)	92.9
5	$BnO(CH_2CH_2O)_4H$ (**10b**)	$BnO(CH_2CH_2O)_4Ts$ (**9h**)	91.0

[a] Pure monofunctionalized diols (**10**) were subjected to THP protection or tosylation.
[b] Pure bifunctional diols (**9**) were prepared from **10**.
[c] Isolated yield.

Table 2
Synthesis of analytically pure monofunctionalized diols (**10**)



Entry	Substrate (**8**+**9**)[a]	Solvent[b]	Product	Yield[c] (%)
1	$TsO(CH_2CH_2O)_4THP$ (**9a**)	MeOH	**10a**	97.0
2	$BnO(CH_2CH_2O)_4THP$ (**9b**)	MeOH	**10b**	90.0
3	$(CH_3CH_2O)_2CHCH_2O(CH_2CH_2O)_4THP$ (**9c**)	EtOH	**10c**	87.0
4	$TsO(CH_2)_4OTHP$ (**9d**)	MeOH	**10d**	84.5
5	$(CH_3CH_2O)_2CHCH_2O(CH_2)_4OTHP$ (**9e**)	EtOH	**10e**	90.5
6	$TsO(CH_2)_6OTHP$ (**9f**)	MeOH	**10f**	85.5
7	$(CH_3CH_2O)_2CHCH_2O(CH_2)_6OTHP$ (**9g**)	EtOH	**10g**	85.9

[a] A mixture of **8** and **9** was subjected to THP deprotection.
[b] Anhydrous MeOH or absolute EtOH from bottle was used.
[c] Isolated yield.

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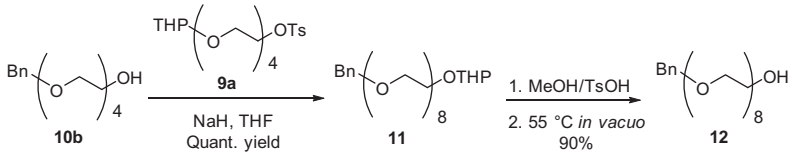

Scheme 2. Synthesis of octa(ethylene glycol) derivatives from mono- and bifunctional diols **10b** and **9a**.

THP ethers for substrates **9c**, **e** and **g** (Table 2, entries 3, 5, and 7). Due to their relatively low boiling points,[10] THP ethers of methanol or ethanol after deprotection step via acetal exchange were readily removed in vacuo using rotary evaporator. Bis-THP protected diols (**8**) released hydrophilic diols after THP deprotection in alcoholic solvents under acidic condition. The hydrophilic diols were simply removed by washing a CH_2Cl_2 or $CHCl_3$ solution of product **10** with aqueous NaCl solution to afford pure monofunctional product **10a-g**.[11] The ease of removing water-soluble α,ω-diols and THP derivatives after deprotection of THP groups of **8** and **9** in methanol or ethanol is the key step to enable a simple and scalable synthesis of monofunctionalized diols (**10a**–**g**) without need of column chromatography. The judicious choice of DHP for its inexpensive source, easy installation and facile deprotection under mild acidic condition[12] further render large-scale synthesis of monofunctionalized diols practical with low cost.

Heterobifunctional α,ω-diol represents an important family of building blocks in organic synthesis and material science. To further extend the application of current methodology for monofunctionalization of water-soluble α,ω-diols, the prepared pure monofunctional diols (**10**) were readily converted to useful heterobifunctional diols following known procedures. To avoid undesired deprotection of α-functional groups during the preparation of heterobifunctional diols, the stability of existing α-functional groups under reaction conditions leading to the ω-functional group formation should be taken into account. For example, monofunctional diols (**10a**, **10b**, **10d** and **10f**) were readily transformed into pure THP-protected bifunctional diols (**9a**, **9b**, **9d** and **9f**) in the presence of catalytic amount of TsOH in high yield (Table 3, entries 1–4). Tetraethylene glycol monobenzyl ether (**10b**) was also tosylated with tosyl chloride to provide valuable heterobifunctional derivative **9h** in a simple manner (Table 3, entry 5).[3b] Moreover, monofunctional diol (**10b**) was deprotonated by NaH and coupled with tosylated heterobifunctional diol (**9a**) to afford chain-length extended octa(ethylene glycol) derivative (**11**) quantitatively (Scheme 2).[1b,13] Column chromatography is not required to purify **11** since only negligible amount of by-product was formed at a relatively large scale (0.25 mol of **10b**) after optimization.[14] The transacetalization of THP-protected **11** in methanol further provided pure monofunctional octa(ethylene glycol) monobenzyl ether (**12**). These results clearly indicate that the presented method can be used to rapidly synthesize monofunctional and bifunctional diol derivatives in large quantity with high purity as useful synthetic building blocks.

In conclusion, we have developed a practical and scalable protocol for the synthesis of monofunctionalized α,ω-diols. Due to its operational simplicity, the current process can be readily scaled up to afford monofunctional diols efficiently without need of column chromatographic separation. The current method paved the road for further versatile elaboration of monofunctionalized diols via heterobifunctionalization and thus the chain-length extension of OEGs, which demonstrated its significance in preparing useful synthetic building blocks.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.066.

Reference and notes

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11. It is worth mentioning that product **10c**, **10e**, and **10g** could not be completely dried (Table 2, entries 3, 5, and 7). Instead, they were stored as solutions in $CHCl_3$ under nitrogen to prevent inter- or intramolecular transacetalization until subjected for further functionalization. However, it was found that pure products **10c**, **10e**, and **10g** can be rapidly recovered by dissolving them in ethanol and stirring the resulting mixtures under nitrogen (100 psi) if inter- or intramolecular transacetalization occurs.
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14. Tosylated bifunctional diol (**9a**, 1.1 equiv) was optimized to afford **11** in a form which can be easily purified in our case.