Efficient asymmetric synthesis of an azasugar in water†

Ulf M. Lindström,* Rui Ding and Olle Hidestål

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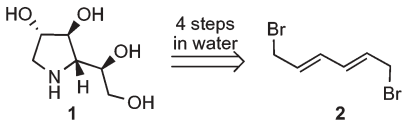
An extremely efficient asymmetric synthesis of a pyrrolidine azasugar was completed in only four steps in water, without the use of protecting groups and in 60% overall yield from a simple, achiral bis-electrophile.

Synthetic chemistry has taken great strides in the last half century and its impact on the development of modern science and society is undisputed. The need for more efficient and less hazardous processes, however, is becoming increasingly urgent in light of the recent growth in environmental concern and awareness. Future chemists will have to meet demands from society that chemical processes must be environmentally friendly, as well as resource- and energy-saving.[1] Organic solvents are obvious targets in the quest to minimize pollution, and with increasing legislative pressure on hazardous solvents, alternatives are rapidly becoming not only desirable, but crucial. Water is a safe and environmentally benign alternative to unnatural solvents. Other advantages of water may be beneficial solvent effects, simplified experimental procedures and reduced need for protecting groups. However, although organic reactions in aqueous media have been the subject of much research lately,[2] the full scope and potential of synthesis in water is still unclear. A significant step forward would be the realization of efficient, multistep aqueous syntheses of precious and useful organic compounds from simple starting materials.

In recent years, some of the most attractive synthetic targets have been polyhydroxylated N-heterocycles, or azasugars, which is reflected by the large number of publications describing their preparation[3] and pharmacologically relevant activity as glycosidase inhibitors.[4] As such they have shown promise as anti-cancer[5] and anti-viral[6] agents. Because of their structural resemblance to sugars, the most common approach towards azasugars has been to use appropriate carbohydrates as starting materials. Asymmetric syntheses of azasugars from cheap, achiral starting materials have been reported less frequently and usually involve lengthy procedures with low overall yield.[7] We can now report an extremely efficient aqueous asymmetric synthesis of the pyrrolidine azasugar **1** from 1,6-dibromodiene, **2**, which is available in one step from cheap, commercially available 1,5-hexadiene-3,4-diol.[8] To the best of our knowledge this is the first asymmetric total synthesis where each step is performed in aqueous media. In keeping with the suggested advantages of using water as solvent, no protecting groups were employed and separation processes were simple, which enabled us to keep the number of synthetic steps and chromatographic purifications to a minimum.

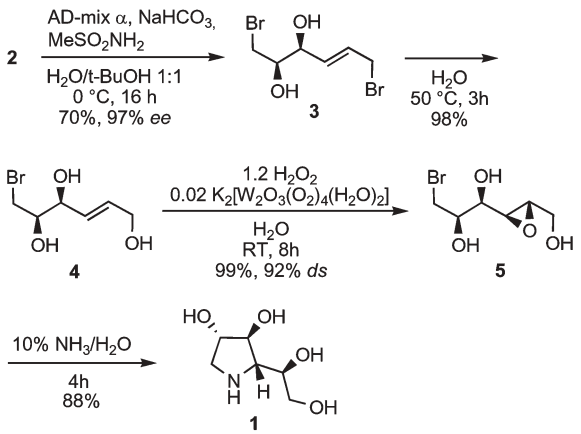
† Electronic supplementary information (ESI) available: experimental details and data for compounds **1**, **4**, and **5**. See http://www.rsc.org/suppdata/cc/b5/b500190k/

*ulf.lindstrom@bioorganic.lth.se



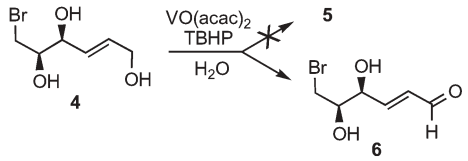
We have recently described a modified Sharpless asymmetric dihydroxylation of **2** to give the chiral bis-electrophilic diol **3**, which was shown to have unique and useful reactivity in water (Scheme 1).[9] For example, we found that the use of the synthetically attractive compounds **2** and **3** is severely limited because of their rapid decomposition in organic solvents. In water, however, they are remarkably stable and in this media their potential can be fully investigated. Following the asymmetric dihydroxylation of **2** (70% yield, 97% ee), selective hydrolysis at the allylic position of dibromide **3** was easily achieved by stirring in water at 50 °C for 3 h, which afforded triol **4** in 98% yield after solid-phase extraction. Further purification was not necessary (>95% pure).

In the following step, the epoxidation of **4** to give epoxy alcohol **5**, we were concerned about the diastereoselectivity because of the presence of two hydroxyl groups of allylic substitution and one of homoallylic, all of which could potentially have a directing effect on the epoxidation and lead to a mixture of diastereomers. Initially we tested the $VO(acac)_2$/*tert*-butyl hydroperoxide (TBHP) reagent, which is known to react highly chemo- and diastereoselectively with allylic alcohols in organic media to give epoxy alcohols. To our surprise, we did not observe any trace of epoxide **5** when using water as solvent for this reaction. Instead we obtained the α,β-unsaturated aldehyde **6**, along with recovered starting material. This reversal of chemoselectivity is a striking example of the unique properties of water that may sometime lead to unexpected reactivity. On the other hand, aldehyde **6** may be highly useful as it



Scheme 1 Synthesis of azasugar **1** in four steps from diene **2**.

sets the stage for addition reactions, many of which are known to proceed well in aqueous media, thus allowing us to reach more complex structures *via* this kind of functionalized bis-electrophile. In addition, **6** contains not only two, but three potential sites for nucleophilic attack.



Attempts at epoxidizing **4** with *m*-CPBA at pH 9 led to fast turnover of starting olefin but only into a complicated mixture of products. Deyong *et al.* have reported diastereoselective epoxidations of cycloalkenols in water using monoperoxyphthalic acid.[10] Unfortunately, when we applied this to **4** it did not give any improvement over the reaction with *m*-CPBA. More recently, Mizuno *et al.* reported efficient epoxidations of allylic alcohols in water catalyzed by a dinuclear peroxotungstate catalyst, $K_2[W_2O_3(O_2)_4(H_2O)_2]$.[11] The use of equimolar amounts of H_2O_2 as oxidant and only 1 mol% of the metal catalyst, which could be recovered and reused, makes this a highly attractive procedure for environmental reasons. The authors reported selectivities similar to those observed for $VO(acac)_2$/TBHP in organic solvents. Gratifyingly, when we applied this method to **4**, the reaction proceeded smoothly at room temperature to afford the desired epoxy alcohol **5** in 99% yield (92% ds), following solid-phase extraction. No further purification was necessary. To obtain this excellent result, however, we had to make a slight modification to the original protocol and use a modest excess (1.2 equiv.) of H_2O_2 and 2 mol% of tungsten catalyst, as the described procedure failed to give complete conversion of olefin into epoxide. In the final step, nucleophilic displacement of the bromide by ammonia (10% in water) was spontaneously followed by an intramolecular ring-opening[12] of the epoxide to give azasugar **1** in 88% yield after flash chromatography. The overall yield of **1** from cheap, achiral starting material was thus 60%. Analytical data were in accordance with those previously published.[13]

In conclusion, we have reported an extremely efficient aqueous asymmetric synthesis of a potentially useful azasugar without the use of protecting groups. Analytically pure product was obtained in high overall yield with minimal use of chromatographic purification. The synthetic strategy based on bis-electrophilic dienes may also be used in the efficient preparation of other heterocycles of interest, such as highly substituted tetrahydrofuran derivatives.[9] Our recent work thus provides unprecedented and compelling experimental evidence that water can act as a superior solvent for green and efficient multistep syntheses of attractive target molecules. Work is now in progress to further develop the scope of bis-electrophilic dienes in aqueous synthesis.

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Ulf M. Lindström,* Rui Ding and Olle Hidestål
Department of Organic Chemistry, Lund University, P. O. Box 124, SE-221 00, Sweden. E-mail: ulf.lindstrom@bioorganic.lth.se; Fax: +46 2228209; Tel: +46 2228211

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