A New General Approach to the 2-Hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one Skeleton via Diisobutylaluminum Hydride Reduction of 2,3-Dioxo-1,4-benzoxazines

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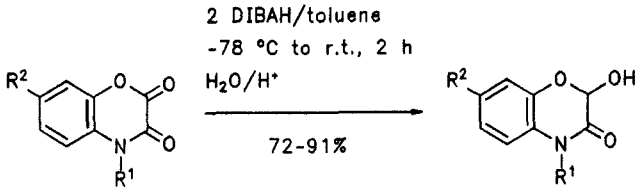
A series of naturally occurring hemiacetals **2a–d** was synthesized by the chemoselective diisobutylaluminum hydride reduction of 2,3-dioxo-4*H*-1,4-benzoxazines **1a,b** and their *N*-hydroxy derivatives **1c,d** precursors. The procedure described represents a new general approach to the 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one skeleton giving rise to the bioactive natural hydroxamic acids 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **(2c)** and 2,4-dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one **(2d)** in only three steps starting from nitrophenols.

Several derivatives of the 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one skeleton have been found to occur in the form of 2-β-D-glucosides as allelochemicals in different plants of Gramineae and Acanthaceae.[1–8] The aglucones are set free by β-glucosidase when the plant is attacked by a pest and can act as plant resistance factors against microbial diseases and insects.[9–10] All the syntheses hitherto known both for 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones **2a–b** and the *N*-hydroxy derivatives **2c–d** have the common feature of generating the lactol OH-group by substitution of an appropriate 2-halogen precursor. In this context we recently reported on a convenient 4-step synthesis of 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **(2c)** (DIBOA)[11] and discussed it in comparison with three hitherto existing methods for DIBOA.[12–14] Unfortunately, this sequence is not applicable for the synthesis of its 7-methoxy derivative **2d** (DIMBOA). Therefore, any efforts to shorten the syntheses of lactols **2a–d** seem promising especially any which improve the generation of the lactol unit.

We have now elaborated an alternative short method for the synthesis of the natural products **2a–d** based on a new general approach to the 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one skeleton. Its feature consists in originating the hemiacetal unit by reduction of the appropriate lactone precursors **1a–d**. In this context we have recently described both the synthesis of 2,3-dioxo-4*H*-1,4-benzoxazines **1a,b** (two steps) and of the 4-hydroxy-2,3-dioxo-1,4-benzoxazines **1c,d** (one step) by reductive cyclization procedures,[15] starting with ethyl 2-nitrophenyl oxalate and ethyl 5-methoxy-2-nitrophenyl oxalate.



1a–d 2a–d

1, 2	R^1	R^2
a	H	H
b	H	OMe
c	OH	H
d	OH	OMe

Thus, both **1a,b** and *N*-hydroxy derivatives **1c,d** are chemoselectively reduced by diisobutylaluminum hydride (DIBAH) in toluene to form exclusively the lactols **2a–d** with no other byproducts detectable by TLC. We have found the use of two equivalents of the hydride most suitable, the first one deprotonating the NH or N–OH functions, the second one reducing the lactone unit. By this means any separate protection–deprotection procedure for the acidic functionality in **1a–d** can be avoided. Once more, diisobutylaluminum hydride proved to be a highly selective reagent, because even on increasing its molar ratio by three neither reduction of the lactam unit nor, in the case of 7-methoxy compounds, ether cleavage is observed under these conditions. Until now, diisobutylaluminum hydride[16,17] is known to be a reliable reagent both for lactone–lactol reductions, e.g. in prostaglandin

synthesis,[18] and lactam–amine reductions, e.g. in alkaloid synthesis.[19] The reduction of **1a–d** is, to the best of our knowledge, the first example for a transformation providing hemiacetals of cyclic glyoxylic hydroxamic acids.

In summary, a new general approach to the 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one skeleton has been achieved by chemoselective reduction of 2,3-dioxo-1,4-benzoxazines **1a–d** with DIBAH to form the hemiacetals **2a–d**. Thus, starting from nitrophenols, the natural hydroxamic acids DIBOA **2c** and DIMBOA **2d** are now accessible in a 3-step procedure.

Melting points were determined on a Boetius micro hotstage, are uncorrected. The starting materials were obtained by literature methods.[15]

2-Hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones 2; General Procedure:
A solution of DIBAH in toluene (17 mL, 1.2 M, 20.0 mmol) was added within 5 min via a syringe to a solution of the appropriate 2,3-dioxo-1,4-benzoxazine **1a–d**, (10.0 mmol) in anhydr. toluene (30 mL) under a N_2 atmosphere at − 78 °C. Without further cooling the mixture was stirred for 2 h allowing it slowly to warm up to r.t. With external cooling in an ice-bath the mixture was hydrolized by slow addition of H_2O (20 mL). $Al(OH)_3$ thus precipitated was then dissolved by acidification with 12 N HCl (p.A. grade) to pH 1. After filtration the aqueous layer was extracted with EtOAc (2 × 10 mL). The extracts were combined with the toluene layer, dried (Na_2SO_4) and the solvents removed in vacuo. The remaining crude product was recrystallized from MeOH to give the 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones **2a–d**, whose IR spectra were identical with authentic samples.

2a; yield: 91%; mp 206–207 °C (MeOH) (Lit.[6] mp 207 °C).

2b; yield: 72%; mp 195–196 °C (MeOH) (Lit.[8] mp 196–198 °C).

2c; yield: 77%; mp 156–157 °C (Et_2O/pentane) (Lit.[13] 157–159 °C).

2d; yield: 75%; mp 168–169 °C (MeOH) (Lit.[12] 168–169 °C).

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