Biomimetic Synthesis of 4-Acetylbenzoxazolin-2(3H)-one Isolated from Zea mays

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Dedicated to Professor Horst Hennig on the occasion of his 60th birthday

4-Acetylbenzoxazolin-2(3H)-one has been prepared biomimetically during attempts to synthesize the hemiacetalic hydroxamic acid 5-acetyl-2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one by the immediate degradation of this unstable compound generated as an intermediate. Thus, 4-acetylbenzoxazolin-2(3H)-one recently isolated from Zea mays kernels, and similar to other benzoxazolin-2(3H)-ones known from plant sources, is assumed to have originated from the degradation of natural 5-acetyl-2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one which in turn could have been enzymatically released by a β-glucosidase from the corresponding 2-β-D-glucoside.

Acetal glucosides of the 2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one lead have been found to occur as allelo chemicals in *Gramineae* [1], *Acanthaceae* [2], *Ranunculaceae* [3], and *Scrophulariaceae* [4]. Among them, (2R)-2-β-D-glucopyranosyloxy-4-hydroxy-2H-1,4-benzoxazin-3(4H)-one [5], its 7-methoxy derivative [6] and the 4-methyl ester of the latter one [7] are of most interest. Hemiacetalic aglycones, like 2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one, its 7-methoxy and 4,7-dimethoxy derivatives, enzymatically released by β-glucosidase after a pest attack, exhibit high bioactivity as plant resistance factors against microbial diseases and insects [8] in rye, maize and wheat and occur in phytotoxic root exudates of quackgrass [9]. Recently, all work directed on the understanding of the molecular mechanisms of the bioactivity was summarized [10]. We have reported on syntheses of the three aglycones mentioned [11-13], on general approaches to substituted 2-hydroxy-

influenced by the substitution of the benzene ring [24]. Recently, the isolation of 4-acetylbenzoxazolin-2(3H)-one from kernels of a *Fusarium*-resistant hybrid of *Zea mays* was reported [25].

We wish to report here on a biomimetic approach to 4-acetylbenzoxazolin-2(3H)-one which allows an assumption on possible precursors of this natural product.

Results and Discussion.

Hitherto all benzoxazolin-2(3H)-ones reported from plant sources have been proven to originate from the degradation of corresponding 2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-ones, which in turn are enzymatically released by β-glucosidase from acetal glucoside precursors. Therefore, it is possible to assume that 4-acetylbenzoxazolin-2(3H)-one reported [25] arises as product of an analogous transformation particularly since during the isolation process no means to inactivate β-glucosidase have been undertaken.

Scheme 1
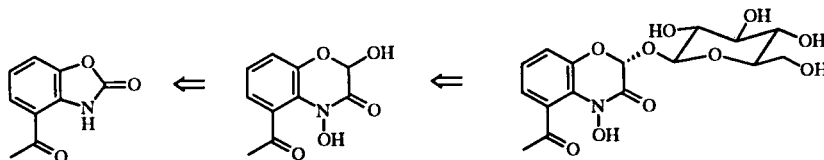
and 2,7-dihydroxy-2H-1,4-benzoxazin-3(4H)-ones [14,15] and on the double diastereoselective glucosidation affording natural acetal glucosides [16]. A well known feature of hemiacetalic cyclic hydroxamic acids with the 2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one skeleton is their degradation in solution to form benzoxazolin-2(3H)-ones and formic acid. Benzoxazolin-2(3H)-one, and its 6-methoxy and 6,7-dimethoxy derivatives have been isolated from natural sources [17-19]. The mechanism of the ring contraction has been extensively investigated [20-23]. The rate of this transformation is

Hence, we have initially been interested in a synthetic approach to the unknown 5-acetyl-2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one, which should undergo degradation to form 4-acetylbenzoxazolin-2(3H)-one. We decided to use 3-hydroxy-2-nitroacetophenone as the precursor for four attempts to synthesize this hemiacetalic hydroxamic acid.

3-Hydroxy-2-nitroacetophenone has been transformed into the starting materials for these pathways by catalytic hydrogenation to form 2-amino-3-hydroxyacetophenone 1, by O-alkylation with methyl bromoacetate to yield

Scheme 2
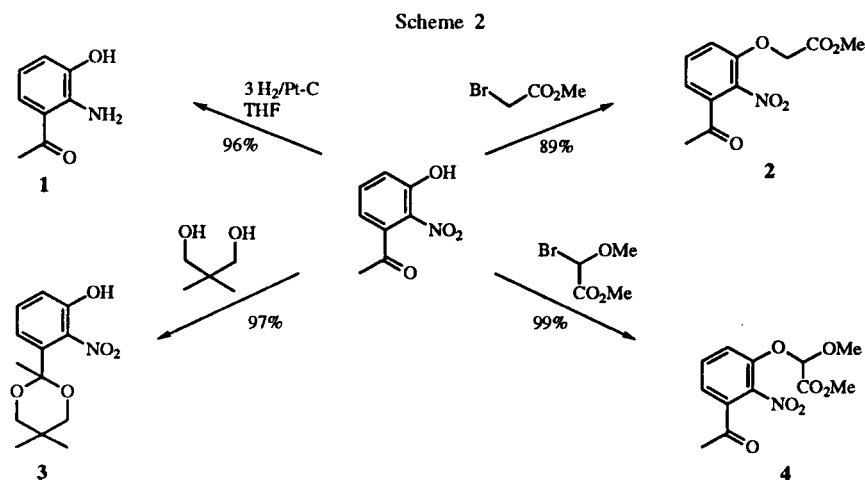
methyl (3-acetyl-2-nitrophenoxy)acetate **2**, by protection of the ketone unit to give rise to 2-(3-hydroxy-2-nitro-phenyl)-2,5,5-trimethyl-1,3-dioxane **3**, and by another *O*-alkylation to afford methyl 2-methoxy-2-(3-acetyl-2-nitrophenoxy)acetate **4**.

It was the intention of the first approach to form the hemiacetal unit in 5-acetyl-2,4-dihydroxy-2*H*-1,4-benzox-azin-3(4*H*)-one by a base catalyzed cyclization of *N*-(2-acetyl-6-hydroxyphenyl)dichloroacetamide **5** according to a method reported [26]. The N-OH function should then be developed by oxidation of the lactam unit in **6**, following another literature procedure [27].

one. The latter one was expected to be a precursor for the generation of the hemiacetal unit in 5-acetyl-2,4-dihy-droxy-2*H*-1,4-benzoxazin-3(4*H*)-one by hydrolysis of the bromide function analogously to our former own method [11].

Initially, catalytic transfer hydrogenation of nitro ester **2** with sodium borohydride as the hydrogen donor for a 3% Pt-C catalyst in connection with the Coutts method [28] was expected to form 5-acetyl-4-hydroxy-2*H*-1,4-benzox-azin-3(4*H*)-one, because this method was successful in the preparation of several 2,7-substituted benzoxazinones [15]. However, in the presence of an acetyl group in **2** we

Scheme 3
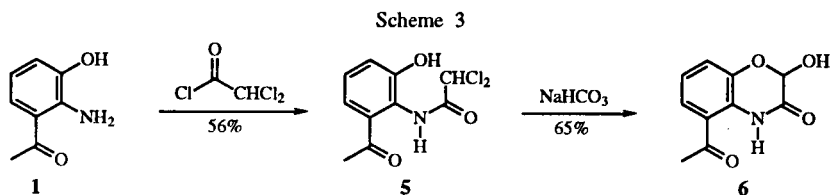
Thus, a solution of 2-amino-3-hydroxyacetophenone **1** in tetrahydrofuran obtained by catalytic hydrogenation was acylated with dichloroacetyl chloride to yield the dichloroacetamide **5**. Base catalyzed cyclization of **5** led to the 5-acetyl-2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **6**, which then should be *N*-oxidized with MoO$_5$(DMF)$_2$ to form the cyclic hydroxamic acid unit. Unfortunately, several attempts to prepare this reagent according to the method reported [27] failed nor did our own variations of the preparation starting from either ammonium or sodium dimolybdate or molybdenum trioxide afford a definite peroxo complex suitable for the oxidation intended.

The second approach was directed to the formation of the cyclic hydroxamic acid 5-acetyl-4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one by reductive cyclization of methyl (3-acetyl-2-nitrophenoxy)acetate **2** followed by an intended regioselective bromination at C-2 leading to 5-acetyl-2-bromo-4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-

observed both reductive cyclization of the intermediate hydroxylamine generated and reduction of the ketone group leading to the undesired 4-hydroxy-5-(1-hydroxy-

Scheme 4
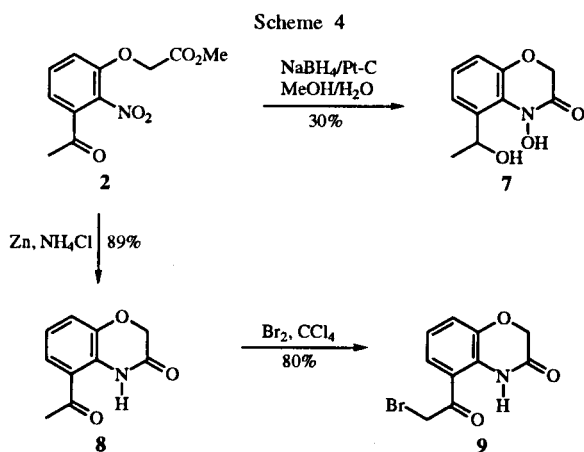
ethyl)-2H-1,4-benzoxazin-3(4H)-one **7** in moderate yield. The reduction of nitroaryls with zinc dust in aqueous ammonium chloride solution is a well known standard method for the generation of arylhydroxylamines. At the same time, the acetyl group should remain intact under these circumstances. Therefore, nitro ester **2** was subjected to zinc dust reduction and indeed reductive cyclization occurred in good yield but with formation of 5-acetyl-2H-1,4-benzoxazin-3(4H)-one **8**, exclusively, without any trace of hydroxamic acid formed. Lactam **8**, though no suitable direct precursor for the 5-acetyl-2,4-

8 under conditions which formerly led to bromination at C-2 in the case of 4-hydroxy-2H-1,4-benzoxazin-3(4H)-one [11] afforded a reaction mixture of *ca.* 80% of 5-(2-bromoacetyl)-2H-1,4-benzoxazin-3(4H)-one **9** with 20% unchanged **8**, as shown by analysis of the ¹H nmr spectrum. Consequently, due to the preferred bromination at the acetyl group the second approach followed would also be unsuccessful in the case of an existing synthesis for 5-acetyl-4-hydroxy-2H-1,4-benzoxazin-3(4H)-one.

In the third approach, the acetyl group was protected by acetalization to form acetal **3** and thus to exclude any

Scheme 5
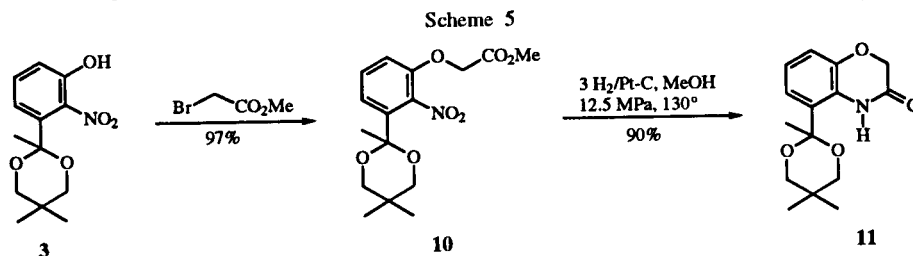
dihydroxy-2H-1,4-benzoxazin-3(4H)-one aimed for, was nevertheless a suitable model to study the regioselectivity of the bromination of the 5-acetyl-2H-1,4-benzoxazin-3(4H)-one skeleton, because the direction of this reaction will not be seriously influenced by the presence of a lactam instead of a N-hydroxylactam moiety. Bromination of

undesired side reactions. Thus, reductive cyclization of **3** was expected to form 4-hydroxy-5-(2,5,5-trimethyl-1,3-dioxan-2-yl)-2H-1,4-benzoxazin-3(4H)-one which should allow a regioselective bromination at C-2. Again, hydrolysis should lead to the hemiacetal moiety in 2,4-dihydroxy-5-(2,5,5-trimethyl-1,3-dioxan-2-yl)-2H-1,4-ben-

Scheme 6
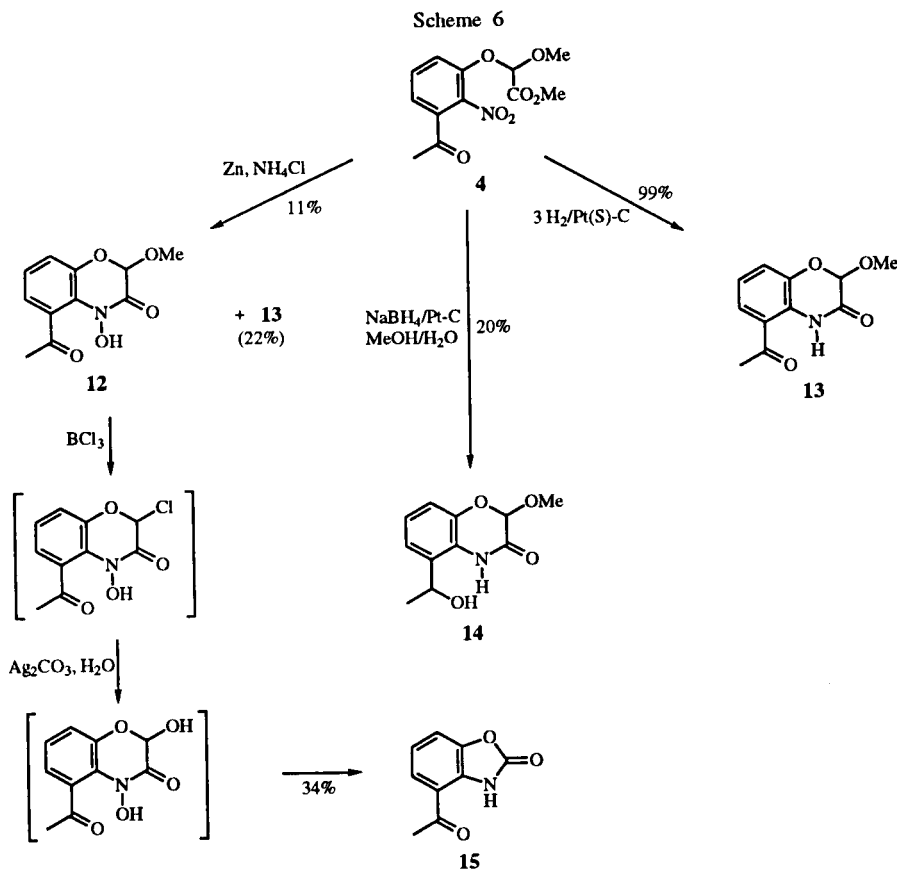
zoxazin-3(4H)-one and deprotection gives rise to 5-acetyl-2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one.

2-(3-Hydroxy-2-nitrophenyl)-2,5,5-trimethyl-1,3-dioxane **3** was transformed into 2-(3-methoxycarbonyl-methylenoxy-2-nitrophenyl)-2,5,5-trimethyl-1,3-dioxane **10** by alkylation with methyl bromoacetate in very good yield. Surprisingly, nitro ester **10** proved to be a compound with an extremely shielded nitro group. Steric hindrance due to both *ortho* substituents of the nitro group prevented reduction of the nitro group under normal conditions, *i.e.* with zinc dust in ammonium chloride solution, with sodium borohydride in the presence of a Pt-C catalyst or with hydrogen over platinum oxide even at a pressure of 12.5 MPa (~127.5 atmospheres). A reduction by catalytic hydrogenation did not occur until the temperature was increased to 130° at 12.5 MPa. Then, the intermediate amine was formed and reductively cyclized to afford 5-(2,5,5-trimethyl-1,3-dioxan-2-yl)-2H-1,4-benzoxazin-3(4H)-one **11**. However, due to its lactam structure, **11** was also unsuitable to reach our initial objective. The steric situation of the nitro group in **10** and related compounds and the consequences for their reactivity have been extensively studied and will be reported elsewhere [29].

Finally, a last approach was started based upon methyl acetal **4**. Reductive cyclization of **4** should afford 5-acetyl-4-hydroxy-2-methoxy-2H-1,4-benzoxazin-3(4H)-one **12** as a very close analogue of 5-acetyl-2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one. A methyl acetal of this type has been reported as a suitable precursor of a hemiacetal to be generated by ether cleavage with boron trichloride and hydrolysis in the synthesis of the natural 2,4-dihydroxy-7-methoxy-2H-1,4-benzoxazin-3(4H)-one [30].

A compound related to **4**, methyl 2-methoxy-2-(5-benzyloxy-2-nitrophenoxy)acetate, was known to be a sensitive but suitable precursor for a reductive cyclization on catalytic transfer hydrogenation to form the 7-benzyloxy-4-hydroxy-2-methoxy-2H-1,4-benzoxazin-3(4H)-one [15] in good yield. However, the presence of a 3-acetyl instead of a 5-benzyloxy group did again change the reactivity of acetal **4**, clearly. Catalytic transfer hydrogenation of **4** gave rise only to 5-(1-hydroxyethyl)-2-methoxy-2H-1,4-benzoxazin-3(4H)-one **14** as a lactam with a reduced acetyl group. Catalytic hydrogenation of **4** in the presence of a deactivated sulfided Pt-C catalyst useful for the synthesis of related hydroxamic acids [31] also only led to 5-acetyl-2-methoxy-2H-1,4-benzoxazin-3(4H)-one **13** as a lactam. Probably, the presence of an acetyl group *ortho* to a hydroxylamino group in a synthetic intermediate causes a significant decrease in its nucleophilicity, which supresses the tendency for ring closure to the cyclic hydroxamic acid. However, on zinc dust reduction of **4** we did finally obtain the desired methyl acetal **12**, although in poor yield and together with lactam **13**. Methyl acetal **12** has been

subjected to an ether cleavage by excess boron trichloride following a literature procedure [30]. Initially, 5-acetyl-2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one was expected as a product of the hydrolytic work-up of the intermediate 5-acetyl-2-chloro-4-hydroxy-2H-1,4-benzoxazin-3(4H)-one. Surprisingly, tlc of the hydrolysis reaction did not show a trace of the typical hydroxamic acid colour reaction with Fe(III) ions. However, an intensive spot of another aromatic compound was observed, which after chromatographic separation proved to be 4-acetylbenzoxazolin-2(3H)-one **15** from its spectroscopic data. The isolation of the ring contracted compound **15** is a clear demonstration of the instability of the hypothetical intermediate 5-acetyl-2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one. Presumably, the driving force for the degradation of this compound is an intramolecular transfer of the hydroxamic acid proton to the acetyl group leading to a zwitterion with an hydroxamate moiety. It is known, that in alkaline medium deprotonated 2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-ones are subject of degradation within a few minutes. Thus, we assume that in our synthesis of **15** the acetyl group acts as an intramolecular proton acceptor and causes the same effect. Interestingly, a similar behaviour of instability was reported for 2,4-dihydroxy-5-methyl-2H-1,4-benzoxazin-3(4H)-one by Atkinson *et al.* [24] which was interpreted in terms of a strain due to steric overlap of the methyl and the N-OH group.

In summary, we believe that the last step of the synthesis of 4-acetylbenzoxazolin-2(3H)-one **15** described here is a biomimetic one, *i.e.* that **15** recently isolated from *Zea mays* kernels [25] has originated from the degradation of 5-acetyl-2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one.

EXPERIMENTAL

2-Amino-3-hydroxyacetophenone (1).

3-Hydroxy-2-nitroacetophenone (3.62 g, 20 mmoles) was hydrogenated in tetrahydrofuran (100 ml) over 5% Pt-C catalyst (100 mg) under normal pressure at room temperature until consumption of 1350 ml of hydrogen (5 hours). The catalyst was fil-

tered and the solvent removed *in vacuo*. The remaining residue was dissolved in ethyl acetate (100 ml), washed with water (2 x 25 ml), dried (magnesium sulfate) and concentrated to a total volume of 4 ml. The precipitate formed was filtered to yield 2.96 g (96%) of a light pink solid of 1, mp 185-187° (lit 184-185° [33]); ^{1}H nmr (DMSO-d_6): δ 2.50 (s, 3H, CH$_3$), 6.43 (dd, 1H, H$_5$, $^3J_{5,6}$ = 8 Hz, $^3J_{5,4}$ = 8 Hz), 6.71 (s, 2H, NH and OH), 6.85 (dd, 1H, H$_4$, $^3J_{5,6}$ = 8 Hz, $^4J_{4,6}$ = 1.3 Hz), 7.26 (dd, 1H, H$_6$, $^3J_{5,6}$ = 8 Hz, $^4J_{4,6}$ = 1.3 Hz), 9.69 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 28.3 (CH$_3$), 114.0 (C-5), 116.9 (C-1), 117.4 (C-4), 122.6 (C-6), 140.9 (C-2), 144.8 (C-3), 200.5 (CO).

2-(3-Hydroxy-2-nitrophenyl)-2,5,5-trimethyl-1,3-dioxane (3).

3-Hydroxy-2-nitroacetophenone (9.05 g, 50 mmoles), 2,2-dimethyl-1,3-propanediol (12.48 g, 0.12 mole) and 4-toluenesulphonic acid (100 mg) were refluxed in toluene (150 ml) for 9 hours in a Dean-Stark apparatus. The solution was cooled to room temperature and washed with water (2 x 250 ml). During washing a solid formed which was filtered, washed again with water and dried to yield 13.0 g (97%) of colourless crystals of 3, mp 178-180° (toluene); ir: ν NO$_2$ 1535 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.59 (s, 3H, CH$_3$), 1.21 (s, 3H, CH$_3$), 1.76 (s, 3H, CH$_3$), 3.30 (d, 2H, OCH$_2$, ^2J = 10.9 Hz), 3.39 (d, 2H, OCH$_2$, ^2J = 10.9 Hz), 6.65 (s, 1H, OH), 7.05 (dd, 1H, H$_4$, $^3J_{4,5}$ = 8.1 Hz, $^4J_{4,6}$ = 1.1 Hz), 7.11 (dd, 1H, H$_6$, $^3J_{5,6}$ = 8.1 Hz, $^4J_{4,6}$ = 1.1 Hz), 7.39 (dd, 1H, H$_5$, $^3J_{5,6}$ = 8.1 Hz, $^3J_{4,5}$ = 8.1 Hz); ^{13}C nmr (deuteriochloroform): δ 22.2 (CH$_3$), 22.9 (CH$_3$), 30.1 (C-5), 31.2 (CH$_3$), 72.9 (C-4, C-6), 99.8 (C-2), 118.4 (C-4'), 121.2 (C-6'), 131.9 (C-5'), 134.9 (C-1'), 139.2 (C-2'), 149.0 (C-3'); ms: m/z 267 (M$^+$, 4), 252 (79), 166 (68),129 (54), 42 (100).

Anal. Calcd. for C$_{13}$H$_{17}$NO$_5$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.42; H, 6.55; N, 5.33.

General Procedure for the Synthesis of the Nitro Esters 2 and 10.

A mixture of 3-hydroxy-2-nitroacetophenone (for 2) (7.24 g, 40 mmoles) or 3 (for 10) (2.67 g, 10 mmoles), methyl bromoacetate (6.15 g (40 mmoles) for 2; 1.53 g (10 mmoles) for 10) and potassium carbonate (5.6 g (40 mmoles) for 2; 1.4 g (10 mmoles) for 10) in dry acetone (75 ml for 2, 50 ml for 10) was refluxed for two hours. The solid was filtered and washed with acetone (3 x 20 ml). The solvent was removed from the combined organic solutions *in vacuo*.

Methyl (3-Acetyl-2-nitrophenoxy)acetate (2).

The solid crude product obtained, was recrystallized from methanol to give 9.0 g (89%) of pale yellow crystals of 2, mp 112-113°; ir: ν CO 1685, 1749 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.63 (s, 3H, CO-CH$_3$), 3.71 (s, 3H, OCH$_3$), 5.06 (s, 2H, OCH$_2$), 7.57 (dd, 1H, H$_6$, $^3J_{5,6}$ = 8.9 Hz, $^4J_{4,5}$ = 1.9 Hz), 7.68 (dd, 1H, H$_5$, $^3J_{5,6}$ = 7.9 Hz, $^3J_{4,5}$ = 7.7 Hz), 7.75 (dd, 1H, H$_4$, $^3J_{4,5}$ = 7.7 Hz, $^4J_{4,6}$ = 1.9 Hz); ^{13}C nmr (DMSO-d_6): δ 28.3 (CH$_3$), 52.3 (OCH$_3$), 65.7 (OCH$_2$), 119.2 (C-6'), 122.9 (C-4'), 130.3 (C-2'), 131.8 (C-5'), 138.3 (C-3'), 149.3 (C-1'), 168.5 (CO), 196.5 (CO); ms: m/z 253 (M$^+$, 7), 238 (6), 207 (45), 164 (12), 121 (7), 42 (100).

Anal. Calcd. for C$_{11}$H$_{11}$NO$_6$: C, 52.16; H, 4.38; N, 5.53. Found: C, 52.10; H, 4.53; N, 5.91.

2-(3-Methoxycarbonylmethylenoxy-2-nitrophenyl)-2,5,5-trimethyl-1,3-dioxane (10).

The remaining colourless oil crystallized rapidly on standing to give 3.29 g (97%) of colourless crystals of 10, mp 89-91°; ir: ν CO 1759 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.59 (s, 3H,

CH$_3$), 1.18 (s, 3H, CH$_3$), 1.64 (s, 3H, CH$_3$), 3.34 (s, 4H, OCH$_2$), 3.78 (s, 3H, CO$_2$CH$_3$), 4.69 (s, 2H, OCH$_2$), 6.91 (dd, 1H, H$_4$, $^3J_{4',5'}$ = 8 Hz, $^4J_{4',6'}$ = 1.1 Hz), 7.16 (dd, 1H, H$_6$, $^3J_{5',6'}$ = 8 Hz, $^4J_{4',6'}$ = 1.1 Hz), 7.4 (dd, 1H, H$_5$, $^3J_{5',6'}$ = 8 Hz, $^3J_{4',5'}$ = 8 Hz); ^{13}C nmr (deuteriochloroform): δ 22.1 (C-8), 22.8 (C-7), 30.1 (C-5), 31.1 (C-9), 52.9 (C-9'), 66.7 (C-7'), 72.9 (C-4, C-6), 99.5 (C-2), 113.9 (C-8'), 121.9 (C-6'), 131.1 (C-5'), 134.8 (C-1'), 140.7 (C-2'), 150.3 (C-3'), 168.8 (C-8'); ms: m/z 339 (M$^+$, 11), 324 (91), 238 (60), 129 (76), 42 (100).

Anal. Calcd. for C$_{16}$H$_{21}$NO$_7$: C, 56.62; H, 6.24; N, 4.13. Found: C, 56.96; H, 6.24; N, 4.34.

Methyl 2-Methoxy-2-(3-acetyl-2-nitrophenoxy)acetate (4).

A mixture of 3-hydroxy-2-nitroacetophenone (1.81 g, 10 mmoles), methyl 2-bromo-2-methoxyacetate (1.83 g, 10 mmoles) and potassium carbonate (1.38 g, 10 mmoles) in dry acetone (50 ml) was refluxed for one hour. The solid was filtered and washed with dry acetone (3 x 20 ml). The combined organic solutions were evaporated *in vacuo* to give a pale brown oil which crystallizes after standing for two days at 5° to yield 2.82 g (99%) of light yellow crystals of 4, mp 76-79°; ir: ν CO 1696, 1763 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.57 (s, 3H, CO-CH$_3$) 3.53 (s, 3H, OCH$_3$), 3.79 (s, 3H, CO$_2$CH$_3$), 5.51 (s, 1H, CH), 7.4-7.6 (m, 3H, aromatics); ^{13}C nmr (deuteriochloroform): δ 28.3 (CH$_3$), 53.5 (2-OCH$_3$), 55.8 (OCH$_3$), 98.9 (CH), 122.2 (C-4'), 123.7 (C-6'), 130.3 (C-2'), 131.6 (C-5'), 132.0 (C-3'), 148.1 (C-1'), 166.1 (C-1), 195.9 (CO); ms: m/z 283 (M$^+$, 2), 224 (44), 165 (48), 104 (100), 75 (76).

Anal. Calcd. for C$_{12}$H$_{13}$NO$_7$: C, 50.89; H, 4.63; N, 4.95. Found: C, 51.20; H, 4.81; N, 4.90.

N-(2-Acetyl-6-hydroxyphenyl)dichloroacetamide (5).

3-Hydroxy-2-nitroacetophenone (3.62 g, 20 mmoles) was hydrogenated in tetrahydrofuran (100 ml) over 5% Pt-C catalyst (100 mg) powder (100 mg) under normal pressure at room temperature until consumption of 1350 ml of hydrogen. The solution was filtered, cooled to 0° and a solution of dichloroacetyl chloride (1.47 g, 10 mmoles) in dry tetrahydrofuran (10 ml) was added dropwise while the temperature was maintained between 5 and 10°. The solution was stirred for one hour, filtered and the solvent removed *in vacuo*. Ethyl acetate (150 ml) was added, washed with water (2 x 100 ml), dried (magnesium sulfate) and evaporated *in vacuo* to give 1.46 g (56%) of a light yellow solid of 5, mp 148-150° (cyclohexane); ir: ν CO 1684, 1657 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.39 (s, 3H, CH$_3$), 6.68 (s, 1H, CH), 7.02-7.17 (m, 3H, ar.), 10.09 (s, 1H, OH), 10.16 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 29.6 (CH$_3$), 67.5 (CH), 119.1 (C-5'), 119.3 (C-3'), 120.9 (C-1'), 128.1 (C-4'), 138.4 (C-2'), 152.8 (C-6'), 162.9 (COCHCl$_2$), 200.4 (COCH$_3$); ms: m/z 261 (M$^+$, 9), 178 (100), 150 (9), 136 (11), 42 (81).

Anal. Calcd. for C$_{10}$H$_9$Cl$_2$NO$_3$: C, 45.98; H, 3.48; N, 5.37. Found: C, 45.72; H, 3.87; N, 4.99.

5-Acetyl-2-hydroxy-2H-1,4-benzoxazin-3(4H)-one (6).

A mixture of 5 (917 mg, 3.5 mmoles), sodium bicarbonate (588 mg, 7.0 mmoles) in water (35 ml) was refluxed for 10 minutes. The solution was cooled, acidified with hydrochloric acid to pH 6 and extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were dried (magnesium sulfate) and evaporated *in vacuo* to give 470 mg (65%) of a light brown solid of 6, mp 170-173° (methanol); ir: ν CO 1698, 1702 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.68 (s, 3H, CH$_3$), 5.63 (d, 1H, H$_2$, ^3J = 6.6 Hz),

7.16 (dd, 1H, H_7, $^3J_{6,7}$ = 8.1Hz, $^3J_{7,8}$ = 8.1 Hz), 7.38 (d, 1H, H_8, $^3J_{7,8}$ = 8.1 Hz), 7.78 (d, 1H, H_6, $^3J_{6,7}$ = 8.1 Hz), 8.23 (d, 1H, OH, ^3J = 6.6 Hz); ^{13}C nmr (DMSO-d_6): δ 28.8 (CH_3), 90.0 (C-2), 120.8 (C-5), 122.8 (C-8), 123.0 (C-6), 125.9 (C-7), 127.6 (C-4a), 141.1 (C-8a), 126.6 (C-3), 202.7 (CO); ms: m/z 207 (M^+, 51), 178 (100), 160 (50), 136 (52), 104 (36).

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.96; H, 4.38; N, 6.76. Found: C, 57.58; H, 4.59; N, 6.45.

General Procedure for the Synthesis of the 1,4-Benzoxazinones 7 and 14 by Catalytic Transfer Hydrogenation of Nitro Esters 2 and 4.

The catalyst (5% Pt-C, 100 mg) and sodium borohydride (1.5 g (40 mmoles) for 7; 0.75 g (20 mmoles) for 14) were suspended in 50% aqueous methanol (30 ml for 7, 15 ml for 14) with vigorous stirring at 0° under a nitrogen atmosphere. After being warmed to 25°, a solution of the corresponding nitro ester 2 (for 7) (2.53 g (10 mmoles) in methanol (25 ml)) or 4 (for 14) (1.42 g (5 mmoles) in dry methanol (10 ml)) was added dropwise within 15 minutes with vigorous stirring maintaining the temperature below 28°. The mixture was then stirred for an additional 35 minutes and excess sodium borohydride and the catalyst were removed by filtration. The filtrate was acidified to pH 1 with concentrated hydrochloric acid *p.A.* grade and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried (magnesium sulfate) and evaporated *in vacuo* to give a brown oil as a crude product in each case.

4-Hydroxy-5-(1-hydroxyethyl)-2H-1,4-benzoxazin-3(4H)-one (7).

Chromatography of the crude product (silica gel 60, ethyl acetate) yielded a colourless oil, which crystallized over night at 5° to give 620 mg (30%) of colourless crystals of 7, mp 130-134°; ir: ν CO 1668 cm⁻¹; ^1H nmr (DMSO-d_6): δ 1.33 (d, 3H, CH_3, ^3J = 6.2 Hz), 4.65 (s, 2H, OCH_2), 5.16 (s, 1H, OH), 5.45 (q, 1H, CH, ^3J = 6.2 Hz), 6.91 (dd, 1H, H_8, $^3J_{7,8}$ = 7.9 Hz, $^4J_{6,8}$ = 1.4 Hz), 7.07 (dd, 1H, H_7, $^3J_{7,8}$ = 7.9 Hz, $^3J_{6,7}$ = 7.9 Hz), 7.37 (dd, 1H, H_6, $^3J_{6,7}$ = 7.9 Hz, $^4J_{6,8}$ = 1.4 Hz), 10.79 (s, 1H, N-OH); ^{13}C nmr (DMSO-d_6): δ 25.9 (CH_3), 64.4 (CH), 69.2 (OCH_2), 114.6 (C-8), 121.5 (C-6), 124.8 (C-7), 126.8 (C-4a), 138.2 (C-5), 146.4 (C-8a), 161.3 (CO); ms: m/z 209 (M^+,17), 191 (29), 146 (100), 134 (9), 42 (23).

Anal. Calcd. for $C_{10}H_{10}NO_4$: C, 57.68; H, 4.84; N, 6.73. Found: C, 57.91; H, 5.18; N, 6.66.

5-(1-Hydroxyethyl)-2-methoxy-2H-1,4-benzoxazin-3(4H)-one (14).

Chromatography of the crude product (silica gel 60, toluene:ethyl acetate = 4:1 (v/v)) yielded 220 mg (20%) of an oil which crystallized on standing overnight at 5° to yield 14 as a colourless solid, mp 110-112°; ir: ν CO 1598 cm⁻¹; ^1H nmr (DMSO-d_6): δ 1.25 (d, 3H, CH_3, ^3J = 6.4 Hz), 3.36 (s, 3H, OCH_3), 4.59 (m, 1H, CH), 5.03 (s, 1H, CH, H_2), 6.57 (dd, 1H, H_8, $^3J_{7,8}$ = 8 Hz, $^4J_{6,8}$ = 1.2 Hz), 6.72-6.74 (m, 2H, H_6 + OH), 7.06 (dd, 1H, H_7, $^3J_{7,8}$ = 8 Hz, $^3J_{6,7}$ = 8 Hz), 9.24 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 26.2 (CH_3), 57.0 (OCH_3), 64.3 (CHOH), 68.3 (C-2), 112.4 (C-8), 113.6 (C-6), 116.2 (C-4a), 129.1 (C-7), 133.8 (C-5), 149.2 (C-8a), 157.4 (CO); ms: m/z 223 (M^+, 20), 195 (27), 180 (41), 123 (29), 95 (100).

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.01; H, 5.58; N, 6.04.

General Procedure for the Synthesis of the 1,4-Benzoxazinones 8 and 12 by Reductive Cyclization of Nitro Esters 2 and 4 with Zinc Dust.

To a solution of the nitro ester 2 (for 8) (2.53 g, 10 mmoles) in ethanol (80 ml) or 4 (for 12) (1.42 g, 5 mmoles) in methanol (40 ml) was added with stirring a solution of ammonium chloride (2.4 g, 44 mmoles) in water (17 ml) for 8, (1.2 g, 22 mmoles) in water (12 ml) for 12 and zinc dust (2.4 g, 37 mmoles) for 8, (720 mg, 11 mmoles) for 12. The mixture was stirred (90 minutes for 8, 1 hour for 12) at room temperature. After filtration the products were isolated from the filtrate.

5-Acetyl-2H-1,4-benzoxazin-3(4H)-one (8).

The filtrate was concentrated *in vacuo* to a total volume of 4 ml. The precipitate was filtered off and recrystallized from methanol to give 1.7 g (89%) 8 as colourless needles, mp 139-140°; ir: ν CO 1685, 1646 cm⁻¹; ^1H nmr (DMSO-d_6): δ 2.61 (s, 3H, CH_3), 4.67 (s, 2H, OCH_2), 7.06 (dd, 1H, H_7, $^3J_{7,8}$ = 8 Hz, $^3J_{6,7}$ = 8 Hz), 7.25 (dd, 1H, H_8, $^3J_{7,8}$ = 8 Hz, $^4J_{6,8}$ = 1.3 Hz), 7.68 (dd, 1H, H_6, $^3J_{6,7}$ = 8 Hz, $^4J_{6,8}$ = 1.3 Hz), 10.76 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 29.4 (CH_3), 67.3 (C-2), 121.5 (C-5), 122.3 (C-8), 123.4 (C-6), 126.4 (C-7), 129.1 (C-4a), 144.4 (C-8a), 165.9 (C-3), 203.5 (CO); ms: m/z 191 (M^+, 56), 176 (33), 162 (13), 148 (13), 42 (100).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.81; H, 4.75; N, 7.33. Found: C, 62.63; H, 4.88; N, 7.66.

5-Acetyl-4-hydroxy-2-methoxy-2H-1,4-benzoxazin-3(4H)-one (12).

The solvent was removed *in vacuo* to give a brown oil which was subjected to chromatography (silica gel 60, toluene:ethyl acetate = 1:1 (v/v)) to yield 131 mg (11%) of 12 as pale yellow oil; ir: ν CO 1658, 1709 cm⁻¹; ^1H nmr (deuteriochloroform): δ 2.71 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 5.48 (s, 1H, CH), 7.22 (dd, 1H, H_7, $^3J_{7,8}$ = 8 Hz, $^3J_{6,7}$ = 7.7 Hz), 7.31 (dd, 1H, H_8, $^3J_{7,8}$ = 8 Hz, $^4J_{6,8}$ = 1.8 Hz), 7.51 (dd, 1H, H_6, $^3J_{6,7}$ = 7.7 Hz, $^4J_{6,8}$ = 1.8 Hz); ^{13}C nmr (deuteriochloroform): δ 30.6 (CH_3), 57.3 (OCH_3), 99.4 (C-2), 121.5 (C-8), 124.7 (C-6), 125.0 (C-7), 127.2 (C-4a), 128.4 (C-5), 142.8 (C-8a), 157.2 (C-3), 202.7 (CO); ms: m/z 237 (M^+, 6), 220 (5), 149 (18), 107 (40), 44 (100).

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.68; H, 4.68; N, 5.91. Found: C, 55.89; H, 5.01; N, 5.67.

Besides hydroxamic acid 12, 245 mg (22%) of lactam 13 was isolated which was identical with 13 from an alternative synthesis described below.

5-(2-Bromoacetyl)-2H-1,4-benzoxazin-3(4H)-one (9).

A solution of bromine (0.4 g, 0.25 mmole) in dry tetrachlormethane (20 ml) was added dropwise to a boiling solution of lactam 8 (477 mg, 0.25 mmole) in dry tetrachloromethane (50 ml) under irradiation with a 500 W photolamp and with vigorous stirring. The bromine was added at a rate allowing the solution only to be slightly reddish coloured. After addition of all of the bromine, the mixture was stirred for one hour at room temperature. Evaporation of the solvent *in vacuo* yielded a dark oil, the composition of which was analyzed by its ^1H nmr spectrum, which proved it to consist of *ca.* 80% of bromoketone 9 and 20% unchanged precursor 8; ^1H nmr (deuteriochloroform): of 9, δ 3.81 (s, 2H, $COCH_2Br$), 4.87 (s, 2H, OCH_2), 6.49 (d, 1H, H_8, $J_{7,8}$ = 7.1 Hz), 6.96 (dd, 1H, H_7, $J_{7,8}$ = 7.1 Hz, $J_{7,6}$ = 8.8 Hz),

7.15 (d, 1H, H_6, $J_{6,7}$ = 8.8 Hz), 11.26 (s, 1H, NH); **9** has not been isolated during this investigation.

5-(2,5,5-Trimethyl-1,3-dioxan-2-yl)-2H-1,4-benzoxazin-3(4H)-one (11).

Nitro ester **10** (1.7 g, 5 mmoles) was hydrogenated in methanol (150 ml) over 5% Pt-C catalyst (100 mg) under high pressure (12.5 MPa) at 130° in a Parr pressure reactor for two hours. The solution was filtered to remove the catalyst. The solvent was removed from the filtrate *in vacuo* to yield 1.25 g (90%) of colourless crystals of **11**, mp 82-84°; ir: ν CO 1701 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.64 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 3.44 (s, 4H, OCH_2), 4.59 (s, 2H, OCH_2), 6.94-7.02 (m, 3H, aromatics), 9.22 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 22.2 (CH_3), 23.1 (CH_3), 30.0 (C-5'), 30.3 (CH_3), 67.3 (C-2'), 72.2 (C-4', C-6'), 100.9 (C-2'), 117.4 (C-8), 122.6 (C-6), 123.9 (C-7), 125.1 (C-5), 126.1 (C-4a), 144.6 (C-8a), 165.5 (C-3); ms: m/z 277 (M+, 72), 262 (62), 191 (92), 176 (100), 149 (35).

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.91; N, 5.05. Found: C, 64.58; H, 6.56; N, 4.74.

5-Acetyl-2-methoxy-2H-1,4-benzoxazin-3(4H)-one (13).

Nitro ester **4** (283 mg, 1 mmole) was hydrogenated in glacial acetic acid (25 ml) over 3% Pt(S)-C catalyst (10 mg) under normal pressure at room temperature until consumption of 70 ml of hydrogen occured. The catalyst was filtered and the solvent was removed *in vacuo* to give 219 mg (99%) of colourless crystals, mp 168-170°; ir: ν CO 1677, 1705 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.65 (s, 3H, CH_3), 3.56 (s, 3H, OCH_3), 5.29 (s, 1H, CH), 7.08 (dd, 1H, H_7, $^3J_{7,8}$ = 8.1 Hz, $^3J_{6,7}$ = 8 Hz), 7.30 (dd, 1H, H_8, $^3J_{7,8}$ = 8.1 Hz, $^4J_{6,8}$ = 1.3 Hz), 7.61 (dd, 1H, H_6, $^3J_{6,7}$ = 8 Hz, $^4J_{6,8}$ = 1.3 Hz); ^{13}C nmr (deuteriochloroform): δ 28.7 (CH_3), 57.1 (OCH_3), 97.0 (C-2), 121.5 (C-5), 122.9 (C-8), 123.2 (C-6), 123.3 (C-7), 126.0 (C-4a), 141.2 (C-8a), 161.3 (C-3), 201.9 (CO); ms: m/z 221 (M+,9), 192 (16), 178 (4.3), 121 (23), 107 (34), 44 (100).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.96; H, 5.13; N, 6.31.

4-Acetylbenzoxazolin-2(3H)-one (15).

To a solution of methyl acetal **12** (119 mg, 0.5 mmole) in dry dichloromethane (20 ml) was added at -78° in an argon atmosphere a precooled solution (at -5°) of boron trichloride (587 mg, 5 mmoles) in dichloromethane (5 ml) within 5 minutes. After one hour the reaction mixture was hydrolized with ice and extracted with ethyl acetate. The combined organic extracts were evaporated *in vacuo*. The residue obtained was dissolved in tetrahydrofuran (10 ml) and added to a suspension of silver carbonate (305 mg, 1.1 mmole) in ice water (10 ml). After stirring for 5 minutes the solution was filtered, the low boiling tetrahydrofuran portion was removed *in vacuo* and the aqueous solution remaining was extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were dried (magnesium sulfate) and the solvent removed *in vacuo* to yield a pale brown oil which was chromatographed (silica gel 60, toluene:ethyl acetate = 7:1 (v/v)) to give 23 mg (34%) of colourless crystals of **15**, mp 199-201° after recrystallization from water (lit 217-218° [25]); ir: ν CO 1672, 1781 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.62 (s, 3H, CH_3), 7.21 (dd, 1H, H_6, $^3J_{6,5}$ = 8 Hz, $^3J_{6,7}$ = 8 Hz), 7.55 (dd, 1H, H_7, $^3J_{6,7}$ = 8 Hz, $^4J_{5,7}$ = 1.1 Hz), 7.77 (dd, 1H, H_5, $^3J_{5,6}$ = 8 Hz, $^4J_{5,7}$ = 1.1 Hz), 11.84 (s, 1H, NH). ^{13}C nmr (DMSO-d_6): δ 27.4

(CH$_3$), 114.1 (C-7), 120.4 (C-4), 121.6 (C-6), 125.1 (C-5), 130.2 (C-3a), 144.1 (C-7a), 154.8 (C-2), 197.5 (CO); ms: m/z 177 (M+, 58), 162 (100), 134 (11), 106 (35).

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