First Syntheses of Natural Products with the 2,7-Dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one Skeleton

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2,7-Dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **11** (DHBOA) and 2,4,7-trihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **14** (TRIBOA) representing aglucones of naturally occurring acetal glucoside type allelo chemicals found in *Gramineae* have been for the first time synthesized by two pathways both involving selective reductive cyclizations of appropriate 7-benzyloxy-2-nitrophenol derivatives as precursors. TRIBOA **14** and its bioactive naturally occurring 7-methyl ether DIMBOA have been found to undergo a hitherto unknown transformation to the corresponding 2,6-dibromo substituted lactam forms **20** and **21** in the presence of hydrogen bromide in acetic acid, which is of value in a better understanding of the possible mode of bioactivity.

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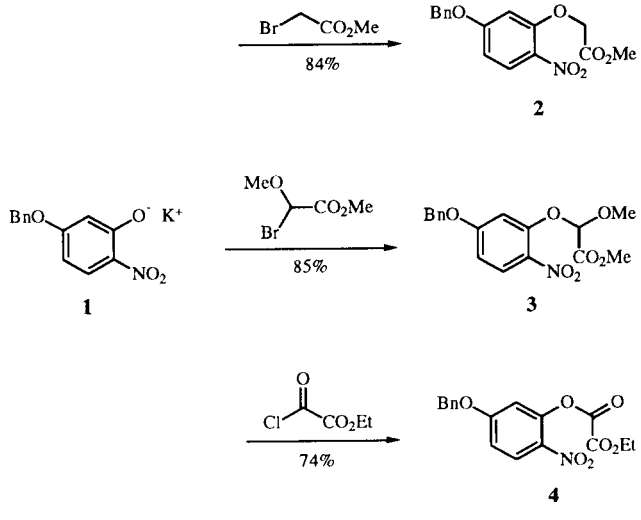
The hemiacetalic cyclic hydroxamic acids 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DIBOA) and 2,4-dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DIMBOA) have been found to occur in the form of 2-β-D-glucosides as allelo chemicals in various species of *Gramineae* [1-3], *Acanthaceae* [4] and *Ranunculaceae* [5]. Recently, we have reported on isolation procedures for the glucosidic precursors 2-β-D-glucopyranosyloxy-4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one from rye (*Secale cereale L.*) [6] and its 7-methoxy derivative from maize (*Zea mays L.*) [7] and have shown that both compounds have 2*R*-configuration. An injury of the plant by a pest attack causes liberation of the aglucone hemiacetals by β-glucosidase. Both hemiacetals have been found to act as plant resistance factors against microbial diseases and insects [8,9]. Hitherto, spectroscopical evidence has also been given for the natural occurrence of 2,4,7-trihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (TRIBOA) [10], a probable biological precursor of the 7-methoxy compound. Similarly, the 2-β-D-glucoside of the corresponding lactam 2,7-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DHBOA) has been isolated from a gramineous plant [3]. Investigations of the bioactive lead prompted several groups to develop independent chemical syntheses both for derivatives of the 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one [11-13] and the 2-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one skeleton [14]. Thus, we have, after describing a special synthesis for DIBOA [15], recently reported on two general synthetic approaches to the 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one skeleton either by chemoselective reduction of appropriate 2,3-dioxo-1,4-benzoxazine precursors [16,17] or by α-hydroxylation of corresponding cyclic hydroxamic acids [18]. In summary, though a number of 7-substituted 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones have been synthesized [19,20] or isolated, neither the 7-hydroxy compound of the natural constitution (TRIBOA) nor the corresponding lactam DHBOA have been described yet.

We wish to report here on the first syntheses of natural products with the 2,7-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one skeleton and some of their derivatives.

Results and Discussion.

We decided to introduce the 7-hydroxy functionality aimed for in the form of a benzyloxy group into the synthetic pathway due to the ease of its deprotection by catalytic hydrogenolysis. This caused a need for the hitherto unknown 5-benzyloxy-2-nitrophenol as starting material. The synthesis of this compound *via* a regioselective nitrosation of 3-benzyloxyphenol followed by a nitric acid oxidation of the pure 5-benzyloxy-2-nitrosophenol thus obtained will be reported elsewhere [21]. Potassium (5-benzyloxy-2-nitrophenolate) **1** was precipitated in very good yield by neutralization of an ethanolic solution of 5-benzyloxy-2-nitrophenol with concentrated potassium hydroxide.

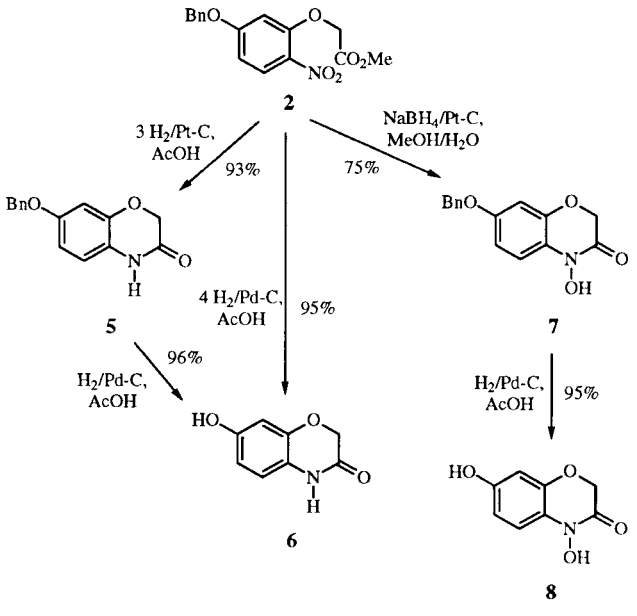
Scheme 1



The dry potassium salt **1** was then reacted with methyl bromoacetate, methyl 2-bromo-2-methoxyacetate and ethyl chloroformylformate to form methyl (5-benzyloxy-2-

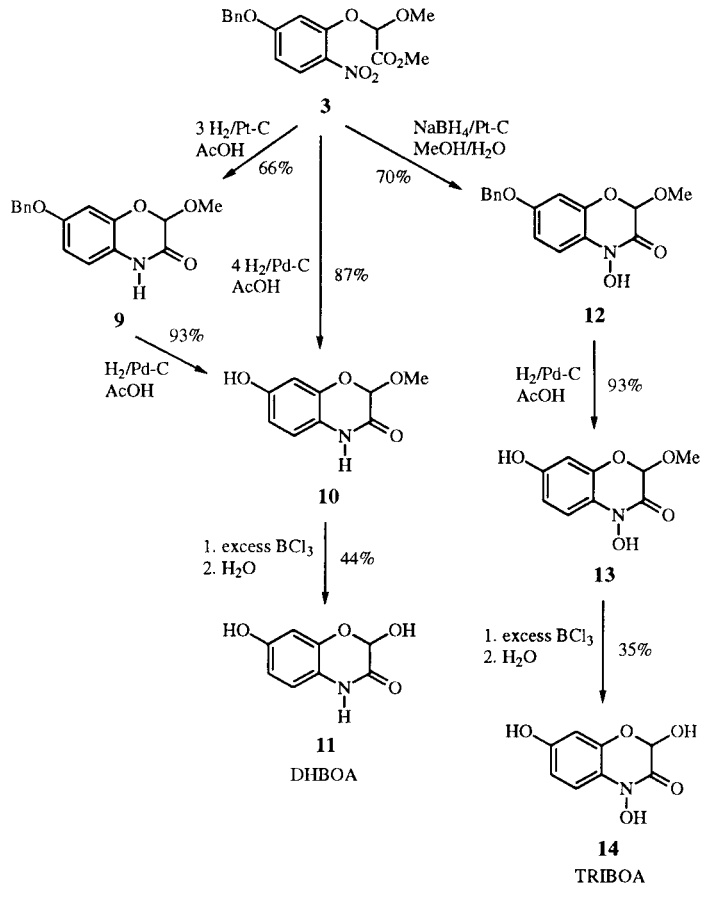
nitrophenoxy)acetate **2**, methyl 2-methoxy-2-(5-benzyloxy-2-nitrophenoxy)acetate **3** and (5-benzyloxy-2-nitrophenyl) ethyl oxalate **4**, respectively, as starting materials intended for the investigation of different synthetic pathways. First, we have been interested in the behavior of the benzyloxy substituent of these esters towards different reducing systems. Therefore, nitro ester **2**, which was expected to be stable against cleavage of its nitrophenyl ether unit has been used as a probe for several reductive cyclizations. Thus, methyl (5-benzyloxy-2-nitrophenoxy)-acetate **2** on catalytic hydrogenation did not undergo reductive cyclization to form a cyclic hydroxamic acid by ring closure of the intermediate hydroxylamine. This finding is in contrast to derivatives of the 2-nitrocinnamoyl series [22]. Hence, hydrogenation over a 3% Pt-C catalyst in acetic acid afforded 7-benzyloxy-2*H*-1,4-benzoxazin-3(4*H*)-one **5**, the protecting group of which was removed by a standard hydrogenolysis procedure using a 10% Pd-C catalyst leading to 7-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **6**. On the other hand, **6** was also accessible directly from catalytic hydrogenation of **2** over this Pd-C catalyst, expectedly. Transfer hydrogenation of **2** by means of sodium borohydride as hydrogen donor for a 3% Pt-C catalyst in connection with the Coutts' method [23] led to 7-benzyloxy-4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **7** without problems. Finally, the 7-hydroxy group was again unmasked by catalytic hydrogenolysis of **7** over Pd-C to afford 4,7-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **8**.

Scheme 2



In contrast to the robust nature of the ether **2** the acetal **3** proved to be more difficult to handle in reductive cyclizations due to its instability towards hydrolytic conditions. Therefore, catalytic hydrogenation of **3** over the Pt-C catalyst gave only rise to 7-benzyloxy-2-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one **9** in acceptable yields on addition of 2,2-dimethoxypropane to the solvent for chemical transformation of the water formed during hydrogenation. 7-Hydroxy-2-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one **10** was available by hydrogenolysis of **9** or directly by catalytic hydrogenation of nitro ester **3** over Pd-C under the precaution against hydrolysis mentioned. The cyclic hydroxamic acid **12** was only accessible by the aqueous procedure of transfer hydrogenation of nitro acetal **3** under strict observation of several parameters for the preparation. Hence, the yield of 7-benzyloxy-4-hydroxy-2-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one **12** depends distinctly on the rate of addition of the nitro compound **3** to the excess sodium borohydride/Pt catalyst suspension prepared. The dropwise addition should take place slowly at a rate not to allow the color of the reaction mixture to turn to yellow, which would indicate the formation of undesired nitrophenol. Furthermore, the rate of addition should be decreased continuously. Unmasking by means of hydrogenolysis gave rise to 4,7-dihydroxy-2-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one **13**, unproblematically.

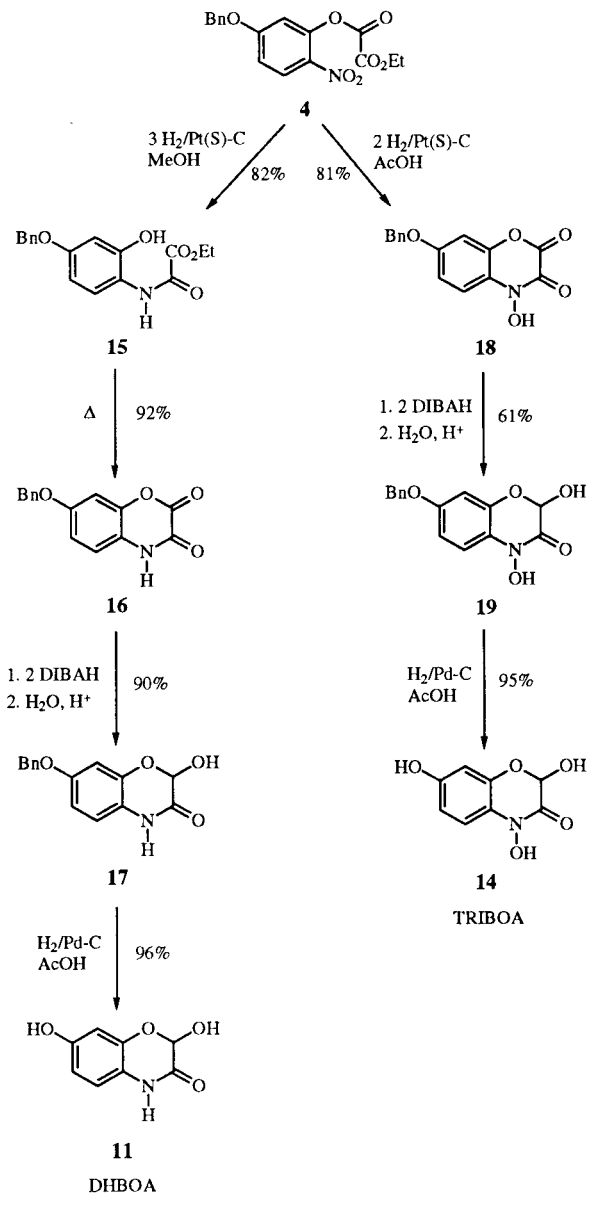
Scheme 3



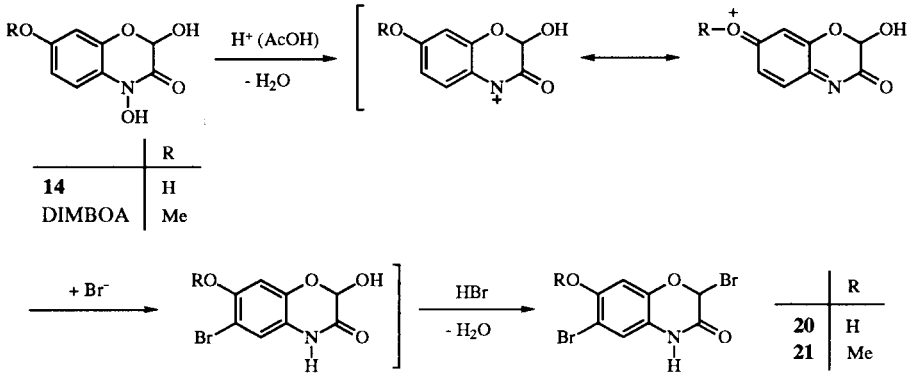
The cyclic methyl acetals **10** and **13** thus obtained can be regarded as direct precursors of DHBOA **11** and TRIBOA **14** if an ether cleavage can be realized. Hence, **10** and **13** have been subjected to an ether cleavage by excess boron trichloride following a literature procedure [12]. DHBOA **11** was obtained in moderate yield when the reaction was not complete until 48 hours. However, examples for such slow cleavages have been reported recently [19]. We found **11** also to be accessible in the same yield by cleavage of **9**, with the benzyl ether being split before the methyl ether, as expected. TRIBOA **14** was obtained also in moderate yield from cleavage of its precursor **13** after 3 hours. Analogously, **14** can also be obtained from **12**. Concerning the synthesis of the hemiacetal units of **11** and **14** by hydrolysis of the intermediate 2-chloro-2*H*-1,4-benzoxazine derivatives formed by the action of boron trichloride it seems worth mentioning that in no case was the use of silver carbonate necessary as described for related cases [12]. Ice-water was sufficient for complete hydrolysis. Hence, the natural aglucones DHBOA and TRIBOA have been for the first time synthesized.

However, the limitation of the yields for DHBOA and TRIBOA obtainable by this substitutive pathway prompted us to investigate an alternative route based upon the generation of the target hemiacetal unit by appropriate reduction of a lactone unit. Therefore, 7-benzyloxy-4*H*-2,3-dioxo-1,4-benzoxazine **16** and 7-benzyloxy-4-hydroxy-4*H*-2,3-dioxo-1,4-benzoxazine **18** have been prepared as precursors starting from the nitrophenyl oxalate **4**. Thus, our procedures recently described for a synthetic route to DIBOA and DIMBOA [16,17] proved to be applicable to the synthesis of the natural products **11** and **14**. Any procedure for the reductive cyclization of **4** has to take into account its extreme sensitivity towards hydrolysis as a feature of a nitrophenyl ester. Hence, a transfer hydrogenation was excluded as the method of choice for the hydroxamic acid **18**. However, **18** could be obtained by catalytic hydrogenation of nitro oxalate **4** in glacial acetic acid over 3% Pt(S)-C in the presence of 2,2-dimethoxypropane for the chemical transformation of the water resulting from the partial hydrogenation of the nitro group. Changing the solvent of the hydrogenation to methanol alone gave rise to the ethyl *N*-(4-benzyloxy-2-hydroxyphenyl)oxalamide **15**. Recently, we have discussed mechanistic aspects of these hydrogenations over a strongly deactivated catalyst in detail [16]. The oxalamide **15** underwent lactonization to form the required lactone **16** on heating in a Kugelrohr apparatus to its melting point. The 4*H*-2,3-dioxo-1,4-benzoxazines **16** and **18** have been chemoselectively reduced by means of diisobutylaluminum hydride in toluene to form 7-benzyloxy-2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **17** and 7-benzyloxy-2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **19**, respectively, as protected forms of **11** and **14**. We have found the use of two equivalents of the reducing agents most suitable, the first one for deprotonation of the acidic functionality, the second one for the lactone-lactol reduction. Attempts to make use of a third equivalent of the hydride for simultaneous unmasking of the 7-hydroxy group proved to be unsuccessful. It was shown by tlc monitoring of the reaction mixture that cleavage of the benzyl ether under this condition only occured at a very low degree, which was still detectable but not of preparative value. Hence, the natural aglucones DHBOA **11** and TRIBOA **14** were liberated by standard hydrogenolyses of **17** and **19**, respectively. In contrast to the substitutive

Scheme 4



Scheme 5



pathway (Scheme 3) all steps of the reductive pathway (Scheme 4) are accompanied with good to excellent yields, thus giving rise to both natural products in acceptable overall yields.

Finally, because of our interest in the synthesis of acetal glucosides [24] and in the mode of bioactivity of cyclic hydroxamic acids, we tried to convert both TRIBOA **14** and DIMBOA into suitable precursors for their acetal glucosides by reaction with excess gaseous bromine-free hydrogen bromide absorbed in glacial acetic acid. As a feature, benzannelated cyclic hydroxamic acids with an unsubstituted position *para* to the N-OH function are known to rearrange in aqueous hydrochloric or hydrobromic acid to form the corresponding *para*-hydroxy or *para*-halogen lactams. Several examples have been reported for 3-amino-3,4-dihydro-1-hydroxycarbostyril [25] as well as for 4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one [26]. However, first of all we did not expect a rearrangement of this type on account of the 7-positions being blocked by a hydroxy or methoxy group in our case. Hence, we aimed for esterification of the hemiacetal hydroxy group to a 2-bromobenzoxazinone derivative which should be able to react under conditions recently described in a synthesis of the natural acetal glucoside blepharin [27]. However surprisingly, work-up yielded 2,6-dibromo-7-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **20** from TRIBOA **14** and 2,6-dibromo-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one **21** from DIMBOA. The mechanism for the formation of both dibrominated lactams has not been investigated yet. Probably, a resonance stabilized cation resulting from protonation of the hydroxamic acid followed by elimination of water [28] may play a central role. It could be stabilized by conjugate addition of bromide to the 6-position of the quinoid system [29]. Eventually, esterification of the hemiacetal unit can happen at the end or at any other stage of this sequence.

Thus, this hitherto unknown reaction of DIMBOA and TRIBOA places emphasis on a feature of both hydroxamic acids that should also be important for understanding their biological activity, *i.e.* the ease of generation of a reactive electrophile by the 7-donor supported elimination of water from the protonated 4-hydroxy group. This behavior shows some analogy to the formation of an electrophile bioactive towards proteins and nucleic acids from 4-acetoxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one [30]. Transformations of cyclic hydroxamic acids into lactams without rearrangements have hitherto been only reported using thiols as reducing agents [19,31].

EXPERIMENTAL

Melting points were determined on a Boetius micro hot-stage apparatus and are corrected. Elemental analyses were performed on a Hereaus CHN-O-Rapid analyzer. The nmr spectra were recorded on a Varian Gemini 200 spectrometer at 199.975 MHz for ^1H and at 50.289 MHz for ^{13}C with hexamethyldisiloxane as the internal standard. The ir spectra were obtained on a Carl Zeiss Jena Specord M 80 spectrometer in potassium bromide. Mass spectra were recorded on a Varian MAT CH6 spectrometer (70 eV EI ionisation, source temperature 200°). Hydrogenation catalysts used have been received from Engelhard De Meern B.V. (3% Pt(S)-C: ESCAT Q118-01; 3% Pt-C: ESCAT 22) and MERCK (10% Pd-C), respectively. 2,4-Dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one used was synthesized according to the literature [16,17].

Potassium (5-Benzyloxy-2-nitrophenolate) (**1**).

5-Benzyloxy-2-nitrophenol (24.5 g, 0.10 mole) was dissolved in ethanol (100 ml) at 50° with stirring. To this solution was added potassium hydroxide (6.7 g, 0.12 mole) in form of a 50% aqueous solution. The precipitate is filtered off and dried at a temperature not exceeding 80° (to avoid thermal decomposition) to yield 26.8 g (95%) of the potassium salt **1** as a pale orange solid.

Methyl (5-Benzyloxy-2-nitrophenoxy)acetate (**2**).

Caution: Do not try to minimize or reduce the amount of methyl bromoacetate used in the following preparation due to the danger of explosion or popping that may happen on uncontrollable overheating of the reaction mixture in the case of a too small amount of the bromo ester!

Powdered potassium (5-benzyloxy-2-nitrophenolate) **1** (28.3

g, 0.10 mole) was suspended in methyl bromoacetate (100.0 g, 0.66 mole) and heated with stirring at 120° in an oil bath. At this temperature the nucleophilic substitution begins with an observable brightening of the suspension from an orange to a yellow color and reaching the reflux temperature of the methyl bromoacetate. After the reaction is completed the suspension is cooled to 20° and diluted with chloroform (150 ml). The potassium bromide precipitated is filtered off. From the filtrate, chloroform and excess methyl bromoacetate are removed *in vacuo*. The remaining solid is recrystallized from methanol to yield 26.5 g (84%) of **2** as pale yellow needles, mp 122-123°; ir: ν CO 1740 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.69 (s, 3H, CH_3), 5.06 (s, 2H, OCH_2CO), 5.22 (s, 2H, Ph-CH_2-O), 6.77-6.90 (m, 2H, 4-H, 6-H), 7.38-7.48 (m, 5H, phenyl), 7.98 (d, 1H, 3-H, J = 9.0 Hz); ^{13}C nmr (DMSO-d_6): δ 52.3 (CH_3), 65.8 (OCH_2CO), 70.5 (Ph-CH_2), 102.0 (C-6), 107.5 (C-4), 128.0 (C-3), 128.2 (C-2', C-6'), 128.5 (C-4'), 128.8 (C-3', C-5), 133.2 (C-2), 136.2 (C-1'), 153.4 (C-1), 163.5 (C-5), 168.6 (CO); ms: m/z 317 (M^+, 34), 258 (14), 180 (10), 137 (10), 91 (100).

Anal. Calcd. for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.76; N, 4.41. Found: C, 60.18; H, 4.77; N, 4.58.

Methyl 2-Methoxy-2-(5-benzyloxy-2-nitrophenoxy)acetate (**3**).

To a suspension of **1** (5.66 g, 20 mmoles) in absolute toluene (80 ml), methyl 2-bromo-2-methoxyacetate (3.65 g, 20 mmoles) in toluene (20 ml) was added rapidly with vigorous stirring. The suspension was heated to reflux until its color turned to pale brown. After cooling to 20° the potassium bromide precipitated was filtered off, the solvent removed *in vacuo* and the remaining oil dissolved in absolute diethyl ether. *n*-Pentane was added to cloudiness and the solution was allowed to stand in the refrigerator overnight whereupon 5.9 g (85%) of colorless crystals of **3** were obtained, mp 56-57°; ir: ν CO 1760 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.49 (s, 3H, CH-OCH_3), 3.78 (s, 3H, CO_2CH_3), 5.25 (s, 2H, Ph-CH_2-O), 6.07 (s, 1H, CH-OCH_3), 6.88-7.03 (m, 2H, 4-H, 6-H), 7.39-7.52 (m, 5H, phenyl), 8.01 (d, 1H, 3-H, J = 9.1 Hz); ^{13}C nmr (DMSO-d_6): δ 52.9 (CO_2CH_3), 55.0 (CH-OCH_3), 70.6 (Ph-CH_2), 98.2 (O-CH(OMe)-CO_2Me), 104.8 (C-6), 108.9 (C-4), 127.9 (C-3), 128.2 (C-2', C-6'), 128.5 (C-4'), 128.8 (C-3', C-5'), 134.1 (C-2), 136.1 (C-1'), 151.4 (C-1), 163.2 (C-5), 166.1 (CO); ms: m/z 347 (M^+, 7), 245 (10), 228 (94), 103 (23), 91 (100).

Anal. Calcd. for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.93; N, 4.03. Found: C, 59.08; H, 4.58; N, 4.11.

(5-Benzyloxy-2-nitrophenyl) Ethyl Oxalate (**4**).

To a suspension of **1** (14.15 g, 50 mmoles) in absolute toluene (80 ml) was dropwise added a solution of ethyl chloroformylformate (6.9 g, 50 mmoles) in toluene (20 ml) at 0° with vigorous stirring. After 1 additional hour of stirring the potassium chloride precipitated was filtered off, the solvent removed *in vacuo* and the remaining pale yellow oil extracted at 40° with absolute cyclohexane. Crystallization of the extract yielded 12.8 g (74%) of colorless crystals of **4**, mp 83-84°; ir: ν CO 1775 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (t, 3H, CH_2CH_3, J = 7.1 Hz), 4.48 (q, 2H, CH_2CH_3, J = 7.1 Hz), 5.15 (s, 2H, Ph-CH_2-O), 6.85-7.03 (m, 2H, 4-H, 6-H), 7.40-7.43 (m, 5H, phenyl), 8.21 (d, 1H, 3-H, J = 9.3 Hz); ^{13}C nmr (deuteriochloroform): δ 14.4 (CH_3), 64.5 (CH_2CH_3), 71.7 (Ph-CH_2), 111.0 (C-6), 114.1 (C-4), 128.1 (C-2', C-6'), 128.8 (C-4'), 129.2 (C-3), 129.4 (C-3', C-5'), 134.6 (C-2), 135.3 (C-1'), 145.8 (C-1), 155.6 (CO-CO_2Et), 156.7 (CO-CO_2Et), 164.2 (C-5); ms: m/z 345 (M^+, 10), 245 (47), 227 (8), 91 (100).

Anal. Calcd. for $C_{17}H_{15}NO_7$: C, 59.13; H, 4.38; N, 4.06. Found: C, 59.09; H, 4.07; N, 4.26.

General Procedure for the Synthesis of the 1,4-Benzoxazinones **5**, **6**, **8-11**, **13-15** and **18** by Catalytic Hydrogenation.

All catalytic hydrogenations were performed in a sealed 250 ml-Erlenmeyer flask fitted with a side inlet for dry hydrogen and a magnetic stirrer under normal pressure at room temperature with 10 mmoles of the appropriate educt (except for **11** and **14** which were prepared on the 5 mmoles scale) in the solvent (100 ml) and with the hydrogenation catalyst (100 mg) cited for each compound. Hydrogenations were run until the hydrogen uptake ceased at the calculated amount which was measured by a graduated column as hydrogen reservoir. The solution was filtered to remove the catalyst. The solvent was removed from the filtrate *in vacuo*. The remaining residue was then treated as described.

7-Benzyloxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**5**).

This compound was obtained on catalytic hydrogenation of nitro ester **2** in glacial acetic acid over 3% Pt-C catalyst. Crystallization of the residue from methanol yielded 2.36 g (93%) **5** as a pale grey solid, mp 152-153°; ir: ν CO 1695 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.54 (s, 2H, OCH_2CO), 5.05 (s, 2H, Ph-CH_2-O), 6.61-6.85 (m, 3H, aromatics), 7.34-7.64 (m, 5H, aromatics), 10.57 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 67.0 (C-2), 69.8 (Ph-CH_2), 103.7 (C-8), 109.0 (C-6), 116.4 (C-5), 121.1 (C-5a), 127.9 (C-2', C-6'), 128.1 (C-4'), 128.7 (C-3', C-5'), 137.3 (C-1'), 144.3 (C-8a), 154.7 (C-7), 164.5 (C-3); ms: m/z 255 (M^+, 74), 164 (27), 136 (25), 108 (17), 91 (100).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.38; H, 5.07; N, 5.43.

7-Hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**6**).

This compound was obtained on catalytic hydrogenation of nitro ester **2** in glacial acetic acid over 10% Pd-C catalyst. The residue was recrystallized from methanol to give 1.56 g (95%) **6** as pale beige crystals, mp 200-202°. Analogously, hydrogenation of compound **5** under the same conditions afforded **6** in 96% yield; ir: ν CO 1655 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.47 (s, 2H, OCH_2CO), 6.34-6.38 (m, 2H, 6-H, 8-H), 6.69 (d, 1H, 5-H, J = 9.2 Hz), 9.28 (s, 1H, OH), 10.42 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 67.0 (C-2), 103.8 (C-8), 109.2 (C-6), 116.5 (C-5), 119.4 (C-5a), 144.3 (C-8a), 153.7 (C-7), 164.4 (C-3); ms: m/z 165 (M^+, 93), 136 (36), 86 (20), 52 (17), 45 (100).

Anal. Calcd. for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.95; H, 4.36; N, 8.42.

4,7-Dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**8**).

This compound was obtained on catalytic hydrogenation of hydroxamic acid **7** in glacial acetic acid over 10% Pd-C catalyst. The residue was recrystallized from acetone to give 1.72 g (95%) **8** as pale grey crystals, mp 185-187°; ir: ν CO 1650 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.68 (s, 2H, OCH_2CO), 6.38-6.49 (m, 2H, 6-H, 8-H), 7.01 (d, 1H, 5-H, J = 8.7 Hz), 9.45 (s, 1H, 7-OH), 10.60 (s, 1H, N-OH); ^{13}C nmr (DMSO-d_6): δ 68.3 (C-2), 103.7 (C-8), 109.1 (C-6), 114.1 (C-5), 122.0 (C-5a), 144.8 (C-8a), 153.3 (C-7), 159.1 (C-3); ms: m/z 181 (M^+, 13), 165 (77), 136 (49), 52 (28), 45 (100).

Anal. Calcd. for $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 53.09; H, 4.10; N, 7.37.

7-Benzyloxy-2-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**9**).

This compound was obtained on catalytic hydrogenation of nitroacetal **3** in glacial acetic acid containing 2,2-dimethoxypropane (2.1 g, 20 mmoles) over 3% Pt-C catalyst. The residue was recrystallized from cyclohexane to give 1.84 g (66%) **9** as pale beige solid, mp 136-138°; ir: ν CO 1715 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.45 (s, 3H, OCH_3), 5.07 (s, 2H, Ph-CH_2-O), 5.32 (s, 1H, C*H*-OCH_3), 6.70-6.92 (m, 3H, aromatics), 7.33-7.45 (m, 5H, aromatics), 10.86 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 55.8 (2-O*C*H_3), 69.9 (Ph-*C*H_2), 96.7 (C-2), 104.8 (C-8), 109.7 (C-6), 116.4 (C-5), 120.5 (C-5a), 128.0 (C-2', C-6'), 128.1 (C-4'), 128.7 (C-3', C-5'), 137.2 (C-1'), 141.0 (C-8a), 154.9 (C-7), 160.5 (C-3); ms: m/z 285 (M^+, 27), 209 (25), 150 (32), 149 (35), 91 (100).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 66.97; N, 5.47; H, 4.76.

7-Hydroxy-2-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**10**).

This compound was obtained on catalytic hydrogenation of nitroacetal **3** in glacial acetic acid in the presence of 2,2-dimethoxypropane (2.1 g, 20 mmoles) over 10% Pd-C catalyst. The residue was recrystallized from toluene to give 1.70 g (87%) **10** as pale beige crystals, mp 219-221°. Analogously, hydrogenation of **9** under the same conditions except the addition of the acetal afforded **10** in 93% yield; ir: ν CO 1695 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.41 (s, 3H, OCH_3), 5.23 (s, 1H, C*H*-OCH_3), 6.42-6.50 (m, 2H, 6-H, 8-H), 6.73 (d, 1H, 5-H, J = 8.5 Hz), 9.33 (s, 1H, OH), 10.67 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 55.7 (2-O*C*H_3), 96.6 (C-2), 104.8 (C-8), 109.9 (C-6), 116.4 (C-5), 118.8 (C-5a), 140.9 (C-8a), 153.9 (C-7), 160.3 (C-3); ms: m/z 195 (M^+, 57), 167 (34), 152 (74), 135 (41), 125 (100).

Anal. Calcd. for $C_9H_9NO_4$: C, 55.39; H, 4.65; N, 7.18. Found: C, 55.25; H, 4.85; N, 7.07.

2,7-Dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**11**).

This compound was obtained on hydrogenation of **17** in glacial acetic acid over 10% Pd-C catalyst following the general procedure on the 5 mmole scale. The residue was recrystallized from diethyl ether/*n*-pentane to give 0.87 g (96%) **11** as colorless solid, mp 140-142° dec; ir: ν CO 1680 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.41 (s, 1H, C*H*-OH), 6.35-6.43 (m, 2H, 6-H, 8-H), 6.74 (d, 1H, 5-H, J = 9.0 Hz), 7.98 (s, 1H, CH-O*H*), 9.03 (s, 1H, 7-OH), 10.50 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 90.7 (C-2), 104.9 (C-8), 109.3 (C-6), 116.2 (C-5), 118.9 (C-5a), 141.7 (C-8a), 153.7 (C-7), 162.2 (C-3); ms: m/z 181 (M^+, 46), 152 (94), 124 (37), 96 (42), 45 (100).

Anal. Calcd. for $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 52.78; H, 4.22; N, 7.44.

4,7-Dihydroxy-2-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**13**).

This compound was obtained on hydrogenation of precursor **12** in glacial acetic acid over 10% Pd-C catalyst. The residue was recrystallized from acetic acid to give 1.96 g (93%) **13** as beige solid, mp 158-159° dec; ir: ν CO 1675 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.40 (s, 3H, OCH_3), 5.44 (s, 1H, C*H*-OCH_3), 6.47-6.53 (m, 2H, 6-H, 8-H), 7.03 (d, 1H, 5-H, J = 9.4 Hz), 9.51 (s, 1H, 7-OH), 10.84 (s, 1H, N-OH); ^{13}C nmr (DMSO-d_6): δ 56.0 (2-OCH_3), 98.5 (C-2), 104.7 (C-8), 109.8 (C-6), 114.2 (C-5), 121.3 (C-5a), 141.2 (C-8a), 154.6 (C-7), 155.2 (C-3); ms: m/z 211 (M^+, 55), 195 (20), 166 (41), 151 (100), 135 (39).

Anal. Calcd. for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.32; H, 4.28; N, 6.94.

2,4,7-Trihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**14**).

This compound was obtained on hydrogenation of **19** in glacial acetic acid over 10% Pd-C catalyst following the general procedure on the 5 mmole scale. The residue was recrystallized from diethyl ether/*n*-pentane to give 0.94 g (95%) **14** as monohydrate in form of a colorless solid, mp 172-174°; ir: ν CO 1650 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.63 (d, 1H, C*H*-OH, J = 6.3 Hz), 6.41-6.65 (m, 2H, 6-H, 8-H), 7.06 (d, 1H, 5-H, J = 8.5 Hz), 8.07 (d, 1H, CH-O*H*), 9.45 (s, 1H, 7-OH), 10.76 (s, 1H, N-OH); ^{13}C nmr (DMSO-d_6): δ 92.7 (C-2), 104.7 (C-8), 109.2 (C-6), 114.1 (C-5), 121.4 (C-5a), 141.9 (C-8a), 154.4 (C-7), 157.0 (C-3); ms: m/z 197 (M^+, 70), 180 (36), 164 (25), 152 (100), 150 (90).

Anal. Calcd. for $C_8H_7NO_5 \times H_2O$: C, 44.66; H, 4.22; N, 6.51. Found: C, 44.17; H, 4.33; N, 6.88.

Ethyl *N*-(4-Benzyloxy-2-hydroxyphenyl)oxalamide (**15**).

This compound was obtained on hydrogenation of nitrooxalate **4** in methanol containing 2,2-dimethoxypropane (2.1 g, 20 mmoles) over 3% Pt(S)-C catalyst. The residue was recrystallized from ethanol to give 2.58 g (82%) **15** as yellow crystals, mp 216-217° (under cyclization to form **16**); ir: ν CO 1725, 1670 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.32 (t, 3H, OCH_2-*C*H_3, J = 7.0 Hz), 4.30 (q, 2H, O*C*H_2-CH_3, J = 7.0 Hz), 5.06 (s, 2H, Ph*C*H_2O), 6.49-6.59 (m, 2H, 3-H, 5-H), 7.37-7.45 (m, 5H, *Phenyl*-CH_2O), 7.75 (d, 1H, 6-H, J = 8.7 Hz), 9.57 (s, 1H, OH), 10.19 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 14.1 (*C*H_3-CH_2-), 62.8 (CH_3-*C*H_2-), 69.6 (Ph-*C*H_2), 102.7 (C-3), 105.3 (C-5), 118.4 (C-6), 122.8 (C-1), 127.9 (C-2', C-6'), 128.1 (C-4'), 128.7 (C-3', C-5'), 137.3 (C-1'), 149.6 (C-2), 154.6 (NH-CO), 156.7 (COO), 160.9 (C-4); ms: m/z 315 (M^+, 64), 269 (15), 206 (11), 124 (37), 91 (100).

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.33; H, 5.24; N, 4.63.

7-Benzyloxy-4-hydroxy-4*H*-2,3-dioxo-1,4-benzoxazine (**18**).

This compound was obtained on hydrogenation of nitro oxalate **4** in glacial acetic acid containing 2,2-dimethoxypropane (2.1 g, 20 mmoles) over 3% Pt(S)-C catalyst. The solid residue remaining after removal of the solvent *in vacuo* was washed with absolute chloroform (10 ml) which was then discarded to give 2.31 g (81%) **18** as yellow crystals, mp 184-185° dec; ir: ν CO 1790, 1670 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.16 (s, 2H, Ph*C*H_2O), 6.99-7.08 (m, 2H, 6-H, 8-H), 7.33-7.46 (m, 6H, 5-H and *Phenyl*-CH_2O), 9.57 (s, 1H, N-OH); ^{13}C nmr (DMSO-d_6): δ 70.1 (Ph-*C*H_2), 103.1 (C-8), 112.2 (C-6), 114.2 (C-5), 121.6 (C-5a), 128.0 (C-2', C-6'), 128.2 (C-4'), 128.7 (C-3', C-5'), 136.9 (C-1'), 138.9 (C-8a), 147.2 (C-2), 154.3 (C-7), 155.4 (C-3); ms: m/z 285 (M^+, 75), 269 (10), 106 (10), 91 (100).

Anal. Calcd. for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.89; H, 4.91. Found: C, 62.87; H, 4.12, N, 5.15.

General Procedure for the Synthesis of the Cyclic Hydroxamic Acids **7** and **12** by Catalytic Transfer Hydrogenation of the Nitro Esters **2** and **3**.

The 3% Pt-C catalyst (100 mg) and sodium borohydride (1.5 g, 0.04 mole) were suspended in 50% aqueous methanol (30 ml) with vigorous stirring at 0° in a nitrogen atmosphere. After being warmed up to 25-30°, a solution of the corresponding nitro ester **2** (for **7**) (10 mmoles in dioxane (30 ml)) or **3** (for **12**) (10 mmoles in methanol (30 ml)) was added dropwise with vig-

orous stirring. The mixture was then stirred for an additional 15 minutes and excess sodium borohydride and the catalyst were removed by filtration. The filtrate was acidified to *p*H 1 with concentrated hydrochloric acid *p.A.* grade under cooling in an ice bath to separate the cyclic hydroxamic acids as crystals.

7-Benzyloxy-4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**7**).

The crude product was recrystallized from methanol/water to give 2.15 g (75%) **7** as colorless crystals, mp 128-130°; ir: ν CO 1700 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.73 (s, 2H, OCH_2CO), 5.06 (s, 2H, Ph-CH_2-O), 6.65-6.75 (m, 2H, 6-H, 8-H), 7.13 (dd, 1H, 5-H, $J_{5\text{-H}/6\text{-H}}$ = 8.0 Hz, $J_{5\text{-H}/8\text{-H}}$ = 1.7 Hz), 7.30-7.47 (m, 5H, phenyl), 10.57 (s, 1H, N-OH); ^{13}C nmr (DMSO-d_6): δ 68.3 (C-2), 69.9 (Ph-*C*H_2), 103.6 (C-8), 108.7 (C-6), 114.0 (C-5), 123.6 (C-5a), 127.9 (C-2', C-6'), 128.1 (C-4'), 128.7 (C-3', C-5'), 137.2 (C-1'), 144.8 (C-8a), 155.2 (C-7), 159.4 (C-3); ms: m/z 271 (M^+, 53), 255 (24), 152 (18), 91 (100), 65 (15).

Anal. Calcd. for $C_{15}H_{13}NO_4$ x H_2O: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.08; H, 4.91; N, 5.06.

7-Benzyloxy-4-hydroxy-2-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**12**).

The crude product was recrystallized from methanol/water to give 2.1 g (70%) **12** as colorless crystals, mp 152-154°; ir: ν CO 1680 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.41 (s, 3H, OCH_3), 5.05 (s, 2H, Ph-CH_2-O), 5.50 (s, 1H, C*H*-OCH_3), 6.74-6.84 (m, 2H, 6-H, 8-H), 7.14 (d, 1H, J = 8.8 Hz), 7.32-7.41 (m, 5H, phenyl), 10.95 (s, 1H, N-OH); ^{13}C nmr (DMSO-d_6): δ 56.1 (2-O*C*H_3), 69.9 (Ph-*C*H_2), 98.4 (C-2), 104.7 (C-8), 109.4 (C-6), 114.1 (C-5), 122.8 (C-5a), 128.0 (C-2', C-6'), 128.1 (C-4'), 128.7 (C-3', C-5'), 137.1 (C-1'), 141.2 (C-8a), 155.4 (C-7), 155.5 (C-3); ms: m/z 301 (M^+, 28), 182 (24), 92 (100), 91 (75).

Anal. Calcd. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.55; H, 4.96; N, 5.00.

General Procedure for the Synthesis of the Cyclic Hemiacetals **11** and **14** by Ether Cleavage of the Methyl Acetals **10** and **13**.

To a suspension of methyl acetals **10** (for **11**) or **13** (for **14**) (5 mmoles) in absolute dichloromethane (50 ml) was added at -78° in a nitrogen atmosphere under stirring a precooled solution (at -5°) of boron trichloride (5.0 g, 42 mmoles) in dichloromethane (20 ml). After 10 minutes the reaction mixture was allowed to warm up to room temperature gradually. Monitoring of the reaction by tlc showed completeness of the reaction for **11** after 48 hours and for **14** after 3 hours, respectively. Excess boron trichloride and most of the solvent were then blown out by a stream of nitrogen. The remaining reddish brown oil was hydrolized with 25 ml of ice-water. The mixture obtained was extracted with ethyl acetate (4 x 25 ml). The combined extracts were dried over sodium sulfate, decolorized with charcoal, filtered and the solvent was removed *in vacuo*. The residual oil was dissolved in diethyl ether (10 ml) and *n*-pentane was added until cloudiness. The product crystallized on standing.

2,7-Dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **11** thus obtained (0.4 g, 44%), mp 140-142°, showed analytical data identical with those described above.

2,4-7-Trihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **14** thus prepared (0.4 g, 37%), mp 172-173° (monohydrate), proved to be identical with **14** synthesized according to the alternative procedure described above.

7-Benzyloxy-4*H*-2,3-dioxo-1,4-benzoxazine (**16**).

The oxalamide **15** (1.58 g, 5 mmoles) was heated in a Kugelrohr apparatus under a pressure of 5 mm Hg slowly at a temperature of 210-220°. Ethanol liberated by the cyclocondensation was collected in the outside bulb. The solid crude product obtained, was recrystallized from acetone to give 1.24 g (92%) **16** as pale brown solid; ir: ν CO 1775, 1745 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.13 (s, 2H, PhCH_2O), 6.93-7.06 (m, 3H, aromatics), 7.37-7.45 (m, 5H, aromatics), 11.78 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 70.1 (Ph-*C*H_2), 103.1 (C-8), 112.3 (C-6), 116.4 (C-5), 119.4 (C-5a), 128.0 (C-2', C-6'), 128.2 (C-4'), 128.7 (C-3', C-5'), 137.0 (C-1'), 141.4 (C-8a), 150.4 (C-2), 154.3 (C-7), 154.6 (C-3); ms: m/z 269 (M^+, 85), 239 (50), 225 (20), 197 (19), 180 (15), 129 (14), 91 (100).

Anal. Calcd. for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.68; H, 4.06; N, 5.23.

General Procedure for the Synthesis of the Cyclic Hemiacetals **17** and **19** by Diisobutylaluminum Hydride Reduction of the 4*H*-2,3-Dioxo-1,4-benzoxazines **16** and **18**.

To a suspension of the lactone precursor **16** (for **17**) or **18** (for **19**) (5 mmoles) in toluene (30 ml) in a nitrogen atmosphere was added at -78° under stirring a solution of diisobutylaluminum hydride in toluene (8.5 ml of a 1.2 *M* solution, 10 mmoles) *via* a syringe. After 10 minutes the reaction was allowed to warm up to room temperature gradually. Monitoring of the reaction by tlc showed completeness of the reaction after 2 hours. The reaction mixture was then hydrolized by dropwise addition of water (20 ml) under cooling in an ice-bath. Concentrated hydrochloric acid (*p.A.* grade) was added until *p*H 1. The resulting suspension was filtered. The toluene phase was separated from the filtrate. The aqueous phase and the filter cake were extracted with ethyl acetate (3 x 25 ml each). The combined organic phases were dried over sodium sulfate, decolorized with charcoal and filtered. The solvent was removed *in vacuo*. The remaining pale yellow oil was dissolved in diethyl ether (10 ml) and *n*-pentane was added until cloudiness. The product crystallized on standing.

7-Benzyloxy-2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**17**).

This compound was obtained as dark yellow crystals (1.22 g, 90%), mp 180-181°; ir: ν CO 1650 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.03 (s, 2H, PhCH_2O), 5.42 (s, 1H, C*H*-OH), 6.65-6.80 (m, 3H, aromatics), 7.33-7.40 (m, 5H, aromatics), 7.93 (s, 1H, CH-O*H*), 10.59 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 69.8 (Ph-*C*H_2), 90.7 (C-2), 104.7 (C-8), 109.1 (C-6), 116.1 (C-5), 120.6 (C-5a), 127.9 (C-2', C-6'), 128.0 (C-4'), 128.7 (C-3', C-5'), 137.3 (C-1'), 141.7 (C-8a), 154.7 (C-7), 162.2 (C-3); ms: m/z 271 (M^+, 35), 241 (90), 124 (30), 91 (100).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.83; N, 5.16. Found: C, 66.18; H, 4.78; N, 4.89.

7-Benzyloxy-2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**19**).

This compound was obtained as pale yellow crystals (0.88 g, 61%), mp 115-117°; ir: ν CO 1680 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.10 (s, 2H, PhCH_2O), 5.68 (s, 1H, C*H*OH), 6.75-6.82 (m, 2H, 6-H, 8-H), 7.18 (d, 1H, 5-H, J = 9.5 Hz), 7.33-7.45 (m, 5H, phenyl), 8.17 (s, 1H, CH-O*H*), 10.84 (s, 1H, N-OH); ^{13}C nmr (DMSO-d_6): δ 69.9 (Ph-*C*H_2), 92.7 (C-2), 104.6 (C-8), 108.9 (C-6), 114.0 (C-5), 123.0 (C-5a), 128.0 (C-2', C-6'), 128.1 (C-4'), 128.7 (C-3', C-5'), 137.2 (C-1'), 141.9 (C-8a), 155.4 (C-7), 157.2 (C-3); ms: m/z 287 (M^+, 15), 271 (30), 269 (38), 241 (85), 124 (40), 91 (100).

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88.

Found: C, 63.05; H, 4.66; N, 4.87.

General Procedure for the Transformation of TRIBOA **14** and DIMBOA into the 2,6-Dibromolactams **20** and **21**.

To a solution of gaseous hydrogen bromide (2.0 g, 25 mmoles) in glacial acetic acid (25 ml) was added the cyclic hydroxamic acid **14** (for **20**) or 2,4-dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (for **21**) (0.5 mmoles). The solution was stirred at room temperature for 24 hours. The solvent was removed *in vacuo*. The remaining residue is sensitive to hydrolysis and was therefore washed with cold, absolute diethyl ether (5 ml), which then was discarded. The oil remaining crystallized during evaporation of traces of ether *in vacuo* and has been analyzed as received.

Due to the extreme sensitivity of **20** and **21** against hydrolysis we had to abstain from an elemental analysis of these compounds.

2,6-Dibromo-7-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**20**).

This compound was obtained as brown crystals (0.132 g, 82%), mp 300-303° dec; ir: ν CO 1705 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.44 (s, 1H, 2-H), 6.63 (s, 1H, 8-H), 7.01 (s, 1H, 5-H), 10.61 (s, 1H, NH); ms: m/z 321 (M^+, 3), 243 (80), 241 (75), 216 (32), 214 (30), 79 (100).

2,6-Dibromo-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**21**).

This compound was obtained as colorless crystals (0.124 g, 74%), mp 205-208° dec; ir: ν CO 1700 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 5.49 (s, 1H, 2-H), 6.85 (s, 1H, 8-H), 7.11 (s, 1H, 5-H), 10.70 (s, 1H, NH); ms: m/z 335 (M^+, 38), 256 (100), 230 (22), 212 (17), 200 (8), 149 (31).

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REFERENCES AND NOTES

[1] A. I. Virtanen and P. K. Hietala, *Acta Chem. Scand.*, **14**, 502 (1960).

[2] J. Hofman and O. Hofmanova, *Eur. J. Biochem.*, **8**, 109 (1969).

[3] T. Nagao, H. Otsuka, H. Kohda, T. Sato, and K. Yamasaki, *Phytochemistry*, **24**, 2959 (1985).

[4] R. B. Wolf, G. F. Spencer, and R. D. Plattner, *J. Nat. Prod.*, **48**, 59 (1985).

[5] S. Özden, T. Özden, J. Attila, and M. Kücükislamoglu, *J. Chromatogr.*, **609**, 402 (1992).

[6] H. Hartenstein and D. Sicker, *Phytochemistry*, **35**, 827 (1994).

[7] H. Hartenstein, J. Klein, and D. Sicker, *Indian J. Heterocyclic Chem.*, **2**, 151 (1993).

[8] H. J. Grambow, J. Lückge, A. Klausener, and E. Müller, *Z. Naturforsch. Teil C*, **41**, 684 (1986).

[9] H. M. Niemeyer, *Phytochemistry*, **27**, 3349 (1988).

[10] M. D. Woodward, L. I. Corcuera, J. P. Helgeson, A. Kelman, and C. D. Upper, *Plant Physiol.*, **63**, 14 (1979).

[11] E. Honkanen and A. I. Virtanen, *Acta Chem. Scand.*, **14**, 504 (1960).

[12] J. L. Jernow and P. Rosen, US Patent 3,862,180 (1975); *Chem. Abstr.*, **82**, 170980e (1975).

[13] S. A. Matlin, P. G. Sammes, and R. H. Upton, *J. Chem. Soc., Perkin Trans 1*, 2481 (1979).

[14] D. Sicker, H. Hartenstein, R. Hazard, and A. Tallec, *J. Heterocyclic Chem.*, **31**, 809 (1994).

[15] D. Sicker, B. Prätorius, G. Mann, and L. Meyer, *Synthesis*, 211 (1989).

[16] H. Hartenstein and D. Sicker, *J. Prakt. Chem.*, **335**, 359 (1993).

[17] D. Sicker and H. Hartenstein, *Synthesis*, 771 (1993).

[18] H. Hartenstein and D. Sicker, *Tetrahedron Letters*, **35**, 4335 (1994).

[19] J. Atkinson, P. Morand, J. T. Arnason, H. M. Niemeyer, and H. R. Bravo, *J. Org. Chem.*, **56**, 1788 (1991).

[20] J. Atkinson, J. Arnason, F. Campos, H. M. Niemeyer, and H. R. Bravo, in Syntheses and Chemistry of Agrochemicals III, ACS Symposium Series, **504**, D. R. Baker, J. G. Fenyes, and J. J. Steffens, eds, American Chemical Society, Washington, DC, 1992, p 349.

[21] R. Maleski, M. Kluge, and D. Sicker, *Synth. Commun.*, in press.

[22] D. Sicker, A. Rabe, A. Zakrzewski, and G. Mann, *J. Prakt. Chem.*, **329**, 1063 (1987).

[23] R. T. Coutts and D. G. Wibberley, *J. Chem. Soc.*, 4610 (1963).

[24] H. Hartenstein, C. Vogt, I. Förtsch, and D. Sicker, *Phytochemistry*, in press.

[25] T. J. McCord, C. P. Crawford, J. A. Rabon, L. D. Gage, J. M. Winter, and A. L. Davis, *J. Heterocyclic Chem.*, **19**, 401 (1982).

[26] C. Mouats, R. Hazard, E. Raoult, and A. Tallec, *Bull. Soc. Chim. France*, **131**, 71 (1994).

[27] L. F. Tietze, M. Beller, A. Terfort, and A. Dölle, *Synthesis*, 1118 (1991).

[28] T. J. McCord, D. H. Kelley, J. A. Rabon, D. C. Foyt, and A. L. Davis, *J. Heterocyclic Chem.*, **9**, 119 (1992).

[29] H. Ulrich and R. Richter in Houben-Weyl, Methoden der organischen Chemie, Band 7, Teil **3a**, C. Gundermann, ed, Georg Thieme Verlag Stuttgart, 1977, p 148.

[30] Y. Hashimoto, T. Ishizaki, and K. Shudo, *Tetrahedron*, **47**, 1837 (1991).

[31] F. J. Perez and H. M. Niemeyer, *Phytochemistry*, **24**, 2963 (1985).