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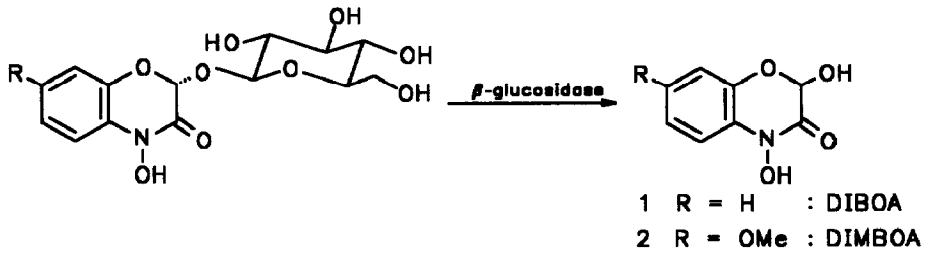
α-Hydroxylation of Cyclic Hydroxamic Acids by Peroxide Oxidation : A Novel Approach to Allelochemicals from *Gramineae*

Holger Hartenstein and Dieter Sicker*

Institut für Organische Chemie, Universität Leipzig, Talstraße 35, 04103 Leipzig, Germany

Abstract : Naturally occurring hemiacetals DIBOA and DIMBOA were synthesized by the first α-hydroxylation of N-hydroxylactams via m-chloroperbenzoic acid oxidation of corresponding cyclosilyl enol ethers.

The cyclic hydroxamic acids 2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one (DIBOA) 1 and 2,4-dihydroxy-7-methoxy-2H-1,4-benzoxazin-3(4H)-one (DIMBOA) 2 have been found to occur in the form of ß-D-glucosides as allelochemicals in different species of the *Gramineae*,[1] *Acanthaceae*[2] and *Ranunculaceae*.[3] Recently, isolation procedures for the glucosidic precursors 2-ß-D-glucopyranosyloxy-4-hydroxy-2H-1,4-benzoxazin-3(4H)-one (GDIBOA) from rye (*Gramineae*)[4] and its 7-methoxy derivative (GDIMBOA) from Coix lachryma jobi (*Gramineae*)[1] and maize (*Gramineae*)[5] have shown that these compounds have 2*R*-configuration. The hemiacetals DIBOA 1 and DIMBOA 2 are set free by ß-glucosidase after injury of the plants and act as plant resistance factors.[6,7] However, both hemiacetals thus obtained were proven to be optically inactive and did not undergo enantioseparation by chiral HPLC[8] or HPCE[9] methods due to a fast racemization of their lactol unit during the separation process.

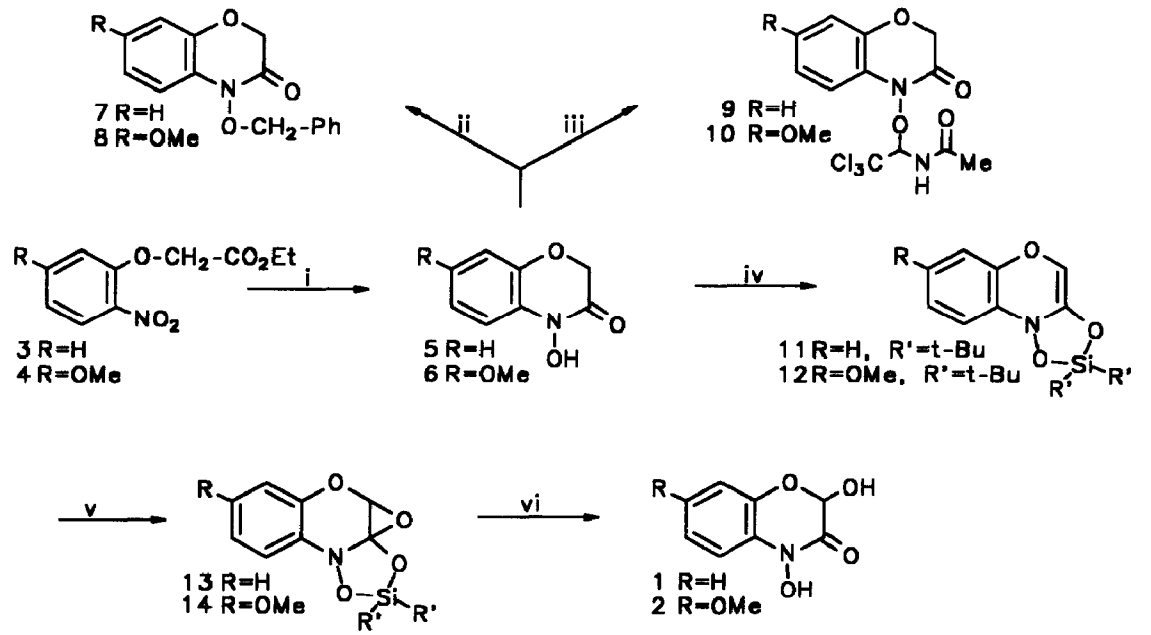


Scheme 1. Enzymatic hydrolysis of 1,4-benzoxazin-3(4H)-one glucosides

This circumstance allows syntheses for both natural products to be racemic. In principle, previous syntheses for 1 and 2 can be divided into two groups according to the way of generating the hemiacetal unit. The feature of the first group consists in hydrolyzing appropriate 2-halogen precursors [10-12] Recently, we reported on a new general synthesis of the 2-hydroxy-2H-1,4-benzoxazin-3(4H)-one skeleton[13] by chemoselective reduction of 2,3-dioxo-1,4-benzoxazines.

It was the aim of this project to develop an oxidative approach for the hemiacetal unit of 1 and 2. Hitherto, oxidations using m-chloroperbenzoic acid for α-hydoxylation were known to give rise to α-hydroxy aldehydes,[14] α-hydroxy ketones,[15] and α-hydroxy carboxylic acids,[16] respectively. Analogous oxidations of N-hydroxylactams have not been cited yet.

The starting 4-hydroxy-2H-1,4-benzoxazin-3(4H)-ones 5 (mp. 169-170°C (lit.[17] 168-169°C), 82%) and 6 (mp. 122-123°C (lit.[9] 121-123°C), 68%) were prepared by reductive cyclization of ethyl 2-nitrophenoxyacetates 3 and 4 with sodium borohydride as recently described for 4-hydroxy-2-methoxy-2H-1,4-benzothiazin-3(4H)-one.[18] The oxidative transformation intended causes a need for protection of the hydroxamic acid moiety. Several kinds of protecting the 4-position have been taken into consideration to yield precursors for oxidizable silylenol ethers. First, 4-acetoxy derivatives have been excluded due to their ability to act as strong electrophiles under heterolysis of the N-O bond.[19] We have found this effect to be enhanced in the presence of the electron-donating 7-methoxy group. Protection of the 4-position has been tried by benzylation of 5 and 6 to yield the 4-benzyloxy derivatives 7 and 8,[20] respectively. However, all attempts to transform them into the corresponding silyl enol ethers by means of LDA/TBDMSCl led to unsuitable decomposition products only.



Reagents and conditions : (i) $NaBH_4$, Pt-C, $MeOH/H_2O$, 25°C, 1h; (ii) BzCl, K_2CO_3, Me_2CO,reflux, 2h; (iii) Cl_3C-CH=N-COMe, THF, 25°C, 30min; (iv) 2 LDA, toluene, -78°C, t-Bu_2SiCl_2, 6h; (v) MCPBA, CH_2Cl_2, -5°C, 2h; (vi) Bu_4NFx3H_2O, THF, 25°C, 2h

Scheme 2. Oxidative generation of hemiacetal units

Bringing to mind the ability of azavinylogous carbonyl compounds like N-(2,2,2-trichloroethylidene)acetamide[21] for the addition of acidic compounds, like shown by us for substituted 2-pyrazolin-5-ones previously,[22] we have then prepared 2-acetylamino-2-(2H-1,4-benzoxazin-3(4H)-on-4-yloxy)-1,1,1-trichloroethane **9** and its 7-methoxy derivative **10**[23] under mild conditions. Unfortunately, both compounds showed a similar tendency to decompose by N-O fission under the silylation conditions following like the 4-acetoxy compounds mentioned above. Eventually, several attempts for silylating the acidic N-OH., e.g. with TBDMSCl/imidazole[24] were unsuccessful. However, two equivalents of lithium diisopropylamide allowed the enolisable hydroxamic acids **5** and **6** to react with di-tert-butyldichlorosilane in absolute toluene to give the protected 1,4-benzoxazines **11** and **12** in form of stable cyclosilylenol ethers.

Oxidation of **11** and **12** with m-chloroperbenzoic acid in methylene chloride formed the intermediate epoxides **13** and **14**. Finally, treatment of **13** and **14** with tetra-n-butylammonium fluoride in THF caused deprotection of the silyl ethers and ring opening of epoxides to yield DIBOA **1** and DIMBOA **2** after separation from the reaction mixture by column chromatography.[25]

In summary, the procedure described here gives for the first time rise to α-hydroxylated cyclic hydroxamic acids by peracid oxidation. Thus, the main naturally occurring hydroxamic acids DIBOA **1** and DIMBOA **2** from *Gramineae* have been synthesized in four steps starting from ethyl 2-nitrophenoxyacetates via m-chloroperbenzoic acid oxidation of di-tert-butyldimethylsilyl protected 4-hydroxy-1,4-benzoxazin-3(4H)-ones.

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References and Notes.

1. a) Wahlroos, Ö.; Virtanen, A. I. *Acta Chem. Scand.* **1959**, *13*, 190; b) Hietala, P. K.; Virtanen, A. I. *Acta Chem. Scand.* **1960**, *14*, 502; c) Nagao, T.; Hideaki, O.; Kohda, H.; Satop, T.; Yamasaki, K. *Phytochemistry*, **1985**, *24*, 2959.
2. Chatterjee, A.; Basa, S. C. *Chem. Ind.* **1969**, 238.
3. Özden, S.; Özden, T.; Attila, I.; Kücükislamoglu, M.; Okatan, A. *J. Chromatogr.* **1992**, *609*, 402.
4. Hartenstein, H.; Sicker, D. *Phytochemistry* **1994**, *35*, 827.
5. Hartenstein, H.; Klein, J.; Sicker, D. *Indian J. Heterocycl. Chem.* **1993**, 151.
6. Niemeyer, H. M. *Phytochemistry* **1988**, *27*, 3349.
7. Bravo, H. R.; Niemeyer, H. M. *Tetrahedron*, **1985**, *41*, 4983.
8. Lippmann, T.; Hartenstein, H.; Sicker, D. *Chromatographia* **1993**, *35*, 302.
9. Thunecke, F.; Hartenstein, H.; Sicker, D.; Vogt, C. *Chromatographia* (in press).
10. Atkinson, J.; Morand, P.; Arnason, T.; Niemeyer, H. M.; Bravo, H. R. *J. Org. Chem.* **1991**, *56*, 1788.
11. Jernow, J. L.; Rosen, P. *US Patent* **1975**, 3,862, 180.
12. Sicker, D.; Prätorius, B.; Mann, G.; Meyer, L. *Synthesis* **1989**, 211.
13. Sicker, D.; Hartenstein, H. *Synthesis*, **1993**, 771.
14. Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427.

15. a) Rubottom, G. M.; Gruber, J. M.; Juve H. D. Jr.; Charleson, D. A. *Org. Synth.* **1986**, *64*, 118; b) Cain, C. M.; Simpkins, N. S. *Tetrahedron Lett.* **1987**, *28*, 3723; c) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987**, *109*, 7575.
16. Rubottom, G. M.; Marrero, R. *J. Org. Chem.* **1975**, *40*, 3783.
17. Honkanen, E.; Virtanen, A.I. *Acta. Chem. Scand.* **1960**, *14*, 1214.
18. Sicker, D.; Hartenstein, H.; Tallec, A.; Hazard, R. **J. Heterocycl. Chem.** (in press).
19. Hashimoto, Y.; Ohta, T.; Shudo, K.; Okamoto, T. *Tetrahedron Lett.* **1979**, *18*, 651.
20. 4-Benzyloxy-2H-1,4-benzoxazin-3(4H)-one **7** and its 7-methoxy derivative **8**, respectively, have been synthesized by refluxing hydroxamic acids **5** and **6** with benzyl chloride/NaI/K_2CO_3 in acetone : **7** (mp.97-98°C (cyclohexane), 74 %), ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.75-7.62 (m, 9H, ar), 5.00 (s, 2H, OCH_2CO), 4.60 (s, 2H, OCH_2Ph) ppm; **8** (mp. 83-84°C (cyclohexane), 82 %), ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.67-7.46 (m, 8H, ar), 5.09 (s, 2H, OCH_2CO), 4.79 (s, 2H, OCH_2Ph), 3.75 (s, 3H, OMe) ppm.
21 Drach, B. S.; Sinitsa, A. D.; Kirsanov, A. W. *Zh. Obshch. Khim.* **1969**, *39*, 2193.
22. Sicker, D.; Böhlmann, W.; Bendler, D.; Mann, G. *Synthesis* **1987**, 493.
23. A general method for this addition consisted in reacting equivalent amounts of hydroxamic acids **5** and **6** with N-(2,2,2-trichloroethylidene)acetamide in absolute tetrahydrofuran at 25°C for 1h, thus yielding **9** (mp. 157-158°C (ethanol), 87 %), ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.46 (d, 1H, J=11Hz, N*H*CH), 7.28-7.60 (m, 4H, ar), 4.18 (d, 1H, J=11 Hz, NHC*H*), 4.97 (s, 2H, CH_2), 2.02 (s, 3H, CH_3) and **10** (mp. 111-113°C (ethanol), 64 %), ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.46 (d, 1H, J=11 Hz, N*H*CH), 6.55-7.67 (m,H, ar), 6.81 (d, 1H, J=11Hz, NHC*H*), 5.02 (s, 2H, CH_2), 3.99 (s, 3H, OCH_3), 2.09 (s, 3H, $COCH_3$) ppm.
24. Greene, Th. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons, Inc.: New York, 1991; 77.
25. Procedure for **1** : To a suspension of 4-hydroxy-2H-1,4-benzoxazin-3(4H)-one **5** (1.65 g, 10 mmol) in toluene (30 ml) a solution of LDA in cyclohexane (10 ml, 2.0 M) was added over 1 min at -70°C and the mixture was stirred for 30 min. A solution of t-Bu_2SiCl_2 (2.20 g, 10 mmol) in toluene (10 ml) was added within 10 min and the mixture was stirred for 3 h and then allowed to warm up to 25°C. The solvents were evaporated in vacuo. The residue remaining was suspended in CH_2Cl_2 (50 ml), neutralized with acetic acid and cooled to -5°C. To this suspension a solution, obtained by dissolving MCPBA (2.3 g of wet 75% MERCK product, 10 mmol) in CH_2Cl_2 (30 ml) and filtering the mixture for drying through a filter pad of Na_2SO_4, was added within 2 min and stirred for 2 h. The solvent was removed and to the solid obtained were added THF (50 ml) and t-Bu_4NFx3H_2O (3.2 g, 10 mmol). The mixture was stirred for 2 h at ambient temperature, then the solvent was evaporated in vacuo. The remaining oil was purified by column chromatography (silica gel 60, toluene:ethyl acetate 1:2, v/v) to yield DIBOA **1** (mp. 155-156°C (lit.[13] 156-157°C), 41%). DIMBOA **2** (mp. 167-169°C (lit.[13] 168-169°C), 32%) was obtained analogously.

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