

Reaction of Alkenes with Hydrogen Peroxide and Sodium Iodide: A Nonenzymatic Biogenic-Like Approach to Iodohydrins

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Abstract: An efficient protocol to synthesize iodohydrins from alkenes is presented. Reactions were conducted in aqueous media using safe and readily available sodium iodide (the most abundant form of the element), and a highly convenient oxidant such as hydrogen peroxide. Addition of a protic acid triggers a faster and efficient process, a role formally related to that played by haloperoxidase enzymes in naturally occurring transformations. The successful application of these conditions to multigram scale preparations and over natural products derivatives is also discussed.

Keywords: alkenes • biomimetic synthesis • electrophilic addition • halogenation • water chemistry

Introduction

The search for efficient preparations of different types of organic compounds is associated many times to the development of new reagents and/or synthetic strategies. Nevertheless, more than often, the consideration of straight approaches relying on activating basic raw sources providing the required components remains scarcely investigated and credited. To this purpose, biomimetic considerations have proved to be very enlightening, offering simple solutions to many synthetic problems. Thus, in approaching the preparation of halogenated compounds halides are of prime interest, as they are key players in those biohalogenation processes^[1] leading to naturally occurring organohalogen compounds.^[2] Haloperoxidases are the enzymes responsible for those reactions^[3] and their catalytic activity has been chemically exploited for different purposes.^[4] In this sense, biosynthetic studies in the marine environment assigned an active role to iodide ions in mediating conversion of alkenes to bi-functional derivatives.^[5] In sharp contrast to this natural trend, safe and highly convenient sodium iodide has been

scantly considered for the conversion of alkenes to iodohydrins.^[6] Furthermore, and oppositely to the situation encountered when preparing halohydrins containing bromine and chlorine, it has been established that the related iodo-hydroxylation process by reaction of an alkene with iodine and water does not represent an efficient alternative.^[7] Therefore, recent efforts towards the preparation of this class of valuable iodinated synthetic intermediates have drawn mainly their attention to the recognition of appropriate starting materials,^[8] better iodine donors,^[9] or even alternative and more elaborated synthetic strategies.^[10] Interestingly, an alkyl iodide can be activated and used as a valuable iodide source to accomplish a synthetically useful conversion of an alkene to the corresponding iodohydrin.^[11] Those leading findings call for the development of a straight conversion of alkenes to iodohydrins that eventually should be based on the combination of a convenient oxidant and a simple salt that acts as the supplier of iodide ions. The validity and scope of such a conceptually simple methodology still remains to be covered.^[12]

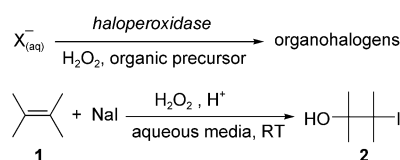
Herein, we report on the iodo-hydroxylation reaction of alkenes **1** with sodium iodide in aqueous media (Scheme 1). The process uses environmentally benign^[13] 33 % aqueous solution of hydrogen peroxide as oxidant.^[14]

Results and Discussion

We initially undertook the search for reaction conditions that promote the incorporation of iodide ions into the alkene. Overall, this would allow for a direct iodo-hydroxylation reaction of the unsaturated hydrocarbon. The enzy-

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Scheme 1. 2-Iodoalkanol **2** from iodo-hydroxylation reaction of alkenes **1** based on biomimetic considerations.

matic synthesis of 2-deoxy-2-halo sugars starting from the parent glycal and the corresponding halide had been previously reported.^[6b] Along those studies an isolated observation on the iodo-hydroxylation of **D**-galactal taking place without requiring any enzymatic catalysis was noticed.^[15] On this basis, we first evaluated the scope of these non-enzymatic conditions over several representative alkenes. Under those conditions, cyclohexene gave rise to a mixture of compounds, yielding the desired iodohydrin in 31 %. Furthermore, 1-hexene afforded exclusively the product that arose from a competitive 1,2-diiodination process. Methyl cinnamate did not react at all, and only traces of the iodo-hydroxylated product were observed upon extending the reaction time up to 60 h. Indene furnished a complex reaction mixture, which suggested that oligomerization reactions took place under those reaction conditions. Thus, as it was early proposed,^[6a] the catalytic action of an enzyme seems to be generally required to promote the efficient incorporation of iodide ions to alkenes, resulting in iodohydrins. The non-enzymatic conditions above referred are useful when electron-rich alkenes are used as precursors, such as the case of the given glycal.^[6b] However, significant drawbacks were found to obtain the desired iodohydrins for the case of other classes of simple alkenes. Searching for a more general synthetic methodology, we attempted to overcome those limitations establishing an alternative way of triggering the process. We used cyclohexene (**1a**) as a model compound to screen the reaction conditions that might simulate the effect of the enzymatic activation step. A graphic summary of relevant data is presented in Table 1.

Table 1. Iodo-hydroxylation of **1a** using NaI and H₂O₂.^[a]

Entry	Molar ratio ^[b] H ₂ O ₂ :HBF ₄ ^[c]	Reaction time [h]	Yield ^[d] [%]
1	1:–	24	1
2	1:1	24	11
3	1:2	24	25
4	3:1	48	27
5	3:2	24	70
6	3:3	4.5	89
7	2:4	4.5	90
8	3:6	2	94
9	3:6	2.5	87 ^[e]

[a] H₂O₂ (33 % aqueous solution) was added to a cooled flask (ice bath) containing a mixture of NaI and **1a** in THF/H₂O (12 mL/5 mL, for 5 mmol of **1a**). [b] Referred to 1:1 molar ratio for **1a**:NaI. [c] Added as 35 % commercial aqueous solution. [d] Based on isolated amounts of **2a** and referred to NaI. [e] For 0.1 mol scale of NaI and using 0.11 mol of **1a** (the reaction mixture was mechanically stirred).

Addition of acid was required to promote an efficient process. First we tested commercially available 35 % aqueous solution of HBF₄, obtaining good results. Entry 8 shows a reasonably fast process and an excellent yield of isolated **2a**, which is generated as a single stereoisomer.^[16] The process was fairly robust when scaled up to 0.1 mol of **1a**, furnishing 19.7 g of **2a** (entry 9, Table 1).

The feasibility of alternative acids was also tested. We chose indene (**1b**), being a more labile alkene under acid conditions, as a convenient substrate to analyze the influence of this experimental variable. In all the cases tested, a single adduct (**2b**) was formed in good yield, and as a single isomer (see Table 2). Interestingly, the reaction can be also executed by the addition of several types of acids routinely used in chemical processes. In general, the observed reaction rate nicely correlates with the pK_a value of the corresponding acid. Thus, stronger acids gave rise to faster reactions than weaker ones. We observed that even H₃PO₄, an acid with a pK_a value in the range of 2, is adequate to promote this iodination chemistry. Remarkably, a solid acid resin (entry 5, Table 2) can be also conveniently employed to furnish **2b**, offering an easily recyclable proton source.

Table 2. Iodo-hydroxylation of **1b** using NaI and H₂O₂.^[a]

Entry	Acid	<i>t</i> [h]	Yield ^[b] [%]
1	HBFB ₄	2	83
2	H ₂ SO ₄	8	84
3	oxalic acid	30	77
4	H ₃ PO ₄	30	69
5	Amberlyst 15 (wet) ^[c]	30	65 ^[d]
6	TFA	20	80

[a] H₂O₂ was added to a cooled flask (ice bath) containing a mixture of NaI, acid and **1b** (5 mmol scale) in THF/H₂O. [b] Based on isolated amount of **2b** and referred to **1b**. [c] Amberlyst 15 (wet) ion-exchange resin is a registered trademark of Rohm and Haas, and was purchased from Aldrich. [d] 2.5 g of resin used.

The scope was further explored, and the results are summarized in Table 3 (unless otherwise noticed, the conditions outlined in Table 1, entry 8, were routinely used).

As depicted, many types of representative alkenes successfully reacted with a predictable selectivity, which follows the already noticed trend for the reactions of **1a** and **1b**. The reactivity of mono-substituted alkenes was explored (Table 1, entries 3 and 4). The nature of the substituent bounded to the alkene controls the regioselectivity of the process. Thus, for the case of an alkyl substituent, the reaction product was formed as a mixture of regioisomers, being Markovnikov's one the major component (5:1 ratio, by GC). However, styrene furnished only one regioisomer. More substituted alkenes were transformed into the corresponding iodohydrin derivatives, including among them an example of a tri-substituted one. When cyclopentene and cycloheptene were assayed under the above defined conditions, the iodo-hydroxylation reaction occurred, but minor

Table 3. Iodohydrins **2** from alkenes **1**, NaI and H₂O₂.^[a]

$ \begin{array}{c} \text{R}^1 \quad \text{R}^2 \\ \diagdown \quad \diagup \\ \text{C} = \text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{R}^3 \end{array} + \text{NaI (1 equiv)} \xrightarrow[\text{THF/H}_2\text{O, 0}^\circ\text{C to RT}]{\text{H}_2\text{O}_2 \text{ (3 equiv), HBF}_4 \text{ (6 equiv)}} \begin{array}{c} \text{R}^2 \\ \\ \text{R}^1 - \text{C} - \text{C} - \text{OH} \\ \quad \\ \text{H} \quad \text{I} \end{array} $				
Entry	Alkene 1	<i>t</i> [h]	Product 2	Yield ^[b] [%]
1		2		94
2		2		83
3		5	 +  (R = Bu)	76 ^[c]
4		5		72 ^[d]
5		60		81
6		2		65
7		6		88 ^[e]
8		8		77 ^[f]
9		22		85 ^[e]
10		4		90 ^[g]
11		4		92 ^[g]

[a] Reaction performed with 5 mmol of the corresponding alkene.

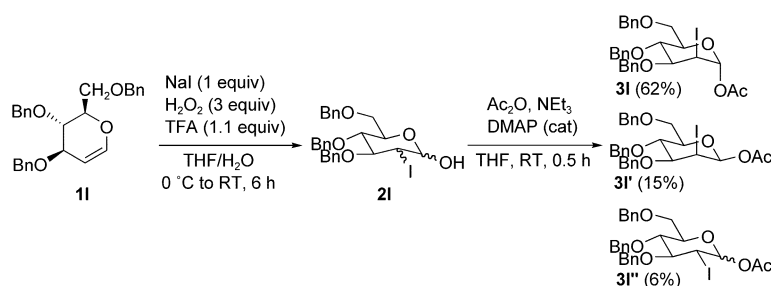
[b] Based on isolated amount of **2** and referred to **1**. [c] Combined yield from the amount of each regiosomer isolated in pure form (**2c** was isolated in 63% upon column chromatography on silica gel using hexane/ethyl acetate:10/1, from a crude reaction mixture containing **2c**:**2c'** in 5:1 ratio by GC analysis). [d] 4 equiv HBF₄ and 4 equiv H₂O₂ were used.[e] CF₃CO₂H (1.1 equiv) instead of HBF₄, and H₂O₂ (6 equiv) were added. [f] Based on crude reaction. Upon chromatography Ph₂C=CHI was isolated. [g] 1.5 equiv H₂O₂ were used.

amounts of 2-iodoperoxides were detected in crude reaction mixtures. The reaction was easily optimized by lowering the amount of H₂O₂ added. Both electron-rich and electron-deficient olefins are efficient partners in this process; the nature of the acid and the reaction time being the only variables that have to be tuned (entries 5 and 7). For the electron-rich 3,4-dihydro-2*H*-pyran (**1g**), the use of the standard conditions resulted in polymerization reactions. In this case, the addition of lower amounts of a weaker acid (TFA) was required to promote an efficient reaction. Under the optimized conditions above established for **1g**, the related tri-*O*-benzyl-D-glucal (**1l**) was also smoothly derivatized, yielding potentially useful iodinated building blocks for carbohydrate chemistry. In this case, the crude mixture isolated from the iodination reaction was rapidly treated with Ac₂O in Et₃N, rendering the mixture of compounds presented in Scheme 2. A remarkable 14:1 ratio for the formation of *manno* over *gluco* isomers was determined by HPLC analysis of the mixture upon acylation.^[17,18]

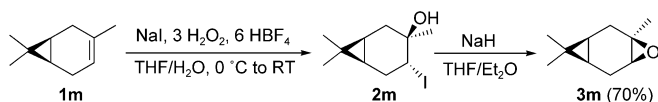
Pure samples of 2-deoxy-2-iodo-mannopyranosyl derivatives, α form **3l** and β form **3l'**, were isolated by standard column chromatography, in the yields given in Scheme 2.

A terpene, (+)-3-carene (**1m**), was easily iodo-hydroxylated using this approach in nearly quantitative conversion, but severe decomposition occurred along the standard chromatographic purification leading to only 43% isolated yield of **2m**. However, the purity in which **2m** is generated in crude reaction mixtures allows its direct use for further synthetic elaboration. Thus, as an example, epoxide **3m** was prepared in 70% overall yield from **1m**, as outlined in Scheme 3. The observed stereochemistry for the epoxide nicely complements that accessible using the direct epoxidation reaction of **1m** with a peracid.^[19]

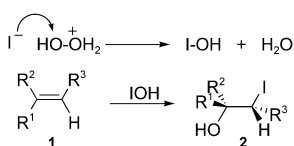
The pattern of reactivity showed by the different alkenes in these transformations, as well as the regio- and stereochemistry observed are those expected for a reaction involving the participation of cyclic iodonium ions as reaction intermediates. These species should be formed upon interaction of **1** with an electrophilic source of iodine.^[20] An appropriate process that would contribute to generate iodonium ions into the given solution could reasonably involve an initial nucleophilic attack of iodide^[21] onto protonated hydrogen peroxide.^[22] As a result, this would afford an active concentration of unstable and productive hypoiodous acid in solution (Scheme 4). Interaction of HOI, or of its protonated form,^[23] with **1** accounts well for the observed formation of iodohydrins **2**.^[24]



Scheme 2. Synthesis of 2-iodo-2-deoxymannopyranosyl derivatives from a protected glucal.



Scheme 3. Sequential iodo-hydroxylation/epoxidation reactions of (+)-3-carene.



Scheme 4. Proposed reaction pathway.

Conclusion

In summary, a truly practicable, efficient and almost unprecedented entry to an important class of iodine containing bi-functional compounds has been devised and executed on the basis of biomimetic considerations.

Among other distinctive features of this synthetically valuable iodo-hydroxylation process are the use of readily available starting materials and that of a safe and convenient oxidant, as diluted solutions of hydrogen peroxide. Furthermore, the easiness in which the process was scaled up to the use of 0.1 mol of starting material represents a worthy and distinctive synthetic attractiveness of this new approach for preparing 2-iodoalkanols, imitating biogenic pathways to functionalize alkenes.

The reaction conditions were successfully applied over a wide set of alkenes, including natural products derivatives. Overall, using common chemicals, an aqueous medium and a very simple synthetic Scheme could now be considered as a solid alternative for preparing iodohydrins, overcoming many problems usually faced under previously reported conditions.

Experimental Section

General: All reactions were carried out under air atmosphere unless otherwise is specified in the text. THF and Et₂O were distilled from sodium/benzophenone under N₂. Analytical thin-layer chromatography plates used were Merck UV-active silica gel 60 F₂₅₄ on aluminium plates. Flash column chromatography was carried out on silica gel 60, 230–240 mesh, using appropriate mixtures of ethyl acetate and hexanes as eluent. ¹H NMR (200, 300, 400 MHz) and ¹³C NMR (50, 75, 100 MHz) spectra were measured at room temperature on a Bruker AC-200, AC-300 and AMX-400 instruments with tetramethylsilane (¹H NMR) or CDCl₃ (¹³C NMR) as internal standard. Carbon multiplicities were assigned by DEPT techniques. High resolution mass spectra (HRMS) were determined on a Finnigan MATT 95 spectrometer. Elemental analysis were carried out on a Perkin–Elmer 2400 microanalyzer. Gas chromatographic analyses were conducted on an HP6890 using a Beta dex 120 Supelco (30 m × 0.25 mm × 0.25 μm) column. HPLC analyses were performed on a Waters LC Module I plus using a Kromasil 100 C8 5 μm 25 × 1.0 column. Melting points were determined on a Büchi-Tottoli and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

General procedure for the preparation of iodohydrins 2a–2c, 2f, and 2m: A 100 mL flask was charged with NaI (0.75 g, 1 equiv, 5 mmol), 1

(1 equiv, 5 mmol) and THF/H₂O (12 mL/5 mL). The mixture was cooled in an ice-water bath and magnetically stirred. To this vigorously stirred mixture HBF₄ (6.12 mL of 35 % aqueous solution, 6 equiv, 30 mmol) and H₂O₂ (1.5 mL, 3 equiv, 15 mmol, 33 % aqueous solution) were sequentially added. An exothermic reaction and development of a dark red colour in solution were noticed. After 15 min, the cooling bath was removed and the reaction mixture further stirred until the solution turned colourless (see Table 3 and Scheme 3). THF was then removed under vacuum, and the resulting mixture was treated with Na₂S₂O₃ (30 mL of 5 % aqueous solution), and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The crude reaction products were purified by column chromatography (hexane/EtOAc) to give pure iodohydrins that gave satisfactory spectroscopic and analytical data. Analytical data for compounds **2a**,^[25] **2b**,^[9d] **2c**,^[26] **2f**^[27] were in complete accordance with literature values.

(1S,3R,4R,6R)-4-Iodo-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol (2m): yellow oil; *R*_f = 0.7 (hexane/ethyl acetate 3:1); [*α*]_D = −73 (*c* = 18, CH₂Cl₂, 20 °C); ¹H NMR (400 MHz, CDCl₃): δ = 4.15 (dd, *J* = 12, 7.2 Hz, 1H; CH), 2.6 (ddd, *J* = 14.9, 12, 8.5 Hz, 1H; CH₂), 2.45 (ddd, *J* = 14.9, 7.2, 0.8 Hz, 1H; CH₂), 2.25 (brs, 1H; O-H), 2.1 (dd, *J* = 14.5, 10.1 Hz, 1H; CH₂), 1.35 (m, 1H), 1.25 (dd, *J* = 1.2, 0.5 Hz, 3H; CH₃), 0.95 (s, 3H; CH₃), 0.85 (s, 3H; CH₃), 0.75 (ddd, *J* = 10.1, 9.1, 4.9 Hz, 1H; CH), 0.45 (ddd, *J* = 9.1, 8.5, 0.8 Hz, 1H; CH); ¹³C NMR (75 MHz, CDCl₃): δ = 70.8 (C), 49.8 (CH), 34.4 (CH₂), 31.1 (CH₂), 28.4 (CH₃), 24.1 (CH₃), 21.9 (CH), 20.1 (CH), 17.5 (C), 15.1 (CH₃); HRMS (EI): *m/z*: calcd for C₁₀H₁₇O: 153.1275; found: 153.1279 [*M*⁺ − I].

General procedure for the preparation of iodohydrins 2j and 2k: A lower amount of H₂O₂ (0.75 mL, 1.5 equiv, 7.5 mmol) was used to avoid competitive formation of hydroperoxides analogues. Analytical data for compounds **2j**,^[28] **2k**^[28] were in complete accordance with literature values.

General procedure for the preparation of iodohydrins 2g–2i and 2l: The best results were obtained employing trifluoroacetic acid (0.42 mL, 1.1 equiv, 5.5 mmol). Analytical data for compounds **2g**,^[29] **2i**^[12e] were in complete accordance with literature values.

1-O-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo- α -mannopyranose (3l): yellow oil; *R*_f = 0.27 (hexane/ethyl acetate 5:1); [*α*]_D = +7.1 (*c* = 7.5, CH₂Cl₂, 20 °C); ¹H NMR (300 MHz, CDCl₃): δ = 7.4–7.1 (m, 15H), 6.4 (d, *J* = 1.4 Hz, 1H; CH), 4.86 (d, *J* = 10.5 Hz, 1H; CH), 4.7 (m, 2H; CH₂), 4.5 (m, 3H), 4.4 (dd, *J* = 4, 1.6 Hz, 1H; CH), 4.0 (m, 2H; CH₂), 3.78 (dd, *J* = 11.1, 4 Hz, 1H; CH₂), 3.68 (dd, *J* = 11.1, 1.6 Hz, 1H; CH₂), 3.22 (dd, *J* = 8.2, 4 Hz, 1H; CH), 2.05 (s, 3H; CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 168.4 (C), 138.1 (C), 137.8 (C), 137.2 (C), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.0 (2 × CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 95.4 (CH), 76.0 (CH), 75.3 (CH), 75.2 (CH₂), 74.7 (CH), 73.4 (CH₂), 70.9 (CH₂), 68.4 (CH₂), 30.9 (CH), 20.4 (CH₃); HRMS (EI): *m/z*: calcd for C₂₉H₃₁O₆: 302.0168; found: 302.0169 [*M*⁺ − I].

1-O-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo- β -mannopyranose (3l′): yellow oil; *R*_f = 0.24 (hexane/ethyl acetate 5:1); [*α*]_D = −3.7 (*c* = 13.7, CH₂Cl₂, 20 °C); ¹H NMR (300 MHz, CDCl₃): δ = 7.4–7.1 (m, 15H), 5.00 (d, *J* = 1.4 Hz, 1H; CH), 4.90 (d, *J* = 10.8 Hz, 1H; CH), 4.70 (m, 3H), 4.60 (dd, *J* = 2.3, 1.4 Hz, 1H; CH), 4.50 (dd, *J* = 11.0, 6.5 Hz, 2H; CH₂), 4.00 (m, 1H), 3.78 (m, 2H; CH₂), 3.68 (ddd, *J* = 9.7, 4.3, 2.3 Hz, 1H; CH), 3.20 (dd, *J* = 8.4, 4.3 Hz, 1H; CH), 2.20 (s, 3H; CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 168.6 (C), 138.0 (C), 137.9 (C), 137.0 (C), 128.4 (CH), 128.2 (2 × CH), 127.9 (2 × CH), 127.7 (2 × CH), 127.6 (CH), 127.4 (CH), 91.2 (CH), 78.9 (CH), 76.9 (CH), 75.2 (CH), 75.1 (CH₂), 73.4 (CH₂), 70.6 (CH₂), 68.4 (CH₂), 36.0 (CH), 21.0 (CH₃); HRMS (EI): *m/z*: calcd for C₂₉H₃₁O₆: 302.0168; found: 302.0166 [*M*⁺ − I].

Procedure for the preparation of 2d: HBF₄ (4.1 mL of 35 % aqueous solution, 4 equiv, 20 mmol) and H₂O₂ (2 mL, 4 equiv, 20 mmol, 33 % aqueous solution) were used. Analytical data for compound **2d**^[26] were in complete accordance with literature values.

Synthesis of epoxide 3m: A crude mixture of **2m** was treated with NaH (1.3 g, ≈ 1 equiv, 5 mmol) in a THF/Et₂O mixture (1:1, 30 mL) under N₂ atmosphere. The reaction was magnetically stirred for 3.5 h and then hydrolyzed with ice. The mixture was extracted with Et₂O (3 × 25 mL) and washed with brine (2 × 50 mL). The combined organic layers were then dried over anhydrous sodium sulphate and volatiles were removed under vacuum. Further purification upon column chromatography (hexane/

EtOAc 50:1) afforded pure **3m** (0.53 g, 3.5 mmol, 70 %). Analytical data for compound **3m**^[30] were in complete accordance with literature values.

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- [1] a) R. Theiler, J. C. Cook, L. P. Hager, J. F. Siuda, *Science* **1978**, *202*, 1094–1096; b) W. Fenical, *Science* **1982**, *215*, 923–928; c) S. L. Neidleman, J. Geigert, *Biohalogenation: Principles, Basic Roles and Applications*, Ellis Horwood, Chichester, **1986**; d) R. I. de la Rosa, M. J. Clague, A. Butler, *J. Am. Chem. Soc.* **1992**, *114*, 760–761; e) G. E. Meister, A. Butler, *Inorg. Chem.* **1994**, *33*, 3269–3275; f) G. J. Coplas, B. J. Hamstra, J. W. Kampf, V. L. Percoraro, *J. Am. Chem. Soc.* **1994**, *116*, 3627–3628; g) V. Conte, F. Di Furia, S. Moro, *Tetrahedron Lett.* **1994**, *35*, 7429–7432; h) B. J. Hamstra, G. J. Coplas, V. L. Percoraro, *Inorg. Chem.* **1998**, *37*, 949–955; i) B. Sels, D. De Vos, M. Buntinx, F. Pierard, A. Kirsch-De Mesmaeker, P. Jacobs, *Nature* **1999**, *400*, 855–857.
- [2] G. W. Gribble, *Acc. Chem. Res.* **1998**, *31*, 141–152.
- [3] a) A. Butler, J. V. Walker, *Chem. Rev.* **1993**, *93*, 1937–1944; b) A. Messerschmidt, R. Wever, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 392–396; c) M. Pickard, J. Gross, E. Lübbert, S. Tölzer, S. Krauss, K.-H. van Pée, A. Berkessel, *Angew. Chem.* **1997**, *109*, 1245–1248; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1196–1199; d) W. Plass, *Angew. Chem.* **1999**, *111*, 960–962; *Angew. Chem. Int. Ed.* **1999**, *38*, 909–912.
- [4] a) E. de Boer, R. Weber, *J. Biol. Chem.* **1988**, *263*, 12326–12332; b) W. Wiesner, K.-H. van Pée, F. Lingens, *J. Biol. Chem.* **1988**, *263*, 13725–13732; c) R. R. Everett, J. R. Kanofsky, A. Butler, *J. Biol. Chem.* **1990**, *265*, 4908–4914; d) T. Haag, F. Lingens, K.-H. van Pée, *Angew. Chem.* **1991**, *103*, 1550–1551; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1487–1488; e) H. Fu, H. Kondo, Y. Ichikawa, G. C. Look, C.-H. Wong, *J. Org. Chem.* **1992**, *57*, 7265–7270; f) E. J. Allain, L. P. Hager, L. Deng, E. N. Jacobsen, *J. Am. Chem. Soc.* **1993**, *115*, 4415–4416; g) S. Kirner, K.-H. van Pée, *Angew. Chem.* **1994**, *106*, 346; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 352; h) A. Zaks, D. R. Dodds, *J. Am. Chem. Soc.* **1995**, *117*, 10419–10424; i) J. S. Martinez, G. L. Carroll, R. A. Tschirret-Guth, G. Altenhoff, R. D. Little, A. Butler, *J. Am. Chem. Soc.* **2001**, *123*, 3289–3294; j) J. N. Carter-Franklin, J. D. Parrish, R. A. Tschirret-Guth, R. D. Little, A. Butler, *J. Am. Chem. Soc.* **2003**, *125*, 3688–3389.
- [5] J. Geigert, S. L. Neidleman, S. K. DeWitt, D. J. Dalietos, *Phytochem.* **1984**, *23*, 287–290.
- [6] Representative exceptions are the enzymatic approach, see: a) J. Geigert, S. L. Neidleman, J. Dalietos, S. K. DeWitt, *Appl. Environ. Microbiol.* **1983**, *45*, 366–374; b) K. K.-C. Liu, C.-H. Wong, *J. Org. Chem.* **1992**, *57*, 3748–3750; and a target oriented preparation, see: c) C. R. LeBlond, K. Rossen, F. P. Gortsema, I. A. Zavialov, S. J. Cianciosi, A. T. Andrews, Y. Sun, *Tetrahedron Lett.* **2001**, *42*, 8603–8606.
- [7] For a review on cohalogenation reactions: J. Rodríguez, J.-P. Dulcère, *Synthesis* **1993**, 1177–1205.
- [8] S. Ma, H. Ren, Q. Wei, *J. Am. Chem. Soc.* **2003**, *125*, 4817–4830.
- [9] a) H. Masuda, K. Takase, M. Nishio, A. Hasegawa, Y. Nishiyama, Y. Ishii, *J. Org. Chem.* **1994**, *59*, 5550–5555; b) M. Smietana, V. Gouverneur, C. Mioskowski, *Tetrahedron Lett.* **2000**, *41*, 193–195; c) D. Dolenc, *Synlett* **2000**, 544–546; d) A. R. De Corso, B. Panunzi, M. Tingoli, *Tetrahedron Lett.* **2001**, *42*, 7245–7247.
- [10] For a review on nucleophilic opening of epoxides by iodide, see: a) C. Bonini, G. Righi, *Synthesis* **1994**, 225–238; for a recent example: b) S. M. Chervin, P. Abada, M. Koreeda, *Org. Lett.* **2000**, *2*, 369–372. For iodoalkylation reactions of carbonyl compounds, see for instance: c) S. Matsubara, M. Yoshioka, K. Utimoto, *Angew. Chem.* **1997**, *109*, 631–633; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 617–618.
- [11] a) A. Bravo, F. Fontana, G. Fronza, F. Minisci, A. Serri, *Tetrahedron Lett.* **1995**, *36*, 6945–6948; b) G. Asensio, C. Andreu, C. Boix-Bernardini, R. Mello, M. E. González-Núñez, *Org. Lett.* **1999**, *1*, 2125–2128.
- [12] While chloro- and bromo-hydroxylation reactions of alkenes employing the corresponding halide salts were proved to be valuable synthetic methodologies, the scope of the related iodo-hydroxylation process has not yet been established. For representative studies on the former reactions, see: a) M. R. Detty, F. Zhou, A. E. Friedman, *J. Am. Chem. Soc.* **1996**, *118*, 313–318; b) C. Francavilla, M. D. Drake, F. V. Bright, M. R. Detty, *J. Am. Chem. Soc.* **2001**, *123*, 57–67; c) B. F. Sels, D. E. De Vos, P. A. Jacobs, *J. Am. Chem. Soc.* **2001**, *123*, 8350–8359; d) M. Abe, Y. You, M. R. Detty, *Organometallics* **2002**, *21*, 4546–4551. For an interesting study on a related intramolecular iodo-etherification reaction using sodium iodide and an organotelluride catalyst, see: e) D. E. Higgs, M. I. Nelen, M. R. Detty, *Org. Lett.* **2001**, *3*, 349–352.
- [13] For some applications see: a) S. Juliá, J. Masana, J. C. Vega, *Angew. Chem.* **1980**, *92*, 968–969; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929–931; b) C. Venturello, R. D'Aloisio, *J. Org. Chem.* **1988**, *53*, 1553–1557; c) W. A. Herrmann, R. W. Fischer, D. W. Marz, *Angew. Chem.* **1991**, *103*, 1706–1709; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1638–1641; d) K. Sato, M. Aoki, R. Noyori, *Science* **1998**, *281*, 1646–1647; e) S. Y. Jonsson, K. Färnegårdh, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2001**, *123*, 1365–1371; f) M. C. White, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 7194–7195; g) A. Berkessel, M. R. M. Andrae, H. Schmickler, J. Lex, *Angew. Chem.* **2002**, *114*, 4661–4664; *Angew. Chem. Int. Ed.* **2002**, *41*, 4481–4484; h) B. S. Lane, M. Vogt, V. J. DeRose, K. Burgess, *J. Am. Chem. Soc.* **2002**, *124*, 11946–11954; i) D. Sloboda-Rozner, P. L. Alsters, R. Neumann, *J. Am. Chem. Soc.* **2003**, *125*, 5280–5281.
- [14] H₂O₂ is an environmentally benign oxidant for chemical processes. a) R. A. Sheldon, *Chemtech* **1994**, 38–47; b) J. H. Clark, *Green Chem.* **1999**, *1*, 1–8.
- [15] This iodination-triggered process uses the H₂O₂/KI reagents combination in a citric-phosphate buffer (pH 3). The reaction time employed for the described iodination was 30 minutes at room temperature.
- [16] Compounds **2** and **3** were characterized by NMR spectroscopy and gave satisfactory analytical and/or HRMS data, in accordance to the assigned structure.
- [17] The mannopyranosyl derivatives were observed in the crude reaction mixture in a ratio of 4:1 for α : β epimers, according to HPLC analysis.
- [18] a) A. Kirschning, C. Plumeier, L. Rose, *Chem. Commun.* **1998**, 33–34; b) W. R. Roush, S. Narayan, C. E. Bennett, K. Briner, *Org. Lett.* **1999**, *1*, 895–897; c) W. R. Roush, C. E. Bennett, *J. Am. Chem. Soc.* **1999**, *121*, 3541–3542; d) A. Kirschning, M. Jesberger, A. Schönbberger, *Org. Lett.* **2001**, *3*, 3623–3626.
- [19] H. C. Brown, A. Suzuki, *J. Am. Chem. Soc.* **1967**, *89*, 1933–1940.
- [20] Bromoperoxidase-catalysed incorporation of bromide to organic compounds has been shown to be an electrophilic process, see: H. S. Soedjak, J. V. Walker, A. Butler, *Biochemistry* **1995**, *34*, 12689–12696.
- [21] R. Curci, J. O. Edwards in *Catalytic Oxidations with Hydrogen Peroxide as Oxidant* (Ed.: G. Strukul), Kluwer, Dordrecht, **1992**, pp. 45–95.
- [22] Å. M. L. Øiestad, A. C. Petersen, V. Bakken, J. Vedde, E. Uggerud, *Angew. Chem.* **2001**, *113*, 1345–1349; *Angew. Chem. Int. Ed.* **2001**, *40*, 1305–1309.
- [23] I. Lengyel, I. R. Epstein, K. Kustin, *Inorg. Chem.* **1993**, *32*, 5880–5882.
- [24] Alternative iodo-hydroxylation promoted by elemental iodine cannot be totally ruled out on this basis, it has been omitted for a matter of simplicity in the graphic. Decomposition of HOI in presence of iodide furnishes iodine. Efficient formation of adduct **2** would assume a reoxidation step of the resulting iodide by-product, see: J. W. Cornforth, D. T. Green, *J. Chem. Soc. C* **1970**, 846–849.
- [25] M. Parrilli, M. Adinolfi, G. Barone, G. Laonigro, L. Mangoni, *Gazz. Chim. Ital.* **1975**, *105*, 1301–1305.
- [26] M. A. Sanseverino, M. C. S. de Mattos, *Synthesis* **1998**, 1584–1586.

- [27] R. C. Cambie, W. I. Noall, G. J. Potter, P. S. Rutledge, P. D. Woodgate, *J. Chem. Soc.* **1977**, 3, 226–230.
- [28] M. D'Auria, F. D'Onofrio, G. Piancatelli, A. Scettri, *Synth. Commun.* **1982**, 12, 1127–1138.
- [29] C. A. Horiuchi, A. Ikeda, M. Kanamori, H. Hosokawa, T. Sujiyama, T. T. Takahashi, *J. Chem. Res. Synop.* **1996**, 60–61.
- [30] M. M. Reddy, T. Punniyamurthy, J. Iqbal, *Tetrahedron Lett.* **1995**, 36, 159–162.

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