One-Pot Synthesis of 1,2,3-Triols from Allylic Hydroperoxides and a Catalytic Amount of OsO_4 in Aqueous Acetone

Cemalettin Alp, Ufuk Atmaca, Murat Çelik, Mehmet Serdar Gültekin*

Faculty of Sciences, Department of Chemistry, Atatürk University, 25240 Erzurum, Turkey
Fax +90(442)2360948; E-mail: gultekin@atauni.edu.tr

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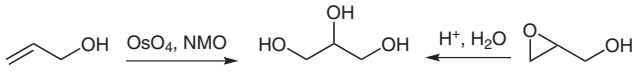
Abstract: Allylic hydroperoxides were converted into the corresponding triols in the presence of a catalytic amount of OsO_4. The present reaction involves regeneration of active osmium species by the hydroperoxide functionality and occurs in a diastereoselective manner to form triols in high yields. A plausible mechanism for the formation of 1,2,3-triols from allylic hydroperoxide is presented.

Key words: osmium tetraoxide, allylic hydroperoxide, triols, intramolecular oxygen transfer

Polyhydroxylated cyclic compounds including conduritols, inositols, allosamidin, and cyclic triols are integral parts of many important natural products and possess a wide range of important biological activities such as glycosidase inhibition.[1,2] Among the cyclitol family, triols[2,3] have attracted much attention due to the fact that they are precursors to many naturally occurring cyclitols. Triols are usually prepared by oxidation of the corresponding allylic alcohols with OsO_4 or by acid-catalyzed epoxide ring opening of epoxy alcohols (Scheme 1).[4]



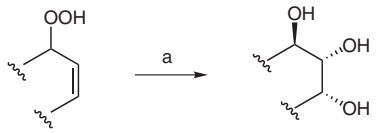
Scheme 1 Synthesis of 1,2,3-triols from allylic alcohols and epoxy alcohols

Due to the high cost and toxicity of OsO_4 and environmental concerns, there is a need to use a catalytic amount of OsO_4 with co-oxidants such as hydrogen peroxide, NMO, $NaIO_4$, or molecular oxygen.[5,6]

In an ongoing project, we have examined the *cis*-dihydroxylation of the double bond of allylic hydroperoxides with OsO_4 without added co-oxidant in water–acetone. We found that the hydroperoxide functionality in allylic hydroperoxides serves as a co-oxidant for regeneration of active osmium species. This oxidation reaction has been employed to effect the synthesis of triols via intramolecular oxygen atom transfer from allyl hydroperoxides.

Allylic hydroperoxides have been synthesized by various methods[7a] (a) from the free-radical autoxidation of olefins, initiated thermally or photolytically; (b) from the autoxidation of organometallic compounds, particularly Grignard reagents; (c) from the reaction of olefins with singlet oxygen; (d) from the solvolysis of alkenyl sulfates (prepared in situ from equimolar quantities of alcohol and sulfuric acid) in hydrogen peroxide; (e) from the solvolysis of allylic mesylates and other sulfonate esters in basic hydrogen peroxide; and (f) from the nucleophilic displacement of allyl halides with basic hydrogen peroxide.

In the initial study, all of the allylic hydroperoxides (Table 1) were synthesized by photooxygenation of the corresponding alkenes. These hydroperoxides were then treated with a catalytic amount of OsO_4 in water–acetone (1:9) solution at room temperature (Scheme 2).



Scheme 2 General reaction of the formation of 1,2,3-triols. *Reagents and conditions*: (a) OsO_4 (0.2 mmol%), H_2O–acetone (1:9), r.t.

cis-Dihydroxylation of **1**[7b,c] with a catalytic amount of OsO_4 at room temperature for 22 hours provided the corresponding *rac*-2,3-dimethylbutane-1,2,3-triol (**2a**)[4c,8,9] in high yield. The cyclic hydroperoxides **3**, **5**, **7**, and **9**, synthesized as described in the literature, were also subjected to *cis*-hydroxylation as reported above to give the *rac*-cyclopentane-1,2,3-triol (**4a**), *rac*-cyclohexane-1,2,3-triol (**6a**), *rac*-cycloheptane-1,2,3-triol (**8a**), and *rac*-cyclooctane-1,2,3-triol (**10a**, Table 1).

For characterization of the products, the triols formed were converted into the corresponding triacetates (**4b**, **6b**, **8b**, and **10b**) as reported in the literature. The comparison of the spectroscopic data of the triacetates was completely in agreement with those given in the literature.[11–17]

Treatment of *rac*-2-hydroperoxy-1,2-dihydronaphthalene (**11**)[18] with OsO_4 under the same reaction conditions gave the expected *rac*-1,2,3,4-tetrahydronaphthalene-1,2,3-triol (**12a**) in moderate yield (61%) along with a mixture of α-naphthol and β-naphthol **12b** (23%) and **12c** (16%), respectively (Scheme 3).

Our attempt to prepare the triacetate derived from triol **12a** failed due to the tendency of the initially formed triacetate to undergo an elimination reaction with base to form naphthalene derivatives.

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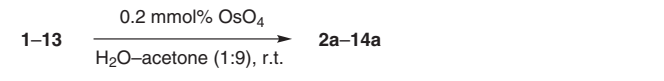
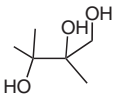
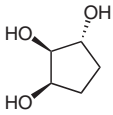
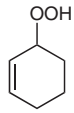
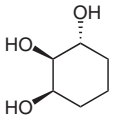
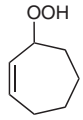
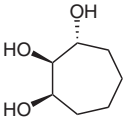
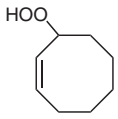
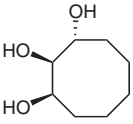
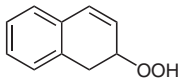
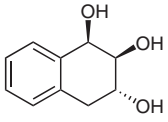
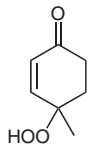
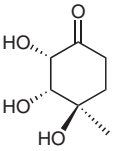
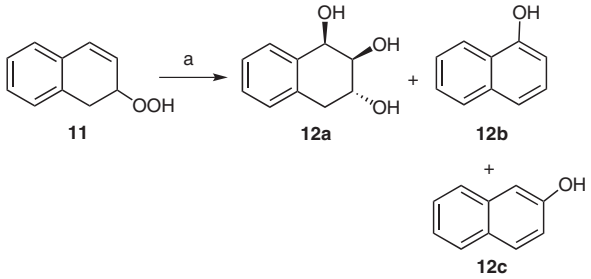
Table 1 The Triols (1,2,3) from Reactions of Allylic Hydroperoxides with a Catalytic Amount of OsO_4



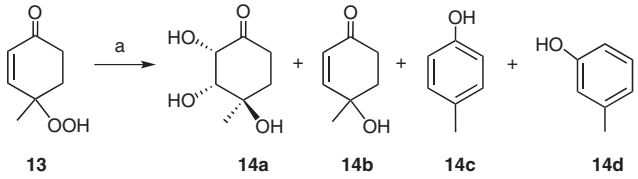
Entry	Substrate[a]	Yield (%)[b]	Triol[c]	Yield (%)[d]	Time (h)
1	 **1**[7]	99[7c]	 **2a**[4,8,9]	86	22
2	 **3**[10]	78[10b]	 **4a**[3,8,11]	84	36
3	 **5**[7a,12]	66[12c]	 **6a**[8,11,13]	94	36
4	 **7**[14]	60[14b]	 **8a**[8,15]	90	37
5	 **9**[19]	80[10b]	 **10a**[8,15,17]	82	28
6	 **11**[18]	53[18b]	 **12a**[8,19]	61	42
7	 **13**[20]	90[20a]	 **14a**[8]	30	65

[a] The references are for the allylic hydroperoxides.
[b] The references are for the isolated yields of allylic hydroperoxides.
[c] The references are for the corresponding triols.
[d] The isolated yields are for triols from allylic hydroperoxides.

Finally, we applied an OsO_4-catalyzed reaction to an alkene **13**[20a] having an electron-deficient double bond. α,β-Unsaturated ketohydroperoxide **13** was reacted with a catalytic amount of OsO_4 as described before. In contrast to the other hydroxylations, the reaction was completed over a longer time (~ 3 d) and in lower yield. Beside the expected *rac*-2,3,4-trihydroxy-4-methylcyclohexanone (**14a**, 30%), the reduction product *rac*-4-hydroxy-4-methylcyclohex-2-enone **14b**,[20a] 51%) was formed as the major product. The aromatization products, *p*-cresol (**14c**, 11%) and *m*-cresol (**14d**, 8%) were formed as the minor products. Again, the acetylation of **14a** failed due to aromatization (Scheme 4).



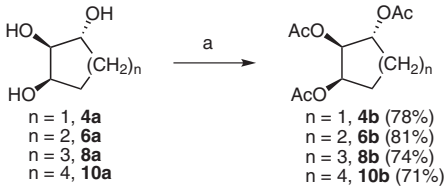
Scheme 3 Oxidation reaction of 2-hydroperoxy-1,2-dihydro-naphthalene (**11**) with a catalytic amount of OsO_4. *Reagent and conditions*: (a) OsO_4 (0.2 mmol%), H_2O–acetone (1:9), 42 h, r.t., 92%, ratios of products **12a/12b/12c** = 6.1:2.3:1.6.



Scheme 4 Oxidation reaction of α,β-unsaturated hydroperoxide **13** with a catalytic amount of OsO_4. *Reagent and conditions*: (a) OsO_4 (0.2 mmol%), H_2O–acetone (1:9), 65 h, r.t., 95%, ratios of products **14a/14b/14c/14d** = 3:5.1:1.1:0.8.

For further characterization, the triols formed (**4a**, **6a**, **8a**, and **10a**) were converted into the corresponding acetates (**4b**, **6b**, **8b**, and **10b**, respectively), the triacetates were prepared as in the literature[4a,12] (Scheme 5).

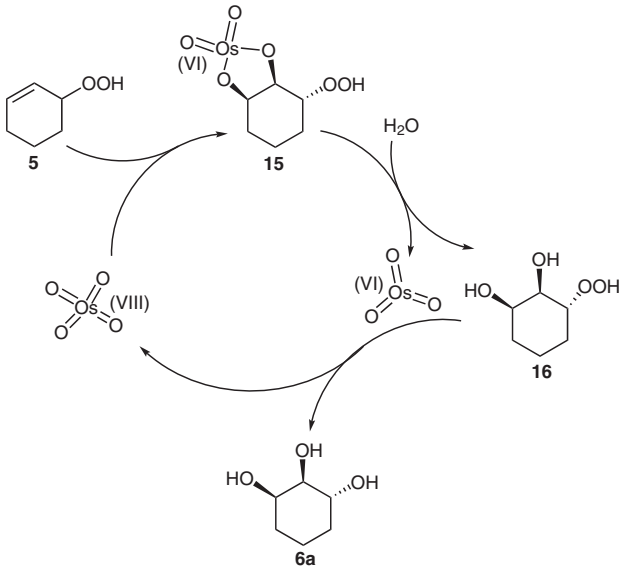
The triols (**4a**, **6a**, **8a**, **10a**, **12a**, and **14a**) were established by comparison of their spectroscopic data with those reported in the references (Table 1).



Scheme 5 Acetylation reaction of cyclic triols. *Reagent and conditions*: (a) pyridine (10 mL), 0 °C, 0.5 h, then Ac_2O (4 equiv), r.t., overnight.

When compounds **12a** and **14a** were treated with pyridine and Ac_2O at room temperature, these molecules were converted into the corresponding aromatic derivatives.

For the formation of triols we suggest the following reaction mechanism (Scheme 6). We assume that OsO_4 first undergoes a stereodirected [3+2] cycloaddition to the double bond. It is well established that the initially formed osmate ester **15** is an energetically more favorable intermediate.[21] The osmate ester **15** undergoes hydrolysis with water to give *cis*-vicinal diol and releases reduced $Os(VI)O_3$, which is reoxidized by the hydroperoxide functionality back to $Os(VIII)O_4$.



Scheme 6 Mechanism for the formation of 1,2,3-triols from allylic hydroperoxides with a catalytic amount of OsO_4

In the methodology described here, it is not necessary to use a co-oxidant. The hydroperoxide group serves as the co-oxidant and that enables the use of a catalytic amount of OsO_4 as a reagent. All of the hydroperoxides are converted into corresponding products in almost quantitative yields.

Thus, our novel triol-synthesis procedure described herein will provide a new alternative method for triols. Application of this triol-synthesis reaction will be presented, particularly in the synthesis of cyclitols in the near future.

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(8) **Typical Procedure for the Formation of Triols**
Allylic hydroperoxide (10 mmol) was dissolved in a mixture of H_2O–acetone (20 mL, 1:9) solution and OsO_4 (0.02 mmol, 5 mg) in acetone (5 mL) was added to the stirring solution of hydroperoxide. The mixture was stirred at r.t. at 22–65 h (examples in Table 1). The reaction was monitored by TLC. The solution was evaporated ($2.7 \cdot 10^{-2}$ bar, r.t.), and then the crude residue was directly purified by column chromatography on silica gel using EtOAc–hexanes as eluent to give the corresponding triols (Table 1).
***rac*-2,3-Dimethylbutane 1,2,3-Triol (2a)**
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (s, 3 H), 1.18 (s, 3 H), 1.21 (s, 3 H), 3.44 (d, *J* = 11.3 Hz, 1 H), 3.83 (d, *J* = 11.3, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 26.6, 27.2, 70.1, 77.5, 77.9 ppm.
***rac*-Cyclopentane-1,2,3-triol (4a)**
^{1}H NMR (200 MHz, CD_3OD): δ = 1.39–1.83 (m, 2 H), 1.91–2.18 (m, 2 H), 3.69–3.79 (m, 1 H), 4.01–4.12 (m, 2 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 31.5, 31.8, 74.6, 79.2, 82.7 ppm.
***rac*-Cyclopentane-1,2,3-triyl Triacetate (4b)**
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.49–1.61 (m, 1 H), 1.74–1.81 (m, 1 H), 2.02 (br s, 9 H, 3 CH_3), 2.23–2.44 (m, 2 H), 5.09–5.23 (m, 2 H), 5.28 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.5, 22.6, 22.8, 28.6, 28.8, 74.1, 77.9, 78.4, 171.8, 171.9, 172.2 ppm.
***rac*-Cyclohexane-1,2,3-triol (6a)**
^{1}H NMR (200 MHz, CD_3OD): δ = 1.20–1.87 (m, 6 H), 3.34 (dd, *J* = 2.7, 8.5 Hz, 1 H), 3.75 (m, 1 H), 4.01 (m, 1 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 21.3, 33.5, 34.9, 72.9, 73.1, 79.1 ppm.
***rac*-Cyclohexane-1,2,3-triyl Triacetate (6b)**
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.57–1.97 (m, 6 H), 2.01 (s, 3 H), 2.05, (s, 3 H), 2.19, (s, 3 H), 4.90 (dd, *J* = 3.0, 9.1 Hz, 1 H), 5.05 (m, 1 H), 5.32 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.3, 22.5, 22.8, 23.9, 29.9, 30.8, 71.9, 72.3, 74.4, 168.1, 171.8, 171.9 ppm.
***rac*-Cycloheptane-1,2,3-triol (8a)**: ^{1}H NMR (200 MHz, CD_3OD): δ = 1.45–1.88 (m, 8 H), 3.55 (dd, *J* = 2.5, 7.1 Hz, 2 H), 3.70 (m, 1 H), 3.96 (m, 1 H) ppm.^{13}C NMR (50 MHz, CD_3OD): δ = 25.4, 26.3, 33.4, 35.8, 74.6, 75.3, 82.2 ppm.
***rac*-Cycloheptane-1,2,3-triyl Triacetate (8b)**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42–1.66 (m, 8 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.97 (s, 3 H), 4.86 (dd, *J* = 2.0, 4.2, 1 H), 4.95 (m, 1 H), 5.06 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.7, 22.8, 22.9, 23.8, 24.0, 29.7, 29.9, 73.9, 74.4, 78.05, 171.8 (2 C), 171.9 ppm.
***rac*-Cyclooctane-1,2,3-triol (10a)**: ^{1}H NMR (200 MHz, CD_3OD): δ = 1.55–1.90 (m, 10 H), 3.65 (dd, *J* = 2.4, 8.5 Hz,

1 H), 3.79 (m, 1 H), 3.96 (m, 1 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 26.1, 27.8, 29.9, 34.0, 36.1, 73.8, 74.8, 80.8 ppm.

***rac*-Cyclooctane-1,2,3-triyl Triacetate (10b)**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45–2.01 (m, 10 H), 1.93 (s, 3 H), 1.96 (s, 3 H), 1.97 (s, 3 H), 4.92–5.23 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9, 24.3, 25.6, 26.5, 28.2, 29.9, 30.9, 31.7, 73.4, 75.3, 76.4, 171.8, 172.0, 172.1 ppm.

***rac*-1,2,3,4-Tetrahydronaphthalene-1,2,3-triol (12a)**: ^{1}H NMR (200 MHz, CD_3OD): δ = 7.18 (m, 4 H), 2.56–3.09 (m, 2 H), 4.64 (m, 1 H), 4.02 (m, 1 H), 3.61 (1 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 38.9, 68.9, 72.8, 76.5, 128.5, 128.9, 129.7, 130.3, 137.3, 138.5 ppm.

***rac*-2,3,4-Trihydroxy-4-methylcyclohexanone (14a)**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.22 (d, *J* = 5.7 Hz, 1 H), 3.72 (d, *J* = 5.7 Hz, 1 H), 2.22–1.84 (m, 4 H), 1.27 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.5, 36.3, 37.4, 74.5, 75.8, 79.9, 209.8 ppm.

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