Highly Regioselective and Diastereoselective Photooxygenation of \(\alpha\)-Cyclogeranyl Derivatives

Constantinos Tsangarakis, Ioannis-Panagiots Zaravinos, Manolis Stratakis*

Department of Chemistry, University of Crete, 71409 Iraklion, Greece
Fax +30(2810)393601; E-mail: stratakis@chemistry.uoc.gr

Received 5 May 2005
Dedicated to the memory of Professor C. S. Foote, a pioneer in the field of singlet oxygen chemistry.

Abstract: Methylene blue-sensitized photooxygenation of several \(\alpha\)-cyclogeranyl derivatives affords the exocyclic allylic hydroperoxides in 94–99% regioselectivity, while the diastereoselectivity varies from 50–97% de in favor of the cis isomer, depending on the substituents. By contrast, the ene reaction with N-phenyltriazolinedione affords significantly different regioselectivity and diastereoselectivity. The often fascinating regiochemistry and diastereoselection in the ene reaction of singlet oxygen (\(^1\)O\(_2\)) with olefins\(^1\) provides an attractive methodology for their selective oxyfunctionalization.\(^2\) Recently, the photooxygenation of alkenes confined in organized media, such as zeolite Y,\(^3\) has gained significant attention due to the remarkable changes in product selectivity compared to the analogous reaction in solution. It has been recognized that for the \(^1\)O\(_2\) ene reactions, steric and electronic interactions contribute significantly to the stability of the product forming transition states. For example,\(^4\) a \(^1\)O\(_2\)--hydroxy steering effect in combination with 1,3-allylic strain (steric effects) lead to remarkable threo diastereoselection in the photooxygenation of chiral allylic alcohols, while by contrast, for the analogous chiral allylic chlorides, repulsive \(^1\)O\(_2\)--halide atom interactions and 1,3-allylic strain as well lead to a highly erythro diastereoselective ene reaction. In addition, a highly diastereoselective and regiososelective ene reaction of \(^1\)O\(_2\) with chiral cyclohexadienes has been reported,\(^5\) where steric repulsions and electronic factors have control substantially the product diastereoselectivity.

In this communication we report a highly regioselective and diastereoselective ene reaction of \(^1\)O\(_2\) with \(\alpha\)-cyclogeranion (1) and its derivatives. Methylene blue-sensitized photooxygenation of 1 in CH\(_2\)Cl\(_2\) affords essentially one out of the three possible regioisomers with >97% cis-diastereoselectivity (1a), as proved by NOE experiments (Scheme 1). Irradiation of the allylic hydrogen atom next to the -OOH functionality in 1a resulted in signal enhancement of the second tertiary allylic hydrogen atom, indicative of a cis stereochemical arrangement.

SYNLETT 2005, No. 12, pp 1857–1860
Advanced online publication: 07.07.2005
DOI: 10.1055/s-2005-871573; Art ID: G15305ST
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Scheme 1 Photooxygenation of \(\alpha\)-cyclogeranion (1)

To explore further this fascinating selectivity, we prepared the \(\alpha\)-cyclogeranyl derivatives 2–7\(^6\) and performed their photooxygenation reaction. The results are presented in Table 1.\(^7\) The allylic hydroperoxides were purified and characterized after flash column chromatography of the crude reaction mixture. Alternatively, PPh\(_3\) was added to the crude reaction mixture immediately after the photooxygenation and the corresponding allylic alcohols were subsequently purified.

The reaction was >97% regioselective with exclusive formation of the ene adduct resulting from hydrogen atom abstraction from the allylic methyl group. The only exception was benzyl ether 5 who gave 5% of the tetrasubstituted allylic hydroperoxide formed by abstraction of the tertiary allylic hydrogen atom. The diastereoselectivity varied from 50–97% de, depending on the substituents X. For the case of aldehyde 4, the reaction rate was approximately an order of magnitude slower compared to 1 or 2, and the product selectivity was determined after reducing the crude reaction mixture with LiAlH\(_4\) to form the corresponding diastereomeric cis- and trans-diols, the major of which was identical with the cis-diol produced by reduction of 1a with PPh\(_3\). All major products 2a–7a exhibited NOE enhancement between the two tertiary allylic hydrogen atoms as observed in 1a, while for the minor diastereomers 3b to 7b it was absent. Adam and co-workers\(^8\) have reported very similar selectivities (90% regioselectivity and relative diastereoselection of 77% in favor of the cis isomer) in the photooxygenation of \(\alpha\)-ionone, a compound structurally related to 6 and 7. It is worthy to emphasize, that the regioselectivity in the photooxygenation of the \(\alpha\)-cyclogeranyl derivatives 1–7 represents a rare example where the so called ‘cis effect’ selectivity\(^9\) is absent.

The remarkable product selectivity can be explained considering the transition states of \(^1\)O\(_2\) attack to the double bond of the more stable conformers of the six-membered ring \(\alpha\)-cyclogeranyl skeleton presented in Scheme 2. The conformation in which the X group possesses a pseudo-
Table 1  Product Selectivity in the Photooxygenation of the α-Cyclogeranyl Derivatives

<table>
<thead>
<tr>
<th>X</th>
<th>Cis:trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CH$_2$OH (1)</td>
<td>&gt;97:3</td>
</tr>
<tr>
<td>-CH$_2$OAc (2)</td>
<td>&gt;97:3</td>
</tr>
<tr>
<td>-CH$_2$Br (3)</td>
<td>87:13</td>
</tr>
<tr>
<td>-CHO (4)</td>
<td>93:7</td>
</tr>
<tr>
<td>-CH$_2$OCH$_2$Ph (5)</td>
<td>86:14$^b$</td>
</tr>
<tr>
<td>-CH$_2$CH$_2$COCH$_3$ (6)</td>
<td>82:18</td>
</tr>
<tr>
<td>-CH$_2$CH$_2$CH$_3$ (7)</td>
<td>75:25</td>
</tr>
</tbody>
</table>

$^a$Typical reaction conditions: O$_2$ gas was bubbled through a solution of 10 mL CH$_2$Cl$_2$, containing 40 mg of each α-cyclogeranyl derivative 1-7 and the dye (10$^{-4}$ M methylene blue). After irradiation with a 300 W Xenon lamp for 30-40 minutes, the starting material had been consumed, except for the case of aldehyde 4 which gave after 60 min of reaction the allylic hydroperoxides in ca. 30% relative yield. The solvent was removed under vacuum and the oily residue was chromatographed to afford the allylic hydroperoxides, or reduced directly to the corresponding alcohols by addition of PPh$_3$ prior to chromatography. The yields for the photooxygenation of 1-3 and 5-7 were 70-75%, either the products isolated as hydroperoxides or alcohols.

$^b$The regiosomeric tetrasubstituted allylic hydroperoxide was formed in 5% relative yield, and was isolated from the product mixture by careful flash chromatography. $^1$H NMR: δ = 7.95 (br s, 1 H), 4.51 (s, 2 H), 4.21 (br t, 1 H), 3.95 (d, 1 H, J = 10.0 Hz), 3.91 (d, 1 H, J = 10.0 Hz), 1.82 (br s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

The higher degree of cis diastereoselectivity obtained in the photooxygenation of α-cyclogeraniol (1) and its acetate 2 can be rationalized in terms of an electrostatic attraction of the positively charged oxygen atom of the perepoxide intermediate and the negatively charged oxygen atom of the hydroxyl or acetate functionality (Scheme 3). This trend is also obvious for the photooxygenation of the aldehyde 4, while for the case of benzyl ether 5, steric reasons may slightly disfavor attack from the top face of conformer A, and the cis diastereoselection becomes lower.

The highly diastereoselective and regioselective photooxygenation of the α-cyclogeranyl derivatives presented herein, resembles the surprising syn-diastereoselective epoxidation of the same compounds with various oxidizing reagents, a selectivity that has been debated in terms of steric and CH–O interactions. For comparison purposes, we examined the product selectivity in the ene reaction of 1, 2 and 5, 6 with the highly reactive enophile N-phenyl-1,3,5-triazoline-2,5-dione (PTAD). The major ene product (ca. 85–90%) was formed in all cases by abstraction of the tertiary allylic hydrogen atom, while the minor product (10–15%) was the trans-exo methylene ene adduct (Scheme 4). The stereochemistry of the minor adduct was tentatively assigned as trans, by the lack of NOE enhancement between the two tertiary allylic hydrogen atoms, as observed in the case of the cis-ene adducts 1a–7a of the photooxygenation reaction.
PTAD, being significantly bulkier compared to singlet oxygen is much more sensitive to steric factors,\(^{14}\) and prefers to attack from the top face of the less stable conformer B. Orientation towards the more substituted side of the double bond to abstract the axially oriented tertiary allylic hydrogen atom leads to the major ene adduct, while most probably orientation towards the less substituted side of the same conformer leads to minor trans ene adduct (Scheme 5). By contrast, the approach of PTAD from the top face in conformer A (see Scheme 3) to abstract a hydrogen atom from the allylic methyl group is hindered from the axially oriented X group.

Scheme 5 Possible product forming transition states in the reaction of α-cyclogeranyl derivatives with PTAD

In conclusion, we have shown that the α-cyclogeranyl carbon skeleton, which appears in a variety of natural products, undergoes a selective ene reaction with singlet oxygen which may be useful for synthetic applications.

Acknowledgment

This work was supported by the European Union and the Greek General Secretariat of Research and Technology (IENEA) 2001.

References

(6) (a) Compounds 1 and 3–5 were prepared by trivial organic methodology from α-cyclogeranyl acetate (2), which was obtained by cyclization of geranyl acetate promoted by zeolite NaY. See: Tsangarakis, C.; Stratakis, M. Adv. Synth. Catal. 2005, in press. (b) Compound 6 (dihydro-α-ionone) is commercially available, while 7 was prepared from 6 by LiAlH\(_4\) reduction followed by mesylation and subsequent reduction by LiAlH\(_4\).
(7) Selected NMR data of the allylic hydroperoxides.

| Compound 1 | \(^{1}H\) NMR: δ = 9.92 (br s, 1 H), 5.25 (d, 1 H, J = 1.5 Hz), 5.08 (d, 1 H, J = 1.5 Hz), 4.43 (m, 1 H), 3.93 (t, J = 10.0 Hz), 3.86 (dd, 1 H, J = 10.0 Hz, J = 7.0 Hz), 2.23 (dd, 1 H, J = 10.0 Hz, J = 7.0 Hz), 1.82 (m, 2 H), 1.69 (m, 1 H), 1.04 (m, 1 H), 0.92 (s, 3 H), 0.88 (s, 3 H). | \(\text{^1}C\) NMR: δ = 143.13, 120.08, 84.52, 62.48, 54.29, 33.43, 29.49, 27.61, 25.74, 26.15. |
| Compound 2a | \(^{1}H\) NMR: δ = 8.97 (s, 1 H), 5.19 (d, 1 H, J = 1.5 Hz), 4.99 (d, 1 H, J = 1.5 Hz), 4.46 (dd, 1 H, J = 10.5 Hz, J = 5.5 Hz), 4.40 (br t, 1 H, J = 3.5 Hz), 4.34 (t, 1 H, J = 10.5 Hz), 2.35 (dd, 1 H, J = 10.5 Hz, J = 5.5 Hz), 2.06 (s, 3 H), 1.85 (m, 2 H), 1.61 (m, 1 H), 1.12 (m, 1 H), 0.96 (s, 3 H), 0.93 (s, 3 H). | \(^{1}C\) NMR: δ = 170.69, 142.38, 118.90, 84.40, 64.74, 50.68, 33.20, 30.26, 30.16, 27.47, 27.17, 26.02. |
| Compound 3a (as alcohol): | \(^{1}H\) NMR: δ = 5.31 (br s, 1 H), 4.88 (br s, 1 H), 4.11 (m, 1 H), 3.73 (dd, 1 H, J = 10.0 Hz, J = 3.5 Hz), 3.61 (t, 1 H, J = 10.0 Hz), 2.21 (dd, 1 H, J = 10.0 Hz, J = 3.5 Hz), 1.90 (m, 1 H), 1.57 (m, 2 H), 1.36 (m, 1 H), 1.03 (s, 3 H), 0.81 (s, 3 H). | \(^{1}C\) NMR: δ = 147.32, 110.39, 72.91, 54.54, 36.54, 34.30, 31.72, 31.20, 28.98, 22.45. |
| Compound 3b (as alcohol; representative signals): | \(^{1}H\) NMR: δ = 5.22 (br s, 1 H), 4.86 (br s, 1 H), 4.24 (m, 1 H, J = 3.5 Hz), 1.73 (dd, 1 H, J = 10.0 Hz, J = 3.5 Hz), 3.38 (t, 1 H, J = 10.0 Hz), 2.58 (dd, 1 H, J = 10.0 Hz, J = 3.5 Hz), 1.05 (s, 3 H), 0.87 (s, 3 H). | \(^{1}C\) NMR: δ = 10.04 (s, 1 H), 7.27–7.35 (m, 5 H), 5.23 (d, 1 H, J = 2.0 Hz), 5.13 (d, 1 H, J = 2.0 Hz), 4.61 (d, 1 H, J = 11.5 Hz), 4.52 (d, 1 H, J = 11.5 Hz), 4.44 (br t, 1 H, J = 4.0 Hz), 4.04 (dd, 1 H, J = 12.0 Hz, J = 9.5 Hz), 3.64 (dd, 1 H, J = 9.5 Hz, J = 7.0 Hz), 2.45 (dd, 1 H, J = 12.0 Hz, J = 9.5 Hz), 1.65–1.85 (m, 3 H), 1.03 (m, 1 H), 0.93 (s, 3 H), 0.87 (s, 3 H). |
| Compound 5b: | \(^{1}H\) NMR: δ = 9.10 (br s, 1 H), 7.27–7.37 (m, 5 H), 5.20 (br s, 1 H), 4.98 (br s, 1 H), 4.54 (dd, 1 H, J = 12.0 Hz), 4.49 (d, 1 H, J = 12.0 Hz), 4.43 (br t, 1 H, J = 4.0 Hz), 3.73 (dd, 1 H, J = 9.5 Hz, J = 3.5 Hz), 3.64 (t, 1 H, J = 9.5 Hz), 2.51 (dd, 1 H, J = 9.5 Hz, J = 3.5 Hz), 1.60–1.85 (m, 3 H), 1.21 (m, 1 H), 1.02 (s, 3 H), 0.76 (s, 3 H). | \(^{1}C\) NMR: δ = 8.63 (br s, 1 H), 5.18 (br s, 1 H), 4.82 (br s, 1 H), 4.34 (br t, 1 H, J = 4.5 Hz), 2.55 (m, 1 H), 2.43 (m, 1 H), 2.17 (m, 3 H), 1.60–1.85 (m, 6 H), 1.18 (m, 1 H), 0.92 (s, 3 H), 0.87 (s, 3 H). |
| Compound 6a | \(^{1}H\) NMR: δ = 8.63 (br s, 1 H), 5.18 (br s, 1 H), 4.82 (br s, 1 H), 4.34 (br t, 1 H, J = 4.5 Hz), 2.55 (m, 1 H), 2.43 (m, 1 H), 2.17 (s, 3 H), 1.60–1.85 (m, 6 H), 1.30 (m, 1 H), 1.01 (s, 3 H), 0.79 (s, 3 H). |
Compound 7a (selected signals): $^1$H NMR: $\delta = 8.02$ (br s, 1 H), 5.14 (br s, 1 H), 4.83 (br s, 1 H), 4.32 (dd, 1 H, $J_1 = 8.5$ Hz, $J_2 = 7.0$ Hz).

Compound 7b (selected signals): $^1$H NMR: $\delta = 7.89$ (br s, 1 H), 5.11 (br s, 1 H), 4.83 (br s, 1 H), 4.45 (br t, 1 H, $J = 5.0$ Hz).


(13) Selected NMR data of the major ene PTAD-adducts.

Compound 1 + PTAD: $^1$H NMR: $\delta = 7.38–7.57$ (m, 5 H), 4.64 (t, 1 H, $J = 6.0$ Hz), 4.16 (d, 1 H, $J = 11.5$ Hz), 4.03 (d, 1 H, $J = 11.5$ Hz), 1.92 (m, 2 H), 1.80 (s, 3 H), 1.66 (m, 1 H), 1.47 (m, 1 H), 1.07 (s, 3 H), 0.98 (s, 3 H).

Compound 2 + PTAD: $^1$H NMR: $\delta = 9.45$ (br s, 1 H), 7.37–7.53 (m, 5 H), 4.72 (t, 1 H, $J = 6.5$ Hz), 4.57 (d, 1 H, $J = 12.0$ Hz), 4.51 (d, 1 H, $J = 12.0$ Hz), 2.01 (s, 3 H), 1.93 (m, 2 H), 1.69 (s, 3 H), 1.61 (m, 1 H), 1.52 (m, 1 H), 1.00 (s, 3 H), 0.99 (s, 3 H). $^{13}$C NMR: $\delta = 171.08, 153.43, 151.72, 140.78, 131.23, 130.85, 128.99, 128.09, 125.27, 60.59, 56.52, 35.97, 34.18, 27.73, 26.87, 23.20, 20.86, 15.97.

Compound 5 + PTAD: $^1$H NMR: $\delta = 7.32–7.58$ (m, 10 H), 4.68 (t, 1 H, $J = 6.5$ Hz), 4.89 (s, 2 H), 3.94 (d, 1 H, $J = 10.0$ Hz), 3.91 (d, 1 H, $J = 10.0$ Hz), 1.92 (m, 2 H), 1.72 (s, 3 H), 1.65 (m, 1 H), 1.51 (m, 1 H), 1.04 (s, 3 H), 1.02 (s, 3 H).

Compound 6 + PTAD: $^1$H NMR: $\delta = 9.17$ (br s, 1 H), 7.36–7.53 (m, 5 H), 4.63 (t, 1 H, $J = 6.0$ Hz), 2.45 (m, 2 H), 2.29 (t, 2 H, $J = 8.0$ Hz), 2.04 (s, 3 H), 1.92 (m, 2 H), 1.63 (m, 1 H), 1.61 (s, 3 H), 1.48 (m, 1 H), 1.00 (s, 3 H), 0.99 (s, 3 H).

$^{13}$C NMR: $\delta = 208.38, 153.35, 151.52, 146.03, 131.34, 129.03, 128.16, 125.52, 123.24, 56.50, 43.26, 35.92, 35.12, 29.71, 27.87, 27.24, 23.68, 22.81, 16.36.

Compound 7 + PTAD (selected peaks): $^1$H NMR: $\delta = 8.55$ (br s, 1 H), 7.35–7.55 (m, 5 H), 4.64 (t, 1 H, $J = 6.0$ Hz), 1.63 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).