Structurally Selective Electrophilic Cyclization of $\alpha,\omega$-Hydroxygeraniol Derivatives by Mercury(II) Trifluoroacetate

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Abstract: An efficient method for the synthesis of polyfunctionalized derivatives of cyclogeraniol from $\alpha,\omega$-hydroxygeraniol derivatives by mercury(II) trifluoroacetate is described.

Key words: cyclizations, stereoselective synthesis, terpenoids, heterocycles, esters

Electrophilic cyclization has been used as an efficient synthetic procedure for the preparation of many otherwise hard-to-access terpenoids.2 The electrophilic cyclization of terpenoids by mercury trifluoroacetate or triflate-$$\text{N},\text{N}$$-dimethylaniline complex salts has been investigated. Whilst the mercury-induced electrophilic cyclization of open-chain monofunctionalized terpenoids takes place in a non-selective way with formation of mixtures of compounds,4 the cyclization of $\alpha,\omega$-bifunctionalized substrates has been less studied.

There are only a few examples of electrophilic cyclization of geraniol derivatives. In the case of 1 or 2, cyclization initiated by superacid5 or by a mercury salt,3d affords compounds 3 and 4, respectively (Scheme 1). The cyclization of the sesquiterpenic $\alpha,\omega$-bifunctionalized substrate 5, under the action of mercury trifluoroacetate was found to give rise to the drimanic compound 63c and the sesquiterpene 7, under the action of a superacid, afforded the epimeric monocyclic compounds 8 and 9.6

Taking into consideration the above findings, we report in the present paper our results on the electrophilic mercury trifluoroacetate induced cyclization of $\alpha,\omega$-bifunctionalized substrates 12–14, obtained from geraniol 10 (Scheme 2). Such electrophilic cyclization of aliphatic $\alpha,\omega$-bifunctionalized terpenoids promoted by mercury salts represents a certain synthetic interest since the possibility of replacing the mercury-containing residue by an oxygen-containing functional group4i,j opens a way to synthetically challenging cyclic terpenoids.

The cyclization of substrate 13 was performed at 0 °C with mercury(II) trifluoroacetate; the reagent was formed in situ from the reaction of mercury oxide with trifluoroacetic anhydride. Subsequent work-up with brine, led to

Scheme 1

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the exclusive formation of the mercurated compound 15 in 88% yield. The structure of 15 was determined by 1H and 13C NMR spectroscopic analysis and the NOE resonance spectrum indicated a β-orientation of both methyl groups, as well as H-2 and H-8 (Figure 1).

Interestingly, compound 15 was also obtained in good yield (74%) through mercury(II) trifluoroacetate induced cyclization of 8-hydroxygeranyl benzoate 12 under the same experimental conditions, whereas the 8-hydroxygeranyl acetate (1) has been reported to afford the monocyclic compound 4.

Subsequent reduction of the mercurated compound 15 with NaBH4/NaOH afforded the bicyclic compound 16. The NOE resonance spectrum of 16 confirmed the α-orientation of the CH2OBz-group (Figure 1).

We also examined the electrophilic mercury trifluoroacetate induced cyclization of the dibenzoate 14 (prepared from 12) and found that cyclization did indeed take place to provide the hydroxyester 18 in 56% yield. However, the dehydrated derivative was also formed, leading to a complex mixture of isomers 17.

The NOE resonance spectrum of compound 18 revealed the β-orientation of the protons at C-1 and C-3 and all NOESY correlations were in accordance with the proposed structure (Figure 1). During the reduction of the mercurated compound 18 by treatment with sodium borohydride, reduction of the ester group also occurred, affording the cyclohexanol compound 19 in 71% yield. Less intense NOE correlations were observed for this compound, which can be attributed to a less rigid conformation of the compound.

In order to rationalize the different regio- and stereochemical outcomes for the cyclization of similarly substituted geranyl derivatives, we propose the mechanism depicted in Scheme 3. Since cyclization of the E-isomer to intermediate II would not be expected to lead to the observed stereocchemistry in the final products, we have assumed that the trisubstituted alkene undergoes rapid isomerization in the presence of Hg(OOCOCF3)2. We propose that the Z-isomer is responsible for the formation of the observed cyclization products. The Z-isomer probably reacts faster than the E-isomer because a ring flip is not required prior to the ether formation through quenching of the carbocation.

According to the nucleophilicity of the OR-group, the intermediate II can react through an intermolecular attack of the oxymethyl substituent to give a bicyclic intermediate (IIa, IIb) that evolves to 15, otherwise, intermediate IIc is formed as a result of the stabilization of the carbocation by the less nucleophilic benzyol derivative. The latter intermediate suffers an intermolecular attack by water giving rise to the hydroxylated compound 18 and mixtures of the dehydration derivative 17.
In conclusion, the mercury(II) trifluoroacetate induced electrophilic cyclization of 8-hydroxygeranyl benzoate (12) and of 8-(tert-butylidimethylsilyloxy)geranyl benzoate (13) were achieved in good yield, affording, for the first time in a diastereoselective manner, the bicyclic ether compound 16 after a reduction step. The cyclization of 8-(benzoyloxy)geranyl benzoate (14) under the same conditions did not give any bicyclic compound and the mercurated cyclohexyl derivative 18 was obtained in a less stereoselective way, along with the mercurated diester 17. An effective method has thus been elaborated for the synthesis of polyfunctionalized derivatives of cyclogeraniol, which provides good synthons for the synthesis of natural terpenoids.

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Mattson Satellite FT-IR spectrometer. 1H and 13C NMR spectra were recorded in CDCl3 on Bruker Avance DPX 500 MHz, Bruker Avance 400 MHz or Bruker Avance DRX 300 MHz spectrometers; chemical shifts (δ) are reported in ppm and are referred to CHCl3 as internal standard (δ = 7.26 ppm for proton and δ = 77.0 ppm for carbon). 1H and 13C NMR assignments were confirmed by homonuclear two-dimensional correlations and DEPT experiments. HRMS data were obtained on a VG Autospec, TRIO 1000 (Fisons) instrument. The ionization mode used in mass spectra was fast atom bombardment (FAB) or chemical ionization (CI) at 70 eV. Flash column chromatography was performed using silica gel (Merck 60, 70–230 mesh). TLC was performed on Merck 60 F254 sheets. The chromatograms were sprayed with 0.1% Ce(SO4)2 in 2 N H2SO4 and heated at 80 °C for 5 min to visualize the spots. All reagents were purchased from Aldrich and used without purification unless stated otherwise. All experiments were made under nitrogen atmosphere. The work-up of the reaction mixtures in organic solvents included exhaustive extraction with EtOAc and washing with H2O up to neutral pH, drying over anhydrous Na2SO4, filtration and removal of the solvent in vacuo.

Scheme 3  Proposed reaction course for cyclization of α,ω-bifunctionalized geranyldiols 12, 13 and 14 by Hg(OOCF3)2

8-Hydroxygeranyl Benzoate (12)

Selenium dioxide (485 mg, 4.369 mmol) was added to a solution of geranyl benzoate* (Ia; 2.253 g, 8.733 mmol) in EtOH (16 mL) and refluxed for 2 h. After cooling to 0 °C, NaBH4 (83 mg, 2.184 mmol) was added and the reaction mixture was stirred at this temperature for 30 min. The reaction mixture was poured into H2O (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL) and concentrated in vacuo to give a yellow oil (2.385 g). The crude product was purified by column chromatography (SiO2, 35 g; hexane–EtOAc, 4:1) to give 8-hydroxygeranyl benzoate (12).

Yield: 865 mg (53%); colorless oil; Rf = 0.50 (EtOAc–hexane, 1:1).

1H NMR (300 MHz): δ = 8.02 (4 H, m), 7.55 (2 H, m), 7.39 (4 H, m), 5.40 (1 H, m, H-2), 5.30 (1 H, m, H-6), 4.76 (2 H, s, CH2-1), 3.98 (2 H, s, CH2-8), 2.07 (4 H, m), 1.77 (3 H, s, CH3-10), 1.63 (3 H, s, CH3-9).

13C NMR (75 MHz): δ = 167.1 (s, C-1), 142.6 (s, C-3), 135.9 (d, C-5), 132.9 (s, C-7 and C-2¢), 129.7 (d, C-3¢ and C-7¢), 128.5 (d, C-4¢ and C-6¢), 125.7 (d, C-4 and C-6), 119.0 (d, C-2), 69.2 (t, C-8), 62.0 (t, C-1), 39.2 (t, C-4), 26.1 (t, C-5), 16.9 (q, C-10), 13.9 (q, C-9).

8-(tert-Butylidimethylsilyloxy)geranyl Benzoate (13)
tert-Butylidimethylsilyl chloride (TBDMSCI; 248.0 mg, 1.645 mmol) was added to a solution of 8-hydroxygeranyl benzoate (12; 370 mg, 1.351 mmol) in anhydrous pyridine (9.0 mL) under nitrogen atmosphere. The reaction mixture was stirred at r.t. for 12 h thenaq H2SO4 (10%, 20 mL) was added. Usual work-up gave a crude reaction product (502 mg), which was purified by column chromatography (SiO2, 7 g; hexane–EtOAc, 97:3) to afford compound 13.

Yield: 435 mg (83%); colorless oil; Rf = 0.78 (EtOAc–hexane, 1:1).

IR (liquid film): 2928, 1732, 1668, 1463, 1271, 1105, 1086, 945, 836 cm−1.

1H NMR (300 MHz): δ = 7.99 (2 H, m, Bz), 7.49 (1 H, m, Bz), 7.37 (2 H, m, Bz), 5.43 (1 H, m, H-2), 5.32 (1 H, m, H-6), 4.79 (2 H, d, J = 7.0 Hz, CH2-1), 3.94 (2 H, s, CH3-8), 2.08 (4 H, m), 1.73 (3 H, s, CH2-10), 1.55 (3 H, s, CH3-9), 0.85 [9 H, s, Si(CH3)3], 0.02 [6 H, s, Si(CH3)2].
**8-Benzoxylgeranyl Benzoate (14)**

Benzoyl chloride (145 mg, 1.034 mmol) was added to a solution of 8-hydroxygeranyl benzoate (12; 150 mg, 0.547 mmol) in anhydrous pyridine (5.0 mL), under a nitrogen atmosphere. The reaction mixture was stirred for 12 h thenaq H2SO4 (10%, 15 mL) was added. usual work-up gave a crude reaction product (206 mg), which was purified by column chromatography (SiO2, 3 g; hexane–EtOAc, 49:1) to afford 8-benzoxylgeranyl benzoate (14).

Yield: 198.7 mg (96%); colorless oil; Rf = 0.66 (EtOAc–hexane, 1:1).

**IR (liquid film):** 2926, 1716, 1601, 1450, 1270 cm⁻¹.

**1H NMR (400 MHz):**
- δ = 7.96 (4 H, m, Bz), 7.44 (2 H, m, Bz), 7.24 (4 H, m, Bz), 5.42 (2 H, m, H-2 and H-6), 4.05 (2 H, d, 1H, CH2-1), 3.89 (2 H, s, CH2-8), 2.10 (2 H, m), 2.07 (2 H, m), 1.69 (3 H, s, CH3-C5), 1.58 (3 H, m, CH3-C1).

**13C NMR (75 MHz):**
- δ = 128.6 (d), 83.2 (s, C-5), 82.8 (t, C-7), 67.9 (t, CH2OBz), 59.7 (d, C-2), 56.9 (d, C-8), 47.5 (s, C-1), 41.5 (t, C-4), 27.8 (t, C-3), 19.3 (q, CH3), 19.7 (q, CH3-C5).

**HRMS-FAB:** m/z [M + H]+ calcd for C21H23O3: 323.1667; found: 323.1667.

Yield: 78.6 mg (74.5%); colorless viscous oil; Rf = 0.62 (EtOAc–hexane, 1:1).

**IR (liquid film):** 2917, 1720, 1460, 1376, 1268, 1112 cm⁻¹.

**1H NMR (300 MHz):**
- δ = 7.87 (2 H, d, J = 8.0 Hz, Bz), 7.44 (1 H, t, J = 8.0 Hz, Bz), 7.33 (2 H, t, J = 8.0 Hz, CH3-HBz), 3.98 (1 H, dd, J = 10.2, 7.5 Hz, CH3-HBz), 3.54 (1 H, d, J = 7.0 Hz, H7), 3.51 (1 H, d, J = 7.0 Hz, H8), 2.52 (1 H, dt, J = 13.5, 3.0 Hz, H-4), 2.20 (1 H, dd, J = 12.0, 7.5 Hz, H-8), 1.75 (4 H, m, H-4, H-3, H-3 and H-2), 1.58 (3 H, s, CH3-C5), 1.26 (1 H, m, H-2), 1.03 (3 H, s, CH3-C1).

**13C NMR (75 MHz):**
- δ = 128.9 (d), 82.7 (s, C-5), 82.6 (t, C-7), 67.9 (t, CH2OBz), 59.7 (d, C-2), 56.9 (d, C-8), 47.5 (s, C-1), 41.5 (t, C-4), 27.8 (t, C-3), 19.3 (q, CH3), 19.7 (q, CH3-C5).

**HRMS-FAB:** m/z [M + H]+ calcd for C21H23O3: 323.1667; found: 323.1667.

Yield: 275.1664 mg; 74.5%.

**Cyclization of 8-Hydroxygeranyl Benzoate (12)**

To a stirred suspension of dried mercury(II) oxide yellow (101 mg, 1.26 mmol) in nitromethane (14 mL) at r.t., TFAA (98 mg, 0.467 mmol) was added dropwise over 30 min. The mixture was stirred at this temperature for an additional 2 h then brine (90 mL) was added and the resulting heterogeneous solution was gradually warmed to r.t. and stirred for another 2 h. The insoluble inorganic materials were filtered, the organic layer was washed with brine to neutral, dried and filtered. Removal of the solvent gave the crude product (1.02 g), which was subjected to chromatography (SiO2, 18 g; hexane–EtOAc, 95:5 then 91:9) to give the starting compound (12) (618 mg, 2.255 mmol) in nitromethane (15 mL) was added dropwise over 30 min. The mixture was stirred at this temperature for an additional 1 h then brine (90 mL) was added and the resulting heterogeneous solution was gradually warmed to r.t. and stirred for another 2 h.

The insoluble inorganic materials were filtered, the organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine to neutral, dried and filtered. Removal of the solvent gave the crude product (1.02 g), which was subjected to chromatography (SiO2, 18 g; hexane–EtOAc, 93:7 then 9:1) to give the starting compound (12) (91.1 mg, 14.7%) and the mercury-containing compound (15) (705 mg, 73.5%) as a colorless solid [mp 69–70 °C (hexane)] the spectral data (MS, IR, 1H and 13C NMR) of which were identical with those of the compound previously obtained from 8-(tert-butyldimethylsilyloxy)geranyl benzoate (13).

**Yield:** 378.1818; 74.5%.


**8-Benzoyloxygeranyl Benzoate (14)**

Yield: 124.6 mg (56.4%); colorless solid; mp 69–70 °C (hexane); Rf = 0.51 (EtOAc–hexane, 1:1).

**IR (liquid film):** 2926, 1708, 1435, 1375, 1280, 1109 cm⁻¹.

**1H NMR (400 MHz):**
- δ = 7.95 (2 H, d, J = 7.0 Hz, Bz), 7.56 (1 H, t, J = 7.0 Hz, Bz), 7.45 (2 H, t, J = 7.0 Hz, H-7), 4.20 (1 H, t, J = 8.0 Hz, CH2-HBz), 3.98 (1 H, dd, J = 11.5, 8.0 Hz, CH3-HBz), 3.63 (1 H, d, J = 7.0 Hz, H-7), 3.52 (1 H, d, J = 7.0 Hz, H-7), 2.69 (1 H, dt, J = 13.3, 3.0 Hz, H-4), 2.54 (1 H, dd, J = 13.0, 4.0 Hz, H-2), 2.44 (1 H, dd, J = 11.5, 7.5 Hz, H-8), 2.27 (1 H, m, H-3), 2.19 (1 H, qd, J = 13.0, 4.0 Hz, H-3), 1.78 (1 H, td, J = 13.0, 5.0 Hz, H-4), 1.68 (3 H, s, CH3-C5), 1.33 (3 H, s, CH3-C1).

**13C NMR (75 MHz):**
- δ = 126.5 (s), 133.1 (d), 131.5 (s), 129.7 (d), 128.6 (d), 83.2 (s, C-5), 82.8 (t, C-7), 67.9 (t, CH2OBz), 59.7 (d, C-2), 56.9 (d, C-8), 47.5 (s, C-1), 41.5 (t, C-4), 27.8 (t, C-3), 19.3 (q, CH3-C5), 19.7 (q, CH3-C1).

**HRMS-FAB:** m/z [M + H]+ calcd for C21H23O3: 323.1667; found: 323.1667.

Yield: 78.6 mg (74.5%); colorless viscous oil; Rf = 0.62 (EtOAc–hexane, 1:1).
IR (liquid film): 3400, 2950, 1712, 1695, 1543, 1381 cm⁻¹.

¹H NMR (500 MHz): δ = 7.91 (2 H, d, J = 7.5 Hz), 7.85 (2 H, d, J = 7.5 Hz), 7.55 (1 H, t, J = 7.5 Hz), 7.40 (1 H, t, J = 7.5 Hz), 7.32 (2 H, t, J = 7.5 Hz), 7.28 (2 H, t, J = 7.5 Hz), 5.00 (1 H, dd, J = 12.0, 2.0 Hz, CH₂-C₃), 4.36 (2 H, m, CH₂-H₂-C₂ and CH₂-H₂-C₃), 4.21 (1 H, d, J = 12.0 Hz, CH₂-H₂-C₆-C₇), 2.85 (1 H, dd, J = 12.5, 4.5 Hz, H₁), 2.67 (1 H, br s, OH), 2.27 (1 H, dd, J = 6.0, 2.0 Hz, H₃), 2.07 (2 H, m, H₂-H₆), 1.91 (1 H, dt, J = 13.0, 3.0 Hz, H₅), 1.50 (1 H, m, H₅), 1.31 (3 H, s, CH₃-C₄), 1.26 (3 H, s, CH₃-C₂).

IR (liquid film): 3400, 2920, 1647, 1549, 1381 cm⁻¹.

¹³C NMR (75 MHz): δ = 167.2 (s), 166.8 (s), 133.6 (s), 133.5 (s), 130.0 (d), 129.9 (d), 129.6 (d), 128.8 (d), 128.7 (d), 128.6 (d), 73.2 (t, CH₂-C₃), 71.9 (s, C-4), 63.8 (d, C-1), 63.6 (t, CH₂-C₃), 52.5 (d, C-3), 45.3 (t, C-5), 43.9 (s, C-2), 27.3 (t, C-6), 24.4 (q, CH₃-C₄), 21.5 (q, CH₃-C₂).


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