Reaction of Dienes with Selenium Dioxide. 2. Unexpected 8-Oxa-3-selenabicyclo[3.2.1]octanes from Linalool

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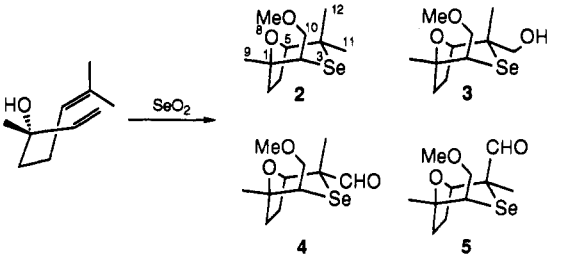
Some time ago[1] we described the reaction of linalyl acetate with SeO_2 in MeOH, which besides the expected products from allylic oxidation, gave some cyclic selenium-containing compounds. The same reaction has been carried out with linalool, but in this case, instead of the allylic oxidation products, some new selenium-containing substances were obtained. Thus, the presence of a free OH group in the molecule prevents the "ene" reaction of SeO_2 (or related species) on the Δ^2 double bond of linalool and changes the course of the double electrophilic attack to the double bonds. So, 8-oxa-3-selenabicyclo[3.2.1]-octanes are obtained through this new double cyclization process.

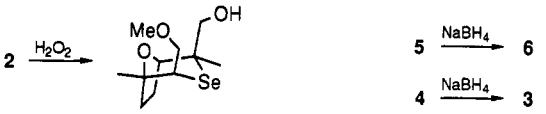
The reaction of linalool (1) with SeO_2 in MeOH was carried out under reflux as previously described for linalyl acetate.[1] After 4 h, the linalool spot was absent in TLC, and the signals of vinyl group or methyls on the double bond were not observed by NMR spectroscopy. The reaction product was a complex mixture from which components 2–5 were isolated (Scheme I). These compounds contain a Se atom, as shown by perchloric acid oxidation followed by reduction with hydrazine to metallic Se[2] and by high-resolution MS measurements.

The main component (2, 22.4%) of the reaction mixture has a molecular formula $C_{11}H_{20}O_2Se$ (HRMS two main M^+ at m/z 264.0649 and 262.0652 for the highest natural abundance isotopes ^{80}Se and ^{78}Se). Its IR, ^1H-NMR, and ^{13}C-NMR spectra indicate that the hydroxyl group is absent and the double bonds of linalool have been replaced by two C–O (76.3 and 87.4 ppm) and two C–Se (40.4 and 43.7 ppm) bonds. The presence of a methoxyl group, from the methanol used as solvent, is also observed. These data allowed us to propose the constitution depicted for 2 in Scheme I. To confirm this structure, compound 2 was oxidized with H_2O_2 in CH_2Cl_2[3] and a single reaction product was obtained (Scheme II). Its HRMS shows two molecular peaks at m/z 280.0558 and 278.0570, which correspond to a molecular formula $C_{11}H_{20}O_3Se$, in agreement with the oxidation of the cyclic selenide 2 to a selenoxide. Instead of the structural changes expected for this oxidation, the spectroscopic properties reveal the transformation of a methyl (3H, s, 1.69 ppm; 32.8 ppm) into a hydroxymethyl group (2H, AB, J = 11 Hz, 3.72 and 3.79 ppm; 69.8 ppm).

Scheme I



Scheme II



The COSY spectrum allows us to observe the aforementioned groupings, while one-bond H–C and long-range H/C two-dimensional correlations confirm the constitution 6 for the oxidation product of 2. The most relevant correlations were: H-5/C-1, which confirms the bridge between these two positions, and $-OCH_3$/C-10 or H-10/CH_3O-, which locate the methoxyl group on C-10. As a result, the Se atom must bridge positions 2 and 4. The relative stereochemistry of C-4 was deduced from the observed NOE's on H-5, H-6α, and H-12 (lower) upon irradiation of Me-11. Other NOE's observed, such as those on H-2, H-10, and H-7β when Me-9 was irradiated, are not definitive enough to deduce the stereochemistry of C-2.

The other three selenium products 3 (7.5%), 4 (2.5%), and 5 (3.1%), obtained from linalool, are very similar to 2 and its oxidation product (6). The spectroscopic data and several NOE experiments confirmed the relative stereochemistries at C-4 and also agree with the same (unknown at that moment) stereochemistry at C-2 for all these compounds. Further evidence of the structural relationships was obtained when $NaBH_4$ reduction of the aldehyde 4 afforded the alcohol 3 and similar treatment of aldehyde 5 yielded compound 6 (Scheme II).

Finally, the crystal structure obtained by X-ray diffraction of 3,5-dinitrobenzoate 7 (prepared by reaction of 3 with 3,5-dinitrobenzoic acid and dicyclohexylcarbodiimide) confirmed the proposed skeleton and the stereochemistry at C-4 and showed the β-disposition of the methoxymethyl grouping at C-2 (Figure 1).

All these compounds and the 8-oxa-3-selenabicyclo-[3,2,1]octane skeleton are described for the first time. While from linalyl acetate the main reaction products are those of allylic oxidation on the Δ^2 double bond, the substances obtained from linalool can be accounted for on the basis of the electrophilic nature of the reagent and its reactive intermediates (Scheme III), as was proposed for the minor products isolated in the treatment of linalyl acetate with SeO_2.[1,4,5]

First, there is an interaction between SeO_2 and hydroxyl groups, as it was observed with SeO_2 and methanol. Thus, the initial stage of the reaction of SeO_2 and linalool would be the formation of a selenite or a complex between the solvent, the reagent, and the substrate. The expected reaction of a selenite grouping (or a SeO_2 associate with

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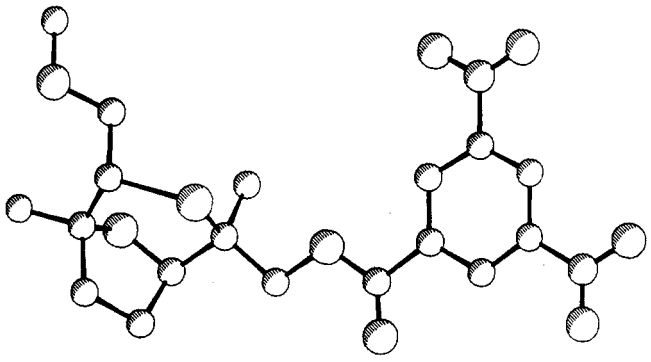

Figure 1.

the hydroxyl group) on the Δ^2 double bond would lead to allylic functionalized products, as it has been proven for other γ-hydroxy olefins.[6] In the case of linalool, the electrophilic attack of the Se atom occurred on the nearest Δ^7 double bond, followed by the entrance of MeOH on C-8. The intermediate so produced through a second electrophilic attack of the Se atom on the Δ^2 double bond would generate the selenoxides 8. Selenoxides have been reported as products from the reactions of olefinic and aromatic compounds with SeO_2.[7] Finally, the reduction[8] of these cyclic selenoxides would produce the selenite 2 as the main reaction product, as has been described for other olefins.[9] Alternatively, selenoxides 8 would undergo *syn* elimination giving the selenenic acid, which in the internal addition to the double bond would generate the oxidized products 3–5. The known *syn* elimination of selenoxides affords olefins and selenic acids that would produce an electrophilic attack in turn leading to hydroxy selenides,[10] and which in the case of cyclic selenoxides exclusively afford hydroxyl derivatives instead of the expected olefins.[11]

Although selenium reagents promote the formation of cyclic compounds from olefins,[12] this reaction is not usually produced by SeO_2. The preferential formation of allylic oxidation products and complex mixtures of selenium derivatives[13] is produced with this reagent. However, this reactivity changes in some instances[7,9] or for certain compounds such as butadiene.[14] The presence of a hydroxyl group influences the reaction of selenium reagents,[15] and in the treatment of linalool with SeO_2 drastically modifies the reaction course to the isolation of new selenium derivatives 2–5.

Experimental Section

General experimental procedures are specified in ref 1. HRMS were obtained at 70 eV (source temperature 200 °C). *J* values are given in Hz.

SeO_2 Treatment of Linalool (1). To a solution of 1 (11 g, 71 mmol) in MeOH (15 mL) was added 11 g (98 mmol) of SeO_2 in 15 mL of MeOH, and the reaction was refluxed for 4 h. After solvent removal, the crude reaction mixture was dissolved in Et_2O and washed with saturated $NaHCO_3$ solution, and water. A 13.2-g portion of the reaction product was so obtained. By flash chromatography (silica gel Merck 9385), 2.95 g of **2** (22.4%, CH_2Cl_2/Et_2O (95:5)), 0.32 g of **4** (2.5%, CH_2Cl_2/Et_2O (96:4)), 0.41 g of **5** (3.1%, CH_2Cl_2/Et_2O (96:4)), and 0.99 g of **3** (7.5%, Et_2O) were isolated. The experiment was repeated several times with the same results.

2-*exo*-(Methoxymethyl)-1,4,4-trimethyl-8-oxa-3-selenabicyclo[3.2.1]octane (2). IR (film) cm^{-1}: 1110, 1090, 945. MS: calcd for $C_{11}H_{20}O_2{}^{80}Se$ 264.0623, found 264.0649; calcd for $C_{11}H_{20}O_2{}^{78}Se$ 262.0631, found 262.0652; fragments (intensity) 126.0658 (59), 108.0127 (100). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.03 (1H, dd, J = 10.0, 7.1), 3.84 (1H, bd, J = 7.2), 3.79 (1H, dd, J = 10.0, 6.0), 3.35 (3H, s), 2.65 (1H, dd, J = 7.1, 6.0), 2.31 (1H, ddd, J = 11.0, 9.5, 5.3), 2.16 (1H, m), 2.00 (1H, ddd, J = 12.4, 11.9, 7.2, 5.3), 1.81 (1H, ddd, J = 11.9, 11.0, 4.6), 1.69 (3H, s), 1.44 (3H, s), 1.14 (3H, s). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 81.84 (1), 43.74 (2), 40.38 (4), 87.45 (5), 28.25 (6), 40.38 (7), 25.82 (9), 76.33 (10), 26.85 (11), 32.81 (12), 58.22 (OMe).

2-*exo*-(Methoxymethyl)-1,4-dimethyl-8-oxa-3-selenabicyclo[3.2.1]octane-4-*endo*-carboxaldehyde (4). IR (film) cm^{-1}: 2740, 1720, 1115, 1085, 945. MS: calcd for $C_{11}H_{18}O_3{}^{80}Se$ 278.0416, found 278.0435; calcd for $C_{11}H_{18}O_3{}^{78}Se$ 276.0424, found 276.0416; fragments (intensity) 250.0426 (21), 247.0453 (17), 232.0146 (6), 216.9952 (6), 200.0082 (25), 198.0109 (13), 185.1265 (16), 169.1207 (16), 147.0802 (34), 111.0819 (89). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.43 (1H, s), 4.28 (1H, m), 4.07 (1H, dd, J = 9.4, 7.2), 3.86 (1H, dd, J = 9.4, 6.3), 3.41 (3H, s), 2.85 (1H, dd, J = 7.2, 6.3), 2.45–2.21 (3H, m), 1.89 (1H, ddd, J = 11.9, 9.2, 6.5), 1.88 (3H, s), 1.52 (3H, s). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 82.40 (1), 44.79 (2), 53.02 (4), 82.00 (5), 29.44 (6), 39.69 (7), 25.84 (9), 76.06 (10), 198.96 (11), 24.80 (12), 58.53 (OMe).

2-*exo*-(Methoxymethyl)-1,4-dimethyl-8-oxa-3-selenabicyclo[3.2.1]octan-4-*exo*-carboxaldehyde (5). IR (film) cm^{-1}: 2740, 1725, 1110, 1080, 950. MS: calcd for $C_{11}H_{18}O_3{}^{80}Se$ 278.0416, found 278.0417; calcd for $C_{11}H_{18}O_3{}^{78}Se$ 276.0424, found 276.0402; fragments (intensity): 250.0239 (8), 246.0216 (11), 217.0832 (13), 140.0865 (52), 98.0731 (80). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.78 (1H, s), 4.40 (1H, m), 3.92 (1H, dd, J = 10.0, 6.8), 3.67 (1H, dd, J = 10.0, 6.3), 3.36 (3H, s), 2.76 (1H, dd, J = 6.8, 6.3), 2.4–2.1 (3H, m), 1.90 (1H, ddd, J = 10.2, 8.9, 7.2), 1.46 (3H, s), 1.20 3H, s). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 81.75 (1), 46.08 (2), 50.01 (4), 80.84 (5), 28.05 (6), 40.58 (7), 25.91 (9), 76.00 (10), 17.41 (11), 196.57 (12), 58.66 (OMe).

2-*exo*-(Methoxymethyl)-1,4-dimethyl-8-oxa-3-selenabicyclo[3.2.1]octan-4-*endo*-methanol (3). IR (film) cm^{-1}: 3430, 1105, 1070, 1020, 950. MS: calcd for $C_{11}H_{20}O_3{}^{80}Se$ 280.0572, found 280.0572; calcd for $C_{11}H_{20}O_3{}^{78}Se$ 278.0580, found 278.0543; fragments (intensity) 249.0350 (5), 221.0084 (19), 125.0958 (97), 109.0658 (90). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.07 (1H, d, J = 7.1), 4.02 (1H, dd, J = 10.1, 6.8), 3.80 (1H, dd, J = 10.1, 6.2), 3.59 (1H, d, J = 12.0), 3.49 (1H, d, J = 12.0), 3.36 (3H, s), 2.70 (1H, dd, J = 6.8, 6.2), 2.30 (1H, ddd, J = 10.0, 9.6, 4.8), 2.20 (1H, ddd, J = 12.4, 9.6, 3.3), 2.03 (1H, dddd, J = 12.4, 11.0, 7.1, 4.8), 1.85 (1H, ddd, J = 11.0, 10.0, 3.3), 1.77 (3H, s), 1.45 (3H, s). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 83.75 (1), 43.95 (2), 45.49 (4), 82.03 (5), 27.60 (6), 40.06 (7), 25.80 (9), 76.30 (10), 68.83 (11), 27.31 (12), 58.29 (OMe).

2-*exo*-(Methoxymethyl)-1,4-dimethyl-8-oxa-3-selenabicyclo[3.2.1]octan-4-*exo*-methanol (6). To an ice-cooled solution of 600 mg of **2** in 25 mL of CH_2Cl_2 was added 0.6 mL of 33% H_2O_2 in 20 mL of CH_2Cl_2. After 30 min at 0 °C and 2 h at room temperature the reaction mixture was washed with 10% aqueous $NaHCO_3$ and brine. By solvent removal and flash chromatography 230 mg (CH_2Cl_2/MeOH (99:1)) of **6** was isolated: IR (film) cm^{-1}: 3430, 1110, 1060, 1020, 945. MS: calcd for $C_{11}H_{20}O_3{}^{80}Se$ 280.0572, found 280.0558; calcd for $C_{11}H_{20}O_3{}^{78}Se$ 278.0580, found 278.0570; fragments (intensity) 263.0535 (64), 261.0576 (31), 249.0392 (6), 231.0001 (29), 125.0969 (100), 109.0673

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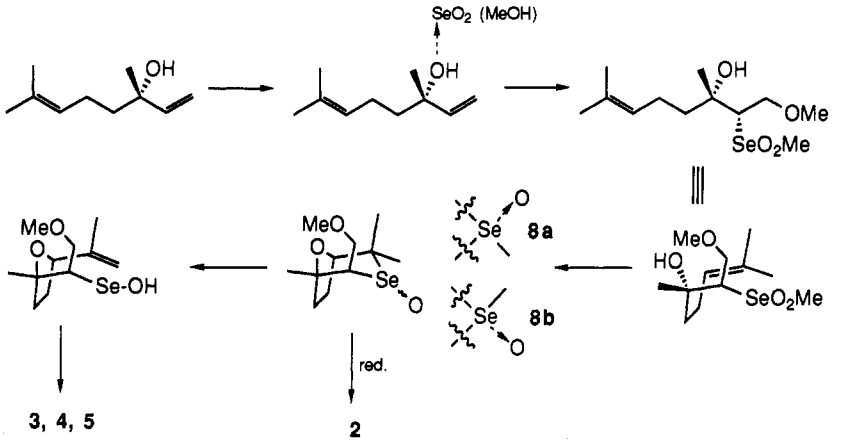
Scheme III



(71). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.18 (1H, d, J = 7.2), 3.92 (1H, dd, J = 9.9, 7.0), 3.79 (1H, d, J = 11.0), 3.72 (1H, d, J = 11.0), 3.70 (1H, dd, J = 9.9, 6.3), 3.34 (3H, s), 2.64 (1H, dd, J = 7.0, 6.3), 2.34 (1H, ddd, J = 9.9, 9.2, 5.0), 2.19 (1H, m), 2.06 (1H, dddd, J = 11.9, 10.9, 7.2, 5.0), 1.85 (1H, ddd, J = 10.9, 9.9, 4.6), 1.42 (3H, s), 1.17 (3H, s). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 81.94 (1), 44.03 (2), 46.98 (4), 81.74 (5), 27.80 (6), 40.53 (7), 25.84 (9), 76.02 (10), 21.34 (11), 69.79 (12), 58.31 (OMe).

$NaBH_4$ Reduction of Aldehydes 4 and 5. A solution of 40 mg (0.14 mmol) of **5** and 14 mg (0.37 mmol) of $NaBH_4$ in 3 mL of MeOH was stirred at room temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2 and washed with water. After solvent removal 24 mg of a compound identical (TLC, spectroscopic data) to **6** were obtained. In a similar process **4** was reduced to **3**.

Synthesis of 3,5-Dinitrobenzoate 7. A solution of 615 mg (2.9 mmol) of 3,5-dinitrobenzoic acid in 10 mL of freshly distilled THF was added to 617 mg (2.22 mmol) of **3**. After addition of 35.4 mg (0.29 mmol) of DMAP and 206 mg (2.9 mmol) of DCC, the mixture was stirred for 5 min at 0 °C and for 20 h at room temperature in argon atmosphere. Then the precipitate was filtered off and the solvent removed. After usual workup 620 mg of crude product was obtained. The esterified derivative **7** (345 mg) was isolated after flash chromatography of crude (*n*-hexane/ethyl acetate (4:1)) and crystallization in ether/CH_2Cl_2 mixtures: yellow needles; mp 150–152 °C; IR (CH_2Cl_2) cm^{-1}: 1735, 1630, 1545, 1460, 1100, 1080, 920. MS *m/z* (intensity): 474 (10), 415 (5), 332 (2), 212 (4), 195 (57), 149 (29), 138 (100), 125 (46), 109 (33). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.24 (1H, t, J = 2.1), 9.12 (2H, d, J = 2.1), 4.45 (1H, d, J = 11.3), 4.35 (1H, d, J = 11.3), 4.14 (1H, d, J = 6.7), 4.05 (1H, dd, J_1 = 10.0, 7.2), 3.83 (1H, dd, J_1 = 10.0, 5.9), 3.38 (3H, s), 2.77 (1H, t, J = 6.2), 2.37–1.95 (4H, m, H-7), 1.90 (3H, s), 1.45 (3H, s). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 25.8 (C-9), 28.0 (C-12), 28.3 (C-6), 40.1 (C-7), 42.2 (C-4), 44.5 (C-2), 58.5 (OMe), 72.3 (C-11), 76.1 (C-10), 82.4 (C-1), 83.6 (C-5), 122.6, 129.4, 133.5, 148.8, 162.1 (C-Ar), 178.1 (COO-). Anal. Calcd for $C_{18}H_{22}O_8N_2Se$: C 45.67; H 4.68; N 5.91. Found: C, 45.82; H, 4.56; N, 5.74.

Caution. Organic selenium compounds and selenium reagents must be handle with care due to their hazardous character.

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