(d, 3 H, J = 6.6 Hz), 1.6-2.0 (m, 2 H), 2.1-2.7 (m, 5 H), 3.63 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 7.78, 17.15, 27.45, 35.94, 38.69, 39.64, 51.57, 176.61, 210.71; $[\alpha]^{25}_D$ +16.8° (c 1.1, $CHCl_3$); IR ($CHCl_3$) 2960, 1735, 1715, 1165 (selected values). Anal. Calcd for $C_9H_{16}O_3$: C, 62.79; H, 9.30. Found: C, 62.68; H, 9.44. ^1H NMR ($CDCl_3$ + $Eu(hfc)_3$): δ 5.50 (s, OCH_3, minor, 0.42 H), 5.58 (s, OCH_3, major, 2.58 H).

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An Unusual Cyclization of a Homoallyl Oxyacetic Acid Dianion[1]

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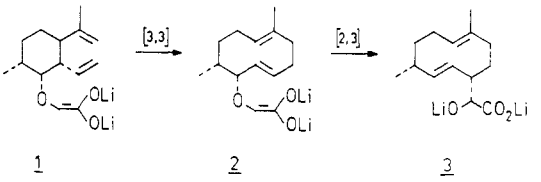
Treatment of the homoallyl oxyacetic acid **7** with excess LDA at −78 °C followed by thermolysis at 185 °C in HMPA provided the unusual cyclization product **8a**. A single-crystal X-ray structure was obtained for the derivative **8c**.

Recently in connection with projects directed toward the synthesis of germacrane sesquiterpenes,[3] we examined a strategy for the synthesis of the 1,6-cyclodecadiene **3** that involved the tandem [3,3]-[2,3]-sigmatropic rearrangement of the homoallyl oxyacetic acid dianion **1**. In this approach, the unfavorable Cope equilibrium between **1** and **2** was to be driven by the [2,3]-sigmatropic rearrangement[4] of the allyl oxyacetic acid dianion **2** to **3** (Scheme I). This strategy is related to our previously reported synthesis of 1,6-cyclodecadienes by tandem Cope-Claisen rearrangements.[5] We now wish to report the results of these studies which led to an unusual cyclization rather than the desired tandem [3,3]-[2,3] transformation.

The requisite acid **7** was prepared as shown in Scheme II. (*R*)-(−)-Carvone (**4**) was converted to **5** in 76% overall yield by reaction first with LDA and (phenylseleno)acetaldehyde and then with triethylamine and methanesulfonyl chloride, by using the procedure of Kowalski.[6] The known axial alcohol **6**[5] was prepared in 45% overall yield by a one-pot procedure which involved 1,4-reduction of **5** with 1 equiv of K-Selectride,[7] addition of 1 equiv of acetic acid, reduction of the resulting ketone with L-Selectride,[8] and workup with basic hydrogen peroxide. This procedure for the preparation of **6** was more convenient than that previously reported.[5] Reaction of **6** with excess chloroacetic acid and NaH gave **7** in 98% yield.

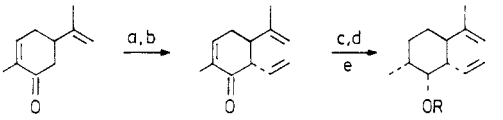
Treatment of **7** with excess LDA at −78 °C, followed by thermolysis in HMPA at 185 °C provided a new isomeric carboxylic acid as the major product. Since purification proved to be difficult, the crude reaction mixture was esterified with diazomethane and purified by flash chromatography to give a 33% yield of a methyl ester which was assigned as **8b** on the basis of NMR, IR, and MS.

Scheme I



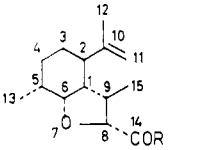
1 2 3

Scheme II[a]



4 5 6 R = H; 7 R = CH_2CO_2H

[a] (a) LDA, $PhSeCH_2CHO$; (b) MsCl, Et_3N; (c) K-Selectride, HOAc; (d) L-Selectride, H_2O_2, NaOH; (e) NaH, $ClCH_2CO_2H$.



8a R = OH
8b R = OCH_3
8c R = NHC_6H_4Br

The 500-MHz ^1H NMR of **8b** showed the isopropylidene protons as singlets at 4.75 and 4.62 ppm. An apparent triplet at 3.92 ppm was assigned to H-6, and a doublet at 3.90 ppm was assigned to H-8. The methyl ester appeared as a singlet at 3.73 ppm. A doublet of quartets at 2.22 ppm was assigned to H-9. The isopropylidene methyl appeared as a singlet at 1.67 ppm. The C-15 methyl group appeared as a doublet at 1.15 ppm, and the C-13 methyl group appeared as a doublet at 1.13 ppm.

Homonuclear decoupling studies with **8b** established the connectivity between C-8, C-9, and C-15. When H-8 was

(1) Synthesis via Sigmatropic Rearrangements. 13. For previous paper in this series see ref 5b.
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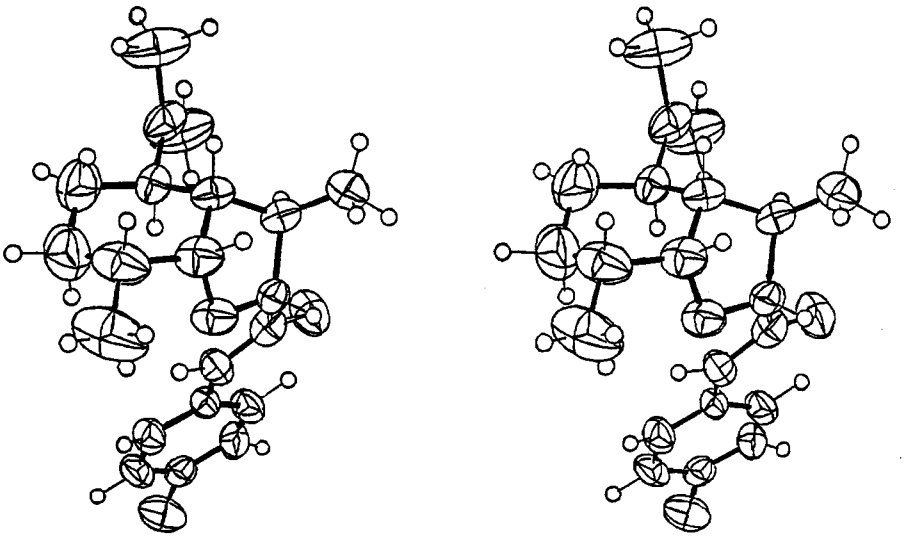

Figure 1.

irradiated, H-9 collapsed from a doublet of quartets to a quartet. When the C-15 methyl was irradiated, H-9 collapsed to doublet. A molecular model of **8b** indicates that H-1 and H-9 are nearly orthogonal, and it is noteworthy that no coupling between these protons was observed. The 2-D COSY ^{1}H NMR of **8b** showed cross peaks between H-6 and H-1, H-8 and H-9, H-1 and H-2, and H-5 and H-13.

Hydrolysis of **8b** with LiOH gave **8a**, which was identical by GC and 500-MHz ^{1}H NMR to the major carboxylic acid obtained from the thermolysis HMPA. Homonuclear decoupling experiments with **8a** also confirmed the connectivity of C-8, C-9, and C-15 by irradiation of H-8, H-9, and H-15.

A single-crystal X-ray was obtained for final structure verification. The *p*-bromoanilide **8c** was prepared by reaction of **8a** with carbonyldiimidazole and *p*-bromoaniline. The cubelike crystals of **8c** proved suitable for single-crystal X-ray analysis. The stereoview ORTEP drawing of **8c** is presented in Figure 1.

The unexpected formation of **8a** may involve the intramolecular addition of the dianion of a carboxylic acid to an unactivated olefin, or it may proceed via a radical anion mechanism. The cyclization ostensibly resembles an ene reaction in which C=C(OLi)$_2$ behaves as the enophile and is related both to the Conia reaction[9] in which an enol is the enophile and to Oppolzer's recently reported cyclizations in which an allylmagnesium moiety acts as the enophile.[10]

Experimental Section

General Procedures. ^{1}H NMR spectra were obtained on a Varian EM-360L (60 MHz) or a Bruker WM-500 (500 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker CXP 200 (50 MHz) spectrometer. Chemical shifts are reported in ppm downfield from Me_4Si, and coupling constants are reported in Hz. IR spectra were recorded on a Beckman Acculab 4. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl, and hexamethylphosphosphoric triamide (HMPA) was distilled from CaH_2. Flash chromatography was performed by the published method.[11]

(5*R*,6*S*)-2-Methyl-5-(2-propenyl)-6-ethenyl-2-cyclohexenone (5). To a solution of diisopropylamine (1.81 g, 18.1 mmol) in THF (15 mL) at −78 °C was added a 2.4 M solution of *n*-BuLi in hexane (7.2 mL, 17 mmol). The reaction was stirred for 15 min at −78 °C, and a solution of (*R*)-(−)-carvone (2.26 g, 15.0 mmol) in THF (4 mL) was added dropwise over 10 min. The reaction was stirred for 10 min at −78 °C, treated with (phenylseleno)acetaldehyde[6] (3.6 g, 20 mmol), and stirred at −78 °C for 1 h. The reaction was quenched at −78 °C by the addition of a solution of acetic acid (0.8 mL) in ether (1.2 mL) and treated with water (25 mL) and ether (25 mL). The aqueous layer was extracted with ether (3 × 25 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give a brown liquid, which was purified by flash chromatography (15% EtOAc–hexanes) to furnish the crude aldol product as a yellow liquid (4.91 g). To a solution of the crude aldol product (4.91 g) in CH_2Cl_2 (15 mL) at 0 °C was added triethylamine (5.9 g, 59 mmol) followed by methanesulfonyl chloride (5.0 g, 44 mmol). The solution was stirred at 0 °C for 35 min, diluted with cold CH_2Cl_2 (60 mL), stirred for 5 min, and then diluted with cold H_2O (50 mL). The CH_2Cl_2 layer was separated, washed with cold pH 6 phosphate buffer and cold brine, dried (K_2CO_3), and evaporated in vacuo. The residue was purified by flash chromatography (7% EtOAc–hexanes) to give the sensitive ketone **5** as a pale yellow oil (2.00 g, 11.4 mmol) in 76% overall yield from **4**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.6–1.9 (m, 6 H), 2.2–3.1 (m, 4 H), 4.7–6.0 (m, 5 H), 6.7–6.8 (s, 1 H).

(1*R*,2*S*,3*R*,6*R*)-2-Ethenyl-3-(2-propenyl)-6-methylcyclohexan-1-ol (6). To a solution of **5** (2.00 g, 11.4 mmol) in THF (15 mL) at −78 °C was added a 1.0 M solution of K-Selectride (13.7 mmol) dropwise over 10 min, and the reaction solution was stirred at −78 °C for 85 min. A solution of acetic acid (823 mg, 13.7 mmol) in THF (2 mL) was added, and the reaction was stirred at −78 °C for 1 h. A 1.0 M solution of L-Selectride (13.7 mL, 13.7 mmol) was then added, and the reaction was stirred at −78 °C for 1 h. The reaction was warmed to 0 °C, treated with 3.0 M NaOH (29.0 mL, 87 mmol), stirred at 0 °C for 30 min, treated with a 30% solution of H_2O_2 (22.0 mL), and stirred at 0 °C for 2.5 h. The reaction mixture was diluted with H_2O (50 mL) and ether (50 mL), and the aqueous layer was extracted with ether (2 × 25 mL). The combined ether extracts were washed with 10% sodium bisulfite (25 mL) and brine, dried (MgSO), and evaporated in vacuo, and the residue was purified by flash chromatography (4% EtOAc–hexanes) to give **6** as a colorless liquid (1.02 g, 5.66 mmol) in 50% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (d, *J* = 4, 3 H), 1.30–1.65 (m, 9 H), 2.11 (dd, *J* = 2, 10, 1 H), 2.40 (dt, *J* = 12, 3, 1 H), 3.72 (s, 1 H), 4.70 (s) and 4.71 (s) (total 2 H), 5.09 (d, *J* = 18, 1 H), 5.10 (d, *J* = 10.5, 1 H), 5.82 (ddd, *J* = 7.5, 10.5, 18, 1 H).

[((1*R*,2*S*,3*R*,6*R*)-2-Ethenyl-3-(2-propenyl)-6-methylcyclohexanyl)-1-oxy]acetic Acid (7). 50% NaH in mineral oil (787 mg, 18.7 mmol) was rinsed with pentane and suspended in THF (2 mL). To the NaH suspension at 0 °C was added a solution of **6** (337 mg, 1.87 mmol), chloroacetic acid (353 mg, 3.7 mmol), and ethanol (8 μL) in THF (4 mL). The ice bath was removed, and the mixture was heated at reflux for 17 h. The reaction mixture was cooled to 0 °C and quenched by the addition of H_2O

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(50 mL). The aqueous layer was washed with ether (3 × 25 mL), and the ether washes were discarded. The aqueous layer was acidified to pH 3 with 2 N HCl and extracted with ether (3 × 25 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo, and the residue was purified by Kugelrohr distillation [200 °C (0.01 mm)] to give **7** as a colorless liquid (445 mg, 1.87 mmol): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (d, J = 7, 3 H), 1.2–1.5 (m, 4 H), 1.60 (s, 3 H), 1.61–1.70 (m, 1 H), 2.1 (dt, J = 10, 2, 1 H), 2.37 (dt, J = 12, 4, 1 H), 3.53 (br s, 1 H), 4.18 (d, J = 15, 1 H), 4.20 (d, J = 15, 1 H), 4.71 (s, 1 H), 4.73 (s, 1 H), 5.05 (d, J = 10.5, 1 H), 5.09 (d, J = 18, 1 H), 5.73 (ddd, J = 9, 10.5, 18, 1 H); HREIMS calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1576.

(1*R*,2*R*,5*R*,6*R*,8*R*,9*R*)-2-(2-Propenyl)-5,9-dimethyl-8-carbomethoxy-7-oxabicyclo[4.3.0]nonane (8b). To a solution of diisopropylamine (49 mg, 0.49 mmol) in THF (0.3 mL) was added a 2.4 M solution of *n*-BuLi in hexane (0.19 mL, 0.46 mmol), and the reaction was stirred for 10 min at 0 °C. A solution of **7** (74 mg, 0.31 mmol) in THF (0.6 mL) was added, the reaction was stirred for 3 min at 0 °C, HMPA (2.5 mL) was added, the reaction mixture was heated to 185 °C, and the THF was allowed to distill off. The reaction mixture was stirred for 45 min at 185 °C and for 14 h at room temperature. The reaction mixture was diluted with H_2O (50 mL) and ether (50 mL). The aqueous layer was washed with ether (2 × 25 mL), and the ether was discarded. The aqueous layer was acidified with 2M HCl and extracted with ether (3 × 25 mL). The combined ether extracts were washed with H_2O (2 × 25 mL) and brine, dried ($MgSO_4$), and evaporated in vacuo to give crude **8a** as a yellow oil (59 mg). The crude **8a** was dissolved in ether (10 mL), treated with a solution of excess diazomethane[12] at 0 °C. The reaction solution was maintained at 0 °C for 40 min, quenched with acetic acid until the yellow color disappeared, washed with saturated aqueous $NaHCO_3$ (3 × 10 mL) and brine, dried ($MgSO_4$), and evaporated in vacuo, and the residue was purified by flash chromatography (5% EtOAc–hexanes) to afford **8b** (25.8 mg, 0.102 mmol) in 33% yield from **7**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.13 (d, J = 8, 3 H), 1.15 (d, J = 7.5, 3 H), 1.2–1.33 (m, 2 H), 1.48–1.59 (m, 2 H), 1.61–1.73 (m, 5 H), 1.95 (dt, J = 12, 3, 1 H), 2.22 (dq, J = 7.5, 4.5, 1 H), 3.73 (s, 3 H), 3.90 (d, J = 4.5, 1 H), 3.92 (t, J = 3, 1 H), 4.62 (s, 1 H), 4.75 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.04 (C-14), 147.54 (C-10), 111.70 (C-11), 83.27 (C-8), 81.13 (C-6), 51.49 (OCH_3), 49.15, 46.01, 43.15, 34.11, 31.39, 28.79, 20.36, 19.58, 18.57; IR (neat) 1775, 1750 cm^{-1}. HREIMS, calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1710.

(1*R*,2*R*,5*R*,6*R*,8*R*,9*R*)-2-(2-Propenyl)-5,9-dimethyl-8-carboxy-7-oxabicyclo[4.3.0]nonane (8a) by Hydrolysis of 8b: LiOH–H_2O (32 mg, 0.75 mmol) was added to a mixture of **8b** (19 mg) in methanol (0.75 mL) and water (0.25 mL), and the mixture was heated at reflux for 10 min, cooled to room temperature, and diluted with H_2O (25 mL) and ether (25 mL). The ether layer was extracted with 0.5 M NaOH (25 mL), the combined aqueous layers were washed with ether, and the ether washes were discarded. The aqueous layer was acidified with 2 M HCl and extracted with ether (3 × 25 mL). The ether extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give **8a** as a pale yellow liquid (19 mg): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.12 (d, J = 7.5, 3 H), 1.21 (d, J = 6, 3 H), 1.22–1.33 (m, 5 H), 1.6–1.7 (m, 4 H), 1.72–1.80 (m, 2 H), 2.45 (m, 1 H), 3.95 (d, J = 4.5, 1 H), 4.13 (t, J = 3, 1 H), 4.68 (s, 1 H), 4.79 (s, 1 H). This NMR was superimposable on the NMR of the crude acid obtained directly from the thermolysis.

(1*R*,2*R*,5*R*,6*R*,8*R*,9*R*)-4′-Bromo-2-(2-propenyl)-5,9-dimethyl-7-oxa-8-bicyclo[4.3.0]nonanemethanilide (8c). To a stirred solution of **8a** (26 mg, 0.11 mmol) in CH_2Cl_2 (0.2 mL) was added carbonyldiimidazole (18 mg, 0.13 mmol), and the solution was cooled to 0 °C, stirred for 10 min, treated with *p*-bromoaniline (23 mg, 0.13 mmol), stirred for 10 min at °C, warmed to 21 °C, and stirred for 14 h. The reaction was treated with water (25 mL) and ether (25 mL). The aqueous layer was acidified with 1 N HCl and extracted with ether (2 × 25 mL). The combined ether layers were washed with 1 N HCl (10 mL), 1 N NaOH (10 mL), and brine and dried ($MgSO_4$). The ether was remove in vacuo, and the resulting solid was purified by flash chromatography (10% EtOAc/hexanes) and crystallized from pentane to give **8c** (32 mg, 0.082 mmol) in 74% yield as colorless cubes: mp 125–128 °C; 500-MHz ^{1}H NMR ($CDCl_3$) δ 1.17 (d, J = 7, 3 H), 1.22 (d, J = 7, 3 H), 1.25–1.33 (m, 3 H), 1.62 (s, 3 H), 1.63–1.70 (m, 3 H), 1.17–1.82 (m, 1 H), 2.32–2.38 (m, 1 H), 3.92 (d, J = 5, 1 H), 4.10 (t, J = 3, 1 H), 4.58 (s, 1 H), 4.75 (s, 1 H), 7.39–7.52 (m, 4 H), 8.38–8.47 (s, 1 H).

Single-Crystal X-ray Structure Determination of 8c. Three dimensional X-ray diffraction data were collected from a colorless crystal of approximate dimension 0.2 × 0.2 × 0.2 mm on a computer-controlled, Enraf-Nonius CAD-4 diffractometer (λ = 0.71069, monochromator, maximum 2θ = 50° ω–2θ scans, scan rate 16°/min in ω, room temperature). Three reflections were recollected at intervals during the data collection to correct for radiation damage. A total of 1958 reflections were measured ($+h,+k,+l$) and averaged to give a set of 1932 unique reflections. The cell parameters, a = 12.316 (4) Å, b = 12.338 (2) Å, c = 12.741 (5) Å, were determined from a least-squares fit to 18 centered reflections. The systematic absences indicated the space group $P2_12_12_1$. Interpretation of the Patterson map located the bromine atom, which served as the initial phasing model. Additional atoms were located in subsequent Fourier and difference Fourier maps. About half of the hydrogen atoms were located in this manner and refined. The remaining hydrogen atoms were placed in their calculated positions. Positional and anisotropic thermal parameters for the non-hydrogen atoms were refined by least squares, using $1/\sigma$ weights, against 1932 reflections (1443 with $F_0 > 4\sigma$). Scattering factors used for C, N, O, and Br were those of Cromer and Mann[13] and for hydrogen were those of Stewart et al.[14] The final $R = (\sum||F_o| - |F_c||/\sum|F_o|)$ was 0.085. The final weighted R was 0.066, the goodness of fit was 3.83, and the maximum shift/error in the last cycle was 0.124. An anomalous dispersion correction was made for the bromine atom. The XRAY system[15] of crystallographic programs was used throughout the analysis. The bond lengths between the non-hydrogen atoms do not indicate any unusual characteristics within the molecule.

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Supplementary Material Available: Tables of atomic positional parameters, atomic thermal parameters, bond lengths, and bond angles for **8c** (2 pages). Ordering information is given on any current masthead page.

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