Brominative Cyclizations of Geranyl Derivatives

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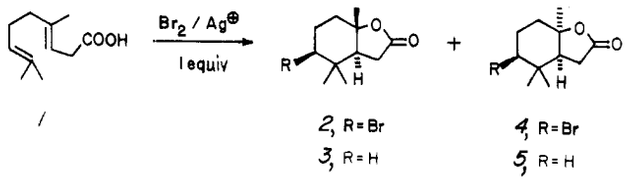
Homogeranic acid (1) and methyl geranylacetoacetate (18) were cyclized with bromine in the presence of silver fluoroborate to the brominated bicyclic compounds 2 and 19, respectively. Proton initiated cyclization competed with the brominative cyclization and gave trans lactone 3 and enol ether 20, respectively. Acid-catalyzed cyclization of 1 to 3 and isomerization of 3 to the cis lactone 5 were investigated. Both 3 and 5 were converted to the natural product dihydroactinidiolide (14).

The reaction of polyenes with a source of positive bromine has been demonstrated to provide a useful method for the incorporation of a bromine atom into various mono- and bicyclic carbon skeletons.[1] Although this transformation is of interest in view of the increasing number of newly discovered halogenated natural products of marine origin, the synthetic applicability is hampered by the low yields (<20%) of purified bromo compounds commonly obtained in this fashion. We would like to present observations which have arisen from some of our studies in this area.



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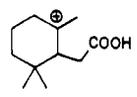
2, R = Br
3, R = H

4, R = Br
5, R = H

When homogeranic acid (1) was allowed to react with a nitromethane solution of 1 equiv each of bromine and silver tetrafluoroborate, the desired trans-fused bromo lactone 2 (11%), a trace of the cis-fused bromo lactone 4 (<1%), and the trans- and cis-fused norbromo lactones 3 (7%) and 5 (17%) were isolated after careful short column chromatography. The stereochemical assignments for 2 and 4 rest on comparison of appropriate spectral data with each other and with the known[2] trans- and cis-fused lactones 3 and 5. This is the first unambiguous establishment of a trans-fused bicyclic product in a bromine-induced cyclization, and compound 2 represents both the first brominated bicyclo[4.3.0] system and lactone to be generated via this route. That the presumably less stable isomer 2 is formed to the near exclusion of 4 is consistent with a concerted cyclization mechanism.

It is of interest to contrast this result with those of Kato and Kitahara,[3] who studied the acid-catalyzed ($SnCl_4$/benzene (1:10), room temperature, 4 h) cyclization of homogeranic acid and esters and reported the exclusive formation of the cis lactone 5. They claimed this result "suggests that the cyclization proceeds via a nonconcerted mechanism and cation [6] could be an intermediate."[3] This was surprising in view of the predominance of the trans-fused compounds 2 and 3 in the present cyclization. The reaction of 1 with a variety of acids was therefore examined in order to shed light on this apparent ambiguity and to determine if the unwanted norbromo products 3 and 5 were arising via a competing cyclization catalyzed by fluoroboric acid that was presumably being generated as the brominative cyclization proceeded. The results of these acid-catalyzed cyclizations of homogeranic acid (1) are shown in Table I and clearly indicate the following points.



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(i) Proton initiated cyclization of homogeranic acid leads to the trans-fused lactone 3 as the kinetically favored product. The trans lactone 3 then isomerizes to the thermodynamically favored cis-fused lactone 5 in the presence of both Lewis and Brönsted acids (entries 1–4, 5–9, 10–12, 15–16, and 18–20). Thus, the results of Kato and Kitahara (vide supra) do not constitute evidence for a nonconcerted reaction pathway. Their reaction conditions certainly would have promoted the 3 to 5 isomerization (cf. entries 5–9).

(ii) Both cyclization of 1 to 3 and isomerization of 3 to 5 are much more facile in nitromethane solution than in a variety of less polar solvents. Furthermore, the rate of isomerization is such that the process could have occurred to a significant extent during the course of our initial brominative cyclization of 1. It was surprising, however, that *trans*-2 to *cis*-4 isomerization of the bromo lactones had occurred to such a minute extent. Indeed, when pure 2 was treated with stannic chloride or stannic bromide in deuterionitromethane, only a slow conversion to several unidentified products, none of which was the cis bromo lactone 4, ensued. A possible rationale for the dichotomous behavior of 2 and 3 under the influence of acid catalysis is available if one assumes that opening of either trans lactone 2 or 3 leads to the planar carbonium ion 6eq (see Chart I), which can only relactonize to the cis lactone 4 or 5 via perpendicular attack on the empty p orbital by the carboxyl group of an axially disposed acetic acid side chain.[4] This necessitates a conformational conversion of 6eq to 6ax, and it is this step which interferes with the overall isomerization in the brominated series (R = Br) due to the severe 1,3-diaxial interaction in 6ax (R = Br) as well as the eclipsing interaction of the bromine and methyl group which intervenes as 6eq converts into 6ax.

(iii) Aqueous fluoroboric acid (48%) *did not* cyclize 1 to 3 or isomerize 3 to 5 in nitromethane solution at a rate that was competitive with the proton incorporation and isomerization in the brominative cyclization. It therefore seemed probable that the rate of proton initiated cyclization was very susceptible to the degree of solvation of the proton itself. That is, water "buffered" the protons in the aqueous fluoroboric acid/nitromethane mixture, thus lowering their electrophili-

Chart I

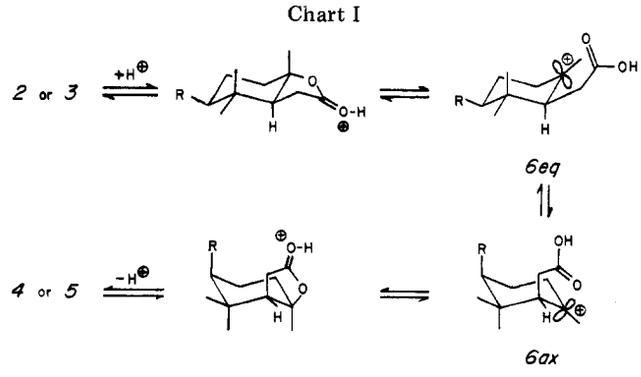


Table I. Acid-Catalyzed Cyclizations of Homogeranic Acid (1)[a]

Entry	Acid	No. of equiv	Solvent	Time	Product ratio[b] 1(S.M.) : 3(trans) : 5(cis) : other[c]			
1	$SnBr_4$ or $SnCl_4$	0.1	CD_3NO_2	5 min	0	2	1	0
2	$SnBr_4$ or $SnCl_4$	0.1	CD_3NO_2	11 min	0	1	2	0
3	$SnBr_4$ or $SnCl_4$	0.1	CD_3NO_2	1 h	0	1	6	0
4	$SnBr_4$ or $SnCl_4$	0.1	CD_3NO_2	2 h	0	0	1	0
5	$SnCl_4$	0.5	C_6D_6	2 min	6	1	Trace	0
6	$SnCl_4$	0.5	C_6D_6	6 min	5	5	1	0
7	$SnCl_4$	0.5	C_6D_6	22 min	7	4	1	0
8	$SnCl_4$	0.5	C_6D_6	2 h	0	1	1	0
9	$SnCl_4$	0.5	C_6D_6	16 h	0	1	4	0
10	$SnBr_4$	0.1	CD_3CN	11 min	7	2	1	0
11	$SnBr_4$	0.1	CD_3CN	40 min	Trace	4	3	0
12	$SnBr_4$	0.1	CD_3CN	3 h	0	2	3	0
13	$SnBr_4$	1.0	$CDCl_3$	2 days	1	4	1	0
14	$SnBr_4$	0.5	C_6D_6	40 h	4	3	2	1
15	HBF_4 (48%)	1.0	CH_3NO_2	1 min	4	1	Trace	1
16	HBF_4 (48%)	1.0	CH_3NO_2	10 min	Trace	6	1	1
17	HNO_3 (70%)	1.0	CD_3NO_2	2.5 h	4	1	0	1
18	$BF_3{\cdot}Et_2O$	0.2	$CDCl_3$	1.5 h	4	1	Trace	0
19	$BF_3{\cdot}Et_2O$	0.2	$CDCl_3$	6 h	4	4	1	0
20	$BF_3{\cdot}Et_2O$	0.2	$CDCl_3$	24 h	1	3	1	0
21	TFA		$CDCl_3$ or CD_3NO_2		No reaction			

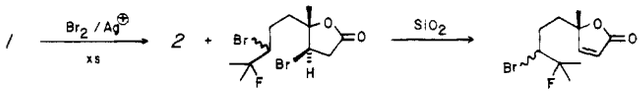
[a] All cyclizations were carried out at ambient temperatures and at concentrations of 0.1–0.2 M in 1. With the exception of entries 15 and 16, the experiments were performed directly in an NMR tube. [b] Product ratios were determined by direct comparison of the relative intensities of the three distinct methyl resonances for 1, 3, and 5 in the NMR spectra of the crude product mixtures. [c] Other unidentified products were occasionally formed as evidenced by the appearance of extraneous methyl absorptions in the crude NMR spectra.

city and ability to induce cyclization relative to the protons in the nonaqueous systems, including the bromine/silver fluoroborate/nitromethane cyclization medium.

This result led us to study the brominative cyclization under a variety of conditions (including the addition of a number of external "buffering" agents) with the hope of minimizing or eliminating the amounts of unwanted **3** and **5**, thereby increasing the yield of bromo lactone **2**. Table II summarizes the conditions which were varied in an attempt to accomplish this objective.

Shortening the reaction time in nitromethane at −10 °C (entry 2) resulted in less **3** to **5** isomerization but the same relative ratio of brominated (**2**) to nonbrominated (**3** + **5**) lactones. Lowering the temperature as well as shortening the reaction time (entries 3–5) finally allowed the reaction to be interrupted before completion. The dramatic rise in the ratio of **2** to **3** + **5** confirmed that the competing proton incorporation was resulting from acid that was being generated as the reaction proceeded. We thus reasoned that the undesired pathway might be swamped out by having excess brominating agent present throughout the course of the reaction. Indeed, when 2–10 equiv of bromine was used (entries 6–8), only small quantities of **3** and **5** were observed. Changing the solvent and/or brominating agent to systems that have been used previously by others[1] gave little or no cyclized bromo lactone (entries 9 and 10). Finally, the addition of external agents designed to buffer the electrophilicity of the protons present (entries 11–14) diminished the amounts of **3** and **5** that were formed; but in all cases, unidentified side products accompanied these attempts to increase the yield of bromo lactone **2**.

It appeared that the most straightforward solution to obtaining the desired bromo lactone **2** on a preparative scale was to use excess brominating agent. Unfortunately, when larger quantities of homogeranic acid (**1**) were cyclized in this fashion, bromo lactone **2** could be isolated in only 15% yield. No trace of **3**, **4**, or **5** was produced, but several new products appeared. Among these were the diastereomeric dibromo fluorides **7**, which underwent elimination of hydrogen bromide



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upon chromatographic purification on silica gel to give **8**, again as a mixture of roughly equal amounts of two diastereomers. Numerous examples of bromofluorination of olefins with bromine/silver fluoride are known.[5a] In one instance, silver fluoroborate has converted a vicinal dichloride to a monochloro monofluoride.[5b] The use of excess brominating agent thus served to provide only a modest improvement in the overall yield of the desired bromo lactone **2**.[6]

Before leaving this discussion of the cyclizations of homogeranic acid, we would like to report the conversion of both the cis and trans lactones **3** and **5** to the naturally occurring dihydroactinidiolide (**14**),[2c,d] which has been synthesized several times.[7] One of those syntheses involved cyclization of 2-phenylsulfonylhomogeranic acid followed by thermal extrusion of benzenesulfinic acid.[8]

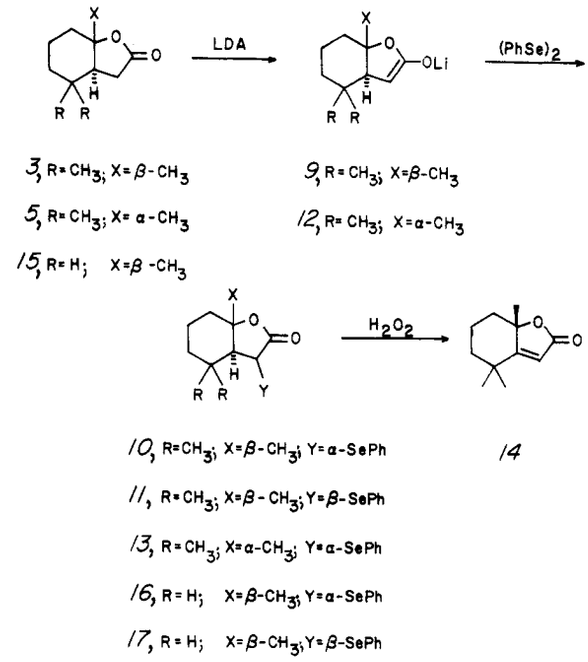
α-Phenylselenylation of the anion of trans lactone **3** with diphenyl diselenide gave a mixture of the selenides **10** and **11** in a 3:1 ratio (see Chart II). Thus, the major isomer (**10**) had arisen from attack of the diselenide on the less hindered α face of anion **9**. Oxidation of this mixture with hydrogen peroxide was followed by thermal extrusion of benzeneselenenic acid to give dihydroactinidiolide (**14**) along with several other components. Presumably, the cis elimination had occurred only from the selenoxide of isomer **10**. In a similar fashion, α-phenylselenylation of anion **12**, generated from cis lactone **5**, gave now only a single selenide, **13**. Oxidation and elimination provided dihydroactinidiolide (**14**) as virtually the sole product due to the isomeric homogeneity of **13**. It is worth noting that the conversions **3** to **10** + **11** and **5** to **13** were never efficient. It is not certain whether this was due to difficulties in generation of the hindered anion intermediates or in the subsequent reaction of these anions with diphenyl diselenide. By way of contrast, the monomethyl trans lactone **15** could be α-phenylselenylated in high yield, under the same condi-

Table II. Brominative Cyclizations of Homogeranic Acid (1)[a]

Entry	Solvent	"Br+" source	Lewis acid	No. of equiv	Temp, °C	Time	Additive (equiv)	Product ratio[b] 1(S.M.):trans Br):3(trans H):5(cis H):other[c]				
1	CH_3NO_2	Br_2	$AgBF_4$	1	−10	15 min		0	2	1	3	1
2	CH_3NO_2	Br_2	$AgBF_4$	1	−10	15 s		0	3	2	2	1
3	n-$PrNO_2$	Br_2	$AgBF_4$	1	−70	5 min		Trace	5	3	1	10
4	n-$PrNO_2$	Br_2	$AgBF_4$	1	−70	1 min		5	15	3	1	20
5	n-$PrNO_2$	Br_2	$AgBF_4$	1	−70	5 s		2	1	0	0	1
6	CH_3NO_2	Br_2	$AgBF_4$	10	−10	5 s		0	3	Trace	Trace	1
7	CH_3NO_2	Br_2	$AgBF_4$	3	−10	1 min		0	2	Trace	Trace	1
8	CH_3NO_2	Br_2	$AgBF_4$	2	−10	1 min		0	8	1	1	4
9	CH_3CN	Br_2	$AgNO_3$	1	−10	15 min		0	0	0	0	1
10	CH_2Cl_2	TBC[d]	$SnBr_4$	1	0	1 h		0	4	8	3	15
11	CD_3NO_2	Br_2	$AgBF_4$	1	−10	5 min	H_2O (5)	0	10	3	1	10
12	CD_3NO_2	Br_2	$AgBF_4$	1	−10	10 min	TMU[e] (1 or 2)	0	0	0	1	2–4
13	CH_3NO_2	Br_2	$AgBF_4$	1	−10	5 min	t-BuOH (1)	0	10	1	1	5
14	CH_3NO_2	Br_2	$AgBF_4$	1	−10	5 min	$NaHCO_3$ (10)	0	3	2	1	2

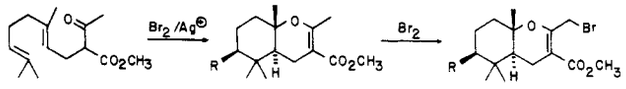
[a] Reactions were run generally on a 0.1–0.5 mmol scale. All reactions were quenched with excess sodium bicarbonate solution to halt further acid-catalyzed processes. [b] Product ratios were determined by comparison of the relative intensities of the three distinct methyl resonances for **1**, **2**, **3**, and **5** in the NMR spectra of the crude product mixtures. [c] Other unidentified products were often formed as evidenced by the appearance of extraneous methyl absorptions in the crude NMR spectra. [d] 2,4,4,6-Tetrabromocyclohexa-2,5-dienone. [e] Tetramethylurea.

Chart II

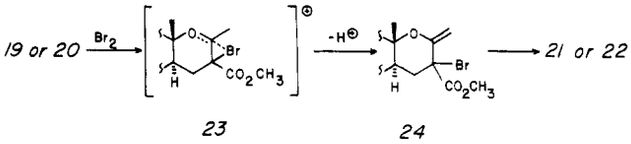


tions used for **3** and **5**, to give isomers **16** and **17** in an isomeric ratio nearly identical with that for the selenides **10** and **11**.[9]

The bromocyclization of β-keto ester **18** was also investigated. With 1 equiv of bromine/silver fluoroborate the reaction produced the brominated vinyl ether **19** (8%) and the proton cyclized enol ether **20** (22%). The latter product could be generated efficiently (83% yield) upon treatment of **18** with aqueous fluoroboric acid in nitromethane for 1 h. Use of 3 equiv of bromine/silver fluoroborate with substrate **18** eliminated the presence of **20** in the product mixture. However, the yield of **19** was not improved due to its further reaction with the excess molecular bromine to form the allylic bromide **21**. In fact, **21** or **22** could be generated from pure **19** (96%) or



20 (98%) by a rapid reaction with 1 equiv of bromine in chloroform at room temperature. These allylic brominations presumably occur via proton loss from the onium ion of partial structure **23** followed by allylic rearrangement of the allyl bromide **24**.



The conclusion to be reached from the preparative scale cyclization of both substrates **1** and **18** with excess brominating agent is that although this procedure eliminated for the most part the appearance of proton cyclized products, the excess brominating reagent provided new reaction pathways which competed with the production of the desired compounds **2** and **19**. The use of organomercurial compounds as precursors to the brominated materials is currently under investigation. Mercuric trifluoroacetate efficiently induces cationic cyclization,[10] and subsequent replacement of the carbon–mercury with a carbon–bromine bond[11] should lead to an effective solution to this problem.

Experimental Section

General Information. Melting points were determined on a Kofler hotstage and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Ariz. Column chromatography was carried out under pressure on silica gel H for TLC (EM 7736, type 60) using a modification of the short column chromatography technique.[12] Infrared spectra were recorded on Perkin-Elmer Model 237 and 257 instruments. Nuclear magnetic resonance spectra were obtained on Varian HFT-80 (proton) and XL-100 (fluorine) instruments in the Fourier transform mode. Mass spectra were determined on AEI MS-30 (electron impact, EI) and Finnigan 4000 (chemical ionization, CI) instruments.

Homogeranic Acid (1). *trans*-Geranyl bromide[13] (53.5 g, 0.25 mol) was dissolved in dry CH_3CN (200 mL). 1,4,7,10,13,16-Hexaoxacyclooctadecane (18-crown-6, 2.5 g, 9.5 mmol) was added followed by KCN (40 g, 0.615 mol). This mixture was stirred in the dark at room temperature for 6 days and filtered. Solvent removal left a residue which was triturated with 3:1 hexane/EtOAc and filtered to separate the 18-crown-6. Solvent removal left homogeranonitrile (geranyl cyanide) as a colorless oil (39 g, 0.24 mol, 96%) of sufficient purity for subsequent hydrolysis. The nitrile could be purified, if necessary, by vacuum distillation [bp 96 °C (0.5 mm) [lit.[14] bp 90–91 °C (0.2 mm)]]: NMR ($CDCl_3$) δ 1.60 (br s, 3 H), 1.68 (br s, 6 H), 2.05 (br s, 4 H), 3.03 (br d, J = 7 Hz, 2 H), 5.1 (m, 2 H); IR (neat) 2140 cm^{-1}; MS m/e (relative intensity) 163 (1), 148 (3), 69 (100).

The crude nitrile (3.5 g, 21.5 mmol) was dissolved in MeOH (27 mL), and an aqueous KOH solution [4.0 g (71 mmol) in 8 mL of H_2O] was added. The reaction mixture was refluxed for 43 h, cooled, diluted with saturated $NaHCO_3$, extracted with ether, acidified with 2 N HCl, and extracted with ether again. The final extracts were dried ($MgSO_4$), filtered, and concentrated to give crude homogeranic acid (**1**)[14] as a light brown oil (3.2 g, 17.6 mmol, 82%). The oil could be purified by elution through a short Florisil column with methylene chloride (>90% recovery): NMR ($CDCl_3$) δ 1.60 (br s, 3 H), 1.67 (br s, 6 H), 2.05 (br s, 4 H), 3.06 (br d, J = 7 Hz, 2 H), 5.04 (m, 1 H), 5.27 (br t, J = 7 Hz, 1 H); IR (neat) 2400–3600 and 1725 cm^{-1}; MS m/e (relative intensity) 182 (2), 167 (2), 69 (100).

Brominative Cyclization of 1. (A) With 1 Equivalent of Br_2/$AgBF_4$. The brominating reagent was prepared by adding Br_2 (210 μL, 3.8 mmol) to a solution of dry $AgBF_4$ (780 mg, 4.0 mmol) in dry CH_3NO_2 (15 mL) under a nitrogen atmosphere. This mixture was cooled to −10 °C, and homogeranic acid (**1**) (690 mg, 3.8 mmol) was added. The solution immediately turned yellow, and a white precipitate appeared. The reaction mixture was stirred for 20 min at −10 °C and quenched by the rapid addition of saturated $NaHCO_3$ (30 mL). This mixture was extracted with ether, and the extracts were washed (saturated NaCl), dried ($MgSO_4$), filtered, and concentrated to leave a crude brown oil (914 mg). Short column chromatography of this oil (100 g of SiO_2, 10% EtOAc/hexane elution) gave the following in order of elution: trans lactone **3**[2a] (51 mg, 0.28 mmol, 7%) [NMR ($CDCl_3$) δ 0.93, 0.96, and 1.34 (s, $3CH_3$'s), 2.00–2.56 (5 line mult, C_3CH and CH_2CO); NMR (CD_3NO_2) δ 0.96 (s, $2CH_3$'s), 1.35 (s, CH_3); NMR (CD_3CN) δ 0.94 (s, $2CH_3$'s), 1.33 (s, CH_3); NMR (C_6D_6) δ 0.43, 0.52, and 0.90 (s, $3CH_3$'s); IR (neat) 1780 cm^{-1}], cis lactone **5**[2d] (117 mg, 0.64 mmol, 17%) [NMR ($CDCl_3$) δ 0.91, 1.03, and 1.52 (s, $3CH_3$'s), 2.00–2.55 (6 line mult, C_3CH and CH_2CO); NMR (CD_3NO_2) δ 0.92, 1.07, and 1.51 (s, $3CH_3$'s); NMR (CD_3CN) δ 0.89, 1.03, and 1.50 (s, $3CH_3$'s); NMR (C_6D_6) δ 0.50, 0.56, and 1.14 (s, $3CH_3$'s); IR (neat) 1765 cm^{-1}], trans bromo lactone **2** (105 mg, 0.40 mmol, 11%), which was recrystallized from hexane/EtOAc to give an analytical sample [mp 112–113 °C; NMR ($CDCl_3$) δ 1.02, 1.08, and 1.38 (s, $3CH_3$'s), 2.05–2.56 (5 line mult, C_3CH and CH_2CO), 3.90 (dd, J = 5 and 11 Hz, CHBr); NMR (CD_3NO_2) δ 1.04, 1.08, and 1.38 (s, $3CH_3$'s), 4.07 (dd, J = 6 and 10 Hz, CHBr); IR (neat) 1770 cm^{-1}; MS m/e (relative intensity) 262 (1), 260 (1), 247 (13), 245 (14) (−CH_3), 219 (13), 217 (12), 181 (12) (−Br), 137 (72), 69 (100). Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.59; H, 6.56. Found: C, 50.62; H, 6.52.], and cis bromo lactone **4** (2 mg, <1%) [NMR ($CDCl_3$) δ 1.07, 1.20, and 1.55 (s, $3CH_3$'s), 2.04–2.15 (7 line mult, C_3CH and CH_2CO), 4.1 (br mult, CHBr); IR (neat) 1760 cm^{-1}; MS m/e (relative intensity) 262 (<1), 260 (<1), 247 (28), 245 (29) (−CH_3), 219 (11), 217 (12), 181 (44) (−Br)].

(B) With Excess Br_2/$AgBF_4$. This experiment was carried out in the same manner as the above one with the following exceptions. Silver fluoroborate (500 mg, 2.5 mmol), Br_2 (132 μL, 2.5 mmol), CH_3NO_2 (7 mL), and homogeranic acid (**1**) (145 mg, 0.80 mmol) were used. The reaction was quenched after 1 min to give the crude product (273 mg). Short column chromatography (25 g of SiO_2, 10% EtOAc/hexane elution) gave the following in order of elution: the diastereomeric dibromo fluorides **7** (23 mg, 0.067 mmol, 8%) [NMR ($CDCl_3$) δ 1.56 (d, J = 22 Hz, CH_3CF), 1.55 (s, CH_3CO), 1.54 (d, J = 22 Hz, CH_3CF), 3.02 (two overlapping ABX systems, J_{AB} = 18 Hz, J_{BX} = J_{AX} = 8 Hz, CH_2CO_2), 3.82 (br mult, $W_{1/2}$ = 16 Hz, $CH_2CHBrCF$), 4.28 (two overlapping dd, J_{XA} = J_{XB} = 8 Hz, C_3CHBr); IR ($CHCl_3$) 1785, 750 cm^{-1}; MS m/e (relative intensity) 261 (3), 259 (3), 237 (3), 235 (3), 207 (22), 205 (21), 179 (78), 177 (63%) (−$C_6H_{11}BrF$); MS m/e (CI, NH_3 reagent gas) 380 (45), 378 (100), 376 (50) (P + NH_4^+)], bromo lactone **2** (30 mg, 0.11 mmol, 15%), and the diastereomeric bromofluorobutenolides **8** (50 mg, 0.19 mmol, 24%) [NMR ($CDCl_3$) δ 1.47 (two d, J = 21 Hz, CH_3CF), 1.49, 1.50 (two s, CH_3CO), 1.52 (two d, J = 21 Hz, CH_3CF), 3.8 (br mult, $CH_2CHBrCF$), 6.0 (two d, J = 5 Hz, $CHCO_2$), 7.3 (two d, J = 5 Hz, $CH{=}CHCO_2$); IR (neat) 1760 cm^{-1}; MS m/e (relative intensity) 237 (6), 235 (6), 179 (22), 123 (20), 97 (100) (−$C_6H_{11}BrF$); MS m/e (CI, NH_3 reagent gas) 298 (100), 296 (95) (P + NH_4^+); fluorine NMR ($CDCl_3$) δ (from $CFCl_3$) 137.975 (8 line m, J = 21 Hz) and 138.062 (8 line m, J = 21 Hz). A fluorine decoupling experiment confirmed the magnitude of J_{HF}'s in the proton NMR spectrum. Compound **8** was not present in the crude reaction product before SiO_2 chromatography (NMR analysis).

Dihydroactinidiolide (14) from Trans Lactone 3. Trans lactone **3** (51 mg, 0.28 mmol) was converted into the anion **9** by reaction with lithium diisopropylamide (LDA) (0.34 mmol, 1.2 equiv) at −78 °C for 30 min in dry THF (1.5 mL) under nitrogen. A THF solution (1 mL) of diphenyl diselenide (105 mg, 0.34 mmol) and HMPA (60 μL, 0.34 mmol) was added. The reaction proceeded at −78 °C for 0.5 h and then at −35 °C for 0.5 h before being quenched with 0.1 N HCl. The solution was extracted with ether, and the extracts were washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated to give a crude oil. Purification by preparative TLC (2 × 200 × 200 mm SiO_2 plate, 20% EtOAc/hexane) gave a colorless oil (55 mg, 0.16 mmol, 59%) which proved to be a 3:1 mixture of selenides **10** and **11**: NMR ($CDCl_3$) (for **10**) δ 0.98, 1.25, and 1.36 (s, $3CH_3$'s), 1.95 (d, J = 14 Hz, C_3CH), 3.85 (d, J = 14 Hz, CHSe), 7.3, 7.7 (mult, ArH); NMR ($CDCl_3$) (for **11**) δ 1.08, 1.29, and 1.60 (s, $3CH_3$'s), 2.29 (d, J = 8 Hz, C_3CH), 3.76 (d, J = 8 Hz, CHSe), 7.3, 7.7 (mult, ArH); IR (neat) 1770 cm^{-1}; MS m/e (relative intensity) 338 (15), 137 (66) (−CO_2–SePh); calcd for $C_{17}H_{22}O_2{}^{80}Se$, 338.0783; found, 338.0800.

This mixture (50 mg, 0.14 mmol) was dissolved in THF (5 mL), cooled to 0 °C under nitrogen, and oxidized with 30% H_2O_2 (150 μL, 1.3 mmol) in the presence of AcOH (500 μL). After 1.5 h at 0 °C, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with Et_2O. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to leave a crude oil (27 mg, 0.15 mmol, 94%) whose major component was dihydroactinidiolide (NMR analysis). This material was purified by preparative TLC (SiO_2, 20% EtOAc/hexane) to give a colorless oil (10 mg, 37% recovery) whose spectral data were identical with those reported[2c,d] for the naturally occurring material.

Dihydroactinidiolide (14) from Cis Lactone 5. This procedure was the same as that reported above for the trans lactone **3** with the following exceptions. Cis lactone **5** (156 mg, 0.86 mmol), LDA (1.0 mmol), THF (4 mL), diphenyl diselenide (321 mg, 1.0 mmol), and HMPA (180 μL, 1.0 mmol) were the quantities used. Anion formation proceeded for 1.3 h at −78 °C. The crude product was purified by short column chromatography (5% EtOAc/hexane elution) and provided selenide **13** (92 mg, 0.27 mmol, 32%) as a white solid which was recrystallized from hexane to provide an analytical sample: mp 88–89 °C; NMR ($CDCl_3$) δ 1.02, 1.22, and 1.37 (s, $3CH_3$'s), 1.98 (d, J = 10 Hz, C_3CH), 3.63 (d, J = 10 Hz, CHSe), 7.3, 7.7 (mult, ArH); IR ($CHCl_3$) 1760 cm^{-1}; MS m/e (relative intensity) 338 (73), 137 (100) (−CO_2–SePh); calcd for $C_{17}H_{22}O_2{}^{80}Se$, 338.0628; found, 338.0676. Anal. Calcd: C, 60.53; H, 6.57. Found: C, 60.52; H, 6.65.

Oxidation of **13** (88 mg, 0.26 mmol) with 30% H_2O_2 (260 μL, 2.3 mmol) in THF (5 mL) containing AcOH (880 μL) at 0 °C for 1.5 h and at room temperature for 3 h gave, after workup as above, dihydroactinidiolide (**14**) (46 mg, 0.25 mmol, 98%).

Methyl Geranylacetoacetate (18). Methyl acetoacetate (2.6 g, 22 mmol) was added to LiH (190 mg, 24 mmol) in dry DMF (50 mL), and the mixture was stirred at room temperature under nitrogen for 0.5 h. Geranyl bromide (5.0 g, 24 mmol) was added, and the mixture was stirred for 3.5 h. The mixture was then diluted with pentane, washed with H_2O (3×) and brine, dried ($MgSO_4$), filtered, and concentrated to give **18** as a pale yellow oil (4.8 g, 19 mmol, 86%) which was vacuum distilled, bp 115–120 °C (0.5 mmHg). An analytical sample was obtained by preparative gas chromatography (10% Carbowax): NMR ($CDCl_3$) δ 1.6 (br s, $2CH_3C{=}C$'s), 1.67 (br s, $CH_3C{=}C$), 2.0 (br s, $2CH_2C{=}C$'s), 2.21 (s, CH_3CO), 2.53 (br t, J = 7 Hz, $C{=}CHCH_2CHC_2$), 3.42 (t, J = 7 Hz, $CH(CO)_2$), 3.70 (s, CO_2CH_3), 5.0 (mult, $2HC{=}C$'s); IR (neat) 1750, 1720 cm^{-1}; MS m/e (relative intensity) 252 (1), 209 (3) (−$COCH_3$), 136 (16) (−$C_5H_8O_3$). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.81.

Bromocyclization of Methyl Geranylacetoacetate (18). Keto

ester **18** (900 mg, 3.6 mmol) was added to a dry CH_3NO_2 (10 mL) solution of $AgBF_4$ (700 mg, 3.6 mmol) and Br_2 (570 mg, 3.6 mmol) at −10 °C under nitrogen. The initially orange solution quickly turned yellow, and a white precipitate appeared. After being stirred for 10 min, the reaction mixture was worked up as for the other bromocyclizations to leave a brown oil (1.15 g). Short column chromatography (125 g of SiO_2, 10% EtOAc/hexane) gave the unbrominated enol ether **20** (200 mg, 0.79 mmol, 22%), which was purified by preparative gas chromatography (10% Carbowax) to give an analytical sample [NMR ($CDCl_3$) δ 0.85, 0.97, and 1.16 (s, $3CH_3$'s), 2.17 (t, J = 1.5 Hz, $CH_3C{=}C$), 3.67 (s, CO_2CH_3); IR (neat) 1705, 1615 cm^{-1}; MS m/e (relative intensity) 252 (22). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.47; H, 9.49.], and the bromo enol ether **19** (100 mg, 0.30 mmol, 8%), which was recrystallized from CH_3OH to provide an analytical sample [mp 108–111 °C; NMR ($CDCl_3$) δ 0.98, 1.14, and 1.17 (s, $3CH_3$'s), 2.17 (t, J = 1.5 Hz, $CH_3C{=}C$), 3.67 (s, CO_2CH_3), 3.93 (dd, J = 10 and 5 Hz, CHBr); IR (KBr) 1700, 1625 cm^{-1}; MS m/e (relative intensity) 332 (4), 330 (4), 251 (13) (–Br). Anal. Calcd for $C_{15}H_{23}O_3Br$: C, 54.39; H, 7.00; Br, 24.12. Found: C, 54.39; H, 7.18; Br, 24.28.].

Acid-Catalyzed Cyclization of Methyl Geranylacetoacetate (18). Keto ester **18** (1.0 g, 4.0 mmol) was dissolved in dry CH_3NO_2 (7 mL) and treated at room temperature with 50% aqueous HBF_4 (700 μL, 4.0 mmol). After 1 h, saturated $NaHCO_3$ was added and the mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give the bicyclic ester **20** (0.83 g, 3.3 mmol, 83%) as a pale yellow oil which was greater than 95% pure by NMR analysis.

Allylic Brominations of 20 and 19. Ester **20** (24 mg, 0.096 mmol) was dissolved in $CDCl_3$ (0.5 mL), and 1 equiv of Br_2 as a 1% solution in CCl_4 was added. The solution rapidly decolorized and was then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to yield the allylic bromide **22** (31 mg, 0.094 mmol, 98%) as a colorless oil: NMR ($CDCl_3$) δ 0.86, 0.98, and 1.18 (s, $3CH_3$'s), 3.73 (s, CO_2CH_3), 4.00 (br d, J = 9 Hz, C**H**HBr), 4.75 (d, J = 9 Hz, CH**H**Br); IR (neat) 1705, 1615 cm^{-1}; MS m/e (relative intensity) 332 (2), 330 (3), 251 (28) (–Br); calcd for $C_{15}H_{23}O_3{}^{81}Br$, 332.0810; found, 332.0813.

In an entirely analogous fashion the bromo ester **19** was brominated to give the dibromide **21** in 97% yield: NMR ($CDCl_3$) δ 0.99, 1.15, and 1.21 (s, $3CH_3$'s), 3.73 (s, CO_2CH_3), 3.9 (mult, C_2CHBr), 4.00 (br d, J = 10 Hz, C**H**HBr), 4.75 (d, J = 10 Hz, CH**H**Br); IR ($CHCl_3$) 1700, 1620 cm^{-1}; MS m/e (relative intensity) 412 (4), 410 (9), 408 (5), 331 (56), 329 (57) (–Br), 249 (15) (–HBr_2); calcd for $C_{15}H_{22}O_3{}^{81}Br_2$, 411.9896; found, 411.9874.

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Registry No.—**1,** 459-85-8; **2,** 66901-56-2; **3,** 37531-07-0; **4,** 66901-57-3; **5,** 37531-06-9; **7** (isomer I), 66901-58-4; **7** (isomer II), 66901-59-5; **8** (isomer I), 66901-60-8; **8** (isomer II), 66901-61-9; **9,** 66901-62-0; **10,** 66901-63-1; **11,** 66901-64-2; **13,** 66901-65-3; **14,** 15356-74-8; **18,** 51933-45-0; **19,** 66901-67-5; **20,** 66901-68-6; **21,** 66901-69-7; **22,** 66901-70-0; *trans*-geranyl bromide, 6138-90-5; homogeranonitrile, 21677-96-3; diphenyl diselenide, 1666-13-3; methyl acetoacetate, 105-45-3.

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