NMR δ 3.67 (s, 2 H) [3.64 (AB q, 2 H, J = 16.6 Hz)], 2.43 (dt, 1 H, J = 4.2, 15.0 Hz) [2.61 (dt, 1 H, J = 4.2, 15.0 Hz), 2.12–1.10 (m, 6 H), 1.02 (s, 3 H) [1.07 (s, 3 H)], 0.98 (s, 3 H) [0.92 (s, 3 H)], 0.90 (s, 3 H); ^{13}C NMR δ 172.4, 101.0, [101.6], 55.6 [54.6], 49.4 [49.0], 47.7, 45.6 [45.1], 33.3 [31.9], 29.6 [31.6], 26.5, 20.5, 20.3 [21.0], 11.6 [9.8]. Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.67; H, 8.01. Found: C, 63.74; H, 7.91.

Hydrolysis and Cyclization of 5b. In exactly the same manner as described above for **5a**, ester **5b** was converted to **6b** (53%). Gas chromatographic analysis of (column B) **6b** again showed two peaks. The NMR spectra clearly indicated the presence of two diastereomers in a ratio of 3:2: ^{1}H NMR δ 4.10 (q, 1 H, J = 7.3 Hz) [3.95 (q, 1 H, J = 7.0 Hz)], 2.65–1.60 (m, 7 H), 1.54 (d, 3 H, J = 6.9 Hz) [1.55 (d, 3 H, J = 7.0 Hz)], 0.97 (s, 3 H) [1.04 (s, 3 H)], 0.93 (s, 3 H) [0.99 (s, 3 H)], 0.91 (s, 3 H) [0.90 (s, 3 H)]. Anal. Calcd for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.38. Found: C, 64.47; H, 8.26.

Preparation and Hydrolysis of 5c. In the same manner as described for the preparation of **5a**, thione 1 was alkylated with ethyl 2-bromophenylacetate to afford, after chromatography (20% ether in petroleum ether as eluant), a 62% yield of **5c** as a 1:1 mixture of diastereomers. The major impurity was diethyl 2,3-diphenylfumarate: ^{1}H NMR δ 7.6–7.1 (m, 5 H), 5.60 (dd, 1 H, J = 16.3, 3.3 Hz), 4.84 (d, 1 H, J = 19.6 Hz), 3.70 (m, 2 H), 2.41 (m, 1 H), 1.90–0.65 (m, 13 H).

Hydrolysis of **5c** according to the method outlined for **5a** and **5b** led to a mixture of compounds. The NMR of this mixture showed only two absorptions in the region of 5.0–6.0. Therefore it can be stated that only two of the four possible stereoisomers of **6c** were formed.

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Registry No. 1, 53402-10-1; **2b**, 623-73-4; **4a**, 105-36-2; (±)-**4b**, 41978-69-2; (±)-**4c**, 2216-90-2; **5a**, 59056-16-5; **5b** (isomer 1), 119593-80-5; **5b** (isomer 2), 119717-06-5; **5c** (isomer 1), 119593-83-8; **5c** (isomer 2), 119677-24-6; **6a** (isomer 1), 119593-81-6; **6a** (isomer 2), 119677-22-4; **6b** (isomer 1), 119593-82-7; **6b** (isomer 2), 119677-23-5; **6c** (isomer 1), 119593-84-9; **6c** (isomer 2), 119677-25-7.

Synthesis of Pelargonic (Nonanoic) and Margaric (Heptadecanoic) Acid Methyl Esters from 1,3-Butadiene[1]

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Introduction

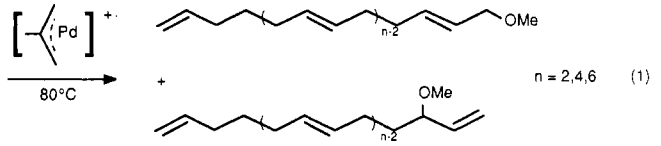
Fatty acids and their derivatives (esters, alcohols, amines) are important chemicals which mostly originate from natural oil and fats except for fatty alcohols which are produced synthetically.[2]

Synthetic fatty acids are available by ethylene oligomerization (Alfen[3] and Shop[4] processes) followed by various oxo processes (hydroformylation, hydrocarbonylation, ...).[5] These methods afford a distribution of linear fatty acids with odd carbon numbers which are often contaminated by less valuable regioisomers.

The preparation of a specific linear carboxylic acid can be achieved by applying the above-mentioned oxo methods to a particular olefin[5,6] and by various chemical methods,[7] the most valuable of which being the oxidative cleavage of the carbon–carbon double bond of a terminal olefin by neutral permanganate under phase-transfer conditions.[8] However, these methods require the synthesis or the separation of a given starting olefin.

We report here an alternative synthesis, based on 1,3-butadiene, of two useful linear carboxylic esters and hence carboxylic acids, namely, pelargonic and margaric acid methyl esters, through a telomerization–carbonylation–hydrogenation sequence.

We previously described that mixtures of 1,3-butadiene and methanol can be easily transformed, with the aid of a cationic palladium catalyst, to telomers with an even number of butadiene units, with predominant formation of C_8 (n = 2; 20%) and C_{16} (n = 4; 34%) telomers (eq 1).[9]



From the reaction mixture, we were able to separate a C_8 fraction which contained 1-methoxyocta-2,7-diene (**1**) (90%) and 3-methoxyocta-1,7-diene (**2**) (10%) and a C_{16} fraction which consisted of 1-methoxyhexadecatetraene **3** (8%), 3-methoxyhexadeca-1,6,10,15-tetraene (**4**) (87%), and a hexadecapentaene (5%) (see Experimental Section).

We therefore envisioned that the carbonylation of these allylic ethers, followed by a hydrogenation step, could be a simple way to produce the corresponding saturated esters (eq 2). Carbonylation of allylic derivatives can be performed by using cobalt,[10] iron,[10] rhodium,[11,12] nickel,[10,13–15] platinum,[11,16] and mainly palladium[11,17–28] catalysts and has

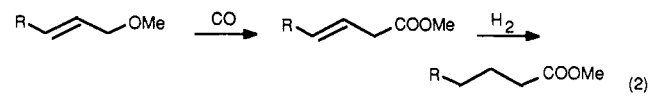


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Table I. Carbonylation of Mixtures of Allylic Ethers 1 + 2[a]

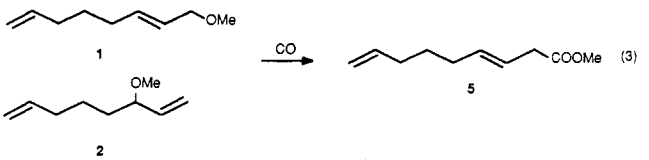
expt	catalyst precursor (mmol)	solvent (mL)	temp, °C	CO pressure, atm	reactn time, h	5,[b] %
1	$Pd(dba)_2$ (0.17) PPh_3 (0.17)	MeOH (2)	80	20	20	0
2	$Pd(dba)_2$ (0.34) PPh_3 (1.33)	MeOH (2) PhMe (8)	80	20	20	0
3	$Pd(dba)_2$ (0.34) PPh_3 (1.33)	PhMe (8)	120	20	20	0
4	$Pd(OAc)_2$ (0.33) PPh_3 (1.33)	MeOH (2) PhMe (8)	120	20	20	0
5	$Pd(OAc)_2$ (0.33) PPh_3 (1.33)	PhMe (8)	120	20	20	10
6	$Pd(OAc)_2$ (0.33) PPh_3 (1.33)	PhMe (8)	120	60	20	0
7	$Pd(OAc)_2$ (0.33) PPh_3 (1.33)	PhMe (8)	150	20	20	0
8	$PdCl_2$ (1.0)	MeOH (2) PhMe (8)	100	30	20	12
9	6 (0.5)	CCl_4 (8) PhMe (8)	100	30	20	25
10	6 (0.5)	CCl_4 (8) MeOH (8)	100	30	20	0
11	6 (0.5)	CCl_4 (8) PhMe (8)	120	30	20	10
12	6 (0.5)	CCl_4 (8) PhMe (8)	100	40	40	50
13	6 (0.5)	MeOH (8)	100	30	20	9
					50	28
14	6 (0.5)	PhMe (8)	100	30	50	52
					90	72
					190	80
15	6 (0.5)	PhMe (8)	120	30	20	17
					90	34

[a] All reactions were carried out with 50 mmol of 1 + 2. [b] Yields were determined by GC analysis.

already been reported in the case of chlorides,[11,13-15,17-19,27] alcohols,[11,16,17,19,23] amines,[11] esters,[17,19,25,26,28] carbonates,[21,22] and phosphates.[12,28] However, the carbonylation of allylic ethers has received much less attention and was examined only for short-chain cases. Tsuji and co-workers first described the carbonylation of allyl ethyl ether to ethyl but-2(or 3)-enoate (total yield 65%) in the presence of 5 mol % of $PdCl_2$ at 80 °C under 100 atm of carbon monoxide.[17] Later, Medema and co-workers reported that the reaction could be more easily performed at 90 °C under 80 atm of carbon monoxide in toluene or CCl_4 as solvent by using $[(\eta^3\text{-allyl})PdCl]_2$ as a catalyst precursor.[19] More recently, Chan disclosed the carbonylation of 1,4-dimethoxybut-2-enes as a route to dimethyl dihydromuconates and hence to dimethyl adipate by the use of chloro-containing palladium compounds in aprotic polar nonbasic solvents,[24] and Hanes and Baugh claimed the carbonylation of 8-methoxy-1,6-octadiene to the corresponding ester in the presence of nickel halides as catalyst at 150 °C under 150 atm of carbon monoxide.[10]

Results and Discussion

The reaction of 1 + 2 mixtures with carbon monoxide (eq 3) was attempted with various palladium catalyst precursors under various conditions in order to optimize the yield of methyl nona-3,8-dienoate (5) (Table I). The



(3)

use of $Pd(0)/PPh_3$ or $Pd(II)/PPh_3$ combinations which were reported to be good catalytic systems for the carbonylation of allylic esters,[26] carbonates,[21] or phosphates[28] completely failed (experiments 1–4, 6, and 7) or gave poor results (experiment 5). Similarly, $PdCl_2$ afforded a low yield of ester 5 (experiment 8). As stated by Medema and co-workers,[19] $[(\eta^3\text{-methyl-2-allyl})PdCl]_2$ (6) was found to be a better carbonylation catalyst. However, working with CCl_4 or CCl_4-containing mixtures as solvent led to low yields of ester 5 although the starting materials 1 + 2 were completely consumed (experiments 9–12). Apart from the ester 5, we were able to characterize by mass spectrometry chlorinated ethers and esters resulting from the addition of CCl_4 to the starting ethers and to the produced ester. This result may be rationalized from the fact that CCl_4 is known to add to olefins in the presence of palladium[29] or ruthenium[30] catalyst and to react with olefins and carbon monoxide in the presence of palladium catalysts.[31] Therefore, the terminal double bonds in 1 and 2 are more reactive toward CCl_4 than the allylic C–O bond toward carbonylation.

Avoiding CCl_4, it appeared that the best solvent was toluene (experiments 13–15). In that solvent (experiment 14), mixtures of ethers 1 + 2 reacted cleanly with carbon

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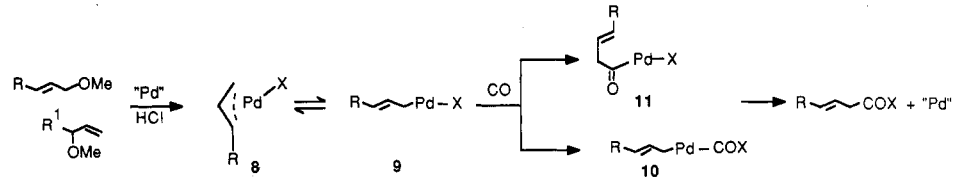
Scheme I[a]

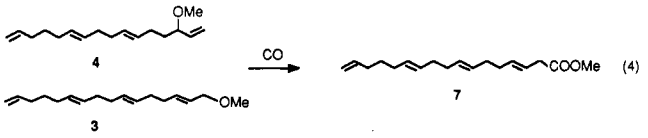


[a] X = OMe, Cl.

monoxide to afford only methyl nona-3,8-dienoate (**5**), which could be easily isolated in fair yields (70%) through distillation. The most crucial reaction parameter is temperature. The highest yield was obtained at 100 °C (experiment 14). At temperatures higher than 100 °C, decomposition of the catalyst precursor **6** to metallic palladium occurred, thus leading to lower yields of ester **5** and to side reactions (experiment 15). Thus, the optimal conditions are 100 °C and 30 atm of carbon monoxide.

The isolated ester **5** was then hydrogenated over Adams platinum to afford quantitatively methyl pelargonate. Taking into account that the methoxyoctadienes **1** + **2** are available in nearly quantitative yields from 1,3-butadiene and methanol mixtures through Pd(0)/PPh_3 catalysis, the above reaction sequence represents an easy and efficient synthesis of either methyl nona-3,8-dienoate or methyl pelargonate from very accessible feedstocks.

The most important feature of the carbonylation reaction is to provide the linear ester **5** from either the linear **1** or the branched **2** allylic ether. We therefore thought that the carbonylation of the above-mentioned C_{16} fraction which contains mostly the branched ether **4** and a small amount of the linear ether **3** could give rise to the same methyl ester of heptadecatetraenoic acid (eq 4). Ac-



(4)

cordingly, carbonylation of the C_{16} fraction under conditions of experiments 14 (Table I) afforded, after 70 h, a single product in 50% isolated yield tentatively described as methyl heptadeca-3,7,11,16-tetraenoate (**7**). Full hydrogenation of the isolated ester **7** furnished in quantitative yield a single product in all respects identical with methyl margarate.

Thus, we have demonstrated that the carbonylation of allylic ethers, easily available from 1,3-butadiene, can be an effective way for a total synthesis of pelargonic and margaric acid methyl esters.

The mechanism of the carbonylation reaction is presently unclear. On the basis of our results, it can be inferred that Pd–Cl bonds are a prerequisite for good catalytic activity to be observed. Their role is possibly to provide the reaction medium with hydrochloric acid, which can activate the oxidative addition of the allylic C–O bond onto a palladium(0) or palladium(II) catalyst by protonation of the oxygen atom giving rise to allylic complexes **8** and **9**. The oxidative addition of allyl acetate or allyl phenyl ethers in the presence of zero-valent palladium[32] or nickel[33] complexes has already been described but does not require the assistance of a proton source. In our case, the presence of hydrochloric acid may be necessary to improve the poor leaving-group character of the methoxy group and to facilitate the formation of **8** and **9**. The intermediacy of complexes **8** and **9** would explain the obtention of only one ester from mixtures of either **1** + **2** or **3** + **4**. From these intermediates, the insertion of carbon monoxide could occur into the Pd–X bond leading to **10** or more probably into the Pd–C bond of the η^1-allylic complex **9** leading to **11** as it has recently been demonstrated[34] by migration of either carbon monoxide or the η^1-allyl group.[35] The final step is the reductive elimination to give the acid derivatives. At the same time, the catalytically active species is regenerated (Scheme I).

Finally, although the catalytic system should be improved with respect to catalyst activity, we feel that it can be applied to other allylic ethers than those described in this paper. As allylic alcohols and therefore allylic ethers are easily available, the carbonylation reaction described here represents a good synthetic method for linear carboxylic acids.

Experimental Section

General Procedure. ^1H NMR spectra were recorded on a Bruker CW 80 spectrometer in $CDCl_3$ solution at 80 MHz using tetramethylsilane as internal standard. Data are reported in the following form: δ value of signal (peak multiplicity, number of protons, attribution). Infrared spectra were obtained on a Perkin-Elmer 597 spectrophotometer as neat liquid. GC analyses were performed on an Intersmat IGC 120 flame ionization detector gas chromatograph fitted with a 1.5 m × $^1/_8$ in. column (10% SE 30 on Gas Chrom Q, 80–100 mesh) working in the range 70–250 °C (10 deg min^{-1}) with N_2 as carrier gas (flow rate 20 mL min^{-1}), the injector and detector temperatures being respectively 300 and 250 °C. Yields of esters **5** and **7** were determined relative to respectively tetradecane and dodecane as internal standards. Reactions under pressure were performed in homemade 100- or 300-mL glass-lined stainless steel autoclaves magnetically stirred and conventionally equipped. Boiling points are uncorrected.

Starting Materials. All solvents were carefully dried, distilled, and stored according to literature procedures.[36] Similarly, all reagents were stored under argon after distillation or recrystallization. Carbon monoxide (N20) and hydrogen U were available from l'Air Liquide. Triphenylphosphine (Janssen Chimica, 98%) was recrystallized from methanol. $PdCl_2$ and $Pd(OAc)_2$ were commercially available from Johnson Matthey, $Pd(dba)_2$[37] and $[(\eta^3\text{-methyl-2-allyl})PdCl]_2$[38] (**6**) were prepared according to the literature.

Synthesis of Mixtures of 1 + 2 and 3 + 4.[9] $Pd(dba)_2$ (0.25 mmol, 115 mg) and [(2-methylallyl)oxy]tris(dimethylamino)-phosphonium hexafluorophosphate[39] (0.25 mmol, 95 mg) were weighed in a 100-mL autoclave under argon. Toluene (10 mL) was added and the mixture stirred for 2 h, a procedure known to generate a cationic (η^3-allyl)palladium complex.[40] Methanol

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(75 mmol, 3 mL) was introduced, and buta-1,3-diene (300 mmol, 16.2 g) was distilled into the autoclave cooled at -20 °C. Heating for 20 h at 80 °C gave rise to a total conversion of butadiene. GC and GC-MS analysis of the crude reaction mixture revealed the formation of small amounts of butadiene dimers (4-vinylcyclohexene, octa-1,3,6- and -1,3,7-triene) (2%), C_8 telomers (m/z = 140) (20%), a small amount of a C_{12} telomer (m/z = 194) (1%), a small amount of a butadiene tetramer (m/z = 216) (3%), and C_{16} telomers (m/z = 248) (34%) together with some higher oligomers and telomers. Distillation of the reaction mixture afforded a low-boiling fraction (bp 50–55 °C, 1 Torr) and a high-boiling fraction (bp 50–60 °C, 10^{-2} Torr).

The low-boiling fraction consisted of a mixture of **1** (90%) and **2** (10%), which were identified by comparison of their GC retention time and spectral data (^{1}H NMR, MS) with those of authentic samples.[41]

The high-boiling fraction was analyzed by GC and GC-MS and found to be a mixture of a butadiene tetramer (m/z = 216) (5%) and two C_{16} telomers (m/z = 248) **3** (8%) and **4** (87%). Distillation of this fraction gave pure compound **4**, which presented the following spectroscopic properties: IR (neat) 1640, 1100, 990, 970, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3–1.7 (m, 4 H, CH_2), 1.8–2.3 (m, 10 H, allylic), 3.3 (s, 3 H, CH_3), 3.55 (q, 1 H, C*H*O, J = 6 Hz), 4.9–6.0 (m, 10 H, *H*C=); mass spectrum, m/z (relative intensity) 248 (M^+, 0.4), 216 (M^+ - MeOH, 0.6), 107 (43), 79 (86), 71 (100), 67 (61), 41 (64).

Hydrogenation of compound **4** over Adams platinum gave quantitatively 3-methoxyhexadecane, which was identical (IR, ^{1}H NMR, MS, GC retention time) with an authentic sample prepared from commercial 3-hexadecanol.

From these data, compound **4** is 3-methoxyhexadeca-1,6-(7),10(11),15-tetraene. However, the characterization of **4** as 3-methoxyhexadeca-1,6,10,15-tetraene is favored on the basis of mechanistic studies.[42]

Column chromatography of a sample of the high-boiling fraction on silica gel eluting with 5% ethyl acetate in cyclohexane afforded a mixture of compounds **3** and **4** (1/3). ^{1}H NMR spectroscopy showed the resonances of compound **4** and resonances as δ 3.25 (s, 3 H, CH_3) and 3.80 (d, 2 H, CH_2O, J = 4 Hz). Hydrogenation of this mixture quantitatively furnished a mixture of 1-methoxyhexadecane and 3-methoxyhexadecane, identified by comparison (GC retention time) with authentic samples prepared from commercial 1- and 3-hexadecanol, respectively. From these data, compound **3** is a 1-methoxyhexadeca-3,x,x,x,-tetraene.

Alternatively, the methoxyoctadienes were synthesized as follows.

Preparation of 1-Methoxyocta-2,7-diene (1) and 3-Methoxyocta-1,7-diene (2). $Pd(dba)_2$ (0.3 mmol, 172 mg) and PPh_3 (0.6 mmol, 157 mg) were weighed in a 300-mL autoclave under argon. Methanol (90 mL) was introduced, and buta-1,3-diene (90 mL, 55 g, 1 mol) was distilled into the autoclave cooled to -20 °C. After heating at 80 °C for 20 h and cooling, the reaction products were submitted to distillation to afford 63 g (90%) of a mixture of **1** (97%) and **2** (3%), bp 62–68 °C (13 Torr), whose spectral data are in agreement with the reported values.[41]

Procedure for the Carbonylation Reaction. The catalyst precursor was weighed in a 100-mL autoclave under argon. A solution of the C_8 fraction (50 mmol, 7 g) or of the C_{16} fraction (20 mmol, 5 g) was introduced, and the autoclave was pressurized with carbon monoxide and heated to the temperature reported in Table I. After the desired reaction time, the products were analyzed by GC or isolated through distillation.

Methyl Nona-3,8-dienoate (5). Distillation of the products of experiment 14 afforded 5.88 g (70%) of methyl nona-3,8-dienoate, bp 90–100 °C (17–18 Torr), which was identical (IR, ^{1}H NMR, GC) with an authentic sample prepared according to ref 43.

Methyl Heptadeca-3,7,11,16-tetraenoate (7). Distillation of the reaction products afforded 2.78 g (50%) of methyl heptadeca-3,7,11,16-tetraenoate, bp 120–124 °C (1 Torr), which presented the following spectroscopic properties: IR (neat) 1740, 1640, 990, 970, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3–1.7 (m, 2 H, CH_2), 1.8–2.3 (m, 12 H, allylic), 3.05 (m, 2 H, CH_2CO_2Me), 3.7 (s, 3 H, CH_3), 4.8–5.1 (m, 2 H, =CH_2), 5.3–5.8 (m, 7 H, *H*C=C*H*).

Hydrogenation of 5 and 7. A solution of compound **5** or **7** (0.5 mmol) in hexane (4 mL) was introduced in a 100-mL autoclave containing Adams platinum (20 mg). The autoclave was pressurized with hydrogen (30 atm) and heated to 50 °C for 4 h. After filtration of the cooled solution through Celite and evaporation of the solvent, a quantitative yield of methyl pelargonate or methyl margarate was obtained. Their IR and ^{1}H NMR spectra and their GC retention times were identical with those of commercial products (Fluka).

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Registry No. **1**, 35702-75-1; **2**, 20202-62-4; **3**, 119595-27-6; **4**, 119595-28-7; **5**, 51122-98-6; **7**, 119595-29-8; $Pd(dba)_2$, 81141-80-2; $[(\eta^3$-methyl-2-allyl)$PdCl]_2$, 12081-18-4; [(2-methylallyl)oxy]tris(dimethylamino)phosphonium hexafluorophosphate, 63936-88-9; buta-1,3-diene, 106-99-0; methyl pelargonate, 1731-84-6; methyl margarate, 1731-92-6.

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1-Silacyclohexan-4-ones and 1-Germacyclohexan-4-ones: Precursors to Metallapharmaceuticals via Boracycles

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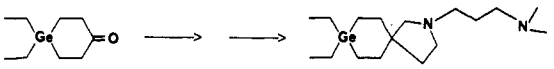
The pioneering studies of Rice and co-workers[2] established that 1-metallacyclohexan-4-ones could be efficiently converted to the pharmacologically important 2-aza-8-metallaspiro[4.5]decanes. "Spirogermanium" (**2**), for example, is reported to have antitumor, antiarthritic, antimalarial, and immunoregulatory activity[3] and is available in several steps from 1,1-diethyl-1-germacyclohexan-4-one (**1d**).[2a]



(eq. 1)

1d **2**

For some time, we have had an interest in the preparation and chemistry of such metallacyclohexan-4-one systems (**1**).[4] After finding the reported methods to this and other ring systems to involve many steps and give low overall yields,[2,5] we took advantage of several newer organoborane-based routes to cyclic ketones and applied

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