1.72 (dd, 1 H, J = 13.5, 6.1 Hz), 1.86 (dd, 1 H, J = 13.5, 10.4 Hz), 2.18 (ddd, 1 H, J = 15.0, 2.6, 2.4 Hz), 2.26 (ddd, 1 H, J = 15.0, 5.7, 5.2 Hz), 2.33 (ddd, 1 H, J = 12.7, 9.0, 2.4 Hz), 2.44 (ddd, 1 H, J = 14.4, 9.7, 9.0 Hz), 2.53 (ddd, 1 H, J = 14.4, 7.9, 2.4 Hz), 2.90 (dd, 1 H, J = 10.4, 6.1 Hz), 3.69 (s, 3 H), 3.90 (dd, 1 H, J = 5.7, 2.6 Hz), 4.78 (dd, 1 H, J = 5.2, 2.4 Hz); ^{13}C NMR (125 MHz) δ 18.80, 19.73, 23.30, 28.41, 39.91, 40.93, 41.08, 50.42, 51.56, 53.62, 57.89, 73.32, 78.23, 83.84, 89.50, 169.33, 173.80; MS m/z 335 (M^+). Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.81; H, 8.71; N, 4.14.

(+)-(1*S*,3*S*,4*S*,8*S*,9*R*,11*S*)-11-*tert*-Butoxy-1,4-dimethyl-9-hydroxy-3-(methoxycarbonyl)-7-oxotricyclo[6.3.0.0^{4,8}]undecane (28A). The 2:1 mixture of isoxazolines **21A** and **21B** (102.0 mg, 0.304 mmol), W-2 Raney Ni (10 mg), and trimethyl borate (0.316 g, 3.04 mmol) in MeOH–H_2O (15:1; 4.8 mL) was stirred for 12.5 h at room temperature under H_2 (1 atm). After filtration through Celite, the filtrate was evaporated under reduced pressure to give a residue, which was partitioned between H_2O and $CHCl_3$. The aqueous layer was thoroughly extracted with $CHCl_3$. The combined extracts were washed with saturated aqueous NaCl, dried, and evaporated under reduced pressure to give a residue, which was adsorbed on silica gel. After being allowed to stand overnight at room temperature, elution with hexane–AcOEt (7:3) afforded a mixture of β-hydroxy ketones **28A** and **28B** (83.5 mg, 83%) in a 2:1 ratio. Recrystallization of the product from hexane provided the major component **28A** as colorless needles, mp 126–127 °C: $[\alpha]^{28}_D$ +96° (c 0.86, $CHCl_3$); IR ($CHCl_3$) 3570 (OH), 1725 (C=O), 1670 (C=O) cm^{-1}; ^{1}H NMR (500 MHz) δ 0.91 (s, 3 H), 1.15 (s, 9 H), 1.28 (s, 3 H), 1.59 (ddd, 1 H, J = 13.8, 8.5, 2.6 Hz), 1.88–2.37 (m, 7 H), 2.40 (d, 1 H, J = 12.2 Hz; disappeared with D_2O), 2.68 (dd, 1 H, J = 12.4, 7.5 Hz), 3.34 (dd, 1 H, J = 11.5, 5.5 Hz), 3.72 (s, 3 H), 4.76 (ddd, 1 H, J = 12.2, 12.2, 5.6 Hz); MS m/z 338 (M^+). Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.46; H, 9.00.

(+)-(1*S*,3*S*,4*S*,5*S*,7*R*,8*R*)-5-*tert*-Butoxy-1,4-dimethyl-7-hydroxy-2-(methoxycarbonyl)-9-methylidenetricyclo[6.3.0.0^{4,8}]undecane (29). To a suspension of Zn powder (14.5 g, 222 mg atom) and CH_2Br_2 (12.4 g, 7.12 mmol) in dry THF (100 mL) was added at −40 °C titanium(IV) tetrachloride (15.0 g, 79.3 mmol) during 8 min. The mixture (Lombardo's reagent) was stirred for 72 h at 5 °C and was used for the following reaction.

A solution of hydroxy ketone **28A** (17.5 mg, 0.052 mmol) in dry CH_2Cl_2 (1.0 mL) was added dropwise to the above Lombardo's reagent in dry THF (0.712 M, 0.25 mL, 0.178 mmol) at room temperature. After being stirred for 9 h at the same temperature, silica gel under ice cooling was added to the resulting mixture. After being stirred for 10 min at room temperature, the mixture was filtered through Celite. The filtrate and washings were combined and evaporated under reduced pressure to afford a residue, which was subjected to chromatography on silica gel. Elution with hexane–AcOEt (17:3) gave olefin **29** (6.5 mg, 37%) as a colorless oil: $[\alpha]^{22}_D$ +11° (c 0.95, $CHCl_3$); IR ($CHCl_3$) 3650 (OH), 1730 (C=O), 1660 (C=C) cm^{-1}; ^{1}H NMR (500 MHz) δ 0.84 (s, 3 H), 1.13 (s, 3 H), 1.16 (s, 9 H), 1.61–2.52 (m, 9 H), 2.58 (dd, 1 H, J = 12.5, 7.0 Hz), 3.39 (dd, 1 H, J = 11.3, 5.2 Hz), 3.69 (s, 3 H), 3.71–3.77 (m, 1 H); MS m/z 336 (M^+); exact mass found M^+ 336.2263, $C_{20}H_{32}O_4$ requires 336.2300.

Acknowledgment. We thank Dr. Y. Ohshima, Miss K. Mushiake, Miss M. Inada, Mrs. A. Satoh, Miss N. Oikawa, and Mr. K. Kawamura of this Institute for spectral measurements and preparation of the manuscript.

Supplementary Material Available: ^{1}H NMR spectra of compounds **15A** and **15B**, **16A** and **16B**, **18A** and **18B**, **21A**, and **29** and listing of bond lengths and angles and torsion angles and two independent molecular structures for **28A** (17 pages). Ordering information is given on any current masthead page.

Sequential Radical Ring Closure–Radical Ring Opening: Use in the Preparation of Benzofurans

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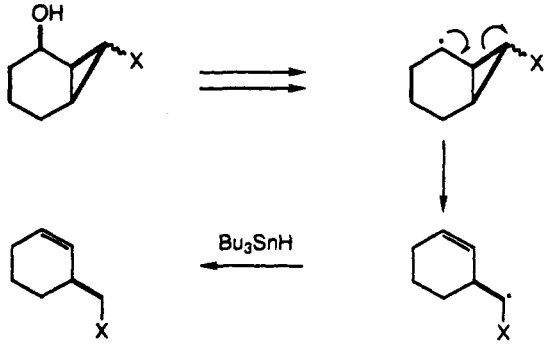
Received February 20, 1991

A radical ring closure–ring opening sequence (Scheme I) was used to prepare benzofuran derivatives.

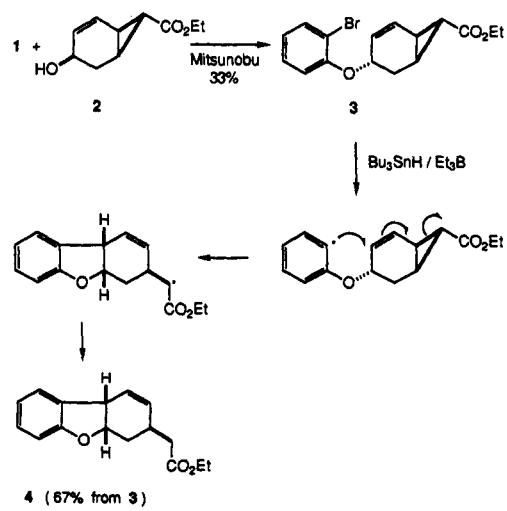
The radical ring opening sequence[1] of eq 1 (where X is, for example, H, alkyl, COOR, $CONMe_2$) represents a procedure for attaching alkyl and substituted-alkyl groups to cyclic structures. We have combined this methodology



Eq. 1

with conventional radical ring closure, as shown in Scheme I, in order to make several benzofuran derivatives required for evaluation as inhibitors[2] of leukotriene biosynthesis.

Scheme I



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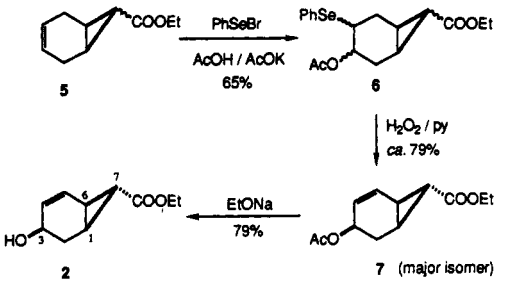
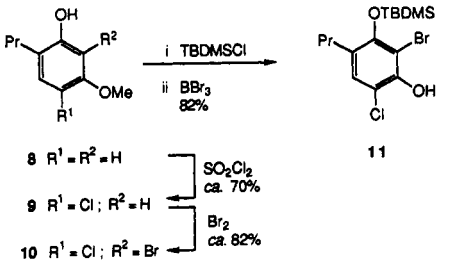
0022-3263/91/1956-5285$02.50/0

Scheme II[a]



[a] The major component of the selenylation corresponded to the stereochemistry shown in 2.

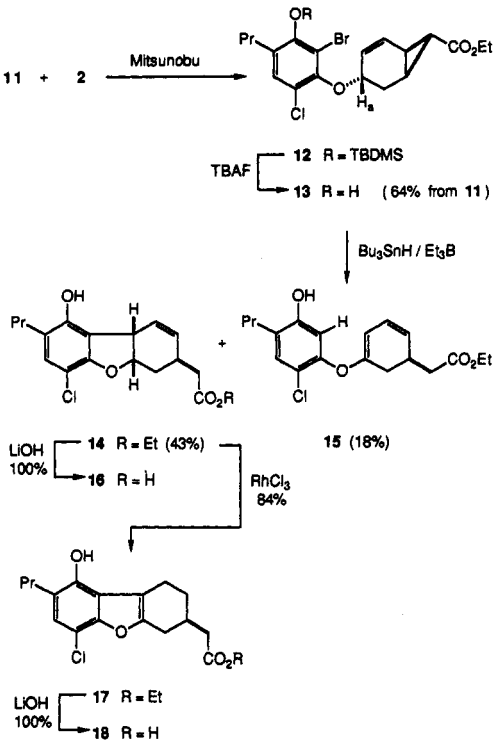
Scheme III



The radical closure–ring opening sequence, as used in the present work,[3] involves Mitsunobu coupling (see Scheme I) of an *o*-bromophenol with the cyclopropane alcohol **2**. Although the coupling in the particular case of **1** and **2** was inefficient, no attempt was made to improve the yield as the coupled product was used only to test the free radical conversion into **4**. That series of steps proceeded in satisfactory yield and so we applied the method to phenol **11** (see Scheme III). The choice of substituents for **11** was based on prior structure–activity studies[2] with simple benzofurans that had been found to inhibit leukotriene biosynthesis.

The cyclopropane alcohol **2** was prepared as summarized in Scheme II, and the stereochemistry of the compound was determined by X-ray analysis[4] of the 3,5-dinitrobenzoate derivative. Epoxidation of the starting olefin **5**[5] under a variety of conditions was not very selective,[6] but the method based on acetoxy selenenylation (**5** → **6**) showed much greater facial discrimination. The presence of an ester substituent on the cyclopropane was dictated by our wish to have a carboxyl group in the final product and had the added advantage of controlling the regiochemistry of cyclopropane opening.[1]

Scheme IV



Phenol **11** was made by the standard methods of Scheme III. Chlorophenol **9** darkened rapidly, but the final product **11** was quite stable and it reacted under Mitsunobu conditions with alcohol **2** to afford the coupled product **12** (Scheme IV). Activation of alcohol **2** must be done at −30 to −20 °C, and not at a higher temperature, in order to avoid elimination of the hydroxyl group. The yield in the coupling was variable, sometimes being as high as 80%. The stereochemistry of **12** (and also of **3**) is a tentative assignment based on the assumption that the normal inversion occurs. Desilylation in the usual way took the route as far as **13**, and treatment with tributylstannyl radicals, arbitrarily generated at room temperature by the triethylborane method,[7] led to the desired product of ring closure and ring opening **14**, together with a minor product (**15**). Presumably, compound **15** arises by abstraction of H_a in **13** to form a radical that then collapses. We detected no byproducts from loss of chlorine, showing that this atom survives the reaction conditions. The stannane-mediated reaction was done at high dilution (0.01 M in starting material and 0.02 M in stannane), and the stannane was added in one portion. The radical sequence with the silylated material **12** was much less clean than that with the unprotected phenol **13**.

Isomerization of **14** with rhodium trichloride under carefully defined conditions[8] gave **17**, and both **14** and **17** were hydrolyzed to the corresponding carboxylic acids **16** and **18**, respectively. These were then evaluated for inhibition of leukotriene biosynthesis,[9] but only marginal activity was found.

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(4) Only low angle diffraction data were collected.

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(6) Cf. Paquette, L. A.; Fristad, W. E.; Schuman, C. A.; Beno, M. A.; Christoph, G. G. *J. Am. Chem. Soc.* **1979**, *101*, 4645.

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(8) Cf. Clive, D. L. J.; Joussef, A. C. *J. Org. Chem.* **1990**, *55*, 1096.

(9) We thank Merck Frosst Canada for the bioassay, which was done by the method of ref 2. Compound **18**: 13% inhibition of leukotriene biosynthesis at 1 μg/mL. Compound **16**: 17% inhibition at 1 μg/mL.

Radical opening of cyclopropanes has been used by itself,[1] or followed by cyclization,[10] and the present work shows that it can also be preceded by ring closure.

Experimental Section

Ethyl (±)-3-Acetoxy-4-(phenylseleno)bicyclo[4.1.0]heptane-7-carboxylate (6). PhSeSePh (8.4 g, 26.9 mmol) was added over 1 min to a solution of Br_2 (4.2 g, 25.2 mmol) in glacial AcOH (80 mL). The mixture was stirred at room temperature for 10 min, and 5[5] (7.75 g, 46.7 mmol) followed by anhydrous AcOK (9.16 g, 93.4 mmol) were added successively, each in one portion.[11] After being stirred at room temperature for 2 h, the mixture was diluted with ether (500 mL), washed with water (1 × 200 mL), saturated aqueous $NaHCO_3$ (1 × 100 mL), and water (1 × 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (7 × 24 cm) using successively 5%, 8%, and 15% EtOAc–hexane afforded 6 (11.56 g, 65%) as a slightly yellow oil that was a mixture of isomers. The major component [ca. 85 mol %, AcO and C(7) syn] had the following: ^1H NMR ($CDCl_3$), 200 MHz) δ 1.27 (t, J = 7.3 Hz, 3 H), 1.50–2.66 (m, including a singlet at δ 1.97, 1 H), 3.72–3.79 (dm, J = 10.0 Hz, 1 H), 4.11 (q, J = 7.3 Hz, 2 H), 4.79–4.94 (m, 1 H), 7.20–7.33 (m, 3 H), 7.46–7.63 (m, 2 H).

Ethyl (±)-3-Acetoxybicyclo[4.1.0]hept-4-ene-7-carboxylate (7). Pyridine (4.69 mL, 58 mmol) and then 30% w/w aqueous H_2O_2 (6.67 mL, 58 mmol) [addition over 15 min (see the caution in ref 12)] were added to a stirred solution of 6 (11.01 g, 29 mmol) in CH_2Cl_2 (130 mL). Stirring was continued for 15 min after the addtion of the H_2O_2, and THF (20 mL) was then added in order to obtain a homogeneous mixture. After a further 2 h (stirring), the mixture was diluted with ether (300 mL), washed with 10% w/v aqueous $Na_2S_2O_3$ (1 × 100 mL) and water (1 × 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 × 17 cm) using 15% EtOAc–hexane afforded 7 (6.05 g, 93%) as an oil. The material was largely (85 mol %; ^1H NMR) a single isomer of the indicated stereochemistry and had the following: ^1H NMR ($CDCl_3$, 300 MHz) (major signals only) δ 1.29 (t, J = 7.2 Hz, 3 H), 1.81 (br t, J = 4.2 Hz, 1 H), 1.92–2.07 (m, including a singlet at δ 2.04, 1 H), 2.20 (dm, J = 16.0 Hz, 1 H), 4.08–4.21 (m, 2 H), 5.27–5.34 (m, 1 H), 5.73 (dd, J = 10.0, 5.7 Hz, 1 H), 6.32–6.39 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.22, 20.96, 21.22, 22.16, 24.68, 31.66, 60.54, 65.56, 122.65, 132.60, 170.37, 172.51; exact mass, m/z calcd for $C_{12}H_{17}O_4$ 225.1127, found 225.1125.

Ethyl (1α,3β,6α,7α)-(±)-3-Hydroxybicyclo[4.1.0]hept-4-ene-7-carboxylate (2). NaH (60% dispersion in oil, 203 mg, 5.08 mmol) was added in several portions over 2 min to a stirred solution of 7 (5.72 g, 25.4 mmol) in anhydrous EtOH. After being stirred at room temperature for 2 h, the mixture was quenched with saturated aqueous NH_4Cl (20 mL) and concentrated (water-pump vacuum) to ca. 40 mL. The concentrate was diluted with ether (400 mL), washed with water (2 × 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 × 21 cm) using 20% EtOAc–hexane afforded the allylic alcohol 2 (3.66 g, 79%) as a slightly yellow oil: FT-IR ($CHCl_3$ cast) 3456 (br), 2981, 2909, 1723, 1702, 1641, 1193 cm^{-1}; ^1H NMR ($CDCl_3$), 300 MHz) δ 1.26 (t, J = 7.0 Hz, 3 H), 1.85–2.01 (m, 4 H), 2.07 (br d, J = 15.2 Hz, 1 H), 2.51 (br s, 1 H), 4.12 (q, J = 7.0 Hz, 2 H), 4.26–4.32 (m, 1 H), 5.76 (dd, J = 9.8, 5.2 Hz, 1 H), 6.23 (dd, J = 9.8, 3.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.14, 21.45, 22.58, 27.29, 32.66, 60.45, 62.52, 127.32, 130.09, 173.06; exact mass, m/z calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0942. A satisfactory combustion analysis could not be obtained.

4-Chloro-5-methoxy-2-propylbenzenol (9). A solution of freshly distilled SO_2Cl_2 (5.58 mL, 69.42 mmol) in dry ether (20 mL) was added dropwise over 15 min (syringe pump) to a stirred solution of 8[13] (11.9 g, 66.1 mmol) in the same solvent (60 mL).[14] After 30 min, more SO_2Cl_2 (1.1 mL, 13.68 mmol) in dry ether (5 mL) was added over 3 min and stirring was continued for 1 h. The mixture was then concentrated (water-pump), diluted with ether (200 mL) and water (200 mL), and stirred for 40 min. The organic layer was separated and washed with water (1 × 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography (twice) of the brown residue over silica gel (7 × 12 cm) using 10% EtOAc–hexane afforded 9 (9.88 g, 70%) as a yellow oil, which becomes black within hours at room temperature but which remains acceptably pure for at least 3 days at room temperature, as judged by ^1H NMR and combustion analysis measurements: FT-IR ($CHCl_3$ cast) 3450, 2960, 1511, 1205, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, J = 7.2 Hz, 3 H), 1.59 (sextet, J = 7.2 Hz, 2 H), 2.47 (t, J = 7.2 Hz, 2 H), 3.78 (s, 3 H), 5.23 (br s, 1 H), 6.41 (s, 1 H), 7.07 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.79, 22.91, 31.01, 56.22, 100.79, 113.36, 121.35, 130.84, 152.85, 153.55; exact mass, m/z calcd for $C_{10}H_{13}{}^{35}ClO$ and $C_{10}H_{13}{}^{37}ClO$, 200.0604 and 202.0575, found 200.0618 and 202.0591. Anal. Calcd for $C_{10}H_{13}ClO$: C, 59.85; H, 6.53. Found: C, 59.66; H, 6.50.

2-Bromo-4-chloro-3-methoxy-6-propylbenzenol (10). Br_2 (7.29 g, 45.53 mmol) in glacial AcOH (25 mL) was added dropwise over 15 min (syringe pump) to a stirred solution of 9 (7.29 g, 33.8 mmol) in the same solvent (70 mL). After 45 min, the solvent was evaporated and the residue was diluted with ether (250 mL), washed with water (2 × 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the resulting red oil over silica gel (70 × 180 mm) using 5% EtOAc–hexane afforded 10 (9.2 g, 92%) as a reddish transparent oil that was 90 mol % pure [^1H NMR, (300 MHz)]: FT-IR ($CHCl_3$ cast) 3507, 2960, 1477, 1431, 1398, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major signals only) δ 0.94 (t, J = 7.2 Hz, 3 H), 1.60 (sextet, J = 7.2 Hz, 2 H), 2.59 (t, J = 7.2 Hz, 2 H), 3.86 (s, 3 H), 5.58 (s, 1 H), 7.09 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.86, 22.61, 32.31, 60.64, 106.87, 119.03, 126.56, 129.73, 149.94, 151.01; mass for $C_{10}H_{12}{}^{79}Br^{35}ClO_2$, $C_{10}H_{12}{}^{79}Br^{37}ClO_2$ and $C_{10}H_{12}{}^{81}Br^{37}ClO_2$ (chemical ionization, NH_3) 296 $(M + 18)^+$, 298 $(M' + 18)^+$ and 300 $(M'' + 18)^+$. Anal. Calcd for $C_{10}H_{12}BrClO_2$: C, 42.96; H, 4.33; O, 11.45. Found: C, 42.44; H, 4.25; O, 11.30.

2-Bromo-6-chloro-3-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4-propylbenzenol (11). t-$BuMe_2SiCl$ (2.67 g, 17.7 mmol) was added in one portion to a stirred solution of 10 (90 mol % pure, 5.0 g, 18.0 mmol) and imidazole (2.52 g, 37.1 mmol) in dry DMF (40 mL). After 1.5 h, the mixture was diluted with ether (350 mL) and washed with water (1 × 200 mL). The aqueous layer was extracted with ether (1 × 150 mL) and the combined organic layers were washed with water (1 × 200 mL), dried ($MgSO_4$), and evaporated. Filtration of the residue through silica gel (7 × 15 cm) using 6% EtOAc–hexane afforded an oil (6.5 g), which was used directly in the next step without further purification.

BBr_3 (1 M in CH_2Cl_2, 20.7 mL, 20.7 mmol) was added over 2 min to a cold (−78 °C) and stirred solution of the above oil (6.5 g, 16.57 mmol) in dry CH_2Cl_2 (100 mL). Stirring at 0 °C was continued for 1.5 h, and the mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL) and diluted with ether (300 mL). The organic extracts were washed with water (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (7 × 18 cm) using 1% EtOAc–hexane afforded pure 11 (5.56, 82% from 10): FT-IR ($CHCl_3$ cast) 3507, 2958, 2930, 1468, 1424, 1191, 833, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.27 (s, 6 H), 0.91 (t, J = 7.2 Hz, 3 H), 1.03 (s, 9 H), 1.54 (sextet, J = 7.2 Hz, 2 H), 2.50 (t, J = 7.2 Hz, 2 H), 4.25–5.75 (br, 1 H), 7.07 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −2.44, 13.78, 18.92, 23.29, 26.20, 32.61, 104.69, 112.64, 127.26, 128.58, 147.24, 150.36; mass for $C_{15}H_{24}{}^{79}Br^{35}ClO_2Si$, $C_{15}H_{24}{}^{79}Br^{37}ClO_2Si$ and $C_{15}H_{24}{}^{81}Br^{37}ClO_2Si$ (chemical ionization, NH_3) 396 $(M + 18)^+$, 398 $(M' + 18)^+$, 400 $(M'' + 18)^+$. Anal. Calcd for $C_{15}H_{24}BrClO_2Si$: C, 47.43; H, 6.37; halogens (based on Cl), 18.66. Found: C, 47.19; H, 6.25; halogens (based on Cl), 18.28.

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Ethyl (1α,3α,6α,7α)-(±)-3-(2-Bromo-6-chloro-3-hydroxy-4-propylphenoxy)bicyclo[4.1.0]hept-4-ene-7-carboxylate (13).[15] Diethyl azodicarboxylate (1.87 g, 1.69 mL, 10.7 mmol) was added over 2 min to a cold (−40 °C) and stirred solution of Ph_3P (2.83 g, 10.8 mmol) in dry THF (60 mL). After 30 min at −40 °C, the mixture became a thick paste and was therefore allowed to attain room temperature (over 30 min) and then diluted with dry THF (30 mL). The suspension, which could now be stirred, was cooled to −30 °C and alcohol **2** (1.98 g, 10.9 mmol) in dry THF (7 mL + 2 mL rinse) was injected over 3 min by cannula. After being stirred at −30 °C for 1 h, and then at −20 °C for 1 h, phenol **11** (1.65 g, 4.35 mmol) in dry THF (5 mL + 2 mL rinse) was added over 2 min by cannula to the suspension. All the solids dissolved as soon as the addition was complete. The solution was stirred at −20 °C for 1 h and the solvents were then evaporated. Flash chromatography of the residue over silica gel (7 × 18 cm) using 4% ether–hexane afforded **12**[15] (1.92 g). The material contained some impurities but was used directly in the next step: FT-IR ($CHCl_3$ cast) 2958, 1726, 1458, 1180, 855 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.28 (s, 6 H), 0.93 (t, J = 7.8 Hz, 3 H), 1.03 (s, 9 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.49–1.61 (m, 3 H), 1.90–1.99 (m, 2 H), 2.03–2.15 (m, 1 H), 2.49–2.61 (m, 3 H), 4.11 (q, J = 7.1 Hz, 2 H), 4.55–4.64 (m, 1 H), 5.89 (br d, J = 10.3 Hz, 1 H), 6.10 (dm, J = 10.3 Hz, 1 H), 7.09 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −2.35, 13.82, 14.25, 18.93, 19.30, 20.46, 23.04, 25.07, 26.21, 26.89, 32.80, 60.58, 75.58, 113.15, 120.84, 126.99, 127.61, 129.29, 131.19, 150.01, 150.75, 172.64; exact mass, for $C_{25}H_{36}{}^{79}Br^{35}ClO_4Si$ (chemical ionization, NH_3) 560 $(M + 18)^+$. Anal. Calcd for $C_{25}H_{36}BrClO_4Si$: C, 55.19; H, 6.67; halogens (based on Cl), 13.04. Found: C, 55.25; H, 6.81; halogens (based on Cl), 12.77.

The reaction is capricious; on a few occasions lower yields (30–70%) were obtained.

Bu_4NF (1 M in THF, 6 mL, 7.06 mmol) was added in one portion to a stirred solution of crude **12** (1.92 g, ca. 3.5 mmol) in dry THF (20 mL). After 1.5 h, the mixture was diluted with ether (200 mL), washed with water (2 × 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography (twice) of the residue over silica gel (4 × 19 cm) using first 8% and then 10% EtOAc–hexane afforded pure **13** (1.19 g, 64% from phenol **11**) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (t, J = 7.8 Hz, 3 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.53–1.87 (m, 3 H), 1.97–2.02 (m, 2 H), 2.03–2.18 (m, 1 H), 2.55–2.70 (m, 3 H), 4.16 (q, J = 7.1 Hz, 2 H), 4.58–4.72 (m, 1 H), 5.65 (s, 1 H), 5.89 (br d, J = 10.3 Hz, 1 H), 6.15 (dm, J = 10.3 Hz, 1 H), 7.11 (s, 1 H).

In a previous run on ca. $^1/_{10}$ scale, the yield from phenol **11** was 75%.

Ethyl (3α,4aα,9bα)-(±)-(6-Chloro-9-hydroxy-8-propyl-3,4,4a,9b-tetrahydrodibenzofuran-3-yl)acetate (14) and Ethyl (±)-[3-(6-Chloro-3-hydroxy-4-propylphenoxy)cyclohexa-3,5-dienyl]acetate (15). Et_3B (1 M in hexane, 0.17 mL, 0.17 mmol) and then Bu_3SnH (47 μL, 0.17 mmol) were added to a solution of **13** (48 mg, 0.111 mmol) in dry benzene (10 mL), and the mixture was stirred for 24 h. The solvent was evaporated and the residue was diluted with ether (3 mL) and stirred with an excess of KF in water. After 1 h, the mixture was diluted with ether (10 mL) and the organic layer was washed with water (3 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 12 cm) using successively 10%, 15%, and 20% EtOAc–hexane afforded **14** (17 mg, 43%) as a white solid and **15** (7 mg, 18%) as colorless oil. Compound **14**: mp 124–130 °C; FT-IR ($CHCl_3$ cast) 3402, 2951, 1714, 1614, 1479, 1280, 1250, 1215, 1195, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.0 (t, J = 7.5 Hz, 3 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.42–1.75 (m, 3 H), 2.35–2.55 (m, 5 H), 2.80–3.0 (m, 1 H), 3.93–4.02 (m, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 4.71 (br s, 1 H), 5.08–5.18 (m, 1 H), 5.76 (d, J = 10.2 Hz, 1 H), 5.88 (dt, J = 10.2, 3.2 Hz, 1 H), 6.86 (s, 1 H); [Irradiation at δ 5.8 caused the signal at δ 3.93–4.02 to collapse to a dd (J = 8.0, 1.2 Hz) and the signal at δ 2.80–3.0 to simplify slightly. Irradiation at δ 3.98 caused the signal at δ 5.88 to collapse to a dd (J = 10.0, 3.2 Hz) and the signal at δ 5.08–5.18 to collapse to a t (J = 3.6 Hz). Irradiation at δ 2.88 caused the signal at δ 1.42–1.75 to simplify, the signal at δ 2.35–2.55 to simplify, the signal at δ 3.93–4.2 to collapse to a dd (J = 7.6, 2.0 Hz), and the signal at δ 5.88 to collapse to a dd (J = 10.0, 3.2 Hz).]; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.82, 14.20, 23.13, 26.61, 31.13, 31.29, 39.87, 40.16, 60.65, 82.17, 106.31, 118.13, 122.14, 125.11, 129.15, 131.15, 149.10, 154.20, 172.54; exact mass, m/z calcd for $C_{19}H_{23}ClO_4$ (^{35}Cl) 350.1285 and (^{37}Cl) 352.1255, found (^{35}Cl) 350.1286 and (^{37}Cl) 352.1263. Anal. Calcd for $C_{19}H_{23}ClO_4$: C, 65.04; H, 6.61; O, 18.24. Found: C, 64.88; H, 6.50; O, 17.97. Compound **15**: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.01 (t, J = 7.2 Hz, 3 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.60–1.80 (m, 2 H), 2.34 (dd, J = 16.0, 8.0 Hz, 1 H), 2.45–2.59 (m) and 2.67 (ddd, J = 16.0, 7.6, 0.8 Hz) [both signals together correspond to 3 H], 2.92–3.12 (m, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 4.95 (d, J = 1 H), 5.14 (s, 1 H), 5.48 (dd, J = 8.8, 4.8 Hz, 1 H), 5.83 (ddd, J = 8.8, 6.0, 1.6 Hz, 1 H), 6.58 (s, 1 H), 7.13 (s, 1 H).

The radical reaction is initiated by traces of oxygen in the solvent.[7] In a subsequent run, where benzene freshly distilled over sodium–benzophenone ketyl, was used the reaction was sluggish and required a large excess of triethylborane and tin hydride.

(3α,4aα,9bα)-(±)-(6-Chloro-9-hydroxy-8-propyl-3,4,4a,9b-tetrahydrodibenzofuran-3-yl)acetic Acid (16). $LiOH·H_2O$ (33 mg, 0.78 mmol) was added to a stirred solution of **14** (55 mg, 0.157 mmol) in 60% THF–water. After 8 h, the mixture was diluted with ether (6 mL) and water (6 mL). The aqueous layer was separated, acidified to pH 2 using 6 M aqueous HCl, and extracted with ether (2 × 6 mL). The organic extracts were dried ($MgSO_4$) and evaporated to yield the desired carboxylic acid **16** (50 mg, 100%) as a brownish solid: mp 176–181 °C; FT-IR (THF cast) 3700–2100, 2959, 1708, 1617, 1473, 1428, 1275, 1235, 1208 cm^{-1}; ^1H NMR (THF-d_8, 200 MHz) δ 0.95 (t, J = 7.1 Hz, 3 H), 1.48–1.68 (m, 3 H), 2.30 (d, J = 7.2 Hz, 2 H), 2.36–2.58 (m, 3 H), 2.68–2.88 (m, 1 H), 3.89–3.99 (m, 1 H), 4.97–5.07 (m, 1 H), 5.70 (d, J = 10.5 Hz, 1 H), 5.81 (dt, J = 10.5, 2.5 Hz, 1 H), 6.78 (s, 1 H), 7.15–8.6 (br, 1 H); exact mass, m/z calcd for $C_{17}H_{19}ClO_4$ 322.0971, found 322.0962.

Ethyl (±)-(6-Chloro-9-hydroxy-8-propyl-1,2,3,4-tetrahydrodibenzofuran-3-yl)acetate (17). $RhCl_3·3H_2O$ (50 mg, 0.21 mmol) was added to a stirred solution of **14** (150 mg, 0.428 mmol) in 20% EtOH–benzene[8] (6 mL) contained in a 10-mL round-bottomed flask equipped with a condenser. The flask was lowered into an oil bath preheated at 65 °C, and the mixture was stirred at that temperature for 18 h, allowed to cool to room temperature, and evaporated. Flash chromatography of the black residue over silica gel (1.5 × 12 cm) using 20% EtOAc–hexane afforded **17** (125 mg, 84%) as a white solid: mp 123–124 °C; FT-IR ($CHCl_3$ cast) 3499, 1717, 1474, 1195, 854 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.01 (t, J = 7.4 Hz, 3 H), 1.32 (t, J = 7.0 Hz, 3 H), 1.68 [sextet (J = 7.5 Hz) superimposed on a m, 3 H], 2.00–2.11 (m, 1 H), 2.40–2.60 (m) and 2.60 (t, J = 7.8 Hz) [both signals together correspond to 6 H], 2.80–3.10 (m, 3 H), 4.20 (q, J = 7.0 Hz, 2 H), 4.79 (s, 1 H), 6.95 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.79, 14.20, 20.74, 23.37, 28.59, 29.14, 30.97, 31.14, 40.08, 60.51, 107.73, 112.02, 118.68, 121.94, 124.57, 145.74, 149.67, 152.20, 172.55; exact mass, m/z calcd for $C_{19}H_{23}ClO_4$ (^{35}Cl) 350.1285 and (^{37}Cl) 352.1255, found (^{35}Cl) 350.1289 and (^{37}Cl) 352.1267. Anal. Calcd for $C_{19}H_{23}ClO_4$: C, 65.04; H, 6.61; O, 18.24. Found: C, 65.15; H, 6.54; O, 18.07.

(±)-(6-Chloro-9-hydroxy-8-propyl-1,2,3,4-tetrahydrodibenzofuran-3-yl)acetic Acid (18). Hydrolysis of **17** (55 mg), under identical conditions with those used for **14**, afforded the acid **18** (50 mg, 100%) as a solid: mp 205–207 °C; FT-IR (THF cast) 3700–2100 (including peak at 3486), 1685, 1474, 1344, 1280, 1184, 852 cm^{-1}; ^1H NMR (THF-d_8, 300 MHz) δ 1.0 (t, J = 7.6 Hz, 3 H), 1.50–1.78 (m, 3 H), 1.95–2.15 (m, 1 H), 2.30–2.60 (m, 4 H), 2.66 (t, J = 7.9 Hz, 2 H), 2.74–3.11 (m, 3 H), 6.92 (s, 1 H), 7.55 (br, 1 H); exact mass, m/z calcd for $C_{17}H_{19}{}^{35}ClO_4$ 322.0972, found 322.0968.

Ethyl (1α,3α,6α,7α)-(±)-3-(2-Bromophenoxy)bicyclo[4.1.0]hept-4-ene-7-carboxylate (3).[15] Diethyl azodicarboxylate (0.21 mL, 1.32 mmol) was added over 2 min to a cold (−40 °C) and stirred solution of Ph_3P (0.35 g, 1.32 mmol) in dry THF (8 mL). After 30 min at −40 °C, the mixture became a thick paste and was therefore allowed to attain room temperature (over 30 min) and diluted with dry THF (5 mL). The suspension, which could now be stirred, was cooled to −40 °C and alcohol **2** (240 mg, 1.32 mmol) in dry THF (2 mL + 1 mL rinse) was injected over 3 min by cannula. After being stirred at −40 °C for 1 h, and then

(15) The stereochemical assignment is tentative: see text.

at −20 °C for 1 h, 2-bromophenol (81 μL, 0.66 mmol) was injected over 2 min. All the solids dissolved as soon as the addition was complete. With the cold bath left in place, the mixture was allowed to attain room temperature (over ca. 1 h), and the solvents were then evaporated. Flash chromatography of the residue over silica gel (2 × 18 cm) using 12% ether–hexane afforded crude 3, which was further purified on a Chromatotron [circular plate coated with a 2-mm-thick adsorbent (silica gel 60 PF_{254} containing gypsum)]. Successive elution with 4%, 8%, and 12% ether–hexane gave pure 3 (72 mg, 33%) as a colorless oil: FT-IR ($CHCl_3$ cast) 1720, 1475, 1183 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.0 Hz, 3 H), 1.63 (t, J = 3.8 Hz, 1 H), 1.82–2.03 (m, 3 H), 2.55–2.70 (m, 1 H), 4.13 (q, J = 7.0 Hz, 2 H), 4.55–4.65 (m, 1 H), 5.72 (br d, J = 10.2 Hz, 1 H), 6.18 (dm, J = 10.2 Hz, 1 H), 6.82–6.93 (m, 2 H), 7.20–7.30 (m, 1 H), 7.50–7.57 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.26, 19.09, 20.39, 24.60, 27.09, 60.71, 71.32, 113.63, 115.77, 122.58, 126.50, 127.94, 128.36, 133.68, 154.31, 172.52; exact mass, m/z calcd for $C_{16}H_{17}{}^{79}BrO_3$ 336.0362, found 336.0350. Anal. Calcd for $C_{16}H_{17}BrO_3$: C, 56.98; H, 5.08; O, 14.23. Found: C, 56.84; H, 4.91; O, 14.28.

Ethyl (3α,4aα,9bα)-(±)-(3,4,4a,9b-Tetrahydrodibenzofuran-3-yl)acetate (4). Et_3B (1 M in hexane, 0.22 mL, 0.22 mmol) and then Bu_3SnH (0.231 mL, 0.878 mmol) were added to a stirred solution of 3 (140 mg, 0.439 mmol) in dry hexanes (18 mL). The mixture was stirred at 35 °C for 24 h. The solvent was then evaporated and the residue was diluted with ether (6 mL) and stirred with an excess of KF in water. After 1 h, the mixture was diluted with ether (20 mL) and the organic layer was washed with water (6 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 12 cm) using 5–10% EtOAc–hexane afforded 4 (71 mg, 67%) and an unidentified side product (12 mg). Compound 4: FT-IR ($CHCl_3$ cast) 2860, 1731, 1597, 1477, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, J = 7.2 Hz, 3 H), 1.58–1.78 (m, 2 H), 2.31–2.41 [m, including a d at δ 2.35, (J = 7.2 Hz), 3 H], 2.72–2.92 (m, 1 H), 3.79 (br d, 7.2 Hz, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 5.06 (m, 1 H), 5.72 (br s, 2 H), 6.77–6.90 (m, 2 H), 7.05–7.12 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.30, 26.90, 31.49, 40.25, 41.06, 60.45, 80.70, 109.94, 120.58, 124.51, 127.19, 128.28, 130.78, 130.86, 159.37, 172.12; exact mass, m/z calcd for $C_{16}H_{18}O_3$ 258.1255, found 258.1252.

Acknowledgment of financial support is made to the Natural Sciences and Engineering Research Council of Canada, to Merck Frosst Canada, and to the University of Alberta. S.D. holds a 1967 Science and Engineering Scholarship (N.S.E.R.C.), a Steinhauer Award of Distinction (Province of Alberta), and scholarships from the F.C.A.R. (Quebec), the A.H.F.M.R. (Alberta), and the University of Alberta. We thank Dr. B. D. Santarsiero (Universitty of Alberta) for the X-ray structure determination.

Registry No. 2, 135189-62-7; 3, 135145-37-8; 4, 135145-38-9; 5, 21449-12-7; 6, 135145-39-0; 7, 135145-40-3; 8, 85696-74-8; 9, 135145-41-4; 10, 135145-42-5; 11, 135145-43-6; 12, 135145-44-7; 13, 135145-45-8; 14, 135145-46-9; 15, 135145-47-0; 16, 135189-63-8; 17, 135145-48-1; 18, 135145-49-2; 2-bromophenol, 95-56-7.

Supplementary Material Available: ^1H NMR spectra of 2, 4, 13, 15, 16, and 18 (6 pages). Ordering information is given on any current masthead page.

$NiCl_2$(dppe)-Catalyzed Geminal Dialkylation of Dithioacetals and Trimethylation of Ortho Thioesters[1]

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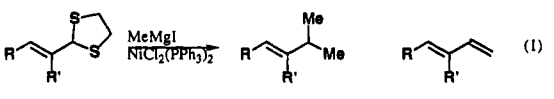
Received February 19, 1991

$NiCl_2$(dppe)-catalyzed cross-coupling of cinnamaldehyde dithioacetals gave the corresponding geminal dimethylation products in excellent yields. Allylic ortho thioesters afforded regioselectively the corresponding trimethylation products. The reaction may occur via an 18-electron π-allyl intermediate, which undergoes facile reductive elimination to afford the geminal dimethylation product. Benzylic dithioacetals having an ortho amino group gave 2-isopropylanilines exclusively. The reaction of benzylic dithioacetals with EtMgBr under the same conditions yielded geminal diethylation products.

We recently reported a series of new nickel-catalyzed olefination reactions of dithioacetals for the synthesis of substituted styrenes, allylsilanes, vinylsilanes, silylated butadienes, and other substituted butadienes.[3] These reactions involve a successive coupling process and a β-elimination step (eq 1). Theoretically, the two carbon–



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sulfur bonds in dithioacetals can both be replaced by carbon–carbon bonds, hence producing *gem*-dialkyl systems. In this case, the catalytic cycle would consist of two sequential reductive elimination steps. The selectivity between geminal dialkylation versus olefination may depend on the nature of the catalyst. It is generally believed that a saturated 18-electron organometallic species would favor reductive elimination over β-elimination, and the

(1) Transition Metal Promoted Reactions. 38.

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