with decyllithium then yields the pheromone.

These results show that the synthetic scope of the ene reaction of acrylate can be considerably extended by this modified Lewis acid catalyst.

Experimental Section

GC analysis was performed on a Hewlett-Packard 402 gas chromatograph with a column packed with 5% FFAP on Chromosorb W at 150–170 °C. The branched ketones were separated from the straight chain ketones on a 3.8% UCW 98 on Chromosorb W column at 240 °C. The isomers **2** and **4** were separated on a PYE GCV apparatus equipped with a CW20M 50 m SCOT column. IR spectra were recorded with Perkin-Elmer 237 and 257 instruments. NMR spectra were obtained in CCl_4 using a Varian EM 360 spectrometer with tetramethylsilane as an internal standard. Melting points were recorded on a hot stage and are uncorrected. All yields are based on isolated products.

Ene Reaction between 1-Octene and Methyl Acrylate. $AlCl_3$ (5.85 g), KCl (0.848 g), and NaCl (0.803 g) were heated while well protected from moisture in a tube of Pyrex glass until a clear solution was obtained. After cooling to room temperature, the glass tube was placed in an acetone–CO_2 bath and 40 mL of methyl acrylate, 17 mL of 1-octene, and a few crystals of hydroquinone were added. When the contents had reached −78 °C, the tube was sealed by melting and put in a boiling water bath for 16 h. The workup procedure consisted of pouring the mixture on ice and dilute hydrochloric acid, extraction with ether, washing of the ether phase, and drying. Evaporation of the solvent and distillation afforded 8.6 g (40%) of 5-hendecenoic acid methyl ester: **2**/**4** ratio was 86:14; IR showed strong absorption at 970 cm^{-1}, suggesting mainly the *E* isomer; NMR δ 5.4–5.15 (m, 2 H), 3.55 (s, 3 H), 2.35–0.80 (m, 17 H), and distorted triplets centered at δ 2.15 and 0.9 corresponding to the allylic CH_2 (s) and the CH_3 at the end of the chain were observed; MS *m/e* 198 ($M^{+\cdot}$), 166 ($M - CH_3OH)^{+\cdot}$, 124 ($C_5H_4CH{=}CHCH{=}CH_2^{+\cdot}$) (McLafferty), 74 ($CH_3O{-}C(OH){-}CH_2^{+\cdot}$) (McLafferty).

Vicinal Bromochloro Ester 3. **2** (1.1 g, 5.55 mmol) was dissolved in 11 mL of CH_2Cl_2, and the solution was cooled to −78 °C in an acetone–CO_2 bath during saturation with HCl gas. Then 1.04 g of *N*-bromosuccinimide, which had been crystallized from water, was added in one portion. The temperature was then allowed to rise to −20 °C, maintaining HCl saturation. After 0.5 h at −20 °C, the mixture was poured on ice–$NaHSO_3$, extracted three times with ether, washed with $KHCO_3$ solution and water, and finally dried. Evaporation of the solvent gave 1.6 g of a colorless oil in 92% crude yield. GLC analysis of the product, which was not purified, showed that it was 93% pure. No olefin remained. IR 1740 cm^{-1} (CO); NMR δ 4.2–3.9 (broad unresolvable multiplet, 2 H), 3.67 (s, 3 H), 2.5–0.8 (m, 17 H). The NMR spectrum was very similar to the spectrum of **2**.

Formation of the Inverted Olefinic Ester Mixture. The product from the above reaction, 1.6 g, was dissolved in 60 mL of dry DMF, and 15 g of NaI was added with stirring. The temperature was then raised to 110–115 °C. After 4 h at this temperature, the mixture was poured out in H_2O and the water–DMF solution was extracted three times with light petroleum. The petroleum phase was then washed with $NaHSO_3$ solution and water and dried with magnesium sulfate. Evaporation of the solvent gave 0.99 g (99%) of a product that contained less than 1% of the bromochloro ester: **2**/**4** ratio was 20:80; IR showed weak absorption at 970 cm^{-1}, attributable to the *E* isomer present; NMR and mass spectra were practically identical with the spectra of the trans compound.

Ester Hydrolysis. The ester (0.81 g) was hydrolyzed in 5 mL of H_2O and 2 mL of EtOH with 0.3 g of KOH for 16 h at room temperature with occasional heating on a water bath at the beginning of the reaction. The usual workup procedure gave 0.77 g (95%) of acid as a colorless oil: IR showed typical broad carboxylic acid bonds at 3000–2000 cm^{-1}; NMR spectrum was similar to the NMR spectrum of the ester, except for the disappearance of the O–CH_3 and the appearance of a COOH proton at δ 11.05.

(*Z*)-6-Heneicosen-11-one (1). To 150 mg of lithium powder in 10 mL of ether was added 2.2 g of decylbromide in 3 mL of ether during 1 h at −10 to −15 °C. After additional stirring for 2 h, GLC analysis after hydrolysis of a sample showed only decane.

This decyllithium solution was then added dropwise at 0 °C with vigorous stirring to a solution of the acid in 10 mL of THF. The mixture was stirred for 16 h at room temperature and refluxed for 0.5 h. The solution was then slowly added to 100 mL of water with vigorous stirring. Extraction of the water phase three times with ether, washing, drying with magnesium sulfate, and evaporation of the ether and the majority of the decane gave 1.4 g of product. Acidification of the water phase and extraction with ether afforded 0.12 g of acid. GC analysis of the ketone revealed the existence of about 3.9% of the branched isomer. This product (0.8 g) was then chromatographed on SiO_2 with 10% ether in light petroleum as eluant. A slight enrichment could be achieved; 0.46 g of ketone was obtained, the GC analysis of which showed 2.5% of the branched isomer. This corresponds to a yield of 62% based on the acid and 75% based on consumed acid.

The *E* and *Z* ketones **7** and **1** could not be satisfactorily separated on any column tried, including the SCOT column. The *E*/*Z* ratio should, however, be 20:80 since neither the hydrolysis nor the reaction with decyllithium concerns the double bond: IR 1720 cm^{-1} (CO) and weak absorption at 970 cm^{-1}; NMR δ 5.25 (m, 2 H), 2.2 (t, 4 H), 1.9 (m, 4 H), 1.8–1.1 (m, 24 H), 1.1–0.8 (overlapping distorted triplets, 6 H); MS (70 eV) *m/e* 308 ($M^{+\cdot}$), 197 ($C_{10}H_{21}CO{-}C_2H_4^{+\cdot}$), 169 ($C_{10}H_{21}CO^{+\cdot}$), 124 ($C_5H_4CH{=}CHCH{=}CH_2^{+\cdot}$) (McLafferty).

(*E*)-6-Heneicosen-11-one (7). By hydrolyzing the ester mixture obtained in the ene reaction, the *E* ketone was synthesized the same way as described above. From 1.84 g (10 mmol) of acid there was obtained after recrystallization from ethanol 1.7 g of **7**: 55% yield based on total acid and 73% yield based on not recovered acid (0.45 g of acid could be recovered); mp 36 °C; IR showed strong absorption at 970 cm^{-1} (trans double bond); NMR and mass spectra were practically identical with the spectra of the cis compound.

Registry No.—**1**, 54844-65-4; **2**, 67270-84-2; **3**, 67254-48-2; **4**, 54471-23-7; **6**, 67270-85-3; **7**, 54844-66-5; methyl acrylate, 96-33-3; 1-octene, 111-66-0; decyl bromide, 112-29-8; $AlCl_3$, 7446-70-0; NaCl, 7647-14-5; KCl, 7447-40-7.

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Stereochemical Control of Transpositional Allylic Oxidation[1,2]

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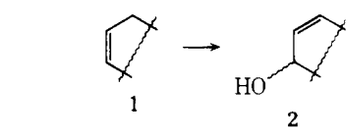
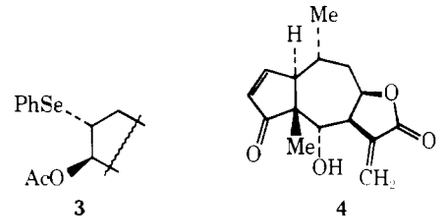
The facility of transpositional allylic oxidation (eq 1) was greatly increased by the discovery by Reich,[4] and also Sharpless[5a] and Clive,[5b] that PhSeX could be utilized for effecting the process. Based on ^1H NMR spectra of intermediates of type **3**, Reich[4] concluded that the PhSeOAc addition to **1** oc-



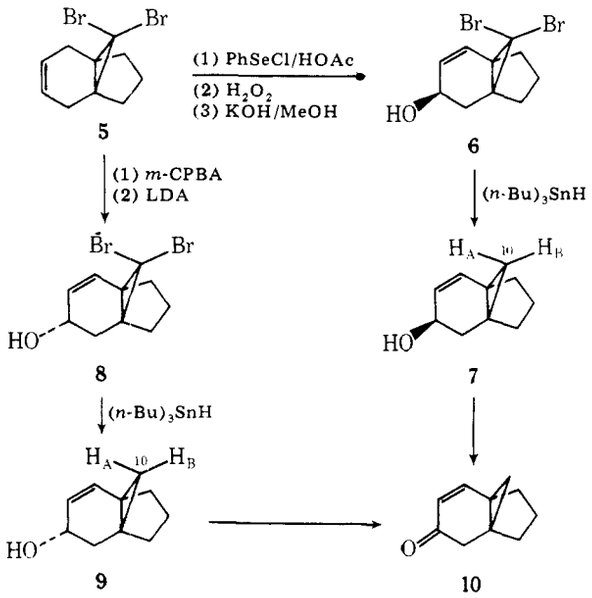
1 2 (1)



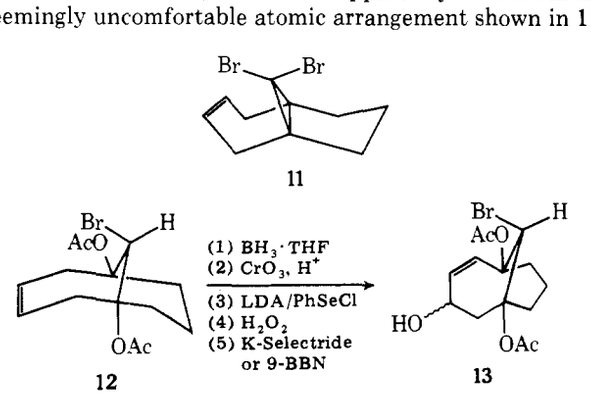
3 4

curred in a trans fashion. If so, the configuration of the hydroxyl group in **2**, as produced from base-mediated epoxide ring-opening,[6] might be epimeric with that formed via the organoselenium adduct.

In the course of our work aimed at the total synthesis of helenalin (**4**),[7] we had occasion to investigate this supposition, the results of which we now report. When 10,10-dibromo[4.3.1]propell-3-ene (**5**)[8] was phenylselenenylated, oxidized, and hydrolyzed, only one allylic alcohol (**6**) was obtained; reduction of **6** with tin hydride afforded **7**. Alternatively, epoxidation of **5** produced a single epoxide, ring opening of which gave **8**; tin hydride reduction of **8** led to **9**, shown to be epimeric with **7** by the fact that both could be oxidized to **10**. Regardless of the stereochemistry of **6** and **8**, it is apparent that the two methods utilized provided the two possible allylic alcohols stereoselectively (i.e., there was no crossover). The stereochemistry of **6** and **8** was proven by measuring the Eu(dpm)$_3$-shifted ^{1}H NMR spectra of **7** and **9**, respectively (see Table I). It is thus concluded that initial attack on **5** occurs from the less hindered side away from the bromine atom; in the case of selenenylation, acetate subsequently attacks from the side syn to the bromine atom.



We note some rather subtle conformational effects are at work in additions to **5**, for attack is apparently initiated in the seemingly uncomfortable atomic arrangement shown in **11**.



On the other hand, the related molecule **12** (known to exist as shown at least in the solid state[9]) did not react with PhSeCl/HOAc, even under forcing conditions. In this case, transpositional allylic oxidation was achieved by the rather circuitous route indicated, where trans additions were avoided.[10] The difficulty with **12** is the bromine atom; its removal afforded a normally reactive olefin.[12]

Table I. Eu(DPM)$_3$-Induced ^{1}H NMR Shifts (LIS) (in ppm)

compd	H	[shift reagent]/[compd] 0.1	0.2	0.3
7[a]	H_A	1.32	4.11	7.28
	H_B	1.05		3.33
9[b]	H_A[c]	0.28	0.73	1.23
	H_B[c]	0.44	0.82	1.09

[a] Measured in CCl_4 solution. [b] Measured in $CDCl_3$ solution. [c] The assignments of H_A and H_B may be reversed.

Experimental Section

Infrared spectra were recorded on a Beckman IR-4250 spectrometer. The proton magnetic resonance spectra were obtained on Varian A-60, Varian HA-100, and Hitachi Perkin-Elmer R-20B spectrometers, using the indicated solvents and tetramethylsilane as an internal standard. The mass spectra were obtained on a high resolution MS-9 mass spectrometer. Some purifications were accomplished with a Waters M-6000 high-pressure liquid chromatograph utilizing 1 ft μ-Porasil or 8 ft Porasil-A preparative columns. Melting points are uncorrected.

***exo*-10,10-Dibromo[4.3.1]propell-2-en-4-ol (6).** To a stirring solution of 2.92 g (10 mmol) of **5**[8] and 1.92 g (10 mmol) of benzeneselenenyl chloride in 10 mL of HOAc was added a solution of 1.96 g (20 mmol) of KOAc in 15 mL of HOAc under nitrogen at room temperature. The initially red solution turned yellow immediately. After stirring for 4 h, the mixture was diluted with H_2O and extracted with ethyl acetate. The combined extracts were washed with H_2O and saturated K_2CO_3 solution, dried, and concentrated to yield a yellow oil which was dissolved in 40 mL of dry THF and cooled in ice; 10 mL of 30% H_2O_2 was then added dropwise at 0–4 °C. Stirring was continued for 17 h. The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined extracts were washed with saturated NaCl solution and dried, and the solvent was removed to afford 3.26 g of solid material. This was recrystallized from ether/hexane to give 2.96 g (85%) of *exo*-10,10-dibromo[4.3.1]propell-2-ene 4-acetate: mp 79–82 °C; IR (CCl_4) 3045, 1745, 1630, 1235 cm^{-1}; ^{1}H NMR (CCl_4) δ 5.7 (brd s, 2 H), 5.35–4.95 (m, H_4), 2.8–1.5 (m, 11 H, including an acetate s at δ 2.0). Anal. Calcd for $C_{12}H_{14}O_2Br_2$: *m/e* 347.9374. Found: *m/e* 347.9361.

To a solution of 2.04 g of the above acetate in 10 mL of MeOH was added 68 mL of a 1.0 M KOH/95% MeOH solution. The resulting reaction mixture was stirred for several hours (or overnight), whereafter H_2O was added, the MeOH evaporated, and 100 mL of $CHCl_3$ added. The $CHCl_3$ layer was washed with H_2O (until neutral) and then dried over K_2CO_3. Filtration and solvent evaporation afforded 1.78 g (99%) of **6**: mp 102.5–103 °C; IR ($CDCl_3$) 3613 (free OH), 3050, 1635, 1088 cm^{-1}; ^{1}H NMR (CCl_4) δ 5.84 (brd s, 2 H), 4.25 (apparent quartet, H_4), 2.8–1.4 (m, 9 H). Anal. Calcd for $C_{10}H_{12}Br_2O$: C, 38.99; H, 3.93. Found: C, 38.87; H, 3.87.

***exo*-[4.3.1]Propell-2-en-4-ol (7).** A mixture of 50 mg (0.16 mmol) of **6** and 118 mg (0.41 mmol) of *n*-Bu_3SnH[13] was heated in an 80 °C oil bath for ca. 7 h. After cooling, the resulting material was chromatographed on a preparative thin-layer plate utilizing 95% ethereal hexane as the developing solvent. Obtained was 19 mg (81%) of **7**: IR (CCl_4) 3630 (s, free OH), 3595–3170 (brd, OH), 3040, 3010, 1640, 1030 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.60 (d, H_2, J = 10 Hz), 5.48 (dd, H_3, J = 5 and 10 Hz), 4.15 (q, H_4, J = 5 Hz), 2.3–1.1 (m, 9 H), 0.76 (center of AB quartet, 2 H_{10}, J = 5 Hz). Anal. Calcd for $C_{10}H_{14}O$: *m/e* 150.1045. Found: *m/e* 150.1042.

***endo*-10,10-Dibromo[4.3.1]propell-2-en-4-ol (8).** To a solution of 7.0 g (23.5 mmol) of **5**[8] in 20 mL of $CHCl_3$ was added, at 0 °C, a solution of 5.0 g (24.5 mmol) of *m*-chloroperbenzoic acid (*m*-CPBA) in 60 mL of $CHCl_3$. After stirring the reaction mixture for 4 h at room temperature, a dilute $NaHSO_3$ solution was added to destroy any excess *m*-CPBA. After dilution with ether, the organic phase was washed with a 5% NaOH solution and a saturated NaCl solution and dried over K_2CO_3. Filtration and evaporation of solvent afforded a white solid identified as *endo*-3,4-epoxy-10,10-dibromo[4.3.1]propellane (7.2 g, 98%): mp 102–104 °C; IR (CCl_4) 1190 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.9 (brd s, 2 H), 2.6–1.4 (m, 10 H). Anal. Calcd for $C_{10}H_{12}Br_2O$: *m/e* 305.9255. Found: *m/e* 305.9256.

A solution of 0.24 mL (3.6 mmol) of Me_2NH in 5 mL of THF was cooled to 0 °C in a flame-dried flask. To this was added 2.7 mL (3.6 mmol) of 1.33 M *n*-BuLi (previously titrated with diphenylacetic acid). After stirring the resulting mixture for 15 min, a solution of 0.74 g (2.4 mmol) of the above synthesized epoxide in 10 mL of THF was

added dropwise via syringe. After completion of the addition, stirring was continued for 5 min, after which the mixture was diluted with ether, washed with 1 N HCl and then a saturated NaCl solution, dried over Na_2CO_3, filtered, and stripped of solvent. The residue was chromatographed on a silica gel column. Elution with 80% ethereal hexane afforded 0.16 g of starting epoxide; further elution with 67% ethereal hexane provided 0.45 g (78%) of **8**: mp 88.5–89.5 °C; IR (KBr) 3500–3100 (OH), 3020, 2920, 1630, 1430, 1010 cm^{-1}; ^1H NMR (CCl_4) δ 5.98 (center of apparent d with 2 Hz splitting, 2 H), 4.15 (m, H_4), 2.5–1.5 (m, 9 H). Anal. Calcd for $C_{10}H_{12}Br_2O$: C, 39.00; H, 3.95; Br, 51.88. Found: C, 39.17; H, 3.93; Br, 51.83.

***endo*-[4.3.1]Propell-2-en-4-ol (9).** Into a dry NMR tube was introduced 0.106 g of benzene (internal standard), 0.354 g (2.0 mmol) of *n*-Bu_3SnH,[13] and 0.083 g (0.27 mmol) of **8**. The mixture became instantly warm, but was then cooled in liquid N_2 and sealed. The tube was then placed in an NMR probe and the reaction followed over a 24-h period (tube was left in probe continuously). After 3 h, integration indicated that ca. 38% of monobromocyclopropyl products and ca. 55% of **9** had been formed. After 24 h, only ca. 8% of monobromocyclopropyl products remained, while ca. 92% of **9** had been produced. The tube was then opened, and pure **9** was isolated via thin-layer chromatography: IR (CCl_4) 3610 (free OH), 3340 (brd, OH), 3060, 3015, 3000, 2920, 1630, 1450, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05 (dd, H_2, $J_{2,3}$ = 10 Hz, $J_{2,4}$ = 2.5 Hz), 5.38 (dd, H_3, $J_{3,4}$ = 1.5 Hz), 4.15 (m, H_4), 2.7–0.8 (m, 9 H), 0.60 (center of AB quartet, 2 H_{10}, J = 5 Hz). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.99; H, 9.40.

[4.3.1]Propell-2-en-4-one (10). The oxidations of **7** and **9** were performed according to the method of Brown.[14]

(1) From 7. To a stirring solution of 38.5 mg (0.26 mmol) of **7** in 1 mL of Et_2O at 0 °C was added 0.17 mL of chromic acid solution (prepared according to Brown[14]). The reaction mixture was stirred for 10 min at 0 °C, following which the cooling bath was removed and the solution allowed to stir for an additional 2 h. The now green solution was diluted with ether, washed with saturated $NaHCO_3$ and then saturated NaCl, and dried over $MgSO_4$. Filtration and evaporation gave 25 mg of crude yellow oil. Thin-layer chromatographic purification (90% ethereal hexane) gave 20.5 mg (54%) of **10**: IR (CCl_4) 3070, 3030, 1680, 1660, 1610, 1400 cm^{-1}; ^1H NMR (CCl_4) δ 7.10 (d, H_2, $J_{2,3}$ = 10 Hz), 5.56 (d, H_3), 2.82 (d, $H_{5\text{-endo}}$, $J_{5\text{-exo},5\text{-endo}}$ = 18 Hz), 2.32 (d, $H_{5\text{-exo}}$), 2.1–1.3 (m, 6 H), 1.17 (d, H_{10A}, $J_{10A,10B}$ = 5 Hz), 0.37 (d, H_{10B}). Anal. Calcd for $C_{10}H_{12}O$ (P − 1, relative intensity 19% of P): *m/e* 147.0810. Found: *m/e* 147.0804.

(2) From 9. The above procedure was used to oxidize 0.039 g (0.26 mmol) of **9** in 3 mL of Et_2O. The yield of **10** was ca. 30 mg (78%).

***syn*-10-Bromo-1,6-diacetoxybicyclo[4.3.1]dec-2-en-4-ol (13).** In a 250-mL flask was dissolved 10 g (30 mmol) of **12** in 80 mL of ether. After cooling to 0 °C, 62 mL (62 mmol) of a 1 M BH_3·THF solution was added dropwise. The solution was then allowed to warm to 25 °C and stirred an additional 2 h. The solution was again cooled to 0 °C, and the excess borane was cautiously destroyed with water. After the addition of 100 mL of ether, a solution of 18 g (60 mmol) of sodium dichromate in 12 mL of concentrated H_2SO_4 and 160 mL of H_2O was added, following which the solution was allowed to warm to 25 °C and stirred for 16 h. The solution was then transferred to a separatory funnel, 100 mL of ether added, and the organic layer washed with two 100-mL portions of H_2O and one 100-mL portion of saturated $NaHCO_3$ solution. The organic solution was then dried over Na_2SO_4, and, after filtering, the solvent was removed on a rotary evaporator. Recrystallization from ether/hexane afforded 8.3 g (80%) of *syn*-10-bromo-1,6-diacetoxybicyclo[4.3.1]decan-3-one as white crystals: mp 93–94 °C; IR ($CDCl_3$) 3000, 2920, 2890, 1740, 1710, 1375, 1240, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (m, H_{10}), 3.21 (center of AB q, J = 14 Hz, 2 H_2), 2.8–1.5 (m, 10 H), 2.02 (s, 6 H, OAc).

In a 50-mL, flame-dried, three-neck flask fitted with an N_2 inlet and outlet (static pressure of N_2 maintained during the reaction) and an addition funnel (septum) was dissolved 5 g (14.5 mmol) of the above ketone in 100 mL of dry THF, and the solution was cooled to −78 °C. In a separate flask was prepared 15 mmol of LDA by the addition of 2.1 mL (15 mmol) of diisopropylamine to 9.4 mL (15 mmol) of 1.6 N *n*-BuLi in 50 mL of dry THF at −10 °C. After stirring for 15 min, the base solution was transferred to the addition funnel and diluted with another 50 mL of ether. The base solution was then added dropwise, and after the addition was complete the solution was stirred at −78 °C for 20 min followed by rapid quenching with a solution of 3.75 g (20 mmol) of phenylselenenyl chloride in 30 mL of dry THF. The solution was then warmed to 0 °C, and a solution of 5 mL of 30% H_2O_2, 5 mL of H_2O, and 0.3 mL of HOAc was added dropwise. After the addition, the solution was allowed to warm to 25 °C and stirred for 5 h. Another 5 mL of H_2O_2 was then added, and the solution was allowed to stir an additional 5 h. Much of the excess solvent was removed on a rotary evaporator, and 100 mL of ether was then added. The solution was transferred to a separatory funnel and the aqueous layer extracted twice with 100-mL portions of ether. The ether fractions were combined, washed twice with 100-mL portions of saturated NH_4Cl solution, and dried over Na_2SO_4. After filtering, the solvent was removed on a rotary evaporator and the product chromatographed on silica gel (hexane/ether) to afford 3 g (60%) of *syn*-10-bromo-1,6-diacetoxybicyclo[4.3.1]dec-2-en-4-one as white crystals: mp 107–108 °C; IR ($CDCl_3$) 2960, 1740, 1670, 1370, 1240, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.42 (dd, H_2, $J_{2,3}$ = 14 Hz, $J_{2,10}$ = 2.5 Hz), 6.02 (d, H_3), 5.76 (narrow m, H_{10}), 3.31 (narrow m, 2 H_5), 2.7–1.5 (m, 6 H), 2.10 (s, 3 H, OAc), 2.02 (s, 3 H, OAc). Anal. Calcd for $C_{14}H_{17}O_5Br$: *m/e* 344.0260. Found: *m/e* 344.0261.

(1) K-Selectride.[15] The above enone (100 mg, 0.3 mmol), dissolved in 10 mL of dry THF, was then placed in a 50-mL, flame-dried, three-neck flask fitted with an N_2 inlet and outlet (static pressure of N_2 maintained during the reaction) and an addition funnel septum). After cooling the solution to −78 °C, 1.2 mL (0.6 mmol) of potassium tri-*sec*-butylborohydride[15] (K-Selectride, 0.5 M in THF) was added dropwise. After the addition was complete, the solution was stirred for 1.5 h at −78 °C followed by quenching with saturated NH_4Cl solution. The solution was then transferred to a separatory funnel and extracted with three 50-mL portions of ether. The ether fractions were combined, washed twice with 50-mL portions of H_2O, and dried over Na_2SO_4. After filtering and removal of the solvent on a rotary evaporator, the resulting oil was purified by LC to afford 75 mg (72%) of **13**, mp 94–96 °C, assigned the endo configuration at C_4 (i.e., hydroxyl away from Br) on the basis of its ^1H NMR spectrum (see below).

(2) 9-BBN.[16] Following Brown's procedure,[16] 1.0 g (2.9 mmol) of the enone in 30 mL of THF was reduced with 9-BBN (6.0 mL, 0.5 M in THF) to afford 0.81 g of crude oil which was chromatographed on silica gel (35% ether/65% hexane as eluent) to give **13a** and **13b.**

syn-10-Bromo-1,6-diacetoxybicyclo[4.3.1]dec-2-en-*endo*-4-ol (**13a**): 121 mg (12%); mp 94–96 °C; IR ($CDCl_3$) 3620, 3460, 2980, 1740, 1295, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.95 (dd, H_2, $J_{2,3}$ = 13 Hz, $J_{2,10}$ = 2.5 Hz), 5.59 (m, H_3, H_{10}), 5.5–5.1 (m, H_4), 3.0–1.5 (m, 9 H), 2.02 (s, 3 H, OAc), 2.01 (s, 3 H, OAc). Anal. Calcd for $C_{14}H_{19}O_5Br$: *m/e* 346.0416. Found: *m/e* 346.0427.

syn-10-Bromo-1,6-diacetoxybicyclo[4.3.1]dec-2-en-*exo*-4-ol (**13b**): 328 mg (33%); mp 124–127 °C; IR ($CDCl_3$) 3620, 3450, 1735, 1250, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80 (brd s, H_2, H_3), 5.67 (brd s, H_{10}), 5.0–4.5 (m, H_4), 3.2–1.4 (m, 9 H), 2.13 (s, 6 H, OAc). Anal. Calcd for $C_{14}H_{19}O_5Br$: *m/e* 346.0416. Found: *m/e* 346.0420.

Registry No.—**5,** 38749-47-2; **6,** 67421-43-6; **7,** 67421-44-7; **8,** 67462-75-3; **9,** 67462-76-4; **10,** 67421-45-8; **12,** 58738-40-2; **13a,** 67421-46-9; **13b,** 67426-17-9; i, 17048-59-8; ii, 67421-49-2; iii, 67462-77-5; *exo*-10,10-dibromo[4.3.1]propell-2-ene 4-acetate, 67421-47-0; *endo*-3,4-epoxy-10,10-dibromo[4.3.1]propellane, 67421-48-1; *syn*-10-bromo-1,6-diacetoxybicyclo[4.3.1]dec-2-en-4-one, 67452-69-1; *syn*-10-bromo-1,6-diacetoxybicyclo[4.3.1]decan-3-one, 67426-16-8.

References and Notes

(1) This is Part 20 of the "Propellanes" series.
(2) This work was supported in part by the NSF, the ISU Research Foundation, and a Departmental Young Faculty Development Award.
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(10) Singlet oxygen did not react with **12,** while the epoxide generated from **12** did not react with LDA/Et_2O or with benzene selenolate anion.[11] Even Br_2 (CH_2Cl_2) did not add to **12,** but rather reacted slowly at room temperature to afford allylic substitution products.
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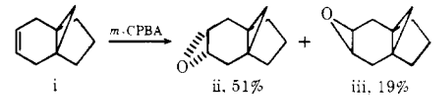
(12) Indeed the high stereoselectivity observed for **5** is also due to the bromines. For example, i affords a mixture of endo (ii) and exo epoxides (iii).



i ii, 51% iii, 19%

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Selective Lithiation/Carbonation of Polyhalobenzenes: An Improved Synthesis of Furosemide-7-^{14}C

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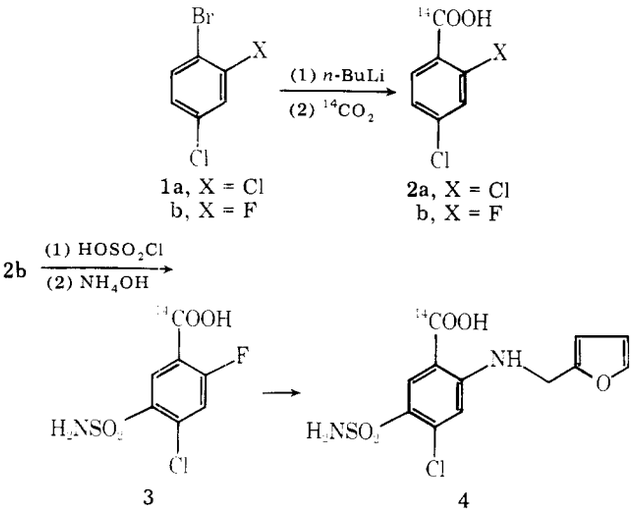
Furosemide (4) usually has been prepared from 4-chloro-2-fluorobenzoic acid (**2b**) by chlorosulfonation and ammonolysis to the sulfonamide (**3**) followed by reaction with furfurylamine.[1-3] In an earlier synthesis of furosemide-7-^{14}C,[4] the required labeled intermediate **2b** was prepared from 4-chloro-2-fluoroaniline and dipotassium diamminocupricyanide-^{14}C by a modified Sandmeyer reaction followed by hydrolysis of the resulting 4-chloro-2-fluorobenzo-^{14}C-nitrile.



The more direct preparation of **2b** from 4-chloro-2-fluorobromobenzene (**1b**) by butyllithium exchange and carbonation was not attempted because the closely related 2,4-dichlorobromobenzene (**1a**) reportedly did not afford 2,4-dichlorobenzoic acid (**2a**) by that procedure.[5]

We now report that, in fact, both **1a** and **1b** do undergo selective lithiation/carbonation to afford the corresponding acids **2a** and **2b** in high yields. The conversion of carbon-14 labeled **2b** to furosemide-7-^{14}C (**4**) by a simplified version of the earlier process[4] is also described.

Reaction of **1a**[6] in ether with *n*-butyllithium at −80 °C for a short time followed by carbonation at −80 °C with carbon-14 dioxide afforded the acid **2a** in 98% yield based on carbon-14 dioxide. Similarly, lithiation/carbonation of **1b**[7] gave **2b** in quantitative radiochemical yield. Treatment of the labeled **2b** with chlorosulfonic acid followed by concentrated ammonium hydroxide afforded labeled **3** in 91.5% yield (crude). Reaction of the crude **3** with furfurylamine gave crude furosemide-7-^{14}C (**4**) in 32% yield.

Experimental Section

Melting and boiling points are uncorrected. Radioactivity was measured by the liquid scintillation technique using a Packard Tricarb Model 2010 spectrometer. Radiochemical purity was determined on thin-layer chromatograms with a Packard Model 7201 radiochromatogram scanner system. Spectra were recorded on standard instruments. All reactions were conducted under nitrogen unless otherwise indicated.

2,4-Dichlorobenzoic-7-^{14}C Acid (2a). A solution of 1-bromo-2,4-dichlorobenzene[8] (**1a**; 1.02 g, 4.5 mmol) in anhydrous diethyl ether (15 mL) contained in an ordinary round-bottom flask was frozen with liquid nitrogen, and a solution of *n*-butyllithium in hexane (3 mL, 2.8 mmol) was added and frozen. The flask was evacuated and then warmed to −80 °C with stirring. From 2 to 5 min after the reaction mixture became a homogeneous solution, it was refrozen with liquid nitrogen and carbon-14 dioxide (1.51 mmol) was transferred into the flask. The mixture was warmed to −80 °C, stirred for 20 min, made alkaline with 0.9 N sodium hydroxide solution (10 mL, 9 mmol), and thoroughly extracted with ether, which was discarded. Acidification of the aqueous phase with dilute sulfuric acid and extraction with ether afforded **2a** (282 mg, 1.48 mmol), 98% yield based on carbon-14 dioxide. Nonradioactive material prepared by the same procedure from ordinary carbon dioxide was found to be identical with authentic 2,4-dichlorobenzoic acid by melting point, IR, and TLC (silica gel; dichloromethane-ethyl acetate–acetic acid, 8:1:1 v/v/v).

4-Chloro-2-fluorobenzoic-7-^{14}C Acid (2b). In the same manner, 4-chloro-2-fluorobromobenzene[7] (**1b**; 440.3 mg, 2.1 mmol) was metalated with *n*-butyllithium (1.17 mmol) and carbonated with carbon-14 dioxide (1.08 mmol; specific activity 59.1 mCi/mmol) to afford **2b** in quantitative yield (209 mg). The product was radiochemically pure (TLC on silica gel; benzene-ethyl acetate–formic acid, 8:1:1 v/v/v). Material prepared with ordinary carbon dioxide in the same way was identical with authentic 4-chloro-2-fluorobenzoic acid.[1]

4-Chloro-2-fluoro-5-sulfamoylbenzoic-7-^{14}C Acid (3). The dry 4-chloro-2-fluorobenzoic-7-^{14}C acid was heated with freshly distilled chlorosulfonic acid (0.635 mL, 9.7 mmol) at 155 °C for 2 h. When cool, the entire reaction mixture was diluted with dichloromethane (4 mL) and transferred to a 10 mL addition funnel using additional dichloromethane (4 mL). The addition funnel was attached to a 100-mL flask containing concentrated ammonium hydroxide (4 mL) cooled to −30 °C, the dichloromethane solution was added dropwise very slowly with stirring, and the mixture was allowed to warm to room temperature. Evaporation of the dichloromethane under reduced pressure left an aqueous phase which was transferred to a liquid–liquid extractor, acidified with 6 N hydrochloric acid (1 mL), and extracted with diethyl ether for 20 h to afford the crude product (**3**; 248 mg, 0.98 mmol). Thin-layer chromatography (silica gel; ethylene dichloride–ethyl acetate, 2:3) showed the product to be approximately 60% of **3**, which was used in the next step without purification.

4-Chloro-*N*-furfuryl-5-sulfamoylanthranilic-7-^{14}C Acid (Furosemide-7-^{14}C; 4). The crude **3** (248 mg) was stirred with dioxane (1 mL) and freshly distilled furfurylamine (0.32 mL) at 110 °C for 2.5 h. Concentration of the reaction mixture under reduced pressure left a dark brown residual oil which was stirred vigorously with ethyl acetate (3 mL) and extracted six times with water (3 mL). Concentration of the aqueous extracts left a residue which was crystallized from methanol–water, 1:1 (4 mL), to give crude **4** (114.5 mg; radiochemical purity 95% by TLC using silica gel plates developed with acetonitrile–acetic acid, 99:1; R_f 0.68). Recrystallization of 15.1 mg of crude **4** with 20.2 mg of unlabeled furosemide (**4**) from methanol–water, 1:1 (2 mL), afforded 23 mg of radiochemically pure **4** of specific activity 57.2 μCi/mg.

Registry No.—**1a**, 1193-72-2; **1b**, 1996-29-8; **2a**, 67700-16-7; **2b**, 54416-83-0; **3**, 54416-84-1; **4**, 54416-85-2; $^{14}CO_2$, 51-90-1; furfurylamine, 617-89-0.

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