mixture became homogeneous. The reaction mixture was immediately cooled to −30 °C, and then 2.23 g (22 mmol) of triethylamine was added. The reaction mixture was stirred at room temperature for 3 days. The precipitate was removed by filtration and the solvent was removed in vacuo. The residue was recrystallized from a heptane–petroleum ether mixture to give 1.82 g (89%) of deep red crystals: mp 243–245 °C (lit. mp 240–241 °C,[15] 245–246 °C,[16] 245–247 °C[17]); ^{1}H NMR (deuteriochloroform) δ 1.33 (s, 36 H), 7.71 (s, 4 H); ^{13}C NMR (deuteriochloroform) δ 29.3 (s, CH_3), 35.7 (s), 126.1 (s), 136.5 (s), 150.9 (s), 186.9 (s, C=O); IR 2960, 2930, 2890, 1600, 1470, 1395, 1370, 1260, 1200, 910, 895 cm^{-1}; MS, m/z 408 ($M^{+\cdot}$). Anal. Calcd for $C_{28}H_{40}O_2$: C, 82.3; H, 9.9. Found: C, 82.2; H, 9.7.

Method B: Dibutylamine. The procedure of method A was followed with 23.7 g (50 mmol) of **1**, 3.9 g (55 mmol) of chlorine, and 25.9 (200 mmol) of dibutylamine in a total of 130 mL of heptane. The residue was triturated with hot petroleum ether (bp 35–60 °C) to give 11.5 g (56%) of deep red crystals identical in every respect with that prepared by method A.

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Registry No. **1**, 6386-58-9; **2**, 93110-24-8; **3**, 2455-14-3; 2,6-di-*tert*-butylphenol, 128-39-2; titanium tetrachloride, 7550-45-0; toluene, 108-88-3; sulfur monochloride, 10025-67-9; carbon tetrachloride, 56-23-5; chlorine, 7782-50-5; heptane, 142-82-5; triethylamine, 121-44-8; dibutylamine, 111-92-2.

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Preparation and Utilization of Corticosteroidal (π-Allyl)palladium Complexes. A Novel Entry to 6α,β-(Carboxymethyl)cortisol

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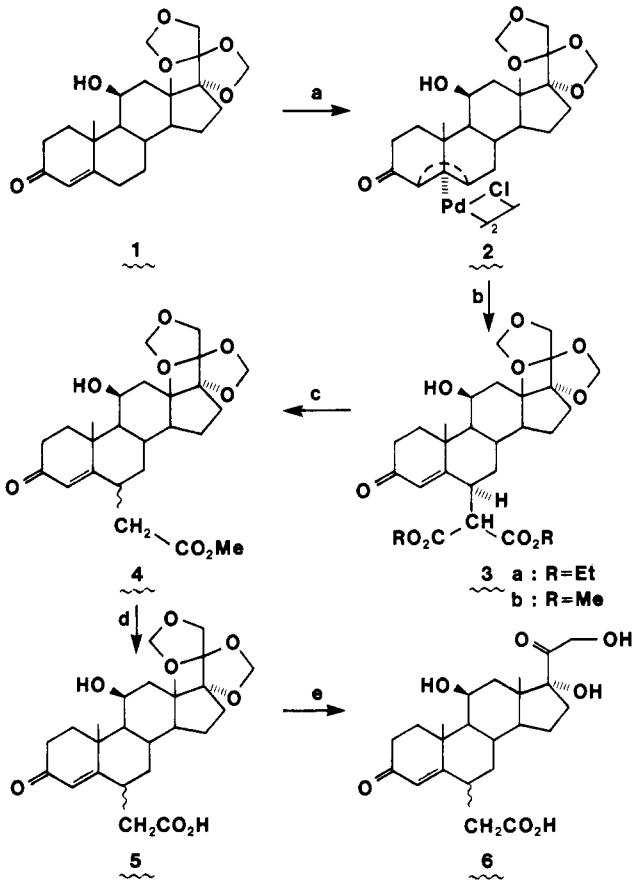
Corticosteroids possessing functionality at C-6 are valuable intermediates for the preparation of immunologically useful protein–hapten conjugates. Antibodies obtained from these conjugates often possess low in vitro cross-reactivities when compared to structurally similar steroids.[1] Thus, there is need for convenient preparations of C-6 functionalized precursors. Some of the more common routes to these compounds entail epoxidation of the 5-ene, 3-one ketal, followed by nucleophilic ring opening and dehydration–deprotection of the 6-substituted 3-one ketal, 4-ol.[1a,2] Many of these routes require several steps and suffer low to moderate yields.

During the past decade, several groups have demonstrated the synthetic utility of steroidal (π-allyl)palladium complexes;[3] however, to the best of our knowledge, no attempts have been made to prepare complexes from 11-substituted 3-oxo-4-ene steroids.

Scheme I



Reagents: a)Na_2PdCl_4/THF; b)$(RO_2C)_2CH_2$/NaH/DMSO; c)LiI/DMF; d)K_2CO_3/KOH/H_2O-MeOH; e)40% HCO_2H

We now wish to report the preparation of the steroidal (π-allyl)palladium complex **2** as an intermediate useful in the preparation of C-6 substituted corticosteroids. Treatment of the bis(methylenedioxy) ether **1**[4] with Na_2PdCl_4 in refluxing THF gave the corresponding complex **2** in 24% yield. The complex was purified by recrystallization and the product characterized by ^{1}H and ^{13}C NMR, as well as elemental analysis.

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The reaction of (π-allyl)palladium complexes with hard and soft nucleophiles has been well documented by Trost.[3g,5] Early attempts to apply this chemistry to a 3-oxo 4–6-η steroid complex gave dienone formation in lieu of the substitution product.[3f,g] More recently, the work of the Jackson group has demonstrated the importance of solvent in the displacement reaction. For example, malonate ion displacement gave the 6-substituted product when anhydrous dimethyl sulfoxide was employed as the reaction solvent, whereas a low yield of the malonate substitution product with concomitant 4,6-dien-3-one formation was observed when dimethyl sulfoxide containing ethanol or methanol was utilized.[3k] In addition, the stereochemistry of the palladation and nucleophilic displacement occurred with complete inversion.[3d,k] With these data in hand, treatment of the complex **2** with either sodium diethyl or dimethyl malonate in anhydrous dimethyl sulfoxide at room temperature gave the corresponding 6α-malonate esters **3a** and **3b** in good yields. In the case of **3b**, LiI-mediated decarbomethoxylation gave the 6-carboxymethyl corticosteroid derivative **4**. Hydrolysis of the ester moiety, followed by removal of the bis(methylenedioxy) ether protecting group gave the epimeric 6-acetic acid derivative **6** (Scheme I). The product was characterized by ^{1}H NMR and high-resolution mass spectrometry.

On the basis of the current body of literature, it is clear that this methodology could be extended to the preparation of other valuable derivatives of corticosteroids.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. TLC plates were developed by spraying with phosphomolybdic acid unless otherwise indicated. ^{1}H NMR spectra were recorded at 60 MHz on a Varian EM-360L spectrometer, and ^{13}C NMR spectra were recorded at 50.13 MHz on a Bruker WP-200SY spectrometer with deuterium lock. In both cases, tetramethylsilane was used as internal reference. IR spectra were recorded on a Perkin-Elmer 283B spectrophotometer. Low-resolution mass spectra were recorded at the North Carolina State University GC/MS Facility on a HP-5985B instrument via the DIP method, while high-resolution mass spectra were recorded at the Research Triangle Institute Mass Spectrometry/Biotechnology Resources Center on a Kratos MS-902 via the DIP method. Both high- and low-resolution mass spectra were recorded in the EI mode at 70 eV unless otherwise indicated. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Bis(μ-chloro)bis[(4-6-η-17α,20,20,21-bis(methylenedioxy)-11β-hydroxy-3-oxopregnenyl)palladium(II)] (2). A mixture of palladium(II) chloride (8.87 g, 50.0 mmol) and sodium chloride (4.39 g, 75.0 mmol) was heated at reflux for 3 h in dry THF (650 mL) under nitrogen. Cortisol–bis(methylenedioxy) ether (18.57 g, 45.97 mmol) was added, and the mixture was heated under mild reflux for 47 h. Residual solids were removed by filtration through a medium-porosity sintered glass funnel, and the filtrate was concentrated in vacuo to give a brown foam. The foam was triturated with Et_2O (700 mL), and the triturant was decanted and concentrated in vacuo to give 4.87 g of starting material. The residue that remained following trituration was dissolved in 50 mL of CH_2Cl_2, and the solution was passed through a pad of silica gel (20 g). The pad was washed with 500 mL of CH_2Cl_2, and the combined washings and filtrate were concentrated to a volume of ca. 30 mL, and Et_2O (500 mL) was added. The resulting bright yellow needles were isolated by vacuum filtration to give 4.71 g of **2**. An additional 1.32 g of product was isolated from the mother liquor upon standing (total 6.03 g, 24%): mp 208.5–210 °C; ^{1}H NMR ($CDCl_3$) δ 5.07 (s, 4, OCH_2O), 4.54 (m, 1, C-11 H), 4.26 (br d, 1, C-6 π-allyl H, J = 4 Hz), 4.03 (s, 2, C-21 CH_2), 3.98 (s, 1, C-4 π-allyl H), 1.53 (s, 3, C-19 CH_3), 1.12 (s, 3, C-18 CH_3); ^{13}C NMR ($CDCl_3$) δ 204.0 (C-3), 134.2 (C-5, π-allyl), 82.6, 64.6 (C-4, C-6, π-allyl); TLC (Si-gel) R_f 0.38 (95:5 CH_2Cl_2/MeOH). Anal. Calcd for $C_{46}H_{62}O_{12}Pd_2Cl_2$: C, 50.65; H, 5.68. Found: C, 50.78; H, 6.20.

Diethyl [17α,20,20,21-Bis(methylenedioxy)-11β-hydroxy-3-oxopregn-4-en-6β-yl]malonate (3a). To a dry two-neck 10-mL round-bottom flask equipped with a stir bar was added NaH as a 57% oil dispersion (7.47 mg, 0.178 mmol). The dispersion was thoroughly washed with hexane in order to remove mineral oil, and dry dimethyl sulfoxide (3 mL) was added under a N_2 blanket. The stirrer was started, and diethyl malonate (54.3 mg, 0.339 mmol) was added. The slurry was warmed to 35 °C, and the bis(π-allyl)palladium complex **2** (103 mg, 0.094 mmol) was added. The reaction mixture immediately turned black, indicating Pd metal precipitation. The mixture was stirred at 35 °C for 18 h at which point 30 mL of H_2O was added. The mixture was partitioned between water and CH_2Cl_2. The organics were separated, and the aqueous phase was extracted with 30 mL of CH_2Cl_2. The combined organics were washed with H_2O (3 × 25 mL) and brine (3 × 25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude product as a yellow oil. The oil was triturated with aqueous ethanol to give 48.23 mg (91%) of **3a** as a pale yellow solid: mp 139–142 °C; ^{1}H NMR ($CDCl_3$)[6] δ 5.72 (s, 1, C-4 vinylic H), 4.95 (s, 4, OCH_2O), 4.23 (q, 4, malonate CH_2), 3.93 (s, 2, C-21 CH_2), 3.24 (br m, 1, $CHCO_2Et$); TLC (silica gel) R_f 0.60 (95:5 CH_2Cl_2/MeOH); mass spectrum, m/z (relative intensity) 564 (15), 563 (56), 562 (100), 489 (9), 488 (10), 403 (36), 384 (54), 372 (65), 354 (29), 339 (21), 284 (26), 266 (32), 251 (48), 225 (52), 161 (48), 131 (48), 115 (58), 105 (63), 91 (80), 69 (71), 55 (92), 43 (97). Anal. Calcd for $C_{30}H_{42}O_{10}$: 562.2777. Found: 562.2779.

Dimethyl 17α,20,20,21-Bis(methylenedioxy)-11β-hydroxy-3-oxopregn-4-en-6β-yl]malonate (3b). Treatment of dimethyl malonate (260.0 mg, 2.01 mmol) with NaH in dimethyl sulfoxide, followed by the (π-allyl)palladium complex **2** (310.0 mg, 0.284 mmol) as outlined for **3a** afforded 116.00 mg of **3b** as an off-white solid: mp 203.5–206.5 °C; ^{1}H NMR ($CDCl_3$) δ 5.78 (s, 1, C-4 vinylic H), 5.00 (s, 4, OCH_2O), 3.96 (s, 2, C-21 CH_2), 3.78 (s, 3, malonate CH_3), 3.65 (s, 3, malonate CH_3), 3.23 (dd, 1, $CHCO_2Me$, $J_{6\alpha,6'}$ = 13 Hz, $J_{6\alpha,7}$ = 4 Hz), 1.52 (s, 3, C-19 CH_3), 1.15 (s, 3, C-18 CH_3); TLC (silica gel) R_f 0.34 (97:3 CH_2Cl_2/MeOH; mass spectrum, m/z (relative intensity) 536 (7), 535 (30), 534 (100), 504 (9), 403 (17), 372 (13), 281 (11), 267 (12), 265 (12), 251 (12), 241 (14), 240 (24), 227 (21), 225 (27), 211 (13), 197 (13), 189 (11), 183 (13), 161 (18), 158 (25), 145 (22), 133 (26), 129 (18), 121 (18), 105 (31), 91 (41), 79 (32), 43 (34). Anal. Calcd for $C_{28}H_{38}O_{10}$: 534.2463. Found: 534.2459.

6α,β-[(Carbomethoxy)methyl]-17α,20,20,21-bis(methylenedioxy)-11β-hydroxy-3-oxopregn-4-ene (4). The dimethyl malonate derivative **3b** (160 mg, 0.30 mmol) was dissolved in 15 mL of dry dimethylformamide, and the solution was placed into a distillation apparatus under N_2 with the receiver dry ice chilled. To the solution was added LiI (78 mg, 0.58 mmol). The solution was heated at 160 °C for 5 h. After being cooled, the golden brown solution was poured onto 30 mL of HCl-acidified ice–CH_2Cl_2. The organics were separated, and the aqueous phase was extracted with 30 mL of CH_2Cl_2. The organics were combined and washed with H_2O (50 mL), 0.1% $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 130 mg (91%) of **4** as a white solid: mp 130 °C (dec 116 °C); ^{1}H NMR ($CDCl_3$) δ 5.78 (br s, 1, C-4 vinylic H), 5.02 (s, 4, OCH_2O), 4.00 (s, 2, C-21 CH_2), 3.67 (s, 3, ester CH_3), 1.52 (s, 3, C-19 CH_3), 1.16 (s, 3, C-19 CH_3); TLC (silica gel) R_f 0.56 (95:5 CH_2Cl_2/MeOH); IR (KBr) 1731 (ester C=O), 1665 (α,β-unsaturated C=O) cm^{-1}; mass spectrum, m/z (relative intensity 478 (6), 477 (28), 476 (100), 446 (6), 428 (6), 404 (7), 339 (5), 281 (10), 239 (18), 173 (16), 158 (18), 131 (17), 91 (34), 79 (24), 43 (23). Anal. Calcd for $C_{26}H_{36}O_8$: 476.2409. Found: 476.2412.

6α,β-[(Carbomethoxy)methyl]-17α,20,20,21-bis(methylenedioxy)-11β-hydroxy-3-oxopregn-4-ene (5). The methyl ester **4** (130 mg, 0.281 mmol) was dissolved in 10 mL of 10% H_2O–MeOH, and K_2CO_3 (1.00 g, 7.24 mmol) was added. The resulting slurry was stirred at room temperature for 18 h at which point H_2O (2 mL) was added, and the mixture was warmed to

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(6) The NMR data and stereochemical assignments are in agreement with data obtained for similar chemistry performed on cholest-4-en-3-one. See ref 3k.

40 °C. Potassium hydroxide (50 mg, 0.891 mmol) was added, and heating continued for 2 h. The mixture was cooled, and the volatiles were removed by rotary evaporation. Water (75 mL) was added, and the solution was extracted with 75 mL of CH_2Cl_2 to remove neutrals. The remaining basic aqueous phase was acidified to pH 2 (HCl) and was extracted with CH_2Cl_2 (3 × 75 mL). The washings were combined, dried ($MgSO_4$), filtered and concentrated to give 60 mg (46%) of the crude acid **5**. The product was purified by preparative TLC (Si gel; 200 × 200 × 2 mm) eluting with 20% MeOH/CH_2Cl_2 and was isolated as a white powder: mp 217–224 °C dec; ^1H NMR ($CDCl_3$) δ 5.70 (distorted s, 1, C-4 vinylic CH), 5.02 (s, 4, OCH_2O), 4.47 (m, 1, C-11 H), 4.02 (s, 2, C-21 CH_2), 1.46 (s, 3, C-19 CH_3), 1.14 (s, 3, C-18 CH_3); TLC (silica gel) R_f 0.41 (85:15 CH_2Cl_2/MeOH, visualized with bromocresol green); IR (KBr) 3520–3020 (br, C-11 OH and CO_2H), 1725 (acid C=O), 1665 (α,β-unsaturated C=O) cm^{-1}; mass spectrum, *m/z* (relative intensity) 464 (6), 463 (29), 462 (100), 444 (12), 432 (45), 414 (23), 396 (7), 384 (9), 344 (17), 326 (11), 325 (11), 323 (11), 319 (13), 316 (10), 311 (11), 300 (22), 285 (21), 281 (18) 267 (15), 265 (15), 253 (16), 241 (24), 239 (45), 225 (24), 211 (18), 195 (15), 182 (23), 173 (25), 158 (53), 145 (35), 131 (30), 119 (36), 115 (40), 105 (49), 91 (59), 79 (39), 55 (25). Anal. Calcd for $C_{25}H_{34}O_8$: 462.2251. Found: 462.2255.

6α,β-[(Carbomethoxy)methyl]-11β,17α,21-trihydroxypregn-4-ene-3,20-dione (6). The protected cortisol carboxylic acid **5** (99.6 mg, 0.216 mmol) was suspended in 9 mL of 40% formic acid, and the mixture was heated at 70 °C under N_2 for 2.5 h. The solution was allowed to cool and was filtered. The filtrate was concentrated in vacuo, and the residue was dissolved in H_2O (50 mL) and the aqueous solution extracted with EtOAc (3 × 50 mL). The organics were dried (Na_2SO_4), filtered, and concentrated to give **6** as a waxy solid (84.7 mg, 93%), virtually pure based on TLC analysis: ^1H NMR (acetone-d_6) δ 5.60 (distorted s, 1, C-4 vinylic H), 4.70–3.80 (m, 6, 11β,17α,21-OH, C-21 CH_2, C-11 CH), 1.51 (s, 3, C-19 CH_3), 0.93 (s, 3, C-18 CH_3); TLC (silica gel) R_f 0.17 (85:15 CH_2Cl_2/MeOH, visualized with bromocresol green); IR (KBr) 3620–3020 (br, OH, CO_2H), 1710 (br, C-20 C=O, acid C=O), 1650 (α,β-unsaturated C=O); mass spectrum (25 eV), *m/z* (relative intensity) 420 (3), 402 (11), 373 (17), 360 (7), 327 (20), 309 (8), 281 (16), 267 (14), 239 (15), 225 (11), 211 (11), 207 (14), 187 (10), 183 (10), 181 (11), 173 (13), 161 (10), 157 (12), 149 (15), 145 (27), 135 (19), 125 (14), 121 (20), 109 (25), 98 (33), 97 (47), 85 (40), 83 (63), 71 (49), 57 (66), 55 (61), 44 (78), 45 (100). Anal (determined for $M^+ - 18$ peak at 70 eV) Calcd for $C_{23}H_{30}O_6$: 402.2041. Found: 402.2046.

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Registry No. 1, 807-05-6; 2, 93134-28-2; **3a**, 93111-63-8; **3b**, 93111-64-9; 4 (isomer 1), 93111-65-0; 4 (isomer 2), 93111-66-1; 5 (isomer 1), 93111-67-2; 5 (isomer 2), 93111-68-3; 6 (isomer 1), 93111-69-4; 6 (isomer 2), 93111-70-7; $PdCl_2$, 7647-10-1; $CH_2(CO_2Et)$, 105-53-3; $CH_2(CO_2Me)$, 108-59-8.

A Simple Synthesis of the Multipurpose Pheromone of *Mus musculus*

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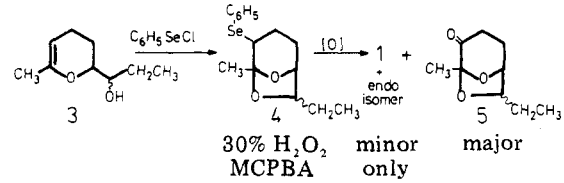
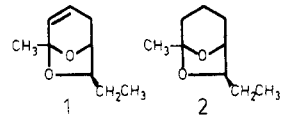
The isolation and identification of **1** as a pheromone of the mouse *Mus musculus*, has recently been reported.[1]

Scheme I. Synthesis of the Mouse Pheromone



The constitution of **1** was verified by its conversion to *exo*-brevicomin (**2**), the aggrevating sex pheromone of the pine bark beetle, *Dendroctonus brevicomis*.



As part of our continuing program into syntheses of natural products having the bicyclic ketal structure,[2] we herein report a simple synthesis of **1** (Scheme I).

The previously prepared and characterized isomeric mixture **3**[3] was treated with phenylselenyl chloride to initiate the cyclization of the neighboring alcohol functionality. The resulting 60:40 exo/endo mixture **4** was then oxidized with MCPBA to smoothly convert the selenide to a mixture of the exo/endo-**1**. This mixture was reduced to the isomeric brevicomins, thus, verifying the identity of the synthetic material.

Experimental Section

Preparation of 4-(Phenylseleno)-5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]octane. A solution of **3** (8.2 g, 0.053 mol) and 100 mL of dry methylene chloride was stirred with 20 g of anhydrous K_2CO_3 at −78 °C under N_2. To this stirred mixture was added, by syringe, phenylselenyl chloride (10 g, 0.052 mol) in 10 mL of methylene chloride. The resulting orange solution was stirred for 4 h at the reduced temperature, after which time it was allowed to warm to room temperature and stir for an additional 24 h. After this time the reaction mixture was filtered, and the filtrate was reduced in volume. The crude reaction product was chromatographed (silica gel, 2.5 × 48 cm column, eluted with methylene chloride). Removal of the methylene chloride left a red oil. This crude product was taken directly to the next step without additional purification.

Oxidation of 4 with Hydrogen Peroxide. In a 125-mL Erlynmeyer flask was placed 4 g of **4** and 75 mL of dry THF. Over a period of 20 min was added 1.36 mL of 30% H_2O_2, *with external cooling to maintain the reaction temperature at 25* °C. After 4 h of stirring the reaction mixture was poured into 250 mL of water, and K_2CO_3 was added to make the pH slightly basic. The resulting solution was extracted with three 150-mL portions of ether, and the combined extracts were dried over anhydrous $MgSO_4$. After removal of solvent, the reaction mixture was distilled to give two products in the ratio of 3:7, with a boiling range of 64–68 °C at 10 mmHg. The minor product **1** was formed as an exo/endo mixture (60:40), and the exo isomer had spectral characteristics (NMR, IR, MS) identical with the product of Chaguin et al.[4] The isomeric **1** was also converted to a 60:40 mixture of the *exo*- and *endo*-brevicomins by catalytic hydrogenation, thus, further establishing its identity.[5] The major

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(4) Chaquin, P.; Morizur, J. P.; Kossanyi, J. *J. Am. Chem. Soc.* **1977**, *99*, 903.

(5) The exo–endo stereochemistry of the C-7 ethyl group is determined by the sodium borohydride reduction of the precursor ethyl ketone.[3] In all of our experiences using this general methodology for the insect pheromones, we have been hindered by the inability to provide a clean preference for one of the isomers.[6] We seem to find a general alcohol isomer ratio of about 60:40, later expressed by a 60:40 ratio of ketals, with the desired exo isomer predominating.

(6) Mundy, B. P.; Schwartz, T. R. *J. Org. Chem.* **1982**, *47*, 576.

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