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.

Acknowledgment. We are indebted to Mr. Gary Campbell of the NCSU GC/MS Facility for low-resolution mass spectra and to Mr. Fred Williams of Research Triangle Institute for high-resolution mass spectra. We wish to thank Becton Dickinson for allowing us to publish this work.

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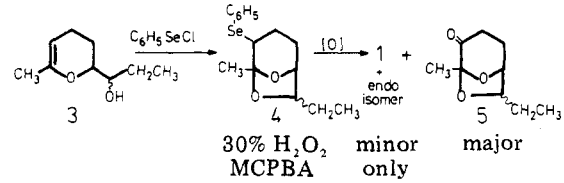
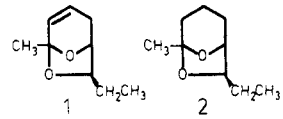
The isolation and identification of **1** as a pheromone of the mouse *Mus musculus*, has recently been reported.[1]

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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(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.

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product 5 exhibited a strong carbonyl infrared absorption at 1767 cm^{-1} and had a proton NMR spectrum consistent with the assigned structure.

Oxidation of 4 with *m*-Chloroperoxybenzoic Acid. To a solution of 1 g of 4 (0.003 mol) in 25 mL of dry methylene chloride was slowly added 0.63 g of *m*-chloroperbenzoic acid. The reaction temperature was maintained at 25 °C over the 30-min addition. After 1 h of additional stirring, the reaction was quenched with 20 mL of 10% sodium sulfite. The methylene chloride layer was separated and dried over anhydrous magnesium sulfate. After removal of solvent, the reaction mixture was distilled (bp_{10} 64 °C) to yield 0.42 g (86%) of the 10:40 exo/endo isomeric mixture 1. There was no 5 found from this procedure.

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Registry No. *endo*-1, 93426-67-6; *exo*-1, 62255-25-8; 3 (isomer 1), 68378-82-5; 3 (isomer 2), 68378-83-6; 4, 93426-68-7; *exo*-5, 93426-69-8; *endo*-5, 93426-70-1.

A Method for the Stereoselective Synthesis of (*E*)-Methylstilbene Retinoids

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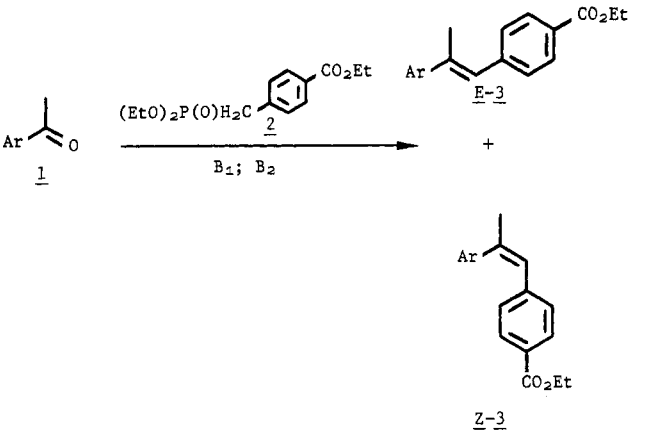
The *E* isomers of stilbenes **3** are a new class of aromatic retinoids that has shown promising activity in controlling the differentiation of epithelial cells and, therefore, may have potential therapeutic value in the treatment of such proliferative diseases of the skin as cancer, psoriasis, and acne.[1-3] Highly stereoselective syntheses of (*E*)-**3** are desirable because the *E* and *Z* isomers in this series are frequently difficult to separate. We have investigated the stereoselectivity of the Horner–Emmons olefination of aryl methyl ketone **1** with the anion of diethyl (4-carbethoxybenzyl)phosphonate (**2**) to form this bond system (Scheme I). The Horner–Emmons olefination is reported to be strongly dependent upon reaction conditions and the relative stability of the initially formed threo and erythro adducts generally leading to product mixtures in which the more stable *E* double-bond isomer predominates.[4,5] Recent reports by Still and Gennari[5] on the stereoselective synthesis of trisubstituted *Z* olefins using a Horner–Emmons olefination and by Ford and co-workers[6] on the double-bond isomeric mixtures obtained using a Wittig olefination have prompted us to report our results.

In the reaction shown in Scheme I, two processes have been found to occur, namely, (a) the olefination leading to a kinetically controlled mixture of isomers (*E*)-**3** and (*Z*)-**3** and (b) the base-catalyzed isomerization of the mixture affording predominately the thermodynamically more stable (*E*)-**3** isomer. The phosphonate anion required

Scheme I



for the olefination was generated by treatment of **2** with a variety of standard bases B_1 (*n*-BuLi/THF, NaH/15-crown-5/THF,[7] $NaCH_2SOCH_3$[8]), which are listed in Table I. For example, by monitoring reaction aliquots by high-performance LC, we have found that the *Z* isomer predominated initially when NaH was used as the base, the amount of *E* isomer increased with time, and the rate of increase was dependent upon the base used. By using deuterated solvents and examining the product mixture by both ^1H NMR and GC–MS, we have found that the isomerization proceeded by deprotonation–protonation of the vinylic methyl group of both bond isomers of **3** by the base (Table II). The base isomerization method afforded a much higher *E*/*Z* isomeric ratio (9:1) than the photoisomerization method reported by Loeliger[2] for (*Z*)-**3a**, in which the *E*/*Z* ratio was 1:1. The isomerization was effected by a variety of strong bases B_2, including the anion of **2**, dimsyl anion, hydride, and ethoxide, as long as the countercation was complexed by the addition of a crown ether or by the solvent. The lithium salt of **2**/THF, NaH/THF, and NaOEt/THF did not isomerize **3a** at any appreciable rate but led to extensive side reactions with time. The sodium salt of **2**/15-crown-5/THF, and $NaCH_2SOCH_3/Me_2SO$ also caused side reactions that reduced the yield. The isomerization was found to be more rapid with ethoxide than with the phosphonate anion in Me_2SO. These results indicate that NaOEt/Me_2SO are the base and solvent of choice for the isomerization to the (*E*)-**3** isomer after the initial olefination reaction. Optimal reaction conditions for this two-step one-pot procedure are reported in the Experimental Section. We have found that this method is applicable to the synthesis of other retinoids. Our results also suggest that the isomer ratios reported by others[6] in the syntheses of retinoids and other trisubstituted olefins in which the double bond is in conjugation with an electron-withdrawing group may not be simply due to the thermodynamics of the olefination reaction but may in part be the result of further base-catalyzed equilibration of the olefinic products.

Experimental Section

Melting points were determined with a hot-stage microscope and are uncorrected. LC analyses were done on a Waters Associates ALC equipped with a RCM-100 module containing a Radialpak B cartridge. Detection was by a Schoeffel Instrument Model 770 variable wavelength UV monitor. Analyses were performed at 260 nm at ambient temperature. Preparative work was done on a Waters Associates Prep/LC System 500 instrument

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