Studies on Terpenes. 4. Synthesis of Optically Active Grandisol, the Boll Weevil Pheromone

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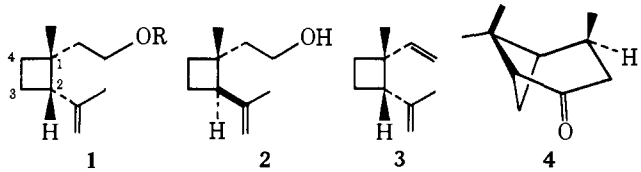
Abstract: (−)-β-Pinene was converted via the alcohol **26** into the ether **27** and, subsequently, the lactone **28.** Reduction of the lactone **28** with lithium triethoxyaluminum hydride gave 6,9-dimethyl-8-hydroxy-7-oxatricyclo[4.3.0.0^{3,9}]nonane (**29**). Treatment of the lactol **29** with triphenylmethylenephosphorane gave the olefin **31** which was hydroborated using bis(3-methyl-2-butyl)borane followed by alkaline hydrogen peroxide to give the diol **33.** Dehydration of the primary monoacetate of the diol **33** gave a mixture of 9-acetoxymethyl-α- and β-pinenes (**41** and **42**). Oxidation of the mixture of **41** and **42** with chromium trioxide in pyridine gave the enone **44**, which was hydrogenated to give 2α*H*-9-acetoxymethylpinan-4-one (**45**). Photolysis of **45** gave the aldehyde **46**, containing approximately 10% of the cyclobutene **47.** Decarbonylation of **46** using chlorotris(triphenylphosphine)rhodium gave grandisol acetate (**1**, R = Ac) (overall yield from (−)-β-pinene (3.5%)) which was converted into (+)-grandisol, (+)-(1*R*,2*S*)-1-methyl-1-(2-hydroxy)ethyl-2-isopropenylcyclobutane.

Grandisol (**1**, R = H) is the major component of the four synergistic compounds of the male boll weevil pheromone.[2] The first synthesis[3a] of grandisol (**1**, R = H) gave a low yield of cis and trans isomers. The cis isomer was spectrally identical with the natural compound. The trans compound **2** was found to be identical with a product synthesized by Corey,[3b] and subsequently isolated from a plant source, *Artemisia fragrans.*[4] Two stereoselective syntheses of racemic grandisol (**1**, R = H)

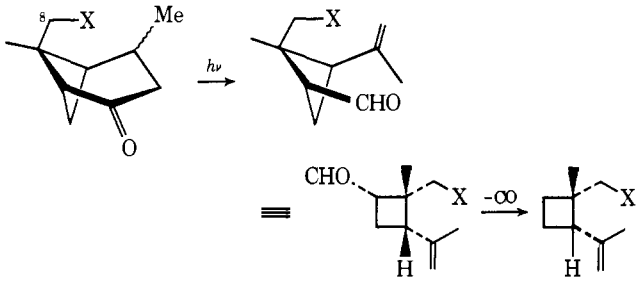


1 **2** **3** **4**

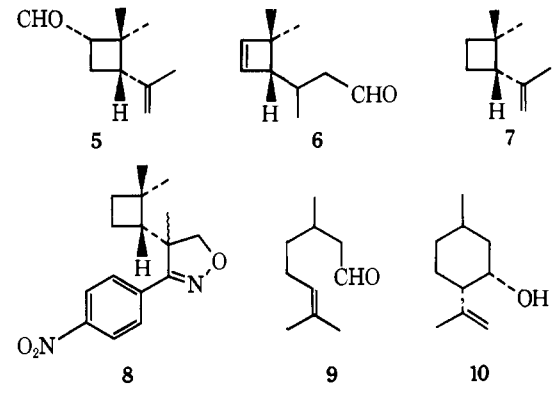
utilizing a (2 + 2) photocycloaddition to construct the cyclobutane ring have been reported.[5] A nonphotochemical approach yielded grandisol in two steps via the zerovalent nickel complex of 1,5-cyclooctadiene catalyzed dimerization of isoprene to the cis diene **3** in 12–15% yield.[6] Stork has developed a general stereospecific synthesis of cyclobutanes which has been applied to grandisol,[7a] and recently other approaches have been described.[7b]

The approach described here utilizes the "abnormal" α cleavage (Norrish type I) of a suitably substituted cyclohexanone, and starts from an optically active starting material containing a cyclobutane ring, namely (−)-β-pinene.[8] The generalized plan is outlined in Scheme I. To test this plaalan

Scheme I



cis-verbanone (**4**)[9] was irradiated (see Experimental Section) in methanol containing sodium hydrogen carbonate. The crude product (64%) contained approximately 75% of **5**, and 10% of the isomer **6.**[10] Decomposition of the aldehyde **5** using chlorotris(triphenylphosphine)rhodium[11] in dichloromethane at reflux gave the volatile hydrocarbon **7**, ν_{max} 1645 and 890

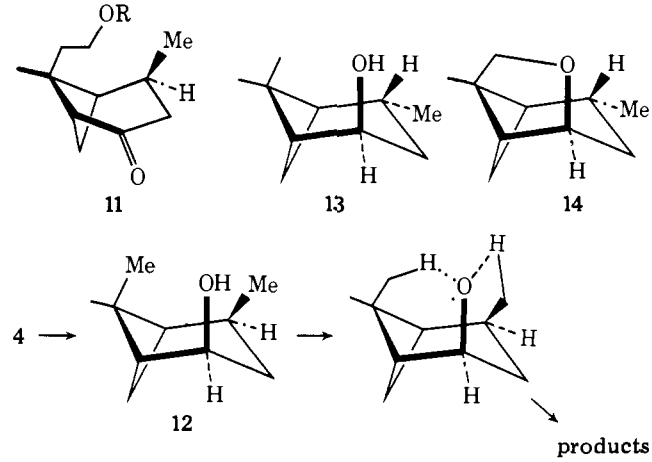


5 **6** **7** **8** **9** **10**

cm^{-1}. Treatment of **7** with *p*-nitrobenzonitrile oxide (generated in situ) gave the crystalline adduct **8.** The alternative reactions of the rhodium(I) reagent with an ω-alkenal to give cyclized products, e.g., **9** → **10**[12] via a rhodium-acyl complex would convert **5** into verbanone **4.** This was not detected (TLC and GLC).

The ketone **11** (referring to Scheme I, X = CH_2OR) would be the ideal precursor; the methyl group is written in the β configuration, since at this stage we knew that *cis*-verbanone (**4**) photolyzed in the desired manner. Unfortunately, to prepare **11** via Scheme II involves an intramolecular oxidation

Scheme II

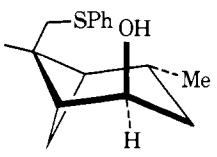


11 **13** **14** **12**

products

which can competitively functionalize the *gem*-methyl group or the β-methyl group, and as a consequence a mixture of

products might be produced. In the event treatment of the alcohol neoisoverbanol[13] (**12**) with bromine-mercuric oxide in pentane at reflux gave a complex mixture of products and was not examined further To avoid this competitive reaction neoverbanol (**13**) was readily cyclized to the required ether **14** (70%) using the bromine-mercuric oxide-$h\nu$ procedure.[14] The ether **14** was cleaved by reaction with phenylthioborane[15] in diglyme to give **15** which was oxidized with *m*-chloroperbenzoic acid to the hydroxy sulfone **16.** Oxidation of the hydroxy



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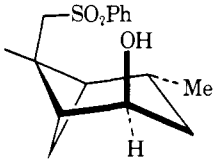

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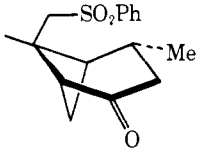

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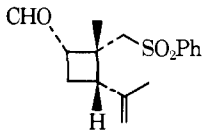

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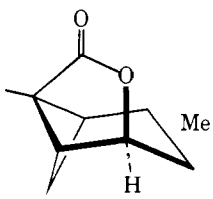
sulfone **16** with chromium trioxide-pyridine in dichloromethane[16] gave the ketone **17**, which is suitably substituted at the *gem*-methyl group (8-Me) for introduction of a one-carbon unit, thus producing the required side chain (Scheme I, X = CH_2OH or an equivalent). Photolysis of the ketone **17** under the same conditions used to produce **5** from *cis*-verbanone gave a complex mixture which contained very little or none of the required cyclobutane **18** (as judged by infrared and NMR). Oxidation of the ether **14** with either chromium trioxide in acetic anhydride[17] or ruthenium tetroxide (RuO_2-KIO_4/H_2O-CCl_4)[18] gave the lactone **19.** Reduction of the lactone **19** with lithium aluminum hydride gave the diol (**20**,



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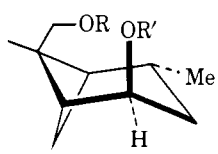

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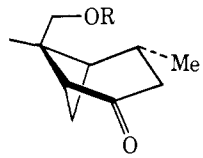

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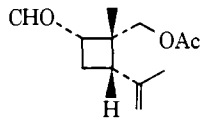
R = R′ = H). The diol **20** (R = R′ = H) was selectively esterified with benzoyl chloride or acetic anhydride in pyridine to give the esters **20** (R = COPh, R′ = H; 85%) and **20** (R = Ac, R′ = H; 68%), respectively. Very little of the dibenzoate **20** (R = R′ = COPh) was obtained, but acetylation was less specific; 22% of the diacetate **20** (R = R′ = Ac) was isolated. Oxidation of the secondary alcohols **20** (R = COPh, R′ = H) and **20** (R = Ac, R′ = H) using the Collins procedure gave the corresponding ketones **21** (R = COPh) and **21** (R = Ac) in excellent yield. The ketones **21** (R = COPh) and **21** (R = Ac) were photolyzed in methanol containing sodium hydrogen carbonate (identical conditions to these used for *cis*-verbanone (**4**)). The benzoate **21** (R = COPh) proved to be virtually inert, whereas the acetate **21** (R = Ac) gave a 64% yield of a mixture of two aldehydes, isolated, but not separable. The ratio of the integrals of the NMR signals in the olefinic, acetate methyl, and -CH_2O multiplets indicated that the two aldehydes are **22** and **23** in the ratio 40-45:55-60. Obviously this does not provide a viable synthetic procedure. The failure of the pho-



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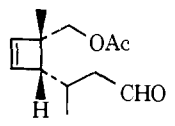

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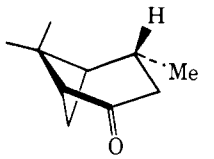
tolysis may be ascribed to two factors that have been changed (cf. *cis*-verbanone (**4**)). The 8-methyl substituent may have some influence on the photochemical α cleavage, or the configuration of the β-methyl group may cause the changes observed. Since *trans*-verbanone (**24**) was readily available,[14] we could examine the effect of the configuration of the β-methyl group on the products of photolysis. The results of Agosta[19] using specifically 3-deuterated cyclohexanones indicate that one might expect little difference between *cis*- and *trans*-verbanone (**4** and **24**). Photolysis of *trans*-verbanone under identical conditions to those used for *cis*-verbanone gave



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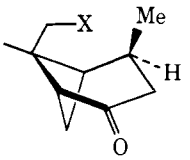

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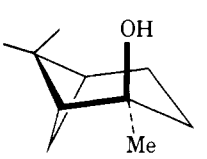

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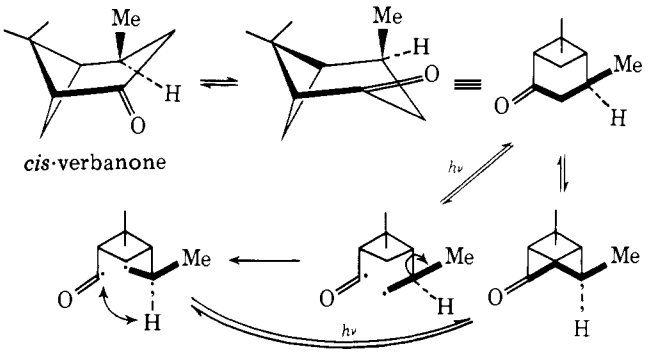
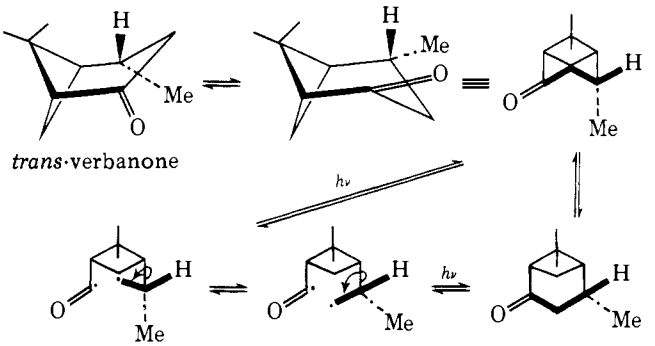
a complex, but consistent mixture of products. The most abundant product has the same retention time as **5**, but was only a small percentage of the total. Other major components coincided with the minor products of photolysis of *cis*-verbanone (**4**). The aldehyde fraction (53% total yield) consisted of a mixture of **5** and **6** in the ratio of 35-40:65-60. This result parallels the observation made with the 8-substituted ketone **21** and indicates that the configuration of the β-methyl substituent plays an important role in determining the ratio of cyclobutane **5** to cyclobutene **6.** The photolysis conditions for *trans*-verbanone were varied to determine whether a change of solvent, wavelength of irradiation, temperature, or extent of reaction affected the yield of the required aldehyde **5.** No useful information was obtained. The observed differences in the photochemical behavior of *cis*- and *trans*-verbanone must have its origins in the conformation of the β-methyl group. Scheme III illustrates this. A new synthetic scheme was re-

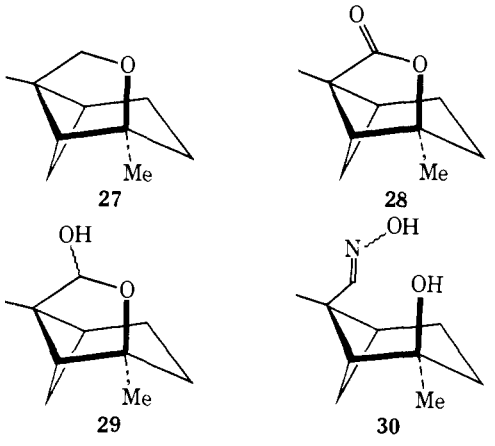
Scheme III



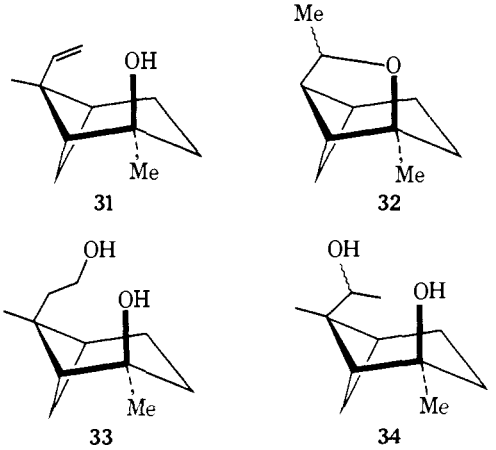


For H migration to take place, rotation about the indicated carbon–carbon bond causes a severe steric interaction between the β-methyl group and the *gem*-methyl group. Consequently, the reversibly-formed diradical may tend to recombine and cleave toward the cyclobutane ring ("normal" α cleavage).

quired that would provide an 8-substituted *cis*-verbanone (**25**). Pinan-2β-ol[20] (**26**) was converted into the cyclic ether **27** by standard procedures.[21] Oxidation of this ether **27** using ruthenium tetroxide[18] (RuO_2-KIO_4) in aqueous carbon tetrachloride gave the lactone **28**[21] (76% from pinan-2β-ol). The lactone **28** was conveniently reduced to the lactol **29** (97%)

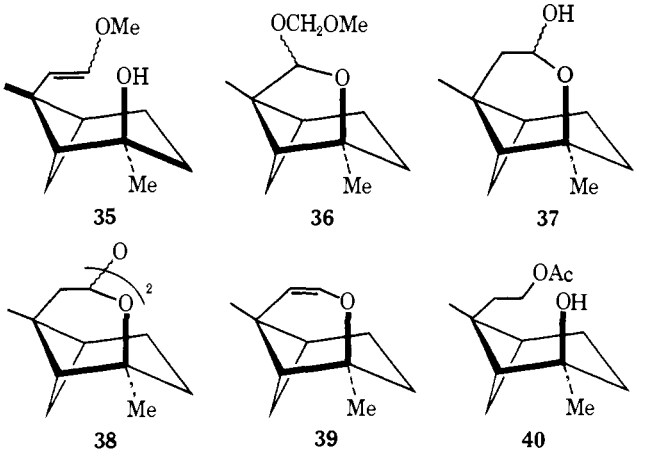


using lithium triethoxyaluminum hydride[22] at −22 °C. Above this temperature further reduction to the corresponding diol occurred. The lactol **29** can be prepared via the nitrite ester of **26**, which on photolysis[23] followed by pyrolysis in isopropyl alcohol at reflux gave the oxime **30** as a mixture of syn and anti isomers. Hydrolysis of the oxime **30** was achieved with 2% aqueous hydrochloric acid in ether-acetone to give the lactol **29.** While less stages are involved in this latter route to the lactol **29**, the overall yield is 51% as compared with 74% via the lactone **28.** Treatment of the lactol **29** with triphenylmethylenephosphorane in dimethyl sulfoxide gave the required olefin **31** (67%). If this reaction was allowed to run for more than 18 h (ca. 85% consumption of lactol), the ether **32** was slowly formed. Apparently **32** is an acid-catalyzed cyclization product derived from the olefin **31**, although it appeared to be formed in the reaction rather than during workup. Hydroboration[24] of the olefin **31** and oxidative workup gave a separable (ca. 3:2) mixture of the required primary alcohol **33** and the secondary

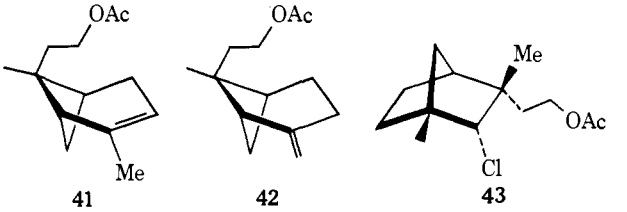


alcohol **34.** Bis(3-methyl-2-butyl)borane[24] reacted with the olefin **31** to give, after oxidative workup, the required diol **33** (95%). An alternative route to the diol **33** was examined. Methoxymethylenetriphenylphosphorane[25] was reacted with the lactol **29**, using potassium *tert*-butoxide in *tert*-butyl alcohol[26] to generate the ylide from the phosphonium salt. The required enol ether **35** was formed, albeit in low yield (36%). The NMR spectrum of **35** demonstrated that a mixture of *Z* and *E* isomers were present in the ratio 3:2.

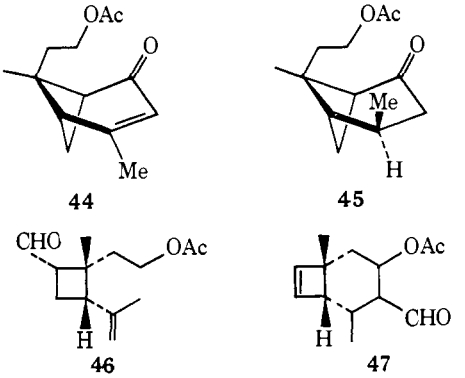
A by-product from the above reaction was isolated and assigned the structure **36** on the basis of its spectral data and hydrolysis to the γ-lactol **29.** Careful hydrolysis of the enol ether **35** at 0° using 1% hydrochloric acid in acetone-water (1:9) gave the δ-lactol **37** as an unstable oil, which was immediately reduced with lithium aluminum hydride at −20° to the required diol **33.** On warming, the δ-lactol was converted into the ethers **38** and **39.** Acetylation of the diol **33** with acetic anhydride in pyridine gave the acetate **40**, which was dehy-



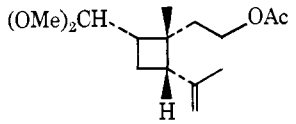
drated using phosphorus oxychloride in pyridine at 0° to give a 2:1 mixture (59%) of the α- and β-pinenes **41** and **42.** Attempted dehydration of the tertiary alcohol **40** with thionyl chloride in pyridine at 0° gave, apart from **41** and **42**, the rearranged product **43.** Oxidation of the mixture of **41** and **42**



with chromium trioxide-pyridine gave the enone **44** (41%). Hydrogenation of the enone **44** over 20% palladium on carbon in ethanol gave the saturated ketone **45** (90%). Photolysis of the ketone **45** in methanol containing 1% sodium hydrogen carbonate gave as the major product (60%) the aldehyde **46**, containing approximately 10% of the cyclobutene **47.** The al-



dehyde **46** was isolated and characterized as its 2,4-dinitrophenylhydrazone derivative, which could be fractionally crystallized until uncontaminated by the corresponding derivative from **47.** If the photolysis of the ketone **45** was carried out in the absence of sodium hydrogen carbonate, the dimethyl acetal **48** was formed along with the dimethyl acetal from the cyclobutene **47.** Decarbonylation of the mixture of aldehydes **46** and **47** with chlorotris(triphenylphosphine)rhodium in dichloromethane gave a mixture (ca. 75%), with grandisol acetate (**1**, R = Ac) as the principal component. Reduction of this mixture with lithium aluminum hydride gave crude grandisol



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(**1**, R = H), which was converted into its corresponding *p*-nitrobenzoate (**1**, R = $COC_6H_4NO_2$-*p*). Crystallization of this derivative to constant physical properties, followed by alkaline hydrolysis and distillation gave grandisol (**1**, R = H), whose spectroscopic properties were identical with a sample of (±-grandisol. Pure synthetic (+)-grandisol has $[\alpha]^{21.5}D$ 18.5° (*c* 1% in *n*-hexane), which is corrected for the optical purity of (−)-β-pinene. Grandisol (**1**, R = H) has the absolute configuration (1*R*,2*S*).

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded for Nujol mulls or liquid thin films on Pye Unicam SP 200 and Perkin-Elmer 257 instruments. Ultraviolet spectra were measured on a Pye Unicam SP 800 spectrometer, and NMR spectra were recorded with a Varian T-60 spectrometer for solutions in [^{2}H] chloroform using Me_4Si as an internal standard unless otherwise indicated. Mass spectra were run on an AEI MS-9 high resolution instrument. Optical rotations were measured as solutions in given solvents on a Perkin-Elmer 141 polarimeter. Analytical and preparative GLC was performed by a Perkin-Elmer F11 and a Pye 105 instrument, respectively. Solvents were dried by standard techniques. Light petroleum refers to the fraction, bp 40–60 °C.

***cis*-1-Formyl-2,2-dimethyl-3-isopropenylcyclobutane (5).** The ketone **4** (5.5 g, 36 mmol) in dry methanol (1 l.) containing sodium hydrogen carbonate (1.0 g) was photolyzed with a 500-W immersion water-cooled medium-pressure quartz jacketed uv lamp under argon at room temperature. After 6 h, the mixture was concentrated at room temperature to a small volume (ca. 20 ml). The residue was diluted with water and extracted twice with light petroleum. The extract was washed with water, dried (Na_2SO_4), and evaporated. The crude aldehyde **5** was purified by distillation, bp 66 °C (17 mmHg), to give a pale yellow liquid (3.5 g, 64%): ir (film) 2750, 1725, 1645, and 895 cm^{-1}; NMR[27] (τ scale) 8.33 (3 H, s), 8.61 (3 H, s), 9.10 (3 H, s), 5.31 (1 H, br s), 5.13 (1 H, br s), and 0.19 (1 H, d, *J* = 2 Hz).

2,2-Dimethylisopropenylcyclobutane (7). The crude distilled aldehyde **5** (600 mg) and chlorotris(triphenylphosphine)rhodium (2.77 g, 3 mmol) in dichloromethane (15 ml) were heated at reflux for 16 h. The solution was cooled, filtered, and the precipitated chlorocarbonylbis(triphenylphosphine)rhodium(I) was washed with dichloromethane (10 ml). Evaporation of the dichloromethane solution and treatment of the residue with ethanol (4 ml) precipitated the remaining rhodium complexes. The filtrate was poured into water and extracted with dichloromethane, dried (Na_2SO_4), and evaporated. Distillation of the residue gave **7**, contaminated with some of the aldehyde **5**, triphenylphosphine, and several minor (<1%) products: ir (film) 1720, 1645, 980, and 775 cm^{-}; *m/e* 152, 123, 109, and 81. To a solution of the crude olefin **7** (74 mg) was added triethylamine (120 mg) in dichloromethane (2 ml), followed by *p*-nitrophenyloximoyl chloride (108 mg) in dichloromethane (4 ml). After 1 h at room temperature, the solution was evaporated and the residue chromatographed on silica, eluting with petroleum ether–ethyl acetate (1:1) to give **8**, mp 110–118 °C: ir (Nujol) 1610, 1605, 1575, 1520, 1320, 1285, 1275, 950, 860, 755, and 695 cm^{-1}; NMR τ 8.88 (3 H, s), 8.83 (3 H, s), 8.68 (3 H), 6.98 (3 H, s), 6.80 (1 H, s), 1.90 (4 H, AB, *J* = 9 Hz).

Anal. ($C_{16}H_{20}N_2O_3$) C, H, N.

2β*H*-9-Phenylsulfonylpinan-4β-ol (16). Sodium borohydride (645 mg, 17 mmol) and thiophenol (2.82 g, 25.6 mmol) in dry diglyme (8 ml) at 0° were treated with redistilled boron trifluoride etherate (1.42 g, 10 mmol).[15] After 10 min at 0°, the ether **14** (200 mg, 1.3 mmol) in diglyme (3 ml) was added. After stirring 15 h at room temperature the mixture was poured into 1 N sodium hydroxide solution and extracted with ether. The ether layer was washed with water (3 × 5 ml), dried (Na_2SO_4), and evaporated. Chromatography of the crude residue on alumina (G3), eluting with light petroleum–ethyl acetate gave unreacted ether **14** (90 mg) and the thioether **15** (95 mg): ir (film) 3450, 1590, 1440, 1030, 745, and 700 cm^{-1}. The crude thioether **15** was stirred with excess *m*-chloroperbenzoic acid in ether for 1 h at room temperature. The ether solution was extracted with saturated aqueous sodium hydrogen carbonate, washed with water, dried (Na_2SO_4), and evaporated. Crystallization of the residue from ethyl acetate gave the sulfone **16** (83 mg), mp 159–161 °C: ir (Nujol) 3600, 1305, 1290, 1150, 1045, 755, and 695 cm^{-1}; NMR τ 8.91 (3 H, d, *J* = 6 Hz), 8.67 (3 H, s), 7.45 (1 H, m), 6.53 (2 H, br s), and 2.00–2.40 (5 H, m).

Anal. ($C_{16}H_{22}SO_3$) C, H, S.

2β*H*-9-Phenylsulfonylpinan-4-one (17). The sulfone alcohol **16** (30 mg) was treated with excess chromium trioxide in pyridine–dichloromethane for 4 h at room temperature in the usual way.[16] Workup gave the ketone **17** (≥90%), mp 148.5–151.0 °C (from ethyl acetate): ir 1720, 1605, 1590, 1290, 1150, 1090, and 1080 cm^{-1}.

Anal. ($C_{16}H_{20}SO_3$) C, H.

4α,9-Dimethyl-7-oxatricyclo[4.3.0.0^{3,9}]nonan-8-one (19). The ether **14** (1.3 g, 8.6 mmol) in acetic anhydride (12 ml) was treated with a solution of chromium trioxide (1.60 g, 16 mmol) in acetic acid (37 ml) and water (4 ml) at 100–110 °C for 4 h. Workup in the usual way gave the lactone **19** (0.65 g, 46%); mp 48–48.5 °C (from light petroleum): ir 1770, 1225, 1075, and 970 cm^{-1}; NMR τ 9.07 (3 H, d, *J* = 6 Hz), 8.62 (3 H, s), 5.05 (1 H, m); $[\alpha]D^{21}$ 119.3° (*c* 4% in $CHCl_3$).

Anal. ($C_{10}H_{14}O_2$) C, H.

The crude ether **14** (6.0 g) was added to a vigorously stirred two-phase mixture of sodium metaperiodate (30 g) in water (300 ml) and carbon tetrachloride (250 ml) to which hydrated ruthenium dioxide (400 mg) had been added. After 36 h of stirring at room temperature, the carbon tetrachloride layer was separated, washed with water, and dried (Na_2SO_4). Ethanol (5 ml) was added to the carbon tetrachloride solution (to reduce RuO_4 to RuO_2) and the mixture was filtered through Celite. The lactone **19** (5.4 g) was isolated as before.

2β*H*-Pinane-4β,9-diol (20, R = R′ = H). The lactone **19** (336 mg) in dry ether (10 ml) was treated with excess lithium aluminum hydride, and the mixture was heated at reflux for 0.5 h. Workup gave the diol **20** (R = R′ = H; 300 mg, 87%), mp 82.5–83.5 °C (from ether–light petroleum): ir 3300, 1030, 1020, and 1005 cm^{-1}; NMR τ 9.11 (3 H, d, *J* = 6 Hz), 8.65 (3 H, s), 5.67 (m), 6.05 (1 H, m), 6.95 (br s); $[\alpha]D^{21}$ −41.0° (*c* 4.9% in $CHCl_3$).

Anal. ($C_{10}H_{18}O_2$) C, H.

2β*H*-9-Benzoyloxypinan-4β-ol (20; R = COPh, R′ = H). The diol **20** (R = R′ = H; 270 mg, 1.59 mmol) in dry pyridine (1 ml) and dry ether (2 ml) at 0° was treated with benzoyl chloride (250 mg, 1.77 mmol) in ether (1 ml). After 15 h at room temperature, workup gave the monobenzoate **20** (R = COPh, R′ = H; 371 mg, 85%), mp 106.5–107.5 °C (from ether–light petroleum): ir (Nujol) 3500, 1705, 1605, 1585, 1290, 1265, 1125, 1030, 960, and 730 cm^{-1}; NMR 9.08 (3 H, d, *J* = 6 Hz), 8.59 (3 H, s), 5.49 (3 H, m), 2.49–1.97 (5 H, m); $[\alpha]D^{21}$ 8.5° (*c* 1.9% in $CHCl_3$).

Anal. ($C_{17}H_{22}O_3$) C, H.

2β*H*-9-Acetoxypinan-4β-ol (20; R = Ac, R′ = H). The diol **20** (R = R′ = H; 400 mg, 2.35 mmol) in pyridine (1.5 ml) and dry ether (5 ml) at room temperature was treated with acetic anhydride (480 mg, 4.7 mmol) in dry ether (2 ml). After 8 h, workup gave after chromatography over alumina (G3) the pure monoacetate **20** (R = Ac, R′ = H; 340 mg, 68%) as a colorless oil, bp 70 °C (3 × 10^{-4} mmHg): ir (film) 3500, 1740, 1725, 1250, 1030, and 1020 cm^{-1}; NMR τ 9.12 (3 H, d, *J* = 6 Hz), 8.75 (3 H, s), 7.97 (3 H, s), 5.77 (2 H, ABq, *J* = 6 Hz) superimposed with 1 H, m; $[\alpha]D^{22}$ −9.0° (*c* 3% in $CHCl_3$).

Anal. ($C_{12}H_{20}O_3$) C, H.

The diacetate **20** (R = R′ = Ac; 22%) was obtained as a colorless oil: ir (film) 1730, 1265, and 915 cm^{-1}; NMR τ 9.11 (3 H, d, *J* = 7 Hz), 8.75 (3 H, s), 8.03 (3 H, s), 7.97 (3 H, s), 5.88 (2 H, s), and 4.78 (1 H, m).

2β*H*-9-Benzoyloxypinan-4-one (21, R = COPh). To a solution of chromium trioxide (1.0 g) in dry pyridine (5 ml) and dry dichloromethane (10 ml) was added the monobenzoate **20** (R = COPh, R′ = H; 371 mg, 1.35 mmol) in dichloromethane (3 ml) at room temperature. After 5 h, ethanol (1 ml) was added to destroy excess reagent and the red solution was decanted. The residue was washed twice with dichloromethane and the combined solution and washings were evaporated. The residue was chromatographed over alumina (G5), eluting with light petroleum–ethyl acetate to give the ketone **21** (R = COPh; 356 mg, 97%) as a pale yellow oil, bp 100 °C (2 × 10^{-4} mmHg): ir (film) 1725, 1610, 1585, 1275, and 725 cm^{-1}; NMR τ 8.93 (3 H, d, *J* = 6 Hz), 8.50 (3 H, s), 5.90 (2 H, d, *J* = 2 Hz), 1.90–2.58 (5 H, m); $[\alpha]D^{24}$ −0.6° (*c* 2% in $CHCl_3$).

Anal. ($C_{17}H_{20}O_3$) C, H.

2β*H*-9-Acetoxypinan-4-one (21, R = Ac). Oxidation of the monoacetate **20** (R = Ac, R′ = H; 200 mg) was carried out exactly as for the monobenzoate **20** (R = COPh, R′ = H). The yield was 192 mg (94%), bp 65 °C (3×10^{-4} mmHg): ir (CCl_4) 1745, 1720, and 1245 cm^{-1}; NMR τ 8.95 (3 H, d), 8.63 (3 H, s), 7.99 (3 H, s), 6.18 (2 H, s); $[\alpha]D^{24}$ 5.5° (*c* 3% in $CHCl_3$).

Anal. ($C_{12}H_{18}O_3$) C, H.

Photolysis of 2β*H*-9-Acetoxypinan-4-one (21, R = Ac). The ketone **21** (R = Ac; 100 mg, 0.48 mmol) in dry methanol (15 ml) containing sodium hydrogen carbonate (ca. 20 mg) was photolyzed for 6 h under N_2 in a water-cooled tube of Vycor glass using an external medium-pressure Hg lamp. The methanol was evaporated at room temperature and the residue was diluted with water (5 ml) and extracted with pentane (2 × 10 ml). The pentane solution was dried (Na_2SO_4), evaporated, and the residue chromatographed on silica, eluting with light petroleum–ethyl acetate. The aldehyde fraction (64 mg, 64%), proved to be a mixture of **22** and **23** in a ratio of 40–45:55–60; ir (CCl_4) 3080, 2715, 1750, 1733, 1725, 1647, 1235, 1035, 900, and 865 cm^{-1}; NMR τ (CCl_4) 9.13 (m), 8.78 (3 H, s), 8.75 (3 H, s), 8.62 (s), 8.30 (3 H, br s), 8.08 (3 H, s), 8.02 (3 H, s), 7.77 (m), 7.40 (m), 6.12 (2 H, m), 5.90 (2 H, d, J = 0 Hz), 5.25 (1 H, br s), 5.12 (1 H, br s), 3.93 (2 H, m), and 0.33 (1 H, m).

Photolysis of *trans*-Verbanone (24). *trans*-Verbanone (350 mg) in methanol (35 ml) containing sodium hydrogen carbonate (35 mg) was photolyzed and worked up under the same conditions as those used for *cis*-verbanone (**4**): The aldehyde fraction (53%) was a mixture of **5** and **6** in the ratio 35–40:60–65 (by NMR): ir (CCl_4) 3075, 3030, 2805, 2710, 1735, 1725, 1645, 915, and 890 cm^{-1}; NMR τ (CCl_4) 9.12 (m), 8.88 (6 H, s), 8.68 (3 H, s), 8.38 (3 H, s), 7.85 (m), 5.37 (1 H, br s), 5.20 (1 H, br s), 3.99 (2 H, q, J = 3.5 Hz), and 0.38 (1 H, m).

6,9-Dimethyl-8-oxo-7-oxatricyclo[4.3.0.0^{3,9}]nonane (28). A two-phase system of water (2 l.), potassium periodate (220 g, 1 mol), carbon tetrachloride (750 ml), hydrated ruthenium dioxide (600 mg, 1%), and the ether **27**[21] (from 66.7 g of pinan-2β-ol **26**) was vigorously stirred at room temperature for 8 days. The organic layer was separated, washed with water, and ethanol (5 ml) added to precipitate ruthenium dioxide. The dried (Na_2SO_4) solution was filtered through Celite, concentrated to 150 ml, and passed through a column (10 cm) of alumina (G3). Evaporation of the eluate and distillation (87–96 °C (2 mmHg)) gave the lactone **28** (58.0 g, 76% overall from **26**), mp 37–38 °C (from light petroleum): ir 1765, 1090, 1050, and 940 cm^{-1}; NMR τ 8.63 (3 H, s), 8.53 (3 H, s); $[\alpha]D^{22}$ (cor)[28] 49.7° (*c* 3% in $CHCl_3$).

Anal. ($C_{19}H_{14}O_2$) C, H.

6,9-Dimethyl-8-hydroxy-7-oxatricyclo[4.3.0.0^{3,9}]nonane (29). A solution of the lactone **28** (10 g) in dry ether (100 ml) at −22° was reduced by the addition of a solution of lithium triethoxyaluminum hydride in ether. The mixture was slowly added to a stirred solution of aqueous ammonium chloride at 0° and filtered. The ether layer was separated and the aqueous phase was extracted with ether. The combined ethereal extracts were washed with water, dried ($MgSO_4$), and evaporated to give the crystalline hemiacetal **29** (9.8 g, 97%), mp 58–60 °C (from light petroleum).

The alcohol **26** (20 g, 0.12 mol) in dry pyridine (250 ml) at 0° was treated with nitrosyl chloride (16.0 g, 0.24 mol) for 1 h. The mixture was allowed to reach room temperature over 2 h, poured into water, and extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated to 200 ml. The ether solution was again washed with water (400 ml), dried ($MgSO_4$), and evaporated. The crude nitrite ether in *n*-hexane (700 ml) was photolyzed for 17 h at room temperature using a glass-jacketed medium pressure lamp. The semisolid precipitate of nitroso dimer was dissolved in isopropyl alcohol and added to the residue from the evaporation of the *n*-hexane. The isopropyl alcohol solution (200 ml) was heated at reflux for 2 h and then evaporated. The residue containing the oxime **30** was dissolved in ether (300 ml) and stirred for 15 h with acetone (50 ml) and 2% aqueous hydrochloric acid (650 ml). The aqueous layer was separated and extracted with ether. The ether extract was washed successively with aqueous saturated sodium hydrogen carbonate solution and aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. Chromatography of the residue on alumina (G3), eluting with light petroleum–ethyl acetate gave the ether **27** (17%) and the hemiacetal **29** (10.3 g, 51% overall from **26**): ir 3450, 1090, 1010, and 990 cm^{-1}; NMR τ 8.75 (3 H, s), 8.65 (3 H, s), and 4.87 (1 H, s).

Anal. ($C_{10}H_{16}O_2$) C, H.

9-Methylenepinan-2β-ol (31). Methyltriphenylphosphonium iodide (189 g, 0.47 mol) was added to dry dimethyl sulfoxide (375 ml) and sodium hydride (12.7 g, 80%, 0.425 mol) under N_2. To this solution was added the hemiacetal **29** (23.5 g) in dimethyl sulfoxide (45 ml) and the mixture was stirred at 65–66 °C for 18 h. The cooled mixture was poured into ice–water (2 kg), extracted with light petroleum (3 × 500 ml), and the extract washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed (after filtering off triphenylphosphine oxide) over alumina (G3), eluting with light petroleum followed by light petroleum–ethyl acetate (99:1) to give the ether **32** (2.5 g, 11%; bp 50 °C (5 mHg)); ir 1145, 1090, 985, 955, and 905 cm^{-1}; NMR τ 8.83 (3 H, s), 8.73 (3 H, s), 9.03–8.77 (3 H, m), [6.29 (1 H, q, J = 7 Hz) and 6.02 (1 H, q, J = 7 Hz), total integral 1 H], *m/e* 166.1351; calcd for $C_{11}H_{18}O$: 166.1358; $[\alpha]D^{24}$ 34.1° (*c* 7.5% in $CHCl_3$); and the hydroxy olefin **31** (13.55 g, 58%; 67% allowing for 2.9 g recovered hemiacetal **29**); mp 50.5–51.5 °C: ir 3330, 1630, 1125, 1005, 925, and 915 cm^{-1}; NMR τ 8.75 (3 H, s), 8.63 (3 H, s), 7.93 (1 H, s exchanged by D_2O), 4.78–5.15 (2 H, m), 3.55 (1 H, dd, J = 18 and 10.5 Hz); $[\alpha]D^{24}$ (cor) −23.5° (*c* 3.5% in $CHCl_3$).

Anal. ($C_{11}H_{18}O$) C, H.

Hydroboration of 31. The olefin **31** (166 mg, 1 mmol) in dry tetrahydrofuran (3 ml) was treated with diborane solution (1.6 ml, 2 mequiv BH_3) at 0°. After 0.5 h at 0°, water (5 ml) was added and the borane worked up oxidatively with 3 N aqueous sodium hydroxide solution (3 ml) and 30% hydrogen peroxide solution (1 ml) at 30–40 °C. Conventional workup followed by chromatography of the residue over alumina (G3), eluting with light petroleum–ethyl acetate (9:1) gave **34** (72 mg, 39%), mp 149–149.5 °C (from light petroleum ether): ir 3330, 1135, and 930 cm^{-1}; NMR τ 8.97 (3 H, d, J = 7 Hz), 8.77 (3 H, s), 8.67 (3 H, s), 5.67 (1 H, g, J = 7 Hz), 2.9 (1 H, br s, exchanged by D_2O); $[\alpha]D^{25}$ (cor) −29.6° (*c* 1% in $CHCl_3$).

Anal. ($C_{11}H_{20}O_2$) C, H.

The following results were for the diol **33** (103 mg, 56%), mp 110–111 °C (from light petroleum ether): ir 3270, 1135, 1080, 965, and 935 cm^{-1}; NMR τ 8.71 (6 H, s), 6.0–6.38 (2 H); $[\alpha]D^{24}$ (cor) −28.5° (*c* 2% in $CHCl_3$).

Anal. ($C_{11}H_{20}O_2$) C, H.

Reaction of the Olefin 31 with Bis(3-methyl-2-butyl)borane. The olefin **31** (18.3 g, 0.110 mol) in tetrahydrofuran (30 ml) at 0° was treated with a tetrahydrofuran solution of bis(3-methyl-2-butyl) borane[24] (285 ml, ca. 0.28 mol, 2.5 equiv). After 18 h at 0°, the mixture was poured into water (300 ml) and aqueous sodium hydroxide solution (335 ml, 3 N) was added, followed by 30% hydrogen peroxide (100 ml). After 3 h at room temperature, the mixture was diluted with water (400 ml) and extracted with ether (3 × 500 ml). The ether extract was washed with water, dried (Na_2SO_4), and evaporated to give the diol **33** (19.2 g, 95%).

9-Methoxymethylenepinan-2β-ol (35). A stirred suspension of methoxymethyltriphenylphosphonium chloride (46.3 g, 0.135 mol) in dry *tert*-butyl alcohol (300 ml) under argon was treated with dry potassium *tert*-butoxide(13.44 g, 0.120 mol) to give a deep red solution of the ylide. After 30 min at 50° a solution of the hemiacetal **29** (5.04 g) in *tert*-butyl alcohol (40 ml) was added and the reaction was allowed to proceed for 40 h at 60–65 °C. The cooled mixture was poured into water (1.5 l.), extracted with ether (3 × 250 ml), dried (Na_2SO_4), and evaporated. The residue was treated with light petroleum and the precipitated triphenylphosphine oxide was removed by filtration. Chromatography of the filtrate over alumina (G3), eluting with light petroleum, gave the ether **36** (2.9 g, 47%), bp 60 °C (0.5 mmHg): ir 1160, 1110, and 1020 cm^{-1}; NMR τ (CCl_4) 8.73 (3 H, s), 8.65 (3 H, s), 6.62 (3 H, s), 5.37 (2 H, q, J = 7 Hz), 5.13 (1 H, s). Further elution gave the enol ether **35** (2.1 g, 36%), bp ca. 50 °C (3×10^{-4} mmHg): ir 3550, 1660, and 1110 cm^{-1}; NMR τ 8.75 (3 H, s), 8.57 (3 H, s), [6.46 (3 H, s), and 6.41 (3 H, s), total integral 3 H], [5.18 (1 H, d, J = 7 Hz) and 4.26 (1 H, d, J = 7 Hz), 4.67 (1 H, d, J = 13 Hz) and 3.56 (1 H, d, J = 13 Hz), total integral 2 H, cis:trans ratio 3:2]; *m/e* 196.1466 (calcd for $C_{12}H_{20}O_2$, 196.1463); $[\alpha]D^{24}$ (cor) 10.9° (*c* 5% in CCl_4).

Hydrolysis of the Enol Ether 35. The enol ether **35** (200 mg, 1 mmol) in ether (5 ml) was stirred at 0° with water (9 ml) containing concentrated hydrochloric acid (0.1 ml)–acetone (1 ml) for 30 min. Workup gave the δ-lactol **37** (137 mg, 74%) as a colorless oil, which rapidly decomposed at room temperature: ir 3400, 1145, 1125, 1105, 1070, and 955 cm^{-1}; NMR τ (CCl_4) 8.83 (3 H, s), 8.75 (3 H, s), 5.15

(1 H, br s, exchanged by D_2O), 4.71 (1 H, m); *m/e* 182.1309 (calcd for $C_{11}H_{18}O_2$, 182.1307).

Reduction of the δ-Lactol 37 to the Diol 33. The δ-lactol (50 mg) in ether (2 ml) was treated with excess lithium aluminum hydride at room temperature. Workup in the usual way gave the diol **33**, mp 110–111 °C, identical in all respects with an authentic sample.

9-Acetoxymethylpinan-2β-ol (40). The diol **33** (19.2 g, 0.104 mol) in dry pyridine (80 ml) and acetic anhydride (16.0 g, 0.157 mol) was stirred at room temperature for 3 h. Workup in the usual way gave the acetate **40** (22.45 g, 95%), bp ca. 80 °C (10^{-3} mmHg): ir (film) 3500, 1750, 1730, 1250, 1055, 1040, and 925 cm^{-1}; NMR τ 8.77 (3 H, s), 8.73 (3 H, s), 7.97 (3 H, s), 5.87 (2 H, t, J = 8 Hz).

Anal. ($C_{13}H_{22}O_3$) C, H.

9-Acetoxymethyl-α- and -β-pinenes (41 and 42). Dropwise addition of phosphorus oxychloride (25.65 g, 0.165 mol) to a stirred solution of the diol monoacetate **40** (24.5 g, 0.108 mol) in dry pyridine (100 ml) at 0°, followed by stirring for 17 h at 0° gave only one product (as judged by TLC). Workup gave an almost pure mixture of the α- and β-pinenes **41** and **42** (2:1, by NMR) (13.3 g, 59%), bp ca. 60 °C (3 × 10^{-4} mmHg): ir 1750, 1650, 1250, 1065, and 1045 cm^{-1}; NMR τ 8.75 (3 H, s), 8.72 (3 H, s), 8.30 (3 H, q, J = 2 Hz), 7.97 (3 H, s), 6.02 (2 H, t, J = 8 Hz), 5.98 (2 H, t, J = 8 Hz), 5.37 (2 H, m), 4.75 (1 H, m); $[\alpha]D^{23}$ (cor) −29.1° (*c* 3% in $CHCl_3$).

Anal. ($C_{13}H_{20}O_2$) C, H.

1,3-Dimethyl-2α-chloro-3α-(2′-acetoxyethyl)norbornane (43). A stirred solution of the diol monoacetate **40** (452 mg, 2 mmol) in dry pyridine (1.5 ml) at 0° was treated with thionyl chloride (310 mg, 2.6 mmol). After 60 h at 0° the mixture was worked up to give 20% of the α- and β-pinenes **41** and **42** (to TLC) along with a new product **43** (185 mg, 38%): ir 1745 and 1240 cm^{-1}; NMR τ 8.95 (3 H, s), 8.91 (3 H, s), 7.99 (3 H, s), 6.40 (1 H, d, J = 2 Hz), 5.91 (2 H, t, J = 7 Hz); *m/e* 244.1240 (calcd for $C_{13}H_{21}O_2Cl$, 244.1230).

9-Acetoxymethylpin-2-en-4-one (44). A stirred solution of the chromium trioxide–pyridine complex (45 g, 32 equiv) in dichloromethane (300 ml) was treated with a mixture of the pinenes **41** and **42** (1.2 g) and the mixture was heated at reflux for 26 h. The supernatant orange solution was decanted from a black semisolid precipitate and the precipitate was washed twice with dichloromethane. The total combined dichloromethane solution was washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue over alumina gave an α,β-unsaturated aldehyde (4%): ir 2720, 1750, 1690, 1250, 1064, and 1045 cm^{-1}; and the enone **44** (520 mg, 41%): ir 1750, 1690, 1630, 1250, 1065, and 1045 cm^{-1}; NMR τ 8.45 (3 H, s), 7.93 (3 H, d, J = 2 Hz), 7.96 (3 H, s), 8.20 (2 H, t, J = 7 Hz), 5.97 (2 H, t, J = 7 Hz), 3.19 (1 H, q); $[\alpha]D^{23}$ (cor) −162.1° (*c* 2% in $CHCl_3$). A sample was microdistilled for analysis, bp ca. 80 °C (3 × 10^{-4} mmHg).

Anal. ($C_{13}H_{18}O_3$) C, H.

2αH-9-Acetoxymethylpinan-4-one (45). The enone **44** (3.0 g) in ethanol (100 ml) containing 20% Pd/C (300 mg) was hydrogenated until 1 equiv of hydrogen was taken up at room temperature and atmospheric pressure (1.5 h). The solution was filtered through Celite and evaporated to give the ketone **45** (2.7 g, 90%): ir 1750, 1720, 1250, and 1060 cm^{-1}; NMR τ 8.77 (3 H, d, J = 6 Hz), 8.58 (3 H, s), 7.92 (3 H, s), 5.90 (2 H, t, J = 7 Hz); $[\alpha]D^{24}$ (cor) −34.5° (*c* 1% in $CHCl_3$). A sample was distilled for micro analysis, bp 75 °C (3 × 10^{-3} mmHg).

Anal. ($C_{13}H_{20}O_3$) C, H.

***cis*-2-(2′-Acetoxyethyl)-*cis*-3-isopropenyl-2-methylcyclobutanecarbaldehyde (46).** The ketone **45** (250 mg, 1.1 mmol) in dry methanol (25 ml) containing sodium hydrogen carbonate (25 mg) in a Vycor glass tube was photolyzed under N_2 employing the usual conditions, until the reaction was 80–90% complete. The methanol was evaporated at room temperature and the residue was treated with water and extracted twice with light petroleum. The extract was washed with water, dried (Na_2SO_4), and evaporated at 30°. The residue was chromatographed over silica, eluting with light petroleum–ethyl acetate (98:2) to give the aldehyde **46** (60%) containing 10% of the cyclobutene isomer **47**. The aldehyde **46** has: ir 3080, 2700, 1735, 1705, 1645, 1245, 1040, and 910 cm^{-1}; NMR τ (CCl_4) 8.58 (3 H, s), 8.30 (3 H, s), 8.07 (3 H, s), 7.47 (1 H, t, J = 7 Hz), 6.12 (2 H, m), 5.23 (1 H, br s), 5.08 (1 H, br s), 0.28 (1 H, d, J = 2 Hz); bp ca. 65 °C (3 × 10^{-4} mmHg).

Anal. ($C_{13}H_{20}O_3$) C, H.

A 2,4-dinitrophenylhydrazone of the aldehyde **46** was prepared by reaction of the crude aldehyde **46** in phosphoric acid–ethanol with 2,4-dinitrophenylhydrazine. The crude derivative was purified by TLC to give the 2,4-DNP derivative, mp 124–125 °C (from ethanol): ir 3280, 1720, 1625, 1590, 1520, 1350, 1310, 1275, 1140, 905, and 900 cm^{-1}; NMR τ 8.70 (3 H, s), 8.28 (3 H, s), 8.02 (3 H, s), 7.20 (1 H, t, J = 9 Hz), 6.03 (2 H, m), 5.25 (1 H, br s), 5.05 (1 H, br s), 2.4–1.60 (3 H, m), and 0.90 (1 H, d, J = 3 Hz).

Anal. ($C_{19}H_{24}N_4O_6$) C, H, N.

Photolysis of 2αH-9-Acetoxymethylpinan-4-one (45) in Methanol in the Absence of Sodium Hydrogen Carbonate. A solution of the ketone **45** (150 mg) in methanol (15 ml) was photolyzed in a Vycor glass tube under nitrogen. After 22 h, the methanol was evaporated at room temperature and the residue was chromatographed over alumina (G3) to give the acetal **48** (46 mg, 37%): ir 1750, 1650, 1250, 1060, 970, and 900 cm^{-1}; NMR τ 8.77 (3 H, s), 8.30 (3 H, s), 7.97 (3 H, s), 6.68 (6 H, s), 6.10–5.57 (3 H, m), 5.32 (1 H, br s), and 5.15 (1 H, br s).

Anal. ($C_{15}H_{26}O_4$) C, H.

Grandisol Acetate (1, R = Ac). The ketone **45** (430 mg, 1.9 mmol) in methanol (40 ml) containing sodium hydrogen carbonate (40 mg) was photolyzed in the usual way to give the crude aldehydes **46** and **47**. This mixture of aldehydes in dichloromethane (6 ml) containing chlorotris(triphenylphosphine)rhodium(I) (1.78 g) and potassium carbonate (100 mg) was heated at reflux under N_2 for 10 h. The dichloromethane was evaporated and the residue extracted with light petroleum, filtered, and evaporated. Chromatography of the residue over alumina, eluting with light petroleum, gave the acetate **1** (R = Ac) (149 mg, 52% overall, allowing for recovered ketone **45**): ir (film) 1735, 1640, 1245, 1040, and 895 cm^{-1}; NMR τ (CCl_4) 8.80 (3 H, s), 8.33 (3 H, s), 8.05 (3 H, s), 7.45 (1 H, t, J = 8 Hz), 6.01 (2 H, t, J = 8 Hz), 5.38 (1 H, br s), 5.18 (1 H, br s).

Reduction of Crude Grandisol Acetate (1, R = Ac). Crude **1** (R = Ac) from the above reaction was treated with excess lithium aluminum hydride at −20° in ether. Workup in the usual way gave impure grandisol (**1**, R = H): ir 3380, 3080, 1645, 1055, 1020, and 900 cm^{-1}; NMR τ (CCl_4) 8.82 (3 H, s), 8.33 (3 H, s) (minor signals at 9.17 and 9.07), 7.56 (1 H, br s exchanged by D_2O), 7.48 (2 H, t, J = 7.5 Hz), 6.46 (3 H, t, J = 7.5 Hz), 5.40 (1 H, br s), 5.22 (1 H, br s), 3.90 (2 H, q, integral 10–15% of 2 H).

The crude grandisol (**1**, R = H; 239 mg) in pyridine (3 ml) was treated with *p*-nitrobenzoyl chloride (415 mg) at 70–80 °C for 0.5 h. The mixture was poured into water and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), and evaporated. The crude *p*-nitrobenzoate (**1**, R = $COC_6H_4NO_2$-*p*) was crystallized three times from light petroleum to give pure **1** (R = $COC_6H_4NO_2$-*p*), mp 73–74 °C: ir (CCl_4) 3050, 1730, 1640, 1605, 1520, 1350, 1275, 1120, 1105, and 895 cm^{-1}; NMR τ (CCl_4) 8.75 (3 H, s), 8.32 (3 H, s), 7.42 (1 H, t, J = 8 Hz), 5.68 (2 H, t, J = 8 Hz), 5.35 (1 H, s), 5.17 (1 H, s), and 1.77 (4 H, s).

Anal. ($C_{17}H_{21}NO_4$) C, H, N.

(+)-Grandisol (1, R = H). Recrystallized grandisol *p*-nitrobenzoate (200 mg) in methanol (2.5 ml)–water (2.5 ml) was treated with potassium hydroxide (600 mg) for 0.5 h at 100°. To the cooled solution solid CO_2 was added and the mixture was extracted with light petroleum. The extract was dried (Na_2SO_4) and evaporated to give (+)-grandisol (**1**, R = H): ir (CCl_4) 3630, 3070, 1645, 1240, 1075, 1045, 990, 890, and 690 cm^{-1}; NMR τ (CCl_4) 8.82 (3 H, s), 8.33 (3 H, s), 8.28 (2 H, br s), 7.93 (1 H, s exchanged by D_2O), 7.48 (1 H, t, J = 7.5 Hz), 6.46 (2 H, t, J = 7.5 Hz), 5.40 (1 H, br s), 5.22 (1 H, br s).[29] Microdistillation at 50–60 °C (1 mmHg) gave 60 mg of (+)-grandisol (**1**, R = H); $[\alpha]D^{21.5}$ (cor) 15.9° (*c* 1% in *n*-hexane); $[\alpha]D^{25}$ (cor) 6.9° (*c* 3% in $CHCl_3$); $[\alpha]D^{25}$ (cor) 12.3° (*c* 3% in EtOH).

The purified pheromone **1** (R = H; 30 mg) was converted back into its *p*-nitrobenzoate, crystallized twice from light petroleum, and hydrolyzed and distilled as before. The very pure sample had $[\alpha]D^{21.5}$ (cor) 18.4° (*c* 1% in *n*-hexane).

Acknowledgment. The Science Research Council is thanked for a research studentship to P.D.H.

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(29) Comparison with spectral data kindly supplied by Dr. C. A. Henrick (Zoecon) of (±)-grandisol showed them to be identical (ir and NMR).

Experimental and Theoretical Studies of the Barrier to Rotation about the N–C^α and C^α–C′ Bonds (ϕ and ψ) in Amides and Peptides

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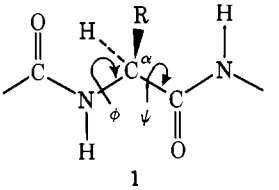
Abstract: The energetics of rotation about the N–C^α (ϕ) and C^α–C′ (ψ) bonds of methyl groups in simple amide and peptide systems have been studied by experimental and theoretical methods. X-Ray crystal structure analyses of 12 molecular conformations indicated that the position of the minimum in ϕ (C′–N–C^α–H) was equal to 180° (i.e., C–H anti to the C′–N bond). In ψ (H–C^α–C′–N) the minimum was found to be 0°, i.e., methyl C–H syn to the C′–N bond, based on analysis of ten molecular structures. Variations from these rotational minima appeared to be induced by crystal forces. In order to better understand these phenomena, ab initio molecular orbital, and empirical force field calculations of the rotational potential surface, and lattice energy calculations of the effect of crystal forces on the conformation were carried out. Minimal basis set molecular orbital calculations as carried out here and by others seem to yield results in disagreement with the experimental observations. When extended basis set calculations were carried out it was found that the calculated rotational potential surface in ϕ is compatible with the experimental results. The location of the minimum in ψ is still not correct, however, although the barrier was found to be almost negligible (0.1–0.2 kcal/mol vs. ~1 kcal/mol in the minimal basis sets). Lattice energy calculations on *N*-methylacetamide indicated that the crystal forces were of the same magnitude as those due to the rotational potential, in agreement with the experimental observation from various crystals that these forces seem to affect the intramolecular conformations. The minimized lattice energies at different ϕ's and ψ's were combined with the rotational potential energies as obtained from the various quantum mechanical methods in order to compare the predicted conformation with that observed. The empirical force field calculations using four previously derived different sets of potential functions (three of which having been obtained from fitting crystal data) all yielded the correct minimum in ϕ. However, in ψ all potentials predicted a minimum in disagreement with the experimental results as in the case of the quantum mechanical calculations. Thus in ψ, all theoretical methods yield the same result, which seems to be at odds with the experimental observations. The results also indicated that a 12th power repulsion may be too "stiff" when applied to the short intramolecular interactions important in determining rotational potentials.

To date the available experimental and theoretical information concerning the energetics of rotation about the N–C^α (ϕ) and C^α–C′ (ψ) bonds[2,3] in simple amide and peptide systems has been very scarce, and as a consequence the properties of these rotations have not been sufficiently well understood. These systems are important as they serve as model compounds for the analogous rotations in biologically important oligopeptides and proteins **1**. The situation is such that up to now not even the position of the minimum energy conformation of



1

the methyl group in model compounds **2** and **3** has been determined unambiguously. In addition, different theoretical