Tetrahedron. Vol 33, pp 373 to 380. Pergamon Press 1977 Printed in Great Britain

THE STEREOCONTROLLED PHOTOADDITION OF ALLENE TO CYCLOPENT-1-ENE-1-CARBOXALDEHYDES. A TOTAL SYNTHESIS OF (±) STEVIOL METHYL ESTER AND ISOSTEVIOL METHYL ESTER

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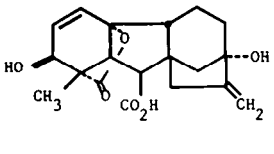
(*Received in the USA* 1 *September* 1976; *received in the UK for publication* 9 *September* 1976)

Abstract—The stereochemistry of the photoaddition of allene to hydroindenal **19** is explored. The stereochemistry is proven by conversion into steviol methyl ester **22b** and isosteviol methyl ester **24**.

The presence of the 1 - hydroxy - 7 - methylene-bicyclo[3.2.1]octane ring system in gibberellic acid **1**[3] and steviol **2**[4] has led to the development of a variety of synthetic techniques applicable to the construction of this functionality.[5]



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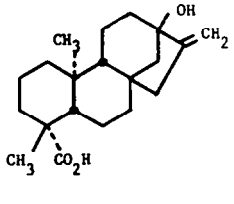

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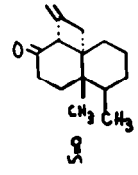
One of our earlier investigations[5h] demonstrated the utility of coupling a photochemical and a solvolytic reaction to provide this ring system as outlined in Scheme 1.

Although this model study produced the expected mode of head-to-head photoadducts which have been produced in cycloalkenone systems,[6,7] it failed to provide useful information regarding stereochemistry, which could only be obtained from a polycyclic aldehyde containing proximate asymmetry.

Photoadducts **8**[6h] and **9**[6d] have been prepared from the corresponding cyclohexenones. In both instances a *trans*-fused juncture is produced. Employing the analysis of Wiesner,[6f,8] a hydroindenal (i.e. **19**) would be expected to provide a *cis*-fused photoadduct necessary to elaborate the stereochemistry present at the B/C ring juncture of steviol.



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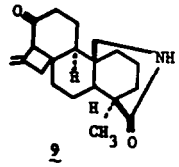

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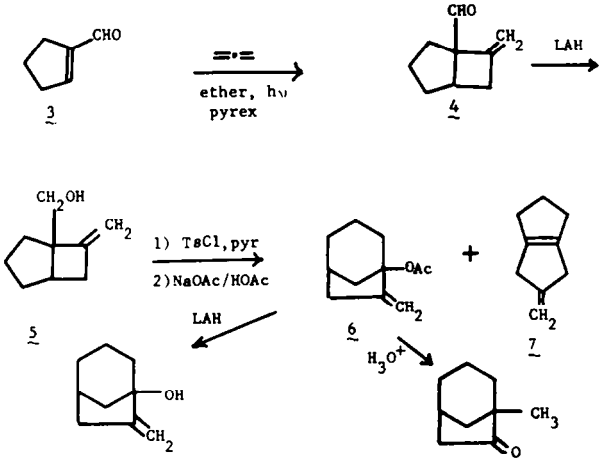
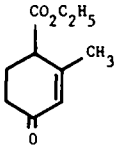


3 **4** **5** **6** **7**

Scheme 1.

As our point of departure, we chose the known[9] tricyclic ketone **12** with the intention of stereoselectively converting it to the acid **15d**,[10] which would subsequently be converted into the critical aldehyde **19**.

At the very outset it proved necessary to make certain modifications in the literature preparation of ketone **12**. Alkylation of the potassium enolate of Hagemann's ester **10** with the mesylate of *m*-methoxyphenethyl alcohol in toluene[11,12] provided the α-alkylated product **11a**, whereas alkylation of the sodio-enolate with the corresponding bromide in benzene-dimethyl-formamide gave *O*-alkylation and *m*-methoxystyrene in addition to the desired product. The crude alkylated material was decarboxylated in aqueous ethanolic sulfuric acid to provide enone **11b** in 66% yield for the two steps.



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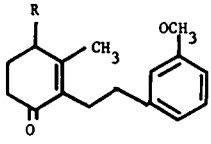
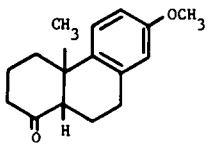


11a, R = $CO_2C_2H_5$

b, R = H

When enone **11b** was subjected to cyclization with 85% phosphoric acid,[9] the desired ketone **12** was obtained in approximately 35% yield while the major material was the naphthalene **13** (45–50%). Moreover, subjection of the tricyclic ketone to the reaction conditions provided the naphthalene, indicating that the ketone was being reversibly formed under the reaction conditions. After examining a veritable plethora of acid catalysts[12] which might form the β-cyclized product under kinetically controlled conditions, it was discovered that treatment of enone **11b** with a 10% solution of phosphorus pentoxide in 91% methane-sulfonic acid[13] at 35° for 52 h afforded a 50% yield of ketone **12**. Although unidentifiable by-products were formed, there was no sign of naphthalene **13**. While hardly a triumph, this did represent a 15% increase in yield over the previous reaction conditions.



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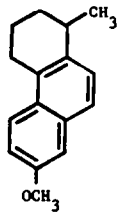

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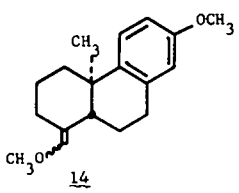
It has been observed by a number[14] of investigators that Wittig reactions conducted in dimethylsulfoxide on *cis*-1-decalones capable of ring juncture epimerization provide the *trans*-fused olefin. Since the ketone **12** exists as a 2:1 (*cis*:*trans*) mixture, it was considered plausible that if the *trans* isomer reacted faster than the *cis* isomer, and the rate of equilibration of the isomers was faster than the olefination of the cis isomer, the required *trans* juncture could be established. Consequently, when ketone **12** was reacted with methoxymethylene triphenylphosphorane[15] in dimethyl sulfoxide, a mixture of enol ethers **14** was obtained, which was subsequently shown to have exclusively the *trans*-fused ring juncture. Moreover, on occasions, it was possible to isolate pure *cis*-ketone **12** from the reaction mixture.



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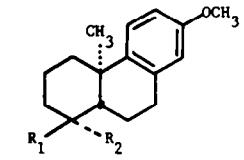


15a, R_1 = H , R_2 = CHO

b, R_1 = CHO, R_2 = H

c, R_1 = CH_3, R_2 = CHO

d, R_1 = CH_3, R_2 = CO_2H

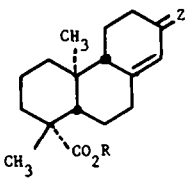
Hydrolysis of the enol ether mixture **14** with aqueous hydrochloric acid provided a single aldehyde **15a** from kinetic protonation. The nuclear magnetic resonance spectrum of this aldehyde revealed the aldehyde proton as a singlet due to restricted rotation imposed by the angular methyl group. Exposure of the axial aldehyde to potassium *tert*-butoxide effected equilibration to the equatorial aldehyde **15b**, whose aldehyde proton appeared as a doublet. Stereocontrolled α-methylation of the aldehyde **15a** (and/or **15b**) proceeded as expected[15,16] to provide a single alkylated aldehyde **15c**.

Further confirmation for this assignment was obtained when the alkylated aldehyde was oxidized with Jones' reagent to the known tricyclic acid **15d**, prepared by two alternate routes by the Japanese workers.[5j] This pathway provided a stereospecific route for establishing the relative stereochemistry at the three asymmetric centers present in the A and B rings of steviol.

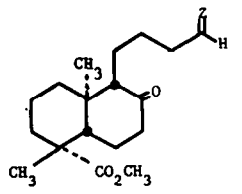
The aromatic tricyclic acid **15d** was subjected to Birch reduction followed by hydrolysis[5j] to provide enone **16a**, which was smoothly transformed into thioketal **16b** with ethanedithiol-boron trifluoride in acetic acid.[17] Since it was necessary to warm the enone in acetic acid to effect solution prior to thioketalization, occasionally some β,γ unsaturated thioketal was formed.

Desulfurization was achieved with lithium in liquid ammonia providing the olefinic acid **16c**, having the double bond in the more substituted position.[18] Exposure of this substance to ethereal diazomethane produced the corresponding methyl ester **16d**.

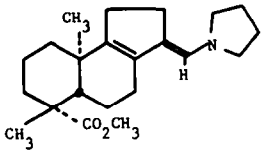
With the olefinic methyl ester in hand, the stage was set for constructing the unsaturated aldehyde **19** as prescribed by the model study sequence. Ozonolysis of the olefinic ester in methanol followed by decomposition with dimethyl sulfide[19] yielded the ketoacetal **17a**, which was readily transformed to the corresponding ketoaldehyde **17b**. The aldolization and dehydration proved to be more perverse than had been anticipated. The aldolization of 2-(4-formylpropyl)-2-benzyloxymethyl cyclohexanone, a monocyclic analog of **17b**, has been effected with sodium carbonate in aqueous ethanol.[20] Under these conditions, only a 29% yield of unsaturated aldehyde could be obtained employing ketoaldehyde **17b**. This low yield was apparently due to the inability of the aldol to undergo dehydration caused by the attendant *trans*-fused A ring. After several unsuccessful forays with other standard catalysts (e.g. acid, DBU, piperidinium acetate),[21] it was found that pyrrolidine in refluxing benzene, with azeo-



16a, Z = O, R = H
b, Z = $-(SCH_2)_2$, R = H
c, Z = H_2, R = H
d, Z = H_2, R = CH_3



17a, Z = OCH_3, OCH_3
b, Z = O



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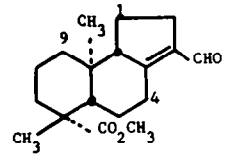
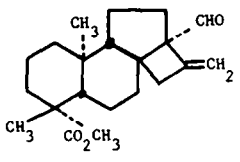


19

tropic removal of water, provided enamine **18**. The kinetically formed[22] aldehyde enamine undergoes aldolization followed by intramolecular elimination of water through the tricyclic enamine of the aldol product. The position of the β,γ double bond was assigned to the ring juncture as opposed to the 3a,4 position (*cisoid* dienamine) since the nuclear magnetic resonance spectrum displayed only the α-vinyl hydrogen. This was as anticipated since the alternate assignment (if formed thermodynamically) would involve severe interactions between the hydrogens at the α and C-4 positions. Hydrolysis of the enamine in aqueous acetic acid-sodium acetate[23] provided aldehyde **19** in 40% yield after chromatography. The 9b-βH geometry follows from equilibration of the unsaturated aldehyde during the hydrolysis.

In aldehyde **19**, the template was now available to test the stereochemistry of allene photoaddition to a hydrindenal system. Irradiation of an ethereal solution of aldehyde **19** in the presence of allene (nitrogen atmosphere, pyrex filter, 450W Hanovia lamp) at −78° caused complete consumption of the starting material, producing after work-up a 14:1 mixture of photoadducts. The crystalline major adduct **20** (*vide infra*) (*m/e* 330 parent) revealed the anticipated NMR absorptions, 0.55 and 1.16 ($-\overset{|}{\underset{|}{C}}-CH_3$), 3.57 ($-CO_2CH_3$), 4.72 and 4.85 (vinyl H) and 9.60 δ(–CHO). The spectral properties of the minor component were similar to those of photoaldehyde **20**, but it was not possible to discern the mode of photoaddition due to limited amounts of material which would have had to be chemically transformed. The prime candidates for the minor isomer are the regioisomeric head-to-tail adduct of **20** or the stereoisomeric head-to-head adduct.

Alcohol **21a** was produced by exposure of the photoaldehyde to ethanolic sodium borohydride at 0°. Whereas, the model alcohol readily formed a tosylate,



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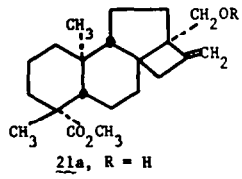
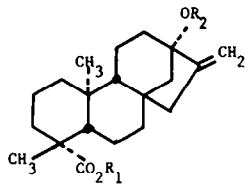


21a, R = H
b, R = Ms

alcohol **21a** was reluctant to follow suit. However, treatment of the alcohol with methanesulfonyl chloride-pyridine provided the corresponding mesylate **21b** without complication. This penultimate product (*m/e* 410, parent) was readily characterized by its NMR spectrum, which displayed, in addition to the two quaternary methyls and the methyl ester, a methyl at 3.13 assigned to the mesylate. Moreover, the carbinyl methylene protons, although inherently diastereotopic, appeared as a two-proton singlet at 4.38δ, insuring that no rearrangement had occurred during the mesylation.

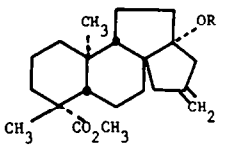
Utilization of refluxing acetic acid–sodium acetate as a solvolytic medium proved to be too severe, producing unrecognizable products. This observation, coupled with the desire not to have to transform the *O*-acetate of steviol methyl ester to methyl steviol, prompted the decision to employ refluxing 50% aqueous acetone in the presence of 2,6-lutidine as the reaction medium. Under these conditions solvolysis gave a mixture of products as witnessed by both TLC and NMR analysis. Preparative thin layer chromatography afforded 3% of (±) steviol methyl ester (**22b**)[24] identical with a sample of optically active steviol methyl ester prepared by esterification of steviol[25] derived from natural stevioside **22a**.[4] Comparison was made by double elution thin layer chromatography in two different solvent systems and by NMR spectroscopy.[26] A second polar crystalline product was isolated and tentatively assigned structure **23a**. The assignment was based upon the mass spectrum which revealed a parent peak at *m/e* 332 with the loss of –OH



22a, R_1 = Glu, R_2 = GluGlu

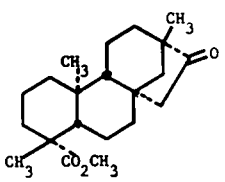
b, R_1 = CH_3, R_2 = H

c, R_1 = CH_3, R_2 = OMs



23a, R = H

b, R = OMs



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and water at *m/e* 314 and 315, respectively. The NMR spectrum revealed the methylene protons as a broad singlet at δ 4.86. Supportive evidence for structure **23a** came from the fact that diene **7** arose as the minor product from migration of the two carbon bridge in the model study.[27,28]

An oily fraction obtained by preparative thin layer chromatography (21%) proved to consist of the internal return mesylate **22c** contaminated by a second mesylate, possibly **23b**, on the basis of its NMR spectrum. The spectrum bore a striking resemblance to steviol methyl ester except for the mesylate methyl at δ3.10. While the mass spectrum of this fraction failed to reveal a parent ion (*m/e* 410), the fragments of highest mass (*m/e* 314 and 315) were the same as those derived from steviol methyl ester. Under the milder reaction conditions employed for this solvolysis, (aqueous acetone–2,6 lutidine at reflux) compared with the more vigorous conditions of refluxing acetic acid-sodium acetate utilized in the model system, bridgehead exchange of the mesylate is a prohibitive process.

Finally, a highly non-polar, non-homogeneous fraction (36%) was isolated whose NMR spectrum showed olefinic protons, a broadened methyl ester region and numerous peaks in the angular methyl region. No definitive information could be obtained concerning the structures of these substances.

Treatment of the contaminated internal return mesylate **22c** with refluxing 20% aqueous hydrochloric acid effected rearrangement (see Scheme 1) to isosteviol methyl ester (**24**),[5,29] providing further evidence for the structure of mesylate **22c**.

Although the solvolytic ring expansion is by no means clean and the reaction is complicated by internal return, the stereochemistry and regioselectivity of the photoaddition in the hydrindenal ring system is highly specific.

EXPERIMENTAL

Microanalyses were performed by Galbraith Laboratories and Atlantic Microlabs. M.pts were obtained on a Fischer-Johns apparatus and are corrected. Infrared (IR) spectra were recorded on a Perkin-Elmer model 421 spectrometer. The nuclear magnetic resonance spectra (NMR) were obtained with Jeolco model JNM-MH-100 and Varian models A-60 and A-60A spectrometers and are given in ppm from an internal tetramethylsilane standard (δ); coupling constants are given in Hz. Mass spectra were determined on a Hitachi RMU-6 instrument. Gas chromatographically purified samples were collected on a 3/8 in. × 20 ft 20% SE-30 on a Chromosorb W(45/60) column using an Aerograph A-90P instrument with helium as the carrier gas.

Solvents used were reagent grade and employed as received, except where noted. Column chromatographies were run with silica gel (Grace, 100–200 Mesh) as the adsorbant eluent, and redistilled solvents as eluants. Preparative thin layer chromatography employed Anal Tech 20 cm × 20 cm × 0.5 mm silica gel plates with fluorescent indicator. In all workup procedures the drying process involved swirling over anhydrous magnesium sulfate and filtering prior to evaporation.

1 - *Cyclopentene* - 1 - *carboxaldehyde* **3**. In a 1 l. flask were combined 20 g (0.25 mol) of cyclohexene and 400 ml of methanol. The mixture was cooled to −60° and ozone was passed through until a deep blue color persisted, indicating the reaction was complete. After flushing the system with nitrogen, 30 g (0.49 mol) of dimethylsulfide was added to the stirred solution. The flask was placed in an ice salt bath; the solution being stirred for 18 h while it came to room temp. When a negative potassium iodide test showed that reduction was complete, the excess dimethylsulfide and methanol were removed on a rotary evaporator. The resulting oil was taken up in 200 ml of 5% hydrochloric acid and stirred for 1.5 h. This suspension was placed in a continuous extractor and extracted with ether for 18 h. After drying a few crystals of *p*-toluene sulfonic acid were added, and the mixture distilled at reduced pressure (b.p. 60–90°/12 mm) affording a cloudy yellow oil. The oil was taken up in ether, and dried over anhydrous magnesium sulfate for 24 h. After filtration, the product was distilled, yielding 11 g (47%) of aldehyde **3**: b.p. 43–46° (7 mm); IR (CCl_4) 2700, 1680 cm^{-1}; NMR (CCl_4) δ 1.80–2.20 (m, 2H), 2.25–2.80 (m, 4H), 6.90 (m, 1H) and 9.75 (s, 1H).

1 - *Formyl* - 7 - *methylenebicyclo*[3.2.0]*heptane* **4**. Into a Pyrex tube flushed with nitrogen and cooled in a dry ice/acetone bath was condensed 10 ml (17.9 g, 0.45 mmol) of allene, followed by the addition of 5.0 g (0.052 mol) of aldehyde **3** with subsequent dilution to 25 ml with dry ether. The mixture was then cooled in liquid nitrogen, degassed, and placed under a nitrogen atmosphere. The tube was sealed, and placed in a water bath cooled by running tap water and photolyzed for 30 h with a 450 Watt Hanovia lamp. Upon completion of the irradiation, the tube was cooled in dry ice/acetone, opened, and slowly brought to room temperature to allow for the gradual evaporation of the excess allene. After removal of the ether on a rotary evaporator, the mixture was distilled, affording 2.85 g (41%) of photoaldehyde **4**: b.p. 63–70° (7 mm); IR (CCl_4) 1710, 1720 cm^{-1}; NMR (CCl_4) δ 1.50–3.20 (m, 9H), 4.90 (m, 2H) and 9.70 (s, 1H). Analysis of 2,4-dinitrophenylhydrazone: calc. for $C_{15}H_{16}O_4N_2$: C, 56.96; H, 5.10. Found: C, 56.79; H, 5.26%.

1 - *Hydroxymethyl* - 7 - *methylenebicyclo*[3.2.0]*heptane* **5**. To a stirred suspension of 1.64 g (0.042 mol) of lithium aluminum hydride in 50 ml of dry ether was added 5.70 g (0.042 mol) of photoaldehyde **4**. After stirring for 2 h, the excess lithium aluminum hydride was decomposed with saturated sodium sulfate solution, the salts were filtered, and the ether removed on a rotary evaporator. Distillation afforded 4.0 g (69%) of bicyclicalcohol **5**: b.p. 78–84° (7 mm); IR (CCl_4) 3600–3100 cm^{-1}; NMR (CCl_4) δ 1.00–3.00 (m, 9H), 3.15 (s, 1H), 3.45 (d, 1H, J = 12 Hz), 3.65 (d, 1H, J = 12 Hz) and 4.79 (m, 2H); mass spectrum, *m/e* (rel. intensity), 138 (11, parent) and 79 (100, base). Calc. for *p*-nitrobenzoate $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.72; H, 6.12; N, 4.79%.

p-Toluenesulfonyl ester of alcohol **5**. To 20 ml of pyridine was added 4.0 g (0.029 mol) of alcohol **5** and the resulting solution was cooled to 10°. To this solution was slowly added 8.4 g (0.043 mol) of *p*-toluenesulfonyl chloride. After storing in a freezer for 18 h, the resulting suspension was poured over a mixture of 30 ml of concentrated hydrochloric acid and 250 ml of iced water. Extraction with ether, drying and removal of the solvent on a rotary evaporator afforded an oil, which crystallized from petroleum ether, yielding 6.75 g (80%) of the *p*-toluenesulfonyl ester: m.p. 74–76°; NMR (CCl_4) δ 1.33–3.13 (m, 8H), 2.53 (s, 3H), 4.13 (s, 2H), 4.81–5.00 (m, 2H), 7.50 (d, 2H, J = 10 Hz) and 7.95 (d,

2H, J = 10 Hz). Calc. for $C_{16}H_{20}O_3S$: C, 65.74; H, 6.90; S, 10.94. Found: C, 65.52; H, 7.09; S, 11.04%.

1 - *Acetoxy* - 7 - *methylenebicyclo*[3.2.1]*octane* **6** *and* Δ1,5-3-*methylenebicyclo*[3.3.0]*octene* **7**. To a solution of 12 g of sodium acetate in 120 ml of glacial acetic acid was added 4.60 g (0.016 mol) of the *p*-toluene-sulfonyl ester of alcohol **5**. After refluxing under nitrogen for 5 h (118°), the solution was cooled, diluted with an equal volume of water, and extracted three times with ether. The ether extracts were combined, neutralized with saturated sodium bicarbonate solution, dried, and concentrated *in vacuo*. The resulting oil was distilled yielding 1.30 g (46%) of acetate **6**: b.p. 88–96° (7 mm); IR (CCl_4) 1735 cm^{-1}; NMR (CCl_4) δ 1.25–2.80 (m, 11H), 1.96 (s, 3H) and 4.90 (m, 2H); mass spectrum *m/e* (rel. intensity), 180 (8, parent) and 95 (100, base). Calc. for $C_{11}H_{14}O_2$ (GLC sample): C, 73.30; H, 8.95. Found: C, 73.60; H, 9.04%. Also obtained was 262 mg (13.8%) of olefin (**7**), single peak by GLC: b.p. 58–62° (7 mm); IR (CCl_4) no carbonyl; NMR (CCl_4) δ 2.13 (s, 6H), 2.96 (broad s, 4H), 5.13 (m, 2H); mass spectrum, *m/e* (rel. intensity), 120 (52, parent) and 91 (100, base).

1 - *Hydroxy* - 7 - *methylenebicyclo*[3.2.1]*octane*. To a stirred suspension of 80 mg (2.1 mmol) of lithium aluminum hydride in 20 ml of ether was added 360 mg (2.0 mmol) of acetate **6**. After addition was complete, the solution was refluxed for 30 min, cooled, and decomposed with saturated sodium sulfate solution. Drying, filtration, and removal of the ether on a rotary evaporator afforded 271 mg (98%) of an oil, which displayed only one peak on GLC. No further attempt was made at purification of the product: IR (CCl_4) 3600, 3550–3200 cm^{-1}; NMR (CCl_4) δ 1.00–3.00 (m, 11H), 3.96–4.33 (broad s, 1H), 4.90 (s, 1H) and 5.15 (1H, s); mass spectrum, *m/e* (rel. intensity) 138 (14, parent) and 95 (100, base). Calc. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.27; H, 10.39%.

5 - *Methyl* - 6 - *oxobicyclo*[3.2.1]*octane*. To 10 ml of 20% hydrochloric acid and 2 ml of tetrahydrofuran was added 200 mg (1.1 mmol) of acetate **6**. The solution was refluxed under nitrogen for 1.5 h, cooled, and extracted with ether. After neutralization with saturated sodium bicarbonate solution, the organic layers were dried and concentrated *in vacuo*, affording 500 mg of an oil, which was purified by VPC to provide 5-methyl-6-oxobicyclo[3.2.1]octane having identical spectral properties with a sample prepared by an alternate route.[30]

m-*Methoxyphenethyl alcohol, methanesulfonyl ester*. In the manner described[31] for the tosylate, the oily mesylate (homogeneous by TLC) was prepared in 92% yield: NMR ($CDCl_3$) δ 2.77 (s, 3H), 2.95 (t, 2H), 3.70 (s, 3H), 4.30 (t, 2H), 6.70 (m, 3H) and 7.10 (m, 1H).

2 - [β - (m - *Methoxyphenethyl*)] - 3 - *methyl* - *cyclohex* - 2 - *en* - 1 - *one* **11b**. A solution of 23.4 g (0.60 mol) of potassium metal dissolved in 600 ml of dry t-butanol under nitrogen was diluted with 2 l freshly dried and distilled toluene and the resulting mixture was distilled until the temperature of the distillate reached 110°. The resulting solution was diluted to 5 l. with more toluene, and heated to 80°. To this solution was added 105.0 g (0.57 mol) of Hagemann's ester **10** dissolved in an equal volume of toluene. After 20 min 148.0 g (0.63 mol) of the mesylate of *m*-methoxyphenethyl alcohol was added and the mixture was vigorously stirred for 18 h at 80°. The mixture was then cooled and poured into an equal volume of water. The layers were separated, the aqueous fraction was acidified with concentrated hydrochloric acid, and extracted with ether. The combined organic layers were dried, and distilled at 1.0 mm until the temperature of the distillate was 140°. The undistilled material (crude ester **11a**) was taken up in 600 ml of ethanol and 2 l of 10% sulfuric acid and refluxed under nitrogen for 48 h. After cooling the reaction mixture was poured into an equal volume of ice cold saturated sodium chloride solution and extracted three times with a total of 1.5 l of ether. After drying and removal of the solvent on a rotary evaporator, the resulting oil was distilled affording 92 g (66%) of enone **11b** (homogeneous by TLC): b.p. 150–155° (6μ); NMR ($CDCl_3$) δ 1.70 (s, 3H), 1.60–2.90 (m, 6H), 2.57 (s, 4H), 3.75 (s, 3H) and 6.60–7.15 (m, 3H).

7 - *Methoxy* - 4a - *methyl* - 3,4,4a,9,10,10a - *hexahydro* - 1(2H)*phenanthrone* **12**. (A) *Phosphoric acid method*. To 150 ml of 85% phosphoric acid was added 30.0 g (0.12 mol) of enone **11b**. The mixture was heated with vigorous stirring under nitrogen at 110° for 12 h. After cooling and dilution with 300 ml of water, the mixture was extracted three times with $CHCl_3$. The organic extracts were combined, dried, and concentrated *in vacuo* to a brown oil. After adsorption on silica gel, this oil was chromatographed on 200 g of silica gel. Elution with benzene until material stopped coming off the column afforded 13.5 g (50%) of an oil, homogeneous by TLC, whose structure was assigned as tetrahydrophenanthrene **13**: NMR ($CDCl_3$) δ 1.26 (d, 3H), 1.4–3.2 (m, 7H), 3.76 (s, 3H), and 6.90–7.86 (m, 5H); IR ($CHCl_3$) no carbonyl. Elution with 10% ether–benzene provided 10.4 g (35%) of ketone **12** as an oily mixture of stereoisomers, (homogeneous by TLC): NMR ($CDCl_3$) δ 1.00 & 1.30 (two singlets, 1:2, 3H), 1.40–3.20 (m, 11H), 3.70 (s, 3H), and 6.40–7.60 (m, 3H); IR($CHCl_3$) 1710 cm^{-1}.

(b) *Methanesulfonic acid method*. To 200 g of 91% methanesulfonic acid in which was dissolved 20 g of phosphorous pentoxide was added 20 g (0.082 mol) of enone **11b**. The resulting mixture was stirred for 5 days at 35° under nitrogen. Similar work-up provided 10 g (50%) of ketone **12**.

7 - *Methoxy* - 1 - *methoxymethylene* - 4aα - *methyl* - 1,2,3,4,4a,9,10,10aβ - *Octahydrophenanthrene* **14**. In a flame-dried 25 ml three necked flask equipped with a thermometer, condenser, and a serum cap was placed 118 mg (2.46 mmol) of 50% sodium hydride dispersion under a N_2 atmosphere. After two hexane washings to remove the mineral oil, 5 ml of freshly dried and distilled dimethylsulfoxide were added via syringe. The resulting suspension was then heated at 75° until gas evolution ceased, whereupon the solution was cooled to room temperature. A solution of 900 mg (2.7 mmol) of the phosphonium salt derived from PPh_3 and chloromethylmethyl ether in 5 ml of dimethylsulfoxide was then added via syringe. After 5 min of stirring a clear, deep red solution was obtained. A solution of 200.0 mg (0.82 mmol) of ketone **12** in 3 ml of dimethylsulfoxide was then added, and the reaction mixture was stirred for 3.5 h. Dilution with 50 ml of water was followed by three ether extractions. The ether extracts were combined, washed three times with water, dried, and concentrated to an oil, which was chromatographed on 20 g of silica gel. Elution with 50% hexane/benzene afforded crystalline Ph_3PO. Subsequent elution with benzene provided 196 mg (88%) of enol ethers **14** as an oil (two spots by TLC): NMR ($CDCl_3$) δ 1.00 & 1.15 (two singlets, 6:1, 3H), 1.20–3.05 (m, 11H), 3.48 & 3.69 (two singlets, 1:6, 3H), 3.77 (s, 3H), 5.70 & 5.95 (two singlets, 6:1, 1H) and 6.60–7.45 (m, 3H).

7 - *Methoxy* - 4aα - *methyl* - 1,2,3,4,4a,9,10,10aβ - *octahydrophenanthrene* - 1α - *carboxaldehyde* **15a**. A solution of 50 mg (0.18 mmol) of enol ethers **14** and 0.25 ml of 35% hydrochloric acid in 2 ml of tetrahydrofuran was allowed to stand at room temperature overnight. After dilution with 5 ml of water, the resulting mixture was extracted with two 8 ml portions of methylene chloride. The organic extracts were combined, washed with saturated sodium chloride solution and dried. Removal of the solvent on a rotary evaporator (bath temp. below 40°) afforded 45 mg (95%) of aldehyde **15a** as on oil (single spot on TLC): NMR ($CDCl_3$) δ 1.03 (s, 3H), 1.00–3.20 (m, 12H), 3.80 (S, 3H), 6.60–7.40 (m, 3H) and 10.35 (s, 1H).

On a preparative scale, less care was exercised in the work-up and the product was chromatographed on silica gel. While the over-all yield was unaffected, the product obtained was a mixture of epimeric aldehydes **15a** and **15b**.

7 - *Methoxy* - 4aα - *methyl* - 1,2,3,4,4a,9,10,10aβ - *octahydrophenanthrene* - 1β - *carboxaldehyde* **15b**. A solution of 45 mg of aldehyde **15a** in 2 ml of t-butanol containing 10 mol percent of potassium t-butoxide was allowed to stand at room temp. 45 min. After dilution with 5 ml of water and acidification with 10% hydrochloric acid, the resulting mixture was extracted with two 8 ml portions of CH_2Cl_2. The organic extracts were combined, washed with saturated NaCl soln and dried. Removal of the solvent on a rotary evaporator afforded 30 mg (67%) of aldehyde **15b** as an oil (homogeneous by TLC): NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.00–3.00 (m, 12H), 3.80 (s, 3H), 6.60–7.40 (m, 3H) and 9.70 (d, 1H).

1β,4aα - *Dimethyl* - 7 - *methoxy* - 1,2,3,4,4a,9,10,10aβ - *octahydrophenanthrene* - 1 - *carboxaldehyde* **15c**. To a mixture of 30 ml of benzene and 57 ml of t-butanol was added 2.31 g

(0.09 mol) of aldehyde **15a** and 2.05 ml MeI. After purging the solution with N_2, 36 ml of 0.5 M potassium t-butoxide in t-butanol was added dropwise, and the resulting solution was stirred at room temperature for 2 h. After dilution with an equal volume of water, the mixture was extracted three times with CH_2Cl_2. The extracts were combined, washed with saturated sodium chloride solution dried, and concentrated *in vacuo*. The resulting oil was triturated with ether–hexane to afford 1.22 g of a white crystalline solid. The mother liquors were chromatographed on silica gel, and treated similarly to yield and additional 0.36 g of solid. The total yield of aldehyde **15c** was 65%: m.p. 84–86°; NMR ($CDCl_3$) δ 1.02 (s, 3H), 1.10 (s, 3H), 1.00–3.10 (m, 11H), 3.78 (s, 3H), 6.60–7.40 (m, 3H) and 9.96 (s, 1H). Calc. for $C_{19}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.18; H, 8.95%.

1β,4aα - *Dimethyl* - 7 - *methoxy* - 1,2,3,4,4a,9,10,10aβ - *octahydrophenanthrene* - 1 - *carboxylic acid* **15d**. A solution of 1.27 g (4.66 mmol) of aldehyde **15c** in 60 ml of acetone was cooled to 5° and treated with a 2-fold excess of Jones' reagent. After stirring at 7° (cold room) for 18 h the excess oxidant was quenched with i-PrOH. The resulting green solution was diluted with an equal volume of water, and extracted three times with 8% NaOH soln. The basic extracts were combined, washed once with ether, cooled in an ice bath and acidified with conc HCl. The suspension was extracted three times with ether. The extracts were combined, dried, and concentrated *in vacuo* to afford 1.20 g (89%) of acid **15d** as a light tan solid. Recrystallization of a sample of this solid from ether afforded white crystals: m.p. 192–193° (lit.[32] 193–194°).

Thioketal of 1β,4aα - *Dimethyl* - 7 - *oxo* - 1,2,3,4,4a,4bβ,5,6,7,9,10,10aβ - *Dodecahydrophenanthrene* - 1 - *carboxylic acid* **16b**. A solution of 2.23 g (7.7 mmol) of ketoacid **16a** in 50 ml of glacial acetic acid was heated to 80°. To this solution was added 10 drops of boron trifluoride etherate and 1.5 ml of ethane dithiol. After an additional 5 min heating, the solution was allowed to cool to room temp. The white crystalline solid which precipitated was filtered, washed with acetic acid, and allowed to dry, affording 2.13 g (78%) of thioketal **16b**: m.p. 243–45°; NMR ($CDCl_3$) δ 0.73 (s, 3H), 1.28 (s, 3H), 0.50–2.60 (m, 16H), 3.23–3.52 (m, 4H), 5.82 (s, 1H) and 10.10 (broad s, 1H); mass spectrum *m/e* (relative intensity): 352 (34), 351 (100), 291 (41), 259 (23), 176 (50), 161 (55), 157 (32), 148 (68), 140 (27), 126 (100), 115 (68), 113 (82), 110 (36), 95 (46) and 81 (78). Calc for $C_{19}H_{28}O_2S_2$: S, 18.19. Found: S, 17.91%.

1β,4aα - *Dimethyl* - 1,2,3,4,4a,4bβ,5,6,7,9,10,10aβ - *Dodecahydrophenanthrene* - 1 - *carboxylic acid, methyl ester* **16d**. To a solution of 2.13 g of thioketal **16b** in 100 ml of tetrahydrofuran was distilled 300 ml of freshly dried ammonia. One g of lithium wire was then added and the mixture was vigorously stirred for 4 h at −33°. After quenching with ammonium chloride, the excess ammonia was allowed to evaporate and the resulting paste was diluted with water. Acidification with concentrated hydrochloric acid was followed by three extractions with ether. The extracts were combined, dried, and concentrated *in vacuo* to an oil. The oil was dissolved in 75 ml of ether, cooled in an ice bath and treated with an excess of ethereal diazomethane for 3 h. After quenching the excess diazomethane with acetic acid, the solution was washed with 5% sodium hydroxide solution, dried, and concentrated *in vacuo* to afford 1.4 g (87%) of an oil. A sample of the oil (homogeneous by TLC) crystallized from methanol/ether: m.p. 86–88°; NMR ($CDCl_3$) δ 0.60 (s, 3H), 1.20 (s, 3H), 1.60–2.40 (m, 18H), 3.61 (s, 3H) and 5.45 (s, 1H); mass spectrum, *m/e* (relative intensity): 276 (24), 275 (93), 216 (100), 201 (31), 147 (27), 95 (29), 93 (46), 91 (42), 81 (35), 79 (61), 67 (41) and 55 (33).

1β,4aα - *Dimethyl* - 5β - (γ - *formylpropyl*) - 6 - *oxo* - *decahydronaphthalene* - 1 - *carboxylic acid, methyl ester* **17b**. A solution of 1.52 g (5.5 mmol) of olefinic ester **16d** in 15 ml of CH_2Cl_2 and 60 ml MeOH was cooled in a dry ice/acetone bath. Ozone was bubbled through the solution until a dark blue color persisted. After purging the solution of excess ozone with N_2, 2 ml of dimethylsulfide was added, and the solution was allowed to come to room temp. When a negative starchiodide test demonstrated that reduction was complete, the solvents were removed on a rotary evaporator. The resulting oil was taken up in ether and washed three times with water. Drying and removal of the solvent afforded keto-acetal **17a** as an oil: NMR ($CDCl_3$) δ 0.51 (s, 3H), 1.24 (s, 3H), 0.60–2.50 (m, 18H), 3.26 (s, 6H), 3.60 (s, 3H) and 4.30 (t, 1H).

Without further purification the oil was taken up in 24 ml of tetrahydrofuran, 20 ml of water, and 5 ml of 10% hydrochloric acid and stirred for 90 min under N_2. The layers were separated and the aqueous layer extracted with ether. The organic extracts were combined, washed with water, dried and concentrated *in vacuo* to afford 1.50 g (89%) of keto-aldehyde **17b** as an oil: (homogeneous by TLC): NMR ($CDCl_3$) δ 0.53 (s, 3H), 1.26 (s, 3H), 0.60–2.60 (m, 18H), 3.60 (s, 3H) and 9.68 (t, 1H).

6 - *Carbomethoxy* - 6β,9aα - *dimethyl* - 2,4,5,5aβ,6,7,8,9,9a,9bβ - *decahydro* - 1H - *benz*[e]*indene* - 3 - *carboxaldehyde* **19**. *Sodium carbonate method.* A solution of 150 mg (0.48 mmol) of ketoaldehyde **17b** and 150 mg of sodium carbonate in 1.2 ml of water and 24 ml of ethanol was heated at 60° for 40 h under N_2. After cooling, the solution was diluted with saturated NaCl soln, and extracted three times with ether. The extracts were combined, washed once with water, dried, concentrated on a rotary evaporator to an oil, and chromatographed on silica gel. The fraction eluted with 5% ether/benzene crystallized from hexane affording 42 mg (29%) (single spot-tlc) of aldehyde **19**: m.p. 114–116°; NMR ($CDCl_3$) δ 0.53 (s, 3H), 1.20 (s, 3H), 0.70–2.60 (m, 16H), 3.56 (s, 3H) and 9.83 (s, 1H); IR ($CHCl_3$) 1680 cm^{-1}; mass spectrum *m/e* (relative intensity): 290 (35), 230 (91), 201 (29), 180 (21), 149 (100), 121 (71), 91 (32), 71 (47), 68 (47), 66 (47), 60 (71), 57 (59), 55 (65), 43 (47), and 41 (59).

Pyrrolidine method. A solution of 150 mg (0.48 mmol) of keto-aldehyde **17b** and 90 mg (1.26 mmol) of pyrrolidine in 33 ml of benzene was refluxed under nitrogen for 18 h with azeotropic removal of water. A solution of ~6 ml of an acetate buffer (prepared by dissolving 10 g of sodium acetate in 20 ml of water and 30 ml of acetic acid) was added at a rate which maintained reflux. After 0.5 h the reaction mixture was allowed to stir at room temperature for another 0.5 h. The solution was diluted with an equal volume of ether and washed twice with water, once with 10% hydrochloric acid, and with saturated $NaHCO_3$ soln until neutral. The resulting solution was combined with the result of two identical reactions, dried, and concentrated *in vacuo*.

The NMR spectrum of the oil thus produced showed it to be approximately 50% aldehydic material (as measured by comparing integration of the aldehyde region with that of the methyl ester). Preparative thin layer chromatography (4 plates, 5% ethyl acetate–benzene) afforded 170 mg (40%) of aldehyde **19**.

Photoaldehyde **20**. One milliliter of a solution of 166 mg (0.57 mmole) of aldehyde **19** in 4 ml of ether was placed in each of four pyrex NMR tubes. Each tube was then cooled in a dry ice–acetone bath and 0.5–1 ml of allene was condensed into each. While still in the bath, the tubes were evacuated and then placed under N_2. The tubes were then sealed and irradiated at −78° (450W Hanovia lamp) for 30 min. This length of time was sufficient to consume all of the starting material. The tubes were opened, and the allene was carefully allowed to evaporate. The remaining solution in the four tubes was combined, concentrated on a rotary evaporator, and purified on two preparative thin layer plates. Elution with 8% ethyl acetate-benzene gave two bands with an R_f of approximately 0.7. A minor photoadduct 5.6 mg (3%) (see text) was obtained as an oil (single spot-TLC): NMR ($CDCl_3$) δ 0.65 (s, 3H), 1.16 (s, 3H), 0.80–2.90 (m, 18H), 3.57 (s, 3H), 4.72 (m, 1H), 4.85 (m, 1H) and 9.62 (s, 1H). The second photoadduct **20**, 78 mg (42%), was obtained as an oil which crystallized on standing: NMR ($CDCl_3$) δ 0.55 (s, 3H), 1.16 (s, 3H), 0.80–2.90 (m, 18H), 3.57 (s, 3H), 4.72 (m, 1H), 4.85 (m, 1H) and 9.60 (s, 1H). A sample of these crystals was triturated with ethanol affording a highly crystalline solid: m.p. 113–116°, mass spectrum, *m/e* (relative intensity), 330 (21), 329 (78), 301 (22), 300 (85), 270 (53), 269 (63), 162 (87), 150 (87), 120 (100), 118 (51), 108 (51), 106 (56), 104 (51), 94 (32), 92 (42), 90 (47), 80 (36), and 78 (31). Calc. for $C_{20}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.20; H, 9.16%.

Alcohol **21a**. A stirred solution of 48 mg (0.146 mmol) of aldehyde **20** in 6 ml of absolute ethanol was cooled in an ice bath under N_2. To this solution was added 6 mg (0.158 mmol) of sodium borohydride and the resulting solution was stirred 0.5 h in the cold. The solution was diluted with twice its volume of

saturated NaCl soln and extracted three times with ether. The extracts were combined, washed once with water, dried and concentrated *in vacuo* to give 48 mg (98%) of alcohol **21** as a colorless oil which displayed one spot on TLC. NMR ($CDCl_3$) δ 0.59 (s, 3H), 1.11 (s, 3H), 0.80–2.60 (m, 18H), 3.53 (s, 3H), 3.66 (s, 2H), 4.77 (m, 2H); IR ($CHCl_3$) 3600–3300 and 1725 cm^{-1}.

Mesylate **21b**. A stirred solution of 130 mg (0.392 mmol) of alcohol **21a** in 15 ml of pyridine was cooled in an ice bath under N_2. To this solution was added 12 drops of methanesulfonyl chloride, and the resulting bright yellow solution was stirred for 0.5 h in an ice bath and then stored in a freezer overnight. The solution was poured over excess cold, 10% hydrochloric acid, and the resulting mixture was extracted three times with ether. The extracts were combined and washed once with cold 10% hydrochloric acid, once with cold 1N sodium hydroxide, and once with water. After drying, the solvent was removed on a rotary evaporator, affording 148 mg (93%) of mesylate **21b** as a colorless oil which displayed one spot on thin layer chromatography: NMR ($CDCl_3$) δ 0.62 (s, 3H), 1.18 (s, 3H), 0.80–2.50 (m, 18H), 3.13 (s, 3H), 3.70 (s, 3H), 4.38 (s, 2H), 4.89 (m, 1H) and 5.00 (m, 1H); mass spectrum, *m/e* (relative intensity), 410 (4.4), 352 (10), 315 (35), 314 (98), 301 (54), 299 (35), 255 (91), 254 (61), 241 (33), 239 (44), 185 (42), 147 (46), 146 (53), 145 (40), 133 (63), 132 (48), 131 (48), 121 (100), 119 (42), 109 (42), 107 (42), 105 (42), 95 (39), 93 (35), 91 (44), 81 (42), 57 (40), 55 (37) and 43 (40).

Solvolysis of mesylate **21b**. A solution of 148 mg (0.363 mmol) of mesylate **21b** and 43 mg (0.4 mmol) of 2,6-lutidine in 20 ml of 50% aqueous acetone was refluxed under nitrogen for 1.5 h. The solution was cooled, diluted with 20 ml of saturated NaCl soln, and extracted three times with ether. The extracts were combined, washed once with water, and dried. Removal of the solvent on a rotary evaporator afforded 127 mg of an oil. The oil was applied to a preparative thin layer plate and doubly eluted with 10% acetate–benzene. Nine distinct bands (fluorescence quenching) were visible. Of these bands four yielded significant amounts of material upon work-up. Listed in order of decreasing R_f, they were characterized as follows: *Band* 1: An oil, 41 mg, whose NMR spectrum was not readily interpreted. It possessed olefinic absorptions, a broadened methyl ester signal, as well as sundry peaks in the angular methyl region. *Band* 2: An oil, 31 mg (21%), characterized as mesylate **22c**: NMR ($CDCl_3$) δ 0.86 (s, 3H), 1.20 (s, 3H), 0.80–2.50 (m, 20H), 3.10 (s, 3H), 3.75 (s, 3H), 5.08 (m, 1H), 5.22 (m, 1H); mass spectrum *m/e* (relative intensity), 133 (40), 131 (39), 121 (100), 120 (44), 109 (44), 106 (42), 95 (38), 93 (38), and 91 (46). *Band* 3: A crystalline solid, m.p. 94–96°, 10 mg (9%), characterized as alcohol **23a**: NMR ($CDCl_3$) δ 0.80 (s, 3H), 1.22 (s, 3H), 0.80–2.50 (m, 20H), 3.76 (s, 3H) and 4.86 (m, 2H); mass spectrum, *m/e* (relative intensity), 332 (40), 315 (72), 314 (48), 272 (79), 255 (39), 217 (100), 199 (42), 133 (70), 120 (93), 118 (53), 109 (56), 107 (74), 105 (42), 95 (42), 93 (44), 91 (49), 81 (44), 79 (44), 67 (40) and 55 (54). *Band* 4: An oil, 4 mg (3%), which identified as steviol methyl ester by double elution thin layer chromatography in two solvent systems (5% ethyl acetate–benzene and 3% isopropanol–hexane) and NMR comparison with a sample prepared from natural steviol.

Isosteviol methyl ester **24**. A solution of 31.0 mg (0.08 mmol) of mesylate **22c** dissolved in 2 ml of methanol and 8 ml of 20% hydrochloric acid was refluxed under nitrogen for 1.5 h. The solution was cooled, diluted with water and extracted two times with ether. These extracts were combined, dried, and concentrated *in vacuo* to afford 17 mg of an oil whose principle component was isosteviol methyl ester identified by NMR and double elution thin layer chromatography in two solvent systems (5% ethylacetate–benzene and 3% isopropanol-hexane) with a sample of isosteviol methyl ester.

Acknowledgement—We are extremely grateful to the Petroleum Research Fund (5854-AC1), the National Science Foundation (GP-30960X, and the National Institutes of Health (CA-08869) for generous, partial support of this work.

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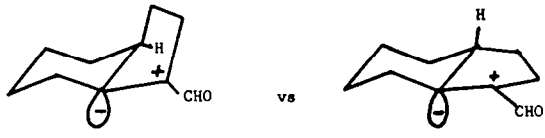

i (cis) ii (trans)

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