CH 80 THESIS:

Investigations into the Use of some Organometallic Complexes in Organic Synthesis

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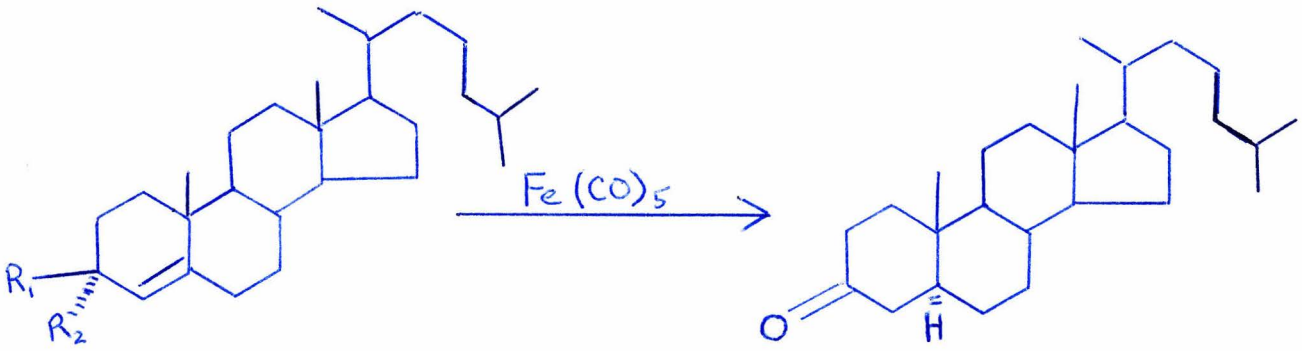
PART I. Iron pentacarbonyl-catalyzed rearrangement of allylic alcohols to saturated ketones.

Problem:

Will iron pentacarbonyl catalyze the isomerization of Δ^4-cholesten-3α-ol (I) and /or Δ^4-cholesten-3β-ol (II) to cholestan-3-one (III)?



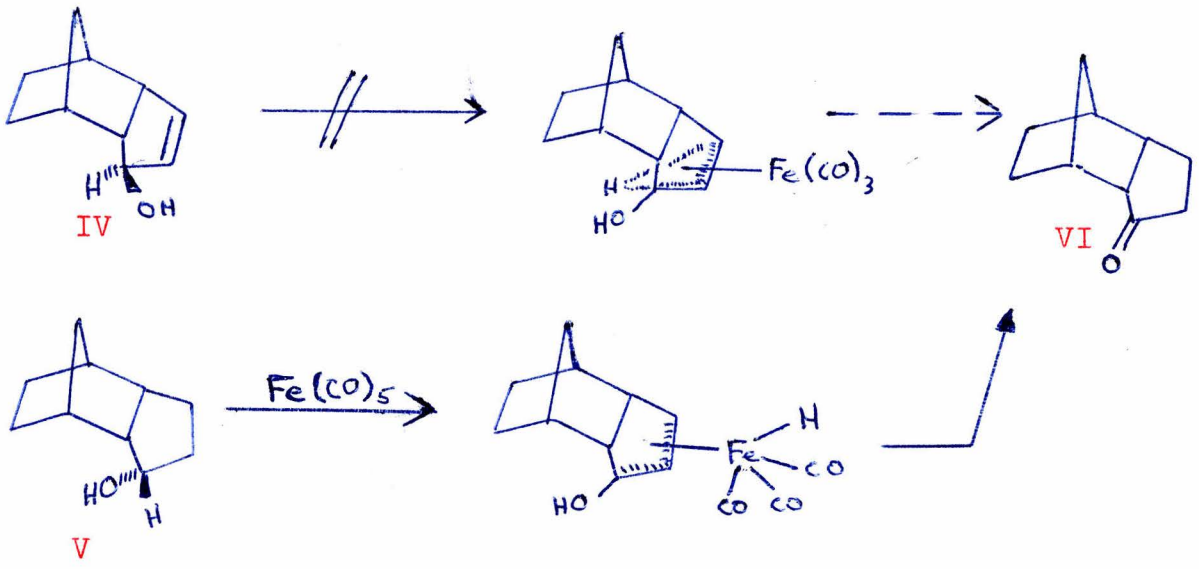
I: R_1=H, R_2=OH
II: R_1=OH, R_2=H

III

History:

F. G. Cowherd and J.L. von Rosenberg [1] investigated the mechanism of 1,3-hydrogen shifts catalyzed by iron pentacarbonyl in order to study apparent violations of the Woodward-Hoffman rules.[2] Normally, hydrogen shifts of order (1,3) are allowed only antarafacially, although the possibility of interaction with d orbitals of a metal ion indicates that such shifts may occur superfacially. In particular, it was found

that endo-α-1-hydroxy-5,6-dihydrodicyclopentadiene IV did not isomerize with iron pentacarbonyl to the ketone VI, while the β- epimer V of IV isomerized in 40% yield when heated at 130°C for 16 hr with 10 mole % $Fe(CO)_5$ under nitrogen.

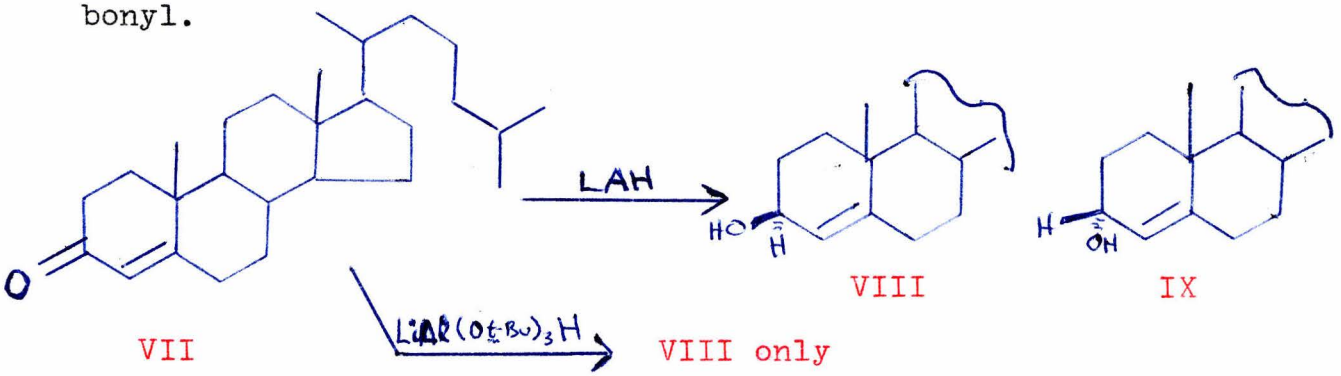


The hypothesis was made that since the iron complex could, for steric reasons, approach from the exo side only, the β-enol only could form the pi-allyl hydro iron tricarbonyl complex intermediate to facilitate the hydrogen transfer required for isomerization.

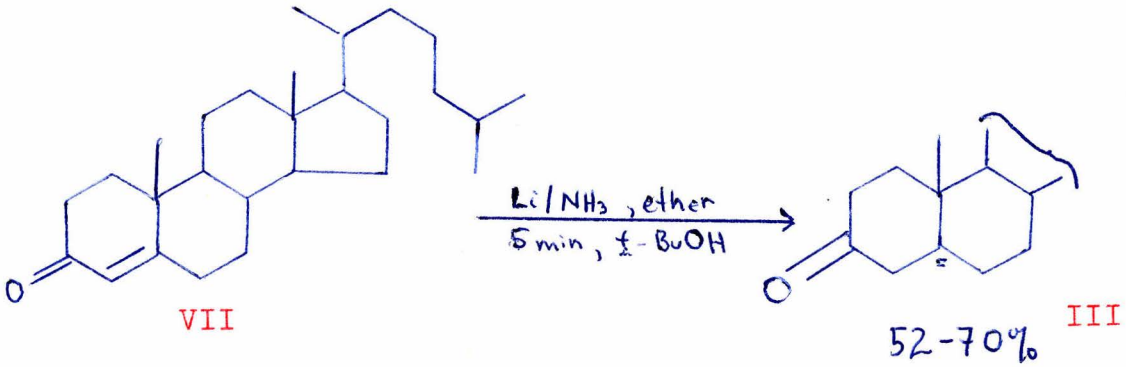
Results:

Cholestenone VII was reduced stereospecifically to the Δ^4-cholesten-3β-ol VIII using lithium aluminum tris(t-butoxy)hydride according to Burgstahler's procedure.[3] The β-alcohol has an

α-hydrogen susceptible to attack by iron pentacarbonyl approaching from underneath, whereas the α-alcohol would have a β-hydrogen requiring unfavorable top-side approach for the 1,3-hydrogen shift. However, the β-alcohol did not rearrange in noticeable yield as expected[4] after extended refluxing at 130-140°C under nitrogen with varying amounts of iron pentacarbonyl.



To test the α-alcohol IX, cholestenone was reduced with lithium aluminum hydride in the usual manner[5], and less that 25% of the α-alcohol was obtained. Still no rearrangement could be induced, either by catalytic amounts or a full equivalent of $Fe(CO)_5$. It was hoped that this partial reduction-isomerization sequence would prove a convenient synthon to replace Barton's Birch reduction[6]:



Experimental Section:

Lithium aluminum tris(t-butoxy) hydride. 10.3g (.271 mole) of lithium aluminum hydride was dissolved in 500 ml ether by refluxing overnight under nitrogen using a Soxhelet extractor. 62g (.830 mole) freshly distilled t-butanol was added slowly with stirring and the mixture refluxed 12 hr. The slurry was filtered through a coarse-fritted glass Buchner funnel and washed twice with ether to remove the excess t-butanol. Yield, after drying in vacuo, 59g (85%) white powder.

Δ^4-Cholesten-3β-ol. After dropwise addition of cold 0°C solution of 7.51g (19.5 mmole) of Δ^4-cholesten-3-one in 100 ml 8:1 ether-benzene to a stirred suspension of 7.1g (60 mmole) lithium aluminum tris(t-butoxy)hydride in dry THF at -40°C, the mixture was allowed to stand 48 hr at 0° and then hydrolyzed with 5N sodium hydroxide, Rochelle salts, and ice. The mixture was extracted with ether, the extracts washed with water and saturated ammonium chloride solution, dried over sodium sulfate, and ether stripped off under aspiration to yield a total of 5.65g(75%) crude product. One recrystallization from ethyl acetate gave white crystals, mp 126-129°C (132° reported).

Attempted rearrangement. 1.76 g(4.57 mmole) of the β-alcohol was dissoved in 20 ml p-xylene (n-octane also tried) in a 50ml 3-necked flask. The system was flushed with nitrogen, and 89mg iron pentacarbonyl was injected and the mixture refluxed 15 hr. Thin-layer chromatography showed less than 5% reaction, so an additional 400mg iron pentacarbonyl was injected and refluxed another 24 hr, following the progress by tlc. Less than 30% of the vpc trace corresponded to cholestanone, the other peaks being starting enol and dehydrated enones.

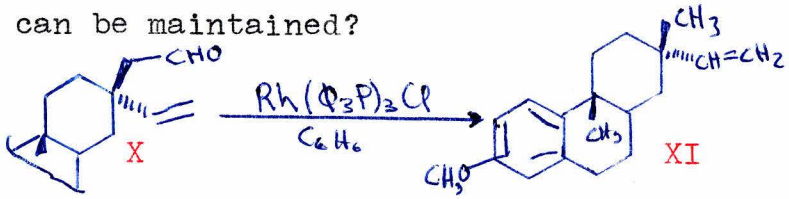
Discussion:

The utility of this synthon as a replacement for the Birch reduction is limited due to low yields, and the project was abandonned on this basis.

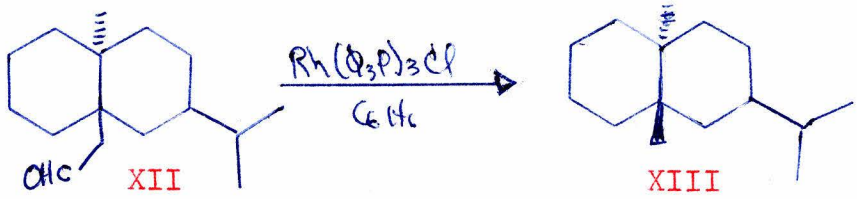
PART II: Rhodium tris(triphenylphosphine) chloride: Decarbonylation vs. Cyclization

Problem A: Will rhodium tris(triphenylphosphine) chloride decarbonylate the aldehyde X to XI? What degree of stereospecificity can be maintained?

History:

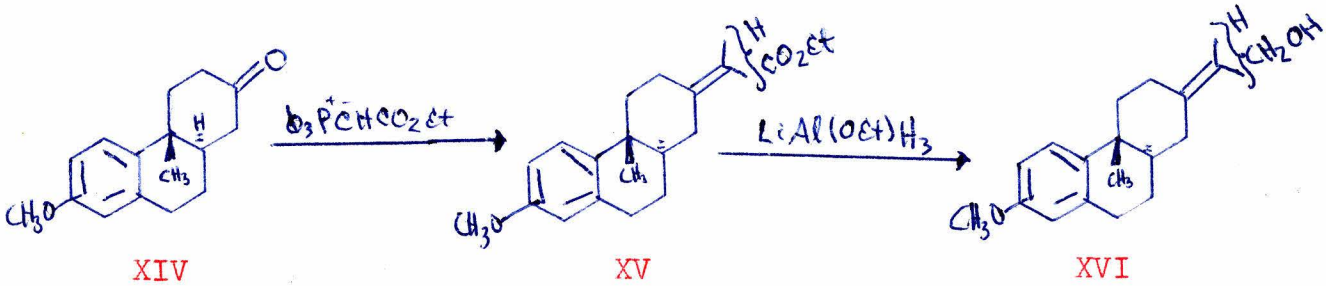


D. Dawson[7] used the catalyst to convert the aldehyde XII to β-vevitone XIII, and it was desired to know if the reaction could be applied in general to more or less rigid and more functionalized systems.

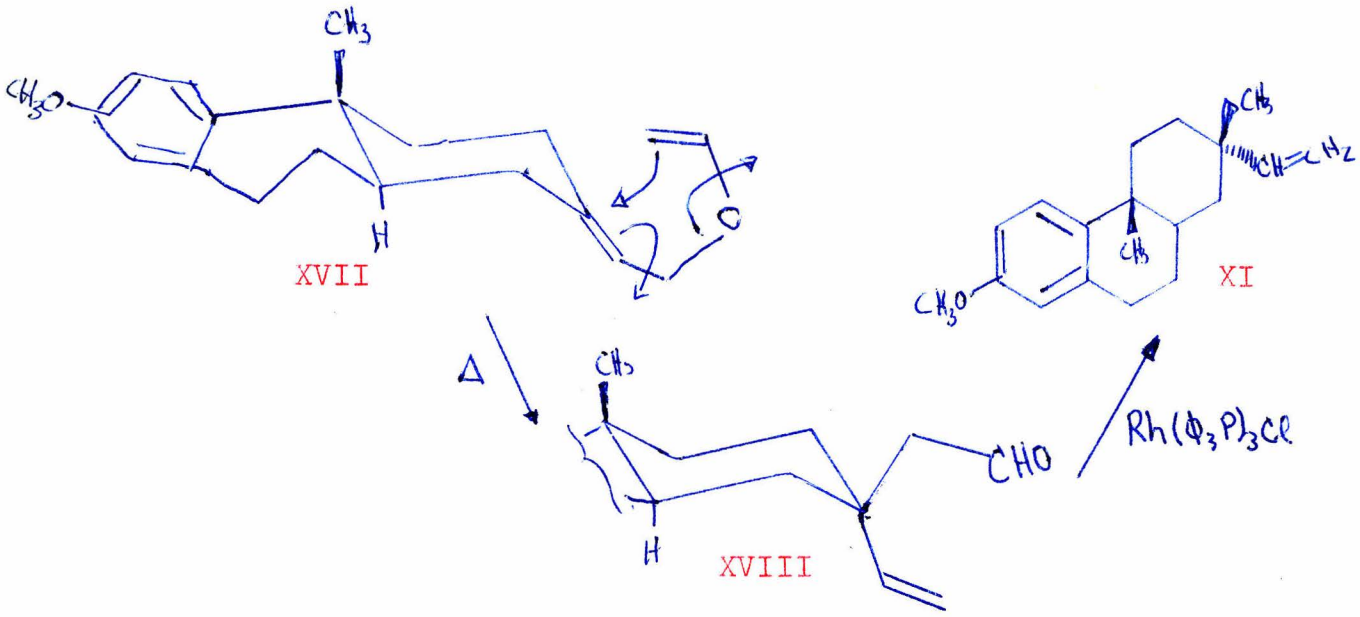


Procedure:

The tricyclic XVI was obtained by the lithium aluminum monoethoxy trihydride reduction[8] of the isomeric mixture of esters XV[9] resulting from an Emmons modification of the Wittig reaction on the tricyclic XIV.[10]



Next the tricyclic allylic alcohol was equilibrated with excess ethyl vinyl ether in the presence of mercuric acetate[11,12] to give the vinyl ether XVII in 32% yield. The vinyl ether was heated in a sealed tube at 196° C for 3 hr to effect a Claisen rearrangement to the vinyl aldehyde XVIII[11,12]. It was expected that regardless of the geometric isomeric mixture of alchols and ethers, the Claisen would be stereoselective to produce an up-aldehyde and a down-vinyl group:



The result on decarbonylation with the rhodium complex should be an up-methyl group.

Experimental Section:

Reduction of α,β-unsaturated ester XV. To a solution of lithium aluminum hydride (2.2g) in ether (freshly distilled from lithium aluminum hydride) was added absolute ethanol (274 mg) in ether (total volume of solution = 100 ml). One ml portions were added at intervals of 1 hr to a stirred ethereal solution of the ester (640 mg crude oil, or 515 mg pure ester) until a total of 4-5 ml had been added. Water was carefully added to decompose excess lithium aluminum hydride, the aluminum salts were filtered off and washed with ether and water, and the combined filtrates were extracted with ether. The ethereal extracts were dried and the ether stripped off in vacuo to give 400 mg of a pale yellow glass, the alcohol XVI.

Equilibration of alcohol XVI with ethyl vinyl ether. To 815 mg enol XVI (some of the enol had already been prepared by D. Muchmore) were added 25 ml ethyl vinyl ether (freshly distilled Eastman Practical Grade from sodium under nitrogen) and 120 mg mercuric acetate (recrystallized from absolute ethanol contaminated with .03 mole % glacial acetic acid). The reaction mixture was refluxed 16 hr under nitrogen, after which potassium carbonate crystals were added and the decanted solution heated on a steam bath to remove excess ethyl vinyl ether. The residue was chromatographed on 60 g Merck alumina and eluted with benzene, yielding 283 mg (23%) of the vinyl ether XVII.

Claisen rearrangement. The vinyl ether XVII (225 mg) was sealed under nitrogen in a Carius tube and heated in reluxing ethylene glycol (196°C) for 3 hr. The vpc trace indicated ≥90% rearrangement and the presence of two isomers, presumably dominated by the epimer XI.

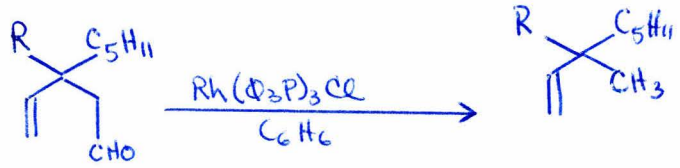
Rhodium tris(triphenylphosphine)chloride.[13] To a warm solution of 6.0 g (22.9mmole) triphenylphosphine in 175 ml ethanol was added 1.0 g (3.8 mmole) rhodium trichloride trihydrate in 30 ml hot absolute ethanol. The mixture was refluxed 1.5 hr under nitrogen with stirring, while reddish-purple crystals precipitated out, topped with a brownish flocculent mass. The crystals were collected and washed twice with ethanol and three times with ether, dried, and stored in vacuo. Yield, 2.52 g reddish-purple crystals.

Attempted Decarbonylation of aldehyde XVIII. To the isomeric mixture of aldehydes (165 mg=0.67 mmole) in 25 ml freshly distilled (from calcium hydride) benzene was added a slight excess of rhodium complex (885 mg), and the resulting red suspension was refluxed under nitrogen for 43 hr, at which time the vpc indicated a single peak at short retention time (215°C oven) and two broad smears at longer time corresponding to the starting material. The reaction mixture was poured onto a double

column of 3-4 g silica gel and 10 g alumina (Merck) (bottom). The IR and nmr spectra of the crude product indicated the absence of vinyl protons and the possibile presence of carbonyl functionality at 1740 cm^{-1} (Ketonic) as opposed to the starting material band at 1720 cm^{-1} (Aldehydic). After preparative tlc on silica gel with 9:1 hexane-ethyl acetate, 167 mg crude yellowish oil was collected and some crystals removed by crystallization from pentane (but no aromaticity in crystals, no product). The yellow oils remaining had a single vpc band with three minor peaks within the band, suggesting optical or geometric isomers. The quantity of material was not sufficient to allow complete analysis.

Discussion: The aromatic fixed-ring system was initially chosen to follow the stereoselctivity of the Claisen, in the hope that an up-methyl group could be generated at that site. Too many problems were involved at once, however, so that a simpler model for the original decarbonylation was sought.

Problem B: In view of the inconclusive results of Problem A, a simpler acyclic system was chosen. In particular, will the 4-penten-1-als XIXA and B decarbonylate to the 1-octenes XXA and B?

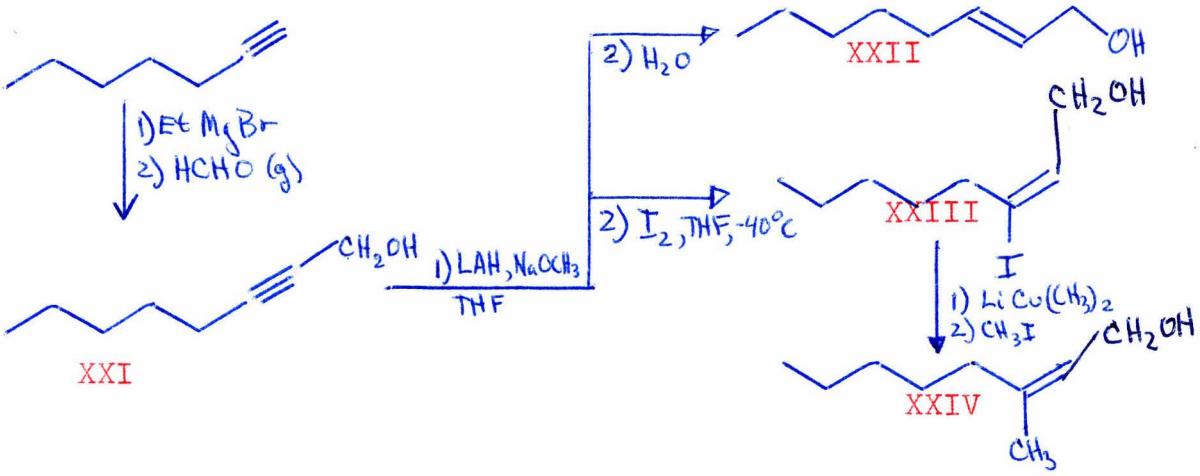


XIX
A: R=H
B: R=CH_3

XX
(no absolute configuration determined)

Procedure:

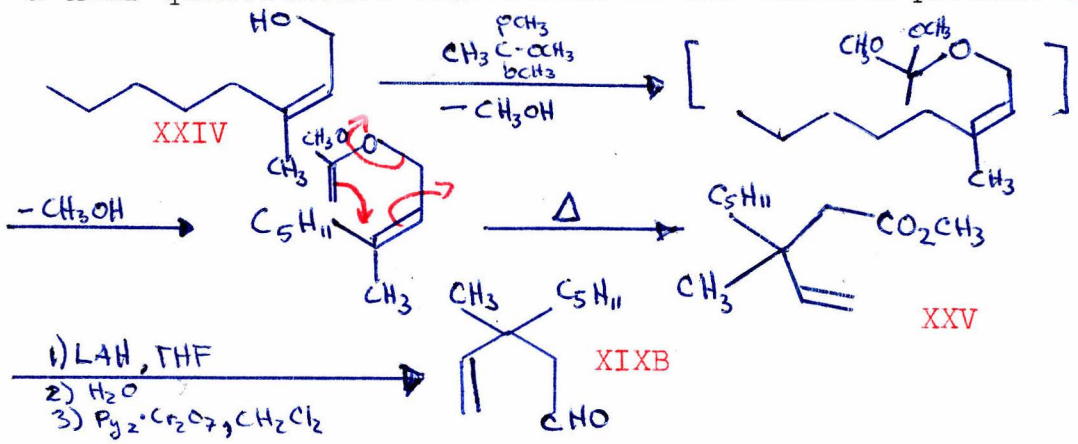
The starting octynol XXI was obtained from K. Cheng, which he had synthesized from 1-heptyne Grignard reagent and dry formaldehyde gas.[14] In the first sequence,



the 2-octyn-1-ol XXI was reduced simply to the 2-octen-1-ol XXII with lithium aluminum hydride and water workup. This sequence was interrupted by the continual loss of products due to volatility, and no aldehyde XIXA was recoverd at the final step. The second sequence is more closely related to the original tetrasubstituted

position in the tricyclic of Problem A, and was pursued to conclusion. Corey's procedure[15] was followed to generate the methylated octenol XXIV by first reduction with iodine workup to give exclusively trans-3-iodo-2-octen-1-ol XXIII followed by lithium dimethyl copper alkylation with methyl iodide workup.

A new reaction was attempted to rearrange the molecular skeleton. Instead of the traditional ethyl vinyl ether-mercuric acetate equilibration followed by a sealed-tube Claisen rearrangement as described for the tricyclic of Problem A, W. S. Johnson's orthoester addition-Claisen[16] was employed . Trimethyl orthoacetate was added in excess to the 3-methyl-2-octen-1-ol XXIV and refluxed overnight; the excess orthoester was then distilled off, and the residue was refluxed under nitrogen overnight. This effected a near quantitative conversion to the Claisen product XXV.



The methyl 4-pentenoate XXV was reduced to the alcohol with lithium aluminum hydride and oxidized to the aldehyde XIXB with pyridinium dichromate.

The final decarbonylation step with rhodium tris(triphenylphosphine)chloride was carried out as in the tricyclic case; however, procedural difficulties were encountered in the final separation and indentification stages. Results are anticipated within a few weeks, and similar research is being continued.

Experimental Section:

Iodination of 2-Octyn-1-ol.XXI. To a heterogeneous solution of 11.4g (.3 mole) lithium aluminum hydride and 32.5g (.6 mole) sodium methoxide in 500 ml THF (freshly distilled from lithium aluminum hydride) under nitrogen was dripped 17.54 g 2-octyn-1-ol in 100 ml dry THF with stirring. The reaction was stirred under reflux 1.5 hr (at which time the vpc showed quantitative conversion) and then cooled to -40° C in dry ice-acetone bath. A solution of 55g sublimed iodine in 300 ml cry THF was dripped slowly over 0.5 hr with stirring before adding saturated sodium thiosulfate-ammonium chloride solution. The iodo-enol was extracted with 3000 ml ether, the ether removed at atmospheric pressure, and the product distilled at bath temp 130±5°C, column temp 64±2°C at 1.5 mm Hg, yielding 5.70 g of pure 3-iodo-2-octen-1-ol, XXIII, which degraded to 90% purity on standing.

Methylation of iodo-enol XXIII. To a vigorously stirred 0°C suspension of 19.1g(.10mole) cuprous iodide in 125 ml ether (freshly distilled) under nitrogen was syringed 100 ml 2.16 M methyllithium in ether (.22 mole). After 15 min, the iodo-enol from above was dissolved in 100 ml dry ether and syringed into the lithium dimethyl copper solution, and then stirred at 0°C for 3 hr. Then 75 ml methyl iodide (freshly distilled from phosphorus pentachloride) were added and the mixture stirred 15 min. Ammonium chloride solution was added to quench the alkylation, and unfortunate bumping was responsible for loss of some product. The yellow ppt. was filtered off and washed with ether and water, and the aqueous blue filtrate extracted 3x with 100 ml ether; solvents were removed under aspiration, and the product vacuum distilled at 1.25mm Hg, to give 1.54g yellow liquid of bp 54-6°C, vpc pure. IR absorptions at 3610 cm^{-1} (strong, OH), 3000 cm^{-1} (weak, olefin), 975 cm^{-1}(med, olefin).

Orthoester addition-Claisen rearrangement. Trimethyl orthoacetate (10 ml) stored over potassium carbonate was distilled under nitrogen into a flask containing 1.54g(10.8 mmole) 3-methyl-2-octen-1-ol XXIC; the flasks were switched and the mixture was refluxed for 18 hr under nitrogen, bath temp. 125±5°C and temperature at the top of 20 cm vigreux column was 65±5°C for removal of methanol. Then the bath temp increased to 230±5°C (column temp 115±5°C) for 18 hr, which distilled off the excess orthoacetate and allowed the neat liquid to reflux and rearrange. The crude product was ≥ 95% pure by vpc and the IR showed absorptions at 1726 cm^{-1}(strong, ester carbonyl), 915 cm^{-1}(med, terminal vinyl, and 1635 cm^{-1} (med, ene stretch).

Reduction of methyl ester XXIV. The unpurified product methyl ester (2.1 g=10 mmole) was dissolved in 100 ml dry THF and dripped into a stirred solution of 0.9 g lithium aluminum hydride in 200 ml dry THF under nitrogen and stirred 2 hr at room temperature. Distilled water was carefully added, lithium and aluminum salts filtered off and washed with ether and water, and the ethereal extracts dried over sodium sulfate. Ether was removed at atmospheric pressure, yielding 1.92 g crude yellow liquid, vpc $\gtrsim$ 90% pure. IR absorptions were at 3620 cm^{-1} (strong, OH), 1625 cm^{-1} (med, ene stretch), and 915 cm^{-1} (terminal vinyl).

Oxidation of alcohol XXV. To a stirred suspension of 30 g. pyridinium dichromate in 250 ml dichloromethane(freshly distilled from phosphorus pentachloride) under nitrogen was added the crude 3-methyl-3-n-pentyl-4-penten-1-ol from above. The reaction was stirred 22 hr at room temperature and then filtered through 100g Florisil in a fritted glass funnel, washing 5x with 100ml dichloromethane. The solvent was distilled off at atmospheric pressure, yielding yellow liquid 90% pure by vpc. IR absorptions were at 1685 cm^{-1} (strong, carbonyl), 1725 cm^{-1} (strong, aldehydic C=O), 1635 cm^{-1} (med, ene stretch) and 915 cm^{-1} (med, terminal vinyl). The 2,4-dinitrophenylhydrazone of the aldehyde XIXB had mp 121-122.5°C after recrystallizing 3x from methanol-acetone.

Decarbonylation of aldehyde XIXB. 285 mg (1.72 mmole) crude aldehyde were dissolved in 50 ml benzene (freshly distilled from calcium hydride),and 1.65g (1.78 mmole) rhodium tris(triphenylphosphine)chloride was added with stirring. The reaction mixture was stirred and refluxed under nitrogen for 23 hr, at which time a tlc of the mixture on silica gel with benzene showed no aldehyde; instead the upper spot corresponded to triphenylphosphine and the lower spot to the product. The mixture was filtered twice through double columns packed with 20g alumina (bottom) and 10g silica gel(top), and eluted with ether. The inorganic were removed in this manner, but the triphenylphosphine remained. The solvents were removed and the residue preparatively tlc'ed on silica gel using benzene.

Discussion:

Although final conclusive decarbonylation has not been verified, the position of the tlc and vpc peaks corresponding to the reaction product suggest the 3,3-dimethyl-1-octene as the product instead of the possible cyclization product, 3-methyl-3-n-pentyl-cyclopentanone. After researching the

peculiarities of rhodium complexes and in particluar tris(tripenylphosphine)halide type coordination complexes, one discovers the extremely high affinity of rhodium complexes to add carbonyl groups as coordinate ligands.[17] Research into the problem is still under way.

(1) F. G. Cowherd and J.L. Rosenberg. J.Am.Chem.Soc. 91 (8), 2157 (1969)

(2) R.B. Woodward and R. Hoffman, J. Am.Chem.Soc. 87, 395,2511, 4389 (1965).

(3) Burgstahler and Nordin, J. Am. Chem Soc. 83, 198 (1961).

(4) J. A. Marshall's group at Northwestern has also found this to be true on similar polycylic or hindered molecules.

(5) H. McKennis and G.W. Griffin. J.Biol. Chem.175, 217 (1948).

(6) Barton, Ives, and Thomas. J. Chem. Soc., 903 (1954).

(7) D. Dawson, notebook, Experiment 169. See also ref's (17)

(8) Davidson, Gunther, Waddington-Feather, and Lythgoe. J Chem. Soc, 4907(1964).

(9) prepared by D. Muchmore

(10) H.O.House. Modern Synthetic Reactions, W.A. Benjamin Co, 1965, p. 250.

(11) R. E. Ireland and J. A. Marshall. J. Org. Chem.27, 1620 (1962).

(12) R.F.Church, R.E. Ireland, and J.A. Marshall. J.Org.Chem 31, 2526 (1966).

(13) D. Dawson, notebook, Experiment 166.

(14) K. Cheng, notebook, p. 79.

(15) E. J. Corey, et.Al. J. Am Chem Soc.89, 3911, 4245 (1967).

(16) A. W.S. Johnson, personal communication to R.E. Ireland.
B. W.S. Johnson, et.al. J. Am. Chem Soc. 92 (3), 741 (1970).

(17) A. Organometallic Chemistry Reviews, 2, 357 (1964).
B. Ibid, 3, 390 (1966).
C. Ibid, 4, 125 (1968).
D. Ibid, 5, 490 (1969).

E. J. Tsyji and K. Ohno. Tetrahedron Letters, 3969 (1965), in which the authors note the ability of Rh $(\phi_3P)_3Cl$ to 'suck' (sic) out a carbonyl from an aldehyde:

$$RCHO + Rh(\phi_3P)_3Cl \longrightarrow RH + \phi_3P + Rh(\phi_3P)_2Cl\ (CO)$$