Ferric Chloride Oxidation. 2-Propyl-4,4,5-trimethoxycyclohexa-2,5-dienone (7). To a *vigorously* stirred solution of 3,4-dimethoxy-6-propylphenol (6) (2.28 g, 11.6 mmol) in methanol (70 mL) containing finely ground potassium carbonate (8.15 g, 58 mmol) was added ferric chloride (15.7 g, 58 mmol) in one portion. The resulting mixture was kept at room temperature with continuous stirring for 30 min, and it was then poured into a saturated sodium bicarbonate solution. The aqueous solution was extracted thoroughly with ether; the combined organic extracts were washed once with brine and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave 2.3 g (88%) of a pale yellow solid which appeared to be pure dienone 7 on the basis of spectroscopic evidence. Recrystallization from ether–pentane gave analytically pure dienone as white rods.

DDQ Oxidation. 2-Allyl-4-methoxy-4,5-methylenedioxycyclohexa-2,5-dienone (4). To a stirred solution of 2-allyl-4,5-methylenedioxyphenol (3) (1.78 g, 10 mmol) in methanol (100 mL) was added 2.5 g (11 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone followed by 100 mg of *p*-nitrophenol. The mixture was stirred at room temperature for 1 h, and the solvent was removed in vacuo. After the residue was taken up in ether, it was washed twice with saturated sodium bicarbonate and once with brine and dried ($MgSO_4$). The ether was then evaporated in vacuo to give an oil which was quickly filtered through a short column of silica gel with 40% ethyl acetate in hexane as solvent. Pure dienone 4 was obtained (1.84 g, 88%) as an oily solid which on recrystallization from ether–pentane gave white rods.

Acknowledgment. We are indebted to the National Institutes of Health (GM 09686) and to the Hoffmann-La Roche Foundation for financial support. High-resolution mass spectra were measured in the National Institutes of Health supported facility at Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann.

Registry No.—**1**, 533-31-3; **2**, 57197-23-6; **3**, 19202-23-4; **4**, 64949-70-8; **5**, 67271-92-5; **6**, 6906-69-0; **7**, 67271-93-6; **8**, 66967-26-8; **9**, 66967-27-9; **10**, 67271-94-7; **11**, 67271-95-8; **12**, 23504-78-1; **13**, 67271-96-9; **14**, 20491-91-2; **15**, 67271-97-0; **16**, 21505-18-0; **17**, 67271-98-1; **18**, 67271-99-2; **19**, 67272-00-8; **20**, 2033-89-8; **21**, 64701-03-7.

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Palladium-Catalyzed Reductions of α,β-Unsaturated Carbonyl Compounds, Conjugated Dienes, and Acetylenes with Trialkylammonium Formates

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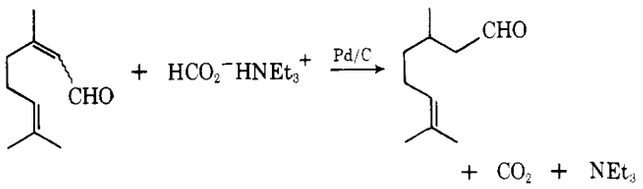
We have reported the convenient reduction of halo- and nitroaromatic compounds with triethylammonium formate and a palladium catalyst.[1] The reaction is quite selective and provides two advantages over catalytic hydrogenation: it can be done in an open flask and it is very simple to measure the exact amount of reducing agent (formic acid) required. We have now found that the trialkylammonium formate–palladium system also is very effective and convenient for reducing α,β-unsaturated carbonyl compounds to saturated carbonyl compounds, and in some instances conjugated dienes and acetylenes to monoenes.

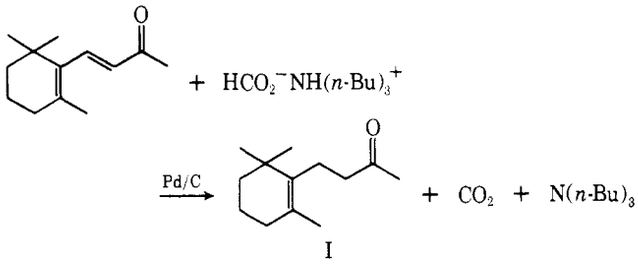
Results and Discussion

α,β-Unsaturated Carbonyl Compounds. A variety of α,β-unsaturated aldehydes, ketones, and esters were reduced at 100 °C with 10% excess formic acid, 30% excess triethyl- or tri-*n*-butylamine, and 1 mol % of palladium in the form of 10% palladium on carbon. The progress of the reductions could easily be monitored by measuring the amount of CO_2 evolved. We did this with several examples by carrying out the reactions in capped, thick-walled Pyrex bottles with a pressure gauge attached to a syringe needle inserted through the rubber liner of the bottle cap. Completion of the reaction was confirmed by GLC analysis. Products were isolated by filtering the solution from the catalyst and distilling the filtrate, or by first washing with aqueous acid and then distilling. The trialkylammonium formates generally form a second liquid phase in the reduction reaction, but dissociate and distill when heated. The compounds reduced by these procedures are listed in Table I.

Citral reduced rather slowly under our usual conditions (44 h) but very cleanly to citronellal in 91% (isolated) yield. Crotonaldehyde reduced more rapidly (8 h). Mesityl oxide, 2-

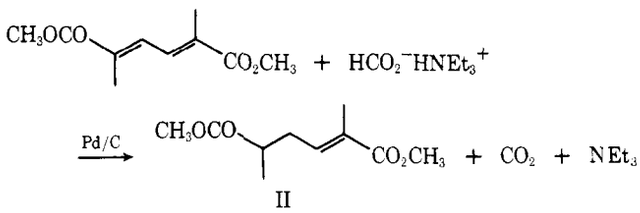


cyclopentenone, 3-methyl-2-cyclopentenone, and benzalacetone all reduced in high yields to the expected saturated ketones. The conjugated dienone, β-ionone, with 1.1 equiv of formic acid produced mainly (69%) the α,β-saturated enone, I. Only 2% of the α,β-unsaturated enone was formed. The remaining product was polymer.



I

Methyl crotonate, methyl cinnamate, and diethyl fumarate reduced to the saturated esters in high yield. Dimethyl (*E,E*)-2,5-dimethyl-2,4-hexadienedioate gave 96% of the monoene, II, under the usual conditions with only 4% completely saturated ester formed. Methyl sorbate gave a mixture of monoenes with methyl 2-hexenoate predominating (65%).



II

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Table I. Reductions with Trialkylammonium Formates[a]

compd	registry no.	amine[b]	time, h	product, % yield	registry no.
citral	5392-40-5	TE	44	citronellal, 91[c]	106-23-0
crotonaldehyde	4170-30-3	TE	8	butanal, 81[c]	123-72-8
mesityl oxide	141-79-7	TE	3	4-methyl-2-pentanone, 84[c]	108-10-1
2-cyclopentenone	930-30-3	TE	1.3	cyclopentanone, 83[c]	120-92-3
3-methyl-2-cyclopentenone	2758-18-1	TE	2.5	3-methylcyclopentanone, 87[c]	1757-42-2
benzalacetone	122-57-6	TB	2.5	4-phenyl-2-butanone, 86[c]	2550-26-7
β-ionone	14901-07-6	TB	20	I, 69[c,e]	17283-81-7
methyl crotonate	18707-60-3	TB	3.3	methyl butanoate, 83[c]	623-42-7
methyl cinnamate	103-26-4	TE	20	methyl hydrocinnamate, 86[c]	103-25-3
diethyl fumarate	623-91-6	TE	2.3	diethyl succinate, 81[c]	123-25-1
dimethyl (*E,E*)-2,5-dimethyl-2,4-hexadienedioate	23119-30-4	TE	2	II, 96[d,f]	67237-56-3
methyl sorbate	1515-80-6	TE	2	methyl 2-hexenoate, 65[d,g]	
methyl sorbate		TB	2	methyl 2-hexenoate, 62[d,g]	
methyl sorbate[h]		TE	2	methyl 2-hexenoate, 38[d]	
methyl sorbate[i]		TE	2	methyl 2-hexenoate, 37[d]	
crotononitrile	4786-20-3	TE	48	butanonitrile, 60[j]	109-74-0
1,3-cyclohexadiene	592-57-4	TE	21	cyclohexene, 72[d]	110-83-8
				cyclohexane, 8[d]	110-82-7
1,3-octadiene	1002-33-1	TE	3	1-octene, 28[c]	111-66-0
				2-octene, 51[c]	111-67-1
diphenylacetylene	501-65-5	TE	2	*cis*-stilbene, 93[c]	645-49-8
				dibenzyl, 2[c]	103-29-7
3-hexyne	928-49-4	TE[k]	1.3	*cis*-3-hexene, 70[c]	7642-09-3
				hexane, 18[c]	110-54-3
3-hexyne[h,m]		TE	30	*cis*-3-hexene, 85[d]	
				hexane, 6[d]	
1-hexyne	693-02-7	43TE[k]	3	1-hexene, 49[c]	
1-octyn-3-ol	818-72-4	TE	4	3-octanol, 56[c,l]	589-98-0
1-hexene	592-41-6	TE	7	hexane, 81[c]	

[a] Generally 20 mmol of substrate was reduced with 22 mmol of 95% formic acid and 0.2 mmol of palladium in the form of 10% palladium on carbon. The mixtures were heated at 100 °C in closed bottles for triethylamine reactions and in open flasks when tri-*n*-butylamine was used. [b] TE = triethylamine; TB = tri-*n*-butylamine. [c] Yield of isolated product or mixture of products. [d] Yield determined by GLC. [e] Also present in the product was 2% of the α,β-unsaturated ketone. [f] About 4% of dimethyl 2,5-dimethylhexanedioate was present. [g] About 35% of an isomeric methyl hexenoate was also formed. [h] The catalyst was 1% $Pd(OAc)_2$ and 2% tri-*o*-tolylphosphine. [i] The catalyst was 1% $Pd(OAc)_2$ and 2% tri(2,5-diisopropylphenyl)phosphine. [j] Only 60% of the crotonitrile had reacted in this time and the reaction appeared to have stopped. [k] Reaction mixture was heated at 75 °C for the time indicated. [l] Yield based upon formic acid. [m] Reacted at room temperature with the equivalent amount of formic acid.

We tried soluble palladium catalysts for this reduction attempting to improve the selectivity. Both diacetatobis(tri-*o*-tolylphosphine)- and diacetatobis(tri[2,5-diisopropylphenyl]phosphine)palladium(II) were less selective than 10% Pd/C as catalysts for this reduction.

Crotonitrile reduced very slowly and incompletely under the usual conditions to butanonitrile.

Conjugated Dienes. Simple conjugated dienes were reduced by the trialkylammonium formate catalysts mainly to monoenes. With a 10% excess of formic acid, 1,3-cyclohexadiene gave 72% cyclohexene and 8% cyclohexane. Similarly, 1,3-octadiene gave 28% 1-octene and 51% 2-octene.

Acetylenes. Diphenylacetylene reduced in 2 h at 100 °C to give 93% *cis*-stilbene and 2% dibenzyl. Other acetylenes did not reduce as cleanly, however. 3-Hexyne, even with exactly 1 equiv of formic acid, gave 70% *cis*-3-hexene and 18% hexane. With the soluble bis(tri-*o*-tolylphosphine)palladium acetate catalyst reduction at room temperature was slow but *cis*-3-hexene was formed in 85% yield with only 6% hexane produced. 1-Hexyne under the usual conditions gave pure 1-hexene but only in 49% yield. The remainder of the product was polymer. 1-Octyn-3-ol also reduced poorly giving only 3-octanol in 56% yield and polymer. No olefin was formed. We carried out a reduction of 1-hexene to compare its reactivity with that of the 1-hexyne. It reduced less than half as rapidly in good yield to hexane (81%).

Summary. The trialkylammonium formate–palladium on carbon catalyst system is a very convenient combination for reducing α,β-unsaturated aldehydes, ketones, and esters to the saturated carbonyl compounds in high yields under mild conditions. Conjugated dienes reduce to monoenes with 1 equiv of reagent fairly selectively while terminal acetylenes give considerable polymer as well as olefin except for 1-octyn-3-ol which gives only 3-octanol. 3-Hexyne and diphenylacetylene give good yields of *cis*-olefins.

Experimental Section

Materials. The 10% palladium on carbon was obtained from the Research Organic/Inorganic Chemical Corp. The palladium acetate and arylphosphines were the materials described previously.[2] The tertiary amines were commercial samples (Aldrich) that were dried over 4 Å molecular sieves before use. Methyl sorbate was prepared by the sulfuric acid catalyzed esterification of sorbic acid (Aldrich) and the (*E,E*)-dimethyl 2,5-dimethyl-2,4-hexadienedioate was prepared by the literature method.[3] All other materials were commercial samples which were used without further purification.

General Procedure for Reductions. Capped Bottle Reactions. Heavy-walled Pyrex bottles of 250-mL capacity were used. In the bottle were placed a magnetic stirring bar, 0.21 g 10% Pd on carbon (0.20 mmol Pd), 20 mmol of the compound to be reduced, and 4 mL (29 mmol) of triethylamine. The bottle was then capped with a self-sealing rubber-lined cap and 0.83 mL (22 mmol) of 95% formic acid was added by microsyringe through the rubber cap liner. A pressure gauge attached to a syringe needle was injected through the cap and the bottle was stirred at 100 °C in a steam bath until the pressure stopped increasing. Completion of the reaction was then confirmed by GLC analysis. Products were isolated by filtration of the catalyst and distillation of the filtrate or concentration of the filtrate and recrystallization.

Reactions in Open Flasks. The same molar quantities of reactants as above were placed in a 50-mL three-necked round-bottomed flask. The mixture was stirred on the steam bath until GLC analysis of a small sample of the reaction mixture showed complete reaction had

occurred. Products were isolated by filtration, rinsing with methylene chloride and washing the filtrate with 10% hydrochloric acid to remove the amine. After drying with anhydrous magnesium sulfate the solution was concentrated and the residue was either distilled or recrystallized.

The properties of products prepared and the means of identification employed are listed in Table II which will appear only in the microfilm edition of this journal.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of the research.

Registry No.—*trans*-methyl 2-hexenoate, 13894-63-8; *cis*-methyl 2-hexenoate, 13894-64-9; Pd, 7440-05-3; TE formate, 585-29-5; TB formate, 7204-61-7.

Supplementary Material Available: Table II, listing the properties of the products prepared (2 pages). Ordering information is given on any current masthead page.

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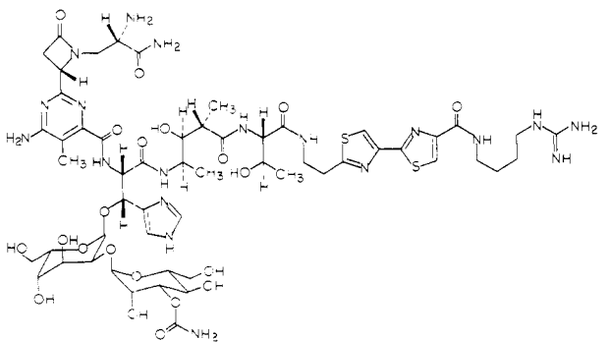
Communications

Synthesis of L-Gulose from D-Glucose via Aldose Interchange

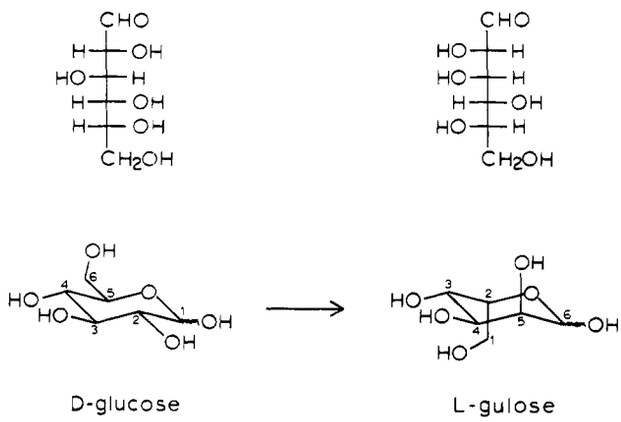
Summary: L-Gulose has been prepared from D-glucose in a form suitable for reconstruction of bleomycin.

Sir: Bleomycin (1) is an antitumor antibiotic possessing clinically useful activity in the treatment of squamous cell carcinomas.[1] Our interest in the total synthesis of bleomycin B_2 (1) has prompted us to consider practical methods for



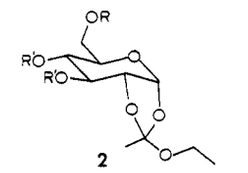
1

preparation of the rare sugar L-gulose in a form suitable for synthetic elaboration of the carbohydrate moiety of bleomycin. Since gulose must be attached stereoselectively to L-*erythro*-β-hydroxyhistidine and 3-*O*-carbamoylmannose via O-1 and O-2, respectively, the sugar must be prepared in a form that permits O-1 and O-2 to be differentiated from each other, and from O-3, O-4, and O-6, in subsequent synthetic transformations. Therefore, while syntheses of L-gulose have been reported,[2] none of these was suitable for our purposes; we report herein an efficient synthesis of an appropriate L-gulose derivative.



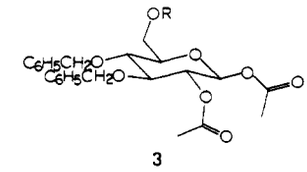
D-glucose L-gulose

Fischer recognized the conceptually simple relationship between the readily available D-glucose and L-gulose, which differ only in oxidation state at C-1 and C-6, and utilized this principle for the preparation of L-gulose from D-glucaric acid in low yield by successive reductions with sodium amalgam.[2a] In the present case, more direct interconversion has been achieved by oxidation of 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-D-glucopyranose (**3b**) to the corresponding 6-aldehydo sugar [isolated as the respective *N,N*-dimethylhydrazone (**4**)] and subsequent borohydride reduction of the latent dialdehyde with sodium borohydride, affording the desired 3,4-di-*O*-benzyl-1-(*N,N*-dimethylhydrazino)-L-gulopyranose (**5**) as a clear oil in 42% overall yield from D-glucose. Verification of structure was accomplished by conversion to 1,6-anhydro



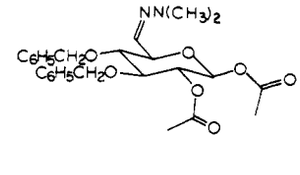
2

a R,R′ = $COCH_3$
b R = $C(C_6H_5)_3$, R′ = H
c R = $C(C_6H_5)_3$, R′ = $CH_2C_6H_5$



3

a R = $C(C_6H_5)_3$
b R = H



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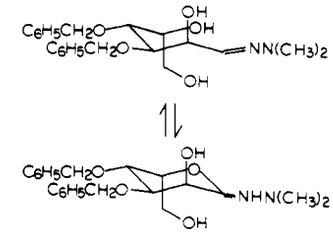

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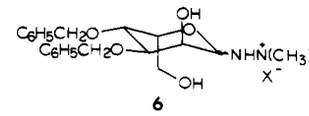

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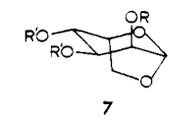

7

a R = H, R′ = $CH_2C_6H_5$
b R, R′ = $COCH_3$
c R, R′ = H

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