(1% Et_3N) to afford 2.74 g (41%) of a colorless syrup: IR (thin film) 3330, 3088, 3062, 3029, 2867, 2102, 1955, 1884, 1810, 1454, 1362, 1302, 1103, 737, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58–1.85 (m, 3 H), 2.60–2.75 (m, 4 H), 3.35 (t, 2 H, J = 5.2), 3.54 (t, 2 H, J = 5.3), 3.58–3.61 (m, 3 H), 3.63–3.66 (m, 8 H), 3.70 (dd, 1 H, J = 2.9, 9.8), 3.75–3.81 (m, 3 H), 3.84 (dd, 1 H, J = 6.6, 13.4), 4.07 (d app t, 1 H, J = 4.2, 8.9), 4.50–4.64 (m, 7 H), 4.71 (d, 1 H, J = 11.4), 7.18–7.20 (m, 2 H), 7.25–7.37 (m, 18 H); ^{13}C NMR ($CDCl_3$) δ 30.00, 46.61, 49.20, 50.56, 69.16, 69.93, 70.25, 70.53, 70.60, 71.41, 71.60, 72.01, 73.18, 73.35, 73.72, 74.87, 75.99, 127.37, 127.50, 127.53, 127.59, 127.74, 127.79, 127.87, 128.19, 128.22, 128.25, 128.26, 138.12, 138.20, 138.24, 138.33; high-resolution mass spectrum (FAB$^+$) calcd for $C_{44}H_{57}O_8N_4$ $(MH)^+$ 769.4176, found 769.4169.

1-Amino-11-[[2-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)ethyl]amino]-3,6,9-trioxaundecane (15). To a solution of 5.99 g (7.79 mmol) of compound 14 in 50 mL of absolute methanol were added 5.41 mL (38.9 mmol) of dry Et_3N and 4.22 g (38.9 mmol) of 1,3-propanedithiol under a nitrogen atmosphere. The solution was stirred at room temperature for 48 h and then concentrated in vacuo. The crude residue was purified by silica gel chromatography eluting with 40:1 chloroform/methanol (0.5% Et_3N) to give 5.15 g (89%) of a colorless oil: IR (thin film) 3316, 3062, 3029, 2916, 2867, 1954, 1880, 1812, 1455, 1363, 1101, 738, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58–1.68 (m, 1 H), 1.73–1.84 (m, 1 H), 2.05 (br s, 3 H), 2.60–2.73 (m, 4 H), 2.82 (t, 2 H, J = 5.3), 3.48 (t, 2 H, J = 5.3), 3.52 (t, 2 H, J = 5.2), 3.55–3.57 (m, 3 H), 3.59–3.63 (m, 6 H), 3.67 (dd, 1 H, J = 2.6, 9.7), 3.74–3.84 (m, 4 H), 4.05 (d app t, 1 H, J = 4.2, 8.9), 4.48–4.62 (m, 7 H), 4.69 (d, 1 H, J = 11.3), 7.16–7.19 (m, 2 H), 7.24–7.35 (m, 18 H); ^{13}C NMR ($CDCl_3$) δ 29.94, 41.61, 46.65, 49.24, 69.19, 70.25, 70.44, 70.49, 71.53, 71.60, 72.13, 73.03, 73.25, 73.43, 73.71, 74.95, 76.12, 77.23, 127.45, 127.57, 127.60, 127.64, 127.67, 127.80, 127.84, 127.94, 128.26, 128.29, 128.31, 128.33, 138.19, 138.25, 138.29, 138.37; high-resolution mass spectrum (FAB$^+$) calcd for $C_{44}H_{59}O_8N_2$ $(MH)^+$ 743.4271, found 743.4270.

1-Amino-11-[[2-(α-D-mannopyranosyl)ethyl]amino]-3,6,9-trioxaundecane (16). To a solution of 3.20 g (4.31 mmol) of compound 15 in 30 mL of dry DME at −42 °C were added 75 mL of liquid ammonia under an atmosphere of ammonia. Sodium metal was added to the solution until a dark blue color persisted. The solution was stirred for 30 min, and the excess sodium was decomposed with a saturated solution of NH_4Cl in methanol. The ammonia was allowed to evaporate at room temperature, and the solution was concentrated in vacuo. The crude residue was dissolved in water/methanol and applied to a 100-mL column of Bio-Rad AG50W-X4 H^+ resin. The column was eluted first with water/methanol and then with 1 M NH_4OH (10% methanol). The fractions containing the product (detected with ninhydrin) were combined and concentrated in vacuo to afford 1.55 g (94%) of a slightly brown oil, which was used in the next step without further purification: IR (Nujol) 3698–2537 (br), 1586, 1154, 1026, 722 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.65–1.77 (m, 1 H), 1.97–2.10 (m, 1 H), 2.68–2.89 (m, 6 H), 3.52–3.78 (m, 16 H), 3.80–3.89 (m, 2 H), 3.95–4.01 (m, 1 H); ^{13}C NMR (D_2O) δ 26.55, 39.33, 45.07, 47.23, 60.91, 67.09, 68.71, 69.09, 69.13, 69.36, 70.45, 71.14, 73.54, 76.30; high-resolution mass spectrum (FAB$^+$) calcd for $C_{16}H_{35}O_8N_2$ $(MH)^+$ 383.2393, found 383.2398.

Mannose–Fluorescein Conjugate (4). Fluorescein isothiocyanate (FITC) (13 mg, 0.03 mmol) was added to a solution of compound 16 (13 mg, 0.03 mmol) in 20 mL of 100 mM $NaHCO_3$ buffer (pH 9). The solution was stirred for 6 h and neutralized with 1 M HCl. The crude reaction mixture was applied to a 10 mL column of Bio-Rad AG50W-X4 H^+ resin, and the column was washed with water and methanol to remove the unreacted FITC. The column was then rinsed with 1.5 M NH_4OH, and the fractions containing the product (detected by an orange color) were concentrated in vacuo to afford a fluffy orange solid. The product was characterized by ^1H NMR and mass spectrometry. Compound 4 also inhibited the mannose-specific adhesion of *E. coli* to yeast cells:[8c] ^1H NMR (400 MHz, D_2O) δ 1.55–1.80 (br m, 1 H), 1.85–2.15 (br m, 1 H), 2.80–3.10 (br m, 2 H), 3.20–3.85 (br m, 23 H), 6.20–6.53 (br m, 5 H), 6.70–7.60 (br m, 6 H); mass spectrum (FAB$^+$) 770 (M^+ − H).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of all new compounds (23 pages). Ordering information is given on any current masthead page.

Selective Hydrogenations Promoted by Copper Catalysts. 1. Chemoselectivity, Regioselectivity, and Stereoselectivity in the Hydrogenation of 3-Substituted Steroids

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Catalytic hydrogenation of steroids has been widely investigated.[1-6] Among many catalytic systems, those based on Pd are of general applications for the specific reduction of olefinic double bonds owing to satisfactory performance in activity and chemoselectivity.

In many cases, however, poor stereoselectivity is observed as, for example, in the hydrogenation of 4-en-3-one steroids, where mixtures of 5α and 5β ketones are obtained. Useful modifications of the catalytic system have been proposed, as the use of acids or bases,[1] to increase the yield of 5β derivatives. Best results were obtained by means of substituted pyridines as solvents.[4]

On the contrary, homogeneous catalysts, based on noble-metal complexes, are of great importance for high chemoselectivity and, particularly, because they allow the preparation of pure 5α derivatives.[7-12] Limitations in their use are low activity and separation problems.

Although copper catalysts are widely used in industrial chemical processes for the hydrogenation of different compounds (e.g., CO to methanol;[13] fat esters and oxo

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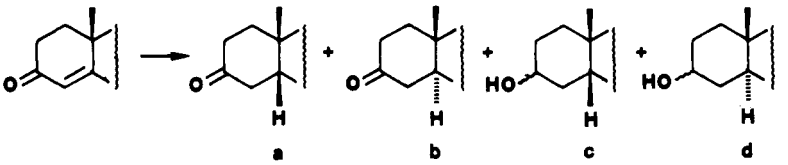
Table I. Hydrogenation of Steroid 4-En-3-ones in the Presence of Cu/Al_2O_3[a]



steroid	equiv of H_2	% conversn	% a	% b	% c	% d	monohydr:dihydr selectivity[b]	stereoselectivity[c]
1	1	87	57	19	8	3	87	75
1	2[d]	100	8	3	57 (86)	25 (88)	-	-
2[e]	1	93	49	14	8	2	86	78
2[e]	2	100	-	-	60 (83)	20 (76)	-	-
3	1	88	65	11	12	-	87	85
3	2	100	-	-	85 (85)	15 (87)	-	-
4	1	95	75	14	5	-	95	84
4	2	100			87 (86)	13 (87)		
5	2	100	62	18	7	2	90	78
5	3		9	3	60 (87)	22 (86)		

[a] Percent of separated products; in parentheses, percent of equatorial epimer. [b] Ketones/(ketones + alcohols). [c] (5β carbonyl derivatives)(5β + 5α carbonyl derivatives). [d] Seven percent diols formed. [e] Twenty percent unidentified products.

aldehydes to alcohols[14]), their use in laboratory-scale hydrogenation is little known.

Recent use of supported copper catalysts for the hydrogenation of polyenes to monoenes,[15,16] alkynes to alkenes,[17] and conjugated enones to saturated ketones[18,19] evidenced a high selectivity in the hydrogen addition to polyunsaturated molecules, which in many cases was comparable to that exhibited by noble-metal catalysts. Consequently, we thought it of interest to investigate the behavior of copper catalysts in the hydrogenation of steroidic molecules in order to extend our previous knowledge on chemo- and regioselectivities to more complex substrates. In particular, the molecular rigidity of condensed rings allows investigations on the stereoselectivity of copper catalysts not yet reported in the literature.

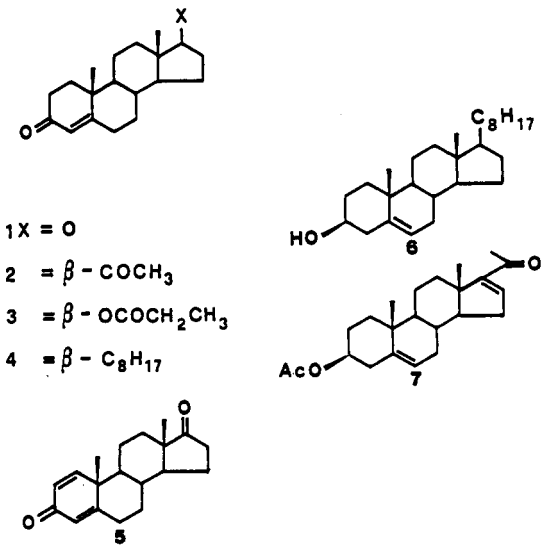
The present paper deals with the activity and selectivity of copper dispersed on alumina, Cu/Al_2O_3, a catalytic system that we have already used and characterized.[17,20]

Two unsaturated functions are present in most of the molecules studied, thus allowing chemoselectivity comparisons. Regioselectivity has been investigated inside the 4-en-3-one group of various 17-substituted steroids (1–4), the 16-en-20-one group (7), and the twice-conjugated, $\Delta^{1,4}$ 3-ketone in 5, whereas stereoselectivity for the hydrogen addition has been evaluated in the course of hydrogenation of the 4,5 olefinic bond and of the 3-oxo group (Chart I).

Results and Discussion

Preliminary tests with four different catalysts prepared by us, namely, 7.2% Cu on SiO_2, 7.5% Cu on Al_2O_3, 11.6% Cu on Cr_2O_3, and 6.3% Cu on MnO_2, showed similar behavior in the hydrogenation of 1. However, Cu/SiO_2 produced a relevant amount of hydrogenolysis byproducts, while Cu/Al_2O_3 was more selective than the others.

Chart I



Therefore all steroidic compounds here investigated were hydrogenated in the presence of 7.5% Cu on Al_2O_3.

Different experimental conditions for the hydrogenation reactions were explored. In the range of 40–160 °C and 0.5–10 atm, regio- and stereoselectivity were little affected by rising T and P, whereas the extent of overreduction gradually increased. For pressures between 10 and 140 atm also the stereoselectivity toward 5β derivatives decreased, particularly with $T > 60$ °C. However, at 1 atm and below 40 °C the hydrogen uptake was very slow. A nonoptimized compromise between activity and selectivity was chosen for most experiments by using a temperature of 60 °C and a hydrogen pressure of 1 atm.

Aliphatic and aromatic hydrocarbons produced very similar results as solvents. In our experiments, toluene was used owing to good solubility of substrates and reaction products in this solvent. Under these conditions, turnover frequencies ranging from 1 to 10 h^{-1} were observed.

Table I shows results obtained in the hydrogenation of different 17-substituted, 4-en-3-one steroids (compounds 1–4). The olefinic bond of the enone moiety is hydrogenated first even when another saturated ketone is present in the molecule (see the first two entries). Thus, when the hydrogen absorption was limited, the corresponding saturated 3-oxo derivatives were obtained in high

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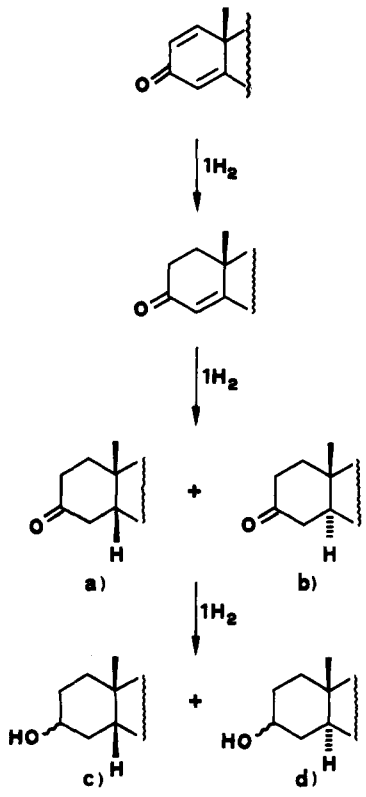
Scheme I. Reaction Pathway for the Hydrogenation of 1,4-Dien-3-one and 4-En-3-one Steroids in the Presence of Cu/Al_2O_3



yield (up to 89%) whereas allylic alcohols were never detected at any stage of the hydrogenation. Small amounts of saturated alcohols, **c** and **d**, resulted from the competition of **a** and **b** with the reagent molecule at high conversion (Scheme I). In all cases, however, a high monohydrogenation:dihydrogenation selectivity was observed.

A particular case of regioselectivity is represented by the hydrogenation of **5**, where two olefinic bonds, both conjugated with the carbonyl group, compete. Figure 1 shows the product distribution versus hydrogen uptake while Scheme I gives the reaction pathway deduced from the above data. The most outstanding result obtained with the copper catalyst is the specific addition of hydrogen to the 1,2 double bond which produced **1** with 93% regioselectivity and allowed its preparation with 74% yield. This performance is superior to any other previously obtained with heterogeneous catalysts, and it is comparable with that reported by Gardi et al.,[21] who used a hydrogen transfer reaction from benzyl alcohol to **5**.

On the other hand, homogeneous hydrogenation catalysts, such as $RhCl(PPh_3)_3$[22] and $RuCl_2(PPh_3)_3$,[8-10] are particularly useful for the selective hydrogenation of **5** to **1**.

To obtain a direct comparison with the copper catalyst, i.e., by using the same analytical techniques, we repeated the hydrogenation of **5** with $RuCl_2(PPh_3)_3$ and with the classical 5% Pd/C. To remove some of the uncertainties about the role played by the support, we also used 1% $Pd/\gamma\text{-}Al_2O_3$. With $RuCl_2(PPh_3)_3$ we operated at 50 °C and 130 atm as suggested by Nishimura to obtain the maximum yield of 4-en-3-one derivative, whereas with Pd/C and Pd/Al_2O_3 we operated at 25 °C and 1 atm of H_2. From the analytical data collected in Table II we can observe

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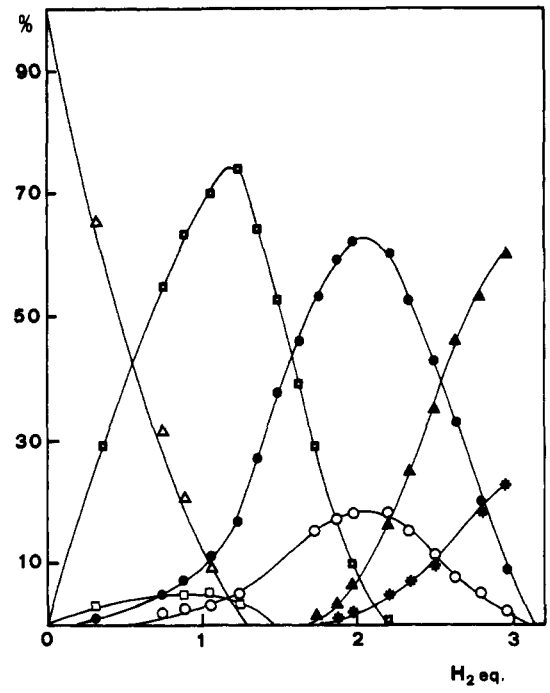


Figure 1. Product distribution versus H_2 uptake during the hydrogenation of **5**: △ = **5**, □ = **1** ■ = 1-en-3-one derivative, ● = **1a**, ○ = **1b**, ▲ = **1c**, * = **1d**.

Table II. Comparison among Different Catalytic Systems in the Hydrogenation of 1,4-Androstadiene-3,17-dione (5)

	Cu/Al_2O_3[a]	Pd/C[b]	Pd/Al_2O_3[b]	$RuCl_2(PPh_3)_3$[c]
conversion	90	79	76	82
% 1	70	25	29	68
regioselectivity[d]	93	42	56	100
monohydrogenation: dihydrogenation[e] selectivity	83	76	68	83
stereoselectivity[f]	78	83	82	-

[a] Toluene, 60 °C, 1 atm of H_2. [b] Dioxane, 25 °C, 1 atm of H_2. [c] Anhydrous benzene, 50 °C, 130 atm of H_2. [d] 4-Ene/(4-ene + 1-ene) (%). [e] Monoenes/(monoenes + saturated diones). [f] Percent 5β after 2 equiv of H_2 consumed.

that the four catalytic systems chemoselectively reduce the dienonic function. However, Cu/Al_2O_3 and $RuCl_2(PPh_3)_3$ are also regiospecific, whereas neither Pd/C nor Pd/Al_2O_3 is able to differentiate between 1,2 and 4,5 double bonds, thus giving a mixture of 4-en-3-one and 1-en-3-one derivatives. In particular, after addition of 1 mol of H_2, Cu/Al_2O_3 produced the highest yield in **1**.

Further addition of H_2 to steroid **5** in the presence of Cu/Al_2O_3 produced a reaction pattern identical with that observed during the hydrogenation of pure **1**.

The stereoselectivity exhibited by Cu/Al_2O_3 in the reduction of the 4-ene unsaturation of the 3-substituted steroids is in agreement with that of other heterogeneous catalysts based on Pd. Thus, the 5β derivatives, having a cis A/B ring junction, are produced as the major products with 75–85% selectivity. In the particular case of cholestenone **4**, a high yield (75%) of 5β-cholestan-3-one could be obtained as a result of both good stereoselectivity and high monohydrogenation:dihydrogenation selectivity.

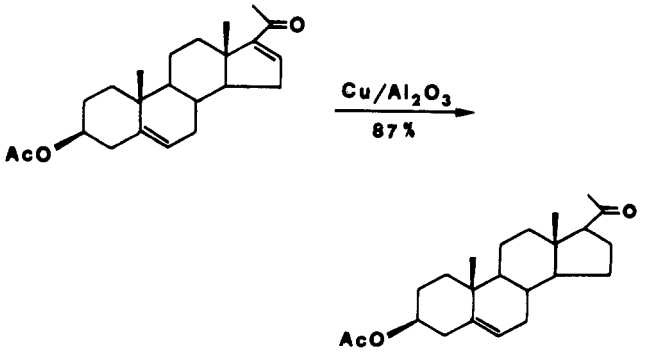
Moreover, it is worth noting that also for the copper catalyst the presence of a ketonic group elsewhere in the molecule decreases selectivity to 5β derivatives as in the case of Pd catalysts.[4] In fact, either the 17-keto or the 20-keto derivatives produced substantially lower yields in 5β isomers.

According to Bonnelle et al.,[18] the regioselectivity of H_2 addition to conjugated enones in the presence of copper chromite can be interpreted by a 1,4 addition process, followed by a prototropic rearrangement. This mechanism reflects the enhanced reactivity of olefinic bonds when conjugated with carbonyl ones in the presence of copper-based catalysts.[23] It may be interesting to note that a 1,4 addition has also been observed when α,β-unsaturated carbonyl compounds were hydrogenated by means of complex copper hydride or hydrido cuprates.[24] Therefore, it can be proposed that the 1,4 hydrogen addition to α,β-unsaturated steroids is mediated by a hydride-like hydrogen present on the copper/alumina surface, whereas the steric control seems to be regulated by the absorption mode of the reagent substrate on the catalyst surface as well documented in the case of Pd catalysts.[2]

After saturation of the 4,5 double bond, the 3-oxo group of **5** began to be hydrogenated according to a second, almost separated step subsequent to the first one as evidenced in Figure 1. The use of several analytical techniques, often in combination, allowed quantification of the epimeric 3-alcohols deriving from 5α and 5β isomers. Table I summarizes the results on the stereochemical course of the hydrogen addition to the unhindered 3-keto group. To the best of our knowledge no previous reports are available on this subject with copper catalysts. The equatorial alcohols were always predominating, both in 5α and 5β series, and the ratio of axial to equatorial alcohol was close to the equilibrium ratio of 16:84.[25] By comparing these results with those reported in the literature for different catalytic systems, we observed that copper on alumina behaves similarly to most heterogeneous catalysts operating in neutral media.[1]

Cholesterol (**6**) was not hydrogenated under the mild conditions used throughout this work and was recovered unchanged after 24 h. This result reflects the reactivity scale reported for the hydrogenation of monofunctional compounds in the presence of copper catalysts and indicates that an isolated olefin is hardly hydrogenated by these catalysts.

Therefore, it is not surprising that 20-oxopregna-5,16-dien-3β-ol acetate (**7**) readily consumed only 1 mol of H_2, producing pregnenolone acetate in high yield (87%) through specific reduction of the 16,17 double bond. Once more the result obtained with Cu/Al_2O_3 is comparable with that observed in the presence of $RhCl(PPh_3)_3$.[22]



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Conclusions

Many efforts are today devoted to the design of new highly active and selective systems for the reduction of unsaturated compounds. Particularly, ever more sophisticated catalysts or reagents, as silicon hydrides in the presence of Pd(0) and $ZnCl_2$[26] or Mo(0)[27] catalysts, diisobutylaluminum hydride in the presence of hexamethylphosphoric triamide and methylcopper(I),[28] have been recently proposed to solve problems of selectivity in the hydrogenation of conjugated polyunsaturated molecules.

In the present investigation, we have found that the inexpensive copper catalyst Cu/Al_2O_3, easily prepared and operating under very mild conditions, shows interesting features of selectivity in the hydrogenation of steroidic enones. In the particular case of 1,4-androstadiene-3,17-dione, the regioselectivity is so high that Cu/Al_2O_3 can be proposed as an effective alternative to homogeneous Rh- and Ru-based catalysts mostly used for the synthesis of 4-en-3-one derivatives from the corresponding 1,4-dien-3-ones. To comparable performance the copper-based system adds the advantages of heterogeneous catalysts, thus avoiding separation procedures.[29]

Experimental Section

Solvents, RPE grade, were used without further purification. Steroids were purchased by Sigma Chemical Co. and Fluka A.G. Samples of allylic alcohols, 17-oxo-4-androsten-3-ol and 20-oxo-4-pregnen-3-ol, were obtained from **1** and **2** by reaction with $NaBH_4$ in tetrahydrofuran at 60 °C for 24 h.[30]

Pd/C (5%) was purchased from Engelhard, and $RuCl_2(PPh_3)_3$ was obtained according to the described procedure.[9] $Pd/\gamma\text{-}Al_2O_3$ (1%) from Girdler (G 129) was reduced at 200 °C for 3 h in an H_2 stream, washed with water until it gave a negative test for chlorides, and dried overnight at 90 °C.

IR spectra were recorded on a Perkin-Elmer 577 instrument; ^{13}C NMR spectra were recorded on a Varian XL 200 instrument. GC analyses were performed on a Hewlett-Packard 5880 instrument, FI detector, equipped with a methyl silicone fluid capillary column (35 m), by using esadecane as internal standard. Thus, to a measured amount of authentic material were added different amounts of esadecane solution in order to obtain samples with different substrate:(internal standard) ratios (in weight). These samples were analyzed at least three times by GC; when the substrate:(internal standard) ratio was plotted versus the (substrate area):(internal standard area) ratio (five points in the range expected for the reaction), calibration curves with $R^2 > 0.99$ were obtained for both ketonic and hydroxylic compounds. GC–MS analyses were performed by using a Hewlett-Packard 5995 C instrument.

Reaction products were identified by comparison of their GC retention times and IR, ^{13}C NMR,[31] and mass spectra[32] with those of commercial samples. The purity of all title compounds was judged to be ≥90% by GC and ^{13}C NMR spectral determination. Authentic samples of 3-oxo-5β- and -5α-androstan-17β-ol propionate (**3a** and **3b**) were obtained through catalytic hydrogenation of **3** with Pd/C (dioxane, 25 °C). Anal. Calcd for $C_{22}H_{33}O_3$: C, 76.48; H, 9.63. Found: C, 76.59; H, 9.95.

3a: ^{13}C NMR ($CDCl_3$) δ 213.1 (C3), 174.6 (C20), 82.4 (C17), 50.8 (C14), 44.3 (C5), 42.8 (C13), 42.3 (C4), 40.8 (C9), 37.2 (C1),

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37.0 (C2 + C12), 35.3 (C8), 35.0 (C10), 27.8 (C21), 27.6 (C16), 26.5 (C7), 25.4 (C6), 23.5 (C15), 22.6 (C19), 20.7 (C11), 12.1 (C18), 9.3 (C22).

3b: ^{13}C NMR δ 211.8 (C3), 174.4 (C20), 82.3 (C17), 53.6 (C9), 50.5 (C14), 46.5 (C5), 44.6 (C4), 42.6 (C13), 38.4 (C1), 38.0 (C2), 36.8 (C12), 35.6 (C10), 35.1 (C8), 31.2 (C7), 28.7 (C6), 27.7 (C21), 27.6 (C16), 23.5 (C15), 20.8 (C11), 12.1 (C18), 11.4 (C19), 9.3 (C22).

Catalyst Preparation. To a solution of $Cu(NO_3)_2 \cdot 3H_2O$ (16 g) in 150 mL of H_2O was added 30% NH_4OH till dissolution of the hydroxide initially formed. To the clear solution was added 20 g of alumina (Riedel-De-Haen), pH 4.5, surface area 200 m^2/g, particle size 70–290 mesh. The suspension was stirred for 10 min and diluted, very slowly, to 2-L volume, stirred for 30 min, and filtered. The solid was dried at 120 °C for 4 h and heated in air at 350 °C for 6 h.

The catalyst was pretreated at 270 °C with H_2 at atmospheric pressure (prereduced catalyst: Cu/Al_2O_3) according to the procedure previously reported for copper chromite,[20] before its use in the hydrogenation reaction. Cu/Al_2O_3 obtained in this way has a copper content of 7–8%, determined by atomic absorption, surface area before the reduction treatment 220–250 m^2/g (BET method[33]), specific Cu(0) area after pretreatment 20–30 m^2/g (N_2O decomposition[34]).

Hydrogenation Procedure. The steroid (0.2 mmol) was dissolved in toluene (6 mL) and the solution heated to 60 °C and then transferred, under H_2, into the reaction vessel where the catalyst (150 mg) had been previously pretreated. The final charge of H_2 was adjusted to 1 atm with a mercury leveling bulb, stirring was begun, and H_2 uptake was measured through a mercury sealed gas buret.

To monitor the product distribution versus H_2 uptake (Figure 1), 20-μL samples were withdrawn from the reacting solution through a viton septum and analyzed by GC. The number of equivalents of hydrogen was calculated on the basis of the molar amount of H_2 consumed by each molecule, e.g., [(74% 4-en-3-one × $1H_2$) + (17% **a** × $2H_2$) + (4% 1-en-3-one × $1H_2$) + (5% **b** × $2H_2$)] = 122% H_2 consumed = 1.2 equiv.

As 5β and 5α stereoisomers give well-separated GC peaks and significative differences in mass spectra, their formation can be monitored during reaction by GC and/or GC–MS. After absorption of 1 or 2 equiv of H_2 (GC monitoring) on a 0.5-g-scale experiment, the reaction mixture was eluted on silica with ethyl ether/hexane or toluene/hexane and the products were identified.

The equatorial:axial ratio was determined inside the separated fractions by digitonide precipitation,[35] GC quantitative determination after silyl derivative formation,[36] and CAD-MIKE spectroscopy following the procedure already described.[37]

Catalytic Hydrogenation of 5. Compound **5** (60 mg, 0.2 mmol) was dissolved in dioxane (6 mL) and the solution added, under H_2, to (a) 5% Pd/C (50 mg) previously dried at 50 °C for 20 min or (b) 1% Pd/Al_2O_3 (150 mg) previously kept under H_2 flow at 200 °C for 5 minutes, in a reaction vessel connected to a gas buret. The reaction mixture was stirred at 25 °C under 1 atm of H_2; after consumption of 1 equiv of H_2 (volumetric), the mixture was analyzed by GC.

Hydrogenation of 5 in the Presence of $RuCl_2(PPh_3)_3$. Steroid **5** (500 mg, 1.8 mmol), $RuCl_2(PPh_3)_3$ (51 mg, 0.05 mmol), NEt_3 (5 mg, 0.05 mmol), and anhydrous benzene (10 mL) were placed in a bomb equipped with a Teflon liner and magnetic stirrer. The bomb was filled with hydrogen (130 atm) and heated at 50 °C, and stirring was begun. After 10 h the reaction was stopped and the benzene solution was passed through alumina to separate the catalyst. Analysis by GC gave the results collected in Table II.

Registry No. **1**, 63-05-8; **1a**, 1229-12-5; **1b**, 846-46-8; **3c** (equatorial), 53-42-9; **1c** (axial), 571-31-3; **1d**, 481-29-8; **2**, 57-83-0; **2a**, 128-23-4; **2b**, 566-65-4; **2c**, 128-20-1; **2d**, 516-55-2; **3**, 57-85-2; **3a**, 18179-14-1; **3b**, 855-22-1; **4**, 601-57-0; **4a**, 601-53-6; **4b**, 566-88-1; **4c**, 516-92-7; **4d**, 80-97-7; **5**, 897-06-3; **6**, 57-88-5; **7**, 979-02-2; 5-pregnen-3β-ol-20-one acetate, 1778-02-5.

Supplementary Material Available: ^{13}C NMR spectra of compounds **3a**, **3b** and pregnenolone acetate (hydrogenation product of compound **7**) and listing of ^{13}C NMR data for the other hydrogenated products (9 pages). Ordering information is given on any current masthead page.

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Reformatsky and Luche Reaction in the Absence of Solvent

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Reformatsky (eq 1) and Luche reactions (eq 2) with Zn provide more economical C–C bond formation methods than Grignard reactions with more expensive Mg metal.

$$R^1R^2C{=}O + BrCH_2COOR^3 \xrightarrow{Zn} R^1R^2C(OH)CH_2COOR^3 \quad (1)$$

$$R^1R^2C{=}O + BrCH_2CH{=}CH_2 \xrightarrow{Zn} R^1R^2C(OH)CH_2CH{=}CH_2 \quad (2)$$

$$\underset{\mathbf{1}}{ArCHO} + \underset{\mathbf{2}}{BrCH_2COOEt} \xrightarrow[NH_4Cl]{Zn} \underset{\mathbf{3}}{ArCH(OH)CH_2COOEt}$$

In addition, we found that Reformatsky and Luche reactions proceed efficiently in the absence of solvent, although Grignard reactions under similar conditions are not very efficient and give more reduction product than the normal carbonyl addition product.[1] The nonsolvent Reformatsky and Luche reactions can be carried out by a very simple procedure and give products in higher yield than with solvent.

In general, the nonsolvent reaction was carried out by mixing aldehyde or ketone, organic bromo compound, and Zn–NH_4Cl in an agate mortar and pestle and by keeping the mixture at room temperature for several hours.

Treatment of the aromatic aldehydes (**1a–e**) with ethyl bromoacetate (**2**) and Zn–NH_4Cl gave the corresponding Reformatsky reaction products (**3a–e**) in the yields shown in Table I. The yield, for example, of **3a** obtained in the nonsolvent reaction (91%) is much better than that obtained by the reaction in dry benzene–ether solution (61–64%).[2] The nonsolvent Reformatsky reaction, which does not require the use of an anhydrous solvent, is thus advantageous.

Synthesis of homoallylic alcohols by the Luche reaction[3] can also be carried out efficiently in the absence of solvent. Treatment of aldehydes (**1a**, **1e**, **5**, **6**) or ketones (**7**, **8**) with 3-bromopropene (**4**) and Zn–NH_4Cl in the absence of solvent gave the corresponding Luche reaction products (**9–14**) in the yields shown in Table II. It has been reported that the Luche reaction of **8** with **4** in water[4] and

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