1 h to ensure complete hydroboration. Acetic acid (20 mmol, 2.0 mL) was added in one portion and the temperature maintained at 110 °C for 3 days. The reaction solution was cooled and transferred to a 250-mL separatory funnel. The flask was rinsed with two 25-mL portions of pentane. The combined organic layers were extracted with four 50-mL portions of cold water and with one 50-mL portion of aqueous $NaHCO_3$ (saturated). The pentane layer was separated and dried over anhydrous magnesium sulfate. The product was isolated by fractional distillation (3.5 g, 50%): bp 44–46 °C (1 mmHg); ^{2}H-decoupled ^{1}H NMR δ 7.07 (s, 5), 2.53 (d, 1, $J_{H^aH^b}$ = 12.5 Hz), 1.53 (d, 1, $J_{H^aH^b}$ = 12.5 Hz), 0.93 (s, 9).

***threo*-1-Phenyl-3,3-dimethylbutane-*1,2*-d_2.** The *E* alkene (**2**; 8.4 mmol, 1.38 g) was hydroborated and protonolyzed as described for the *Z* isomer. The product was isolated by distillation (0.62 g, 45%): bp 52–54 °C (1 mmHg); ^{2}H-decoupled ^{1}H NMR δ 7.07 (s, 5), 2.53 (d, 1, $J_{H^aH^b}$ = 5.0 Hz), 1.53 (d, 1, $J_{H^aH^b}$ = 5.0 Hz), 0.93 (s, 9).

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Registry No. 1, 71486-30-1; **2**, 71486-31-2; *erythro*-**3**, 71486-32-3; *threo*-**4**, 71486-33-4; 1-phenyl-3,3-dimethyl-1-butyne, 4250-82-2; 3,3-dimethyl-1-butyne, 917-92-0; iodobenzene, 591-50-4.

Lanthanoids in Organic Synthesis. 4.[1] Selective Ketalization and Reduction of Carbonyl Groups

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The transformation of aldehydes and ketones to cyclic or noncyclic ketals is one of the easiest and most efficient protective methods for carbonyl groups against nucleophilic reagents.[2] This reaction is usually performed in the presence of various acidic catalysts. During the synthesis of complex molecules, a situation may occur in which one carbonyl group must be selectively transformed in the presence of another. This desired result can often be obtained by blocking a given carbonyl group, so that it is important from a synthetic viewpoint to know specific ketalization processes and catalysts.

We recently reported the efficient ketal formation from aldehydes under mild conditions in the presence of lanthanoid ions.[1] As the yields are excellent and the reaction is very easy to accomplish, it was of interest to further investigate the ketalization process with ketones and bifunctional molecules. The results reported in this note emphasize the sharp contrast between aldehyde and ketone ketalization when rare-earth chlorides are used as catalysts.

Aromatic ketones (e.g., acetophenone, benzophenone, and benzosuberone) and α-enones[3] remain unaffected under the reaction conditions. The reactivity of aliphatic and alicyclic ketones, however, is less straightforward for reasons which still remain obscure. Whereas cyclohexanone and its 4-*tert*-butyl analogue yield the corresponding ketal quantitatively in the presence of $NdCl_3$, other ketones gives unexpected results with various lanthanoid ions. Attempts to isolate the ketal or to determine its concentration in the reaction mixture frequently gave substantially different results according to the analytical method used;[4] these discrepancies remain unexplained. Instead of ketals, hemiketals may be involved, but it has not been possible to obtain direct evidence for such intermediates.

Irrespective of the actual carbonyl protecting species, the preceding results implied that selective ketalization of aldehydes in the presence of ketones would thus be possible in many cases. Addition of excess $NaBH_4$ to the same reaction mixture should result in the reduction of the free keto group. Deprotection during workup would then afford secondary alcohols and aldehydes (or hydroxyaldehydes). In fact, this is the case, and the net result is that our procedure allows a one-pot specific reduction of a keto group in the presence of an aldehyde.[5] A satisfactory selectivity can thus be obtained as shown in Table I. For best results, the proper choice of catalyst is important. It was previously observed that the ketal yield increases with the atomic number of the rare-earth ion.[1] For many aldehydes, including aromatic aldehydes, and hindered ketones, heavier lanthanoids can be used suc-

Table I. Reduction of Ketones in the Presence of Aldehydes[a]

entry	initial mixture or compd	ketalization catalyst	recovered starting matl, %	reduction prod, %
1	cyclohexanecarboxaldehyde	$NdCl_3$	70	30
	cyclododecanone		8	92
2	cyclohexanecarboxaldehyde	$CeCl_3$	48	52
	benzyl methyl ketone		56	44
3	**1**	$ErCl_3$		70[b] (**2**)
4	**5**	$ErCl_3$		76[c] (**6**)
5	benzaldehyde	$ErCl_3$	93	7
	cycloheptanone		17	83
6	benzaldehyde	$CeCl_3$	83	17
	5-nonanone		16	84
7	benzaldehyde	$ErCl_3$	95	5
	2-cyclohexenone		18	82
8	*p*-anisaldehyde	$ErCl_3$	98	2
	acetophenone		20	80

[a] Yields are calculated from the VPC analysis of the crude mixture. For compounds **2** and **6**, the figures are isolated yields of purified product. [b] One stereoisomer could be detected by NMR in the presence of shift reagents. The absolute configuration of the secondary alcohol function was determined by Horeau's method.[12] [c] 1:1 mixture of the epimeric alcohols.

(1) Previous paper in this series: J. L. Luche and A. L. Gemal, *J. Chem. Soc., Chem. Commun.*, 976 (1978). Contribution No. 42 from the Laboratoire de Chimie Organique, CERMO. For No. 41 see: A. E. Greene and J. P. Deprès, submitted for publication.

(2) For example see: E. Schmitz and I. Eichhorn, *Chem. Ether Linkage*, 309 (1967); Y. Ogata and A. Kawasaki, *Chem. Carbonyl Group*, **2**, 1 (1970); H. J. E. Lowenthal in "Protective Groups in Organic Chemistry", J. F. W. McOmie, Ed., Plenum Press, London, 1973, p 323.

(3) J. L. Luche, *J. Am. Chem. Soc.*, **100**, 2226 (1978); J. L. Luche, L. Rodriguez-Hahn, and P. Crabbé, *J. Chem. Soc., Chem Commun.*, 601 (1978).

(4) As an example, camphor (2 mmol) was submitted to ketalization conditions in the presence of erbium chloride. The resulting solution was separated into two parts. One was treated as described for the isolation of the ketal (see Experimental Section). NMR analysis showed that the initial material was quantitatively recovered. The other half was treated with excess $NaBH_4$ (2–10 equiv), and then aqueous HCl was added (pH 3). After the usual workup, the crude mixture was analyzed by VPC and shown to contain 80% of initial material and only 20% of the reduction products (borneol and isoborneol). Similar behavior was observed with other ketones such as 2-octanone, 2-methylcyclohexanone, 5-nonanone.

(5) For another process with a similar selectivity but with different scope and mechanism see: J. L. Luche and A. L. Gemal *J. Am. Chem. Soc.*, in press.

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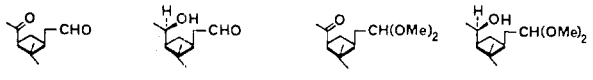
Table II. Selective Reductions of Ketones

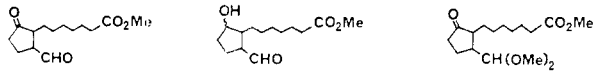
entry	initial mixture or compd	ketalization catalyst	recovered starting matl, %	reduction prod, %
1	cyclohexanone	$NdCl_3$	95	5
	5-nonanone		20	80
2	cyclohexanone	$LaCl_3$	88	12
	cyclopentanone		25	75
3	cyclohexanone	$NdCl_3$	95	5
	2-methylcyclohexanone		35	65
4	cyclohexanone	$NdCl_3$	86	14
	2-cyclohexenone		5	95
5	2-octanone	$ErCl_3$	64	36
	cyclododecanone		4	96
6	acetophenone	$ErCl_3$	76	24
	benzyl methyl ketone		25	75
7	camphor	$CeCl_3$	87	13
	benzyl methyl ketone		26	74
8	8	$ErCl_3$		95[a] (9)
9	12	$CeCl_3$[b]	17[c]	40[c] (14)
			25[d]	48[d]

[a] Isolated yield. For other cases, see Table I, footnote a. [b] No trimethyl orthoformate was added, as comparative experiments showed that it had no effect. [c] At room temperature; isolated yields. [d] At −20 °C; isolated yields.

cessfully. Lighter ions (Ce^{3+} and Nd^{3+}) give satisfactory results when the aldehyde–ketone discrimination becomes more difficult. The intramolecular examples (**1** and **5**) of



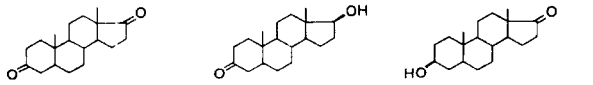
1 **2** **3** **4**



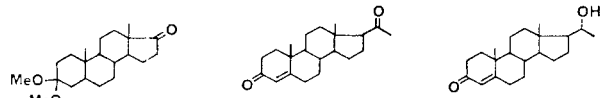
5 **6** **7**

the method are most significant, and in both cases, intermediate monoketals **3** and **7** could be isolated in high yield. However, it must be pointed out that the procedure has some limitations (Table I, entry 2) but is applicable in a large number of cases.

In addition, the different reaction rates for ketones are also of interest, and ketone vs. ketone selective reductions can also be performed by the same process. Results of some competitive experiments, listed in Table II, are illustrative of the type of selectivity which can be reached by the in situ protection of the more reactive carbonyl group. Intramolecular selectivity is observed with androstane-3,17-dione (**8**), which yields 17β-hydroxyandrostan-3-one (**9**) in 95% yield. In this case, the intermediate monoketal **11** could be isolated and characterized.[6]

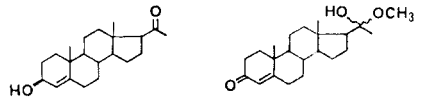


8 **9** **10**



11 **12** **13**

This result is representative of the reversal of reduction selectivity obtained in this process. The typical reduction using $NaBH_4$ in methanol yields a preponderance of 3β-hydroxyandrostan-17-one **10**.[7] Similarly, reduction of progesterone (**12**) with $NaBH_4$ yields mainly **13**,[8] but in the presence of $CeCl_3$, 3β-hydroxypregnen-20-one (**14**) is obtained in 40% yield.[3] In this case, it was not possible



14 **15**

to isolate any ketal. The yield of **14** increases to 48% (66% after substraction of recovered starting material) when the reaction temperature is lowered to −20 °C. As the formation of hemiketals and ketals is known to be favored at low temperature,[2,9] the in situ protection of the C(20) carbonyl group in compound **12** can be rationalized by the formation of a labile species **15**, although no direct evidence could be obtained.

In summary, the one-pot, convenient process described here permits, in most cases, a selective reduction of the less reactive carbonyl group in the presence of a more reactive one. Even if the exact nature of the protective species is not yet known, this procedure should find many applications in organic syntheses.

Experimental Section

Lanthanoid chloride hydrates ($LnCl_3 \cdot 6H_2O$) were obtained from Alfa-Ventron Corp. and were used without purification. Methanol (Prolabo RP) of reagent grade quality was used as received. Infrared spectra were recorded on a Beckmann Acculab 4 instrument as a film or in Nujol suspension. NMR spectra were taken at room temperature on a 60-MHz PMX 60 spectrometer, with $CDCl_3$ containing Me_4Si as an internal standard. Chemical shifts are quoted in ppm downfield from Me_4Si. GLC analyses were obtained on a Carlo Erba Fractovap chromatograph equipped with a Carbowax 20 M, 10% Chromosorb WAW column. Mass spectra were run in CERMAV, Grenoble, on a MS 30 AEI spectrometer by Mr. C. Bosso, whose assistance is acknowledged. Melting points were determined with a Büchi Tottoli apparatus. Optical rotations were measured on a Perkin-Elmer Model 141 electronic polarimeter at 22 °C.

General Procedure for Ketalization. The carbonyl compound (1 mmol) was dissolved in a 0.4 M methanol solution of $LnCl_3 \cdot 6H_2O$ (2.5 mL) and 750 mg (~7 mmol) of trimethyl orthoformate added. The mixture was kept for 15 min at room temperature and then poured into 20 mL of 5% aqueous $NaHCO_3$. Extraction with ether, drying of the organic phase (Na_2SO_4), and evaporation of the solvent yielded a crude mixture which was analyzed by NMR. Purification of the product was accomplished by chromatography (neutral Al_2O_3). Identifications were made by comparison with authentic samples prepared by conventional methods.[2]

Competitive Reduction of Two Carbonyl Compounds. The two investigated compounds (1 mmol each) were dissolved in 2.5 mL of the $LnCl_3 \cdot 6H_2O$ methanolic solution, and 750 mg (~7 mmol) of trimethyl orthoformate was added. The mixture was left for 15 min at room temperature. $NaBH_4$ (80 mg, 2 equiv) was then added in one portion with stirring. A vigorous reaction occurred. After 5 min the solution was acidified (pH 3) by addition of 1 N aqueous HCl. After 20 min, saturated aqueous NaCl was added, and the mixture was extracted with ether. Drying of the organic solution and evaporation of the solvent gave a mixture which was analyzed by GLC. Identification of the peaks was made

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by coinjection of authentic material with the crude reaction mixture.

Reduction of Ketoaldehyde 1 to Hydroxyaldehyde 2.[10] One-Step Procedure. Compound **1** (150 mg, 0.88 mmol), prepared by ozonolysis of (+)-α-pinene,[11] was dissolved in 2.5 mL of methanolic 0.4 M $ErCl_3 \cdot 6H_2O$ solution and 0.7 mL of trimethyl orthoformate. The mixture was heated to 50 °C for 2 min and then left at room temperature for 15 min. After the addition of excess $NaBH_4$ (60 mg) and workup, the crude oil was dissolved in acidified acetone. After hydrolysis of the ketal was complete (TLC), the reaction was worked up as usual to obtain 125 mg of a colorless oil which was purified on silica gel. A pure fraction (110 mg, 70% yield) of hydroxy aldehyde **2** was obtained: IR 3400, 2840, 2720, 1720 cm^{-1}; NMR 9.5 (1 H, br s), 3.9–3.1 (1 H, br m), 1.1 (3 H, s), 1.05 (3 H, d, J = 6 Hz), 1 ppm (3 H, s); $[\alpha]_D$ −13.1° (MeOH); mass spectrum, m/e 100 (ring cleavage), 85, 69.

Isolation of the Reaction Intermediates 3 and 4. Repetition of the first step of the above procedure from 150 mg of **1** yielded 180 mg of the keto ketal **3** in high purity (yield 94%): IR 1700, 1180, 1130, 1060 cm^{-1}; NMR 4.2 (1 H, t), 3.25 (6 H, s), 2.0 (3 H, s), 1.3 (3 H, s), 0.83 ppm (3 H, s); mass spectrum, m/e 214, 183, 151, 124, 84, 75, 43; $[\alpha]_D$ +35.5° (benzene). Compound **3** was not further purified, due to its instability. Reduction of **3** (40 mg) with excess $NaBH_4$ (15 mg) yielded 40 mg of an oil which was assigned structure **4** (quantitative yield): IR 3440, 1140, 1105, 1090, 1070 cm^{-1}; NMR 4.2 (1 H, t), 3.9–3.2 (1 H, m), 3.2 (6 H, s), 1.1–0.9 ppm (9 H); mass spectrum m/e 185, 166, 151, 119, 109, 91, 85, 75; $[\alpha]_D$ −3.5° (benzene).

A 20-mg sample of **4** was used in Horeau's method[12] for the determination of the absolute configuration of the secondary alcohol. The final α-phenylbutyric acid was dextrorotatory ($[\alpha]_D$ +1°), allowing the assignment of configuration **4** to the reduction product from **3**.

Reduction of Ketoaldehyde 5 to Hydroxyaldehyde 6.[13] One-Step Procedure. Compound **5**[14] (160 mg, 0.63 mmol) was dissolved in 1.6 mL of methanolic 0.4 M $CeCl_3 \cdot 6H_2O$ solution and 487 mg (4.41 mmol) of trimethyl orthoformate added. The mixture was left at room temperature for 2.5 h, and then $NaBH_4$ (70 mg, 1.89 mmol) was added with stirring. After 5 min the solution was acidified by addition of 1 N aqueous HCl and 15 mL of acetone. After 6 h and workup as usual, 150 mg of an oil was obtained and purified on a silica gel column. A pure fraction (123.5 mg, 76%) of **6** was obtained: IR 3480, 2960, 2880, 2840, 1735, 1460 cm^{-1}; NMR 9.36 (1 H, br s), 3.36 (3 H, s), 4.16 (1 H, br s), 2.5–1.16 (18 H); mass spectrum m/e 238, 204 (metastable peak), 193 (metastable peak), 177, 145, 105, 57, 44, 43.

Compound **5** (75 mg, 0.29 mmol) was ketalized as previously described. Treatment with aqueous $NaHCO_3$ and usual workup yielded 87 mg (100% yield) of an oil which was identified as the keto ketal **7** by comparison with an authentic sample.[14]

Reduction of Androstane-3,17-dione 8 to 17β-Hydroxyandrostan-3-one 9. One-Step Procedure. Androstane-3,17-dione (288 mg, 1 mmol) was dissolved in 5 mL of methanolic $ErCl_3 \cdot 6H_2O$ (0.2 M) and 750 mg (7 mmol) of trimethyl orthoformate added. The solution was left at room temperature for 15 min, and then 80 mg (2 equiv) of $NaBH_4$ was added in one portion with stirring. The mixture was left for 5 min, and then the pH was brought to ~2 with aqueous 1 N HCl. After a further 20 min period, water was added and the mixture extracted with ether. The organic phase was washed (saturated aqueous NaCl) and dried (Na_2SO_4) and the solvent evaporated, leaving an oil (300 mg) which crystallized readily; mp 176–178 °C. After recrystallization (CH_2Cl_2, hexane), 275 mg (95%) of **9**, mp 178–179 °C (lit.[15] mp 180–181 °C), was obtained with physical data identical with those of an authentic sample.

3,3-Dimethoxyandrostan-17-one.[6] Androstane-3,17-dione (**8**; 60 mg, 0.20 mmol) was dissolved in 1 mL of methanolic $ErCl_3 \cdot 6H_2O$ (0.2 M) and 100 mg of trimethyl orthoformate added. The solution was left at room temperature for 15 min and then poured into 5% aqueous $NaHCO_3$. After extraction (CH_2Cl_2), drying of the organic solution (Na_2SO_4), and evaporation, 60 mg of an oil (86%) was obtained and crystallized readily. Recrystallization from MeOH gave pure compound: mp 124–125 °C (lit.[6] mp 128 °C), $[\alpha]_D$ +85° ($CHCl_3$) [lit.[6] +85.5° ($CHCl_3$)].

17β-Hydroxyandrostan-3-one 9. Compound **11** (50 mg) in 1 mL of methanolic $ErCl_3 \cdot 6H_2O$ (0.2 M) was treated with 30 mg of $NaBH_4$ and then left for 5 min at room temperature. Water was then added and the mixture extracted with CH_2Cl_2. After the mixture was dried (Na_2SO_4) and evaporated, 56 mg of a white solid was recovered: mp 177–180 °C (lit.[16] mp 180–182 °C), $[\alpha]_D$ + 12.5° (lit.[16] +14°). Hydrolysis of the preceding compound (MeOH, aqueous 1 N HCl, 20 min, room temperature) led to 42 mg (98%) of 17β-hydroxyandrostan-3-one (**9**), identical in all respects with an authentic sample.

Reduction of Progesterone (12) to 3β-Hydroxypregnen-20-one (14). Progesterone (90 mg, 0.28 mmol) and 100 mg (1 equiv) of $CeCl_3 \cdot 6H_2O$ were dissolved in 1.5 mL of MeOH and cooled to −20 °C. $NaBH_4$ (5 mg, 0.5 equiv) was added and the mixture stirred for 10 min. Acetone (1 mL) was added, and the temperature was allowed to reach ambient temperature. After the usual workup, 87 mg of an oil was obtained, which was chromatographed (SiO_2, CH_2Cl_2–MeOH). Starting material (25 mg, 28%) was recovered in addition to 43 mg (48%) of compound **14**: mp 161–162 °C, $[\alpha]_D$ +140° (lit.[17] mp 155–161 °C, $[\alpha]_D$ +136°). A third fraction (17 mg, 20%) containing impure pregnene-3,20-diol was isolated. The diol was identified by TLC and comparison with an authentic sample.[8]

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Registry No. **1**, 71628-89-2; **2**, 71582-31-5; **3**, 71582-32-6; **4**, 71582-33-7; **5**, 61659-10-7; **6**, 58282-89-6; **7**, 71582-34-8; **8**, 5982-99-0; **9**, 29873-50-5; **11**, 71628-90-5; **12**, 57-83-0; **14**, 566-66-5; 3,3-dimethoxy-17β-hydroxyandrostane, 71582-35-9; 3β,20-dihydroxy-4-pregnene, 71628-91-6; cyclohexanecarboxaldehyde, 2043-61-0; cyclododecanone, 830-13-7; benzyl methyl ketone, 103-79-7; benzaldehyde, 100-52-7; cycloheptanone, 502-42-1; 5-nonanone, 502-56-7; 2-cyclohexenone, 930-68-7; *p*-anisaldehyde, 123-11-5; acetophenone, 98-86-2; cyclohexanemethanol, 100-49-2; cyclododecanol, 1724-39-6; α-methylbenzeneethanol, 698-87-3; benzyl alcohol, 100-51-6; cycloheptanol, 502-41-0; 5-nonanol, 623-93-8; 2-cyclohexen-1-ol, 822-67-3; 4-methoxybenzenemethanol, 105-13-5; α-methylbenzenemethanol, 98-85-1; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; 2-methylcyclohexanone, 583-60-8; 2-octanone, 111-13-7; camphor, 76-22-2; cyclohexanol, 108-93-0; cyclopentanol, 96-41-3; 2-methylcyclohexanol, 583-59-5; 2-octanol, 123-96-6; 1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol, 10385-78-1.

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Chiral (Arene)tricarbonylchromium Complexes: Resolution of Aldehydes

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Functionalized chiral metallocenes are of great potential interest for asymmetric synthesis. However, the scope of their use is at present limited because of the difficulties encountered in the resolution of racemates.

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