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Selective Reduction of the Exomethylene Group of α-Methylene γ- or δ-Lactones with $CdCl_2$–Mg–MeOH–H_2O†‡

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The strained exomethylene group of the α-methylene γ- or δ-lactone moiety in sesquiterpenoids can be selectively reduced with the $CdCl_2$–Mg–MeOH–H_2O reagent system.

In continuation of our interest[1] in metal–metal salt reductions and also to devise a cheap method for the reduction of the exomethylene group in arteannuin B **1**,[2] we studied its reaction with the $CdCl_2$–Mg–MeOH–H_2O system. A mixture of two products was obtained which were separated by preparative TLC. The more polar major product, mp 180–182 °C, was identified as the dihydro compound **2** by direct comparison with an authentic sample.[2] The less polar minor product, mp 128–130 °C, was identified as the methyl ester **3** by spectral data. In order to examine the generality of this procedure, the reactions of other substrates with $CdCl_2$–Mg–MeOH–H_2O were studied and the results are given in Table 1.

The reaction[3] of δ-lactone **4** with the above-mentioned reagent combination furnished a mixture of C-11-epimers (**5** and **6**) in the ratio of 4:1. The stereochemistry of the C-11-methyl group was assigned on the basis of chemical shift difference studies and coupling constant.[4] Reduction of compound[2] **7** with this reagent combination furnished only one major product **8** in 90% yield.

The reduction of δ-lactones[3,5] (entries 7 and 8) also furnished a mixture of C-11-epimers (**13**, **14**) and (**16**, **17**) in the ratio of 1:4 and 4:1, respectively.

The substrates in entries 4 and 5 did not undergo any reduction and the starting material was recovered quantitatively. However, the substrate in entry 6 underwent reduction to give dihydroarteannuin B **2** as the major product.

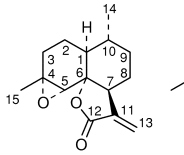
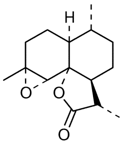
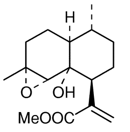
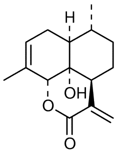
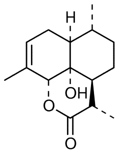
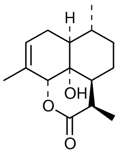
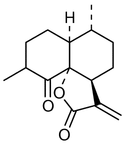
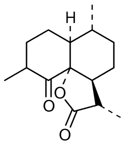
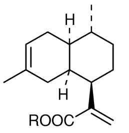
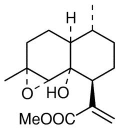
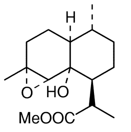
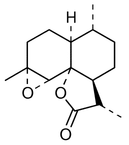
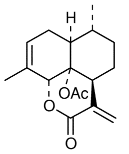
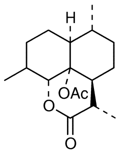
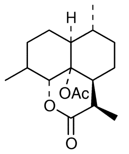
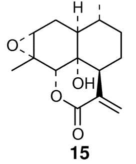
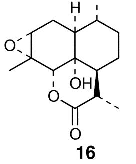
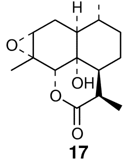
From the experimental results discussed above, it appears that the strained exomethylene group of the α-methylene γ- or δ-lactone moiety undergoes smooth reduction with $CdCl_2$–Mg–MeOH–H_2O. To account for the formation of product **11** in the case of entry 6, it appears that the methyl ester **3** is first converted into the γ-lactone, *i.e.* arteannuin B **1**, which undergoes reduction and opening of the lactone ring (see entry 1).

It is pertinent to mention here that the carbonyl function is not reduced under these reaction conditions (see entry 3).[6]

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded for thin films on a Perkin Elmer 1710 FT-IR spectrometer. ^1H NMR spectra were recorded in deuteriochloroform with tetramethylsilane as internal standard on a Varian FT-80 (80 MHz) or a Bruker WM-400 (400 MHz) spectrometer. Chemical shifts are expressed as δ in ppm, and *J* values in Hz. Most of the coupling constants were determined by decoupling experiments. Mass spectra were recorded under electron impact at 70 eV on a JEOL JMS D-100 spectrometer. TLC and preparative TLC were performed on silica gel G (E. Merck, India).

Table 1 Reduction by $CdCl_2$–Mg–MeOH–H_2O

Entry	Substrate	Products[a]		Yields[b] (%)	t/ min
1	 **1**	 **2**	 **3**	95:5 (98)	15
2	 **4**	 **5**	 **6**	80:20 (88)	15
3	 **7**	 **8**		(90)	15
4	 **9** R = H	No reaction			
5	**10** R = Me	No reaction			
6	 **3**	 **11**	 **2**	5:95 (90)	15
7	 **12**	 **13**	 **14**	20:80 (92)	15
8	 **15**	 **16**	 **17**	80:20 (90)	15

[a]All the product(s) gave satisfactory elemental analyses and spectral data. [b]All the yields refer to isolated chromatographically pure compounds.

General Procedure.—To a solution of the substrate (0.40 mmol) in 3 ml of MeOH was added, with stirring, anhydrous $CdCl_2$ (5.45 mmol) and Mg powder (32.91 mmol). Then H_2O (111.11 mmol)

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

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was added dropwise to this reaction mixture over a period of 5 min when an instantaneous exothermic reaction took place with the liberation of hydrogen. After 15 min, the reaction mixture was diluted with 200 ml of CH_2Cl_2, washed with water and dried. Evaporation of the solvent under reduced pressure produced a residue which on purification by preparative TLC (EtOAc–hexane, 1:4 or 1:9) furnished the product(s) characterized by spectral analysis and direct comparison with authentic samples.

Selected NMR data.—Compound **12**: ^1H NMR (80 MHz, $CDCl_3$): δ 6.50 (dd, *J* 1.7 and 1.7, H-13a), 5.60 (dd, *J* 1.7 and 1.7, H-13b), 5.42 (br s, H-3), 5.12 (br s, H-5), 1.95 (s, OAc), 1.80 (s, H-15), 0.92 (d, *J* 7, H-14); compound **13**: ^1H NMR (400 MHz, $CDCl_3$): δ 5.44 (br s, H-3), 5.18 (s, H-5), 2.84 (m, H-11), 2.09 (s, OAc), 1.80 (s, H-15), 1.22 (d, *J* 7, H-13), 0.95 (d, *J* 7, H-14). Irradiation of the signal at δ 1.22 (d, *J* 7, H-13) collapsed the multiplet at δ 2.84 (H-11) into a doublet (*J* 6.76); compound **14**: ^1H NMR (400 MHz, $CDCl_3$): δ 5.55 (br s, H-3), 4.96 (s, H-5), 2.21 (m, H-11), 2.01 (s, OAc), 1.83 (s, H-15), 1.27 (d, *J* 7, H-13) 0.94 (d, *J* 7, H-14). Irradiation of the doublet (*J* 7) at δ 1.27 (H-13) collapsed the multiplet at δ 2.21 (H-11) into a doublet (*J* 3.44).

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2 A. K. Bhattacharya, D. C. Jain, R. P. Sharma, R. Roy and A. T. McPhail, *Tetrahedron*, 1997, **53**, 14975. Arteannuin B **1** is the biogenetic precursor of artemisinin, a potent antimalarial drug; *e.g.* S. S. Zaman and R. P. Sharma, *Heterocycles*, 1991, **32**, 1593.

3 For preparatiaon of compounds **4** and **15**, see A. K. Pathak, D. C. Jain, R. S. Bhakuni, P. K. Choudhuri and R. P. Sharma, *J. Nat. Prod*., 1994, **57**, 1708.

4 C. R. Narayanan and N. K. Venkatasubramanian, *J. Org. Chem*., 1968, **33**, 3156.

5 Acetate **12** was prepared from compound **4** using BF_3–Ac_2O.

6 For comparison with Ni_2B reduction, see–(*a*) C. A. Brown, *Chem. Commun*., 1969, 952 and references cited therein; (*b*) C. A. Brown and V. K. Akuja, *J. Org. Chem*., 1973, **38**, 2226; (*c*) C. A. Brown, *J. Org. Chem*., 1970, **35**, 1900.