nitrogen atmosphere. After being stirred for 1 h, the solution was cooled in an ice bath and 15 mL of 10% NaOH and then 10 mL of 30% hydrogen peroxide were added. The solution was stirred at room temperature for 2 h and extracted with ether. The ether extract was washed with water and saturated NaCl and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the residue was chromatographed on a silica gel column. Elution with hexane–benzene (1:2.5) gave 350 mg of the less polar alcohol **2a:** mp 115–116.5 °C; NMR (60 MHz) δ 1.15 (3 H, d, J = 6.5 Hz, 29-Me), 2.73 (1 H, m, 6-H), 3.27 (3 H, s, MeO), 3.7 (1 H, m, 28-H). Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.19; H, 11.76. Further elution with hexane–benzene (1:3) gave 300 mg of the more polar isomer **3a** as an oil: NMR (60 MHz) spectrum of **3a** was quite similar to that of **2a;** MS m/e 444 (M^+), 429 ($M^+ - Me$), 412 ($M^+ - MeOH$), 389 ($M^+ - C_4H_7$). Compound **2a** showed the same mass spectrum. Anal. Calcd for $C_{30}H_{52}O_2$: M^+ m/e 444.3966. Found: M^+ m/e 444.3963.

Application of Modified Horeau's Method to 2a and 3a. A solution of 5 mg of **2a** in 65 μL of pyridine was treated with 5 μL of α-phenylbutyric anhydride at room temperature overnight. To the solution was added 6 μL of (+)-α-methylbenzylamine, and the resulting precipitate was diluted with ethyl acetate and analyzed by GLC (OV-17 at 190 °C). **3a** (5 mg) was treated similarly. The ratio of the peak height on GLC with the shorted retention time to that with the longer one was 1.11:0.89 for the sample from **2a** and 0.92:1.08 for the sample from **3a.**

(24*R*)-24-Ethylcholesterol (Sitosterol) (4a). To a solution of 100 mg of **2a** in 3 mL of pyridine was added 80 μL of methanesulfonyl chloride (MsCl) with cooling in an ice bath. After being stirred for 1 h at room temperature, the reaction mixture was poured into ice water and extracted with ether. The organic layer was washed with dilute HCl, saturated $NaHCO_3$, and saturated NaCl and dried over $MgSO_4$. Evaporation of the solvent gave the mesylate as an oil: NMR (60 MHz) δ 1.39 (3 H, d, J = 6.5 Hz, 29-Me), 2.75 (1 H, m, 6-H), 2.95 (3 H, s, MeS), 3.29 (3 H, s, MeO), 4.9 (1 H, m, 28-H). The mesylate was used for the next step without purification.

A mixture of the mesylate, 2 mL of HMPA, and 50 mg of $NaBH_4$ was heated at 80 °C for 2 h under argon. After being cooled, the reaction mixture was added to cold water and extracted with ether. The extract gave an oily product which was found to contain 70% of the 3,5-cyclo derivative of **4a** and 30% of the elimination product (3,5-cyclo derivative of isofucosterol) by GLC analysis. To a solution of the crude product in 10 mL of CH_2Cl_2 was added 100 mg of m-chloroperbenzoic acid with cooling in an ice bath. After being stirred for 30 min at 0–5 °C, dilute NaOH was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and dried over $MgSO_4$, and the solvent was evaporated. The product was purified by silica gel chromatography to give 75 mg of the 3,5-cyclo derivative of **4a** (eluted with hexane–benzene, 2:1): NMR (60 MHz) δ 2.75 (1 H, m, 6-H), 3.30 (3 H, s, MeO).

A mixture of the product, 2 mL of dioxane, 0.7 mL of water, and a catalytic amount of p-TsOH was stirred at reflux for 3 h. Extraction with ether, the usual workup, and crystallization from methanol gave 60 mg of (24*R*)-24-ethylcholesterol (**4a**), mp 136.5–138 °C (lit.[7a] mp 139–140 °C).

(24*S*)-Ethylcholesterol (Clionasterol) (5a). When 100 mg of **3a** was treated in the same manner as described for **2a,** 55 mg of **5a** was obtained, mp 141–142.5 °C (from methanol) (lit.[7a] mp 142–143 °C).

6β-Methoxy-3,5-cycloergost-24(28)-ene (1b). When 495 mg of 24-methylenecholesterol was treated in the same manner as described for **1a,** 330 mg of **1b** was obtained as an oil: NMR (60 MHz) δ 0.2–0.7 (1 H, m, 3-H), 2.75 (1 H, m, 6-H), 3.3 (3 H, s, MeO), 4.7 (2 H, broad s, 28-H). Anal. Calcd for $C_{29}H_{48}O$: M^+ m/e 412.3705. Found: M^+ m/e 412.3717.

(24*R*)- and (24*S*)-6β-Methoxy-3,5-cycloergost-28-ol (2b and 3b). Hydroboration–oxidation of 50 mg of **1b** using the same procedure described for **1a** gave an epimeric mixture of **2b** and **3b,** which was separated by preparative TLC (four times of development) with benzene–ethyl acetate (25:1) to give 15 mg of the less polar alcohol **2b** and 12 mg of the more polar isomer **3b.** NMR (60 MHz) and mass spectra of the separated **2b** and **3b** are almost the same: NMR (60 MHz) δ 2.75 (1 H, m, 6-H), 3.29 (3 H, s, MeO), 3.53 (2 H, m, 28-H); MS m/e 430 (M^+), 415 ($M^+ - CH_3$), 398 ($M^+ - MeOH$), 375 ($M^+ - C_4H_7$).

(24*R*)-Methylcholesterol (Campesterol) (4b). Compound **2b** (15 mg) was converted to the corresponding mesylate by treatment with MsCl (10 μL)–pyridine (0.5 mL). To a suspension of 15 mg of $LiAlH_4$ in dry ether was added the mesylate in 1 mL of dry ether under argon. The mixture was refluxed for 3 h and cooled. Moist ether and dilute HCl were added to the mixture. Extraction with ether and the usual workup gave 13 mg of the product. Acid treatment of the product as described above gave 10 mg of **4b,** mp 160.5–161 °C (methanol) (lit. mp 159–160[7b] and 160–161 °C[7a]).

(24*S*)-Methylcholesterol (Dihydrobrassicasterol) (5b). When 12 mg of **3b** was treated in the manner described for **2b,** 8 mg of **5b** was obtained, mp 158.5–160 °C (from methanol) (lit. mp 157–158[7b] and 158–159 °C[7a]).

Registry No.—**1a,** 68844-30-4; **1b,** 68844-31-5; **2a,** 68844-32-6; **2a** mesylate, 68844-33-7; **2b,** 68844-34-8; **2b** mesylate, 68844-35-9; **3a,** 68889-64-5; **3b,** 6889-65-6; **4a,** 83-46-5; **4a** 3,5-cyclo derivative, 53139-46-1; **4b,** 474-62-4; **5a,** 83-47-6; **5b,** 4651-51-8; fucosterol, 17605-67-3; fucosterol tosylate, 68844-36-0; isofucosterol 3,5-cyclo derivative, 66461-40-3; 24-methylenecholesterol, 474-63-5.

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Bromination of 3-Cyclopentyl-2-butenolide

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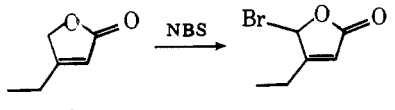
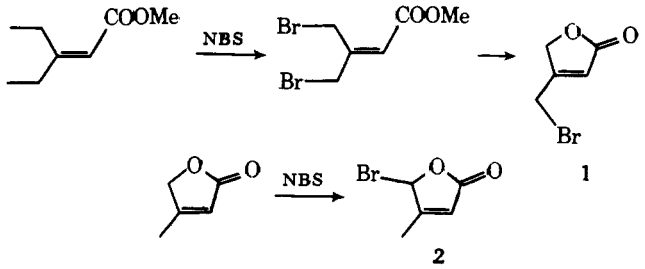
Recently Martin et al. reported the synthesis of the simple brominated butenolides **1** and **2** shown in Scheme I.[1] In particular, we note that the NBS bromination of the 3-methyl-2-butenolide occurs α to the oxygen. Steyn and co-workers had earlier found the same results, and in addition they found that 3-ethyl-2-butenolide (**3**) also underwent an NBS bromination α to the oxygen (eq 1).[2] We have investigated the bromination



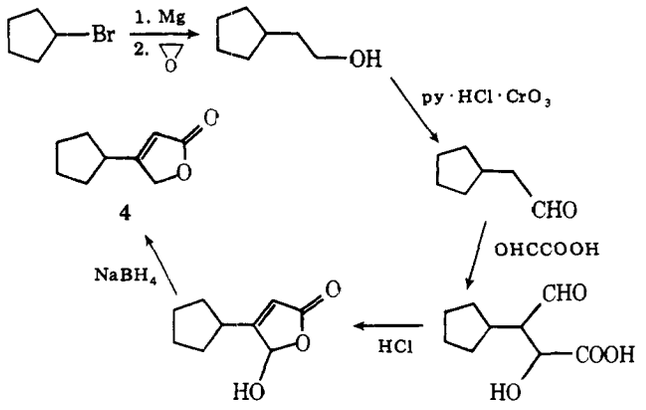
(1)[2]

3

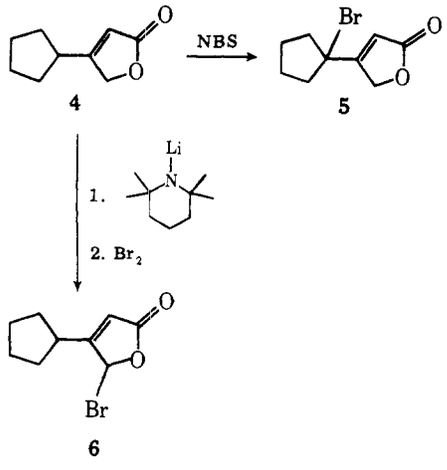
Scheme I. Synthesis of 3-Methyl Brominated Butenolides[1]



Scheme II. Synthesis of 3-Cyclopentyl-2-butenolide (4)



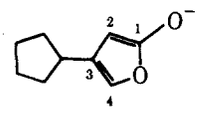
Scheme III. Bromination of 3-Cyclopentyl-2-butenolide (4)



of substituted butenolides with the eventual goal being the preparation of brominated cardenolides,[3] which would be used to probe the mode of action of these cardiotonic steroids. Our results with the bromination of the model compound 3-cyclopentyl-2-butenolide (4) are significantly different from those reported above, such that we would like to present them at this time. 3-Cyclopentyl-2-butenolide (4), as prepared in Scheme II, was used in our studies. The Grignard reagent from cyclopentyl bromide was treated with ethylene oxide to produce 2-cyclopentylethanol[4] in 25% yield. This alcohol was oxidized to the corresponding aldehyde in 72% yield with pyridinium chlorochromate.[5] Condensation of this aldehyde with glyoxylic acid according to the procedure of Debono and co-workers[6] and dehydration with HCl in CH_2Cl_2 produced 3-cyclopentyl-4-hydroxy-2-butenolide in 73% yield for these two steps. Finally, reduction of the hemiacetal with $NaBH_4$[7] gave 4 in 93% yield.

N-Bromosuccinimide (NBS) bromination of the butenolide 4 gave the bromo compound **5** in 74% yield (Scheme III). It was obvious from the spectral data that bromination had occurred at the tertiary carbon, and we could not detect any other bromination products.

We anticipated that deprotonation of **4** should occur at the secondary position under either kinetic or equilibrium conditions. Bromination of the resulting anion could occur at either the 2 or 4 positions. Although most conjugated anions are trapped by electrophiles at the α carbon, the anion from **4**, shown as one resonance structure **7**, might be expected to show electrophilic attack at carbon 4, which is α to the ring oxygen of the furan.[8] Indeed, reaction of carbanion **7** with Br_2 gave the 4-bromo-3-cyclopentyl-2-butenolide (**6**) in 67% yield.



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We could not detect any α-bromobutenolide in the NMR spectrum of the crude product. A related example of a Michael addition from carbon 4 of the anion from some 4-substituted butenolides has recently been reported.[9] Alkylation of anions of 2- and 3-substituted butenolides yields mixtures of products resulting from alkylation at carbon 2 and 4.[10]

The difference in reactivity of 3-methyl-, 3-ethyl-, and 3-cyclopentyl-2-butenolide toward NBS reflects the difference in reactivity of primary, secondary, and tertiary hydrogens toward free radical abstraction.[11] This effect probably dominates any radical stabilization by an adjacent oxygen.[12]

Experimental Section

Melting points, which were determined on a Kofler hot stage microscope, and boiling points are uncorrected. All IR spectra were recorded in $CHCl_3$ solution using a Perkin-Elmer Model 700 spectrophotometer and were calibrated with the 1601-cm^{-1} band of polystyrene. The ^1H NMR spectra were recorded in $CDCl_3$ solution on either a Varian Model T-60 or HA-100 spectrometer. The signal positions are reported using the δ scale with tetramethylsilane as an internal standard. The multiplicity, coupling constants, and integrated peak areas are indicated in parentheses after each signal. The mass spectra were obtained using an Atlas CH-4B mass spectrometer, and high-resolution determinations were obtained using an AEI MS-9 or MS-50 spectrometer. Both instruments were operated at an ionizing potential of 70 eV. Elemental microanalyses were performed by Mr. Peter Borda, University of British Columbia. The silica gel used was obtained from E. Merck, and that used for thin-layer chromatography (TLC) was the grade PF_{254}.

2-Cyclopentylacetaldehyde. To a solution of 21.7 g (101 mmol) of pyridinium chlorochromate[5] in 300 mL of dry methylene chloride was added 7.65 g (67.1 mmol) of cyclopentylethanol[4] over 5 min. The deep red solution turned dark, and a black precipitate formed within a few minutes. The resulting mixture was stirred (magnetic stirrer) for 2 h at room temperature and then worked up by filtering through a short pad of Florisil and washing the residue with 2 × 150 mL of ether. The combined filtrates were washed with 250 mL of 5% HCl, 250 mL of 10% $NaHCO_3$, and 250 mL of brine and dried over anhydrous $MgSO_4$. After removal of solvent, the crude product was distilled to give 5.41 g (72%) of 2-cyclopentylacetaldehyde, bp 53–54 °C/12 mm (lit.[13] bp 53 °C/12 mm).

Condensation of 2-Cyclopentylacetaldehyde with Glyoxylic Acid. To a solution of 4.14 g (37 mmol) of 2-cyclopentylacetaldehyde in 400 mL of methanol–water (1:1) was added 8.40 g (114 mmol) of glyoxylic acid hydrate in one portion, followed by 5.50 g (136 mmol) of NaOH pellets in several portions. The resulting solution was stirred for 22 h at room temperature and then acidified with glacial acetic acid to pH 6. The solution was extracted with 3 × 200 mL of ether, and the extracts were washed with 300 mL of brine and dried over anhydrous $MgSO_4$. After removal of solvent and vacuum drying, a white solid residue (4.9 g) was obtained. The spectral data for this material indicated that it contained hydroxy acid along with some dehydrated product and some butenolide. This mixture was used directly in the next step.

3-Cyclopentyl-4-hydroxy-2-butenolide. The crude product (4 g) obtained in the previous reaction was dissolved in 180 mL of methylene chloride saturated with anhydrous HCl, and the solution was stirred for 5 h at room temperature. The reaction was worked up by diluting with 100 mL of ether, washing the organic phase with 75 mL each of 10% $NaHCO_3$ and brine, and drying the extracts over anhydrous $MgSO_4$. The crude product obtained after removal of solvent was distilled (Kugelrohr) to give 3.73 g (73% yield from 2-cyclopentylacetaldehyde) of 3-cyclopentyl-4-hydroxy-2-butenolide: bp 100–103 °C/0.6 mm; IR ($CHCl_3$) 3200–3700, 1760, and 1640 cm^{-1}; NMR ($CDCl_3$) δ 6.00 (s, 1 H), 5.72 (s, 1 H), 5.3 (broad s, exchangeable with D_2O, 1 H), 2.8 (m, 1 H), 1.4–2.4 (m, 8 H); mass spectrum, *m/e* (relative intensity) 168 (0.6), 150 (5), 139 (4), 122 (100), 100 (51), 94 (28), 79 (21).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.42; H, 7.30.

3-Cyclopentyl-2-butenolide (4). 3-Cyclopentyl-4-hydroxy-2-butenolide (3.65 g, 21.7 mmol) was dissolved in 250 mL of metha-

nol–water (1:1) containing 3 g of NaOH. Sodium borohydride (2.5 g, 65.1 mmol) was added to the solution with stirring at room temperature. After 2 h, the reaction was worked up by acidifying with concentrated HCl to pH 1 and extracting with 2 × 200 mL of ether. The combined extracts were washed with 100 mL each of 10% $NaHCO_3$ and saturated brine and then dried over anhydrous $MgSO_4$ to yield 3.20 g of liquid residue after removal of solvents. Distillation (Kugelrohr) of the crude product gave 3.01 g (91% yield) of **4**: bp 108–110 °C/0.8 mm; IR ($CHCl_3$) 1785, 1745, 1640, 1040, 1030, 895, and 860 cm^{-1}; NMR ($CDCl_3$) δ 5.82 (q, J = 2 Hz, 1 H), 4.78 (d, J = 2 Hz, 2 H), 3.8 (m, 1 H), 1.2–2.2 (m, 8 H); mass spectrum, *m/e* (relative intensity) 152 (60), 123 (100), 107 (67), 95 (35), 93 (43), 69 (53), 68 (75), 67 (75), 60 (70), 55 (75), 41 (70).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.98; H, 7.95.

Bromination of 4 with *N*-Bromosuccinimide. A 31-mg (0.02-mmol) sample of **4**, 36 mg (0.2 mmol) of NBS (Fisher Chemical Co.), and a small crystal of azobis(isobutyronitrile) were stirred with 2 mL of dry carbon tetrachloride in a 5-mL round-bottom flask fitted with a condenser and a drying tube ($CaSO_4$). The mixture was exposed to a 275-W sun lamp with a filter (Corning no. 7380, $\lambda > 340$ nm) for 45 min. The resulting suspension was filtered and the filtrate evaporated. The solid residue obtained was recrystallized from isopropyl ether–ether to give 34 mg (74% yield) or 3-(1-bromocyclopentyl)-2-butenolide (**5**) as colorless plates: mp 69–70 °C; IR ($CHCl_3$) 1795, 1760, 1635, 1050, 895, and 860 cm^{-1}; NMR ($CDCl_3$) δ 6.00 (t, J = 2 Hz, 1 H), 5.08 (d, J = 2 Hz, 2 H), 1.6–2.5 (m, 8 H); mass spectrum, *m/e* (relative intensity) 231 (0.3), 229 (0.4), 167 (2), 151 (100), 123 (20), 107 (12), 105 (9), 95 (10), 93 (12), 91 (7), 67 (8).

Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.77; H, 4.76; Br, 34.60. Found: C, 46.77; H, 4.86; Br, 34.40.

Bromination of the Anion from 4. To a solution of 0.19 mL (1.1 mmol) of 2,2,6,6-tetramethylpiperidine in 3 mL of dry tetrahydrofuran was added 0.45 mL (1.0 mmol) of *n*-butyllithium solution (2.2 M in hexane).[14] The solution was stirred under N_2 for 1 h at room temperature. A solution of 152 mg (1.0 mmol) of **4** in 0.5 mL of dry tetrahydrofuran was then introduced, and the mixture was stirred for another 1 h. The resulting solution was syringed dropwise into a solution of Br_2 (0.1 mL, 2 mmol) in 1 mL of dry tetrahydrofuran under an N_2 atmosphere. The bromine solution decolorized rapidly with a white precipitate forming. After being stirred for 15 min, the mixture was diluted with 20 mL of ether, washed with 10 mL of 5% HCl, 10 mL of $NaHSO_4$ (10%) solution, and 10 mL of brine, and then dried over anhydrous $MgSO_4$. The crude product obtained after removal of the solvents was chromatographed by TLC ($CHCl_3$–CCl_4, 4:1) to give 155 mg (67% yield) of 4-bromo-3-cyclopentyl-2-butenolide (**6**): bp 85–90 °C/0.6 mm (Kugelrohr); IR ($CHCl_3$)[15] 1795, 1760, 1635, 1020, 875, and 855 cm^{-1}; NMR ($CDCl_3$) δ 6.82 (s, 1 H), 5.95 (d, J = 1 Hz, 1 H), 2.9 (m, 1 H), 1.4–2.3 (m, 8 H); mass spectrum, *m/e* (relative intensity) 231 (3), 229 (3), 151 (100), 137 (9), 135 (9), 133 (8), 123 (8), 95 (6), 67 (80), 55 (39), 41 (75).

Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.77; H, 4.76; Br, 34.60. Found: C, 46.49; H, 4.86; Br, 34.40.

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Registry No.—**4**, 68867-09-4; **4** anion, 68867-13-0; **5**, 68867-10-7; **6**, 68867-11-8; 2-cyclopentylacetaldehyde, 5623-81-4; cyclopentylethanol, 766-00-7; glyoxylic acid, 298-12-4; 3-cyclopentyl-4-hydroxy-2-butenolide, 68867-12-9; cyclopentyl bromide, 137-43-9.

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(15) Although the position of the carbonyl bands in the IR spectra of the two brominated products is similar, the intensities are quite different and appear to be useful in distinguishing isomers in this case.

Selective Reduction of Mono- and Disubstituted Olefins by Sodium Borohydride and Cobalt(II)

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Application of transition metal hydrides in organic synthesis has attracted increasing attention in recent years.[1] Although the complexed reagents, presumably transition metal hydrides, prepared from transition metal salts, e.g., Fe(II), Ti(IV), Zr(IV), etc., and metal hydrides, e.g., $LiAlH_4$ and NaH, have been reported to reduce alkenes and alkynes,[2] $NaBH_4$ has not been used extensively in the preparation of such complexed reducing reagents.[3] We now wish to report our observation that the complex species prepared from Co(II) salt and $NaBH_4$ reduced alkenes and alkynes in high yields, and that this reagent displays an extremely high steric selectivity in the reduction of alkenes.[4]

As shown in Table I, monosubstituted terminal olefins (entries 1–3) are most easily reduced by this reagent, the reactions being complete in 1 h. Disubstituted olefins (entries 4–10) are in general more slowly reduced, although reduction of norbornene and norbornadiene is exceptionally facile. It is also noteworthy that the reduction rates are significantly different for *cis*- and *trans*-stilbenes, with the cis isomer being more easily reduced (entries 7 and 8). While mono- and disubstituted olefins are efficiently reduced by this reagent, the more highly substituted olefins (entries 11–15) are virtually inert to these reducing conditions. The potential synthetic utility of this reducing agent is well demonstrated in the reduction of limonene (entry 9), in which the disubstituted side-chain olefin is selectively reduced in the presence of the trisubstituted endocyclic double bond. The observed selectivity in the reduction (mono- > di- > tri- and tetrasubstituted) can be best explained in terms of steric effects, although the involvement of the electronic effect to a minor degree cannot be excluded.

Alkynes are also facilely reduced to alkanes (entries 16–18). Although the partial reduction of alkyne to alkene could be easily achieved by limiting the amount of $NaBH_4$ in the case of 1-octyne (entries 16 and 17), apparently this is not general (entry 18).[5]

Alcoholic $NaBH_4$ was reported to react with Co(II) to produce, depending on the reaction conditions, Co metal, $Co(BH_4)_2$, or complexed cobalt hydrides.[6] It is reasonable to assume that the species responsible for the selective reduction of alkenes and alkynes is most likely a cobalt hydride. The isotope labeling results in the reduction of 1-dodecene (Table II) seem to support this assumption. The results can be best accommodated by the following mechanistic picture. The reaction of Co(II) and $NaBH_4$ produces a cobalt hydride species which is capable of exchanging H ligands with the medium or hydrated water (see the difference of d_0 between entries 1–3). The reduction of the olefin presumably involves the initial hydrocobaltation followed by reductive cleavage

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