Experimental Section[13]

(*E*)-1,2-Bis(bromomethyl)cyclododecene (2). To a solution of 5.80 g (30.2 mmol) of 1,2-dimethylenecyclododecane[6] (1) in 18 mL of chloroform at −10 °C was added dropwise with stirring a solution of 1.6 mL (30.8 mmol) of bromine in 16 mL of chloroform. After 1.5 h, the mixture was washed with saturated aqueous sodium bisulfite, dried, and concentrated under reduced pressure to give 10.4 g (98%) of solid dibromide 2, which was of suitable purity for use in the subsequent coupling reaction. Recrystallization from pentane gave 6.37 g of white solid: mp 56–57 °C; δ_{Me_4Si} ($CDCl_3$) 4.15 (AB, J_{AB} = 9 Hz, CH_2Br), 2.35 (m, allylic CH_2), and 1.2 (envelope, ring CH_2).

(*E*)-1,2-Dimethylcyclododecene (3). To a stirred solution of 0.10 g (0.29 mmol) of dibromide 2 in 5 mL of tetrahydrofuran (THF) at −80 °C was added 1.3 mL (0.65 mmol) of 0.50 M potassium tri-*sec*-butylborohydride[8] in THF via hypodermic syringe. The solution was allowed to stir with warming for 2 h, whereupon 2.5 mL of 20% sodium hydroxide and 2.5 mL of 30% hydrogen peroxide were added at 0 °C. After 2 h, the product was isolated by ether extraction to give 0.055 g (98%) of (*E*)-1,2-dimethylcyclododecene, identified by spectral and chromatographic comparison with an authentic sample:[9] δ_{Me_4Si} ($CDCl_3$) 1.70 (s, vinyl CH_3) and 1.2 (envelope, ring CH_2).

(*E*)-1,2-Di-3-butenylcyclododecene (4). To a stirred solution of 0.07 g (0.20 mmol) of dibromide 2 in 1 mL of hexamethylphosphoric triamide at room temperature was added dropwise 1 mL (0.5 mmol) of 0.50 M allylmagnesium chloride in THF. After 4 h, the product was isolated by extraction with hexane and filtration through 20 g of neutral alumina. Distillation afforded 0.025 g (65%) of dimethylenecyclododecane (1), bp 40–65 °C at 0.02 torr, and 0.16 g (30%) of triene 4: bp 70–120 °C at 0.02 torr; δ_{Me_4Si} ($CDCl_3$) 5.8–5.0 (vinyl H), 2.1 (allylic CH_2), and 1.4 (envelope, ring CH_2).

Anal. Calcd for $C_{20}H_{34}$: C, 87.51; H, 12.49. Found: C, 87.21; H, 12.84.

(*E*)-1,2-Bis(4-hydroxybutyl)cyclododecene (5). To a stirred solution of 4.4 mL of 2-methyl-2-butene in 50 mL of THF was added 16.5 mL of 1.0 M diborane in THF. After 15 min, 1.48 g of triene 4 in 5–10 mL of THF was added. The reaction mixture was stirred at room temperature for 3.5 h and treated with 4.8 mL of water. After 3.7 mL of 40% aqueous sodium hydroxide had been added, 6.2 mL of 30% aqueous hydrogen peroxide was added over a 10-min period with continuous stirring. Occasional cooling was necessary to control the exothermic reaction. The resulting mixture was heated at 45–50 °C for 5 h. After cooling, the organic layer was separated and the water layer was extracted with ethyl acetate. Filtration and removal of solvent gave 3.3 g of a colorless oil. The 3-methyl-2-butanol was removed by vacuum distillation, leaving a colorless solid residue of 1.8 g (95%) which was normally used without further purification. Recrystallization from hexane gave material with mp 95–98 °C: IR (film) 3370, 2950, 2890, 1470, 1060 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 1.05–1.75 (m, CH_2), 1.75–3.00 (m, allylic CH_2 and OH), 3.58 (m, CH_2–O).

Anal. Calcd for $C_{20}H_{38}O_2$: C, 77.36; H, 12.33. Found: C, 77.62; H, 12.35.

(*E*)-1,2-Bis(4-cyanobutyl)cyclododecene (7). A solution containing 1.8 g of crude diol 5 in 10–15 mL of pyridine was added to a stirred solution of 2.5 g of *p*-toluenesulfonyl chloride in 18 mL of pyridine. After 1 h at 0 °C, the mixture was placed in a freezer overnight and then poured onto ice and extracted with ether. Filtration and removal of solvent gave 3.5 g of a colorless ditosylate 6, which was used without further purification: IR (film) 2950, 2880, 1600, 1370, 1180 cm^{-1}.

This sample of ditosylate 6, 2 g of sodium cyanide, and 40 mL of dimethyl sulfoxide were heated under argon with stirring at 135 °C for 1 h. After being cooled, the mixture was poured into water and extracted with ether. Filtration and removal of solvent gave 1.69 g of dinitrile 7 as a light yellow oil which was used without further purification: IR (film) 2950, 2880, 2250, 1460, 1120 cm^{-1}.

The dicarboxylic acid derivative, mp 150–152 °C, was prepared by saponification using potassium hydroxide in ethylene glycol at 190 °C for 5 h.

Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.09; H, 10.75. Found: C, 71.99; H, 10.39.

[10.10]Betweenanene (10). To a stirred solution of 0.82 g (5.0 mmol) of dinitrile 7 in 80 mL of ether at 0 °C was added dropwise 6.0 mL of 1 M diisobutylaluminum hydride in hexane. After 3 h, 50 mL of saturated aqueous ammonium chloride was added to the cold solution followed, after 20 min, by 50 mL of 5% aqueous hydrochloric acid. The product was isolated by ether extraction, giving 0.60 g (72%) of dialdehyde 8 sufficiently pure for use in the next step: δ_{Me_4Si} ($CDCl_3$) 9.7 (t, J = 2 Hz, –CHO) and 2.38 (m, CH_2CHO).

To a well-stirred mixture of 4.1 g of zinc–copper couple and 4.2 g of titanium trichloride in 40 mL of refluxing 1,2-dimethoxyethane was added a solution of 0.44 g (1.32 mmol) of dialdehyde 8 in 50 mL of DME over a 34-h period.[11] Heating was continued for an additional 14 h, whereupon the cooled mixture was filtered, concentrated under reduced pressure, and eluted through 20 g of silica gel with hexane to afford 0.16 g (40%) of diene 9: δ_{Me_4Si} ($CDCl_3$) 5.4 (m, vinyl H), 2.1 (m, allylic H), and 1.4 (envelope, ring CH_2).

A solution of 0.15 g (0.50 mmol) of the above diene 9 in 8 mL of ethyl acetate was stirred for 2 h at room temperature with 0.1 g of 5% platinum-on-carbon under a hydrogen atmosphere. Filtration followed by concentration and chromatography (silica gel) afforded 0.14 g (93%) of solid [10.10]betweenanene (**10**), mp 63.5–64.5 °C, after recrystallization from acetone: δ_{Me_4Si} ($CDCl_3$) 2.8–1.8 (m, allylic CH_2) and 1.25 (envelope, ring CH_2).

Anal. Calcd for $C_{22}H_{40}$: C, 86.76; H, 13.24. Found: C, 86.90; H, 13.33.

The sample thus obtained was identical with material previously synthesized by an independent route.[1]

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Registry No.—1, 41613-91-3; 2, 69309-09-7; 3, 56491-46-4; 4, 63240-80-2; 5, 63240-82-4; 6, 63240-84-6; 7, 63240-86-8; 8, 69309-10-0; 9, 69309-11-1; 10, 63269-60-3; allylmagnesium chloride, 2622-05-1; (*E*)-1,2-bis(4-carboxybutyl)cyclododecene, 63240-88-0.

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(12) Cf. K. Nakanishi and P. H. Solomon, "Infrared Absorption Spectroscopy", Holden-Day, San Francisco, 1977, pp 17–18.
(13) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses", Collect. Vol. 4, Wiley, New York, 1963, p 132) was used to maintain an argon atmosphere. The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with water and saturated brine solution, and drying the extracts over anhydrous sodium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Nuclear magnetic resonance spectra were recorded with Varian CFT-20 or Perkin-Elmer R20B spectrometers. Signals are reported as the chemical shift downfield from tetramethylsilane (Me_4Si) in parts per million of the applied field. Coupling constants are reported in hertz. Melting points were determined on a calibrated Thomas capillary melting point apparatus. Melting points are not corrected.

Facile Synthesis of Codeine from Thebaine[1]

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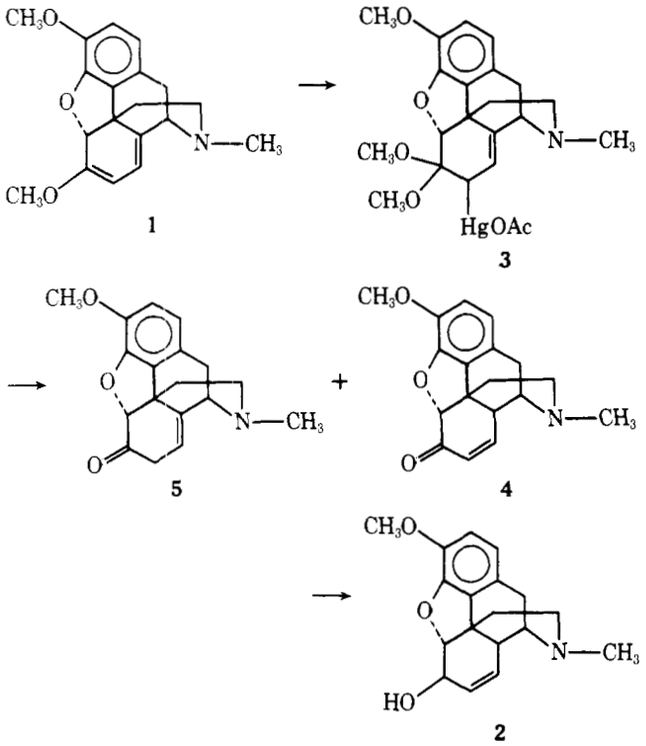
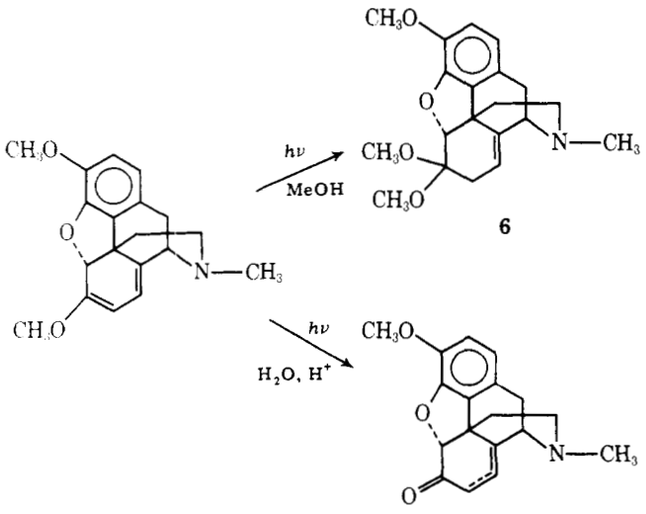
The conversion of thebaine (1) to codeine (2) has recently received attention since the former alkaloid could have become the principal domestic raw material for the analgesic

agents in this alkaloid series.[2] The most facile method for this conversion was first reported, in 1963,[3] to proceed in 75% yield and the process involved the addition of anhydrous hydrogen bromide to thebaine, followed by dehydrobromination and hydride reduction.[4] A more complex process which has been reported[5] to proceed in 85% yield involved oxymercuration of thebaine in methanol to give a mercurated neopinone dimethyl ketal (**3**), followed by subsequent reduction and hydrolysis to give a 3:1 mixture of codeinone (**4**) and neopinone (**5**), a mixture which through two more steps has been converted to codeine (**2**).



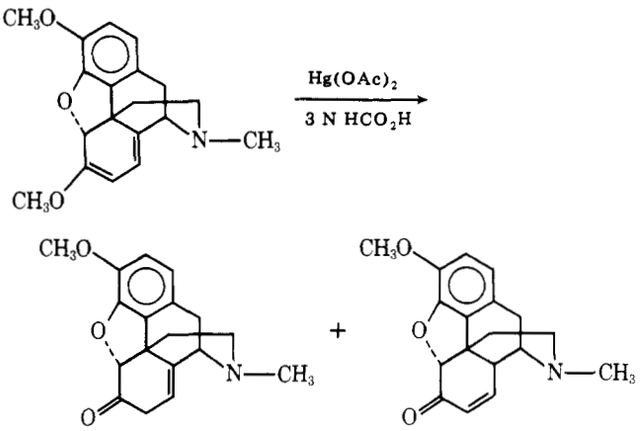
In the course of studies of the photochemistry of *s-cis*-1,3-dienes, the photochemistry of thebaine was investigated. It had been reported that *s-trans*-dienol ethers upon irradiation in alcohol yielded the related β,γ-unsaturated ketal.[6] Thebaine, an *s-cis*-dienol methyl ether, was irradiated in methanol using a 450-W Hanovia lamp and a Corex filter to give neopinone dimethyl ketal (**6**) in 78% yield. In view of this efficient addition of methanol to the dienol ether moiety, thebaine as its hydrochloride was irradiated in a slightly acidic aqueous solution under the same conditions to yield, directly, a 9:1 mixture of neopinone and codeinone in 80% yield. Thus,



the photochemical conversion under extremely mild reaction conditions of thebaine to neopinone dimethyl ketal or, directly, to the neopinone and codeinone mixture offers a new process to convert thebaine to codeine since these photochemically produced materials are known to be converted readily to codeine.[5]

It has been reported that neopinone dimethyl ketal, formed by the oxymercuration procedure,[5] upon reaction with 3 N formic acid at room temperature for 4 days gives a 3:1 mixture of neopinone and codeinone in 90% yield. When the photochemically produced neopinone dimethyl ketal was subjected to the same reaction conditions, a 2:1 mixture of starting ketal and mixed enones resulted. This puzzling result necessitated further study of the hydrolysis reaction. Realizing that the ketal utilized in the original study[5] had been obtained by the oxymercuration of thebaine in methanol, a catalytic amount of mercuric acetate (0.7 mol %) was added to the hydrolysis solution of the photochemically produced ketal. Such an addition completely changed the composition of the hydrolysis mixture, there being obtained upon 80% reaction the formation of an enone mixture in a corrected yield of 89%.

This finding of the catalytic effect of mercuric salts upon the hydrolysis of a ketal was next extended to the hydrolysis of thebaine, itself. It was found that the hydrolysis of thebaine at room temperature for 4 days in 3 N formic acid containing 13.3 mol % of mercuric acetate yielded a 3:1 mixture of codeinone and neopinone. When the mercuric acetate was omitted, no enones were formed under the same hydrolysis conditions. Further investigation of the hydrolysis reaction showed that the reaction occurred, albeit slowly, with only 2.7 mol % of mercuric acetate.



The optimized reaction conditions were found to be the utilization of a 6.7 mol % of mercuric acetate in 3 N formic acid and a reaction time at 6.5 h at room temperature.[7] Under these reaction conditions, and not purifying any intermediates, thebaine was converted to codeine in an overall yield of 71%. The steps for the conversion of the initial enone mixture included the addition of hydrogen chloride, followed by dehydrochlorination under nonequilibrating conditions, and sodium borohydride reduction of the crude codeinone.[5] The codeine prepared by direct mercuric acetate catalyzed hydrolysis of thebaine contained only 22 ppm mercury.[8]

Experimental Section

Melting points were determined on a Mel-temp apparatus and are uncorrected. ^{1}H-NMR spectra were determined on a Varian Associates T-60 spectrometer. Gas-phase chromatographic analyses were performed on a Hewlett-Packard 402 high-efficiency gas chromatograph, equipped with a 6 ft × ⅛ in. column packed with 3% OV-225, Chromosorb W, AW DMCS, 100–120 M, at a temperature of 230 °C, using a flame ionization detector.

Photochemical Formation of Neopinone Dimethyl Ketal (6).

A solution of 623 mg (2 mmol) of thebaine in 150 mL of methanol, freshly distilled from $Mg(OMe)_2$, was deoxygenated with a stream of dry nitrogen. This solution was irradiated with a Hanovia 450-W lamp through a Corex filter under a nitrogen purge for 2 h, at which time TLC analysis (silica gel, $CHCl_3$–MeOH, 85:15) showed that all the starting material had been consumed. The solution was rotary evaporated and the residue purified by column chromatography (silica gel, $CHCl_3$–MeOH, 94:6) to yield 538 mg (78%) of neopinone dimethyl ketal as a light golden oil. The crude product was Kugelrohr distilled to give 420 mg (61%) of the methanol adduct: bp 105–110 °C (0.02 mm Hg) [lit. bp 90 °C (0.01 mm Hg)]; NMR ($CHCl_3$) δ 1.80–2.90 (m, 11 H), 2.93 (s, 3 H), 3.50 (s, 3 H), 3.88 (s, 3 H), 4.65 (s, 1 H), 5.36 (d, d, 1 H, J = 6.3 Hz), 6.66 (m, 2 H).

Photochemical Formation of a Neopinone–Codeinone Mixture. A suspension of 643 mg (2.07 mmol) of thebaine in 165 mL of water was deoxygenated with a stream of dry nitrogen. To the solution there was added 250 mL of 1 N HCl (2.5 mmol) and the thebaine hydrochloride which formed slowly dissolved. The solution was irradiated with a Hanovia 450-W lamp through a Corex filter for 2.5 h, at which time TLC analysis ($CHCl_3$–MeOH, 85:15) showed that all the starting material had been consumed. To the aqueous solution there was added 1.0 g of anhydrous Na_2CO_3 and the resulting suspension was extracted with $CHCl_3$. The organic extract was washed with water, dried (Na_2SO_4), and rotary evaporated to yield 500 mg (81%) of a brown oil, which was shown by NMR analysis of the 5β proton[5] to be a 9:1 mixture of neopinone and codeinone.

Hydrolysis of Photochemically Formed Neopinone Dimethyl Ketal (6). A solution of 300 mg (0.875 mmol) of photochemically formed neopinone dimethyl ketal (**6**) in 20 mL of 3 N formic acid was stirred under nitrogen at room temperature for 4 days. A 100-mL portion of a saturated aqueous solution of K_2CO_3 was added and the solution was extracted with $CHCl_3$. The organic extract was washed with water, dried (Na_2SO_4), and rotary evaporated to yield a 2:1 mixture of starting material and enones **4** and **5**.

This same reaction procedure was repeated with the addition of 2 mg (0.006 mmol, 0.7 mol %) of $Hg(OAc)_2$ to yield 240 mg of a 1:5 mixture of starting material and enones; the corrected yield for enones **4** and **5** was 89%.

Hydrolysis of Thebaine (1). A solution of 234 mg (0.75 mmol) of thebaine and 31.9 mg (0.1 mmol, 13.3 mol %) of $Hg(OAc)_2$ in 20 mL of 3 N formic acid was stirred, under nitrogen, at room temperature for 4 days. The solution was diluted with 100 mL of a saturated aqueous solution of K_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4), and rotary evaporated to give a straw-colored solid in 100% yield. The composition of this material was determined by NMR analysis of the 5β proton and by GC chromatography and it was shown to be a 3:1 mixture of codeinone (**4**) and neopinone (**5**).

Following the same procedure with varying amounts of $Hg(OAc)_2$ resulted in the formation of these two enones during the first 24 h, as analyzed by GC chromatography. When no $Hg(OAc)_2$ was added, no enones were produced in 5 days and the addition of only 0.8 mol % of $Hg(OAc)_2$ resulted in complete conversion of thebaine to the enone mixture in 18 days; however, in this latter case the yield of enones was low (~30%) and other byproducts were formed.

Conversion of Thebaine (1) to Codeine (2). A solution of 1.17 g (3.75 mmol) of thebaine (**1**) and 79.8 mg (0.25 mmol, 6.7 mol %) of $Hg(OAc)_2$ in 100 mL of 3 N formic acid was stirred, under nitrogen, for 6.5 h. The solution was diluted with 100 mL of saturated aqueous K_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4), and rotary evaporated.

The residue was dissolved in 5.3 mL of $CHCl_3$ and allowed to react with 5.3 mL of a solution of 1.1 g of hydrogen chloride in 10 mL of ether. A precipitate formed immediately. The reaction was allowed to continue for 30 min and then diluted with 2.5 mL of CH_2Cl_2 and 2.5 mL of the above solution of hydrogen chloride in ether. The reaction was allowed to continue for an additional 15 min and then 250 mL of cold 0.2 N NaOH solution and 50 mL of $CHCl_3$ were added. The aqueous layer was reextracted with $CHCl_3$ and the organic extracts were washed with water, dried (Na_2SO_4), and rotary evaporated.

The residue was dissolved in 60 mL of methanol, 3.02 g (79 mmol) of $NaBH_4$ in 73 mL of methanol was added, under nitrogen, and the reduction was allowed to proceed for 15 h. The solution was concentrated to a volume of 60 mL, diluted with 60 mL of 10% NaOH solution, and heated to reflux. The reaction mixture was further diluted with 50 mL of water and extracted with $CHCl_3$. The organic extract was washed with water, dried (Na_2SO_4), and rotary evaporated to yield 890 mg (79%) of crude white codeine (**2**). GC analysis of this material indicated a 90% purity. The crude product was sublimed (100 °C, 0.03 mm Hg) to give codeine in 80% yield, mp 151–154 °C (lit.[4] mp 153–157 °C). The NMR spectrum was identical with a commercial sample of codeine.

Registry No.—**1**, 115-37-7; **2**, 76-57-3; **4**, 467-13-0; **5**, 509-66-0; **6**, 32398-20-2.

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(1) This work was supported by Grant No. AM 00 709, National Institute of Arthritis, Metabolism and Digestive Diseases. The thebaine was kindly supplied by E. I. duPont and Co., Inc.
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(7) With smaller amounts of $Hg(OAc)_2$, the reaction required long reaction times which, in turn, led to the formation of a large number of products.
(8) We wish to thank Ralph D. McLaughlin of the Lawrence Berkeley Laboratory for the determination of the amount of mercury by his atomic absorption procedure.

Ring Opening of Steroid Epoxides by Dichlorobis(benzonitrile)palladium(II)

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Epoxides are an important class of compounds by virtue of the versatility of their reactions. The opening of the oxirane ring by hydrogen halides leads to the formation of halohydrins, which can be converted into a number of other derivatives.[1]

We have found that a group of oxidocholestanes may be easily and quantitatively converted into the corresponding chlorohydrin derivatives using $Pd(PhCN)_2Cl_2$ in benzene. These reactions offer an example of the original reactivity of the coordination compound, which is acting through two concomitant effects, i.e., the activation of the reaction site by coordination and the participation of its ligands, which is proved by their presence in the reaction product.

The stereochemistry of the ring opening by dichlorobis(benzonitrile)palladium(II) appears to be the expected trans diaxial type and is similar to that observed for the same reactions in the presence of a large excess of hydrochloric or hydrobromic acids (Table I).[2-4]

The action pathway of the palladium complex probably involves the coordination of the oxirane oxygen through substitution of the labile benzonitrile ligands followed by nucleophilic attack of the chloride coordinated to another molecule of the complex.[5] This mechanism appears to be in agreement with the stereoelectronic features of the nucleophilic opening of the epoxide ring, where the attacking nucleophile approaches the ring carbons from a periplanar direction.[4,6]

The epoxide ring opening by $Pd(PhCN)_2Cl_2$ employs conditions milder than those in saturated solutions of hydrochloric or hydrobromic acids, and the chlorohydrin yields are essentially quantitative. Only the OH group at C-3 may give a competitive reaction with the epoxide opening since 3-cholestanols and coprostanols are transformed by the $Pd(PhCN)_2Cl_2$ into the 3-chloro derivatives in few hours, at 70 °C.[5]

As proved by compounds II–V, the carbonyl and ester groups are insensitive to $Pd(PhCN)_2Cl_2$ (at variance with the

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