(3) Oxidation reactions of oximes are known to yield α-functionalized (acetoxy, nitro, halo) tertiary nitroso compounds: (a) ref 3c, Chapter 16, p 383; (b) J. P. Freeman, *Chem. Rev.*, **73**, 283 (1973).

(4) The Eschenmoser group has provided several elegant examples of the generation of vinylogous *C*-nitroso compounds via the intramolecular C-alkylation of unsaturated oxime anions: (a) J. Schreiber, M. Pesaro, W. Leimgruber, and A. Eschenmoser, *Helv. Chim. Acta*, **41**, 2103 (1958); (b) D. Felix, P. Jakober, and A. Eschenmoser, *Chimia*, **19**, 538 (1965). See also (c) P. Wieland and G. Anner, *Helv. Chim. Acta*, **52**, 121 (1969); (d) E. R. Krajniak, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **26**, 1337 (1973).

(5) E. Wenkert, P. Bakuzis, R. J. Baumgarten, C. L. Leicht, and H. P. Schenk, *J. Am. Chem. Soc.*, **93**, 3208 (1971).

(6) This compound exhibited satisfactory spectral (IR, ^{13}C NMR and/or ^{1}H NMR, mass spectrometry) and analytical properties (exact mass and/or combustion analysis).

(7) Yields refer to isolated material of >95% purity.

(8) Oxime stereochemistry assigned by ^{13}C NMR (C. A. Bunnell and P. L. Fuchs, *J. Org. Chem.*, **42**, 2614 (1977)) and ^{1}H NMR (G. J. Karabatos, R. A. Taller, and F. M. Vane, *J. Am. Chem. Soc.*, **85**, 2326, 2327 (1963)).

(9) Acid-catalyzed (commercial CDCl$_3$) isomerization of the syn oxime yields the anti isomer for the purposes of spectral comparison.[8]

(10) The preparation of potassium diphenyl-4-pyridylmethide follows. Potassium hydride (55.0 mmol, 12.0 mL of 4.6 M oil suspension) was placed in a dry flask under nitrogen. Hexane (50 mL) was added, and the mixture was stirred for several minutes. The mixture was then allowed to settle and the hexane was removed via syringe. The process was repeated four times and the residual solvent removed under vacuum leaving a dry powder. Diphenyl-4-pyridylmethane (Chem Samples,[10a] 50.0 mmol, 12.3 g) dissolved in THF (50 mL) was added (slightly exothermic) and the resulting deep red solution was stirred until H$_2$ evolution was complete (1–2 h). The solution is conveniently titrated by adding the reagent solution (via a 1.0-mL syringe) to a known amount of benzoic acid (~80 mg) dissolved in THF (10 mL). Potassium benzoate precipitates from the colorless solution and a very sharp change (colorless to bright orange) is observed at the end point. Three such titrations gave an average of 0.97 M (0.95, 0.98, 0.99). The reagent solution is stable for at least 1 month if kept in a refrigerator. Since all triarylmethide anions react readily with oxygen,[10b] the reagent must be maintained under an inert atmosphere. (a) At the conclusion of our work we were informed that Chem Samples no longer intended to supply diphenyl-4-pyridylmethane. This material can be easily made by the procedure of Tschitschibabin (*Chem. Ber.*, **61**, 547 (1928)). Alternatively, we have found that potassium diphenyl-2-pyridylmethide (diphenyl-2-pyridylmethane is available from Aldrich) serves equally well in these reactions. (b) T. J. Kiess and L. L. Moore, *J. Heterocycl. Chem.*, **9**, 1161 (1972).

(11) Potassium triphenylmethide (J. W. Huffman, P. L. Harris, *Synth. Commun.* **7**, 137 (1977)) also serves as a base in this reaction, but the ease of removal of diphenylpyridylmethane (5% HCl) makes KDPPM a far more convenient reagent to use.

(12) The cyclopentyl oxime (mp 139–140 °C) is prepared from the known ketol (A. Hamon, B. Lacoume, G. Pasquet, and W. R. Pilgrim, *Tetrahedron Lett.*, 211 (1976)) via the standard two-step procedure.

(13) After 12 h at reflux in THF with KDPPM, 90% of the cyclopentyl oxime is recovered.

(14) Oxime **9** (mp 127–128 °C) is prepared from the ketal alcohol via successive reaction with benzenesulfonyl chloride–pyridine, 3.5% aqueous HClO$_4$ in THF, and hydroxylamine hydrochloride–25% pyridine–ethanol. Synthesis of the ketal alcohol is to be published by D. A. Clark and P. L. Fuchs; see also D. A. Clark, Ph.D. Thesis, Purdue University, 1978.

(15) This observation suggests that the rate-determining step in the **9** → **11** transformation is the nitrosocyclopropane → α-isopropylidene oxime rearrangement, while in the case of the reaction with the cyclohexyl substrate (**6** → **8**) the internal alkylation is rate limiting. Experiments are in progress to more carefully delineate these parameters.

(16) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

(17) An authentic mixture of **16***Z* and **16***E* was prepared via the reaction of (*Z*)- + (*E*)-2-butenyl cuprates (66% *Z*) with 2-chlorocyclopentanone oxime by the method of Corey, Melvin, and Haslanger (*Tetrahedron Lett.*, 3117 (1975)). Comparison of the ^{13}C NMR of this mixture with that of the product from ring contraction of **12b** allows a lower limit of 80% to be placed upon the olefinic specificity. Experiments are currently in progress to refine this number.

(18) A similar geometric preference is seen in the high-temperature thermolysis of cyclopropyl esters: D. E. McGreer and N. W. K. Chiu, *Can. J. Chem.*, **46**, 2217, 2226 (1968).

(19) Oxime **17** (mp 120–122 °C) is prepared from the known[5,19a,b] ketol via the standard two-step procedure: (a) W. C. Lumma, Jr., and O. H. Ma, *J. Org. Chem.*, **35**, 2391 (1970); (b) F. Nerdel, D. Frank, and H. Marschall, *Chem. Ber.*, **100**, 720 (1967).

(20) Oxygen alkylation is apparently prevented because of the anti geometry of oxime **17**. Nitrogen alkylation would yield a four-membered-ring nitrone and is presumably not produced in this case because of kinetic preference for cyclopropane formation. A study of substrates which *can* undergo C-, N-, and O-alkylation is currently underway.

(21) Preparation of these materials is to be published, D. A. Clark and P. L. Fuchs; see also D. A. Clark, Ph.D. Thesis, Purdue University, 1978.

(22) Melting points for oxime benzenesulfonates; **20** (mp 136–138 °C); **21** (mp 153–155 °C); **22** (mp 158–160 °C); **23** (mp 133–135 °C).

(23) (a) H. Feuer, Ed., "The Chemistry of the Nitro and Nitroso Group", Part I. Wiley-Interscience, New York, 1969; (b) P. A. S. Smith, "Open-chain Nitrogen Compounds", Vol. 2, W. A. Benjamin, New York, 1966, Chapter 13, pp 355–390; (c) A. T. Blomquist, Ed., "Organic Functional Group Preparations", Vol. II, Academic Press, New York, 1971, Chapter 16, p 383.

(24) In addition to the dimers, 2% of the tertiary tricyclic nitro compound could be isolated from this reaction.

(25) Extended thermolysis of the syn oxime or acid-catalyzed (commercial CDCl$_3$) isomerization yields the anti oxime for the purposes of spectral comparison.[8] TLC analysis (SiO$_2$, 30% THF-C$_6$H$_{14}$) always shows syn oximes to have smaller R_f values than anti oximes in this series.

(26) The same rearrangement occurs at the melting point of the dimer (which melts without exhibiting the typical blue color associated with the nitroso monomers).

(27) Note that these nitrosocyclobutanes rearrange at temperatures ~150 °C higher than the analogous nitrosocyclopropanes.

(28) Graduate Research Associate; David Ross Fellow, 1975–1977; Phillips Petroleum Fellow, 1977–1978.

(29) Postdoctoral Research Associate.

(30) Alfred P. Sloan Fellow, 1977–1979.

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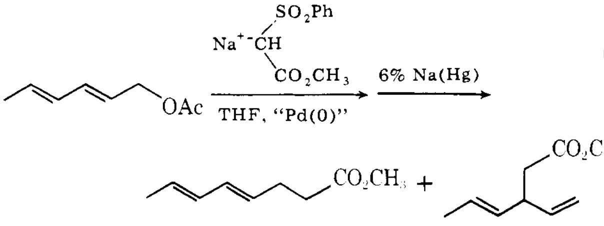
Steric Steering with Supported Palladium Catalysts

Sir:

The development of useful reactions catalyzed by soluble transition metals has led to interest in evolving "insolubilized" versions of these catalysts for ease of recovery and workup.[1] Frequently, such supported catalysts will lose some reactivity and/or selectivity. We report that supporting a palladium(0) species on both silica gel and cross-linked polystyrene not only does not lose reactivity but, because of steric steering, provides important enhanced selectivity over the solubilized forms.

Phosphinylated silica gel was prepared by treating granular silica gel (Ventron 89 346, 8–12 mesh, 300-m^2/g surface area, 1-mL/g pore volume) with 3-chloropropyltrimethoxysilane in hot toluene followed by TMS-chloride and then lithium diphenylphosphide in THF.[2] The phosphinylated silica gel[3] was refluxed with tetrakis(triphenylphosphine)palladium in deoxygenated benzene to give the deep red silica gel catalyst. Phosphinylated polystyrene[4] was prepared in the usual fashion starting with Dow polystyrene cross-linked with 2% divinylbenzene (50–100 mesh).[5] Analysis indicates that chloromethylation led to 94% ring substitution[6a] and phosphide displacement[6b] led to 94% of the chlorides displaced. Palladation of the support as above gave the bright red polystyrene catalyst containing 1.62% palladium[6c] (equiv mol wt, ~6200 per palladium).[7] Both catalysts should be stored in the *absence* of solvent. Remarkably, in the dry state, both are fairly stable toward air, retaining activity even up to 2 months' storage, in contrast to tetrakis(triphenylphosphine)palladium which rapidly decomposes in air.

In the case of carbon nucleophiles in allylic alkylation,[8,9] some increase in regioselectivity is noted. For example, sorbyl acetate showed an increased preference for alkylation at the less hindered terminus as summarized in eq 1.[10] However,



(1)

$(Ph_3P)_4Pd$	69	31
Ⓟ-Pd[11]	80	20

utilization of nitrogen nucleophiles provided dramatic illustrations of the beneficial effect of the supported catalysts.[12]

Treatment of *cis*-3-acetoxy-5-carbomethoxy-1-cyclohexene (**1**) with diethylamine and the soluble palladium catalyst led to a mixture of both the *cis*- and *trans*-3-diethylamino-5-carbomethoxy-1-cyclohexenes[10,13] (**3** and **4** (see eq 2)) with

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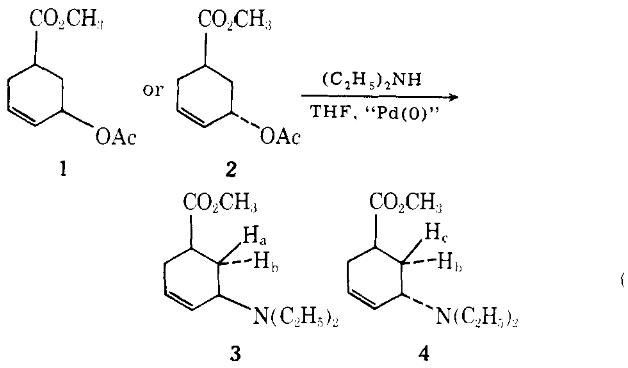
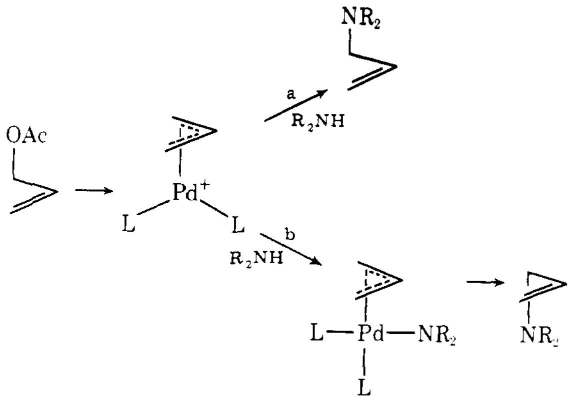


(2)

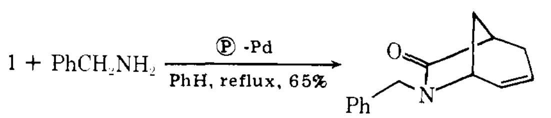
		3	4	% yield
1	$(Ph_3P)_4Pd$	67	33	85
1	Ⓟ-Pd^{II}	100	0	83
1	(Si)-Pd^{II}	100	0	72
2	$(Ph_3P)_4Pd$	35	65	60
2	Ⓟ-Pd^{II}	0	100	86

the cis isomer predominating.[14] Similarly, the trans allylic acetate **2** led to a mixture enriched in the trans amine **4**. The diminished stereospecificity contrasts with the case of carbon nucleophiles in which such crossover does not occur.[9b] The crossover presumably results from a mixed mechanism in which the nucleophile attacks carbon directly to give the product of net retention of configuration (eq 3, path a) and



(3)

attacks palladium which, after reductive elimination, gives the product of inverted configuration with respect to starting acetate (eq 3, path b). If the palladium in the π-allyl complex is bound to a polymer, which should effectively shield the metal from coordinating with the nucleophile, path b should be excluded. Indeed as indicated in eq 2, both types of polymer bound catalysts show complete stereospecificity. This high specificity is also observed with primary amines as illustrated in eq 4. This example also illustrates the important role solvent

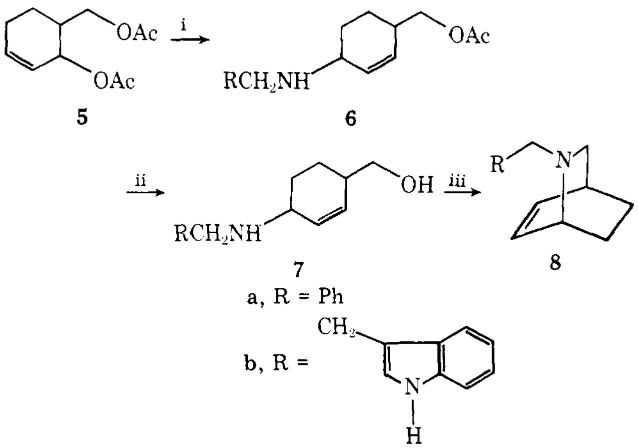


(4)

plays with supported catalysts. Use of THF led to essentially recovered starting material after 13 h, whereas, use of benzene (preferred) or acetonitrile gave complete reaction in this same period.[15] This dramatic rate effect was not so pronounced for secondary amines.

The availability of a clean retention pathway for nitrogen nucleophiles allowed the development of a convenient isoquinuclidine synthesis as outlined in Scheme I.[12] The diacetate **5**, available from the Diels-Alder adduct of 1-acetoxy-1,3-butadiene and methyl acrylate by reduction and acetylation, undergoes regio- and stereospecific amination in benzene to give **6a** (58%) contaminated with **7a** (29%). The acetate **6a** was quantitatively hydrolyzed to the amino alcohol **7a** with refluxing 5% methanolic potassium hydroxide. Chromatographic and spectral criteria showed **7a** to be homogeneous. The regio- and stereochemistry was proven by cyclization using bromotriphenylphosphonium bromide to give *N*-benzylisoquinuclidine in 77% yield after distillation. It was identical with an authentic sample previously prepared in these laboratories.[12]

Scheme I. Isoquinuclidine Synthesis[a]



[a] (i) Ⓟ-Pd (0.018 mol % Pd to substrate), PhH, or 1 : 1 PhH–THF, RCH_2NH_2, reflux, 87%–Q. (ii) 5%, KOH, CH_3OH, reflux, Q–76%. (iii) Ph_3PBr_2, CH_3CN, $(C_2H_5)_3N$, reflux, 77–81%.

Repetition of this sequence using tryptamine required a benzene-THF mixture[16] to dissolve the amine and effect alkylation to give a quantitative yield of **6b** and **7b**. Subjection of **7b** to the bromophosphonium salt cyclization gave the crystalline isoquinculidine **8b**, mp 122.5–123.5 °C, which was identical with an authentic sample.[12] Since we have already showed that **8b** could be cyclized to desethylibogamine, this route represents an alternative synthesis of this family of alkaloids. While this route is slightly longer than our original approach, it is experimentally somewhat simpler and gives purer product with less difficulty.

Obviously, these supported catalysts have the same advantages as other supported reagents in that they can be simply removed and recovered. A flow reactor was also developed which allowed passage of a solution of the reagents through a jacketed column containing the catalyst. However, a special advantage of the supported catalyst stems from the steric protection of the catalyst which allows more effective steering of the nucleophile. The use of this effect in enhancing the scope of nucleophiles for allylic alkylation is another potential application. The applicability of this principle for other transition metal catalyzed reactions is of interest for exploration.

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(1) For some leading discussions see the following. Pitman, C. U.; Evans, G. O. *Chem. Tech.* **1973**, 560. Overberger, C. G.; Sannes, K. N. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 99. Leznoff, C. C. *Chem. Soc. Rev.* **1974**,

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(2) Allum, K. G.; Hancock, R. D.; Howell, I. V.; McKenzie, S.; Pitkethly, R. C.; Robinson, P. J. *J. Organomet. Chem.* **1975,** *87,* 203.

(3) Analysis indicated: C, 12.60; H, 1.54; Cl, 1.38; P, 1.73.

(4) (a) For a review see Frechet, J. M. J.; Farrall, M. J. In "Chemistry and Properties of Crosslinked Polymers", Academic Press: New York, 1977; pp 59–83. (b) The polystyrene was purified by the method recommended by Hartley, F. R.; Vezey, P. N. *Adv. Organomet. Chem.* **1977,** *15,* 189.

(5) (a) Pepper, K. W.; Paisely, H. M.; Young, M. A. *J. Chem. Soc.* **1953,** 4097. For 30 g of resin, 150 g of chloromethyl methyl ether and 7.5 g of stannic chloride for 1.5 h at reflux were employed. (b) Phosphide displacement was adapted from Regen, S. L.; Lee, D. P. *J. Org. Chem.* **1975,** *40,* 1669. (c) Capka, M.; Svoboda, P.; Hetflejs, J. *Collect. Czech. Chem. Commun.* **1973,** *38,* 1242. Capka, M.; Hetflejs, J. *Ibid.* **1974,** *39,* 154. After submission of our paper, the following two reports of reactions catalyzed by Pd(0) on polymer supports appeared. Card, R. J.; Neckers, D. C. *J. Org. Chem.* **1978,** *43,* 2958. Pittman, C. U.; Ng, Q. *J. Organomet. Chem.* **1978,** *153,* 85.

(6) (a) Anal. Cl, 21.98, 22.04. (b) Anal. Cl, 0.70, 0.80; P, 8.95, 9.02. (c) Anal. P, 7.75, 7.90; Pd, 1.57, 1.62.

(7) In the continuous extractions of the palladated catalyst with benzene as a purification, use of paper thimbles in a Soxhlet extractor led to substantial decomposition. All glass systems must be used for maximum results.

(8) For a recent review see Trost, B. M. *Tetrahedron.* **1977,** *33,* 2615.

(9) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1976,** *98,* 630. (b) *J. Org. Chem.* **1976,** *41,* 3215. (c) *J. Am. Chem. Soc.* **1977,** *99,* 3867. (d) *Ibid.* **1978,** *100,* 3435. (e) Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977,** *42,* 2036.

(10) All new compounds have been characterized.

(11) Ⓟ-Pd denotes the polystyrene catalyst; Ⓢi-Pd denotes the silica gel catalyst.

(12) Trost, B. M.; Genet, J. P. *J. Am. Chem. Soc.* **1976,** *98,* 8516. Trost, B. M.; Godleski, S.; Genet, J. P. *Ibid.* **1978,** *100,* 3930.

(13) As in the related series,[9b] couplings of H_a and H_b in **3** and **4** allow assignment. In **3** H_a appears at δ 1.5 (q, J = 12 Hz) indicative of an axial proton with only geminal and axial-axial couplings. In **4**, both H_a and H_b appear as a pseudotriplet (J = 6 Hz) at δ 1.9 indicative of conformationally averaged couplings.

(14) Determined by VPC analysis on a 10 ft × 0.25 in 20% SE-30 on Chromosorb P column at 150 °C.

(15) Apparently in THF the primary amine is preferentially absorbed onto the polymer and the dissociation is very slow. In benzene, this equilibrium appears to be fast and reversible thereby allowing the allylic acetate to compete.

(16) In this case, THF was required to dissolve tryptamine. Use of either solvent alone led to poor results.

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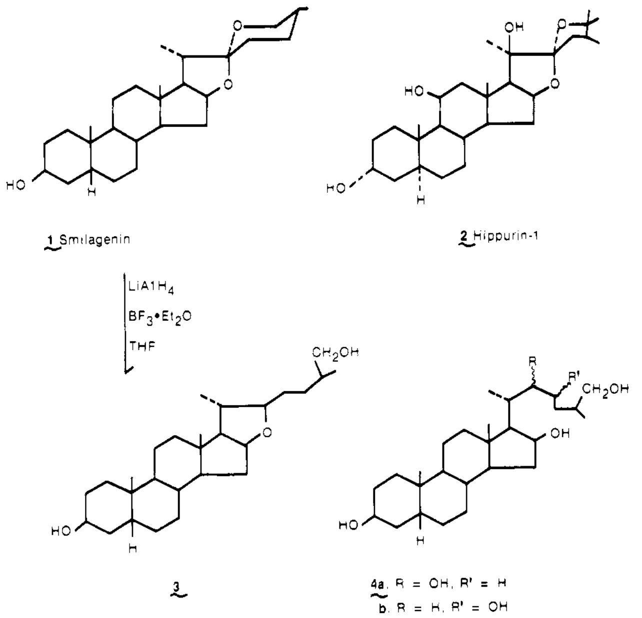
Synthesis of 3β,16β,23(*R*),26-Tetrahydroxy-5β-cholestane[1]

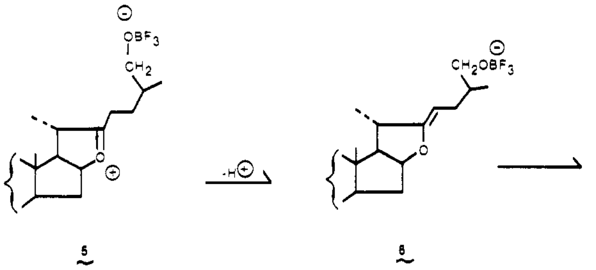
Sir:

Steroidal sapogenins[2] bearing spiro ketal systems such as smilagenin (**1**) are well-known plant constituents and even occur (cf. **2**) in certain marine animals.[3] Some 20 years ago we[4] found that a reagent prepared from lithium aluminum hydride and boron trifluoride in ethyl ether would readily cleave the spiro ketal unit to yield the corresponding dihydrosapogenin and a series of new products. For example, application of the reduction reaction to smilagenin (**1**) afforded dihydrosmilagenin (**3**) and a mixture of polyhydroxy steroids.[5] We now report that the latter substances correspond to the hitherto unknown and potentially important C-22 and C-23 epimeric tetraols **4a** and **4b**. The novel introduction of oxygen (presumably a new hydroboration sequence) was found to be general for such spiro ketal systems and is illustrated in the sequel utilizing smilagenin.



Boron trifluoride etherate (11 mL) in tetrahydrofuran (40 mL) was slowly (10–15 min) added to a cold (ice bath) mixture of smilagenin (**1**, 1.0 g) and lithium aluminum hydride (1.0 g) in tetrahydrofuran (50 mL). After 2 h the mixture was heated at reflux for 3 h, cooled, and allowed to stand at room temperature for 18 h. The reaction was terminated by addition of water (100 mL) and the boron-containing steroids and dihydrosmilagenin were isolated by extraction with ether. After solution in ethanol (10 mL) and addition of potassium hydroxide (1.0 g), water (0.5 mL), and hydrogen peroxide (1 mL, 30%), the mixture was warmed. The products were isolated by dilution with water, extraction with ether, and careful chromatographic separation (through silica gel columns in series at 50 psi, elution with 4:1 chloroform-acetone, and flame ionization detection). Recyrstallization using acetone-methanol led to dihydrosmilagenin (0.5 g), and two sets of tetrahydroxy sterols epimeric at C-22 (**4a,** 0.147 g of 22*R*, mp 137–138.5 °C, and 0.071 g of 22*S*, mp 115.5–119.5 °C, absolute configurational assignments provisional) and C-23 (**4b,** 0.241 g of 23*R*, mp 196–202.5 °C with sintering from 193 °C, and 0.050 g of 23*S*, mp 229.5–231 °C). Structural elucidation by X-ray crystallographic methods of the tetraol melting at 196–202.5 °C allowed the unequivocal assignment 3β,16β,23(*R*),26-tetrahydroxy-5β-cholestane (**4b,** 23*R*). Comparison and interpretation of other physical measurements (principally NMR and mass spectral), elemental composition, and chemical degradation (e.g., to 5β-cholestane) results for this substance with that obtained for the other isomers allowed the structural assignments noted above.

Based on our earlier mechanistic studies[6,7] concerned with metal hydride reduction of the steroidal sapogenin spiro ketal, the lithium aluminum hydride-boron trifluoride etherate catalyzed formation of dihydrosmilagenin (**3**) most probably proceeds by an intermolecular hydride insertion (**5** → **3**) from the least hindered side of intermediate **5** to yield the 22*R* derivative. The competitive production of tetraols **4a** and **4b** may



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