Regiocontrolled Coupling of (π-Allylic)palladium Complexes with Organozirconium Species

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Abstract: A carbon–carbon bond-forming reaction has been developed involving coupling between an alkenylzirconium(IV) complex, prepared by hydrozirconation of the corresponding terminal acetylene, and (η^3-allylic)palladium chloride dimers, prepared from olefins, to give 1,4 dienes. A stereospecific synthesis of 20(R)-cholestan-3-one is described. Bis(η^5-cyclopentadienyl)chloro(4′-methylpent-1′-en-1′-yl)zirconium reacts with di-μ-chloro-bis[η^3-16,17,20-(3-oxopregn-17(20)(Z)-en-16-yl ethylene ketal)]dipalladium in the presence of maleic anhydride. A mixture is obtained consisting of 1,4 dienes produced by addition of the alkenyl group to either the C(20) or C(16) terminus, respectively, of the allylic system. Hydrogenation of the C(20)-coupled product and deketalization yielded 20(R)-cholestanone exclusively. Transfer of the organic group from zirconium to palladium precedes carbon–carbon bond formation; this result is shown to be valid both in the presence and in the absence of added ligand. Coupled product thus obtained has stereochemistry opposite to that formed by stabilized anion attack on η^3-allylic complexes of palladium. The analogous sequence, starting from the epimeric di-μ-chloro-bis[η^3-16,17,20-(3-oxopregn-17(20)(E)-en-16-yl ethylene ketal)]dipalladium, yielded 20(S)-cholestanone exclusively. It was observed that regioselectivity of coupling depends on the nature of palladium ligands present. This phenomenon is rationalized by postulating the intermediacy of isomeric square-planar (η^3-allyl)palladium(alkenyl)(ligand) complexes, which subsequently reductively eliminate allyl–alkenyl (1,4 diene) with concomitant extrusion of palladium(0).

To efficiently and specifically form a C–C in place of a C–H bond at an allylic site of an olefin is a subject of continuing interest to synthetic organic chemists. One approach to this problem which has met with some success involves the activation of the allylic C–H bond by coordination of an olefin to a transition metal ion. Indeed, the use of (η^3-allylic)Pd complexes as synthetic intermediates has been exploited attractively and has resulted in high-yield regioselective and stereoselective transformations[1-4] in which the key C–C bond-forming step has been regarded as an S_N2-like attack by added nucleophile on a terminus of the allylic unit, on that face of the ligand *opposite* to that to which the metal is bound; the metal acts as a leaving group.[5] The scope of this procedure is limited: only stabilized anions can be employed; "harder" anions (anions of thioacetals, enolates of simple ketones, or esters), and certain organometallic species (e.g., lithium dimethylcuprate, methyllithium and alkylzinc derivatives) are reported not to lead to allylic addition products.[6]

In principle, organometallic reagents could react by attack *at Pd(II)* to yield an (allylic)Pd(II) intermediate which, on reductive elimination of the C–C bond, would give product of *opposite* configuration at the reactive allylic terminus to that obtained by the trans-nucleophilic attack described above. The formation of allylic C–C bonds by the reaction of (η^3-allylic) complexes of Pd(II) with organometallic systems has, in fact, been noted: thallium aryls[7] and dimethylcadmium are reported to achieve this reaction successfully.[6,8] These reactions were limited to transfer of simple groups and no studies aimed at elucidating the stereochemical path of carbon–carbon bond formation were reported. Organozirconium species have been noted to transfer an alkenyl ligand to Pd(II);[9] a transmetalation–reductive elimination sequence (see Scheme I, M = $Cp_2Zr(Cl)-$) invoving (η^3-allylic PdCl) species and organozirconium complexes could be utilized to generate a C–C bond. This scheme requires that the organic group derived from the organozirconium species be delivered to the *same* face of the allylic ligands to which the palladium is bound. For testing this hypothesis, the coupling reaction was employed in the synthesis of a steroidal product and a preliminary account of this work has appeared.[10]

Results

Synthesis and Characterization of Di-μ-chloro-bis[η^3-16,17,20-(3-oxopregn-17(20)(Z)-en-16-yl ethylene ketal)]dipalladium (6). Ketalization of 17β-hydroxy-5α-androstan-3-one (**1**) occurred under standard procedures to give the corresponding ketal **2** in 95% yield, which was then oxidized with pyridinium chlorochromate to give androstan-3,17-dione 3-ethylene ketal (**3**) in 96% yield. Wittig olefination with a slurry of potassium *tert*-butoxide and ethyltriphenylphosphonium bromide in THF gave 3-oxopregn-17(20)(Z)-ene ethylene ketal (**4**) contaminated with a trace of the (E) isomer (**5**) in 81% yield; **3** was also recovered in 12% yield.[11]

Solid bis(acetonitrile) dichloropalladium was added to a stirred suspension of sodium carbonate and sodium chloride in CH_2Cl_2 containing dissolved **4** (**5**) and 1,4,7,10,13-pentaoxacyclopentadecane (15-crown-5). This yielded di-μ-chloro-bis[η^3-16,17,20-(3-oxopregn-17(20)(Z)-en-16-yl ethylene ketal)]dipalladium (**6**) contaminated with 5–7% of the (E) isomer (**7**) in 96% isolated yield.[12] Crystallization from acetone/hexane gave pure **6**, and ^{13}C NMR data showed **6** to be a single compound. LC separation of the mother liquor also gave a pure sample of **7**.

Scheme III shows how purified **4** can afford both **6** and a trace of the epimeric **7**. The α attack (pathway a) is favored for steric reasons and affords the major product, **6**. The (Z)-(η^3-allylic)-palladium chloride dimer formed by β attack (pathway b) seems to be unstable under these reaction conditions. It is isomerized as shown in Scheme III to the more stable (E)-(η^3-allylic)palladium chloride dimer, **7**, in which the palladium is bonded to the less crowded α face. Indeed, we find that reduction of **7** with

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(2) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615.
(3) Trost, B. M.; Strege, P. E.; Weber, L.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3407.
(4) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.
(5) Åkermark, B.; Åkermark, G.; Hegedus, L. S.; Zetterberg, K. *J. Am. Chem. Soc.* **1981**, *103*, 3037.
(6) Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3416. Methylmagnesium bromide has been noted to *fail* in this reaction.
(7) Numata, S.; Kurosawa, H. *J. Organomet. Chem.* **1977**, *131*, 301.
(8) Castanet, Y.; Petit, F. *Tetrahedron Lett.* **1979**, 3221. Methylmagnesium bromide is noted to *succeed* in this reaction.
(9) (a) Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett.* **1977**, 1303. (b) Okukado, N.; Van Horn, D. E.; Klima, W. L.; Negishi, E. I. *Ibid.* **1978**, 1027.
(10) Temple, J. S.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 7381.
(11) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435.
(12) Published procedures were slightly modified: (a) Morelli, D.; Ugo, R.; Conti, F.; Donati, M. *Chem. Commun.* **1967**, 801. (b) Conti, F.; Donati, M.; Pregaglia, G. F.; Ugo, R. *J. Organomet. Chem.* **1971**, *30*, 421. (c) Ketley, A. D.; Braatz, J. *Chem. Commun.* **1968**, 169. (d) Jones, D. N.; Knox, S. D. *J. Chem. Soc., Chem. Commun.* **1975**, 165. (e) Collins, D. J.; Jackson, W. R.; Timms, R. N. *Aust. J. Chem.* **1977**, *30*, 2167.

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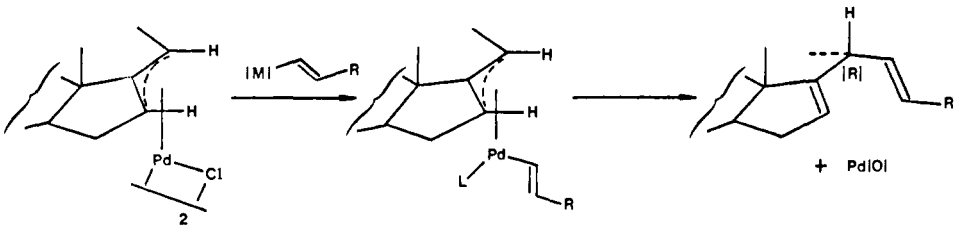
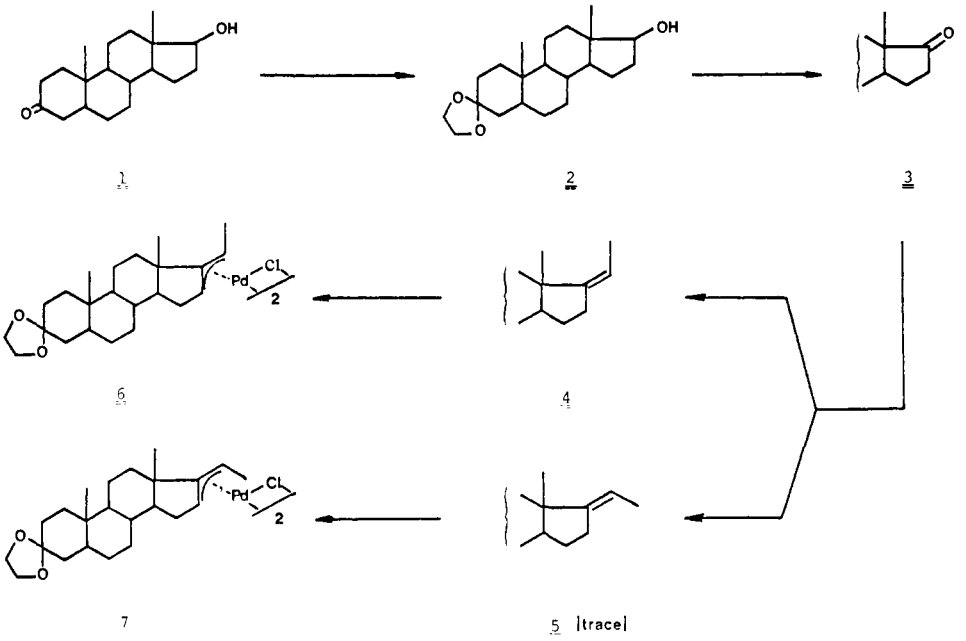
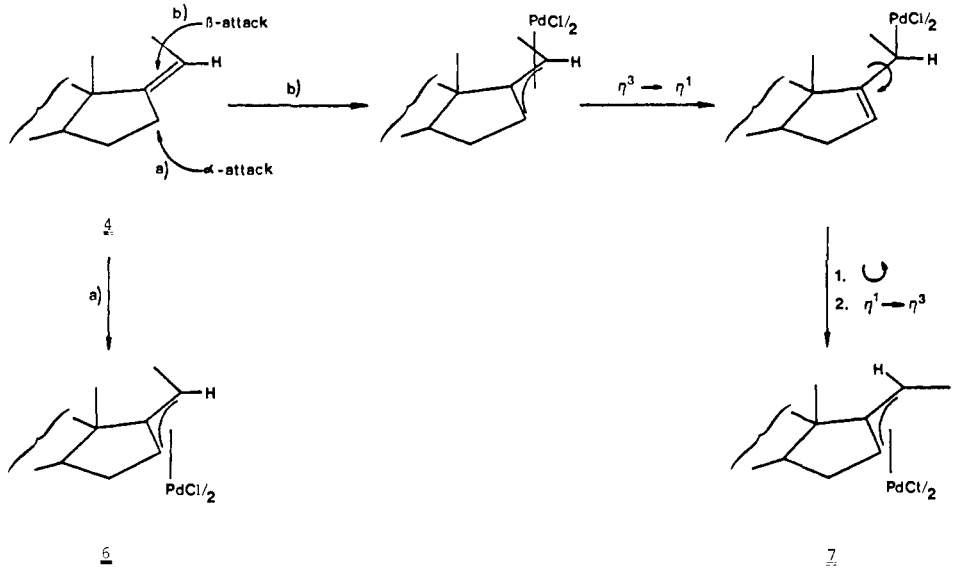
Scheme I



Scheme II



Scheme III

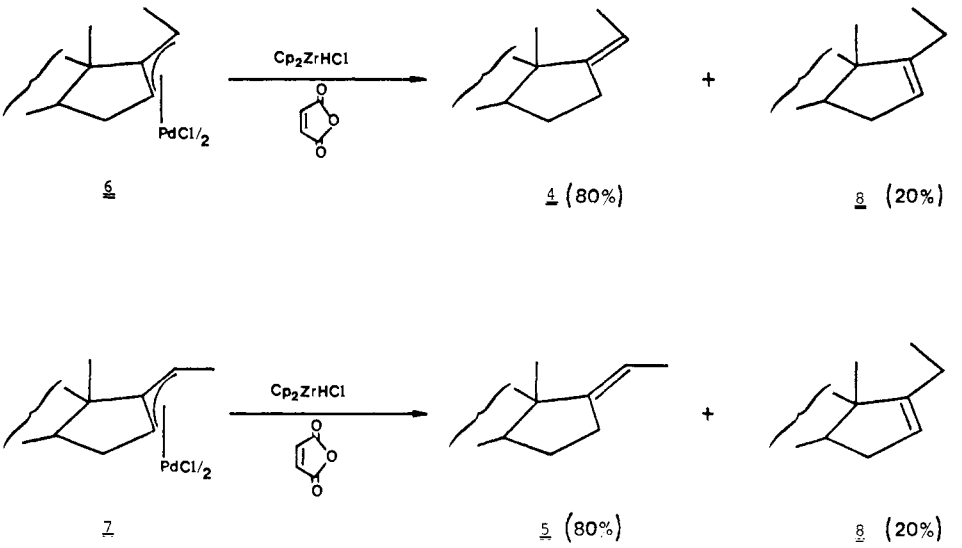


Cp_2ZrHCl affords olefin **5**, and reduction of **6**, affords olefin **4** [both contaminated with olefin **8** (20%)]. This proves that both (η^3-allylic)pallaldium chloride dimers **6** and **7** have the Pd bonded to the same face: the only difference is the stereochemistry at C(20).

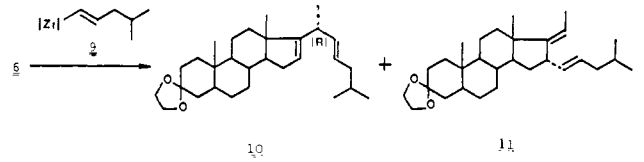
The Coupling Reaction betweeen 6 and 9. Synthesis of 20-(*R*)-Cholestan-3-one (14). With use of an optimized procedure, it was possible to obtain coupled products **10** and **11** in a ratio of 7:1 and to avoid formation of any uncoupled product. Equilibration of **6** (at −78 °C) with 3 equiv of maleic anhydride in THF was followed by dropwise addition (over 2 h) of a THF solution of **9**. The reaction mixture was allowed to warm to room temperature overnight; coupled product was isolated in 96% yield. Separation by a combination of crystallization and LC yielded **10** in 78% yield. Analysis by ^{13}C NMR showed that **10** and **11** were each single isomers, consistent with a stereospecific carbon–carbon bond-forming process.

Ligand Effects on Reductive Elimination Rates. The rate of overall coupling (at room temperature) is retarded by addition of a phosphine: in the presence of 4 equiv of triphenylphosphine, no trace of coupling was measured after 1 h at room temperature. In contrast, monitoring the reaction by ^1H NMR between **6** and

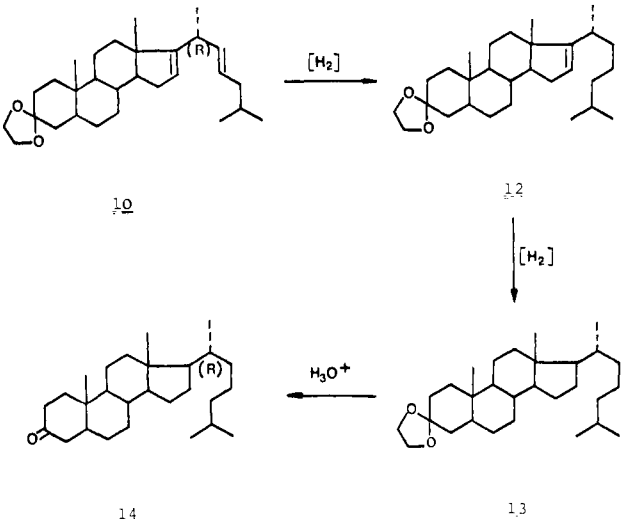
Scheme IV



Scheme V



Scheme VI

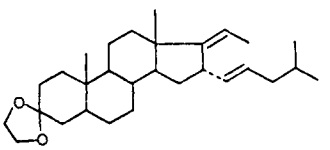


9 in the presence of maleic anhydride showed that coupling was complete (and that 1 equiv of Cp_2ZrCl_2 had been formed) in less than 5 min at −78 °C. In the absence of an added ligand, a mixture of coupled products **10** and **11** (51%, ratio 2:3) and noncoupled olefins **4** and **8** (34%) was formed. The origin of "noncoupled" olefins **4** and **8** was attributed to the fact that the intermediary Pd(II) species could undergo β-hydrogen elimination from the alkenyl ligand (to generate an allylic palladium hydride) at a rate competitive with reductive elimination of the 1,4 diene.

Coupling Regiochemistry. It was found that maleic anhydride or *p*-benzoquinone (π-acid ligands) promoted coupling preferentially at C(20). The effect of solvent (THF, acetonitrile, hexane, glyme, methylene chloride, or toluene) on the regiochemistry of the coupling reaction (in the presence of 3 equiv of maleic anhydride per palladium) was measured, but little solvent dependence was noticed. A temperature dependence of the coupling reaction performed in the presence of maleic anhydride was noted [**10**/**11** = 1.5 (25 °C), 5.0 (−40 °C), ≥7.0 (−78 °C)]. That the high regioselectivity obtained under optimized conditions results indeed from a ligand effect and not just from one of temperature was demonstrated by observations made in Pd-catalyzed coupling reactions of both simple and steroidal olefin-derived (allylic) complexes. Under *isothermal* conditions high selectivity for coupling at the less hindered terminus of the allylic unit occurred *only* in the presence of maleic anhydride; in its absence, or when a phosphine was used instead of it, no such high selectivity was noted.[13]

Completion of the Synthesis of the Steroid. Hydrogenation of **10** (via **12**) afforded the saturated ketal **13** which was hydrolyzed by refluxing in aqueous THF acidified with *p*-toluene sulfonic acid monohydrate. The product **14** was purified in 94% yield by LC. The spectral properties of this synthetic cholestanone, **14** (^{1}H and ^{13}C NMR, IR, MS), were identical with those of an authentic sample. Since steroids show ^{1}H and ^{13}C NMR chemical shifts which are sensitive to the configuration at C(20),[14] markedly different spectra would be expected for the 20(*R*) and 20(*S*) isomers of cholestan-3-one or its precursors. Indeed, we note[13] that the 20(*S*) isomer, **15**, displays C(21) methyl resonance at 1.13 (vs. δ 1.09 for **10**) and 20(*S*)-cholestan-3-one, **18**, at 0.81 (vs. δ 0.90 for **14**). NMR analysis showed no contamination by the 20(*S*) isomers in the preparation of **10** and **14**, respectively, described herein.

The Coupling Reaction between 7 and 9. Synthesis of 20-(*S*)-Cholestan-3-one (18). In the analogous reaction, starting from the (*E*) isomers of **7** and **9** in the presence of maleic anhydride, coupling occurred predominantly at C(20) over the temperature range −78 to 25 °C. ^{1}H NMR analysis of the crude coupling product, **15** (yield 85% at −78 °C or 89% at 25 °C), showed contamination by only a trace (≤5%) of C(16)-coupled product, **16**. *No temperature dependence of the coupling regioselectivity,*



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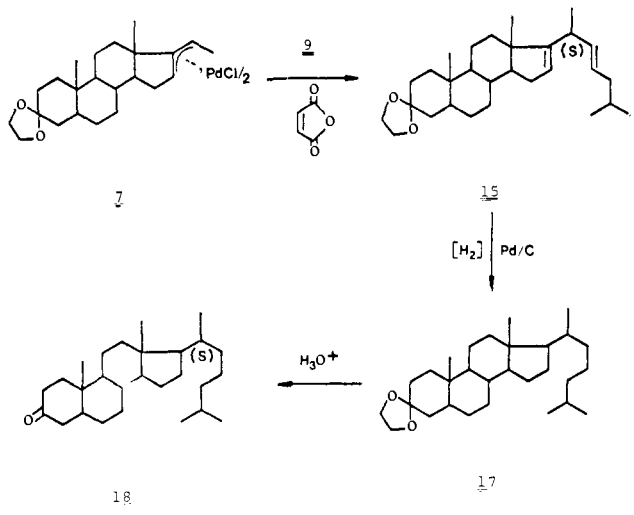
as described in the case of the (Z) isomer, **6**, *could be detected.* It should be pointed out that these products (**15** and **16**) were epimeric at C(20) with those formed (**10** and **11**) starting from

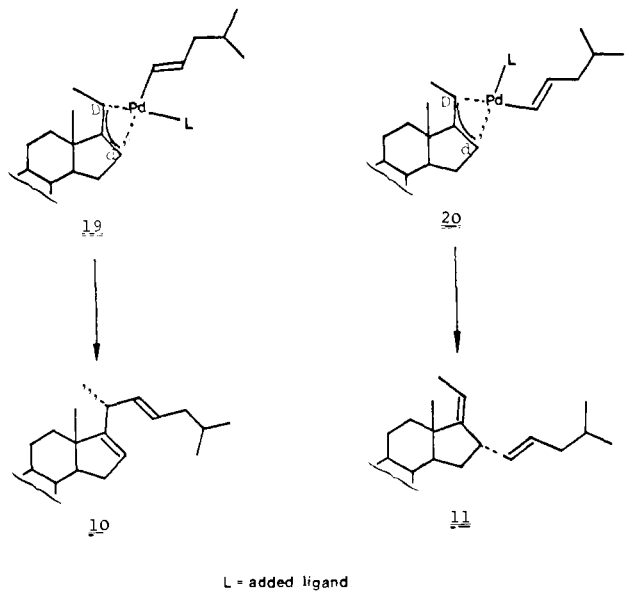
(13) Hayasi, Y.; Riediker, M.; Temple, J. S.; Schwartz, J. *Tetrahedron Lett.* **1981**, 2629.

(14) (a) Platak, D. M.; Wicha, J.; *Chem. Rev.* **1978**, *78*, 199. (b) Letourneux, Y.; Khuong-Huu, Q.; Gut, M.; Lukacs, G. *J. Org. Chem.* **1975**, *40*, 1674. (c) Van Antwerp, C. L.; Eggert, H.; Meakins, G. D.; Miners, J. O.; Djerassi, C. *J. Org. Chem.* **1977**, *42*, 789.

Scheme VII



Scheme VIII



the (η^3-allylic) palladium chloride dimer, **6**. Compounds **15** and **16** show markedly different C(21) methyl resonances from those in the corresponding compounds **10** and **11** (see Table II). NMR analysis of the crude product showed no contamination by a 20(*R*) isomer (**10** or **11**) in the preparation of **15** described herein.

Hydrogenation of **15** over Pd/C in ethanol yielded in 95% yield the saturated ketal, **17**, which was hydrolyzed by refluxing in aqueous THF acidified with *p*-toluenesulfonic acid monohydrate. The spectral properties of this synthetic 20(*S*)-cholestanone (**18**) were markedly different from those of the natural 20(*R*)-cholestanone (**14**) as shown in Table II. Structural determination was made by comparing the ^{1}H NMR data of **18** with published data of 3-hydroxy-20(*S*)-Δ^5-cholestane[15] (Table II) and by knowing the steric course of this coupling reaction as shown in the previous sections.

Discussion

Reductive Elimination. The reductive elimination of the 1,4 diene from its Pd(allylic)alkenyl precursor is assumed to be an intramolecular process by analogy with thermal studies of an (aryl)Pd(allylic) analogue.[7] Investigation[16] of the thermally induced formation of ethane from dimethyl Pd(II) systems has concluded that a cis orientation of the participating methyl groups is required.

The rate of the overall coupling reaction is dependent on the nature of the ligands for palladium and increases for L = PPh_3 < Cl–(Zr) < maleic anhydride, consistent with the notion that the metal center undergoes a formal reduction concomitant with carbon–carbon bond formation. A donor ligand should suppress this process; an acceptor ligand should enhance it.[6,7]

Ligand Effects on the Regiochemistry of Coupling. An acceptor ligand, L, can cause preferential coupling of an alkenyl group to the exocyclic C(20) terminus of the steroidal η^3-allylic ligand of **6**. Since coupling is believed to proceed with a cis geometry about the metal, the geometric distribution of ligands in the Pd(II) complexes immediately preceding formation of the carbon–carbon bond should determine the product ratio. The effect of an acceptor ligand on this distribution can be discussed with reference to simple bonding arguments for square-planar complexes.

An unsymmetrically substituted η^3-allylic ligand, by virtue of unsymmetrical bonding to the metal, should exert unequal trans influences[17] upon the other ligands, L(1) and L(2), in a square-planar complex; the thermodynamically favored situation would place the weaker σ donor (or stronger acceptor) ligands (L(1) or L(2) trans to the more strongly donating (closer) terminus of the allylic ligand.[18]

In η^3-allylic intermediates derived from **6**, palladium, with its complement of ligands, is postulated to be preferentially disposed toward the somewhat less sterically congested allylic terminus (the side chain one), so that the distance Pd–C(20) would be less than the distance Pd–C(16); in other words, the exocyclic C(20)–allylic terminus should exert a slightly stronger electron-donation interaction ("*D*") toward palladium than should the more sterically hindered endocyclic C(16)–allylic terminus ("*d*") (Scheme VIII). By this argument an acceptor ligand (maleic anhydride) should favor **19** and a donor (μ-Cl species) should favor **20**. Phosphine ligands are probably intermediate in their bonding properties;[19] barring large steric effects (for large cone angle phosphines), little regiochemical control might be expected of them. Coupling selectivities for reactions involving **6** and **7** are slightly different (although the effect of added ligand is the same); this suggests that the pattern of alkyl group substitution at the allylic termini affects relative crowding at them.[20,21]

Conclusions

Although ^{1}H and ^{13}C NMR spectral investigations (in CD_2Cl_2 at room temperature) of a solution of **6** and 1 equiv of maleic anhydride per palladium showed that the equilibrium between dimer **6** and any monomeric maleic anhydride adduct greatly favors the dimer, from a multitude of chemical observations it is clear that the maleic anhydride is indeed bound to Pd(II) in the coupling step itself:

(1) In the absence of added maleic anhydride, significant β-hydride elimination (which requires a vacant coordination site on palladium) occurs when **6** is treated with **9**; however, in the presence of maleic anhydride, β-hydride elimination is completely suppressed.

(2) The rate for reductive elimination of the carbon–carbon bond in the presence of maleic anhydride is greatly enhanced compared with that which is noted in the absence of the ligand. (At −78 °C in the absence of maleic anhydride, even though transmetalation from **6** is rapid, no carbon–carbon bond formation occurs. In contrast, in the presence of maleic anhydride, reductive

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(16) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933.
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(18) (a) Faller, J. W.; Incorvia, M. J. *J. Organomet. Chem.* **1969**, *19*, P13. (b) Faller, J. W.; Mattina, M. J. *Inorg. Chem.* **1972**, *11*, 1296.
(19) Cristoph, G. G.; Halpern, J.; Khare, G. P.; Koh, Y. B.; Romanowski, C. *Inorg. Chem.* **1981**, *20*, 3029.
(20) In the absence of crystallographic data for **6** and **7**, the mechanisms through which this is manifested can be discussed only speculatively.
(21) Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642.

Table I. NMR Data for Epimeric Olefins 4 and 5 and (η^3-Allylic)palladium Chloride Dimers 6 and 7

		H-C(16)	3 H-C(18)	H-C(20)	3 H-C(21)
C_6D_6	4		0.87	5.21	1.69
	5		0.77	5.14	1.59
$CDCl_3$	4		0.86	5.11	1.64
	5		0.72	5.01	1.53
C_6D_6	6	3.34	0.64	3.39	1.22
	7	4.09	0.57	4.18	0.93
$CDCl_3$	6	3.66	0.98	3.70	1.27
	7	4.38	0.89	4.28	1.11

elimination occurs rapidly even at −78 °C.)

(3) The regiochemistry of coupling in the presence of maleic anhydride is markedly different from that observed in its absence regardles of temperature.

Thus although the bulk of the initial mass balance of **6** is in equilibrium with only a minute proportion of monomer, **19** or **20** (where L = maleic anhydride), this monomer may be reactive enough to act as a funnel for the whole reservoir of **6**.

Experimental Section

General. All experiments, unless aqueous reagents were directly employed, were performed under an atmosphere of purified nitrogen. Solvents were distilled just prior to use, under nitrogen, from an appropriate drying agent.

Mass spectra are reported in the order: molecular ion (intensity), four highest peaks (intensities).

Elemental analyses were performed by Hoffmann-LaRoche, Inc., Nutley, NJ, or by Analytische Laboratorien Elbach, Englskirchen, Germany; molecular weight determinations were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Preparation of Alkenylzirconium Compound (9). This compound was prepared according to a published procedure.[22] ^{1}H NMR (C_6D_6) δ 6.64 (d, 1, J = 18 Hz), 5.71 (s, 10), 5.57 (m, 1), 1.87 (t, 2, J = 7 Hz), 1.60 (m, 1), 0.75 (d, 6, J = 7 Hz).

Preparation of 17β-Hydroxy-5α-androstan-3-one Ethylene Ketal (2).[11] A solution of 17β-hydroxy-5α-androstan-3-one (**1**) (Aldrich, 10.1 g, 37.7 mmol) in benzene (300 mL), to which ethylene glycol (4.0 g, 64.5 mmol) and p-toluenesulfonic acid monohydrate (0.120 g, 0.631 mmol) were added, was heated to reflux for 3 h in a flask equipped with a Dean-Stark trap. The pale pink reaction mixture was partitioned between ether and saturated aqueous $NaHCO_3$. The organic fractions were combined and dried over sodium sulfate and filtered and the solvent was removed in vacuo to give 11.0 g of **2** (95% yield). ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 4), 3.70 (t, 1, J = 7 Hz, 0.9–2.0 (m, 23), 0.85 (s, 3), 0.75 (s, 3).

Preparation of Androstan-3,17-dione 3-Ethylene Ketal (3). A solution of **2** (11.0 g, 32.9 mmol) in methylene chloride (100 mL) was added to a stirred suspension of pyridinium chlorochromate (20.4 g, 94.6 mmol) and anhydrous sodium acetate (3.25 g, 38.1 mmol) in methylene chloride (150 mL). After 2 h the mixture was diluted with anhydrous ether and passed through a column of florisil. The colorless organic fractions were concentrated and the residual oil was purified by HPLC to give 9.75 g of **3** (97% yield). ^{1}H NMR (CCl_4) δ 3.8 (s, 4), 0.95–2.5 (m, 22), 0.8 (s, 6).

Preparation of 3-Oxopregn-17(20)(Z)-ene Ethylene Ketal (4).[11] Potassium *tert*-butoxide (11.2 g, 100 mmol) and ethyltriphenylphosphonium bromide (25.5 g, 68.7 mmol) were stirred for 1 h in THF (200 mL). A solution of **3** (9.75 g, 29.34 mmol) in 50 mL of THF was added over 20 min, and the orange slurry was refluxed for 11 h. The reaction mixture was added to 150 mL of ice water, extracted with 5 × 30 mL of ether, and dried over magnesium sulfate. The solvent was removed to give a viscous oil whch was purified by LC to give **4** (8.17 g, 81% yield) and **3** (1.13 g, 11.6%). NMR analysis shows 4 to be contaminated by a trace of the (E) isomer, **5**. Compound **5** can be removed by a published procedure.

Preparation of Di-μ-chloro-bis[η^3-16,17,20-(3-oxopregn-17(20)(Z)-en-16-yl ethylene ketal)]dipalladium (6). Sodium chloride (3.5 g, 60 mmol), sodium carbonate (3.5 g, 33.0 mmol), 1,4,7,10,13-pentaoxacyclopentadecane (15-crown-5) (1.0 g, 4.5 mmol), and 4 (5.31 g, 15.43 mmol) were stirred in methylene chloride (200 mL) for 1 h. Bis(acetonitrile)dichloropalladium (5.5 g, 21.2 mmol) was added as a solid over 1 h, and the suspension was refluxed for 15 h. The crude reaction mixture was filtered through a pad of basic aluminum oxide (Beckman Activity grade 1), and the solid residue was washed with chloroform until the washings became colorless. The pale yellow fractions were combined and the solvent was removed in vacuo to give an orange oil which was purified by LC to yield **6** (7.179 g, 96% yield based on 4). NMR analysis showed **6** to be contaminated by a trace of the (E) isomer, **7**. A combination of crystallization (acetone/hexane) and LC (SiO_2, ether/hexane 1:2) gave pure samples of **6** and **7**.

6: ^{1}H NMR (C_6D_6) δ 3.60 (s, 4), 3.39 (q, 1, J = 7.6 Hz), 3.34 (br d, 1, J = 2.7 Hz), 1.22 (d, 3, J = 7.6 Hz), 0.9–2.1 (br m, 20), 0.64 (s, 6). Proton homonuclear decoupling shows that irradiation of the doublet (δ 1.22) caused the quartet (δ 3.39) to collapse to a singlet. ^{13}C NMR (CD_2Cl_2) δ 138.1 (C-3), 109.5 (C-17), 79.2 (C-20), 68.9 (C-16), 64.5 (ketal), 55.8, 54.6, 45.9, 44.1, 38.4, 36.6, 34.6, 32.0, 31.7, 31.4, 28.8, 21.6, 17.0, 14.4, 11.5. Off-resonance decoupling split δ 79.2, 68.9 into doublets and δ 64.5 into a triplet. δ 138.1, 109.1 remained singlets. IR (CCl_4) 2942, 2884, 2861, 1380, 1362; mp 215 °C dec.

7: ^{1}H NMR (C_6D_6) δ 3.60 (s, 4), 4.18 (q, 1, J = 6.6 Hz), 4.09 (br m, 1), 0.93 (d, 3, J = 6.6 Hz), 0.9–2.1 (br m, 20), 0.64 (s, 3), 0.57 (s, 3).

Reduction of 6 wtih Cp_2ZrHCl. A solution of 70 mg (0.144 mmol) of **6** and 43 mg (0.433 mmol) of maleic anhydride is 5 mL of THF was cooled to −78 °C. The hydride Cp_2ZrHCl (80% purity) (70 mg, 0.217 mmol) was added as a solid and the slurry was warmed to room temperature for 6 h. Evaporation of THF and LC (basic alumina, CH_2Cl_2) afforded 41 mg (0.199 mmol, 83% yield) of olefin as a 4:1 mixture of 4 and **8**. **8**: ^{1}H NMR (C_6D_6) δ 0.76 (s, 6, CH_3(18) + CH_3(19)), 1.08 (t, 3, J = 7 Hz, CH_3(21)), 3.60 (s, 4), 5.34 (m, 1, H-C(16)). The same reaction without maleic anhydride afforded a 1:1 mixture of **4** and **8**.

Reaction of 7 with Cp_2ZrHCl. The hydride Cp_2ZrHCl (35 mg, 0.108 mmol) was dissolved in 10 mL of THF and cooled to −78 °C. A solution of 20 mg (0.041 mmol) of **7** and 21 mg (0.21 mmol) of maleic anhydride in 5 mL of THF was added at once. Filtration through Celite and LC (basic alumina, activity III, CH_2Cl_2) afforded 13 mg (0.038 mmol, 92% yield) of olefin as a 4:1 mixture of **5** and **8**. The same reaction without maleic anhydride afforded a 1:1 mixture **5** and **8**.

Coupling Reactions of 6 with 9 in the Presence of Maleic Anhydride. Optimized Procedure. A THF (30 mL) solution of **9** (0.550 g, 0.618 mmol) was added over a period of 2 h to a solution of 560 mg (1.16 mmol) of **6** and 340 mg (3.46 mmol) of maleic anhydride in 250 mL of THF at −78 °C. The reaction mixture was allowed to warm to room temperature overnight. The THF solvent was removed in vacuo and the oily black residue was filtered through basic alumina (activity III, CH_2Cl_2) and finally purified by LC to give coupled steroidal product in 96% field. ^{1}H NMR integration of the C(18) methyl signals showed the ratio **10**/**11** to be ≥7.0. The mixture of coupled products was separated by fractional crystallization (ethanol/ethyl acetate) to give **10** in 52% yield. The mother liquor was separated by HPLC (vide supra) to give an additional 26% of **10** (78% combined yield of **10**). The mother liquor (18%) contained **10**/**11** in the ratio 0.5 (^{1}H NMR integration).

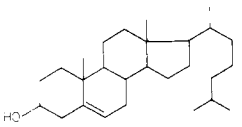
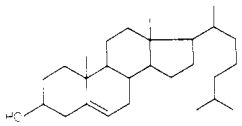
10: ^{1}H NMR ($CDCl_3$) δ 5.22–5.42 (m, 3), 3.92 (s, 4), 2.81 (br m, 1), 1.0–2.0 (br m, 23), 1.09 (d, 3, J = 8 Hz), 0.87 (d, 6, J = 6 Hz), 0.83 (s, 3), 0.77 (s, 3). Proton homonuclear decoupling showed that irradiation of the doublet (δ 1.09) caused the multiplet (δ 2.81) to sharpen. Irradiation of the multiplet (δ 2.81) caused the doublet (δ 1.09) to collapse to a singlet and the olefinic multiplet (δ 5.22–5.42) to sharpen dramatically. ^{13}C NMR ($CDCl_3$) δ 160.5, 137.4, 127.4, 122.1, 109.9, 78.9, 64.6, 58.1, 55.2, 47.6, 44.4, 42.3, 38.5, 36.6, 36.4, 36.2, 35.6, 34.6, 32.3, 31.7, 31.5, 29.1, 22.9, 22.8, 21.5, 21.4, 17.0, 11.9; IR (CCl_4) 975 cm^{-1}; mp 92–93 °C. Anal. ($C_{29}H_{46}O_2$) C, H. Mass spectra 426 (19), 315 (100), 99 (74), 125 (23), 411 (20).

11: ^{1}H NMR (C_6D_6) δ 5.46 (br m, 2), 5.32 (d × q, 1, J = 2 × 7 Hz), 3.60 (s, 4), 3.17 (br m, 1), 1.74 (d × d, 3, J = 1.7 × 7 Hz), 1.2–2.3 (br m, 23), 0.92 (d, 6, J = 6 Hz), 0.92 (s, 3), 0.74 (s, 3). Proton homonuclear decoupling showed that irradiation of the multiplet (δ 3.17) caused the broad doublet (δ 1.74) to sharpen and also caused the olefinic quartet (δ 5.32) to sharpen. Irradiation of the olefinic region caused the multiplet (δ 3.17) to sharpen and the broad doublet (δ 1.74) to collapse to a broad singlet. Irradiation of the broad doublet (δ 1.74) caused the multiplet (δ 3.17) to sharpen and the quarted (δ 5.32) to collapse to a broad singlet. ^{13}C NMR (C_6D_6) δ 136.9, 127.7, 116.0, 109.4, 64.2, 54.3, 53.7, 46.0, 45.2, 43.8, 42.2, 38.7, 37.8, 36.3, 35.8, 35.3, 34.4, 32.6, 32.2, 32.1, 31.9, 28.9, 22.5, 21.7, 21.2, 17.6, 13.4, 11.5; IR (CCl_4) 972 cm^{-1}. Mass calcd for $C_{29}H_{46}O_2$: 426.3498. Found: 426.3497 ± 0.0021. Mass spectra 426 (37), 99 (100), 411 (50), 397 (40), 125 (29).

Hydrogenation of 10. A suspension of platinum oxide (Adams catalyst, 0.023, g, 0.1 mmol) in 20 mL of ethyl acetate was stirred for 2 h under 1 atm of hydrogen. Crystals of **10** (0.0553 g, 0.13 mmol) were added, and hydrogenation was continued for 26 h under 100 psig H_2 in a Fisher-Porter apparatus. The solution was filtered and the solvent was removed, yielding 20(R)-cholestan-3-one ethylene ketal, **13**, as a crude

(22) (a) Carr, D. B. Ph.D. Dissertation, Princeton University, Princeton, N.J., 1978. (b) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1979**, *101*, 3521.

Table II. NMR Data of the C(20) Epimeric Compounds

		H–C(16)	3 H–C(18)	H–C(20)	3 H–C(21)
C_6D_6	**10**	5.44	0.88	2.91	1.23
	15	5.43	0.83	2.86	1.25
$CDCl_3$	**10**	5.31	0.77	2.81	1.09
	15	5.32	0.77	2.78	1.13
C_6D_6	**11**	3.17	0.92	5.32	1.74
	16	3.30	0.82	5.31	1.60
$CDCl_3$	**11**	3.01	0.90	5.06	1.67
	16	3.23	0.76	5.15	1.53
C_6D_6	**14**		0.64		1.00
	18		0.66		0.91
$CDCl_3$	**14**		0.68		0.90
	18		0.67		0.81
$CDCl_3$			0.69		0.91 (ref 15)
$CDCl_3$			0.69		0.81 (ref 15)

solid (0.0559 g), identified by ^1H NMR comparison with an authentic sample.

13: ^1H NMR (C_6D_6) δ 3.60 (s, 4), 0.85–2.05 (m, 40), 1.00 (d, 3, J = 6 Hz), 0.93 (d, 6, J = 6 Hz), 0.76 (s, 3), 0.66 (s, 3); mass spectra 430 (11), 99 (100), 125 (31), 112 (14), 100 (14). When the reaction was stopped after 2 h, the 16(17)-monoolefin, **12**, could be recovered.

12: ^1H NMR ($CDCl_3$) vinylic resonance (1 H) seen as a multiplet at δ 5.18–5.26; mass spectra 428 (2), 99 (100), 315 (40), 55 (34), 43 (30).

Hydrolysis of 13: The crude solid, **13**, obtained by hydrogenation of **10**, was dissolved in THF (15 mL) to which *p*-toluenesulfonic acid monohydrate (0.010 g, 0.053) mmol) and distilled water (2 mL) had been added and refluxed for 20 min. The reaction mixture was cooled to room temperature, diluted with 20 mL of ether, and washed with 2 × 10 mL of saturated aqueous $NaHCO_3$ and 3 × 10 mL of water, and dried over magnesium sulfate. Evaporation of ethyl acetate/ether and subsequent LC purification yielded 5α-20(*R*)-cholestan-3-one, **14** (0.0584 g, 94% yield based on **10**). The IR and ^1H NMR spectra of **14** were superimposable with those of an authentic sample; the ^{13}C NMR chemical shifts were identical with the nearest δ 0.1. ^1H NMR (C_6D_6) δ 0.8–2.2 (br m, 31), 1.00 (d, 3, J = 7 Hz, 0.93 (d, 6, J = 6 Hz), 0.64 (s, 6); ^{13}C NMR (C_6D_6 δ 208.4, 56.8, 56.5, 54.0, 46.6, 44.8, 42.9, 40.3, 40.0, 38.6, 38.2, 36.7, 36.2, 35.6, 32.0, 29.2, 28.6, 28.4, 24.5, 24.4, 23.0, 22.8, 21.7, 19.1, 12.3, 11.3; IR (CCl_4) 1719 cm^{-1} (strong, sharp); mass spectra 386 (16), 43 (100), 55 (90), 41 (82), 231 (78); mp 128.0–129.0 °C; mmp 128.0–129.0 °C.

Reaction of 7 with 9 in the Presence of Maleic Anhydride. A solution of 51 mg (0.0105 mmol) of **7** and 31 mg (0.315 mmol) of maleic anhydride in 8 mL of THF was added in a period of 60 min to a solution of 138 mg (0.404 mmol) of **9** in 5 mL of THF at −78 °C. The reaction mixture was allowed to warm to room temperature overnight. The THF solvent was removed in vacuo; the oily black residue was filtered through basic alumina (activity III, CH_2Cl_2) and finally purified by LC to give 38 mg (0.089 mmol, 85% yield) of coupled steroidal product, **15**. ^1H NMR showed **15** to be contaminated only by a trace (≤5%) of C(16)-coupled product, **16**.

5α-20(*S*)-Cholesta-16(17),22(23)-dien-3-one ethylene ketal (15): ^1H NMR ($CDCl_3$) δ 0.77 (s, CH_3 (18)), 0.83 (s, CH_3 (19)), 0.87 (d, 6, J = 6 Hz), 1.13 (d, J = 7 Hz, CH_3 (21)), 2.78 (m, H–C(20)), 3.92 (s, 4), 5.32 (m, H–C(16) + H–C(22) + H–C(23)); ^1H NMR (C_6D_6) δ 0.76 (s, CH_2 (19)), 0.83 (s, CH_2 (18)), 0.91 (d, 6, J = 6 Hz), 1.25 (d, J = 7 Hz, CH_2 (21)), 2.86 (m, H–C(20)), 3.59 (s, 4), 5.43 (m, H,–C(16) + H–C(22) + H–C(23)).

5α-Pregna-16-(4′-methylpent-1′-en-1′-yl)-17(20)-en-3-one ethylene ketal (16): ^1H NMR ($CDCl_3$) δ 0.76 (s, CH_3 (18)), 0.82 (s, CH_3 (19)), 0.86 (d, 6, J = 7 Hz), 1.53 (d × d, J = 1 Hz, J' = 7 Hz, CH_3 (21)), 3.23 (m, H–C(16)), 3.92 (s, 4), 5.15 (d × q, J = 2.5 Hz, J' = 7 Hz, H–C-(20)), 5.32 (m, 2); ^1H NMR (C_6D_6) δ 0.74 (s, CH_3 (19)), 0.82 (s, CH_3 (18)), 0.91 (d, 6, J = 6 Hz), 1.60 (d × d, J = 1 Hz, J' = 7 Hz, CH_3 (21)), 3.30 (m, H–C(16)), 3.59 (s, 4), 5.31 (d × q, J = 2.5 Hz, J' = 7 Hz, H–C(20)), 5.45 (m, 2). The same reaction at room temperature starting from 32 mg (0.066 mmol) of **7** afforded 25 mg (0.059 mmol, 89%) of coupled steroidal product, **15**, contaminated only by a trace (<5%) of C(16)-coupled product, **16**.

Hydrogenation of 15. A suspension of 27 mg of 5% Pd/C in 6 mL of EtOH was stirred for 1 h under 1 atm of hydrogen. Compound **15** (33 mg, 0.078 mmol) was added, and stirring was continued for another 4 h under 1 atm of hydrogen. The solution was filtered and the solvent was removed, yielding 32 mg (0.074 mmol, 95%) of 5α-20(*S*)-cholestan-3-one ethylene ketal (**17**). ^1H NMR ($CDCl_3$) δ 0.65 (s, CH_3 (18)), 0.81 (s, CH_3 (19)), 0.81 (d, J = 6 Hz, CH_3 (21)), 0.87 (d, 6, J = 6.4), 3.92 (s, 4); ^1H NMR (C_6D_6) δ 0.67 (s, CH_3 (18)), 0.75 (s, CH_3 (19)), 0.91 (d, J = 6 Hz, CH_3 (21)), 0.93 (d, 6, J = 6 Hz), 3.59 (s, 4).

Hydrolysis of 5α-20(*S*)-Cholestan-3-one Ethylene Ketal (17). The crude solid, **17** (32 mg, 0.074 mmol), obtained by hydrogenation of **16** was dissolved in THF (15 mL), to which *p*-toluenesulfuric acid monohydrate (0.010 g, 0.053 mmol) and distilled water (2 mL) had been added, and refluxed for 20 min. The reaction mixture was cooled to room temperature, diluted with 20 mL of ether, washed with 2 × 10 mL of saturated aquesous $NaHCO_3$, and dried over magnesium sulfate. Evaporation of solvent and subsequent LC purification yielded 5α-20-(*S*)-cholestan-3-one (**18**) (27 mg, 0.070 mmol, 95%). ^1H NMR ($CDCl_3$) δ 0.67 (s, CH_3 (18)), 0.81 (d, J = 6 Hz, CH_3 (21)), 0.87 (d, 6, J = 6 Hz), 1.00 (s, CH_3 (19)); ^1H NMR (C_6D_6) δ 0.64 (s, CH_3 (19)), 0.66 (s, CH_3 (18)), 0.91 (d, J = 6 Hz, CH_3 (21)), 0.93 (d, 6, J = 6 Hz).

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Registry No. 1, 521-18-6; **2**, 1046-35-1; **3**, 1046-36-2; 4, 67493-93-0; **5**, 80594-48-5; **6**, 80657-80-3; **7**, 80657-39-2; **8**, 80584-67-4; **9**, 75862-51-0; **10**, 80655-82-9; **11**, 80629-89-6; **12**, 80584-68-5; **13**, 1858-14-6; **14**, 566-88-1; **15**, 80629-90-9; **16**, 80629-91-0; **17**, 80629-92-1; **18**, 80629-93-2; Cp_2ZrHCl, 37342-97-5; maleic anhydride, 108-31-6.