hedron Lett., 3019 (1972); J. Meinwald, A. M. Chalmers, T. E. Pliske, and T. Eisner, Chem. Commun., 86 (1969).
(16) B. M. Trost and L. S. Melvin Jr., J. Am. Chem. Soc., 98, 1204 (1976).
(17) E. J. Corey, N. W. Gilman, and B. E. Ganem, J. Am. Chem. Soc., 90, 5616 (1968).
(18) (a) O. P. Vig, J. C. Kapur, J. Singh, and B. Vig, Indian J. Chem., 674 (1969); (b) B. A. Nagasampagi, L. Yankov, and S. Dev, Tetrahedron Lett., 189 (1967).
(19) For alternative syntheses of geranylgeraniol, see L. Ruzicka and G. Firmenich, Helv. Chim. Acta, 22, 392 (1939); A. Caliezi and H. Schinz, Helv. Chim. Acta, 35, 1649 (1952); J. N. Nazarov, B. P. Gussev, and V. I. Gunar, Zh. Obshch. Khim, 28, 1444 (1958) (Chem. Abstr., 53, 1102i (1959)); L. J. Altman, L. Ash, R. C. Kowerski, W. W. Epstein, B. R. Larsen, H. C. Rilling, F. Muscio, and D. E. Gregonis, J. Am. Chem. Soc., 94, 3257 (1972).
(20) Y. Takahashi, S. Sakai, and Y. Ishii, Chem. Commun., 1092 (1967); Y. Takahashi, K. Tsukiyama, S. Sakai, and Y. Ishii, Tetrahedron Lett., 1913 (1970).
(21) M. Julia and J. M. Paris, Tetrahedron Lett., 4833 (1973).

Stereocontrolled Approach to Steroid Side Chain via Organopalladium Chemistry. Partial Synthesis of 5α-Cholestanone

Barry M. Trost* and Thomas R. Verhoeven

Contribution from the Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received October 20, 1977*

Abstract: Stereocontrolled introduction of an acyclic unit onto a cyclic system was accomplished using π-allylpalladium chemistry. Using stoichiometric palladium chemistry, methyl 3-methoxy-19,24-bisnor-20-isocholane-1,3,5(10)-tetraenoate was synthesized from estrone methyl ether. Thus, steroids epimeric at C(20) to the natural series are available from the 17-keto compounds. Alternatively, steroids possessing the natural configuration at C(20) are available from the starting materials via a catalytic palladium reaction. Estrone methyl ether was converted to methyl 3-methoxy-19,24-bisnorcholane-1,3,5(10)-tetraenoate. A partial synthesis of 5α-cholest-24-enone and 5α-cholestanone was achieved from testosterone.

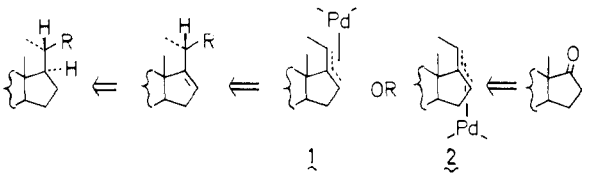
Introduction

The total synthesis of steroids represents one of the great challenges to synthetic chemists and has culminated in several elegant and practical approaches to this ring system.[1,2] One problem in steroid synthesis that has received considerably less attention is the stereocontrolled introduction of the cholesteryl side chain. The importance of this problem is heightened by the interest in ecdysones (insect molting hormones), the metabolites of vitamin D, and other unusual steroids possessing substituted side chains. Biosynthetic and metabolism studies of cholesterol have generated a need for modified side chains. Furthermore, the stereocontrolled attachment of an acyclic side chain onto a ring system constitutes an oftentimes encountered problem. The methodology developed for the steroid system should have broader applicability.

The problem factors down into two major concerns—(1) the ability to add the necessary carbon framework with appropriate substitution for further elaboration and (2) the creation of stereochemistry at C(17) and C(20). To circumvent the latter difficulty, several approaches have used a bisnorcholanic acid derivative in which both these centers already exist in the proper stereochemistry.[3] Indeed, a recent synthesis of a 24,25-dihydroxy system employed this strategy.[4] The center at C(17) is not a major problem since catalytic reduction of Δ^{16} or $\Delta^{17(20)}$ steroids does introduce hydrogen in the 17α configuration.[5] The main difficulty rests in the creation of C(20).

Reduction of $\Delta^{17(20)}$ or $\Delta^{20(22)}$ unsaturated steroids has led to the *R* configuration at C(20) with varying degrees of control.[5,6] Most recently, the formation of the (*E*)-$\Delta^{20(22)}$ unsaturated isomer via a wittig reaction on a 17-acetyl steroid followed by catalytic hydrogenation has been claimed to give only the natural configuration at C(20),[7] although this has been questioned.[7c] Alkylation of the enolate of a 17β-carbomethoxymethyl steroid with 4-methylpentyl bromide is also reported to give a single epimer.[8] A most elegant solution to the problem involved the introduction of the side chain with correct stereochemistry via a Claisen–Johnson rearrangement concomitant with creation of the D ring.[9]

The fact that the reduction of Δ^{16} unsaturated steroids provides the desired configuration at C(17) allows simplification of the problem to one of allylic alkylation with stereochemical control at an acyclic carbon. Using palladium as a template to provide conformational rigidity to direct the stereochemistry appeared to be a reasonable approach to the general problem of stereocontrol in conformationally nonrigid (e.g., acyclic or macrocyclic) systems. Depending upon the stereochemistry of formation of the new C–C bond with the complexed species, either **1** or **2** would be required. The requisite complexes should be available from olefination procedures on a C(17) ketone. Indeed, the ready availability of 17-keto steroids makes them most attractive as starting materials. We, therefore, undertook an investigation of the stereochemistry of alkylation of π-allylpalladium complexes which has resulted in the ability to form either epimer.[10]



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Results

Our investigation began with estrone methyl ether (**3**) which was converted to the 17-ethylidene derivative **4** via the Wittig reaction.[11] We find that use of potassium *tert*-butoxide in refluxing THF to be the better conditions (81%) compared with dimsylsodium in Me_2SO (5%) in our hands. The *Z* configuration is assigned in analogy to the literature. A small amount of the *E* isomer is detectable in the NMR spectrum (δ 0.78) of the crude mixture which was removed in the subsequent

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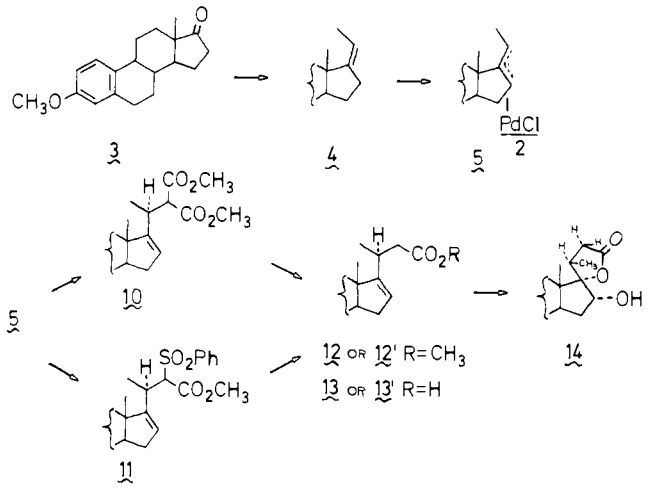
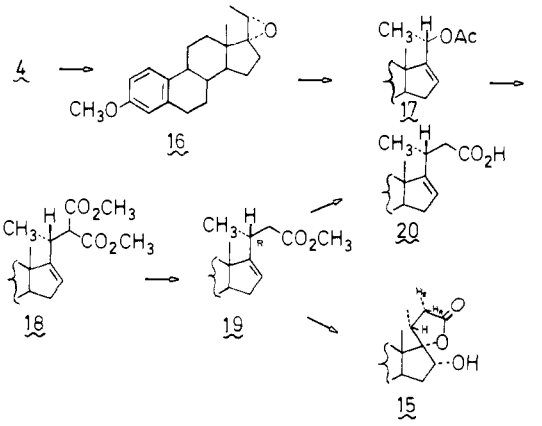
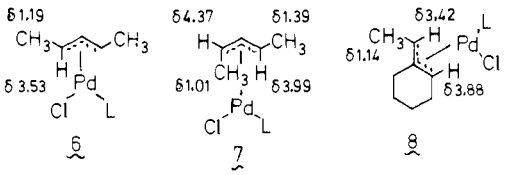
Scheme I. Preparation and Alkylation of Bis[chloro(16,17,19-η^3-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene)palladium(II)]

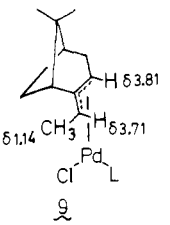


Scheme II. Preparation and Alkylation of (20*S*)-3-Methoxy-acetoxynorpregna-1,3,5(10),16-tetraene (17)



recrystallization. Treatment with sodium tetrachloropalladite under our standard conditions[12] gave the π-allylpalladium complex **5** in 67% isolated yield. NMR spectroscopy allows the assignment of the syn stereochemistry.[13] In particular, anti protons or methyl groups are shielded by the palladium relative to the syn substituents. Thus, in complexes **6** and **7** this effect

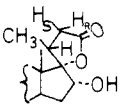




is clearly seen and is independent of ligand.[13c] The stereochemistry of **9** has been independently established by x-ray crystallography.[14] In **5**, the signals for the methyl protons, H_a, and H_b appear at δ 1.26, 3.56, and 3.74—in excellent accord with the shifts expected for the syn *not* anti isomer. The assignment of the palladium on the α face is based upon steric considerations and the fact the absorption for the angular methyl group (δ 1.00) is almost the same as in the starting olefin **4**. A strong shielding by palladium would be expected if it were on the β face.

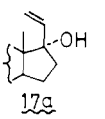
Alkylation of **5** required activation by phosphorus ligands.[15] While triphenylphosphine, hexamethylphosphorous triamide, and bis(1,2-diphenylphosphino)ethane (**6**) can be employed, best results were obtained with the bidentate ligand **6**. Both the sodium salt of dimethyl malonate and methyl phenylsulfonylacetate led to alkylation exclusively at C(20) to give **10** and **11** in 81 and 82% yield, respectively. To determine the configuration at C(20), **10** was decarbomethoxylated to **12** with lithium iodide–sodium cyanide in hot DMF (46%)[16] or preferably with tetramethylammonium acetate in HMPA at 100 °C (87–91%).[17] Desulfonylation of **11** with calcium in refluxing liquid ammonia gave a compound **12′** identical by NMR and IR spectroscopy with that obtained by decarbomethoxylation of **10**. Because of the known difficulty in differentiating isomers at C(20), both samples of **12** (i.e., **12** and **12′**) from **10** and **11**, respectively, were hydrolyzed to the crystalline acids **13** and **13′** (Scheme I). The melting points of the two samples were identical, but, most significantly, the mixture melting (which ultimately proved to be the best technique to differentiate the C(20) isomers) led to no depression.

To discern the stereochemistry, hydroxylation and lactonization gave the crystalline hydroxy lactone **14** (mp 250–251 °C). On the basis of cis-α-hydroxylation, the stereochemistry at C(16) and C(17) is assigned as shown. Europium(+3) induced shifts differentiates between 20*S* and 20*R*. In particular, in the 20*S* configuration, the C(21) methyl group should be more deshielded than the C(18) methyl group because of its closer proximity to the europium which complexes preferentially to the hydroxyl group. On the other hand, in the 20*R* isomer **15**, the distances for nearest approach for the C(18) and



C(21) methyl groups are ~4.8 and 5.0 Å (from Dreiding models) and similar shifts are anticipated (vide infra). Table I summarizes the shift data which clearly attest to the *S* configuration. Thus, alkylation of the π-allyl complex proceeds on the face opposite palladium.[14]

An alternative approach to allylic alkylation generates the intermediate π-allylpalladium complex from allylic derivatives such as allylic acetates upon treatment with a palladium(0) complex.[18,19] For this approach, the allylic acetate must be available in a stereocontrolled fashion. Scheme II outlines the sequence. Epoxidation gives a single crystalline (mp 90.5–92 °C) epoxide **16** in quantitative yield assigned the α configuration based upon steric approach control. Base catalyzed epoxide ring opening was sensitive to reaction conditions.[20,21] In most cases, a mixture of **17** and the vinyl alcohol **17a** re-



sulting from anti-Markownikoff elimination toward the methyl group was observed. However, addition of 5 equiv of lithium diethylamide in hexane to a solution of **16** in hexane containing 2 equiv of HMPA gave a 74% yield of a homogeneous crystalline acetate (mp 124.5–126 °C) after workup with acetyl chloride. The stereochemistry at C(20) is unaffected by this reaction and thus can be assigned *S*.

Addition of the allylic acetate to a THF solution of tetrakis(triphenylphosphine)palladium and excess triphenylphos-

Table I. Eu(dpm)$_3$[a] Induced Proton Shifts[b] on **14**

Substituent	% Eu(dpm)$_3$ 0	3.3	7.8	11.0	16.7	23.4	33.4	Total shift, Hz
C-18 methyl	0.80	0.82	0.85	0.92	1.06	1.32	1.67	87
C-21 methyl	1.27	1.27	1.33	1.45	1.65	2.02	2.57	130
C-16 methine	4.53	4.64	4.92	5.32	6.10	7.20	9.40	487

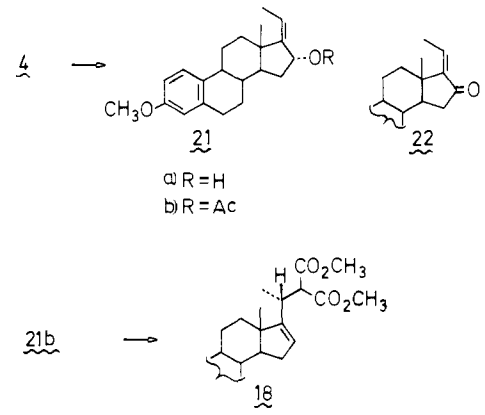
[a] Europium tris(dipivaloylmethide). [b] All shifts are in parts per million internal Me_4Si at 100 MHz unless otherwise stated.

Table II. Eu(dpm)$_3$[a] Induced Proton Shifts[b] on **15**

Substituent	% Eu(dpm)$_3$ 0	0.9	2.6	8.0	11.6	15.2	17.0	22.4	30.0	Total shift, Hz
C-18 methyl	0.96	0.96	0.97	1.11	1.15	1.22	1.32	1.47	1.81	85
C-21 methyl	1.15	1.16	1.19	1.30	1.37	1.44	1.53	1.67	1.98	83
C-16 methine	4.30	4.33	4.40	5.26	5.50	5.96	6.53	7.51	9.39	509
21-H_R	3.19	3.20	3.26	3.78	3.91	4.18	4.50	5.05	6.17	298

[a] Europium tris(dipivaloylmethide). [b] All shifts are in parts per million from internal Me_4Si at 100 MHz unless otherwise stated.

Scheme III. Preparation and Alkylation of (*Z*)-3-Methoxy-16α-acetoxynorpregna-1,3,5(10),17(20)-tetraene

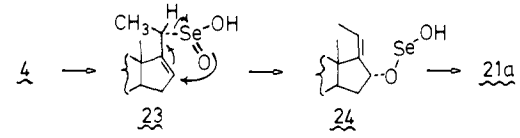


phine at room temperature followed by addition of a solution of dimethyl sodiomalonate in THF led after refluxing for 20 h to an 83% yield of a homogeneous alkylation product **18**. However, the great similarity of its properties, chromatographic and spectroscopic, to those of **10** did not allow us to conclude their identity or nonidentity. Decarbomethoxylation using the tetramethylammonium acetate procedure produced **19** whose properties also very closely resembled those of **12**. Hydrolysis led to a crystalline carboxylic acid whose melting point (162.5–164 °C) was virtually identical with that of **13**; however, a mixture melting point led to a severe melting point depression (mmp 139–155 °C). *Thus, alkylation via the catalytic procedure gave a different stereochemistry from and complementary stereochemistry to that from the stoichiometric procedure!*

To confirm the epimeric nature of **19**, it was converted to the hydroxy lactone **15**, mp 202–203 °C, which was clearly quite distinct in its properties from those of **14**. Most significantly, the europium(+3) induced ^1H NMR shifts (see Table II) gave a similar overall shift of the 18- and 21-methyl groups as expected (vide supra). In this case the H_R proton at C(21) could be easily discerned as a dd (J = 16, 7 Hz) at δ 3.19. The fact that it shifts ~3.5 times more than the C-21 methyl group confirms the conclusion based upon the relative shifts of the two methyl groups.

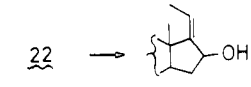
To confirm the catalytic activity of the palladium(0) complex, a control experiment involved alkylation of **17** under identical conditions but in the absence of the complex. Only elimination product was observed, it being formed at a very slow rate. It is interesting to note the regiospecificity of this allylic alkylation. The fact that the new carbon–carbon bond formed at the same carbon that bore acetate raised the question of the intermediacy of a true π-allylpalladium complex. To answer this question the allylically related acetate **21b** was synthesized and alkylated (see Scheme III).

Oxidation of olefin **4** with selenium dioxide[22] gave the allylic alcohol **21a** in 65% yield contaminated by the corresponding



ketone **22** (26% yield). The alcohol was directly converted to the allylic acetate **21b** (mp 108–109 °C) in usual fashion. The stereochemistry of **21b** was assigned on the basis of NMR spectroscopy and mechanistic considerations. The *Z* configuration of the olefin was clearly indicated by the similarity of the proton shifts. In particular, the C(18) and C(21) methyl groups experience a deshielding due to steric compression in the *Z* isomer compared to the *E* isomer. For example, **4** exhibits the C(18) methyl at δ 0.92, whereas the corresponding *E* isomer exhibits this methyl group at δ 0.79. The appearance of the 18- and 21-methyl groups of **21b** (δ 0.90 and 1.74) at virtually the identical positions with those of **4** suggests the same olefin configuration. Europium(+3) induced shifts (18.8 mol %) also support this assignment since the vinyl proton at C(20) ($\Delta\delta$ = 240 Hz) shifts four times more than the 21-methyl group ($\Delta\delta$ = 59 Hz).

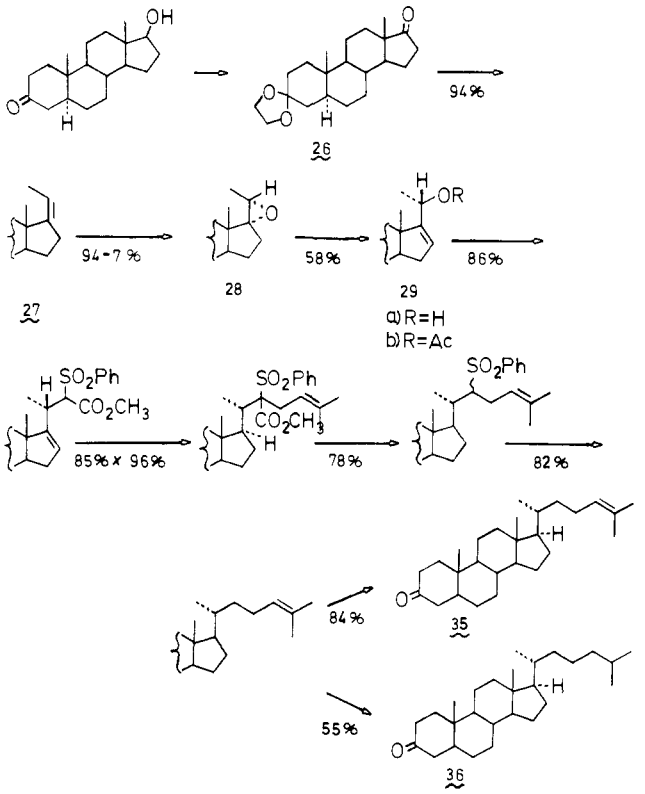
Mechanistically, initial attack of selenium dioxide should occur on the α face to give allylselenic acid **23**.[22b] Sigmatropic rearrangement on the β face would lead to the 16β-hydroxy $E-\Delta^{17(20)}$ isomer; 2,3 shift on the less hindered α face should produce 16α-hydroxy Z-$\Delta^{17(20)}$ isomer. The fact that the olefin geometry is clearly *Z* suggests that the configuration of the hydroxyl group is α. Confirmation of this conclusion came from reduction of enone **22** with DIBAL which gave a mixture



of alcohols in which one isomer greatly predominated and differed from **21a**. Based upon the antieipated preference for α hydride attack, it was assigned the 16β configuration **25** (δ 5.54 (1 H, q), 4.42 (1 H, m), 1.77 (3 H, d), 1.07 (3 H, s)).

Alkylation of **21b** proved substantially more difficult than that of **17**. No reaction occurred in THF under conditions identical with that used for **17**. To achieve partial alkylation, heating in Me_2SO at 120 °C with dimethyl sodiomalonate and

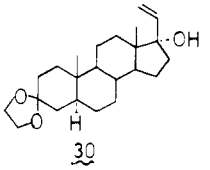
Scheme IV. Synthesis of 5α,Δ[24]-Cholestenone and 5α-Cholestanone



tetrakis(triphenylphosphine)palladium was required. Reaction occurred regiospecifically to give only **18,** identical with the previously prepared alkylation product.

With the availability of producing either configuration at C(20), final confirmation of the stereochemical course of the allylic alkylation was envisioned to involve correlation with a known steroid, 5α-cholestanone (see Scheme IV). In addition, this exercise illustrates the utility and flexibility of this approach to acyclic side chains as well as the application of this approach to a practical problem.

4,5α-Dihydrotestosterone was converted to the monoketal **26** of androstane-3,17-dione by standard procedures. Wittig olefination proceeded as before to give the *Z* isomer **27,** mp 121–123 °C. Epoxidation gave a single epoxide **28,** mp 149–150.5 °C. In this case, ring opening with lithium diethylamide in hexane (in the absence of HMPA) followed by acetyl chloride led to a mixture of three compounds, the allylic alcohol **29a** (mp 183–184.5 °C), the allylic acetate **29b** (mp 151–153 °C), and the anti-Markownikoff allylic alcohol **30**.



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By subjecting **29a** to acetylation with acetic anhydride in pyridine, the desired allylic acetate **29a** was isolated in 58% yield from **28**.

Alkylation with the sodium salt of methyl phenylsulfonylacetate in refluxing THF containing a catalytic amount of palladium(0) complex proceeded smoothly and in high yield to give **31** which is, based upon the earlier example, epimerically pure at C(20). This compound as well as **32** and **33** are solids of broad melting point ranges due to the epimeric nature of C(22).

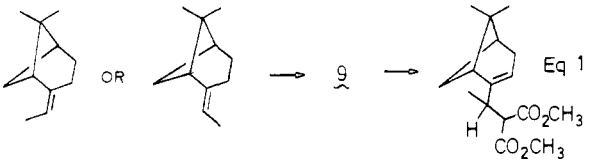
Catalytic hydrogenation of **31** over rhodium on alumina effected desulfonylation but no double-bond reduction. Reduction with palladium on charcoal led to substantial product loss. On the other hand, use of 5% palladium on barium carbonate proceeded smoothly. That only a single epimer at C(17) was produced was suggested by the appearance of only a single set of absorptions for the methyl groups (δ 0.67 (s), 0.79 (s), 1.21 (d)). Final confirmation was achieved by the ultimate success of this route.

Introduction of the remaining carbons of the side chain was accomplished by simple alkylation using sodium hydride and 1-bromo-3-methyl-2-butene in HMPA to give **32**. Decarboxylation as above to **33** was not complicated by the presence of the ketal at C(3). Desulfonylation uncomplicated by elimination reactions required the use of 6% sodium amalgam in the presence of disodium hydrogen phosphate as a buffer.[23] For solubility, a mixture of methanol and 1,2-dimethoxyethane was employed. Hydrolysis of **34** gave 5α-cholest-24-en-3-one (**35**), $[\alpha]_D^{CHCl_3}$ +37.4° (*c* 0.545), as a sharp melting crystalline solid, mp 117.5–118.5 °C, homogeneous by all criteria. While this compound is known in the literature,[24] its properties have not heretofore been reported. It potentially can serve as an important intermediate in the synthesis of many modified steroids.

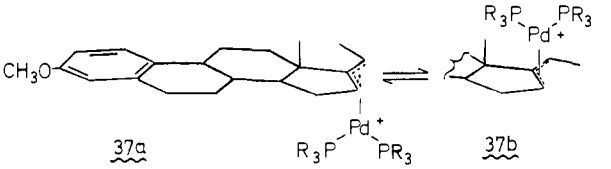
Catalytic hydrogenation of **34** followed by hydrolysis gave 5α-cholestan-3-one, mp 126.5–128 °C, $[\alpha]_D^{CHCl_3}$ +40.5° (*c* 0.850). Mixture melting point, chromatographic properties, and ^1H NMR spectra confirmed the identity with an authentic sample. The sensitivity of the ^{13}C NMR spectrum to configuration led us to compare the synthetic and authentic samples by this technique as well and again the identity was confirmed.

Discussion

The utility of allylic alkylation via organopalladium complexes requires a knowledge of the stereochemistry and degree of stereochemical control. Previous results[14] with the pinene derivative **9** (eq 1) had indicated that, in the stoichiometric



reaction, formation of the π-allyl complex is controlled by thermodynamics and thus is independent of the geometry of the starting olefin. Either isomer or a mixture is satisfactory and only one complex is normally formed. The nucleophile approached from the face opposite palladium. These conclusions are confirmed here. The complex formed represents what would be expected to be the thermodynamically more stable one. However, the stereochemistry of alkylation is actually determined by the next intermediate. As in all the cases, the requirement for phosphine ligands suggests the intermediacy of the cationic complex **37**. Potentially such a complex can be an equilibrium mixture of **37a** and **37b**. The unfavorable anti

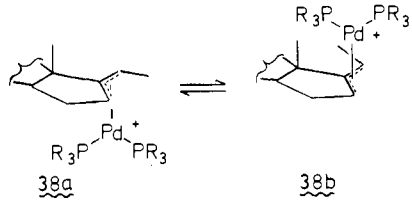


configuration of the methyl group and the location of the palladium on the congested β face of the steroid would argue against any appreciable concentration of **37b**. Nevertheless, the stereochemistry of reaction at the acyclic carbon in either complex leads to the *same* stereoisomer at C(20) since the relative stereochemistry of palladium to this carbon is unchanged by this interconversion. The formation of **10** and **11** as the sole products of alkylation confirms that the nucleophile

approaches on the face opposite palladium and this stereochemical event is the *same* for both the malonate and sulfonyl ester systems. The absence of the alternative epimer further indicates that isomerization of **37** to **38** does not occur under these conditions. Thus, the palladium provides a somewhat rigid template which enforces stereochemical control on the "absorbed" species.

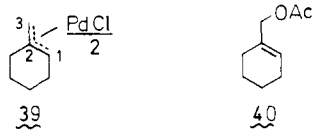
The stereochemical course of the catalytic reaction is both surprising and pleasing. *The replacement of the acetate group by the carbon nucleophile proceeded with retention of configuration.* Thus, this alkylation method complements the normal S_N2 methods which involve inversion of configuration. The ready availability and chemical stability of the acetates make them quite attractive substrates. Elimination reactions do not appear to compete with the substitution reaction. With more normal leaving groups, such reactions are frequently problematical.

Several mechanistic deductions about the catalytic reaction appear reasonable from these results. First, cationic complexes like **38a** and **38b** are involved. The obtention of the same al-



38a **38b**

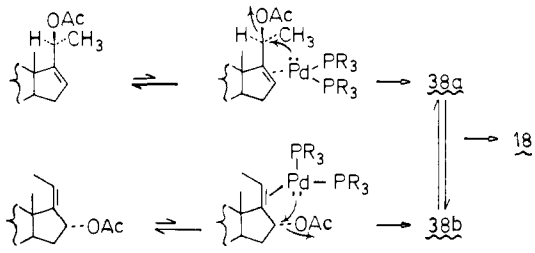
kylation product from both **17** and **21b** suggests that fact. More significantly, we have established that the product ratios (i.e., attack at 1 vs. 3) for alkylation of **39** with various phosphines is identical with those in the catalytic alkylation of **40** with the



39 **40**

same phosphines.[25] Since we have established that the carbon–carbon bond-forming reaction for these cationic complexes proceeds on the face opposite to that of palladium, the oxidative addition of the Pd^0 and the allylic acetate must occur with inversion of configuration[26] to give a net overall retention (i.e., a double inversion). The absence of **10** or **11** as products in the alkylation of **17** indicates that isomerization of **38** to **37** is slow relative to the carbon–carbon bond-forming reaction.

We suggest that the initial step is the formation of an olefin–palladium(0) complex[27] which induces the elimination of acetate by back-side displacement in the rate-determining step of the reaction. Interconversion of **38a** and **38b** would be ex-



pected to be fast,[13,28,29] but, as pointed out before, is immaterial with respect to the stereochemistry of reaction at the acyclic carbon. The striking difference in rate of reaction of allylic acetates **17** and **21b** is in accord with this scheme. Since equilibration of **38a** and **38b** is expected to be fast, the bond-forming step is identical in both cases. The large difference in rate then suggests that initial formation of the π-allylpalladium complexes is rate determining. For **17**, the palladium can coordinate to the less hindered α face to initiate the oxidative addition, but for **21b** it must coordinate to the sterically congested β face. The severe steric interactions associated with the palladium and the angular methyl group strongly retards the process for **21b**. While the scheme presented is not "proven", it does accommodate the present results and related results. From the fact that we have found it to have useful predictive power, we believe it is a useful and realistic working hypothesis.

For the problem presented herein, clearly either epimer at C(20) is available in a fully stereocontrolled fashion. The virtue that this approach has lies in the flexibility offered for modified side chains. Indeed, partially hydroxylated side chains related to ecdysones have been introduced.[19c,30] Recently, a natural steroid possessing the epimeric configuration at C(20) corresponding to that obtained in the stoichiometric palladium procedure was isolated.[31] This procedure offers a stereocontrolled approach to this new type of steroid. Furthermore, this approach may have applicability beyond the steroid cases since the rigidity of the steroid framework is not required for the stereochemical control. Stereochemically controlled additions of acyclic units onto ring systems appear to be reasonable by this approach. More generally, the ability to form carbon–carbon bonds in conformationally ill-defined systems may be at hand. Aspects of this question are being examined.

Experimental Section

All reactions were run under a positive nitrogen pressure. Solvents were distilled before use: Me_2SO, amines, and hexane from calcium hydride; THF from sodium benzophenone ketyl. Silica gel (PF-254) was used for all analytical and preparative thin layer chromatography. Column chromatography was done using W. R. Grace silica gel, grade 62, 60–200 mesh. NMR spectra were run on a Varian T-60 or Jeolco MH-100 spectrometers. IR spectra were taken on a Perkin-Elmer 267 spectrometer. Mass spectra were obtained on a MS9. Melting points are uncorrected.

Preparation of 3-Methoxy-*cis*-19-norpregna-1,3,5(10),17(20)-tetraene (4). Potassium *tert*-butoxide (5.092 g, 45.46 mmol) and ethyltriphenylphosphonium bromide (11.681 g, 31.48 mmol) were stirred in 60 mL of THF for 15 min. Estrone methyl ether (3.481 g, 12.25 mmol) was added and the mixture was refluxed for 30 h. The reaction mixture was partitioned between water and ether. The ether was washed with a 10% aqueous hydrogen peroxide solution and then dimethyl sulfide, dried over $MgSO_4$, and filtered, and the solvent removed in vacuo, to give 13.65 g as a crude yellow oil. Purification by column chromatography (silica gel, 140 g; hexane, 2 L; 5:1 hexane–ethyl acetate, 1 L) gave 2.95 g (81%) of a white solid which was recrystallized from methanol–ether: mp 77.5–79 °C (lit.[11] mp 76.5–77.5 °C); R_f 0.66 (5:1 hexane–ethyl acetate); NMR (CCl_4) δ 7.12 (d, 7 Hz, 1 H), 6.60 (dd, J = 7, 1 Hz, 1 H), 6.53 (br, 1 H), 5.15 (q (7 Hz) of m, 1 H), 3.74 (s, 3 H), 2.82 (m, 2 H), 2.34–1.36 (m, 15 H), 1.70 (d (7 Hz) of t (1 Hz) 3 H), 0.92 (s, 3 H); IR (CCl_4) 2860, 1610, 1500 cm^{-1}; UV (C_2H_5OH) λ_{max} 286 nm (ϵ 2558), 276 (2190), 237 (sh, 5800), 232 (sh, 9900); mass calcd for $C_{21}H_{28}O$ 296.2140, found 296.2149.

Preparation of Bis[chloro-(16,17,20-η^3-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene)palladium(II)] (5). Cupric chloride dihydrate (2.461 g, 14.43 mm) was heated at 90–100 °C under vacuum for 1 h. Palladium dichloride (0.7543 g, 4.25 mmol), sodium acetate (2.238 g, 27.28 mmol), sodium chloride (1.696 g, 29.01 mmol), and acetic anhydride (2 mL) in 32 mL of glacial acetic acid were heated for 3 h at 100 °C. The reaction mixture was cooled to 60 °C and the ethylidene derivative **4** (2.0071 g, 6.78 mmol) was added and the mixture heated for 60 h at 70 °C. The reaction mixture was filtered and partitioned between ether and water. The ether was neutralized with saturated aqueous sodium carbonate, washed with water, dried over magnesium sulfate, and filtered and the solvent removed in vacuo to give 2.64 g of a crude solid. Purification via column chromatography (silica gel, 150 g; hexane, 100 mL; 5:1 hexane–chloroform, 135 mL; 2.5:1 hexane–chloroform, 350 mL; 3:5 hexane–chloroform, 400 mL) gave 1.246 g (67% based on Pd) of the solid yellow complex, R_f 0.18 (5:1 hexane–ethyl acetate), mp 161–182 °C dec, and 0.383 g of starting olefin. Yellow complex: NMR (CCl_4) δ 6.94 (d, J = 8 Hz,

1 H), 6.56 (d, J = 8 Hz, 1 H), 6.51 (br, 1 H), 3.74 (br s, 4 H), 3.56 (m, 1 H), 2.82 (m, 2 H), 2.4–0.9 (m, 1 H), 1.28 (d, J = 8 Hz), 1.00 (s, 3 H); IR (CCl_4) 2850, 1610, 1570, 1495 cm^{-1}; UV (C_2H_5OH) λ_{max} 287 nm (ϵ 3441), 278 (3570), 248 (sh, 13 500), 222 (sh, 27 900). Anal. ($C_{42}H_{54}O_2Pd_2Cl_2$) C, H, Cl.

Alkylation of 5, With Malonate to 10. To sodium hydride (27.7 mg, 1.157 mm) in 4 mL of THF was added dimethyl malonate (152 mg. 1.157 mm) and the mixture was stirred for 45 min at room temperature. The palladium complex (202.1 mg, 0.323 mm) and bis(1,2-diphenylphosphino)ethane (184.7 mg, 0.464 mm) were stirred in 4 mL of THF at room temperature for 45 min. This was added in one portion to the former and the combined mixture was stirred at room temperature for 43 h. The reaction mixture was partitioned between ether and water, extracted 4 × 30 mL with ether, dried over sodium sulfate, and filtered and the solvent removed in vacuo. Purification via preparative TLC (3:1 hexane–ethyl acetate) gave 160.1 mg (81%) of a yellow oil (R_f 0.25): NMR (CCl_4) δ 6.96 (d, J = 8 Hz, 1 H), 6.46 (d, J = 8 Hz, 1 H), 6.41 (br s, 1 H), 5.37 (m, 1 H), 3.66 (s, 3 H), 3.63 (s, 3 H), 3.60 (s, 3 H), 3.40 (d, J = 9 Hz), 2.80 (m, 2 H), 2.4–1.2 (m, 11 H), 1.14 (d, J = 9 Hz, 3 H), 0.85 (s, 3 H); IR (CCl_4) 2840, 1765, 1739, 1610, 1495 cm^{-1}; UV (C_2H_5OH) λ_{max} 287 nm (ϵ 1280), 278 (1340), 220 (sh, 5284); mass calcd for $C_{26}H_{34}O_5$ 426.2406, found 426.2400.

With Sulfone Ester to 11. Sodium hydride (39.6 mg, 1.65 mmol) was added to 5 mL of THF followed by the addition of methyl phenylsulfonylacetate (313.6 mg, 1.47 mmol) in 2 mL of THF. The π-allyl complex **5** (203.5 mg, 0.233 mmol) and bis(diphenylphosphino)ethane (184.9 mg, 0.465 mmol) were stirred in 4 mL of THF for 20 min. This was added in one portion and stirring continued at room temperature for 24 h. Workup and purification as above gave 194.5 mg (82%) of a white solid: R_f 0.78; mp 62–68.5 °C; NMR (CCl_4) 7.83 (m, 2 H), 7.52 (m, 3 H), 7.01 (d, J = 8 Hz, 1 H), 6.52 (d, J = 8 Hz, 1 H), 6.46 (s, 1 H), 5.40 (m, 1 H), 4.03 and 4.00 (2d, J = 8, 7 Hz, respectively, total 1 H), 3.65 (s, 3 H), 2.48 and 2.25 (2s, total 3 H), 3.08 (m, 1 H), 2.76 (m, 2 H), 1.1–2.2 (m, 14 H) including 2d at 1.41 and 1.32, 0.82 and 0.77 (2s, 3 H); IR (CCl_4) 2870, 1741, 1609, 1500 cm^{-1}; mass calcd for $C_{30}H_{36}O_5S$ 508.2283, found 508.2283.

Preparation of Methyl 3-Methoxy-19,24-bisnor-20-isocholane-1,3,5(10),16-tetraenoate (12). From 10. Diester **10** (120 mg, 0.282 mmol) and anhydrous tetramethylammonium acetate (224.7 mg, 1.68 mmol) were heated at 95 °C for 13 h in 3.0 mL of dry HMPA. The reaction mixture was cooled and partitioned between ether and water, extracted with 3 × 30 mLof ether, dried over magnesium sulfate, and evaporated in vacuo to a yellow oil. Purification by preparative TLC (3:1 hexane–ethyl (acetate) gave 90 mg (87% yield) of product: NMR (CCl_4) δ 6.96 (d, J = 8 Hz, 1 H), 6.48 (dd, J = 8, 2 Hz, 1 H), 6.44 (br, 1 H), 5.32 (m, 1H), 3.71 (s, 3 H), 3.61 (s, 3 H), 1.2–3.0 (m, 16 H), 1.10 (d, J = 7 Hz, 3 H), 0.85 (s, 3 H); IR (CCl_4) 2868, 2862, 1739, 1609, 1570, 1498 cm^{-1}; mass calcd for $C_{24}H_{32}O_3$ 368.2351, found 368.2343.

From 11. Ammonia was refluxed over sodium for 20 min and then distilled into a flame-dried round-bottom flask containing calcium (14.4 mg, 0.36 mm) cooled to −78 °C. The phenyl sulfone **11** (28.5 mg, 0.0584 mm), dissolved in 2 mL of ether, was added in one portion and the mixture allowed to gently reflux for 10 min. After the mixture was cool to −78 °C, sodium benzoate was added until the blue reaction mixture turned clear (yellow tint). Ammonium chloride was added and the solvent was allowed to evaporate. The solid residue was partitioned between ether and water, extracted with ether, dried (Na_2SO_4), and filtered and the solvent removed in vacuo to give 20.1 mg of a yellow oil. Purification via preparative layer chromatography (3:1 hexane–ethyl acetate) gave 12.6 mg of product (R_f 0.60) (4:1 hexane–ethyl acetate) for a 61% yield. Spectral properties (NMR, IR) were identical with those of the above sample.

Hydrolysis of 12. Preparation of 13. The ester **12** (32 mg, 0.0869 mm) was dissolved in a 5% degassed solution of potassium hydroxide in 2.5:1 methanol–water, and heated at reflux for 18 h. The reaction mixture was cooled, and the methanol removed in vacuo. The remaining liquid was acidified with 2 N HCl and extracted with 4 × 20 mL of ether. The combined organic extracts were dried ($MgSO_4$) and filtered and the solvent removed in vacuo. Purification via preparative layer chromatography, (3:1 hexane–ethyl acetate with 0.5% formic acid) gave 23 mg of a solid acid for a 72% yield. Recrystallization from hexane–$CHCl_3$ gave white crystals, mp 161–162.5 °C. The sample of ester **12** obtained from **11** was similarly hydrolyzed to give an identical acid: mp and mmp 161–162.5 °C; NMR ($CDCl_3$) δ 7.5 (v br, 1 H), 7.18 (d, J = 8 Hz, 1 H), 6.70 (dd, J = 8, 2 Hz, 1 H), 6.64 (br, 1 H), 5.46 (m, 1 H), 3.83 (s, 3 H), 1.25–3.0 (m, 16 H), 1.19 (d, J = 7 Hz, 3 H), 0.88 (s, 3 H); IR (CCl_4) 2400–3500, 2880, 1711, 1608, 1570, 1500 cm^{-1}; mass calcd for $C_{23}H_{30}O_3$ 354.2195, found 354.2195. Anal ($C_{23}H_{30}O_3$) C, H.

Hydroxylation and Lactonization of 12. Preparation of 14. The monoester (50 mg, 0.136 mmol) dissolved in 1 mL of dry ether was added in one portion to a solution of osmium tetroxide (63 mg, 0.254 mmol) dissolved in 3 mL of ethyl ether and 0.3 mL of pyridine (distilled from calcium hydride). The brown mixture was stirred at room temperature for 7.5 h. Sodium bisulfite (105 mg) in 1.25 mL of water and 0.8 mL of pyridine was added and vigorous stirring maintained for 4 h. The reaction mixture was partitioned between ether and water, extracted 4 × 30 mL with ether, dried (Na_2SO_4), and filtered and the solvent removed in vacuo to give a yellow oil, which was heated under vacuum (60 °C) for 1 h to remove the remaining pyridine. The residue was dissolved in 15 mL of benzene, 8 mg of p-toluenesulfonic acid monohydrate was added, and the mixtuu7re was refluxed (Dean-Stark trap) for 40 min. The reaction mixture was partitioned between ether and water, washed 2 × 10 mL with saturated aqueous solution of sodium bicarbonate, dried, (Na_2SO_4), and filtered and the solvent removed in vacuo. Purification via preparative layer chromatography (1:1 hexane–ethyl acetate), gave 23.6 mg of lactonized product (R_f 0.25) for a 47% overall yield. Recrystallization for acetone–hexane gave white crystals: mp 250–251 °C: NMR ($CDCl_3$) δ 7.20 (d, J = 8 Hz, 1 H), 6.75 (dd, J = 8, 2 Hz, 1 H), 6.68 (br, 1 H), 4.65 (m, 1 H), 3.81 (s, 3 H), 1.4–3.0 (m, 16 H), 1.30 (d, J = 5 Hz, 3 H), 0.83 (s, 3 H); IR (CCl_4) 3610, 3480, 2885, 1780, 1740, 1608, 1575, 1503 cm^{-1}; mass calcd for $C_{23}H_{30}O_4$ 370.2144, found 370.2147. Anal. ($C_{23}H_{30}O_4$) C, H.

Preparation of 3-Methoxy-17α,20α-epoxy-19-norpregna-1,3,5(10)-triene (16). m-Chloroperbenzoic acid (0.7447 g, 4.31 mmol) in 5 mL of chloroform was stirred at 0 °C. The ethylidene derivative **4** (1.025 g, 3.46 mmol) was added and the mixture stirred at 0 °C for 5 h. The reaction mixture was diluted with chloroform, extracted with 5% aqueous sodium hydroxide solution, washed with water, dried over sodium sulfate, and filtered and the solvent removed in vacuo to give 1.070 g (99%) of a white solid: mp 90.5–92 °C; R_f 0.47 (5:1 hexane–ethyl acetate); NMR (CCl_4) δ 7.03 (d, J = 8 Hz, 1 H), 6.54 (dd, J = 8, 2 Hz, 1 H), 6.49 (br, 1 H), 3.71 (s, 3 H), 2.81 (m, 3 H), 1.2–2.4 (m, 13 H), 1.35 (d, J = 7 Hz, 3 H), 0.89 (s, 3 H); IR (CCl_4) 2860, 1606, 1571, 1499 cm^{-1}; mass calcd for $C_{21}H_{28}O_2$ 312.2089, found 312.2089.

Preparation of (20S)-3-Methoxyacetoxy-19-norpregna-1,3,5(10),16-tetraene (17). The 17α,20α-epoxide **16** (380 mg, 1.21 mmol) was dissolved in a mixture of 4.5 mL of hexane and 520 μL of hexamethylphosphoric triamide and stirred for 15 min at room temperature. n-Butyllithium (4.4 mL, 6.4 mmol) was added to a solution of diethylamine (441 mL, 6.4 mmol, freshly distilled from calcium hydride) in 5 mL of hexane at −78 °C, which was then allowed to warm to room temperature. The epoxide solution was added and the mixture stirred at room temperature for 10 h. After the reaction mixture cooled to −78 °C, 5 mL of acetyl chloride was added and the mixture was allowed to stir at room temperature for 10 hr. The reaction mixture was partitioned between ether and a saturated aqueous sodium bicarbonate solution and the aqueous layer extracted 4 × 40 mL with ether. The combined organic extracts were dried over magnesium sulfate and filtered and the solvent removed in vacuo to give 1.214 g of a yellow oil. Purification by preparative layer chromatography (3:1 hexane–ethyl acetate) gave 320 mg of the desired secondary acetate (R_f 0.34) for a 74.3% yield: mp 124.5–126 °C; NMR (CCl_4) δ 6.93 (d, J = 8 Hz, 1 H), 6.44 (dd, J = 8, 2 Hz, 1 H), 6.37 (br, 1 H), 5.52 (m, 1 H), 5.28 (q, J = 7 Hz, 1 H), 3.64 (s, 3 H), 2.75 (m, 2 H), 1.3–2.4 (m, 11 H), 1.93 (s, 3 H), 1.30 (d, J = 6 Hz, 3 H), 0.87 (s, 3 H); IR (CCl_4) 2860, 1738, 1610, 1575, 1499 cm^{-1}; mass calcd for $C_{23}H_{30}O_3$ 354.2195, found 354.2189.

Alkylation of 17 with Dimethyl Malonate. Preparation of 18. The allylic acetate **17** (180 mg, 0.508 mmol), triphenylphosphine (93.2 mg, 0.356 mmol), and tetrakis(triphenylphosphine)palladium(0) (41.0 mg, 0.0356 mmol) were stirred under argon in 5 mL of degassed tetrahydrofuran for 20 min. Dimethyl malonate (440 mg, 381 μL, 3.34 mmol) was added to a slurry of sodium hydride (80.3 mg, 3.34 mmol) in 5 mL of tetrahydrofuran and stirred for 15 min. The solution of the sodiomalonate was added in one portion to the former and the combined portions were stirred at reflux for 20 h. The reaction mixture was partitioned between ether and water, extracted 4 × 30 mL with

ether, dried over magnesium sulfate, and filtered and the solvent removed in vacuo to give 500 mg of a yellow oil. Purification via preparative layer chromatography (2.5:1 hexane–ethyl acetate) gave 180.1 mg (83% yield) of an oil identified as the alkylated product: NMR (CCl_4) δ 6.96 (d, J = 8 Hz, 1 H), 6.46 (br d, J = 8 Hz, 1 H), 6.39 (br, 1 H), 5.27 (m, 1 H), 3.68 (s, 6 H), 3.55 (s, 3 H), 3.40 (d, J = 10 Hz, 1 H), 2.78 (m, 3 H), 1.2–2.4 (m, 11 H), 1.03 (d, J = 7 Hz, 3 H), 0.76 (s, 3 H); IR (CCl_4) 2860, 2845, 1768, 1740, 1610, 1575, 1500 cm^{-1}; UV (C_2H_3OH) λ_{max} 285 nm (ϵ 1256), 276 (1370), 272 (sh, 1200), 218 (sh, 5840); mass calcd for $C_{26}H_{34}O_5$ 426.2406, found 426.2408.

Preparation of Methyl 3-Methoxy-19,24-bisnorcholane-1,3,5(10),16-tetraenoate (19). As described above for the preparation of **12**, 180.1 mg (0.423 mmol) of diester **18** and 333 mg (2.48 mmol) of tetramethylammonium acetate, in 4.5 mL of HMPA, were heated at 100 °C for 13 h to give 94 mg (91% yield) of **19** after the usual workup and purification: NMR (CCl_4) δ 7.10 (d, J = 8 Hz, 1 H), 6.60 (dd, J = 8, 2 Hz, 1 H), 6.53 (br, 1 H), 5.40 (m, 1 H), 3.73 (s, 3 H), 3.61 (s, 3 H), 1.2–3.0 (m, 16 H), 1.10 (d, J = 7 Hz, 3 H), 0.81 (s, 3 H); IR (CCl_4) 2862, 2868, 1738, 1609, 1570, 1498 cm^{-1}.

Preparation of 3-Methoxy-19,24-bisnorcholane-1,3,5(10),-16-tetraenic Acid (20). As described above for the preparation of **13**, 32 mg (0.087 mmol) of ester **19** was hydrolyzed by refluxing in a 5% degassed solution of potassium hydroxide in 2.5:1 methanol–water for 18 h to give 22 mg (72.8% yield) of crystalline acid: mp 162.5–164 °C (hexane–$CHCl_3$); a mixture melting point of **13** and **20** showed a severe depression, mmp 139–155 °C; NMR ($CDCl_3$) δ 8.9 (b, 1 H), 7.16 (d, J = 8 Hz, 1 H), 6.70 (dd, J = 8, 2 Hz, 1 H), 6.65 (br, 1 H), 5.42 (m, 1 H), 3.80 (s, 3 H), 1.1–3.0 (m, 16 H), 1.12 (d, J = 8 Hz), 0.81 (s, 3 H): IR (CCl_4) 3500–2600 (br, 2875, 1711, 1609, 1570, 1499 cm^{-1}; mass calcd for $C_{23}H_{30}O_3$ 354.2195, found 354.2195.

Hydroxylation and Lactonization of 19. Preparation of 15. As described for **14**, 55 mg (0.15 mmol) of ester **19** was hydroxylated using 43 mg (0.17 mmol) of osmium tetroxide in 0.2 mL of pyridine and 3.5 mL of ether for a reaction time of 14 h. Lactonization was performed for 2 h to give after purification 29.4 mg (53% yield) of crystalline hydroxylactone: mp 202–203 °C (acetone–hexane); NMR ($CDCl_3$) δ 7.10 (d, J = 8 Hz, 1 H), 6.66 (dd, J = 8, 2 Hz, 1 H), 6.61 (br, 1 H), 4.30 (m, 1 H), 3.80 (s, 3 H), 3.19 (dd, J = 16, 7 Hz, 1 H), 2.80 (m, 2 H), 2.64 (m, 2 H), 1.1–2.4 (m, 12 H), 1.18 (d, J = 7 Hz, 3 H), 0.96 (s, 3 H); IR (CCl_4) 3605, 3455, 2860, 1780, 1755, 1606, 1575, 1500 cm^{-1}; mass calcd for $C_{23}H_{30}O_4$ 370.2144, found 370.2144.

Preparation of 3-Methoxy-16α-acetoxy-*cis*-19-norpregna-1,3,5(10),17(20)-tetraene. Selenium dioxide (149 mg, 1.35 mmol) was dissolved in 50 mL of 95% ethanol. 3-Methoxy-*cis*-19-norpregna-1,3,5(10),17(20)-tetraene (400 mg, 1.35 mmol) was added and the mixture heated at reflux for 8 h. The solvent was removed in vacuo, and the residue partitioned between ether and water, extracted 4 × 40 mL with ether, dried over magnesium sulfate, and filtered, and the solvent removed in vacuo to give 462 mg of a yellow oil. Purification via preparative thin layer chromatography (3:1 hexane–ethyl acetate) gave 275 mg of the 16α-hydroxy product **21a** (R_f 0.22) for a 65% yield and 109.9 mg of a slightly impure fraction (R_f 0.85) identified as the 16-oxo derivative. **21a**: NMR ($CDCl_3$) δ 7.21 (d, J = 8 Hz, 1 H), 6.73 (dd, J = 8, 2 Hz, 1 H), 6.67 (br, 1 H), 5.65 (q, J = 6 Hz, 1 H), 4.49 (m, 1 H), 3.78 (s, 3 H), 2.88 (m, 2 H), 1.2–2.6 (m, 12 H), 1.78 (br d, J = 6.5 Hz, 3 H), 0.90 (s, 3 H); IR (CCl_4) 2845, 1550, 1500 cm^{-1}.

Alcohol **21a** (300 mg, 0.96 mmol) was stirred at room temperature in 6 mL of freshly distilled acetic anhydride and 2.5 mL of pyridine (distilled from calcium hydride) for 24 h. The reaction mixture was partitioned between ether and water, dried over magnesium sulfate, and filtered and the solvent removed in vacuo to give 336 mg of a yellow oil. Preparative layer chromatography (3.5:1 hexane–ethyl acetate) gave 268 mg of a yellow solid (R_f 0.75) identified as the allylic acetate (79%). Recrystallization from ethanol gave white crystals: mp 108–109 °C; NMR (CCl_4) δ 7.00 (d, J = 8 Hz, 1 H), 6.52 (dd, J = 8, 2 Hz, 1 H). 6.46 (br, 1 H), 5.46 (q, J = 7 Hz, 1 H), 5.42 (br, 1 H), 3.70 (s, 3 H), 2.77 (m, 2 H), 1.2–2.5 (m, 11 H), 1.99 (s, 3 H), 1.74 (d, J = 7 Hz, 3 H), 0.94 (s, 3 H); IR (CCl_4) 2860, 1735, 1609, 1570, 1500 cm^{-1}; UV (C_2H_5OH) λ_{max} 285 nm (ϵ1900), 276 (2000); mass calcd for $C_{23}H_{30}O_3$ 354.2195, found 354.2189.

Alkylation of 3-Methoxy-16α-acetoxy-*cis*-19-norpregna-1,3,5(10),17(20)-tetraene with Dimethyl Malonate. Allylic acetate **21b** (53 mg, 0.15 mmol), triphenylphosphine (27.2 mg, 0.104 mmol), and tetrakis(triphenylphosphine)palladium(0) (8.1 mg, 7.02 × 10^{-3} mmol) were stirred in 2 mL of degassed Me_2SO (freshly distilled from calcium hydride) under argon at room temperature for 10 min. Dimethyl malonate (119 mg, 103 μL, 0.902 mmol) was added to a slurry of sodium hydride (21.6 mg, 0.902 mmol) in 2 mL of Me_2SO and the mixture stirred at room temperature for 15 min. The malonate solution was added in one portion to the former and the mixture was stirred at 80 °C for 13 h and 110 °C for 15 h. Additional tetrakis(triphenylphosphine)palladium(0) (11.1 mg, 9.63 × 10^{-3} mmol) was introduced and heating continued for 8 h and then at 120 °C for 2 h. Workup in the usual manner gave 182 mg of a yellow oil. Purification by preparative layer chromatography (3.5:1 hexane–ethyl acetate) gave 17.9 mg of starting acetate (34% recovery) and 20.0 mg of an oil (36%) corresponding to the alkylated product. It was identical with the product prepared via the catalytic alkylation of **17**.

Preparation of 4,5α-Dihydrotestosterone Ethylene Ketal. 4,5α-Dihydrotestosterone (1.84 g, 6.34 mmol) was dissolved in 130 mL of benzene, ethylene glycol (0.71 ml, 12.69 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg) were added, and the mixture was refluxed with a Dean-Stark trap for 2 h. The reaction mixture was partitioned between benzene and a saturated solution of sodium bicarbonate. The aqueous phase was extracted with 3 × 50 mL of benzene, the combined organic extracts were dried over sodium sulfate and filtered, and the solvent was removed in vacuo to give 1.985 g of a white solid (93%). Recrystallization from hexane–chloroform–carbon tetrachloride gave white needles: mp 166.5–168 °C; NMR ($CDCl_3$) δ 3.93 (s, 4 H), 3.61 (t, J = 6 Hz, 1 H), 0.9–2.1 (m, 23 H), 0.83 (s, 3 H), 0.73 (s, 3 H); IR (CCl_4) 3645, 3400, 955 cm^{-1}; mass calcd for $C_{21}H_{34}O_3$ 334.2508, found 334.2497.

Preparation of Androstane-3,17-dione 3-Ethylene Ketal (26). To a suspension of pyridinium chlorochromate (3.398 g, 15.76 mm) and anhydrous sodium acetate (551 mg, 6.71 mm) in 30 mL of methylene chloride was added the above alcohol (1.825 g, 5.46 mm) dissolved in 40 mL of methylene chloride. The mixture was stirred at room temperature for 1.5 h and diluted with 70 mL of anhydrous ether. The mixture was filtered through a 10-cm pad of Florisil and washed with a total of 200 mL of ether. The solvent was removed in vacuo to give 1.769 g (97% yield) of white solid: mp 149–151 °C after recrystallization from ethanol; NMR (CCl_4) δ 3.91 (s, 4 H), 1.0–2.4 (m, 22 H), 0.88 (s, 6 H); IR (CCl_4) 1745, 1415, 960 cm^{-1}; mass calcd for $C_{21}H_{32}O_3$ 332.2351, found 332.2352.

Preparation of 3-Oxo-*cis*-pregna-17(20)-ene Ethylene Ketal (27). Potassium *tert*-butoxide (2.249 g, 20.1 mmol) and ethyltriphenylphosphonium bromide (7.66 g, 20.6 mmol) were added to 55 mL of dry THF to give an orange slurry. The ketone **26** (1.769 g, 5.33 mmol) was added and the mixture was refluxed for 10 h. The reaction mixture was partitioned between ether and water, extracted with 4 × 75 mL of ether, dried over magnesium sulfate, and filtered and the solvent removed in vacuo. Purification via preparative layer chromatography (5:1 hexane–ethyl acetate) gave 1.725 g (94% yield) of colorless crystals: mp 121–123 °C (pentane); NMR (CCl_4) δ 5.05 (br q, J = 7 Hz, 1 H), 3.80 (s, 4 H), 2.22 (m, 2 H), 1.8–1.0 (br, 23 H), 0.84 (s, 3 H), 0.80 (s, 3 H); IR (CCl_4) 1377, 1362, 950 cm^{-1}; mass calcd for $C_{23}H_{26}O_2$ 344.2715, found 344.2710.

Preparation of 3-Oxo-17α,20α-epoxypregnane Ethylene Ketal (28). The olefin **27** (1.725 g, 5.01 mmol) was dissolved in 50 mL of chloroform and cooled to 0 °C. *m*-Chloroperbenzoic acid (85% technical) (1.50 g, 7.39 mmol) was added in one portion and stirring continued at 0 °C for 1 h. The reaction mixture was partitioned between 5% aqueous sodium hydroxide and chloroform (200 mL). The organic phase was washed again with 5% aqueous sodium hydroxide, washed with water, dried over sodium sulfate, and filtered and the solvent removed in vacuo, to give a white solid (1.691 g), for a 94% yield. Recrystallization from ethanol gave white crystals: mp 149–150.5 °C; NMR (CCl_4) δ 3.89 (s, 4 H), 2.89 (q, J = 6 Hz, 1 H), 0.9–2.3 (m, 25 H), 1.32 (d, J = 6 Hz, 3 H), 0.88 (s, 3 H), 0.83 (s, 3 H); IR (CCl_4): 112, 955 cm^{-1}. Calcd for $C_{23}H_{36}O_3$: 360.2664. Found: 360.2658.

Preparation of (20*S*)-3-Oxoacetoxypregna-16-ene Ethylene Ketal (29b). To the epoxy ketal **28** (902.2 mg, 2.50 mmol), dissolved in 16 mL of hexane at 0 °C was added a solution of lithium diethylamide prepared from 3.5 mL (33.8 mmol) of diethylamine in 2 mL of hexane and 10.5 mL of 1.42 M (14.91 mmol) *n*-butyllithium in hexane. The mixture was stirred at room temperature for 24 h and cooled to −78 °C and 3 mL of acetyl chloride slowly added. The reaction mixture was partitioned between ether and water, extracted with 4 × 35 mL of ether, dried over magnesium sulfate, and filtered and the solvent removed in vacuo. Purification via preparative layer chromatography (2:1 hexane–ethyl acetate) gave 312.0 mg (31%) of (20*S*)-3-oxoa-

cetoxypregna-16-ene ethylene ketal (**29b**), 248.5 mg (28%) of (20*S*)-3-oxohydroxypregn-16-ene ethylene ketal (**29a**), and 165.8 mg (18%) of 3-oxo-17α-hydroxypregn-20-ene ethylene ketal (**30**).

The hydroxy ketal **29a** (220 mg, 0.61 mm) was stirred in 4 mL of acetic anhydride and 1.5 mL of pyridine at room temperature for 9.5 h. The reaction mixture was partitioned between ether and water, extracted with 4 × 25 mL of ether, dried over magnesium sulfate, and filtered and the solvent removed in vacuo. Purification via preparative layer chromatography (2:1 hexane–ethyl acetate) gave 236.8 mg (96% yield) of the acetate **29b** for a combined yield of 58%.

(20*S*)-3-Oxoacetoxypregn-16-ene ethylene ketal: mp 151–153 °C; NMR (CCl_4) δ 5.60 (m, 1 H), 5.36 (q, J = 7 Hz, 1 H), 3.91 (s, 4 H), 2.02 (s, 3 H), 1.0–1.9 (m, 20 H), 1.32 (d, J = 7 Hz, 3 H), 0.88 (s, 3 H), 0.86 (s, 3 H); IR (CCl_4) 1740, 1625, 950, 887 cm^{-1}; mass calcd for $C_{25}H_{38}O_4$ 402.2770, found 402.2770.

(20*S*)-3-Oxohydroxypregn-16-ene ethylene ketal: mp 183–184.5 °C; NMR ($CDCl_3$) δ 5.60 (m, 1 H), 4.27 (q, J = 7 Hz, 1 H), 3.90 (s, 4 H), 1.0–2.3 (m, 23 H), 1.30 (d, J = 7 Hz, 3 H), 0.89 (s, 3 H), 0.86 (s, 3 H); IR (CCl_4) 3618, 870 cm^{-1}; mass calcd for $C_{23}H_{36}O_3$ 360.2664, found 360.2664.

Alkylation of (20*S*)-3-Oxoacetoxypregn-16-ene Ethylene Ketal with Methyl Phenylsulfonylacetate. Preparation of 31. The allylic acetate **39b** (430 mg, 1.069 mmol), triphenylphosphine (138 mg, 0.527 mmol), and tetrakis(triphenylphosphine)palladium(0) (80.1 mg, 0.969 mmol) were stirred in 3 mL of tetrahydrofuran at room temperature for 20 min. To sodium hydride (111.5 mg, 4.847 mmol) in 15 mL of THF was added a solution of methyl phenylsulfonylacetate (1.237 g, 5.78 mmol) in 2 mL of THF over a 10-min period and the resultant mixture stirred at room temperature for an additional 15 min. This was then added to the former mixture in one portion and the combined portions were refluxed for 42 h. The reaction mixture was partitioned between ether and water, extracted with 4 × 50 mL of ether, dried over magnesium sulfate, and filtered and the solvent removed in vacuo. Purification via preparative layer chromatography (5:3.2 hexane–EtOAc) gave 508.9 mg (86% yield). Recrystallization from ethanol gave a white powder: mp 164–172 °C; NMR ($CDCl_3$) δ 7.83 (m, 2 H), 7.52 (m, 3 H), 5.29 (m, 1 H), 4.20 and 4.16 (2d, J = 10 Hz, 1 H), 3.97 (s, 4 H), 3.56 and 3.27 (2s, 3 H), 3.10 (m, 1 H), 1.0–2.2 (m, 23 H), 0.81 (s, 3 H), 0.65 and 0.77 (2s, 3 H); IR (CCl_4) 1750, 1335, 1142 cm^{-1}; UV (C_2H_5OH) λ_{max} 273 nm (ε 1110), 266 (1110), 258 (860), 252 (860), 252 (860), 218 (9140); mass calcd for $C_{32}H_{44}O_6S$ 556.2859, found 556.2866.

Preparation of Methyl 3-Oxo-22-phenylsulfonylnorcholanoate Ethylene Ketal. The alkylation product **31** (289 mg 0.52 mmol), dissolved in 5 mL of ethyl acetate and 25 mL of absolute ethanol, was shaken with 800 mg of 5% palladium on barium carbonate at 30 psi of hydrogen for 29 h. The mixture was filtered through a pad of Celite and washed with ethyl acetate and the solvent removed in vacuo to give a white solid. Purification via preparative layer chromatography (2:1 hexane–ethyl acetate) gave 280 mg (96% yield) of product. Recrystallization from ethanol gave white crystals: mp 197–204 °C; NMR ($CDCl_3$) δ 7.96 (m, 2 H), 7.64 (m, 3 H), 4.0 (d, J = 12 Hz, 1 H). 3.91 (s, 4 H), 3.65 and 3.55 (2s, 3 H), 2.27 (m, 1 H), 0.9–2.2 (m, 23 H), 1.20 (d, J = 6 Hz, 3 H), 0.79 (s, 3 H), 0.67 (s, 3 H); IR (CCl_4) 1755, 1740, 1330, 1150, 945, 875 cm^{-1}; mass calcd for $C_{32}H_{46}O_6S$ 558.3015, found 558.3004. Anal. ($C_{32}H_{46}O_6S$) C, H, S.

Preparation of 22-Phenylsulfonyl-22-carbomethoxy-5α-cholest-24-en-3-one Ethylene Ketal (32). To methyl 3-oxo-22-phenylsulfonylnorcholanoate ethylene ketal (190.5 mg, 0.341 mmol) dissolved in 2.0 ml of HMPA, was added sodium hydride (100 mg of a 57% oil dispersion, 2.3 mmol) in one portion. After stirring for 15 min at room temperature, 1-bromo-3-methylbut-2-ene (400 μl, 3.4 mmol) was added in one portion and the mixture stirred at room temperature for 6 h. The reaction mixture was partitioned between ether and water, extracted with 4 × 25 mL of ether, dried over magnesium sulfate, and filtered and the solvent removed in vacuo to give a yellow oil. Purification via preparative layer chromatography (10:7 hexane–ethyl acetate) gave 178.8 mg (84% yield) of a white foam. Recrystallization from ethanol gave a white solid: mp 162–172.5 °C; NMR ($CDCl_3$) δ 7.8–81 (m, 2 H), 7.58 (m, 3 H), 4.94 (br t, J = 6 Hz, 1 H), 3.96 (s, 4 H), 3.58 (s, 3 H), 2.83 (m, 2 H), 1.0–2.4 (m, 27 H), 1.63 (s, 6 H), 0.68, 0.77, and 0.84 (3 s, 6 H); IR (CCl_4) 1745, 1675, 1585, 1485, 1330, 1315, 1150 cm^{-1}; mass calcd for $C_{37}H_{54}O_6S$ 626.3641, found 626.3676.

Preparation of 22-Phenylsulfonylcholest-24-en-3-one Ethylene Ketal (33). To ketal **32** (174.0 mg, 0.278 mmol), dissolved in 2 mL of HMPA, was added tetramethylammonium acetate (410 mg, 3.08 mmol) and the mixture heated at 100–105 °C for 15 h. The reaction mixture was cooled, poured in 25 mL of water, extracted with 5 × 20 mL of ether, dried over magnesium sulfate, and filtered and the solvent removed in vacuo. Purification via preparative layer chromatography (10:7 hexane–ethyl acetate) gave 123.7 mg of a white solid (78%). Recrystallization from ethanol gave crystals: mp 205–214 °C dec; NMR ($CDCl_3$) δ 7.86 (m, 2 H), 7.54 (m, 3 H), 4.79 (br t, J = 6 Hz, 1 H), 3.92 (s, 4 H), 3.09 (m, 1 H), 2.2 (m, 2 H, 0.9–2.1 (m, 27 H), 1.59 (s, 3 H), 1.39 (s, 3 H), 0.80 (s, 3 H), 0.60 (s, 3 H); IR (CCl_4) 1675, 1327, 1312, 1150, 948, 878 cm^{-1}; mass calcd for $C_{35}H_{52}O_4S$ 568.3586, found 568.3626.

Preparation of 5α-Cholest-24-en-3-one Ethylene Ketal (34). Sulfone ketal **33** (114.8 mg, 0.202 mm) was dissolved in 8 mL of methanol and 3.5 mL of dimethoxyethane by heating to 50 °C. The solution was cooled to room temperature and anhydrous disodium hydrogen phosphate (800 mg) was added. After 5 min, 6% sodium amalgam (2.1 g) was added and stirring continued for 30 min. The reaction mixture was filtered and the solid washed with 60 ml of ether. The organic solution was washed with 2 × 20 mL of a saturated aqueous solution of sodium chloride, 1 × 15 mL of a 5% aqueous solution of sodium hydroxide, and 1 × 15 mL of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, and filtered and the solvent removed in vacuo to give a white solid. Purification via preparative layer chromatography (3:1 hexane–ethyl acetate) gave 70.6 mg (82%) of a white solid. Recrystallization from ethanol gave white crystals: mp 103–109 °C; NMR ($CDCl_3$) δ 5.12 (t, 6 Hz, 1 H), 3.92 (s, 4 H), 0.8–2.0 (m, 28 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 0.92 (d, J = 5 Hz, 3 H), 0.80 (s, 3 H), 0.64 (s, 3 H); IR (CCl_4) 946, 878 cm^{-1}; mass calcd for $C_{29}H_{48}O_2$ 428.3654, found 428.3647.

Preparation of 5α-Cholest-24-ene-3-one (35). 5α-Cholest-24-en-3-one ethylene ketal (39.5 mg, 0.092 mm) was refluxed in a mixture of 5 mL of benzene, 2 mL of water, and 3 drops of concentrated hydrochloric acid for 1.5 h. The reaction mixture was partitioned between ether and a saturated sodium bicarbonate solution, extracted with 3 × 25 mL of ether, dried over magnesium sulfate, and filtered and the solvent removed in vacuo to give 29.8 mg (84% yield) of a white solid. Recrystallization from ethanol gave white crystals: mp 117.5–118.5 °C; $[\alpha]_D^{CHCl_3}$ +37.4° (c 0.545); NMR ($CDCl_3$) δ 5.06 (t, J = 6 Hz, 1 H), 2.3 (m, 2 H), 0.7–2.2 (m, 26 H), 1.66 (s, 3 H), 1.59 (s, 3 H), 1.0 (s, 3 H), 0.90 (d, J = 6 Hz, 3 H), 0.67 (s, 3 H); IR (CCl_4) 1725, 1425 cm^{-1}; mass calcd for $C_{27}H_{44}O$ 384.3392, found 384.3391.

Preparation of 5α-Cholestan-3-one (36). The unsaturated ketal **34** (59.8 mg, 0.139 mmol), dissolved in 10 mL of absolute ethanol, was shaken under 32 psi of hydrogen over 200 mg of 5% palladium on barium carbonate for 6 h. The reaction mixture was filtered through a pad of Celite and the latter washed with ethanol and ether. The solvent was removed in vacuo to give 78 mg of a white solid. The crude product was dissolved in 5 mL of benzene, 5 mL of water, and 1 mL of acetone with 5 drops of concentrated hydrochloric acid added. After stirring vigorously under reflux for 30 min, the reaction mixture was partitioned between ether and a saturated aqueous sodium bicarbonate solution, extracted with 4 × 20 mL of ether, dried over magnesium sulfate, and filtered and the solvent removed in vacuo to give 67 mg of a white solid. Purification via preparative layer chromatography gave 30.1 mg (55%) of a white solid, mp 115–121 °C. Recrystallization from absolute ethanol gave white needles: mp 126.5–128 °C and mmp 126.5–128 °C with authentic sample; $[\alpha]_D^{CHCl_3}$ +40.5° (c 0.850) (lit.[32] +41°). All spectral properties (^1H NMR, IR, mass spectrum, ^{13}C NMR) were identical with those of an authentic sample of 5α-cholestan-3-one.

Acknowledgment. We wish to express out appreciation to the National Science Foundation and the National Institutes of Health (General Medical Sciences) for their generous support of our programs. We also thank Dr. J. Mathieu of Roussel Uclaf and Dr. J. Fried of Syntex for generous gifts of steroid precursors.

References and Notes

(1) A. A. Akhrem and Y. A. Titov, "Total Steroid Synthesis", Plenum Press, New York, N.Y., 1970; R. T. Blickenstaff, A. C. Ghosh, and G. C. Wolf, "Total Synthesis of Steroids", Academic Press, New York, N.Y., 1974.
(2) For most recent work, see (a) W. S. Johnson, *Bioorg Chem.*, **5**, 51 (1976); (b) S. Danishefsky and P. Cain, *J. Am. Chem. Soc.*, **98**, 4975 (1976), and

earlier references in the series; (c) G. Neif and R. Weichert, *Chem. Ber.*, **109**, 3025 (1976); (d) U. Eder, H. Gibian, G. Haffer, G. Neef, G. Sauer, R. Wiechert, *Chem. Ber.*, **109**, 2948 (1976); (e) T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, and K. Fukumoto, *J. Am. Chem. Soc.*, **98**, 3378 (1976); (f) A. R. Daniewski and M. Kocor, *J. Org. Chem.*, **40**, 3136 (1975), and earlier references in the series; (g) G. Sauer, U. Eder, G. Haffer, G. Neef, and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, **14**, 417 (1975); (h) R. A. Michell, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. A. Scott, and P. A. Wehrle, *J. Org. Chem.*, **40**, 675 (1975); (i) N. Cohen. B. L. Banner, W. F. Eichel, D. R. Parrish, G. Saucy, J. M. Cassal, W. Meier, and A. Furst, *ibid.*, **40**, 681 (1975).
(3) For a few early examples, see (a) W. Cole and P. L. Julian, *J. Am. Chem. Soc.*, **67**, 1369 (1945); (b) A. Romeo and R. Williotti, *Ann. Chim. (Rome)*, **47**, 618 (1957); (c) K. Tsuda and K. Sakai, *Chem. Pharm. Bull.*, **9**, 529 (1961); (d) U. Kerb, G. Schulz, P. Hocks, R. Wiechert, A. Furlenmeier, A. Furst, A. Langemann, and G. Waldvogel, *Helv. Chim. Acta*, **49**, 1601 (1966). For a few recent examples, see (e) S. C. Eyley and D. H. Williams, *J. Chem. Soc., Perkin Trans. 1*, 727 (1976); (f) W. Suerow and W. Littmann, *Chem. Ber.*, **109**, 2884 (1976).
(4) J. J. Partridge, V. Toome, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **98**, 3739 (1976).
(5) (a) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952); (b) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953); (c) W. S. Johnson, J. A. Marshall, J. F. W. Keana, R. W. Franck, D. G. Martin, and V. J. Bauer, *Tetrahedron, Suppl.*, **8** (2), 541 (1966).
(6) P. Kurath and M. Capezzuto, *J. Am. Chem. Soc.*, **78**, 3527 (1956).
(7) (a) J. P. Schmit, M. Piraux, and J. F. Pilette, *J. Org. Chem.*, **40**, 1586 (1975); (b) T. C. McMorris and S. R. Schow, *ibid.*, **41**, 3759 (1976); (c) W. R. Nes, T. E. Varkey, and K. Krevitz, *J. Am. Chem. Soc.*, **99**, 260 (1977).
(8) J. Wicha and K. Ba, *J. Chem. Soc., Chem. Commun.*, 968 (1975).
(9) I. J. Bolton, R. G. Harrison, and B. Lythgoe, *J. Chem. Soc. C*, 2950 (1971).
(10) For a preliminary report of a portion of this work, see B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **98**, 630 (1976).
(11) Cf (a) A. M. Krubiner and E. P. Oliveto, *J. Org. Chem.*, **31**, 24 (1966); (b) A. Krubiner, N. Gottfried, and E. Oliveto, *ibid.*, **33**, 1715 (1968).
(12) B. M. Trost and P. E. Strege, *Tetrahedron Lett.*, 2603 (1974).
(13) (a) H. C. Volger, *Recl. Trav. Chim. Pays-Bas*, **88**, 225 (1969); (b) K. Vireze, H. C. Volger, and P. W. N. M. van Leeuwen, *Inorg. Chim. Acta Rev.*, **3**, 109 (1969); (c) J. W. Faller, M. E. Thomsen, and M. J. Mattina, *J. Am. Chem. Soc.*, **93**, 2642 (1971).
(14) B. M. Trost and L. Weber, *J. Am. Chem. Soc.*, **97**, 1611 (1975).
(15) B. M. Trost and T. J. Fullerton, *J. Am. Chem. Soc.*, **95**, 292 (1973).
(16) For a review see J. E. McMurry, *Org. React.*, **24**, 187 (1976).
(17) Adapted from a procedure of W. S. Johnson, private communication.
(18) K. E. Atkins, W. E. Walker, and R. M. Manyik, *Tetrahedron Lett.*, 3821 (1970); K. Takahashi, A. Miyake, and G. Hata, *Bull. Chem. Soc. Jpn.*, **45**, 230 (1972); H. Onoue, I. Moritani, and S. I. Murahashi, *Tetrahedron Lett.*, 121 (1973).
(19) (a) B. M. Trost and T. R. Verhoeven, *J. Org. Chem.*, **41**, 3215 (1976); (b) B. M. Trost and P. E. Strege, *J. Am. Chem. Soc.*, **99**, 1649 (1977); (c) B. M. Trost and Y. Matsumura, *J. Org. Chem.*, **42**, 2036 (1977).
(20) A. C. Cope and J. K. Heeren, *J. Am. Chem. Soc.*, **87**, 3125 (1965), and earlier references; J. K. Crandall and L. C. Lin, *J. Org. Chem.*, **33**, 2375 (1968), and earlier references; C. L. Kissel and B. Rickborn, *J. Org. Chem.*, **37**, 2060 (1972).
(21) For differential regioselectivity, see B. M. Trost and S. Kurozumi, *Tetrahedron Lett.*, 1929 (1974); A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **96**, 6514 (1974); C. G. Pitt, M. S. Fowler, S. Sathe, S. C. Srivastava, and D. L. Williams, *ibid.*, **97**, 3798 (1975).
(22) (a) V. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 4835 (1971); (b) for a review, see N. Rabjohn, *Org. React.*, **24**, 261 (1976); (c) also see D. Arigoni, A. Vasella, K. B. Sharpless, and H. P. Jensen, *J. Am. Chem. Soc.*, **95**, 7917 (1973).
(23) B. M. Trost, H. C. Arndt, P. E. Strege, and T. R. Verhoeven, *Tetrahedron Lett.*, 3477 (1976).
(24) T. J. Scallen and W. Kreuger, *J. Lipid Res.*, **9**, 120 (1968).
(25) P. E. Strege and T. R. Verhoeven, unpublished work in these laboratories.
(26) Cf. K. S. Y. Law, P. K. Wong, and J. K. Stille, *J. Am. Chem. Soc.*, **98**, 5832 (1976); J. K. Stille and K. S. Y. Law, *ibid.*, **98**, 5841 (1976); A. V. Kramer, J. A. Labinger, J. S. Bradley, and J. A. Osborn, *ibid.*, **96**, 7145 (1974); A. V. Kramer and J. A. Osborn, *ibid.*, **96**, 7832 (1974).
(27) For information of the first stable olefin–palladium(0) complex, see R. van der Linde and R. O. de Jongh, *Chem. Commun.*, 563 (1971).
(28) K. Vrieze, "Dynamic NMR Spectroscopy", Academic Press, New York, N.Y., 1975, p 441.
(29) The rate of this reaction relative to the rate of alkylation is clearly substrate dependent. If interconversion requires formation of a σ bond to a tertiary carbon, interconversion is slow relative to alkylation.[19a] On the other hand, such is not the case if formation of a σ bond to a secondary carbon is involved (T. R. Verhoeven, unpublished results).
(30) B. M. Trost and Y. Matsumura, submitted for publication.
(31) D. J. Vanderah and C. Djerassi, *Tetrahedron Lett.*, 683 (1977).
(32) L. F. Fieser and M. Fieser, "Steroids", Reinhold New York, N.Y., 1959.

A Highly Enantioselective Synthesis of Cyclopropane Derivatives through Chiral Cobalt(II) Complex Catalyzed Carbenoid Reaction.[1] General Scope and Factors Determining the Enantioselectivity

Akira Nakamura,*[2a] Akira Konishi,[2b] Yoshitaka Tatsuno,[2b] and Sei Otsuka*[2b]

Contribution from the Department of Polymer Science, Faculty of Science, and the Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka, Japan 560. *Received May 23, 1977*

Abstract: Optically active cyclopropane derivatives, e.g., *cis*- and *trans*-2-phenylcyclopropanecarboxylic acid, were prepared by carbenoid type reactions between olefins and diazoalkanes catalyzed by bis[(−)-camphorquinone-α-dioximato]cobalt(II). A high enantioselectivity (maximum 88% optical yield) was achieved with a high chemical yield (90–95%) for the preparation of neopentyl *trans*-2-phenylcyclopropanecarboxylate, using a 3 mol % catalyst concentration at 0 °C. The reaction occurs selectively at a terminal double bond conjugated with a vinyl, aryl, or alkoxycarbonyl group. Diazo compounds containing electron-attracting groups (CO_2R, COR, or CN) can be used. The (1*S*) enantiomer was always in large excess (60–80% ee) in the 2-substituted cyclopropanecarboxylates thus obtained with this catalyst.

Optically active cyclopropane derivatives have been prepared,[3] for example, by the reaction of olefins with stoichiometric amounts of chiral sulfonium ylides (maximum optical yield 30%),[4] by the Simmons–Smith reactions (CH_2X_2/Zn) employing chiral substrates (optical yield 9.3%),[5] or by catalytic olefin cyclopropanation with diazoalkanes under the influence of chiral copper complexes (maximum optical yield 8%).[6,7] In the course of our study on the interaction of diazo compounds with transition metal compounds,[8] we have been interested in the asymmetric carbenoid reaction of diazo compounds catalyzed by chiral metal complexes. Among many complexes examined, bis(α-camphorquinonedioximato)-cobalt(II) was found to be an active catalyst for the formation of optically active cyclopropanes with over 80% optical yield. The chemical yield is often in the range 80–95% and only a small amount (1 mol % relative to diazo compound) of catalyst is required. The ready availability of the chiral camphorquinonedioxime ligand from natural sources is also an advantage. Recently, communications[9] have appeared describing cyclopropanation of 2,5-dimethyl-2,4-hexadiene with various chiral

0002-7863/78/1500-3443$01.00/0