4.01 (dd, $J_{3,4}$ = 8.4 Hz, $J_{3,2}$ = 3.2 Hz, 3-H(α,β)), 3.58 (q, $J_{\alpha,\beta}$ = 7.0 Hz, α-H(α')), 3.50 (q, $J_{\alpha,\beta}$ = 7.15 Hz, α-H(α)), 3.10 (dt, $J_{4,3}$ = $J_{4,5}$ = 8.1 Hz, $J_{4,5'}$ = 4.1 Hz, 4-H(α')), 1.45 (d, $J_{\beta,\alpha}$ = 7.15 Hz, β-H$_3$(α,β)), 1.35 (d, $J_{\beta,\alpha}$ = 7.0 Hz, β-H$_3$(α'). ^{1}H NMR (400 MHz, D_2O, pH $\geq$12): δ 4.48 (dd, $J_{2,3}$ = 8.1 Hz, $J_{2,1}$ = 4.8 Hz, 2-H(α')), 4.28 (d, $J_{1,2}$ = 4.8 Hz, 1-H(α')), 3.82 (dd, $J_{5,5'}$ = 11.5 Hz, $J_{5,4}$ = 6.1 Hz, 5-H(α')), 3.75 (dd, $J_{5',5}$ = 11.5 Hz, $J_{5',4}$ = 3.8 Hz, 5'-H(α')), 3.49 (ddd, $J_{4,3}$ = 8.4 Hz, $J_{4,5}$ = 6.1 Hz, $J_{4,5'}$ = 3.8 Hz, 4-H(α')), 3.36 (q, $J_{\alpha,\beta}$ = 7.1 Hz, α-H(α')), 3.00 (dd, $J_{3,4}$ = 8.4 Hz, $J_{3,2}$ = 8.1 Hz, 3-H(α')), 1.35 (d, $J_{\beta,\alpha}$ = 7.1 Hz, β-H$_3$(α')). ^{13}C NMR (100.6 MHz, D_2O, pH $\approx$0, GASPE): δ 174.2 (α-C=O(α,β)), 173.5 (α-C=O(α')), 96.7 (C-1(β)), 96.5 (C-1(α)), 72.7/72.2 (C-3(α)), 72.7 (C-1(α'), C-3(α')), 71.8/71.5 (C-3(β)), 71.5 (C-2(α')), 70.1 (C-2(β)), 69.0 (C-2(α), C-4(α')), 63.4 (C-α(α')), 63.1 (C-5(β)), 59.8/59.7 (C-5(α)), 58.0 (C-4(α)), 57.9 (C-4(β)), 56.8 (C-α(α)), 56.3 (C-α(β)), 55.9 (C-5(α')), 16.9 (C-β(α,β)), 13.2 (C-β(α')). ^{13}C NMR (100.6 MHz, D_2O, pH $\approx$8, GASPE): δ 178.3 (α-C=O(α')), 96.7 (C-1(α)), 73.2 (C-3(α')), 72.3 (C-1(α')), 72.1 (CH_2), 71.9 (C-2(α')), 68.3 (C-4(α')), 65.4 (C-α(α')), 64.3 (CH), 61.3 (C-5(β)), 59.9 (C-5(α)), 55.8 (C-5(α')), 19.9 (C-β(β)), 18.8 (C-β(α)), 14.8 (C-β(α')). $C_8H_{15}NO_6$ (221.2). Anal. Calcd: C, 43.44; H, 6.84; N, 6.33. Found: C, 32.52; H, 5.06; N, 4.79.

1-L-Alanino-1,4-anhydro-1-deoxy-L-lyxitol (14). **9** (200 mg, 0.64 mmol) was completely dissolved in 10–15 mL of H_2O and hydrogenated to completion in the presence of 200 mg catalyst (10% Pd on charcoal, Merck) at 1 atm H_2 (about 2 h). Charcoal was added, and the mixture was filtered through Celite. After freeze-drying, **14** was obtained as a brown syrupy mass. $[\alpha]^{21}_D$ +46.0° (*c* 1, H_2O); $[\alpha]^{21}_D$ +47.7° (*c* 0.5, H_2O); R_f(C) 0.56. ^{13}C NMR (100.6 MHz, D_2O, GASPE): δ 174.0 (α-C=O), 73.0 (C-3), 71.7 (C-2), 68.9 (C-4), 65.6 (C-α), 59.3 (C-1), 55.6 (C-5), 14.2 (C-β). $C_8H_{15}NO_5$ (205.2). Anal. Calcd: C, 46.82; H, 7.37; N, 6.83. Found: C, 41.62; H, 7.74; N, 6.65.

3-L-Alanino-3-desoxy-D-xylose (15). **10** (200 mg, 0.64 mmol) was dissolved in methanol/water (1/2) and hydrogenated as described above for **14** (about 2.5 h). After repeated freeze-drying, **15** was obtained as a white, fluffy powder, dec above 120–125 °C; $[\alpha]^{23}_D$ +49.3° (*c* 2, H_2O); R_f(C) 0.50. ^{1}H NMR (400 MHz, D_2O): δ 5.22/5.21 (d, $J_{1,2}$ = 3.6 Hz, 1-H(α)), 4.66/4.64 (d, $J_{1,2}$ = 7.6 Hz, 1-H(β)), 4.23 (q, $J_{\alpha,\beta}$ = 7.2 Hz, α-H(α)), 4.19 (q, $J_{\alpha,\beta}$ = 7.2 Hz, α-H(β)), 4.02/4.00 (dd, $J_{5,5'}$ = 11.3 Hz, $J_{5,4}$ = 5 Hz, 5-H(β)), 4.00 (ddd, $J_{4,5'}$ = 10.5 Hz, $J_{4,3}$ = 9.55 Hz, $J_{4,5}$ = 5 Hz, 4-H(α,β)), 3.96 (dd, $J_{5',5}$ = 11.3 Hz, $J_{5',4}$ = 10.5 Hz, 5'-H(α)), 3.84/3.75 (dd, $J_{2,3}$ = 10.65 Hz, $J_{2,1}$ = 3.6 Hz, 2-H(α)), 3.75 (dd, $J_{5,5'}$ = 11.3 Hz, $J_{5,4}$ = 5 Hz, 5-H(α)), 3.56/3.50 (dd, $J_{2,3}$ = 10.4 Hz, $J_{2,1}$ = 7.6 Hz, 2-H(β)), 3.43 (dd, $J_{5',5}$ = 11.3 Hz, $J_{5',4}$ = 10.5 Hz, 5'-H(β)), 3.41 (dd, $J_{3,2}$ = 10.4 Hz, $J_{3,4}$ = 10.2 Hz, 3-H(β)), 3.30/3.29 (dd, $J_{3,2}$ = 10.65 Hz, $J_{3,4}$ = 9.55 Hz, 3-H(α)), 1.57 (d, $J_{\beta,\alpha}$ = 7.2 Hz, β-H$_3$(α,β)). ^{13}C NMR (100.6 MHz, D_2O, GASPE): δ 177.3 (α-C=O(α,β)), 99.2/99.1 (C-1(β)), 93.8/93.7 (C-1(α)), 72.6 (C-2(β)), 70.4 (C-2(α)), 68.6/68.5 (C-5(β)), 68.2 (C-4(β)), 68.7 (C-4(α)), 65.8 (C-3(β)), 63.4/63.0 (C-3(α)), 63.3 (C-5(α)), 60.5/60.4 (C-α(β)), 60.2 (C-α(α)), 18.4/17.8 (C-β(α)), 18.2 (C-β(β)). $C_8H_{15}NO_6$ (221.2). Anal. Calcd: C, 43.44; H, 6.84; N, 6.33. Found: C, 38.22; H, 6.50; N, 5.93.

New Stereoselective Synthesis of 20*S* and 20*R* Steroidal Side Chains. Remarkable Stereoselectivity Differences between Saturated and α,β-Unsaturated Steroidal Esters

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Reaction of (*E*)-ethyl 3β-(*tert*-butyldimethylsiloxy)pregna-5,17(20)-dien-21-oate (**5**), (*E*)-ethyl 3β-(*tert*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate (**13**), and (*E*)-ethyl 6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-en-21-oate (**16**) with lithium diisopropylamide followed by alkyl halides results in the highly predominant formation of Δ^{16}-(20*S*) alkylation products **6a**, **6b**, **14**, and **17** in isolated yields of 82% or higher. Synthetic applications to both 20*S* and 20*R* steroidal side chains are described. Contrary to the conventional rule, 20-H$_\alpha$-Δ^{16}-steroids consistently exhibit the diagnostic C(20) methyl resonance signal at 0.05–0.1 ppm higher than the 20-H$_\beta$-Δ^{16}-steroids. In addition, it was found that stereochemistry at the C(20) position of ethyl 20-alkylpregn-16-en-21-oates could easily be assigned by circular dichroism measurements.

The recent discovery of biologically interesting steroids with modified side chains,[1] such as insect molting hormones (ecdysones),[2] plant anticancer sterols,[3] metabolites of vitamin D,[4] shark repellents,[5] plant growth promoting brassinolides,[6] and marine sterols with "unusual" configurations at C(20),[7] has stimulated the development of

Scheme I

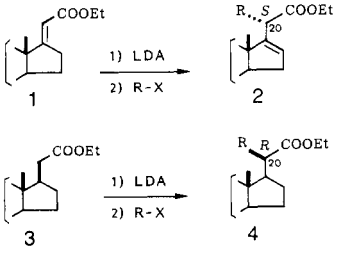

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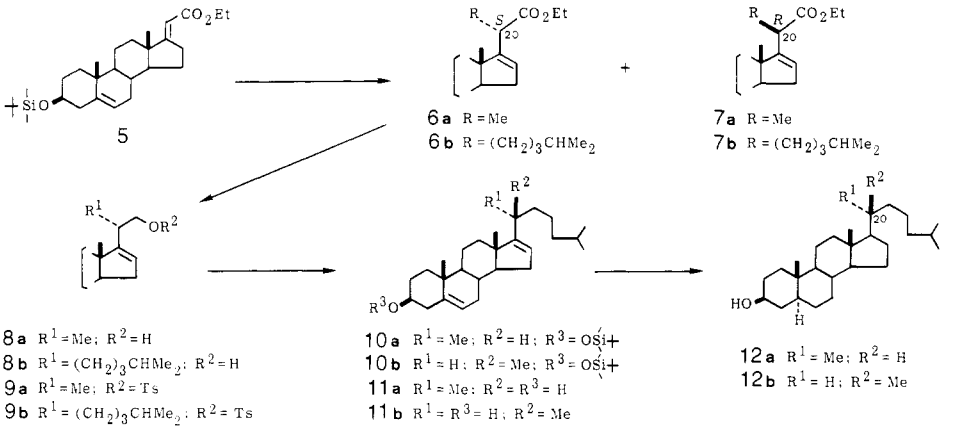
Table I. Stereoselective Alkylation of the α,β-Enoates 5, 13, and 16 with Alkyl Halides[a]

substrate	alkyl halide	20S product (% yield)[b]	20R product (% yield)[b]	ratio 20S:20R	20S + 20R: % yield[b]
5	MeI	**6a** (88)	**7a** (5.4)	96:4	94
5	$Me_2CH(CH_2)_3I$	**6b** (92)	**7b** (6)	94:6	98
13	MeI	**14** (85)	**15** (4)	95:5	89
16	MeI	**17** (82)	**18** (12)	87:13	94

[a] Reaction conditions are detailed in the Experimental Section. [b] All yields are isolated yields for purified compounds.

Scheme II



efficient methods to introduce such modified side chains into readily available steroids.

Recently described synthetic methods for construction of the C(20) chiral center have involved the use of organocopper,[8] organopalladium,[9] and organoboron reagents,[10] ene reactions,[11] the α-alkylation of esters,[12] sigmatropic rearrangements,[13] and chirality transfer reactions.[14]

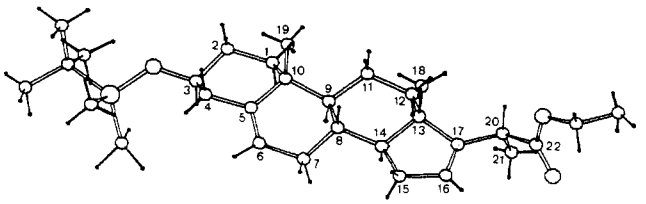


Figure 1. Crystal structure and solid-state conformation of (20S)-ethyl 3β-(*tert*-butyldimethylsiloxy)-20-methylpregna-5,16-dien-21-oate (**6a**).

Catalytic hydrogenation of the 17(20)- or 20(22)-double bond gave rise to product mixtures.[15] The main goal of any such synthesis is the highly stereoselective introduction of the chiral center at the C(20) position.

The large-scale availability of inexpensive 17-keto steroids which are produced via efficient microbial methods from soybean sitosterol and campesterol makes them attractive starting materials.[1b,16] We report here that alkylation of α,β-unsaturated ester **1**, easily derived from a 17-keto steroid, yields the 20S isomer **2** with very high stereoselectivity (up to 96% diastereoselection, 92% isolated chemical yield),[17] while the analogous alkylation of saturated ester **3** has been reported to yield the 20R isomer **4** preferentially[12] as shown in Scheme I. Further, we detail important diagnostic data from ^1H NMR analyses and circular dichroism studies which allow determination of the stereochemistry at the C(20) chiral center in Δ^{16}-steroids.

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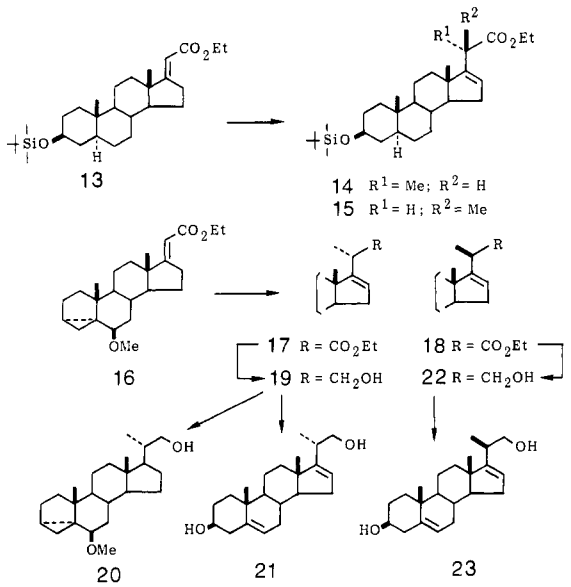
Scheme III

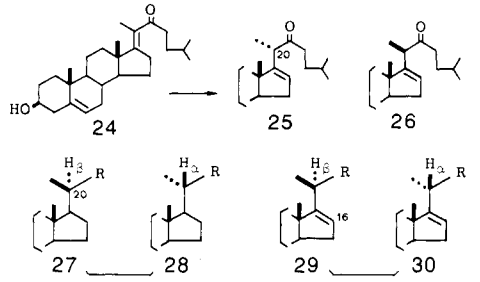


Results and Discussion

Stereoselective Introduction of a C(20) Chiral Center into a Steroidal Side Chain. The requisite (*E*)-α,β-enoates **5**, **13**, and **16** for the present study were readily prepared in high yields from the known 3β-(*tert*-butyldimethylsiloxy)androst-5-en-17-one,[18] 3β-(*tert*-butyldimethylsiloxy)-5α-androstan-17-one,[19] and 6β-methoxy-3α,5-cyclo-5α-androstan-17-one,[20] respectively, by treatment with triethyl phosphonoacetate–sodium ethoxide according to the usual method.[12] The *E* stereochemistry of the enoates **5**, **13**, and **16** was inferred from the well-known fact that reaction of 17-keto steroids with stabilized ylides such as the sodium salt of triethyl phosphonoacetate leads to the more stable *E* isomers.[21,22]

Compounds **5**, **13**, and **16** are suitable starting materials for the alkylation reaction. Thus, treatment of **5** with a slight excess of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C for 1 h, followed by alkylation with methyl iodide in the presence of hexamethylphosphoric triamide (HMPA), furnished methylated products **6a** and **7a** (ratio 94:6) in 94% combined yield (Scheme II, Table I). The stereochemistry of the C(20) chiral center in the major product was assigned on the basis of the following evidence. Successive treatment of **6a** with lithium aluminum hydride ($LiAlH_4$), *p*-toluenesulfonyl chloride–pyridine, (3-methylbutyl)magnesium bromide–dilithium tetrachlorocuprate,[23] and aqueous hydrogen fluoride gave the known cholesta-5,16-dien-3β-ol (**11a**),[24,25]

Scheme IV



which on catalytic hydrogenation over platinum dioxide afforded 5α-cholestan-3β-ol (**12a**).[15]

X-ray diffraction analysis confirmed the 20*S* stereochemistry of **6a** (Figure 1).

In a similar manner, **5** was alkylated with LDA and 1-iodo-4-methylpentane. Two products (**6b** and **7b**) (ratio 94:6) were obtained in 98% combined yield. The absolute configuration at the C(20) chiral center of **6b** was determined to be *S* by its conversion to the known (20*S*)-5α-20-isocholestan-3β-ol (**12b**)[25-27] via alcohol **8b**, *p*-toluenesulfonate **9b**, silyl ether **10b**, and alcohol **11b**.

Analogously, enoate **13** or **16** gave methylated products (**14**:**15** = 95:5, 89% combined yield, or **17**:**18** = 87:13, 94% combined yield) with the 20*S* product predominating in each case (Scheme III). Stereochemistry at the C(20) position in **14** and **15** was established to be *S* and *R*, respectively, by ^{1}H NMR analysis (**14**, 20-CH_3, δ 1.254; **15**, 20-CH_3, δ 1.318). The 20*S* isomer shows its C(20)-methyl signal upfield relative to that of the 20*R* isomer. Furthermore, since we found that the opposite sign in the circular dichroism (CD) of (20*S*)- and (20*R*)-20-alkylpregn-16-en-21-oates, epimeric at C(20) (e.g., **14**, negative Cotton effect, versus **15**, positive Cotton effect), was retained regardless of the bulk of the C(20) position by measurement of the CD Cotton effect of the alkylated products. A more detailed discussion of the ^{1}H NMR and CD results leading to this conclusion is presented below.

The 20*S* stereochemistry of the major alkylation product **17** was determined by its conversion to known steroids **20**[7e,28] and **21**[11c] via alcohol **19** in the usual way. Spectral data, as well as the melting point of the stereoisomeric diol **23** derived from the minor product **18** via alcohol **22** differ from those of published data for alcohol **21**.[11c]

Interestingly, the 20*S* stereochemistry of the major product **2** obtained via the present alkylation of the α,β-unsaturated ester **1** is opposite to that (20*R*) of the major alkylation product **4** derived from the saturated ester **3** under similar reaction conditions.[12]

Determination of Absolute Configuration of the C(20)-Methyl Group in Δ^{16}-Steroids by ^{1}H NMR Analysis. We next report a method for determining stereochemistry at the C(20) position of a Δ^{16} steroidal side chain. At present, a great deal of information on the ^{1}H NMR spectral properties of the C(20) chiral center of steroid side chain stereoisomers is available. It has been reported by Gut and co-workers[25] that isomerization of the α,β-unsaturated ketone **24** under alkaline conditions resulted in the formation of a mixture of **25** (major: C-(20)-CH_3, δ 1.15) and **26** (minor: C(20)-CH_3, δ 1.216)

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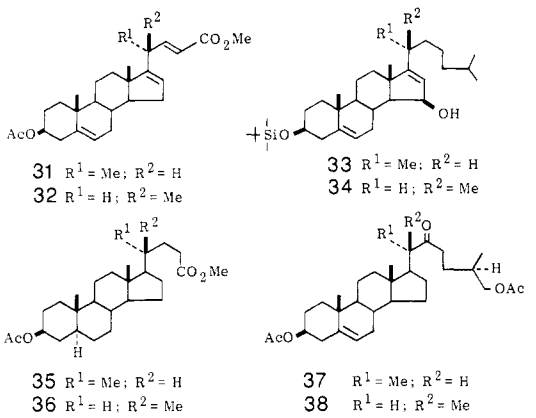
Table II. Some Representative ^1H NMR Chemical Shifts for C(21)-Protons of Steroids Epimeric at C(20)[a]

entry	20-H_α isomer (δ)	20-H_β isomer (δ)	δ 20-H_β − δ 20-H_α	ref
1	**6a** (1.266)	**7a** (1.330)	+0.064	*b*
2	**10a** (0.987)	**10b** (1.045)	+0.058	*b*
3	**11a** (0.988)	**11b** (1.046)	+0.058	*b*
4	**14** (1.254)	**15** (1.318)	+0.064	*b*
5	**17** (1.262)	**18** (1.330)	+0.068	*b*
6	**19** (1.039)	**22** (1.125)	+0.086	*b*
7	**21** (1.039)	**23** (1.125)	+0.086	*b*
8	**25** (1.15)	**26** (1.216)	+0.066	25
9	**31** (1.17)	**32** (1.22)	+0.05	11a, 11d
10	**33** (0.97)	**34** (1.11)	+0.14	8b
11	**12a** (0.896)	**12b** (0.806)	−0.090	*b*
12	**35** (0.92)	**36** (0.83)	−0.09	7e, 11d
13	**37** (1.11)	**38** (1.02)	−0.11	30

[a] Structures **31**–**38** are presented in Scheme V. For designations H_α and H_β, see ref 29. [b] This study.

Scheme V



(Scheme IV). The 20*S* stereochemistry of the major product (**25**) was deduced from chemical evidence. However, Wicha and co-workers raised doubts regarding the assigned C(20) stereochemistry in **25** and hence in **26** on the basis of the chemical shift of the C(20)-methyl resonance.[1a,12a] In fact, it has been well documented that 20-H_β (20-iso series) steroids **27**[29] consistently exhibit the C-(20)-methyl resonance at 0.05–0.1 ppm higher than the corresponding 20-H_α (20-normal series) steroids **28**.[1a] This conventional rule has frequently been used for determination of the C(20) stereochemistry of synthetic and natural steroids.[7e,8c] Our results, however, support the stereochemical assignments of Gut and co-workers. Confirmation of the 20*S* and 20*R* formulations for **25** and **26** come from a comparison of ^1H NMR shifts for their C-(20)-methyls with data for the group of Δ^{16}-steroids listed in Table II. Table II contains a listing of ^1H NMR shifts for both the Δ^{16}-unsaturated (entries 1–10) and saturated (entries 11–13) steroids.

As shown in Table II (entries 1–10), the 20-H_β-Δ^{16}-steroids [C(20) stereochemistry is depicted in **29**] always exhibit the C(20)-methyl signal at 0.05–0.1 ppm lower than the 20-H_α-Δ^{16}-steroids [C(20) stereochemistry is depicted in **30**]. This tendency is independent of the substituent at C(15) (entry 10) or C(22) (entries 1–7 and 9). This trend has previously been recognized in some Δ^{16}-steroids.[8c,11d] It should be clearly noted that this tendency is reversed in the absence of the 16(17)-double bond, as can be seen from entries 11–13 (for structures **31**–**38**, see Scheme V).[30]

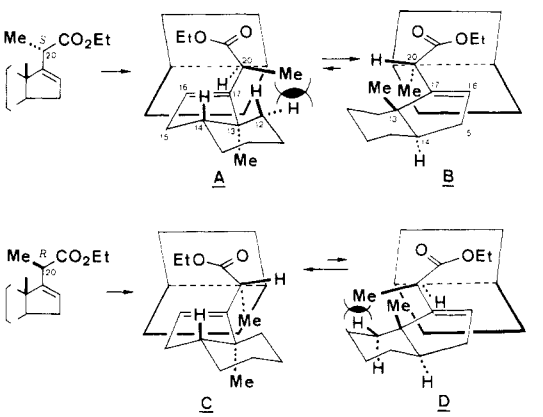
(29) *Pure Appl. Chem.* **1972**, *31*, 283. This convention (α and β) has been accepted for the C(20) position in the IUPAC–IUB 1971 Definite Rules for Steroid Nomenclature.

Table III. CD Data for the n → π* Transition in Ethyl 20-Alkylpregn-16-en-21-oates

compd	stereochem at C(20)	λ, nm ($\Delta\epsilon$)[a]
6a	*S*	208 (0), 217 (−2.42), 255 (0)
6b	*S*	211 (0), 219 (−3.66), 255 (0)
14	*S*	206 (0), 217 (−2.67), 255 (0)
17	*S*	211 (0), 219 (−2.54), 255 (0)
7a	*R*	210 (0), 219 (+4.63), 250 (0)
7b	*R*	208 (0), 219 (+3.33), 255 (0)
15	*R*	206 (0), 216 (+3.96), 250 (0)
18	*R*	211 (0), 217 (+4.76), 255 (0)

[a] In isooctane at 30 °C.

Scheme VI



The C(20)-methyl group of the major product (**25**) resonates at 0.07 ppm higher in the ^1H NMR spectrum than the C(20)-methyl group of the major product (**26**) (entry 8). Accordingly, the stereochemistry at the C(20) position of the major product (**25**) should be assigned as *S*, whereas the minor product (**26**) should receive the *R* configuration, as suggested by Gut and co-workers.[25]

Determination of Stereochemistry at the C(20) Position of Ethyl 20-Alkylpregn-16-en-21-oates by Circular Dichroism. It has been well documented that most chiral β,γ-unsaturated carbonyl compounds,[31–33] including α-phenylacetic acids,[34,35] their esters,[35] and the corresponding α-phenyl ketones,[33] exhibit unusually high CD ellipticities and ORD amplitudes.[36] The enhancement of the Cotton effect associated with the n → π^* transition of the carbonyl group is due to homoconjugation of the carbonyl group with the β,γ-double bond. The carbonyl group should adopt a suitable conformation, which allows a favorable disposition of the interacting chromophores. Previous studies regarding the factors that contribute to the chiroptical properties of β,γ-unsaturated carbonyl compounds have led to a so-called "extended" or "generalized" octant rule.[33,36,37] To the best of our

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(33) Moscowitz, A.; Mislow, K.; Glass, M. A. W.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 1945.

(34) Steyn, P. S.; Wessels, P. L.; Holzapfel, C. W.; Potgieter, D. J. J.; Louw, W. K. A. *Tetrahedron* **1972**, *28*, 4775.

(35) Korver, O. *Tetrahedron* **1970**, *26*, 5507.

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knowledge, application of ORD or CD for determining the stereochemistry at the C(20) position of steroidal side chains has been limited only to special compounds such as corollatadiol, which exhibits a plain negative ORD curve.[1a] We found in the present study that highly diagnostic CD Cotton effects are observed, permitting stereochemical assignments of the C(20) chiral center of the ethyl 20-alkylpregn-16-en-21-oates. As shown in Table III, whereas (20*R*)-β,γ-enoates **7a**, **7b**, **15**, and **18** show positive Cotton effects around 216–219 nm, the 20*S* isomers **6a**, **6b**, **14**, and **17** exhibit negative effects at about 217–219 nm. According to the "extended" or "generalized" octant rule, conformers A (prediction: positive Cotton effect) and D (prediction: negative Cotton effect) would predominate in the equilibria, as shown in Scheme VI.[33,36,37]

Surprisingly, for conformers A and D, severe unfavorable interactions between the β-hydrogen at the C(12) position and the C(20)-methyl group are present. In fact, computations of conformer A, based on X-ray analysis of **6a**, disclosed that the interatomic distance between the C-(12)-H_β and one of the hydrogens of the C(20)-methyl group is only 1.77 Å. Clearly in conformation A crowding is at a maximum and the real molecule cannot resemble this structure. Molecular models, CD spectral data (Table III), the above interatomic distance, and the X-ray analytical data for **6a** all suggest that conformers B and C are demanded sterically. Thus conformers B (20*S* series) and C (20*R* series) would explain the negative and positive Cotton effects, respectively. These results show unequivocally that, for these first examples of ethyl 20-alkylpregn-16-en-21-oates, Cotton effects are negative for the 20*S* and positive for the 20*R* compounds.

In summary, we are now in a position to prepare both 20*S* and 20*R* steroidal side chains via a very facile alkylation process simply by starting from either the unsaturated or saturated ester precursor. Furthermore, two methods of differentiating Δ^{16}-(20*S*)- and Δ^{16}-(20*R*)-steroids by means of ^{1}H NMR analysis and CD are presented.

Experimental Section

General Methods. All melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. Infrared spectra were obtained on a Shimadzu Model IR-400 spectrometer. Nominal and exact mass spectra were recorded on a JEOL JMS-01SG-2 mass spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AM-400 (400 MHz) and/or a JEOL FX-200 (200 MHz) spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million downfield from internal Me_4Si (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet). Elemental analyses were carried out by the Microanalytical Center of Kyoto University. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Circular dichroisms were measured with a JASCO J-500A spectrometer in isooctane at 30 °C. For flash chromatographies, silica gel 60H (silica gel for thin-layer chromatography, Merck) or silica gel 60 (finer than 230 mesh, Merck) was employed.

(*E*)-Ethyl 3β-(*tert*-Butyldimethylsiloxy)pregna-5,17(20)-dien-21-oate (5). A solution of 3β-(*tert*-butyldimethylsiloxy)androst-5-en-17-one[18] (1.3 g, 3.23 mmol) and triethyl phosphonoacetate (7.23 g, 32.3 mmol) in a mixture of EtOH (10 mL) and tetrahydrofuran (THF) (10 mL) under argon was treated dropwise with stirring at 30 °C with a solution of 5% NaOEt (15.6 mL, 32.3 mmol). The mixture was refluxed for 10 h, and after cooling, it was concentrated under reduced pressure and diluted with water, and the product was extracted with Et_2O. The extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried over $MgSO_4$. The solvent was evaporated off, and the residue was recrystallized from a mixture of MeOH–Et_2O (1:1) to give **5** (1.52 g, 99% yield) as colorless crystals. **5**: mp 129 °C; $[\alpha]^{30}_D$ −49.6° (*c* 1.92, $CHCl_3$); IR ($CHCl_3$) 2949, 2910, 2870, 1695, 1652, 1466, 1373, 1346, 891, 872, 840 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.057 (s, 6 H), 0.83 (s, 3 H), 0.89 (s, 9 H), 1.02 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H), 3.48 (m, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 5.33 (doubletoid m, 1 H), 5.54 (t, J = 2.3 Hz, 1 H).

Anal. Calcd for $C_{29}H_{48}O_3Si$: C, 73.68; H, 10.24. Found: C, 73.41; H, 10.40.

(*E*)-Ethyl 3β-(*tert*-Butyldimethylsiloxy)-5α-pregn-17-(20)-en-21-oate (13). By the same procedure described above, 3β-(*tert*-butyldimethylsiloxy)-5α-androstan-17-one[19] (1.2 g, 3 mmol) was converted into **13** (1.39 g, 98.6% yield). **13**: mp 118 °C [colorless needles from Et_2O–MeOH (1:2)]; $[\alpha]^{29}_D$ +12.5° (*c* 0.77, $CHCl_3$); IR ($CHCl_3$) 2950, 2875, 1695, 1650, 1466, 1450, 1373, 1348, 1290, 1258, 1185, 1170, 1135, 1092, 1058, 873, 841 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.047 (s, 6 H), 0.805 and 0.820 (s, each 3 H), 0.88 (s, 9 H), 1.28 (t, J = 7.08 Hz, 3 H), 2.81 (m, 2 H), 4.14 (q, J = 7.08 Hz, 2 H), 5.52 (t, J = 2.20 Hz, 1 H).

Anal. Calcd for $C_{29}H_{50}O_3Si$: C, 73.36; H, 10.62. Found: C, 73.41; H, 10.91.

(*E*)-Ethyl 6β-Methoxy-3α,5-cyclo-5α-pregn-17(20)-en-21-oate (16). By the same procedure described above, 6β-methoxy-3α,5-cyclo-5α-androstan-17-one[20] (3 g, 10 mmol) was transformed into **16** (3.66 g, 99% yield). **16**: colorless syrup; $[\alpha]^{30}_D$ + 54.8° (*c* 1.50, $CHCl_3$); IR ($CHCl_3$) 2950, 2900, 1694, 1650, 1453, 1372, 1346, 1325, 1294, 1263, 1180, 1153, 1105, 1091, 1075, 1035, 1020, 865 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.459 (dd, J = 8.06, 5.13 Hz, 1 H), 0.667 (dd, J = 5.13, 3.67 Hz, 1 H), 0.875 (s, 3 H), 1.05 (s, 3 H), 1.28 (t, J = 7.08 Hz, 3 H), 3.34 (s, 3 H), 4.15 (q, J = 7.08 Hz, 2 H), 5.53 (t, J = 2.44 Hz, 1 H).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.22; H, 9.88.

Stereoselective Alkylation of the α,β-Enoates 5, 13, and 16 with LDA–Alkyl Halides. (20*S*)-Ethyl 3β-(*tert*-Butyldimethylsiloxy)-20-methylpregna-5,16-dien-21-oate (6a) and Its 20*R* Isomer 7a. The following procedure for the synthesis of **6a** and **7a** is representative. To a stirred solution of 0.264 mL (2.2 mmol) of diisopropylamine in 10 mL of dry THF under an argon atmosphere at −78 °C was added dropwise 1.18 mL (2.2 mmol) of 1.6 M butyllithium in hexane. After 15 min, a solution of the enoate **5** (944 mg, 2 mmol) in 2 mL of dry THF was added dropwise to the above mixture, and the mixture was stirred for 1 h at −78 °C. A mixture of methyl iodide (0.7 mL) and HMPA (2 mL) was added by means of a syringe. The mixture was stirred at −78 °C for 3 h, and the temperature was allowed to rise to −40 °C and the mixture stirred for 1 h. Saturated NH_4Cl solution (5 mL) was added with stirring to the above mixture at −78 °C. The mixture was extracted with Et_2O, and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water, dried over $MgSO_4$, and concentrated to leave a crystalline residue. The residue was recrystallized from MeOH–Et_2O (5:1) to yield the diastereoisomerically pure ester **6a** (770 mg, 79% yield). The mother liquor was concentrated in vacuo to leave a mixture of semisolid, which was separated by flash column chromatography with hexane–EtOAc (10:1) to yield the minor alkylation product **7a** (52 mg, 5.4% yield) and **6a** (94 mg, 9.6% yield). The total yield of the major product **6a** amounted to ca. 88%.

6a: colorless crystals; mp 126 °C; $[\alpha]^{30}_D$ −18.9° (*c* 0.72, $CHCl_3$); IR ($CHCl_3$) 2950, 2920, 2870, 1723, 1468, 1438, 1375, 1252, 1181, 1090, 1009, 961, 891, 873, 840 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.059 (s, 6 H), 0.80 (s, 3 H), 0.89 (s, 9 H), 1.03 (s, 3 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.266 (d, J = 7.08 Hz, 3 H), 3.48 (m, 1 H), 4.11 (q, J = 7.1 Hz, 2 H), 5.33 (m, 1 H), 5.57 (m, 1 H); ^{13}C NMR (100 MHz) δ −4.52, 14.15, 15.93, 17.80, 18.25, 19.37, 20.80, 25.96, 30.61, 31.19, 31.61, 32.15, 34.61, 36.88, 37.39, 38.42, 42.92, 47.15, 50.86, 57.45, 60.35, 72.60, 120.90, 124.77, 141.88, 154.21, 174.96.

Anal. Calcd for $C_{30}H_{50}O_3Si$: C, 74.02; H, 10.35. Found: C, 74.10; H, 10.50.

7a: mp 44–45 °C (crystallized on long standing as colorless crystals that could not be recrystallized); $[\alpha]^{25}_D$ −49.0° (*c* 0.47, $CHCl_3$); IR ($CHCl_3$) 2950, 2920, 2870, 1723, 1468, 1438, 1375, 1252, 1181, 1090, 1009, 961, 891, 873, 840 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.057 (s, 6 H), 0.80 (s, 3 H), 0.89 (s, 9 H), 1.03 (s, 3 H), 1.25 (t, J = 7.08 Hz, 3 H), 1.33 (d, J = 7.08 Hz, 3 H), 3.48 (m, 1 H), 4.12 (q, J = 7.08 Hz, 2 H), 5.33 (m, 1 H), 5.58 (m, 1 H); nominal mass

(37) Mislow, K.; Glass, M. A. W.; Moscowitz, A.; Djerassi, C. *J. Am. Chem. Soc.* **1961**, *83*, 2771.

spectrum, m/z 486 (M^+), 471, 429 (base peak), 327, 281, 253, 75; exact mass spectrum m/z calcd for $C_{30}H_{50}O_3Si$ 486.3524, found 486.3540.

(20*S*)-Ethyl 3β-(*tert*-Butyldimethylsiloxy)-20-isocholesta-5,16-dien-21-oate (6b) and Its 20*R* Isomer 7b. By the same procedure described above, the α,β-enoate **5** (472 mg, 1 mmol) was transformed into **6b** (515 mg, 92% yield) and **7b** (34 mg, 6% yield) by treatment with LDA–4-methylpentyl iodide.

6b: mp 76–77 °C [colorless crystals from Et_2O–MeOH (1:9)]; $[\alpha]^{34}_D$ −29.02° (*c* 1.83, $CHCl_3$); IR ($CHCl_3$) 2940, 2880, 1722, 1463, 1373, 1256, 1180, 1093, 1008, 961, 891, 873, 840 cm^{-1}; ^1H NMR (400 MHz) δ 0.058 (s, 6 H), 0.780 (s, 3 H), 0.852 (d, *J* = 6.64 Hz, 6 H), 0.89 (s, 9 H), 1.03 (s, 3 H), 1.24 (t, *J* = 7.16 Hz, 3 H), 2.95 (dd, *J* = 9.64, 5.16 Hz, 1 H), 3.48 (m, 1 H), 4.12 (q, *J* = 7.16 Hz, 2 H), 5.32 (m, 1 H), 5.60 (m, 1 H); ^{13}C NMR (100 MHz) δ −4.55, 14.20, 15.95, 18.25, 19.36, 20.76, 22.50, 22.65, 25.74, 25.95, 27.78, 30.58, 31.26, 31.59, 32.11, 33.20, 34.48, 36.65, 37.36, 38.73, 42.88, 44.21, 47.21, 50.85, 57.17, 60.26, 72.58, 120.91, 125.03, 141.84, 152.97, 174.50.

Anal. Calcd for $C_{35}H_{60}O_3Si$: C, 75.74; H, 10.91. Found: C, 75.61; H, 11.08.

7b: colorless syrup; $[\alpha]^{27}_D$ −26.8° (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 2940, 2880, 1722, 1463, 1373, 1256, 1180, 1093, 1008, 961, 891, 873, 840 cm^{-1}; ^1H NMR (200 MHz) δ 0.056 (s, 6 H), 0.78 (s, 3 H), 0.854 (d, *J* = 6.59 Hz, 6 H), 0.89 (s, 9 H), 1.03 (s, 3 H), 1.25 (t, *J* = 7.08 Hz, 3 H), 2.98 (t, *J* = 7.02 Hz, 1 H), 3.48 (m, 1 H), 4.12 (q, *J* = 7.08 Hz, 2 H), 5.34 (m, 1 H), 5.59 (m, 1 H); nominal mass spectrum, m/z 556 (M^+), 541, 499 (base peak), 453, 425, 351, 327, 253, 75; exact mass spectrum m/z calcd for $C_{35}H_{60}O_3Si$ 556.4306, found 556.4302.

(20*S*)-Ethyl 3β-(*tert*-Butyldimethylsiloxy)-20-methyl-5α-pregn-16-en-21-oate (14) and Its 20*R* Isomer 15. By the same procedure, **13** (475 mg, 1 mmol) was transformed into **14** (415 mg, 85% yield) and **15** (20 mg, 4% yield).

14: mp 122–123 °C [colorless needles from Me_2CO–MeOH (4:1)]; $[\alpha]^{27}_D$ +27.7° (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 2950, 2870, 1723, 1465, 1450, 1378, 1253, 1186, 1091, 1070, 1054, 1010, 873, 859, 840 cm^{-1}; ^1H NMR (200 MHz) δ 0.048 (s, 6 H), 0.759 (s, 3 H), 0.823 (s, 3 H), 0.883 (s, 9 H), 1.236 (t, *J* = 7.08 Hz, 3 H), 1.254 (d, *J* = 7.08 Hz, 3 H), 3.09 (m, 1 H), 3.53 (m, 1 H), 4.11 (q, *J* = 7.08 Hz, 2 H), 5.54 (m, 1 H).

Anal. Calcd for $C_{30}H_{52}O_3Si$: C, 73.71; H, 10.72. Found: C, 73.63; H, 10.93.

15: colorless syrup; IR ($CHCl_3$) 2910, 2860, 1720, 1463, 1452, 1374, 1362, 1323, 1251, 1173, 1131, 1084, 1067, 1049, 1029, 1004, 988, 957, 940, 912, 896, 870, 845, 836 cm^{-1}; ^1H NMR (200 MHz) δ 0.046 (s, 6 H), 0.752 (s, 3 H), 0.820 (s, 3 H), 0.880 (s, 9 H), 1.242 (t, *J* = 7.08 Hz, 3 H), 1.318 (d, *J* = 7.08 Hz, 3 H), 3.10 (m, 1 H), 3.54 (m, 1 H), 4.11 (q, *J* = 7.08 Hz, 2 H), 5.56 (m, 1 H); nominal mass spectrum, m/z 488 (M^+), 473, 433, 432, 431 (base peak), 417, 416, 415, 388, 387, 355, 329, 284, 283, 255, 243, 208, 171, 161, 159, 147, 145, 133, 131, 121, 119, 109, 107, 105, 95, 93, 91, 75, 73; exact mass spectrum m/z calcd for $C_{30}H_{52}O_3Si$ 488.3680, found 488.3685.

(20*S*)-Ethyl 6β-Methoxy-20-methyl-3α,5-cyclo-5α-pregn-16-en-21-oate (17) and Its 20*R* Isomer 18. By the same procedure described above, the α,β-enoate **16** (975 mg, 2.61 mmol) was transformed into **17** (826 mg, 82% yield) and **18** (123 mg, 12% yield).

17: colorless syrup; $[\alpha]^{23}_D$ +69.4° (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 2950, 2890, 2880, 1724, 1455, 1378, 1329, 1301, 1186, 1092, 1053, 1022, 1006, 964, 948, 920, 865, 832 cm^{-1}; ^1H NMR (400 MHz) δ 0.452 (dd, *J* = 7.98, 5.10 Hz, 1 H), 0.666 (dd, *J* = 4.94, 3.86 Hz, 1 H), 0.836 (s, 3 H), 1.056 (s, 3 H), 1.243 (t, *J* = 7.16 Hz, 3 H), 1.262 (d, *J* = 7.04 Hz, 3 H), 2.79 (m, 1 H), 3.11 (m, 1 H), 3.35 (s, 3 H), 4.12 (q, *J* = 7.16 Hz, 2 H), 5.55 (m, 1 H); ^{13}C NMR (100 MHz) δ 13.12, 14.14, 16.38, 17.83, 19.25, 21.44, 22.37, 24.94, 29.11, 31.11, 33.16, 34.88, 35.10, 35.45, 38.39, 43.63, 47.43, 48.65, 56.63, 57.46, 60.35, 82.34, 124.61, 154.37, 175.00; nominal mass spectrum, m/z 386 (M^+), 372, 371, 355, 354, 341, 340, 339, 332, 331, 286, 285, 281, 265, 254, 253 (base peak), 252, 237, 227, 199, 197, 173, 171, 161, 160, 159, 147, 145, 143, 121, 119, 117, 107, 105, 95, 93, 91, 81, 79, 77; exact mass spectrum m/z calcd for $C_{25}H_{38}O_3$ 386.2820, found 386.2829.

18: colorless syrup; $[\alpha]^{23}_D$ +59.4° (*c* 0.65, $CHCl_3$); IR ($CHCl_3$) 2950, 2890, 1724, 1465, 1455, 1448, 1440, 1378, 1350, 1330, 1301, 1248, 1181, 1165, 1092, 1051, 1022, 968, 950, 920, 870, 832 cm^{-1}; ^1H NMR (400 MHz) δ 0.447 (dd, *J* = 7.96, 5.1 Hz, 1 H), 0.662 (dd, *J* = 4.94, 4.83 Hz, 1 H), 0.827 (s, 3 H), 1.059 (s, 3 H), 1.252 (t, *J* = 7.16 Hz, 3 H), 1.330 (d, *J* = 7.12 Hz, 3 H), 2.79 (m, 1 H), 3.11 (m, 1 H), 3.346 (s, 3 H), 4.117 (dq, *J* = 7.16, 1.0 Hz, 2 H), 5.57 (m, 1 H); ^{13}C NMR (100 MHz) δ 13.12, 14.19, 16.47, 17.53, 19.24, 21.44, 22.39, 24.93, 29.13, 31.12, 33.16, 34.66, 35.10, 35.42, 38.51, 43.62, 47.42, 48.55, 56.63, 56.98, 60.41, 82.37, 124.78, 154.00, 175.21; nominal mass spectrum, m/z 386 (M^+), 372, 371, 355, 354, 340, 339, 332, 331, 313, 286, 285, 265, 254, 253 (base peak), 252, 237, 159, 157, 147, 145, 135, 133, 131, 121, 119, 107, 105, 95, 93, 91, 81, 79, 77, 71; exact mass spectrum m/z calcd for $C_{25}H_{38}O_3$ 386.2820, found 386.2828.

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Registry No. **5**, 115019-36-8; **6a**, 115019-37-9; **6b**, 115019-38-0; **7a**, 115019-39-1; **7b**, 115075-04-2; **8a**, 115019-40-4; **8b**, 115019-41-5; **9a**, 115019-42-6; **9b**, 115019-43-7; **10a**, 115019-44-8; **10b**, 115075-05-3; **11a**, 21903-15-1; **11b**, 115075-06-4; **12a**, 80-97-7; **12b**, 105119-51-5; **13**, 115019-45-9; **14**, 115019-46-0; **15**, 115019-47-1; **16**, 64338-43-8; **17**, 115019-48-2; **18**, 115019-49-3; **19**, 81481-33-6; **20**, 51231-23-3; **21**, 80115-46-4; **22**, 101387-33-1; **23**, 115019-50-6; 3β-(*tert*-butyldimethylsiloxy)androst-5-en-17-one, 42151-23-5; 3β(-*tert*-butyldimethylsiloxy)-5α-androstan-17-one, 57711-44-1; 6β-methoxy-3α,5-cyclo-5α-androstan-17-one, 14425-92-4.

Supplementary Material Available: Synthetic method and spectral data (IR, ^1H NMR, and MS) for **8a,b**, **9a,b**, **10a,b**, **11a,b**, **12a,b**, and **19–23**, CD curves of **6a,b**, **7a,b**, **14**, **15**, **17**, and **18**, and crystal data, atomic parameters for non-hydrogen atoms, fractional coordinates and anisotropic thermal parameters for hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, bond length and valence angles, and torsion angles for **6a** (16 pages); observed and calculated structure factors for **6a** (12 pages). Ordering information is given on any current masthead page.