4.20 (1 H, d, J = 11.4 Hz, H-24a), 4.30 (1 H, dd, J = 7.0 and 9.2 Hz, H-25b), 4.44 (1 H, dd, J = 7.7 and 9.2 Hz, H-25a), 5.11 (br t, J = 6.2 Hz, H-10), and 5.37 (1 H, t, J = 8.4 Hz, H-6); EIMS m/z 404 (M^+), 387, 371, and 137; HREIMS m/z 404.2924 (M^+, $C_{25}H_{40}O_4$, 404.2926).

Reduction of (6Z)-Neomanoalide (7) with $NaBH_4$. To the cooled EtOH solution (1.5 mL) of $NaBH_4$ (10.2 mg) was added (Z)-neomanoalide (7, 18.9 mg) in 0.5 mL of EtOH and stirred at room temperature for 90 min. The same workup and purification as described above gave 3 [8.3 mg, $[\alpha]_D^{17}$ +3.9° (c 0.8, $CHCl_3$)] and 8 [3.4 mg, $[\alpha]_D^{17}$ +3.8° (c 0.3, $CHCl_3$)].

Oxidation of 2,3-Dihydroluffariolide B (8) with PCC. To a solution of 8 (2.0 mg) in CH_2Cl_2 (0.5 mL) was added PCC (4.5 mg) and powdered molecular sieves (4A, 8.9 mg), and the mixture was stirred at room temperature for 2 h. Et_2O (5 mL) was added, and the reaction mixture was filtered with a membrane filter and washed with Et_2O (5 mL × 2). The residue was subjected to a silica gel column (Wako gel C-300, 0.5 × 10 cm) with hexane/EtOAc (2:1) to give luffariolide E [5, 1.2 mg, $[\alpha]_D^{17}$ +9.8° (c 0.17, $CHCl_3$)].

Oxidation of Luffariolide D (4) with PCC. To the CH_2Cl_2 solution (0.5 mL) of luffariolide D (4, 1.0 mg) was added molecular sieves (4A, 9.3 mg) and PCC (3.5 mg, and the mixture was stirred at room temperature for 1 h. Et_2O (5 mL) was added to the reaction mixture, filtered with a membrane filter, and washed with Et_2O (5 mL × 2). The filtrate was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column (0.5 × 8 cm) with hexane/EtOAc (6:4) to afford luffariolide E [5, 0.7 mg, $[\alpha]_D^{17}$ +9° (c 0.07, $CHCl_3$)].

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Supplementary Material Available: EIMS, HREIMS, IR, UV, 2D J-resolution, and NOESY spectra of 1–5 and 2D NMR correlation data of 1–5 (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

An Efficient, Highly Stereoselective Synthesis of (Z)-16α-Hydroxy-17-ethylidene Steroids

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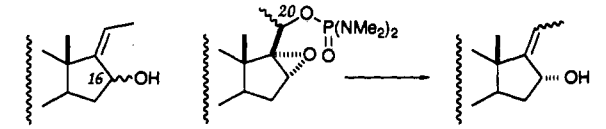
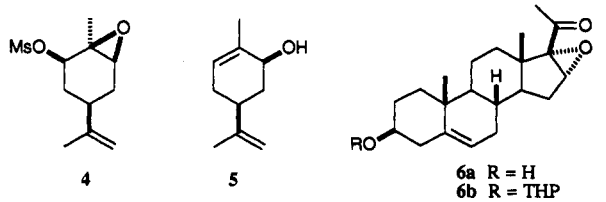
Both Z and E isomers of the 17-ethylidene derivatives of steroids and their 16-hydroxylated analogues serve as pivotal intermediates for the stereoselective introduction of steroid side chains.[1] While there are a number of multistep syntheses of these ethylidene compounds described in the literature,[2] the stereoselective synthesis of (Z)-16-hydroxy-17-ethylidene steroids 1 has remained problematic.[2,3] In the following paper, we show that such an ethylidene derivative can be synthesized efficiently, with complete stereoselectivity, by the use of a four-step sequence from the readily available 16α,17α-epoxypregnenolone (6a).

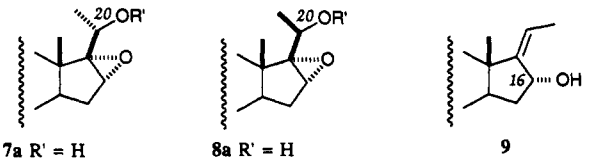
The present study was initiated with the aim of examining the effect of the stereochemistry at C-20 upon the stereochemical outcome of the reductive epoxide ring opening of epoxy phosphorodiamidates (see 2 → 3). The extent of the stereochemical preservation, if any, during the carbanion formation by dissolving metal reduction of a phosphorodiamidate, together with the timing of the epoxide-ring opening, were of great interest to us. In this context, it should be noted that Yamamoto reported, as a means for stereoselective 1,3-transposition of allylic alcohols, that a similar reduction of epoxy alcohol methanesulfonate 4 with Na–NH_3 or Na-naphthalene produced allylic alcohol 5 in high yield.[4] This overall syn elimination of the epoxy–mesylate unit seems to provide considerable mechanistic insight into the reaction, since, unlike acyclic 2,3-epoxy-1-alkanol mesylates, the reaction must proceed either by epoxide-ring opening of the *cis*-epoxy carbanion or possibly by that of the *trans*-epoxy carbanion.



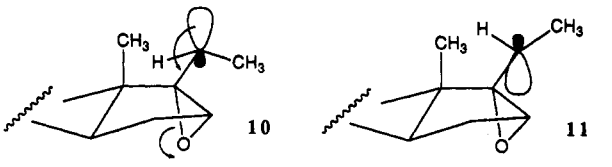
1 2 3



4 5 6a R = H 6b R = THP



7a R' = H 7b R' = P(=O)(NMe2)2 8a R' = H 8b R' = P(=O)(NMe2)2 9



10 11

The requisite epoxy phosphorodiamidates 7b[5] and 8b were obtained in stereochemically pure form from the commercially available 16α,17α-epoxypregnenolone (6a). Thus, sodium borohydride reduction of epoxypregnenolone tetrahydropyranyl (THP) ether 6b,[3c,d,6] prepared from 6a with dihydropyran/p-TsOH/CH_2Cl_2 in 93% yield, provided quantitatively a 3:1 mixture of 20R- and 20S-epoxy alcohols, 7a and 8a, respectively. The stereochemical assignments of these alcohols were made by comparison of the proton NMR spectra of 7a and 8a with those re-

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0022-3263/92/1957-3507$03.00/0

ported for the identical, with the exception of the protecting group for the 3-hydroxy group, epoxy alcohols of known C-20-configuration.[7] Thus, the most diagnostic differences were found for the chemical shifts of 16- and 21-H's, exhibiting singlets at δ 3.32 (20*R*) and 3.50 (20*S*) and doublets at δ 1.11 (20*R*) and 1.32 (20*S*), respectively. The formation of the phosphorodiamidate derivatives of the two purified 20-hydroxy compounds was achieved almost quantitatively (98 and 96% yields for **7b** and **8b**, respectively) by their treatment with *n*-butyllithium, followed by bis(dimethylamino)phosphorochloridate. Dissolving-metal reduction of each of the stereochemically pure epoxy phosphorodiamidates **7b** and **8b** with lithium in ethylamine[8] at 0 °C afforded the same, configurationally clean 16α-hydroxyl (*Z*)-17,20-ethylidene steroid **9**[3c,d,6] in high yields (81% and 75% yields from **7b** and **8b**, respectively). This intriguing, highly stereoselective formation of olefin **9** from either diastereomer of phosphorodiamidates **7b** and **8b** might be envisoned as the result of trans epoxide-ring opening of the stereoselectively generated epoxy carbanion (see **10**). Moreover, in view of lower stereoselectivity observed for the formation of 16α-hydroxy-17,20-ethylidene (2:1 *Z*/*E*) by the C-20-radical-initiated epoxide-ring opening for the same system, although the reaction was carried out at refluxing toluene temperature,[9] it may be reasonable to assume that the present reductive epoxide-ring opening with lithium and ethylamine takes place after the stereoselective formation of a carbanionic species, i.e., **10**. However, the possibility exists that the phosphorodiamidates **7b** and **8b** stereospecifically produce carbanions **10** and **11**, which undergo highly stereoselective trans and cis epoxide-ring opening, respectively, to yield (*Z*)-ethylidene alcohol **9**.

These observations on the stereoselective formation of olefin **9** eliminated the need for the separation of the stereoisomers of 20-alcohols **7a** and **8a**. Therefore, the four-step sequence for the stereoselective synthesis of olefin **9** from **6a** can be achieved without separation of a mixture of **7a** and **8a**, providing the olefin **9** in 70% overall yield.

Experimental Section

Multiplicities associated with ^{13}C NMR chemical shifts were obtained by off-resonance decoupling. Multiplicities of several carbons in **7b** and **8b** could not be definitively assigned owing to extensive overlap; those with asterisks indicate ^{13}C–^{31}P couplings. Pairs of ^{13}C NMR chemical shifts in brackets represent those of resolved diastereomeric carbon atom resonances from the tetrahydropyranyl anomeric center.

Sodium Borohydride Reduction of 3β-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-16α,17α-epoxy-5-pregnen-20-one (6b). To a solution of ketone **6a** (3.50 g, 8.44 mmol) (purchased from Sigma Chemical Co., Ltd., St. Louis, MO) in dry methanol (120 mL) was added $NaBH_4$ (0.319 g, 8.44 mmol, 1.00 mol equiv) in portions with magnetic stirring, under N_2 at 0 °C. The solution was allowed to warm to rt. After 2 h at that temperature, the reaction mixture was treated with water (50 mL), and the methanol was removed by rotary evaporation. The resulting aqueous mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organic solutions were washed with brine (50 mL), dried (Na_2SO_4), and concentrated by rotary evaporation. Purification of the crude products by flash column chromatography (silica gel, hexanes/ethyl acetate, gradient elution) gave 2.41 g (71%) of the less polar 20*R*-alcohol **7a** and 0.961 g (29%) of the more polar 20*S*-alcohol **8a**, both as white crystalline solids.

(20*R*)-3β-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-16α,17α-epoxy-5-pregnen-20-ol (7a): mp 169–170 °C (95% ethanol); $[\alpha]^{23}_D$ −88.2° (*c* 1.37, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3 H, 18-H), 1.03 (s, 3 H, 19-H), 1.11 (d, 3 H, *J* = 6.4 Hz, 21-H), 3.32 (s, 1 H, 16β-H), 3.44–3.57 (m, 2 H, CH_2OCHO), 3.85–3.97 (m, 1 H, 3α-H), 4.36 (dq, 1 H, *J* = 8.6, 6.4 Hz, 20-H), 4.70 (apparent br t, 1 H, *J* = 3.1 Hz, CH_2OCHO), 5.33 ppm (br, dd, 1 H, *J* = 5.2, 4.9 Hz, 6-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.64 (q), 19.34 (q), 20.08 (t), 20.64 (q), 25.57 (t), 27.44 (t), 29.72 (t), 30.37 (d), 31.37 (t), 31.62 (t), 32.78 (t), 37.08 (s), 37.44 (t), 38.89 (t), 40.34 (t), 41.79 (s), 45.75 (d), 50.66 (d), 60.24 (d), 62.86 (t), 64.09 (d), 72.84 (s), 76.04 (s), 97.09 (d), 121.12 (d), 141.39 ppm (s); IR (KBr) 3471 (br, s, νOH), 1109, 1058, 1033, 1021 cm^{-1} (m). Anal. Calcd for $C_{28}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 74.81; H, 9.82.

(20*S*)-3β-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-16α,17α-epoxy-5-pregen-20-ol (8a): mp 175–176 °C (95% ethanol); $[\alpha]^{23}_D$ −39.4° (*c* 1.51, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3 H, 18-H), 1.02 (s, 3 H, 19-H), 1.32 (d, 3 H, *J* = 6.4 Hz, 21-H), 3.44–3.58 (m, 2 H, CH_2OCHO), 3.50 (s, 1 H, 16β-H), 3.85–3.95 (m, 1 H, 3α-H), 4.21 (dq, 1 H, *J* = 7.2, 6.6 Hz, 20-H), 4.71 (apparent br t, 1 H, *J* = 4.4 Hz, CH_2OCHO), 5.34 ppm (br dd, 1 H, *J* = 5.2, 4.9 Hz, 6-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.65 (q), 19.32 (q), 20.05 (t), 20.73 (q), 25.56 (t), 26.93 (t), 29.70 (t), 30.24 (d), 31.34 (t), 31.54 (t), 33.07 (t), 36.96 (s), 37.40 (t), 38.85 (t), 40.30 (t), 41.19 (s), 46.37 (d), 50.41 (d), 58.96 (d), 62.84 (t), 63.05 (d), 73.60 (s), 76.01 (d), [96.99 and 97.10] (d), [121.12 and 121.18] (d), [141.22 and 141.38] ppm (s); IR (KBr) 3473 (br, νOH), 1058, 1033 cm^{-1} (m). Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 74.98; H, 9.87.

Preparation of *N*,*N*,*N*′,*N*′-Tetramethylphosphorodiamidates. To a solution of the 20-hydroxy steroid (0.10 M in THF/TMEDA (4:1)) under N_2 at −78 °C was added, with magnetic stirring, *n*-butyllithium (1.05 equiv of a 1.60 M solution in hexanes). The solution was stirred at that temperature for 20 min prior to the addition of bis(dimethylamino)phosphorochloridate (1.00 equiv). The reaction mixture was then allowed to warm to rt before the addition of a saturated aqueous NH_4Cl solution. The resulting mixture was extracted with ethyl acetate three times, and the combined organic solutions were washed with brine, dried (Na_2SO_4), and concentrated by rotary evaporation. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate (3:1)) afforded the phosphorodiamidate derivative as a white solid.

(20*R*)-3β-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-[(*N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidyl)oxy]-16α,17α-epoxy-5-pregnene (7b). Prepared from **7a** (2.00 g, 4.80 mmol), yield 2.59 g (98%). **7b**: mp 118–120 °C; $[\alpha]^{23}_D$ −10.9° (*c* 1.44, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3 H, 18-H), 1.02 (s, 3 H, 19-H), 1.23 (d, 3 H, *J* = 6.4 Hz, 21-H), 2.64 [d, 12 H, $^3J_{PH}$ = 9.6 Hz, $P(N(CH_3)_2)_2$], 3.24 (s, 1 H, 16β-H), 3.42–3.57 (m, 2 H, CH_2OCHO), 3.85–3.96 (m, 1 H, 3α-H), 4.71, (apparent br t, 1 H, *J* = 4.5 Hz, CH_2OCHO), 5.01 (dq, 1 H, $^3J_{PH}$ = 7.2 Hz, *J* = 6.4 Hz, 20-H), 5.33 ppm (br dd, 1 H, *J* = 4.9, 4.8 Hz, 6-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.37 (q), 17.70 (q), 19.30 (q), 20.04 (t), 20.73 (t), 25.56 (t), 27.12 (t), 28.05 (t), 29.71 (t), 30.30, 31.34, 31.59, 32.96 (t), 36.70 (q), 37.01, 37.19, 37.42, 38.87 (t), 40.32 (t), 42.07 (s), 46.15 (d), 50.54 (d), 59.09 (d), 62.83 (t), 70.40 (s, d*, $^3J_{PC}$ = 8.2 Hz), 70.56 (d, d*, $^2J_{PC}$ = 4.2 Hz), 76.05 (d), [96.96 and 97.08] (d), [121.04 and 121.10] (d), [141.37 and 141.54] ppm (s); IR (KBr) 1216, 1114, 1059, 1033, 1024, 1002 cm^{-1}. Anal. Calcd for $C_{30}H_{51}N_2O_5P$: C, 65.43; H, 9.34; N, 5.09. Found: C, 65.14; H, 9.29; N, 5.29.

(20*S*)-3β-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-[(*N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidyl)oxy]-16α,17α-epoxy-5-pregnene (8b). Prepared from **8a** (0.802 g, 1.93 mmol), yield 1.02 g (96%). **8b**: mp 129–130 °C; $[\alpha]^{23}_D$ − 36.9° (*c* 1.49, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3 H, 18-H), 1.02 (s, 3 H, 19-H), 1.39 (d, 3 H, *J* = 6.4 Hz, 21-H), 2.62 [d, 12 H, $^3J_{PH}$ = 9.8 Hz, $P(N(CH_3)_2)_2$], 3.43–3.55 (m, 2 H, CH_2OCH), 3.55 (s, 1 H, 16β-H), 3.85–3.96 (m, 1 H), 4.70 (apparent br t, 1 H, *J* = 4.2 Hz, CH_2OCHO), 4.91 (dq, 1 H, $^3J_{PH}$ = 8.6 Hz, *J* = 6.4 Hz, 20-H), 5.33 ppm (br dd, 1 H, *J* = 4.9, 4.4 Hz, 6-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.84 (q), 19.30 (q), 19.32 (q), 20.03 (t), 20.65 (t), 25.56 (t), 27.24 (t), 28.04 (t), 29.70 (t), 30.29, 31.33, 31.57, 32.70 (t), 36.57 (q), 37.00, 37.18, 37.42, 38.87 (t), 40.31 (t), 40.31 (t), 41.57 (s), 45.96 (d), 50.46 (d), 59.66 (d), 62.79 (t), 67.67 (d, d*, $^2J_{PC}$ = 4.0 Hz),

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73.35 (s, d*, $^3J_{PC}$ = 6.5 Hz), 76.01 (d), [96.97 and 97.06] (d), [121.04 and 121.11] (d), 141.24 ppm (s); IR (KBr) 1226, 1059, 1032 cm^{-1}. Anal. Calcd for $C_{30}H_{51}N_2O_5P$: C, 65.43; H, 9.34; N, 5.09. Found: C, 65.19; H, 9.22; N, 5.28.

Reductive Epoxide-Ring Opening of Phosphorodiamidate Derivatives. Ethylamine (30 mL) was dried by passing through a chamber of NaOH and condensed under N_2 at −78°C. Lithium wire (45 mg, 6.77 mmol, cut into small pieces and flattened with a hammer) was then added to ethylamine with magnetic stirring over a period of 10 min. When virtually all of the lithium had dissolved (ca. 20 min), a solution of the steroidal phosphorodiamidate (0.125 g, 0.227 mmol) in 5 mL of dry THF was added to the dark blue solution dropwise through a syringe over a period of 2 min and then the dry ice/2-propanol bath was replaced with an ice–water bath, and the solution was allowed to warm to 0 °C. After 60 min at 0 °C, water (10 mL) was added, and the reaction mixture was allowed to warm to rt and was kept under continued stirring until most of the ethylamine had evaporated. The remaining aqueous solution was extracted with ethyl acetate (3 × 35 mL), and the combined organic solutions were washed with brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, gradient elution) provided exclusively the (*Z*)-allylic alcohol **9**[3c,d,6] as a crystalline white solid: mp 144–146 °C (lit.[1] oil) (74 mg, 81% from the 20*R*-isomer; 68 mg, 75% from the 20*S*-isomer; and 70 mg, 77% from a 3:1 mixture of 20*R* and 20*S* stereoisomers).

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1,6- and 1,8-Addition Reactions of Organocuprates to Michael Acceptors: NMR-Spectroscopic Observation of the Intermediates and Conclusions about the Reaction Mechanism

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The 1,4-addition of organocuprates to enones and enoates is one of the most important C–C bond-forming processes in organic chemistry.[1] This is due to the usually very high reactivity which allows broad applications of this reaction; furthermore, the importance of this process is enhanced by the use of diastereoselective[2] as well as enantioselective variants[3] (using cuprates with chiral ligands). In contrast to the large number of applications of addition reactions of organocuprates, the understanding of the reaction mechanisms is poor; the knowledge of the mechanistic picture is prerequisite, however, for the fine-tuning of a reaction, e.g., for choosing chiral ligands suitable for enantioselective addition reactions.

The mechanism of the 1,4-addition reaction of cuprates to enones and enoates has been investigated using NMR spectroscopy.[4] It was found that at low temperature attack of the cuprate at the C–C double bond of the Michael acceptor **1** gives rise to the formation of the π-complex **2** which is characterized by the bond between a copper atom and the π-system of the double bond and the interaction of a lithium atom with the carbonyl oxygen atom.[5] Upon warming, the spectra of the lithium enolate **5** were obtained; intermediates formed during the transformation of **2** to **5** could not be detected by NMR spectroscopy. It has been postulated that this transformation proceeds via organocopper compound **3**; herein, the copper atom has the unstable oxidation state +3, and rapid reductive elimination of RCu should give the enolate **5**.[4] This mechanism has been challenged by Berlan et al. who proposed the formation of species **4** by 1,2-addition of the cuprate across the C–C double bond; reductive elimination of RCu should again yield enolate **5**.[6] In both cases it is assumed that the formation of the enolate **5** occurs by *intramolecular* addition of the cuprate bound in the π-complex;[7] this assumption is also the basis for the mechanistic rationalizations of diastereoselective[2] and enantioselective[3] cuprate additions. In this paper, it is shown that the 1,6- and 1,8-additions of organocuprates to Michael acceptors are also occurring via π-complexes of type **2**; in these cases, the formation of the addition products might proceed by *intermolecular* attack of a second cuprate at these π-complexes.

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