Reduction of 17α-Hydroxy-20-keto Steroids: Convenient Synthesis of (E)-3β-Hydroxy-5,17(20)-pregnadiene 3-Pivaloate and (Z)-3β,16α-Dihydroxy-5,17(20)-pregnadiene 3-Pivaloate

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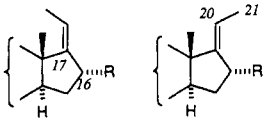
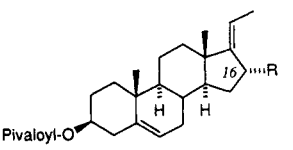
Reduction of the 20-keto group of both 17α-hydroxy- and 16α-alkoxy-17α-hydroxy steroids has been examined with various hydride reagents in a number of different solvent systems. For each of these steroids, specific conditions have been established to cleanly reduce to (20*R*)-17α,20-α-diols. These conditions have been applied to the synthesis of (*E*)-3β-hydroxy-5,17(20)-pregnadiene 3-pivaloate (**5**) and (*Z*)-3β,16α-dihydroxy-5,17(20)-pregnadiene 3-pivaloate (**6**) from commercially available 3β,17α-dihydroxy-5-pregnen-20-one (**7a**) and 3β-hydroxy-5,16-pregnadien-20-one (**11a**), respectively. The pivaloate derivative of **7a** was reduced with L-Selectride in THF to provide, after mild acid treatment and oxidative workup, (20*R*)-17α,20-diol **9** as a single stereoisomer in 86% yield. Subsequent syn-dideoxygenation of its thionocarbonate derivative with triethyl phosphite afforded pure (*E*)-ethylidene **5** in 56% overall yield from **7a**. [2-(Trimethylsilyl)ethoxy]methyl (SEM) ether derivative of the 16α-hydroxy group of 3β,16α,17α-trihydroxy-5-pregnen-20-one 3-pivaloate (**13b**), obtained in two steps from **11a**, was reduced with $(n\text{-Bu})_4NBH_4$ in THF to provide, after mild acid treatment of the quenched solution, (20*R*)-17α,20-diol **14b** as a single stereoisomer in 90% yield. Similar dideoxygenation of the diol followed by deprotection of the SEM group with CsF gave 16α-hydroxylated (*Z*)-17-ethylidene **6** in 48% overall yield from **11a**. In addition, results on stereoselective syn-deoxygenation of (20*S*)-17α,20-epoxides are also discussed.

Stereochemically pure 17-ethylidene steroids[1,2] and their 16-oxygenated analogues[1,3] are pivotal intermediates for the stereocontrolled construction of steroid side chains. While (*Z*)-17-ethylidene **1**[2] and its 16α-hydroxylated derivative (*E* isomer) **2**[3] are obtainable stereoselectively, their geometric isomers **3** and **4** are not as readily accessible at present. A variety of multistep approaches toward **3** are described in the literature, often without experimental procedures.[4] Among these, the best method appears to be a six-step synthesis of (*E*)-3β-hydroxy-5,17(20)-pregnadiene tetrahydropyranyl ether from dehydroisoandrosterone reported by Midland.[4g] In contrast, the only available means to access its 16α-hydroxylated analogue **4** is either through laborious chromatographic separation of the minor component of the product mixture obtained from the Wharton reaction[5a] of 16α,17α-epoxy-20-one steroids,[3,5] or through chromatographic separation of an about 1:1 mixture of (*Z*)-3β,16α- and -3β,16β-dihydroxy-5,17(20)-pregnadiene diacetates (10–13% each), obtained from the acid-catalyzed rearrangement reaction of 3β,20-dihydroxy-5,16-pregnadiene diacetate (1:1 epimeric mixture at C-20).[5b] Herein described are results on the reduction of 17α-hydroxy-20-keto steroids with various hydride reagents in several different solvent systems and their application to the convenient synthesis of these olefins (*E*)-3β-hydroxy-5,17(20)-pregnadiene 3-pivaloate (**5**) and its selectively protected 16α-hydroxy analogue (*Z*)-3β,16α-dihydroxy-5,17(20)-pregnadiene 3-pivaloate (**6**). Furthermore, discussed below are some observations on the stereocontrolled deoxygenation of the trisubstituted (20*S*)-17α,20-epoxides in connection with the attempted synthesis of the geometric isomers of **5** and **6**.





1 R = H
2 R = OH

3 R = H
4 R = OH

5 R = H
6 R = OH

Our initial efforts were directed toward establishing the conditions for stereoselective reduction of a 17α-hydroxy-20-keto steroid to a 17α,20-diol, from which stereospecific dideoxygenation at both C-17 and C-20 could be achieved. To this end, a number of reducing agents such as $LiAlH_4$, $NaBH_4$, and 9-BBN were examined for the reduction of the 20-ketone of 3-pivaloate derivative **7b** of the commercially available 3β,17α-dihydroxy-5-pregnen-20-one (**7a**). While these reagents generally gave one of the 20-hydroxy epimers as a major product, their stereoselectivity was not satisfactory, i.e., typically a 2/1–5/1 ratio. Interestingly, the reaction of **7b** with L-Selectride at −78 °C followed by aqueous NH_4Cl workup resulted in the smooth formation of boronate **8**[6] in 86% yield as a 1:1 epimeric mixture at the α-carbon to the boron atom. The

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(6) Structures **8–10** and **12–21** all share the same A–C ring structure as **5**.

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Table I. Reduction of 3β,16α,17α-Trihydroxy-5-pregnen-20-one 16-(Methoxymethyl ether) (13a)

run[a]	hydride reagent	conditions	% total yield of diols	% composition of diols[b] 14a[c]	15[d]	16[e]
1	$NaBH_4$	MeOH/THF (6:1), room temperature, 0.5 h	98	25	75	–
2	$NaBH_4$	EtOH/THF (2:1), room temperature, 14 h	31	60	–	40
3	$NaB(OMe)_3H$	THF, room temperature, 22 h	54	53	–	47
4	$NaBH_4$	H_2O/THF (1:62.5), −23 °C, 2 h	84	40	46	14
5	$NaB(OAc)_3H$	AcOH, 45 °C, 2 days	30	–	100	–
6	$(n\text{-}Bu)_4NBH_4$	THF; MeOH, room temperature, H_2O quench (see text)	90	80	–	20
7	$(n\text{-}Bu)_4NBH_4$	THF; MeOH, room temperature, H_2O/H^+ quench (see text)	90	100	–	–

[a] Millimoles of steroid **13a**, hydride reagent, and the total solvent volume for runs 1–5 are: run 1, 0.105, 0.625, and 3.5 mL; run 2, 0.0734, 0.185, and 3 mL; run 3, 0.105, 0.133, and 3 mL; run 4, 0.210, 0.529, and 5.08 mL; run 5, 0.105, 0.126, and 4 mL. Experimental procedures employed in runs 6 and 7 are identical with those described for the $(n\text{-}Bu)_4NBH_4$ reduction of **13b**. Note, however, in run 6 treatment with 10% aqueous HCl was omitted after the aqueous ammonium chloride quench. [b] Determined by 300-MHz ^1H NMR spectra (in $CDCl_3$) of the mixture of diols. [c] For **14a**: mp 173–175 °C; $[\alpha]^{23}_D$ −119° (*c* 0.36, $CHCl_3$); ^1H NMR (300 MHz) δ 0.841 (s, 3 H), 1.032 (s, 3 H), 1.181 (s, 9 H), 3.033 (s, 1 H, OH), 3.405 (s, 3 H), 3.887 (m, 2 H), 4.573 (m, 1 H), 4.633 (d, 1 H, *J* = 6.8 Hz), 4.747 (d, 1 H, *J* = 6.8 Hz), 5.361 (br d, 1 H, *J* = 3.8 Hz); ^{13}C NMR (75.3 MHz) δ 15.06 (q), 18.78 (q), 19.37 (q), 20.25 (t), 27.19 (q, 3 C), 27.70 (t), 31.69 (d), 31.85 (t), 32.00 (t), 32.63 (t), 36.68 (s), 36.97 (t), 38.08 (t), 38.64 (s), 47.39 (s), 48.84 (d), 49.73 (d), 56.72 (q), 70.16 (d), 73.55 (d), 78.74 (d), 83.65 (s), 96.28 (t), 122.04 (d), 140.11 (s), 177.95 (s); IR (KBr) 3413, 1722, 1166 cm^{-1}. [d] For **15**: ^1H NMR (300 MHz) δ 0.675 (s, 3 H), 1.043 (s, 3 H), 1.181 (s, 9 H), 1.411 (d, 3 H, *J* = 6.5 Hz), 3.418 (s, 3 H), 3.639 (s, 1 H, OH), 4.382 (q, 1 H, *J* = 6.5 Hz), 4.447 (m, 1 H), 4.627 (m, 1 H), 4.648 (d, 1 H, *J* = 6.9 Hz), 4.728 (d, 1 H, *J* = 6.9 Hz), 5.364 (br d, 1 H, *J* = 3.5 Hz). [e] For **16**: mp 181–183 °C; $[\alpha]^{23}_D$ −82.0° (*c* 0.69; $CHCl_3$; ^1H NMR (300 MHz) δ 0.744 (s, 3 H), 1.022 (s, 3 H), 1.180 (s, 9 H), 1.215 (d, 3 H, *J* = 6.2 Hz), 3.156 (br s, 1 H, OH), 3.408 (s, 3 H), 3.846 (q, 1 H, *J* = 6.2 Hz), 4.223 (dd, 1 H, *J* = 2.4, 7.7 Hz), 4.569 (m, 1 H), 4.700 (d, 1 H, *J* = 6.4 Hz), 4.767 (d, 1 H, *J* = 6.4 Hz), 5.360 (br d, 1 H, *J* = 4.4 Hz); ^{13}C NMR (75.3 MHz) δ 14.29 (q), 18.35 (q), 19.37 (q), 20.09 (t), 27.19 (q, 3 C), 27.70 (t), 31.16 (t), 31.39 (d), 31.90 (t), 32.98 (t), 36.65 (s), 36.94 (t), 38.07 (t), 38.65 (s), 46.02 (s), 49.42 (d), 49.55 (d), 56.19 (q), 72.03 (d), 73.50 (d), 82.30 (d), 83.43 (s), 96.62 (t), 122.11 (d), 139.99 (s), 177.94 (s); IR (KBr) 3506, 1720, 1168 cm^{-1}.

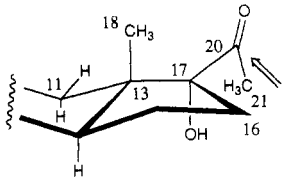
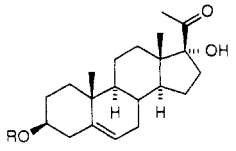
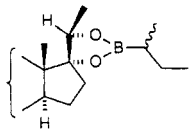


Figure 1.

oxidative aqueous workup with H_2O_2 of the same reaction afforded 17α,20-diol **9** in 86% yield as a single stereoisomer. The C-20 stereochemistry of **9** could not be assigned



7a R = H
7b R = pivaloyl



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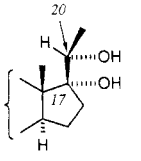

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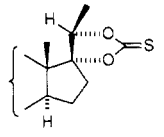
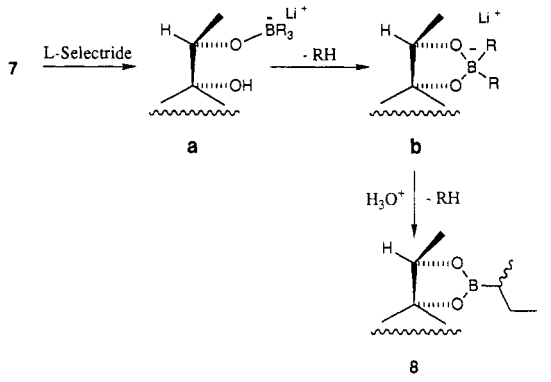


10

at this stage, but was subsequently deduced as 20*R* based on the results on the stereospecific syn-dideoxygenation to **5** as described below. The complete stereoselectivity observed at C-20 may be rationalized by the approach trajectory of the "hydride" to C-20 as indicated in Figure 1. The results of molecular mechanics calculations (MAXIMIN program) as well as the lack of the intramolecular hydrogen bonding between the 17α-hydroxyl and the carbonyl as judged by its IR and ^1H NMR spectra suggest the conformation of **7b** shown in Figure 1 to be the most stable; the torsional angle between C_{13}—C_{17} and C_{20}=O was calculated to be 89.6°. Bulky L-Selectride (Aldrich) reduces the 20-ketone directly without involving the initial reaction with the highly congested 17α-hydroxyl. The lithium "ate" complex a is likely to react with the 17α-

Scheme I[a]



[a] R = *sec*-butyl.

hydroxyl to give rise to the cyclic ate complex b, which upon aqueous workup affords boronate **8** (Scheme I). It is of interest to note that the similar boronate formation from 1,2-diols with lithium trialkylborohydrides has recently been reported.[7]

The synthesis of **5** from diol **9** was readily achieved by stereospecific syn-dideoxygenation of its thionocarbonate derivative **10**.[8,9] Thus, refluxing thionocarbonate **10**, obtained from **9** and thophosgene in 74% yield, in triethyl phosphite for 20 h resulted in the smooth formation of (*E*)-ethylidene **5** (91%) whose 300-MHz ^{1}NMR was void of the peaks assignable to its *Z* isomer.[10]

The above dideoxygenation approach was also applied to the synthesis of *Z*-allylic alcohol **6**. The 3-pivaloate derivative **11b** of readily available 3β-hydroxy-5,16-pregnadien-20-one (**11a**) was first converted selectively to its 16α,17α-diol **12** with $KMnO_4$,[11] which was then protected as its 16-methoxymethyl (MOM) ether **13a**. The reduction of the ketone of **13a** was first attempted as above with L-Selectride, which proceeded slowly at room temperature,

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(8) Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677.
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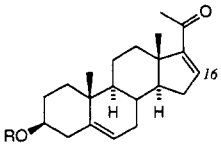
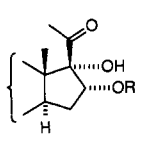
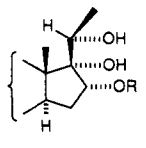
and only deacylated product was isolated. Therefore, several smaller and reactive $NaBH_4$ and related reagents were next examined in various solvent systems (Table I).



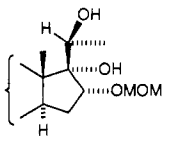
11a R = H
11b R = pivaloyl



12 R = H
13a R = MOM
13b R = SEM



14a R = MOM
14b R = SEM



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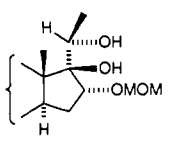

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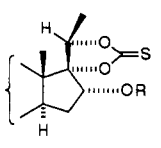
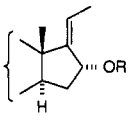


17a R = MOM
17b R = SEM

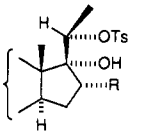
Reduction of **13a** with $NaBH_4$ in MeOH/THF afforded a 1:3 mixture of C-20 epimers **14a** and **15** in 98% yield. Somewhat surprisingly, when EtOH/THF was used as the solvent, the reaction proceeded very sluggishly and a 1.5:1 mixture of **14a** and compound **16**,[12] tentatively assigned as 17β-epimer of **14a** based on spectroscopic evidence (see footnote *e*, Table I), was isolated in low yield. Similar results were obtained upon reduction of **13a** with $NaB(OMe)_3H$ in THF (see Table I). As it was felt that the steric hindrance imposed by the 16-MOM group is likely to impede the reduction at C-20, **13a** was treated with $NaBH_4$ in H_2O/THF.[13] Unfortunately, while the reduction proceeded rapidly and highly efficiently, a mixture of all three diols was produced. Stereochemical assignment of three diols was made on the basis of the experimental observation that: (1) stereospecific syn-dideoxygenation of **14a** provided *Z*-allylic alcohol derivative **18a** (vide infra) and (2) aqueous acid treatment of **16** resulted in the smooth conversion into **14a**. Apparently, isomerization at C-17, which must take place prior to the reduction of the ketone, is caused due to the basic nature of the reaction medium, and the ratio of the three diol products depends upon the relative rates of isomerization at C-17 and reductions of the ketone group of **13a** and its 17β-epimer. It is of interest to note that the reduction of the latter ketone appears to produce only 20*R* isomer **16**.

In a somewhat different vein, efforts were then made to reduce the 20-ketone through the use of a possible 17α-hydroxy-assisted intramolecular process. Thus, hydroxy ketone **13a** was treated with $NaB(OAc)_3H$ in THF,[14] the condition that is postulated to undergo hydroxy-assisted intramolecular delivery of a hydride to ketones. However, the reaction at room temperature with this reagent did not yield detectable amounts of products. Even at 45 °C, the reduction of the 20-ketone proceeded very sluggishly, providing diol **15** as a single diol stereoisomer in low yield (see Table I). In an attempt to reduce the size of the hydride reagent, **13a** was stirred with 2 equiv of $(n\text{-Bu})_4NBH_4$ in THF[15] for 24 h, at which point a large excess of methanol was added to the reaction mixture. Aqueous quench of the reaction gave a 4:1 mixture of **14a** and **16** in 90% yield. However, it was subsequently found that the minor diol, **16**, could be completely converted into **14a** simply by treating the above aqueous solution with dilute HCl for a period of 6 h at room temperature, providing **14a** in 90% yield from **13**. Mechanistic details of this surprisingly facile acid-catalyzed isomerization of the 17β-hydroxyl of **16** remain unclear. In this regard it is interesting to note that reexamination of the reduction of **7b** with L-Selectride revealed that the aqueous ammonium chloride treatment of the resulting boronate was essential for obtaining boronate **8**. Thus, omitting this overnight acid treatment resulted in the formation of a mixture of boronates which upon H_2O_2 treatment gave an approximately 1:1 mixture of 17,20-diols. But it was found that this mixture of diols could also be cleanly epimerized into a single diol **9** as above.

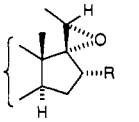
For the synthesis of *Z*-allylic alcohol **6**, α-diol **14a** was first converted to thionocarbonate **17a** (77%), which upon refluxing in triethyl phosphite afforded (*Z*)-17-ethylidene **18a** in quantitative yield. However, deprotection of **18a** under a variety of acidic conditions failed, invariably accompanied by a significant degree of stereochemical scrambling at C-20. Accordingly, [2-(trimethylsilyl)ethoxy]methyl (SEM) ether **13b** was prepared and reduced with $(n\text{-Bu})_4NBH_4$ followed by acid treatment as before, providing α-diol **14b** in 86% overall yield from **12**. A similar dideoxygenation sequence was repeated with **14b** to afford the 16-SEM-protected (*Z*)-17-ethylidene **18b** in 78% overall yield from **14b**. Treatment of **18b** with CsF in refluxing DMF resulted in the clean deprotection of the SEM group without even a trace of stereochemical scrambling of the 17,20-double bond to provide pure *Z*-alylic alcohol **6** in 80% yield.



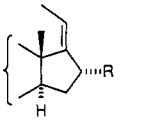
18a R = MOM
18b R = SEM



19a R = H
19b R = OSEM



20a R = H
20b R = OSEM



21a R = H
21b R = OSEM

Anti stereospecific dideoxygenation of 17α,20-diols **9** and **14b** would provide (*E*)-ethylidene **21a** and (*Z*)-16-hydroxyethylidene **21b**, respectively. To this end, two diols were converted into epoxides **20a** and **20b** by treatment of their corresponding tosylates **19a** and **19b** with NaH in 97% and 72% overall yields, respectively. Stereocontrolled deoxygenation of epoxides with retention of stereochemistry is described in the literature. However, most of these methods are applied to either disubstituted epoxides or epoxides of cyclic trisubstituted olefins.[16] Therefore, stereochemical preservation during the deoxygenation of

(12) A small amount of diol **16** was isolated and was converted into its 17,20-thionocarbonate (50% yield) whose ^1H and ^{13}C NMR spectra were distinctly different from those of **17b**.

(13) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2718.

(14) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Evans, D. A.; Chapman, K. T. *Ibid.* **1986**, *27*, 5939. (c) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. While the concept of the 17α-hydroxy-assisted reduction of the 20-ketone is highly attractive, it must be emphasized that the possibility still exists that this ketone reduction of **13a** with $(n\text{-Bu})_4NBH_4$ may not necessarily involve such an intramolecular process.

(15) (a) Raber, D. J.; Guida, W. C. *J. Org. Chem.* **1976**, *41*, 690. (b) Sorrell, T. N.; Pearlman, P. S. *Tetrahedron Lett.* **1980**, 3963. (c) Raber, D. J.; Guida, W. C.; Shoenberger, D. C. *Ibid.* **1981**, *22*, 5107 and references cited therein.

(16) See: Ogawa, A.; Miyake, J.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* **1985**, *26*, 669 and references cited therein.

epoxides **20a** and **20b** could not be assessed a priori with certainty. Treatment of **20a** with WCl_6/n-BuLi[17] and $[(n\text{-Bu})_3SnAlMe]Li$[18] resulted in the formation of 17-ethylidene in 51% and 47% yields, but with considerable scrambling of the olefin stereochemistry, i.e., 1.2:1 and 3.5:1 mixtures of *Z*:*E*-ethylidenes, respectively. The only literature precedent where trisubstituted spiro epoxides are demonstrated to undergo deoxygenation with complete retention of stereochemistry appears to be the method with P_2I_4 reported by Mori et al.[19] Deoxygenation of epoxide **20a** with P_2I_4 in CH_2Cl_2 at room temperature indeed produced pure (*E*)-ethylidene **21a**. However, the yield for its formation was only 30–35%. Similar treatment of 16-oxygenated epoxide **20b** resulted in complete recovery of the starting epoxide or the formation of a complex mixture of products when the reaction was conducted at room temperature or at reflux in CH_2Cl_2, respectively.

In conclusion, reduction of the 20-ketone of both 17α-hydroxy and 16α-alkoxy-17α-hydroxy steroids has been studied with various hydride reagents in several different solvent systems. For each of these steroids, specific conditions have been established for reduction to (20*R*)-17α,20-diols with complete stereoselectivity. These (20*R*)-17α,20-diols were subsequently converted by the use of the stereospecific syn-dideoxygenation sequence to stereochemically pure (*E*)-3β-hydroxy-5,17(20)-pregnadiene 3-pivaloate (**5**) and selectively protected (*Z*)-3β,16α-dihydroxy-5,17(20)-pregnadiene 3-pivaloate (**6**), thus constituting convenient syntheses of these synthetically highly versatile olefins in 56% and 48% overall yields from commercially available 3β,17α-dihydroxy-5-pregnen-20-one (**7a**) and 3β-hydroxy-5,16-pregnadien-20-one (**11a**), respectively.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra were recorded on either a Bruker WM360 or a AM300 spectrometer in $CDCl_3$. The multiplicity indicated for each ^{13}C NMR chemical shift represents the observed splitting pattern of the corresponding ^{13}C peak when run in an off-resonance decoupling mode. The off resonance ^{13}C NMR spectrum was not taken of the epimeric mixture of boronate 8. IR data are reported in wavenumbers (cm^{-1}).

Melting points were taken on a hot stage apparatus and are uncorrected. Column chromatographic separation was performed with the method of flash column chromatography with Merck 230–400 mesh silica gel.[20] Reactions were monitored by thin-layer chromatography (TLC) with Analtech 250 plates with fluorescent indicator. Spots were detected by ultraviolet light (254 nm), iodine vapor, and ceric ammonium sulfate–sulfuric acid.

Air- and/or moisture-sensitive reactions were performed under a static pressure of dry nitrogen after flushing the reaction vessel with a stream of dry nitrogen. All glassware was oven-dried. Reagents and solvents were transferred by standard syringe techniques through rubber septa. The following solvents were dried and purified under dry nitrogen atmosphere just prior to use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Methylene chloride and pyridine were distilled from calcium hydride.

Energy minimization of **7b** was carried out by use of the MAXIMIN molecular mechanics methods within the SYBYL software package.

3β,17α-Dihydroxy-5-pregnen-20-one 3-Pivaloate (7b). To a solution of 2.50 g (7.52 mmol) of 3β,17α-dihydroxy-5-pregnen-20-one (**7a**) (purchased from Steraloids, Inc, Wilton, NH) in 12 mL of pyridine was added 2.75 mL (22.6 mmol) of pivaloyl chloride in 2.5 mL of pyridine over the course of 1 h, and the mixture was allowed to stir overnight, at which point methylene chloride (ca. 50 mL) was added. The resulting mixture was washed successively with 10% aqueous HCl (3 × ca. 50 mL), saturated aqueous $NaHCO_3$ (3 × ca. 20 mL), and brine (1 × ca. 50 mL). The organic layer was then dried ($MgSO_4$), filtered, and evaporated under reduced pressure, leaving 3.00 g of **7b** (96%) as a white solid: mp 209–210 °C (95% ethanol); $[\alpha]^{23}_D$ −64.5° (*c* 1.81, $CHCl_3$); ^1H NMR (300 MHz) δ 0.738 (s, 3 H), 1.037 (s, 3 H), 1.183 (s, 9 H), 2.276 (s, 3 H), 4.577 (m, 1 H), 5.377 (br d, 1 H, *J* = 5.3 Hz); ^{13}C NMR (90.56 MHz) δ 15.30 (q), 19.30 (q), 20.65 (t), 24.16 (t), 27.22 (q, 3 C), 27.68 (q), 27.75 (t), 30.34 (t), 32.03 (t and d, 2 C), 33.80 (t), 36.77 (s), 37.14 (t), 38.68 (t), 48.16 (s), 49.83 (d), 50.94 (d), 73.55 (d), 90.23 (s), 122.21 (d), 139.98 (s), 177.95 (s), 211.18 (s); IR (KBr) 3389, 1723, 1707, 1691, 1171 cm^{-1}; high-resolution MS (CI; NH_3) calcd for $C_{26}H_{44}O_4N$ $(M + NH_4)^+$ *m/z* 434.3270, found *m/z* 434.3279. Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 74.89; H, 9.70.

(20*R*)-3β,17α,20-Trihydroxy-5-pregnen-20-one 3-Pivaloate 17,20-*sec*-Butylboronate (8). A solution of pivaloate **7b** (2.98 g, 7.15 mmol) in 12 mL of THF under dry N_2 was cooled to −78 °C. Over the course of 30 min, 18 mL of 1 M L-Selectride in THF was added dropwise at −78 °C, and the solution was kept stirring at that temperature for 3 h, after which time it was allowed to warm slowly to room temperature and stir for an additional hour. The reaction was quenched by the addition of 20 mL of saturated aqueous ammonium chloride and allowed to stir overnight, and the THF was evaporated off. To the resulting solid residue was added 50 mL of methylene chloride. The solution was washed with water (50 mL) and brine (25 mL), dried ($MgSO_4$), filtered, and evaporated, leaving 2.97 g of **8** as a white solid (86%): mp 128–129 °C (95% ethanol); $[\alpha]^{23}_D$ −55.9° (*c* 1.58, $CHCl_3$); ^1H NMR (360 MHz) δ 0.657 (s, 3 H), 0.908 (t, 3 H, *J* = 7.4 Hz), 0.973 (d, 3 H, *J* = 1.3 Hz), 1.041 (s, 3 H), 1.184 (s, 9 H), 1.246 (d, 3 H, *J* = 6.5 Hz), 4.358 (q, 1 H, *J* = 6.5 Hz), 4.556 (m, 1 H), 5.386 (d, 1 H, *J* = 4.5 Hz); ^{13}C NMR (90.56 MHz) δ 12.34, 14.27, 15.26, 15.42, 19.45, 20.39, 20.47, 22.61, 26.27, 27.24, 27.83, 29.78, 31.83, 31.87, 32.33, 36.87, 37.20, 38.18, 46.24, 50.06, 50.15, 73.64, 74.13, 77.23, 94.61, 107.66, 107.72, 122.42, 140.00, 177.94; IR (KBr) 1720, 1181 cm^{-1}; MS (CI, NH_3) *m/z* 502 $(M + NH_4)^+$. Anal. Calcd for $C_{30}H_{49}O_4B$: C, 74.37; H, 10.19; B, 2.23. Found: C, 74.40; H, 10.23; B, 2.14.

(20*R*)-3β,17α,20-Trihydroxy-5-pregnene 3-Pivaloate (9). A solution of 3.00 g (7.20 mmol) of alcohol **7b** in 20 mL of THF was cooled under N_2 to −78 °C. Over the course of 30 min, 18 mL of 1 M L-Selectride in THF was added dropwise at that temperature. The solution was kept stirring at −78 °C for 2 h and at room temperature for 1 h. The solution was quenched with 40 mL of saturated aqueous ammonium chloride, and the resulting mixture was allowed to stir overnight. The THF was evaporated off under reduced pressure, and 50 mL of CH_2Cl_2 was added. The solution was washed with water (40 mL) and brine (25 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated off. The resulting solid was redissolved in 50 mL of THF and recooled to 0 °C, at which time the flask was evacuated and charged with oxygen, and 9 mL of 30% aqueous hydrogen peroxide was then added very slowly (*caution*: much gas is evolved). The resulting solution was left to stir at that temperature for 30 min and at room temperature for 30 min. The reaction was quenched with 20 mL of saturated aqueous sodium bicarbonate solution, the THF was evaporated off, 75 mL of methylene chloride was added, and the organic phase was washed with brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated, leaving 2.56 g of **9** (86%) as a white solid: mp 234–236 °C (95% ethanol); $[\alpha]^{23}_D$ −63.0° (*c* 1.23, $CHCl_3$); ^1H NMR (360 MHz) δ 0.823 (s, 3 H), 1.043 (s, 3 H), 1.180 (d, 3 H, *J* = 6.1 Hz), 1.182 (s, 9 H), 4.023 (q, 1 H, *J* = 6.1 Hz), 4.574 (m, 1 H), 5.378 (br d, 1 H, *J* = 3.6 Hz); ^{13}C NMR (90.56 MHz) δ 15.08 (q), 18.76 (q), 19.41 (q), 20.86 (t), 24.05 (t), 27.24 (q, 3 × C), 27.80 (t), 32.09 (t), 32.29 (t), 32.35 (d), 34.15 (t), 36.78 (s), 37.18 (t), 38.15 (t), 38.70 (s), 47.31 (s), 49.98 (d), 50.67 (d), 70.57 (d), 73.70 (d), 85.36 (s), 122.42 (d), 139.97 (s), 178.01 (s); IR (KBr) 3566, 3535, 1697, 1191 cm^{-1}. Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.52; H, 10.19.

(17) Sharpless, K. B.; Umbreit, M. A.; Nieh, M. T.; Flood, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 6538.
(18) Matsubara, S.; Nonaka, T.; Okuda, Y.; Kanemoto, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1480.
(19) Mori, M.; Uozumi, Y.; Kimura, M.; Ban, Y. *Tetrahedron* **1986**, *42*, 3793.
(20) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

(20*R*)-3β,17α,20-Trihydroxy-5-pregnene 3-Pivaloate 17,20-Thionocarbonate (10). Diol **9** (200 mg, 0.478 mmol) was dissolved under N_2 in 3 mL of methylene chloride containing 141 mg (1.15 mmol) of 4-(dimethylamino)pyridine. The solution was cooled to 0 °C, 0.05 mL (0.656 mmol) of thiophosgene was added, and the reaction mixture was left to stir at that temperature for 30 min, warmed to room temperature, and allowed to stir for another 2 h. Approximately 2 g of silica gel was added to the reaction mixture, and the excess solvent was evaporated off. The resulting solid was placed on top of a silica gel column and eluted with 20% ethyl acetate/hexanes, and the solid thus obtained recrystallized from 95% ethanol to give 162 mg of **10** (74%) as white needles: mp 250–252 °C; $[\alpha]^{23}_D$ –64.8° (*c* 1.28, $CHCl_3$); ^1H NMR (300 MHz) δ 0.747 (s, 3 H), 1.035 (s, 3 H), 1.182 (s, 9 H), 1.462 (d, 3 H, *J* = 6.6 Hz), 4.682 (m, 1 H), 4.860 (q, 1 H, *J* = 6.6 Hz), 5.378 (br d, 1 H, *J* = 5.2 Hz); ^{13}C NMR (90.56 MHz) δ 14.24 (q), 17.55 (q), 19.40 (q), 20.21 (t), 23.33 (t), 27.22 (q, 3 C), 27.71 (t), 29.72 (t), 31.56 (t, 2 C), 32.16 (t), 32.16 (d), 36.76 (s), 37.08 (t), 38.07 (t), 38.67 (s), 46.93 (s), 49.60 (d), 50.22 (d), 73.42 (d), 79.28 (d), 102.84 (d), 121.92 (d), 139.99 (s), 177.85 (s), 190.55 (s); IR (KBr) 1785, 1718, 1162 cm^{-1}. Anal. Calcd for $C_{27}H_{40}O_4S$: C, 70.39; H, 8.75; S, 6.96. Found: C, 70.06; H, 8.63; S, 7.04.

[17(20)*E*]-3β-Hydroxy-5,17(20)-pregnadiene 3-Pivaloate (5). A dry, N_2-purged, 10-mL, round-bottomed flask was charged with 250 mg (0.543 mmol) of thionocarbonate **10** and 5 mL of triethyl phosphite, and the flask was fitted with a condenser and allowed to reflux for 20 h. The reaction mixture was concentrated under reduced pressure, 2 mL of methylene chloride was added, and the solution was placed on top of a silica gel column and eluted with methylene chloride to yield 190 mg of **5** (91%) as a white solid; mp 135–136 °C (95% ethanol); $[\alpha]^{23}_D$ –59.5° (*c* 1.12, $CHCl_3$); ^1H NMR (300 MHz) δ 0.754 (s, 3 H), 1.047 (s, 3 H), 1.183 (s, 9 H), 1.542 (dd, 3 H, *J* = 1.4, 6.6 Hz), 4.589 (m, 1 H), 5.047 (m, 1 H), 5.287 (br d, 1 H, *J* = 3.9 Hz); ^{13}C NMR (90.56 MHz) δ 13.76 (q), 18.82 (q), 19.43 (q), 21.11 (t), 24.45 (t), 26.39 (t), 27.21 (q, 3 × C), 27.78 (t), 31.84 (d), 31.90 (t), 36.07 (t), 36.88 (t), 37.14 (t), 38.14 (t), 38.67 (s), 43.53 (s), 50.71 (d), 55.14 (d), 73.59 (d), 110.39 (d), 122.38 (d), 140.06 (s), 152.51 (s), 177.94 (s); IR (KBr) 1728, 1168 cm^{-1}; high-resolution MS (CI, NH_3) calcd for $C_{26}H_{44}O_2N$ ($M + NH_4$)$^+$ *m/z* 402.3372, found *m/z* 402.3372. Anal. Calcd for $C_{26}H_{40}O_2$: C, 81.19; H, 10.48. Found: C, 80.81; H, 10.43.

3β-Hydroxy-5,16-pregnadien-20-one 3-Pivaloate (11b). A solution of 1.23 g (3.91 mmol) of 3β-hydroxy-5,16-pregnadien-20-one (**11a**; purchased from Sigma Chemical Co., St. Louis, MO) in 6 mL of pyridine was treated with 1.5 mL (12.2 mmol) of pivaloyl chloride dissolved in 1.2 mL of pyridine over the course of 1.5 h, and the reaction mixture was allowed to stir at room temperature for 6 h. The reaction was quenched by the addition of 20 mL of methylene chloride and 20 mL of 10% aqueous HCl solution. The organic layer was washed with two more portions of 20 mL of 10% aqueous HCl, with 20 mL of saturated aqueous sodium bicarbonate solution (2 × 20 mL) and finally with brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated, leaving 1.52 g of **11b** (97%) as a whitish solid: mp 192–195 °C (dec; recrystallized from 95% aqueous acetonitrile); $[\alpha]^{23}_D$ –29.5° (*c* 1.23, $CHCl_3$); ^1H NMR (300 MHz) δ 0.914 (s, 3 H), 1.016 (s, 3 H), 1.177 (s, 9 H), 2.259 (s, 3 H), 4.566 (m, 1 H), 5.372 (br d, 1 H, *J* = 5.6 Hz), 6.703 (dd, 1 H, *J* = 2.1, 3.2 Hz); ^{13}C NMR (90.56 MHz) δ 15.74 (q), 19.28 (q), 20.71 (t), 27.07 (q), 27.17 (q, 3 C), 27.67 (t), 30.26 (d), 31.61 (t), 32.26 (t), 34.70 (t), 36.85 (s), 36.94 (t), 38.10 (t), 38.60 (s), 46.15 (s), 50.49 (d), 56.45 (d), 73.44 (d), 121.79 (d), 140.41 (s), 144.03 (d), 155.45 (s), 177.81 (s), 196.47 (s); IR (KBr) 1725, 1683, 1666, 1166 cm^{-1}; high-resolution MS (CI, NH_3) calcd for $C_{26}H_{39}O_3$ ($M + H$)$^+$ *m/z* 399.2899, found *m/z* 399.2911. Anal. Calcd for $C_{26}H_{38}O_3$: C, 78.35; H, 9.61. Found: C, 78.07; H, 9.58.

3β,16α,17α-Trihydroxy-5-pregnen-20-one 3-Pivaloate (12). Pivaloate **11b** (2.50 g, 6.27 mmol) was dissolved in 300 mL of acetone (distilled over potassium permanganate) containing 1.2 mL of formic acid. *Finely ground* potassium permanganate (1.40 g, 8.86 mmol) was dissolved in 25 mL of water and 100 mL of acetone. Both solutions were cooled to 0 °C, the potassium manganate solution was added to the steroid solution, the mixture was stirred for approximately 5 s (usually until the purple solution turns brown, at which point most of the purple hue of the solution is gone), and the reaction was quenched with 10 mL of 10% aqueous $Na_2S_2O_4$ solution. The manganese dioxide produced was filtered off, and the filtrate was concentrated to remove most of the acetone. Brine (100 mL) was added, and the mixture was extracted with methylene chloride (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated, leaving 2.46 g of **12** (91%) as a white solid: mp 239–241 C (95% ethanol); $[\alpha]^{23}_D$ –57.3° (*c* 1.16, $CHCl_3$); ^1H NMR (300 MHz) δ 0.694 (s, 3 H), 1.022 (s, 3 H), 1.181 (s, 9 H), 2.255 (s, 3 H), 3.806 (s, 1 H), 4.569 (m, 1 H), 5.054 (m, 1 H), 5.362 (br d, 1 H, *J* = 3.8 Hz); ^{13}C NMR (90.56 MHz) δ 14.89 (q), 19.38 (q), 20.20 (t), 27.20 (q, 3 C), 27.44 (q), 27.70 (t), 31.03 (t), 31.64 (d), 31.85 (t), 33.93 (t), 36.70 (s), 36.96 (t), 38.06 (t), 38.68 (s) 47.23 (s), 49.60 (d), 49.71 (d), 72.48 (d), 73.53 (d), 89.01 (s), 122.10 (s), 139.98 (s), 178.03 (s), 211.29 (s); IR (KBr) 3508, 1725, 1704, 1174 cm^{-1}. Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.08; H, 9.23.

3β,16α,17α-Trihydroxy-5-pregnen-20-one 3-Pivaloate 16-[[2-(Trimethylsilyl)ethoxy]methyl ether] (13b). Diol **12** (6.00 g, 13.9 mmol) was dissolved at room temperature in 75 mL of methylene chloride containing 9.5 mL (54.5 mmol) of diisopropylethylamine and 4.5 mL (25.4 mmol) of [2-(trimethylsilyl)ethoxy]methyl chloride (SEM chloride). The reaction mixture was allowed to stir at that temperature for 4 h, at which point 300 mL of methylene chloride and 150 mL of 10% aqueous HCl solution were added. The organic layer was washed successively with 150 mL of 10% aqueous HCl, 200 mL of saturated aqueous sodium bicarbonate, and 100 mL of brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated, leaving a reddish solid, which was placed on top of a silica gel column and eluted with 15% ethyl acetate in hexanes as the eluent to give 7.53 g of **13b** (96%) as a white solid: mp 188–190 °C (95% ethanol); $[\alpha]^{23}_D$ –118.7° (*c* 1.26, $CHCl_3$); ^1H NMR (360 MHz) δ 0.015 (s, 9 H), 0.642 (s, 3 H), 1.019 (s, 3 H), 1.181 (s, 9 H), 2.220 (s, 3 H), 3.523 (m, 2 H), 3.657 (s, 1 H), 4.557 (m, 1 H), 4.558 (d, 1 H, *J* = 6.3 Hz), 4.638 (d, 1 H, *J* = 6.3 Hz), 4.914 (dd, 1 H, *J* = 2.2, 9.3 Hz), 5.361 (br d, 1 H, *J* = 4.1 Hz); ^{13}C NMR (90.56 MHz) δ –1.44 (q, 3 C), 14.84 (q), 18.17 (t), 19.38 (q), 20.30 (t), 27.21 (q, 3 C), 27.41 (q), 27,73 (t), 31.03 (t), 31.73 (d), 31.87 (t), 32.10 (t), 36.70 (s), 36.99 (t), 38.09 (t), 38.66 (s), 47.19 (s), 49.59 (d), 49.69 (d), 65.65 (t), 73.48 (d), 79.34 (d), 89.16 (s), 95.24 (t), 122.12 (d), 140.01 (s), 177.94 (s), 210.88 (s); IR (KBr) 3503, 1718, 1706, 1171 cm^{-1}. Anal. Calcd for $C_{32}H_{54}O_6Si$: C, 68.29; H, 9.67. Found: C, 68.16; H, 9.88.

(20*R*)-3β,16α,17α,20-Tetrahydroxy-5-pregnene 3-Pivaloate 16-[[2-(Trimethylsilyl)ethoxy]methyl ether] (14b). SEM ether **13b** (4.24 g, 7.53 mmol) and tetra-*n*-butylammonium borohydride (4.00 g, 15.5 mmol) were dissolved in 150 mL of THF, and the solution was allowed to stir at room temperature for 24 h. The solution was then cooled to 0 °C and treated with 50 mL of methanol, and the mixture was allowed to stir at that temperature for another 8 h. The reaction mixture was poured into a solution of 30 mL of saturated aqueous ammonium chloride, 30 mL of water, and 5 mL of 10% aqueous HCl, and the mixture was allowed to stir for 6 h. The resulting mixture was concentrated, and 100 mL of methylene chloride was added. The organic layer was washed first with saturated aqueous sodium bicarbonate (50 mL) and then with brine (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the resultant solid was placed on top of a silica gel column and eluted with 20% ethyl acetate in hexanes to give 3.82 g of **14b** (90%) as a white solid: mp 176–177 °C (95% ethanol); $[\alpha]^{23}_D$ –104.1° (*c* 1.16, $CHCl_3$); ^1H NMR (300 MHz) δ 0.019 (s, 9 H), 0.840 (s, 3 H), 0.906 (dd, 1 H, *J* = 1.5, 7.7 Hz), 0.937 (dd, 1 H, *J* = 1.4, 7.7 Hz), 1.030 (s, 3 H), 1.118 (d, 3 H, *J* = 6.4 Hz), 1.180 (s, 9 H), 3.033 (s, 1 H), 3.623 (m, 2 H), 3.890 (br d, 1 H, *J* = 5.8 Hz), 3.900 (q, 1 H, *J* = 6.4 Hz), 4.530 (m, 1 H), 4.672 (d, 1 H, *J* = 7.0 Hz), 4.763 (d, 1 H, *J* = 7.0 Hz), 5.358 (br d, 1 H, *J* = 3.5 Hz); ^{13}C NMR (90.56 MHz) δ –1.43 (q, 3 C), 15.05 (q), 18.15 (t), 18.73 (q), 19.36 (q), 20.25 (t), 27.18 (q, 3 × C), 27.69 (t), 31.68 (d), 31.84 (t), 31.98 (t), 32.55 (t), 36.66 (s), 36.95 (t), 38.08 (t), 38.62 (s), 47.37 (s), 48.80 (d), 49.71 (d), 66.44 (t), 70.15 (d), 73.53 (d), 76.72 (d), 83.62 (s), 94.22 (t), 122.04 (d), 140.07 (s), 177.88 (s); IR (KBr) 3392, 1724, 1170 cm^{-1}. Anal. Calcd for $C_{32}H_{56}O_6Si$: C, 68.04; H, 9.99; Si, 4.97. Found: C, 67.97; H, 9.95; Si, 4.82.

(20*R*)-3β,16α,17α,20-Tetrahydroxy-5-pregnene 3-Pivaloate 16-[[2-(Trimethylsilyl)ethoxy]methyl ether] 17,20-Thionocarbonate (17b). Diol **14b** (1.50 g, 2.66 mmol) and 1.8 g of

4-(dimethylamino)pyridine (1.80 g, 14.7 mmol) were dissolved in 30 mL of methylene chloride containing 0.22 mL (2.89 mmol) of thiophosgene. The solution was allowed to stir overnight, after which time 10 g of silica gel was added and the solvent was evaporated off. The solid thus obtained was placed on top of a silica gel column and eluted with methylene chloride to give 1.26 g of **17b** (78%) as a white solid: mp 197–199 °C (95% ethanol); $[\alpha]^{23}_D$ –82.3° (*c* 1.15, $CHCl_3$); ^1H NMR (360 MHz) δ 0.026 (s, 9 H), 0.751 (s, 3 H), 0.925 (m, 2 H), 1.033 (s, 3 H), 1.182 (s, 9 H), 1.584 (d, 3 H, *J* = 6.6 Hz), 3.596 (ddd, 1 H, *J* = 6.5, 10.2, 10.4 Hz), 3.723 (ddd, 1 H, *J* = 5.8, 10.3, 10.4 Hz), 4.577 (m, 2 H), 4.719 (s, 2 H), 4.774 (q, 1 H, *J* = 6.6 Hz), 5.370 (br d, 1 H, *J* = 5.0 Hz); ^{13}C NMR (90.56 MHz) δ –1.40 (q, 3 C), 14.18 (q), 16.43 (q), 18.18 (t), 19.37 (q), 19.59 (t), 27.18 (q, 3 C), 27.60 (t), 29.56 (t), 30.63 (t), 31.27 (t), 31.68 (d), 36.70 (s), 36.84 (t), 37.98 (t), 38.62 (s), 66.20 (t) 73.27 (d), 75.91 (d), 79.12 (d), 93.99 (t), 100.41 (s), 121.81 (d), 139.93 (s), 177.84 (s), 190.88 (s); IR (KBr) 1801, 1723, 1168 cm^{-1}. Anal. Calcd for $C_{33}H_{54}O_6SSi$: C, 65.31; H, 8.97; S, 5.22; Si, 4.63. Found: C, 64.92; H, 8.88; S, 5.20; Si, 4.63.

[17(20)*Z*]-3β,16α-Dihydroxy-5,17(20)-pregnadiene 3-Pivaloate 16-[[2-(Trimethylsilyl)ethoxy]methyl ether] (18b). A solution of thionocarbonate **17b** (130 mg, 0.214 mmol) in 6 mL of triethyl phosphite was allowed to reflux under N_2 overnight, after which time most of the triethyl phosphite was removed with the aid of a vacuum pump. The resultant slurry was placed on top of a silica gel column and eluted with hexanes to give 113 mg of **18b** (quantitative) as a white solid: mp 98–100 °C (absolute ethanol); $[\alpha]^{23}_D$ –68.1° (*c* 1.16, $CHCl_3$); ^1H NMR (300 MHz) δ 0.013 (s, 9 H), 0.758 (s, 3 H), 0.955 (br t, 2 H, *J* = 8.7 Hz), 1.041 (s, 3 H), 1.180 (s, 9 H), 1.725 (d, 3 H, *J* = 6.9 Hz), 3.681 (m, 2 H), 4.716 (br t, 1 H, *J* = 4.4 Hz), 4.734 (d, 1 H, *J* = 7.4 Hz), 4.805 (d, 1 H, *J* = 7.4 Hz), 5.382 (br d, 1 H, *J* = 3.7 Hz), 5.407 (dq, 1 H, *J* = 1.8, 7.0 Hz); ^{13}C NMR (90.56 MHz) δ –1.42 (q, 3 C), 14.47 (q), 18.22 (t), 19.37 (q), 20.54 (q), 21.04 (t), 27.17 (q, 3 C), 27.70 (t), 31.09 (d), 31.89 (t), 32.42 (t), 36.42 (t), 36.84 (s), 37.00 (t), 38.06 (t), 38.63 (s), 43.37 (s), 50.48 (d), 51.97 (d), 65.80 (t), 73.52 (d), 77.27 (d), 94.29 (t), 118.71 (d), 122.16 (d), 140.09 (s), 152.86 (s), 177.97 (s); IR (KBr) 1719, 1163 cm^{-1}; high-resolution MS (CI, NH_3) calcd for $C_{32}H_{58}NO_4Si$ $(M + NH_4)^+$ *m/z* 548.4135, found *m/z* 548.4150. Anal. Calcd for $C_{32}H_{54}O_4Si$: C, 72.41; H, 10.21. Found: C, 72.49; H, 10.47.

[17(20)*Z*]-3β,16α-Dihydroxy-5,17(20)-pregnadiene 3-Pivaloate (6). Diene **18b** (50 mg, 0.094 mmol) and cesium fluoride (150 mg, 0.987 mmol) were dissolved in 5 mL of DMF. The reaction mixture was heated to reflux, and refluxing was continued for 16 h. The reaction was quenched by the addition of 5 mL of brine, and the resulting mixture was extracted with methylene chloride (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant slurry was placed on top of a silica gel column and eluted first with hexanes followed by 20% ethyl acetate in hexanes to give 30 mg of **6** (80%) as a white solid: mp 146–149 °C (dec; 95% ethanol); $[\alpha]^{23}_D$ –163.2° (*c* 1.98, $CHCl_3$); ^1H NMR (300 MHz) δ 0.754 (s, 3 H), 1.046 (s, 3 H), 1.183 (s, 9 H), 1.787 (d, 3 H, *J* = 7.0 Hz), 4.578 (m, 1 H), 4.802 (br d, 1 H, *J* = 4.6 Hz), 5.338 (dq, 1 H, *J* = 1.6, 6.9 Hz), 5.385 (br d, 1 H, *J* = 5.0 Hz); ^{13}C NMR (90.56 MHz) δ 14.59 (q), 19.40 (q), 20.33 (q), 21.04 (t), 27.20 (q, 3 C), 27.72 (t), 31.81 (t), 31.87 (d), 36.10 (t), 36.65 (t), 36.87 (s), 37.03 (t), 38.08 (t), 38.66 (s), 43.95 (s), 50.54 (d), 51.98 (d), 71.28 (d), 73.50 (d), 117.76 (d), 122.28 (d), 140.02 (s), 156.14 (s), 177.99 (s); IR (KBr) 3535, 1712, 1174 cm^{-1}; high-resolution MS (CI, NH_3) calcd for $C_{26}H_{44}NO_3$ *m/z* 418.3321, found *m/z* 418.3322. Anal. Calcd for $C_{26}H_{40}O_3$: C, 77.95; H, 10.07. Found: C, 77.64; H, 10.10.

(20*R*)-3β,17α,20-Trihydroxy-5-pregnene 3-Pivaloate 20-Tosylate (19a). To a solution of 500 mg (1.20 mmol) of (20*R*)-diol **9** in 7 mL of pyridine, 400 mg (2.10 mmol) of freshly recrystallized *p*-toluenesulfonyl chloride was added. The reaction mixture was protected from light and allowed to stir overnight. The reaction was quenched with 25 mL of water, and the mixture was extracted with methylene chloride (2 × 25 mL). The combined organic layers were washed successively with 10% aqueous HCl (2 × 25 mL), saturated aqueous $CuSO_4$ (20 mL), saturated aqueous sodium bicarbonate (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated, leaving 660 mg of **19a** (97%) as a white solid: mp 126–130 °C dec; $[\alpha]^{23}_D$ –51.4° (*c* 1.22, $CHCl_3$); ^1H NMR (300 MHz) δ 0.833 (s, 3 H), 1.031 (s, 3 H), 1.184 (s, 9 H), 1.219 (d, 3 H, *J* = 6.2 Hz), 2.446 (s, 3 H), 4.556 (m, 1 H), 5.013 (q, 1 H, *J* = 6.2 Hz), 5.356 (br d, 1 H, *J* = 3.7 Hz), 7.333 (d, 2 H, *J* = 8.2 Hz), 7.791 (d, 2 H, *J* = 8.2 Hz); ^{13}C NMR (75.3 MHz) δ 14.03 (q), 15.82 (q), 19.32 (q), 20.62 (t), 21.60 (q), 23.62 (t), 27.16 (q, 3 C), 27.66 (t), 30.91 (t), 31.87 (t), 32.09 (d), 33.83 (t), 36.60 (s), 37.00 (t), 38.01 (t), 38.59 (s), 47.26 (s), 49.63 (d), 50.53 (d), 73.46 (d), 83.03 (d), 85.19 (s), 122.16 (d), 127.57 (d, 2 C), 129.69 (d, 2 C), 135.31 (s), 139.78 (s), 144.54 (s), 177.85 (s); IR (KBr) 3516, 1708, 1358, 1176 cm^{-1}. Anal. Calcd for $C_{33}H_{48}O_6S$: C, 69.20; H, 8.45. Found: C, 68.86; H, 8.52.

(20*S*)-3β-Hydroxy-17α,20-epoxy-5-pregnene 3-Pivaloate (20a). A solution of 600 mg (1.05 mmol) of tosylate **19a** and 250 mg (10.4 mmol) of sodium hydride was heated to reflux for 2 h. The solution was allowed to cool to room temperature and was poured into 50 mL of wet ether, and the mixture was washed with 10 mL of water and 10 mL of brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the remaining solid was purified by silica gel chromatography with 10% ethyl acetate/hexanes as the eluent to give 420 mg of **20a** (quantitative) as a white solid: mp 158–160 °C (95% ethanol); $[\alpha]^{23}_D$ –62.0° (*c* 1.09, $CHCl_3$); ^1H NMR (300 MHz) δ 0.898 (s, 3 H), 1.033 (s, 3 H), 1.183 (s, 9 H), 1.379 (d, 3 H, *J* = 5.7 Hz), 2.977 (q, 1 H, *J* = 5.7 Hz), 4.576 (m, 1 H), 5.383 (br d, 1 H, *J* = 4.8 Hz); ^{13}C NMR (90.56 MHz) δ 14.56 (q), 14.83 (q), 19.39 (q), 20.64 (t), 24.20 (t), 27.21 (q, 3 C), 27.72 (t), 31.64 (t), 31.80 (d), 32.35 (t), 34.08 (t), 36.68 (s), 37.04 (t), 38.09 (t), 38.65 (s), 41.67 (s), 49.81 (d), 54.34 (d), 57.04 (d), 73.23 (s), 73.48 (d), 122.28 (d), 139.87 (s), 177.88 (s); IR (KBr) 1722, 1169 cm^{-1}. Anal. Calcd for $C_{26}H_{40}O_3$: C, 77.95; H, 10.06. Found: C, 77.89; H, 10.11.

(*Z*)-3β-Hydroxy-5,17(20)-pregnadiene 3-Pivaloate (21a). Epoxide **20a** (150 mg, 0.374 mmol) was dissolved in a mixture of 10 mL of dry methylene chloride and 5 mL of pyridine, and the solution was treated with 215 mg (0.378 mmol) of P_2I_4 at room temperature. The mixture was allowed to stir at that temperature for 16 h, at which point the solution was diluted with 25 mL of methylene chloride, and the reaction quenched with 25 mL of 5% aqueous HCl. The aqueous layer was extracted with methylene chloride (2 × 50 mL), and the combined organic extracts were washed first with 20 mL of 1% aqueous $Na_2S_2O_3$ and then with 20 mL of brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the resulting yellow viscus oil was purified by silica gel chromatography with 10% ethyl acetate/hexanes as the eluent to give 52 mg (35%) of **21a** as a yellowish solid, which showed identical ^1H and ^{13}C NMR spectra with those of the authentic sample prepared by the method of Trost.[2a]

(20*S*)-3β,16α-Dihydroxy-17α,20-epoxy-5-pregnene 3-Pivaloate 16-[[2-(Trimethylsilyl)ethoxy]methyl ether] (20b). Diol **14b** (200 mg, 0.35 mmol) and *p*-toluenesulfonyl chloride (200 mg, 1.05 mmol) were dissolved in 7 mL of pyridine, and the mixture was allowed to stir at room temperature for 20 h. The reaction was quenched with 20 mL of water. The resultant mixture was vigorously shaken in a separatory funnel and extracted with 50 mL of methylene chloride. The organic layer was then washed successively with 25 mL of 10% aqueous HCl, 25 mL of saturated aqueous $CuSO_4$, 25 mL of saturated sodium bicarbonate, and 10 mL of brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Although TLC seemed to indicate the presence of only one compound, ^1H NMR revealed the presence of the epoxide as well as the tosylate. The crude solid was dissolved in 5 mL of THF in a 10-mL, round-bottomed flask fitted with a condenser, and the solution was treated with 85 mg of NaH (10 equiv). The solution was allowed to reflux for 4 h after which time the reaction mixture was poured into 30 mL of methylene chloride, and the mixture was washed with 10 mL of saturated aqueous ammonium chloride and 10 mL of brine. The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated off. The resultant solid was purified by silica gel chromatography with 20% ethyl acetate in hexanes as the eluent to give 140 mg of **20b** (72%) as a white solid: mp 160–161 °C (95% ethanol); $[\alpha]^{23}_D$ –103.4° (*c*, 1.18, $CHCl_3$); ^1H NMR (300 MHz) δ 0.010 (s, 9 H), 0.897 (m, 1 H), 0.917 (s, 3 H), 1.020 (s, 3 H), 1.174 (s, 9 H), 1.402 (d, 3 H, *J* = 5.7 Hz), 2.946 (q, 1 H, *J* = 5.7 Hz), 3.583 (m, 2 H), 4.333 (br d, 1 H, *J* = 7.7 Hz), 4.557 (m, 1 H), 4.598 (d, 1 H, *J* = 7.1 Hz), 4.696 (d, 1 H, *J* = 7.1 Hz), 5.366 (d, 1 H, *J* = 4.7 Hz); ^{13}C NMR (90.56 MHz) δ –1.41 (q, 3 C), 14.44 (q), 15.28 (q), 18.15 (t), 19.36 (q), 20.20 (t), 27.18

(q, 3 C), 27.65 (t), 31.39 (t), 31.47 (d), 32.17 (t), 33.83 (t), 36.63 (s), 36.86 (t), 38.03 (t), 38.62 (s), 41.57 (s), 49.57 (d), 51.71 (d), 55.35 (d), 65.14 (t), 72.23 (s), 73.41 (d), 75.28 (d), 94.36 (t), 122.06 (d), 139.92 (s), 177.88 (s); IR (KBr) 1721, 1171 cm^{-1}; high-resolution MS (CI, NH_3) calcd for $C_{36}H_{58}NO_5Si$ $(M + NH_4)^+$ m/z 564.4084, found m/z 564.4069. Anal. Calcd for $C_{32}H_{54}O_5Si$: C, 70.28; H, 9.95. Found: C, 70.04; H, 10.10.

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Registry No. **5**, 123487-32-1; **6**, 123487-33-2; **7a**, 387-79-1; **7b**, 123487-34-3; **8**, 123487-35-4; **9**, 123487-36-5; **10**, 123487-37-6; **11a**, 1162-53-4; **11b**, 123487-38-7; **12**, 123487-39-8; **13a**, 123487-40-1; **13b**, 123487-41-2; **14a**, 123487-42-3; **14b**, 123487-43-4; **15**, 123487-44-5; **16**, 123538-42-1; **17b**, 123487-45-6; **18b**, 123487-46-7; **19a**, 123487-47-8; **20a**, 123487-48-9; **20b**, 123487-49-0; **21a**, 123487-50-3; SEM chloride, 76513-69-4; pivaloyl chloride, 3282-30-2.

Approaches to the Total Synthesis of the Antitumor Antibiotic Echinosporin

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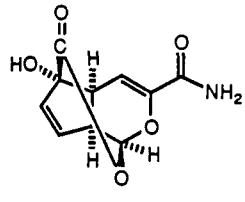
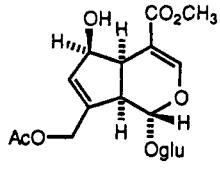
A strategy for the total synthesis of the structurally unique microbial metabolite echinosporin (1) has been tested. Readily available bromo ester **6** has been converted in a few steps to the TCBOC-protected α-keto ester norbornene system **14**. An alternative, shorter, but less reliable route to **14** has also been investigated starting from keto ester **15**. Cleavage of the unconjugated olefinic double bond of **14** yielded diacid **21a**, which was subsequently converted to α-keto ester **22**. Intermediate **22** was transformed to the key enol lactone **24**, which possesses the full carbon skeleton and two of the four chiral centers of echinosporin. Further manipulation of lactone **24** gave acetal unsaturated diester **29**. Despite considerable effort, **29** could not be converted to the required α-hydroxy ester **31** via dienolate **30**. Moreover, mesylate **33**, prepared from **29**, could not be eliminated to produce **31**. Thus, a modified route will have to be developed to construct the α-hydroxy-β,γ-unsaturated cyclopentenyl ester system of 1.

In 1981 Sato and co-workers reported the isolation of echinosporin from the actinomycete *Streptomyces echinosporus* discovered in the microbial screening of a Mexican soil sample.[1] A combination of chemical and spectroscopic studies established structure 1 for this compound, and subsequent X-ray crystallographic analysis confirmed the original formulation.[2] Echinosporin was found to possess antimicrobial activity as well as antitumor activity against systems such as leukemia P388, P388/VCR, and fibrosarcoma Meth 1.[3]



1



2

Echinosporin has a unique structure reminiscent of iridoids such as daphylloside (2).[4,5] However, it seems unlikely that these compounds share a common biogenetic origin.[5] To date, no studies on the biosynthesis of echinosporin have appeared.

Despite its similarity to the iridoids, echinosporin (1) poses a unique set of synthetic problems, in part due to its exceptionally high level of functionality.[6] In addition, most routes to echinosporin that one can devise would seem to require quite a number of chemoselective transformations. We envisioned a total synthesis of 1 shown retrosynthetically in Scheme I. We hoped to prepare 1 from lactone **3** via selective reduction of the enol lactone carbonyl group and α-hydroxylation of the cyclopentenyl ester functionality. Compound **3** would be synthesized from the nearly symmetrical tetracarbonyl compound **4**, which seemed accessible from oxidative double-bond cleavage of norbornyl system **5** or its equivalent. Intermediate **5** incorporates the requisite stereochemistry for enol lactone **3**. In this paper is described our progress in executing the strategy shown in Scheme I.

The synthetic route commenced with known bromo ester **6**, readily available from norbornadiene,[7] which was reduced to alcohol **7** (93%) and eliminated[7] to norbornene **8** (80%) (Scheme II). PCC/alumina oxidation[8] of **8** afforded aldehyde **9** (73%). A two-carbon homologation of

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