Neurosteroid Analogues. 2. Total Synthesis and Electrophysiological Evaluation of Benz[e]indene Analogues of the Anesthetic Steroid Alphaxalone

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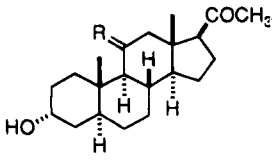
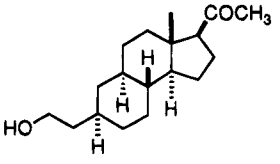
Anesthetic steroid **1a** and benz[e]indene **2** are known to have potent pharmacological actions at $GABA_A$ receptors. Anesthetic 11-ketosteroids such as alfaxalone (**1b**) are also known to have this activity. Evaluation of corresponding 5*H*-benz[e]inden-5-one analogs of 11-ketosteroids necessitated the development of an efficient route to these compounds. Accordingly, total synthesis of the 5*H*-benz[e]inden-5-ones **3** and **4** from the known 5*H*-inden-5-one precursor **5** is described. The structure of compound **3** has been verified by X-ray diffraction analysis. Electrophysiological evaluations of compounds **3** and **4** indicate that, unlike benz[e]indene **2**, these compounds have weak pharmacological actions at $GABA_A$ receptors.

Introduction

We have described previously the synthesis of a series of benz[e]indenes and phenanthrenes having modulatory actions at $GABA_A$ receptors.[1] These tricyclic compounds are analogues of 3α-hydroxy-5α-pregnan-20-one (**1a**), a compound known to have anesthetic activity.[2] Electrophysiological evidence supports the hypothesis that positive allosteric modulation of $GABA_A$ receptor function by steroid **1a** explains this anesthetic activity.[3] Because of the interesting electrophysiological actions of benz[e]-indene **2**,[1a] we are interested in further structure–activity studies of additional benz[e]indene modulators of $GABA_A$ receptors. This article reports the synthesis and electrophysiological activity of 5*H*-benz[e]inden-5-one analogues **3** and **4**. The structure of compound **3** has been established unambiguously by single crystal X-ray diffraction analysis.[2a] The compounds are of particular interest because they are analogues of the clinically-used intravenous anesthetic steroid alphaxalone (3α-hydroxy-5α-pregnane-11,20-dione, **1b**).[4]



1a: R = H_2
1b: R = O



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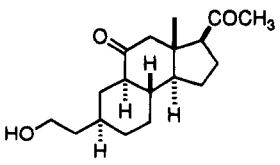

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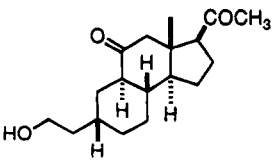

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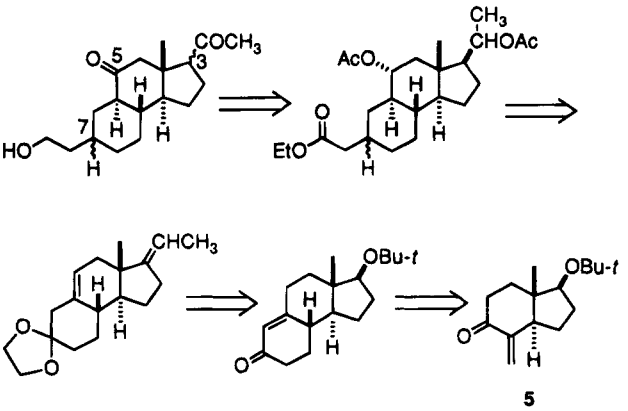
The synthesis of benz[e]indene **2** is achieved efficiently by partial removal of the A-ring of 19-nortestosterone, followed by introduction of the C-3 (benz[e]indene numbering system) side chain.[1c,5] This synthetic strategy was not practical for the synthesis of compounds **3** and **4** because of the lack of available 19-nor-11-oxygenated steroids. Hence, a total synthesis strategy was chosen to obtain the desired 5*H*-benz[e]inden-5-ones. As shown by the retrosynthetic analysis in Scheme 1, the final products are derived by modification of a triester intermediate. The C-7 side chain of the triester is introduced by a Wittig reaction after the oxygen functionalites on C-5 and the side chain at C-3 are elaborated by bis-hydroboration of a diene precursor. The diene precursor is obtained from the previously described bicyclic compound **5**.[6]

Scheme 1



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‡ Departments of Psychiatry, and Anatomy and Neurobiology.
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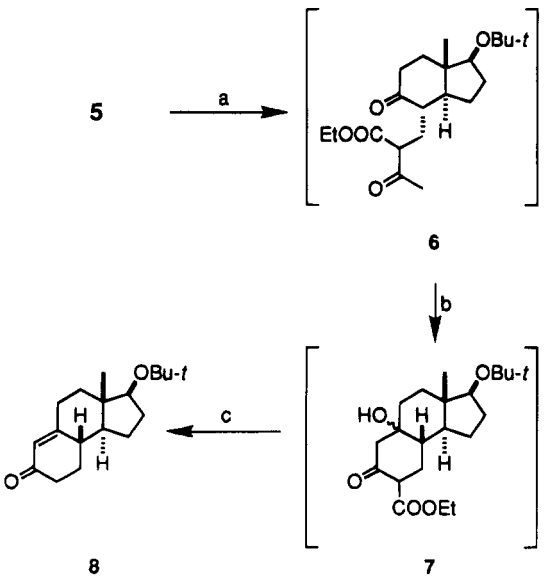
Scheme 2[a]



[a] Reagents: (a) CH_3COCH_2COOEt, 0.11 N NaOMe, MeOH, rt, overnight; (b) 5 N aqueous NaOH, 1 h; 6 N aqueous HCl; (c) heating at 80 °C in high vacuum, 3 h.

Results and Discussion

Preparation of Benz[*e*]indene 8. Numerous synthetic methodologies utilizing benz[*e*]indene intermediates have been developed for total steroid synthesis.[7] However, for the most part, these benz[*e*]indene intermediates contain a substituent at C-6 that is used subsequently to elaborate the A-ring of the steroid ring system.[6,8] In those instances where benz[*e*]indenes like compound **8**, which do not have a substituent at C-6, were prepared either as a target compound or as a byproduct, the methods reported were not optimal for our needs.[9] Hence, an efficient method to synthesize benz[*e*]indene **8** from precursor **5** was developed (Scheme 2). In a one-pot procedure, compound **5** was reacted with ethyl acetoacetate to give intermediate **6** which initially cyclized to intermediate **7** and then underwent dehydration and decarboxylation reactions to yield benz[*e*]indene **8** in 77% yield.

Bis-Hydroboration of Benz[*e*]indene 12. The next steps in the synthesis of benz[*e*]indenes **3** and **4** involve the introduction of oxygen functionalities at C-5 (C-11 in steroids) and C-1′ (C-20 in steroids) of the two carbon side-chain at C-3. Many efficient methods for introducing an oxygen functionality at either C-11 or C-20 during steroid synthesis have been developed.[10-12] From these reported methods, only those involving the hydroboration of double bonds[12] are readily adapted to the simultaneous introduction of the C-5 and C-1′ oxygen functionalities into a benz[*e*]indene intermediate. Although we could not find a precedent for the bis-hydroboration of steroids containing the $\Delta^{9(11),17(20)}$ diene system, reports of the bis-hydroboration of other dienes to yield diol products estabished the feasibility of the reaction.[13] Accordingly, compound **8** (Scheme 3) was hydrolyzed in 6 N aqueous HCl to give enone **9** (90%), and this product was converted subsequently into ketal **10** (88%).[14] Oxidation of compound **10** by PCC[15] buffered with NaOAc yielded product **11** (91%), which was converted into diene **12** (81%) by reaction with (ethyl)triphenylphosphonium bromide and NaH in DMSO.[12b] Although not indicated in Scheme 3, product **12**, as isolated after flash chromatography, only contained the exocyclic double bond at C-3 in the *Z* configuration.[16] The bis-hydroboration of diene **12** with BH_3·THF followed by oxidation with H_2O_2 gave crude product **13** which was, without isolation, hydrolyzed and acetylated to give products **15** and **16** (63% overall for the three steps) in the ratio of ~12:1. These diacetates were separated by HPLC as described in the Experimental Section.

Previous studies of the hydroboration of steroids containing $\Delta^{9(11)}$ or $\Delta^{17(20)}$ double bonds have shown that these reactions are highly regio- and stereoselective yielding as the major products the 11α- and 20(*S*)-alcohol, respectively.[12b,17] By analogy, the major diacetate derived from the bis-hydroboration of diene **12** was expected to be diacetate **15**. This expectation, with regard to the stereochemistry of hydroboration of the Δ^5 double bond of compound **12**, was supported by NMR experiments comparing the NOE between the hydrogens of the C-3a methyl group and the C-5 hydrogen of compounds **15** and **16**.[18,19] In dynamic NOE experiments, irradiation of the methyl group hydrogens led to a faster NOE build up for the C-5 hydrogen of the major diacetate derived from the hydroboration reaction. Since the shortest distance

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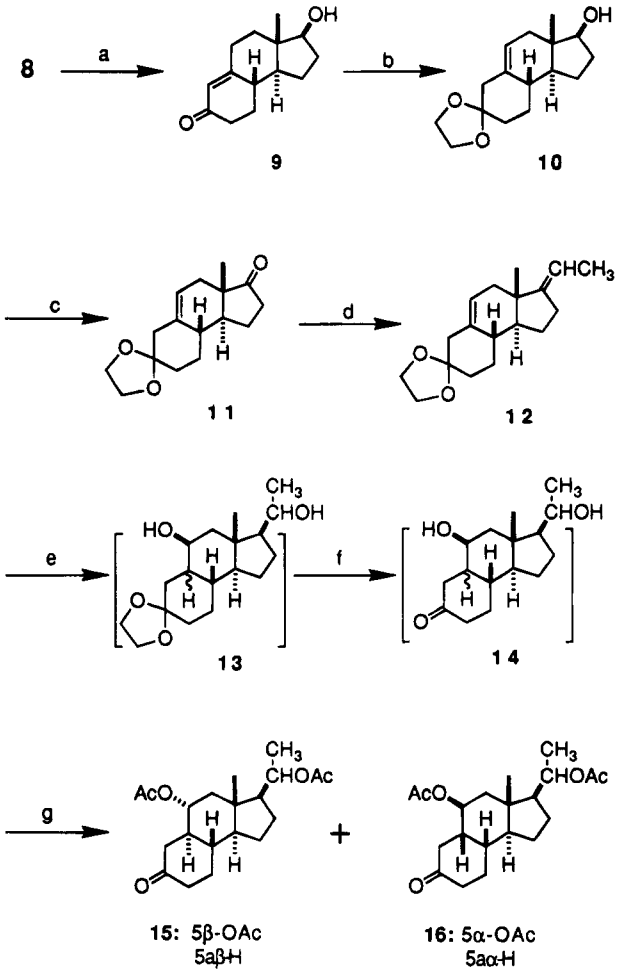
(16) The assignment of the *Z* configuration for the olefin was made by analogy based on the stereochemistry observed when this reaction was carried out on a 17-ketosteroid.[12b]

(17) Nussim, M.; Mazur, Y.; Sondheimer, F. *J. Org. Chem.* **1964**, *29*, 1120.

(18) Based on a literature analogy,[12b] the *S* configuration was assigned to the acetyloxy group in the C-3 side chain. No experiments were carried out to confirm this assignment because the acetyloxy stereocenter is eliminated in the last step of the synthetic sequence.

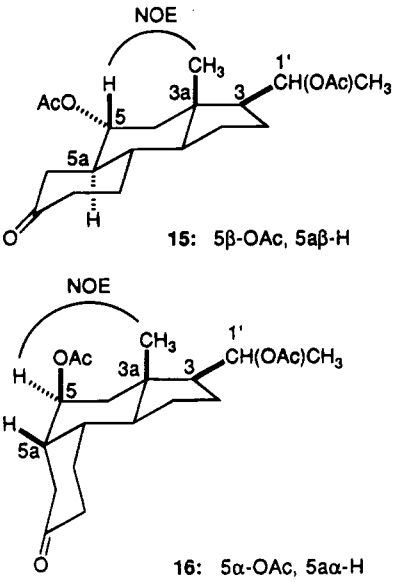
Scheme 3[a]



[a] Reagents: (a) 6 N aqueous HCl, EtOH, reflux, 2.5 h; (b) $HOCH_2CH_2OH$–TsOH, C_6H_6, reflux, 1.5 h; (c) PCC–NaOAc, CH_2Cl_2, room temperature, 2 h; (d) $Ph_3P^+CH_2CH_3Br^-$, NaH, DMSO, 60–70 °C, 22 h; (e) BH_3·THF, THF, room temperature, 3 h; 10% NaOH, 30% H_2O_2, 0 °C, 2 h; (f) 2 N aqueous HCl, THF, room temperature, overnight; (g) $(CH_3CO)_2O$–pyridine, 100 °C, 3 h.

between these hydrogens is found in structure **15**, the major diacetate was assigned this structure. The assigned stereochemistry at C-5a in compounds **15** and **16** follows from the established *cis* stereochemical course of hydroboration reactions.

Introduction and Selective Protection of the 2-Hydroxyethyl Group at C-7. A carbethoxyolefination reaction[20] was used to introduce the required side chain at C-7. Heating compound **15** with (carbethoxymethylene)triphenylphosphorane overnight at 160 °C in the absence of solvent produced an isomeric mixture of (*E*)-**17** and (*Z*)-**18** in 63% yield (Scheme 4).[21,22] Although (*E*)-**17** could be obtained easily from this mixture by crystallization (see Experimental Section), in practice, the



isomeric mixture was hydrogenated (550 psi, 65 °C, 20 h) using a Pd–C catalyst to obtain a 1:1 ratio of the saturated products **19** and **20** in near quantitative yield. Crystallization (5% EtOAc in hexane, −10 °C, overnight) of this product mixture yielded ~80–85% of the total amount of compound **19** present in the initial product mixture. The remainder of the product mixture was separated completely by HPLC. The reduction of either triester **19** or triester **20** with DIBALH gave the corresponding triols **21** (85%) and **22** (91%).

Previously, we found that NaOCl (bleach) in acetic acid could be used to selectively oxidize (in moderate yield) a secondary alcohol at the benz[*e*]indene C-3 position in the presence of a primary alcohol group located in a 2-hydroxyethyl substituent at C-7.[1c] In the present case, when we attempted to selectively oxidize the secondary hydroxyl groups at C-3 and C-5 in triol **21** with this oxidant using several different reaction conditions, an unidentified mixture of products was obtained. A different selective oxidant, $(NH_4)_2Ce(NO_3)_6$–$NaBrO_3$ in aqueous acetonitrile,[23] also failed to convert triol **21** into the desired product.

The alternative approach of protecting the primary hydroxyl groups in triols **21** and **22** before oxidation of the secondary hydroxyl groups also was investigated. The reaction of triols **21** and **22** with 3-pivaloylthiazolidine-2-thione, a reagent known to react selectively with primary alcohols,[24] proceeded with very good selectivity and in moderate yield in refluxing THF (10 h) to give trimethylacetates **23** (70%) and **24** (55%), respectively.[25] Oxidation of **23** and **24** by Jones reagent proceeded smoothly to yield products **25** (92%) and **26** (93%), respectively. Finally, the trimethylacetate group was removed from compounds **25** and **26** using NaOH in MeOH. Since enolization of the C-3 acetyl group also occurred under these reaction conditions, compound **25** gave a mixture of benz[*e*]indene products **3** and **27** which were obtained in yields of 41 and 21%, respectively, after HPLC separation. Similarly, saponification of compound

(19) According to the IUPAC rules of nomenclature, the α-side of the reference plane is that side on which the preferred substituent lies at the lowest-numbered stereogenic position. Accordingly, the C-3 substituent defines the α-side of the plane and groups on the same side of the plane as the C-3 substituent are assigned α descriptors. A different IUPAC rule governs the nomenclature of steroids wherein substituents above the plane of the steroid are assigned β descriptors.

(20) (a) Sugasawa, S.; Matsuo, H. *Chem. Pharm. Bull. Jpn.* **1960**, *8*, 819. (b) Fodor, G.; Tomoskozi, I. *Tetrahedron Lett.* **1961**, 579.

(21) The assignments of *E*/*Z* configuration were made by analogy to the configuration of a product derived from the carbethoxyolefination of [3*S*-(3α,3aα,9aα,9bβ)]-3-(1,1-dimethylethoxy)dodecahydro-3a-methyl-7*H*-benz[*e*]inden-7-one whose absolute stereochemistry was determined by X-ray diffraction analysis.

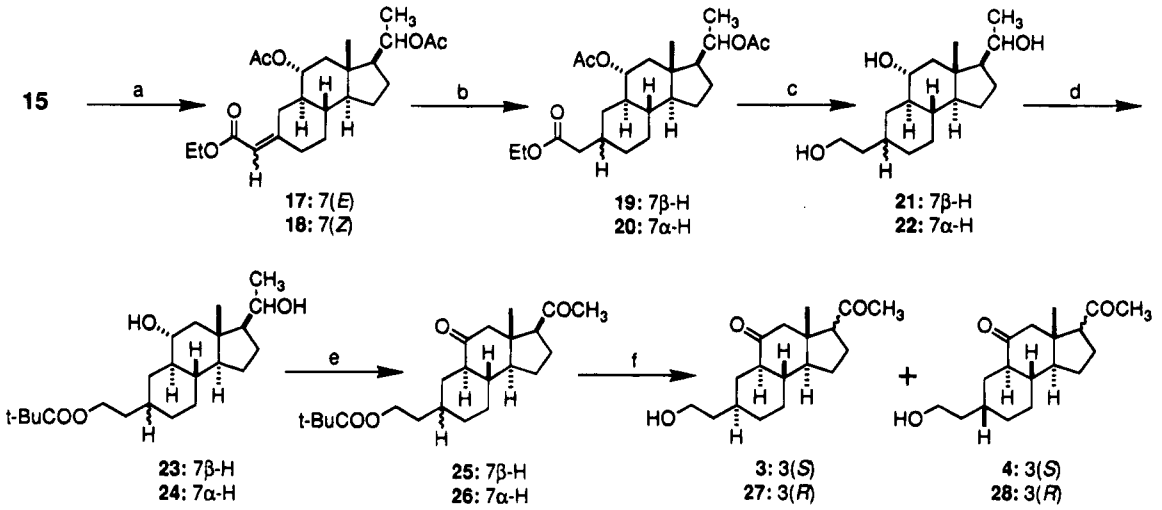
(22) Because the *E*/*Z* pair of carbethoxyolefination products derived from compounds **15** and **16** are easily separated by column chromatography, compounds **15** and **16** need not be separated by HPLC before the carbethoxyolefination reaction.

(23) Kanemoto, S.; Tomioka, H.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 105.

(24) Yamada, S. *J. Org. Chem.* **1992**, *57*, 1591.

(25) No reaction occurred at room temperature, the reaction temperature specified in ref 24.

Scheme 4[a]



[a] Reagents: (a) Ph_3P=CHCOOEt, 160 °C, 15 h; (b) Pd–C, H_2, 550 psi, 65 °C, 20 h; (c) DIBALH, toluene, room temperature, 1 h; (d) 3-pivaloythiazolidine-2-thione, NaH, THF, 55–60 °C, 10 h; (e) Jones reagent, acetone, −5 °C, 5 min; (f) KOH, MeOH, rt, 60 h.

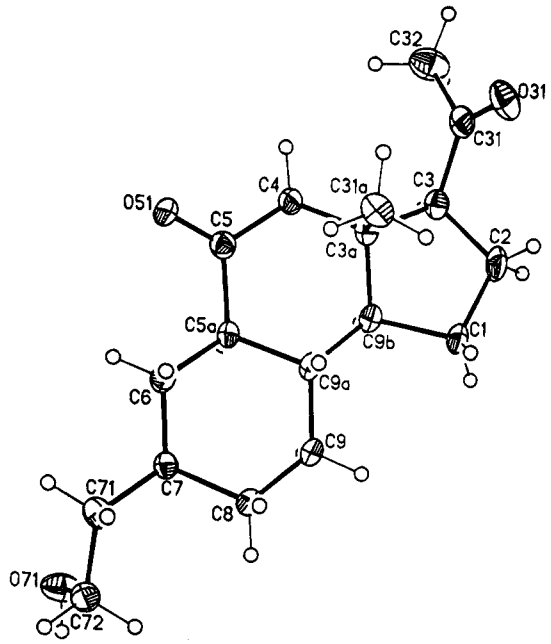


Figure 1. ORTEP drawing of [3*S*-(3α,3aα,5aβ,7α,9aα,9bβ)]-3-Acetyldodecahydro-7-(2-hydroxyethyl)-3a-methyl-5*H*-benz[*e*]-inden-5-one (**3**).

26 gave benz[*e*]indenes **4** (45%) and **28** (19%). The structure of benz[*e*]indene **3** was established by single crystal X-ray diffraction analysis (Figure 1). The structures of benze[*e*]indenes **4** and **19**–**28** follow from the IR and NMR data reported in the Experimental Section and deductive reasoning based on the crystal structure of benz[*e*]indene **3**.

Electrophysiological Evaluations. The results of the electrophysiological evaluations of the target 5*H*-benz[*e*]inden-5-ones **3** and **4**, as well as their corresponding 3(*R*)-diastereomers **27** and **28**, on $GABA_A$ receptor function using cultured rat hippocampal neurons are shown in Table 1. The compounds were evaluated at a concentration of 1 μM for their ability to potentiate chloride currents mediated by 1 μM GABA, and at a concentration of 10 μM for their ability to directly initiate (i.e., gate) a chloride current in the absence of GABA. For comparison, the evaluations of the steroids **1a**, **1b**, and **29** (3α-hydroxy-5β-pregnane-11,20-dione) as well as benz[*e*]indene **2** are also reported.

Table 1. Electrophysiological Effects of Benz[*e*]indenes and Steroids on $GABA_A$ Receptor Function

compd	N[a]	compd (1 μM) potentiation % response relative to current produced by GABA[b]	compd (10 μM) gated current[c]
1a	5	523 ± 87[d]	30 ± 6[e]
1b	6	348 ± 19	196 ± 7
29	5	413 ± 22	238 ± 29
2	12[e]	489 ± 19[e]	NR[e,f]
3	5	110 ± 12	NR
3	5	172 ± 26[g]	NR
4	5	118 ± 7	NR
27	6	103 ± 5	NR
28	4	99 ± 4	NR

[a] N = Number of cells examined. [b] To calculate the % response, the magnitude of the peak current produced by 1 μM GABA plus 1 μM compound was normalized with respect to the peak current produced by 1 μM GABA alone on the same cell. A % response of 100% reflects no change in the current compared to 1 μM GABA alone. 1 μM GABA is a concentration at the foot of the dose–response curve in cultured postnatal rat hippocampal neurons. These experiments were conducted at −60 mV, and compounds were applied by pressure ejection for 500 ms. [c] The compound-gated current reflects the peak current directly gated by 10 μM compound in the absence of GABA compared to the response obtained from the same cell in response to 1 μM GABA alone. [d] Values are the mean ±SEM. [e] Values reported are from ref 1b. [f] NR denotes no response. Compounds that increased current by ≤5% of the response to 1 μM GABA in the same cells were considered to give no response. [g] This table entry indicates the potentiating effect of this compound at 10 μM on currents mediated by 1 μM GABA.

The results shown in Table 1 indicate that, under the conditions chosen for comparison, steroids **1b** and **29** have similar potencies as potentiators of GABA-mediated currents. These steroids also have similar potencies for direct gating of current. These steroids are somewhat less active in the potentiation assay and somewhat more potent in the gating assay than steroid **1a**. By contrast, 5*H*-benz[*e*]inden-5-ones **3** and **4** are much less potent as potentiators of GABA-mediated currents than benz[*e*]-indene **2**. As expected from a previous structure–activity study showing that the hydrogen bond acceptor substituent at the benz[*e*]indene C-3 position must have the *S* configuration for the compounds to have potent activity,[1c] the 3(*R*)-compounds **27** and **28** were found to be inactive as potentiators of GABA-mediated currents. None of the tricyclic compounds gated a current by itself.

An explanation for why the introduction of a carbonyl group at the C-11 position of a steroid is compatible with potent electrophysiological activity whereas the introduction of a carbonyl group into the corresponding C-5 position of a benz[*e*]indene greatly diminishes electrophysiological activity is not readily apparent. The explanation cannot be that the structures of the 5*H*-benz[*e*]inden-5-ones are incorrect since the structure of compound **3** was unambiguously established by X-ray diffraction analysis. Moreover, modeling sudies (not shown) indicate that the carbonyl at C-5 does not adversely effect the ability of the 2-hydroxyethyl group at C-7 to attain the low energy conformation needed for compound **3** to sterically mimic steroid **1b**.

Some pharmacological studies of steroids **1b** and **29** support the hypothesis that these steroids occupy a different binding site on $GABA_A$ receptors than steroid **1a**.[26] If this is indeed the case, then it may be that the 5*H*-benz[*e*]inden-5-ones **3** and **4** do not bind as effectively to the site occupied by anesthetic steroids having an 11-keto substituent as benz[*e*]indene **2** binds to the other site occupied by anesthetic steroids lacking the 11-keto substituent. This could explain the large decrease in activity found for compounds **3** and **4**. Future pharmacological studies are needed to evaluate this hypothesis.

Experimental Section

General Methods. NMR spectra, IR spectra, and melting points were obtained by methods described previously.[1c] X-ray diffraction analysis was performed on a fee for service basis in the X-Ray Crystallography Facility of the Department of Chemistry, Washington University. The diffraction data were collected using a Siemens P4 diffractometer. The strucutre was solved by direct methods using the program SHELXTL PLUS. The 2-methyl-1,3-cyclopentanedione used as a starting material to prepare compound **5** was purchased from Fluka Chemical Co., Ronkonkoma, NY. The 3α-hydroxy-5α-pregnane-11,20-dione (**1b**) was purchased from Research Biochemical Inc., Natick, MA, and 3α-hydroxy-5β-pregnan-11,20-dione (**29**) was purchased from Steraloids, Inc., Wilton, NH. The Econosil silica and Econonsil C18 HPLC columns were purchased from Alltech Associates, Inc., Deerfield, IL. Flash chromatography was performed using silica gel (32–63 μm) purchased from Scientific Adsorbants, Atlanta, GA. Elemental analysis were carried out by M-H-W Laboratories, Phoenix, AZ.

[3*S*-(3α,3aα,9aα,9bβ)]-3-(1,1-Dimethylethoxy)-1,2,3,3a,4,5,8,9,9a,9b-decahydro-3a-methyl-7*H*-benz[*e*]inden-7-one (8). To a solution of ethyl acetoacetate (65 g, 0.5 mol) in a solution of 0.11 N sodium methoxide (880 mg of Na in 350 mL of MeOH) was added dropwise a solution of [1*S*-(1α,3aβ,7aα)]-1-(1,1-dimethylethoxy)octahydro-7a-methyl-4-methylene-5*H*-inden-5-one[6] (**5**, 50 g, 0.21 mol) in MeOH (200 mL) within 1.5 h. After the mixture was stirred overnight (ca. 20 h) at room temperature, a solution of 5 N NaOH (100 mL) was added and stirred for another 1 h. Most of the MeOH was removed on a rotary evaporator and the residue was diluted with water (100 mL). The mixture was extracted with toluene (100 mL), and the aqueous phase was cooled and acidified to pH 3 with 6 N HCl. The aqueous phase was extracted with EtOAc (3 × 150 mL), and all combined organic extracts were dried over Na_2SO_4. The solvent was removed to give an oil, which was a mixture of compounds **7** and **8**. Complete decarboxylation was brought about by heating this mixture at 80 °C (ca. 3 h) under high vacuum (~0.5 mm) until no further loss of weight occurred. The crude product was purified by chromatography (silica, 30% EtOAc in hexane) to give product **8** (45 g, 77%) as white crystals: mp 125–127 °C (lit.[9e,27] mp 122–123.5 °C; 125–128 °C); IR 2939, 2869, 1666, 1609, 1393, 1199, 1065, 1034 cm^{-1}; ^1H NMR δ 5.86 (s, 1H), 3.41 (t, J = 8.2 Hz, 1H), 1.14 (s, 9H), 0.89 (s, 3H); ^{13}C NMR δ 199.4, 166.65, 124.96, 79.75, 72.18, 50.33, 42.44, 38.11, 36.69, 36.11, 31.36, 30.98, 28.49 (3×), 27.14, 23.68, 10.72. Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.15; H, 9.98.

[3*S*-(3α,3aα,9aα,9bβ)]-1,2,3,3a,4,5,8,9,9a,9b-Decahydro-3-hydroxy-3a-methyl-7*H*-benz[*e*]inden-7-one (9). A solution of compound **8** (25 g, 90 mmol) in EtOH (250 mL) and 6 N HCl (60 mL) was refluxed for 2.5 h. Then the mixture was chilled and the pH was adjusted to pH 5. Most of the EtOH was removed, the residue was extracted with toluene (2 × 100 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed to give the crude product which was purified by chromatography (silica, 30% EtOAc in hexane) to yield product **9** (18 g, 90%) as white crystals: mp 109–110 °C (from MeOH–EtOEt–hexane) (lit.[14] mp 109 °C from diisopropyl ether); IR: 3413, 2948, 2868, 1661, 1615, 1449, 1426, 1354, 1331, 1053 cm^{-1}; ^1H NMR δ 5.84 (s, 1H), 3.67 (t, J = 8.5 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR δ 199.69, 166.96, 124.39, 79.80, 50.00, 42.48, 37.76, 36.16, 35.34, 31.01, 29.48, 26.65, 22.84, 9.95. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.44; H, 9.29.

[3*S*-(3α,3aα,9aα,9bβ)]-1,2,3,3a,4,6,8,9,9a,9b-Decahydro-3a-methylspiro[7*H*-benz[*e*]inden-7,2′-[1,3]dioxolan]-3-ol (10). A stirred mixture of dry benzene (50 mL) and ethylene glycol (620 mg, 10 mmol) was heated under reflux until all the water was removed. To this mixture was added a solution of compound **9** (220 mg, 1.0 mmol) in dry benzene (10 mL) followed by TsOH (11 mg, 5% by w). After the mixture was refluxed for 1.5 h (monitored by TLC), it was cooled to room temperature and washed with saturated Na_2CO_3 (50 mL) and brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated to give an oil which was purified by chromatography (silica, 25% EtOAc in hexane) to give product **10** (229 mg, 88%) as a colorless oil: (lit.[14] mp 109 °C from MeOH–H_2O–C_5H_5N); IR 3431, 2943, 2873, 1421, 1362, 1108, 1073, 1053 cm^{-1}; ^1H NMR δ 5.39–5.31 (m, 1H), 3.95–3.86 (m, 4H), 3.68 (t, J = 8.7 Hz, 1H), 0.69 (s, 3H); ^{13}C NMR δ 136.08, 121.46, 109.13, 81.48, 64.36, 64.12, 47.26, 43.23, 42.05, 38.99, 37.88, 33.98, 30.33, 28.65, 23.80, 10.63.

[3a*S*-(3aα,9aα,9bβ)]-1,2,4,6,8,9,9a,9b-Octahydro-3a-methylspiro[7*H*-benz[*e*]indene-7,2′-[1,3]dioxolan]-3(3a*H*)-one (11). To a stirred suspension of PCC (2.26 g, 10.5 mmol) and sodium acetate (1.23 g, 15 mmol) in dichloromethane (150 mL) was added compound **10** (1.82 g, 7.0 mmol) at room temperature under nitrogen. After 2 h, the mixture was filtered with a Buchner funnel and the solid was washed with dichloromethane (2 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), and dried over Na_2SO_4. The solvent was evaporated to give a yellowish solid, which was purified by chromatography (silica, 40% EtOAc in hexane) to give product **11** (1.64 g, 91%) as colorless crystals: mp 118–119 °C (from EtOEt, lit.[14] mp 122 °C from MeOH–C_5H_5N); IR 2954, 2934, 2916, 2888, 1733, 1374, 1241, 1105 cm^{-1}; ^1H NMR δ 5.38–5.31 (m, 1H), 3.93–3.90 (m, 4H), 0.84 (s, 3H); ^{13}C NMR δ 221.35, 136.48, 120.85, 108.93, 64.46, 64.25, 47.86, 46.61, 43.28, 38.28, 36.15, 33.88, 32.95, 28.19, 22.45, 14.05. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.00; H, 8.27.

[3a*S*-[3(*E*),3aα,9aα,9bβ]]-3-Ethylidene-1,2,3,3a,4,6,8,9,9a,9b-decahydro-3a-methylspiro[7*H*-benz[*e*]indene-7,2′-[1,3]dioxolane] (12). A solution of NaH (600 mg, 2.5 mmol) in dry DMSO (20 mL) was warmed to 75–80 °C for 45 min under nitrogen. The resulting solution was cooled in an ice–water bath and (ethyl)triphenylphosphonium bromide (9.28 g, 25 mmol) in DMSO (30 mL) was added. After 10 min at room temperature, a solution of compound **11** (1.3 g, 5 mmol) in DMSO (20 mL) was added and the mixture was stirred overnight (22 h) at 60–70 °C under nitrogen. The mixture then was cooled to room temperature, poured into water (500 mL), and extracted with hexane (5 × 50 mL). The combined

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(27) Scott, J.; Vetter, W.; Oberhansli, W. E.; Furst, A. *Tetrahedron Lett.* **1972**, 1719.

(28) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

organic layers were evaporated to give an oil which was purified by chromatography (silica, 30% EtOAc in hexane) to give product **12** (1.1 g, 81%) as a colorless oil: IR 2941, 2871, 1437, 1369, 1106 cm^{-1}; ^1H NMR δ 5.38–5.31 (m, 1H), 5.22–5.17 (m, 1H), 3.97–3.92 (m, 4H), 1.64 (d, J = 5.5 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR δ 149.52, 136.32, 122.04, 114.38, 109.15, 64.39, 64.12, 52.67, 43.19, 42.64, 38.94, 37.94, 33.99, 31.91, 28.98, 25.19, 16.98, 14.05.

[3*S*-[3α(*S),3aα,5*β*,5a*β*,9aα,9b*β*]]-5-(Acetyloxy)-3-[1-(acetyloxy)ethyl]dodecahydro-3a-methyl-7*H*-benz[*e*]inden-7-one (15) and [3*S*-[3α(*S**),3aα,5α,5aα,9aα,9b*β*]]-5-(Acetyloxy)-3-[1-(acetyloxy)ethyl]dodecahydro-3a-methyl-7*H*-benz[*e*]inden-7-one (16).** To a stirred solution of compound **12** (4.8 g, 17.5 mmol) in dry THF (100 mL) was added a borane–THF complex (1.0 M borane solution in THF, 50 mL, 50 mmol) at room temperature. After an additional 3 h, the mixture was cooled to 0 °C and 10% aqueous NaOH (50 mL) was added cautiously followed by addition of 30% H_2O_2 (50 mL) within 20 min. After stirring at 0 °C for 2 h, the mixture was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with brine (2 × 50 mL) and dried over Na_2SO_4. Evaporation of solvent gave hydroboration product **13** as an oil.

The foregoing crude product **13** was dissolved in THF (25 mL) and 2 N aqueous HCl (10 mL). The solution was stirred overnight at room temperature under nitrogen. Most of the THF was removed under vacuum, the aqueous layer was extracted with EtOAc (3 × 60 mL), and the combined organic layers were dried over Na_2SO_4. Evaporation of solvent gave hydrolysis product **14** as an oil.

The foregoing crude product **14** was dissolved in acetic anhydride (20 mL) and pyridine (10 mL), and the mixture was warmed to 100 °C for 3 h. The excess acetic anhydride and pyridine were evaporated to give an oil which was purified by chromatography (silica, 30% EtOAc in hexane) to give a mixture of isomers **15** and **16** in the ratio of ~12:1 as a colorless oil. The isomers were separated by HPLC (Alltech Econosil silica column, 250-mm × 10-mm, 30% EtOAc in hexane, 3.0 mL/min).

Compound **15** (3.54 g, 58%) was obtained as a colorless oil: IR 2958, 2877, 1733, 1432, 1371, 1246 cm^{-1}; ^1H NMR δ 4.97–4.88 (m, 2H), 2.03 (s, 3H), 2.01 (s, 3H), 1.23 (d, J = 6.1 Hz, 3H), 0.86 (s, 3H); ^{13}C NMR δ 209.69, 170.26, 170.07, 73.42, 72.06, 54.83, 53.84, 47.63, 43.65, 43.57, 42.72, 40.78, 37.24, 30.44, 25.22, 23.00, 21.07, 20.86, 20.26, 13.28. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.55; H, 8.63. Found: C, 68.29; H, 8.36.

Compound **16** (280 mg, 5%) was obtained as colorless crystals: mp 147–149 °C; IR 2957, 2876, 1729, 1432, 1371, 1249 cm^{-1}; ^1H NMR δ 4.87–4.79 (m, 2H), 2.03 (s, 3H), 2.02 (s, 3H), 1.16 (d, J = 6.1 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR δ 210.12, 170.56, 170.35, 74.12, 72.48, 54.44, 53.65, 47.94, 44.17, 44.00, 43.46, 41.04, 37.71, 30.77, 25.46, 23.56, 21.43, 21.13, 19.75, 13.41. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.55; H, 8.63. Found: C, 68.52; H, 8.46.

[3*S*-[3α(*S),3aα,5*β*,5a*β*,7(*E*),9aα,9b*β*]]-3-[1-(Acetyloxy)-ethyl]-7-[(ethoxycarbonyl)methylene]dodecahydro-3a-methyl-1*H*-benz[*e*]inden-5-ol Acetate (17) and [3*S*-[3α(*S**),3aα,5*β*,5a*β*,7(*Z*),9aα,9b*β*]]-3-[1-(Acetyloxy)ethyl]-7-[(ethoxycarbonyl)methylene]dodecahydro-3a-methyl-1*H*-benz[*e*]inden-5-ol Acetate (18).** A stirred solid mixture of **15** (140 mg, 0.39 mmol) and (carbethoxymethylene)triphenylphosphorane (280 mg, 0.8 mmol) was heated to 160 °C overnight (ca. 15 h) under nitrogen. The resultant brown colored liquid was cooled to room temperature, and EtOAc (50 mL) was added. The solution was washed with water (50 mL) and brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvent yielded a gum which was purified by chromatography (silica, 15% EtOAc in hexane) to give a mixture of *E*- and *Z*-isomers as an oil (110 mg, 63%). The *E*-isomer **17** can be crystallized (see below for spectroscopic and analytical data) from the mixture upon storage in a refrigerator overnight, whereas the *Z*-isomer **18** can not be purified in this manner. In practice, the product was used for the next reaction without separation of the isomers.

Product **17**, obtained as described above, was recrystallized from EtOEt and isolated as colorless crystals: mp 129–131 °C; IR 2953, 2880, 1733, 1650, 1446, 1370, 1246 cm^{-1}; ^1H NMR δ 5.56–5.54 (m, 1H), 4.94–4.87 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 2.05 (s, 3H), 2.01 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.22 (d, J = 7.1 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR δ 171.67, 170.64, 170.36, 130.15, 124.49, 75.11, 72.59, 55.12, 55.05, 43.90, 43.37, 43.07, 42.72, 33.95, 32.25, 30.85, 25.63, 23.11, 21.29 (2×), 20.52, 14.17, 13.29. Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.70; H, 8.65.

[3*S*-[3α(*S),3aα,5*β*,5a*β*,7α,9aα,9b*β*]]-5-(Acetyloxy)-3-[1-(acetyloxy)ethyl]dodecahydro-3a-methyl-1*H*-benz[*e*]indene-7-acetic Acid Ethyl Ester (19) and [3*S*-[3α(*S**),3aα,5*β*,5a*β*,7*β*,9aα,9b*β*]]-5-(Acetyloxy)-3-[1-(acetyloxy)ethyl]dodecahydro-3a-methyl-1*H*-benz[*e*]indene-7-acetic Acid Ethyl Ester (20).** A stirred solution of compounds **17** and **18** (200 mg, 0.46 mmol) and Pd catalyst (10% Pd on carbon, 20 mg) in EtOAc (20 mL) was hydrogenated (H_2, 550 psi) in a Paar Model 4561 Minireactor (300 mL) at 65 °C for 20 h. The mixture was cooled to room temperature, the solution was filtered, and the solvent was evaporated to yield crude product which was purified by chromatography (silica gel, 15% EtOAc in hexane) to give in quantitative yield a mixture of isomers **19** and **20** (~1:1) as a colorless oil. The isomer mixture was dissolved in 5% EtOEt in hexane and stored at −20 °C for 20 h. Most of isomer **19** crystallized from the solution as colorless crystals. The remaining mixture of isomers was separated by HPLC (Alltech Econosil C18 column, 250-mm × 10-mm, 65% acetone in water, 3.5 mL/min).

Compound **19** was obtained as colorless crystals: mp 107–8 °C (from EtOEt–hexane); IR 2931, 1734, 1446, 1372, 1245 cm^{-1}; ^1H NMR δ 4.93–4.78 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.03 (s, 3H), 2.00 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.22 (d, J = 6.1 Hz, 3H), 0.77 (s, 3H); ^{13}C NMR δ 172.58, 170.47, 170.15, 73.86, 72.45, 59.88, 55.08, 54.44, 47.47, 44.06, 42.63, 41.75, 38.13, 34.72, 34.21, 32.07, 30.33, 25.49, 22.92, 21.13, 21.05, 20.35, 14.09, 13.33. Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.42; H, 9.12.

Compound **20** was obtained as colorless crystals: mp 66–68 °C (from hexane); IR 2931, 1734, 1447, 1371, 1246 cm^{-1}; ^1H NMR δ 4.95–4.72 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 2.01 (s, 3H), 2.00 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H), 0.77 (s, 3H); ^{13}C NMR δ 172.95, 170.44, 170.17, 73.86, 72.48, 59.93, 55.11, 54.47, 44.12, 42.60, 42.23, 38.76, 36.83, 32.25, 29.62, 29.05, 25.51, 25.16, 22.77, 21.13, 21.01, 20.34, 14.10, 13.35. Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.44; H, 9.33.

[3*S*-[3α(*S),3aα,5*β*,5a*β*,7α,9aα,9b*β*]]-Dodecahydro-5-hydroxy-3-(1-hydroxyethyl)-3a-methyl-1*H*-benz[*e*]indene-7-ethanol (21).** To a solution of compound **19** (470 mg, 1.07 mmol) in dry toluene (100 mL) was added a solution of DIBALH in toluene (1.0 M solution in toluene, 20 mL, 20 mmol) at −5 °C under nitrogen. After addition of DIBALH, the mixture was allowed to warm to room temperature. After 1 h, the mixture was cooled to 0–5 °C, saturated NH_4Cl (50 mL) and 2 N HCl (25 mL) were added, and the mixture was stirred until clear. The organic layer was separated, and the aqueous layer was saturated with NaCl and extracted with THF (2 × 50 mL) and EtOAc (50 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed to give a solid which was recrystallized from MeOH to give product **21** (318 mg, 85%) as white needles: mp 183–185 °C; IR 3307, 2910, 1446, 1039 cm^{-1}; ^1H NMR δ 3.67–3.61 (m, 3H), 3.50–3.42 (m, 1H), 1.27 (d, J = 6.1 Hz, 3H), 0.75 (s, 3H); ^{13}C NMR δ 72.45, 70.84, 60.78, 59.61, 56.38, 52.14, 49.58, 43.89, 41.40, 40.16, 36.86, 35.29, 34.11, 32.20, 27.53, 24.43, 24.00, 14.03. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 73.00; H, 10.68.

[3*S*-[3α(*S),3aα,5*β*,5a*β*,7*β*,9aα,9b*β*]]-Dodecahydro-5-hydroxy-3-(1-hydroxyethyl)-3a-methyl-1*H*-benz[*e*]indene-7-ethanol (22).** Using the same reduction procedure described immediately above, compound **20** (1.0 g, 2.3 mmol) was converted to a solid which was purified by recrystallization from MeOH–EtOAc to yield product **22** (620 mg, 91%) as white crystals: mp 174–176 °C; IR 3392, 2931, 1451, 1371, 1048 cm^{-1}; ^1H NMR δ 3.63–3.54 (m, 3H), 3.43–3.32 (m, 1H), 1.21 (d, J = 6.2 Hz, 3H), 0.70 (s, 3H); ^{13}C NMR δ 72.41, 70.78, 61.60, 59.57, 56.32, 49.59, 46.44, 43.84, 40.62, 35.56, 33.91, 30.52, 27.54, 26.86, 24.31, 24.04, 14.12. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.75; H, 10.68.

[3S-[3α(S*),3aα,5β,5aβ,7α,9aα,9bβ]]-Dodecahydro-5-hydroxy-3-(1-hydroxyethyl)-3a-methyl-1H-benz[e]indene-7-ethanol Trimethylacetate (23). A mixture of compound **21** (750 mg, 2.5 mmol), 3-pivaloylthiazolidine-2-thione[24] (3.4 g, 17 mmol), and NaH (240 mg, 10 mmol) was stirred at 55–60 °C for 10 h under nitrogen. The mixture was diluted with EtOAc (100 mL) and washed with saturated NH_4Cl (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed to give an oil. The crude product was purified by chromatography (silica, 50% EtOAc in hexane) to give product **23** (523 mg, 70%) as white crystals: mp 111–113 °C (from Et_2O–hexane); IR 3399, 2925, 1729, 1713, 1480, 1370, 1160 cm^{-1}; ^1H NMR δ 4.13–4.08 (m, 2H), 3.70–3.66 (m, 1H), 3.53–3.44 (m, 1H), 1.24 (d, J = 6.2 Hz, 3H), 1.19 (s, 9H), 0.69 (s, 3H); ^{13}C NMR δ 178.60, 71.61, 70.00, 62.49, 58.04, 54.72, 50.79, 48.19, 42.75, 38.59, 38.41, 35.89, 35.37, 34.30, 32.43, 30.65, 27.07 (3×), 25.88, 23.43, 23.24, 13.67. Anal. Calcd for $C_{23}H_{40}O_4$: C, 72.59; H, 10.59. Found: C, 72.73; H, 10.52.

[3S-[3α(S*),3aα,5β,5aβ,7β,9aα,9bβ]]-Dodecahydro-5-hydroxy-3-(1-hydroxyethyl)-3a-methyl-1H-benz[e]indene-7-ethanol Trimethylacetate (24). Using the same selective esterification procedure described immediately above, compound **22** (500 mg, 1.69 mmol) gave a solid which was purified by recrystallization from EtOEt–hexane to yield product **24** (350 mg, 55%) as white crystals: mp 81–83 °C; IR 3379, 2917, 1728, 1712, 1480, 1369, 1164 cm^{-1}; ^1H NMR δ 4.12–4.05 (m, 2H), 3.71–3.66 (m, 1H), 3.55–3.43 (m, 1H), 1.24 (d, J = 6.2 Hz, 3H), 1.19 (s, 9H), 0.70 (s, 3H); ^{13}C NMR δ 178.74, 71.75, 70.11, 63.41, 58.12, 54.74, 48.26, 45.39, 42.79, 38.98, 38.65, 32.63, 30.36, 29.54, 29.36, 27.14 (3×), 25.91, 25.37, 23.46, 23.15, 13.75. Anal. Calcd for $C_{23}H_{40}O_4$: C, 72.59; H, 10.59. Found: C, 72.70; H, 10.64.

[3S-(3α,3aα,5aβ,7α,9aα,9bβ)]-3-Acetyl-7-[2-(trimethylacetyloxy)ethyl]dodecahydro-3a-methyl-5H-benz[e]inden-5-one (25). Jones reagent (8 N solution, 0.5 mL) was added to a stirred solution of compound **23** (420 mg, 1.1 mmol) in acetone (100 mL) at −5 °C. After 5 min (monitored by TLC), the reaction was quenched with 2-propanol (1.0 mL), and EtOAc (50 mL) and H_2O (50 mL) were added. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL) and dried over Na_2SO_4. The solvent was removed to give a solid, which was recrystallized from EtOEt–hexane to give product **25** (384 mg, 92%) as white crystals: mp 107–109 °C; IR 2926, 1725, 1707, 1480, 1361, 1284, 1159 cm^{-1}; ^1H NMR δ 4.10 (t, J = 6.6 Hz, 2H), 2.77 (t, J = 9.1 Hz, 1H), 2.11 (s, 3H), 1.19 (s, 9H), 0.59 (s, 3H); ^{13}C NMR δ 210.59, 208.0, 178.47, 62.30, 58.04, 54.72, 50.79, 48.19, 42.75, 38.59, 38.41, 35.37, 34.30, 32.43, 30.65, 27.12 (3×), 25.88, 23.43, 23.24, 14.56. Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.55; H, 9.47.

[3S-(3α,3aα,5aβ,7β,9aα,9bβ)]-3-Acetyl-7-[2-[(trimethylacetyl)oxy]ethyl]dodecahydro-3a-methyl-5H-benz[e]inden-5-one (26). Using the same oxidation procedure as immediately above, compound **24** (350 mg, 0.92 mmol) gave a solid which was purified by recrystallization from EtOEt to yield product **26** (320 mg, 93%) as white crystals: mp 121–123 °C; IR 2928, 1726, 1706, 1480, 1361, 1285, 1158 cm^{-1}; ^1H NMR δ 4.06 (t, J = 6.8 Hz), 2.79 (t, J = 9.2 Hz, 1H), 2.12 (s, 3H), 1.19 (s, 9H), 0.60 (s, 3H); ^{13}C NMR δ 210.90, 207.93, 178.36, 63.08, 62.04, 54.85, 54.21, 48.68, 47.27, 41.56, 38.49, 31.16, 29.96, 29.16, 28.70, 28.46, 26.99 (3×), 26.15, 23.17, 23.08, 14.46. Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.38; H, 9.54.

[3S-(3α,3aα,5aβ,7α,9aα,9bβ)]-3-Acetyldodecahydro-7-(2-hydroxyethyl)-3a-methyl-5H-benz[e]inden-5-one (3) and [3R-(3α,3aβ,5aα,7β,9aβ,9bα)]-3-Acetyldodecahydro-7-(2-hydroxyethyl)-3a-methyl-5H-benz[e]inden-5-one (27). A solution of compound **25** (180 mg, 0.48 mmol) and KOH (20 mg) in MeOH (20 mL) was stirred at room temperature for 60 h under nitrogen and then cooled to 0 °C and acidified to pH 2 with 3 N HCl. The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed to give a yellow oil which was purified by chromatography (silica, 60% EtOAc in hexane) to give a mixture of isomeric products **3** and **27** as an oil (116 mg, 83%). The isomeric products were separated by HPLC (Alltech Econosil silica column, 250-mm × 10-mm, 60% EtOAc in hexane, 3.3 mL/min).

Compound **3** (58 mg, 41%) was obtained as colorless crystals (from EtOEt): mp 84.5–86.5 °C; IR 3383, 2923, 1703, 1445, 1360, 1268, 1225, 1055 cm^{-1}; ^1H NMR δ 3.72 (t, J = 6.5 Hz, 2H), 2.77 (t, J = 9.1 Hz, 1H), 2.11 (s, 3H), 0.60 (s, 3H); ^{13}C NMR δ 211.08, 208.29, 61.90, 59.90, 54.57, 54.13, 53.85, 47.22, 41.05, 39.68, 33.09, 32.01, 31.41, 31.11, 30.97, 23.14 (2×), 14.37. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.97; H, 9.57.

Compound **27** (24.9 mg, 21%) was obtained as a colorless oil: IR 3403, 2926, 1704, 1445, 1360, 1270, 1225, 1176, 1056 cm^{-1}; ^1H NMR δ 3.72 (t, J = 6.6 Hz, 2H), 2.83 (dd, J = 2.5 Hz, J = 5.9 Hz, 1H), 2.13 (s, 3H), 0.85 (s, 3H); ^{13}C NMR δ 212.22, 211.60, 60.40, 59.45, 53.65, 51.37, 48.68, 48.58, 41.28, 39.94, 33.26, 32.65, 32.30, 31.95, 31.20, 25.25, 24.82, 21.92. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.90; H, 9.50.

[3S-(3α,3aα,5aβ,7β,9aα,9bβ)]-3-Acetyldodecahydro-7-(2-hydroxyethyl)-3a-methyl-5H-benz[e]inden-5-one (4) and [3R-(3α,3aβ,5aα,7α,9aβ,9bα)]-3-Acetyldodecahydro-7-(2-hydroxyethyl)-3a-methyl-5H-benz[e]inden-5-one (28). Using the same procedure described immediately above, compound **26** (200 mg, 0.53 mmol) was converted to an oil (100 mg, 64%) which was a mixture of isomeric products **4** and **28** in a ratio of ~4:1. Purification and separation of the products was achieved by column chromatography (silica, 80% EtOAc in hexane) followed by HPLC (Alltech Econosil silica column, 250-mm × 10-mm, 70% EtOAc in hexane, 3.0 mL/min).

Compound **4** (70 mg, 45%) was obtained as colorless crystals (from EtOEt–hexane): mp 82–83 °C; IR 3482, 2924, 1703, 1447, 1361, 1270, 1229, 1054 cm^{-1}; ^1H NMR δ 3.65 (t, J = 6.9 Hz, 2H), 2.78 (t, J = 9.1 Hz, 1H), 2.12 (s, 3H), 0.59 (s, 3H); ^{13}C NMR δ 211.23, 208.15, 62.19, 61.32, 54.98, 54.41, 48.92, 47.36, 41.70, 34.28, 31.20, 29.14, 28.64, 28.60, 26.41, 23.35, 23.21, 14.53. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.93; H, 9.42.

Compound **28** (30 mg, 19%) was obtained as colorless crystals (from EtOEt): mp 159–160 °C; IR 3406, 2925, 1702, 1447, 1361, 1270, 1229, 1184, 1054 cm^{-1}; ^1H NMR δ 3.63 (t, J = 6.7 Hz, 2H), 2.83 (dd, J = 2.6 Hz, J = 5.5 Hz, 1H), 2.13 (s, 3H), 0.85 (s, 3H); ^{13}C NMR δ 212.09, 211.84, 61.37, 59.54, 51.57, 48.79, 48.59, 41.78, 34.31, 32.64, 29.22, 28.63, 28.58, 26.84, 25.31, 24.74, 21.97. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.77; H, 9.60.

Electrophysiological Methods. The methods used were identical to those described in an earlier study.[1c] References for the culturing of rat hippocampal neurons, patch clamp techniques, and methods of data analysis are also reported there.

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