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Neurosteroid analogues. Part 13: Synthetic methods for the preparation of 2β-hydroxygonane derivatives as structural mimics of *ent*-3α-hydroxysteroid modulators of $GABA_A$ receptors

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Abstract—Many different 3α-hydroxysteroids in the androstane and pregnane steroid series enhance the actions of γ-aminobutyric acid (GABA) at GABA type-A ($GABA_A$) receptors in the mammalian central nervous system. Recent studies have shown that (3α,5α)-3-hydroxy-androstan-17-one (androsterone) is less active at these receptors than its enantiomer *ent*-androsterone. Further structure–activity relationship (SAR) studies are needed to explore the structural features of *ent*-androsterone that are important for its enhanced action at these receptors. Molecular modeling shows that 2β-hydroxysteroids are similar in three-dimensional shape to the enantiomers of 3α-hydroxysteroids. The development of synthetic methods to gain access to C_{17}-substituted analogues of 2β-hydroxygonanes for SAR studies is demonstrated with the synthesis of (2β,5α,14β)-2-hydroxygonan-17-one.

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1. Introduction

The steroid (3α,5α)-3-hydroxypregnan-20-one (allopregnanolone, Fig. 1) and many analogues of it are known to be potent enhancers of γ-aminobutyric acid (GABA) at GABA type-A ($GABA_A$) receptors.[1–4] These neuroactive GABAergic steroids have activity as general anesthetics, anticonvulsants, sedative hypnotics, and anxiolytics; and there is considerable current interest in the development of new analogues as pharmaceuticals having these activities.

As part of our ongoing studies of the enantioselectivity of neurosteroid action at $GABA_A$ receptors, we recently investigated the enantioselectivity for (3α,5α)-3-hydroxy-androstan-17-one (androsterone, Fig. 1) effects at these receptors.[5] Androsterone has only weak actions on $GABA_A$ receptor function[6,7] and, based on our previous results from enantioselectivity studies of allopregnanolone,[8] we expected that *ent*-androsterone (Fig. 1) would have even weaker actions than androsterone. Unexpectedly, we found that *ent*-androsterone was more active than androsterone. Moreover, a 17-spiroepoxide derivative of *ent*-androsterone (Fig. 1) was shown to have actions comparable to those of allopregnanolone.[5]

Additional steroid analogues are needed for future structure–activity relationship (SAR) studies of *ent*-androgen action at

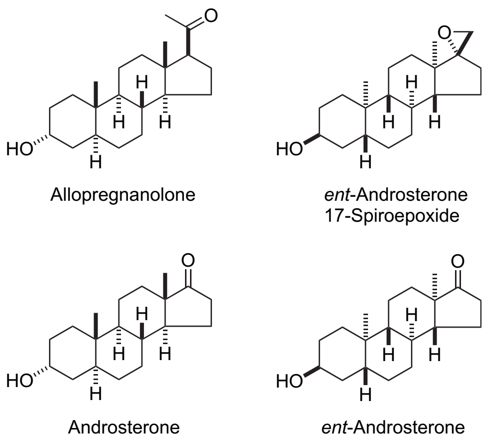

Figure 1. Structures of steroid modulators of $GABA_A$ receptor function. Allopregnanolone and *ent*-androsterone 17-spiroepoxide potently enhance the actions of GABA at $GABA_A$ receptors. Androsterone is a weak enhancer of GABA action. *ent*-Androsterone has activity higher than that of androsterone but less than that of the other two steroids.

Keywords: 2β-Hydroxygonanes; Abnormal Beckmann rearrangement; Neurosteroids; Phenanthrenes.

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GABA$_A$ receptors. In this regard, we were intrigued by the structural similarity between 2β-hydroxysteroids and the enantiomers of 3α-hydroxysteroids. Figure 2A shows the structure of (2β,5α,13β,14β)-2-hydroxygonan-17-one (**1**) and *ent*-androsterone. Figure 2B shows a three-dimensional overlay of molecular models of steroid **1** and *ent*-androsterone. Both steroids are shown with their β face down because in this orientation the compounds most closely resemble the highly active 3α-hydroxysteroid allopregnanolone. As presented in Figure 2, each of the four steroid rings of one compound is proximate to the corresponding ring of the other compound. The O_2 and O_3 atoms of the two molecules are 0.68 Å apart and the O_{17} atoms are 0.54 Å from each other in this overlay.

Two additional design criteria were considered in the decision to select steroid **1** as an initial potential structural mimic of *ent*-androsterone. Previous SAR studies have shown that having methyl groups on the steroid α face decreases the activity of 3α-hydroxysteroid modulators of GABA$_A$ receptors.[9,10] When aligned as shown in Figure 2B, the C_{18} and/or C_{19} methyl groups of steroids in the androstane, estrane (19-norandrostane), and 18-norandrostane series would be located below the plane of the steroid rings (i.e., they would occupy positions similar to those occupied by methyl groups on the α face of 3α-hydroxysteroids, and therefore could be expected to negatively affect pharmacological activity). By choosing a steroid in the gonane class as a synthetic target, worries about unfavorable steric effects of these methyl groups are avoided.

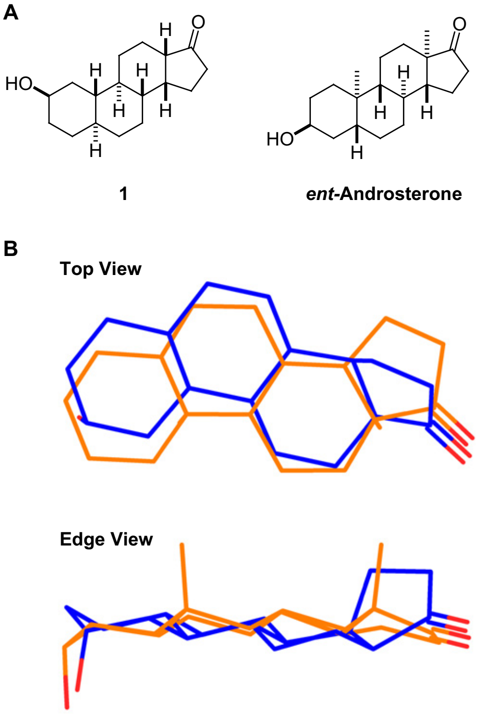
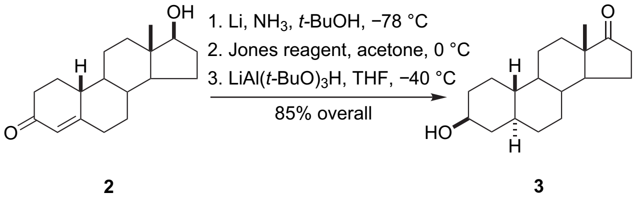


Figure 2. Panel A: structures of (2β,5α,14β)-2-hydroxygonan-17-one (**1**) and *ent*-androsterone. Panel B: an overlay of steroid **1** (blue structure) and *ent*-androsterone (orange structure). The structures were overlaid using an rms fit of atoms C_9, C_{11}, C_{12}, C_{14}, O_3, and O_{17} in each structure for the alignment. The O_2–O_{17} (9.37 Å) distance in steroid **1** is shorter than the O_3–O_{17} distance (9.67 Å) in *ent*-androsterone.

The decision to have the 13β,14β-cis C,D-ring fusion present in steroid **1** was made because this cis ring fusion places the C_{17} carbonyl group further above the plane of the steroid rings (when oriented as shown in Fig. 2B) than it would be in the corresponding 13β,14α-trans ring fusion. This was considered to be desirable since previous SAR studies indicate that the D-ring hydrogen bonding groups need to be above the plane of the steroid rings for high pharmacological activity.[1,6,7]

2. Results and discussion

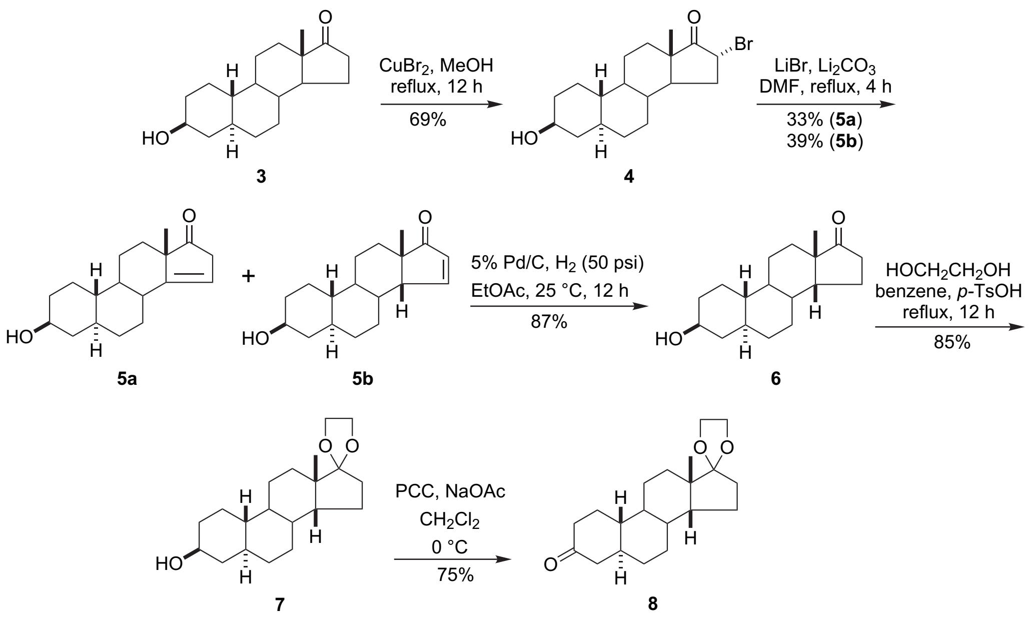
The starting material, (3β,5α)-3-hydroxyestran-17-one (**3**), was prepared in three steps by known methodology[11,12] from commercially available 19-nortestosterone (**2**) in 85% total yield (Scheme 1). Steroid **3** was brominated selectively in the C_{16} position using $CuBr_2$[13,14] to give compound **4** in 69% yield (Scheme 2). HBr was eliminated from steroid **4** using $LiBr/Li_2CO_3$[15] to give compounds **5a** (33%) and **5b** (39%). For characterization purposes, some spectroscopic data were collected on each of these products after their separation by chromatography. For synthetic purposes, products **5a** and **5b** were not separated and the mixture was subjected to catalytic hydrogenation to give compound **6** in 87% yield. The 17-keto group was ketalized in the standard way[16] to afford compound **7** in 85% yield. Oxidation of the 3β-hydroxyl group of compound **7** using PCC in the presence of NaOAc[17] gave compound **8** (75%).



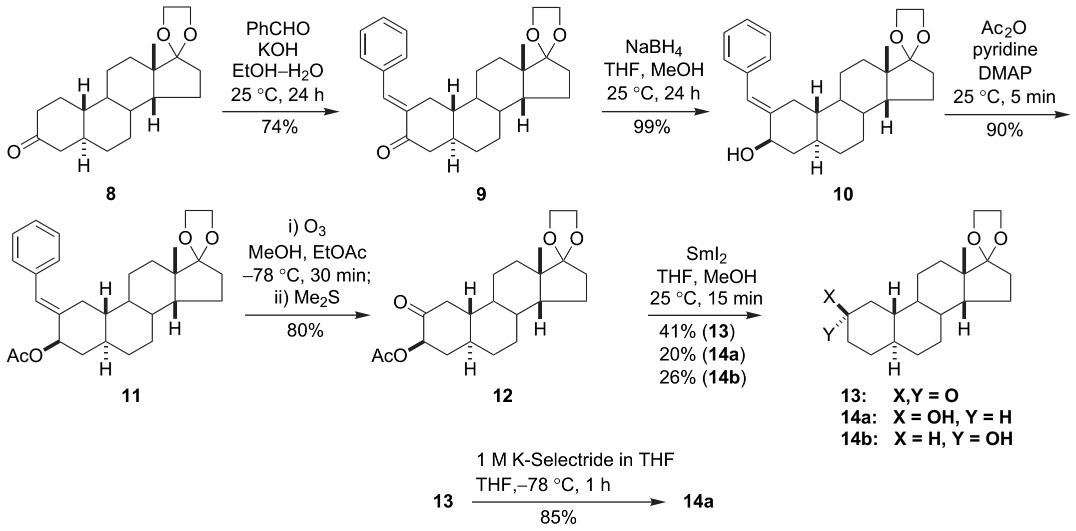
Scheme 1.

When treated with 10% ethanolic KOH at room temperature for 24 h, compound **8** underwent an aldol condensation[18] to give compound **9** in 74% yield (Scheme 3). Reduction of the 3-ketone group with $NaBH_4$ at room temperature led to the 3β-hydroxysteroid **10** (99%), and acetylation of the hydroxyl group gave the acetate derivative **11** in 90% yield. Compound **11** was treated with ozone in the usual manner[18] to give steroid **12** (80%). Samarium(II) iodide/THF mediated reductive removal of the 3-acetyloxy group from compound **12** gave 2-ketosteroid **13** (41%), 2β-hydroxysteroid **14a** (20%), and 2α-hydroxysteroid **14b** (26%). Reduction of compound **13** with K-Selectride in THF at −78 °C gave additional amounts of compound **14a** (85%).

The hydroxyl group of 2β-hydroxysteroid **14a** was reacted with acetic anhydride and pyridine in the presence of a catalytic amount of 4-dimethylaminopyridine to afford 2-(acetyloxy)steroid **15** (92%) after 5 min at room temperature (Scheme 4). The 17-ketal of compound **15** was readily removed using *p*-TsOH in acetone at room temperature for 12 h to give, in quantitative yield, steroid **16**. The reaction of compound **16** with $NH_2OH \cdot HCl$ and NaOAc gave oxime **17** (97%). Oxime **17** underwent an abnormal Beckmann rearrangement[19] upon treatment with $CH(OCH_3)_3$/TFA in



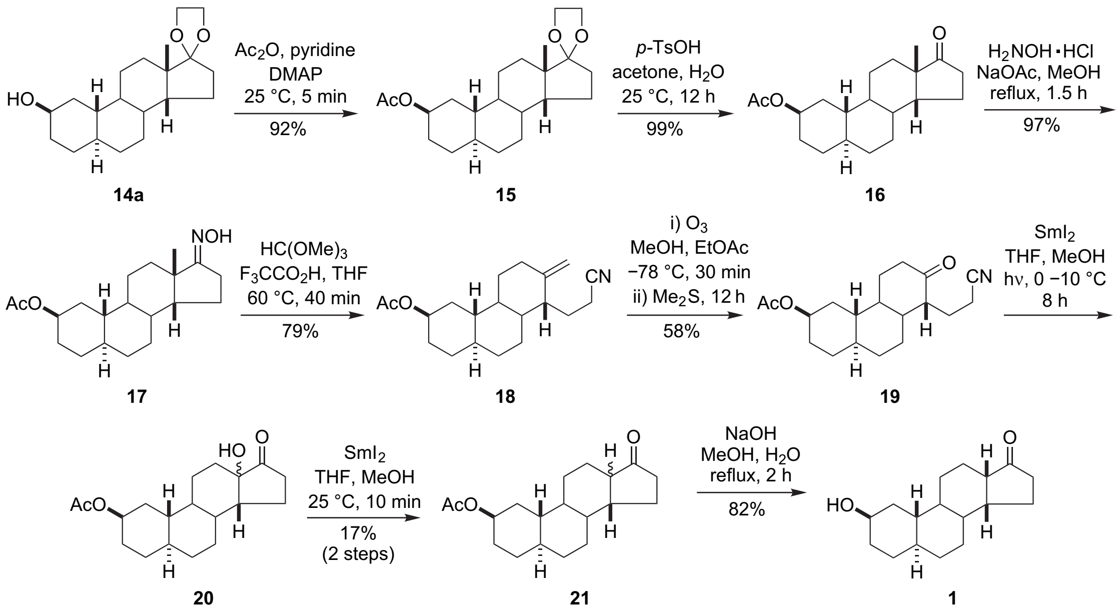
Scheme 2.



Scheme 3.

THF to give carbonitrile **18** (79%). Ozonolysis of compound **18** at −78 °C yielded ketone-nitrile **19** (58%). Treatment of compound **19** with SmI_2 in THF and irradiation with a 500 W lamp[20] at 0–10 °C for 8 h gave crude 13-hydroxysteroid **20**. After isolation, crude product **20** was again treated with SmI_2 in THF at room temperature for 10 min to give compound **21** (17%, from compound **19**). Finally, base-catalyzed hydrolysis of the 3-acetyloxy group of compound **21** and column chromatography to remove the presumed 13α,14β stereoisomer gave compound **1** (82%). The structure of steroid **1** was confirmed by single crystal X-ray diffraction analysis (Fig. 3).[21]

Using methods reported previously,[22] the actions of compound **1** as a modulator of $GABA_A$ receptor function were compared to those of *ent*-androsterone. Whereas *ent*-androsterone allosterically displaced 50% of [^{35}S]-*tert*-butylbicyclophosphorthionate bound to the picrotoxin binding site on $GABA_A$ receptors at a concentration of 0.31 μM,[5] no displacement of [^{35}S]-*tert*-butylbicyclophosphorthionate occurred at concentrations up to 30 μM of compound **1**. *ent*-Androsterone (10 μM) enhances 2 μM GABA-mediated chloride currents at rat $\alpha_1\beta_2\gamma_{2L}$ GABA receptors expressed in *Xenopus laevis* oocytes.[5] Compound **1** at concentrations up to 10 μM does not enhance 2 μM GABA-mediated chloride currents at these expressed receptors. Finally, *ent*-androsterone causes 50% loss of righting reflex for tadpoles at a concentration of 3.38 μM.[5] By contrast, compound **1** did not cause loss of righting reflex in tadpoles at a concentration as high as 10 μM. Thus, despite the similarities in the overall



Scheme 4.

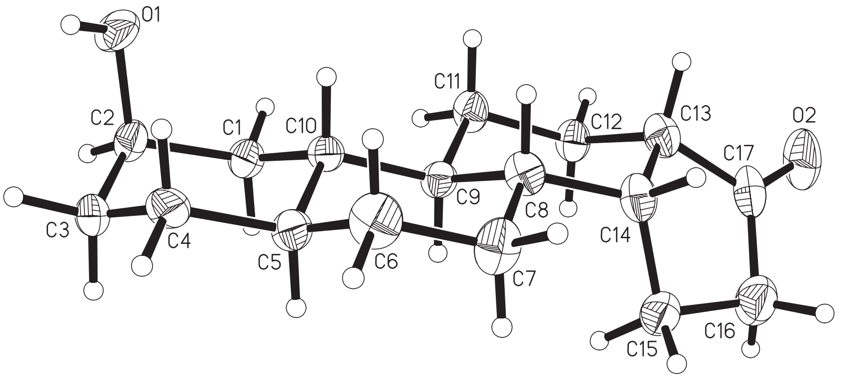


Figure 3. Projection view of one of the two unique molecules of steroid **1** shown with 50% thermal ellipsoids for non-hydrogen atoms.

shapes of the two steroids, only *ent*-androsterone is effective as a positive modulator of GABA$_A$ receptors at concentrations below 10 μM.

3. Conclusion

We have described the synthesis and crystal structure of (2β,5α,14β)-2-hydroxygonan-17-one (**1**) from commercially available 19-nortestosterone. Novel features of the synthetic route developed include the first use of a SmI$_2$-promoted reaction to remove a 3-acetyloxy group from a 2-keto-3-(acetyloxy)steroid, the first report of the abnormal Beckmann rearrangement on steroids having the 13β,14β-cis C,D-ring fusion, and the first use of SmI$_2$-promoted reactions to prepare 18-norsteroids having a 13β,14β-cis C,D-ring fusion. Omission of the part of the reported synthetic sequence that was used to construct the 13β,14β-cis C,D-ring fusion would also allow other 2β-hydroxygonane analogues with the 13β,14α-trans C,D-ring fusion to be prepared using methods reported previously for the synthesis of (13β,14α)-18-norsteroids.[20,23]

4. Experimental

4.1. General methods

Melting points were determined on a Kofler micro hot stage and are uncorrected. NMR spectra were recorded in CDCl$_3$ at 300 MHz (^{1}H) or 75 MHz (^{13}C). IR spectra were recorded as films on a NaCl plate. Elemental analyses were carried out by M-H-W Laboratories, Phoenix, AZ.

4.1.1. (3β,5α,16α)-16-Bromo-3-hydroxyestran-17-one (4). A mixture of known compound **3**[24] (1.40 g, 5.07 mmol) and copper bromide (3.06 g, 13.7 mmol) in methanol (35 mL) was stirred under reflux for 12 h. Then the solvent was removed under reduced pressure to give a residue and water (25 mL) was added. The product was extracted with CH$_2$Cl$_2$ (25 mL), the organic layer was washed with water (2×10 mL) and brine (20 mL), and dried over Na$_2$SO$_4$. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel; CH$_2$Cl$_2$/EtOAc, 10:1) to give compound **4** (1.24 g, 69%) as white crystals. Mp 108–110 °C (EtOAc/

hexanes); $[\alpha]_D^{20}$ +59.1 (*c* 0.30, $CHCl_3$); ^1H NMR δ 4.56 (m, 1H), 3.56 (br s, 1H), 3.05 (s, 1H), 2.18 (m, 2H), 0.91 (s, 3H); ^{13}C NMR δ 13.6, 24.4, 27.7, 29.0, 31.7, 32.5, 33.3, 34.9, 39.2, 40.4, 42.4, 45.4, 46.0, 46.5, 47.2, 47.3, 69.3, 213.0; IR ν_{max} 3400, 2920, 2853, 1748, 1448, 1023 cm^{-1}. Anal. Calcd for $C_{18}H_{27}BrO_2$: C 60.85, H 7.66. Found: C 60.78, H 7.87.

4.1.2. (3β,5α)-3-Hydroxyestr-14-en-17-one (5a) and (3β,5α,14β)-3-hydroxyestr-15-en-17-one (5b). The mixture of compound **4** (0.65 g, 1.8 mmol), LiBr (0.42 g, 5.0 mmol), and Li_2CO_3 (0.35 g, 5.0 mmol) in DMF (30 mL) was stirred under reflux for 4 h. Afterward, the reaction mixture was chilled to room temperature and poured into water (50 mL), the mixture was extracted with EtOAc (2×30 mL), the combined organic extract was washed with saturated $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure. The products were purified by column chromatography (silica gel; CH_2Cl_2/EtOAc, 10:1) to give compound **5a** (0.17 g, 33%; R_f=0.47, CH_2Cl_2/EtOAc, 10:1) and compound **5b** (0.20 g, 39%; R_f=0.33, CH_2Cl_2/EtOAc, 10:1). Compound **5a** was obtained as an oil, ^1H NMR δ 5.47 (d, *J*=1.8 Hz, 1H), 3.59 (m, 1H), 2.86 (m, 2H), 2.29 (s, 1H), 1.12 (s, 3H); ^{13}C NMR δ 19.7, 25.2, 27.8, 28.0, 32.9, 33.0, 35.4, 40.8, 41.0, 41.3, 43.0, 46.5, 48.6, 50.7, 70.0, 112.3, 152.8, 222.7; IR ν_{max} 3400, 3059, 2921, 2855, 1744, 1641, 1449, 1046 cm^{-1}.

Compound **5b** was obtained as an oil, ^1H NMR δ 7.64 (dd, *J*=6.0, 2.4 Hz, 1H), 6.15 (dd, *J*=6.0, 2.4 Hz, 1H), 3.57 (m, 1H), 2.63 (m, 1H), 1.11 (s, 3H); ^{13}C NMR δ 21.3, 24.8, 28.0, 30.1, 31.7, 33.4, 35.5, 39.7, 39.8, 40.8, 42.9, 47.3, 47.5, 54.4, 70.2, 132.2, 163.3, 215.2; IR ν_{max} 3400, 2921, 2854, 1705, 1585, 1449, 1052 cm^{-1}. Compounds **5a** and **5b** were not purified further and used in the next step directly.

4.1.3. (3β,5α,14β)-3-Hydroxyestran-17-one (6). A mixture of compounds **5a** and **5b** (3.90 g, 14.2 mmol) was dissolved in EtOAc (50 mL) and hydrogenated under H_2 (50 psi) in the presence of 5% Pd–C (400 mg) at room temperature overnight. The reaction mixture was filtered through a pad of Celite 545® to remove catalyst and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel; EtOAc/hexanes, 1:1) to give compound **6** (3.81 g, 97%) as white crystals. Mp 116–118 °C (EtOAc); $[\alpha]_D^{20}$ +92.0 (*c* 0.27, $CHCl_3$); ^1H NMR δ 3.56 (m, 1H), 3.27 (br s, 1H), 2.45 (dd, *J*=19.2, 8.1 Hz, 1H), 2.13 (dd, *J*=19.2, 9.9 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR δ 18.1, 19.3, 24.6, 27.6, 27.7, 30.0, 33.4, 35.1, 35.6, 39.1, 40.0, 40.6, 42.7, 46.2, 47.5, 47.8, 69.6, 222.8; IR ν_{max} 3401, 2917, 2854, 1732, 1448, 1048 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_2$: C 78.21, H 10.21. Found: C 78.42, H 9.97.

4.1.4. (3β,5α,14β)-3-Hydroxyestran-17-one cyclic-(1,2-ethanediyl acetal) (7). A solution of compound **6** (0.41 g, 1.49 mmol), ethylene glycol (2.2 g, 35 mmol), and *p*-TsOH (60 mg, 0.32 mmol) in benzene (35 mL) was refluxed using a Dean–Stark trap for 12 h. The mixture was cooled to room temperature, diluted with ether (50 mL), and washed with saturated $NaHCO_3$ (2×20 mL) and brine (2×20 mL). The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a crude product, which was purified by column chromatography (silica gel; EtOAc/hexanes, 1:1) to yield compound **7** (406 mg, 85%) as an oil. $[\alpha]_D^{20}$ +73.9 (*c* 0.065, $CHCl_3$); ^1H NMR δ 3.86 (m, 4H), 3.55 (m, 1H), 0.92 (s, 3H); ^{13}C NMR δ 16.1, 19.7, 25.3, 27.8, 28.9, 30.3, 32.1, 33.6, 35.3, 39.4, 39.7, 40.8, 43.0, 45.1, 46.4, 46.8, 63.7, 65.0, 69.9, 120.4; IR ν_{max} 3368, 2920, 2856, 1447, 1367, 1031 cm^{-1}. Anal. Calcd for $C_{20}H_{32}O_3$: C 74.96, H 10.06. Found: C 75.12, H 9.86.

4.1.5. (5α,14β)-Estrane-3,17-dione cyclic-17-(1,2-ethanediyl acetal) (8). To a solution of compound **7** (406 mg, 1.27 mmol) in CH_2Cl_2 (25 mL) were added NaOAc (0.46 g, 5.6 mmol) and PCC (0.72 g, 3.35 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h and allowed to stand overnight. Then the reaction mixture was diluted with Et_2O (100 mL) and the mixture was filtered through a pad of silica gel. Removal of solvent gave a residue, which was purified by column chromatography (silica gel; hexanes/EtOAc, 5:1) to give compound **8** (302 mg, 75%) as white crystals. Mp 85–86 °C (hexanes/EtOAc); $[\alpha]_D^{20}$ +103.9 (*c* 0.28, $CHCl_3$); ^1H NMR δ 3.90 (m, 4H), 2.29 (m, 4H), 0.94 (s, 3H); ^{13}C NMR δ 16.3, 19.8, 25.7, 29.0, 30.0, 30.1, 32.2, 34.2, 39.4, 39.7, 41.1, 43.4, 45.2, 46.1, 46.9, 48.5, 63.9, 65.2, 120.4, 211.6; IR ν_{max} 2935, 2880, 1714, 1470, 1448 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O_3$: C 75.43, H 9.50. Found: C 75.63, H 9.38.

4.1.6. (5α,14β)-2-(Phenylmethylene)estrane-3,17-dione cyclic-17-(1,2-ethanediyl acetal) (9). A mixture of compound **8** (1.60 g, 5.03 mmol), benzaldehyde (1.75 g, 16.5 mmol), and KOH (400 mg, 7.14 mmol) in EtOH (30 mL) and water (5 mL) was stirred at room temperature in the dark for 24 h. Then the reaction mixture was poured into ice-water (50 mL), and the product was extracted with CH_2Cl_2 (2×25 mL), the organic phase was washed with water (15 mL) and brine (15 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a residue, which was purified by column chromatography (silica gel; hexanes/EtOAc, 6:1) to give compound **9** (1.51 g, 74%) as light yellow crystals. Mp 153–155 °C (EtOAc); $[\alpha]_D^{20}$ +43.0 (*c* 0.33, $CHCl_3$); ^1H NMR δ 7.47 (d, *J*=2.1 Hz, 1H), 7.40 (m, 5H), 3.89 (m, 4H), 3.36 (dd, *J*=16.2, 2.7 Hz, 1H), 2.63 (dd, *J*=16.8, 4.2 Hz, 1H), 0.91 (s, 3H); ^{13}C NMR δ 16.4, 19.9, 25.7, 29.0, 29.9, 32.3, 33.2, 33.7, 39.0, 39.1, 40.8, 44.4, 45.3, 47.0, 47.4, 64.0, 65.3, 120.5, 128.3 (2×C), 128.5, 130.3 (2×C), 135.4, 135.6, 135.8, 201.5; IR ν_{max} 2918, 2860, 1682, 1594, 1572, 1491, 1085, 735 cm^{-1}. Anal. Calcd for $C_{27}H_{34}O_3$: C 79.76, H 8.34. Found: C 79.66, H 8.35.

4.1.7. (3β,5α,14β)-3-Hydroxy-2-(phenylmethylene)estran-17-one cyclic-(1,2-ethanediyl acetal) (10). To a solution of compound **9** (1.51 g, 3.72 mmol) in THF (40 mL) and MeOH (25 mL) was added $NaBH_4$ (70 mg, 1.85 mmol) at room temperature. The mixture was stirred for 30 min. Most of solvent was removed under reduced pressure and EtOAc (35 mL) was added to the residue. The organic phase was washed with water (20 mL) and brine (20 mL) and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel; hexanes/EtOAc, 3:1) to give compound

10 (1.50 g, 99%) as a thick oil. $[\alpha]_D^{20}$ +67.2 (*c* 0.49, $CHCl_3$); ^1H NMR δ 7.34 (m, 5H), 6.57 (s, 1H), 4.12 (m, 1H), 3.88 (m, 4H), 3.10 (dd, *J*=13.5, 2.4 Hz, 1H), 2.43 (br s, 1H), 0.91 (s, 3H); ^{13}C NMR δ 16.4, 19.9, 25.3, 29.0, 30.3, 31.2, 32.3, 33.2, 39.3, 40.3, 41.4, 44.7, 45.3, 47.0, 48.5, 63.9, 65.2, 72.4, 118.3, 120.6, 125.9, 128.0 (2×C), 128.8 (2×C), 137.9, 144.1; IR ν_{max} 3435, 2917, 2859, 1445, 1087 cm^{-1}; Anal. Calcd for $C_{27}H_{36}O_3$: C 79.37, H 8.88. Found: C 79.54, H 8.96.

4.1.8. (3β,5α,14β)-3-(Acetyloxy)-2-(phenylmethylene)estran-17-one cyclic-(1,2-ethanediyl acetal) (11). A mixture of compound **10** (1.50 g, 3.67 mmol), acetic anhydride (4.5 mL, 480 mmol), pyridine (4.5 mL), and 4-dimethylaminopyridine (10 mg, 0.082 mmol) was stirred at room temperature for 5 min. The reaction mixture was poured into ice-water (50 mL) and was extracted with EtOAc (2×30 mL). The combined organic extract was washed with water (2×20 mL), 10% $NaHCO_3$ (10 mL), and brine (20 mL) and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel; hexanes/EtOAc, 4:1) to give compound **11** (1.48 g, 90%) as white crystals. Mp 141–143 °C (hexanes/EtOAc); $[\alpha]_D^{20}$ +105.0 (*c* 0.20, $CHCl_3$); ^1H NMR δ 7.33 (m, 5H), 6.36 (s, 1H), 5.32 (m, 1H), 3.88 (m, 4H), 3.24 (dd, *J*=13.5, 3.3 Hz, 1H), 2.16 (s, 3H), 0.91 (s, 3H); ^{13}C NMR δ 16.4, 19.9, 21.2, 25.3, 29.1, 30.3, 31.5, 32.3, 33.1, 39.5, 40.3, 41.0, 41.2, 45.3, 47.0, 48.3, 64.0, 65.3, 73.8, 118.9, 120.6, 126.2, 128.1 (2×C), 128.8 (2×C), 137.5, 139.3, 170.1; IR ν_{max} 2931, 2860, 1738, 1599, 1241, 1046 cm^{-1}. Anal. Calcd for $C_{29}H_{38}O_4$: C 77.30, H 8.50. Found: 77.50, H 8.61.

4.1.9. (3β,5α,14β)-3-(Acetyloxy)estrane-2,17-dione cyclic-17-(1,2-ethanediyl acetal) (12). A solution of compound **11** (1.48 g, 3.29 mmol) in MeOH (60 mL) and EtOAc (30 mL) was treated with ozone at −78 °C until a blue color persisted (ca. 30 min). Oxygen was passed through the solution for 20 min until the blue color disappeared, Me_2S (10 mL) was added to the solution, and the reaction mixture was stirred overnight at −78 °C to room temperature. Solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel; hexanes/EtOAc, 3:1) to give compound **12** (0.98 g, 80%) as white crystals. Mp 188–189 °C (hexanes/EtOAc); $[\alpha]_D^{20}$ +125.0 (*c* 0.45, $CHCl_3$); ^1H NMR δ 5.20 (m, 1H), 3.88 (m, 4H), 2.70 (d, *J*=13.2 Hz, 1H), 2.13 (s, 3H), 0.91 (s, 3H); ^{13}C NMR δ 16.1, 19.6, 20.3, 25.0, 28.6, 29.8, 32.0, 32.1, 38.5, 38.7, 39.9, 40.6, 43.3, 45.0, 46.5, 48.0, 63.7, 65.0, 75.5, 120.1, 169.5, 203.8; IR ν_{max} 2933, 2863, 1748, 1728, 1238, 1092 cm^{-1}. Anal. Calcd for $C_{22}H_{32}O_5$: C 70.18, H 8.57. Found: C 69.93, H 8.80.

4.1.10. (5α,14β)-Estrane-2,17-dione cyclic-17-(1,2-ethanediyl acetal) (13), (2β,5α,14β)-2-hydroxyestran-17-one cyclic-(1,2-ethanediyl acetal) (14a) and (2α,5α,14β)-2-hydroxyestran-17-one cyclic-(1,2-ethanediyl acetal) (14b). Iodine (2.06 g, 8.12 mmol) in dried THF (30 mL) was added to samarium filings (1.50 g, 10 mmol) by syringe under Ar. The mixture was stirred at room temperature for 30 min to give a black-blue solution. Then compound **12** (0.92 g, 2.45 mmol) in dried THF (15 mL) and MeOH (5 mL) was added to the SmI_2/THF solution and the reaction mixture was stirred for 15 min. The reaction mixture was poured into 10% Na_2CO_3 (70 mL) and extracted with EtOAc (3×30 mL), the combined organic extract was washed with water (20 mL) and brine (20 mL), and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel; CH_2Cl_2/EtOAc, 10:1) to give compounds **13** (0.32 g, 41%), **14a** (0.16 g, 20%), and **14b** (0.20 g, 26%).

Compound **13** was obtained as white crystals. Mp 143–145 °C (hexanes/EtOAc); $[\alpha]_D^{20}$ +91.4 (*c* 0.45, $CHCl_3$); ^1H NMR δ 3.89 (m, 4H), 2.59 (dd, *J*=15.6, 2.7 Hz, 1H), 2.35 (m, 2H), 0.91 (s, 3H); ^{13}C NMR δ 16.2, 19.8, 24.9, 28.8, 30.0, 32.2, 32.6, 33.3, 38.8, 41.0, 41.1, 41.2, 45.0, 45.1, 46.7, 47.7, 63.9, 65.1, 120.4, 211.7; IR ν_{max} 2948, 2858, 1714, 1455, 1088 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O_3$: C 75.43, H 9.50. Found: C 75.29, H 9.70.

Compound **14a** was obtained as white crystals. Mp 136–138 °C (hexanes/EtOAc); $[\alpha]_D^{20}$ +105.5 (*c* 0.12, $CHCl_3$); ^1H NMR δ 4.13 (m, 1H), 3.89 (m, 4H), 0.91 (s, 3H); ^{13}C NMR δ 16.4, 19.9, 25.1, 27.6, 29.1, 30.5, 32.3, 32.5, 33.8, 36.3, 39.7, 40.1, 40.8, 42.6, 45.2, 47.2, 64.0, 65.2, 66.6, 120.8; IR ν_{max} 3436, 2918, 2860, 1305, 1095 cm^{-1}. Anal. Calcd for $C_{20}H_{32}O_3$: C 74.96, H 10.06. Found: C 74.94, H 9.94.

Compound **14b** was obtained as white crystals. Mp 141–143 °C (hexanes/EtOAc); $[\alpha]_D^{20}$ +81.2 (*c* 0.07, $CHCl_3$); ^1H NMR δ 3.89 (m, 4H), 3.55 (m, 1H), 0.91 (s, 3H); ^{13}C NMR δ 16.4, 20.0, 25.3, 29.2, 30.5, 32.0, 32.4, 33.3, 35.4, 39.2, 39.5, 40.0, 41.9, 45.3, 45.8, 47.1, 64.0, 65.3, 71.2, 120.8; IR ν_{max} 3368, 2920, 2857, 1305, 1097, 1031 cm^{-1}. Anal. Calcd for $C_{20}H_{32}O_3$: C 74.96, H 10.06. Found: C 74.92, H 10.18.

4.1.11. (2β,5α,14β)-2-Hydroxyestran-17-one cyclic-(1,2-ethanediyl acetal) (14a). To a solution of compound **13** (406 mg, 1.28 mmol) in dried THF (35 mL) was added 1 M K-Selectride (6.5 mL, 6.5 mmol) in THF at −78 °C under N_2 and the mixture was stirred for 1 h at this temperature. Then the reaction was quenched by adding 10% NaOH (8 mL) and 30% hydrogen peroxide (8 mL), and the reaction was continued for another 30 min. The mixture was extracted with EtOAc (3×30 mL). The combined organic phase was washed with water (10 mL) and brine (2×10 mL) and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel; CH_2Cl_2/EtOAc, 10:1) to give compound **14a** (346 mg, 85%) whose properties were identical to those for this product when isolated directly from the SmI_2 reduction.

4.1.12. (2β,5α,14β)-2-(Acetyloxy)estran-17-one cyclic-(1,2-ethanediyl acetal) (15). A mixture of compound **14** (476 mg, 1.49 mmol), acetic anhydride (2 mL), dry pyridine (2 mL), and 4-dimethylaminopyridine (10 mg) was stirred at room temperature for 5 min. The reaction mixture was poured into ice-water (15 mL) and extracted with EtOAc (2×15 mL). The organic phase was washed successively with saturated $NaHCO_3$ (5 mL), water (5 mL), 10% aqueous HCl (5 mL), water (5 mL), and brine (5 mL) and dried over

Na_2SO_4. The solvent was removed under reduced pressure to give oily compound **15** (496 mg, 92%) that was not purified and directly converted to compound **16**.

4.1.13. (2β,5α,14β)-2-(Acetyloxy)estran-17-one (16). The mixture of compound **15** (496 mg, 1.37 mmol), *p*-TsOH (50 mg, 0.26 mmol), and water (36 mg, 2 mmol) in acetone (15 mL) was stirred at room temperature overnight. After the solvent was removed under reduced pressure, EtOAc (35 mL) was added to the residue and the organic phase was washed with saturated $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL) and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by re-crystallization (hexanes/EtOAc) to give compound **16** (430 mg, 99%) as white crystals. Mp 144–146 °C (hexanes/EtOAc); $[\alpha]_D^{20}$ +92.3 (*c* 0.12, $CHCl_3$); ^1H NMR δ 5.10 (s, 1H), 2.44 (dd, J=18.6, 7.2 Hz, 1H), 2.05 (s, 3H), 1.08 (s, 3H); ^{13}C NMR δ 18.2, 19.4, 21.1, 24.3, 27.7, 28.0, 29.4, 30.0, 33.1, 33.4, 35.6, 39.2, 40.2, 41.3, 41.9, 47.4, 48.1, 69.6, 170.1, 222.3; IR ν_{max} 2910, 2850, 1727, 1250, 1020 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O_3$: C 75.43, H 9.50. Found: C 75.27, H 9.39.

4.1.14. (2β,5α,14β)-2-(Acetyloxy)estran-17-one oxime (17). The mixture of compound **16** (460 mg, 1.47 mmol), hydroxylamine hydrochloride (1.00 g, 14.4 mmol), and NaOAc (1.15 g, 14.0 mmol) in MeOH (35 mL) was refluxed for 1.5 h. The solvent was removed partially under reduced pressure. Water (20 mL) was added to the residue. Then the mixture was extracted with EtOAc (2×20 mL), the combined organic extract was washed with water (20 mL) and brine (20 mL), and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by re-crystallization (hexanes/EtOAc) to give compound **17** (476 mg, 97%) as white crystals. Mp 186–188 °C (hexanes/EtOAc); $[\alpha]_D^{20}$ +76.4 (*c* 0.89, $CHCl_3$); ^1H NMR δ 9.44 (s, 1H), 5.10 (s, 1H), 2.06 (s, 3H), 1.18 (s, 3H); ^{13}C NMR δ 20.7, 21.5, 21.8, 25.2, 25.3, 28.2, 29.6, 31.0, 32.0, 33.5, 33.8, 39.1, 40.3, 41.7, 42.2, 43.9, 50.3, 70.1, 173.0, 176.4; IR ν_{max} 3305, 2918, 2857, 1737, 1369, 1242, 937 cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_3$: C 72.04, H 9.37, N 4.20. Found: C 72.18, H 9.12, N 4.10.

4.1.15. (1*R*,4a*R*,4b*S*,6*S*,8a*S*,10a*S*)-6-(Acetyloxy)tetradecahydro-2-methylene-1-phenanthrenepropanenitrile (18). To a solution of compound **17** (476 mg, 1.43 mmol) and trimethyl orthoformate (2.8 mL, 25.6 mmol) in dried THF (35 mL) was added dropwise trifluoroacetic acid (0.26 mL, 3.5 mmol) at 60 °C for 10 min, and the reaction was continued for another 30 min. Then saturated Na_2CO_3 (4.5 mL) was added, the solvent was partially removed under reduced pressure and EtOAc (50 mL) was added. The organic phase was washed with saturated $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL) and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel; hexanes/EtOAc, 4:1) to give compound **18** (356 mg, 79%) as white crystals. Mp 103–105 °C (EtOAc); $[\alpha]_D^{20}$ +21.5 (*c* 0.13, $CHCl_3$); ^1H NMR δ 5.10 (s, 1H), 4.74 (t, J=2.1 Hz, 1H), 4.72 (d, J=9.0 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR δ 15.3, 21.5, 22.0, 28.2, 29.7, 29.9, 30.2, 31.7, 33.6, 33.7, 40.2, 42.1, 42.4, 46.7, 47.8, 70.0, 109.7, 112.0, 149.2, 170.6; IR ν_{max} 2920, 2856, 2244, 1733, 1647, 1246 cm^{-1}. Anal. Calcd for $C_{20}H_{29}NO_2$: C 76.15, H 9.27, N 4.44. Found: C 76.13, H 9.32, N 4.19.

4.1.16. (1*R*,4a*R*,4b*S*,6*S*,8a*S*,10a*R*)-6-(Acetyloxy)tetradecahydro-2-oxo-1-phenanthrenepropanenitrile (19). A solution of compound **18** (356 mg, 1.13 mmol) in MeOH (60 mL) and EtOAc (35 mL) was treated with ozone at −78 °C until a blue color persisted (ca. 30 min). Oxygen was passed through the solution for 20 min until the blue color disappeared, and Me_2S (4.5 mL) was added at −78 °C and the resultant mixture was stirred overnight while warming to room temperature. Solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel; hexanes/EtOAc/CH_2Cl_2, 4:1:1) to give compound **19** (206 mg, 58%) as white crystals. Mp 157–159 °C (hexanes/EtOAc); $[\alpha]_D^{20}$ +24.4 (*c* 0.13, $CHCl_3$); ^1H NMR δ 5.11 (s, 1H), 2.46 (m, 1H), 2.04 (s, 3H); ^{13}C NMR δ 15.1, 21.2, 22.6, 27.7, 29.2, 29.4, 30.4, 33.0, 33.6, 37.2, 39.1, 41.5, 41.7, 45.8, 54.5, 69.5, 118.8, 170.3, 213.1; IR ν_{max} 2922, 2850, 2244, 1727, 1699, 1379, 1241 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_3$: C 71.89, H 8.57, N 4.41. Found: C 71.64, H 8.73, N 4.49.

4.1.17. (2β,5α,14β)-2-(Acetyloxy)-13-hydroxy-18-norestran-17-one (20) and (2β,5α,14β)-2-(acetyloxy)gonan-17-one (21). Iodine (240 mg, 0.95 mmol) in dried THF (30 mL) was added to samarium filings (225 mg, 1.50 mmol) by syringe under Ar. The mixture was stirred at room temperature for 30 min to give a black-blue solution. Then a solution of compound **19** (93 mg, 0.30 mmol) and 2-methyl-2-propanol (38 mg, 0.51 mmol) in THF (10 mL) was added to the freshly made SmI_2/THF solution under Ar at 0 °C. The reaction mixture was stirred at 0–10 °C while irradiated with a 500 W tungsten lamp for 8 h and then the reaction mixture was poured into 5% aqueous HCl (10 mL), and extracted with EtOAc (2×15 mL). The combined organic extract was washed with water (10 mL), 10% $NaHCO_3$ (10 mL), and brine (10 mL) and dried over Na_2SO_4. Solvent removal gave crude compound **20** (46 mg), which was used without purification or characterization.

Under Ar, a solution of crude compound **20** in dried THF (5 mL) and MeOH (0.5 mL) was added to a freshly made SmI_2/THF (0.1 M, 15 mL) solution by syringe. The reaction mixture was stirred at room temperature for 10 min, quenched by adding 5% aqueous HCL (10 mL), and extracted with EtOAc (2×10 mL). The combined organic extract was washed with water (10 mL), 10% $NaHCO_3$ (10 mL), and brine (10 mL) and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel; CH_2Cl_2/EtOAc, 20:1) to give compound **21** (15.6 mg, 17% from compound **19**) as white crystals. Mp 118–120 °C (EtOAc); ^1H NMR δ 5.11 (s, 1H), 2.38 (dd, J=18.9, 8.1 Hz, 1H), 2.05 (s, 3H). From the ^{13}C NMR data this product was determined to be a 9:1 mixture of epimers at C_{14}. The ^{13}C NMR resonances for the major isomer were δ 20.7, 21.5, 22.9, 28.0, 28.3, 29.7, 30.2, 33.5, 33.7, 37.1, 40.6, 41.5, 41.7, 41.8, 42.3, 49.2, 70.0, 170.6, 221.4; IR ν_{max} 2918, 2855, 1738, 1245 cm^{-1}.

4.1.18. (2β,5α,14β)-2-Hydroxygonan-17-one (1). The mixture of compound **21** (15.6 mg, 0.05 mmol), NaOH (2 mg, 0.05 mmol), and water (18 mg, 1 mmol) in MeOH

(12 mL) was refluxed for 2 h. The reaction mixture was chilled, and most of the MeOH was removed under reduced pressure to give a residue to which was added EtOAc (20 mL). The organic phase was washed with 10% aqueous HCl (5 mL), water (5 mL), and brine (5 mL) and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel; hexanes/CH_2Cl_2/EtOAc, 3:1:1) to give compound **1** (11 mg, 82%) as white crystalline needles. Mp 123–124 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ +140 (*c* 0.30, $CHCl_3$); ^1H NMR δ 4.16 (m, 1H), 2.38 (dd, J=18.9, 8.1 Hz, 1H); ^{13}C NMR δ 20.7, 23.0, 27.6, 28.0, 30.3, 32.5, 33.7, 36.3, 37.2, 40.6, 40.8, 41.7, 41.8, 42.6, 49.2, 66.7, 221.5; IR ν_{max} 3565, 2923, 2851, 1720 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_2$: C 77.82, H 9.99. Found: C 77.68, H 10.02.

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