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Synthesis of 6,19-Sulfamidate Bridged Pregnanes

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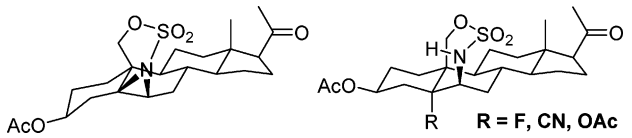
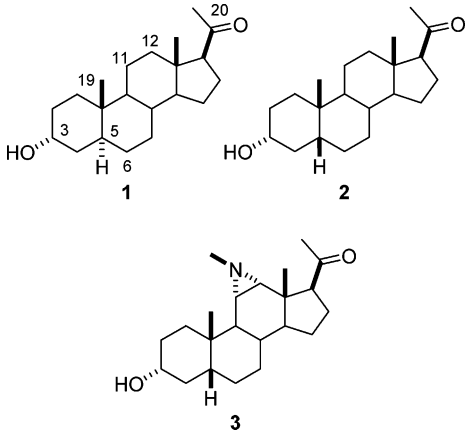


Conformationally restrained substituted pregnane-20-one derivatives were obtained by an intramolecular nitrene addition onto a C-5/C-6 double bond involving a tethered C-19 sulfamoyl moiety. The resulting aziridine underwent regioselective nucleophilic ring opening at C-5 at room temperature with cyanide, fluoride, and acetate. In the isolated case of acetate, a reversal of regioselectivity was observed at higher temperatures, a result attributed to a rearrangement process involving aziridine ring opening at the C-5 position and subsequent migration of the acetyl moiety to C-6.

Over the past 2 decades there has been a resurgence of interest in steroids as potential therapeutics for central nervous system disorders. This interest followed the discovery that neurosteroids and neuroactive steroids are potent modulators of $GABA_A$ receptor function.[1] Endogenously occurring steroids such as 3α-hydroxy-5α-pregnan-20-one (allopregnanolone, **1**) and its 5β-isomer (pregnanolone, **2**) may be considered as prototypical. Such neurosteroids and their synthetic analogues have been found to exhibit anesthetic,[2] hypnotic,[3] anxiolytic,[4] or anticonvulsant[5] activities in vivo. An important advance in this area was the finding that relatively large, polar substituents, which confer water-solubility to these lipophilic steroids, could be incorporated at a number of different positions on the steroid nucleus without loss of anesthetic activity.[6] This has led to an increasing interest in developing new strategies to introduce these functional groups into specific positions. In this context, transition-metal-catalyzed reactions have proven to be versatile tools.[7]



Although the effect of conformational changes on the biological activity of steroidal hormones has been the subject of several studies,[8] little is known about their effect on the activity of neurosteroids.[9] In this context, we have recently synthesized 11α,12α-aziridinosteroid **3**, which combines the presence of a polar group (for water solubility) with a certain degree of conformational rigidity.[10] Compounds of type **3** are of interest per se as inhibitors of various enzymes or as ligands of neuroreceptors, but they can also be considered as precursors of amino steroids after nucleophilic ring opening. In particular, the presence of an aziridine ring over the β-face in the 5,6 position would be interesting since the regioselective opening of this moiety by nucleophiles would give access to 6β-aminopregnenolone with different patterns of substitution at the 5α position. Whereas the incorporation of a methyl group at C-5 eliminates or diminishes neuroinhibitory activity and a 6β-methyl group enhances activity irrespective of the stereochemistry at C-5,[11a,b] to our knowledge there are no examples of the effect of other substituents at C-5 and/or C-6 on this activity. When the entire 6-CH_2 group is replaced by oxygen[12] or nitrogen,[13] a drastic reduction in activity is observed.

We now report the synthesis of a rigid analogue of allopregnanolone having a sulfamoyl aziridine moiety on the β-face at the C-5−C-6 position (compound **9**), using the intramolecular aziridination reaction starting from primary and secondary homoallylic alcohols recently

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(1) *Neurosteroid Effects in the Central Nervous System: The Role of the GABA-A Receptor*; Smith, S. S., Ed.; CRC Press: Boca Raton, 2003.

(2) Mok, W. M.; Herschkowitz, S.; Krieger, N. R. *J. Neurochem.* **1991**, *57*, 1296−1301.

(3) Mendelson, W. B.; Martin, J. V.; Perlis, M.; Wagner, R.; Majewska, M. D.; Paul, S. M. *Psychopharmacology* **1987**, *93*, 226−229.

(4) (a) Bitran, D.; Hilvers, R. J.; Kellogg, C. K. *Brain Res.* **1991**, *561*, 157−161. (b) Brot, M. D.; Akwa, Y.; Purdy, R. H.; Koob, G. F.; Britton, K. T. *Eur. J. Pharmacol.* **1997**, *325*, 1−7. (c) Rodgers, R. J.; Johnson, N. J. T. *Pharmacol. Biochem. Behav.* **1998**, *59*, 221−232.

(5) (a) Belelli, D.; Bolger, M. B.; Gee, K. W. *Eur. J. Pharmacol.* **1989**, *166*, 325−329. (b) Kokate, T. G.; Svensson, B. J.; Rogawski, M. A. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 1223−1229. (c) Veleiro, A. S.; Rosenstein, R. E.; Jaliffa, C. O.; Grilli, M. L.; Speroni, F.; Burton, G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 343−346.

(6) Anderson, A.; Boyd, A. C.; Campbell, A. C.; Gemmel, D. K.; Hamilton, N. M.; Hill, D. R.; Hill-Venning, C.; Lambert, J. J.; Maidment, M. S.; May, V.; Marshall, R. J.; Peters, J. A.; Rees, D. C.; Stevenson D. *J. Med. Chem.* **1997**, *40*, 1668−1681.

(7) Skoda-Foldes, R.; Kollar, L. *Chem. Rev.* **2003**, *103*, 4095−4129.

(8) Burton, G.; Galigniana, M. D.; de Lavallaz, S.; Brachet-Cota, A. L.; Sproviero, E. M.; Ghini, A. A.; Lantos, C. P.; Damasco, M. C. *Mol. Pharmacol*, **1995**, *47*, 535−543.

(9) See for example: *CNS Neurotransmitters and Neuromodulators. Neuroactive Steroids*; Stone, T. W., Ed.; CRC Press: Boca Raton, 1996; Chapters 2 and 4.

(10) Di Chenna, P. H.; Dauban, P.; Ghini, A. A.; Baggio, R.; Garland, M. T.; Burton, G.; Dodd, R. H. *Tetrahedron* **2003**, *59*, 1009−1014.

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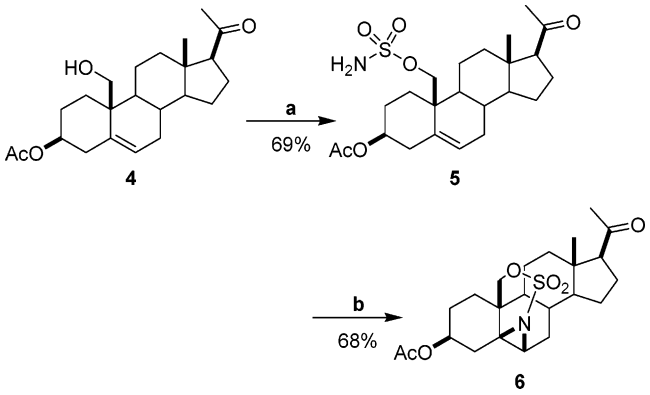
SCHEME 1. Synthesis of Aziridinosulfamidate 6[a]



[a] Reagents and conditions: (a) $ClSO_2NCO$, HCO_2H, DMA, 0 °C to 20 °C; (b) PhIO, $Cu(CH_3CN)_4PF_6$, acetonitrile, 20 °C.

developed by us.[14] In this case, an important point would be the expected total facial stereoselectivity in the delivery of the nitrene tethered to the C-19 moiety on the β-face, therefore leading to the 5β,6β-aziridinosteroid. Several steroid derivatives with a cyclic sulfamidate moiety in their structures (compounds **10**, **11**, **12**, and **13**) were also obtained by ring-opening of the aziridine **6** with different nucleophiles (fluoride, cyanide, and acetate).

The key intermediate in this synthetic approach was the aziridinosulfamidate **6** (Scheme 1). The starting 19-hydroxypregnene **4** was synthesized from commercially available pregnenolone acetate in three steps (50% yield) following essentially our previously described procedure.[15,16] Compound **4** was transformed into the polar unsaturated steroidal sulfamate **5** in 69% yield (77% based on consumed starting material) by reaction with sulfamoyl chloride generated in situ from chlorosulfonyl isocyanate.[17] The one-pot intramolecular aziridination procedure (1.5 equiv of PhI=O, 10% $Cu(CH_3CN)_4PF_6$)[18] was then applied to compound **5**, giving the aziridinosulfamidate **6** as the sole isolable product in 68% yield.[19]

Because active neurosteroids require a 3α-hydroxyl function,[20] compound **6** was transformed into the target analogue **9** in a straightforward way using the Mitsunobu reaction (Scheme 2). Thus, **6** was deacetylated with potassium carbonate to give the 3β-hydroxy derivative **7** in almost quantitative yield. Subsequent treatment with DEAD/Ph_3P/HCO_2H gave the 3α-formyloxy pregnane **8**, which was deprotected with potassium hydroxide in acetonitrile to furnish compound **9** in 93% yield. The coupling pattern for the resonances of H-4β (δ 1.83, J = 14.1 and 5.2 Hz) and H-4α (δ 1.88, J = 14.1 and 7.6 Hz) in the ^{1}H NMR spectrum of **9** showed no axial-axial partition, thereby indicating the sought axial orientation of the hydroxyl group at C-3.

With the aim of synthesizing neurosteroid analogues having a cyclic sulfamidate moiety and different substituents at C-5, aziridine ring opening of compound **6** was investigated with several nucleophiles (Scheme 2). The reagents, i.e., cyanide, fluoride, and acetate, were chosen as a function of their potential to provide active steroids and also in order to broaden the scope of the selective ring-opening reaction of sulfamoylaziridines previously described by us.[14] Thus, treatment of compound **6** with either tetra-*n*-butylammonium fluoride (TBAF), potassium cyanide, or cesium acetate at room temperature afforded the corresponding seven-membered cyclic sulfamidates (**10**, **11**, and **12**) resulting from regioselective aziridine ring opening at the most substituted position (Table 1, entries 1, 3, and 4). In all cases, good yields (ranging from 68% to 81%) were obtained and the regioselectivity matched that observed in our preceding experiments with different types of nucleophiles.[14] All structures were unambiguously determined with the aid of 2D NMR experiments.

trans-Diaxial opening of the aziridine ring may account for the regioselectivity of this reaction.[21] However, when the reaction with cesium acetate was run at 100 °C, an unexpected reversal of regioselectivity was observed, a 2:1 mixture of ring-opened products being obtained in favor of the six-membered cyclic sulfamidate **13** (Table 1, entry 5). The structure of compound **13** was inferred from 2D NMR (COSY-45 and HETCOR) and mass spectra. Particularly diagnostic were the double doublet at δ 5.97, the singlet at δ 5.74, and the broad signal at δ 5.28 corresponding to the 6α-H, NH, and 3α-H (equatorial in this compound) clearly different from the resonances at δ 4.44, 4.90, and 4.78 for these hydrogens in the isomeric cyclic sulfamidate **12**. Significant shifts were also observed in the ^{13}C NMR spectrum where C-5 and C-6 appeared at 63.5 (C) and 69.5 ppm (CH) (86.0 ppm (C) and 52.0 ppm (CH), respectively, in **12**).

In contrast to acetate, reaction of aziridine **6** with cesium fluoride at 100 °C afforded the same C-5 ring-opened product as at 20 °C, that is, sulfamidate **10** (46% yield, Table 1, entry 2). This suggests that the reversal of regioselectivity observed in the case of the acetate is the result of a rearrangement process with migration of the acetate group from C-5 to C-6 to give the more stable six-membered cyclic sulfamidate **13**[22] (Figure 1) and not due to attack of the nucleophile at C-6. This was confirmed by heating compound **12** with a catalytic amount (0.2 equiv) of cesium acetate in DMF at 100 °C for 20 min. Under these conditions complete isomerization occurred, and the rearranged 5-amino-6-acetyl derivative **13** was isolated in 64% yield. It is expected that ring opening of **6** by axial attack at C-5 should afford the seven-membered cyclic sulfamidate, **12** being the kinetically favored product[21b] and resulting in the 10:1 product

(11) (a) Han, M.; Zorumski, C. F.; Covey, D. F. *J. Med. Chem.* **1996**, *39*, 4218−4232. (b) Zeng, C.-M.; Benz, A.; Howell, M.; Manion, B.; Evers, A. S.; Zorumski, C. F.; Mennerick, S.; Covey, D. F. *Abstracts of Papers*, 222nd National Meeting of the American Chemical Society, Chicago, IL, August 26−30, 2001; American Chemical Society: Washington, DC, 2001.

(12) Nicoletti, D.; Ghini, A. A.; Furtmüller, R.; Sieghart, W.; Dodd, R. H.; Burton, G. *Steroids* **2000**, *65*, 349−356.

(13) Kasal, A.; Matyas, L.; Budesinsky, M. *Tetrahedron* **2005**, *61*, 2269−2278.

(14) Durán, F. J.; Leman, L.; Ghini, A. A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett*. **2002**, *4*, 2481−2483.

(15) Joselevich, M.; Ghini, A. A.; Burton, G. *Org. Biomol. Chem.* **2003**, *1*, 939−943.

(16) Eduardo, S. L.; Ghini, A. A.; Burton, G. *ARKIVOC* **2003**, Part X, 468−476.

(17) (a) Appel, R.; Berger, G. *Chem. Ber.* **1958**, *91*, 1339−1341. (b) Okada, M.; Iwashita, S.; Koizumi, N. *Tetrahedron Lett.* **2000**, *41*, 7047−7051.

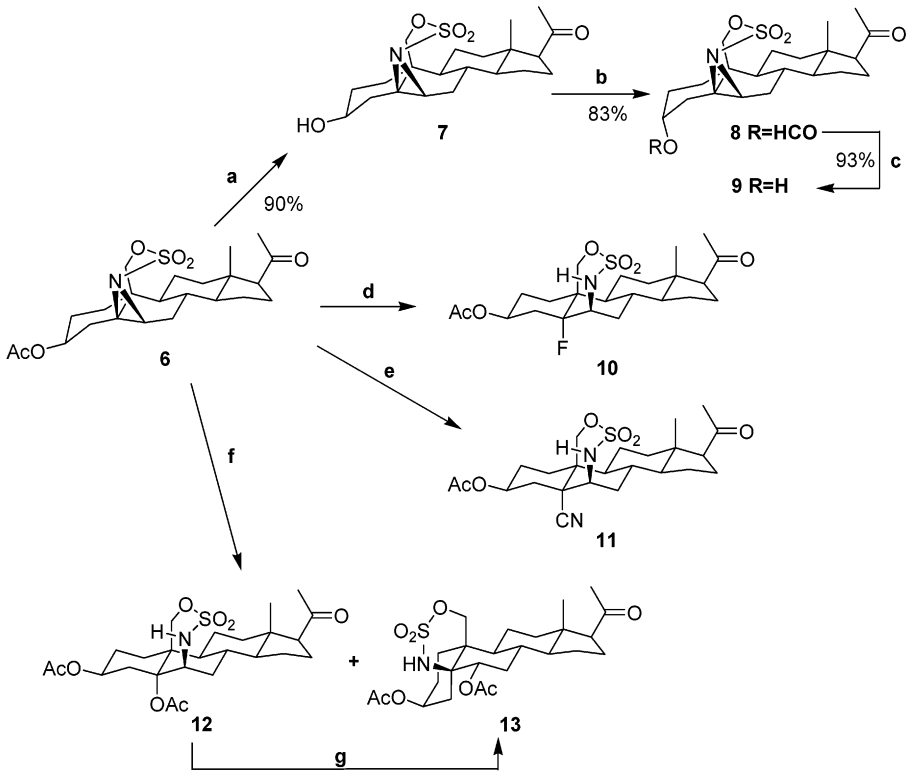
(18) Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707−7708.

(19) Compound **5** decomposed on silica gel; it was purified by flash chromatography on Florisil.

(20) Gee, K. W.; Bolger, M. B.; Brinton, R. E.; Coirini, H.; McEwen, B. S. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 803−812.

(21) The regiochemistry of the opening of conformationally rigid unsymmetrical epoxides and other three-membered heterocycles follows the Fürst-Plattner rule with exclusive formation of the diaxial product under kinetically controlled conditions. See for example: (a) Valls, J.; Toromanoff, E. *Bull. Soc. Chim. Fr.* **1961**, 758−764. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 165−166.

SCHEME 2. Synthesis of Neurosteroid Analogue 9 and Nucleophilic Aziridine Opening of 6[a]



[a] Reagents and conditions: (a) K_2CO_3, MeOH, 0 °C; (b) Ph_3P, HCO_2H, DEAD; (c) KOH, acetonitrile, 0 °C; (d−f) see Table 1; (g) CsOAc (0.2 equiv), DMF, 100 °C.

TABLE 1. Nucleophilic Opening of Aziridinosulfamidate 6

entry	reagent	conditions	products (% yield)[a]
1	TBAF/THF	20 °C, 6 h	**10** (81)
2	CsF/DMF	100 °C, 6 h	**10** (46)
3	KCN/DMF	20 °C, 2 h	**11** (68)
4	CsOAc/DMF	20 °C, 6 h	**12** (79) + **13** (8)
5	CsOAc/DMF	100 °C, 15 min	**12** (19) + **13** (42)

[a] Yields correspond to isolated products.

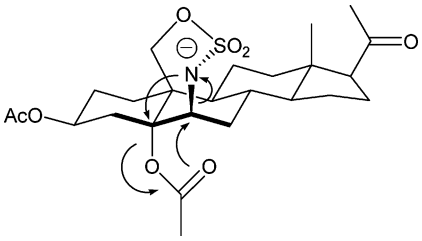


FIGURE 1. Proposed mechanism for the rearrangement of **12** into **13** under base-catalyzed conditions.

ratio observed when the reaction was carried out at room temperature (Table 1, entry 4).

The scope of our one-pot intramolecular copper-catalyzed aziridination for the preparation of cyclic sulfamidates has now been extended to unsaturated sulfamates derived from a homoallylic alcohol, allowing the isolation of a new conformationally locked aziridinosteroid. The aziridine in turn underwent regioselective nucleophilic ring opening to give access to rigid analogues of allopregnanolone possessing a cyclic sulfamidate moiety and various substituents at the C-5 position or at the C-6 position depending on the reaction temperature. To the best of our knowledge, this is the first synthesis of a steroid having a cyclic sulfamidate moiety in its structure. Work is in progress to apply this methodology to other unsaturated steroids.

(22) AM1 calculations show that **13** is more stable than **12** by ca. 7.8 kcal/mol (see Supporting Information).

Experimental Section

3β-Acetyloxy-20-oxopregn-5-en-19-yl Sulfamate (5). Formic acid (0.088 mL, 2.300 mmol) was added dropwise to neat chlorosulfonyl isocyanate (0.200 mL, 2.300 mmol) at 0 °C with rapid stirring. Gas evolution was observed during the addition process. The resulting viscous suspension was stirred for 18 h at room temperature. The reaction mixture was cooled to 0 °C, DMA (0.7 mL) was added, and the solution was stirred for 5 min. A solution of 3β-acetyloxy-19-hydroxypregn-5-en-20-one (**4**, 430 mg, 1.148 mmol) in DMA (0.7 mL) was added dropwise, and the reaction was allowed to warm to 20 °C over a 3 h period. The reaction was quenched by the successive addition of EtOAc (10 mL) and brine (5 mL). The mixture was poured into EtOAc (20 mL) and water (10 mL), the organic phase was collected, and the aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash chromatography on Florisil (hexanes−EtOAc gradient) gave 43.0 mg (10%) of the starting steroid **4** and compound **5** (359.2 mg, 69% yield). Physical data of compound **5**: mp 169−171 °C (hexanes−EtOAc). IR ν_{max} KBr cm^{-1}: 3287, 2930, 2854, 1732, 1697, 1448, 1366, 1267, 825, 567. ^1H NMR ($CDCl_3$−CD_3OD 9:1, 500.13 MHz) δ: 0.68 (3H, s), 1.05 (1H, dt, J = 4.5, 11.8 Hz), 1.11 (1H, m), 1.26 (1H, m), 1.43 (1H, dt, J = 4.2, 12.6 Hz), 1.91 (1H, m), 2.03 (3H, s), 2.13 (3H, s), 2.33 (1H, br t, J = 13.2 Hz), 2.45 (1H, ddd, J = 13.3, 4.9, 2.0 Hz), 2.53 (1H, t, J = 8.9 Hz), 4.15 (1H, d, J = 10.2 Hz), 4.33 (1H, d, J = 10.2 Hz), 4.64 (1H, m), 5.67 (1H, m). ^{13}C NMR ($CDCl_3$−CD_3OD 9:1, 125 MHz) δ: 13.2, 21.3, 21.6, 22.8, 24.3, 27.6, 31.2, 31.4, 32.5, 32.7, 37.9, 38.9, 39.9, 44.1, 49.8, 57.3, 63.6, 70.0, 73.2, 127.5, 133.6, 170.9, 210.3. MS (EI) *m/z* (%): 453 (M^+, 2.8), 355 (3.3); MS (ES) *m/z* (%): 476 (M + Na^+, 33), 467 (7.5),

411 (3.1), 379 (100). HRMS: calcd for $C_{23}H_{35}NO_6SNa$ 476.2083, found 476.2083.

3β-Acetyloxy-5β,6β-iminopregnan-20-one *N*,19-Sultone (6). To a solution of compound **5** (340.0 mg, 0.750 mmol) in dry acetonitrile (4.0 mL) containing activated 3 Å molecular sieves (0.2 g) were added iodosylbenzene (509.0 mg, 2.32 mmol) and $Cu(CH_3CN)_4PF_6$ (58.0 mg, 0.154 mmol) under nitrogen at 20 °C. The reaction mixture was stirred at 20 °C for 20 h, the molecular sieves were removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes−EtOAc 6:4 to 3:7) to give compound **6** (230.3 mg, 68% yield). Physical data of compound **6**: mp 147−149 °C (hexanes−EtOAc). IR ν_{max} KBr cm^{-1}: 3447, 2944, 2875, 1732, 1700, 1364, 1242, 1181, 1026, 997, 788, 737. ^1H NMR ($CDCl_3$−CD_3OD 9:1, 500.13 MHz) δ: 0.66 (3H, s), 1.03 (2H, m), 1.85 (1H, dd, J = 14.9, 5.4 Hz), 2.01 (1H, dd, J = 14.9, 4.3 Hz), 2.12 (6H, s), 2.17 (1H, m), 2.48 (1H, t, J = 9.1 Hz), 2.53 (1H, dd, J = 16.3, 7.2 Hz), 2.62 (1H, d, J = 6.1 Hz), 4.31 (1H, d, J = 12.3 Hz), 4.68 (1H, dd, J = 12.3, 1.1 Hz), 5.12 (1H, m). ^{13}C NMR ($CDCl_3$−CD_3OD 95:5, 125 MHz) δ: 13.4, 20.9, 21.1, 22.9, 23.7, 24.2, 25.0, 26.0, 30.6, 31.2, 31.9, 35.7, 38.3, 44.1, 45.8, 46.1, 52.9, 58.6, 63.2, 66.8, 72.8, 171.5, 209.7. MS (EI) m/z (%): 451 (M^+, 1.5), 328, 310, 294, 251. MS (ES) m/z (%): 474 (M + Na^+, 100), 475 (7.5). HRMS: calcd for $C_{23}H_{33}NO_6SNa$ 474.1926, found 474.1970.

3β-Acetyloxy-5α-fluoro-*S*,*S*-dioxo-19,6-(epoxythioimino)-pregnan-20-one (10). Method A. Aziridine **6** (25.0 mg, 0.055 mmol) was dissolved in anhydrous THF (0.75 mL), and TBAF (29.0 mg, 0.111 mmol) was added at 20 °C under nitrogen. After 6 h, the THF was removed under reduced pressure, and the oily residue was purified by flash chromatography on silica gel using hexane−EtOAc (6:4) as eluent, to give compound **10** as a white solid (21.1 mg, 81% yield). Physical data of compound **10**: mp 199−201 °C (hexanes−EtOAc). IR ν_{max} KBr cm^{-1}: 3278, 2938, 2879, 1733, 1699, 1454, 1362, 1178, 1088, 1030, 987, 764, 741. ^1H NMR ($CDCl_3$, 500.13 MHz) δ: 0.70 (3H, s), 1.16 (1H, m), 2.04 (3H, s), 2.09 (1H, dd, J = 13.4, 8.7 Hz), 2.11 (3H, s), 2.39 (1H, ddd, J = 42.6, 13.4, 11.4 Hz), 2.50 (1H, m), 2.51 (1H, t, J = 9.0 Hz), 3.31 (1H, br d, J = 4.6 Hz), 4.27 (1H, dd, J = 13.7, 4.6 Hz), 4.65 (1H, d, J = 13.7 Hz), 4.80 (1H, d, J = 4.6 Hz), 5.07 (1H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.0, 21.2, 23.0, 23.6, 26.8, 28.8, 29.2, 31.3, 32.0, 35.9 (d, J_{C-F} = 22.0 Hz), 39.2, 42.3 (d, J_{C-F} = 19.5 Hz), 44.8, 46.3 (d, J_{C-F} = 3.4 Hz), 56.7 (d, J_{C-F} = 32.2 Hz), 57.4, 63.4, 69.0 (d, J_{C-F} = 3.4 Hz), 71.9 (d, J_{C-F} = 5.9 Hz), 97.0 (d, J_{C-F} = 176.3 Hz), 170.3, 209.1. ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −157.48 (br d, J_{H-F} = 41.7 Hz). MS (ES) m/z (%): 494 (M + Na^+, 100), 582 (17.5), 495 (5.0), 474 (5.6). HRMS: calcd for $C_{23}H_{34}FNO_6SNa$ 494.1989, found 494.1983.

Method B. Aziridine **6** (10.0 mg, 0.022 mmol) was dissolved in anhydrous DMF (0.30 mL), and CsF (10.0 mg, 0.066 mmol) was added at 20 °C under nitrogen. The reaction vessel was placed in a silicon bath at 100 °C for 6 h and then allowed to come to room temperature, poured into brine (5.0 mL), and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with NaCl saturated solution, dried over Na_2SO_4, and evaporated under vacuum. Purification by preparative TLC (cyclohexanes−EtOAc 4:6) gave compound **10** (4.8 mg, 46% yield) identical (TLC and ^1H NMR) to that obtained above.

3β-Acetyloxy-5α-cyano-*S*,*S*-dioxo-19,6-(epoxythioimino)-pregnan-20-one (11). Aziridine **6** (50.0 mg, 0.111 mmol) was dissolved in anhydrous DMF (1.5 mL) and KCN (21.0 mg, 0.323 mmol) was added at 20 °C under nitrogen. After 2 h the reaction mixture was carefully poured into a solution of 20% NaOH (15 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated under vacuum. The white solid obtained was purified by flash chromatography on silica gel using hexanes−EtOAc (90:10), to give compound **11** (40.8 mg, 68% yield). Physical data of compound **11**: mp 147−148 °C (hexanes−EtOAc). IR ν_{max} KBr cm^{-1}: 3271, 2942, 2877, 1736, 1699, 1444, 1366, 1340, 1238, 1178, 1070, 1027, 765, 740; ^1H NMR ($CDCl_3$, 500.13 MHz) δ: 0.71 (3H, s), 1.25 (H, m), 1.97 (1H, dt, J = 14.4, 3.4 Hz), 2.06 (3H, s), 2.11 (3H, s), 2.26 (1H, ddd, J = 15.3, 5.9, 1.6 Hz), 2.32 (1H, dd, J = 13.0, 11.6 Hz), 2.53 (1H, t, J = 9.1 Hz), 2.66 (1H, m), 3.47 (1H, m), 4.16 (1H, d, J = 13.9 Hz), 4.77 (1H, dd, J = 13.9, 1.0 Hz), 5.16 (1H, d, J = 5.1 Hz), 5.19 (1H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.1, 21.1, 21.5, 23.1, 23.5, 26.5, 29.4, 31.3, 31.5, 32.7, 33.8, 39.0, 40.5, 44.9, 48.9, 50.1, 55.6, 57.5, 63.1, 68.9, 69.4, 120.1, 170.1, 209.1. MS (ES) m/z (%): 501 (M + Na^+, 100), 420 (25), 421 (8.8), 502 (3.1), 589 (8.1). HRMS: calcd for $C_{24}H_{34}N_2O_6SNa$ 501.2035, found 501.2067.

Reaction of Aziridine 6 with Cesium Acetate. Method A. Aziridine **6** (20.0 mg, 0.044 mmol) was dissolved in anhydrous DMF (0.45 mL), and cesium acetate (43.0 mg, 0.221 mmol) was added at 20 °C. After 6 h, the reaction mixture was poured into NaCl saturated solution (5.0 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated under vacuum. The resulting white solid was purified by preparative TLC (hexanes−EtOAc 1:1) to give 3β,5α-diacetyloxy-*S*,*S*-dioxo-19,6-(epoxythioimino)pregnan-20-one (**12**) (18.0 mg, 79% yield) and 3β,6α-diacetyloxy-*S*,*S*-dioxo-19,5-(epoxythioimino)pregnan-20-one (**13**) (1.8 mg, 8% yield). Physical data of compound **12**: mp 142−143 °C (hexanes−EtOAc). IR ν_{max} KBr cm^{-1}: 3323, 2954, 2878, 1743, 1701, 1431, 1374, 1359, 1238, 1185, 1028, 942, 779, 738. ^1H NMR ($CDCl_3$, 500.13 MHz) δ: 0.71 (3H; s), 1.07 (1H, m), 2.03 (3H, s), 2.11 (3H, s), 2.13 (3H, s), 2.16 (1H, m), 2.26 (1H, dd, J = 13.5, 11.8 Hz), 2.51 (1H, t, J = 9.2 Hz), 2.60 (1H, m), 2.90 (1H, ddd, J = 13.5, 4.5, 1.6 Hz), 4.15 (1H, d, J = 13.7 Hz), 4.44 (1H, br t, J = 5.3 Hz), 4.78 (1H, m), 4.80 (1H, d, J = 13.7 Hz), 4.90 (1H, d, J = 5.3 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.2, 21.2, 21.4, 22.1, 23.0, 23.5, 26.8, 27.2, 29.2, 30.6, 31.3, 31.9, 39.4, 42.5, 45.1, 46.1, 52.0, 58.3, 63.3, 68.9, 71.2, 86.0, 169.6, 170.3, 209.2. MS (ES) m/z (%): 534 (M + Na^+, 100), 622 (62.5), 474 (18.8), 453 (18.8), 363 (39.4). HRMS: calcd for $C_{25}H_{37}NO_8SNa$ 534.2138, found 534.2131. Physical data of compound **13**: mp 158−160 °C (hexanes−EtOAc). IR ν_{max} KBr cm^{-1}: 3288, 2941, 2879, 1735, 1703, 1435, 1367, 1335, 1240, 1177, 1028, 987, 737. ^1H NMR ($CDCl_3$, 500.13 MHz) δ: 0.62 (3H, s), 1.10 (1H, q, J = 12.3 Hz), 1.52 (1H, dt, J = 3.6, 13.6 Hz), 1.59 (1H, br d, J = 15.0 Hz), 1.71 (1H, br t, J = 14.8 Hz), 1.89 (1H, br d, J = 14.8 Hz), 1.98 (1H, br d, J = 16.2 Hz), 2.08 (3H, s), 2.09 (1H, br d, J = 16.2 Hz), 2.11 (3H, s), 2.12 (1H, d, J = 12.3 Hz), 2.14 (3H, s), 2.41 (1H, td, J = 15.0, 3.9 Hz), 2.47 (1H, t, J = 9.1 Hz), 4.15 (1H, d, J = 12.1 Hz), 4.98 (1H, d, J = 12.1 Hz), 5.28 (1H, br s, $W_{1/2}$ = 8.6 Hz), 5.74 (1H, s), 5.97 (1H, dd, J = 12.1, 5.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.2, 20.1, 21.0, 21.1, 21.4, 23.0, 23.4, 24.1, 29.6, 31.3, 32.8, 33.5, 38.3, 38.6, 41.2, 43.6, 56.5, 63.2, 63.5, 68.5, 69.5, 74.0, 169.0, 169.7, 208.7. MS (ES) m/z (%):1046 (27.5), 1045 (2M + Na^+, 100), 622 (11.9), 534 (M + Na^+, 25.6). HRMS (ES): calcd for $C_{25}H_{37}NO_8SNa$ 534.2138, found 534.2131.

Method B. Aziridine **6** (18.0 mg, 0.040 mmol) was dissolved in anhydrous DMF (0.45 mL), and cesium acetate (38.0 mg, 0.200 mmol) was added at 20 °C under nitrogen. The reaction vessel was placed in a silicon bath at 100 °C for 15 min and then allowed to come to room temperature, poured into brine (5.0 mL), and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated under vacuum. Purification by preparative TLC (hexanes−EtOAc 1:1) gave compound **12** (4.2 mg, 19% yield) and compound **13** (8.3 mg, 42% yield) identical (TLC and ^1H NMR) to that obtained above.

Isomerization of 3β,5α-Diacetyloxy-*S*,*S*-dioxo-19,6-(epoxythioimino)pregnan-20-one (12). Compound **12** (8.0 mg, 0.016 mmol) was dissolved in anhydrous DMF (0.20 mL), and cesium acetate (0.6 mg, 0.003 mmol) was added at 20 °C under nitrogen. The reaction vessel was placed in a silicon oil bath at 100 °C for 20 min and then allowed to cool to room temperature, poured into brine (5.0 mL), and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated under vacuum. Purification by preparative TLC (hexanes−EtOAc 1:1) gave compound **13** (5.2 mg, 64% yield), identical (TLC and ^1H NMR) to that obtained above.

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Supporting Information Available: General experimental methods; procedure for the preparation of **9** (Scheme 2); complete NMR spectral assignments of compounds **5**, **6**, and **9**−**13**; AM1 calculated structures of compounds **12** and **13**; and ^{13}C NMR spectra of compounds **5**, **6**, and **9**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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