Heterocycles. 13. Synthesis of [1,2-*d*]Triazolo Steroids [1, 2]

Philip M. Weintraub

Marion Merrell Dow Research Institute, 2110 E. Galbraith Rd, Cincinnati, Ohio 45215, USA

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Reaction of 1,2-epoxy-5α-3-ketosteroids with sodium azide produces a mixture of expected 2-azido-5α-Δ^1-3-ketosteroids and novel [1,2-*d*]triazolosteroids. A possible pathway for formation of the latter involving 1,3-dipolar cycloaddition of sodium azide is discussed.

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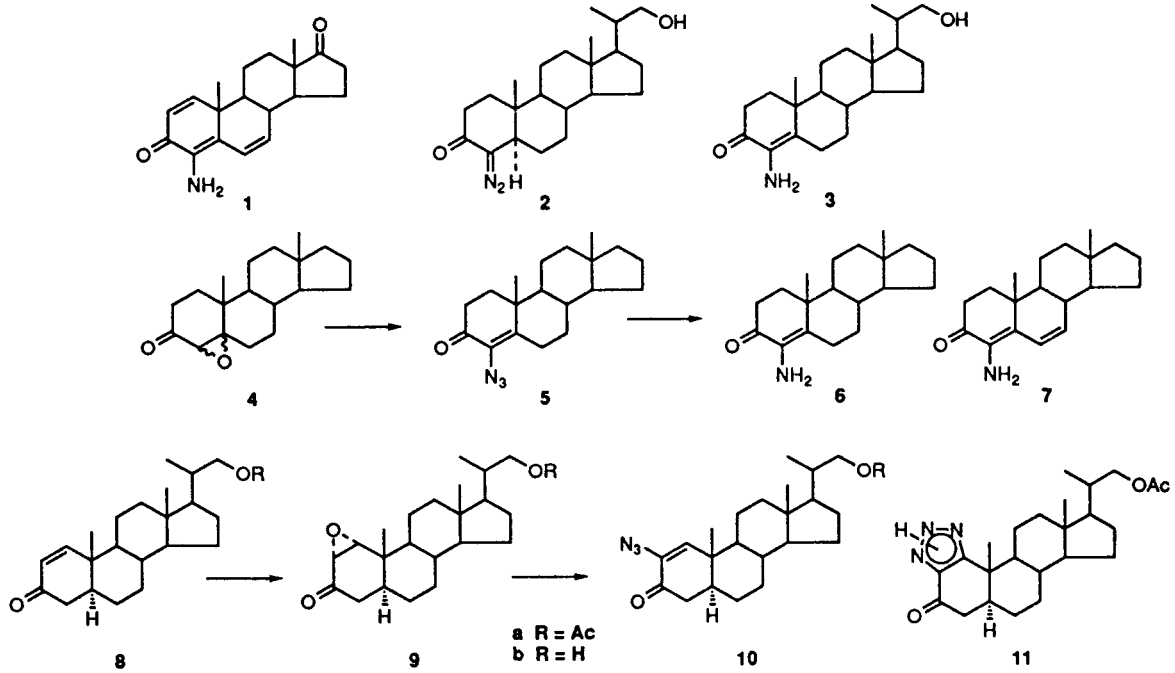
4-Aminoandrosta-1,4,6-triene-3,17-dione (FCE 24928, **1**) is reported to be a potent, *in vivo*, irreversible inhibitor of the enzyme steroid aromatase [3]. We reported that steroids **2** [4] and **3** [5] bearing a nitrogen on the C_4-carbon are potent inhibitors of the enzyme steroid 5α-reductase. 4-Aminosteroids **6** may be prepared from the corresponding 4,5-epoxy-3-ketosteroids **4** by reaction with sodium azide at 60° followed by reduction of the intermediate azidosteroids **5**. Interestingly, when this reaction is carried out at 100° the corresponding 4-amino-$\Delta^{4,6}$-3-ketosteroids are formed [3].

Using a similar reaction sequence we hoped to prepare the analogous 2-aminosteroids **14b** and **15**. Epoxidation of 21-acetyloxy-20-(S)-methyl-5α-pregn-1-en-3-one (**8a**) gave **9a** as a single stereoisomer [6]. Reaction of this epoxide with sodium azide in dimethyl sulfoxide at 60° for 1.5 hours gave a two component mixture. The less polar material was determined to be the desired vinyl azide **10a** [7]. Structure proof was straightforward. The ^{1}H nmr spectrum had both a singlet at 6.61 ppm for the C_1-vinyl proton and an acetyl methyl singlet at 2.06 ppm. Additionally, the infrared spectrum showed a strong absorption at 2112 cm^{-1} characteristic of an azide [9]. The second, more polar component showed an acetate methyl at 2.08 ppm in the ^{1}H nmr spectrum and the absence of a vinyl proton. Additionally, the infrared spectrum exhibited a strong signal at 3132 cm^{-1}, but no azide absorption at 2112 cm^{-1}. The mass spectrum of this material showed a parent ion at 414 amu (M^++1, 100%), isomeric with azide **10a**. This was confirmed by elemental analyses. From these data we were able to deduce the structure of the by-product as the novel triazole **11**.

It was initially difficult to reconcile the ^{13}C nmr of triazole **11** with the assigned structure. In deuteriochloroform the only downfield signal was the acetate carbonyl (197.9 ppm). The possibility of some intermediate rate tautomerism was eliminated as variable temperature experiments failed to evince the C_1, C_2 and C_3 carbons. Upon

Scheme I

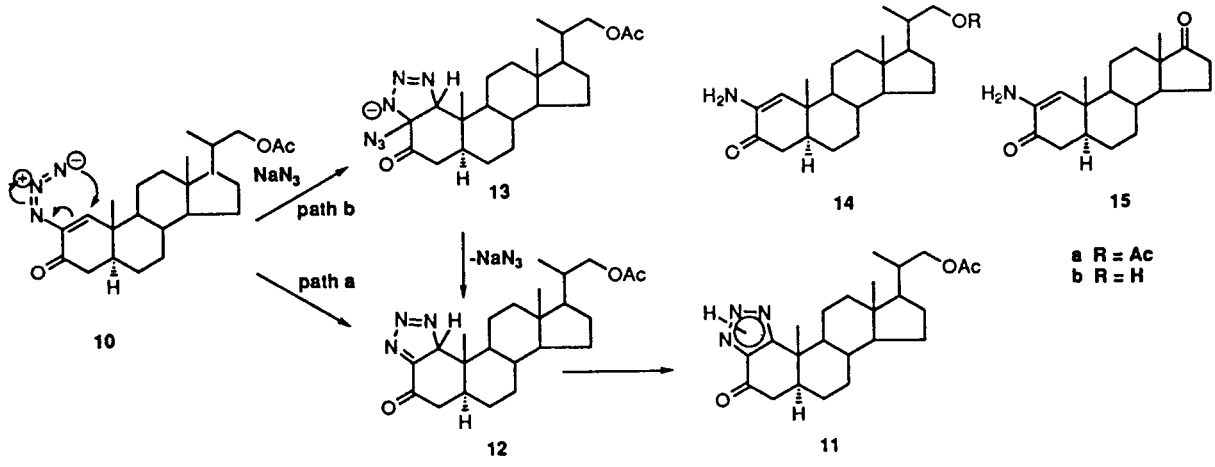


addition of chromium(III) acetylacetonate three additional downfield signals appeared: at 192.5 ppm for the C_3-carbonyl carbon, at 139.1 ppm (broadened) and at 162.0 ppm (slightly broadened) for carbons C_1 and C_2 (unassigned). This experiment demonstrates these carbons have long T_1's. The resulting long relaxation times obscure these carbons in "normal" ^{13}C experiments.

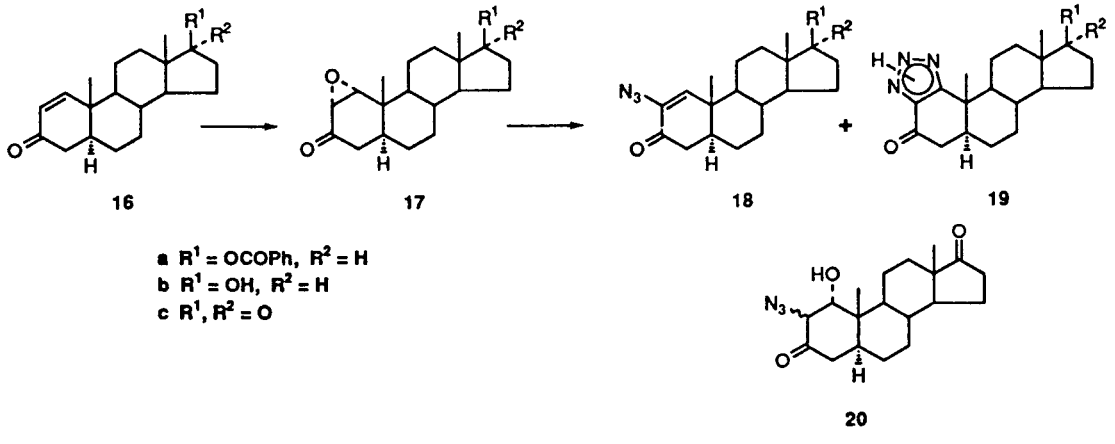
occurred as indicated by thin layer chromatography. When the reaction was repeated, but with the addition of two equivalents of sodium azide, the azide **10a** slowly disappeared and triazole **11** was formed. From these experiments we concluded that path b was the operative reaction pathway.

In subsequent experiments the reaction time was

Scheme II



Scheme III



We felt **11** was most likely formed from the vinyl azide **10** by either intramolecular 1,5-electrocyclization (path a, Scheme II) or by addition of a second molecule of azide ion followed by loss of the first azide ion (path b) [10]. Conversion of vinyl azides to triazoles (path a) generally requires a driving force such as enhanced nucleophilic character of the ß-carbon [11] or irreversible loss of a stable species [12]. Sodium azide is known to add to acetylenes [13] or to olefins [14, 15] bearing an electron-withdrawing group, although these reactions can be hazardous [16].

The origin of **11** was addressed by heating a sample of vinyl azide **10a** in dimethylsulfoxide at 60°. No reaction

extended and less vinyl azide was obtained which is consistent with the proposed reaction pathway. The generality of the reaction is shown by the preparation of triazoles **19a-c** (Scheme III). In the androstenedione series **16-19** (R^1,R^2 = O), we isolated the intermediary hydroxy azide **20** which appears to be a reasonably stable molecule.

EXPERIMENTAL

The nmr spectra were obtained with a Varian VXR 300 Magnetic Resonance spectrophotometer with tetramethylsilane as an internal solvent. Infrared (ir) spectra (potassium bromide pellets) were obtained with a Perkin-Elmer 180 FTIR spec-

trophotometer. The ultraviolet (uv) spectra were recorded with a Perkin-Elmer Lambda 4C spectrophotometer in ethanol. The standard drying agent was magnesium sulfate and the solvents were removed under vacuum on a rotary evaporator. Melting points were determined in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. All chromatographic separations were effected using flash chromatography [17] with E. Merck 230-400 mesh silica gel 60.

General Procedure for Epoxidation of 5α–Δ^1-3-Ketosteroids.

A solution of 5α-Δ^1-3-ketosteroid (0.108 mole) in methanol (200 ml), dichloromethane (75 ml) and 30% hydrogen peroxide (30 ml) was cooled to 15° in a water bath. An aqueous 4 normal sodium hydroxide solution was slowly added keeping the temperature below 17°. After 4 hours, most of the solvent was removed. The residue was dissolved in dichloromethane (500 ml) and was washed with brine. The aqueous layer was separated and extracted with dichloromethane (200 ml). The organic layers were combined, dried, treated with charcoal, filtered through a celite pad, and concentrated to a solid which was purified by chromatography.

21-Acetyloxy-1α,2α-epoxy-20-(S)-methyl-5α-pregnan-3-one (**9a**) and 1α,2α-Epoxy-21-hydroxy-20-(S)-methyl-5α-pregnan-3-one (**9b**).

These compounds were obtained after chromatography (toluene and toluene-1 to 5% ethyl acetate). The acetate eluted first (52%), mp 140-142° (aqueous acetone); ir: υ 1732, 1716, 1254 cm^{-1}; ^1H nmr: δ 0.72 (s, 3H, C_{18}-CH_3), 0.88 (s, 3H, C_{19}-CH_3), 1.03 (d, 3H, C_{22}-CH_3), 2.07 (s, Ac-CH_3), 3.24 (d, 1H, C_1-H), 3.53 (d, 1H, C_2-H), 3.78 (dd, 1H, C_{21}-H), 4.08 (dd, 1H, C_{21}-H); ms: m/z 388 (85%, M⁺+1), 329 (100%, M⁺+1-AcOH).

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.20; H, 9.59.

The alcohol eluted next (13%), mp 179-181° (acetone); ir: υ 3402, 1722 cm^{-1}; ^1H nmr: δ 0.72 (s, 3H, CH_{18}-CH_3), 0.88 (s, 3H, C_{19}-CH_3), 1.06, (d, C_{22}-CH_3), 3.24 (d, 1H, C_1-H), 3.37 (dd, 1H, C_{21}-H), 3.53, (d, 1H, C_2-H), 3.65 dd, 1H, C_{21}-H); ms: m/z 347 (100%, M⁺+1), 329 (75%, M⁺+1-H_2O).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.44; H, 9.88.

17β-Benzoyloxy-1α,2α-epoxy-5α–androstan-3-one (**17a**).

This compound was obtained after chromatography (toluene and toluene-2% ethyl acetate, 74%), mp 206-207° (dichloromethane-acetone, boiling off dichloromethane; lit [18] mp 182-184°); ir: υ 1714, 1278 cm^{-1}; ^1H nmr: δ 0.92 (s, 3H, C_{18}-CH_3), 0.97 (s, C_{19}-CH_3), 3.25 (d, 1H, C_1-H), 3.52 (d, 1H, C_2-H), 4.87 (t, 1H, C_{17}-H), 7.44 (t, 2H), 7.57 (t, 1H), 8.06 (dd, 2H); ms: m/z 409 (100%, M⁺+1), 287 (80%, M⁺+1-$PhCO_2H$).

Anal. Calcd. for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 76.15; H, 7.96.

1α,2α-Epoxy-5α-androstan-17β-ol-3-one (**17b**).

To a magnetically stirred mixture of the above benzoate (15.04 g, 36.8 mmoles) in methanol (200 ml) and dichloromethane (100 ml) was added lithium hydroxide hydrate (1.70 g, 40.5 mmoles). After 24 hours, half the solvent was removed and the resulting mixture diluted with water. The solids were collected by filtration, washed with water, sucked dry and purified by chromatography (toluene and toluene-5 to 10% ethyl acetate).

The first compound off the column was recovered starting material (5.4 g, 35%).

The next compound off the column was identified as 1-methoxy-5α-androst-1-en-17β-ol-3-one benzoate (1.8 g, 11.6%), mp 192-193° (aqueous acetone); ir: υ 1714, 1696, 1610, 1280, 1120 cm^{-1}; uv: λ max (log ε) 230 (4.157), 264 (3.950); ^1H nmr: δ 0.98 (s, C_{18}-CH_3), 1.06 (s, C_{19}-CH_3), 3.57 (s, 3H, CH_3O), 4.85 (t, 1H, C_{17}-H), 6.02 (1H, s, C_1-H), 7.86 (t, 2H), 7.57 (t, 1H), 8.05 (dd, 2H); ms: m/z 422 (50%, M⁺), 105 (100%, PhCO).

Anal. Calcd. for $C_{27}H_{34}O_4$: C, 76.74; H, 8.11. Found: 76.66, H, 8.20.

The next material off the column was the title compound (3.3 g, 29%), mp 163-164° (aqueous acetone) lit [19] mp 161-162°; ir: υ 3466, 1712 cm^{-1}; ^1H nmr: δ 0.78 (s, 3H, C_{18}-CH_3), 0.91 (s, C_{19}-CH_3), 3.24 (d, 1H, C_1-H), 3.53 (d, 1H, C_2-H), 3.67 (t, 1H, C_{17}-H); ms: m/z 304 (98%, M⁺), 245 (100%).

Anal. Calcd. for $C_{19}H_{28}O_3$: C,74.96, H, 9.27. Found: C, 75.02; H, 9.54.

1α,2α-Epoxy-5α-androstane-3,17-dione (**17c**).

To a solution of the above alcohol (14.5 g, 47.6 mmoles) in acetone (1 ℓ) cooled to -1° was added slowly a solution of Jones reagent [20]. The solids were removed by filtration and washed with acetone. The combined filtrate and wash was concentrated to blue-green solid which was purified by chromatography (toluene and toluene-10% ethyl acetate) 2.1 g (14%), mp 243-245° (acetone) lit [19] mp 246-247°; ir: υ 1738, 1696 cm^{-1}; ^1H nmr: δ 0.89 + 0.90 (s + s, 6H, C_{18}-CH_3 + C_{19}-CH_3), 3.24 (d, 1H, C_1-H), 3.52 (d, 1H, C_2-H); ms: m/z 303 (80%, M⁺+1), 285 (100%, M⁺+1-H_2O).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.60; H, 8.57.

General Procedure for Reaction of Epoxyketones with Azide.

A mixture of epoxyketone (10 mmoles) in dimethyl sulfoxide (135 ml) was heated in an oil bath to 60°. Solid sodium azide was added and the vigorously stirred mixture was treated dropwise with concentrated sulfuric acid (1.8 ml) [21]. After the appropriate time, the reaction was cooled to room temperature. It was poured into cold water (1.4 ℓ) [22]. The resulting solids were collected by filtration, washed with water and sucked dry. This crude material was purified by chromatography.

21-Acetyloxy-2-azido-20-(S)-methyl-5α-pregn-1-en-one (**10a**) and 21-Acetyloxy-20-(S)-methyl-1'H-5α-pregn-1-eno[1,2-*d*]triazol-3-one (**11**).

The reaction was run for 1.5 hours. The first material off the column (toluene-5% ethyl acetate and toluene-25% ethyl acetate) was the vinyl azide (34%); ir: υ 2112. 1742, 1678, 1606, 1246 cm^{-1}; uv: λ max (log ε) 277 (3.892); ^1H nmr: δ 0.72 (s, 3H, C_{18}-CH_3) 1.02 + 1.04 (d + s, C_{22}-CH_3 + C_{19}-CH_3), 2.06 (s, 3H, Ac-CH_3), 3.77 (dd, 1H, C_{21}-H), 4.08 (dd, 1H, C_{21}-H), 6.61 (s, 1H, C_1-H); ms: m/z 414 (25%, M⁺+1), 386 (30%, M⁺+1-N_2), 326 (100%, 386-AcOH); ^{13}C nmr: (downfield lines only) 171.9; (with Cr(AcAc) added): 139.1 (broadened), 162.0 (slightly broadened), 171.2. 192.5.

Anal. Calcd. for $C_{24}H_{35}N_3O_3$: C, 69.70; H, 8.53; N, 10.16. Found: C, 69.71; H, 8.81; N, 10.19.

The next material off the column was the triazole (57%), mp 249-250° (aqueous acetone); ir: υ 3132, 1738, 1702, 1684, 1654, 1246 cm^{-1}; uv: λ max (log ε) 248 (3.884); ^1H nmr: δ 0.77

(s, 3H, C_{18}-CH_3), 1.03 (d, C_{22}-CH_3), 1.22 (s, C_{19}-CH_3), 2.08 (s, 3H, Ac-CH_3), 2.89 (v br, 1H, NH), 3.78 (dd, 1H, C_{21}-H), 4.05 (dd, 1H, C_{21}-H); ^{13}C nmr (dimethyl sulfoxide-d_6): (downfield signals only) δ 191.9; ^{13}C nmr (dimethyl sulfoxide-d_6 + chromium acetylacetonate): δ 139.1, 162.0, 171.9, 192.5; ms: m/z 414 (100%, M^++1), 354 (75%, M^++1-AcOH).

Anal. Calcd. for $C_{24}H_{35}N_3O_3$: C, 69.70; H, 8.53; N, 10.16. Found: C, 69.55; H, 8.88; N, 9.91.

2-Azido-17β-benzoyloxy-5α-androst-1-en-3-one (**18a**) and 17β-Benzoyloxy-1'H-5α-androst-1-eno[1,2-*d*]triazol-3-one (**19a**).

The reaction was run for 2 hours. The first material off the column was the vinyl azide (9.4%) mp 138-139° dec (aqueous acetone); ir: υ 2116, 1712, 1686, 1602, 1278 cm^{-1}; uv: λ max (log ε) 229 (4.225), 275 (3.917); ^1H nmr: δ 0.97 (s, C_{18}-CH_3), 1.05 (s, C_{19}-CH_3), 4.86 (t, 1H, C_{17}-H), 6.61 (s, 1H, C_1-H), 7.45 (t, 2H), 7.56 (m, 1H), 8.03 (pr d, 2H); ms: m/z 434 (35%, M^++1), 406 (100%, M^++1-N_2), 284 (85%, 406-$PhCO_2H$).

Anal. Calcd. for $C_{26}H_{31}N_3O_3$: C, 72.03; H, 7.21; N, 9.69. Found: C, 72.11; H, 7.69; N, 9.10.

The next material off the column was the triazole (23%), mp 320-321° dec (dichloromethane-acetone by boiling off the dichloromethane); ir: υ 3250-3130, 1716, 1684 sh, 1654, 1278 cm^{-1}; uv: λ max (log ε) 230 (4.258); ^1H nmr: δ 0.99 (s, C_{18}-CH_3) 1.16 (s, C_{19}-CH_3), 2.94 (br, 1H, NH), 4.77 (t, 1H, C_{17}-H), 7.54 (t, 2H), 7.67 (m, 1H), 7.98 (d, 2H); ms: m/z 434 (75%, M^++1), 312 (100%, M^++1-$PhCO_2H$).

Anal. Calcd. for $C_{26}H_{31}N_3O_3$: C, 72.03; H, 7.21; N, 9.69. Found: C, 72.06; H, 7.49; N, 9.54.

2-Azido-17β-hydroxy-5α-androst-1-en-3-one (**18b**) and 17β-Hydroxy-1'H-5α-androst-1-eno[1,2-*d*]triazol-3-one (**19b**).

The reaction was run for 1 hour. The first material off the column (toluene and toluene-20 to 75% ethyl acetate) was the vinyl azide (23%) mp 236-240° dec (aqueous acetone); ir: υ 3412, 1608, 1522 cm^{-1}; uv: λ max (log ε) 277 (3.827); ^1H nmr: δ 0.77 (s, C_{18}-CH_3) 1.03 (s, C_{19}-CH_3), 3.67 (t, C_{17} -H), 6.62 (s, C_1-H), a small amount of impurity can be seen in this sample; ms: m/z 330 (30%, M^++1), 302 (100%, M^++1-N_2), 284 (50%, 302-H_2O).

Anal. Calcd. for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.75. Found: C, 69.46; H, 8.39; N, 12.70.

The next material off the column was the triazole (27%), mp 286-287° dec (dichloromethane-acetone by boiling off the dichloromethane); ir: υ 3424, 3138, 1692 cm^{-1}; uv: λ max (log ε) 248 (3.849); ^1H nmr (dimethyl sulfoxide-d_6): δ 0.72 (s, 3H, C_{18}-CH_3) 1.13 (s, C_{19}-CH_3), 3.44 (t + br s, C_{17}-H + H_2O), 4.49 (br s, 1H, NH), on deuterium oxide exchange the br s at 3.44 and at 4.49 disappear; ms: m/z 330 (100%, M^++1), 302 (45%, M^+ +1-H_2O).

Anal. Calcd. for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.75. Found: C, 68.72; H, 8.55; N, 11.90.

2-Azido-5α-androst-1-ene-3,17-dione (**18c**) and 1'H-5α-Androst-1-eno[1,2-*d*]-triazol-3,17-dione (**19c**) and 2-Azido-1α-hydroxy-5α-androstan-3,17-dione (**20**).

The reaction was run for 1 hour. The first material off the column (toluene and toluene-5 to 50% ethyl acetate) was the vinyl azide (7.9%) mp 134-135° dec (aqueous methanol): ir: υ 2121, 1746, 1682, 1642 cm^{-1}; uv: λ max (log ε) 277 (3.881); ^1H nmr: δ 0.90 (s, 3H, C_{18}-CH_3) 1.06 (s, C_{19}-CH_3), 6.59 (s, 1H, C_1-H); ms: m/z 328 (50%, M^++1), 300 (100%, M^++1-N_2).

Anal. Calcd. for $C_{19}H_{25}N_3O_2$: C, 69.70; H, 7.70; N, 12.83. Found: C, 70.00; H, 7.79; N, 12.56.

The next material off the column was the hydroxy azide (10%), mp 210-211° dec (aqueous acetone); ir: υ 3498, 2108, 1730 cm^{-1}; uv: λ max (log ε) 285 (2.396); ^1H nmr: δ 0.88 (s, 3H, C_{18}-CH_3) 1.07 (s, C_{19}-CH_3), 4.02 (t, 1H, C_1-H), 4.21 (d, 1H, C_2-H); ms: m/z 346 (35%, M^++1), 318 (100%, M^++1-N_2), 300 (50%, 318-H_2O).

Anal. Calcd. for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.16. Found: C, 66.46; H, 8.09; N, 12.01.

The next material off the column was the triazole (18%), mp 311-312° dec (methanol); ir: υ 3448, 3130, 1738, 1700, 1682, 1656 cm^{-1}; uv: λ max (log ε) 248 (3.856); ^1H nmr (dimethyl sulfoxide-d_6): δ 0.87 (s, C_{18}-CH_3), 1.17 (s, C_{19}-CH_3), 15.46 (br s, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 229.5 [23]; ms: m/z 328 (100%, M^++1), 310 (30%, M^++1-H_2O).

Anal. Calcd. for $C_{19}H_{25}N_3O_2$: C, 69.70; H, 7.70; N, 12.83. Found: C, 69.13,; H, 7.61; N, 12.19.

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