Regio- and Stereospecific Total Synthesis of a Racemic A,19-Dinorsteroid

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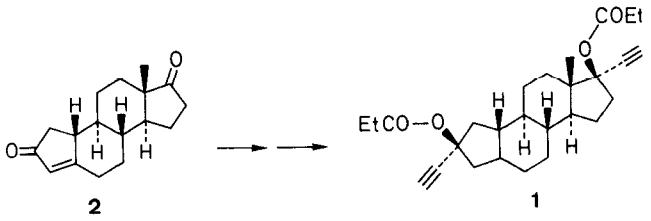
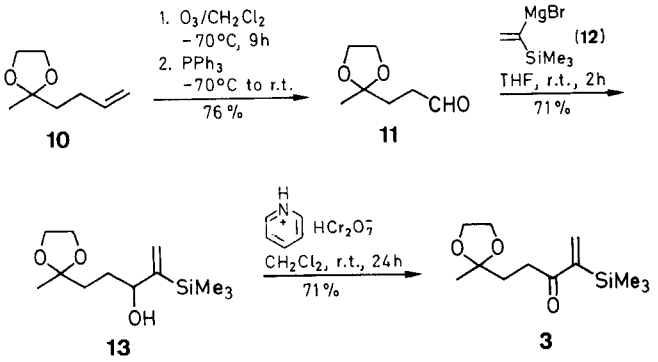
DL-A-nor-estr-3(5)-ene-2,17-dione is regio- and stereospecifically synthesized from 1-acetal-protected 7a-methyl-2,3,5,6,7,7a-hexahydroindene-1,5-dione in five steps in ca. 23% overall yield. The key step is the regiospecific trapping of an enolate of the dione with 6,6-(1,2-ethanediyldioxy)-2-trimethylsilyl-3-oxo-1-heptene.

The A-norsteroids form a class of non-natural compounds with unusual chemical and biological properties. It has been reported[1] that A-norandrostanes[2] exhibit implantation inhibiting activity. Several A-nor-[3] and A,19-dinorsteroids[4] have hence been synthesized. Among them, dinordrin **(1)** is by far the most active compound. Its remarkable biological activities and specific chemical structure have led many laboratories to synthesize this substance.[4]



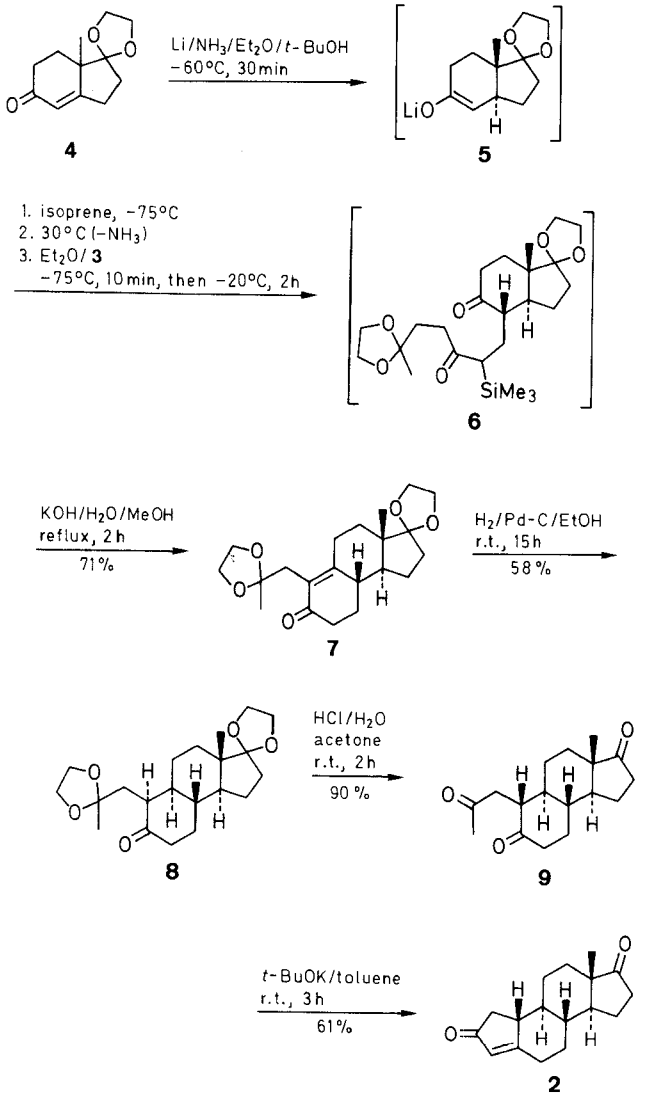
2 **1**

We here report an efficient synthesis of the A-19-dinorsteroid **2**, which is the precursor of **1**, by utilizing the regiospecific reductive Michael addition[5] of the 2-silylated electrophile **3** to the 1-protected endione **4**.[6] The 6-protected 2-trimethylsilyl-1-heptene-3,6-dione **3** is used to construct the rings A and B of **2**; it is prepared from 2-(3-butenyl)-2-methyl-1,3-dioxolane **(10)** in three steps using known methodology.[8]



10 **11** **13** **3**

The route to diketone **2** starts from 7a-methyl-2,3,5,6,7,7a-hexahydroindene-1,5-dione (**4**). Reduction of **4** with lithium in liquid ammonia and replacement of the ammonia by diethyl ether, followed by reaction of the resultant enolate (**5**) solution with 1.38 equivalent of **3** at $-75\,^{\circ}C$ and then allowing the mixture to come to $-20\,^{\circ}C$ afforded, on workup, the crude Michael adduct **6**. Subsequent treatment with aqueous potassium hydroxide in methanol at reflux temperature gave, after chromatographic purification, a single annulated product **7** in 71% yield with a positive solvent effect in ^{1}H-NMR spectrometry ($\Delta^{CCl_3}_{CDCl_3} = +0.16$), indicating *trans* C, D ring fusion.[6] Catalytic hydrogenation of **7** in alkaline medium in the presence of palladium on charcoal afforded **8** in 58% yield. Treatment of **8** with 1 N hydrochloric acid in acetone and then with potassium *tert*-butoxide in anhydrous toluene effected deacetalization to give **9** in 90% yield. Cyclocondensation of **9** afforded the title compound **2** in 61% yield. The coupling constant for H-9 to H-10 is $J_{9,10} = 14.4$ Hz so that the configuration at C-10 in **9** can be assigned as *S*.[7] The overall yield of the five-step synthesis of **2** based on **4** as starting material is about 23%.



Thus, the combination of the regiospecific generation of an enolate such as **5** by reduction, followed by trapping with a silylated enone such as **3** provides a useful method for the rapid, regio- and stereospecific construction of A-nor steroids. This methodology is finding increasing use in the synthesis of naturally occurring compounds.[5,9]

Mass Spectra were recorded on Shimadzu GCMS-QP1000 or Finigan GCMS-4021 spectrometers. IR spectra were recorded on Perkin-Elmer-683 or Shimdazu IR-440 spectrophotometers. ^{1}H-NMR spectra on Varian EM-360L (60 MHz) or Varian XL-200 (200 MHz) spectrometers.

In the following, PE refers to petroleum ether (bp 60–90 °C).

4,4-(1,2-Ethanediyldioxy)pentanal (11):

A solution of 2-(3-butenyl)-2-methyl-1,3-dioxolane [**10** (prepared by acetalization of 5-hexen-2-one[10] with 1,2-ethanediol; yield: 95%); 10 g, 70.4 mmol] in CH_2Cl_2 (120 mL) is cooled to $-70\,^{\circ}C$ and O_3 is introduced into the stirred solution for about 9 h. The solution is then swept with N_2 for 30 min to remove excess O_3, PPh_3 (18.6 g) is added, and the mixture is allowed to gradually come to r.t., and the solvent is evaporated. Hexane (50 mL) is added to the residue and the precipitate was removed by filtration and washed well with hexane and Et_2O. The combined filtrate is evaporated and the crude product is immediately distilled to give aldehyde **11**; yield: 7.7 g (76%); bp 50–52 °C/1 Torr. (Lit.[10] bp 42 °C/0.3 Torr).

$C_7H_{12}O_3$ (144.2)

MS (EI, 70 eV): *m/z* (%) = 145 ($M^+ + 1$, 22), 144 (M^+, 1), 143 ($M^+ - 1$, 12), 99 (30), 87 (100).

IR (film): $\nu = 1721$ (C=O), 1060 cm^{-1}.

^{1}H-NMR (CCl_4/TMS): $\delta = 1.23$ (s, 3H, H-5), 1.93 (t, 2H, $J = 6$ Hz, H-3), 2.33 (m, 2H, H-2), 3.83 (s, 4H, OCH_2CH_2O), 9.60 (s, 1H, H-1).

6,6-(1,2-Ethanediyldioxy)-3-hydroxy-2-trimethylsilyl-1-heptene (13):

A solution of 1-trimethylsilylvinylmagnesium bromide (35.6 mmol) in anhydrous THF (40 mL) is prepared from 1-bromovinyl-(trimethyl)silane (6.38 g, 35.6 mmol) and magnesium turnings (1.10 g, 44.6 mmol).[11] This solution is stirred at 0 °C, the freshly distilled aldehyde **11** (7.6 g, 52.5 mmol) is added dropwise, and stirring is continued at r.t. for 2 h. The mixture is then diluted with Et_2O (30 mL) and quenched with sat. NH_4Cl solution (15 mL). The separated H_2O layer is extracted with Et_2O (3 × 30 mL). The combined organic phases are dried (Na_2SO_4) and evaporated. The residue is column chromatographed on silica gel (EtOAc/PE, 3:7) to afford **13** as an oil; yield: 6.2 g (71%).

$C_{12}H_{24}O_3Si$ (244.2)

MS (EI, 70 eV): *m/z* (%) = 244 (M^+, 1), 227 ($M^+ - 17$, 17), 183 (25), 87 (100).

IR (film): $\nu = 3468$ (OH), 3052 (C=C), 1064 cm^{-1}.

^{1}H-NMR (CCl_4/TMS): $\delta = 0.15$ (s, 9H, $3CH_3$), 1.25 (s, 3H, H-7), 1.60 (m, 4H, H-4, H-5), 2.43 (s, 1H, OH), 3.87 (s, 4H, OCH_2CH_2O), 4.15 (m, 1H, H-3), 5.35 (br, 1H, H-1), 5.68 (br, 1H, H-1).

6,6-(1,2-Ethanediyldioxy)-2-trimethylsilyl-1-hepten-3-one (3):

To a stirred solution of aldehyde **13** (3.8 g, 15.6 mmol) in dry CH_2Cl_2 (25 mL) is added pyridinium dichromate (8.8 g, 1.5 equiv) and stirring is continued at r.t. for 24 h. The mixture is then diluted with Et_2O (20 mL), filtered, washed with Et_2O (3 × 15 mL), dried (Na_2SO_4), and evaporated. The crude product is column chromatographed on silica gel (EtOAc/PE, 3:7) to afford **3** as an oil; yield: 2.66 g (71%).

$C_{12}H_{22}O_3Si$	calc.	C 59.46	H 9.15
(242.4)	found	58.97	9.17

MS (EI, 70 eV): *m/z* (%) = 243 ($M^+ + 1$, 3), 227 (2), 87 (100).

IR (film): $\nu = 3062$ (C=C), 1660 (conjugated C=O), 1048 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.12 (s, 9H, $3CH_3$), 1.33 (s, 3H, H-7), 2.00 (t, 2H, J = 6 Hz, H-5), 2.74 (t, 2H, J = 6 Hz, H-4), 3.94 (s, 4H, OCH_2CH_2O), 6.14 (d, 1H, J = 2 Hz, H-1), 6.48 (d, 1H, J = 2 Hz, H-1).

***dl*-A-Nor-3,5-seco-estr-9-ene-2,5,17-trione 2,17-Bis(1,2-ethanediyl) Acetal (7):**

To a solution of Li (120 mg, 15 mmol) in dry NH_3 (50 mL) under N_2 is added dropwise a stirred solution of **4**[6] 1.04 g, 5 mmol) in dry Et_2O (20 mL) containing *t*-BuOH (0.377 mL) at −60 °C, and stirring at −60 °C is continued for 30 min under N_2. The excess Li is destroyed by addition of isoprene (0.1 mL). Then, NH_3 is evaporated on a water bath (30 °C) and the residue is vacuum-dried to give a white solid. This product is diluted with Et_2O (40 mL) and stirred at −75 °C for 10 min. Then, a solution of ketone **3** (1.68 g, 6.9 mmol) in Et_2O (20 mL), stirring is continued at −75 °C for 10 min, the mixture is allowed to warm to −20 °C, stirred at −20 °C for 2 h, and quenched with sat. NH_4Cl solution (10 mL). The separated H_2O layer is extracted with Et_2O (3 × 20 mL). The combined organic phases are washed with brine, dried (Na_2SO_4), and evaporated to give the crude product **6**.

To this product are added MeOH (100 mL) and 6% aq KOH solution (20 mL). The mixture is heated at reflux for 2 h, then allowed to cool, neutralized with AcOH (1.4 mL), and MeOH evaporated. The residue is diluted with Et_2O (40 mL) and the separated aq layer is extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and evaporated. The crude product is column-chromatographed on silica gel (EtOAc/PE, 3:7) to afford **7** as an oil; yield: 1.28 g (71%).

$C_{21}H_{30}O_5$ (362.4)

MS (EI, 70 eV): *m/z* (%) = 364 (M^+ + 2, 8), 363 (M^+ + 1, 33), 187 (20), 171 (14), 141 (56), 99 (45), 87 (62), 43 (100).

Exact Mass: *m/z* calc. 362.2094, found 362.2108.

IR (film): ν = 1664 (conjugated C=O), 1608 cm^{-1}.

^{1}H-NMR (CCl_4/TMS): δ = 1.06 (s, 3H, H-18), 1.20 (s, 3H, H-3), 1.30–1.60 (m, 4H, H-15, H-16), 1.67–2.01 (m, 5H, H-7, H-12, H-14), 2.20–2.60 (m, 5H, H-6, H-8, H-11), 2.70 (s, 2H, H-1), 3.90 (s, 8H, $2OCH_2CH_2O$).

***dl*-A-Nor-3,5-seco-estrane-2,5,17-trione 2,7-Bis(1,2-ethanediyl) Acetal (8):**

To absolute EtOH (20 mL) are added **7** (320 mg, 0.88 mmol), Et_3N (0.1 mL), and 10% Pd on charcoal (100 mg). The mixture hydrogenated (10–15 atm) at r.t. for 15 h. The catalyst is filtered off, the solution is evaporated, and the crude product is column chromatographed on silica gel (EtOAc/PE, 3:7) to give **8** as an oil; yield: 186 mg (58%).

$C_{21}H_{32}O_5$ (364.5).

MS (EI, 70 eV): *m/z* (%) = 365 (M^+ + 1, 1), 349 (M^+ − 15, 1), 99 (78), 87 (100).

Exact Mass: *m/z* calc. 364.2251, found 364.2263.

IR (film): ν = 1713 (C=O) cm^{-1}.

^{1}H-NMR (CCl_4/TMS): δ = 0.92 (s, 3H, H-18), 1.26 (s, 3H, H-3), 1.17–1.50 (m, 12H, H-1, H-7, H-11, H-12, H-15, H-16), 1.72 (m, 3H, H-8, H-9, H-14), 2.07–2.65 (m, 3H, H-6, H-10); 3.83 (s, 8H, $2OCH_2CH_2O$).

***dl*-A-Nor-3,5-seco-estrane-2,5,17-trione (9):**

Ketone **8** (132 mg, 0.363 mmol) is dissolved in acetone (12 mL), 1 N aq HCl (0.6 mL) is added, and the mixture is stirred at r.t. for 2 h. Then, sat. $NaHCO_3$ solution (1 mL) is added and the mixture is evaporated. The residue is diluted with CH_2Cl_2 (15 mL) and washed with H_2O. The separated H_2O layer is extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases are dried (Na_2SO_4) and evaporated. The crude product is column chromatographed on silica gel (EtOAc/PE, 3:7) to afford product **9**; yield: 90 mg; mp 102–103 °C.

$C_{17}H_{24}O_3$ (276.4)

MS (EI, 70 eV): *m/z* (%) = 277 (M^+ + 1, 46), 276 (M^+, 4), 261 (1), 233 (4), 219 (100), 95 (58), 55 (29).

Exact Mass: *mz* calc. 276.1725, found 276.1753.

IR (KBr): ν = 1740 (five-membered ring C=O), 1710 cm^{-1} (six-membered ring C=O, MeC=O).

^{1}H-NMR ($CDCl_3$/TMS, 400 MHz): δ = 0.99 (s, 3H, H-18), 1.15 (m, 4H, H-11, H-12), 1.52–1.65 (m, 4H, H-7, H-15), 1.91 (m, 2H, H-8, H-14), 2.21 (s, 3H, H-3), 2.12–2.61 (m, 7H, H-1, H-6, H-9, H-16), 2.82 (m, 1H, $J_{9,10}$ = 14.4 Hz, H-10).

***dl*-A-Nor-estr-3(5)-ene-2,17-dione (2):**

To a stirred solution of the trione **9** (30 mg, 0.11 mmol) in dry toluene (4 mL) is added, under N_2, a cooled suspension of *t*-BuOK (20 mg, 0.18 mmol) in dry toluene (1 mL), and stirring is continued at r.t. for 3 h. The mixture is then quenched with sat. NaH_2PO_4 solution (2.5 mL). The H_2O layer is extracted with EtOAc (3 × 10 mL). The combined organic phases are washed with brine (2 mL), dried (Na_2SO_4), and evaporated. The crude product is column chromatographed on silica gel (EtOAc/hexane, 5:5) to afford product **2**; yield: 17 mg (61%); mp 156–157 °C.

$C_{17}H_{22}O_2$ (258.35)

MS (EI, 70 eV): *m/z* (%) = 259 (M^+ + 1, 9), 258 (M^+, 48), 241 (8), 214 (8), 202 (9), 41 (100).

Exact Mass: *m/z* calc. 258.1619, found 258.1611.

IR (KBr): ν = 1740 (five-membered ring C=O), 1700 (conjugated C=O), 1620 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.95 (s, 3H, H-18), 1.10–1.45 (m, 8H, H-7, H-11, H-12, H-15), 1.80 (m, 3H, H-8, H-9, H-14), 2.02–2.72 (m, 7H, H-1, H-6, H-10, H-16), 5.82 (s, 1H, H-3).

Received: 23 November 1989; revised: 6 April 1990

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