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ORIGINAL PAPER

Synthesis and Crystal Structure of a New Mestranol Acetate

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Abstract A new mestranol acetate, 17α-ethinyl-17-hydroxy-3-methoxyestra-1,3,5(10)-triene-6-one-17-acetate, was synthesized by an efficient three-step sequence starting from norethindrone. The structure of the new steroid was characterized by ^{1}H NMR, ^{13}C NMR, MS, IR spectrum and X-ray single crystal diffraction. It crystallizes in the triclinic system, space group P1. The molecules are arranged in a head-to-tail fashion without intra- and intermolecular hydrogen bonding.

Keywords Mestranol · Acetate · Synthesis · X-ray · Crystal structure

Introduction

As common components of widely used hormone regulation and therapy medications, mestranol has been proved to be stable in air. Nevertheless, stability samples of formulated drug products containing mestranol stored for years under ambient laboratory conditions were observed to contain several oxidative transformation products of the parent compound which were not present at the beginning of the study. It was also found that decomposition of mestranol in the solid state could be accelerated at elevated temperature in the presence of air, as a result of auto-oxidation. Up until now, little is known about the decomposition products of mestranol. In view of providing authentic samples and steroidal compounds with antitumor activity and potential value in the radioimmunoassay [1–4], the chemical synthesis and structural characterization of the decomposition products of mestranol and related compounds is of great importance. Recently we reported efficient synthesis and structural characterization of a series of mestranol decomposition products [5]. As a continuation of the study on steroidal compounds [6], we present herein efficient synthesis and crystal structure of a new mestranol acetate.

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Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer. $CDCl_3$ was used as solvent and chemical shifts recorded were internally referenced to Me_4Si (0 ppm). All chemical shifts (δ) were given in ppm and coupling constants (J) in Hz. IR spectra were obtained on a Thermo Electron Corporation Nicolet 380 FT-IR spectrophotometer. Mass spectra were recorded on a Finnigan-MAT-8430 instrument using electron ionization (EI) at 70 eV. Melting points were determined on a WRS-2A capillary melting apparatus and the quoted temperatures were uncorrected.

All chemical reagents were purchased from commercial sources and used as received unless other statements.

Synthesis of 3,17β-Dihydroxy-19-norpregna-1,3,5(10)-triene-20-yne-6-one (**2**)

Norethindrone (17.9 g, 60 mmol) and anhydrous potassium acetate (9.5 g, 96 mmol) in dry DMF (120 mL) was

heated to 120 °C and stirred for 20 h while oxygen or air was bubbled through the solution. The reaction mixture was poured onto ice water (100 mL) containing methylene chloride (300 mL). Hydrochloric acid (1 N, 150 mL) was added then the organic layer was separated. The aqueous phase was extracted with methylene chloride (150 mL × 3). The organic phases were combined and washed with 150 mL each of 1 N hydrochloric acid, water, and brine then dried over $MgSO_4$. After evaporation to remove solvent, the crude product was purified by column chromatography on silica gel with 20% ethyl acetate in petroleum ether (bp 60–90 °C) to afford **2** (11.4 g, 61%) as pale yellow solid. M.p.: 228.6–229.5 °C (literature [7] value: 229–230 °C); $R_f = 0.25$ (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.53$ (d, J = 2.9 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.07 (dd, J = 8.5 and 2.9 Hz, 1H), 5.24 (s, 1H), 2.74 (dd, J = 16.9 and 3.3 Hz, 1H), 2.64 (s, 1H), 2.22–2.55 (m), 1.74–2.08 (m), 1.57–1.66 (m), 1.24–1.43 (m), 0.90 (s, 3H) ppm; IR (KBr) $\nu = 3563$, 3388, 3277, 2965, 2945, 2891, 2865, 1664, 1607, 1498, 1385, 1311, 1259, 1215, 1178, 1133, 1045 cm^{-1}.

Synthesis of 17α-Ethinyl-17-hydroxy-3-methoxyestra-1,3,5(10)-triene-6-one (**3**)

A mixture consisting of **2** (4.34 g, 14 mmol), anhydrous potassium carbonate (6.36 g, 46 mmol), methyl iodide (6 mL, 13.7 g, 97 mmol), and acetone (40 mL) was stirred at room temperature for 36 h then refluxed for 6 h. The reaction mixture was allowed to cool to room temperature and poured into water (150 mL). The mixture was extracted with ethyl acetate (80 mL × 4) and the combined organic phase was dried over Na_2SO_4. After evaporation to remove solvent, the crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent or by recrystallization from methylene dichloride/hexane to give **3** (4.3 g, 95%) as pale yellow needles. M.p.: 161.8–162.5 °C (literature [1] value: 162–163 °C from ether); $R_f = 0.57$ (petroleum

Table 1 Crystal data and experimental crystallographic details

Empirical formula	$C_{23}H_{26}O_4$
Formula weight	366.44
Temperature	293(2) K
Radiation, wavelength	MoKα, 0.71073 Å
Habit, colour	Prism, colorless
Crystal system, space group	Triclinic, P1
Unit cell dimensions	
a	7.1491(19) Å
b	11.872(3) Å
c	12.792(3) Å
α	109.668(5)°
β	98.096(5)°
γ	94.114(5)°
Volume	1003.9(5) $Å^3$
Z, calculated density	2, 1.212 g cm^{-3}
Absorption coefficient	0.082 mm^{-1}
F(000)	392
Crystal size	0.507 × 0.420 × 0.327 mm
θ range for data collection	1.72–26.00°
Limiting indices	$-8 \le h \le 8$, $-14 \le k \le 12$, $-15 \le l \le 14$
Reflections collected/unique	5525/3868 [R(int) = 0.1316]
Absorption correction	Empirical
Max. and min. transmission	1.0000 and 0.8127
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3868/3/493
Goodness-of-fit on F^2	0.955
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0611$, $wR_2 = 0.1307$
R indices (all data)	$R_1 = 0.0730$, $wR_2 = 0.1372$
Largest diff. peak and hole	0.265 and −0.257 e $Å^{-3}$

Table 2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **4**

Atom	x	y	z	*U*eq
O(1)	−692(5)	5480(4)	−2199(3)	84(1)
O(2)	5030(5)	3461(4)	−2248(3)	87(1)
O(3)	285(4)	10009(3)	4506(2)	60(1)
O(4)	−2168(6)	11001(3)	5025(3)	81(1)
O(5)	−1565(5)	2938(4)	10695(3)	87(1)
O(6)	1454(6)	3658(4)	14740(3)	93(1)
O(7)	4294(4)	−2666(3)	7158(2)	61(1)
O(8)	3563(5)	−3372(3)	5282(3)	69(1)
C(1)	3636(6)	4710(4)	550(4)	54(1)
C(2)	4664(6)	4086(4)	−272(4)	61(1)
C(3)	4106(6)	4019(4)	−1359(4)	58(1)
C(4)	2538(7)	4499(4)	−1663(4)	60(1)
C(5)	1504(6)	5110(4)	−840(3)	52(1)
C(6)	−169(6)	5608(4)	−1222(3)	56(1)
C(7)	−1208(6)	6323(4)	−327(3)	55(1)
C(8)	103(5)	6931(4)	805(3)	43(1)
C(9)	993(5)	5953(4)	1194(3)	47(1)
C(10)	2072(5)	5227(3)	302(3)	47(1)
C(11)	2196(6)	6482(4)	2363(3)	56(1)
C(12)	1204(6)	7345(4)	3245(3)	53(1)
C(13)	472(5)	8311(4)	2827(3)	45(1)
C(14)	−881(5)	7700(4)	1705(3)	44(1)
C(15)	−1877(7)	8728(5)	1499(4)	62(1)
C(16)	−1927(6)	9615(4)	2676(4)	60(1)
C(17)	−893(5)	9109(4)	3516(3)	48(1)
C(18)	2138(6)	9156(4)	2751(4)	63(1)
C(19)	−2213(6)	8394(4)	3899(3)	55(1)
C(20)	−3287(7)	7804(5)	4173(4)	68(1)
C(21)	−498(8)	10888(4)	5191(4)	63(1)
C(22)	938(9)	11683(5)	6153(4)	86(2)
C(23)	6552(8)	2863(5)	−2019(5)	84(2)
C(24)	4036(7)	2088(4)	12570(4)	65(1)
C(25)	3534(8)	2650(5)	13612(4)	74(1)
C(26)	1834(7)	3136(5)	13672(4)	69(1)
C(27)	668(7)	3075(4)	12721(4)	67(1)
C(28)	1175(6)	2482(4)	11648(4)	56(1)
C(29)	−166(6)	2411(4)	10644(4)	61(1)
C(30)	216(6)	1624(4)	9526(4)	60(1)
C(31)	1507(5)	677(4)	9601(3)	49(1)
C(32)	3355(5)	1336(4)	10422(3)	49(1)
C(33)	2865(6)	1980(4)	11575(4)	53(1)
C(34)	4932(6)	532(4)	10432(3)	56(1)
C(35)	5233(6)	−198(4)	9252(3)	55(1)
C(36)	3386(5)	−924(4)	8538(3)	47(1)
C(37)	1916(5)	−75(4)	8456(3)	48(1)
C(38)	280(6)	−881(5)	7559(4)	65(1)
C(39)	1227(6)	−1859(4)	6748(4)	60(1)
C(40)	3339(6)	−1602(4)	7249(3)	51(1)
C(41)	2688(8)	−1857(5)	9028(4)	69(1)
C(42)	4389(6)	−854(4)	6757(3)	56(1)
C(43)	5123(7)	−271(5)	6321(4)	72(1)
C(44)	4344(6)	−3468(4)	6121(4)	57(1)
C(45)	5473(9)	−4440(6)	6199(5)	90(2)
C(46)	−209(10)	4225(8)	14855(6)	116(2)

U(eq) is defined as one-third of the trace of the orthogonalized U^{ij} tensor

ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.57$ (d, J = 2.9 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.12 (dd, J = 8.6 and 2.9 Hz, 1H), 3.85 (s, 3H), 2.75 (dd, J = 16.9 and 3.3 Hz, 1H), 2.63 (s, 1H), 2.23–2.57 (m), 1.72–2.05 (m), 1.56–1.66 (m), 1.26–1.49 (m), 0.90 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 197.8$ (C=O), 158.2 (3-C), 139.5 (10-C), 133.4 (5-C), 126.6 (1-C), 121.6 (2-C), 109.7 (4-C), 87.2 (21-C), 79.6 (17-C), 74.4 (22-C), 55.5 (OCH_3), 49.3 (13-C), 46.9 (14-C), 44.0 (9-C), 42.6 (7-C), 40.7 (8-C), 38.9 (16-C), 32.4 (12-C), 25.7 (11-C), 22.5 (15-C), 12.5 (CH_3) ppm; IR (KBr) $\nu = 3523$, 3275, 2946, 1674, 1605, 1493, 1327, 1286, 1246, 1224, 1038 cm^{-1}; MS (EI, 70 eV): *m/z* (%) 324 (M^+, 77), 256 (50), 241 (68), 227 (12), 214 (15), 200 (60), 188 (100), 174 (19), 161 (23), 145 (10), 128 (12), 115 (18), 103 (11), 91 (11), 77 (13).

Synthesis of 17α-Ethinyl-17-hydroxy-3-methoxyestra-1,3,5(10)-triene-6-one-17-acetate (**4**)

A mixture consisting of **3** (2.79 g, 8.6 mmol), pyridine (3 mL, 2.93 g, 37.1 mmol), and acetic anhydride (7 mL, 7.56 g, 74.1 mmol) was heated to 80 °C and stirred for 5 h. The reaction mixture was allowed to cool to room temperature and poured into water (30 mL). The mixture was extracted with ethyl acetate (40 mL × 3) and the combined organic phase was dried over Na_2SO_4. After evaporation the crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (4:1) as eluent to give **4** (2.56 g, 81%) in addition to the starting material **3** (0.28 g, 10%) as colorless prismatic crystals. M.p.: 167.5–168.5 °C; $R_f = 0.71$ (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.60$ (d, J = 2.9 Hz, 1H, 4-H), 7.39 (d, J = 8.6 Hz, 1H, 1-H), 7.15 (dd, J = 8.6 and 2.9 Hz, 1H, 2-H), 3.88 (s, 3H, OCH_3), 2.76 (m, 2H), 2.69 (s, 1H, C≡CH), 2.12–2.54 (m, 3H), 2.10 (s, 3H, $COCH_3$), 1.92–2.08 (m, 4H), 1.60–1.69 (m, 2H), 1.29–1.48 (m, 2H), 0.89 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 200.0$ (C=O), 171.8 (O–C=O), 160.6 (3-C), 141.7 (10-C), 135.7 (5-C),

129.0 (1-C), 123.9 (2-C), 112.0 (4-C), 86.5 (17-C or 19-C), 85.4 (19-C or 17-C), 77.6 (≡CH), 57.8 (OCH_3), 50.1 (14-C), 46.3 (13-C), 44.8 (9-C), 42.7 (7-C), 39.6 (8-C), 35.2 (16-C), 33.2 (12-C), 27.9 (11-C), 25.3 (22-C or 15-C), 23.7 (15-C or 22-C), 15.6 (18-C) ppm; IR (KBr) $\nu = 3266$, 2940, 2872, 2125, 1742, 1730, 1686, 1675, 1606, 1492, 1445, 1422, 1369, 1319, 1290, 1262, 1248, 1028, 714 cm^{-1}; MS (EI, 70 eV): *m/z* (%) 366 (M^+, 91), 351 (M^+–CH_3, 37), 324 (29), 306 (15), 291 (12), 264 (12), 256 (21), 254 (21), 241 (49), 213 (11), 200 (18), 188 (60), 187 (62), 174 (19), 161 (22), 131 (10), 115 (13), 91 (15), 77 (12), 53 (10), 43 (100).

Measurement of Crystal Structure

The X-ray diffraction experiment for compound **4** was carried out on a Bruker Smart CCD diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.710\,73$ Å) at 293(2) K. Data collection, cell refinement, data reduction and correction for absorption were all performed using Bruker programs [8]. The structure was solved by direct methods and refined anisotropically by full-matrix least-squares calculations on F^2 with SHELXTL for the non-hydrogen atoms [9]. The hydrogen atoms were assigned based on the expected bonding geometry and were refined isotropically in the final least-squares cycles. The crystal data and experimental details for compound **4** were summarized in Table 1. Atomic coordinates and equivalent isotropic displacement parameters were provided in Table 2.

Results and Discussion

The target compound, 17α-ethinyl-17-hydroxy-3-methoxyestra-1,3,5(10)-triene-6-one-17-acetate (**4**), was synthesized

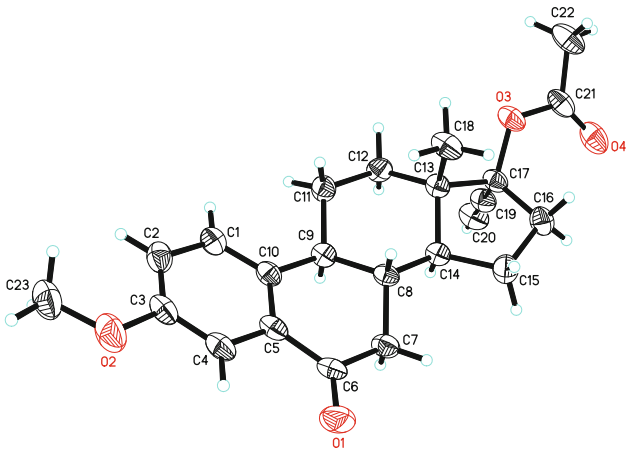


Fig. 1 A view of the molecule of compound **4**. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii

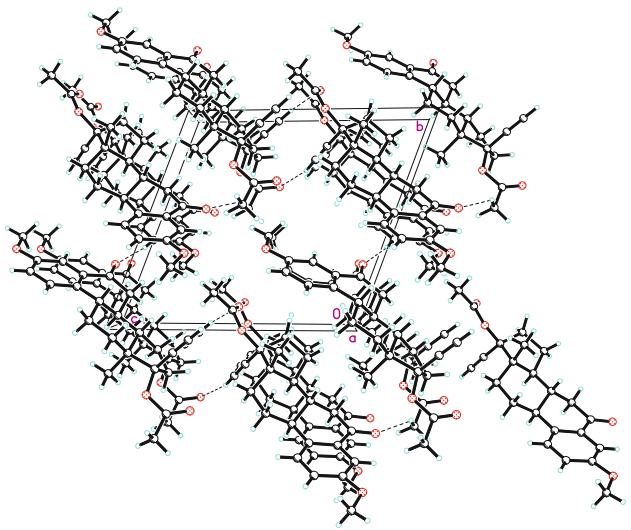
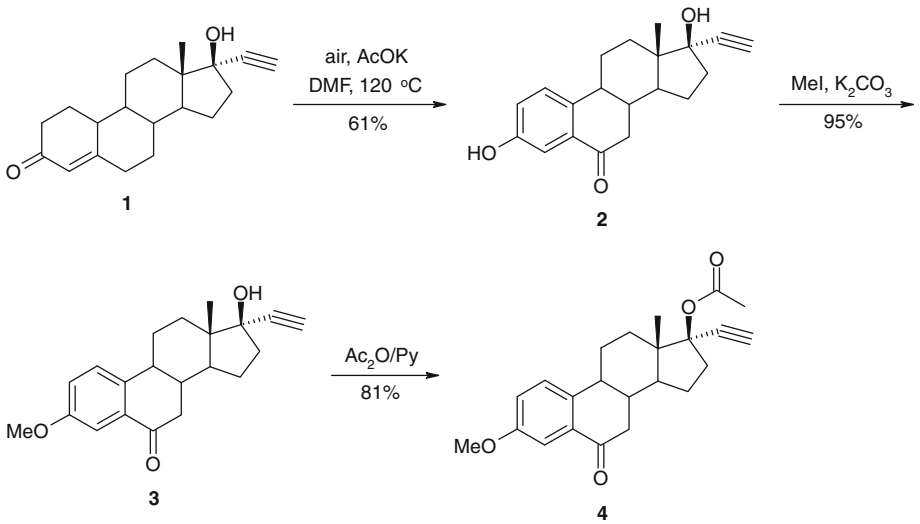


Fig. 2 Unit cell packing of compound **4**, viewed along a axis

Scheme 1 Synthetic route of the mestranol acetate **4**



starting from norethindrone (**1**). It was first reported by Wiechert and co-workers [10] that norethidrone could be oxidized to 6-keto ethinyl estradiol (**2**) by oxygen in DMF containing potassium acetate at 120 °C. This procedure was followed and the yield of compound **2** was about 40% [7, 11]. We found that the yield of **2** could be improved up to 61% by prolonging the reaction time. Moreover, the oxidation procedure could be simplified by replacing oxygen with air without substantial decrease in yields (Scheme 1). Methylation of compound **2** with methyl iodide in the presence of potassium carbonate afforded **3**, the minor degradation product of mestranol, in high yield (95%). Acetylation of **3** with acetic anhydride and pyridine gave **4** in good yield (81%). Thus, the efficient three-step sequence starting from norethindrone produced compound **4** in an overall yield of 47%.

Table 3 Selected bond lengths (Å) and angles (°)

Bond lengths (Å)	
O(1)–C(6)	1.207(5)
O(2)–C(3)	1.392(5)
O(3)–C(21)	1.334(6)
O(3)–C(17)	1.454(5)
C(1)–C(10)	1.363(6)
C(1)–C(2)	1.402(6)
C(1)–H(1)	0.9300
C(5)–C(10)	1.416(5)
C(5)–C(6)	1.466(6)
C(6)–C(7)	1.502(6)
C(7)–C(8)	1.521(5)
C(7)–H(7A)	0.9700
C(11)–C(12)	1.542(6)
C(13)–C(17)	1.562(5)
C(19)–C(20)	1.169(6)
C(20)–H(20)	0.9300
C(21)–C(22)	1.478(7)
Bond angles (°)	
C(23)–O(2)–C(3)	117.1(4)
C(10)–C(1)–C(2)	122.6(4)
C(3)–C(2)–H(2)	120.6
C(2)–C(3)–O(2)	124.7(4)
O(1)–C(6)–C(5)	122.8(4)
C(5)–C(6)–C(7)	116.7(3)
C(14)–C(8)–C(9)	109.8(3)
C(10)–C(9)–C(8)	109.1(3)
C(9)–C(11)–H(11A)	108.8
C(13)–C(14)–C(15)	104.1(3)
C(16)–C(15)–C(14)	104.7(3)
C(15)–C(16)–H(16A)	110.4
C(16)–C(17)–C(13)	103.2(3)
C(20)–C(19)–C(17)	178.0(4)
C(19)–C(20)–H(20)	180.0
C(21)–C(22)–H(22A)	109.5
O(2)–C(23)–H(23C)	109.5

Single crystals of compound **4** suitable for X-ray diffraction were obtained by slow evaporation of a solution in petroleum ether and ethyl acetate (2:1). The crystal structure and the packing of the molecules in the unit cell of **4** were showed in Figs. 1, 2, respectively. The selected bond lengths and angles were listed in Table 3. Compound **4** crystallizes in the triclinic system with unusual space group P1. There are two molecules in the asymmetric unit and it appears that the two unique molecules only differ by a small change in their configurations. P1 is a chiral space group and the molecules are chiral. But the absolute configuration for the structure is not determined and the structure presented represents a postulated absolute configuration. Although there are no hydrogen bonds, there are numerous short contacts. For example, the attraction of H43–O4 and H20–O8 make a close pair of the two molecules. The steroid skeleton does not significantly differ from mestranol as observed in the crystal structure [12]. The molecules are arranged in a head-to-tail fashion, similar to that in 17α-ethinyl-3-methoxyestra-1,3,5(10),9(11)-tetraene-17-ol [13] but different from the head-to-head fashion as observed in mestranol [12] without intra- and intermolecular hydrogen bonding. In the molecular structure, rings B, C and D adopt distorted chair, approximately planar, and envelope conformation, respectively.

In conclusion, 17α-ethinyl-17-hydroxy-3-methoxyestra-1,3,5(10)-triene-6-one-17- acetate was synthesized by an efficient three-step sequence starting from norethindrone. X-Ray crystal structure of the new mestranol acetate revealed the head-to-tail molecular arrangement fashion and ring conformation.

Supplementary Material

CCDC-699083 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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References

1. Rao PN (1974) Steroids 23:173
2. Kazhnitková H, Zamrazilová L, Hill M, Lapčík O, Pouzar V, Hampl R (2007) Steroids 72:342

3. Jordan VC, Brodie AMH (2007) Steroids 72:7
4. Saxena HO, Faridi U, Kumar JK, Luqman S, Darokar MP, Shanker K, Chanotiya CS, Gupta MM, Negi AS (2007) Steroids 72:892
5. Li H, Song Y, Peng X (2008) Steroids 73:488
6. Li J, Li H, Li Y (2010) Chem Cent J 4:18
7. Ekhato IV, Hurley T, Lovdahl M, Revitte TJ, Guo L, Huang Y, Clipper S, Colson C (2002) Steroids 67:165
8. Bruker (2001) SMART and SAINT. Bruker AXS Inc, Madison
9. Sheldrick GM (2008) Acta Crystallogr A64:112
10. Hofmeister H, Laurent H, Wiechert R (1973) Chem Ber 106:723
11. Cotter ML, Levine SD, Mallory R, Shaw C (1978) Tetrahedron Lett (22):1939
12. Steiner T, Lutz B, van der Maas J, Veldman N, Schreurs AMM, Kroon J, Kanters JA (1997) Chem Commun (2):191
13. Li H, Song Y, Ge F (2008) Acta Crystallogr E 64:o783