Tetrahedron 66 (2010) 4068–4072

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

One-pot ethynylation and catalytic desilylation in synthesis of mestranol and levonorgestrel

Fung Fuh Wong [a,*], Shih Hsien Chuang [b], Sheng-chuan Yang [b], Yu-Hsiang Lin [b], Wen-Che Tseng [a], Shao-Kai Lin [c], Jiann-Jyh Huang [b,*]

[a] Graduate Institute of Pharmaceutical Chemistry, China Medical University, No. 91, Hsueh-Shih Rd., Taichung, Taiwan 40402, ROC
[b] Development Center for Biotechnology, No. 101, Lane 169, Kangning St., Xizhi City, Taipei County, Taiwan 221, ROC
[c] Sustainable Environment Research Center, National Cheng Kung University, No. 500, Sec. 3, An-ming Rd., Tainan City, Taiwan 709, ROC

ARTICLE INFO

Article history:
Received 22 December 2009
Received in revised form 1 April 2010
Accepted 2 April 2010
Available online 8 April 2010

Keywords:
Ethynylation
Catalytic desilylation
Propargyl alcohol
Trimethylsilylacetylide
One pot

ABSTRACT

A one-pot ethylnylation and catalytic desilylation reaction was developed for the synthesis of mestranol and levonorgestrel. Addition of trimethylsilylacetylide to the carbonyl group at C-17 of the steroids yielded the C-17α-trimethylsilylacetylenyl adducts, which were desilylated with a catalytic amount of TBAF (0.050 equiv) in one pot to provide the corresponding mestranol and levonorgestrel both in 90% yields. A plausible mechanism was proposed for the catalytic desilylation through the regeneration of the fluoride ion from the reaction of alkoxide on the steroid with Me_3SiF. The one-pot ethynylation and catalytic desilylation methodology provided an alternative route and avoided the traditional use of flammable and explosive acetylene gas toward the synthesis of mestranol and levonorgestrel.

1. Introduction

Trimethylsilylacetylide is mono-protected acetylene, which can introduce a terminal ethynyl group onto a molecule through nucleophilic substitution or addition reaction followed by subsequently removal of the silyl group. It forms propargyl alcohols when reacting with aldehydes or ketones, which are the key intermediates for the synthesis of natural products such as prostaglandins,[1] steroids,[2] carotenoids,[3] and leukotrienes.[4] In some synthetic steroids, the equipped propargyl alcohol moiety is to delay their being hepatic inactivation and to reduce the androgenic effects.[5] Mestranol[6] and levonorgestrel[7] are two important steroidal oral contraceptives possessing the structure feature at their C-17 position.

Mestranol and levonorgestrel are traditionally prepared by the use of metal acetylide from explosive acetylene gas.[8] As a safer ethynylation agent, trimethylsilylacetylide was only used to synthesize some structurally related compounds[9] and the reaction conditions for the desilylation step are not well-studied. Methanolic NaOH, ethanolic KOH,[10] or sodium or potassium carbonate in MeOH[11] was used for desilylation in most of the cases if the substrate is tolerate to the alkaline condition. Tetrabutylammonium fluoride (TBAF)[12] is a good substitute for its good solubility in organic solvent. However, desilylation with TBAF often requires at least one molar equivalent or excess of the reagent.[9]

In this paper, we reported our research on the catalytic desilylation of trimethylsilylacetylenyl group by TBAF. The reaction only proceeded in one-pot condition without the isolation of adducts from the reaction of the steroids with lithium trimethylsilylacetylide. In control experiment where the isolation of adducts were conducted, the catalytic desilylation did not occur. We proposed a plausible mechanism accounting for the result by the regeneration of the desilylating fluoride from the Me_3SiF to deprotect the Me_3Si-equipped steroids consecutively.

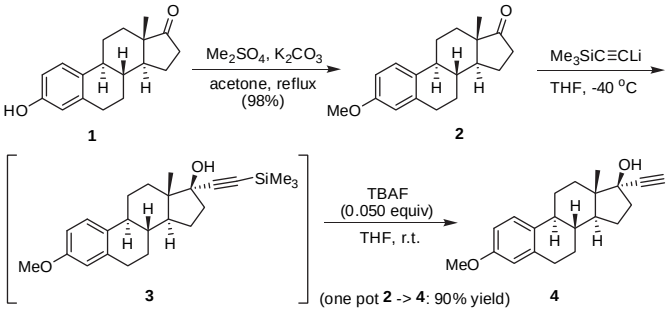
2. Result and discussion

For the synthesis of mestranol (**4**), estrone (**1**) was treated with dimethylsulfate in the presence of K_2CO_3 to provide 3-*O*-methylated-estrone **2** in 98% yield (see Scheme 1).[13] Compound **2** was served as a model for the study of one-pot enthynylation and desilylation. We first optimized the enthynylation step by treating compound **2** with 1.0, 2.0, 3.0, and 4.0 equiv of the freshly prepared lithium trimethylsilylacetylide ($LiC{\equiv}CSiMe_3$) in THF at −40 °C for 1.0 h and at room temperature for 30 min. The C-17α-trimethylsilylacetylenyl adduct **3** was isolated in 75%, 92%, 98%, and 95% yields, respectively. As a result, the use of lithium trimethylsilylacetylide

* Corresponding authors. Tel.: +886 2 2695 6933x2501; fax: +886 2 2695 7474; e-mail address: lukehuang0226@gmail.com (J.-J. Huang).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.04.008

was fixed to 3.0 equiv for the following study. For the one-pot reaction, compound **2** was reacted with lithium trimethylsilylacetylide followed by addition of different equivalents of TBAF (Scheme 1). After warmed up to room temperature and stirred for additional 1.0 h, the reaction gave the resultant mestranol (**4**)[6] in different yields as show in Table 1. We found the use of 0.050 equiv of TBAF provided **4** in satisfactory yields (90%, **2**→**4**) and the excess addition of TBAF did not improve the yield significantly.



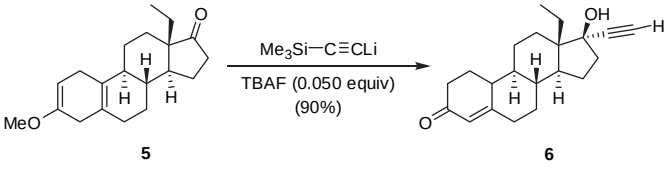
Scheme 1.

Table 1
Reaction of compound **2** with 3.0 equiv of lithium trimethylsilylacetylide followed by different equivalents of TBAF

Equivalents of TBAF	1.0	0.50	0.10	0.050	0.030
Yield of **4** (%)	91	90	92	90	83

In control experiment, the isolated compound **3** was allowed to react with 0.050 equiv of TBAF. The reaction provided only trace amount mestranol (**4**). It required at least 1.2 equiv of TBAF to give 92% yield of the product **4** from **3** and consistent with the results from conventional desilylation of propargyl alcohol by TBAF from literature.[14,15] When 1.0 equiv of *n*-BuLi was added to compound **3** followed by addition of catalytic amount of TBAF (0.050 equiv) at −40 °C, the reaction proceeded smoothly to give **4** in 90% yield. The results indicated that the presence of strong alkaline was crucial for the conversion of **2** to **4** by catalytic desilylation. We envisioned that the regeneration of fluoride might occur in one-pot condition after the catalytic amount TBAF was consumed to form Me_3SiF.

The same method could also be applied to the synthesis of levonorgetrel (**6**, see Scheme 2). 3-Methoxy-18-methylandrosta-2,5-10-dien-17-one (**5**) was treated with 3.0 equiv of lithium trimethylsilylacetylide followed by 0.050 equiv of TBAF in one pot. Levonorgetrel (**6**) was obtained in 90% yield and its physical properties and spectroscopic characteristics were consistent with the published data.[16] The one-pot reaction provided mestranol (**4**) and levonorgetrel (**6**) in comparable yields with the stepwise synthesis (for **4**, 90–89%; for **6**, 90–91%).



Scheme 2.

Application of the one-pot desilylation reaction to epiandrosterone (**7**), dehydroepiandrosterone (**8**), and pregnenolone (**9**) also generated the corresponding steroidal propargyl alcohols **10**, **11**, and **12** in 65%, 71%, and 75% yield, respectively (Chart 1). Four equivalents of $LiC{\equiv}CSiMe_3$ were used in the reaction considering the presence of acidic hydroxyl group at the C-3 position of compounds **7**–**9**. The result demonstrated substrates with hydroxyl group and alkene moiety were tolerable in the reaction. Moreover, high diastereoselectivity was also obtained on steroid **9** with acyclic carbonyl group to provide compound **12** as the sole product.

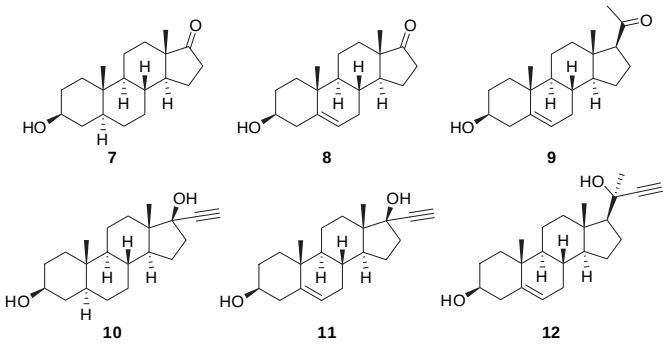
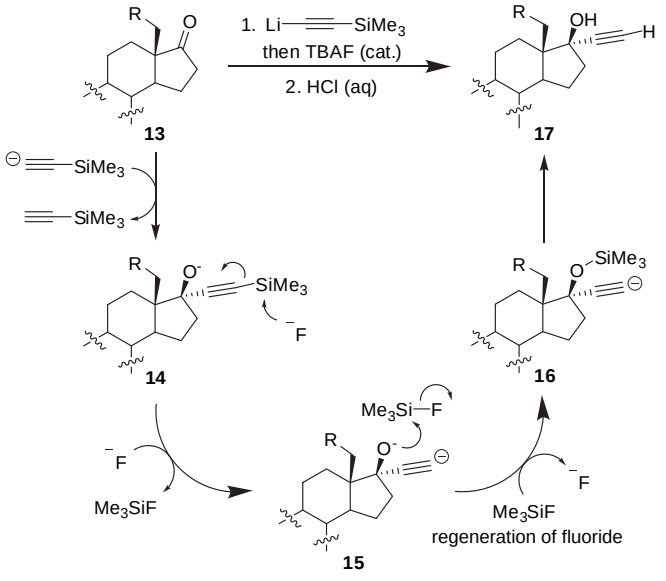


Chart 1.

A plausible mechanism for the one-pot ethynylation and catalytic desilylation reaction was proposed in Scheme 3. Trimethylsilylacetylide underwent nucleophilic addition to the carbonyl group on steroid **13** to generate intermediate **14**, which was desilylated by an organic-soluble fluoride from the subsequently added TBAF to generate dianion **15** and trimethylsilyl fluoride (Me_3SiF). The alkoxide in dianion **15** would replace the fluoride in Me_3SiF to form intermediate **16** and regenerate the fluoride ion to desilylate another **14**. Upon workup, the removal of $SiMe_3$ group from **16** by H_2O took place to form the final product **17**. Since Me_3SiF was reported to react with NaOH in cold ether solution to give Me_3SiOH for preparative purpose,[17] we considered the reaction step for the regeneration of fluoride was feasible. Another evidence comes from the reaction of 1-trimethylsilyl-2,2-difluorocyclopropane derivative with benzaldehyde in the presence of catalytic amount TBAF reported by Shibuya et al.[18] A mechanism for the regeneration of TBAF from Me_3SiF is also proposed.



Scheme 3.

In summary, we developed a one-pot synthesis of mestranol (**4**) and levonorgetrel (**6**) by use of lithium trimethylsilylacetylide followed by a catalytic amount of TBAF. The reaction provided mestranol (**4**) and levonorgetrel (**6**) both in 90% yield, which were similar to that in stepwise synthesis by isolating

C-17α-trimethylsilylacetylenyl adducts. A plausible mechanism was proposed for catalytic desilylation through the regeneration of fluoride from the nucleophilic replacement of Me_3SiF by alkoxide in the reaction mixture. This one-pot ethynylation and catalytic desilylation avoided the traditional use of flammable and explosive ethynyl gas for the introduction of acetylene group onto the steroids.

3. Experimental section

3.1. General procedure

All chemicals were reagent grade and used as purchased. All reactions were carried out under argon or nitrogen atmosphere and monitored by TLC. Flash column chromatography was carried out on silica gel (230–400 mesh). Ethyl acetate and hexanes, purchased from Mallinckrodt Chemical Co., were dried and distilled from CaH_2. Tetrahydrofuran (THF, reagent grade, from Mallinckrodt Chemical Co.) was dried by distillation from CaH_2 and subsequently distilled from sodium benzophenone ketyl under nitrogen. Acetone was distilled from CaH_2 and stored over 4 Å molecular sieves under nitrogen. Potassium carbonate was purchased from Showa Chemical Co. Dimethylsulfate and tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF) were purchased from Arcos Organics. Estron (**1**) and 3-methoxy-18-methylesta-2,5-10-dien-17-one (**5**) were purchased from Ashland Specialty Chemical Company. Epiandrosterone (**7**), dehydroepiandrosterone (**8**), and pregnenolone (**9**) were purchased from TCI. The following compounds and reagents were purchased from Aldrich Chemical Co.: *n*-butyllithium (1.6 M solution in hexanes), absolute ethanol, and trimethylsilylacetylene.

Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254) purchased from Merck Inc. Mixtures of ethyl acetate and hexanes were used as eluants. Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene absorption at 1601 cm^{-1}. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (400 MHz or 500 MHz) spectrometer by use of $CDCl_3$ as solvent. Carbon-13 NMR spectra were obtained on a Bruker (100 MHz) spectrometer by used of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). ESIMS spectra were obtained from an Applied Biosystems API 300 mass spectrometer. High-resolution mass spectra were obtained by means of a JEOL JMS-HX110 mass spectrometer.

3.2. Preparation of lithium trimethylsilylacetylide

To a solution of trimethylsilylacetylene (3.0 equiv to compounds **2** and **5**; 4.0 equiv to compounds **7**–**9**) in THF was added *n*-butyllithium (1.6 M solution in hexanes, 2.9 equiv to compounds **2** and **5**) at −40 °C. The reaction mixture was warmed up to −20 °C and stirred for 1.0 h to give the desired lithium trimethylsilylacetylide solution.

3.3. 3-Methoxy-estra-1,3,5(10)-trien-17-one (2)

To a solution of estron (**1**, 100 g, 0.370 mol, 1.0 equiv) in acetone (1.2 L) was added potassium carbonate (511 g, 3.70 mol, 10 equiv) and dimethylsulfate (233 g, 1.85 mol, 5.0 equiv). The reaction mixture was heated at reflux for 2.0 h and the desired crude product was precipitated by slow addition of H_2O (1.6 L). The solution was cooled and stirred in ice-bath for 1.0 h and the precipitate was collected, washed with cold water (800 mL), and dried in vacuum oven at 50–60 °C for 12 h to give **2** (104 g, 0.366 mmol) as white solids in 99% yield: mp (recrystallized from ethanol) 172–174 °C; TLC R_f 0.43 (40% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (s, 3H, CH_3), 1.40–1.61 (m, 7H), 1.90–2.40 (m, 4H), 2.45–2.58 (m, 2H), 2.88–2.92 (d, *J*=11.6 Hz, 2H, C(=O)CH_2), 3.78 (s, 3H, OCH_3), 6.65 (d, *J*=3.6 Hz, 1H, ArH), 6.73 (dd, *J*=11.6, 3.6 Hz, 1H, ArH), 7.21 (d, *J*=11.6 Hz, 1H, ArH); IR (diffuse reflectance) 2914 (w, C=C–H), 1903 (m), 1737 (s, C=O), 1504 (s, C=C), 1452 (s), 1315 (s), 1245 (s), 1164 (m), 1164 (m), 1037 (s), 1014 (m), 960 (m), 906 (m), 845 (m), 819 (m), 787 (m), 704 (m), 641 (m), 578 (m), 559 (m), 493 (m),451 (s) cm^{-1}; MS *m*/*z* (relative intensity) 284 (M^+, 100), 256 (4), 227 (9), 199 (30), 187 (15), 174 (10),160 (25), 159 (10), 148 (7), 134 (6), 115 (6), 91 (5), 55 (3).

3.4. 17α-Trimethylsilylacetylenyl-3-methoxy-1,3,5(10)-estratrien-17β-ol (3)

3-Methoxy-estra-1,3,5(10)-trien-17-one (**2**, 20.0 g, 70.4 mmol, 1.0 equiv) was dissolved in anhydrous THF (200 mL) and reacted with lithium trimethylsiylacetylide solution (3.0 equiv) at −40 °C for 1.0 h. The reaction mixture was warmed up to room temperature and stirred for another 30 min. The solution was neutralized with aqueous HCl (3.0 N) and H_2O (200 mL) was then added. The organic solvents were removed under vacuum and the resultant solution was extracted with EtOAc (300 mL). The organic layer was washed with brine (50 mL×2), dried over $MgSO_4$ (s), filtered, and concentrated under reduced pressure to give **3** (26.5 g, 68.9 mmol) as off-white solids in 98% yield: TLC R_f 0.35 (25% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.18 (s, 9H, 3×CH_3), 0.87 (s, 3H, CH_3), 1.36–1.58 (m, 4H), 1.64–2.04 (m, 8H), 2.16–2.48 (m, 3H), 2.85 (br s, 1H, OH), 3.78 (s, 3H, OCH_3), 6.63 (d, *J*=3.6 Hz, 1H, ArH), 6.71 (dd, *J*=11.2, 3.6 Hz, 1H, ArH), 7.23 (d, *J*=11.2 Hz, 1H, ArH); IR (diffuse reflectance) 3484 (br, OH), 2932 (w, C=C–H), 2158 (s, C≡C), 1738 (m), 1609 (s, C=C), 1583 (m), 1499 (s), 1454 (m), 1282 (m), 1250 (s), 1145 (m), 1042 (s), 975 (m), 934 (m), 888 (m), 842 (b), 781 (m), 760 (m), 721 (m), 702 (m), 627 (m), 566 (m), 452 (s) cm^{-1}; MS *m*/*z* (relative intensity) 384 (M^+, 10), 369 (65), 368 (10), 294 (5), 245 (75), 229 (15), 206 (15), 153 (22), 115 (30), 105 (30), 99 (44), 91 (52), 73 (100), 65 (28); HRMS calcd for $C_{24}H_{34}O_2Si$ 382.2328, found 382.2331.

3.5. Mestranol (4)

Compound **2** (12.5 g, 44.0 mmol, 1.0 equiv) was dissolved in anhydrous THF (100 mL) and reacted with lithium trimethylsiylacetylide solution (3.0 equiv) at −40 °C for 1.0 h. The reaction was added with TBAF (1.0 M solution in THF, 0.050 equiv, 2.20 mL) and warmed up to room temperature and stirred for 1.0 h. The reaction mixture was neutralized with aqueous HCl (1 N) and concentrated under reduced pressure to remove THF. The aqueous solution was then added with additional H_2O (100 mL) and extracted with EtOAc (200 mL×2). The organic layer was washed with brine (50 mL×2) and concentrated under reduced pressure. The resultant light yellow solids were recrystallized from ethanol to give the desired **4** (12.3 g, 39.6 mmol) in 90% yield: mp (recrystallized from ethanol) 151–154 °C; TLC R_f 0.27 (25% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (s, 3H, CH_3), 1.39–1.56 (m, 4H), 1.64–2.08 (m, 8H), 2.10–2.42 (m, 3H), 2.81 (s, 1H, C≡C–H), 2.85 (br s, 1H,, OH), 3.78 (s, 3H, OCH_3), 6.63 (d, *J*=3.6 Hz, 1H, ArH), 6.71 (dd, *J*=11.4, 3.6 Hz, 1H, ArH), 7.21 (d, *J*=11.4 Hz, 1H, ArH); IR (diffuse reflectance) 3525 (br, OH), 3287 (s, C≡C–H), 2977 (s, C=C–H), 2092 (m, C≡C), 1612 (s, C=C), 1506 (m), 1448 (m), 1324 (m), 1254 (m), 1254 (s), 1061 (m), 1036 (s), 962 (m), 904 (m), 843 (m), 832 (b), 788 (m), 655 (m), 620 (m) cm^{-1}; MS *m*/*z* (relative intensity) 310 (M^+, 44), 284 (4), 263 (2), 253 (4), 242 (23), 227 (100), 213 (10), 199 (12), 186 (13), 174 (35), 159 (14), 147 (24), 129 (10), 115 (11), 97 (12), 83 (12), 69 (13), 55 (18).

3.6. Levonorgestrel (6)

Compound **5** (13.4 g, 44.6 mmol, 1.0 equiv) was dissolved in anhydrous THF (100 mL) and reacted with lithium trimethylsilylacetylide solution (3.0 equiv) at −40 °C for 1.0 h. The reaction was added with TBAF (1.0 M solution in THF, 0.050 equiv, 2.25 mL) and warmed up to room temperature and stirred for 1.0 h. The reaction mixture was neutralized with aqueous HCl (1 N) and concentrated under reduced pressure to remove THF. The aqueous solution was then added with additional H_2O (100 mL) and extracted with EtOAc (200 mL×2). The organic layer was washed with brine (50 mL×2) and concentrated under reduced pressure. The resultant light yellow solids were recrystallized from ethanol to give the desired **4** (12.6 g, 40.3 mmol) in 90% yield: mp (recrystallized from ethanol) 171–174 °C; TLC R_f 0.26 (25% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02 (s, 3H, CH_3), 0.80–1.11 (m, 4H), 1.00 (t, J=10.0 Hz, 3H, CH_3), 1.12–1.80 (m, 3H), 1.60 (q, J=10.0 Hz, 2H, CH_2), 1.64 (br s, 1H, OH), 1.82–2.56 (m, 12H), 2.60 (s, 1H, C≡C–H), 5.89 (s, 1H, C(=O)CH=C); IR (diffuse reflectance) 3347 (br, OH), 2932 (w, C=C–H), 1653 (s, C=O), 1617 (m, C=C), 1451 (m),1364 (m), 1270 (m), 1210 (m), 1131 (m), 1066 (s), 969 (m), 925 (m), 887 (m), 854 (b), 814 (m), 766 (m), 691 (s), 657 (s), 608 (m), 564 (m), 512 (m), 465 (m) 428 (m) cm^{-1}; MS m/z (relative intensity) 312 (M^+, 100), 283 (20), 265 (12), 245 (76), 229 (35), 217 (15), 203 (16), 187 (18), 160 (22), 135 (27), 105 (44), 91 (70), 79 (46), 67 (32), 55 (28).

3.7. 5α,17α-Pregn-20-yne-3β,17β-diol (10)[19]

Compound **7** (503 mg, 1.74 mmol, 1.0 equiv) was dissolved in anhydrous THF (20 mL) and reacted with lithium trimethylsiylacetylide solution (4.0 equiv) at −40 °C for 1.0 h. The reaction was added with TBAF (1.0 M solution in THF, 0.050 equiv, 87 μL) and warmed up to room temperature and stirred for 1.0 h. The reaction mixture was neutralized with aqueous HCl (1 N) and concentrated under reduced pressure to remove THF. The aqueous solution was then added with additional H_2O (20 mL) and extracted with EtOAc (50 mL×2). The organic layer was washed with brine (10 mL×2) and concentrated under reduced pressure. The resultant light yellow solids were purified by column chromatography on silica gel (20% EtOAc in hexanes as eluant) to give the desired **10** (358 mg, 1.13 mmol) in 65% yield: mp (recrystallized from EtOAc) 261–262 °C; TLC R_f 0.12 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.82 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.92–1.95 (m, 22H), 2.56 (s, 1H, C≡C–H), 3.56–3.61 (m, 1H, C-3H); IR (diffuse reflectance) 3429 (br, OH), 3264 (s), 2929 (s), 2857 (s), 1468 (m), 1446 (m), 1381 (s), 1127 (s), 1051 (s), 1025 (s), 976 (m), 841 (m), 701 (s), 638 (m), 615 (m), 554 (m), 473 (m) cm^{-1}; ESIMS m/z 315.0 $(M-H)^-$.

3.8. 17α-Ethynylandrost-5-ene-3β,17β-diol (11)[20]

Compound **8** (512 mg, 1.78 mmol, 1.0 equiv) was dissolved in anhydrous THF (20 mL) and reacted with lithium trimethylsiylacetylide solution (4.0 equiv) at −40 °C for 1.0 h. The reaction was added with TBAF (1.0 M solution in THF, 0.050 equiv, 89 μL) and warmed up to room temperature and stirred for 1.0 h. The reaction mixture was neutralized with aqueous HCl (1 N) and concentrated under reduced pressure to remove THF. The aqueous solution was then added with additional H_2O (20 mL) and extracted with EtOAc (50 mL×2). The organic layer was washed with brine (10 mL×2) and concentrated under reduced pressure. The resultant light yellow solids were purified by column chromatography on silica gel (15% EtOAc in hexanes as eluant) to give the desired **11** (398 mg, 1.27 mmol) in 71% yield: mp (recrystallized from acetone/ether) 241–242 °C; TLC R_f 0.19 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.02–2.31 (m, 19H), 2.56 (s, 1H, C≡C–H), 3.49–3.54 (m, 1H, C-3H); 5.35 (d, J=5.0 Hz, 1H, C=CH); IR (diffuse reflectance) 3430 (br, OH), 3263 (s), 2936 (s), 2897 (s), 2859 (m), 2826 (m), 1650 (w), 1459 (m), 1436 (m), 1383 (s), 1249 (m), 1200 (w), 1162 (w), 1134 (m), 1053 (s), 1038 (s), 1023 (s), 842 (s), 701 (s), 623 (m), 582 (w), 553 (w), 483 (w); ESIMS m/z 313.0 $(M-H)^-$.

3.9. 24-Norchol-5-en-22-yn-3β-ol (12)[21]

Compound **9** (533 mg, 1.68 mmol, 1.0 equiv) was dissolved in anhydrous THF (20 mL) and reacted with lithium trimethylsiylacetylide solution (4.0 equiv) at −40 °C for 1.0 h. The reaction was added with TBAF (1.0 M solution in THF, 0.050 equiv, 84 μL) and warmed up to room temperature and stirred for 1.0 h. The reaction mixture was neutralized with aqueous HCl (1 N) and concentrated under reduced pressure to remove THF. The aqueous solution was then added with additional H_2O (20 mL) and extracted with EtOAc (50 mL×2). The organic layer was washed with brine (10 mL×2) and concentrated under reduced pressure. The resultant light yellow solids were purified by column chromatography on silica gel (20% EtOAc in hexanes as eluant) to give the desired **11** (432 mg, 1.26 mmol) in 75% yield: mp (recrystallized from EtOH) 144–146 °C; TLC R_f 0.13 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.10–2.30 (m, 23H), 2.52 (s, 1H, C≡C–H), 3.50–3.54 (m, 1H, C3-H), 5.35 (d, J=5.5 Hz, 1H, C=CH); IR (diffuse reflectance) 3391 (br, OH), 2931 (s), 2898 (s), 2868 (s), 1672 (w), 1623 (w), 1450 (m), 1370 (s), 1249 (w), 1195 (w), 1127 (m), 1042 (s), 1024 (s), 953 (m), 919 (m), 870 (m), 841 (s), 808 (m), 759 (w), 736 (w), 651 (m), 592 (w), 571 (w), 500 (w), 457 (w); ESIMS m/z 341.0 $(M-H)^-$.

Acknowledgements

We are grateful to the China Medical University (CMU96-126 & CMU98-S-40) and the National Science Council of Republic of China (NSC98-2221-E-039-003-) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.04.008. This data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Nicolau, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 3548–3551.
2. Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8341–8343.
3. Chan, K.-K.; Cohen, N. C.; DeNoble, J. P.; Specian, A. C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497–3505.
4. Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 8323–8325.
5. (a) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Butterworth: London, 1988; (b) Krouse, I. H.; Wenthold, P. G. *J. Am. Soc. Mass Spectrom.* **2005**, *16*, 697–707.
6. El-Obeid, H. A.; Al-Badr, A.; Mestranol, A. *Anal. Profiles Drug Subs.* **1982**, *11*, 375–406.
7. Tuba, Z.; Bardin, C. W.; Dancsi, A.; Francsics-Czinege, E.; Molnár, C.; Csörgei, J.; Falkay, G.; Koide, S. S.; Kumar, N.; Sundaram, K.; Dukát-Abrók, V.; Balogh, G. *Steroids* **2000**, *65*, 266–274.
8. For the use of acetylene to synthesize mestranol (**4**) and levonorgestrel (**6**), see: (a) Colton, F. B.; Nysted, L. N.; Riegel, B.; Raymond, A. L. *J. Am. Chem. Soc.* **1957**, *79*, 1123–1127; (b) Djerassi, C.; Miramontes, L.; Rosenkranz, G.; Sondheimer, F. *J. Am. Chem. Soc.* **1954**, *76*, 4092–4094; (c) Kanojia, R. M.; Allen, G. O.; Killinger, J. M.; McGuire, J. L. *J. Med. Chem.* **1979**, *22*, 1538–1541; (d) Peters, R. H.; Crowe, D. F.; Avery, M. A.; Chong, W. K. M.; Tanabe, M. *J. Med. Chem.* **1988**, *31*, 572–576; (e) Rosernberger, M.; Fraher, T. P.; Saucy, G. *Helv. Chim. Acta* **1971**, *54*, 2857–2870; (f) Baier, H.; Dürner, G.; Quinkert, G. *Helv. Chim. Acta* **1985**, *68*, 1054–1068; (g) FerriñTo, S.; López-Tapia, F.; Salgado-Zamora, H. *Synth. Commun.* **1996**, *26*, 1461–1465.
9. For examples, see: (a) Sierra, M. A.; Torres, M. R. *J. Org. Chem.* **2007**, *72*, 4213–4219; (b) Page, P. C. B.; Hussain, F.; Bonham, N. M.; Morgan, P.; Maggs, J. L.; Park, B. K. *Tetrahedron* **1991**, *47*, 2871–2878; (c) Ramírez-López, P.; de la Torre, M. C.;

Montenegro, H. E.; Asenjo, M.; Sierra, M. A. *Org. Lett.* **2008**, *10*, 3555–3558; (d) Jones, G. B.; Hynd, G.; Wright, J. M.; Purohit, A.; Plourde, G. W., II; Huber, R. S.; Mathews, J. E.; Li, A.; Kilgore, M. W.; Bubley, G. J.; Yancisin, M.; Brown, M. A. *J. Org. Chem.* **2001**, *66*, 3688–3695.

10. For the use of methanolic NaOH or ethanolic KOH for desilylation, see: (a) Tamura, Y.; Yakura, T.; Haruta, J.-i.; Kita, Y. *Tetrahedron Lett.* **1985**, *26*, 3837–3840; (b) Grangier, G.; Trigg, W. J.; Lewis, T.; Rowan, M. G.; Potter, B. V. L.; Blagbrough, I. S. *Tetrahedron Lett.* **1998**, *39*, 889–892; (c) Johnson, W. S.; Frei, B.; Gopalan, S. A. *J. Org. Chem.* **1981**, *46*, 1512–1513.
11. For the use of sodium or potassium carbonate in MeOH for desilylation, see: (a) Arndt, H.-D.; Polborn, K.; Koert, U. *Tetrahedron Lett.* **1997**, *38*, 3879–3882; (b) Trost, B. M.; Rhee, Y. H. *J. Am. Soc. Chem.* **2002**, *124*, 2528–2533; (c) Nomura, I.; Mukai, C. *J. Org. Chem.* **2004**, *69*, 1803–1812.
12. For the use TBAF as desilylating agent, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, NY, 1999.
13. Nishino, H.; Tsunoda, K.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 545–550.
14. McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304–4309.
15. Lin, M.-Y.; Das, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 9340–9341.
16. Smith, H.; Hughes, G. A.; Douglas, G. H.; Wendt, G. R.; Buzby jun, G. C.; Edgren, R. A.; Fisher, J.; Foell, T.; Gadsby, B.; Hartley, D.; Herbst, D.; Jansen, A. B. A.; Ledig, K.; McMenamin, J.; McMenamin, J.; Pattison, T. W.; Phillips, P. C.; Rees, J.; Siddall, J.; Siuda, J.; Smith, L. L.; Tokolics, J.; Watson, D. H. P. *J. Chem. Soc.* **1964**, 4472–4492.
17. Sommer, L. H.; Pietrusza, E. W.; Whitmore, F. C. *J. Am. Chem. Soc.* **1946**, *68*, 2282–2284.
18. Shibuya, A.; Pietz, S.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 5537–5540.
19. Salman, M.; Chamness, G. C. *J. Med. Chem.* **1991**, *34*, 1019–1024.
20. Marwah, P.; Marwah, A.; Lardy, H. A.; Miyamoto, H.; Chang, C. *Bioorg. Med. Chem.* **2006**, *14*, 5933–5947.
21. Burger, A.; Colobert, F.; Hetru, C.; Luu, B. *Tetrahedron* **1988**, *44*, 1141–1152.