Steroids 77 (2012) 467–470

Contents lists available at SciVerse ScienceDirect

Steroids

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

A simple and convenient synthesis of 2-methoxyestradiol from estrone

A.P. Prakasham, Karuna Shanker, Arvind S. Negi *

Chemical Sciences Division, Central Institute of Medicinal and Aromatic Plants (CIMAP–CSIR), P.O. CIMAP, Kukrail Picnic Spot Road, Lucknow, 226015 UP, India

ARTICLE INFO

Article history:
Received 21 November 2011
Received in revised form 24 December 2011
Accepted 6 January 2012
Available online 16 January 2012

Keywords:
2-Methoxyestradiol
Breast cancer
Total synthesis

ABSTRACT

A simple and straightforward synthesis of 2-methoxyestradiol have been achieved in nine synthetic steps with 21% of overall yield. Being a convenient process, it can be upscaled to industrial process.

1. Introduction

Oestrogens play an important role in the physiology of female [1]. They function as oestrogen action mediators in reproductive tissues as well as cardiovascular, bone, brain and liver [2]. Hence, they exhibit several interesting biological activities and have been developed as pharmaceuticals for fertility regulation, osteoporosis, breast cancer, inflammation etc. [3]. 2-Methoxyestradiol (**1**, 2ME2) a potent anticancer agent, has shown antiproliferative activity against breast cancer [4], prostate cancer and ovarian cancer [5] in preclinical and clinical studies [6]. It exerts microtubule depolymerisation after binding to the colchicine binding site of tubulin [7] and exhibits antiangiogenic and proapoptotic activity [8]. In a recent study, 2-methoxyestradiol was found to be a promising radiosensitizer in the treatment of radioresistant breast cancer cells [9]. Some of its analogues like ENMD-1198 and STX140, have shown impressive potency in reducing breast cancer induced osteolysis and tumour burden [10] and are under further evaluations. Being an important anticancer drug candidate, several researchers have put their efforts towards the synthesis of 2-methoxyestradiol [11a–h].

In the recent past, eight different syntheses of 2-methoxyestradiol have been developed. Different strategies were adopted to introduce a suitable group at 2-position of estradiol. Leese et al. [11a] used BuLi as a superbase in the key step for introducing an aldehyde group at 2-position at −78 °C. In another method, Kiuru et al. [11b] used superbase (LIDAKOR) for the insertion a hydroxyl group directly at 2-position of substituted estradiol. Fries rearrangement was a crucial step in the methodology by Rao et al. [11c] for introducing an acetyl group at 2-position of estradiol by using $ZrCl_4$. Chen et al. [11d] and Luo et al. [11e] both synthesized 2-methoxyestradiol through 2-bromoestradiol. Wang et al. [11f] transformed 2-formyl bis (MOM) ethers of estradiol to 2-methoxyestradiol in excellent yields. Xin et al. [11g] reported a five step short synthesis of 2-methoxyestradiol, here cupric bromide was used in the key step to introduce a bromo group at 2-position of estradiol unit. Very recently, Akselsen and Hansen [11h] used $MgCl_2$–Et_3N along with paraformaldehyde to formylate 2-position of estradiol. In some of these methods either reaction conditions were very harsh or overall yields were very low. Most of these methodologies are hampered by problems and are not easily adoptable for industrial production. Herein, we report a simple and straight forward methodology for the preparation of 2-methoxyestradiol.

2. Experimental

2.1. General procedures

Estrone was procured from Sigma chemicals, USA. Melting points were determined on E-Z Melt automated melting point apparatus, Stanford Research System, USA and were uncorrected. Reactions were monitored on Merck silica gel thin layer chromatography (TLC, $UV_{254\ nm}$) aluminium sheets. TLC visualization was accomplished by spraying with a solution of 2% ceric sulphate in 10% aqueous sulphuric acid and charring at 80–100 °C. Column chromatography was carried out on silica gel (100–200 mesh, Thomas Baker). Concentration and evaporation of the solvents after reaction or extraction were carried out in rotavapour at reduced pressure. Dry solvents were prepared as per standard methods. NMR experiments (^1H NMR, ^{13}C NMR, DEPT etc.) were obtained

* Corresponding author. Tel.: +91 522 2359632; fax: +91 522 2342666.
E-mail address: arvindcimap@rediffmail.com (A.S. Negi).

0039-128X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.steroids.2012.01.005

on Bruker Avance-300 MHz instrument. Chemical shifts are given in δ ppm with tetramethylsilane (TMS) as an internal standard. The abbreviations of signal patterns are as; s, singlet; d, doublet; t, triplet, m, multiplet & bs, broad singlet. All the ^{1}H and ^{13}C spectral data are reported. Electrospray ionization (ESI) mass spectra were recorded on Shimadzu LC–MS after dissolving the compounds in methanol. FT-IR spectra were recorded on Perkin–Elmer SpectrumBX after making KBr pellets. Nomenclature of steroid derivatives has been given as per the recommendations published by the Joint Commission on the Biochemical Nomenclature (JCBN) of IUPAC [12].

2.2. Chemical synthesis

2.2.1. 2-Formyl, 3-methoxyestra-1,3,5(10)-trien-17-acetate (**5**)

To a stirred cold solution of Estra 1,3,5(10)-trien-3,17-diol-3-methyl ether, 17-acetate (**4**), (1000 mg, 3.04 mmol) in dry dimethylformamide (5 mL, 64 mmol), phosphorus oxychloride (3 mL, 32 mmol) was added dropwise. It was kept at 0–10 °C temperature for 1 h and then heated at 90–100 °C for 4 h. After completion, the reaction mixture was poured into crushed ice and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with water, dried over anhydrous sodium sulphate and concentrated in vacuum. The residue thus obtained was purified through silica gel (100–200 mesh) column by eluting with 5–6% ethyl acetate–hexane. Compound **5** was recrystallised with hexane–chloroform (4:1) to get a creamish white solid (652 mg).

Yield 60%, m.p. 177–178 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.82 (s, 3H, 18-CH_3), 2.05 (s, 3H, OAc), 1.20–2.39 (m, 13H, rest of the 5× CH_2 and 3× CH of steroidal ring), 2.90 (bs, 2H, 6-CH_2), 3.88 (s, 3H, OCH_3), 4.67 (t, 1H, 17-CH, J = 8.40 Hz), 6.67 (s, 1H, 4-CH), 7.73 (s, 1H, 1-CH), 10.38 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.4, 21.6, 23.6, 26.4, 27.3, 27.9, 30.8, 37.1, 38.7, 43.2, 43.9, 50.1, 56.0, 83.0, 112.1, 123.1, 126.0, 133.4, 146.6, 160.2, 171.6, 190.1. Electrospray mass (MeOH): 357.0 $[M+H]^+$, 379 $[M+Na]^+$, 395 $[M+K]^+$; Negative mode: 355 $[M-H]^-$; IR: 3006, 2932, 1729, 1673, 1607, 1494, 1270, and 1041 cm^{-1}.

2.2.2. 2-Formyl, 3-hydroxyestra-1,3,5(10)-trien-17-acetate (**6**)

Compound **5** (500 mg, 1.40 mmol) was dissolved in dry dichloromethane (15 mL). To this stirred solution anhydrous aluminium chloride (600 mg, 4.49 mmol) was added in portions. The reaction mixture was further stirred for 4 h at room temperature. On completion the solvent was evaporated and quenched with dil. HCl (5%, 10 mL), extracted with ethyl acetate (20mL × 3). Organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The residue thus obtained was charged on silica gel column and eluted with ethyl acetate-hexane to get desired product **6** as white solid (378 mg). It was recrystallised with chloroform–hexane (1:3).

Yield 79%, m.p. 177–179 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84 (s, 3H, 18-CH_3), 2.06 (s, 3H, OAc), 1.22–2.35 (m, 13H, rest of the 5× CH_2 and 3× CH of steroidal ring), 2.89 (bs, 2H, 6-CH_2), 4.70 (t, 1H, 17-CH, J = 8.4 Hz), 6.70 (s, 1H, 4-CH), 7.42 (s, 1H, 1-CH), 9.82 (s, 1H, CHO), 10.78 (s, 1H, exchangeable, OH phenolic). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.0, 21.1, 23.2, 26.0, 26.7, 27.5, 30.1, 36.6, 38.1, 42.8, 43.2, 49.7, 82.5, 116.9, 118.9, 130.5, 132.5, 147.9, 159.2, 171.2, 196.1. Electrospray mass (MeOH): 343 $[M+H]^+$, 365 $[M+Na]^+$; IR: 3049, 2966, 2870, 1727, 1652, 1571, 1412, and 1253 cm^{-1}.

2.2.3. 2-Formyl, estra-1,3,5(10)-trien-3,17-diacetate (**7**)

Compound **6** (600 mg, 1.75 mmol) was dissolved in dry pyridine (2 mL). To this solution acetic anhydride (0.5 mL, 5.29 mmol) was added. The reaction mixture was left as such overnight (14–16 h) at room temperature. On completion the reaction mixture was poured into crushed ice, acidified with dil. HCl (5%, 5 mL) and extracted with ethyl acetate (15mL × 3). Organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue thus obtained was recrystallised with chloroform–hexane to get **7** as white crystalline solid (634 mg).

Yield 94%, m.p. 152–153 °C. ^{1}H NMR ($CDCl_3$, 300 MHz):δ 0.84 (s, 3H, 18-CH_3), 2.07 (s, 3H, 17-OAc), 1.20–2.41 (m, 13H, rest of the 5× CH_2 and 3× CH of steroidal ring), 2.38 (s, 3H, 3-OAc), 2.92 (bs, 2H, 6-CH_2), 4.70 (t, 1H, 17-CH, J = 8.4 Hz), 6.87 (s, 1H, 4-CH), 7.77 (s, 1H, 1-CH), 10.1 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.0, 20.8, 21.1, 23.2, 25.9, 26.6, 27.5, 29.8, 36.6, 37.9, 42.8, 43.6, 49.7, 82.5, 123.3, 125.5, 128.8, 138.9, 145.8, 149.0, 169.6, 171.2, 188.8 Electrospray mass (MeOH): 407 $[M+Na]^+$; IR: 2941, 2877, 2765, 1774, 1731, 1687, and 1490 cm^{-1}.

2.2.4. 2-Hydroxy, estra-1,3,5(10)-trien-3,17-diacetate (**8**)

Compound **7** (500 mg, 1.30 mmol) was taken in dry dichloromethane (10 mL). The reaction mixture was stirred with cooling (0–10 °C) for 15 min. To this stirred solution 1 mL saturated Na_2HPO_4 and *m*-chloroperbenzoic acid (1000 mg, 70%, 4.1 mmol) were added. The reaction mixture was further stirred overnight at room temperature. On completion the solvent was evaporated. The residue was dissolved in ethyl acetate (40 mL), washed with 10% sodium bicarbonate solution (20mL × 2). Organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue thus obtained was purified through silica gel column and eluted with ethyl acetate-hexane to get desired product **8** as white crystalline solid (386 mg).

Yield 80%, m.p. 164–165 °C. ^{1}H NMR ($CDCl_3$, 300 MHz):δ 0.82 (s, 3H, 18-CH_3), 2.06 (s, 3H, 17-OAc), 1.26–2.29 (m, 13H, rest of the 5× CH_2 and 3× CH of steroidal ring), 2.34 (s, 3H, 3-OAc), 2.78 (bs, 2H, 6-CH_2), 4.69 (t, 1H, 17-CH, J = 8.1 Hz), 5.17 (bs, 1H, exchangeable, 2-OH, phenolic), 6.71 (s, 1H, 4-CH), 6.95 (s, 1H, 1-CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.4, 21.3, 21.6, 23.6, 26.6, 27.5, 27.9, 29.4, 37.2, 38.6, 43.3, 44.1, 50.1, 83.2, 118.0, 119.6, 133.6, 136.0, 136.9, 144.9, 170.3, 171.9; ESIMS (MeOH): m/z = 395 $[M+Na]^+$; IR: 3415, 2930, 2864, 1766, 1735, 1590, 1506, and 1269 cm^{-1}.

2.2.5. 2-Methoxy, estra-1,3,5(10)-trien-3,17-diacetate (**9**)

Compound **8** (200 mg, 0.54 mmol) was taken in dry acetone (20 mL). To this solution anhydrous potassium carbonate (1 g) and dimethyl sulphate (0.2 mL, 2.1 mmol) were added. The reaction mixture was refluxed for 1 h. On completion, solvent was filtered and evaporated to dryness. The residue was dissolved in ethyl acetate (30 mL), washed with water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue was passed through a small silica gel column and eluted with ethyl acetate-hexane. Compound **9** was obtained as oil (185 mg).

Yield 89%, m.p. oil. ^{1}H NMR ($CDCl_3$, 300 MHz):δ 0.81 (s, 3H, 18-CH_3), 2.05 (s, 3H, 17-OAc), 1.25–2.29 (m, 13H, rest of the 5× CH_2 and 3× CH of steroidal ring), 2.30 (s, 3H, 3-OAc), 2.83 (bs, 2H, 6-CH_2), 3.84 (s, 3H, OCH_3), 4.68 (bs, 1H, 17-CH), 6.56 (s, 1H, 4-CH), 6.93 (s, 1H, 1-CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.4, 21.1, 21.6, 23.6, 26.5, 27.6, 27.9, 29.1, 37.2, 38.6, 43.3, 44.1, 50.1, 56.27, 83.1, 113.1, 120.1, 133.1, 135.55,137.9, 149.1, 169.9, 171.6; ESIMS (MeOH): m/z = 387 $[M+H]^+$, 409 $[M+Na]^+$.

2.2.6. 2-Methoxy, estra-1,3,5(10)-trien-3,17-diol (**10**)

Compound **9** (100 mg, 0.26 mmol) was taken in 5% methanolic KOH (10 mL). The reaction mixture was refluxed for 1 h. On completion the reaction mixture was acidified with 5% dil. HCl with cooling. It was extracted with ethyl acetate (3 × 20 mL), washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The residue thus obtained was purified through silica gel

column by eluting with chloroform–hexane. Compound **10** was obtained as white crystalline solid (64 mg).

Yield 82%, mp 188–189 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.78 (s, 3H, 18-CH_3), 1.18–2.31(m, 13H, rest of the 5× CH_2 and 3× CH of steroidal ring), 2.77 (bs, 2H, 6-CH_2), 3.73 (bs, 1H, 17-CH), 3.86 (s, 3H, 2-OCH_3), 5.43 (s, 1H, exchangeable, Phenolic OH), 6.64 (s, 1H, 4-CH), 6.79 (s, 1H, 1-CH): ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.5, 23.5, 27.0, 27.7, 29.4, 31.0, 37.1, 39.2, 43.7, 44.7, 50.4, 56.4 82.3, 108.5, 115.0, 129.9, 132.1, 143.9, 145.0: ESIMS (MeOH): 325 $[M+Na]^+$, negative mode:301 $[M-H]^-$; IR: 3482, 3404, 2927, 1508, 1274,1207, and 1118 cm^{-1}.

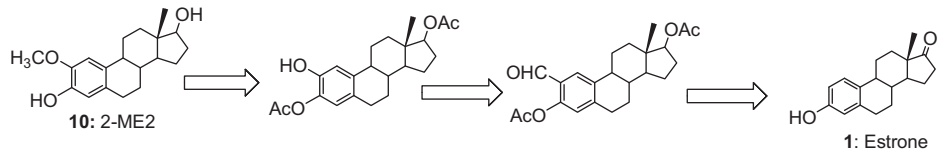
2.3. HPLC analysis of 2-methoxyestradiol

The purity profile of synthesized 2-methoxyestradiol was checked by reverse phase HPLC (Schimadzu) using C-18 (Phenomenex, 4.6 × 250 mm , 5 μm) column and water:acetonitrile = 40:60 as mobile phase with flow rate of 1 mL/min. The 2-ME2 procured from Sigma was used as standard. Retention time (t_R) of 2ME2 was 6.09 min. The absorbance of the compound λ_{max} was determined as 254 nm in PDA. The purity of the synthesized 2ME2 was found to be 91% (% area basis).

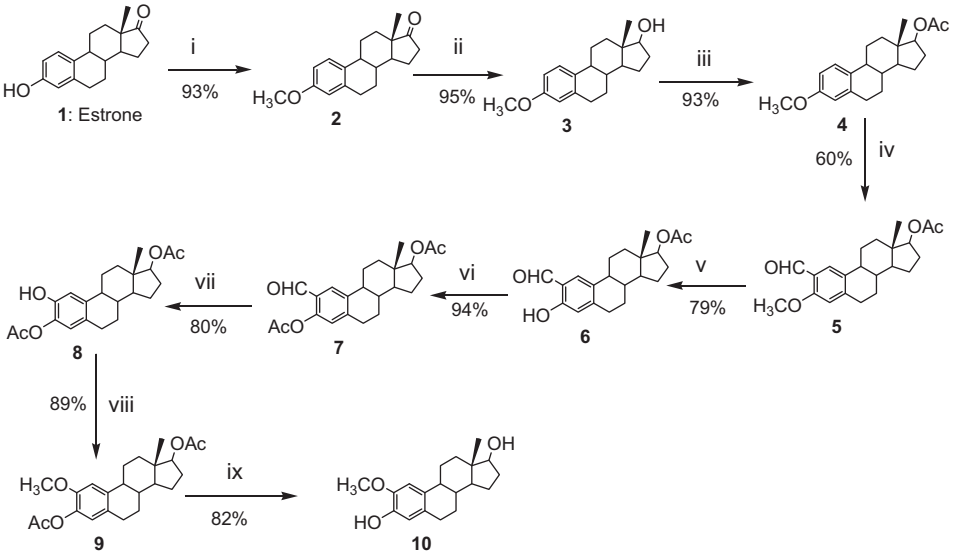
3. Results and discussion

A retrosynthetic plan is as depicted in Scheme 1. For total synthesis (Scheme 2), estrone (**1**) was methylated to estrone 3-methyl ether (**2**) by using dimethyl sulphate/anhydrous potassium carbonate in dry acetone- chloroform (1:1) under reflux conditions. The 17-ketone of estrone 3-methyl ether (**2**) was reduced to alcohol by using sodium borohydride in methanol-dichloroform (1:1) to afford estradiol 3-methyl ether, 17-ol (**3**). The 17-hydroxyl was acetylated with acetic anhydride in dry pyridine to yield estradiol 3-methyl ether, 17-acetate (**4**). A formyl group was introduced at 2-position of **4** by applying Vilsmeier–Haack formylation reaction. Compound **4** was treated with dry DMF-$POCl_3$ system to get the 2-formyl estradiol 3-methyl ether, 17-acetate (**5**) in 60% yield [13]. Aldehyde **5** was demethylated by stirring it with anhydrous aluminium chloride in dry dichloromethane ($AlCl_3$–DCM) at room temperature to get 2-formyl, estradiol 17-acetate (**6**) in 79% yield [14]. The phenolic hydroxyl of **6** was protected as acetyl derivative using dry pyridine-acetic anhydride combination at room temperature to yield 2-formyl, estradiol 3,17-diacetate (**7**) in 94% yield. Compound **7** underwent Baeyer–Villiger oxidation in presence of *m*-chloroperbenzoic acid in the buffered solution of Na_2HPO_4-dichloromethane to yield directly 2-hydroxy estradiol 3,17-diacetate (**8**) in 80% yield. This was a hydrolysed product of estradiol 3,17-diacetate 2-formate. Compound **8** was methylated to 2-methoxy estradiol 3,17-diacetate (**9**) by using dimethyl sulphate in dry acetone in anhydrous potassium carbonate. Compound **9**, on alkaline hydrolysis afforded the desired product 2-methoxyestradiol (**10**) in 82% yield.

In the recent past, several methods were developed to synthesize 2ME2. Some of the methods are good but in most of these either complex reagents or drastic reaction conditions were used. Except one or two, in most of these methodologies total yield are also low. We prepared 2ME2 through a straight forward and simple route. Under the optimized reaction conditions, it was synthesized in 21% of overall yield. In our methodology, there are nine synthetic steps with no drastic reaction conditions. Most of the conversions are very efficient with an average yield of 85% and overall yield of the 21%. The methodology is based on simple and



Scheme 1. Retrosynthetic analysis of 2-methoxyestradiol **1**.



Scheme 2. Reagents and conditions: (i) Me_2SO_4, anhyd. K_2CO_3, acetone:chloroform (1:1), reflux, 93%; (ii) $NaBH_4$, MeOH–DCM (1:1), RT, 95%; (iii) pyridine, Ac_2O, RT, overnight, 93%; (iv) DMF-$POCl_3$, 0–10 °C for 1 h, 90–100 °C for 4 h, 60%; (v) Anhydrous $AlCl_3$–DCM, RT, 3 h, 79%; (vi) pyridine, Ac_2O, RT, overnight, 94%; (vii) *m*-CPBA, DCM, sat. Na_2HPO_4, 0 °C-RT, overnight, 80%; (viii) Me_2SO_4, anhydrous K_2CO_3, acetone, reflux, 1 h, 89%; (ix) 5% KOH in MeOH, reflux, 1 h, 82%.

common reagents. All the steps can be up-scaled to industrial process. The purity of the final product was found to be 91% by RP-HPLC.

In conclusion, a simple and straight forward synthesis of 2-methoxyestradiol has been achieved starting from estrone with an overall yield of 21% in nine steps. No drastic reaction condition was used. This route might provide a new access to the synthesis of new analogues of 2-methoxyestradiol as well which is presently in process.

Acknowledgements

The authors are thankful to Director CSIR-CIMAP for constant help and support. This work was financially supported by CSIR. CSIR Research Internship to AP Prakasham is duly acknowledged.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.steroids.2012.01.005.

References

[1] (a) Katzenellenbogen JA, Katzenellenbogen JA. The 2010 Philip S. Portoghese Medicinal Chemistry Lectureship: addressing the "core issue" in the design of estrogen receptor ligands. J Med Chem 2011;54:5271–82;
(b) Minutolo F, Macchia M, Katzenellenbogen BS, Katzenellenbogen JA. Estrogen receptor β ligands: recent advances and biomedical applications. Med Res Rev 2011;31:364–442.
[2] Sherwin BB. Estrogen and cognitive functioning in women. Endocr Rev 2003;24:133–51.
[3] (a) Ray S, Dwivedy I. Development of estrogen antagonists as pharmaceutical agents. Adv Drug Res 1997;29:171–270;
(b) Jordan VC. Antiestrogens and selective estrogen receptor modulators as multifunctional medicines. 1. Receptor interactions. J Med Chem 2003;46:883–908.
[4] Cho JK, Hong KY, Park JW, Yang HK, Song SC. Injectable delivery system of 2-methoxyestradiol for breast cancer therapy using biodegradable thermosensitive poly(organophosphazene) hydrogel. J Drug Target 2011;19:270–80.
[5] Kato S, Sadarangani A, Lange S, Ana M, Delpiano AM, Vargas M, Brañes J, Carvajal J, Owen GI, Owen GI. 2-Methoxyestradiol mediates apoptosis through caspase-dependent and independent mechanisms in ovarian cancer cells but not in normal counterparts. Reprod Sci 2008;15:878–94.
[6] Nehal J, Lakhani NJ, Sarkar MA, Venitz J, Figg WD. 2-Methoxyestradiol, a promising anticancer agent: metabolism of estrogens. Pharmacotherapy 2003;23:165–72.
[7] (a) D'Amato RJ, Lin CM, Flynn E, Folkman J, Hamel E. 2-Methoxyestradiol, an endogenous mammalian metabolite, inhibits tubulin polymerization by interacting at colchicine site. Proc Natl Acad Sci USA 1994;91:3964–8;
(b) Hamel E, Lin CM, Flynn E, D'Amato RJ. Interactions of 2-methoxyestradiol, an endogenous mammalian metabolite, with unpolymerized tubulin and with tubulin polymer. Biochemistry 1996;35:1304–10.
[8] (a) Fotsis T, Zhang Y, Pepper MS, Adlercreutz H, Montesano R, Nawroth PP, Schweigerer L. The endogenous oestrogen metabolite 2-methoxyestradiol inhibits angiogenesis and suppresses tumour growth. Nature 1994;368:237–9;
(b) Pribluda Jr VS, Gubish ER, LaVallee TM, Treston A, Swartz GM, Green SJ. 2-Methoxyestradiol, a promising anticancer agent:antitumour activity of 2-methoxyestradiol. Cancer Metastasis Rev 2000;19:173–9;
(c) Fukai M, Song J, Zhu BT. Mechanism of 2-methoxyestradiol induced apoptosis and growth arrest in human breast cancer cells. Mol Carcinogen 2009;48:66–78.
[9] Salama S, Diaz-Arrastia C, Patel D, Botting S. Hatch S.2-Methoxyestradion, an endogenous estrogen metabolite, sensitizes radioresistance MCF-7/FIR breast cancer cells through multiple mechanism. Int J Radiat Oncol Biol Phys 2011;80:e231–239.
[10] Thomas JA, Mol IM, Que I, Kaijzel EL, Lowik CWGM. 2-Methoxyestradiol analogue ENMD-1198 reduces breast cancer-induced osteolysis and tumour burden both in vitro and in vivo. Mol Can Ther 2011;10:874–82.
[11] (a) Leese MP, Hejaz HA, Mahon MF, Newman S, Purohit A, Reed MJ, Potter BVL. A ring substituted estrogen-3-O-sulfamates: potent multitargeted anticancer agents. J Med Chem 2005;48:5243–56;
(b) Kiuru PS, Wahala K. Short synthesis of 2-methoxyestradiol and 2-hydroxyestradiol. Steroids 2003;68:373–5;
(c) Rao PN, Cessac JW. A new practical synthesis of 2-methoxyestradiol. Steroids 2002;67:1065–70;
(d) Chen SH, Luo GR, Wu XS, Chen M, Zhao HM. A new synthetic route to 2- and 4-methoxyestradiols by nucleophilic substitution. Steroids 1986;47:63–6;
(e) Luo GR, Chen SH, Zhang HM. Effects of components of crown-CuI mixed catalyst on nucleophilic substitution of bromoestrogen. Chin J Org Chem 1989;9:266–8;
(f) Wang Z, Cushman M. An optimized synthesis of 2-methoxyestradiol, a naturally occurring human metabolite with anticancer activity. Synth Commun 1998;28:4431–7;
(g) Xin M, You Q, Xiang H. An efficient practical synthesis of 2-methoxyestradiol. Steroids 2010;75:53–6;
(h) Akselsen OW, Hansen TV. Ortho-formylation of estrogens. Synthesis of the anti-cancer agent 2-methoxyestradiol. Tetrahedron 2011;67:7738–42.
[12] IUPAC. Joint Commission on Biochemical Nomenclature (JCBN). Nomenclature of steroids. Pure Appl Chem 1989;61:1783–822.
[13] Vilsmeier A, Haack A. Chem Ber 1927;60:119.
[14] Negi AS, Chattopadhyay SK, Srivastava S, Bhattacharya AK. A simple regioselective demethylation of p-aryl methyl ethers using aluminium chloride-dichloromethane system. Synth Commun 2005;35:15–21.