Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5723–5726

A novel and stereoselective synthesis of 7α-alkynylestra-1,3,5(10)-triene-3,17β-estradiol

Naseem Ahmed and Johan E. van Lier*

Department of Nuclear Medicine and Radiobiology, Faculty of Medicine and Health Sciences, Universite' de Sherbrooke, Sherbrooke, Québec, Canada J1H 5N4

Received 4 June 2007; revised 15 June 2007; accepted 19 June 2007
Available online 23 June 2007

Abstract—Different stereoselective synthetic routes for the preparation of 7α/β-substituted estradiol derivatives, that is, 7α-alkynylestra-1,3,5(10)-triene-3,17β-estradiol (**13**) and its 17β-acetate derivative (**14**), are explored. These steroids are key starting materials for Pd-catalyzed Sonogashira cross-coupling reactions to yield potential estrogen receptor (ER) antagonists, ER-based imaging ligands and other multi-functional agents. Initial preparation of 7α-alkynyl nortestosterone derivatives followed by various approaches to aromatize the A-ring, failed. Instead, stereoselective 7α-cyanation before A-ring aromatization, followed by 7α-cyano reduction to the 7α-aldehyde, dibromomethylenation and dehydrobromination of the aldehyde, gave the desired 7α-alkynyl derivatives **13** and **14** in good yield.

Estrogens act as endocrine growth factors for at least 60–70% of breast cancers, and their effects are mediated via the estrogen receptor (ER) pathway. Several approaches have been adopted to treat hormone-sensitive breast cancer. In pre-menopausal women these include reducing circulating estrogen by ovarian ablation or by inhibiting ovarian estrogen production. In post-menopausal women, the mainstays of therapy are the prevention of estrogen binding to its receptor using an anti-estrogen or lowering estrogen levels with aromatase inhibitors.[1]

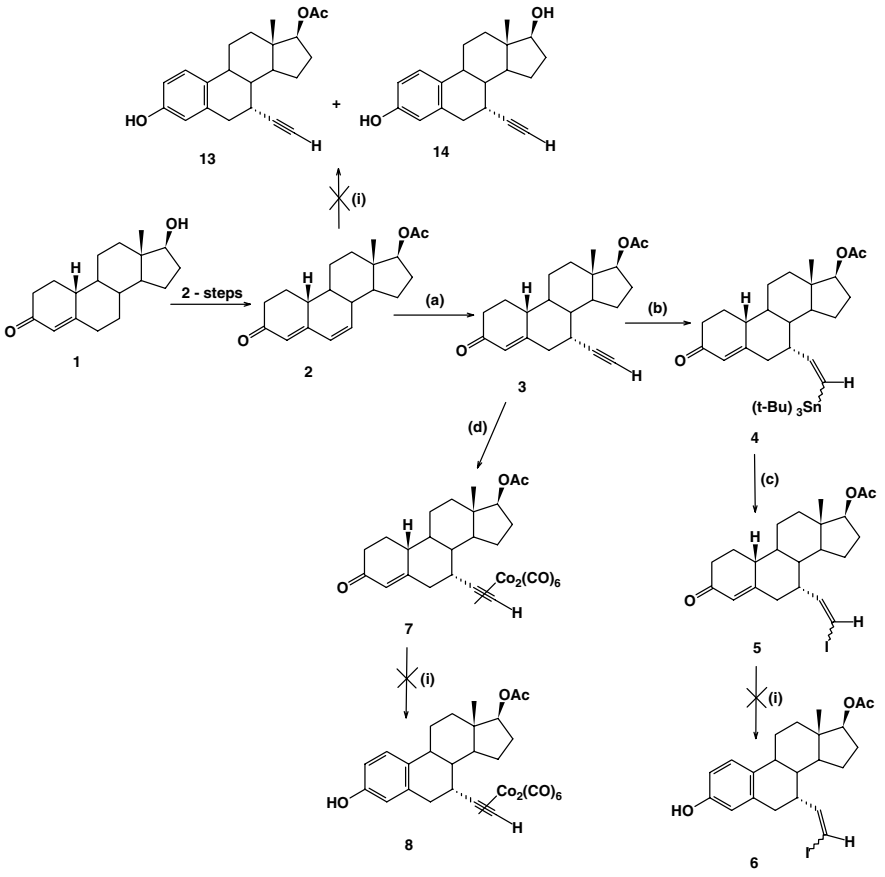
The use of ER antagonists is a common strategy in the treatment of ER-positive human breast cancer.[2] Tamoxifen, a well-known antagonist of the human ER, which also retains weak agonistic activity for the same receptor, is commonly prescribed for this purpose.[2,3] However, partly because of its inherent partial agonistic activity (albeit very weak), breast cancer patients chronically treated with tamoxifen often experience relapse of the cancer. More recently, pure ER antagonists that are devoid of any ER agonistic activity, such as ICI-182,780 (fulvestrant) and ICI-164,384 have been developed as effective alternatives to tamoxifen.[4] Studies have shown that human breast cancer cells that became resistant to tamoxifen were still sensitive to the anticancer effect of fulvestrant, which was recently approved by FDA for treatment of post-menopausal, ER-positive progressive breast cancers.[4b,d] Structurally, these ER antagonists contain the 17β-estradiol (E2) core with a long side chain attached to the 7α-position. Many of the 7α-substituted derivatives of E2, are highly useful intermediates for the rational design and synthesis of high-affinity ER antagonistic analogs as well as ER-based imaging ligands for human breast cancers or other ER-based multi-functional agents.[5]

Therefore, it is critical to understand the phenomena of regulation of E2 derivatives within the organism for the diagnosis and treatment of estrogen related illness.[6] A variety of E2 derivatives have been prepared via functionalization mainly at C-2, C-6, C-7, C-11, and C-16 positions for use as probes to study the estrogen binding proteins responsible for the concentration of physiological levels of E2 in target tissues. Compounds prepared via functionalization at the C-7 position of estradiol showed both high binding affinity for estrogen binding proteins and significant anti-estrogenic activity.[7]

Different synthetic pathways for C-7 substituted estradiols and estrones have been pursued, either starting from estradiol[8] or 19-nortestosterone[9] nuclei. Most of these

Keywords: Chemical synthesis; Conjugate addition; Estrogen receptor antagonist; 7α-Ethenyl-3,17β-estradiol and its 17β-acetate derivative.
* Corresponding author. Tel.: +1 819 564 5409; fax: +1 819 564 5442; e-mail: johan.e.vanlier@usherbrooke.ca

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.06.098



Scheme 1. (a) Reagents and conditions: H–C_2MgBr, CuCl, THF, −10 °C, 1 h; K_2CO_3–MeOH; (b) (*t*-Bu)$_3$SnH, AIBN or Et_3B, rt, 24 h; (c) I_2, $CHCl_3$; (d) $Co_2(CO)_8$, Et_2O, rt, 1.5 h; (i) $CuBr_2$, LiBr, CH_3CN, rt, 48 h. Yield: **2**—66% (overall), **3**—60%, **4**—45%, **5**—92%, **7**—70%.

pathways have limitations when applied to large-scale production of the desired intermediates, such as the paucity of the expensive starting reagents or the need of multi-steps synthetic routes.[10]

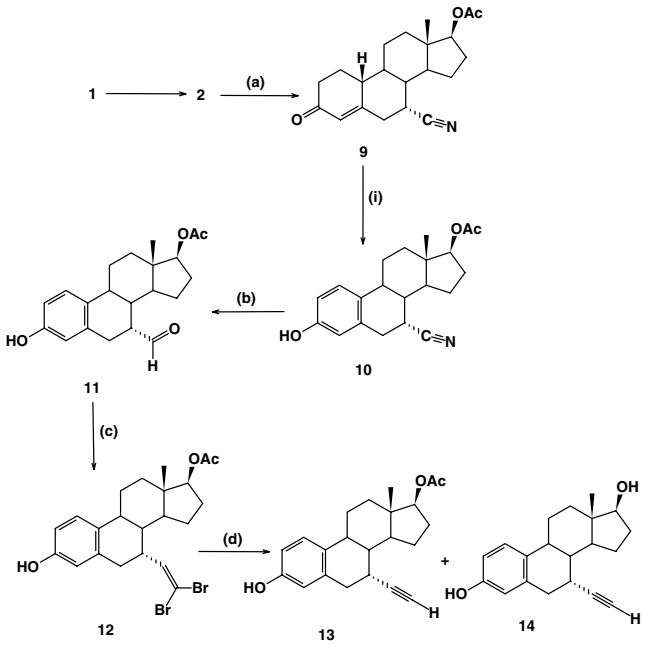
In search of improved ER binding agents useful for the management of estrogen-dependent pathologies, we and others previously synthesized[11] 7α-substituted steroid derivatives **9** and tested their ER binding affinity and cytotoxicity towards ER-positive animal tumors. Here, we report a new and stereoselective synthetic approach for the preparation of 7α/β-ethenyl substituted estrogens. These derivatives are useful intermediates for the conjugation of estradiol with different organic moieties coupled via alkyne tethers at the 7α-position to yield analogs with potentially improved binding affinity for the ER.

Our first attempt to stereoselective synthesize the 7α/β-ethenyl-substituted estradiols **13** and **14**, involved a simple, two-step reaction path[7a,b] starting from 19-nortestosterone (**1**) to afford the intermediate dienone **2**. The Grignard reaction of **2** with ethynyl magnesium bromide in the presence of CuCl catalyst gave the 7α-ethenyl **3** in good yield. However, subsequent attempts to aromatize the A-ring in **3** by using $CuBr_2$ and LiBr catalysts[12] failed (Scheme 1).

In a second approach to aromatize the A-ring of **3**, the 7α-ethenyl group was protected with dicobalt octacarbonyl [$Co_2(CO)_8$] in diethyl ether to afford compound **7**.[13] However attempts to aromatize **7** likewise failed, even after prolonging the reaction time up to 48 h. We then converted the 7α-ethenyl group of intermediate **3** with tri-*t*-butyltin hydride and AIBN or Et_3B, which gave the vinyl tri-*t*-butyltin **4** in good yield. Subsequent quenching of **4** with iodine in $CHCl_3$, afforded the 7α-iodovinyl derivatives **5**. Again, attempts to aromatize the A-ring of **5** to give **13**, failed. At higher reaction temperatures decomposition products were detected along with unreacted starting materials.

In order to circumvent the failing aromatization steps with the 7α-functionalized compounds **3**, **5**, and **7**, we explored an alternative route via the more stable 7α-cyano analog.

Subsequent A-ring aromatization in the presence of $CuBr_2$ and LiBr catalyst, gave the 7α-cyanoestradiol derivative **10** in good yield. Reduction of the cyano group in **10** with DIBAL-H in toluene followed by acid hydrolysis gave a mixture of 7α-/β-aldehyde diastereomers **11**, in up to 60% yield. The isomers were separated by silica gel flash column chromatography and the principal 7α-isomer was treated with CBr_4 and triphenylphosphine (PPh_3) to yield the 7α-dibromoethenyl substituted estradiol **12** in good yield.[14] Finally, the dibromovinylidene **12** was treated with *n*-butyl lithium at −78 °C, followed by water hydrolysis, to give the



Scheme 2. Reagents and conditions: Et_2AlCN, THF–toluene, 1 h, aq NaOH; (i) $CuBr_2$, LiBr, CH_3CN, rt, 30 min; (b) DIBAL-H, toluene, 3 h, MeOH–HCl; (c) CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt, 18 h; (d) *n*-BuLi, −78 °C to rt, H_2O, 4 h.

desired products **13** and **14** in 3:1 ratio (Scheme 2). The latter products were separated by silica gel flash column chromatography and characterized on the basis of their spectroscopic data (^{1}H NMR, EIMS, and HRMS).[15] These findings contrast the earlier reported inhibiting effect on A-ring aromatization by cyano substitution at the 11β-position of nortestosterone derivatives.[11b]

In summary, we explored different synthetic routes for the preparation of 7α-substituted estradiol derivatives, that is, 7α-alkynylestra-1,3,5(10)-triene-3,17β-estradiol (**13**) and its 17β-acetate **14**, which are useful intermediates for the development of high-affinity, ER antagonists. Various approaches to aromatize the A ring of 7α-substituted 19-nortestosterone derivatives failed. Instead, products **13** and **14** were prepared stereoselectively and in good yield via a 7α-cyanoestradiol intermediate.

Acknowledgment

This work was supported by the Canadian Institutes of Health Research (CIHR, Grant MOP-44065).

References and notes

1. (a) Paulmurugan, R.; Gambhir, S. S. *PNAS* **2006**, *103*, 15883; (b) Lippman, M. E.; Allegra, J. C. *New Engl. J. Med.* **1978**, *299*, 930; (c) Fisher, B.; Osborne, C. K.; Margolese, R.; Bloomer, W. In *Cancer Medicine*, 4th ed.; Williams & Wilkins: Baltimore, 1997; Vol. 1, p 2349.
2. (a) Jordan, V. C.; Brodie, A. M. H. *Steroids* **2007**, *72*, 7; (b) MacGregor, J. I.; Jordan, V. C. *Pharmacol. Rev.* **1998**, *50*, 151.
3. Top, S.; El-Hafa, H.; Vessieres, A.; Quivy, J.; Vassermann, J.; Hughes, D. W.; McGlinchey, M. J.; Mornon, J.-P.; Thoreau, E.; Jaouen, G. *J. Am. Chem. Soc.* **1995**, *117*, 8373.
4. (a) Osborne, C. K.; Wakeling, A.; Nicholson, R. I. *Br. J. Cancer* **2004**, *90*, S2–S6; (b) Bowler, J.; Lilley, T. J.; Pittam, J. D.; Wakeling, A. E. *Steroids* **1989**, *54*, 71; (c) Thompson, M. J.; Hutchinson, E. J.; Stratford, T. H.; Bowler, W. B.; Blackburn, G. M. *Tetrahedron Lett.* **2004**, *45*, 1207; (d) Jones, S. E. *Semin. Oncol.* **2003**, *30*, 14.
5. (a) Adamczyk, M.; Johnson, D.; Reddy, E. A. *Steroids* **1997**, *62*, 771; (b) Hussey, S. L.; He, E.; Peterson, B. R. *Org. Lett.* **2002**, *4*, 415; (c) Skaddan, M. B.; Wust, F. R.; Katzenellenbogen, J. A. *J. Org. Chem.* **1999**, *64*, 8108; (d) Mitra, K.; Marquis, J. C.; Hillier, S. M.; Rye, P. T.; Zayas, B.; Lee, A. S., et al. *J. Am. Chem. Soc.* **2002**, *124*, 1862; (e) Hussey, S. L.; Muddana, S. S.; Peterson, B. R. *J. Am. Chem. Soc.* **2003**, *125*, 3692.
6. (a) Osborne, C. K.; Schiff, R. *J. Clin. Oncol.* **2005**, *23*, 1616; (b) Beauregard, J.; Turcotte, E.; Benard, F. *PET Clin.* **2006**, *1*, 51; (c) Mankoff, D. A.; Tewson, T. J.; Eary, J. F. *Nucl. Med. Biol.* **1997**, *24*, 341; (d) Gosling, J. P. *Clin. Chem.* **1990**, *36*, 1408; (e) Wild, D. *The Immunoassay Handbook*; Stockton Press: New York, 1994, p 366.
7. (a) Martynow, J.; Krupa, M.; Les, A.; Kutner, A.; Szelejewski, W. *Org. Process Res. Dev.* **2004**, *8*, 846; (b) Bucourt, R.; Vignau, M.; Torelli, V.; Richard-Foy, H.; Geynet, C.; Secco-Millet, C.; Redeuilh, G.; Baulieu, E. E. *J. Biol. Chem.* **1978**, *253*, 8221; (c) Muhelenbruch, B.; Kirmeier, F.; Roth, H. J. *Arch. Pharm. (Weinheim)* **1986**, *319*, 177; (d) Bowler, J.; Lilley, T. J.; Pittam, J. D.; Wakeling, A. E. *Steroids* **1989**, *54*, 71; (e) Levesque, C.; Merand, Y. *Steroids* **1989**, *54*, 71; (f) Levesque, C.; Merand, Y.; Dufour, J.-M.; Labrie, C.; Labrie, F. *J. Med. Chem.* **1991**, *34*, 1624; (g) Hauptmann, H.; Paulus, B.; Kaiser, T.; Luppa, T. B. *Bioconjugate Chem.* **2000**, *11*, 537.
8. (a) French, A. N.; Wilson, S. R.; Welch, M. J.; Katzenellenbogen, J. A. *Steroids* **1993**, *58*, 157; (b) Kunzer, H.; Thiel, M.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1994**, *35*, 1691; (c) Kunzer, H.; Thiel, M.; Peschke, B. *Tetrahedron Lett.* **1996**, *37*, 1771; (d) Spera, D.; Cabrera, G.; Fiaschi, R.; Carlson, K. E.; Katzenellenbogen, J. A.; Napolitano, E. *Bioorg. Med. Chem.* **2004**, *12*, 4393; (e) Luyt, L. G.; Bigott, H. M.; Welch, M. J.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2003**, *11*, 4977; (f) VanBrocklin, H. F.; Liu, A.; Welch, M. J.; O'Neil, J. P.; Katzenellenbogen, J. A. *Steroids* **1994**, *59*, 34; (g) Morais, G. R.; Oliveira, M. C. D. N.; Thiemann, T. *Lett. Org. Chem.* **2006**, *3*, 214; (h) Blazejewski, J. C.; Wilmshurst, M. P.; Popkin, M. D.; Wakselman, C.; Nonclercq, G. D.; Ma, Y.; Seoc, H. S.; Leclercq, G. *Bioorg. Med. Chem.* **2003**, *11*, 335.
9. (a) Neeman, M.; Osawa, Y. *Tetrahedron Lett.* **1963**, *4*, 1987; (b) Wintersteiner, O.; Moore, M.; Cohen, A. I. *J. Org. Chem.* **1964**, *29*, 1325; (c) Thiemann, T.; Umeno, K.; Imai, M.; Shima, Y.; Mataka, S. *J. Chem. Res. (S)* **2002**, 1; (d) Lovely, C. J.; Gilbert, N. E.; Liberto, M. M.; Sharp, D. W.; Lin, Y. C.; Brueggemeier, R. W. *J. Med. Chem.* **1996**, *39*, 1917; (e) Labaree, D. C.; Zhang, J.-X.; Harris, H. A.; O'Connor, C.; Reynolds, T. Y.; Hochberg, R. B. *J. Med. Chem.* **2003**, *46*, 1886; (f) van der Louw, J.; Leysen, D.; Bursi, R. B. U.S. Patent 6,756,366,B1, 2004.
10. Jiang, X.-R.; Sowell, J. W.; Zhu, B. T. *Steroids* **2006**, *71*, 334.
11. (a) Ahmed, N.; Dubuc, C.; Rousseau, J.; Benard, F.; van Lier, J. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3212; (b) Ali, H.; Rousseau, J.; Ahmed, N.; Guertin, V.; Hochberg, R. B.; van Lier, J. E. *Steroids* **2003**, *68*, 1163; (c) Ali, H.; van Lier, J. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2847;

(d) Ali, H.; Rousseau, J.; Paquette, B.; Dubé, C.; Marko, B.; van Lier, J. E. *Steroids* **2003**, *68*, 1189; (e) Seimbille, Y.; Benard, F.; van Lier, J. E. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2275; (f) DaSilva, J. N.; van Lier, J. E. *J. Med. Chem.* **1990**, *33*, 430; (g) Ali, H.; Rousseau, J.; van Lier, J. E. *J. Med. Chem.* **1993**, *36*, 264; (h) Nickisch, K.; Bittler, D.; Laurent, H.; Losert, W.; Nishino, Y.; Schillinger, E.; Wiechert, R. *J. Med. Chem.* **1990**, *33*, 509; (i) Labaree, D. C.; Zhang, J.-X.; Harris, H. A.; O'Connor, C.; Reynolds, T. Y.; Hochberg, R. B. *J. Med. Chem.* **2003**, *46*, 1886.

12. Rao, P. N.; Cessac, J. W.; Kim, H. K. *Steroids* **1994**, *59*, 621.
13. (a) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911; (b) Seyferth, D.; Nestle, M. O.; Wehman, A. T. *J. Am. Chem. Soc.* **1975**, *97*, 7417.
14. Watanabe, M.; Mataka, S.; Thies Thiemann, T. *Steroids* **2005**, *70*, 856.
15. *General procedure:* (a) Synthesis of **3** (Grignard reaction): To a stirred solution of **2** (0.9 g, 3 mmol) and cuprous chloride (350 mg) in THF (35 mL) was added ethynyl magnesium bromide (16 mL, 0.5 M in THF, 3.6 mmol, Aldrich) under argon at −10 °C. The mixture was stirred for 1–1.5 h and monitored by TLC. The reaction mixture was quenched with water and aq HCl (0.5 N), extracted in $CHCl_3$, and the organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of hexane–EtOAc (8:2) as the eluent to afford compound **3** in 65% yield: mp: 115–117 °C (lit 117-121 °C[9f]); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83 (s, 3H), 2.6 (s, 1H), 3.72 (t, 1H), 5.78 (br s, 1H); MS *m*/*z* M^+ 298. (b) *Synthesis of 7α-ethenylestra-1,3,5(10)-triene-3,17β-estradiol* (**13**) *and its 17β-acetate derivative* (**14**): (i) A solution of carbon tetrabromide (CBr_4) (249 mg, 0.75 mmol) in dry CH_2Cl_2 (3 mL) was added to **11** (192 mg, 0.5 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred at rt for 18 h and monitored by TLC. The reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography using hexane–ether (4:1) to give **12** in 62% yield: ^{1}H NMR (CDCl3, 300 MHz) δ 0.87 (s, 3H), 2.08 (s, 3H), 2.29 (s, 3H), 2.78 (m, 1H), 4.43 (t, 1H), 6.89 (m, 2H), 7.29 (d, 1H), 7.12 (s, 1H). (ii) A solution of *n*-butyl lithium in pentane (1.58 M, 2 mL) was added to **12** (540 mg, 1 mmol) in dry THF (15 mL) at −78 °C under an argon atmosphere and the resulting mixture was stirred for 4 h at −78 °C. To the green solution was added water (5 mL) and it was warmed to rt. After 30 min, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography using hexane–EtOAc (6:1) to give products **13** and **14** (1:3 ratio) in overall 80% yield as yellowish solids. Product **13**: mp 130–135 °C: ^{1}H NMR (CDCl3, 300 MHz) δ 0.82 (s, 3H), 3.1 (s, 1H), 3.73 (t, 3H) and 6.89 (m, 2H), 7.29 (d, 1H); EI MS *m*/*z* M^+ 338; HRMS calcd for $C_{22}H_{26}O_3$ (M^+) 338.1882, found 338.1891. Product **14**: 0.82 (s, 3H), 2.06 (s, 3H, acetate), 3.1 (s, 1H), 4.13 (t, 1H), 6.89 (m, 2H), 7.29 (d, 1H); EI MS *m*/*z* M^+ 296; HRMS calcd for $C_{20}H_{24}O_2$ (M^+) 296.1776, found 296.1782.