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Concise synthesis of 12a-methyl-11-aryl-1,2-dihydrobenzo[*f*]pyrrolo[1,2-*a*]quinolin-3(12a*H*)-ones as racemic 14-azaestrogen analogs

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ABSTRACT

A concise method for the synthesis of 14-azasteroid analogs with angular methyl group at C-13 of the steroidal nucleus has been reported in this paper. We have developed an interesting cascade reaction of arylacetylenes and *N*-(naphthalen-2-yl)pent-4-ynamides under gold (III)-catalysis to produce novel tetracyclic 12a-methyl-11-aryl-1,2-dihydrobenzo[*f*]pyrrolo[1,2-*a*]quinolin-3(12a*H*)-ones which may be viewed as 14-azaestrogen analogs.

1. Introduction

Numerous hormones are known to have tetracyclic steroidal framework. These are classified as mineralocorticoids, glucocorticoids, androgens, estrogens and progestogens based on the receptors to which they bind to elicit their biological response [1]. Research on steroids enjoys utmost attention in pure and applied sciences worldwide [2]. Estrogens (Fig. 1), a category of the steroidal hormone system having an aromatic ring, bind with and activate the Estrogen Receptors (ER) promoting a variety of physiological responses such as bone maturation, blood lipid profile, neuroprotective effects, reproductive functions and breast cell proliferation [3].

Heterosteroids are man-made polycyclic steroidal systems where one or more carbons are replaced by heteroatom(s) [4]. Owing to the structural and topological similarity with natural steroids, heterosteroids are a subject of intense research that reports syntheses of new congeners and unveils interesting and useful properties that they possess [5–9]. A large number of heterosteroids have been clinically studied; some have culminated into successful drugs [5–9]. Fig. 2 includes several notable examples *viz.*, finasteride (antihyperplastics) [10], candocuronium iodide (muscle relaxants) [11], danazol (antiestrogen) [12], and RU-5135 (antagonist of GABA in the CNS) [13]. A large number of N-containing heterosteroids have been studied as azaestrogens [14,15]. Considering the fact that any minor modification in the chemical structure of the steroid often results in a huge change in their biological activities and applications; medicinal chemists employ it as a tool in design and development of new drugs [5–9].

Since this investigation deals with synthesis of 14-azasteroids, it is pertinent to briefly describe strategies adopted in past to assemble this nucleus. There are only a handful of reports describing synthesis of 14-azasteroids [16–24]. Three related procedures employed [4+2] hetero-Diels–Alder approach between alkenes and *N*-acyliminium ions derived from 2-naphthylamine and γ-keto acids [16,17] (or by borohydride reduction of *N*-2-naphthylimide [18]). In two endeavors with somewhat similar strategy [19,20], cross Claisen condensation between ethyl acetate and ethyl 8-methoxybenzo[*f*]quinoline-3-carboxylate, prepared from 6-methoxy-2-naphthalenamine in 3 steps, led to the formation of a β–keto ester. This β–keto ester underwent intramolecular reductive cycloamidation to produce 14-azasteroid skeleton. Falling and Rapoport [21] reported the synthesis of a 14-azasteroid analog as a minor product starting from 1,4-naphthoquinone and homoproline ester, through oxidative Michael addition, reductive O-acetylation, aryl ether formation, ester hydrolysis and intramolecular nuclear acylation sequence. Singh and Panda [22] have reported an asymmetric approach to the synthesis of 14-azasteroids from

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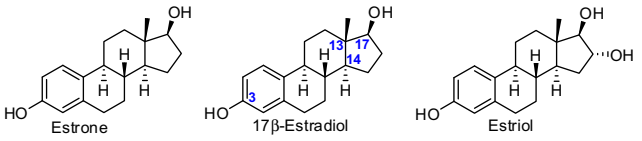


Fig. 1. Molecular structures of natural estrogens.

2-tetralone and L-proline derived aldehyde. 1-Bromo-3,4-dibydronaphthalene, obtained from 2-tetralone, was lithiated and then reacted with BOC-protected L-homoproline aldehyde. Removal of the BOC-group resulted in intramolecular cyclization to diastereomeric 14-azasteroids [22]. Loven and Speckamp subjected 3-hydroxymethyl-*N*-tosyl-octahydrobenzo[*f*]quinoline to a sequence of side chain oxidation to aldehyde, Wittig reaction with triethyl phosphonoacetate, alkene hydrogenation, $LiAlH_4$-induced detosylation and ester reduction, and finally $PBr_3/NaHCO_3$ cyclization of the amino-alcohol to yield 14-azasteroid [24]. In another interesting endeavor Sokolov et al. [23] have reported an interesting approach to 14-aza-17-thiasteroids by stereoselectively adding thiirane and methyl thiirane across C=N of 8-methoxy-3-methylhexahydrobenzo[f]quinolone. Thus, there are mainly six distinct approaches to synthesize 14-azasteroid nucleus.

In continuation of our efforts of developing domino methodologies to complex heterocyclic systems [18,25–30], we herein report a concise synthesis of 14-azasteroids, namely 12a-methyl-11-aryl-1,2-dihydrobenzo[*f*]pyrrolo[1,2-*a*]quinolin-3(12a*H*)-ones, in three simple steps.

2. Experimental

2.1. General remarks

All the chemicals and solvents for this work were obtained from commercial sources and were used as such. TLCs were performed on pre-coated Merck silica gel $60F_{254}$ plates with the spots detected under UV light. Silica gel (230–400 mesh) was used for column chromatography. Melting points were measured with a MEL-TEMP®, an electrothermal melting point apparatus and are uncorrected. Microwave experiments were carried out in a CEM® Discover microwave reactor. Q-Block-35 and Q-tube® 35 ml were used to run the high pressure reactions. ^1H and ^{13}C NMR spectra were recorded using a Bruker® AC-300 Avance spectrometer at 300 MHz and 75 MHz, respectively, in $CDCl_3$ or DMSO-d_6. ^1H NMR spectra were reported relative to residual $CHCl_3$ (δ 7.26) or DMSO (δ 2.50). ^{13}C NMR spectra were reported relative to $CHCl_3$ (δ 77.2) or DMSO (δ 39.5). High-resolution mass spectra (HRMS) were recorded in the positive ion mode using a microTOF (Bruker Daltonics) spectrometer at Dalhousie University.

2.2. Chemical synthesis

2.2.1. Synthesis of 2-naphthylamines

Ammonium hydroxide aqueous solution (841 mg, 27.8 mmol, 2 equiv.) was added to a freshly prepared aqueous solution of ammonium sulfite monohydrate (3.2 g, 27.8 mmol, 2 equiv.) in a 35 ml high pressure reaction vessel. Appropriate 2-naphthol analog (**1a** or **1b**) (13.9 mmol, 1 equiv.) was added, and the mixture was stirred for 17 h at 120 °C. The reaction mixture was filtered and the precipitate was washed with cold 5% aq. NaOH and then dissolved in DCM. The organic layer was again washed with 5% aq. NaOH (3 × 30 mL) and dried over anh. sodium sulfate to afford 2-naphthylamines after the removal of solvent *in vacuo*.

*2.2.1.1. 2-Naphthylamine (**2a**).* Purple solid; yield 49%; m.p. 111–113 °C (lit. m.p. 109–111 °C [31]). The ^1H and ^{13}C NMR data of this compound was found to be identical to those reported in the literature [31].

*2.2.1.2. 6-Bromo-2-naphthylamine (**2b**).* Brownish solid; yield 21%; m.p. 124–126 °C (lit. m.p. 127–128 °C [32]). The ^1H and ^{13}C NMR data of this compound was found to be identical to those reported in the literature [32].

2.2.2. General procedure for the preparation of N-(naphthalen-2-yl)pent-4-ynamides (**3**)

4-Pentynoic acid (1.38 g, 14.01 mmol, 1 equiv.) was dissolved in DCM (2 mL) then added to an ice-cold solution of EDC (4.026 g, 21 mmol, 1.5 equiv.) and HOBt (2.649 g, 19.59 mmol, 1.4 equiv.) in DCM (25 mL). A solution of appropriate 2-naphthylamine (21 mmol, 1.5 equiv.) in DCM (20 mL) was then added to the reaction mixture and stirred. Triethylamine (2.13 g, 21 mmol, 1.5 equiv.) was added drop-wise over 10 min. then the reaction temperature was allowed to increase gradually to room temperature. The reaction mixture was stirred for 17 h. The reaction mixture was then diluted with 20 ml DCM, washed with water, 5% aq. HCl, saturated Aq. sodium bicarbonate solution, and brine solution. The organic layer was dried over anh. sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude was purified by column chromatography to afford the corresponding *N*-(naphthalen-2-yl)pent-4-ynamides.

*2.2.2.1. N-(Naphthalen-2-yl)pent-4-ynamide (**3a**).* Colorless solid; yield 76%; m.p. 126–128 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.18 (s, 1H), 2.67 (brs, 4H), 7.40–7.60 (m, 4H), 7.77–7.83 (m, 3H), 8.24 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.6, 33.2, 66.5, 79.6, 113.6, 116.7, 121.8, 123.3, 124.3, 124.4, 125.5, 127.6, 130.7, 131.9, 166.0. ESI-HRMS calcd. for $C_{15}H_{13}NO$: 224.1075 $[M+H]^+$; found: 224.1080.

*2.2.2.2. N-(6-Bromonaphthalen-2-yl)pent-4-ynamide (**3b**).* Colorless solid; yield 81%; m.p. 185–187 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.10 (s, 1H), 2.67 (brs, 4H), 7.40–7.75 (m, 5H), 7.94 (s, 1H), 8.25 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.6, 33.2, 66.6, 79.5, 113.5, 115.7, 117.6, 124.6, 126.0, 126.3, 126.7, 128.5, 129.2, 132.2, 166.2. ESI-HRMS calcd. for $C_{15}H_{12}BrNO$: 302.0181 $[M+H]^+$; found: 302.0183.

2.2.3. General procedure for gold-catalyzed tandem synthesis of 15-oxo-14-azasteroids (**4a–l**)

To a solution of appropriate *N*-naphthylpent-4-ynamide (1 mmol) and alkyne (4 mmol) in toluene (10 mL), $AuBr_3$

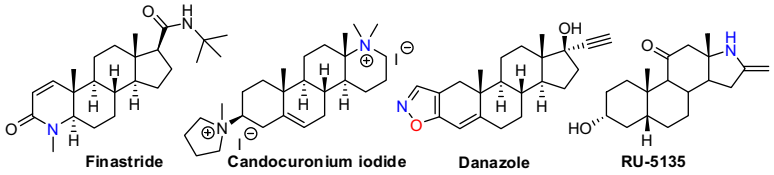


Fig. 2. Examples of biologically active heterosteroids.

(3 mol%) and $AgSbF_6$ (5 mol%) were added in a 35 mL microwave vessel equipped with a magnetic stir bar. The overhead space was flushed with argon before placing the cap. The resulting mixture was placed in the microwave cavity and it was irradiated at 120 °C for 4 h with constant stirring. Toluene was removed under reduced pressure. The residue was purified by flash column chromatography (hexanes/ethyl acetate 20:1) to isolate the desired product and to recover the unreacted amide starting material.

*2.2.3.1. 12a-Methyl-11-phenyl-1,2-dihydrobenzo[f]pyrrolo[1,2-a]quinolin-3(12aH)-one (**4a**).* Light Yellow liquid; yield 21%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (s, 3H), 2.20–2.40 (m, 2H), 2.53–2.68 (m, 1H), 2.72–2.85 (m, 1H), 5.98 (s, 1H), 7.06 (t, *J* = 8.1 Hz, 1H), 7.19–7.41 (m, 7H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 8.48 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.9, 30.4, 32.4, 60.1, 120.6, 121.5, 124.5, 124.9, 127.3, 127.4, 127.6, 127.7, 128.4, 128.6, 129.7, 131.8, 133.1, 134.4, 136.0, 142.0, 173.6. ESI-HRMS calcd. for $C_{23}H_{19}NO$: 326.1545 $[M+H]^+$; found: 326.1539.

*2.2.3.2. 8-Bromo-12a-methyl-11-phenyl-1,2-dihydrobenzo[f]pyrrolo[1,2-a]quinolin-3(12aH)-one (**4b**).* Colorless viscous liquid; yield 15%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (s, 3H), 2.20–2.40 (m, 2H), 2.53–2.64 (m, 1H), 2.72–2.85 (m, 1H), 6.00 (s, 1H), 6.90–7.35 (m, 7H), 7.75–7.95 (m, 2H), 8.45 (t, *J* = 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.7, 26.4, 29.2, 56.7, 117.5, 118.5, 121.1, 121.6, 124.0, 124.5, 125.0, 125.3, 125.5, 127.0, 128.9, 130.4, 131.1, 131.4, 138.6, 139.0, 170.1. ESI-HRMS calcd. for $C_{23}H_{18}BrNO$: 404.0650 $[M+H]^+$; found: 404.0645.

*2.2.3.3. 11-(4-Ethylphenyl)-12a-methyl-1,2-dihydrobenzo[f]pyrrolo[1,2-a]quinolin-3(12aH)-one (**4c**).* Yellow liquid; yield 24%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.80–0.95 (dist. t, 3H), 1.27 (s, 3H), 2.19–2.38 (m, 2H), 2.52–2.84 (m, 4H), 5.98 (s, 1H), 6.95–7.54 (m, 5H), 7.80 (d, *J* = 7.5 Hz, 2H), 7.88 (d, *J* = 9.0 Hz, 2H), 8.48 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.1, 19.7, 25.3, 26.4, 29.2, 56.8, 117.4, 118.5, 121.1, 121.6, 123.2, 124.3, 124.7, 125.1, 125.5, 126.3, 127.5, 128.6, 129.9, 130.7, 136.2, 140.3, 170.1. ESI-HRMS calcd. for $C_{25}H_{23}NO$: 354.1858 $[M+H]^+$; found: 354.1854.

*2.2.3.4. 8-Bromo-11-(4-ethylphenyl)-12a-methyl-1,2-dihydrobenzo[f]-pyrrolo[1,2-a]quinolin-3(12aH)-one (**4d**).* Colorless viscous liquid; yield 27%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.27 (s, 3H), 2.20–2.35 (m, 2H), 2.51–2.83 (m, 4H), 5.98 (s, 1H), 6.90–7.35 (m, 6H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.94 (s, 1H), 8.48 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.0, 19.72, 25.3, 26.4, 29.2, 56.8, 115.2, 117.4, 118.5, 121.1, 121.6, 124.3, 124.8, 125.2, 125.7, 126.9, 129.8, 130.3, 130.9, 132.5, 135.8, 140.5, 170.1. ESI-HRMS calcd. for $C_{25}H_{22}BrNO$: 432.0963 $[M+H]^+$; found: 432.0965.

*2.2.3.5. 11-(4-Methoxyphenyl)-12a-methyl-1,2-dihydrobenzo[f]pyrrolo[1,2-a]quinolin-3(12aH)-one (**4e**).* Yellow liquid; yield 29%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27 (s, 3H), 2.20–2.39 (m, 2H), 2.52–2.84 (m, 2H), 3.85 (s, 3H), 5.94 (s, 1H), 6.84–7.42 (m, 7H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 8.48 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.7, 27.1, 29.2, 52.0, 56.7, 110.8, 117.4, 117.7, 121.1, 121.3, 121.6, 123.3, 124.1, 125.1, 125.5, 126.3, 126.6, 130.0, 130.1, 131.4, 156.9, 170.1. ESI-HRMS calcd. for $C_{24}H_{21}NO_2$: 356.1651 $[M+H]^+$; found: 356.1629.

*2.2.3.6. 8-Bromo-11-(4-methoxyphenyl)-12a-methyl-1,2-dihydrobenzo[f]pyrrolo[1,2-a]quinolin-3(12aH)-one (**4f**).* Colorless viscous liquid; yield 33%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27 (s, 3H), 2.20–2.39 (m, 2H), 2.51–2.81 (m, 2H), 3.84 (s, 3H), 5.93 (s, 1H), 6.90–7.31 (m, 6H), 7.75–7.95 (m, 2H), 8.44–8.52 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ19.7, 27.0, 29.2, 52.0, 56.7, 111.0, 117.5, 118.5, 121.1, 124.0, 124.9, 125.0, 125.2, 125.5, 125.7, 127.0, 130.1, 130.4, 131.0, 132.1, 156.2, 170.0. ESI-HRMS calcd. for $C_{24}H_{20}BrNO_2$: 434.0756 $[M+H]^+$; found: 434.0750.

*2.2.3.7. 11-(4-tert-Butylphenyl)-12a-methyl-1,2-dihydrobenzo[f]pyrrolo[1,2-a]quinolin-3(12aH)-one (**4g**).* Yellow liquid; yield 25%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (s, 3H), 1.35 (s, 9H), 2.20–2.35 (m, 2H), 2.51–2.85 (m, 2H), 5.98 (s, 1H), 6.95–7.35 (m, 7H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 8.48 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.7, 27.1, 28.1, 29.2, 31.3, 56.7, 117.5, 118.5, 121.0, 121.5, 122.1, 124.0, 124.1, 125.0, 126.2, 126.7, 128.7, 130.0, 130.6, 132.9, 135.9, 147.3, 170.1. ESI-HRMS calcd. for $C_{27}H_{27}NO$: 382.2171 $[M+H]^+$; found: 382.2153.

*2.2.3.8. 8-Bromo-11-(4-tert-butylphenyl)-12a-methyl-1,2-dihydrobenzo[f]pyrrolo[1,2-a]quinolin-3(12aH)-one (**4h**).* Colorless viscous liquid; yield 22%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27 (s, 3H), 1.35 (s, 9H), 2.20–2.36 (m, 2H), 2.51–2.82 (m, 2H), 5.98 (s, 1H), 6.90–7.36 (m, 6H), 7.75–7.80 (m, 2H), 8.48 (t, *J* = 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.7, 27.0, 28.1, 29.2, 31.3, 56.7, 117.5, 118.5, 121.0, 121.4, 122.3, 124.0, 124.8, 125.2, 125.8, 126.2, 126.9, 128.7, 130.6, 131.0, 135.5, 147.6, 170.1. ESI-HRMS calcd. for $C_{27}H_{26}BrNO$: 460.1276 $[M+H]^+$; found: 460.1265.

*2.2.3.9. 11-(4-Butylphenyl)-12a-methyl-1,2-dihydrobenzo[f]pyrrolo[1,2-a]quinolin-3(12aH)-one (**4i**).* Yellow liquid; yield 29%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (t, *J* = 6.9 Hz, 3H), 1.27 (s, 3H), 1.29–1.48 (m, 4H), 2.20–2.37 (m, 2H), 2.51–2.81 (m, 4H), 5.98 (s, 1H), 6.90–7.35 (m, 7H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 8.48 (d, *J* = 9.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ10.5, 19.0, 26.4, 27.1, 29.2, 30.2, 32.0, 56.7, 117.4, 121.1, 121.5, 123.2, 124.1, 124.3, 125.0, 125.3, 126.2, 126.7, 128.7, 130.0, 130.5, 132.9, 136.1, 138.9, 170.0. ESI-HRMS calcd. for $C_{27}H_{27}NO$: 382.2171 $[M+H]^+$; found: 382.2169.

*2.2.3.10. 8-Bromo-11-(4-butylphenyl)-12a-methyl-1,2-dihydrobenzo[f]pyrrolo[1,2-a]quinolin-3(12aH)-one (**4j**).* Colorless viscous liquid; yield 21%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (t, *J* = 6.9 Hz, 3H), 1.27 (s, 3H), 1.32–1.46 (m, 4H), 2.16–2.39 (m, 2H), 2.51–2.85 (m, 4H), 5.98 (s, 1H), 6.96–7.35 (m, 6H), 7.77–7.98 (m, 2H), 8.48 (t, *J* = 9.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ10.6, 19.0, 26.4, 27.0, 29.2, 30.2, 32.1, 56.7, 115.2, 117.4, 118.5, 121.1, 124.2, 124.8, 125.1, 125.3, 125.5, 125.8, 126.9, 129.8, 130.9, 132.5, 135.7, 139.2, 170.2. ESI-HRMS calcd. for $C_{27}H_{26}BrNO$: 460.1276 $[M+H]^+$; found: 460.1261.

*2.2.3.11. 12a-Methyl-11-(4-pentylphenyl)-1,2-dihydrobenzo[f]pyrrolo[1,2-a]quinolin-3(12aH)-one (**4k**).* Yellow liquid; yield 13%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (t, *J* = 6.9 Hz, 3H), 1.27 (s, 3H), 1.29–1.48 (m, 4H), 1.60–1.75 (m, 2H), 2.18–2.40 (m, 2H), 2.52–2.83 (m, 4H), 5.98 (s, 1H), 6.96–7.35 (m, 7H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 8.48 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ10.6, 19.2, 26.3, 27.1, 27.6, 28.1, 29.2, 32.3, 56.7, 117.4, 118.4, 121.0, 121.4, 124.1, 124.2, 125.0, 125.2, 126.2, 126.6, 128.6, 130.0, 130.5, 132.9, 136.1, 138.9, 170.0. ESI-HRMS calcd. for $C_{28}H_{29}NO$: 396.2327 $[M+H]^+$; found: 396.2314.

*2.2.3.12. 8-Bromo-12a-methyl-11-(4-pentylphenyl)-1,2-dihydrobenzo[f]pyrrolo[1,2-a]quinolin-3(12aH)-one (**4l**).* Colorless viscous liquid; yield 12%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (t, *J* = 6.9 Hz, 3H), 1.27 (s, 3H), 1.29–1.48 (m, 4H), 1.55–1.80 (m, 2H), 2.20–2.37 (m, 2H), 2.51–2.82 (m, 4H), 5.98 (s, 1H), 7.00–7.35 (m, 6H), 7.75–7.95 (m, 2H), 8.48 (t, *J* = 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ10.7, 19.2, 26.4, 27.1, 27.7, 28.2, 29.2, 32.3, 56.7, 115.2, 117.4, 118.5, 121.1, 121.5, 124.2, 124.8, 125.2, 125.3, 125.5, 125.8, 127.0, 130.1, 132.5, 135.8, 139.3, 170.1. ESI-HRMS calcd. for $C_{28}H_{28}BrNO$: 474.1433 $[M+H]^+$; found: 474.1423.

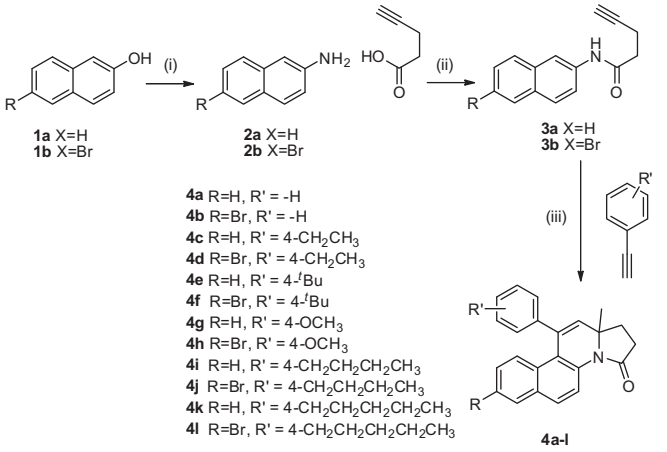
3. Results and discussions

We envisioned a synthetic route to 14-azasteroids with general structure **A**, retrosynthetic analysis of which is presented in Scheme 1. Intramolecular *6-endo-dig* hydroarylation of alkyne **B** with C-1 position of naphthalene ring will generate target compounds **A** [33]. Compounds **B** can be prepared from nucleophilic addition of aryl alkynes onto the *N*-acyliminium ion **C** or the enamide **D** [34]. The enamide **D** can, in turn, be formed from *N*-(naphthalen-2-yl)pent-4-ynamides **E** via *5-exo-dig* hydroamidation reaction [35]. Amide bond formation between 2-naphthylamines and 4-pentynoic acid will produce ynamides **E**. Commercially available 2-naphthol analogs can be converted to corresponding 2-naphthylamines via Bucherer reaction [31].

Several transition metal catalysts are known to catalyze hydroamination and hydroarylation reactions [33,35], gold-based catalysts have emerged as highly efficient and versatile to catalyze both of these reactions, even in tandem when feasible [36,37]. Thus, we selected to perform the proposed hydroamidation and hydroarylation sequence using $AuBr_3/AgSbF_6$ catalyst combination [37]. It is well-recognized that intramolecular formation of one new carbon–nitrogen and two new carbon–carbon bonds to make a tricyclic ring system in a one-pot reaction is particularly challenging because the regio- and chemoselectivity must be well-controlled to avoid formation of mixture of homo- and heterocoupled compounds.

Scheme 2 shows the synthetic strategy adopted to prepare desired 14-azasteroids. Precursors 2-naphthalenamine (**2a**) and 6-bromo-2-naphthalinamine (**2b**) were synthesized *via* Bucherer reaction on corresponding naphthols (**1a**, **1b**) [31]. The ynamides **3a** and **3b** were synthesized from corresponding 2-naphthalenamine (**2a** or **2b**) and 4-pentynoic acid using peptide coupling reagents EDC and HOBt in dichloromethane. These ynamides were then subjected to tandem hydroamination and hydroarylation reactions using $AuBr_3$ (3 mol%) and $AgSbF_6$ (5 mol%) catalyst system in toluene [37] under microwave irradiation conditions.

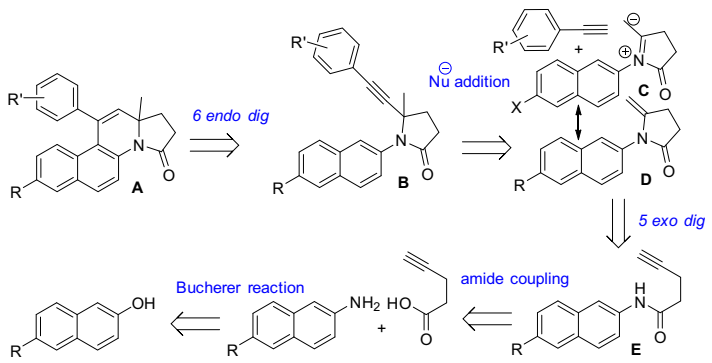
The Bucherer reaction for converting naphthols to naphthylamines and the subsequent amide bond formation with 4-pentynoic acid to obtain compounds **3a** and **3b** were straightforward. Compound **3a** was then reacted with phenylacetylene using somewhat modified conditions than what was reported in the literature for performing a similar reaction under $AuBr_3/AgSbF_6$-catalysis [37]. The reported procedure used heating the reaction contents in a sealed tube to perform the reaction whereas we employed microwave irradiation as the heat source and the reaction was performed under pressurized reaction vials. The progress of the reaction was monitored by tlc initially at 30 min interval for up to 4 h and then at 1 h interval for up to 9 h. Even with the use of 4 equivalents phenylacetylene, the starting ynamide **3a** was not completely consumed after 9 h of heating at 120 °C in the microwave reactor.



Scheme 2. Reagents and conditions: (i) ammonium sulfite monohydrate $(NH_4)_2SO_3{\cdot}H_2O$, ammonium hydroxide NH_4OH, H_2O, 120 °C, high pressure vessel, 17 h; (ii) EDC, HOBt, Et_3N, DCM, 0 °C – rt, 17 h; (iii) anh. $AuBr_3$ (cat.), $AgSbF_6$ (cat.), toluene, 120 °C, microwave (MW) under argon protection, 4 h.

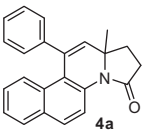
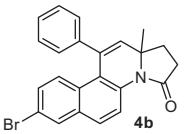
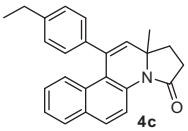
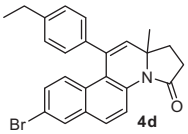
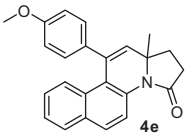
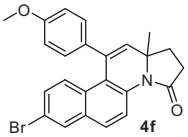
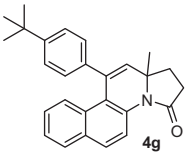
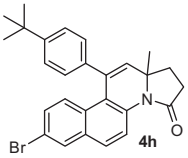
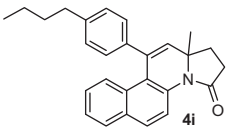
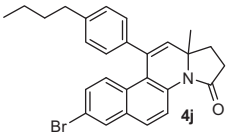
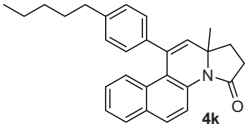
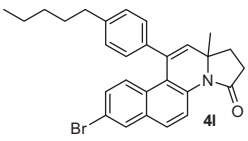
Based on the tlc observations, a new product was formed with R_f slightly lower than the precursor ynamide and the reaction progress virtually appeared to have stalled after 4 h of heating. The reaction was worked-up and the new product was purified by column chromatography. To our delight, the product was identified as the desired product where intramolecular formation of one new carbon–nitrogen and two new carbon–carbon bonds to make 14-azasteroid ring in a one-pot reaction was regio- and chemoselectively achieved in 52% yield (based on consumed ynamide **3a**). In the interest of time, we decided to proceed with these conditions to make analogs using variously substituted phenylacetylenes on **3a** and **3b** to test the generality of this reaction. The results are presented in Table 1. All 14-azasteroids reported in this manuscript are new to chemical literature and have been completely characterized by spectroscopic means.

As can be noticed in Table 1, highly electron donating $-OCH_3$ at the *para* position of the substituted phenylacetylene appeared to favor the formation of the desired compound. Relatively less electron donating long alkyl groups posted comparatively lower yields. The reaction did not work when *m*-flourophenylacetylene was used. The observation appeared to suggest that the inductive electron withdrawing effects of the fluoro-substituent was detrimental for the reaction. Also, the use of 1-hexyne and 1-heptyne did not yield any product. Similar observation was made previously [37]. Use of *o*- and *p*-substituted haloacetylenes did yield desired products in the previous report where m-substituted haloacetylenes were not used [37]. Also, the use of electron poor



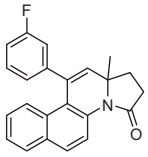
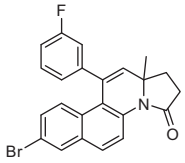
Scheme 1. Retro-synthetic analysis for the synthesis of 14-azasteroids A.

Table 1
14-Azasteroids.

Entry	R	R′	Product	Yield[a]
1	H	H	 **4a**	52
2	Br	H	 **4b**	43
3	H	4-CH_2CH_3	 **4c**	59
4	Br	4-CH_2CH_3	 **4d**	66
5	H	4-OCH_3	 **4e**	67
6	Br	4-OCH_3	 **4f**	71
7	H	4-^{t}Bu	 **4g**	63
8	Br	4-^{t}Bu	 **4h**	56
9	H	4-$CH_2CH_2CH_2CH_3$	 **4i**	68
10	Br	4-$CH_2CH_2CH_2CH_3$	 **4j**	55
11	H	4-$CH_2CH_2CH_2CH_2CH_3$	 **4k**	38
12	Br	4-$CH_2CH_2CH_2CH_2CH_3$	 **4l**	36

(*continued on next page*)

Table 1 (*continued*)

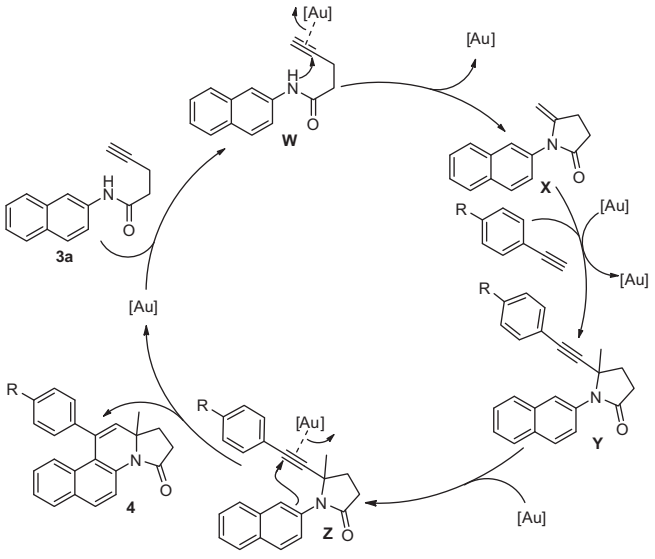
Entry	R	R′	Product	Yield[a]
13	H	3-F		NR[b]
14	Br	3-F		NR[b]

[a] Yield based on consumed starting material.
[b] NR – no reaction.

2-pyridylacetylene did not yield any product in the previous report. These observations can shed light on the possible reaction mechanism for the cyclization step.

Gold salts with complex counter anions such as –OTf or $–SbF_6$ are unstable and are generally obtained *in situ* by addition of AgOTf or $AgSbF_6$ as co-catalysts [38]. These bulky anions create relatively free Au cations that can freely coordinate with alkenes and alkynes [38]. We propose the catalytic cycle for the gold (III)-catalyzed intramolecular hydroamidation transformation, nucleophilic addition and intramolecular hydroarylation cascade (Scheme 3), which is similar to the gold-catalyzed tandem reactions reported before [36,37]. The terminal alkyne moiety of **3a** is first activated by the $AuBr_3/AgSbF_6$ catalyst system to generate intermediate **W**, which then converts to enamide intermediate **X** via intramolecular hydroamination. Attack on enamide **X** by nucleophilic arylalkynes in the presence of $AuBr_3/AgSbF_6$ generates a propargylamide **Y**. The nucleophilicity of the arylalkynes depends on the electron donating nature of the aryl substituents. Thus, electron withdrawing substituents negatively impact the reaction outcome. Finally, the propargylamide **Y** is also activated by Au/Ag-salt catalyst to generate **Z**, which undergoes intramolecular hydroarylation to yield the final product **4**.

One can argue that intermediate **X** can resonate to generate *N*-acyliminium ion (**C**, shown in Scheme 1), which can then undergo a [4+2] inverse electron demand aza-Diels–Alder reaction with arylacetylenes to produce 14-azasteroids in a concerted manner [18]. However, [Au] is known to catalyze hydroarylation reaction between alkynes and electron rich arenes [33] and therefore the proposed catalytic cycle in Scheme 3 appears more probable.



Scheme 3. A plausible mechanism for gold-catalyzed cyclization.

4. Conclusion

In conclusion, we have devised a concise synthesis of 14-azasteroids with angular methyl group at the C-13 position in three steps from cheaply available 2-naphthol analogs. Employing Bucherer reaction, naphthol analogs were converted to corresponding naphthylamines, which in turn were conjugated with 4-pentynoic acid under peptide coupling conditions. The resulting ynamides were reacted with arylacetylenes under $AuBr_3/AgSbF_6$ catalyst system to produce the title compounds in moderate to good yields.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.steroids.2015.03.010.

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