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Article

Concise Synthesis of Naphthalene-based 14-Aza-12-Oxasteroids

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Abstract: A concise, transition metal free four step synthetic pathway has been developed for the synthesis of tetracyclic heterosteroidal compounds, 14-aza-12-oxasteroids, starting from readily available 2-naphthol analogues. After conversion of 2-naphthols to 2-naphtylamines by the Bucherer reaction, subsequent selective C-acetylation was done *via* the Sugasawa reaction and reduction of the acetyl group using borohydride, resulted into corresponding amino-alcohols. The naphthalene based amino-alcohols underwent double dehydrations and double intramolecular cyclisation with oxo-acids leading to one-pot formation of a C-N bond, a C-O bond and an amide bond in tandem, to generate two additional rings completing the steroidal framework. A series of 14-aza-12-oxasteroids were synthesized by our developed synthetic strategy, in moderate yields and structure of one of the final products, 12a-Methyl-11-phenyl-11,12a-dihydro-1H-naphtho[2,1-d]pyrrolo[2,1-b][1,3]oxazin-3(2H)-one, was further confirmed by single crystal X-ray crystallography.

Keywords: heterosteroids; 14-aza-12-oxosteroid; Sugasawa reaction; Dean-Stark condensation; double dehydration

1. Introduction

Steroids serve as an important class of natural products by virtue of their ability to penetrate cells and bind to membrane and nuclear receptors [1]. Steroidal hormones are classified as glucocorticoids, mineralocorticoids, estrogen, progestogens and androgens because of their binding to a particular receptor to express their biological response [2]. Estrogens (Figure 1), an aromatic ring containing steroidal hormone, binds with estrogen receptors (ER) and trigger them in promoting a variety of physiological responses such as bone maturation, neuroprotective effects, reproductive functions, modulation of blood lipid profile, and breast cell proliferation [3]. Progesterone is a pro-gestational steroid hormone secreted by the female reproductive system. It is associated to the menstrual cycle, pregnancy, and development of an embryo (Figure 1) [4]. Medicinal chemists are intrigued with the biological activities of various modified steroids for drug design and development process. While retaining the steroidal framework, the structural modifications allow for modulation of the biological activities for the resulting molecules. The naturally occurring steroidal frameworks have been modified in various ways with the aim of identifying active compounds with improved efficacy and reduced toxicity. Heterosteroids is one such modification of the natural steroids, where one or more carbons are replaced by heteroatom(s). Medicinal chemistry of heterosteroids have been extensively studied [5]. A few of heterosteroids have already been culminated into successful drugs, such as stanozolol (hereditary angioedema) [6], danazol (antiestrogen) [7], RU-5135 (antagonist of GABA in the CNS) [8], finasteride (antihyperplastics) [9], and dutasteride (benign prostatic hyperplasia) [10] (Figure 1).

Although, synthesis of these structurally complex molecules in a short route from readily available starting materials is a challenge in the field of organic chemistry, several aza and oxa-steroids have been synthesized by various research groups in past by following different synthetic protocols. Oumzil *et al.* [11], reported total synthesis of 11-oxasteroid having pyridine ring as the A

ring, using intramolecular Diels-Alder reaction. Singh and Panda [12] described an efficient approach for the synthesis of 14-azasteroids using L-proline *via* intramolecular S_N2' cyclization reaction as a key step for the construction of nitrogen containing ring C. Bernath *et al.* [13], reported the stereospecific synthesis of 8-aza-12-oxasteroids. In continuation of our efforts of developing complex heterosteroids [14], mainly 14-azasterogen analogues, we herein report a concise synthesis of 14-aza-12-oxasteroids in four simple steps. We have previously reported the synthesis of tricyclic 7-oxa-2-azatricyclo[7.4.0.02,6]trideca-1(9),10,12- trien-3-ones and their homologs, by the reaction of keto acids with methyl chloroformate and variously substituted o-aminobenzyl alcohols using triethylamine as a base in toluene at room temperature [15], a similar type of synthesis with a different approach is reported here.

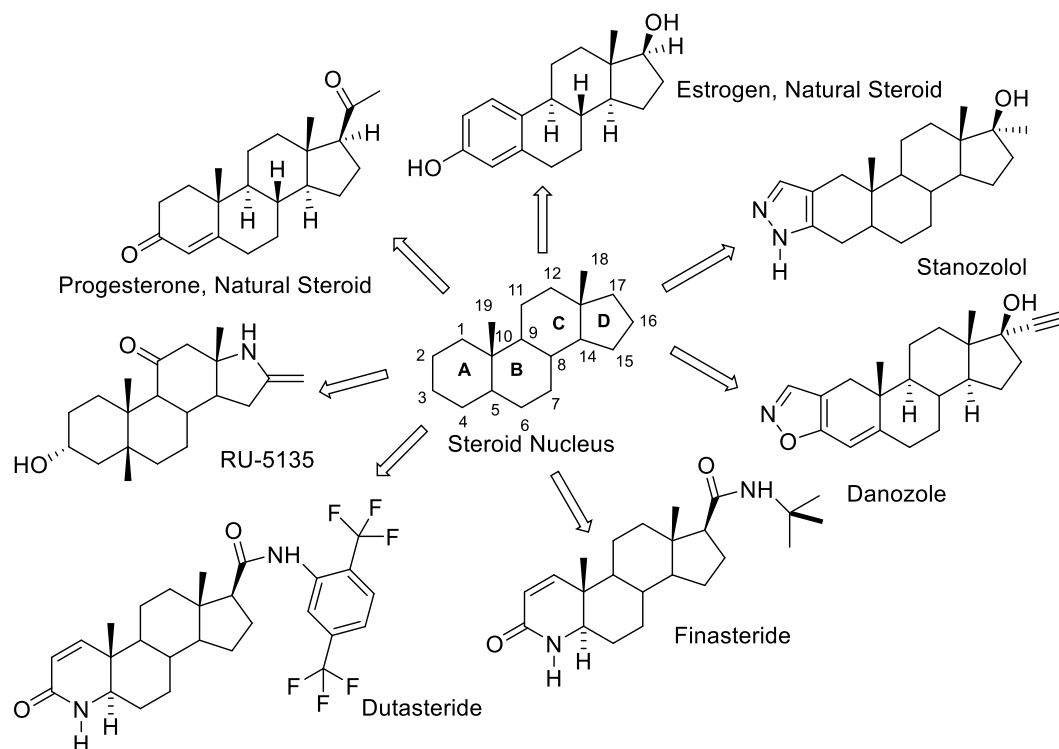
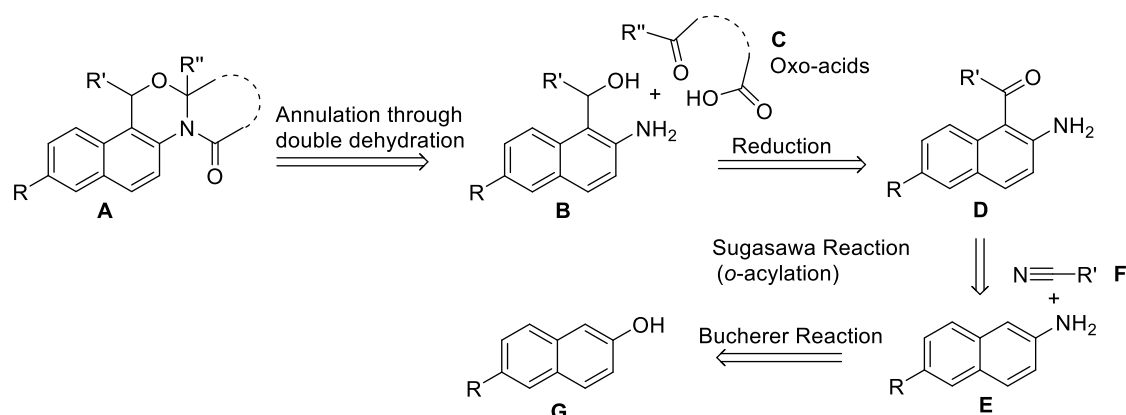


Figure 1. Representative natural steroids and clinically used heterosteroids.

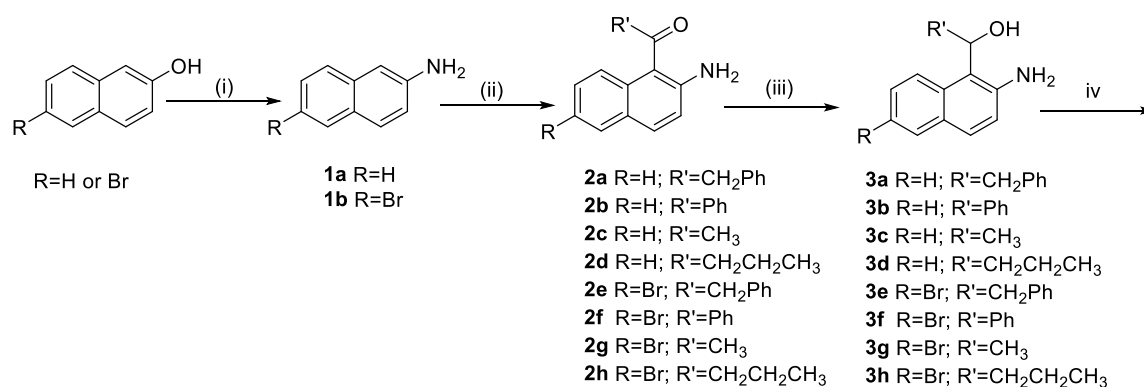
2. Results

We envisioned a synthetic strategy to obtain our designed 14-aza-12-oxasteroids with general structure **A**, retrosynthetic analysis of which is presented in Scheme 1. Double dehydration and cyclization between **B** and oxo acids **C** would yield the target 14-aza-12-oxasteroids **A**. Naphthalene-based amino-alcohols **B** can be prepared by the reduction of 1-acyl-2-aminonaphthalenes **D**, which in turn can be synthesized *via* Sugasawa reaction [16] of **E** with various aryl and alkyl nitriles **F**. 2-Aminonaphthalenes **E** can be obtained from commercially available 2-naphthols **G** *via* Bucherer reaction [17].



Scheme 1. Retrosynthetic analysis for the synthesis of 14-aza-12-oxasteroids **A**.

Our synthetic scheme started from commercially available 2-naphthol and 6-bromo-2-naphthol (Scheme 2), which were converted into 2-naphthylamine (**1a**, 78% yield) and 6-bromo-2-naphthylamine (**1b**, 85% yield), respectively by using Bucherer reaction [14a, 17]. The Friedel-Craft acylation is a common technique to attach acetyl groups on aromatic rings [18]. However, in an aniline system, coordination of the amino group with the Lewis acid results in a deactivated aromatic system. Sugasawa [16] took a unique approach to achieve *ortho*-acylation of anilines by using nitriles and two Lewis acids for the reaction. We successfully achieved *ortho*-acylation of 2-naphthylamines (**1a** & **1b**) by using various nitriles (benzyl nitrile, benzonitrile, acetonitrile and butyronitrile) by the Sugasawa protocol employing the BCl_3 and AlCl_3 system to obtain our desired amino-ketone compounds **2a-h** (Scheme 2). The reactions were performed under inert atmosphere since moisture in the air would react with the Lewis acids to form respective hydroxides. During the work-up of this reaction, dilute acid was used to convert imine intermediate to the desired ketones. Although in case of compounds **2b** and **2f**, extensive amounts of conc. acids and significantly longer heating times were required. Requirement of the forcing conditions for imine hydrolysis was probably due to greater stability of these imines having conjugation with naphthalene and benzene rings. The *ortho*-acylated compounds **2a-h** were obtained in 50-95 % yields after purification by column chromatography. Further, these acylated 2-aminonaphthalenes **2a-h** were reduced to corresponding amino alcohol analogues **3a-h**, by borohydride reduction.¹⁹ The crude compounds **3a-h** were obtained in 93-98 % yields, these compounds were used for the next reaction without further purification. A greener approach without involving any reagent, with recoverable solvent and lesser reaction time was explored to induce the double dehydration reaction between keto acids and the amino alcohols **3a-h** utilising a Dean-Stark apparatus as compared to our previous report for the synthesis of similar tricyclic compounds [15]. It was gratifying that the attempt to achieve the double dehydration and subsequent formation of three bonds in tandem between naphthalene-based amino alcohols **3a-h** and various keto acids (levulinic acid/ 2-carboxybenzaldehyde/ 4-acetylbutyric acid/ (2-oxopropyl sulfanyl)- acetic acid) were successful. Formation of new C-N, C-O and amide bond along with double cyclization reaction leads to the synthesis of our desired 14-aza-12-oxasteroid compounds **4a-l**, in moderate yields (30-78 %, Scheme 2, Table1). The structures of all the synthesized compounds **1a-b**, **2a-2h**, **3a-3h** and **4a-4l** were unambiguously established based on their spectral (^1H -, ^{13}C NMR and HRMS) data analysis. The structures of known compounds **1a** and **1b** were further confirmed on the basis of comparison of their physical and spectral data with those reported in the literature [14a, 17].

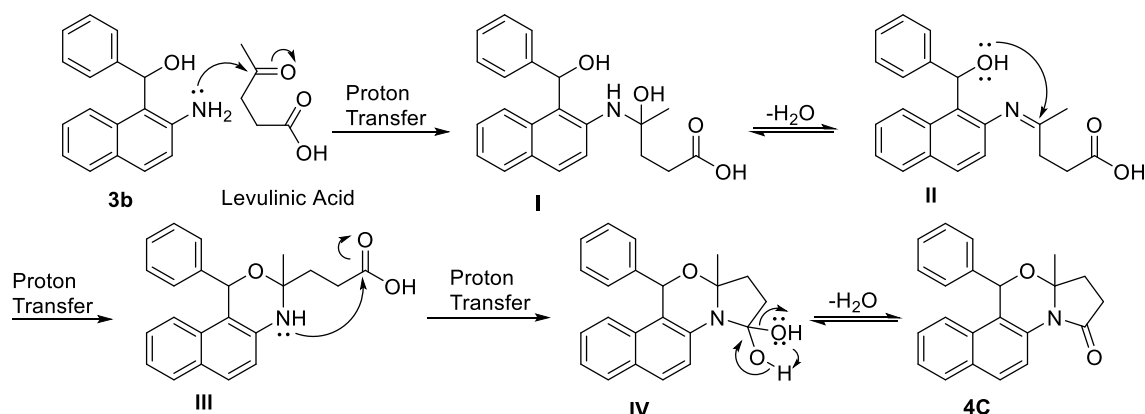


Compd No.	R	R'	R''	R'''
4a	H	CH ₂ Ph	CH ₃	CH ₂ CH ₂
4b	Br	CH ₂ Ph	CH ₃	CH ₂ CH ₂
4c	H	Ph	CH ₃	CH ₂ CH ₂
4d	Br	Ph	CH ₃	CH ₂ CH ₂
4e	H	CH ₃	CH ₃	CH ₂ CH ₂
4f	Br	CH ₃	CH ₃	CH ₂ CH ₂
4g	H	CH ₂ CH ₂ CH ₃	CH ₃	CH ₂ CH ₂
4h	Br	CH ₂ CH ₂ CH ₃	CH ₃	CH ₂ CH ₂
4i	H	CH ₃	H	Ph
4j	Br	CH ₃	H	Ph
4k	H	CH ₃	CH ₃	CH ₂ CH ₂ CH ₂
4l	H	CH ₃	CH ₃	CH ₂ SCH ₂

Scheme 2. Reagents and conditions: (i) (NH₄)₂SO₃, aq. NH₃, 100 psi, 150 °C (ii) (a) R'CN, BCl₃, AlCl₃, inert, toluene; (b) 1.0 M HCl; (iii) NaBH₄, MeOH, THF, inert condition; (iv) Keto-acids [levulinic acid/ 2-carboxybenzaldehyde/ 4-acetylbutyric acid/ (2-oxopropyl sulfanyl)-acetic acid], toluene, reflux, Dean-Stark distillation.

3. Discussion

The most plausible mechanism for the cyclization and dehydration reaction is shown in Scheme 3, taking **4c** as a representative example. The amino alcohol **3b** contains two nucleophiles with varying nucleophilicity. The amine group is more nucleophilic than the alcohol group, therefore it attacks the electrophilic ketone carbonyl on levulinic acid first, leading to dehydration and imine formation (**I** and **II**). Subsequent nucleophilic attack from the hydroxy group to the imine center resulted in intramolecular cyclisation, forming the amino-acetal C-ring in **III**. After proton transfer, the last nucleophilic attack from the secondary amino group to the carboxylic acid center carried out another intramolecular dehydration, forming the lactam as the D-ring in **4c**.



Scheme 3. A plausible mechanism for synthesis of 14-aza-12-oxasteroids considering synthesis of **4c** as the representative example.

The heterosteroidal products **4a-l** obtained following this synthetic pathway were expected to give a mixture of up-to four stereoisomeric products: the (*R,R*) and (*S,S*) enantiomeric pair and the (*R,S*) and (*S,R*) enantiomeric pair, as we did not incorporate any means for enantioselection. In most cases (except in **4i** and **4j**) there was no evidence for the formation of mixtures of diastereomers in the NMR data. The final compounds **4a-h** and **4k-l** showed only one set of peaks in their NMR spectra (see Supporting Information), which indicates that these molecules were synthesized as racemic enantiomeric pairs. The analysis of the X-ray crystallographic data of compound **4c** reveals that the unit cell has non-centrosymmetric space group and thus it cannot be a racemic mixture. This observation can be possibly due to the preferential crystallization of the C6-*R*, C4-*S* enantiomer which was randomly selected for crystallography. Also, from the crystal structure of compound **4c** (Figure 2), it can be visualized that the methyl group of C4 and the phenyl group of C6 are in a *trans* geometry indicating the most thermodynamically stable product. This, along with NMR spectra, confirm that only one enantiomeric pair (*R,S* and *S,R*) was diastereoselectively formed in the reaction. In case of compounds **4i** and **4j**, where R'' is H (instead of methyl group), mixture of diastereomers was obtained as evident from the NMR data. It appears that higher amount of steric hinderance caused by the presence of angular methyl group led to exclusive diastereoselectivity in case of compounds **4a-h** and **4k-l**. However, lower amount of steric hinderance in case of **4i** and **4j**, allowed for the formation of mixture of diastereomers albeit with some selectivity (see Experimental). The ratio of formation of these diastereomers was established by the proton NMR spectroscopy. The crystallographic data of compound **4c** was deposited in the Cambridge Crystallographic Data Centre with CCDC no. 2006680. The ORTEP diagram of compound **4c** is shown in Figure 2.

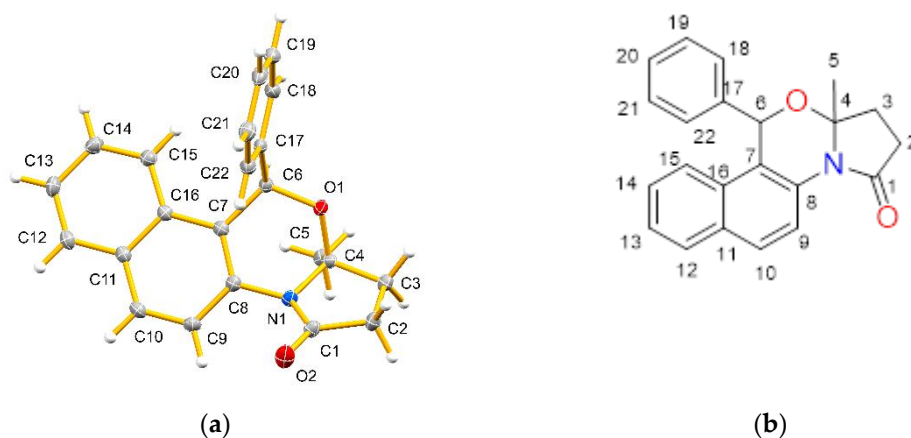


Figure 2. (a) Ortep diagram, of compound **4c** drawn in 50 % thermal probability ellipsoids; (b) chemical structure of **4c** with similar numbering pattern as X-ray crystal structure.

4. Materials and Methods

General: All the chemicals and solvents used for these syntheses were obtained from commercial sources and were used without modification, except for toluene and methanol. Toluene was dried with sodium metal overnight and distilled before reactions. Methanol was dried with molecular sieves overnight before use. Among the various keto acids used for our synthesis, levulinic acid, 2-carboxybenzaldehyde and 4-acetylbutyric acids were obtained from A.K. Scientific, Inc. USA. (2-Oxopropyl sulfanyl)-acetic acid was synthesized by following a literature procedure [20] starting from mercaptoacetic acid (obtained from Sigma Aldrich). TLCs were performed on pre-coated Merck silica gel 60F254 plates with the spots detected under UV light. The silica gel used in column chromatography was 230-400 mesh. NMR spectra were recorded using a Bruker AC-300 Avance spectrometer at 300 MHz for ^1H NMR and 75 MHz for $^{13}\text{C}\{^1\text{H}\}$ NMR. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded in either CDCl_3 or $\text{DMSO}-d_6$ solvents. ^1H NMR spectra were reported relative

to CHCl₃ (δ: 7.26) or DMSO (δ: 2.50). ¹³C{¹H} NMR spectra were reported relative to CDCl₃ (δ: 77.16) or DMSO-d₆ (δ: 39.52). HRMS (ESI) spectra were recorded using Orbitrap Q-exactive analyser. In X-ray crystallography, the crystal chosen was attached to the tip of a MicroLoop with Paratone-N oil. Measurements were made on a Bruker D8 VENTURE diffractometer equipped with a PHOTON III CMOS detector using monochromated Cu Kα radiation (λ = 1.54178 Å) from an Incoatec micro-focus sealed tube at 100 K. Among the various keto acids used for our synthesis, levulinic acid, 2-carboxybenzaldehyde and 4-acetylbutyric acids were obtained from a commercial supplier, A.K. Scientific, Inc. USA. (2-Oxopropyl sulfanyl)-acetic acid was synthesized by following a literature procedure starting from mercaptoacetic acid,²⁰ which in turn was obtained from Sigma Aldrich, USA.

General procedure for the synthesis of 1-acyl-2-aminonaphthalenes (**2a-h**): In a N₂-flushed 250 mL round bottom flask, 2-naphthylamines (2.00 g, **1a**: 13.96 mmol; **1b**: 9.01 mmol, 1 eq.) and AlCl₃ (1.2 eq.) were added. The flask was flushed again with N₂. Toluene was added to the reaction mixture followed by BCl₃ heptane solution (1.0 M, 1.2 eq.). The R'CN (acetonitrile/butyronitrile/benzonitrile/ benzyl nitrile, 6.5 eq) was then added to the reaction mixture. The mixture was refluxed and was monitored with TLC (**2a-b**: 3.5 h, **2c-d**: 2 h, **2e-f**: 4 h, **2g-h**: 2.5 h). After cooling to room temperature, aq. HCl (1.0 M, 1.2 eq., **2b** and **2f**: 12.0 M, 500 eq.) was added to the resultant mixture forming a yellow-orange mixture, which was heated at 80 °C for 30 mins (4 hrs for **2b** and **2f**). During the work up, the reaction mixture was cooled to room temperature and the yellow-orange mixture was poured into ice-water (ca. 50 mL). This was followed by the addition of aq. NaOH (5.0 M) until pH >13. More ice and NaOH pellets were used as needed with **2b** and **2f**, to bring the pH >13. The mixture was extracted with EtOAc (3 × 50 mL). The organic layers were added together and washed with brine (50 mL) and dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo* to form the crude product. The crude product was purified by column chromatography to yield **2a-h**.

1-(2-Aminonaphthalen-1-yl)-2-phenylethanone (**2a**): Dark orange solid; 50% yield (1.81 g); m.p. 72-73°C; ¹H NMR (CDCl₃, 300 MHz): δ 7.85 (d, *J* = 9.0 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.39-7.28 (m, 6H), 6.83 (d, *J* = 9.0 Hz, 1H), 5.48 (brs, 2H), 4.36 (s, 2H); ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 203.6, 146.0, 135.6, 133.4, 129.4, 128.7, 128.4, 127.4, 126.6, 124.1, 122.6, 122.6, 119.2, 115.4, 50.0; **ESI-HRMS**: calcd. C₁₈H₁₆NO: 262.1226 [M+H]⁺; found 262.1227.

(2-Aminonaphthalen-1-yl)(phenyl)methanone (**2b**): Yellow crystals; 60% yield (2.06 g); m.p. 166-167°C. ¹H NMR (DMSO, 300 MHz): δ 7.78 (d, *J* = 9.0 Hz, 1H), 7.71 (d, *J* = 6.0 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 2H), 7.59 (t, *J* = 6.0 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.17-7.06 (m, 4H), 5.93 (brs, 2H); ¹³C{¹H} NMR (DMSO, 75 MHz): δ 197.8, 145.7, 138.6, 132.8, 132.2, 131.4, 129.0, 128.5, 128.0, 126.3, 125.9, 123.3, 121.2, 118.9, 112.4; **ESI-HRMS**: calcd. C₁₇H₁₄NO: 248.1070 [M+H]⁺; found 248.1070.

1-Acetyl-2-aminonaphthalene (**2c**): Orange solid; 63% yield (1.62 g); m.p. 107-108 °C. ¹H NMR (CDCl₃, 300 MHz): δ 7.82 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 6.0 Hz, 1H), 7.65 (d, *J* = 6.0 Hz, 1H), 7.46 (t, *J* = 9.0 Hz, 1H), 7.27 (t, *J* = 9.0 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 5.80 (brs, 2H), 2.70 (s, 3H); ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 202.9, 146.4, 133.8, 132.6, 128.7, 127.7, 127.4, 124.4, 122.6, 119.5, 115.2, 32.3.

1-(2-Aminonaphthalen-1-yl)butan-1-one (**2d**): Orange oil; 50% yield (1.33 g); ¹H NMR (CDCl₃, 300 MHz): δ 7.74-7.68 (m, 2H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.46 (t, *J* = 9.0 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 5.17 (brs, 2H), 2.99 (t, *J* = 7.5 Hz, 2H), 1.86 (sx, *J* = 7.8 Hz, 2H), 0.97 (t, *J* = 6.0 Hz, 3H); ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 207.7, 144.8, 132.8, 131.2, 128.6, 127.6, 127.2, 124.0, 122.5, 119.6, 116.4, 46.2, 19.3, 13.8; **ESI-HRMS**: calcd. C₁₄H₁₆NO: 214.1226 [M+H]⁺; found 214.1231.

1-(2-Amino-6-bromonaphthalen-1-yl)-2-phenylethanone (**2e**): Dark purple solid; 75% yield (2.29 g); m.p. 101-102°C; ¹H NMR (CDCl₃, 300 MHz): δ 7.84 (s, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.55 (m, 2H), 7.34-7.26 (m, 5H), 6.83 (d, *J* = 12.0 Hz, 1H), 5.46 (brs, 2H), 4.26 (s, 2H); ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 203.2, 146.0, 135.3, 132.3, 130.6, 130.4, 129.3, 128.7, 128.5, 126.8, 125.7, 120.3, 115.9, 50.1; **ESI-HRMS**: calcd. C₁₈H₁₅BrNO: 340.0332 [M+H]⁺; found 340.0335.

(2-Amino-6-bromonaphthalen-1-yl)(phenyl)methanone (**2f**): Yellow crystals; 65% yield (1.90 g); m.p. 120-121°C; ¹H NMR (DMSO, 300 MHz): δ 7.97 (d, *J* = 1.5 Hz, 1H), 7.77 (d, *J* = 12.0 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 2H), 7.60 (d, *J* = 6.0 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 6.0 Hz, 1H), 7.16 (d, *J* = 9.0 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 6.03 (s, 2H); ¹³C{¹H} NMR (DMSO, 75 MHz): δ 197.6, 146.4, 138.6,

133.3, 131.1, 130.9, 129.9, 129.3, 128.9, 127.4, 125.6, 120.4, 113.9, 112.3; **ESI-HRMS**: calcd. $C_{17}H_{13}BrNO$: 326.0175 $[M+H]^+$; found 326.0184.

1-Acetyl-2-amino-6-bromonaphthalene (**2g**): Orange solid; 95% yield (2.25 g); m.p. 135-137 °C. 1H NMR ($CDCl_3$, 300 MHz): δ 7.80 (s, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 1H), 5.94 (brs, 2H), 2.66 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 202.3, 147.0, 132.7, 131.2, 130.6, 130.4, 130.0, 128.8, 128.2, 125.9, 120.6, 32.2.

1-(2-Amino-6-bromonaphthalen-1-yl)butan-1-one (**2h**): Brown solid; 60% yield (1.57 g); m.p. 42-43 °C; 1H NMR ($CDCl_3$, 300 MHz): δ 7.81 (s, 1H), 7.59-7.47 (m, 3H), 6.86 (d, J = 9.0 Hz, 1H), 5.02 (brs, 2H), 2.92 (t, J = 7.5 Hz, 2H), 1.79 (q, J = 9.0 Hz, 2H), 0.95 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 207.1, 145.1, 131.8, 130.7, 130.5, 130.2, 128.7, 125.6, 120.3, 116.1, 115.7, 46.2, 19.3, 13.8; **ESI-HRMS**: calcd. $C_{14}H_{13}BrNO$: 292.0332 $[M+H]^+$; found 292.0337.

General procedure for the synthesis of 1-(1-hydroxyalkyl)-2-aminonaphthalenes (**3a-h**): In a 50 mL flask, **2a-h** (500 mg, 1 eq.) were dissolved in a 1:1 mixture of methanol and THF solution (10 mL). The reaction flask was flushed with N_2 gas and cooled to 0 °C in an ice bath. While stirring, $NaBH_4$ powder (6 eq., except **2b** & **2f**: 12 eq) was added in small batches. The reaction was stirred in a round bottom flask with a N_2 balloon for 5 mins in the ice bath, and further stirred at room temperature until no starting material was observed on the TLC (ca. 1 hr). The solvent was removed *in vacuo* leaving a solid. Distilled water (ca. 5 mL) was added and the products were extracted with EtOAc (2 × 25 mL) and washed with distilled water (2 × 10 mL). The organic layer was dried with anhydrous Na_2SO_4 and the solvent was removed *in vacuo* yielding the products in pure form.

1-(2-Aminonaphthalen-1-yl)-2-phenylethanol (**3a**): Orange solid; 93% yield (467 mg); m.p. 129-131 °C; 1H NMR ($CDCl_3$, 300 MHz): δ 7.82 (d, J = 6.0 Hz, 1H), 7.73 (d, J = 6.0 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.39-7.25 (m, 6H), 6.89 (d, J = 9.0 Hz, 1H), 5.85 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 3.81 (brs, 3H), 3.39 (dd, J = 15.0 Hz, 9.0 Hz, 1H), 3.12 (dd, J = 12.0 Hz, 3.0 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 143.1, 138.6, 131.8, 129.5, 129.1, 128.8, 128.5, 128.1, 126.6, 126.6, 121.8, 120.6, 120.3, 115.9, 72.0, 40.7; **ESI-HRMS**: calcd. $C_{18}H_{18}NO$: 264.1383 $[M+H]^+$; found 264.1383.

(2-Aminonaphthalen-1-yl)(phenyl)methanol (**3b**): Pale orange solid; 94% yield (474 mg); m.p. 131-133 °C; 1H NMR (DMSO, 300 MHz): δ 7.97 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 9.0 Hz, 1H), 7.59 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 6.0 Hz, 2H), 7.31-7.23 (m, 3H), 7.19-7.09 (m, 2H), 7.02 (d, J = 9.0 Hz, 1H), 6.62 (s, 1H), 6.16 (s, 1H), 5.61 (brs, 2H); $^{13}C\{^1H\}$ NMR (DMSO, 75 MHz): δ 144.7, 144.4, 132.8, 128.4, 128.3, 127.8, 127.0, 126.3, 126.0, 125.9, 122.1, 120.6, 119.9, 116.0, 68.5; **ESI-HRMS**: calcd. $C_{17}H_{16}NO$: 250.1226 $[M+H]^+$; found 250.1214.

1-(1-Hydroxyethyl)-2-aminonaphthalene (**3c**): Colourless solid; 98% yield (499 mg); m.p. 89.9-91.2 °C. 1H NMR ($CDCl_3$, 300 MHz): δ 7.78 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 9.0 Hz, 1H), 7.41 (t, J = 6.0 Hz, 1H), 7.23 (t, J = 6.0 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 5.91 (q, J = 7.5 Hz, 1H), 4.82 (brs, 1H), 3.33 (brs, 2H), 1.65 (d, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 142.8, 131.6, 128.8, 128.7, 127.9, 126.6, 121.8, 120.6, 120.2, 117.4, 67.0, 20.2. **ESI-HRMS**: calcd. for $C_{12}H_{14}NO$: 188.1070 $[M+H]^+$; found 188.1068.

1-(2-Aminonaphthalen-1-yl)butan-1-ol (**3d**): Orange solid; 95% yield (480 mg); m.p. 86-88 °C; 1H NMR (DMSO, 300 MHz): δ 7.87 (d, J = 6.0 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 5.64 (brs, 2H), 5.53 (brs, 2H), 2.01-1.89 (m, 1H), 1.73-1.62 (m, 1H), 1.57-1.46 (m, 1H), 1.34-1.23 (m, 1H), 0.89 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (DMSO, 75 MHz): δ 144.5, 132.2, 128.4, 127.7, 126.9, 121.2, 120.5, 120.0, 116.5, 68.1, 37.8, 19.1, 14.1; **ESI-HRMS**: calcd. $C_{14}H_{18}NO$: 216.1383 $[M+H]^+$; found 216.1386.

1-(2-Amino-6-bromonaphthalen-1-yl)-2-phenylethanol (**3e**): Purple solid; 93% yield (468 mg); m.p. 144-146 °C; 1H NMR (DMSO, 300 MHz): 7.86 (s, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 7.25-7.21 (m, 4H), 7.18-7.12 (m, 2H), 7.06 (d, J = 9.0 Hz, 1H), 5.80 (brs, 2H), 5.61 (brs, 1H), δ 5.69 (s, 1H), 3.20 (dd, J = 15.0 Hz, 9.0 Hz, 1H), 2.96 (dd, J = 12.0 Hz, 6.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (DMSO, 75 MHz): δ 145.1, 140.5, 139.3, 130.7, 129.9, 129.5, 128.4, 128.2, 127.9, 127.3, 125.8, 121.1, 115.9, 113.0, 69.6, 40.4; **ESI-HRMS**: calcd. $C_{18}H_{17}BrNO$: 342.0488 $[M+H]^+$; found 342.0495.

(2-Amino-6-bromonaphthalen-1-yl)(phenyl)methanol (**3f**): Very pale orange solid; 94% yield (474 mg); m.p. 171-172 °C; 1H NMR (DMSO, 300 MHz): δ 7.94-7.89 (m, 2H), 7.58 (d, J = 9.0 Hz, 1H),

7.34 (d, $J = 9.0$ Hz, 3H), 7.25 (t, $J = 7.5$ Hz, 2H), 7.16 (t, $J = 6.0$ Hz, 1H), 7.06 (d, $J = 9.0$ Hz, 1H), 6.54 (s, 1H), 6.17 (s, 1H), 5.72 (brs, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO, 75 MHz): δ 145.2, 144.2, 131.4, 129.8, 128.4, 127.8, 127.7, 126.3, 125.9, 124.9, 120.9, 116.1, 113.1, 68.2; **ESI-HRMS**: calcd. $\text{C}_{17}\text{H}_{15}\text{BrNO}$: 328.0332 $[\text{M}+\text{H}]^+$; found 328.0319.

1-(1-Hydroxyethyl)-2-amino-6-bromonaphthalene (**3g**): Colourless solid; 98% yield (495 mg); m.p. 120-123 °C. ^1H NMR (DMSO- d_6 , 300 MHz): δ 7.90 (s, 1H), 7.87 (d, $J = 3.0$ Hz, 1H), 7.50 (d, $J = 9.0$ Hz, 1H), 7.39 (d, $J = 3.0$ Hz, 1H), 6.99 (d, $J = 9.0$ Hz, 1H), 5.74 (brs, 2H), 5.59 (q, $J = 6.0$ Hz, 1H), 5.52 (brs, 1H), 1.41 (d, $J = 6.0$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 , 75 MHz): δ 144.6, 130.3, 129.9, 128.4, 128.2, 126.9, 123.7, 121.0, 117.1, 112.9, 64.4, 21.1; **ESI-HRMS**: calcd. for $\text{C}_{12}\text{H}_{13}\text{BrNO}$: 266.0175 $[\text{M}+\text{H}]^+$; found 266.0173.

1-(2-Amino-6-bromonaphthalen-1-yl)butan-1-ol (**3h**): Brown solid; 98% yield (493 mg); m.p. 138-140 °C; ^1H NMR (DMSO, 300 MHz): δ 7.87 (d, $J = 1.5$ Hz, 2H), 7.52 (d, $J = 9.0$ Hz, 1H), 7.40 (d, $J = 9.0$ Hz, 1H), 7.01 (d, $J = 9.0$ Hz, 1H), 5.80 (brs, 2H), 5.61 (brs, 1H), 5.42 (t, $J = 6.0$ Hz, 1H), 1.96-1.84 (m, 1H), 1.69-1.56 (m, 1H), 1.54-1.42 (m, 1H), 1.30-1.18 (m, 1H), 0.87 (t, $J = 7.5$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO, 75 MHz): δ 144.7, 130.8, 129.9, 128.4, 127.0, 121.1, 116.9, 113.0, 68.0, 36.9, 19.1, 14.1; **ESI-HRMS**: calcd. $\text{C}_{14}\text{H}_{17}\text{BrNO}$: 294.0488 $[\text{M}+\text{H}]^+$; found 294.0490.

General procedure for the synthesis of 14-aza-12-oxasteroid analogs (**4a-l**): In a 50 mL round bottom flask with a stir bar, **3a-h** (200 mg, 1 eq.) were dissolved in toluene (ca. 5 mL), and then appropriate keto acid [levulinic acid/2-carboxybenzaldehyde/4-acetylbutyric acid/(2-oxopropyl sulfanyl)-acetic acid, 1.5 eq.] was added. The reaction mixture was refluxed for 2 hrs with a Dean-Stark apparatus, with dry toluene filled in the vertical column. The solvent was removed from the reaction mixture *in vacuo* and the crude product was purified using column chromatography to yield respective 14-aza-12-oxasteroid analogs.

11-Benzyl-12a-methyl-11,12a-dihydro-1*H*-naphtho[2,1-*d*]pyrrolo[2,1-*b*][1,3]oxazin-3(2*H*)-one (**4a**): Orange solid; 40% yield (104 mg); m.p. 124-126 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 8.16 (d, $J = 9.0$ Hz, 1H), 7.93 (t, $J = 7.5$ Hz, 2H), 7.84 (d, $J = 9.0$ Hz, 1H), 7.62 (t, $J = 7.5$ Hz, 1H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.27-7.22 (m, 3H), 7.07 (d, $J = 3.0$ Hz, 2H), 5.85 (d, $J = 3.0$ Hz, 1H), 3.43 (d, $J = 12.0$ Hz, 1H), 3.06 (dd, $J = 15.0$ Hz, 6.0 Hz, 1H), 2.58 (t, $J = 7.5$ Hz, 2H), 2.37-2.20 (m, 2H), 1.42 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO, 75 MHz): δ 172.1, 137.7, 131.4, 129.5, 129.1, 128.4, 127.8, 126.5, 126.5, 124.9, 122.6, 121.8, 120.7, 89.3, 72.1, 42.8, 32.6, 29.8, 22.4; **ESI-HRMS**: calcd. $\text{C}_{23}\text{H}_{22}\text{NO}_2$: 344.1645 $[\text{M}+\text{H}]^+$; found 344.1644.

11-Benzyl-8-bromo-12a-methyl-11,12a-dihydro-1*H*-naphtho[2,1-*d*]pyrrolo[2,1-*b*][1,3]oxazin-3(2*H*)-one (**4b**): Purple solid; 33% yield (82 mg); m.p. 106-108 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 8.16 (d, $J = 9.0$ Hz, 1H), 8.05 (d, $J = 1.5$ Hz, 1H), 7.79 (d, $J = 9.0$ Hz, 1H), 7.72 (d, $J = 9.0$ Hz, 1H), 7.66 (d, $J = 9.0$ Hz, 1H), 7.23-7.19 (m, 3H), 7.00-6.99 (m, 2H), 5.79 (dd, $J = 6.0$ Hz, 3.0 Hz, 1H), 3.36 (dd, $J = 15.0$ Hz, 3.0 Hz, 1H), 3.04 (dd, $J = 15.0$ Hz, 6.0 Hz, 1H), 2.56 (t, $J = 7.5$ Hz, 2H), 2.18-2.34 (m, 2H), 1.40 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO, 75 MHz): δ 172.0, 137.2, 132.3, 131.7, 131.0, 129.8, 129.4, 127.8, 127.5, 126.6, 124.4, 122.0, 121.8, 118.8, 71.9, 89.3, 42.8, 32.6, 29.8, 22.3; **ESI-HRMS**: calcd. $\text{C}_{23}\text{H}_{21}\text{BrNO}_2$: 421.0677 $[\text{M}+\text{H}]^+$; found 421.0740.

12a-Methyl-11-phenyl-11,12a-dihydro-1*H*-naphtho[2,1-*d*]pyrrolo[2,1-*b*][1,3]oxazin-3(2*H*)-one (**4c**): Yellow-orange powder; 45% yield (119 mg); m.p. 189-191 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 8.46 (d, $J = 9.0$ Hz, 1H), 7.90 (d, $J = 9.0$ Hz, 1H), 7.83 (d, $J = 9.0$ Hz, 1H), 7.48 (d, $J = 9.0$ Hz, 1H), 7.36 (t, $J = 6.0$ Hz, 1H), 7.32-7.26 (m, 6H), 6.45 (s, 1H), 2.71-2.66 (m, 2H), 2.29 (t, $J = 9.0$ Hz, 2H), 1.64 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO, 75 MHz): δ 172.6, 141.6, 132.3, 131.5, 129.7, 129.5, 129.2, 129.0, 129.0, 128.8, 126.6, 125.2, 124.6, 120.7, 120.6, 90.6, 75.8, 33.1, 30.6, 22.0; **ESI-HRMS**: calcd. $\text{C}_{22}\text{H}_{20}\text{NO}_2$: 330.1489 $[\text{M}+\text{H}]^+$; found 330.1489.

8-Bromo-12a-methyl-11-phenyl-11,12a-dihydro-1*H*-naphtho[2,1-*d*]pyrrolo[2,1-*b*][1,3]oxazin-3(2*H*)-one (**4d**): Purple-brown solid; 30% yield (75 mg); m.p. 203-205 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 8.49 (d, $J = 9.0$ Hz, 1H), 7.97 (s, 1H), 7.79 (d, $J = 9.0$ Hz, 1H), 7.31-7.27 (m, 5H), 7.23-7.21 (m, 2H), 6.39 (s, 1H), 2.70-2.65 (m, 2H), 2.29 (t, $J = 6.0$ Hz, 2H), 1.64 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO, 75 MHz): δ 172.2, 140.9, 132.3, 132.2, 130.6, 129.5, 128.9, 128.5, 128.1, 127.8, 125.9, 121.4, 120.3, 118.8, 90.2, 75.2, 32.7, 30.1, 21.6; **ESI-HRMS**: calcd. $\text{C}_{22}\text{H}_{19}\text{BrNO}_2$: 408.0594 $[\text{M}+\text{H}]^+$; found 408.0584.

11,12a-Dimethyl-11,12a-dihydro-1H-naphtho[2,1-d]pyrrolo[2,1-b][1,3]oxazin-3(2H)-one (**4e**): Viscous orange liquid; 34% yield (96 mg); ¹H NMR (CDCl₃, 300 MHz): δ 8.35 (d, *J* = 1.5 Hz, 1H), 7.87-7.78 (m, 3H), 7.53-7.43 (m, 2H), 5.66 (q, *J* = 6.0 Hz, 1H), 2.67 (t, *J* = 9.0 Hz, 2H), 2.30 (t, *J* = 9.0 Hz, 2H), 1.65 (d, *J* = 6.0 Hz, 3H), 1.47 (s, 3H); ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 172.1, 131.2, 130.2, 129.2, 128.9, 128.2, 126.2, 124.8, 123.3, 123.1, 120.4, 89.3, 68.0, 32.8, 30.1, 23.1, 21.5; **ESI-HRMS**: calcd. for C₁₇H₁₈NO₂: 268.1332 [M+H]⁺; found 268.1328.

8-Bromo-11,12a-dimethyl-11,12a-dihydro-1H-naphtho[2,1-d]pyrrolo[2,1-b][1,3]-oxazin-3(2H)-one (**4f**): Viscous orange liquid; 35% yield (92 mg); ¹H NMR (CDCl₃, 300 MHz): δ 8.35 (d, *J* = 1.5 Hz, 1H), 7.98 (s, 1H), 7.69-7.39 (m, 3H), 5.58 (q, *J* = 6.0 Hz, 1H), 2.65 (t, *J* = 7.5 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 1.59 (d, *J* = 6.0 Hz, 3H), 1.43 (s, 3H); ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 172.2, 132.3, 130.7, 129.4, 127.7, 127.2, 124.8, 123.5, 121.4, 119.0, 118.7, 89.3, 67.7, 32.7, 30.0, 23.1, 21.4; **ESI-HRMS**: calcd. for C₁₇H₁₇BrNO₂: 346.0437 [M+H]⁺; found 346.0433.

12a-Methyl-11-propyl-11,12a-dihydro-1H-naphtho[2,1-d]pyrrolo[2,1-b][1,3]oxazin-3(2H)-one (**4g**): Orange solid; yield 45% (123 mg); m.p. 123-125 °C; ¹H NMR (CDCl₃, 300 MHz): δ 8.27 (d, *J* = 9.0 Hz, 1H), 7.87-7.76 (m, 3H), 7.52 (t, *J* = 9.0 Hz, 1H), 7.45 (t, *J* = 9.0 Hz, 1H), 5.58 (dd, *J* = 6.0 Hz, 1.5 Hz, 1H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.12-2.01 (m, 1H), 1.87-1.75 (m, 1H), 1.55-1.44 (m, 1H), 1.44 (s, 3H), 1.32-1.21 (m, 1H), 0.87 (t, *J* = 6.0 Hz, 3H). ¹³C{¹H} NMR (DMSO, 75 MHz): δ 172.3, 131.2, 131.0, 129.2, 128.9, 128.1, 126.2, 124.8, 122.9, 122.6, 120.5, 89.3, 71.3, 38.8, 32.8, 30.1, 21.9, 18.0, 13.9; **ESI-HRMS**: calcd. C₁₉H₂₂NO₂: 296.1645 [M+H]⁺; found 296.1631.

8-Bromo-12a-methyl-11-propyl-11,12a-dihydro-1H-naphtho[2,1-d]pyrrolo[2,1-b][1,3]-oxazin-3(2H)-one (**4h**): Purple oil; 40% yield (102 mg); ¹H NMR (CDCl₃, 300 MHz): δ 8.29 (d, *J* = 9.0 Hz, 1H), 7.99 (d, *J* = 1.5 Hz, 1H), 7.70-7.62 (m, 2H), 7.56 (d, *J* = 9.0 Hz, 1H), 5.53 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.06-1.95 (m, 1H), 1.82-1.70 (m, 1H), 1.51-1.39 (m, 1H), 1.43 (s, 3H), 1.23-1.15 (m, 1H), 0.85 (t, *J* = 7.5 Hz, 3H); ¹³C{¹H} NMR (DMSO, 75 MHz): δ 172.3, 132.4, 131.3, 130.8, 129.4, 127.6, 127.2, 124.6, 122.7, 121.5, 118.7, 89.3, 71.1, 38.8, 32.8, 30.0, 21.8, 17.9, 13.8; **ESI-HRMS**: calcd. C₁₉H₂₁BrNO₂: 374.0750 [M+H]⁺; found 374.0739.

7-Methyl-7H-naphtho[2',1':4,5][1,3]oxazino[2,3-a]isoindol-13(8aH)-one (**4i**): Viscous orange liquid; 78% yield (249 mg). Mixture of two diastereomers (6:4). Data for the major diastereomer are presented here; ¹H NMR (CDCl₃, 300 MHz): δ 8.56 (d, *J* = 1.5 Hz, 1H), 7.94-7.43 (m, 9H), 5.95 (q, *J* = 9.0 Hz, 1H), 5.79 (s, 1H), 1.72 (d, *J* = 9.0 Hz, 3H); ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 164.8, 140.2, 132.7, 130.2, 128.9, 128.5, 126.6, 126.4, 124.7, 124.6, 124.0, 123.5, 123.2, 123.1, 122.4, 120.8, 119.0, 83.1, 72.4, 23.3; **ESI-HRMS**: calcd. for C₂₀H₁₆NO₂: 302.1176 [M+H]⁺; found 302.1173.

4-Bromo-7-methyl-7H-naphtho[2',1':4,5][1,3]oxazino[2,3-a]isoindol-13(8aH)-one (**4j**): Colourless solid; 40% yield (112 mg); m.p. 230-233 °C. Mixture of two diastereomers (8:2). Data for the major diastereomer are presented here; ¹H NMR (CDCl₃, 300 MHz): δ 8.58 (d, *J* = 9.0 Hz, 1H), 8.03 (s, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 8.03-7.59 (m, 6H), 5.94 (q, *J* = 6.0 Hz, 1H), 5.87 (s, 1H), 1.70 (d, *J* = 6.0 Hz, 3H); ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 164.9, 140.2, 132.9, 132.2, 131.0, 130.5, 130.0, 129.7, 128.2, 127.7, 124.9, 124.2, 123.6, 122.5, 120.3, 118.6, 83.2, 72.3, 23.4; **ESI-HRMS**: calcd. for C₂₀H₁₅BrNO₂: 380.0281 [M+H]⁺; found 380.0284.

12,13a-Dimethyl-1,2,3,13a-tetrahydronaphtho[2,1-d]pyrido[2,1-b][1,3]oxazin-4(12H)-one (**4k**): Viscous orange liquid; 30% yield (91 mg); ¹H NMR (CDCl₃, 300 MHz): δ 7.87-7.70 (m, 4H), 7.55-7.46 (m, 2H), 5.65 (q, *J* = 6.0 Hz, 1H), 2.63 (t, *J* = 9.0 Hz, 2H), 2.13 (t, *J* = 9.0 Hz, 2H), 1.63 (d, *J* = 6.0 Hz, 3H), 1.38 (s, 3H), 0.83 (t, *J* = 9.0 Hz, 2H); ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 170.1, 132.8, 131.6, 128.9, 128.8, 127.6, 127.1, 126.2, 125.2, 122.5, 86.1, 67.3, 37.0, 34.1, 25.0, 23.5, 17.0.

12,13a-Dimethyl-12,13a-dihydro-1H-naphtho[2,1-d][1,4]thiazino[3,4-b][1,3]oxazin-4(3H)-one (**4l**): Viscous orange liquid; 30% yield (92 mg); ¹H NMR (CDCl₃, 300 MHz): δ 7.87-7.66 (m, 4H), 7.56-7.47 (m, 2H), 5.65 (q, *J* = 7.5 Hz, 1H), 3.60 (m, 2H), 3.06 (s, 2H), 1.68 (d, *J* = 7.5 Hz, 3H), 1.54 (s, 3H); ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 165.6, 132.1, 131.6, 128.8, 128.7, 127.2, 126.3, 125.5, 124.6, 122.5, 87.7, 67.5, 39.0, 33.8, 23.4, 23.3; **ESI-HRMS**: calcd. for C₁₇H₁₈NO₂S: 300.1053 [M+H]⁺; found 300.1047.

5. Conclusions

We have devised a concise synthesis of 14-aza-12-oxasteroids, **4a-l** in four simple steps, starting from cheaply available 2-naphthol analogues. Bucherer reaction was employed to convert naphthol analogues to their corresponding naphthylamines, which in turn were ortho-acylated using Sugasawa reaction. Further, the 1-acylated-2-aminonaphthylenes were reduced to corresponding amino-alcohols. Double dehydrations and double intramolecular cyclisation of the synthesized amino-alcohols with four different oxo-acids resulted into one-pot formation of a C-N bond, a C-O bond and an amide bond in tandem. A series of twelve, 14-aza-12-oxasteroid analogs were synthesized in moderate yields. The structure, stereochemistry and connectivity of the bonds was further confirmed by X-ray crystal structure determination of one of the analogue *i.e.*, 12a-methyl-11-phenyl-11,12a-dihydro-1H-naphtho[2,1-d]pyrrolo[2,1-b][1,3]oxazin-3(2H)-one (**4c**).

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Data Availability Statement: All spectroscopic and x-ray data obtained during this research are included in the Supplementary Materials (see above).

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