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A CONVENIENT METHODOLOGY FOR THE *IN SITU* OXIDATION OF 4-SUBSTITUTED URAZOLES. SETTING UP A ONE-POT PROCEDURE FOR THE EFFICIENT PROTECTION OF DIENES

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Abstract – The oxidation of 4-substituted urazoles to the corresponding 1,2,4-triazoline-3,5-diones can be performed selectively in the presence of dienic systems by the action of the nitrosonium ion, formed *in situ* by stoichiometric amounts of sodium nitrite and acetic acid. This convenient methodology is mild, fast, and allows the efficient protection of dienic systems in a one-pot procedure. The dienes were not affected whatsoever by the nitrosonium ion, and react extremely fast with triazolinediones; promptly forming the corresponding Diels-Alder cycloadducts in good to excellent yields. The reaction medium did not affect steroids having an extra double bond at the side chain or an acid-labile spiroketal moiety.

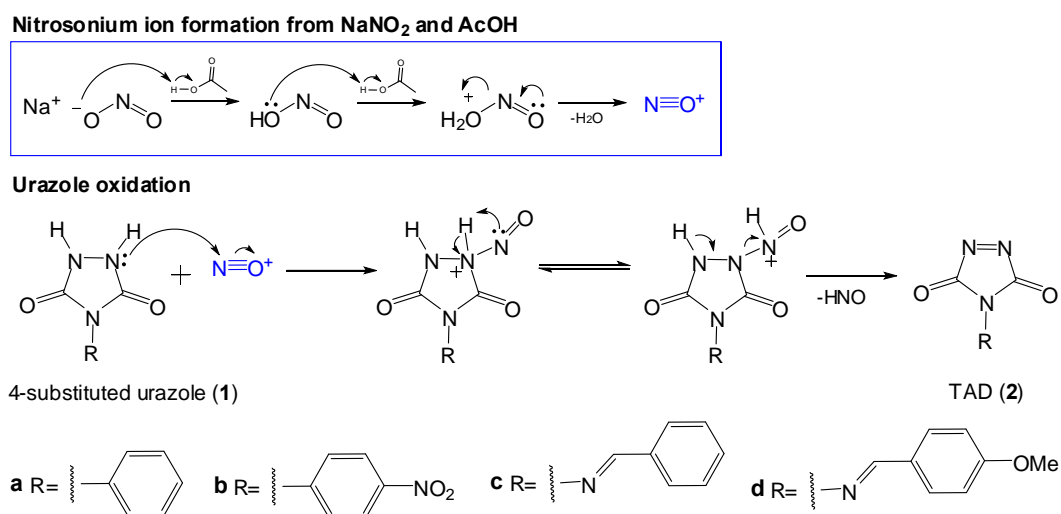
INTRODUCTION

The 4-substituted 1,2,4-triazoline-3,5-diones (TADs) are very versatile reagents in various organic reactions including Diels-Alder reactions,¹ electrophilic aromatic substitutions,² dehydrogenations,³ oxidations of alcohols or thiols,⁴ and condensations.⁵ The formation of Diels-Alder cycloadducts is essential, for instance, for multicomponent strategies and in the field of the chemistry of protecting groups, among others. In order to protect labile dienes, many dienophiles have been employed, and among them 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) displayed notable preference because its ability to form Diels-Alder cycloadducts at low temperatures; although it might participate in ene reactions.⁶ It has been reported that PTAD; the “Cookson reagent”,⁷ is an extremely reactive dienophile; for example, it has demonstrated to be 1000 times more reactive than tetracyanoethylene,⁸ and 2000 times more reactive than maleic anhydride.⁹ Most of TADs are obtained in moderate to good yields; however, in spite of the fact that a variety of methodologies for the preparation of TADs have been reported so far, this transformation is challenging. Commonly, TADs are prepared from the oxidation of the corresponding urazoles and

several reagents for the oxidation of urazoles have been reported, such as 1,3,4,6-tetrachloro-3 α ,6 α -diphenylglycoluril (also known as iodogen),¹⁰ iodobenzene diacetate,¹¹ *t*-butyl hypochlorite,¹² calcium hypochlorite,¹³ potassium dichromate,¹⁴ phenylseleninic anhydride and phenylseleninic acid,¹⁵ NBS,¹⁶ OXONE (potassium peroxomonosulfate),¹⁷ triphenylbismuth carbonate,¹⁸ among others. Many of those reagents involve: long reaction times, special care to be manipulated, high costs, higroscopicity, photosensitivity, lack of selectivity, dangerousness, and tedious or fancy preparation/work-up procedures. To date, most reagents currently used in the preparation of TADs result in the formation of by-products that either decompose or are difficult to remove. TADs are very useful but highly reactive and sensitive. It is of interest, therefore, to search for new mild synthetic methods.

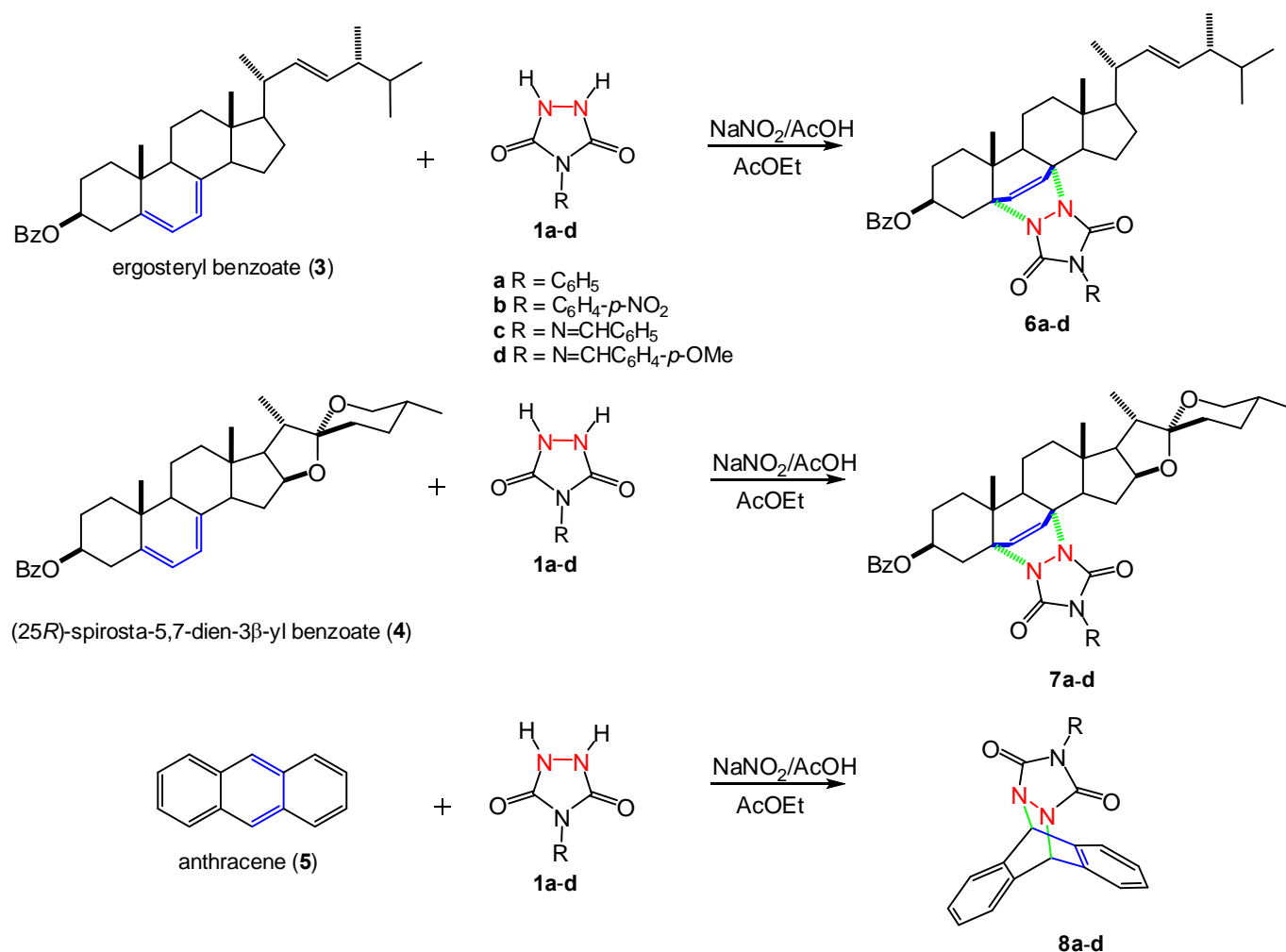
RESULTS AND DISCUSSION

We were interested in developing a mild method for the preparation of 1,2,4-triazoline-3,5-dione derivatives. For this purpose, we found that upon stoichiometric quantities of nitrosonium ion (generated from sodium nitrite and acetic acid), urazoles **1a-d** can readily be transformed into the corresponding TADs **2a-d**. A plausible mechanism for this reaction involves the *in situ* generation of the nitrosonium ion acting as the oxidizing species. Subsequent elimination of nitroxyl then yields the 1,2,4-triazoline-3,5-dione moiety (Scheme 1). The oxidation reactions were performed in ethyl acetate at room temperature, since urazoles exhibited high solubility under such conditions. In our hands, ethyl acetate showed to be the best solvent for urazoles, providing excellent yields and reaction times. Other solvents currently employed (as methylene chloride or THF), did not dissolve urazoles rapidly; hence poor yields and long reaction times were obtained instead.



Scheme 1. A plausible mechanism for the formation of the nitrosonium ion, and the subsequent oxidation of urazoles to TADs.

Due to their high reactivity, TADs are difficult to purify and decompose easily. Nevertheless, we trapped such dienophiles *in situ* through a Diels-Alder cycloaddition using the dienes ergosteryl benzoate (**3**), (25*R*)-spirosta-5,7-dien-3 β -yl benzoate (**4**), and anthracene (**5**). This convenient one-pot method made available a series of cycloadducts (**6-8**) in excellent yields, involving two *in situ* reactions and without by-products. Reactions were readily performed at room temperature, and the resulting cycloadducts were purified by column chromatography and properly characterized (Scheme 2).



Scheme 2. *In situ* formation of Diels-Alder cycloadducts.

The reaction times and yields of the resulting Diels-Alder cycloadducts using 4-substituted urazoles are presented in Table 1. Entries 1-4 and 5-8 show cycloadducts derived from steroidal dienes (**3** and **4**) showing excellent yields in short reaction times. For anthracene cycloadducts (entries 9-12), yields were lower under the same tested conditions. Anthracene (**5**) is a more stable diene which was slowly dissolved in ethyl acetate, and when a mixture of solvents was used in equal amounts (EtOH/CH₂Cl₂ 1:1) anthracene cycloadducts were improved obtaining quantitative yields.

Table 1. Reaction times and yields for the Diels-Alder cycloadducts series 6-8.

Entry	Urazole	Diene	Cycloadduct	Time (min)	Yield (%) ^a
1	1a	3	6a	5	98
2	1b		6b	7	99
3	1c		6c	5	98
4	1d		6d	5	96
5	1a	4	7a	5	97
6	1b		7b	7	96
7	1c		7c	5	98
8	1d		7d	5	98
9	1a	5	8a	8	88
10	1b		8b	15	80
11	1c		8c	12	82
12	1d		8d	12	75

^a Yields are reported after purification by column chromatography.

It is worth noting that for urazoles **1c-d**, the imino group was not attacked by the nitrosonium ion in any case. In this fashion, substituted arylidenaminourazoles could be selectively obtained, due to the fact that 4-aminourazole can be easily synthesized from non-expensive reagents, and readily reacts with aldehydes.¹⁹ In order to evaluate the selective oxidation of urazoles and the subsequent formation of the corresponding cycloadducts, the NMR spectra of all products were recorded. The C-22 double bond of **3** did not undergo the addition of the nitrosonium ion. In the case of spirostans, it is reported that, in the presence of an acidic medium, the C-23 could be rapidly attacked by the nitrosonium ion; and the resulting intermediate can be hydrolyzed to provide 23-oxospirostans.²⁰ NBS could have reacted in allylic positions of **3** and **4**. On the other hand, oxidizing agents like OXONE, *t*-butyl hypochlorite, and potassium dichromate readily react with the spiroketal moiety of **4**. These side-reactions were not observed when the steroidal dienes were employed under the abovementioned conditions; hence, high regioselectivity was found in the proposed methodology; since most of oxidizing agents are not selective

with other functional groups. It means that the nitrosonium ion exclusively and rapidly reacts with urazoles. In our hands, PTAD was isolated,²¹ but yields were poor. If TADs are trapped *in situ* as the proposed methodology suggests, yields of the cycloadducts become excellent instead. The formation of the steroidal cycloadducts can be confirmed by the characteristic signals for H-6 and H-7 for **6a** and **7a** which are shifted towards 6.20-6.50 ppm as an AB system. For **8a** the signal for H-9 and H-10 is displayed in 6.34 ppm as a sharp singlet. In the range of 7.00-8.00 ppm, aromatic protons appear for all compounds. The steroidal angular methyls (Me-18 and Me-19) showed singlet signals for a unique compound. The same condition was observed for the doublets assigned to Me-21, Me-24¹, Me-26 and Me-27.

To the best of our knowledge, the protective power of urazoles is related to the substituent at position 4; thus, an electron withdrawing group diminishes the electron density of the resulting double bond in the cycloadduct. In the same way, deprotection reactions are facilitated by the presence of such electron withdrawing group.²² In this context, the retro-Diels-Alder reactions were performed for all adducts, under the action of DBU in toluene, and in all cases the starting dienes **3-5** were successfully recovered.

CONCLUSIONS

The oxidation of 4-substituted urazoles under the action of the nitrosonium ion provides an efficient, mild and rapid methodology to successfully attain TADs. The one-pot procedure developed here allowed the *in situ* formation of the nitrosonium ion (using sodium nitrite and acetic acid in stoichiometric amounts), the chemo-oxidation of the urazole building blocks, and the subsequent formation of the corresponding cycloadducts in a rapid and stereoselective way. Furthermore, the retro-Diels-Alder reaction proceeded successfully under standard basic conditions, providing the regeneration of dienes. The labile groups attached in the steroidal side chains were not affected at all.

EXPERIMENTAL

General

¹H and ¹³C-NMR spectra were recorded at 400 and 100 MHz respectively on a Varian Mercury spectrometer. The spectra were registered in CDCl₃ and referenced to TMS. The chemical shift values are reported as ppm units and coupling constants are expressed in Hertz (Hz). All assignments were confirmed with the aid of two dimensional experiments (COSY, HSQC and HMBC). HRMS data were obtained from a JEOL The MStation spectrometer. Infrared spectra were recorded on a Nicolet 380 FT-IR spectrometer. UV-Visible data were recorded on a Beckman DU-7500 UV-Vis spectrophotometer. 4-aminourazole (*p*-urazine) was prepared according to the procedure described by Lenoir.¹⁹

General procedure for the synthesis of arylideniminourazoles

4-Aminourazole (8.6 mmol) was dissolved in 30 mL of hot water. Then the corresponding aldehyde (benzaldehyde or anisaldehyde, 17.2 mmol) was added dropwise. The reaction mixture was refluxed for 30 min, next cooled and the resulting precipitate was filtered off, washed with ethyl ether and dried under vacuum to yield quantitatively **1c-d** as thin needles.

General procedure for the synthesis of cycloadducts

To a solution of the selected diene (**3-5**, 0.18 mmol) in 0.5 mL of EtOAc, urazole (**1a-d**, 0.18 mmol) and NaNO₂ (12.4 mg, 0.18 mmol) were added. The reaction mixture was maintained under an argon atmosphere and then, AcOH (20.5 μ L, 0.36 mmol) was added. The resulting solution was stirred at room temperature for an established period of time (Table 1) where the formation of the nitrosonium ion can be observed (brown gas) and the characteristic red color of the corresponding TAD appeared next but readily vanished.²¹ The crude was washed once with a saturated aqueous solution of NaHCO₃ (30 mL) and once with distilled water (30 mL), dried over Na₂SO₄, and evaporated under reduced pressure. The resulting product was purified by column chromatography over silica gel (hexane/EtOAc, 8:2) generating **6-8** in good to excellent yields (see Table 1).

(22E)-5 α ,8 α -(4'-Phenyl)urazoloergosta-6,22-dien-3 β -yl benzoate (6a).²³ ¹H-NMR (400 MHz, CDCl₃) δ 8.03 (2H, m, H-ortho Bz), 7.52 (1H, m, H-para Bz), 7.42 (2H, m, H-ortho), 7.42 (2H, m, H-meta Bz), 7.42 (2H, m, H-meta), 7.28 (1H, m, H-para), 6.43 (1H, d, $J_{7-6} = 8.3$ Hz, H-7), 6.26 (1H, d, $J_{6-7} = 8.3$ Hz, H-6), 5.73 (1H, m, H-3), 5.24 (1H, m, H-23), 5.18 (1H, m, H-22), 3.39 (1H, dd, $J_{4eq-3} = 4.5$ Hz, $J_{gem} = 13.9$ Hz, H-4eq), 2.51 (1H, m, H-15a), 2.36 (1H, m, H-14), 2.36 (1H, m, H-4ax), 2.27 (1H, m, H-2eq), 2.06 (1H, m, H-20), 2.06 (1H, m, H-12eq), 1.04 (3H, d, $J_{21-20} = 6.0$ Hz, CH₃-21), 1.04 (3H, s, CH₃-19), 0.91 (3H, d, $J_{24}^{1-24} = 6.8$ Hz, CH₃-24¹), 0.83 (3H, d, $J_{26-25} = 6.9$ Hz, CH₃-26), 0.82 (3H, s, CH₃-18), 0.82 (3H, d, $J_{27-25} = 6.8$ Hz, CH₃-27). ¹³C-NMR (100 MHz, CDCl₃) δ 33.6 (C-1), 26.0 (C-2), 71.1 (C-3), 31.0 (C-4), 41.1 (C-5), 135.0 (C-6), 129.2 (C-7), 43.8 (C-8), 52.8 (C-9), 65.3 (C-10), 22.3 (C-11), 38.0 (C-12), 64.8 (C-13), 49.2 (C-14), 23.3 (C-15), 27.4 (C-16), 55.0 (C-17), 13.2 (C-18), 17.4 (C-19), 39.5 (C-20), 21.2 (C-21), 135.1 (C-22), 132.3 (C-23), 42.7 (C-24), 17.5 (C-24¹), 33.0 (C-25), 19.9 (C-26), 19.6 (C-27), 165.5 (PhCO₂-3), 148.9 (C-3'), 146.4 (C-5'), 132.6 (C-para Bz), 131.7 (C-ipso), 130.6 (C-ipso Bz), 129.5 (C-ortho Bz), 128.7 (C-meta Bz), 128.1 (C-ortho), 126.1 (C-meta), 127.6 (C-para). HRMS: calcd. for C₄₃H₅₄N₃O₄, 676.4114, [M+H]⁺; found, 676.4107. $[\alpha]_D = -89.7^\circ$ (1.0 CHCl₃). IR 3049, 2926, 1774, 1714, 1603 cm⁻¹.

(22E)-5 α ,8 α -(4'-p-Nitrophenyl)urazoloergosta-6,22-dien-3 β -yl benzoate (6b). ¹H-NMR (400 MHz, CDCl₃) δ 8.26 (2H, m, H-meta), 8.04 (2H, m, H-ortho Bz), 7.84 (2H, m, H-ortho), 7.55 (1H, m, H-para Bz), 7.43 (2H, m, H-meta Bz), 6.47 (1H, d, $J_{7-6} = 8.3$ Hz, H-7), 6.31 (1H, d, $J_{6-7} = 8.3$ Hz, H-6), 5.72 (1H,

m, H-3), 5.25 (1H, m, H-23), 5.20 (1H, m, H-22), 3.36 (1H, dd, $J_{4eq-3} = 4.4$ Hz, $J_{gem} = 14.0$ Hz, H-4eq), 1.07 (3H, s, CH₃-19), 1.05 (3H, d, $J_{21-20} = 6.8$ Hz, CH₃-21), 0.91 (3H, d, $J_{24}^1-24 = 6.8$ Hz, CH₃-24¹), 0.84 (3H, d, $J_{26-25} = 6.8$ Hz, CH₃-26), 0.83 (3H, s, CH₃-18), 0.82 (3H, d, $J_{27-25} = 6.8$ Hz, CH₃-27). ¹³C-NMR (100 MHz, CDCl₃) δ 33.6 (C-1), 25.7 (C-2), 70.8 (C-3), 30.9 (C-4), 41.2 (C-5), 135.4 (C-6), 129.3 (C-7), 43.8 (C-8), 52.7 (C-9), 65.6 (C-10), 22.4 (C-11), 37.9 (C-12), 65.2 (C-13), 49.1 (C-14), 23.3 (C-15), 27.5 (C-16), 55.0 (C-17), 13.1 (C-18), 17.5 (C-19), 39.6 (C-20), 21.2 (C-21), 134.9 (C-22), 132.4 (C-23), 42.7 (C-24), 17.5 (C-24¹), 33.0 (C-25), 19.9 (C-26), 19.6 (C-27), 165.6 (PhC=O-3), 147.5 (C-NO₂), 145.9 (C-3'), 144.8 (C-5'), 137.7 (C-*ipso*), 132.8 (C-*para* Bz), 130.4 (C-*ipso* Bz), 129.6 (C-*ortho* Bz), 128.2 (C-*meta* Bz), 125.7 (C-*ortho*), 124.0 (C-*meta*). HRMS calcd. for C₄₃H₅₃N₄O₆, 721.3965, [M+H]⁺; found, 721.3960. $[\alpha]_D = -34.6^\circ$ (1.0 CHCl₃). IR 3048, 2928, 1750, 1705, 1600, 1523, 1347, 748 cm⁻¹.

(22E)-5 α ,8 α -(4'-Benzalamino)urazoloergosta-6,22-dien-3 β -yl benzoate (6c). ¹H-NMR (400 MHz, CDCl₃) δ 9.47 (1H, s, H-imine), 8.06 (2H, m, H-*ortho* Bz), 7.80 (2H, m, H-*ortho*), 7.55 (1H, m, H-*para* Bz), 7.41 (2H, m, H-*meta* Bz), 7.41 (2H, m, H-*meta*), 7.41 (1H, m, H-*para*), 6.41 (1H, d, $J_{7-6} = 8.3$ Hz, H-7), 6.23 (1H, d, $J_{6-7} = 8.3$ Hz, H-6), 5.76 (1H, m, H-3), 5.25 (1H, m, H-23), 5.19 (1H, m, H-22), 3.38 (1H, dd, $J_{4eq-3} = 5.0$ Hz, $J_{gem} = 14.0$ Hz, H-4eq), 2.52 (1H, m, H-15a), 2.36 (1H, m, H-14), 2.36 (1H, m, H-4ax), 2.26 (1H, m, H-2eq), 2.06 (1H, m, H-20), 2.06 (1H, m, H-12eq), 1.04 (3H, d, $J_{21-20} = 6.8$ Hz, CH₃-21), 1.03 (3H, s, CH₃-19), 0.92 (3H, d, $J_{24}^1-24 = 6.8$ Hz, CH₃-24¹), 0.85 (3H, d, $J_{26-25} = 6.7$ Hz, CH₃-26), 0.83 (3H, d, $J_{27-25} = 6.8$ Hz, CH₃-27), 0.82 (3H, s, CH₃-18). ¹³C-NMR (100 MHz, CDCl₃) δ 33.5 (C-1), 25.9 (C-2), 70.9 (C-3), 30.9 (C-4), 41.1 (C-5), 135.1 (C-6), 129.2 (C-7), 43.8 (C-8), 52.7 (C-9), 65.3 (C-10), 22.4 (C-11), 38.0 (C-12), 64.9 (C-13), 49.1 (C-14), 23.2 (C-15), 27.5 (C-16), 55.0 (C-17), 13.2 (C-18), 17.5 (C-19), 39.5 (C-20), 21.2 (C-21), 135.1 (C-22), 132.3 (C-23), 42.7 (C-24), 17.5 (C-24¹), 33.0 (C-25), 19.9 (C-26), 19.6 (C-27), 165.5 (PhC=O-3), 156.2 (C-imine), 147.2 (C-3'), 144.6 (C-5'), 133.8 (C-*ipso*), 132.7 (C-*para* Bz), 131.1 (C-*para*), 130.6 (C-*ipso* Bz), 129.6 (C-*ortho* Bz), 128.5 (C-*meta* Bz), 128.2 (C-*ortho*), 128.1 (C-*meta*). HRMS calcd. for C₄₄H₅₅N₄O₄, 703.4223, [M+H]⁺; found, 703.4214. $[\alpha]_D = -40.7^\circ$ (1.0 CHCl₃). IR 3279, 3050, 2925, 1760, 1710, 1605, 1052, 806 cm⁻¹.

(22E)-5 α ,8 α -(4'-Anisalamino)urazoloergosta-6,22-dien-3 β -yl benzoate (6d). ¹H-NMR (400 MHz, CDCl₃) δ 9.33 (1H, s, H-imine), 8.06 (2H, m, H-*ortho* Bz), 7.75 (2H, m, H-*ortho*), 7.54 (1H, m, H-*para* Bz), 7.43 (2H, m, H-*meta* Bz), 6.90 (2H, m, H-*meta*), 6.40 (1H, d, $J_{7-6} = 8.3$ Hz, H-7), 6.23 (1H, d, $J_{6-7} = 8.2$ Hz, H-6), 5.75 (1H, m, H-3), 5.25 (1H, m, H-23), 5.19 (1H, m, H-22), 3.83 (3H, s, OCH₃), 3.38 (1H, dd, $J_{4eq-3} = 4.9$ Hz, $J_{gem} = 13.9$ Hz, H-4eq), 2.53 (1H, m, H-15a), 2.35 (1H, m, H-14), 2.35 (1H, m, H-4ax), 2.26 (1H, m, H-2eq), 2.04 (1H, m, H-20), 2.04 (1H, m, H-12eq), 1.04 (3H, d, $J_{21-20} = 7.6$ Hz, CH₃-21), 1.03 (3H, s, CH₃-19), 0.92 (3H, d, $J_{24}^1-24 = 6.8$ Hz, CH₃-24¹), 0.84 (3H, d, $J_{26-25} = 6.7$ Hz, CH₃-26), 0.83 (3H, d, $J_{27-25} = 7.0$ Hz, CH₃-27), 0.82 (3H, s, CH₃-18). ¹³C-NMR (100 MHz, CDCl₃) δ 33.6 (C-1), 26.0

(C-2), 71.0 (C-3), 30.9 (C-4), 41.1 (C-5), 135.1 (C-6), 129.2 (C-7), 43.8 (C-8), 52.7 (C-9), 65.3 (C-10), 22.4 (C-11), 38.0 (C-12), 64.9 (C-13), 49.2 (C-14), 23.2 (C-15), 27.5 (C-16), 55.0 (C-17), 13.2 (C-18), 17.5 (C-19), 39.5 (C-20), 21.2 (C-21), 135.1 (C-22), 132.3 (C-23), 42.7 (C-24), 17.5 (C-24¹), 33.0 (C-25), 19.9 (C-26), 19.6 (C-27), 165.5 (PhCO₂-3), 156.7 (C-imine), 147.4 (C-3'), 144.9 (C-5'), 126.4 (C-*ipso*), 132.7 (C-*para* Bz), 162.1 (C-OCH₃), 55.3 (OCH₃), 130.6 (C-*ipso* Bz), 129.6 (C-*ortho* Bz), 128.2 (C-*meta* Bz), 129.9 (C-*ortho*), 114.0 (C-*meta*). HRMS calcd. for C₄₅H₅₇N₄O₅, 733.4329, [M+H]⁺; found, 733.4319. [α]_D = -24.9° (1.0 CHCl₃). IR 3290, 3048, 2926, 1760, 1715, 1615, 1247, 1051, 1040, 860 cm⁻¹.

(25R)-5α,8α-(4'-Phenyl)urazolospirost-6-en-3β-yl benzoate (7a). ¹H-NMR (400 MHz, CDCl₃) δ 8.03 (2H, m, H-*ortho* Bz), 7.53 (1H, m, H-*para* Bz), 7.42 (2H, m, H-*ortho*), 7.42 (2H, m, H-*meta* Bz), 7.42 (2H, m, H-*meta*), 7.30 (1H, m, H-*para*), 6.43 (1H, d, *J*₇₋₆ = 8.3 Hz, H-7), 6.27 (1H, d, *J*₆₋₇ = 8.2 Hz, H-6), 5.71 (1H, m, H-3), 4.58 (1H, dd, *J*₁₆₋₁₇ = 14.8 Hz, *J*₁₆₋₁₅ = 7.1 Hz, H-16), 3.45 (1H, ddd, *J*_{26eq-25} = 4.4 Hz, *J*_{gem} = 12.8 Hz, *J*_{26eq-24eq} = 1.6 Hz, H-26eq), 3.41 (1H, ddd, *J*_{4eq-3} = 4.8 Hz, *J*_{gem} = 14.0 Hz, *J*_{4eq-2eq} = 1.2 Hz, H-4eq), 3.33 (1H, dd, *J*_{26ax-25} = 11.0 Hz, *J*_{gem} = 12.8 Hz, H-26ax), 2.90 (1H, ddd, *J*₁₅₋₁₄ = 4.8 Hz, *J*₁₅₋₁₆ = 7.1 Hz, *J*_{gem} = 11.8 Hz, H-15a), 2.44 (1H, dd, *J*_{14-15a} = 4.8 Hz, *J*_{14-15b} = 13.2 Hz, H-14), 2.38 (1H, dd, *J*_{4ax-3} = 11.6 Hz, *J*_{gem} = 14.0 Hz, H-4ax), 2.27 (1H, m, H-2eq), 1.04 (3H, s, CH₃-19), 1.00 (3H, d, *J*₂₁₋₂₀ = 6.6 Hz, CH₃-21), 0.91 (3H, s, CH₃-18), 0.78 (3H, d, *J*₂₇₋₂₅ = 6.4 Hz, CH₃-27). ¹³C-NMR (100 MHz, CDCl₃) δ 33.7 (C-1), 26.1 (C-2), 71.0 (C-3), 31.3 (C-4), 41.2 (C-5), 135.0 (C-6), 129.1 (C-7), 41.1 (C-8), 52.6 (C-9), 65.6 (C-10), 22.0 (C-11), 38.3 (C-12), 63.9 (C-13), 48.7 (C-14), 31.1 (C-15), 79.5 (C-16), 61.2 (C-17), 17.2 (C-18), 17.5 (C-19), 41.1 (C-20), 14.5 (C-21), 109.1 (C-22), 31.5 (C-23), 28.7 (C-24), 30.2 (C-25), 66.6 (C-26), 17.1 (C-27), 165.5 (PhCO₂-3), 149.6 (C-3'), 147.0 (C-5'), 132.7 (C-*para* Bz), 131.6 (C-*ipso*), 130.6 (C-*ipso* Bz), 129.5 (C-*ortho* Bz), 128.8 (C-*meta*), 128.1 (C-*para*), 127.7 (C-*meta* Bz), 126.1 (C-*ortho*). HRMS calcd. for C₄₂H₅₀N₃O₆, 692.3700, [M+H]⁺; found, 692.3695. [α]_D = -72.9° (1.0 CHCl₃). IR 3047, 2925, 1770, 1718, 1602 cm⁻¹.

(25R)-5α,8α-(4'-*p*-Nitrophenyl)urazolospirost-6-en-3β-yl benzoate (7b). ¹H-NMR (400 MHz, CDCl₃) δ 8.26 (2H, m, H-*meta*), 8.04 (2H, m, H-*ortho* Bz), 7.84 (2H, m, H-*ortho*), 7.55 (1H, m, H-*para* Bz), 7.43 (2H, m, H-*meta* Bz), 6.46 (1H, d, *J*₇₋₆ = 8.3 Hz, H-7), 6.30 (1H, d, *J*₆₋₇ = 8.2 Hz, H-6), 5.72 (1H, m, H-3), 4.61 (1H, dd, *J*₁₆₋₁₇ = 14.8 Hz, *J*₁₆₋₁₅ = 7.2 Hz, H-16), 3.47 (1H, dd, *J*_{26eq-25} = 4.0 Hz, *J*_{gem} = 10.8 Hz, H-26eq), 3.38 (1H, m, H-4eq), 3.36 (1H, dd, *J*_{26ax-25} = 11.2 Hz, *J*_{gem} = 10.8 Hz, H-26ax), 2.83 (1H, ddd, *J*₁₅₋₁₄ = 4.8 Hz, *J*₁₅₋₁₆ = 7.2 Hz, *J*_{gem} = 11.6 Hz, H-15a), 2.45 (1H, m, H-14), 2.40 (1H, m, H-4ax), 2.25 (1H, m, H-2eq), 1.06 (3H, s, CH₃-19), 1.01 (3H, d, *J*₂₁₋₂₀ = 6.5 Hz, CH₃-21), 0.92 (3H, s, CH₃-18), 0.79 (3H, d, *J*₂₇₋₂₅ = 6.3 Hz, CH₃-27). ¹³C-NMR (100 MHz, CDCl₃) δ 33.6 (C-1), 26.0 (C-2), 70.7 (C-3), 31.2 (C-4), 41.2 (C-5), 135.3 (C-6), 129.3 (C-7), 41.2 (C-8), 52.6 (C-9), 66.0 (C-10), 22.1 (C-11), 38.3 (C-12), 64.2 (C-13), 48.5 (C-14), 31.0 (C-15), 79.5 (C-16), 61.2 (C-17), 17.2 (C-18), 17.5 (C-19), 41.2 (C-20),

14.5 (C-21), 109.3 (C-22), 31.5 (C-23), 28.7 (C-24), 30.2 (C-25), 66.7 (C-26), 17.1 (C-27), 165.6 (PhCO₂-3), 148.2 (C-NO₂), 146.0 (C-3'), 145.4 (C-5'), 137.7 (C-*ipso*), 132.8 (C-*para* Bz), 130.5 (C-*ipso* Bz), 129.6 (C-*ortho* Bz), 128.2 (C-*meta* Bz), 125.7 (C-*ortho*), 124.0 (C-*meta*). HRMS calcd. for C₄₂H₄₉N₄O₈, 737.3550, [M+H]⁺; found, 737.3543. [α]_D = -67.4° (1.0 CHCl₃). IR 3079, 2926, 1765, 1700, 1612, 1520, 1342, 751 cm⁻¹.

(25R)-5α,8α-(4'-Benzalamino)urazolospirost-6-en-3β-yl benzoate (7c). ¹H-NMR (400 MHz, CDCl₃) δ 9.46 (1H, s, H-imine), 8.06 (2H, m, H-*ortho* Bz), 7.81 (2H, m, H-*ortho*), 7.55 (1H, m, H-*para* Bz), 7.42 (2H, m, H-*meta* Bz), 7.42 (2H, m, H-*meta*), 7.42 (1H, m, H-*para*), 6.41 (1H, d, *J*₇₋₆ = 8.3 Hz, H-7), 6.24 (1H, d, *J*₆₋₇ = 8.2 Hz, H-6), 5.74 (1H, m, H-3), 4.62 (1H, dd, *J*₁₆₋₁₇ = 14.4 Hz, *J*₁₆₋₁₅ = 7.6 Hz, H-16), 3.49 (1H, dd, *J*_{26eq-25} = 3.6 Hz, *J*_{gem} = 10.8 Hz, H-26eq), 3.38 (1H, dd, *J*_{26ax-25} = *J*_{gem} = 10.8 Hz, H-26ax), 3.38 (1H, m, H-4eq), 2.93 (1H, ddd, *J*₁₅₋₁₄ = 4.9 Hz, *J*₁₅₋₁₆ = 7.6 Hz, *J*_{gem} = 11.6 Hz, H-15a), 2.45 (1H, dd, *J*_{14-15a} = 4.9 Hz, *J*_{14-15b} = 14.0 Hz, H-14), 2.38 (1H, dd, *J*_{4ax-3} = 11.4 Hz, *J*_{gem} = 13.2 Hz, H-4ax), 2.26 (1H, m, H-2eq), 1.04 (3H, s, CH₃-19), 1.01 (3H, d, *J*₂₁₋₂₀ = 6.5 Hz, CH₃-21), 0.90 (3H, s, CH₃-18), 0.80 (3H, d, *J*₂₇₋₂₅ = 6.3 Hz, CH₃-27). ¹³C-NMR (100 MHz, CDCl₃) δ 33.6 (C-1), 26.0 (C-2), 70.9 (C-3), 31.3 (C-4), 41.2 (C-5), 135.0 (C-6), 129.1 (C-7), 41.1 (C-8), 52.5 (C-9), 65.7 (C-10), 22.0 (C-11), 38.3 (C-12), 64.0 (C-13), 48.6 (C-14), 31.0 (C-15), 79.6 (C-16), 61.2 (C-17), 17.2 (C-18), 17.5 (C-19), 41.1 (C-20), 14.5 (C-21), 109.2 (C-22), 31.5 (C-23), 28.8 (C-24), 30.2 (C-25), 66.7 (C-26), 17.1 (C-27), 165.5 (PhCO₂-3), 156.5 (C-imine), 147.8 (C-3'), 145.2 (C-5'), 133.7 (C-*ipso*), 132.7 (C-*para* Bz), 131.2 (C-*para*), 130.6 (C-*ipso* Bz), 129.6 (C-*ortho* Bz), 128.5 (C-*meta* Bz), 128.2 (C-*ortho*), 128.2 (C-*meta*). HRMS calcd. for C₄₃H₅₁N₄O₆, 719.3809, [M+H]⁺; found, 719.3801. [α]_D = -76.4° (1.0 CHCl₃). IR 2924, 1763, 1710, 1610, 1047, 865 cm⁻¹.

(25R)-5α,8α-(4'-Anisalamino)urazolospirost-6-en-3β-yl benzoate (7d). ¹H-NMR (400 MHz, CDCl₃) δ 9.27 (1H, s, H-imine), 8.01 (2H, m, H-*ortho* Bz), 7.71 (2H, m, H-*ortho*), 7.50 (1H, m, H-*para* Bz), 7.39 (2H, m, H-*meta* Bz), 6.86 (2H, m, H-*meta*), 6.35 (1H, d, *J*₇₋₆ = 8.3 Hz, H-7), 6.19 (1H, d, *J*₆₋₇ = 8.2 Hz, H-6), 5.68 (1H, m, H-3), 4.58 (1H, m, H-16), 3.78 (3H, s, OCH₃), 3.44 (1H, ddd, *J*_{26eq-25} = 3.6 Hz, *J*_{gem} = 11.2 Hz, *J*_{26eq-24eq} = 1.6 Hz, H-26eq), 3.34 (1H, dd, *J*_{26ax-25} = *J*_{gem} = 11.2 Hz, H-26ax), 3.34 (1H, m, H-4eq), 2.89 (1H, m, H-15a), 2.40 (1H, dd, *J*_{14-15a} = 4.8 Hz, *J*_{14-15b} = 13.2 Hz, H-14), 2.33 (1H, dd, *J*_{4ax-3} = *J*_{gem} = 14.0 Hz, H-4ax), 2.21 (1H, m, H-2eq), 1.03 (3H, s, CH₃-19), 0.97 (3H, d, *J*₂₁₋₂₀ = 6.6 Hz, CH₃-21), 0.90 (3H, s, CH₃-18), 0.76 (3H, d, *J*₂₇₋₂₅ = 6.3 Hz, CH₃-27). ¹³C-NMR (100 MHz, CDCl₃) δ 33.5 (C-1), 26.0 (C-2), 70.9 (C-3), 31.2 (C-4), 41.1 (C-5), 134.9 (C-6), 129.0 (C-7), 41.1 (C-8), 52.5 (C-9), 65.6 (C-10), 21.9 (C-11), 38.2 (C-12), 63.9 (C-13), 48.5 (C-14), 31.0 (C-15), 79.5 (C-16), 61.1 (C-17), 17.2 (C-18), 17.4 (C-19), 41.0 (C-20), 14.5 (C-21), 109.1 (C-22), 31.4 (C-23), 28.7 (C-24), 30.1 (C-25), 66.7 (C-26), 17.1 (C-27), 165.5 (PhCO₂-3), 156.8 (C-imine), 148.0 (C-3'), 145.4 (C-5'), 126.3 (C-*ipso*), 132.7

(C-*para* Bz), 162.1 (C-OCH₃), 55.3 (OCH₃), 130.5 (C-*ipso* Bz), 129.5 (C-*ortho* Bz), 128.1 (C-*meta* Bz), 129.9 (C-*ortho*), 113.9 (C-*meta*). HRMS calcd. for C₄₄H₅₃N₄O₇, 749.3914, [M+H]⁺; found, 749.3908. [α]_D = -72.0° (1.0 CHCl₃). IR 2926, 1760, 1713, 1604, 1274, 1100, 1010, 858 cm⁻¹.

9,10-(4'-Phenyl)urazolo-9,10-dihydroanthracene (8a). ¹H-NMR (400 MHz, CDCl₃) δ 7.48 (4H, m, aromatics), 7.34 (2H, m, H-*meta*), 7.29 (4H, m, aromatics), 7.29 (1H, m, H-*para*), 7.19 (2H, m, *ortho*), 6.34 (2H, s, H-9 and H-10). ¹³C-NMR (100 MHz, CDCl₃) δ 156.0 (C-3', C-5'), 136.4 (C-4a, C-8a, C-9a, C-10a), 131.0 (C-*ipso*), 128.3 and 124.0 (C-1 and C-8), 125.3 (C-*ortho*), 129.0 (C-*meta*), 128.3 (C-*para*), 60.4 (C-9 and C-10). HRMS calcd. for C₂₂H₁₆N₃O₂, 354.1243, [M+H]⁺; found, 354.1237. IR 3054, 2927, 1757, 1703, 1612 cm⁻¹.

9,10-(4'-*p*-Nitrophenyl)urazolo-9,10-dihydroanthracene (8b). ¹H-NMR (400 MHz, CDCl₃) δ 8.22 (2H, m, H-*meta*), 7.66 (2H, m, H-*ortho*), 7.54-7.27 (8H, m, H-aromatics), 6.35 (2H, s, H-9 and H-10). ¹³C-NMR (100 MHz, CDCl₃) δ 154.3 (C-3', C-5'), 146.3 (C-NO₂), 137.1 (C-*ipso*), 136.4 (C-4a, C-8a, C-9a, C-10a), 128.6 and 124.1 (C-1 and C-8), 124.7 (C-*ortho*), 124.3 (C-*meta*), 60.4 (C-9 and C-10). HRMS calcd. for C₂₂H₁₅N₄O₄, 399.1093, [M+H]⁺; found, 399.1085. IR 2926, 1765, 1695, 1451, 1395, 732 cm⁻¹.

9,10-(4'-Benzalamino)urazolo-9,10-dihydroanthracene (8c). ¹H-NMR (400 MHz, CDCl₃) δ 9.28 (1H, s, H-imine), 7.74 (2H, d, *J* = 7.4 Hz, H-*ortho*), 7.52 and 7.24 (8H, m, H-aromatics), 7.42 (1H, m, H-*para*), 7.40 (2H, m, H-*meta*), 6.32 (2H, s, H-9 and H-10). ¹³C-NMR (100 MHz, CDCl₃) δ 157.5 (C-imine), 153.9 (C-3', C-5'), 136.5 (C-4a, C-8a, C-9a, C-10a), 132.9 (C-*ipso*), 131.8 (C-*para*), 128.6 (C-*meta*), 128.5 and 124.1 (C-1 and C-8), 128.4 (C-*ortho*), 60.2 (C-9 and C-10). HRMS calcd. for C₂₃H₁₇N₄O₂, 381.1352, [M+H]⁺; found, 381.1347. IR 3290, 2925, 1760, 1705, 1040, 845 cm⁻¹.

9,10-(4'-Anisalamino)urazolo-9,10-dihydroanthracene (8d). ¹H-NMR (400 MHz, CDCl₃) δ 9.14 (1H, s, H-imine), 7.69 (2H, m, H-*ortho*), 7.47 and 7.28 (8H, m, H-aromatics), 6.88 (2H, m, H-*meta*), 6.32 (2H, s, H-9 and H-10), 3.82 (3H, s, OCH₃). ¹³C-NMR (100 MHz, CDCl₃) δ 157.7 (C-imine), 154.1 (C-3', C-5'), 136.5 (C-4a, C-8a, C-9a, C-10a), 125.5 (C-*ipso*), 128.8 (C-*para*), 114.1 (C-*meta*), 128.4 and 124.1 (C-1 and C-8), 130.2 (C-*ortho*), 60.2 (C-9 and C-10), 55.3 (OCH₃). HRMS calcd. for C₂₄H₁₉N₄O₃, 411.1457, [M+H]⁺; found, 411.1452. IR 3287, 2920, 1762, 1711, 1250, 1045, 1038, 855 cm⁻¹.

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