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Electrophile-induced generation of cyclic azomethine imines from steroidal δ-alkenyl hydrazones

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ABSTRACT

Novel δ-alkenyl phenylhydrazones were synthesized in both the estrone and the 13α-estrone series. Electrophile-induced cyclizations of alkenyl phenylhydrazones with phenylselenyl bromide furnished cyclic iminium salts, via attack of the imino nitrogen atom on the intermediate seleniranium ion. Hydride reduction of the iminium salts led to novel aminophenyl-substituted aza-D-homoestrones. The structures of the new products were determined by NMR (one- and two-dimensional) and MALDI-MS techniques, with C_{70} fullerenes as matrix in the latter case.

1. Introduction

Cyclofunctionalizations based on the reaction of an electrophilic reagent with an alkene possessing a suitably positioned nucleophilic group are unchangedly receiving attention. Organoselenium reagents are often used as electrophiles, owing to their ready availability, the mild reaction conditions, and the numerous chemical modifications which can be performed on the selenium moiety. Amines, imidates, imines, azides, and amino acids, for instance, have been used as internal *N* nucleophiles in selenocyclizations of alkenes [1–4]. The phenylselenyl bromide-induced cyclization of alkenyl oximes or oxime ethers leads to the seleniranium ion, which can be attacked by the *O* or the *N* atom of the ambident nucleophile [5–9]. Our previous work revealed the nucleophilic attack of the oxime *O* or *N* atom of steroidal secooximes or oxime ethers, yielding oxazepines and cyclic nitrones, which underwent intermolecular 1,3-dipolar cycloaddition with each other [9]. The resulting non-symmetrical steroid dimers contained 16-halomethyl- or phenylselenylmethyl-substituted six- and seven-membered D rings.

Azomethine imines are usually generated by thermal, microwave-, or acid-induced 1,2-prototropy from the terminal *N* to the central *N* atom [10–17]. We recently described the Lewis-acid induced formation and subsequent cyclization of steroidal azomethine imines [18].

Our present goal was to synthesize *D*-secophenylhydrazones in both the estrone and the 13α-estrone series. Additionally, the phenylselenyl bromide-induced cyclizations of the hydrazones, yielding cyclic azomethine imine salts, are discussed.

2. Experimental

Melting points (mps) were determined with a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed with a PerkinElmer CHN analyzer model 2400. Thin-layer chromatography: silica gel 60 F_{254}; layer thickness 0.2 mm (Merck); detection with iodine or UV (365 nm) after spraying with 5% phosphomolybdic acid in 50% aqueous phosphoric acid and heating at 100–120 °C for 10 min. Flash chromatography: silica gel 60, 40–63 μm (Merck). ^{1}H NMR spectra were recorded in $CDCl_3$ solution (if not otherwise stated) with a Bruker DRX-500 instrument at 500 MHz, with Me_4Si as internal standard. ^{13}C NMR spectra were recorded with the same instrument at 125 MHz under the same conditions. The mass spectrometer used was an Autoflex II TOF/TOF (Bruker Daltonics, Bremen, Germany) operated in reflector mode. The ions were accelerated under delayed extraction conditions (80 ns) in positive and negative ion modes, with an acceleration voltage of 20.00 kV. The instrument uses a 337 nm pulsed (50 Hz) nitrogen laser. 1 μL aliquots of the standard solutions were loaded onto the target

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plate (MTP 384 target plate ground steel TF, Bruker Daltonics, Bremen, Germany) by mixing with the same volume of a saturated matrix solution prepared by dissolving C_{70} fullerenes in toluene. EI-MS spectra were measured on a Varian MAT 311A instrument.

2.1. General procedure for the synthesis of steroidal phenylhydrazones

Secoaldehyde **1** or **2** [19] (375 mg, 1.00 mmol) was dissolved in methanol (5 mL), and phenyl- or substituted phenylhydrazine hydrochloride (1.00 mmol) and a methanolic solution (5 mL) of sodium acetate (200 mg, 2.44 mmol) were added. The mixture was stirred for 0.5 h at rt. The white or yellow precipitate was filtered off, washed with cold methanol, and dried.

2.2. Reaction of *1* with phenylhydrazine hydrochloride

According to Section 2.1, **1** (375 mg, 1.00 mmol), phenylhydrazine hydrochloride (145 mg, 1.00 mmol) and sodium acetate (200 mg, 2.44 mmol) in methanol were allowed to react. After work-up, **3a** was obtained as a white solid (395 mg, 85%). mp 137–139 °C; R_f = 0.54 (60% CH_2Cl_2/40% hexane). Anal. Calcd. for $C_{32}H_{36}N_2O$: C, 82.72; H, 7.81. Found: C, 82.90; H, 8.02. ^{1}H NMR ($CDCl_3$): δ = 1.16 (s, 3H, 18-H_3), 2.83 (m, 2H, 6-H_2), 4.93 (m, 2H, 16a-H_2), 5.03 (s, 2H, OCH_2), 5.84 (m, 1H, 16-H), 6.71 (d, 1H, J = 2.4 Hz, 4-H), 6.77–6.82 (overlapping multiplets, 2H, 2-H and 4′-H), 6.86 (s, 1H, 17-H), 6.99 (d, 2H, J = 8.1 Hz, 2′-H and 6′-H), 7.13 (s, 1H, NH), 7.19–7.24 (overlapping multiplets, 3H, 1-H, 3′-H and 5′-H), 7.30 (t, 1H, J = 7.3 Hz, 4″-H), 7.37 (t, 2H, J = 7.3 Hz, 3″-H and 5″-H), 7.42 (d, 2H, J = 7.3 Hz, 2″-H and 6″-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.2 (C-18), 26.1, 27.5, 30.3, 34.2, 38.2, 41.1, 42.3 (C-13), 43.4, 47.8, 70.0 (OCH_2), 112.5 (3C, C-2, C-2′ and C-6′), 114.5 (C-16a), 114.6 (C-4), 119.4 (C-4′), 126.4 (C-1), 127.4 (2C) and 128.5 (2C): C-2″, C-3″, C-5″ and C-6″, 127.8 (C-4″), 129.2 (2C, C-3′ and C-5′), 132.8 (C-10), 137.3 (C-1″), 138.0 (C-5), 140.1 (C-16), 145.6 (C-1′), 149.7 (C-17), 156.8 (C-3). MS positive mode: 463 (20% $[M-H]^+$), 91 (100%, benzylic cation).

2.3. Reaction of *1* with 4-tolylhydrazine hydrochloride

According to Section 2.1, **1** (375 mg, 1.00 mmol), 4-tolylhydrazine hydrochloride (159 mg, 1.00 mmol) and sodium acetate (200 mg, 2.44 mmol) in methanol were allowed to react. After work-up, **3b** was obtained as a white solid (417 mg, 87%). mp 149–152 °C; R_f = 0.57 (60% CH_2Cl_2/40% hexane). Anal. Calcd. for $C_{33}H_{38}N_2O$: C, 82.80; H, 8.00. Found: C, 82.53; H, 7.92. ^{1}H NMR ($CDCl_3$): δ = 1.15 (s, 3H, 18-H_3), 2.26 (s, 3H, tolyl-CH_3), 2.83 (m, 2H, 6-H_2), 4.92 (m, 2H, 16a-H_2), 5.02 (s, 2H, OCH_2), 5.84 (m, 1H, 16-H), 6.71 (d, 1H, J = 2.0 Hz, 4-H), 6.78 (dd, 1H, J = 8.6 Hz, J = 2.0 Hz, 2-H), 6.84 (s, 1H, 17-H), 6.90 (d, 2H, J = 8.3 Hz, 2′-H and 6′-H), 7.02 (d, 2H, J = 8.3 Hz, 3′-H and 5′-H), 7.20 (d, 1H, J = 8.6 Hz, 1-H), 7.30 (t, 1H, J = 7.1 Hz, 4″-H), 7.37 (t, 2H, J = 7.1 Hz, 3″-H and 5″-H), 7.42 (d, 2H, J = 7.1 Hz, 2″-H and 6″-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.2, 20.5, 26.1, 27.5, 30.3, 34.2, 38.3, 41.1, 42.2, 43.4, 47.8, 70.0 (OCH_2), 112.5 (C-2), 112.7 (2C, C-2′ and C-6′), 114.4 (C-16a), 114.5 (C-4), 126.4 (C-1), 127.4 (2C) and 128.5 (2C): C-2″, C-3″, C-5″ and C-6″, 127.8 (C-4″), 128.6 (C-4′), 129.6 (2C, C-3′ and C-5′), 132.8 (C-10), 137.4 (C-1′), 138.0 (C-5), 140.1 (C-16), 143.5 (C-1′), 149.3 (C-17), 156.8 (C-3). MS positive mode: 477 (20% $[M-H]^+$), 91 (100%, benzylic cation).

2.4. Reaction of *1* with 4-cyanophenylhydrazine hydrochloride

According to Section 2.1, **1** (375 mg, 1.00 mmol), 4-cyanophenylhydrazine hydrochloride (170 mg, 1.00 mmol) and sodium acetate (200 mg, 2.44 mmol) in methanol were allowed to react. After work-up, **3c** was obtained as a white solid (400 mg, 82%). mp 173–175 °C; R_f = 0.18 (60% CH_2Cl_2/40% hexane). Anal. Calcd. for $C_{33}H_{35}N_3O$: C, 80.95; H, 7.20. Found: C, 81.07; H, 7.05. ^{1}H NMR ($CDCl_3$): δ = 1.16 (s, 3H, 18-H_3), 2.83 (m, 2H, 6-H_2), 4.94 (m, 2H, 16a-H_2), 5.03 (s, 2H, OCH_2), 5.83 (m, 1H, 16-H), 6.72 (d, 1H, J = 2.0 Hz, 4-H), 6.79 (dd, 1H, J = 8.6 Hz, J = 2.0 Hz, 2-H), 6.93 (s, 1H, 17-H), 6.98 (d, 2H, J = 8.3 Hz, 2′-H and 6′-H), 7.19 (d, 1H, J = 8.6 Hz, 1-H), 7.31 (t, 1H, J = 7.1 Hz, 4″-H), 7.37 (t, 2H, J = 7.1 Hz, 3″-H and 5″-H), 7.42 (d, 2H, J = 7.1 Hz, 2″-H and 6″-H), 7.47 (d, 2H, J = 8.3 Hz, 3′-H and 5′-H), 7.54 (s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.1 (C-18), 26.0, 27.4, 30.3, 34.2, 38.0, 41.0, 42.5 (C-13), 43.3, 47.7, 70.0 (OCH_2), 101.0 (C-4′), 112.2 (2C, C-2′ and C-6′), 112.5 (C-2), 114.5 (C-4), 114.7 (C-16a), 120.1 (CN), 126.4 and 127.4 (2C) and 127.8 and 128.5 (2C): C-1, C-2″, C-3″, C-4″, C-5″ and C-6″, 132.5 (C-10), 133.6 (2C, C-3′ and C-5′), 137.2 (C-1″), 137.9 (C-5), 139.8 (C-16), 148.5 (C-1′), 152.5 (C-17), 156.8 (C-3). MS negative mode: 488 (10% $[M-H]^-$), 117 (100% $[NHPhCN]^-$); positive mode: 489 (10% $[M]^+$), 270 (100%), 91 (30%, benzylic cation).

2.5. Reaction of *1* with 4-nitrophenylhydrazine hydrochloride

According to Section 2.1, **1** (375 mg, 1.00 mmol), 4-nitrophenylhydrazine hydrochloride (190 mg, 1.00 mmol) and sodium acetate (200 mg, 2.44 mmol) in methanol were allowed to react. After work-up, **3d** was obtained as a yellow solid (510 mg, 90%). mp 186–188 °C; R_f = 0.25 (60% CH_2Cl_2/40% hexane). Anal. Calcd. for $C_{32}H_{35}N_3O_3$: C, 75.41; H, 6.92. Found: C, 75.27; H, 7.17. ^{1}H NMR ($CDCl_3$): δ = 1.18 (s, 3H, 18-H_3), 2.84 (m, 2H, 6-H_2), 4.95 (m, 2H, 16a-H_2), 5.04 (s, 2H, OCH_2), 5.82 (m, 1H, 16-H), 6.72 (d, 1H, J = 2.4 Hz, 4-H), 6.79 (dd, 1H, J = 8.5 Hz, J = 2.4 Hz, 2-H), 6.98 (overlapping multiplets, 3H, 2′-H, 6′-H and 17-H), 7.20 (d, 1H, J = 8.5 Hz, 1-H), 7.31 (t, 1H, J = 7.2 Hz, 4″-H), 7.38 (t, 2H, J = 7.2 Hz, 3″-H and 5″-H), 7.42 (d, 2H, J = 7.2 Hz, 2″-H and 6″-H). 7.73 (s, 1H, NH), 8.13 (d, 2H, J = 8.3 Hz, 3′-H and 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.1 (C-18), 26.0, 27.4, 30.3, 34.2, 38.0, 41.0, 42.6 (C-13), 43.3, 47.6, 70.0 (OCH_2), 111.3 (2C, C-2′ and C-6′), 112.5 (C-2), 114.5 (C-4), 114.7 (C-16a), 126.2 (2C, C-3′ and C-5′), 126.4 and 127.4 (2C) and 127.9 and 128.5 (2C): C-1, C-2″, C-3″, C-4″, C-5″ and C-6″, 132.5 (C-10), 137.3 (C-1″), 137.9 (C-5), 139.7 (C-16), 139.8 (C-4′), 150.2 (C-1′), 153.7 (C-17), 156.8 (C-3). MS negative mode: 508 (60% $[M-H]^-$); positive mode: 508 (40% $[M-H]^+$); 91 (100%, benzylic cation).

2.6. Reaction of *2* with phenylhydrazine hydrochloride

According to Section 2.1, **2** (375 mg, 1.00 mmol), phenylhydrazine hydrochloride (145 mg, 1.00 mmol) and sodium acetate (200 mg, 2.44 mmol) in methanol were allowed to react. After work-up, **4a** was obtained as a white solid (465 mg, 86%). mp 100–102 °C; R_f = 0.60 (60%CH_2Cl_2/40% hexane). Anal. Calcd. for $C_{32}H_{36}N_2O$: C, 82.72; H, 7.81. Found: C, 82.65; H, 7.98. ^{1}H NMR ($CDCl_3$): δ = 1.27 (s, 3H, 18-H_3), 2.85 (m, 2H, 6-H_2), 4.99 (m, 2H, 16a-H_2), 5.03 (s, 2H, OCH_2), 5.87 (m, 1H, 16-H), 6.71 (d, 1H, J = 2.2 Hz, 4-H), 6.77–6.82 (overlapping multiplets, 2H, 2-H and 4′-H), 6.95 (d, 2H, J = 7.9 Hz, 2′-H and 6′-H), 7.12 (s, 1H, NH), 7.18–7.23 (overlapping multiplets, 4H, 1-H and 17-H and 3′-H and 5′-H), 7.31 (t, 1H, J = 7.1 Hz, 4″-H), 7.38 (t, 2H, J = 7.1 Hz, 3″-H and 5″-H), 7.42 (d, 2H, J = 7.1 Hz, 2″-H and 6″-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.1 (C-18), 27.2, 27.5, 30.4, 33.4, 39.5, 41.6, 42.4, 43.6, 51.1, 70.0 (OCH_2), 112.5 (3C, C-2, C-2′ and C-6′), 114.5 (C-4), 114.7 (C-16a), 119.4 (C-4′), 126.5 and 127.4 (2C) and 127.8 and 128.5 (2C): C-1, C-2″, C-3″, C-4″, C-5″ and C-6″, 129.2 (2C, C-3′ and C-5′), 132.9 (C-10), 137.3 (C-1″), 137.9 (C-5), 139.9 (C-16), 144.7 (C-17), 145.5 (C-1′), 156.8 (C-3). MS positive mode: 464 (20% $[M]^+$), 91 (100%, benzylic cation).

2.7. Reaction of **2** with 4-tolylhydrazine hydrochloride

According to Section 2.1, **2** (375 mg, 1.00 mmol), 4-tolylhydrazine hydrochloride (159 mg, 1.00 mmol) and sodium acetate (200 mg, 2.44 mmol) in methanol were allowed to react. After stirring for 30 min, the reaction mixture was cooled to −18 °C, when a light-yellow precipitate of **4b** appeared (480 mg, 92%). mp 86–88 °C; R_f = (50% CH_2Cl_2/50% hexane). Anal. Calcd. for $C_{33}H_{38}N_2O$: C, 82.80; H, 8.00. Found: C, 82.76; H, 7.84.

^{1}H NMR ($CDCl_3$): δ = 1.28 (s, 3H, 18-H_3), 2.27 (s, 3H, tolyl-CH_3), 2.84 (m, 2H, 6-H_2), 5.00 (m, 2H, 16a-H_2), 5.04 (s, 2H, OCH_2), 5.87 (m, 1H, 16-H), 6.72 (d, 1H, J = 2.3 Hz, 4-H), 6.80 (dd, 1H, J = 8.4 Hz, J = 2.3 Hz, 2-H), 6.88 (d, 2H, J = 8.3 Hz, 2′-H and 6′-H), 7.03 (d, 2H, J = 8.3 Hz, 3′-H and 5′-H), 7.18 (s, 1H, 17-H), 7.21 (d, 1H, J = 8.4 Hz, 1-H), 7.32 (t, 1H, J = 7.1 Hz, 4″-H), 7.39 (t, 2H, J = 7.1 Hz, 3″-H and 5″-H), 7.44 (d, 2H, J = 7.1 Hz, 2″-H and 6″-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.5 (tolyl-CH_3), 27.1 (C-18), 27.3, 27.6, 30.4, 33.4, 39.6, 41.6 (C-13), 42.4, 43.7, 51.2, 70.0 (OCH_2), 112.5 (C-2), 112.6 (2C, C-2′ and C-6′), 114.5 (C-4), 114.6 (C-16a), 126.5 and 127.8: C-1 and C-4″, 127.4 (2C) and 128.5 (2C) and 129.6 (2C): C-2″, C-3″, C-5″, C-6″, C-3′ and C-5′), 128.7 (C-4′), 133.0 (C-10), 137.4 (C-1″), 137.9 (C-5), 140.0 (C-16), 143.4 (C-1′), 144.4 (C-17), 156.8 (C-3). MS positive mode: 477 (30% $[M-H]^+$), 91 (100%, benzylic cation).

2.8. Reaction of **2** with 4-cyanophenylhydrazine hydrochloride

According to Section 2.1, **2** (375 mg, 1.00 mmol), 4-cyanophenylhydrazine hydrochloride (170 mg, 1.00 mmol) and sodium acetate (200 mg, 2.44 mmol) in methanol were allowed to react. After work-up, **4c** was obtained as a white solid (392 mg, 80%). mp 135–136 °C; R_f = 0.21 (60% CH_2Cl_2/40% hexane). Anal. Calcd. for $C_{33}H_{35}N_3O$: C, 80.95; H, 7.20. Found: C, 81.11; H, 7.36. ^{1}H NMR ($CDCl_3$): δ = 1.23 (s, 3H, 18-H_3), 2.79 (m, 2H, 6-H_2), 4.98 (m, 2H, 16a-H_2), 5.00 (s, 2H, OCH_2), 5.80 (m, 1H, 16-H), 6.67 (d, 1H, J = 2.0 Hz, 4-H), 6.73 (dd, 1H, J = 8.6 Hz, J = 2.0 Hz, 2-H), 6.91 (d, 2H, J = 8.3 Hz, 2′-H and 6′-H), 7.15 (d, 1H, J = 8.6 Hz, 1-H), 7.20 and 7.21 (2×s, 2×1H, 17-H and NH), 7.27 (t, 1H, J = 7.1 Hz, 4″-H), 7.33 (t, 2H, J = 7.1 Hz, 3″-H and 5″-H), 7.37 (d, 2H, J = 7.1 Hz, 2″-H and 6″-H), 7.41 (d, 2H, J = 8.3 Hz, 3′-H and 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.9 (C-18), 27.2, 27.4, 30.3, 33.3, 39.3, 41.9 (C-13), 42.3, 43.5, 50.9, 70.0 (OCH_2), 100.9 (C-4′), 112.1 (2C, C-2′ and C-6′), 112.5 (C-2), 114.5 (C-4), 115.0 (C-16a), 120.1 (CN), 126.4 and 127.4 (2C) and 127.8 and 128.5 (2C): C-1, C-2″, C-3″, C-4″, C-5″ and C-6″, 132.7 (C-10), 133.6 (2C, C-3′ and C-5′), 137.2 (C-1″), 137.8 (C-5), 139.4 (C-16), 147.9 (C-17), 148.4 (C-1′), 156.8 (C-3). MS negative mode: 488 (20% $[M-H]^-$); positive mode: 490 (20% $[M+H]^+$), 91 (100%, benzylic cation).

2.9. Reaction of **2** with 4-nitrophenylhydrazine hydrochloride

According to Section 2.1, **2** (375 mg, 1.00 mmol), 4-nitrophenylhydrazine hydrochloride (190 mg, 1.00 mmol) and sodium acetate (200 mg, 2.44 mmol) in methanol were allowed to react. After work-up, **4d** was obtained as a yellow solid (510 mg, 90%). mp 132–134 °C; R_f = 0.73 (CH_2Cl_2). Anal. Calcd. for $C_{32}H_{35}N_3O_3$: C, 75.41; H, 6.92. Found: C, 75.48; H, 7.06. ^{1}H NMR ($CDCl_3$): δ = 1.28 (s, 3H, 18-H_3), 2.84 (m, 2H, 6-H_2), 4.97–5.04 (overlapping multiplets, 4H, OCH_2 and 16a-H_2), 5.80 (m, 1H, 16-H), 6.70 (d, 1H, J = 2.0 Hz, 4-H), 6.78 (dd, 1H, J = 8.6 Hz, J = 2.0 Hz, 2-H), 6.92 (d, 2H, J = 9.2 Hz, 2′-H and 6′-H), 7.19 (d, 1H, J = 8.6 Hz, 1-H), 7.29 (s, 1H, 17-H), 7.30 (t, 1H, J = 7.1 Hz, 4″-H), 7.37 (t, 2H, J = 7.1 Hz, 3″-H and 5″-H), 7.41 (d, 2H, J = 7.1 Hz, 2″-H and 6″-H), 7.63 (s, 1H, NH), 8.10 (d, 2H, J = 9.1 Hz, 3′-H and 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.9, 27.2, 27.4, 30.3, 33.3, 39.3, 42.0, 42.3, 43.5, 50.9, 70.0 (OCH_2), 111.2 (2C, C-2′ and C-6′), 112.5 (C-2), 114.5 (C-4), 115.1 (C-16a), 126.2 (2C, C-3′ and C-5′), 126.5 (C-4″), 127.4 (2C, C-2″ and C-6″), 127.8 (C-1), 128.5 (2C, C-3″ and C-5″), 132.7 (C-10), 137.2 (C-1″), 137.8 (C-5), 139.3 (C-16), 139.7 (C-4′), 149.3 (C-17), 150.1 (C-1′), 156.8 (C-3). MS negative mode: 508 (80% $[M-H]^-$); positive mode: 508 (40% $[M-H]^+$), 91 (100%, benzylic cation).

2.10. General procedure for the synthesis of 16-phenylselenylmethyl-17aza-D-homoestrones

Hydrazone **3** (1.00 mmol) or **4** (1.00 mmol) was dissolved in dry acetonitrile (10 mL), and phenylselenyl bromide (236 mg, 1.00 mmol) was added in an ice-water bath under a nitrogen atmosphere. The mixture was stirred for 0.5 h, the solvent was evaporated off, the crude product was dissolved in dichloromethane (5 mL), methanol (5 mL) was added, and the reduction was carried out with potassium borohydride (216 mg, 4 mmol) during 24 h at room temperature under stirring. The mixture was diluted with dichloromethane (30 mL) and washed with water. The dichloromethane solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The resulting oil was purified by flash chromatography.

2.11. Cyclization of **3a**

According to Section 2.10, hydrazone **3a** (502 mg, 1.00 mmol) and phenylselenyl bromide (236 mg, 1.00 mmol) were allowed to react in acetonitrile (10 mL). After reduction, the crude product was subjected to chromatographic purification on a silica gel column with light petroleum/dichloromethane (50:50) as eluent, but **15** remained as an oil (430 mg, 69%). R_f = 0.40 (50% CH_2Cl_2/50% hexane). Anal. Calcd. for $C_{38}H_{42}N_2OSe$: C, 73.41; H, 6.81. Found: C, 73.62; H, 6.95. ^{1}H NMR ($CDCl_3$): δ = 1.12 (s, 3H, 18-H_3), 1.94 (d, 1H, J = 10.1 Hz) and 2.89 (d, 1H, J = 10.1 Hz): 17a-H_2, 2.58 (m, 1H, 16-H), 2.84 (m, 2H, 6-H_2), 3.14 (dd, 1H, J = 11.9 Hz, J = 7.3 Hz) and 3.41 (dd, 1H, J = 11.9 Hz, J = 2.9 Hz): 16a-H_2, 4.04 (s, 1H, NH), 5.04 (s, 2H, OCH_2), 6.72 (d, 1H, J = 2.6 Hz, 4-H), 6.78 (overlapping multiplets, 2H, 2-H and 4′-H), 6.91 (d, 2H, J = 7.6 Hz, 2′-H and 6′-H), 7.18–7.22 (overlapping multiplets, 6H, aromatic protons), 7.31 (t, 1H, J = 7.1 Hz, 4″-H), 7.38 (t, 2H, J = 7.1 Hz, 3″-H and 5″-H), 7.43 (d, 2H, J = 7.1 Hz, 2″-H and 6″-H), 7.47 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.6 (C-18), 25.7, 26.2, 30.0, 31.1, 32.8, 35.4, 37.7, 38.6, 43.6, 47.6, 66.3 (C-16), 70.0 (OCH_2), 70.4 (NCH_2), 112.4 (C-2), 113.5 (2C, C-2′ and C-6′), 114.6 (C-4), 119.2 (C-4′), 126.1, 126.3, 127.4 (2C), 127.8, 128.5 (2C), 128.9 (2C), 129.1 (2C), 131.9 (3C), 133.0 (C-10), 137.3 (C-1″), 137.9 (C-5), 148.3 (C-1′), 156.8 (C-3). MS (EI); m/z (%): 622 (100, M^+).

2.12. Cylization of **3b**

According to Section 2.10, hydrazone **3b** (480 mg, 1.00 mmol) and phenylselenyl bromide (236 mg, 1.00 mmol) were allowed to react in acetonitrile (10 mL). After reduction, the crude product was subjected to chromatographic purification on a silica gel column with light petroleum/dichloromethane (50:50) as eluent, yielding **16** as a white solid (458 mg, 72%). mp 150–152 °C; R_f = 0.40 (CH_2Cl_2). Anal. Calcd. for $C_{39}H_{44}N_2OSe$: C, 73.68; H, 6.98. Found: C, 73.85; H, 7.21. ^{1}H NMR ($CDCl_3$): δ = 1.08 (s, 3H, 18-H_3), 1.87 (d, 1H, J = 10.1 Hz) and 2.86 (d, 1H, J = 10.1 Hz): 17a-H_2, 2.23 (s, 3H, tolyl-CH_3), 2.54 (m, 1H, 16-H), 2.81 (m, 2H, 6-H_2), 3.12 (dd, 1H, J = 11.8 Hz, J = 7.2 Hz) and 3.39 (dd, 1H, J = 11.8 Hz, J = 2.8 Hz): 16a-H_2, 3.90 (s, 1H, NH), 5.00 (s, 2H, OCH_2), 6.69 (d, 1H, J = 2.6 Hz, 4-H), 6.75 (dd, 1H, J = 8.5 Hz, J = 2.6 Hz, 2-H), 6.80 (d, 2H, J = 8.2 Hz, 2′-H and 6′-H), 6.98 (d, 2H, J = 8.2 Hz, 3′-H and 5′-H), 7.14–7.21 (overlapping multiplets, 4H, 1-H and three other aromatic protons), 7.28 (t, 1H, J = 7.2 Hz, 4″-H), 7.35 (t, 2H, J = 7.2 Hz, 3″-H and 5″-H), 7.40 (d, 2H, J = 7.2 Hz, 2″-H and 6″-H), 7.44 (m, 2H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.6 (C-18), 20.5, 25.7, 26.2, 30.0, 31.1, 32.9, 35.4, 37.7, 38.5, 43.6, 47.6, 66.2 (C-16), 70.0 (OCH_2), 70.3 (NCH_2), 112.4 (C-2), 113.7 (2C, C-2′ and C-

6′), 114.6 (C-4), 126.1 (2C), 126.2, 127.4 (2C), 127.8, 128.5 (2C), 128.7, 129.6 (2C, C-3′ and C-5′), 131.2 (C-1‴), 131.9 (2C), 132.9 (C-10), 137.2 (C-1″), 137.8 (C-5), 145.8 (C-1′), 156.7 (C-3). MS positive mode: 635 (10% $[M]^+$), 530 (60% $[M-105]^+$), 91 (100%, benzylic cation).

2.13. Cyclization of **3c**

According to Section 2.10, hydrazone **3c** (490 mg, 1.00 mmol) and phenylselenyl bromide (236 mg, 1.00 mmol) were allowed to react in acetonitrile (10 mL). After reduction, the crude product was subjected to chromatographic purification on a silica gel column with light petroleum/dichloromethane (50:50) as eluent, yielding a 1:1.2 mixture of **18a** (16β) and **18b** (16α) (453 mg, 70%). In order to obtain the pure diastereomers, the diastereoisomeric mixture of **18a** and **18b** was separated on a second silica gel column with the same eluent.

Data for **18a**: oil, $R_f = 0.75$ (CH_2Cl_2). Anal. Calcd. for $C_{39}H_{41}N_3OSe$: C, 72.43; H, 6.39. Found: C, 72.55; H, 6.42. ^{1}H NMR ($CDCl_3$): $\delta = 1.12$ (s, 3H, 18-H_3), 2.05 and 2.78 (2×d, 2×1H, $J = 10.1$ Hz): 17a-H_2, 2.60 (m, 1H, 16-H), 2.83 (m, 2H, 6-H_2), 3.10 (m, 1H) and 3.22 (dd, 1H, $J = 11.9$ Hz, $J = 2.7$ Hz): 16a-H_2, 4.54 (s, 1H, NH), 5.03 (s, 2H, OCH_2), 6.73 (d, 1H, $J = 2.4$ Hz, 4-H), 6.79 (dd, 1H, $J = 8.6$ Hz, $J = 2.4$ Hz), 6.88 (d, 2H, $J = 8.1$ Hz, 2′-H and 6′-H), 7.18–7.24 (overlapping multiplets, 4H, 1-H, aromatic protons), 7.32 (t, 1H, $J = 7.1$ Hz, 4″-H), 7.39 (t, 2H, $J = 7.1$ Hz, 3″-H and 5″-H), 7.43 (overlapping multiplets, 6H, 3′-H, 5′-H, 2″-H, 6″-H and two other aromatic protons) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 17.6$ (C-18), 25.7, 26.1, 29.9, 30.9, 32.5, 35.4, 37.6, 38.5, 43.6, 47.4, 66.3 (C-16), 70.0 (OCH_2), 70.5 (NCH_2), 100.8 (C-4′), 112.4 (2C, C-2′ and C-6′), 112.5 (C-2), 114.6 (C-4), 120.2 (CN), 126.0, 126.1 (2C), 127.4 (2C), 127.8, 128.5 (2C), 129.0, 131.3 (C-1‴), 132.2 (2C), 132.8 (C-10), 133.6 (2C, C-3′ and C-5′), 137.3 (C-1″), 137.8 (C-5), 151.5 (C-1′), 156.8 (C-3). MS negative mode: 117 (100% [NH-Ph-CN]$^-$); positive mode: 646 (10% $[M-H]^+$), 530 (20% $[M-117]^+$), 91 (100%, benzylic cation).

Data for **18b**: oil, $R_f = 0.73$ (CH_2Cl_2). Anal. Calcd. for $C_{39}H_{41}N_3OSe$: C, 72.43; H, 6.39. Found: C, 72.58; H, 6.45. ^{1}H NMR ($CDCl_3$): $\delta = 1.14$ (s, 3H, 18-H_3), 2.43 and 2.59 (2×d, 2×1H, $J = 10.4$ Hz): 17a-H_2, 2.83 (m, 2H, 6-H_2), 3.12 (m, 1H) and 3.27 (dd, 1H, $J = 12.0$ Hz, $J = 3.6$ Hz): 16a-H_2, 3.50 (m, 1H, 16-H), 5.03 (s, 2H, OCH_2), 5.43 (s, 1H, NH), 6.73 (d, 1H, $J = 2.4$ Hz, 4-H), 6.79 (dd, 1H, $J = 8.6$ Hz, $J = 2.4$ Hz), 6.83 (d, 2H, $J = 8.1$ Hz, 2′-H and 6′-H), 7.18–7.24 (overlapping multiplets, 4H, 1-H and three other aromatic protons), 7.32 (t, 1H, $J = 7.1$ Hz, 4″-H), 7.39 (t, 2H, $J = 7.1$ Hz, 3″-H and 5″-H), 7.43 (overlapping multiplets, 4H, 2″-H, 6″-H and two other aromatic protons), 7.49 (m, 2H, 3′-H and 5′-H) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 17.7$ (C-18), 22.8, 25.6, 26.0, 27.1, 29.8, 35.5, 37.9, 38.1, 41.5, 43.7, 60.2 (C-16), 62.9 (NCH_2), 70.0 (OCH_2), 100.6 (C-4′), 112.4 (C-2), 112.6 (2C, C-2′and C-6′), 114.5 (C-4), 120.2 (CN), 126.6 (2C), 127.2, 127.4 (2C), 127.8, 128.5 (2C), 129.2, 130.1 (C-1‴), 132.6 (2C), 132.9 (C-10), 133.6 (2C, C-3′ and C-5′), 137.3 (C-1″), 137.9 (C-5), 151.2 (C-1′), 156.8 (C-3). MS negative mode: 117 (100% [NH-Ph-CN]$^-$); positive mode: 646 (10% $[M-H]^+$), 530 (20% $[M-117]^+$), 91 (100%, benzylic cation).

2.14. Cyclization of **3d**

According to Section 2.10, hydrazone **3d** (510 mg, 1.00 mmol) and phenylselenyl bromide (236 mg, 1.00 mmol) were allowed to react in acetonitrile (10 mL). After reduction the crude product was subjected to chromatographic purification on a silica gel column with dichloromethane as eluent, yielding **17** as a yellow solid (494 mg, 74%). mp 188–190 °C; $R_f = 0.68$ (CH_2Cl_2). Anal. Calcd. for $C_{38}H_{41}N_3O_3Se$: C, 68.46; H, 6.20. Found: C, 68.31; H, 6.42.

^{1}H NMR ($CDCl_3$): $\delta = 1.15$ (s, 3H, 18-H_3), 2.09 and 2.77 (2×d, 2×1H, $J = 10.4$ Hz): 17a-H_2, 2.63 (m, 1H, 16-H), 2.83 (m, 2H, 6-H_2), 3.08 (dd, 1H, $J = 12.0$ Hz, $J = 6.9$ Hz) and 3.19 (dd, 1H, $J = 12.0$ Hz, $J = 2.8$ Hz): 16a-H_2, 4.80 (s, 1H, NH), 5.03 (s, 2H, OCH_2), 6.72 (d, 1H, $J = 2.4$ Hz, 4-H), 6.79 (dd, 1H, $J = 8.4$ Hz, $J = 2.4$ Hz, 2-H), 6.84 (d, 2H, $J = 7.0$ Hz, 2′-H and 6′-H), 7.17–7.23 (overlapping multiplets, 4H, 1-H and three other aromatic protons), 7.31 (t, 1H, $J = 7.3$ Hz, 4″-H), 7.37 (t, 2H, $J = 7.3$ Hz, 3″-H and 5″-H), 7.42 (overlapping multiplets, 4H, 2″-H, 6″-H and two other aromatic protons), 8.08 (d, 2H, $J = 9.1$ Hz, 3′-H and 5′-H) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 17.6$ (C-18), 25.6, 26.1, 29.9, 30.9, 32.5, 35.4, 37.6, 38.5, 43.6, 47.4, 66.4 (C-16), 70.0 (OCH_2), 70.6 (NCH_2), 111.4 (2C, C-2′ and C-6′), 112.5 (C-2), 114.6 (C-4), 126.1, 126.2, 126.8, 127.4 (2C), 127.8 (2C), 128.5 (2C), 129.0 (2C), 131.2 (C-1‴), 132.3 (2C), 132.7 (C-10), 137.3 (C-1″), 137.8 (C-5), 139.5 (C-4′), 153.4 (C-1′), 156.8 (C-3). MS positive mode: 666 (10% $[M]^+$), 91 (100%, benzylic cation).

2.15. Cyclization of **4a**

According to Section 2.10, hydrazone **4a** (502 mg, 1.00 mmol) and phenylselenyl bromide (236 mg, 1.00 mmol) were allowed to react in acetonitrile (10 mL). After reduction, the crude product was subjected to chromatographic purification on a silica gel column with light petroleum/dichloromethane (50:50) as eluent, yielding **25** as an oil (442 mg, 71%). $R_f = 0.37$ (50% CH_2Cl_2/50% hexane). Anal. Calcd. for $C_{38}H_{42}N_2OSe$: C, 73.41; H, 6.81. Found: C, 73.22; H, 6.68.

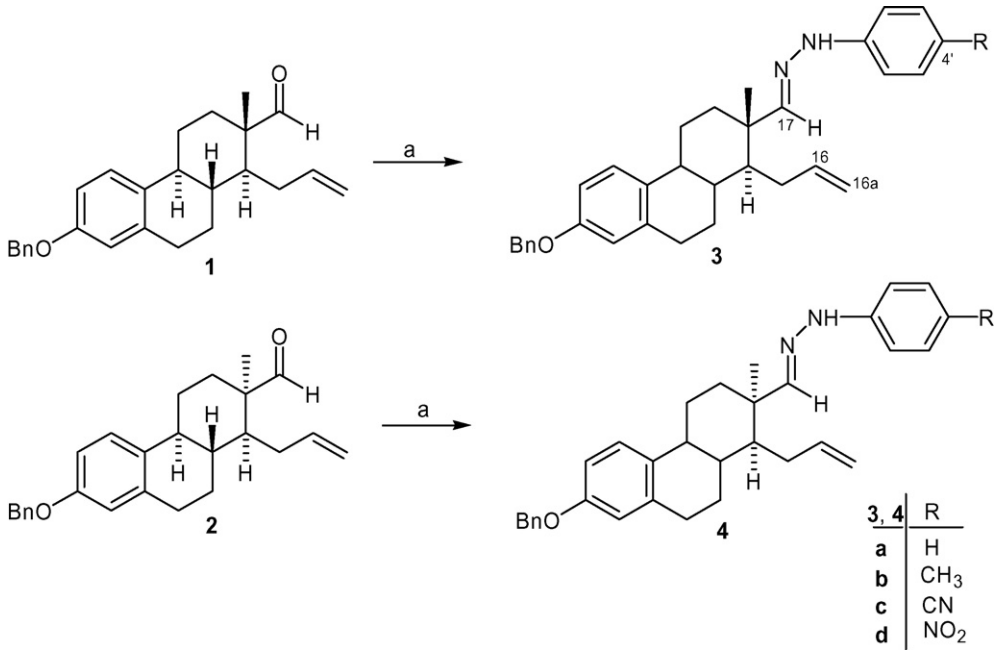
^{1}H NMR ($CDCl_3$): $\delta = 1.29$ (s, 3H, 18-H_3), 2.26 and 2.54 (2×d, 2×1H, $J = 12.5$ Hz): 17a-H_2, 2.82 (m, 2H, 6-H_2), 2.94 (dd, 1H, $J = 12.0$ Hz, $J = 7.8$ Hz) and 3.42 (dd, 1H, $J = 12.0$ Hz, $J = 2.9$ Hz): 16a-H_2, 3.96 (s, 1H, NH), 5.04 (s, 2H, OCH_2), 6.72 (d, 1H, $J = 2.4$ Hz, 4-H), 6.77 (overlapping multiplets, 2H, 2-H and 4′-H), 6.88 (d, 2H, $J = 7.6$ Hz, 2′-H and 6′-H), 7.16–7.22 (overlapping multiplets, 6H, 1-H, 3′-H, 5′-H and three other aromatic protons), 7.32 (t, 1H, $J = 7.3$ Hz, 4″-H), 7.38 (t, 2H, $J = 7.3$ Hz, 3″-H and 5″-H), 7.43 (d, 2H, $J = 7.3$ Hz, 2″-H and 6″-H), 7.47 (m, 2H) ppm. MS (EI); m/z (%): 622 (100, M^+).

2.16. Cyclization of **4b**

According to Section 2.10, hydrazone **4b** (480 mg, 1.00 mmol) and phenylselenyl bromide (236 mg, 1.00 mmol) were allowed to react in acetonitrile (10 mL). After reduction, the crude product was subjected to chromatographic purification on a silica gel column with light petroleum/dichloromethane (50:50) as eluent, yielding **26** as a white solid (503 mg, 79%). mp 85–87 °C; $R_f = 0.41$ (50% CH_2Cl_2/50% hexane). Anal. Calcd. for $C_{39}H_{44}N_2OSe$: C, 73.68; H, 6.98. Found: C, 73.95; H, 6.82. ^{1}H NMR ($CDCl_3$): $\delta = 1.28$ (s, 3H, 18-H_3), 1.51 (d, $J = 3.0$ Hz) and 2.53 (d, $J = 3.0$ Hz): 17a-H_2, 2.26 (s, 3H, tolyl-CH_3), 2.83 (m, 2H, 6-H_2), 2.96 (dd, 1H, $J = 11.9$ Hz, $J = 7.8$ Hz) and 3.43 (dd, 1H, $J = 11.9$ Hz, $J = 2.9$ Hz): 16a-H_2, 3.86 (s, 1H, NH), 5.05 (s, 2H, OCH_2), 6.73 (d, 1H, $J = 2.5$ Hz, 4-H), 6.78 (overlapping multiplets, 3H, 2-H, 2′-H and 6′-H), 7.01 (d, 2H, $J = 8.2$ Hz, 3′-H and 5′-H), 7.17 (d, 1H, $J = 8.6$ Hz, 1-H), 7.20 (overlapping multiplets, 3H, 3‴-H, 4‴-H and 5‴-H), 7.33 (t, 1H, $J = 7.1$ Hz, 4″-H), 7.39 (t, 2H, $J = 7.1$ Hz, 3″-H and 5″-H), 7.43 (d, 2H, $J = 7.1$ Hz, 2″-H and 6″-H), 7.48 (overlapping multiplets, 2H, 2‴-H and 6‴-H) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 20.5$, 26.6, 26.8, 28.6, 29.2, 30.2, 32.8, 35.0, 37.5, 38.4, 42.8, 44.9, 59.9 (C-16), 61.1 (C-17a), 70.0 (OCH_2), 112.4 (C-2), 113.5 (2C, C-2′ and C-6′), 114.5 (C-4), 126.4 (2C), 127.4 (2C), 127.8, 128.4 (C-4′), 128.5 (2C), 128.9 (2C), 129.6 (2C, C-3′ and C-5′), 131.7 (C-1‴), 132.2 (2C), 133.0 (C-10), 137.3 (C-1″), 138.1 (C-5), 146.0 (C-1′), 156.8 (C-3). MS positive mode: 635 (10% $[M]^+$), 530 (50% $[M-105]^+$), 91 (100%, benzylic cation).

2.17. Cyclization of **4c**

According to Section 2.10, hydrazone **4c** (490 mg, 1.00 mmol) and phenylselenyl bromide (236 mg, 1.00 mmol) were allowed to react in acetonitrile (10 mL). After reduction, the crude product was subjected to chromatographic purification on a silica gel column



Scheme 1. Reagents and conditions: (a) Ph-NH-NH_2·HCl or R-Ph-NH-NH_2·HCl, NaOAc, MeOH, rt.

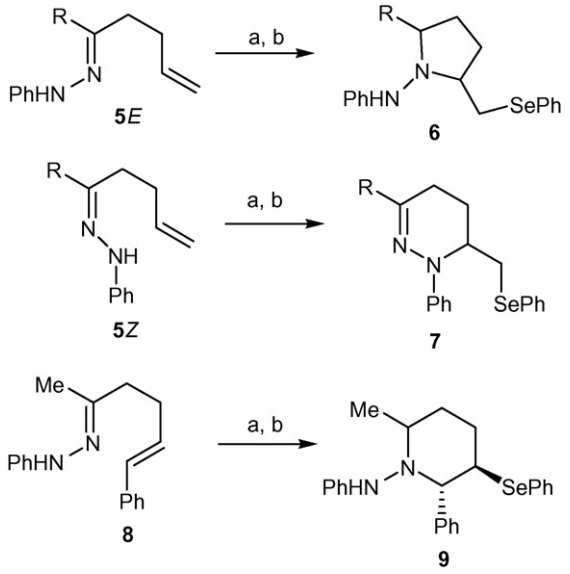
with light petroleum/dichloromethane (50:50) as eluent, yielding **27** as an oil (472 mg, 73%). R_f = 0.78 (CH_2Cl_2). Anal. Calcd. for $C_{39}H_{41}N_3OSe$: C, 72.43; H, 6.39. Found: C, 72.58; H, 6.27. ^{1}H NMR ($CDCl_3$): δ = 1.30 (s, 3H, 18-H_3), 2.42 and 2.67 (2×d, 2×1H, J = 10.7 Hz): 17a-H_2, 2.83 (m, 2H, 6-H_2), 2.90 (dd, 1H, J = 12.2 Hz, J = 7.6 Hz) and 3.22 (dd, 1H, J = 12.2 Hz, J = 2.8 Hz): 16a-H_2, 4.45 (s, 1H, NH), 5.04 (s, 2H, OCH_2), 6.73 (d, 1H, J = 2.6 Hz, 4-H), 6.79 (dd, 1H, J = 8.5 Hz, J = 2.6 Hz, 2-H), 6.84 (d, 2H, J = 8.2 Hz, 2′-H and 6′-H), 7.17 (d, 1H, J = 8.5 Hz, 1-H), 7.22 (overlapping multiplets, 2H, aromatic protons), 7.32 (t, 1H, J = 7.1 Hz, 4″-H), 7.38 (t, 2H, J = 7.1 Hz, 3″-H and 5″-H), 7.42–7.44 (overlapping multiplets, 5H, 2″-H, 6″-H and three other aromatic protons) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.6, 26.8, 28.5 (C-18), 29.0, 30.2, 32.4, 35.0, 37.5, 38.3, 42.8, 44.6, 60.0 (C-16), 61.4 (NCH_2), 70.0 (OCH_2), 100.7 (C-4′), 112.5 (3C, C-2, C-2′ and C-6′), 114.5 (C-4), 120.2 (CN), 126.4, 126.8, 127.4 (2C), 127.8, 128.5 (2C), 129.0 (2C), 130.9 (C-1‴), 132.5 (2C), 132.8 (C-10), 133.6 (2C, C-3′ and C-5′), 137.2 (C-1″), 138.0 (C-5), 151.6 (C-1′), 156.8 (C-3). MS negative mode: 530 (20% [M−117]$^-$), 117 (100% [NH-PH-CN]$^-$); positive mode: 530 (20% [M−117]$^+$), 91 (100%, benzylic cation).

2.18. Cyclization of *4d*

According to Section 2.10, hydrazone **4d** (510 mg, 1.00 mmol) and phenylselenyl bromide (236 mg, 1.00 mmol) were allowed to react in acetonitrile (10 mL). The crude iminium salt **24d** was filtered off, washed with cold acetonitrile, and directly subjected to NMR measurements. ^{1}H NMR ($CDCl_3$): δ = 1.68 (s, 3H, 18-H_3), 2.85 (m, 2H, 6-H_2), 3.36 (dd, 1H, J = 13.0 Hz, J = 9.1 Hz) and 3.54 (dd, 1H, J = 13.0 Hz, J = 2.6 Hz): 16a-H_2, 4.38 (m, 1H, 16-H), 5.05 (s, 2H, OCH_2), 6.69 (d, 1H, J = 2.5 Hz, 4-H), 6.75 (dd, 1H, J = 8.7 Hz, J = 2.5 Hz, 2-H), 6.80 (d, 2H, J = 9.0 Hz, 2′-H and 6′-H), 7.07 (d, 1H, J = 8.7 Hz, 1-H), 7.13 (m, 2H, aromatic protons), 7.28 (t, 1H, J = 7.0 Hz, 4″-H), 7.30–7.40 (overlapping multiplets, 6H, aromatic protons), 8.04 (d, 2H, J = 9.0 Hz, 3′-H and 5′-H), 9.04 (s, 1H, 17a-H), 11.7 (s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.5, 26.6, 28.4 (C-18), 28.7, 29.7, 29.9, 37.9, 40.9, 41.3, 41.4, 43.3, 61.5 (C-16), 70.0 (OCH_2), 113.0 (C-2), 114.7 (C-4), 115.5 (2C, C-2′ and C-6′), 126.0 (2C), 126.6, 127.4 (2C), 127.5 (C-1‴), 127.9, 128.3, 128.5 (2C), 129.6 (2C), 130.1 (C-10), 133.4 (2C), 137.0 (C-1″), 137.1 (C-5), 143.2 (C-4′), 146.9 (C-1′), 157.2 (C-3), 187.5 (C-17a). After reduction, the crude product was subjected to chromatographic purification on a silica gel column with light petroleum/dichloromethane (50:50) as eluent, yielding **28** as an oil (467 mg, 70%). R_f = 0.65 (CH_2Cl_2). Anal. Calcd. for $C_{38}H_{41}N_3O_3Se$: C, 68.46; H, 6.20. Found: C, 68.72; H, 6.05. ^{1}H NMR ($CDCl_3$): δ = 1.31 (s, 3H, 18-H_3), 2.41 and 2.71 (2×d, 2×1H, J = 10.6 Hz): 17a-H_2, 2.65 (m, 1H, 16-H), 2.80 (m, 2H, 6-H_2), 2.90 (dd, 1H, J = 12.2 Hz, J = 7.5 Hz) and 3.19 (m, 1H): 16a-H_2, 4.75 (s, 1H, NH), 5.04 (s, 2H, OCH_2), 6.74 (d, 1H, J = 2.4 Hz, 4-H), 6.78 (overlapping multiplets, 3H, 2-H and 2′-H and 6′-H), 7.17 (d, 1H, J = 8.6 Hz, 1-H), 7.22 (overlapping multiplets, 3H, aromatic protons), 7.31 (t, 1H, J = 7.0 Hz, 4″-H), 7.38 (t, 2H, J = 7.0 Hz, 3″-H and 5″-H), 7.42–7.44 (overlapping multiplets, 4H, 2″-H, 6″-H and two other aromatic protons), 8.07 (d, 2H, J = 8.9 Hz, 3′-H and 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.6, 26.8, 28.5 (C-18), 29.0, 30.2, 32.3, 35.0, 37.4, 38.2, 42.7, 44.5, 60.1 (C-16), 61.4 (NCH_2), 70.0 (OCH_2), 111.2 (2C, C-2′, C-6′), 112.4 (C-2), 114.4 (C-4), 126.2 (2C), 126.5, 126.9, 127.4 (2C), 127.9, 128.5 (2C), 129.1 (2C), 130.7 (C-1‴), 132.6 (2C), 132.7 (C-10), 137.2 (C-1″), 138.0 (C-5), 139.4 (C-4′), 153.4 (C-1′), 156.8 (C-3). MS positive mode: 666 (10% [M]$^+$), 530 (50% [M−136]$^+$), 91 (100%, benzylic cation).

3. Results and discussion

Steroidal hydrazones **3** and **4** were prepared from D-secoaldehydes **1** and **2**, which are available in four steps from estrone or 13α-estrone 3-benzyl ether, respectively [19]. In the estrone series, reaction of the appropriate 4-substituted phenylhydrazine hydrochloride and sodium acetate in methanol took place in a few minutes, and the products **3a–d** were formed as precipitates (Scheme 1). The resulting hydrazones **3a–d** were washed with methanol and subjected directly to NMR measurements, which confirmed their structure. In the 13α-estrone series, the reaction with 4-tolylhydrazine hydrochloride proceeded in a different manner. Under the same reaction conditions as described for the estrone derivatives, no precipitate was formed. After stirring for 30 min, the reaction mixture was cooled to −18 °C, when a light-yellow precipitate of **4b** appeared, which needed no purification. In both estrone series, four differently substituted phenylhydrazones, **3a–d** and **4a–d**, were synthesized.



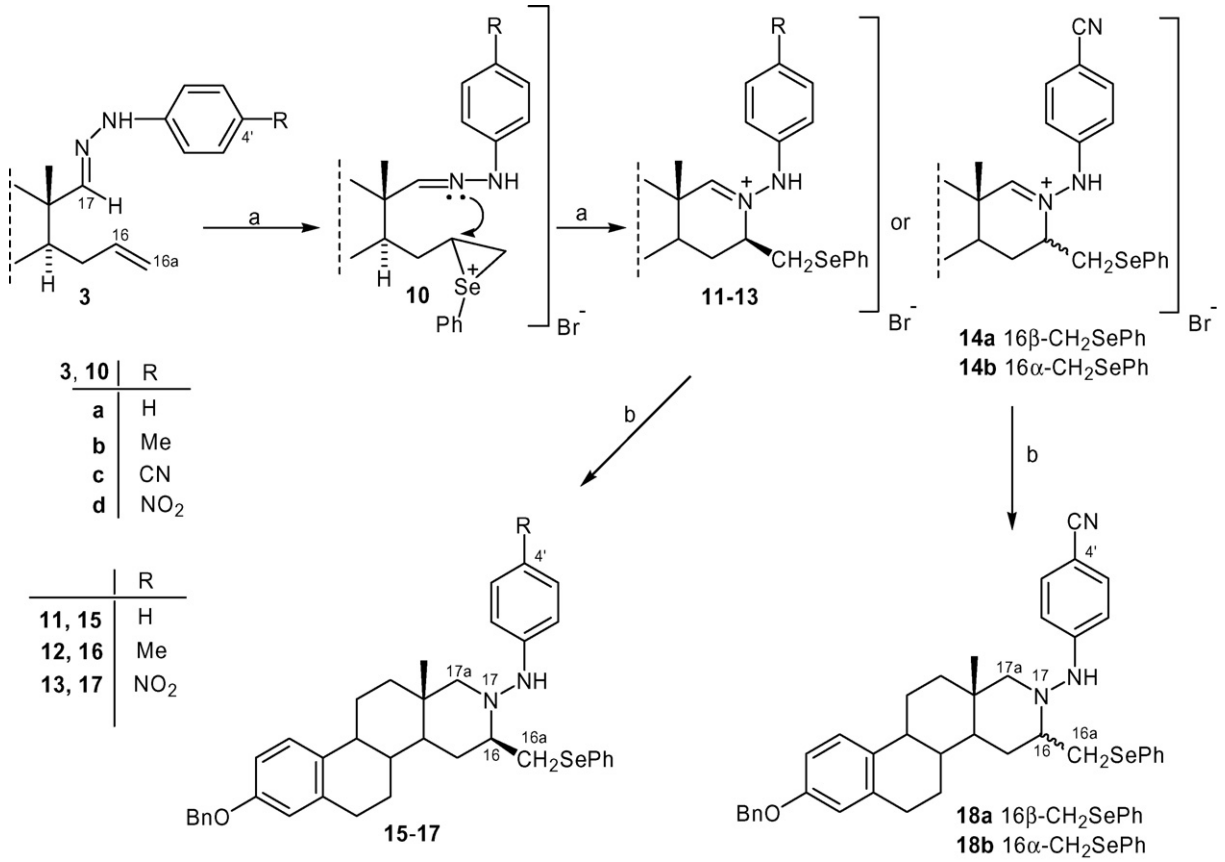
Scheme 2. Reagents and conditions: (a) PhSeBr, CH_2Cl_2, rt; (b) $NaBH_4$, CH_2Cl_2, MeOH, rt.

Tiecco et al. investigated the selenium-induced cyclizations of γ-alkenyl phenylhydrazones (**5***E*, **5***Z*, **8**, Scheme 2) [20]. The hydride reductions of the initially formed iminium salts led to pyrrolidinamine (**6**), piperidinamine (**9**) or tetrahydropyridazine (**7**) derivatives. They concluded that the cyclization is a regioselective process and that the structure of the product is strongly determined by the geometry of the starting phenylhydrazone.

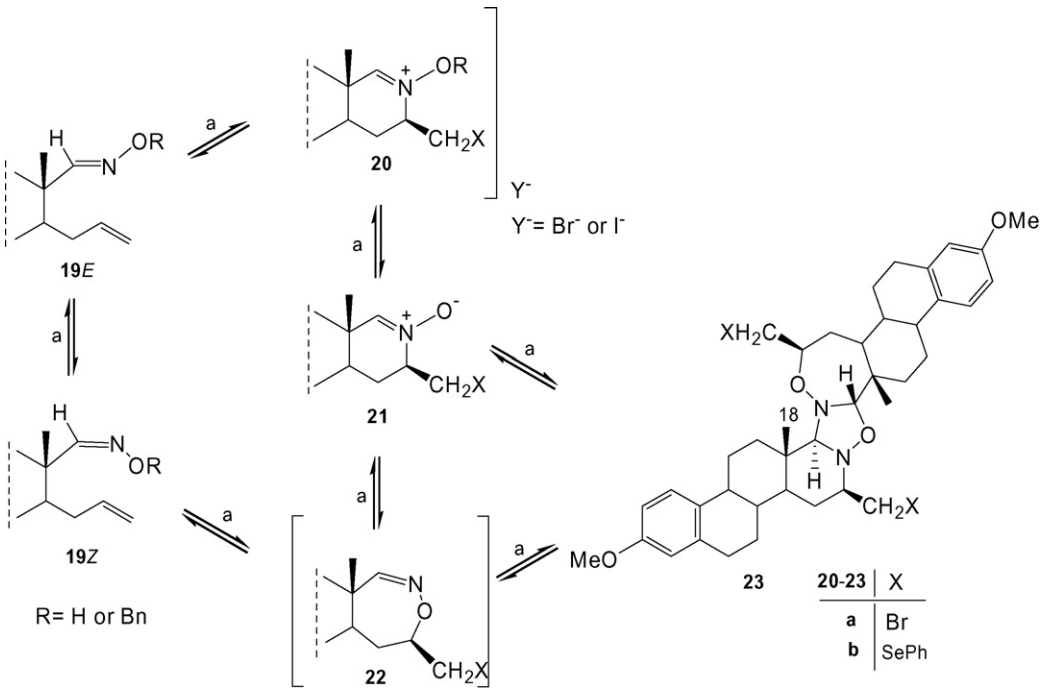
First, the estrone phenylhydrazones **3a**–**d** were subjected to cylization, with phenylselenyl bromide as electrophile trigger (Scheme 3). Iminium salt formation was carried out in acetonitrile solution with 1 equiv. of phenylselenyl bromide, the reaction mixture being stirred in an ice-water bath [9]. The intermediate seleniranium ion **10a**–**d** was trapped via the imino *N* atom of the phenylhydrazone **3a**–**d**. Iminium salts **11**–**14** were formed immediately. After the starting hydrazone **3a**–**d** had reacted completely, the solvent was evaporated off. The crude salt **11**–**14** was dissolved in dichloromethane, methanol was added and the C=N double bond was reduced with 4 equiv. of potassium borohydride, the reaction mixture being stirred for 24 h at room temperature, which yielded 17-phenylamino- or substituted 17-phenylamino aza-D-homoestrones **15**–**18**. The selenocyclizations proceeded in a stereoselective manner, furnishing the 16β-phenylselenylmethyl-aza-D-homo derivative **15**–**17**, except for the cyclization of **3c**, which led to a diastereoisomeric mixture of the products **18a**,**b**.

We recently reported the halogen- and phenylselenyl-induced synthesis of nitrone dipoles from steroidal δ-alkenyl oximes and oxime ethers in both the estrone and the 13α-estrone series [9]. Oximes or oxime ethers **19** of estrone 3-methyl ether behaved as ambident nucleophiles: the attack of the *N* atom of the *E* isomer led to the thermodynamically stable cyclic nitrone **21**, but the attack of the *O* atom of the *Z* isomer afforded the oxazepine derivative **22**. Additionally, a nonsymmetrical steroidal dimer **23** was formed by the intermolecular 1,3-dipolar cycloaddition of **21** and **22** (Scheme 4).

It was of particular interest to investigate whether the phenylhydrazones of estrone benzyl ether give different types of products under the conditions employed, since the internal nucleophile is an ambident group: it can act with the imino or amino *N* as the reactive site. Side-products containing a seven-membered D ring have not



Scheme 3. Reagents and conditions: (a) PhSeBr, CH_3CN, ice-water bath, N_2; (b) KBH_4, CH_2Cl_2-MeOH, rt.



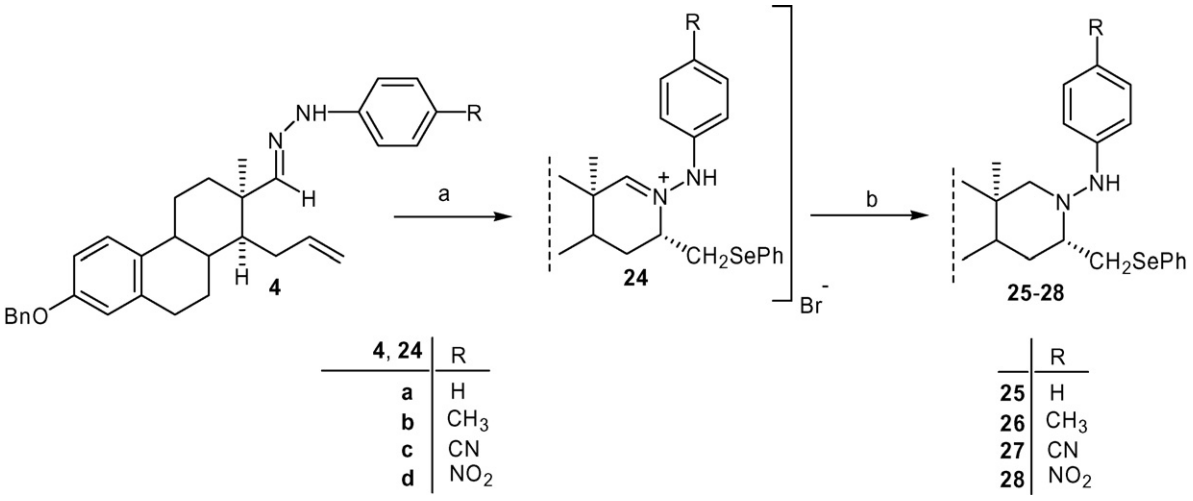
Scheme 4. Reagents and conditions: (a) NBS or PhSeBr, MeCN, rt, N_2.

been isolated. Nucleophilic attack of the amino *N* on C-16 would lead to tetrahydrodiazepine derivatives, but attack of the imino *N* on C-16a would lead to the azepanilamine derivative. To summarize the results in the estrone series, no reaction involving the nucleophilic attack of the amino *N* atom took place. Additionally, all the reactions proceeded with similar rates and yields, irrespective of the aromatic substituent.

Following the cyclizations in the estrone series, the reactions of the 13α-phenylhydrazones **4a**–**d** were carried out under the same reaction conditions as described for the estrone series (Scheme 5). All the reactions were regio- and stereoselective, 16α-phenylselenylmethyl aza-D-homo-13α-estrones **25**–**28** being formed in high yields. Similarly to the results obtained in the estrone series, side-products with seven-membered D rings were not isolated in the reactions of the 13α-estrone phenylhydrazones.

The structures of the new products were determined with one- and two-dimensional NMR and MALDI-MS techniques. The ^{1}H NMR spectra of **3a**–**d** reveal the singlet of 17-H at 6.9 ppm and of NH at >7 ppm. In the ^{13}C NMR spectra, the signals of C-17 are observed in the range 150–154 ppm. In the spectra of **4a**–**d**, there is an upfield shift of the singlet of 17-H (7.2 ppm) and a downfield shift of the signal of C-17 (144–150 ppm). Fig. 1 shows representative ^{1}H NMR spectra of hydrazones **3c** and **4c**.

The ^{1}H NMR spectra of the estrone aza-D-homo derivatives **15**–**17** and **18a** display the two doublets of 17a-H_2 at ∼1.9 and 2.8 ppm with a coupling constant of 10 Hz, the multiplet of 16-H at ∼2.6 ppm, and 16a-H_2 gives two readily distinguishable double doublets at ∼3.1 and 3.3 ppm. In the ^{13}C NMR spectra, C-16 and C-17a are seen at ∼66.2 and 70.5 ppm. The ^{1}H NMR spectra of the 13α-estrone-D-homo derivatives **25**–**28** show similarities between the pairs **25**–**26** and **27**–**28**. The two doublets of 17a-H_2 appear at ∼1.5 and 2.5 ppm, with different coupling constants in the spectra of **25** and **26**, but at 2.4 and 2.7 ppm in the spectra of **27** and **28**. Fig. 2 shows representative ^{1}H NMR spectra of aza-D homoe-



Scheme 5. Reagents and conditions: (a) PhSeBr, CH_3CN, ice-water bath, N_2; (b) KBH_4, CH_2Cl_2-MeOH, rt.

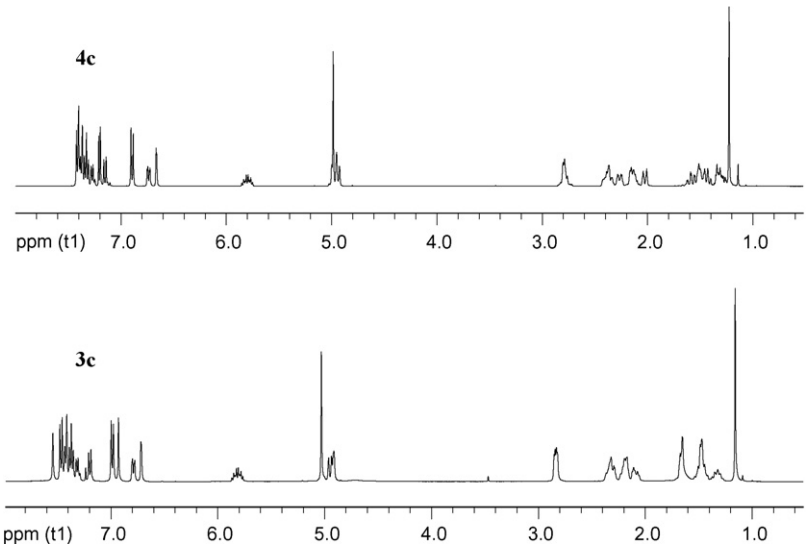


Fig. 1. ^{1}H NMR spectra of hydrazones **3c** and **4c**.

strones **16** and **26**. The downfield shift of C-16 (60 ppm) and C-17a (61 ppm) of 13α-estrone derivatives **25**–**28** can be observed from a comparison of the ^{13}C NMR spectra of the 13-epimer pairs. The iminium salt **24d** of the 4-nitrophenylhydrazone could be isolated as a stable precipitate and subjected to NMR measurements. The ^{1}H NMR spectrum of **24d** displayed a multiplet at 4.38 ppm, due to 16-H, with the singlets of N-H and 17a-H at 9.04 and 11.73 ppm. In the ^{13}C spectrum, the signals of C-16 and C-17a appeared at 61.5 and 187.5 ppm. The configurations of C-16 were determined by means of NOESY experiments. The results were in good agreement with our previous findings on the halo- and selenocyclizations of oximes and oxime ethers [8,9].

Neutral steroids are difficult to analyze by desorption/ionization methods coupled with mass spectrometry, and there are only a few literature reports on the analysis of derivatized steroids through MALDI TOF mass spectrometry [21–23]. In our preliminary study, heterocyclic estrone derivatives were efficiently measured by MALDI TOF mass spectrometer using C_{70} fullerenes as matrix without further chemical derivatization, since all the steroids contained endo- or exocyclic amino *N* atoms which were capable of protonation [9]. Accordingly, MALDI TOF measurements of the synthesized phenylhydrazones **3** and **4** and their cyclic derivatives **16**–**18**, and **26**–**28** were carried out in both negative and positive mode with C_{70} fullerenes as matrix. In the negative mode detection, only fragment ions, but no molecular or quasimolecular ions generally appeared, except for **3c**,**d** and **4c**,**d**, where the negatively charged quasimolecular ions $[M-H]^-$ were detected. In some cases, fragment ions which arose from the cleavage of the aminophenyl or substituted aminophenyl function from the phenylhydrazone were observed, *e.g.*, at m/z = 117 Da $[NHPhCN]^-$ in the spectrum of **27**. In the positive mode detection, the positively charged quasimolecular ions $[M-H]^+$ formed through the cleavage of one hydrogen atom from the amino group were detected in the spectra of phenylhydrazones **3a**–**d** and **4a**–**d**. Molecular ions appeared in many cases: **3c**, **16**, **17**, **18a**,**b**; **26** and **28**. Additionally, two other fragment ions were observed: that of the benzylic cation and one with a mass of 530, from the steroid residue obtained by cleavage of the substituted phenylamino function, *e.g.*, in the spectrum of **27**. Fig. 3 shows the representative mass spectrum of hydrazone **4d** in negative mode.

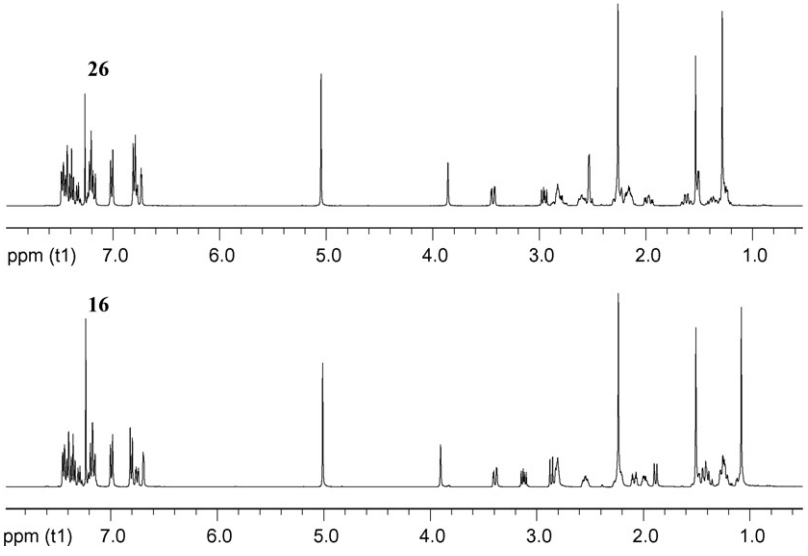


Fig. 2. ^{1}H NMR spectra of aza D-homo derivatives **26** and **16**.

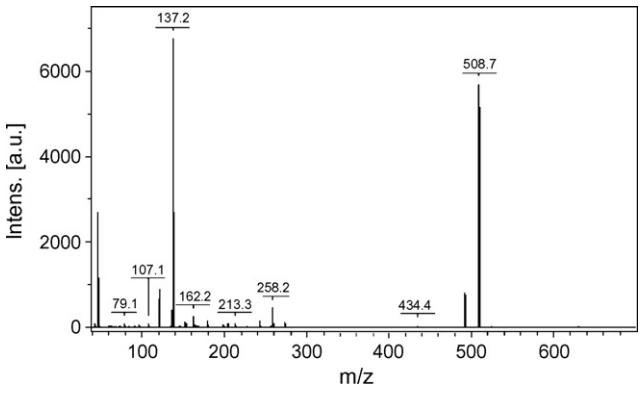


Fig. 3. Mass spectrum of hydrazone **4d**.

4. Conclusions

Secoaldehydes of estrone and 13α-estrone were effectively transformed into δ-alkenyl phenylhydrazones **3** and **4**, phenylselenyl bromide-induced cyclization of which led to cyclic iminium salts. Subsequent hydride reduction yielded new aza-D-homoestrone 3-benzyl ethers **15**–**18** and **25**–**28**. The 3-benzyl-protected secohydrazones **3**, **4** and aza-D-homoestrones **15**–**18** and **25**–**28** undergo facile transformation into the 3-unprotected derivatives, which are promising candidates for pharmacological testing. Many examples have been reported of the cytostatic and antileukemic activity of aza-D-homoestrones [24,25], but there do not appear to have been any biological examinations of 13α-aza-D-homoestrones. Structure determinations of the new synthesized compounds were carried out with one- and two-dimensional NMR and MALDI-TOF measurements.

Acknowledgements

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