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Органічна хімія

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SYNTHESIS OF NEW HETEROLIGNANOLIDES WITH FURO[2,3-*f*]-ISOINDOLONE SCAFFOLD VIA TANDEM ACYLATION/DIELS–ALDER REACTION

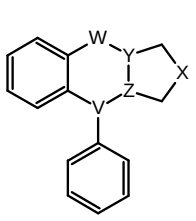
Yu. Homza, R. Lytvyn, Yu. Horak, M. Obushak

Ivan Franko National University of Lviv,
Kyryla & Mefodiya Str., 6, 79005 Lviv, Ukraine
e-mail: homzayuriy@gmail.com

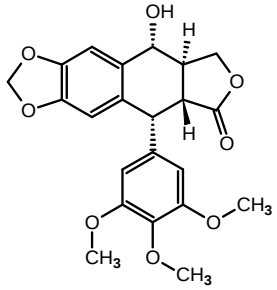
The new method of obtaining heterolignanolides with (4*RS*,4a*SR*,7a*SR*)-4a,5,6,7,7a,8-hexahydro-5*H*-furo[2,3-*f*]isoindol-5-one moiety via Acylation/Intramolecular Diels-Alder reaction based on interaction between *N*-[3-(2-furyl)prop-2-en-1-yl]-4-methoxyaniline and 3-substituted acrylic acid chloranhydrides have been developed.

Key words: heterolignanolides, furo[2,3-*f*]-isoindolone, intramolecular Diels-Alder reaction.

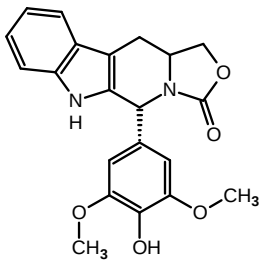
The lignans are natural group of organic polyphenolic compounds found in plants and derived from phenylalanine via dimerization of substituted cinnamic alcohols [1]. They provide various biological activity [2, 3], and analogues of lignans, where one or few benzene rings are replaced with heterocycles, so called heterolignanolides, are known for anticancer ability [4]. The most studied representatives of this class of compounds is podophillotoxins with purgative, vesicant, antirheumatic, antiviral, and antitumor activities [5] and azatoxins [6], which are mainly used as antineoplastic agents. As investigation of biological activity showed, replacement of C atoms in lignans on heteroatoms, such as N, O, S or exchange of phenyl cycles on heterocycles allows to develop anticancer drugs [7, 8]. Thus, development of new methods of obtaining lignanolides is important task of preparative organic chemistry:



HETEROLIGNANOLIDES
V,W,X,Y,Z - C or heteroatom

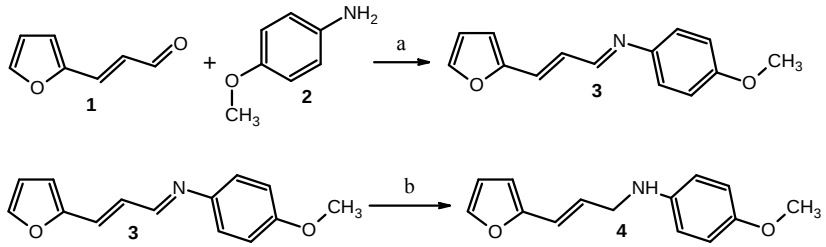


PODOPHILLOTOXIN



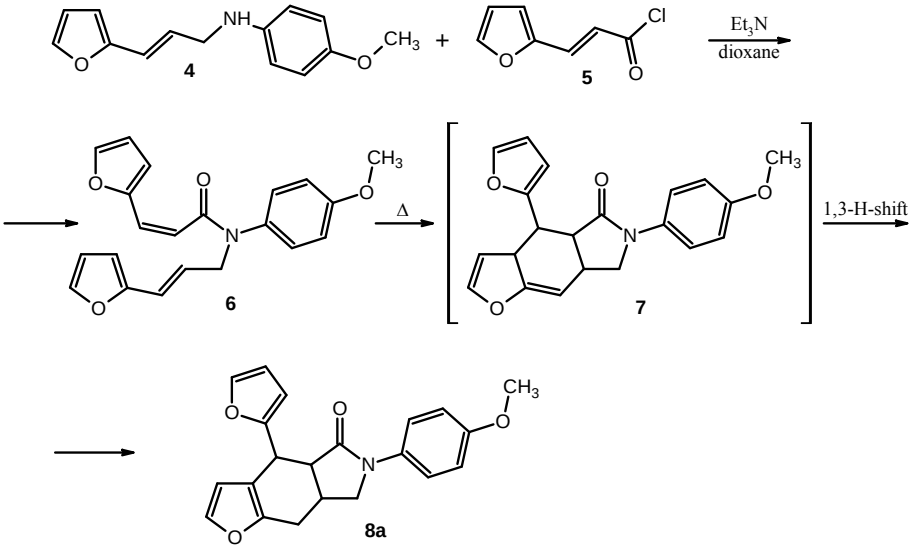
AZATOXIN

In present work we research the possibility of synthesis heterolignanolides via tandem Acylation/Diels–Alder reaction [9] using *N*-[3-(2-furyl)prop-2-en-1-yl]-4-methoxyaniline **4**, obtained from corresponding 3-(2-furyl)-acrylaldehyde **1** by simple sequence of reactions. Treatment of furylacrolein **1** with 4-methoxyaniline **2** in presence of sodium acetate gives Shiff base, *N*-[3-(2-furyl)prop-2-en-1-ylidene]-4-methoxyaniline **3**. C=N double bond of imine **3** were selectively reduced with system $NaBH_4$/HCl in THF:

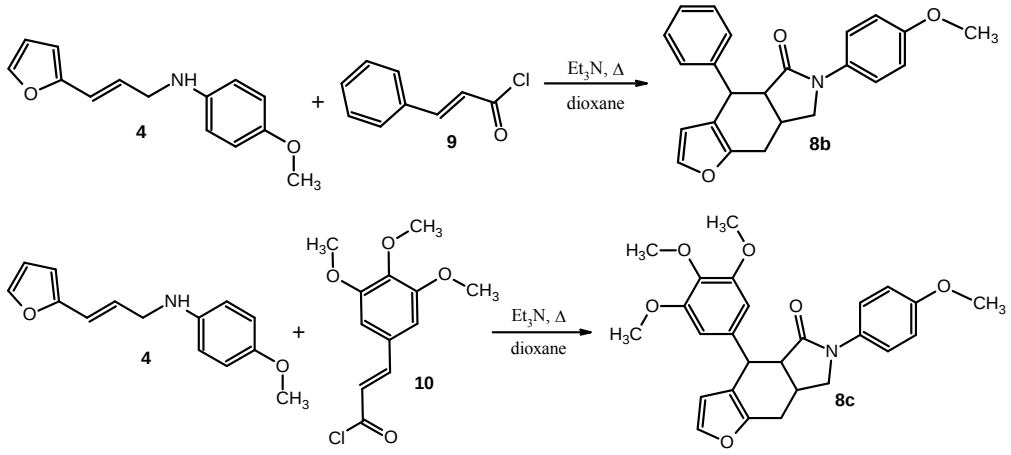


Conditions: a – EtOH, AcONa, reflux, 3h; b – THF, $NaBH_4$, aqueous HCl.

Then we tried *N*-[3-(2-furyl)prop-2-en-1-yl]-4-methoxyaniline **4** in reaction with 3-(2-furyl)-acroleil chloride **5**; product of "acylation step" 3-(2-furyl)-*N*-[3-(2-furyl)prop-2-en-1-yl]-*N*-(4-methoxyphenyl)acrylamide **6** has diene moiety and dienophilic fragment and undergoes intramolecular [2+4] cycloaddition, forming tricyclic scaffold in intermediate 4-(2-Furyl)-6-(4-methoxyphenyl)-3a,4a,5,6,7,7a-hexahydro-5*H*-furo[2,3-*f*]isoindol-5-one **7**. The latter undergoes 1,3-H-shift after Diels–Alder reaction giving desire 4-(2-furyl)-6-(4-methoxyphenyl)-4a,5,6,7,7a,8-hexahydro-5*H*-furo[2,3-*f*]isoindol-5-one **8a**:



Then we enlarged chemical space of this transformation by using cynnamoyl chlorides **9** and **10** in developed synthetic scheme, interaction with *N*-[3-(2-furyl)prop-2-en-1-yl]-4-methoxyaniline **4** lead to lignanolides **8b-c**:



Usually Diels–Alder reaction is reversible, especially at higher temperatures, but in our case because of 1,3-H-shift and rearomatization of furan nucleus this step becomes irreversible, significantly increasing yields of final products.

So, we developed a new method of obtaining lignans analogues via Acylation/Intramolecular Diels–Alder reaction, moreover, we succesfully managed three-step sequence as one-pot process without changing reaction conditions. Also group of new furyllignanolides with potential antitumor activity were synthesized.

Experimental section

All reagents and solvents were purchased from commercial suppliers (Acros Organics, Aldrich, Alfa Aesar, and AstaTech) and used without further purification. No reactions require absolute solvents (CH_2Cl_2, o-xylene, PhH, EtOH) or an inert atmosphere. IR spectra were obtained in KBr pellets using an Infralum FT-801 IR-Fourier spectrometer. Thin layer chromatography was carried out on aluminum backed silica plates Sorbfil. The plates were visualized under UV light (254 nm) or in I_2 vapors. Organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Mass spectra were taken on Kratos MS-30 (UK) (electron ionization, 70 eV, ion source temperature was 200 °C, direct inlet probe) spectrometer, Thermo Focus DSQ II (electron ionization, 70 eV, ion source temperature 200 °C, gas chromatographic inlet with Varian FactorFour VF-5ms column) or on Agilent 1 100 series LC/MSD spectrometer with an API-ES/APCI ionization mode. NMR spectra were run in deuterated (> 99 %) solvents on Bruker Avance 500 (500 MHz for ^1H and 125 MHz for ^{13}C) or Varian Gemini (200 MHz for ^1H and 50 MHz for ^{13}C) spectrometers for 2–8% solutions in $CDCl_3$ or DMSO-d_6 at 23–25 °C using TMS as internal standard.

4,4a,6,7,7a,8-Hexahydro-5*H*-furo[2,3-*f*]isoindol-5-one (8). General Procedure.

The solution of 3-(furan-2-yl)acryloyl or cinnamoyl chloride (3.0 mmol) in dioxane (5 mL) was added to the mixture of *N*-[3-(2-furyl)prop-2-en-1-yl]-4-methoxyaniline **4** (~ 3.0 mmol) and triethylamine (0.44 mL, 3.1 mmol) in dioxane (10 mL). The resulting mixture was heated at reflux for 4 h (TLC and GCMS monitoring), cooled to r.t, diluted with water (50 mL), and extracted with ethyl acetate (3 × 50 mL). The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue solidified on standing and further recrystallization from hexane–EtOAc or EtOH−DMF mixtures afforded the corresponding furoisoindolones **8** as white or light-brown crystals.

(4*RS*,4a*SR*,7a*RS*)-4-(2-Furyl)-6-(4-methoxyphenyl)-4a,5,6,7,7a,8-hexahydro-5*H*-furo[2,3-*f*]isoindol-5-one (8a). Yield – 63 %; light-brown powder; mp = 177–178 °C (EtOH/DMF). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.54–2.90 (m, 2H, H-7a and H-4a), 2.88–3.06 (m, 2H, H-8), 3.73 (s, 3H, OCH_3), 3.75–3.87 (m, 2H, H-7), 4.10 (d, $J_{4,4a}$ = 10.1 Hz, 1H, H-4), 6.23 (d, $J_{2,3}$ = 1.7 Hz, 1H, H-3), 6.32 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-3 Furyl), 6.42 (dd, $J_{4,5}$ = 1.8 Hz, $J_{3,4}$ = 3.2 Hz, 1H, H-4 Furyl), 6.93 (br. d, $J_{2(6),3(5)}$ = 9.0 Hz, 2H, H-3 and H-5 C_6H_4), 7.54 (d, $J_{2,3}$ = 1.7 Hz, 1H, H-2), 7.56 (d, $J_{2(6),3(5)}$ = 9.0 Hz, 2H, H-2 and H-6 C_6H_4), 7.62 (dd, $J_{4,5}$ = 1.8 Hz, $J_{3,5}$ = 0.7 Hz, 1H, H-5 Furyl). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.9 (C-8), 36.4 (C-7a), 41.4 (C-4), 44.9 (C-4a), 50.9 (C-7), 55.2 (CH_3O), 105.6, 109.9, 110.4 (C Ar), 113.8 (2 C, C-3 and C-5 C_6H_4), 119.4 (C Ar), 121.0 (2 C, C-2 and C-6 C_6H_4), 132.8, 142.1, 142.2, 149.5, 154.6, 155.7 (C Ar), 172.2 (C-5). MS (APCI): *m/z* = 350 $[M + H]^+$. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.03; H, 5.37; N, 4.20.

(4*RS*,4a*SR*,7a*SR*)-6-(4-Methoxyphenyl)-4-phenyl-4a,5,6,7,7a,8-hexahydro-5*H*-furo[2,3-*f*]isoindol-5-one (8b). Yield – 72%; white powder; mp = 188–189 °C (EtOH/DMF). ^{1}H NMR (500.1 MHz, DMSO-d_6): δ = 2.55–2.67 (m, 1H, H-7a), 2.81 (ddd, *J* = 2.7, $J_{7a,8A}$ = 11.2 Hz, $J_{8B,8A}$ = 14.5 Hz, 1H, H-8A), 2.90-2.98 (m, 1H, H-8B), 2.94 (dd, $J_{4,4a}$ = 10.8 Hz, $J_{4a,7a}$ = 12.8 Hz, 1H, H-4a), 3.70 (t, $J_{7A,7a} = J_{7B,7A}$ = 9.1 Hz, 1H, H-7A), 3.72 (s, 3H, OCH_3), 3.88 (dd, $J_{7B,7A}$ = 9.1 Hz, $J_{7B,7a}$ = 7.0 Hz, 1H, H-7B), 3.98 (d, $J_{4,4a}$ = 10.8 Hz, 1H, H-4), 5.79 (d, $J_{2,3}$ = 1.8 Hz, 1H, H-3), 6.89 (d, $J_{2(6),3(5)}$ = 9.2 Hz, 2H, H-2 and H-6 C_6H_4), 7.18–7.22 (m, 1H, H-4 Ph), 7.25-7.30 (m, 4H, H-Ar), 7.43 (d, $J_{2,3}$ = 1.8 Hz, 1H, H-2), 7.50 (d, $J_{2(6),3(5)}$ = 9.2 Hz, 2H, H-3 and H-5 C_6H_4). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 26.2 (C-8), 37.0 (C-7a), 40.7 (C-4a), 50.8 (C-4), 51.0 (C-7), 55.2 (CH_3O), 110.1 (C-3), 113.7 (2 C, C-3 and C-5 C_6H_4), 120.7 (2 C, C-2 and C-6 C_6H_4), 122.1 (C-3a), 126.1 (C-4 Ph), 127.9 (2 C, C-2 and C-6 Ph), 128.6 (2 C, C-3 and C-5 Ph), 133.0 (C-1 C_6H_4), 141.9, 142.8 (C-1 Ph and C-2), 149.4 (C-8a), 155.5 (C-4 C_6H_4), 172.0 (C-5). MS (APCI): *m/z* = 360 $[M + H]^+$. Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.65; H, 5.97; N, 3.75.

(4*RS*,4a*SR*,7a*SR*)-6-(4-Methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-4a,5,6,7,7a,8-hexahydro-5*H*-furo[2,3-*f*]isoindol-5-one (8c). Yield – 56%; white powder; mp = 237–238 °C (EtOH/DMF). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.56–2.66 (m, 1H, H-7a), 2.84 (ddd, *J* = 2.7 Hz, $J_{7a,8A}$ = 11.1 Hz, $J_{8A,8B}$ = 14.7 Hz, 1H, H-8A), 2.94 (ddd, *J* = 1.4 Hz, $J_{7a,8B}$= 5.4 Hz, $J_{8A,8B}$ = 14.7 Hz, 1H, H-8B), 2.99 (dd, $J_{7A,7a}$ = 12.8 Hz, $J_{7A,7B}$ = 9.8 Hz, 1H, H-7A), 3.66 (s, 3H, $C_6H_4OC\underline{H}_3$), 3.72 (s, 3H, 4-OCH_3 C_6H_2), 3.73 (s, 6H, 3-OCH_3 and 5-OCH_3 C_6H_2), 3.88 (dd, $J_{7B,7A}$ = 9.8 Hz, $J_{7B,7a}$ = 7.0 Hz, 1H, H-7B), 3.93 (d, $J_{4,4a}$ = 10.7 Hz, 1H, H-4), 5.90 (d, $J_{2,3}$ = 1.8 Hz, 1H, H-3), 6.57 (s, 2H, H-2 and H-6 C_6H_2), 6.91 (d, $J_{2(6),3(5)}$ = 9.2 Hz, 2H, H-2 and H-6 C_6H_4), 7.43 (d, $J_{2,3}$ = 1.8 Hz, 1H, H-2), 7.52 (d, $J_{2(6),3(5)}$ = 9.2 Hz, 2H, H-3 and H-5 C_6H_4). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 26.2 (C-8), 37.1 (C-7a), 41.1.

(C-4a), 50.6 (C-4), 50.9 (C-7), 55.1 (CH_3O), 55.8 (2C, OMe), 59.8 (OMe), 106.0 (2 C, C-2 and C-6 C_6H_2), 110.3 (C-3), 113.7 (2 C, C-3 and C-5 C_6H_4), 120.8 (2 C, C-2 and C-6 C_6H_4), 122.1 (C-3a), 133.1 (C-1 C_6H_4), 136.0, 138.5, 141.8 (C-2, C-1 and C-4 C_6H_2), 149.3 (C-8a), 152.5 (2 C, C-3 and C-5 C_6H_2), 155.6 (C-4 C_6H_4), 172.0 (C-5). MS (APCI): *m/z* = 450 $[M + H]^+$. Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.28; H, 5.96; N, 3.03.

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СИНТЕЗ НОВИХ ГЕТЕРОЛІГНАНОЛІДІВ З ФУРО[2,3-*f*]-ІЗОІНДОЛОНОВИМ ЯДРОМ З ВИКОРИСТАННЯМ ТАНДЕМНОЇ РЕАКЦІЇ АЦИЛЮВАННЯ/ДІЛЬСА – АЛЬДЕРА

Ю. Гомза, Р. Литвин, Ю. Горак, М. Обушак

Львівський національний університет імені Івана Франка,
вул. Кирила і Мефодія, 6, 79005 Львів, Україна
e-mail: homzayuriy@gmail.com

Розроблено новий метод одержання гетеролігнанолідів з (4*RS*,4a*SR*,7a*SR*)-4a,5,6,7,7a,8-гексагідро-5*H*-фуро[2,3-*f*]ізоіндол-5-оновим фрагментом з використа-нням реакції ацилювання та внутрішньомолекулярної реакції Дільса–Альдера на основі взаємодії між *N*-[3-(2-фурил)проп-2-ен-1-іл]-4-метоксианіліном та хлор-ангідридами 3-заміщених акрилових кислот.

Ключові слова: гетеролігнаноліди, фуро[2,3-*f*]-ізоіндолон, внутрішньо-молекулярна реакція Дільса–Альдера.

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