Letters to the Editor

Synthesis of crownophane with the bicyclo[2.2.2]octane core

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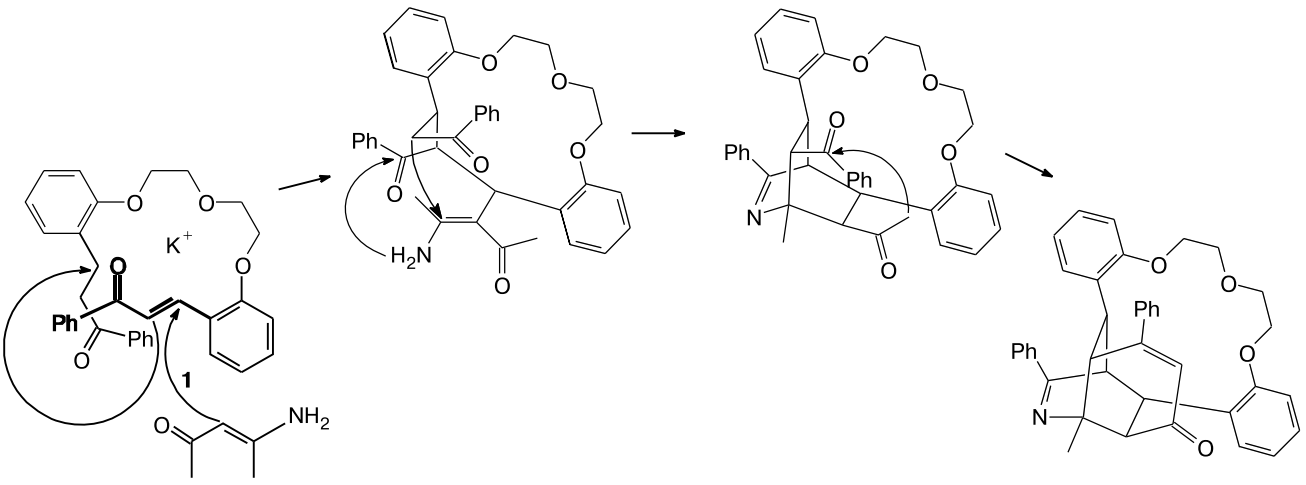
Synthesis of polycyclic structures, such as alkaloids and terpenoids, often includes the use of poly-component cascade reactions.[1—3] Performing cascade transformations is stipulated by the presence of certain functional groups in the starting reactants or key intermediates. For instance, α,β-unsaturated ketones, well known as the Michael acceptors, were used in the target synthesis of prostaglandins[4] and in the assembling of complex pentacyclic alka-

Scheme 1



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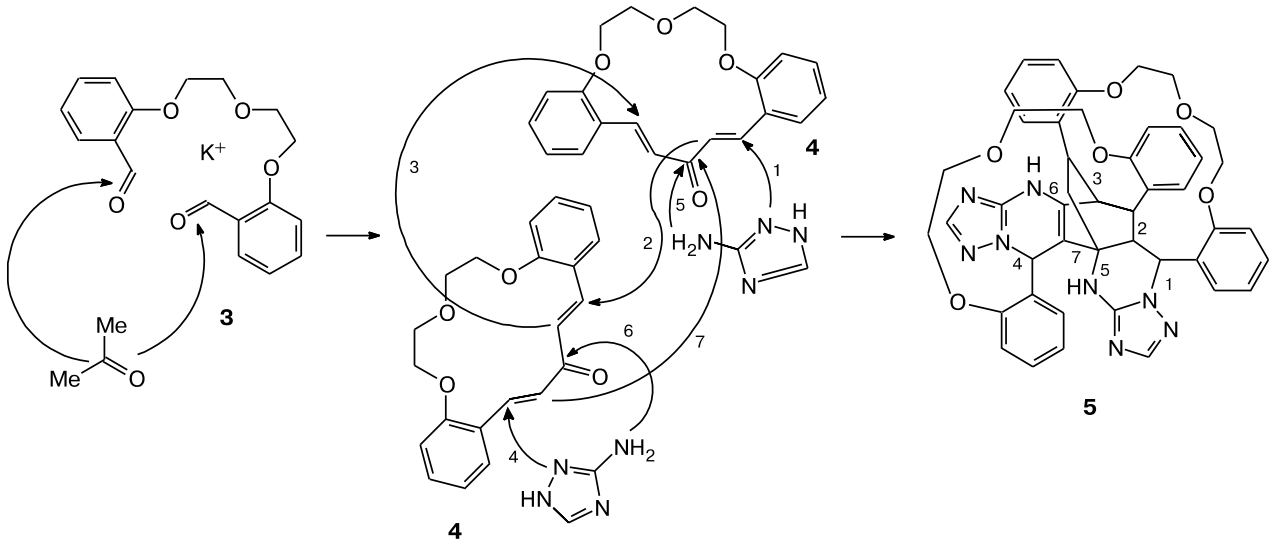
Scheme 2



loid methylhomosecodafnifillate.[3,5] We found an ability of acyclic analogs of crown ethers, chalcone podands (the Michael acceptors), to be involved into the domino-sequence of nucleophilic addition reactions to the double C=C and C=O bonds. The reaction of chalcone podands **1** with 4-aminopent-3-en-2-one leads to the formation of the alkaloid-like crownophane **2** with 2-azabicyclo[2.2.2]-oct-2-enoic core, resembling the natural alkaloid dafnezomin[6] (Scheme 1). The high stereoselectivity observed on the formation of the polycyclic skeleton of crownophane **2** was due to the concerted action of the template effect of the alkali metal ions present in solution and *gauche*-effect of the oligooxyethylene fragment in chalcone podand.

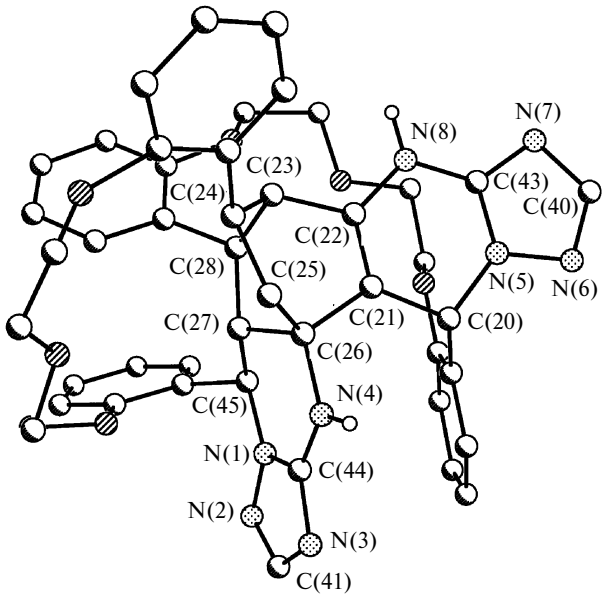


Fig. 1. Molecular structure of crownophane **5** according to the X-ray diffraction data.

The present work shows that crown ethers, whose oligooxyethylene and polyene fragments are combined in the same macrocycle, can be also involved into the cascade reactions (Scheme 2). Thus, the reaction of (16*E*,19*E*)-dibenzo[*h*,*o*][1,4,7]trioxacyclohexadeca-16,19-dien-18-one (**4**), obtained by the template synthesis from formyl podand **3** and acetone (see Ref. 7), with aminotriazole furnishes compound **5** containing the bicyclo[2.2.2]octane core fused with two azolopyrimidine fragments (Scheme 2 shows a cascade of the Michael addition reactions). The structure of crownophane **5**, isolated from the reaction mixture in 32% yield, was confirmed by X-ray crystallography (Fig. 1, Table 1).

In conclusion, development of new synthetic approaches to the preparation of complex polycyclic compounds, such as **2** and **5**, can become not only the basis of new methodology for the construction of macrocyclic caged structures and directed synthesis of natural compounds and their synthetic analogs, but also enrich chemistry with new class of alkaloid-like crownophanes.

IR spectrum was recorded on a Spectrum One IR Fourier-spectrometer (Perkin—Elmer) using a Diffuse Reflectance Sampling Accessory. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 and 100 MHz, respectively) relatively to Me_4Si (^{1}H) and DMSO-d_6 (^{13}C) as internal standards. Melting point was measured on a Boetius microheating stage. Reaction progress and purity of compounds were monitored by TLC on Silufol-254 plates, visualized in iodine vapors.

17,20,23,39,42,45-Hexaoxa-4,6,8,9,53,54,56,58-octaaza-dodecacyclo[28.28.1.1^{1,32}.0^{2,10}.0^{3,31}.0^{5,9}.0^{11,16}.0^{24,29}.0^{33,38}.0^{46,51}.0^{52,59}.0^{53,57}]hexaconta-3,5,7,11(16),12,14,24(29),25,

Table 1. Crystallographic data and parameters of X-ray diffraction experiment for compound **5**

Parameter	Value
Molecular formula	$C_{46}H_{44}O_6N_8 \cdot C_3H_7NO \cdot C_2H_6O$
Molecular weight	924.06
Crystal system	Triclinic
Z	2
Space group	$P\bar{1}$
a/Å	11.6809(5)
b/Å	12.2675(8)
c/Å	18.5577(10)
α/deg	72.445(5)
β/deg	81.961(4)
γ/deg	70.352(5)
V/Å^3	2385.6(2)
d_{calc}/g cm^{-3}	1.285
F(000)	980
μ(MoKα)/mm^{-1}	0.089
Crystal size/mm	0.36×0.25×0.19
Range of scanning θ/deg	2.70—28.28
Range of h, k, l	$-15 \le h \le 13$ $-16 \le k \le 14$ $-22 \le l \le 24$
Number of measured reflections	19971
Number of independent reflections	11211
R_{int}	0.0272
Number of reflections with $I > 2\sigma(I)$	4456
R-factors (on $I > 2$ (I))	
R_1	0.0443
wR_2	0.0850
R-factors (on all the reflections)	
R_1	0.1165
wR_2	0.0900
Q-factor on F^2	0.994
Residual electron density (min/max)/e Å^3	−0.328/0.303

27,33(38),34,36,46,48,50,54,56-heptadecane (5). A solution of compound **4** (0.25 g, 0.7 mmol) and 3-amino-1,2,4-triazole (0.063 g, 0.7 mmol) in DMF (15 mL) was heated in the presence of KOH (0.7 mmol) for 35 h at 80 °C, followed by addition of water to the reaction mixture. A precipitate formed was filtered off and washed with several portions of water on the filter. The product was isolated by column chromatography (SiO_2), eluting with the mixture chloroform—ethyl acetate—isopropanol (10 : 10 : 2), followed by recrystallization from chloroform. The yield was 0.17 g (32%), m.p. >350 °C. ^{1}H NMR (70 °C), δ: 1.88 (m, 1 H, CH_2); 2.81 (m, 1 H, CH_2); 3.52—4.42 (m, 21 H, OCH_2, CH); 4.73 (dd, 1 H, CH, J = 11.3 Hz, J = 1.7 Hz); 5.61 (d, 1 H, CH, J = 11.4 Hz); 6.43 (td, 1 H, Ar, J = 7.4 Hz, J = 0.8 Hz); 6.50 (td, 1 H, Ar, J = 7.4 Hz, J = 1.3 Hz); 6.61 (d, 1 H, Ar, J = 8.2 Hz); 6.75—6.86 (m, 6 H, Ar, HC=N); 6.92 (m, 2 H, Ar); 7.00 (dd, 1 H, Ar, J = 8.0 Hz, J = 1.0 Hz); 7.11 (m, 2 H, Ar); 7.26 (s, 1 H, NH); 7.45 (dd, 1 H, Ar, J = 7.6 Hz, J = 1.0 Hz); 7.54 (m, 2 H, Ar); 7.66 (s, 1 H, HC=N). ^{13}C NMR (70 °C), δ: 30.11, 36.30, 37.60, 40.51, 44.99, 48.36, 53.76, 55.03, 61.77, 67.14, 67.50, 69.46, 69.49, 70.39, 70.56, 70.72, 71.34, 110.99, 111.03, 116.84, 117.24, 118.79, 119.78, 121.49, 122.34, 124.17, 125.64, 126.26, 126.50, 126.59, 126.68, 128.64, 128.71, 130.92, 131.28, 131.98, 134.89, 147.35, 149.52, 151.89, 154.93, 155.57, 156.11, 156.16, 182.73. IR, ν/cm^{-1}: 752, 800 (Ar); 1048, 1064, 1115, 1241 (ν^s, ν^{as}, C_{Ar}—O—C_{Alk}, C_{Alk}—O—C_{Alk}); 1335, 1353, 1373, 1397, 1453, 1489, 1515, 1541, 1555, 1602, 1634 (C=C, C=N); 2824, 2872, 2924, (C_{Ar}—H); 3041, 3069 (C_{Ar}—H); 3254, 3409 (N—H). Calculated (%): C, 68.65; H, 5.47; N, 13.93. $C_{46}H_{44}O_6N_8$. Found (%): C, 68.70; H, 5.62; N, 14.03.

X-ray diffraction study. Crystals of crownophane **5** were obtained by slow concentration of the solution of this compound in DMF—EtOH. X-ray diffraction analysis was performed on a Xcalibur 3 automatic diffractometer with a CCD-detector (ω-scanning, MoKα-radiation, λ = 0.71073 Å, graphite monochromator, T = 295 K). The structure was solved by the direct method and refined by the full-matrix least squares method first in isotropic and then in anisotropic approximation on F^2 for all the nonhydrogen atoms using the SHELXS-97 and SHELXL-97 program packages.[8] Crystallographic data and parameters of the X-ray diffraction experiment are given in Table 1. The details of the X-ray diffraction experiment for the structure **5** were deposited with the Cambridge Structural Database with the number CCDC 822752.

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