Synthesis of 8,9-(1,3-benzodioxolo-5,6)-5-azatricyclo[8.2.1.0^{1,5}]tridec-11-en-6-one. A convenient route to structural analogs of the alkaloid cephalotaxine*

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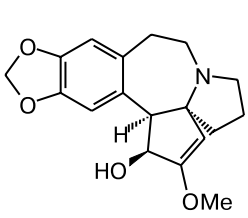
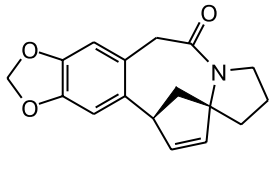
A synthetic route to 8,9-(1,3-benzodioxolo-5,6)-5-azatricyclo[8.2.1.0^{1,5}]tridec-11-en-6-one structurally isomeric to the pentacyclic cephalotaxine nucleus is suggested. The route is based on the sequence including diallylboration of 2-pyrrolidinone and intramolecular metathesis of the resulting 2,2-diallylpyrrolidine, giving rise to 1-azaspiro[4.4]non-7-ene. This product was *N*-acylated with 6-bromohomopiperonylic acid chloride and then subjected to intramolecular cyclization according to the Heck reaction.

Key words: cephalotaxine, Heck reaction, palladacycles, polycyclic compounds, 1-azaspiro[4.4]non-7-ene, intramolecular metathesis, X-Ray diffraction analysis.

In recent years, a large number of alkaloids whose molecules contain spiro-coupled (hetero)cycles have been isolated from various natural objects.[1] Among these alkaloids, a special part belongs to pentacyclic cephalotaxine and a number of its esters (harringtonine, homoharringtonine, isoharringtonine, and deoxyharringtonine). All these alkaloids are produced by yew trees (*Cephalotaxus harrigtonia* var. *drupacae*), which grow in China and in Japan. Cephalotaxine esters possess high antileucaemia (myeloid leucaemia)[2a] and antimalarial activities;[2b] pharmaceuticals based on them are now under clinical trials.[2] Previously, several research groups have synthesized the parent cephalotaxine and some of its close analogs (see, for example, Ref. 3).



Cephalotaxine



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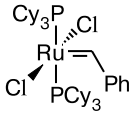
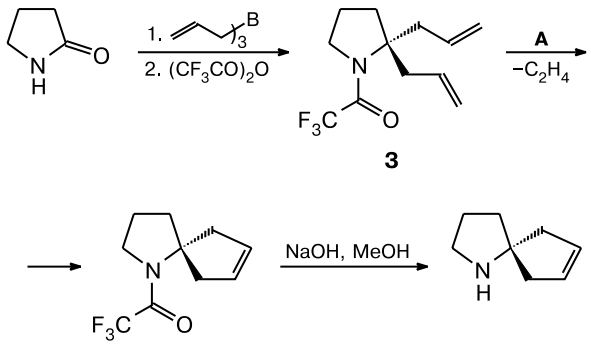
In this communication we propose a route to polycyclic amide **1**. This compound can be used to prepare the previously unknown pentacyclic system, which is isomeric to the alkaloid cephalotaxine. The key step of the synthesis is the design of 1-azaspiro[4.4]non-7-ene (**2**). This product was prepared by reductive diallylation of 2-pyrrolidinone with triallylborane[4] followed by intramolecular metathesis of the *N*-trifluoroacetyl derivative **3** in the presence of the Grubbs catalyst (**A**) (0.5 mol.%, CH_2Cl_2)[5] (Scheme 1). The protective group in **4** was removed by treatment with alkali in methanol, and bicyclic amine **2** was isolated by distillation in 74% yield.



A

Scheme 1



3 **4** **2**, 74%

The other fragment of the molecule was prepared according to Scheme 2. Commercially available homopiperonylic acid was brominated into position 6 with *N*-bromosuccinimide[6a] in dichloromethane for 2 h; the use of this reagent proved to be more convenient than

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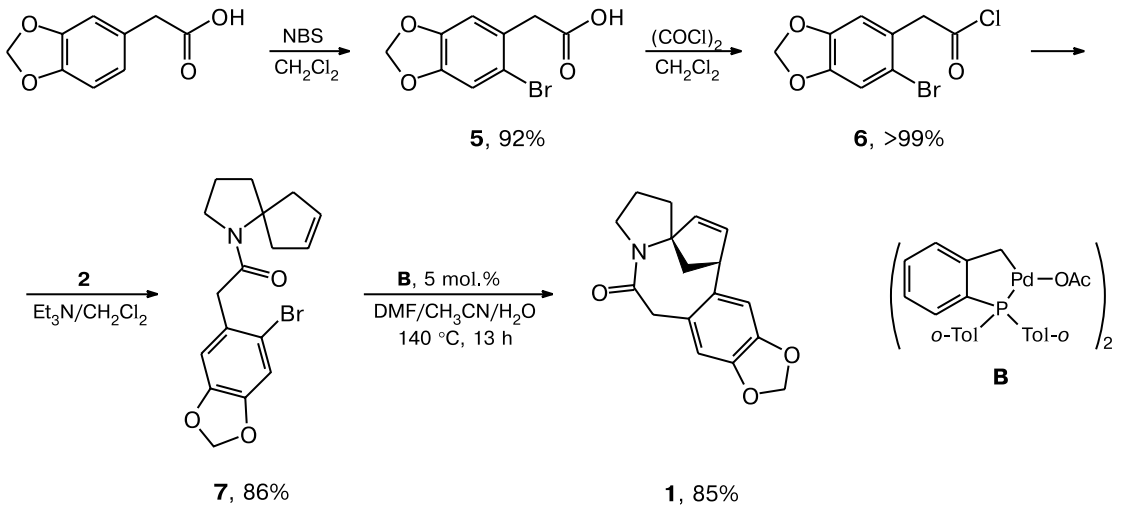
Scheme 2



treatment with bromine (this has been described previously[6b]). The resulting bromo acid **5** was heated with oxalyl chloride in dichloromethane, which gave acyl chloride **6** in a quantitative yield.[3b]

The acylation of bicyclic amine **2** with chloride **6** was carried out in the presence of triethylamine; the amide **7** thus formed was isolated by chromatography on silica gel. The final step made use of the Heck cyclization (*cf.* Ref. 3b, in which the double bond in the product of similar cyclization is also nonconjugated with the aromatic nucleus). Heating of amide **7** with palladium complex **B** as the catalyst for 13 h at 140 °C affords compound **1** (85%) (see Scheme 2).

The structure of pentacyclic compound **1** was determined by X-ray diffraction analysis (Fig. 1). Compound **1** has two asymmetric centers, C(1) and C(17). The crystal of **1** is racemic, the relative configuration of these centers being (1*S**, 17*R**). The structure of the nitrogen-containing tricyclic fragment is shown in Fig. 2: the 9-membered ring has a boat conformation (the C(11), C(18), and C(19) atoms deviate from the mean plane of the other atoms of the ring by −0.909, −1.493, and −1.468 Å, respectively), the 8-membered ring has a chair conformation (the C(11) and C(20) atoms deviate from the mean plane of the other ring atoms by −0.909 and +0.798 Å, respectively), and the 5-membered ring has an envelope conformation (the C(20) atom deviates from the plane of the other ring atoms by 0.405 Å).

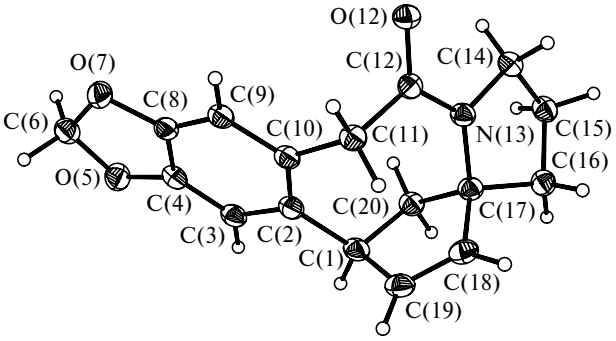


Fig. 1. Molecular structure of compound **1** (ellipsoids of thermal vibrations are given with 50% probability).

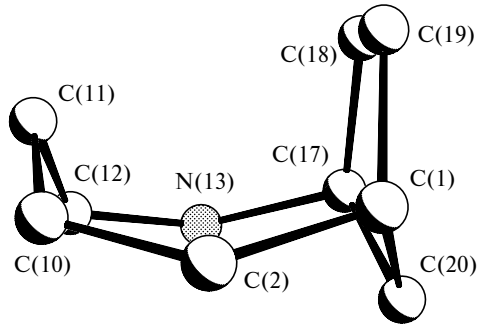


Fig. 2. Conformation of the tricyclic fragment in compound **1**.

Thus, using the sequence including diallylboration of 2-pyrrolidinone, intramolecular metathesis, and the Heck cyclization, we synthesized pentacyclic compound **1** whose further transformations allow the synthesis of a structural isomer of the alkaloid cephalotaxine. The change in the size of the nitrogen-containing fragment of the spiro-coupled heterocycle, which may take place in our method, allows one to prepare a number of new cephalotaxine analogs.

Experimental

The reactions were carried out in an atmosphere of pure argon. All solvents were purified and dried according to stan-

dard procedures. The NMR spectra were recorded on Bruker AMX-400 and Avance-300 spectrometers. Column chromatography was carried out using silica gel 60—230 mesh (Merck). Aluminum plates with silica gel 60 F_{254} (Merck) were used for thin layer chromatography. Catalyst **A** was received from Fluka. Complex **B** was prepared from palladium acetate and tri-*o*-tolylphosphine according to a published procedure.[7] Homopiperonylic acid was purchased from Acros. Compound **4** was prepared according to a reported procedure.[4,5]

1-Azaspiro[4.4]non-7-ene (2). Bicyclic amide **4** [4] (12.3 g, 56.0 mmol) was dissolved in MeOH (60 mL), a solution of NaOH (10 *M*, 20 mL, 0.2 mol) was added, and the mixture was refluxed for 2 h, the course of the reaction being monitored by TLC (hexane—AcOEt, 4 : 1). Methanol was removed *in vacuo*, the residue was extracted with ether (3×20 mL), and the combined extracts were dried with K_2CO_3 and concentrated on a rotary evaporator. Distillation gave amine **2** (5.1 g, 74%) as a colorless liquid, b.p. 69—70 °C (12 Torr). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.54 (s, 2 H); 2.87 (t, 2 H, J = 7.0 Hz); 2.25 (s, 4 H); 1.71 (m, 2 H); 1.60 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 125.13 (2 CH=); 65.22 (C); 41.89 (2 CH_2); 41.20 (CH_2); 34.65 (CH_2); 20.75 (CH_2).

(6-Bromo-1,3-benzodioxol-5-yl)acetic acid (5). *N*-Bromosuccinimide (5.3 g, 30 mmol) was added in portions at +5 °C over a period of 15 min (see Ref. 7) to a solution of homopiperonylic acid (5 g, 27.7 mmol) in CH_2Cl_2 (80 mL). The mixture was stirred for 2 h at room temperature. Water (100 mL) was added, the organic layer was separated, and the solvent was evaporated on a rotary evaporator. The resulting precipitate was filtered off, washed with hexane and water, and dried in air for ~12 h to give brominated acid **5** (6.6 g, 92%) as a white powder, m.p. 190—191 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 12.45, 7.17, 6.98 (all s, 1 H each); 6.04, 3.62 (both s, 2 H each). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 171.58, 147.22, 146.99, 128.09, 114.87, 112.04, 111.60, 101.92, 40.83. Acid **5** was converted into the corresponding acyl chloride **6** by a reported procedure.[3b]

1-(1-Azaspiro[4.4]non-7-en-1-yl)-2-(6-bromo-1,3-benzodioxol-5-yl)ethan-1-one (7). Solid chloride **6** (4.85 g, 17.5 mmol) was added with stirring and water-bath cooling (~20 °C) to a solution of amine **2** (2.0 g, 16.2 mmol) and triethylamine (2.0 g, 2.78 mL, 20.0 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred for 2 h and treated with water (40 mL). The organic layer was separated, washed with a solution of $NaHCO_3$, water, and a solution of 3 *M* HCl (10 mL), and dried with Na_2SO_4. The solvent was evaporated and the oil thus formed was chromatographed on silica gel with a hexane—AcOEt (2 : 1) system to give amide **7** (5.07 g, 86%) as a white crystalline powder, m.p. 102—103 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.96, 6.80 (both s, 1 H each); 5.91, 5.62, 3.60, 3.56 (all s, 2 H each); 3.19 (d, 2 H, J = 15.2 Hz); 2.09 (d, 2 H, J = 15.0 Hz); 1.89 (br.s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 167.74, 147.34, 147.26, 128.76 (2 CH), 128.49, 115.04, 112.42, 110.93, 101.66, 69.82, 48.65, 43.97 (2 CH_2), 43.14, 42.95, 23.37. Found (%): C, 56.07; H, 4.94; N, 3.82. $C_{17}H_{18}BrNO_3$. Calculated (%): C, 56.06; H, 4.98; N, 3.85.

8,9-(1,3-Benzodioxolo-5,6)-5-azatricyclo[8.2.1.0^{1,5}]tridec-11-en-6-one (1). Catalyst **B** (47 mg, 0.05 mmol, 5 mol %), AcONa (0.21 g, 2.6 mmol), and amide **7** (0.36 g, 1 mmol) were charged into a 25-mL two-necked flask under argon, and CH_3CN (5 mL), DMF (5 mL), and water (1 mL) were added. The mixture was degassed through three freezing—evacuation—argon filling—thawing cycles. The flask was plugged with stoppers secured by springs and heated on an oil bath for 13 h at 140 °C. The solvents were evaporated *in vacuo*, the residue was diluted with water, and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). After concentrating the extracts, the residue was purified by chromatography on silica gel with a AcOEt—hexane system, 2 : 1 (R_f = 0.23) to give compound **1** (0.24 g, 85%) as a white crystalline powder, m.p. 149—150 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.77, 6.63 (both s, 1 H each); 6.11 (dd, 1 H, J = 2.9, J = 5.3 Hz); 5.91, 5.88 (both d, 1 H, J = 1.3 Hz); 5.81 (d, 1 H, J = 5.4 Hz); 4.94 (d, 1 H, J = 13.1 Hz); 3.82 (dd, 1 H, J = 2.1 Hz, J = 8.8 Hz); 3.73 (ddd, 1 H, J = 3.4 Hz, J = 8.4 Hz, J = 12.2 Hz); 3.47 (ddd, 1 H, J = 7.4 Hz, J = 9.1 Hz, J = 12.2 Hz); 3.15 (d, 1 H, J = 13.1 Hz); 2.32 (m, 1 H); 3.27 (dd, 1 H, J = 8.8 Hz, J = 13.0 Hz); 1.98—1.72 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 171.36, 146.59, 146.15, 134.98, 134.78, 134.42, 128.16, 113.85, 110.21, 101.00, 73.65, 52.99, 49.09, 47.78, 40.88, 40.76, 21.42. Found (%): C, 72.04; H, 5.94; N, 4.94. $C_{17}H_{17}NO_3$. Calculated (%): C, 72.07; H, 6.05; N, 4.94.

X-Ray diffraction analysis of compound 1 ($C_{17}H_{17}NO_3$, M = 283.32). The crystals of **1** are monoclinic, space group $P2_1/n$; at T = 120 K: a = 7.1808(13), b = 18.046(3), c = 10.3917(18) Å, β = 99.352(3)°, V = 1328.7(4) Å^3, Z = 4, d_c = 1.416 g cm^{-13}, $F(000)$ = 600, μ = 0.097 mm^{-1}. The unit cell parameters and the intensities of 12317 reflections (R_{int} = 0.026) were measured on a Bruker SMART 1000 CCD automated diffractometer equipped with a Oxford CryoSystem low-temperature unit (T = 120 K, Mo-Kα radiation, graphite monochromator, φ and ω scan mode, $2\theta_{max}$ = 54°). The structure was solved by the direct method and refined by the full-matrix least-squares calculations in the anisotropic approximation for nonhydrogen atoms. The hydrogen atoms were located in the difference Fourier syntheses and refined isotropically. The final R-factors: R_1 = 0.044 for 2196 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.115 for all 2898 independent reflections. All calculations were performed using the SHELXTL PLUS software (Version 5.10).[8]

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