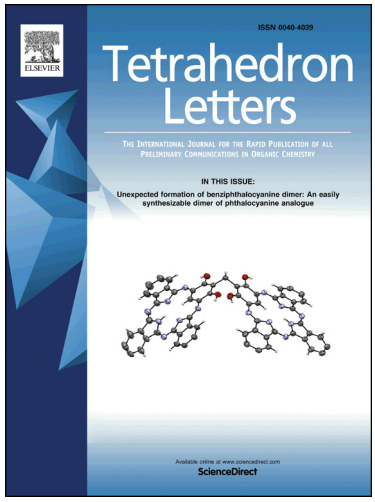

Rearrangement of 2-azanorbornenes to tetrahydrocyclopenta[*c*]pyridines under the action of activated alkynes – a short pathway for construction of the altemicidin core.

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Graphical Abstract

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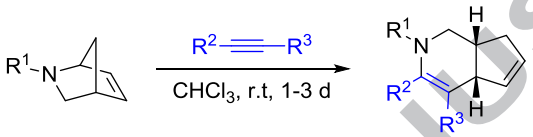

R^1 = Alkyl, Allyl, Bn, Cycloalkyl; R^2 = H, CO_2Alkyl;
R^3 = CO_2Alkyl, $CONH_2$ (*18 examples, 33-88% yield*)

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Rearrangement of 2-azanorbornenes to tetrahydrocyclopenta[*c*]pyridines under the action of activated alkynes – a short pathway for construction of the altemicidin core.

Dinara K. Nasirova[a], Anastasia V. Malkova[a], Kirill B. Polyanskii[a], Kristina Yu. Yankina[a], Prince N.-A. Amoyaw[b], Irina A. Kolesnik[c], Alexey V. Kletskov[c], Ivan A. Godovikov[d], Eugeniya V. Nikitina[a], Fedor I. Zubkov[a,*]

[a] *Department of Organic Chemistry, Peoples' Friendship University of Russia (RUDN University), 6 Miklukho-Maklaya St., Moscow, 117198, Russian Federation*
[b] *Division of Liberal Arts and Sciences, State University of New York at Delhi, Delhi, New York, 13753, USA*
[c] *Institute of Physical Organic Chemistry, National Academy of Sciences, 13 Surganov St., Minsk, 220072, Belarus*
[d] *A. N. Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences, 28 Vavilova St., Moscow, 119991, Russian Federation*

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ABSTRACT

A simple approach to a series of 2,4a,7,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridines was proposed on the basis of the amino-Claisen rearrangement of readily accessible 2-azabicyclo[2.2.1]hept-5-enes under the action of dialkyl acetylenedicarboxylates, methyl propiolate or propiolamide. The rearrangement is highly diastereoselective and leads to the formation of only one isomer with *cis*-annulation of the five- and six-membered rings in satisfactory yields. Using the developed method, close analogs of the altemicidin and SB-203207 cores were synthesized.

Partially hydrogenated cyclopenta[*c*]pyridine is the main structural element of a number of alkaloids and a common motif in the plant kingdom. Nearly 30 years ago the first natural products possessing the cyclopenta[*c*]pyridine structure were isolated and documented.[1-4] For example, nepetalactam[1] was isolated from the oil of *Nepeta cataria* (catnip), lindenialine[2] was obtained from the leaves of *Lindenia austro-caledonica* Brongn, and dinklageine[3] was found in the leaves of *Strychnos dinklagei* Gilg. (Fig. 1). However, until recently, the previously mentioned alkaloids or their heterocyclic cores have not attracted significant attention.

In 2000, the SmithKline Beecham group published the structure of SB-203207, which was isolated from a *Streptomyces* species, and established that it inhibits isoleucyl *t*RNA synthetase with an IC_{50} value below 2 nM.[5] This discovery has highlighted the potent biological activities of the cyclopenta[*c*]pyridine skeleton, establishing it as a challenging structural goal for target oriented synthesis. Currently, many approaches to altemicidin derivatives have been proposed,[6] including the enantioselective synthesis of SB-203207.[7]

Herein, we report a short synthetic route for the synthesis of partly hydrogenated cyclopenta[*c*]pyridines with structures similar to the natural alkaloids (Fig. 1).

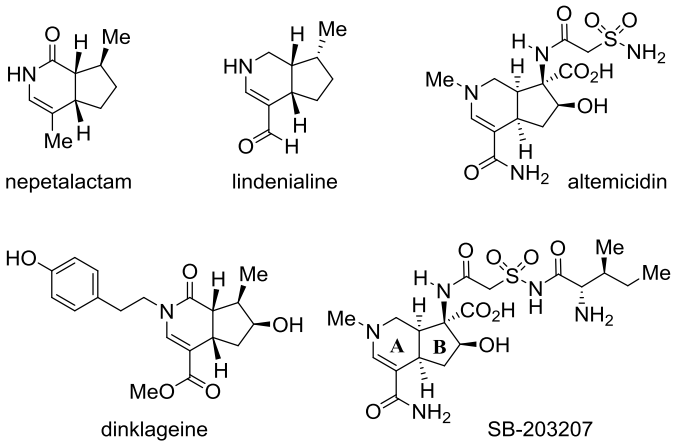


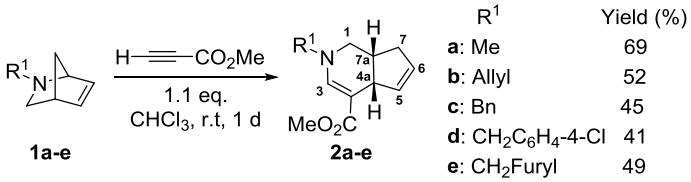
Figure 1. Selected naturally occurring cyclopenta[*c*]pyridines.

N-Substituted 2-azabicyclo[2.2.1]heptenes, which are easily obtained by a three-component aza-Diels-Alder reaction between the corresponding primary alkylamines, formaldehyde and cyclopentadiene,[8] are building-blocks commonly used in the stereoselective synthesis and in the synthesis of natural products.[9]

* Corresponding author. Tel.: +7-495-955-0729; fax: +7-495-952-2644; e-mail: fzubkov@sci.pfu.edu.ru

These building-blocks are attractive not only because of their ready availability, but also due to the fact that they are available in optically pure form.[10]

Through extensive literature review, we found only one example of the sigmatropic rearrangement of the 2-azabicyclo[2.2.1]hept-5-ene core (**1a**) to a cyclopenta[*c*]pyridine under the action of methyl propiolate (MP).[11] The reaction was carried out in acetonitrile at reflux and the target product of the rearrangement **2a** (R^1 = Me) was isolated in 19% yield (Scheme 1).[11a]

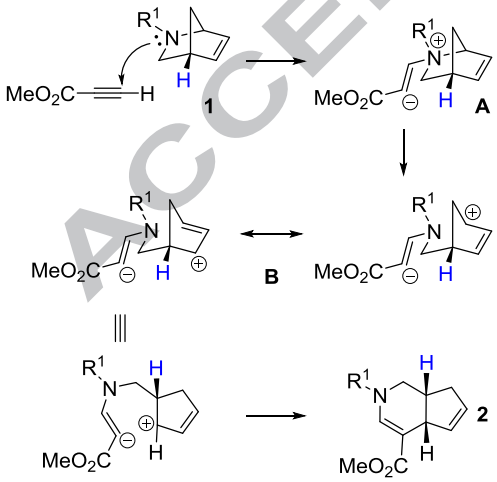


R^1	Yield (%)
a: Me	69
b: Allyl	52
c: Bn	45
d: $CH_2C_6H_4$-4-Cl	41
e: CH_2Furyl	49

Scheme 1. Amino-Claisen rearrangement of 2-azanorbornenes under the action of MP.

Taking into account the close similarity of compound **2a** (R^1 = Me) and the structures of the natural compounds (Fig. 1), we attempted to optimize the conditions for its preparation. Thus, we discovered that increasing the reaction temperature above room temperature, in order to speed up the reaction between the activated alkyne and 2-azanorbornene **1a**, led to significant polymerization, thereby resulting in a dramatic reduction in the yield of the desired product **2a**. Protic solvents (MeOH, CF_3CH_2OH) render impossible or inhibit the rate of reaction between MP and **1a**, and the best yields were achieved in $CHCl_3$ at r.t. Although other solvents (MeCN, CH_2Cl_2, PhH, THF) were also found to be suitable, the reaction proceeds slowly and affords only moderate yields of **2a**. It is possible the most polar $CHCl_3$ facilitates the formation of zwitterion **B** (Scheme 2). The optimized parameters were then used for the synthesis of compounds **2a-e**.

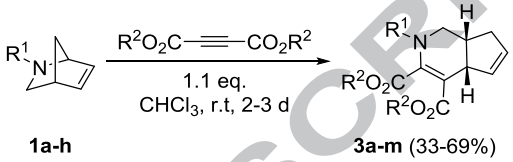
A plausible reaction mechanism for the rearrangement is shown in Scheme 2.



Scheme 2. Proposed mechanism for the diastereoselective amino-Claisen rearrangement of 2-azabicyclo[2.2.1]heptenes (**1**).

The first step involves the initial addition of methyl propiolate to bicycle **1** to form zwitterion **A**, the relative configuration of which does not affect the spatial structure of the final product **2**, formed *via* the resonance-stabilized bipolar ion **B**. The formation of a new σ-bond completes the amino-Claisen rearrangement. For obvious structural reasons, the cyclization in cation **B** proceeds diastereospecifically and leads to the formation of a single diastereoisomer of compound **2** with *cis*-annulation of the five- and six-membered rings. However, strong evidence for the proposed mechanism cannot be provided at this time and an alternative synchronous process can also be envisioned.

Reactions involving the addition of dimethyl, diethyl or di-*t*-butyl acetylenedicarboxylates to 2-azabicyclo[2.2.1]heptenes (**1**) also proceeded in a similar fashion, affording adducts **3a-m** in moderate yields under the same reaction conditions (Scheme 3, Table 1).



Scheme 3. Amino-Claisen rearrangement of 2-azanorbornenes **1** under the action of acetylenedicarboxylic acid esters.

The spatial structures of cyclopenta[*c*]pyridines **2** and **3** were established based on their NMR spectroscopic data. The most noticeable signals in the ^{1}H NMR spectra are a doublet of doublets at δ 2.6-2.8 ppm belonging to the ABX system of the NCH_2CH group (^2J ~11-12, ^3J ~5-6 and 10-11 Hz) and two multiplets of the CH=CH fragment at δ ~5.6 and 5.9 ppm. The ^{13}C NMR spectra are characterized by signals for the carbon atoms of the double bonds at δ ~97 (C-4), 125, 136, and 146 ppm (see ESI).

Table 1. Substituents R^1, R^2 and isolated yields of cyclopenta[*c*]pyridines **3**.

Compound **3**	R^1	R^2	Yield **3** (%)
a	Me	Me	69
b	Allyl	Me	56
c	Bn	Me	64
d	$CH_2C_6H_4$-4-Cl	Me	60
e	CH_2Furyl	Me	33
f	Cyclohexyl	Me	55
g	*n*-$C_{12}H_{25}$	Me	58
h	Cyclopropyl	Me	41
i	*i*-Pr	Me	65
j	Me	Et	67
k	Bn	Et	63
l	$CH_2C_6H_4$-4-Cl	Et	48
m	Me	*t*-Bu	42

The *cis*-annulation of the rings in compounds **3** was proven by single crystal X-ray analysis using di-*tert*-butyl ester **3m** as a representative example. The spatial structures of compounds **2** and **4** were assigned by analogy.

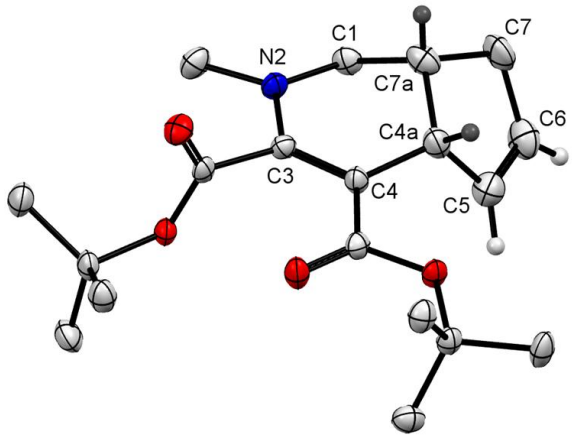
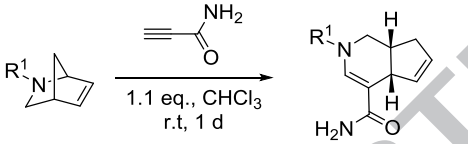


Figure 2. Crystal structure for compound **3m**. Displacement ellipsoids are shown at the 50% probability level. Almost all H atoms of the molecule were deleted for clarity, H-4a, H-5, H-6 and H-7a atoms are shown as small spheres of arbitrary radii.

The single crystal X-ray structure of di-*tert*-butyl ester **3m** (R^1 = Me, R^2 = *t*-Bu) is shown in Figure 2. Compound **3m** comprises of the fused bicyclic system containing five-membered (cyclopentene) and six-membered (piperidine) rings. The five-membered ring possess a *flat envelope* conformation, and the six-membered ring adopts a *distorted flat boat* conformation. The nitrogen atom is almost planar (sum of the bond angles are 356.9°). The dihedral angle between H-4a and H-7a is 31.5(6)°.

In order to synthesize structures more closely related to altemicidin and SB-203207, we demonstrated that propiolamide (PA)[12] can also be involved in the rearrangement (Scheme 4).



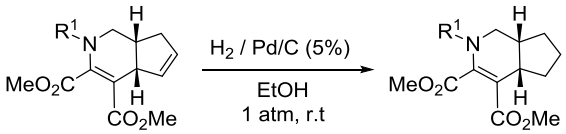
1a,**c**

4a: R^1 = Me (61%);
4b: R^1 = Bn (57%).

Scheme 4. Amino-Claisen rearrangement of 2-azanorbornenes (**1**) under the action of propiolamide.

Amides **4a** and **4b** were isolated in moderate yields. In the case of R^1 = Me, a compound resembling the A ring of SB-203207 (Fig. 1) was generated in one step.

We also attempted to perform further modifications of the unsubstituted double bond in cyclopenta[*c*]pyridines **2**-**4**, in order to develop routes to access the target natural products. Unfortunately, the Prilezhaev oxidation of compounds **2a**, **3a**, and **4a** with *m*-CPBA did not occur over a broad temperature range (0–70 °C), and instead of the desired epoxides a multicomponent mixture formed. However, the reduction of cyclopenta[*c*]pyridines (**3**) proceeded chemospecifically at the least substituted and more electronically enriched double bond of the five-membered ring, leading to derivatives **5**, possessing the core of nepetalactam and lindenialine, in good yields (Scheme 5).



3a,**c**

5a: R^1 = Me (88%);
5b: R^1 = Bn (85%).

Scheme 5. Selective reduction of cyclopenta[*c*]pyridines **3a**,**c**.

In conclusion, during the course of this investigation the reaction between 2-azanorbornenes and activated alkynes was carried out. The obtained results revealed that the reaction proceeds *via* the stereoselective amino-Claisen rearrangement. This simple protocol may be useful in the synthesis of natural-like products possessing a cyclopenta[*c*]pyridine core.

Acknowledgments

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13. **General procedure for the preparation of substituted tetrahydro-cyclopenta[*c*]pyridines (2-4)**. 2-Azanorbornene **1** (2 mmol) was dissolved in dry $CHCl_3$ (15 mL) at ambient temperature, then the substituted acetylene (2.2 mmol) was added to the solution and the homogenous mixture stirred at r.t (24 h for MP and PA; 72 h for dialkyl acetylene dicarboxylates; TLC monitoring). Evaporation of the solvent under reduced pressure gave a crude brown oil which was purified by silica gel column chromatography (hexane-EtOAc with increasing polarity as eluent) to provide products **2-4** as colorless oils or white powders. In the case of the reaction with MP, the obtained products **2a-e** were unstable at r.t in air (quickly became dark), but relatively stable under a N_2 atmosphere at –16 °C.
General procedure for the preparation of hexahydrocyclopenta[*c*]pyridines (5). A moderate hydrogen flow (one bubble per second) was passed through a solution of compound **3** (2 mmol) and 5% Pd/C (70 mg) in EtOH (10 mL) for 1 h at r.t. The reaction mixture was purged with argon and filtered through a thin layer of celite. The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography to give cyclopenta[*c*]pyridines **5a**,**b**.
14. The colorless crystal of **3m** ($C_{19}H_{29}NO_4$, M = 335.43) is orthorhombic, space group *Pna21*, a = 9.903(2) Å, b = 17.692(4) Å, c = 10.573(3) Å, V = 1852.3(7) Å^3, Z = 4, T = 120 K, μ (MoKα) = 0.083 mm^{-1}, d_{calc} = 1.203 g/cm^3. 20411 total reflections were measured ($4.488° \leq 2\Theta \leq 61.008°$), 5622 unique reflections (R_{int} = 0.0851, R_{sigma} = 0.0829) which were used in all calculations. The final R_1 was 0.0652 ($I > 2\sigma$ (I)) and wR_2 was 0.1619 (all data). Crystallographic data (excluding structure factors) for the structure of **3m** reported herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1556691. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

Supplementary Material

Supplementary data (characterization data, copies of ^{1}H and ^{13}C NMR spectra for compounds **2-5**, and X-ray data for compound **3m** associated with this article can be found in the online version, at ESI.

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Highlights

- Amino-Claisen rearrangement of azabicyclo[2.2.1]heptenes under the action of alkynes
- Diastereoselective pathway to altemicidin and dinklageine core analogs
- Effective synthesis of 2,4a,7,7a-tetrahydrocyclopenta[*c*]pyridines under mild conditions
- Short pathway for construction of the altemicidin core