Tetrahedron 96 (2021) 132388

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The first synthesis of benzo[*e*]cycloalk[g]oxazocinone atropisomers *via* lactonization of *N*-mesyl- or *N*-arylsulfonyl-*N*-[2-(1-cycloalken-1-yl)-6-methylphenyl]glycines

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ARTICLE INFO

Article history:
Received 31 May 2021
Received in revised form
2 August 2021
Accepted 6 August 2021
Available online 12 August 2021

Keywords:
Bromocyclization
Glycine
Atropisomerism
Axial chirality
Benzoxazepine
Benzoxazocine

ABSTRACT

The article describes an efficient access to cycloalkene-annulated benzoxazocines displaying both axial and central chiralities, *via* a domino halogenation-lactonization reaction of substituted glycine precursors. Upon interaction between *N*-[2-(1-cyclohexen-1-yl)-6-methylphenyl]-*N*-mesyl- or -*N*-arylsulfonylglycines and bromine an axially chiral mixture of (a*R*,*R*)- and (a*S*,*S*)-enantiomers of heterocycles with benzo[*e*]cyclohexa[*g*][1,4]oxazocine core is formed as the main reaction product, which slowly transforms into the corresponding mixture of (a*S*,*R*)- and (a*R*,*S*)-enantiomers. The reaction of *N*-tosyl analog of these glycines with iodine under the same conditions leads to the heterocycle of spiro[4,1-benzoxazepin-5,1′-cyclohexane] structure. Upon treatment of the cyclopentenyl homologue *N*-tosylate of these glycines with molecular bromine or iodine, in both cases, a compound with the benzoxazocinone backbone is obtained as the only reaction product.

1. Introduction

In the some natural and synthetic aryl fused carbo- [1] and heterocycles [2], axial chirality can also be present, which leads to pronounced differences in their properties, but such compounds are not so common. The appearance of axial chirality promotes the existence of these molecules in the form of an equilibrium mixture or one of the atropisomers, which is stable under normal conditions. The configuration of a stereogenic element (center or axis) may lead to differences in biological activities [2e,h]. There is only scant information about such aryl fused representatives of the oxazocine series and the heterocycles shown in Fig. 1 exist in the form of an equilibrium mixture in the ratio 96–98 : 4-2 depending on the solvent and have the low energy of mutual transition [2f]. Remarkably, enantiomers exhibit different antagonistic activity towards NK_1 receptors. The isomers with the predominant (a*R*,3*S*)-configuration are 50–200 times more active than the (3*R*)-analogs, where a*S* stereochemistry predominates. This could indicate that axial chirality is important for receptor recognition. A necessary condition for the existence of equilibrium atropisomerism in these oxazocines is the presence of the phenyl substituent at the pyridine fragment. There are known heterocycles of the benzoxazocine series, in whose molecules the signs of axial isomerism are absent, but, nevertheless, these compounds also exhibit certain types of biological activity. Some synthetic representatives have been investigated as inhibitors of cellular receptors [3], efficient as antithrombotic agents [4] or have analgesic properties [5] (Fig. 2a–c).

The heterocycle with the backbone of N-(2-hydroxyethyl)isoindolone (*porritoxin*), isolated from natural raw materials, was initially mistakenly assigned the structure shown in Fig. 2 (d) [6a]. Ten years later, the same authors have corrected the formula [6b], the heterocycle has phytotoxin properties.

The choice of the method for constructing the benzoxazocine backbone is quite wide and depends on the mutual arrangement of nitrogen and oxygen atoms in the heterocycle, regio localization and stereochemistry of substituents [7]. For this purpose, approaches involving halogene source can also be used, among which the results of studies on the synthesis of benzoxazocines from aminoaryl-substituted alkenes also attract an attention [8]. It should be noted that the set of compounds with the benzoxazocine nucleus obtained by cohalogenation of such alkenes is still scarce. Although approaches to the lactonization of unsaturated carboxylic acid derivatives or their amides, intramolecular halogenamidation

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https://doi.org/10.1016/j.tet.2021.132388
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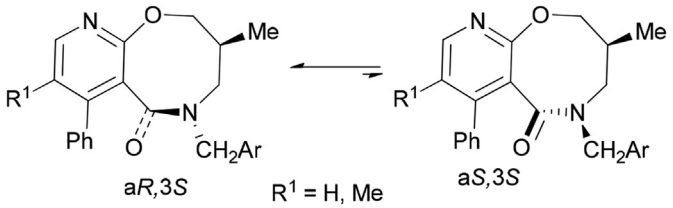


Fig. 1. An atropisomeric aryl-fused oxazocinones, in which the a*R* isomer predominates.

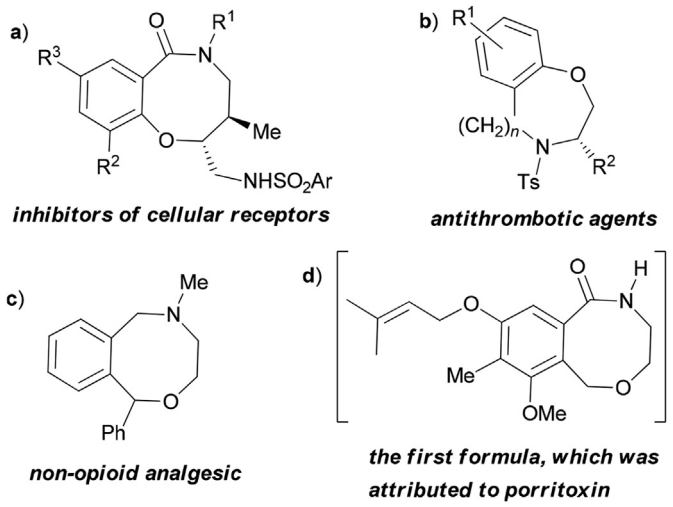


Fig. 2. Synthetic bioactive benzoxazoheterocycles.

of alkenyl-(thio)ureas under the action of halogens has proven itself well in the preparation of five-, six-, or seven-membered heterocyclic systems [9].

In this publication, we report on the first synthesis of axially chiral representatives of benzoxazocinone heterocycles by the reaction of *N*-[2-(1-cycloalken-1-yl)-6-methylphenyl]-*N*-mesyl- or -*N*-arylsulfonylglycines with molecular iodine or bromine. In this reaction, unexpectedly, a non-trivial direction of lactonization with the formation of eight-membered heterocycles was realized, and the halogen atom, which is its mediator, is absent in the esterification product. In the cycloalkene fragment annulated with benzoxazocinone, a double bond is induced during the reaction, with the emergence of which the potential prerequisites for the subsequent easy functionalization of the obtained compounds are laid.

2. Results and discussion

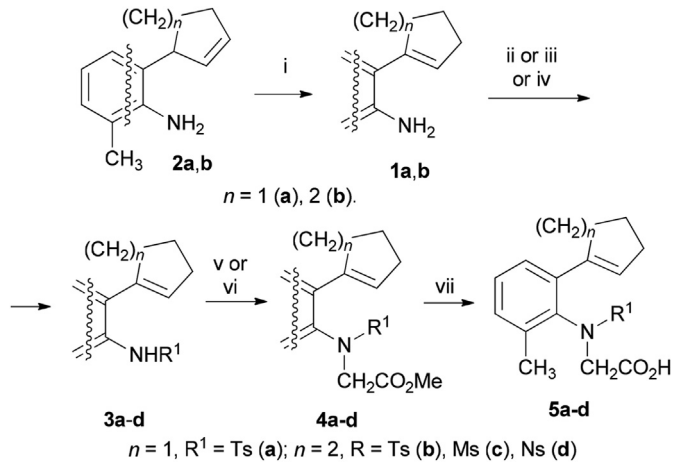
The required for this study amines **1a** [10] and **1b** (see ESI) were obtained by heating of allylic regio isomers **2a**,**b** with potassium hydroxide. Upon interaction of these amines with tosyl-, mesyl- or (2-nitrobenzene)sulfonylchloride sulfonylamides **3a** [11], **3b-d** were synthesized. Heating tosylamides **3a**,**b** with metallic sodium gave their sodium salts, the addition of methyl bromoacetate to which led to esters **4a**,**b**. When esters **4a**,**b** were prepared by this method, a certain amount of starting tosylate **3a**,**b** remained in the reaction mixture. The presence of an impurity of the starting amide does not interfere with the alkaline hydrolysis of the resulting esters to give the corresponding acids **5a**,**b**. During the subsequent work-up of the reaction mixture, all water-insoluble organic impurities are removed by extraction. We have also discovered an approach to the synthesis of esters **4a-d** without the use of metallic sodium. For this goal, sulfonylamide **3a-d** was stirred with methyl bromoacetate in THF in the presence of KOH and triethylbenzylammonium bromide (TEBAB). In this case, complete conversion of the starting amide was achieved with the formation of methyl ester **4a-d** as the only reaction product (see Scheme 1).

Next, we studied the interaction of glycines **5a-d** with Br_2 and iodine. The dropwise addition of molecular bromine to a stirred suspension of compound **5a** and potassium carbonate in methylene chloride or stirring with molecular iodine under analogous conditions leads to cyclopenta[*g*]benzoxazocinone *M**-**6** in racemic form (as a mixture of heterocycles a*R*,*S*-**6** and a*S*,*R*-**6**) (Scheme 2). When the compound *M**-**6** is kept at room temperature in the form of a powder or in $CHCl_3$ for 3 months, as well as when heated at 55 °C in $CHCl_3$ for 30 h, no changes occur in the spectra.

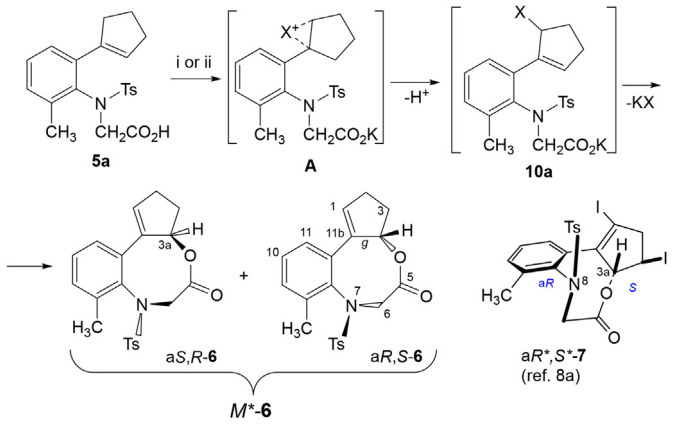
Below, using the example of cyclohexenyl homologues (Schemes 3), we show the initial formation of a mixture of a*R*,*R*- and a*S*,*S*-enantiomers, which at room temperature slowly isomerize into a mixture of a*S*,*R*- and a*R*,*S*-analogs, respectively. Therefore, and in the case of the cyclization of glycine **5a**, one would expect the appearance in the reaction mixture of the diastereomer *P**-**6** with a*R*,*R*- and a*S*,*S*-configuration of substituents. However, the signals of this supposed compound were not detected in the NMR spectra, or the *P**-analogue almost instantly isomerized to give the heterocycle *M**-**6**.

Analysis of the structure of the *M**-**6** molecule using a ball-and-stick model and programs built into the graphical editors of a set of chemical schemes made it possible to establish that the Overhauser effect can be observed between the protons of the tosyl aromatic ring and the H-3a proton. At the same time, what is important, these protons are located on one side of the oxazocine ring. The simulation data are in good agreement with the previously obtained parameters of X-ray diffraction studies of the diiodinated heterocycle a*R**,*S**-**7** [8a], whose tricyclic framework is identical to the skeleton of compound *M**-**6** (Scheme 2). In these experiments it was found that in the compound a*R**,*S**-**7** the tosyl group and the H-3a proton are located quite close to each other. And in the $^1H-^1H$ NOESY spectrum of this compound there is a noticeable cross-peak of the spatial interaction between the tosyl aromatic ring protons H-2′,6′ and the H-3a proton (a doublet signal, ESI, Page 43).

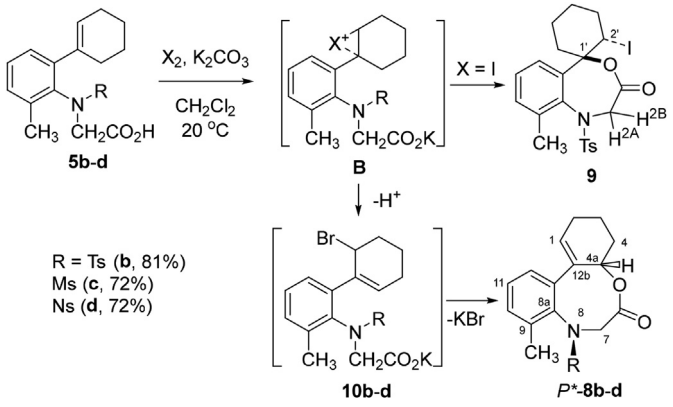
The $^1H-^1H$ NOESY NMR spectrum of benzoxazocinone *M**-**6** also shows a similar cross-peak of the triplet signal of the H-3a



Scheme 1. Synthesis of starting carboxylic acids **5a-d**. Reagents and conditions: i) KOH, 305 °C, 1 h (89–95%); ii) TsCl, Py, 20 °C, 24 h (80%); iii) MsCl, Py, 20 °C, 24 h (75%); iv) NsCl, Py, 20 °C, 48 h (94%); v) 1. Na, C_6H_6, reflux. 2. $BrCH_2CO_2CH_3$, reflux (4b, 69%); vi) KOH, TEBAB, THF, $BrCH_2CO_2CH_3$, 20 °C, 12 h (89–95%); vii) LiOH, THF-H_2O, 3:1 v/v, 20 °C, 4 h (40–79%)..



Scheme 2. Synthesis of benzoxazocinone *M**-**6** and the proposed mechanism of its formation, as well as the formula of the previously synthesized heterocycle a*R**,*S**-**7**. Reagents and conditions: i) Br_2, K_2CO_3, 20 °C, 3 h, 57%; ii) I_2, K_2CO_3, 20 °C, 24 h, 82%.



Scheme 3. Formation of benzoxazocinones *P**-**8b-d** or benzoxazepinone **9** upon interaction between glycines **5b-d** and molecular bromine or iodine.

proton (δ 5.96 ppm) with the doublet signal of the tosyl protons H-2′,6′ (δ 7.60 ppm) (ESI, Page 42).

Upon interaction between cyclohexenyl homologues **5b-d** and molecular bromine, heterocycles *P**-**8b-d** (Scheme 3) are initially formed, which are a mixture of (a*R*,*R*)- and (a*S*,*S*)-enantiomers with the stereogenic axis at the N8—C8a bond and the chirality center at the C4a atom. At room temperature or with slight heating, *P**-**8b-d** heterocycles slowly transform into axial isomers *M**-**8b-d** as a mixture of (a*S*,*R*)- and (a*R*,*S*)-enantiomers. It is known [12] that in such cyclizations, in some cases, the direction of conversion of N-acyl-2-(1-alken-1-yl)anilines depends on the structure of the olefin unit, the nature of substituent at the nitrogen atom, the halogen used, and the reaction conditions. This development of transformations was no exception and in this study. The interaction of acid **5b** with molecular iodine gave spirocyclic compound **9** with a benzoxazepinone structure.

Fig. 3 shows the procedure for determining whether axial isomers belong to *M*- or *P*-stereoisomers. The sulfonyl group is considered the senior substituent. The line of the arrow from this senior substituent is directed to the second most senior carbon atom C-12a of benzoxazocinone (Fig. 3).

Comparison of the spectra of individual compounds **8b-d** and spectra recorded at certain time intervals after exposure at room temperature and at 55°C gives a visually beautiful picture of the dynamics of changes in the peak intensity caused by axial transformations in these compounds.

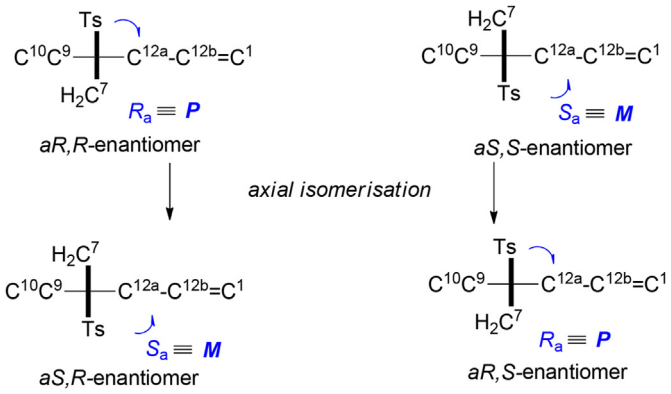


Fig. 3. An assignment of stereochemical descriptors to the corresponding atropisomers of heterocycles **8b-d**.

Probably, the tosyl derivative of 1,4-benzoxazocionone *P**-**8b** is more resistant to isomerization, since in the NMR spectra recorded after ≈18 h, no signals of the *M**-isomer **8b** were detected. The half-transformation time $\tau_{1/2}$ of the supposed *P**-isomer **8b** into the atropisomer *M**-**8b** at room temperature, according to ^{1}H NMR spectra, is *ca.* 60 days. After boiling this compound in ethanol for ≈9 h, the isomerization is almost complete, and upon cooling, crystals of the *M**-**8b** diastereomer precipitate.

In the case of bromination of analogs **5c**,**d**, in the NMR spectra recorded after ≈18 h, along with the signals of the main atropisomer *P**-**8c**,**d**, the signals of the axial isomer *M**-**8c**,**d** are also detected [a pairwise ratio of atropisomers *P**-**8c**: *M**-**8c** ≈ 8:1 (Fig. 4, *b*) and *P**-**8d**: *M**-**8d** ≈ 4:1 (Fig. 5, *a*)].

To obtain axial diastereomers *M**-**8c**,**d**, solutions with these ratios of atropisomers in deuterochloroform were kept at 55 °C for 21 h. However, residual signals of protons of the initial *P**-isomer are recorded in the ^{1}H NMR spectrum of the reaction mixture, even with longer heating. After removal of $CDCl_3$, the residue was crystallized from ethanol, and pure *M**-**8c**,**d** was isolated. Fig. 4 shows the change in the ratio of integrals of the most clearly distinguished signals of axial diastereomers *M**-**8c** and *P**-**8c** with time in the spectral region from 3.8 to 7.0 ppm, using compound **8c** as an example. Fig. 5 shows, for comparison, the same spectral range for compounds *P**-**8d** (Fig. 5, *a*) and *M**-**8d** (Fig. 5, *b*).

Hence, it can be seen that the general picture of changes in this region of the spectra of these compounds is practically the same, if we do not take into account the small differences in the values of chemical shifts. The transformation of heterocycles *P**-**8b-d** into axial isomers *M**-**8b-d**, as can be seen in Figs. 4 and 5, is accompanied by the disappearance of the signal attributed to the aromatic H-12 proton (δ 6.85—6.97 ppm) from this segment of the spectrum due to the shift to the weak field. A similar downfield shift is observed for the H-1, H-4a, H-7A and H—7B protons in the product of axial isomerization *M**-**8b-d**.

The structures of benzoxazocinones **8b-d** by the example of heterocycles *P**-**8c** and *M**-**8c** were analyzed using ball-and-stick models as in the case of compound *M**-**6**. From this, we assumed that, first, in the *P**-**8c** isomer, the protons of the O_2SCH_3 group and the H-4a proton are located at a great distance from each other, where the Overhauser effect is possible, but can be very weak. Second, the discussed protons are located on opposite sides of the osazocine cycle. After axial isomerization to the *M**-**8c** diastereomer, the protons of the O_2SCH_3 group and the H-4a proton are located on one side of the oxazocine ring and approach significantly to distances sufficient to record the manifestations of the Overhauser effect (Fig. 6). Ball-and-stick modeling of the structure of

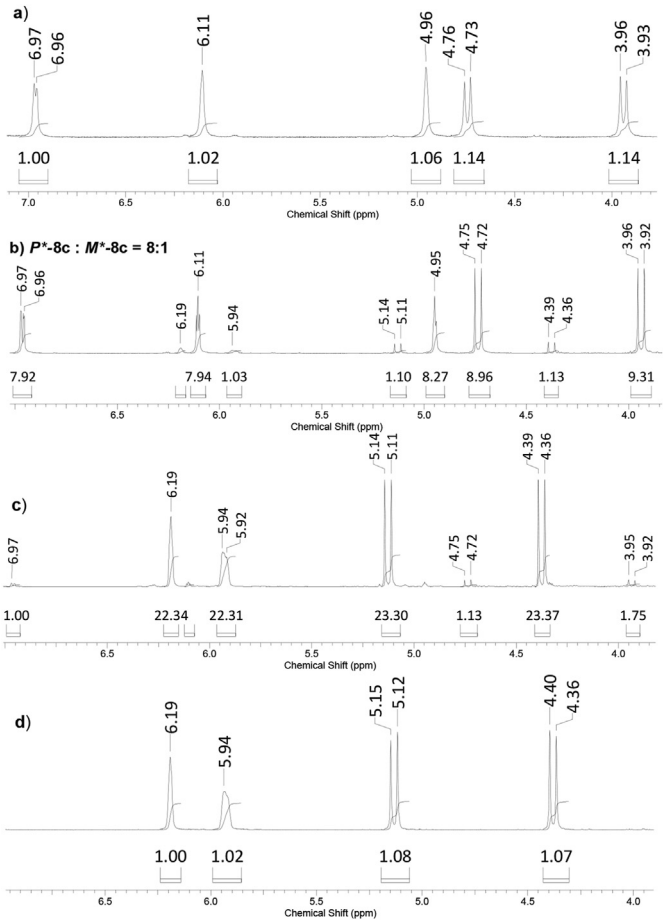


Fig. 4. Changes in the ratio of atropisomers *P**-**8c** and *M**-**8c** with time and upon heating. The most distinct signals of H-1, H-4a, H-7A, H–7B, and H-12 protons are shown in the range of 3.8–7.0 ppm in the spectra of compounds: a) *P**-**8c**, purified by crystallization from MeOH; b) *P**-**8c** after 18 h at 20 °C; c) the same solution after 21 h at 55 °C; d) *M**-**8c**, purified by crystallization from EtOH.

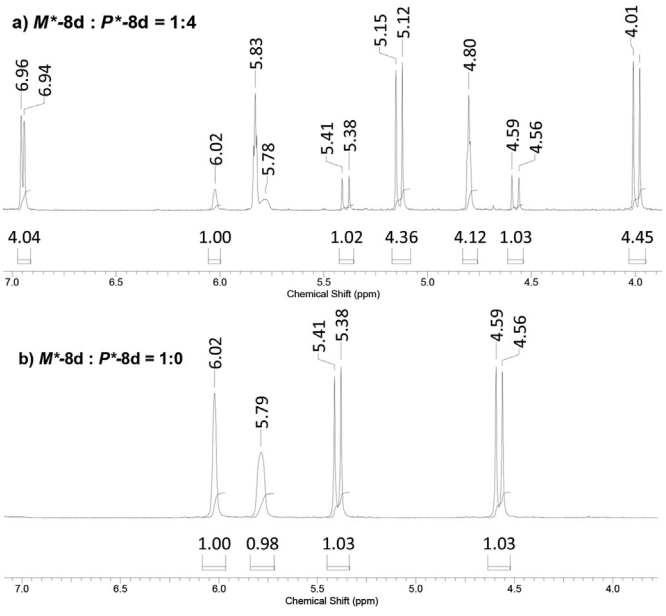


Fig. 5. Spectrum region of atropisomers *P**-**8d** and *M**-**8d** after 18 h at 20°C (a) and pure compound *M**-**8d** (b).

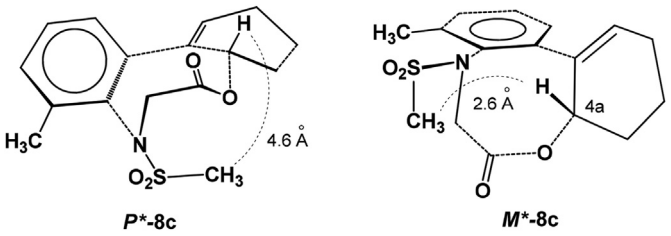


Fig. 6. The assumed configurations of substituents of the oxazocine nucleus in accordance with the ball-and-stick models of *P**-**8c** and *M**-**8c** molecules.

these atropisomers made it possible to reveal one more point that deserves attention. In the atropisomer *P**-**8c**, the olefin group C^1=C [12b] is located almost perpendicular to the aromatic ring. Whereas in the *M**-**8c** diastereomer, this fragment and the aromatic ring become planar, which, in general, can facilitate their π-conjugation.

Indeed, in the ^{1}H–^{1}H NOESY NMR spectra of benzoxazocinones in the case of the *M**-**8c** isomer, a cross-peak between the protons of the O_2SCH_3 group (δ 3.04 ppm) and a multiplet signal of the H-4a proton (δ 5.95–5.92 ppm) was found (ESI, Page 59, a, b). In the NOESY spectrum of the *P**-**8c** isomer, such cross-peak between the O_2SCH_3 protons (δ 3.08 ppm) and the triplet signal of the H-4a proton (δ 4.96 ppm) is absent (ESI, Page 54, b). Based on these observations, with a high degree of probability, the structure of these six benzoxazocinones was assigned to the corresponding axial isomers *P**-**8b-d** and *M**-**8b-d**.

The mechanistic aspects of the formation of benzoxazocinones *M**-**6**, *P**-**8b-d** are considered from the point of view of classical concepts of halocyclization reactions. Probably, both in the case of N-(2-cyclopentenyl)aryl substituted glycine **5a**, and in the case of cyclohexenyl homologues **5b-d**, the heterocyclization proceeds through the stage of generating halogenonium complexes **A** (Scheme 2) or **B** (Scheme 3). When molecular bromine is involved in the cyclization reaction, as shown in both Schemes 2 and 3, a pseudoallyl bromination product **10a** (Scheme 2) or **10b-d** (Scheme 3) is formed. After substitution of a bromine atom for a carboxyl group in these allyl halides, benzoxazocinones *M**-**6** (Scheme 2) or *P**-**8** (Scheme 3) are formed.

A similar mechanism of the lactonization reaction passing through the stage of formation of allyl iodide **10a** (X = I) is reproduced in the case of glycine **5a** when molecular iodine is used as a cyclizing agent (Scheme 2). The formation of allyl iodide can be confirmed by an example, where the generation of a similar intermediate iodide **C** was previously assumed [13] upon the interaction of ethanimidamide **D** with iodine. In this reaction, 2-ethyl-3-methyleneindole **E** was unexpectedly obtained (Fig. 7).

The iodonium complex **B** generated from the cyclohexene derivative **5b**, in contrast to the cyclopentene homologue **A**, is transformed *via* the 7-*exo*-cyclization route to form spiro-fused benzoxazepinone **9** (Scheme 3). Probably, the latter direction in this case is realized faster than the formation of allyl iodide. Dry heterocycle **9**, according to NMR spectra, practically did not undergo any changes, when stored at temperatures up to 30 °C for 2 years. When dissolved in $CDCl_3$, benzoxazepinone **9** was rapidly transformed into the starting acid **5b**. The mechanism of this retro transformation is unknown; apparently, water, which is present in commercial deuterochloroform, participates in this process.

Assumptions about the mutual arrangement in space of the RO_2S–N–CH_2CO_2H fragment and the cyclohexene ring in glycines **5b-d** before the interaction with bromine also remain controversial. The segment of the aromatic ring C-1-C-2-C-6 in these glycines is overloaded with substituents, and this tightness creates certain restrictions on their rotation along the axis $C_{Ar}(1'')$—N and

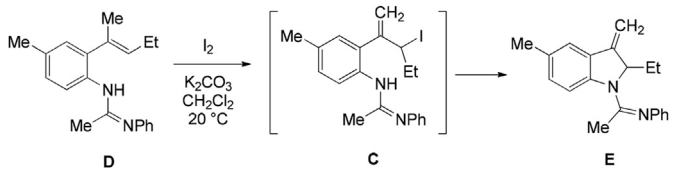


Fig. 7. A known example of the supposed formation of allylic iodide **C**.

$C_{Ar}(2'')$—$C_{CyHex}(1''')$. As is known [14], such axial isomerism can contribute to the direction of cyclization reactions. For this reaction, it can be assumed that for the initial formation of heterocycles *P**-**8b-d**, there must be an *anti*-arrangement of the olefin fragment of the cyclohexene ring and the sulfonyl group. In other words, acids **5b-d** in this reasoning should be designated as *anti*-**5b-d**, along the N—C1" and C2″—C1‴ axes, of which *P**,*P**-axial isomerism exists (Fig. 8). It was found that in the ^{1}H NMR spectra of esters **4b-d** and acids **5b-d** due to the magnetic nonequivalence of the methylene protons of the glycine fragment, the chemical shifts of their doublet signals differ significantly. We assume that the reason for this may be the existence of these acids as a stable atropisomer of *anti*-**5b-d**, caused by restriction of the rotation of fragments of this molecule around the N—C1" and C2″—C1‴ axes.

3. Conclusions

In summary, we have proposed a simple approach to the synthesis of benzo[*e*]cycloalk[*g*]oxazocinones *via* the one-pot halogenation-lactonization reaction of N-mesylates or N-arylsulfonates of N-[2-(1-cycloalken-1-yl)phenyl]glycines. In the case of the cyclopentenyl homologue, the molecular bromine or iodine can be used as a cyclizing agent. In this reaction a single atropisomer of benzoxazocinone is formed, which does not undergo subsequent axial transformations. In the case of cyclohexenyl analogs, the structure of the reaction product depends on the nature of the halogen. Upon interaction with bromine, a compound of the benzoxazocine structure was obtained. While using molecular iodine in this reaction, a heterocycle with a spiro[4,1-benzoxazepin-5,1′-cyclohexane] backbone is formed. The initially formed benzoxazocinones [*g*]-annulated with cyclohexene are a mixture of (a*R*,*R*)- and (a*S*,*S*)-enantiomers, which undergo subsequent slow irreversible axial isomerization into the corresponding mixture of (a*S*,*R*)- and (a*R*,*S*)-analogs.

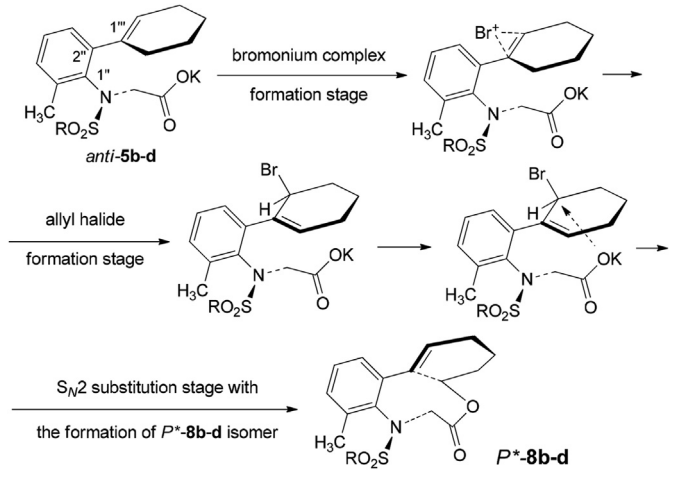


Fig. 8. The assumed mutual arrangement of the cyclohexene and N-tosylglycine fragments in the molecule of the starting tosylates **5b-d** and the subsequent stages of bromination, formation of allyl bromide and intramolecular nucleophilic substitution, resulting from this, leading to the formation of stereoisomeric heterocycles *P**-**8b-d**.

3.1. Experimental section

All common reagents and solvents were used as obtained from commercial suppliers without further purification. Preparative chromatographic separations were performed on silica gel MN 60 (35–75 μm) and reactions followed by TLC analysis using silica gel plates Sorbfil ZAO Sorbpolimer, Krasnodar, Russia, the substances were detected with iodine vapor. The spectral analyses were performed on the equipment of the Center of joint usage of the Ufa Institute of Chemistry, Russian Academy of Sciences. Melting points were determined on a table Boetius and are uncorrected. The IR spectra were recorded on a spectrophotometer with Fourier transformer IR Prestige-21 Shimadzu. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III instrument at 500.13 and 125.13 MHz, respectively. The internal standard - TMS. Spectra methods of homo- and heteronuclear correlation COSY, HMBC were used for correct assignment of signals in the NMR spectra. Chemical shift in ppm is quoted relative to solvent signals calibrated as follows for $CDCl_3$: δ_H ($CHCl_3$) = 7.26, δ_C ($CDCl_3$) = 77.2. Mass spectra (APCI, 20 eV) were obtained on a Shimadzu LCMS-2010EV instrument, with Luna 5μ C(18) 150 × 4.6 mm column and octadecylsilan as sorbent. Elemental analysis was performed on the device CHNS Elemental Analyzer EURO EA-3000. The iodine content was determined by the Schoeniger flask technique, followed by potentiometric titration.

3.1.1. Methyl N-(2-cyclopent-1-en-1-yl-6-methylphenyl)-N-[(4-methylphenyl)sulfonyl]glycinate (**4a**)

Compound **3a** (0.99 g, 3 mmol), TEBAB (0.49 g, 0.6 mmol), and KOH (0.171 g, 3.05 mmol) were intensively stirred in THF (10 mL) for 10 min on a magnetic stirrer. Thereafter, methyl bromoacetate (0.55 g, 3.6 mmol) was added to the mixture in one portion and stirring was continued for 24 h. A light powdery precipitate of potassium bromide is gradually formed. Then, *t*-BuOMe (90 mL) and water (20 mL) were added to the reaction mixture, stirred until homophase and transferred to a separatory funnel. The organic layer was separated, washed with water (10 mL) and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to obtain 1.2 g (100%) of compound **4a** in the form of a syrupy mass, practically pure according to NMR spectra for the subsequent hydrolysis reaction. The entire sample was purified on a silica gel column (20 g) from possible resinous impurities. Yield: 1.12 g (93%), as viscous oil, R_f 0.5 (C_6H_6 – *t*-BuOMe, 200:1). ^{1}H NMR: δ 7.72 (d, J = 8.1 Hz, 2 H, H3′,5′), 7.30 (d, J = 8.1 Hz, 2 H, H2′,6′), 7.19 (t, J = 7.5 Hz, 1 H, H4″), 7.12–7.09 (m, 2 H, ArH), 5.78 (s, 1 H, H2‴), 4.66 (d, J = 17.6 Hz, 1 H, H2A), 4.12 (d, J = 17.6 Hz, 1 H, H2B), 3.66 (s, 3 H, OCH_3), 2.45 (s, 3 H, $ArCH_3$), 2.18 (s, 3 H, $ArCH_3$), 2.72–2.55, 1.98–1.89 (m, 6H, 3 CH_2). ^{13}C NMR: δ 169.34 (C1), 143.44, 141.17, 140.22, 139.90, 138.46, 136.92 (C1′, C4′, C1″, C2″, C6″, C1‴), 130.97, 130.26, 128.16, 127.86 (C3″, C4″, C5″, C2‴), 129.01, 128.14 (C2′,6′, C3′,5′), 53.81 (C2), 52.05 (OCH_3), 37.68, 33.73, 23.72 (C3‴, C4‴, C5‴), 21.58, 19.65 (2 $ArCH_3$). MS (MeCN/H_2O, 83/17), ($I_{rel.}$, %): m/z = 244.1 [M – $H_3CC_6H_4SO_2$]$^+$ (65), 400.2 [M + H]$^+$ (100), 523.2 (25).

3.1.2. Methyl N-(2-cyclohex-1-en-1-yl-6-methylphenyl)-N-[(4-methylphenyl)sulfonyl]glycinate (**4b**)

Metallic sodium (0.04 g, 1.74 mmol) was added to a solution of tosylate **3b** (0.59 g, 1.74 mmol) in benzene (10 mL). The solution was heated at reflux until the metal disappeared, then methylbromoacetate (0.23 g, 1.74 mmol) was added to the flask and heating was continued for additional 2 h. The reaction mixture was cooled to room temperature, water (10 mL) was added and the

reaction mixture was stirred. The reaction product was extracted with benzene (50 mL), dried over $MgSO_4$, the solvent was evaporated *in vacuo*. The residue was chromatographed on a silica gel column (20 g, C_6H_6). Yield: 0.5 g (69%), as viscous oil, R_f 0.25 (C_6H_6). IR (KBr): 1789, 1463, 1372, 1089, 1040. ^{1}H NMR: δ 7.71 (d, J = 7.9 Hz, 2 H, H3′,5′), 7.28 (d, J = 7.9 Hz, 2 H, H2′,6′), 7.14 (t, J = 7.6 Hz, 1 H, H4″), 7.08 (d, J = 7.6 Hz, 1 H, ArH), 6.96 (d, J = 7.3 Hz, 1 H, ArH), 5.57 (s, 1 H, H2‴), 4.59 (d, J = 17.7 Hz, 1 H, H2A), 4.14 (d, J = 17.7 Hz, 1 H, H2B), 3.59 (s, 3 H, OCH_3), 2.42 (s, 3 H, $ArCH_3$), 2.27 (s, 3 H, $ArCH_3$), 2.38–2.32, 2.12–2.05, 2.02–1.94, 1.72–1.55 (m, 8H, 4 CH_2). ^{13}C NMR: δ 169.33 (C1), 140.29, 143.42, 139.94, 137.70, 136.92, 136.04 (C1′, C4′, C1″, C2″, C6″, C1‴), 129.87, 129.83, 129.19, 128.09, 128.05, 127.86 (C2′,6′, C3′,5′, C3″, C4″, C5″, C2‴), 53.55 (C2), 52.00 (OCH_3), 30.55, 25.28, 23.10, 21.76 (C3‴, C4‴, C5‴, C6‴), 21.55, 20.02 (2 $ArCH_3$). MS (MeCN/H_2O, 95/5), ($I_{rel.}$, %): m/z = 428 (60), 414 [M + H]$^+$ (100), 342 [M − $CH_2CO_2CH_3$ + H]$^+$ (20), 273 (40), 259 [M − $CH_3C_6H_4SO_2$ + H]$^+$ (90).

3.1.3. Methyl N-(2-cyclohex-1-en-1-yl-6-methylphenyl)-N-(methylsulfonyl)glycinate (**4c**)

Was synthesized according to a similar procedure for the preparation of compound **4a** by stirring methanesulfonylamide **3c** (1.06 g, 4 mmol), TEBAB (1.08 g, 4 mmol), KOH (0.24 g, 4.2 mmol), and methyl bromoacetate (0.68 g, 4.4 mmol) in THF (10 mL). The yield of a crude viscous syrupy mass is 1.2 g (89%), which crystallizes upon standing, m. p. 76–77°C (EtOH). IR, KBr, ν, cm^{-1}: 1751 (C=O), 1331, 1323, 1208, 1145, 876, 788, 771. ^{1}H NMR: δ 7.16–7.09 (m, 2 H, ArH), 6.96 (d, J = 6.2 Hz, 1 H, ArH), 5.66 (s, 1 H, H2″), 4.39 (dd, J = 4.6 Hz, J = 18.0 Hz, 1 H, H2A), 4.18 (dd, J = 4.6 Hz, J = 18.0 Hz, 1 H, H2B), 3.73 (s, 3 H, OCH_3), 3.28 (s, 3 H, SCH_3), 2.48 (s, 3 H, $ArCH_3$), 2.32–2.30, 2.20–2.12, 1.69–1.63 (m, 8H, 4 CH_2). ^{13}C NMR: δ 169.73 (C1), 145.17, 138.84, 138.31, 136.85 (C1′, C2′, C6′, C1″), 129.97, 128.16, 128.02, 127.72 (C3′, C4′, C5', C2″), 53.67 (C2), 51.96 (OCH_3), 42.92 (SCH_3), 30.41, 25.28, 22.99, 21.89 (C3″, C4″, C5″, C6″), 19.75 ($ArCH_3$). MS (MeCN/H_2O, 100/0), ($I_{rel.}$, %): m/z = 259 [M − CH_3SO_2 +H]$^+$ (100).

3.1.4. Methyl N-(2-cyclohex-1-en-1-yl-6-methylphenyl)-N-[(2-nitrophenyl)sulfonyl]glycinate (**4d**)

Was synthesized by a similar procedure for the preparation of compound **4a** by stirring sulfonylamide **3d** (1.36 g, 3.64 mmol), TEBAB (0.98 g, 3.64 mmol), KOH (0.23 g, 4.0 mmol) and $BrCH_2CO_2CH_3$ (0.62 g, 4.04 mmol). Yield 1.59 g (95%) of crude ether in the form of a viscous yellowish mass. R_f 0.24 (C_6H_6). IR, KBr, ν, cm^{-1}: 1761 (C=O), 1546, 1437, 1371, 1360, 1199, 1163, 1126, 1085, 875, 852, 785, 774, 752, 598, 569. ^{1}H NMR: δ 7.98 (dd, J = 1.2 Hz, J = 7.6 Hz, 1 H, ArH), 7.68–7.60 (m, 2 H, ArH), 7.55 (dd, J = 1.2 Hz, J = 7.6 Hz, 1 H, ArH), 7.17 (t, J = 7.6 Hz, 1 H, H4″), 7.08 (d, J = 7.6 Hz, 1 H, ArH), 6.96 (d, J = 7.6 Hz, 1 H, ArH), 5.52 (s, 1 H, H2‴), 4.77 (d, J = 18.3 Hz, 1 H, H2A), 4.16 (d, J = 18.3 Hz, 1 H, H2B), 3.66 (s, 3 H, OCH_3), 2.28 (s, 3 H, $ArCH_3$), 2.16–2.02, 1.75–1.61 (m, 8H, 4 CH_2). ^{13}C NMR: δ 168.85 (C1), 148.64, 145.74, 139.32, 136.58, 136.04, 134.52 (C1′, C2′, C1″, C2″, C6″, C1‴), 133.23, 131.93, 130.95, 130.07, 128.41, 128.32, 127.99, 123.79 (C3′, C4', C5′, C6', C3″, C4″, C5″, C2‴), 54.22 (C2), 51.86 (OCH_3), 30.84, 25.36, 23.09, 21.79 (C3‴, C4‴, C5‴, C6‴), 20.10 ($ArCH_3$). MS (MeCN/H_2O, 100/0), ($I_{rel.}$, %): m/z = 445.1 [M + H]$^+$ (100), 259.1 [M + H − $NO_2C_6H_4SO_2$]$^+$ (30).

3.1.5. N-(2-cyclopent-1-en-1-yl-6-methylphenyl)-N-[(4-methylphenyl)sulfonyl]glycine (**5a**)

To the stirring solution of **4a** (1.06 g, 2.65 mmol) in THF − H_2O (3:1, 80 mL) at 20 °C the LiOH·H_2O (0.34 g, 8.0 mmol) was added. After 3 h *t*-BuOMe (70 mL) and water (60 mL) were added. The aqueous phase was separated and extracted with *t*-BuOMe (2 × 15 mL). To the aqueous phase hydrochloric acid (10 mL, 1 N) was added, extracted with *t*-BuOMe (80 mL). The organic layer was dried over $MgSO_4$, solvent was evaporated *in vacuo*. Yield: 0.81 r (79%), as viscous oil, R_f 0.15 (C_6H_6 − *t*-BuOMe, 50:1). ^{1}H NMR: δ 9.68 (br. s, 1 H, COOH), 7.65 (d, J = 8.1 Hz, 2 H, H3′,5′), 7.25 (d, J = 8.1 Hz, 2 H, H2′,6′), 7.15 (t, J = 7.5 Hz, 1 H, H4″), 7.06–7.03 (m, 2 H, ArH), 5.73 (s, 1 H, H2‴), 4.53 (d, J = 17.9 Hz, 1 H, H2A), 4.13 (d, J = 17.9 Hz, 1 H, H2B), 2.44 (s, 3 H, $ArCH_3$), 2.06 (s, 3 H, $ArCH_3$), 2.71–2.65, 2.58–2.51, 1.95–1.89 (m, 6H, 3 CH_2). ^{13}C NMR: δ 173.70 (C1), 143.33, 141.28, 140.61, 139.43, 137.71, 136.63 (C1′, C4′, C1″, C2″, C6″, C1‴), 130.99, 130.26, 129.16, 128.25, 128.20, 127.85 (C2′,6′, C3′,5′, C3″, C4″, C5″, C2‴), 53.87 (C2), 37.92, 33.71, 23.67 (C3‴, C4‴, C5‴), 21.57, 19.54 (2 $ArCH_3$). MS (MeOH/H_2O, 100/0), ($I_{rel.}$, %): m/z = 231.1 [M + H − $H_3CC_6H_4SO_2$]$^+$ (20), 386.1 [M + H]$^+$ (100); 326.1 [M − CH_2COOH] (20), 384.2 [M − H]$^-$ (100).

3.1.6. N-(2-cyclohex-1-en-1-yl-6-methylphenyl)-N-[(4-methylphenyl)sulfonyl]glycine (**5b**)

Was synthesized according to a similar procedure for the preparation of acid **5a** from ester **4b** (0.2 g, 0.48 mmol). Yield: 0.12 r (62%), as viscous oil, R_f 0.2 ($CHCl_3$–MeOH, 95:5). ^{1}H NMR: δ 7.69 (d, J = 8.3 Hz, 2 H, H3′,5′), 7.29 (d, J = 8.3 Hz, 2 H, H2′,6′), 7.18 (t, J = 7.3 Hz, 1 H, H4″), 7.08 (d, J = 7.3 Hz, 1 H, ArH), 6.99 (d, J = 7.3 Hz, 1 H, ArH), 5.55 (s, 1 H, H2‴), 4.41 (d, J = 18.0 Hz, 1 H, H2A), 4.25 (d, J = 18.0 Hz, 1 H, H2B), 2.43 (s, 3 H, $ArCH_3$), 2.09 (s, 3 H, $ArCH_3$), 2.38–2.32, 2.00–1.94, 1.73–1.56 (m, 8H, 4 CH_2). ^{13}C NMR: δ 172.78 (C1), 145.86, 143.99, 139.15, 136.65, 136.45, 136.19 (C1′, C4′, C1″, C2″, C6″, C1‴), 130.02, 129.48, 128.33, 128.20, 128.15 (C2′,6′, C3′,5′, C3″, C4″, C5″, C2‴), 53.71 (C2), 30.65, 25.21, 23.03, 21.72 (C3‴, C4‴, C5‴, C6‴), 21.59, 19.74 (2 $ArCH_3$). MS (MeCN/H_2O, 95/5), ($I_{rel.}$, %): m/z = 400 [M + H]$^+$ (100), 245 [M − $CH_3C_6H_4SO_2$ + H]$^+$ (90); 398 [M − H] (100), 434 [M −H + $2H_2O$] (25).

3.1.7. N-(2-cyclohex-1-en-1-yl-6-methylphenyl)-N-(methylsulfonyl)glycine (**5c**)

Was synthesized according to a similar procedure for the preparation of acid **5a** from ester **4c** (0.94 g, 2.79 mmol). Yield: 0.36 g (40%) as colorless crystals, m. p. 169–174 °C, R_f 0.2 ($CHCl_3$–MeOH, 95:5). IR, Vaseline oil, ν, cm^{-1}: 1787, 1729, 1329, 1314, 1247, 1183, 1146, 1120, 1072, 964, 881, 789, 622, 557, 519. ^{1}H NMR: δ 7.96 (br. s, 1 H, COOH), 7.20–7.15 (m, 2 H, ArH), 7.01 (d, J = 6.1 Hz, 1 H, ArH), 5.69 (s, 1 H, H2″), 4.55 (d, J = 18.6 Hz, 1 H, H2A), 4.25 (d, J = 18.6 Hz, 1 H, H2B), 3.28 (s, 3 H, O_2SCH_3), 2.48 (s, 3 H, $ArCH_3$), 2.33–1.66 (m, 8H, 4 CH_2). ^{13}C NMR: δ 174.47 (C1), 145.12, 138.97, 137.80, 136.71 (C1′, C2′, C6′, C1″), 130.17, 128.47, 128.20, 128.08 (C3′, C4′, C5', C2″), 53.47 (C2), 42.83 (SCH_3), 30.45, 25.25, 22.94, 21.79 (C3″, C4″, C5″, C6″), 19.77 ($ArCH_3$). MS (MeCN/H_2O, 100/0), ($I_{rel.}$, %): m/z = 324.1 [M + H]$^+$ (100), 245.1 [M − CH_3SO_2 + H]$^+$ (90), 198.1 (80); 322.2 [M − H]$^-$ (100).

3.1.8. N-(2-Nitrobenzenesulfonyl)-N-[6-(1-cyclohexen-1-yl)-2-methylphenyl]glycine (**5d**)

Was synthesized according to a similar procedure for the preparation of acid **5a** from ester **4d** (1.52 g, 3.42 mmol). Yield: 0.76 g (52%). Amorphous mass in the form of foam. R_f 0.2 ($CHCl_3$–MeOH, 95:5). IR, Vaseline oil, ν, cm^{-1}: 1732, 1589, 1546, 1296, 1268, 1240, 1197, 1162, 1126, 1117, 1085, 1067, 876, 851, 776, 752, 738, 597. ^{1}H NMR: δ 8.23 (br s, 1 H, COOH), 7.91 (d, J = 7.6 Hz, 1 H, ArH), 7.69 (t, J = 7.6 Hz, 1 H, ArH), 7.62 (t, J = 7.6 Hz, 1 H, ArH), 7.59 (d, J = 7.6 Hz, 1 H, ArH), 7.20 (t, J = 7.6 Hz, 1 H, H4″), 7.10 (d, J = 7.6 Hz, 1 H, ArH), 6.99 (d, J = 7.6 Hz, 1 H, ArH), 5.49 (s, 1 H, H2‴), 4.76 (d, J = 18.3 Hz, 1 H, H2A), 4.29 (d, J = 18.3 Hz, 1 H, H2B), 2.24 (s, 3 H, $ArCH_3$), 2.30–2.27, 2.15–1.97, 1.72–1.58 (m, 8H, 4 CH_2). ^{13}C NMR: δ 173.67 (C1), 148.38, 145.81, 139.28, 136.23, 135.97, 133.90 (C1′, C2′, C1″, C2″, C6″, C1‴), 133.79, 131.75, 131.38, 130.23, 128.67, 128.47, 128.28, 124.01 (C3′, C4', C5′, C6', C3″, C4″, C5″, C2‴), 54.14

(C2), 30.80, 25.31, 23.04, 21.69 (C3‴, C4‴, C5‴, C6‴), 20.03 ($ArCH_3$). MS (MeCN/H_2O, 100/0), ($I_{rel.}$, %): m/z = 431.1 $[M + H]^+$ (100), 472.1 $[M + H + CH_3CN]^+$ (50); 429.5 $[M - H]^-$ (100), 372.6 (90).

3.1.9. 8-Methyl-7-[(4-methylphenyl)sulfonyl]-3,3a,6,7-tetrahydrobenzo[e]cyclopenta[g][1,4]oxazocin-5-(2H)-one (*M**-**6**)

A) To the stirring suspension of **5a** 0.193 g (0.5 mmol) and K_2CO_3 (0.8 g, 5.8 mmol) in CH_2Cl_2 (10 mL) molecular bromine (0.08 g, 0.5 mmol) in CCl_4 (2 mL) was added. The reaction mixture was stirred for 24 h, sodium thiosulfate (5%, 5 mL) solution was added and stirred for additional 10 min. The product was extracted with CH_2Cl_2 (40 mL), washed with water (10 mL), dried over $MgSO_4$. Solvent was evaporated *in vacuo*. The residue (0.15 g) was purified on silica gel column (3 g, C_6H_6). Yield: 0.11 g (57%), m. p. 125–130 °C (EtOH), R_f 0.15 (C_6H_6 - $PhCH_3$, 20:1). IR, Vaseline oil, ν, cm^{-1}: 1739, 1345, 1302, 1162, 1116, 1092, 1052, 901, 814, 796, 784, 735, 706, 664, 573, 544, 536. ^1H NMR: δ 7.60 (d, J = 8.2 Hz, 2 H, H2′,6′), 7.31–7.24 (m, 4 H, ArH), 7.15 (d, J = 7.3 Hz, 1 H, H11), 6.25 (t, J = 1.3 Hz, 1 H, H1), 5.96 (dt, J = 7.6 Hz, J = 1.5 Hz, 1 H, H3a), 5.18 (d, J = 16.6 Hz, 1 H, H6A), 4.38 (d, J = 16.6 Hz, 1 H, H6B), 2.44 (s, 3 H, $ArCH_3$), 2.43–2.40, 2.34–2.28, 2.23–2.18, 1.96–1.87 (m, 4H, CH_2CH_2), 2.03 (s, 3 H, $ArCH_3$). ^{13}C NMR: δ 167.40 (C5), 144.28 (C4'), 142.72 (C11b), 139.91 (C8), 136.69 (C1'), 136.13, 133.09 (C1), 132.62 (C7a, C11a), 131.30 (C9), 130.07, 127.90 (C10, C11), 129.83, 127.47 (C2′,6′, C3′,5′), 83.95 (C3a), 52.52 (C6), 31.91, 29.35 (C2, C3), 21.60, 17.67 (2 $ArCH_3$). MS (MeCN/H_2O, 99/1), ($I_{rel.}$, %): m/z = 767.1 [2 M + H]$^+$ (100), 612.2 $[2 M + H - CH_3C_6H_4SO_2]^+$ (25), 384.1 $[M + H]^+$ (50), 228.0 $[M - CH_3C_6H_4SO_2]^+$ (25); 382.1 $[M - H]^-$ (100).

B) A suspension of glycine **5a** (0.73 g, 1.9 mmol), K_2CO_3 (0.42 g, 3 mmol) and molecular iodine (0.56 g, 2.2 mmol) in CH_2Cl_2 (15 mL) was stirred on a magnetic stirrer for 24 h, then sodium thiosulfate (5%, 20 mL) was added and stirred for additional 10 min. The product was extracted with CH_2Cl_2 (50 mL), washed with water (2 × 10 mL), dried over $MgSO_4$. Solvent was evaporated *in vacuo*. The yield of practically pure crude product *M**-**6** is 0.65 g (86%). After clarification by chromatography on a silica gel column (1 g), 0.6 g (82%) of the heterocycle *M**-**6** was isolated as a white powder. The NMR characteristics of the compound obtained by this method are identical to the data given at point A.

3.1.10. 9-Methyl-8-[(4-methylphenyl)sulfonyl]-2,3,4,4a,7,8-hexahydro-6H-dibenzo[e,g][1,4]oxazocin-6-one (as a mixture of (aR,R)- and (aS,S)-enantiomers) (*P**-***8b***)

Was synthesized in a similar way according to procedure A for the preparation of the previous heterocycle *M**-**6**. Molecular bromine (0.32 g, 2 mmol) in CCl_4 (2 mL) was added to the suspension of glycine **5b** (0.8 g, 2 mmol) and K_2CO_3 (0.7 g, 5 mmol) under stirring. Yield of the crude residue 0.8 g (100%). Crystallization from ethanol gives 0.64 g (81%) colorless crystals of the heterocycle *P**-**8b**, m. p. 137–139 °C (EtOH). ^1H NMR: δ 7.58 (d, 2H, J = 7.6 Hz, ArH), 7.26–7.21 (m, 4H, ArH), 6.85 (d, 1H, J = 7.0 Hz, ArH), 5.70 (s, 1H, H1), 4.93 (d, 1H, J = 15.8 Hz, H7A), 4.57 (br. s, 1H, H4a), 4.00 (d, 1H, J = 15.8 Hz, H7B), 2.45 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.00–1.22 (m, 6H, $3CH_2$). ^{13}C NMR: δ 171.77 (C6), 144.30, 143.40, 140.60, 137.05, 136.49, 135.47 (C8a, C9, C12a, C12b, C1′, C4′), 134.73, 131.11, 129.48, 129.43 (C1, C10, C11, C12), 129.04, 128.21 (C3′,5′, C2′,6′), 75.77 (C4a), 54.90 (C7), 29.60, 25.38, 15.21 (C2, C3, C4), 21.56, 19.21 (2 CH_3). MS (MeCN/H_2O, 95/5), ($I_{rel.}$, %): m/z = 398.2 $[M + H]^+$ (100), 242.0 $[M - CH_3C_6H_4SO_2]^+$ (78).

3.1.11. 9-Methyl-8-[(4-methylphenyl)sulfonyl]-2,3,4,4a,7,8-hexahydro-6H-dibenzo[e,g][1,4]oxazocin-6-one (as a mixture of (aS,R)- and (aR,S)-enantiomers) (*M**-***8b***)

A solution of the heterocycle *P**-**8b** (0.4 g, 1 mmol) in EtOH (5 mL) was heated at reflux for 9 h; after cooling, very small colorless crystals of the isomer *M**-**8b** were filtered off. Yield: 0.2 g (50%), m. p. 171–174 °C (EtOH). ^1H NMR: δ 7.67 (d, 2H, J = 7.8 Hz, ArH), 7.30 (d, 2H, J = 7.8 Hz, ArH), 7.26 (t, 1H, J = 7.6 Hz, ArH), 7.17 (d, 1H, J = 7.6 Hz, ArH), 7.12 (d, 1H, J = 7.6 Hz, ArH), 5.98 (s, 1H, H1), 5.20 (br. s, 1H, H4a), 5.01 (d, 1H, J = 15.7 Hz, H7A), 4.42 (d, 1H, J = 15.7 Hz, H7B), 2.45 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.20–1.16 (m, 6H, $3CH_2$). ^{13}C NMR: δ 167.08 (C6), 144.21, 140.60, 139.83, 138.46, 136.94, 132.80 (C8a, C9, C12a, C12b, C1', C4'), 131.09 (C1), 130.95, 127.95 (C10, C12), 130.23 (C11), 129.66, 127.61 (C3′,5′, C2′,6′), 76.31 (C4a), 52.44 (C7), 29.78, 25.33, 19.61 (C2, C3, C4), 21.57, 18.09 (2 CH_3). MS (MeCN/H_2O, 95/5), ($I_{rel.}$, %): m/z = 398.3 $[M + H]^+$ (100), 242.2 $[M - CH_3C_6H_4SO_2]^+$ (50).

3.1.12. 9-Methyl-8-methylsulfonyl-2,3,4,4a,7,8-hexahydro-6H-dibenzo[e,g][1,4]oxazocin-6-one (as a mixture of (aR,R)- and (aS,S)-enantiomers) (*P**-***8c***)

Was synthesized in a similar way according to procedure A for the preparation of the previous heterocycle *M**-**6** from glycine **5c** (0.285 g, 0.88 mmol) and molecular bromine (0.14 g, 0.88 mmol) in the presence of K_2CO_3 (0.4 g, 2.9 mmol) in CH_2Cl_2 (10 mL). The residue (0.27 g) was purified on silica gel column (2 g, $CHCl_3$). The heterocycle *P**-**8c** 0.203 g (72%) was obtained containing *ca.* 15% (according to ^1H NMR data) impurity of the isomer *M**-**8c**. Crystallization from ethanol gave 0.13 g of pure (according to NMR data) compound *P**-**8c**, m. p. 165–170 °C (EtOH). R_f 0.2 ($CHCl_3$). IR, Vaseline oil, ν, cm^{-1}: 1727, 1351, 1313, 1239, 1201, 1151, 974, 885, 804, 773, 750, 582, 517. ^1H NMR: δ 7.28–7.20 (m, 2H, ArH), 6.97 (dd, 1H, J = 2.0 Hz, J = 7.0 Hz, ArH), 6.11 (t, 1H, J = 3.9 Hz, H1), 4.95 (t, 1H, J = 3.7 Hz, H4a), 4.74 (d, 1H, J = 15.9 Hz, H7A), 3.94 (d, 1H, J = 15.9 Hz, H7B), 3.08 (s, 3H, O_2SCH_3), 2.43 (s, 3H, CH_3), 2.35–2.17, 1.95–1.65 (m, 6H, $3CH_2$). ^{13}C NMR: δ 172.75 (C6), 142.97 (C12a), 140.56, 137.42, 135.60 (C8a, C9, C12b), 134.54 (C1), 131.47, 129.77, 129.74 (C10, C11, C12), 76.94 (C4a), 55.02 (C7), 42.00 (SCH_3), 29.41, 25.36, 16.71 (C2, C3, C4), 19.02 (CH_3). MS (MeCN/H_2O, 100/0), ($I_{rel.}$, %): m/z = 322.1 $[M + H]^+$ (70), 243.1 $[M + H - CH_3SO_2]^+$ (100).

3.1.13. 9-Methyl-8-methylsulfonyl-2,3,4,4a,7,8-hexahydro-6H-dibenzo[e,g][1,4]oxazocin-6-one (as a mixture of (aS,R)- and (aR,S)-enantiomers) (*M**-***8c***)

A solution of compound *P**-**8c** (30 mg) in deuterochloroform (1.0 mL) in an ampoule for taking the NMR spectra of the NORELL® 508 UP brand was kept at 55 °C for 21 h. After this time, according to the measured integrals in the ^1H NMR spectra, the signal ratio *M**-**8c**:*P**-**8c** ≈ 22:1 is achieved. The solution was transferred to a flask, the solvent was evaporated *in vacuo*, the residue in the form of a white powder was dissolved in boiling ethanol (5 mL), very fine colorless crystals of the *M**-**8c** isomer precipitated after cooling were filtered off and dried in air. Yield: 25 mg (83%), m. p. 190–193°C (EtOH). IR, Vaseline oil, ν, cm^{-1}: 1725, 1351, 1335, 1308, 1259, 1159, 1113, 1031, 960, 909, 802, 774, 562, 537, 516. ^1H NMR: δ 7.29 (dt, 1H, J = 0.9 Hz, J = 7.6 Hz, ArH), 7.21 (d, 2H, J = 7.6 Hz, ArH), 6.19 (s, 1H, H1), 5.95–5.92 (m, 1H, H4a), 5.14 (d, 1H, J = 15.9 Hz, H7A), 4.39 (d, 1H, J = 15.9 Hz, H7B), 3.04 (s, 3H, O_2SCH_3), 2.40 (s, 3H, CH_3), 2.39–2.27, 2.01–1.98, 1.83–1.72 (m, 6H, $3CH_2$). ^{13}C NMR: δ 167.06 (C6), 141.07, 138.63, 138.47, 132.18 (C8a, C9, C12a, C12b), 131.84, 131.14, 130.49, 128.36 (C1, C10, C11, C12), 76.43 (C4a), 52.33 (C7), 40.71 (O_2SCH_3), 30.04, 25.61, 20.48 (C2, C3, C4), 18.27 ($ArCH_3$). MS (MeCN/H_2O, 100/0), ($I_{rel.}$, %): m/z = 322.1 $[M + H]^+$ (100), 243.1 $[M + H - CH_3SO_2]^+$ (100), 242.1 $[M - CH_3SO_2]^+$ (50).

3.1.14. 9-Methyl-8-(2-Nitrobenzenesulfonyl)-2,3,4,4a,7,8-hexahydro-6H-dibenzo[e,g][1,4]oxazocin-6-one (as a mixture of (aR,R)- and (aS,S)-enantiomers) (*P**-***8d***)

Was synthesized in a similar way according to procedure A for the preparation of the previous heterocycle *M**-**6** from glycine **5d**

(0.43 g, 1.0 mmol) and molecular bromine (0.16 g, 1.0 mmol) in the presence of K_2CO_3 (0.84 g, 5.8 mmol) in CH_2Cl_2 (10 mL). The residue (0.38 g), along with the heterocycle *P**-**8d**, contains *ca.* 20% (according to ^{1}H NMR data after 18 h) impurity of the *M**-**8d** isomer. This residue was chromatographed on a silica gel column (11 g, $CHCl_3$), yielding 0.31 g (72%) pure heterocycle *P**-**8d** as a white foam. R_f 0.35 ($CHCl_3$ – *t*-BuOMe, 50:1). IR, Vaseline oil, ν, cm^{-1}: 1731, 1546, 1166, 1127, 1087, 1034, 972, 888, 777, 755, 746, 606, 604, 573. ^{1}H NMR: δ 7.85 (d, J = 8.0 Hz, 1 H, ArH), 7.67 (t, J = 7.3 Hz, 1 H, ArH), 7.60 (t, J = 7.3 Hz, 1 H, ArH), 7.55 (d, J = 7.6 Hz, 1 H, ArH), 7.27 (t, J = 7.6 Hz, 1 H, H4″), 7.21 (d, J = 7.3 Hz, 1 H, ArH), 6.95 (d, J = 7.3 Hz, 1 H, ArH), 5.83 (t, 1 H, J = 3.7 Hz, H1), 5.14 (d, 1H, J = 15.6 Hz, H7A), 4.80 (t, 1 H, J = 3.7 Hz, H4a), 3.94 (d, 1 H, J = 15.6 Hz, H7B), 2.19 (s, 3 H, CH_3), 2.03–1.68, 1.58–1.43 (m, 6 H, 3 CH_2). ^{13}C NMR: δ 172.82 (C6), 148.40, 144.17, 139.73, 136.26, 134.65, 133.72 (C8a, C9, C12a, C12b, C1', C2'), 135.04 (C1), 133.66, 131.72, 131.44, 131.28, 130.41, 130.09, 123.66 (C10, C11, C12, C3', C4', C5', C6'), 76.26 (C4a), 55.51 (C7), 29.44, 25.52, 16.58 (C2, C3, C4), 18.58 (CH_3). MS (MeCN/H_2O, 100/0), ($I_{rel.}$, %): m/z = 429.1 [M + H]$^+$ (50), 242.1 [M – $O_2NC_6H_4SO_2$]$^+$ (95), 196.1 (40), 83.0 (100).

3.1.15. 9-Methyl-8-(2-Nitrobenzenesulfonyl)-2,3,4,4a,7,8-hexahydro-6H-dibenzo[e,g][1,4]oxazocin-6-one (as mixture of (aS,R)- and (aR,S)-enantiomers) (*M**-**8d**)

A solution of compound *P**-**8d** (55 mg) in deuterochloroform in a NORELL® 508 UP ampoule was kept at 55 °C for 21 h. After this time, the signals of the *P**-isomer were practically absent in the NMR spectra. Crystallization from ethanol gives pure compound *M**-**8d**, 43 mg (78%), m. p. 162–165°C (EtOH). IR, Vaseline oil, ν, cm^{-1}: 1737, 1541, 1314, 1292, 1193, 1166, 1088, 1030, 942, 912, 799, 611, 567. ^{1}H NMR: δ 7.73 (t, J = 7.9 Hz, 1 H, ArH), 7.65 (d, J = 7.9 Hz, 1 H, ArH), 7.64 (d, J = 7.9 Hz, 1 H, ArH), 7.55 (t, J = 7.9 Hz, 1 H, ArH), 7.30 (t, J = 7.9 Hz, 1 H, H4″), 7.18 (d, J = 7.9 Hz, 1 H, ArH), 7.15 (d, J = 7.9 Hz, 1 H, ArH), 6.02 (s, 1 H, J = 3.7 Hz, H1), 5.79–5.75 (m, 1 H, H4a), 5.39 (d, 1 H, J = 16.5 Hz, H7A), 4.57 (d, 1H, J = 16.5 Hz, H7B), 2.10 (s, 3H, $ArCH_3$), 2.17–2.12, 2.00–1.65 (m, 6H, 3CH_2). ^{13}C NMR: δ 167.13 (C6), 147.88, 140.63, 139.25, 138.29, 133.30, 131.96 (C8a, C9, C12a, C12b, C1′, C2′), 134.17 (C1), 132.21, 131.67, 131.69, 131.09, 130.60, 128.20, 123.77 (C10, C11, C12, C3′, C4′, C5′, C6′), 76.24 (C4a), 53.70 (C7), 29.81, 25.41, 20.010 (C2, C3, C4), 17.61 (CH_3). MS (MeCN/H_2O, 95/5), ($I_{rel.}$, %): m/z = 429.1 [M + H]$^+$ (70), 242.1 [M – $O_2NC_6H_4SO_2$]$^+$ (100), 196.1 (30), 83.0 (100).

3.1.16. (2′*R**,5*S**)-2′-Iodo-9-methyl-1-[(4-methylphenyl)sulfonyl]-1,2-dihydro-3H-spiro[4,1-benzoxazepine-5,1′-cyclohexan]-3-one (***9***)

To stirring suspension of glycine **5b** (0.12 г, 0.3 mmol) and K_2CO_3 (0.138 g, 1 mmol) in CH_2Cl_2 (10 mL) molecular iodine (0.18 g, 0.7 mmol) was added. The reaction mixture was stirred for 24 h, sodium thiosulfate (5%, 20 mL) was added and stirred for additional 10 min. The product was extracted with CH_2Cl_2 (40 mL), washed with water (10 mL), dried over $MgSO_4$. The solvent was evaporated *in vacuo*. The reaction product was isolated by chromatography on silica gel column (2 g, C_6H_6). Yield: 0.11 г (70%), R_f 0.42 ($CHCl_3$ – *t*-BuOMe, 99:1). Colorless crystals from MeOH, m.p. 122–125 °C (decomp.). ^{1}H NMR: δ 7.89 (d, J = 8.2 Hz, 2 H, H3″,5″), 7.37 (d, J = 8.2 Hz, 2 H, H2″,6″), 7.33–7.28 (m, 3 H, ArH), 5.07 (s, 1 H, H2'), 4.97 (d, J = 18.4 Hz, 1 H, H2A), 3.94 (d, J = 18.4 Hz, 1 H, H2B), 2.86 (dt, J = 3.5 Hz, J = 14.0 Hz, 1 H, H3′A), 2.45 (s, 3 H, $ArCH_3$), 2.31 (s, 3 H, $ArCH_3$), 2.11–2.04, 1.75–1.45 (m, 7H, H3′B, $CH_2CH_2CH_2$). ^{13}C NMR: δ 167.90 (C3), 144.64, 139.64, 138.83, 137.15, 136.83 (C5a, C9, C9a, C1″, C4″), 133.21, 130.03, 128.17, 127.48, 127.41 (C6, C7, C8, C2″,6″, C3″,5″), 87.34 (C5,1′), 52.35 (C2), 38.15 (C2'), 33.18, 31.21, 21.19, 20.84 (C3', C4', C5', C6'), 21.60, 20.34 (2 $ArCH_3$). MS (MeCN/H_2O, 95/5), ($I_{rel.}$, %): m/z = 526 [M + H]$^+$ (60), 398 [M – I]$^+$ (100), 244 [M – I – $CH_3C_6H_4SO_2$ + H]$^+$ (45).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was performed in the scope of the "Design, directed synthesis and study of biological activity of functionalized benzo fused heterocycles, polyheteromono-, bicyclic N,N-, N,O-, S,O-containing systems and uracil derivatives" governmental task (topic no. AAAA-A19-119011790021-4).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132388.

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