Bis(oxiranes) Containing Cyclooctane Core: Synthesis and Reactivity towards NaN₃

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Abstract: Reactions of oxirane ring opening provide a powerful tool for regio- and stereoselective synthesis of polyfunctional and heterocyclic compounds, widely used in organic chemistry and drug design. Cyclooctane, alongside other medium-sized rings, is of interest as a novel molecular platform for the construction of target-oriented leads. Additionally, cyclooctane derivatives are well known to be prone to transannular reactions, which makes them a promising object in the search for novel approaches to polycyclic structures. In the present work, a series of cyclooctanediones was studied in Corey-Chaykovsky reactions, and novel spirocyclic bis(oxiranes) containing cyclooctane core, namely, 1,5-dioxadispiro[2.0.2.6]dodecane and 1,8-dioxadispiro[2.3.2.3]dodecane, were synthesized. Ring opening of the obtained bis(oxiranes) upon treatment with sodium azide was investigated, and it was found that the reaction path is determined by the reciprocal orientation of oxygen atoms in the oxirane moieties. Diastereomers of the bis(oxiranes) with cis-orientation underwent independent ring opening, supplying corresponding diazidodiols, while in the case of stereoisomers with trans-orientation, domino-like reactions occurred, including intramolecular nucleophilic attack and the formation of a novel three- or six-membered O-containing ring. Summarily, a straightforward approach to polyfunctional compounds containing cyclooctane or oxabicyclo[3.3.1]nonane cores, employing bis(oxiranes), was elaborated.

Keywords: oxiranes; cyclooctanes; nucleophilic ring opening; domino reactions; azides; polyols; oxabicyclo[3.3.1]nonanes; polyfunctional compounds

1. Introduction
Transformations of strained electron-deficient oxirane rings represent a powerful tool in drug design and organic synthesis. Oxirane rings occur in a number of medicinal drugs and bioactive natural compounds (Figure 1) and are widely used for the construction of novel drug candidates, particularly as an alkylating agent [1–5]. Synthetic approaches towards such drugs as atazanavir (HYV protease inhibitor), linezolid (antibiotic), diltiazem (antihypertensive drug), and a number of others include transformations of oxirane moiety [6]. Reactions of oxirane ring opening are widely used as a regio- and stereoselective approach to polyfunctional and heterocyclic compounds, and novel reactions and synthetic procedures employing oxiranes are still being developed [7–14]. The presence of two or more oxirane moieties in a molecule creates the opportunity for a straightforward synthesis of polyfunctional compounds, and for the use of such a molecule as a linker in the construction of multivalent ligands.

Cyclooctane, alongside other medium rings, is characterized by an optimal balance of conformational rigidity and flexibility and is of interest as a novel molecular platform for the design of target-oriented leads [15–18]. On the other hand, the synthetic application of ring-closure reactions to medium rings is often limited because of the entropy factor disfavoring ring closure. Therefore, the search for simple preparative approaches to the functionalization of already existing cyclooctane moiety poses an important problem [19,20].
Additionally, a number of transannular reactions can proceed due to cyclooctane conformational transitions, including those starting from oxirane ring-opening processes [21,22].

This work is therefore aimed at the synthesis of novel bis(oxiranes) A, containing cyclooctane core, the investigation of the reactions with azide anion, and the preparation of polyfunctional compounds B starting from the bis(oxiranes) (Scheme 1).

Scheme 1. Ring opening of bis(oxiranes) A, containing cyclooctane core.

2. Results and discussion

2.1. Synthesis of Bis(oxiranes) via Corey-Chaykovsky Reaction of Cyclooctanediones

In order to obtain previously unknown bis(oxiranes), cyclooctanediones 1–5 were investigated in a Corey-Chaykovsky reaction using sulfur ylide derived from trimethylsulfonium iodide and potassium tert-butoxide (Scheme 2).

Bis(oxirane) 6 was obtained from cyclooctane-1,2-dione (1) as a mixture of diastereomers in good yield (Scheme 2). In order to study the difference in the reactivity of stereomers of compound 6, individual diastereomer 6a (meso form) and 6b (as racemate) were isolated via preparative column chromatography.

The interaction of cyclooctane-1,3-dione (2) and sulfur ylide produced no bis(oxirane), which is probably due to the tendency of 1,3-diketone to produce enolate under basic conditions. As such, 1,3-diketone 3, containing a spirocyclopropane moiety between the carbonyl groups, was employed in a Corey-Chaykovsky reaction, yielding bis(oxirane) 7 as a mixture of meso form 7a and racemate 7b in ratio 3:1 (Scheme 2). The reaction proceeded in low yield and a decrease in the reaction time down to 1 h was required in order to prevent the decomposition of the products. The lability of compounds 7a,b prevented their isolation via column chromatography, and full description of NMR spectra could be accomplished only for the isomer 7a prevailing in the reaction mixture.

Cyclooctane-1,4-dione (4), in the presence of potassium tert-butoxide and sulfur ylide, which may also act as a base, underwent a well-known [23,24] intramolecular condensation, producing bicyclic ketone 8 instead of the corresponding bis(oxirane) (Scheme 2).

Finally, cyclooctane-1,5-dione (5) was found to smoothly react with sulfur ylide, producing bis(oxirane) 9 in good yield (Scheme 2). Individual diastereomers 9a and 9b were isolated via column chromatography.

The relative configuration of compounds 6a,b was determined using a calculation of $^{13}$C NMR chemical shifts. The assignments of configuration for 7a,b and 9a,b were made on the basis of NMR spectra, taking into account differences in the symmetry of molecules (see Supplementary Materials for details).
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![Diagrams](https://example.com/diagrams.png)

Scheme 2. Investigation of diketones 1–5 in Corey-Chaykovsky reaction.

2.2. Ring Opening of Bis(oxiranes) with Sodium Azide

In order to compare the reactivity of bis(oxiranes) with different reciprocal positions of three-membered rings, compounds 6a,b and 9a,b were investigated by the treatment with a well-known nucleophile: sodium azide. It should be mentioned that organic azides are of the utmost interest as versatile intermediates in organic synthesis and can be found in a variety of pharmaceuticals and biologically active compounds, such as Zidovudine, Azidamfenicol, Azidocillin, and others [25–28].

The conditions of the ring opening of oxiranes containing spiroannelated cyclooctane moiety were probed for model oxaspirodecane 10. It was found that the reaction of compound 10, with a four-fold excess of sodium azide in water under reflux, produces azidoalcohol 11 as a sole product (Scheme 3).

![Diagrams](https://example.com/diagrams.png)

Scheme 3. Ring opening of oxirane 10 with sodium azide.

Under the same conditions, compound 6a interacted with sodium azide, producing predominantly product 12, resulting from the opening of one of two oxirane rings, which was obtained as a poorly separable mixture with diazidodiol 13 (see Section 3.3 and Supplementary Materials). To obtain diazidodiol 13 as the sole product, an additional optimization of reaction conditions was conducted (see Supplementary Materials). Varying solvents, reaction times and reagents ratios demonstrated that for the full conversion of compound 6a into diazidodiol 13, 16-fold excess of nucleophilic agent and reflux in water for 30 h are required (Scheme 4).
When the reaction time was shorter, a mixture of compounds 16 and 17 was obtained, with diazidodiol 17 prevailing (see Section 3.3 and Supplementary Materials).

The reaction of bis(oxirane) 9b, containing trans-oriented oxygen atoms, with sodium azide required shorter time (2 h) and lower excess of nucleophile (4 eq), and again proceeded in an unexpected way, producing oxabicyclononane 18 in good yield (Scheme 5). The formation of oxabicyclononane 18 presumably resulted from the ring opening of an oxirane moiety, producing anion II, and subsequent intramolecular nucleophilic attack of oxygen on the second oxirane ring. It should be noted that no examples of the formation of tetrahydropyran moiety via domino ring opening of bis(oxiranes) has been found in earlier research. This reaction opens the way to hardly accessible oxabicyclononane derivatives,
which, like bicyclononanes [31,32] and azabicyclononanes [33], represent promising 3D scaffolds for drug design.

Thus, it was demonstrated that diastereomers of bis(oxiranes) with cyclooctane cores possess different reactivity towards azide anion. Compounds 6a and 9a, containing cis-oriented oxygen atoms, are less reactive and undergo independent ring opening of oxirane moieties, whereas compounds 6b and 9b, containing oxygen atoms in trans-position, undergo relatively fast domino-type ring opening of oxirane rings and generate products of intramolecular nucleophilic attack 14,18.

3. Materials and Methods

3.1. General Remarks

1H and 13C NMR spectra were recorded on a 400 MHz spectrometer Agilent 400-MR (400.0 and 100.6 MHz for 1H and 13C, respectively) at r.t. in CDCl3, while chemical shifts δ were measured with reference to the solvent (CDCl3, δH = 7.26 ppm, δC = 77.16 ppm). When necessary, assignments of signals in NMR spectra were made using 2D techniques (see Supplementary Materials). Accurate mass measurements (HRMS) were obtained on Bruker micrOTOF II with electrospray ionization (ESI). Analytical thin-layer chromatography was carried out with silica gel plates supported on aluminum (Macherey-Nagel, ALUGRAM Xtra SIL G/UV 254), with inspection using a UV lamp (254 nm). Column chromatography was performed on silica gel (Macherey-Nagel, Silica 60, 0.015–0.04 mm). Cyclooctanediones 1,4-diketone (2CH(C(CH3)=O)) in 40 mL of dry DMSO was added dropwise. The reaction mixture was stirred for 16 h at r.t., then it was poured into icy water (60 mL) and extracted with pentane (3 × 20 mL). Combined organic layers were quickly dried over MgSO4; the solvent was evaporated under reduced pressure. The products were isolated via preparative column chromatography (SiO2).

3.2. Synthesis of Bis(oxiranes) (General Method)

To the solution of trimethylsulfonium iodide (6.6 g, 32.4 mmol) in 60 mL of dry DMSO, the solution of corresponding cyclooctanedione (1.4 g, 10 mmol) in 5 mL of dry DMSO was added dropwise at stirring under argon. Then the solution of potassium tert-butoxide (3.36 g, 30 mmol) in 40 mL of dry DMSO was added dropwise. The reaction mixture was stirred for 16 h at r.t., then it was poured into icy water (60 mL) and extracted with pentane (3 × 20 mL). Combined organic layers were quickly dried over MgSO4; the solvent was evaporated under reduced pressure. The products were isolated via preparative column chromatography (SiO2).

(3R,4S)-1,5-Dioxadispiro[2.0.2.6]dodecane (6a).

Yield 2% (34 mg), yellowish liquid, Rf = 0.38 (CH2Cl2:light petrol 3:1).

1H NMR (400 MHz, CDCl3, 25 °C): δ = 1.51–1.85 (m, 10H, 6CH2), 1.85–1.96 (m, 2H, 2CH2), 2.63 (d, 2J = 5.3, 2H, 2CH2O), 2.85 (dd, 2J = 5.3, 3J = 0.9, 2H, 2CH2O); 13C NMR (101 MHz, CDCl3, 25 °C): δ = 22.8 (2CH2β), 25.9 (2CH2γ), 33.8 (2CH2α), 53.1 (2CH2O), 60.3 (2Cspiro).

HRMS (ESI+), 70 eV, m/z): calculated for C10H16O2 [M+H]+: 169.1223; found: 169.1229.

(3R,4R)/15-Dioxadispiro[2.0.2.6]dodecane (6b).

Yield 3% (50 mg), yellowish liquid, Rf = 0.18 (CH2Cl2:light petrol 3:1).

1H NMR (400 MHz, CDCl3, 25 °C): δ = 1.43–1.67 (m, 4H, 4CH2), 1.69–1.84 (m, 6H, 6CH2), 1.90–2.01 (m, 2H, 2CH2), 2.59 (d, 2J = 5.7, 2H, 2CH2O), 2.87 (d, 2J = 5.7, 2H, 2CH2O); 13C NMR (101 MHz, CDCl3, 25 °C): δ = 21.4 (2CH2β), 25.4 (2CH2γ), 32.3 (2CH2α), 52.3 (2CH2O), 58.7 (2Cspiro).

HRMS (ESI+), 70 eV, m/z): calculated for C10H18O2 [M+H]+: 169.1223; found: 169.1229.

1,8-Dioxadispiro[2.0.2.5]tetradecane (7).

Yield 16% (310 mg), obtained as a mixture of diastereomers 7a:7b 3:1, colorless liquid, Rf = 0.27 (CH2Cl2)
7a: 1H NMR (400 MHz, CDCl$_3$, 25 °C): $\delta = 0.39-0.45$ (m, 2H, CH$_2$, cy-Pr), 0.65-0.71 (m, 2H, CH$_2$, cy-Pr), 1.38-1.46 (m, 2H, C$_{10}$H$_5$, C$_{14}$H$_2$), 1.52-1.71 (m, 2H, C$_{11}$H$_2$, C$_{13}$H$_2$ + 2H, C$_{12}$H$_2$), 1.89-1.96 (m, 2H, C$_{11}$H$_2$, C$_{13}$H$_2$), 1.99-2.07 (m, 2H, C$_{10}$H$_2$, C$_{14}$H$_2$), 2.61 (s, 4H, 2CH$_2$O); 13C NMR (101 MHz, CDCl$_3$, 25 °C): $\delta = 6.5$ (CH$_2$, cy-Pr), 8.8 (CH$_2$, cy-Pr), 22.4 (C$_{11}$H$_2$, C$_{13}$H$_2$), 26.6 (C$_4$), 26.7 (C$_{12}$H$_2$), 34.1 (C$_{10}$H$_2$, C$_{14}$H$_2$), 54.2 (2CH$_2$O), 59.0 (C$_3$C$_3$).

7b: 1H NMR (400 MHz, CDCl$_3$, 25 °C): $\delta = 0.40-0.47$ (m, 4H, CH$_2$, cy-Pr), 1.47-1.56 (m, 2H, C$_{10}$H$_2$, C$_{14}$H$_2$), 1.60-1.66 (m, 2H, C$_{12}$H$_2$), 1.71-1.80 (m, 4H, C$_{11}$H$_2$, C$_{13}$H$_2$), 2.0-2.06 (m, 2H, C$_{10}$H$_2$, C$_{14}$H$_2$); 13C NMR (101 MHz, CDCl$_3$, 25 °C): $\delta = 7.3$ (2CH$_2$, cy-Pr), 24.5 (C$_{11}$H$_2$, C$_{13}$H$_2$), 25.5 (C$_{12}$H$_2$), 25.9 (C$_4$), 34.7 (C$_{10}$H$_2$, C$_{14}$H$_2$), 54.6 (2CH$_2$O), 58.99 (C$_3$C$_3$).

HRMS (ESI$^+$, 70 eV, m/z): calculated for C$_{12}$H$_9$O$_2$ [M+H$^+$]: 195.1380; found: 195.1384.

3.4,5,6-Tetrahydropentalen-1(2H)-one (8) [23].

Yield 20% (244 mg), colorless oil, R$_f$ = 0.19 (light petrol:EtOAc 10:3).

1H NMR (400 MHz, CDCl$_3$, 25 °C): $\delta = 2.25-2.38$ (m, 4H, 2CH$_2$2), 2.43-2.56 (m, 4H, 2CH$_2$2), 2.66-2.76 (m, 2H, CH$_2$); 13C NMR (101 MHz, CDCl$_3$, 25 °C): $\delta = 24.5$ (CH$_2$), 25.7 (CH$_2$), 27.9 (CH$_2$), 32.1 (CH$_2$), 41.2 (CH$_2$), 149.0 (C), 187.4 (C), 204.0 (C=O).

13C NMR (101 MHz, CDCl$_3$, 25 °C): $\delta = 1.47$ (ddd, 4H, 2$\delta$ = 14.4, 3$\delta$ = 9.0, 3$\gamma$ = 3.6, 4CH$_2$), 1.55–1.66 (m, 2H, 2CH$_2$), 1.79–1.92 (m, 2H, 2CH$_2$), 2.01 (ddd, 4H, 2$\delta$ = 14.4, 3$\delta$ = 8.8, 3$\gamma$ = 3.4, 4CH$_2$), 2.63 (s, 4H, 2CH$_2$O); 13C NMR (101 MHz, CDCl$_3$, 25 °C): $\delta = 22.4$ (2CH$_2$), 34.8 (4CH$_2$), 54.9 (2CH$_2$O), 59.6 (2 C$_{spiro}$).

HRMS (ESI$^+$, 70 eV, m/z): calculated for C$_{10}$H$_{12}$O$_2$ [M+Na$^+$]: 191.1043; found: 191.1042.

Yield 17% (286 mg), yellowish liquid, R$_f$ = 0.49 (light petrol:EtOAc 3:1).

1H NMR (400 MHz, CDCl$_3$, 25 °C): $\delta = 1.62-1.85$ (m, 12H, 6CH$_2$2), 2.67 (s, 4H, 2CH$_2$O); 13C NMR (101 MHz, CDCl$_3$, 25 °C): $\delta = 21.7$ (2CH$_2$), 34.6 (4CH$_2$), 55.6 (2CH$_2$O), 59.1 (2 C$_{spiro}$).

HRMS (ESI$^+$, 70 eV, m/z): calculated for C$_{10}$H$_{12}$O$_2$ [M+Na$^+$]: 169.1223; found: 169.1228.

3.3. Ring Opening of Oxiranes upon Treatment with Sodium Azide (General Method)

To the solution of sodium azide (2–32 mmol) in water (2 mL), the corresponding oxirane (1 mmol) was added. The reaction mixture was stirred under reflux for 2–3 h, cooled down to r.t. and extracted with ethyl acetate (3 × 3 mL). The organic layers were combined; the solvent was evaporated under reduced pressure. The products were isolated via preparative column chromatography (SiO$_2$).

1-(Azidomethyl)cyclooctanol (11).

Obtained from oxirane 10 and sodium azide (0.26 g, 4 mmol). Reaction time 5 h. Yield 52% (95 mg), colorless oil, R$_f$ = 0.32 (light petrol:EtOAc 10:1).

1H NMR (400 MHz, CDCl$_3$, 25 °C): $\delta = 1.35-1.72$ (m, 12H, 7CH$_2$), 1.72–1.83 (m, 2H, 2CH$_2$), 3.26 (s, 2H, CH$_2$N$_3$); 13C NMR (101 MHz, CDCl$_3$, 25 °C): $\delta = 22.1$ (2CH$_2$), 24.9 (CH$_2$), 28.2 (2CH$_3$), 33.9 (2CH$_2$), 60.8 (CH$_2$N$_3$), 75.3 (C).

HRMS (ESI$^+$, 70 eV, m/z): calculated for C$_8$H$_{17}$N$_3$O [M+Na$^+$]: 206.1264; found: 206.1253.

(3R,4S)/(3S,4R)-4-(Azidomethyl)-1-oxaspiro[2.7]decan-4-ol (12).

Obtained from bis(oxirane) 6a and sodium azide (0.52 g, 8 mmol). Reaction time 3 h. Yield 16% (33 mg), colorless oil, R$_f$ = 0.55 (light petrol:EtOAc 6:1).

1H NMR (400 MHz, CDCl$_3$, 25 °C): 1.34–1.95 (m, 12H, 6CH$_2$), 2.47 (s, 1H, OH), 2.61 (d, 1H, $\delta$ = 4.9, CH$_2$O), 3.08 (d, 1H, $\delta$ = 4.9, CH$_2$O), 3.25 (s, 2H, CH$_2$N$_3$); 13C NMR (101 MHz, CDCl$_3$, 25 °C): 21.3 (CH$_2$), 24.9 (CH$_2$), 25.0 (CH$_2$), 25.7 (CH$_2$), 30.3 (CH$_3$), 31.6 (CH$_2$), 53.5 (CH$_2$O), 51.3 (CH$_2$N$_3$), 58.1 (CH$_2$N$_3$), 1(C$_{14}$ = 141), 61.0 (C), 73.9 (C).

HRMS (ESI$^+$, 70 eV, m/z): calculated for C$_{10}$H$_{17}$N$_3$O [M+Na$^+$]: 234.1213; found: 234.1220.

(1R,2S)/(1S,2R)-1,2-Bis(azidomethyl)cyclooctane-1,2-diol (13).
 Obtained from bis(oxirane) 6a and sodium azide (1.04 g, 16 mmol). Reaction time 30 h. Yield 54% (136 mg), yellow oil, Rf = 0.76 (light petrol:EtOAc 4:1).

1H NMR (400 MHz, CDCl3, 25 °C): δ = 1.41–1.54 (m, 4H, 2CH2), 1.55–1.70 (m, 4H, 2CH2), 1.74–1.90 (m, 2H, 2CH2), 1.94–2.04 (m, 2H, 2CH2), 2.87 (s, 2H, 2 OH), 3.29 (d, 2H, J = 12.4, 2CH2N3), 3.51 (d, 2H, J = 12.4, 2CH2N3); 13C NMR (101 MHz, CDCl3, 25 °C): δ = 21.6 (2CH2), 28.1 (2CH2), 32.6 (2CH2N3), 57.3 (2CH2N3), 77.3 (2 C).

HRMS (ESI+, 70 eV, m/z): calculated for C10H18N4O2 [M+Na]+: 277.1383; found: 277.1387.

((1R,8S)/(1S,8R)-8-(Azidomethyl)-9-oxabicyclo[6.1.0]nonan-1-yl)methanol (14).

 Obtained from bis(oxirane) 6b and sodium azide (0.52 g, 8 mmol). Reaction time 2 h. Yield 40% (84 mg), yellow oil, Rf = 0.10 (light petrol:EtOAc 4:1).

1H NMR (400 MHz, CDCl3, 25 °C): δ = 1.40–1.70 (m, 10H, 6CH2), 1.90 (br.m, 1H, OH), 2.24–2.37 (m, 2H, 2CH2), 3.52 (d, 1H, J = 13.5, CH2N3), 3.62 (d, 1H, J = 13.5, CH2N3), 3.72 (dd, 1H, J = 12.2, J = 4.6, CH3O), 3.86 (dd, 1H, J = 12.2, J = 5.4, CH3O); 13C NMR (101 MHz, CDCl3, 25 °C): δ = 25.1 (CH2), 25.4 (CH2), 26.49 (CH2), 26.51 (CH2), 29.57 (CH2), 29.63 (CH2), 52.3 (CH2N3), 62.5 (CH2O), 66.0 (C), 66.3 (C).

HRMS (ESI+, 70 eV, m/z): calculated for C19H19N3O3 [M+Na]+: 252.1319; found: 252.1315.

(3S,7S)-7-(Azidomethyl)-1-oxaspiro[2.7]decan-7-ol (16).

 Obtained from bis(oxirane) 9a and sodium azide (0.26 g, 4 mmol). Reaction time 2 h. Yield 14% (30 mg), yellowish liquid, Rf = 0.27 (light petrol:EtOAc 3:1).

1H NMR (400 MHz, CDCl3, 25 °C): δ = 1.41–1.53 (m, 2H, 2CH2), 1.60–1.74 (m, 4H, 4CH2), 1.74–1.91 (m, 6H, 6CH2), 2.62 (s, 2H, CH2O), 3.26 (s, 2H, CH2N3); 13C NMR (101 MHz, CDCl3, 25 °C): δ = 19.2 (2CH2), 34.1 (2CH2), 35.7 (2CH2), 55.4 (CH2O), 58.9 (Cspiro), 60.9 (CH2N3), 75.1 (C).

HRMS (ESI+, 70 eV, m/z): calculated for C10H19N2O2 [M+Na]+: 234.1213; found: 234.1215.

(1S,5S)-1,5-Bis(azidomethyl)cyclooctane-1,5-diol (17).

 Obtained from bis(oxirane) 9a and sodium azide (0.52 g, 8 mmol). Reaction time 6 h. Yield 82% (208 mg), yellowish liquid, Rf = 0.17 (light petrol:EtOAc 3:1).

1H NMR (400 MHz, CDCl3, 25 °C): δ = 1.45–1.62 (m, 6H, 6CH2), 1.81–1.96 (m, 6H, 6CH2), 2.28 (br.s, 2H, 2 OH), 3.21 (s, 4H, 2CH2N3); 13C NMR (101 MHz, CDCl3, 25 °C): δ = 17.9 (2CH2), 36.4 (4CH2), 62.6 (2CH2N3), 74.1 (2 C).

HRMS (ESI+, 70 eV, m/z): calculated for C10H17N2O2 [M+H]+: 255.1564; found: 255.1570.

[5-(Azidomethyl)-9-oxabicyclo[3.3.1]non-1-yl]methanol (18).

 Obtained from bis(oxirane) 9b and sodium azide (0.26 g, 4 mmol). Reaction time 2 h. Yield 64% (136 mg), yellowish liquid, Rf = 0.37 (CH2Cl2).

1H NMR (400 MHz, CDCl3, 25 °C): δ = 1.31–1.48 (m, 4H, C2H2, C4H2, C6H2, C8H2), 1.59–1.76 (m, 6H, C2H2, C4H2, C6H2, C8H2, C10H2, C12H2), 1.93–2.13 (m, 3H, C3H2, C7H2, OH), 3.03 (s, 2H, CH2N3), 3.34 (d, 2H, J = 6.4, CH2OH); 13C NMR (101 MHz, CDCl3, 25 °C): δ = 18.4 (C3H2, C5H2), 29.5 (C1H2, C6H2), 31.0 (C1H2, C6H2), 61.4 (CH2N3), 71.4 (CH2OH), 72.9 (C1), 73.9 (C2).

HRMS (ESI+, 70 eV, m/z): calculated for C10H17N3O2 [M+H]+: 212.1394; found: 212.1388.

3.4. Synthesis of (1R,8S)/(1S,8R)-1-(Azidomethyl)-8-(methoxymethyl)-9-oxabicyclo[6.1.0]nonane (15)

To the solution of alcohol 14 (0.21 g, 1 mmol) and methyl iodide (0.72 g, 0.33 mL, 5.7 mmol) in dry DMF (12 mL), NaH (60% suspension in oil; 0.14 g, 3.6 mmol) was added. The reaction mixture was stirred for 12 h at r.t., quenched with saturated aqueous NH4Cl (10 mL), and extracted with EtOAc (3 × 5 mL). Combined organic layers were dried over MgSO4; the solvent was evaporated under reduced pressure. The product was isolated via preparative column chromatography (SiO2).
Yield 16% (36 mg), brown oil, R<sub>f</sub> = 0.38 (CH<sub>2</sub>Cl<sub>2</sub>:light petrol 1:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C): δ = 1.36–1.66 (m, 10H, 6CH<sub>2</sub>), 2.23–2.35 (m, 2H, 2CH<sub>2</sub>), 3.36 (s, 3H, CH<sub>3</sub>), 3.431 (d, J<sub>2</sub> = 11.1, CH<sub>2</sub>O), 3.438 (d, J<sub>2</sub> = 13.4, CH<sub>2</sub>N<sub>3</sub>), 3.53 (d, J<sub>2</sub> = 13.4, CH<sub>2</sub>N<sub>3</sub>), 3.73 (d, J<sub>2</sub> = 11.1, CH<sub>2</sub>O);

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, 25 °C): δ = 25.2 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 29.9 (CH<sub>2</sub>), 52.8 (CH<sub>2</sub>N<sub>3</sub>), 59.3 (CH<sub>3</sub>O), 64.6 (C), 65.1 (C), 74.2 (CH<sub>2</sub>O).

HRMS (ESI<sup>+</sup>, 70 eV, m/z): calculated for C<sub>11</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub> [M+Na]<sup>+</sup>: 248.1369; found: 248.1369.

4. Conclusions

To summarize, novel bis(oxiranes), containing cyclooctane core, were synthesized and investigated upon treatment with sodium azide. Configuration of bis(oxiranes) was found to drastically influence on their reactivity towards azide anion. A novel pathway of the reaction of 1,3-bis(oxiranes) with a nucleophile, producing oxabicyclononane moiety, was found. Preparative approaches towards a series of novel cyclooctane and oxabicyclononane derivatives, containing azido and hydroxy groups, starting from spirocyclic oxiranes and employing simple and convenient methods, were realized.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27206889/s1, assignment of relative configuration of diastereomers of bis(oxiranes); optimization of conditions of the ring opening of 6a and 9a; copies of NMR spectra of the novel compounds [40–45].

Author Contributions: Conceptualization, K.N.S. and E.B.A.; investigation, K.N.S., O.V.R., S.A.S., S.V.K., Y.K.G., A.D.A. and I.P.G.; data curation, Y.K.G.; writing—original draft preparation, O.V.R. and K.N.S.; writing—review and editing, A.D.A. and E.B.A.; visualization, Y.K.G. and I.P.G.; project administration, E.B.A.; funding acquisition, E.B.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by The Ministry of Science and Higher Education of the Russian Federation (Agreement with Zelinsky Institute of Organic Chemistry RAS No 075-15-2020-803).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The study was fulfilled using the NMR spectrometer Agilent 400-MR, purchased by the MSU Development Program.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of all the described compounds are available from the authors.

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