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Haloiminolactonization of Cyclopentene α,α-Dichlorocarboxamides. Tandem Rearrangement of Iminolactones in Epoxylactones

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Abstract—Electrophilic cyclization initiated by NBS and I_2 of 2,2-dichloro-2-[(1*R*,5*S*)- and 2,2-dichloro-2-[(1*S*,5*R*)-5-hydroxy-2-cyclopent-2-en-1-yl]-*N*-[(1*R*)-1-phenylethyl]acetamides was investigated. Stable under conditions of chromatography on SiO_2 bicyclic iminoesters, (2*Z*,3a*S*,4*S*,6*S*,6a*S*)-6-bromo-3,3-dichloro- and (2*Z*,3a*S*,4*S*,6*S*,6a*S*)-3,3-dichloro-6-iodo-2-{[(1*R*)-1-phenylethyl]imino}hexahydro-2*H*-cyclopenta[*b*]furan-4-ols were isolated and characterized, and a possible version was suggested of their step-by-step recyclization transformations. The halocyclization of carboxamides in water-organic mixtures afforded bicyclic epoxylactones (1a*R*,2a*S*,5a*S*,5b*S*)- and (1a*S*,2a*R*,5a*R*,5b*R*)-5,5-dichlorohexahydro-4*H*-oxireno[3,4]cyclopenta-[1,2-*b*]furan-4-ones, whose reductive dechlorination proceeded stepwise with successive removal of Cl atoms and led to the formation of (1a*R*,2a*S*,5a*S*,5b*S*)- and (1a*S*,2a*R*,5a*R*,5b*R*)-hexahydro-4*H*-oxireno[3,4]cyclopenta-[1,2-*b*]furan-4-ones.

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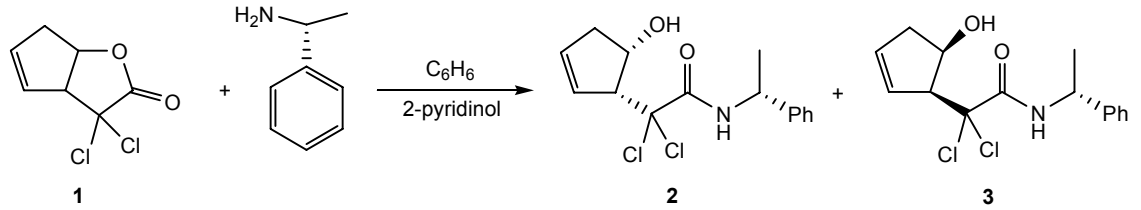
Electrophilic cyclizations of α,β-, β,γ-, γ,δ-unsaturated amides initiated by sources of a positive halogen atom are well known [1–6]. Cyclization proceeds mainly along the permitted Baldwin [7] routes, the structure of the compound and the substituents at the double bond influence the stereo- and regioselectivity of the process [8, 9]. The carbonium intermediate generated by the attack of the electrophile on the double bond depending on conditions can intra-molecularly react both with the oxygen atom (*O*-attack) and the *N*-function (*N*-attack) resulting in lactams, amines, lactones, esters etc. [1]. Due to the low nucleophilicity of the amide nitrogen atom the *N*-cyclization is difficult under common conditions, and mainly the *O*-alkylation products are obtained. A successful halolactamization of unsaturated carboxamides requires a preliminary activation (increase in the nucleophilicity) of the amide nitrogen atom that is provided by the preparation of *N*-, *O*-bis-TMS-imidates (Knapp method [10]), or through *N*-lithium salts (Corey method [11]) followed by the treatment with the halogen source (NBS, I_2, Br_2). Enantioselective reactions of halolactonization, haloesterification, and haloamination were developed [12–16]. These reactions are widely applied to the directional synthetic approaches to bioactive and other structures [1, 11].

In this work aiming to obtain vicinally tetrasubstituted chiral cyclopentane blocks we investigated the electrophilic cyclization of cyclopentene carboxamides **2** and **3** prepared from dichlorolactone **1** [13] with NBS and I_2 in MeCN and THF in the presence or absence of $NaHCO_3$ and water.

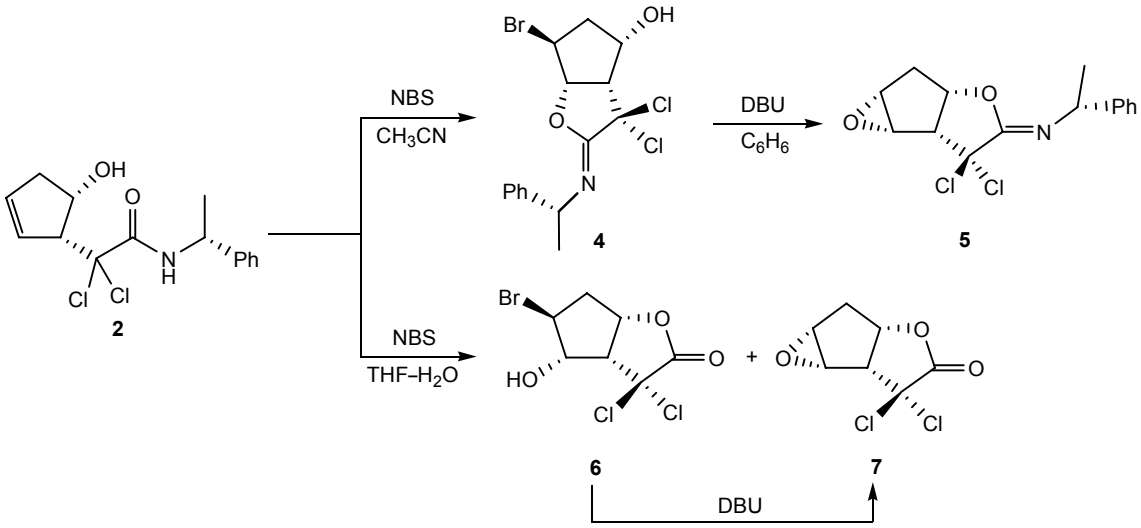
Carboxamides **2** and **3** were prepared in ~34% yield by the opening of the lactone ring of compound **1** at treating with (+)-α-methylbenzyl amine. Carboxamides **2** and **3** have different R_f values and are easily separated by chromatography on SiO_2 (Scheme 1).

The cyclization of carboxamides for the preparation of the most popular 5- and 6-membered rings are carried out in a mixture THF–H_2O to obtain therewith the corresponding lactones, however, the postulated intermediates of the intramolecular *O*-attack, iminium salts or iminoesters, were not isolated [1]. The lability of γ-iminolactones obtained in another way is also

Scheme 1.



Scheme 2.



mentioned in [14]. The intramolecular electrophilic cyclization of compound **2** with NBS in MeCN afforded in good yield iminoester **4**, whose structure was confirmed by NMR and mass spectra, and also by the data of 2D ^{1}H NMR spectrum (Scheme 2, Fig. 1).

The dehydrobromination of compound **4** using DBU in boiling benzene or *t*-BuOK in THF at room temperature occurred cleanly giving epoxyiminolactone **5**. The *anti*-configuration of imine **5** was proved by X-ray diffraction analysis (Fig. 2).

The reaction of carboxamide **2** with NBS in a medium THF–H_2O led to the formation of a mixture of dichloroepoxylactone **7** with the minor less polar compound **6**. At the dehydrobromination of this crude mixture by stirring with DBU (20°C, 3 h) minor compound **6** was converted in epoxylactone **7**, which was obtained in over 60% yield.

The result of the electrophilic cyclization of amide **2** under the action of I_2 also depends on the reaction conditions. For instance, in MeCN in the presence of

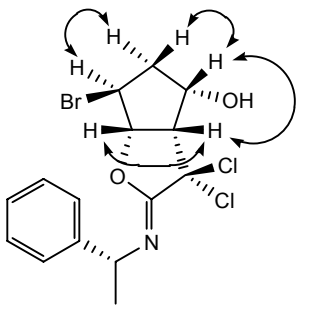


Fig. 1. NOE-interactions in (2*Z*,3a*S*,4*S*,6*S*,6a*S*)-6-bromo-3,3-dichloro-2-{[(1*R*)-1-phenylethyl]imino}hexahydro-2*H*-cyclopenta[*b*]furan-4-ol **4**.

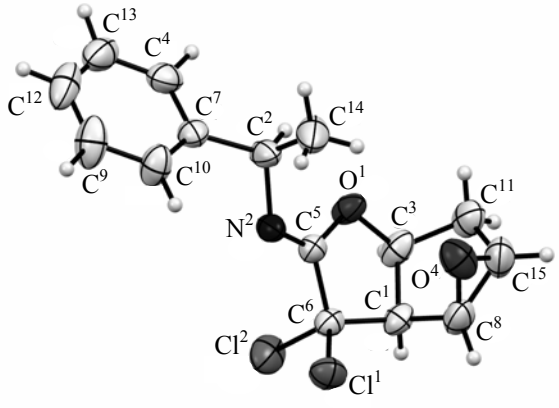
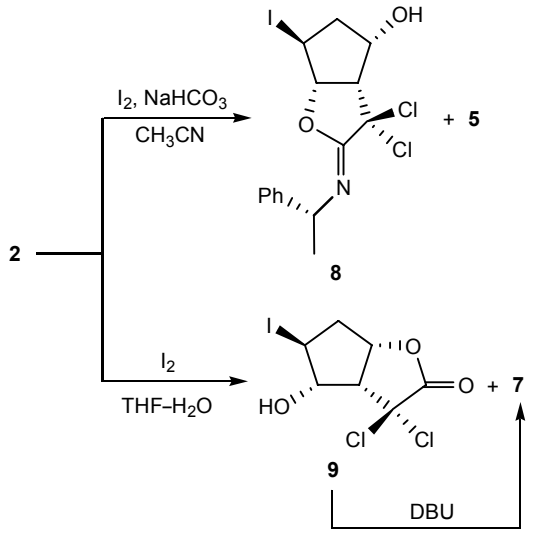


Fig. 2. Molecular arrangement of (1*R*)-*N*-[(1a*R*,2a*S*,4*Z*,5a*S*,5b*S*)-5,5-dichlorohexahydro-4*H*-oxireno[3,4]cyclopenta[1,2-*b*]-furan-4-ylidene]-1-phenylethanamine

$NaHCO_3$ along with the expected iminoester **8** the formation of epoxylactone **5** obtained in the previous experiment was observed, and in aqueous THF a mixture of dichloroepoxylactone **7** with iodolactone **9** appeared; its treatment with DBU provided exclusively epoxylactone **7** in 75% yield (Scheme 3).

Scheme 3.



In the studied transformations of compound **2** especially interesting is the formation in anhydrous conditions of stable at chromatography on SiO_2 exocyclic iminoesters **4** and **8**, and also their recyclization into epoxyimine **5**.

Presumably the formation of epoxyiminoester **5** from halohydrins **4** and **8** begins with the intramolecular attack of γ-hydroxide-anion on the spatially available imine bond in compound **10** and with the generation of a charged tricyclic intermediate **11**. The subsequent selective cleavage of one C–O bond in the latter and the S_N2-substitution of the halogen in the arising imine **12** with the closure of the epoxy ring complete the formation of stable epoxylactone **5** (Scheme 4).

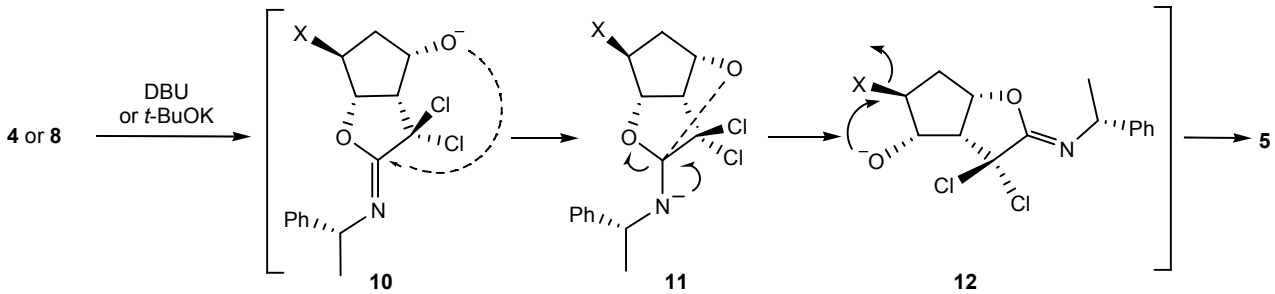
The exocyclic oxyimino esters are fairly labile [14], and the relative stability of the exocyclic iminoester **5** is evidently due to steric and electronic effects of the *gem*-dichloro function.

It may be stated that we have discovered a new tandem rearrangement of γ-hydroxyiminolactones into epoxyiminolactones followed by hydrolysis (in the presence of water) to the corresponding epoxylactones. We have found in the literature only three "distant" precedents of this rearrangement reminding the conversions "oxyimino→lactam" [8, 9].

In the study of reductive dechlorination of compound **5** with Zn-Cu couple in MeOH in the presence of NH_4Cl we found that the reaction proceeded stepwise with the formation of the dechlorination and hydration products in the imine part of molecule **7** and **13–15**. The latter products we succeeded to isolate in the individual state by treating the reaction mixture just after total consumption of initial iminolactone **5**. If the reaction is not stopped the intermediate compounds **7** and **13** are gradually converted into the main epoxylactone **14** that forms in 50% yield. The reaction of the individual dichloro derivative **7** made it possible to considerably reduce its duration and to increase the yield of epoxylactone **14** to 60% (Scheme 5).

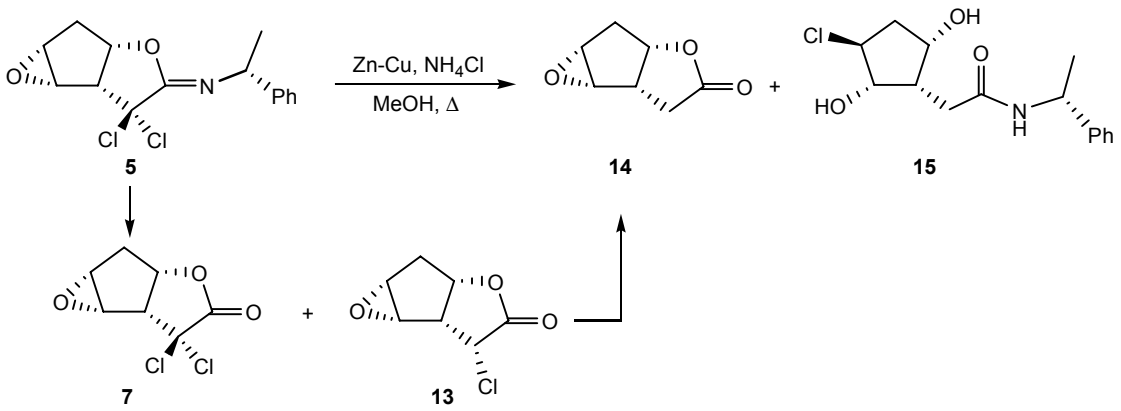
The structure of monochlorolactone **13** presented in Scheme 5 follows unambiguously from the data of ^1H and ^{13}C NMR spectra. The strong NOE-interaction between the *cis*-protons at the atoms C^5 and C^{5a} (*J* 8.6 Hz) indicates the *exo*-orientation of the C^5–Cl bond (Fig. 3). Consequently, the reductive dechlorination with zinc occurs first of all with the sterically more accessible atom 5β-Cl of dichlorolactone **7**.

Scheme 4.

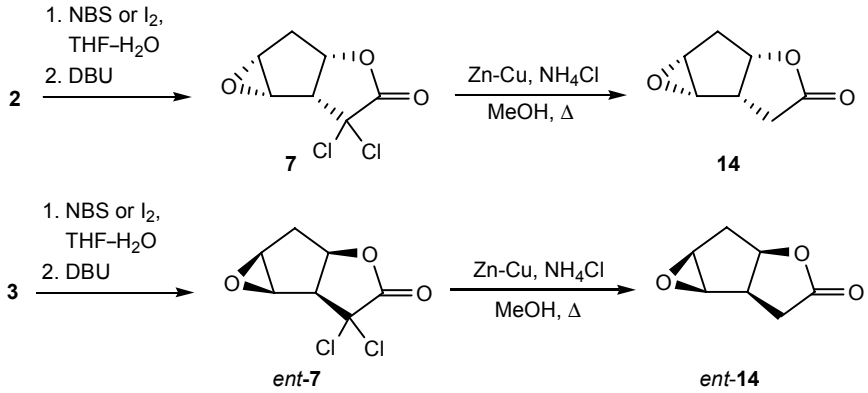


X = I, Br.

Scheme 5.



Scheme 6.



As seen from the structure of epoxylactone **14** the vicinally tetrasubstituted cyclopentane block is obviously of synthetic interest for developing approach to cyclopentanoids [19–23]. Chiral epoxylactone **14** was described for the first time and applied to prostaglandins synthesis in [24]. In [25] compound **14** was obtained from 5-substituted cyclopentadiene derivative via a fairly whimsy stage of chirality introduction resulting in the preparation of Grieco (–)-lactone. This compound was obtained by a multistage synthesis from D-glucose [26]. In [27] the spectral data of compound **14**, prepared from racemic Grieco lactone in the course of the synthesis of natural macrolide auriside were published.

The output of our study consists in the development of a new practical procedure for the preparation of synthetically important epoxylactone **14** and its enantiomer *ent*-**14** proceeding from easily accessible carboxamides **2** and **3** in two stages with an overall yield 40% (Scheme 6).

Thus as a result of our investigation we characterized the primary adducts of carboxamide **2** *O*-cyclization: iminolactones **4** and **8**, described their recyclization transformations promoted by γ-hydroxy-anion and the reactions of reductive dechlorination of **5**, dichlorolactones **7** and *ent*-**7** with the preparation of correct configuration of chiral sites of the bicyclic blocks for cyclopentanoids: epoxylactones **14** and *ent*-**14**.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Shimadzu IR Prestige-21 from films or mulls in mineral oil. NMR spectra were registered on spectrometers Bruker AM-300 [operating frequencies

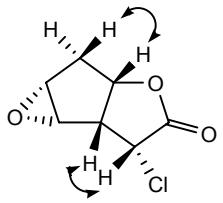


Fig. 3. NOE-interactions in 2,2-dichloro-2-[(1*S*,5*R*)-5-hydroxycyclopent-2-en-1-yl]-*N*-[(1*R*)-1-phenylethyl]acetamide **13**.

300.13 (^{1}H) and 75.47 (^{13}C) MHz] or Bruker Avance-500 [operating frequencies 500.13 (^{1}H) and 125.77 (^{13}C) MHz] in $CDCl_3$ (δ_H 7.27, δ_C 77.00 ppm) or acetone-d_6 (δ_H 2.07, δ_C 28.83 ppm). Mass spectra were obtained on an instrument Thermo Finnigan MAT 95XP, ionizing electrons energy 70 eV. XRD experiment on a single crystal of compound **5** was performed on a diffractometer Xcalibur E (Agilent Technologies). The reaction progress was monitored by TLC on Sorbfil plates, spots visualized with 10% solution of anisealdehyde in ethanol with sulfuric acid added, or with alkaline solution of $KMnO_4$. Rotation angles were measured on a polarimeter Perkin-Elmer 241 MC. We used (+)-α-methylbenzylamine purchased from Fluka, $[\alpha]_D^{25}$ +38.5°.

Reaction of lactone (1) with (+)-α-methylbenzylamine. To a solution of 0.3 g (1.6 mmol) of compound **1** in 10 mL of anhydrous C_6H_6 in an argon atmosphere at 20°C while stirring was added 0.15 g (1.60 mmol) of 2-pyridinol and 0.4 mL (3.2 mmol) of (+)-α-methylbenzylamine. The reaction mixture was stirred for 48 h, the end of the process was determined by TLC monitoring. The reaction mixture was diluted with ethyl acetate (30 mL), washed with H_2O (3 × 5 mL), dried with Na_2SO_4, concentrated in a vacuum, and the residue was chromatographed on a column packed with SiO_2 (eluent petroleum ether–ethyl acetate, 20 : 1). Yield 0.33 g (34%) of compound **2** and 0.33 g (34%) of compound **3**.

2,2-Dichloro-2-[(1*R*,5*S*)-5-hydroxy-2-cyclopent-2-en-1-yl]-*N*-[(1*R*)-1-phenylethyl]acetamide (2). Light-yellow crystals, R_f 0.31 (petroleum ether–ethyl acetate, 8 : 2, triple elution), mp 35°C, $[\alpha]_D^{20}$ –10° (*c* 1.0, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3312 (NH), 3313 (OH), 2951, 2853, 1922, 1635 (C=O), 692 (CCl_2). ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 1.26 d (3H, Me, *J* 7.1 Hz), 2.38 br.d (1H, OH, *J* 7.0 Hz), 2.45 d.d.q (1H, H^{5a}, *J* 17.1, 4.4, 2.3 Hz), 2.68 d.d.t.d (H^{5b}, *J* 17.1, 7.4, 1.1, 2.3 Hz), 3.91 d.d.q (1H, H^2, *J* 6.2, 1.1, 2.3 Hz), 4.60 d.d.d.d (1H, H^1, *J* 7.4, 4.6, 7.0, 6.2 Hz), 5.07 quintet (1H, H$^{2'}$, *J* 7.1 Hz), 5.88 d.q (1H, H^3, *J* 6.0, 2.2 Hz), 6.00 d.q (1H, H^4, *J* 6.0, 2.3 Hz), 7.11 d (1H, NH, *J* 7.1 Hz), 7.26–7.32 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$, 75 MHz), δ, ppm: 21.38 (Me), 41.13 (C^5), 50.17 ($CHCl_2$), 60.31 (C^2), 72.55 (C^1), 87.16 (C$^{1'}$); 126.01, 127.69, 128.97, 141.95 (C_6H_5); 128.35 (C^3), 132.75 (C^4), 166.18 (COO). Found, %: C 57.51; H 5.15; Cl 22.37; N 4.51. $C_{15}H_{17}NCl_2O_3$. Calculated, %: C 57.34; H 5.35; Cl 22.47; N 4.46.

2,2-Dichloro-2-[(1*S*,5*R*)-5-hydroxycyclopent-2-en-1-yl]-*N*-[(1*R*)-1-phenylethyl]acetamide (3). Light yellow oily substance, R_f 0.45 (petroleum ether–ethyl acetate, 8 : 2, triple elution), $[\alpha]_D^{20}$ +106.8° (*c* 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3312 (NH), 3313 (OH), 2951, 2853, 1922, 1635 (C=O), 692 (CCl_2). ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 1.26 d (1H, Me, *J* 7.1 Hz), 2.14 br.d (1H, OH, *J* 5.6 Hz), 2.42 d.d.q (1H, H^{5a}, *J* 16.9, 4.6, 2.3 Hz), 2.63 d.d.t (1H, H^{5b}, *J* 16.9, 7.4, 1.0 Hz), 3.96 d.q (1H, H^2, *J* 6.2, 0.9 Hz), 4.61 d.d.d.d (1H, H^1, *J* 7.4, 4.6, 6.2, 7.1 Hz), 5.04 quintet (1H, H$^{2'}$, *J* 7.1 Hz), 5.88 d.q (1H, H^3, *J* 6.2, 2.0 Hz), 5.99 d.q (1H, H^4, *J* 6.2, 2.3 Hz), 7.13 d (1H, NH, *J* 7.1 Hz), 7.26–7.32 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$, 75 MHz), δ, ppm: 21.57 (Me), 40.99 (C^5), 50.33 ($CHCl_2$), 60.08 (C^2), 72.66 (C^1), 87.21 (C$^{1'}$); 126.01, 127.65, 128.80, 142.16 (C_6H_5); 122.96 (C^4), 128.26 (C^3), 166.30 (CO).

(2*Z*,3a*S*,4*S*,6*S*,6a*S*)-6-Bromo-3,3-dichloro-2-{[(1*R*)-1-phenylethyl]imino}hexahydro-2*H*-cyclopenta[*b*]furan-4-ol (4). To a solution of 0.25 g (0.80 mmol) of amide **2** in 8 mL of CH_3CN was added 0.31 g (1.75 mmol) of NBS, and the mixture was stirred for 2 h at 20°C, the solvent was evaporated, the residue was chromatographed on a column packed with SiO_2 (petroleum ether–ethyl acetate, 9 : 1). Yield 0.30 g (95%), R_f 0.26 (eluent petroleum ether–ethyl acetate, 8 : 2, double elution). Light yellow crystals, mp 180°C, $[\alpha]_D^{20}$ +77.7° (*c* 1.0, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3228, 1689, 1456, 1035. ^{1}H NMR spectrum (acetone-d_6, 500 MHz), δ, ppm: 1.25 d (3H, CH_3, *J* 6.7 Hz), 2.82 d.d (1H, H^{5A}, *J* 7.3, 16.3 Hz), 3.00 d.d.d (1H, H^{5B}, *J* 2.8, 6.0, 16.3 Hz), 3.76 d.d (1H, H^{3a}, *J* 4.3, 5.8 Hz), 4.46 d (1H, H^6, *J* 6.0 Hz), 4.58 d (1H, H^{6a}, *J* 4.0 Hz), 4.77 q (1H, CHN, *J* 6.7 Hz), 5.25 m (1H, H^4); 7.25 (1H), 7.30 (2H), 7.40 (2H, C_6H_5). ^{13}C NMR spectrum (acetone-d_6, 125 MHz), δ, ppm: 23.49 (CH_3), 41.88 (C^5), 54.16 (C^6), 55.54 (CHN), 59.60 (C^{3a}), 77.83 (C^4), 82.37 (C^{6a}), 82.78 (C^3); 126.22, 126.28, 126.30, 127.80, 128.00, 145.08 (C_6H_5); 156.94 (C^2). Mass spectrum, *m/z* (I_{rel}, %): 391 (60) $[M]^+$, 376 (20) $[M - CH_3]^+$, 105 (100) $[C_6H_5CHCH_3]^+$. Found: 391.9742 $[M]^+$. $C_{15}H_{16}BrCl_2NO_2$. Calculated 391.9736.

(1*R*)-*N*-{(1a*R*,2a*S*,4*Z*,5a*S*,5b*S*)-5,5-Dichlorohexahydro-4*H*-oxireno[3,4]cyclopenta[1,2-*b*]furan-4-ylidene}-1-phenylethanamine (5). *a*. To a solution of 0.20 g (0.51 mmol) of bromide **4** in 7 mL of anhydrous C_6H_6 was added 0.083 mL (0.56 mmol) of DBU. The reaction mixture was boiled for 1 h (TLC monitoring), concentrated, the residue was chroma-

tographed on a column packed with SiO_2 eluent petroleum ether–ethyl acetate, 9 : 1). Yield 0.12 g (76%).

b. To a solution of 0.78 g (0.2 mmol) of bromide **4** in 6 mL of anhydrous THF at 0°C was added by portions 0.034 mg (0.3 mmol) of *t*-BuOK. The reaction mixture was stirred for 10 min (TLC monitoring), THF was evaporated, the residue was diluted with ethyl acetate (20 mL), washed with H_2O, with brine, dried with Na_2SO_4, concentrated in a vacuum, and the residue was chromatographed on a column packed with SiO_2 (eluent petroleum ether–ethyl acetate, 8 : 2). Yield 0.025 g (40%). White crystals, mp 160ºC, $[\alpha]_D^{20}$ +53.4° (*c* 1.0, CH_2Cl_2). R_f 0.31 (petroleum ether–ethyl acetate, 8 : 2, triple elution). IR spectrum, ν, cm^{-1}: 1705, 1464, 1451, 1042, 705. ^1H NMR spectrum (acetone-d_6, 500 MHz), δ, ppm: 1.35 d (3H, CH_3, *J* 6.6 Hz), 2.30 d.d.d (1H, H^{2A}, *J* 0.9, 16.0 Hz), 2.45 d (1H, H^{2B}, *J* 16.0 Hz), 3.70 br.s (1H, H^{5b}), 3.74 d.d (1H, H^{5a}, *J* 1.3, 6.0 Hz), 3.80 br.s (1H, H^{1a}), 4.75 q (1H, CHN, *J* 6.6 Hz), 5.06 t (1H, H^{2a}); 7.15–7.20 m (1H, Ph), 7.30 t (2H, Ph, *J* 7.3 Hz), 7.40 d (2H, Ph, *J* 7.5 Hz). ^{13}C NMR spectrum ($CDCl_3$, 75 MHz), δ, ppm: 23.34 (Me), 34.52 (C^2), 56.51 (C^{5a}), 58.41 (CHN), 59.70, 59.95 (C^{1a}, C^{5b}), 82.52 (C^{2a}), 83.57 (C^5); 127.16, 127.25, 128.3, 146.76 (C_6H_5); 157.45 (C^4). Mass spectrum, *m/z* (I_{rel}, %): 311 (60) $[M]^+$, 296 (100) $[M - CH_3]^+$, 276 (10) $[M - Cl]^+$, 105 (92) $[C_6H_5CHCH_3]^+$. Found: 311.0470 $[M]^+$. $C_{15}H_{15}Cl_2NO_2$. Calculated: *M* 311.0474.

(1a*R*,2a*S*,5a*S*,5b*S*)-5,5-Dichlorohexahydro-4*H*-oxireno[3,4]cyclopenta[1,2-*b*]furan-4-one (7). *a*. To a solution of 0.21 g (0.68 mmol) of amide **2** in 10 mL of a mixture THF–H_2O, 8 : 2, was added 0.37 g (2.10 mmol) of NBS, the mixture was stirred for 12 h (TLC monitoring). THF was evaporated, the residue was extracted with ethyl acetate (3 × 40 mL), the combined organic extracts were washed with brine, dried with Na_2SO_4, concentrated in a vacuum. The residue was diluted with benzene, 0.2 mL (1.30 mmol) of DBU was added, and the mixture was stirred for 2 h. Then benzene was evaporated, the residue was chromatographed on a column packed with SiO_2 (eluent petroleum ether–ethyl acetate, 8 : 2). Yield 0.084 g (65%), R_f 0.44 (petroleum ether–ethyl acetate, 1 : 1), light yellow crystals, mp 121°C, $[\alpha]_D^{20}$ –94.2° (*c* 1.0, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 1791, 1135, 1180, 1025. ^1H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 2.20 d.d (1H, H^{2A}, *J* 6.1, 16.1 Hz), 2.64 d.d (1H, H^{2B}, *J* 16.1 Hz), 3.61 d (1H, H^{5a}, *J* 6.1 Hz); 3.74 s (1H) and 3.80 s (1H, H^{1a}, H^{5b}); 5.05 d (1H, H^{2a}, *J* 6.1 Hz). ^{13}C NMR spectrum ($CDCl_3$, 75 MHz), δ, ppm: 33.67 (C^2); 57.58, 57.76, 59.68 (C^{5a}, C^{5b}, C^{1a}); 78.18 (C^5), 79.99 (C^{2a}), 167.40 (C^4). Mass spectrum, *m/z* (I_{rel}, %): $[M]^+$ was not observed, 296 (60) $[M - CO_2 - Cl]^+$, 65 (100). Found, %: C 40.10; H 2.71; Cl 33.18. $C_7H_6Cl_2O_3$. Calculated, %: C 40.22; H 2.89; Cl 33.92.

Reaction of amide (2) with I_2 in the presence of $NaHCO_3$. To a solution of 0.3 g (0.96 mmol) of amide **2** in 15 mL of CH_3CN was added 0.98 g (3.90 mmol) of I_2 and 1.23 g (14.40 mmol) of $NaHCO_3$, and the mixture was stirred for 72 h at 20°C. The reaction mixture was quenched by adding 7 mL of a saturated solution of Na_2SO_3, concentrated to a 1/3 of volume, and extracted with ethyl acetate (3 × 40 mL), the combined organic extracts were washed with water, with brine, dried with $MgSO_4$. After concentrating the solution and column chromatography of the residue on SiO_2 (eluent petroleum ether–ethyl acetate, 9 : 1) we obtained 0.074 g (17%) of iodide **8** and 0.12 g (41%) of iminolactone **5**.

(2*Z*,3a*S*,4*S*,6*S*,6a*S*)-3,3-Dichloro-6-iodo-2-{[(1*R*)-1-phenylethyl]imino}hexahydro-2*H*-cyclopenta[*b*]-furan-4-ol (8). White crystals, mp 65°C, R_f 0.58 (petroleum ether–ethyl acetate, 8 : 2, triple elution), $[\alpha]_D^{20}$ –66° (*c* 0.2, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3223, 1691, 1458, 1036. ^1H, NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 1.42 d (3H, CH_3, *J* 6.6 Hz), 2.75 d.d (1H, H^{5A}, *J* 7.2, 15.8 Hz), 3.10 d.d.d (1H, H^{5B}, *J* 3.1, 6.8, 15.8 Hz), 4.10 d.d (1H, H^{3a}, *J* 3.8, 4.6 Hz), 4.25 d (1H, H^6, *J* 6.6 Hz), 4.80 q (1H, CHN, *J* 6.6 Hz), 5.15 m (1H, H^{6a}); 7.25 (1H), 7.30 (2H), 7.40 (2H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$, 75 MHz), δ, ppm: 23.47 (CH_3), 27.10 (C^6), 43.87 (C^5), 55.70 (C^{3a}), 59.80 (CHN), 79.92 (C^4), 81.91 (C^3), 82.42 (C^{6a}); 126.22, 126.28, 126.30, 127.80, 128.00, 145.08 (C_6H_5); 154.57 (C^2). Found, %: C 40.22; H 3.89; Cl 15.92; I 28.35; N 3.03. $C_{15}H_{16}Cl_2INO_2$. Calculated, %: C 40.94; H 3.66; Cl 16.11; I 28.84; N 3.18.

Reaction of carboxamide (2) with I_2 in the system THF–H_2O. To a solution of 0.23 g (0.73 mmol) of amide **2** in 20 mL of a mixture THF–H_2O, 8 : 2, was added 1.90 g (7.30 mmol) of I_2. The mixture was stirred for 2 h (TLC monitoring), THF was evaporated, the residue was extracted with ethyl acetate (3 × 50 mL), the combined organic extracts were washed with saturated solution of Na_2SO_3 and with brine, dried with Na_2SO_4, concentrated in a vacuum, and the residue was chromatographed on a column packed with SiO_2 (eluent petroleum ether–ethyl acetate, 8 : 2). Yield 0.031 g (31%) of iodide **9** and 0.096 g (63%) of dichloroepoxylactone **7**.

(3a*R*,4S,5*S*,6a*S*)-3,3-Dichloro-4-hydroxy-5-iodohexahydro-2*H*-cyclopenta[*b*]furan-2-one (9). Light yellow oily substance, R_f 0.36 (petroleum ether–ethyl acetate, 8 : 2, double elution). IR spectrum, ν, cm^{-1}: 3600–3200, 1793, 1023, 973. ^1H NMR spectrum (acetone-d_6, 300 MHz), δ, ppm: 2.95 d.d (1H, H^{6A}, *J* 7.0, 16.3 Hz), 3.15 d.d.d (1H, H^{6B}, *J* 2.8, 6.0, 16.3 Hz), 4.10 t (1H, H^{3a}, *J* 4.5 Hz), 4.45 d (1H, H^6, *J* 6.7 Hz), 4.65 m (1H, H^4), 5.40 m (1H, H^{6a}). ^{13}C NMR spectrum (acetone-d_6, 75 MHz), δ, ppm: 28.86 (C^5), 43.12 (C^6), 58.66 (C^{3a}), 79.67 (C^4), 80.17 (C^3), 82.84 (C^{6a}), 176.40 (CO). Found, %: C 25.01; H 1.95; Cl 21.53; I 37.35. $C_7H_7Cl_2IO_3$. Calculated, %: C 24.95; H 2.09; Cl 21.04; I 37.66.

Compound **7**. *b*. To a solution of 0.076 g (0.23 mmol) of iodohydrin **9** in 5 mL of anhydrous C_6H_6 was added 0.068 mL (0.45 mmol) of DBU. The reaction mixture was stirred for 3 h at room temperature (TLC monitoring), concentrated, and the residue was chromatographed on a column packed with SiO_2 (eluent petroleum ether–ethyl acetate, 8 : 2). Yield 0.019 g (40%).

Reaction of epoxyiminoester (5) with Zn-Cu couple. To a solution of 0.18 g (0.59 mmol) of compound **5** in 8 mL of anhydrous MeOH in an argon atmosphere at stirring was added 0.02 g (0.3 mmol) of NH_4Cl and 0.19 g (3 mmol) of Zn-Cu couple. The reaction mixture was stirred for 2 h at boiling (TLC monitoring), the precipitate was filtered off, the mother liquor was concentrated, and the residue was chromatographed on a column packed with SiO_2 (eluent petroleum ether–ethyl acetate, 8 : 2). Yield 0.006 g (5%) of dichlorolactone **7**, 0.025 g (25%) of monochlorolactone **13**, 0.018 g (22%) of dechlorinated lactone **14**, and 0.013 g (8%) of compound **15**.

(1a*R*,2a*S*,5a*S*,5b*S*)-5-Chlorohexahydro-4*H*-oxireno[3,4]cyclopenta[1,2-*b*]furan-4-one (13). White crystals, mp 133°C, R_f 0.31 (petroleum ether–ethyl acetate, 1 : 1, triple elution), $[\alpha]_D^{20}$ –126.2°C (*c* 0.5, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 1767, 1262, 1377, 1172, 1022, 837. ^1H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 2.15 d.d.d (1H, H^{2A}, *J* 1.4, 6.1, 16.1 Hz), 2.53 d (1H, H^{2B}, *J* 16.1 Hz), 3.30 d.d.d (1H, H^{5a}, *J* 1.6, 6.4, 8.8 Hz), 3.65 t (1H, H^{2a}, *J* 1.4 Hz), 3.72 d.d (1H, H^{1a}, *J* 1.4, 1.6 Hz), 4.69 d (1H, H^5, *J* 8.8 Hz), 4.86 t (1H, H^{2a}, *J* 6.4 Hz). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 34.69 (C^2), 46.41 (C^{5a}), 52.32 (C^5), 57.92 (C^{5b}), 59.39 (C^{1a}), 80.08 (C^{2a}), 171.08 (CO). Mass spectrum, *m/z* (I_{rel}, %): $[M]^+$ was not observed, 139 (4) $[M - Cl]^+$, 95 (88) $[M - Cl - CO_2]^+$, 67 (100). Found: 139.0393 $[M - Cl]^+$. $C_7H_7O_3$. Calculated $[M - Cl]$ 139.0390.

(1a*R*,2a*S*,5a*S*,5b*S*)-Hexahydro-4*H*-oxireno[3,4]-cyclopenta[1,2-*b*]furan-4-one (14). White crystals, mp 77°C (76–77°C [24, 25]), $[\alpha]_D^{20}$ –107°C (*c* 1.0, CH_2Cl_2) {–115°C (*c* 1.0, $CHCl_3$) [24], –108°C (*c* 1.0, $CHCl_3$) [25]}, R_f 0.27 (petroleum ether–ethyl acetate, 1 : 1, triple elution). IR spectrum, ν, cm^{-1}: 1751, 1031. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.10 d.d.d (1H, H^{2A}, *J* 1.6, 7.1, 16.2 Hz), 2.50 d (1H, H^{2B}, *J* 16.2 Hz), 2.70 d (2H, H^5, *J* 5.3 Hz), 3.00 m (1H, H^{5a}), 3.60 br.s (1H) and 3.70 br.s (1H, H^{1a}, H^{5b}), 5.00 t (1H, H^{2a}, *J* 6.6 Hz). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 30.20 (C^5), 34.38 (C^2), 40.08 (C^{5a}), 60.06 and 60.78 (C^{1a} and C^{5b}), 83.38 (C^{2a}), 176.21 (CO). Mass spectrum, *m/z* (I_{rel}, %): 140 (70) $[M]^+$, 112 (20) $[M - H_2O]^+$, 97 (100). Found: 140.0467 $[M]^+$. $C_7H_8O_3$. Calculated *M* 140.0468.

2-[(1*S*,2*S*,3*S*,5*S*)-3-Chloro-2,5-dihydroxycyclopentyl]-*N*-[(1*R*)-1-phenylethyl]acetamide (15). Transparent oily substance, R_f 0.11 (petroleum ether–ethyl acetate, 1 : 1, double elution), $[\alpha]_D^{20}$ +51.7°C (*c* 1.0, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3400–3200, 1632, 1560, 1100. ^1H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 1.50 d.d.d (3H, CH_3, *J* 3.9, 6.1, 15.0 Hz), 1.80–1.90 m (1H, H^{4A}), 2.20–2.30 m (1H, H^{4B}), 2.40–2.60 m (2H, H^2), 3.25 m (1H, H^1), 3.42 br.s (2H, 2OH), 3.85 d.d.d (1H, H^3, *J* 2.7, 3.7, 7.3 Hz), 3.97 br.s (1H, H^5), 4.40 br.s (1H, H^2), 5.20 quintet (1H, CHN, *J* 7.0 Hz), 6.30 d (1H, NH, *J* 7.6 Hz), 7.25–7.20 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$, 75 MHz), δ, ppm: 21.77 (CH_3), 32.07 (C^2), 40.45 (C^4), 44.62 (C^{6a}), 49.00 (CHN), 57.06 (C^3), 74.07 (C^5), 87.05 (C^2), 126.01, 127.41, 128.68, 142.94 (C_6H_5), 172.69 (CO). Found, %: C 60.08; H 6.59; Cl 11.33; N 4.92. $C_{15}H_{20}ClNO_3$. Calculated, %: C 60.50; H 6.77; Cl 11.97; N 4.70.

Dechlorination of dichloroepoxylactone (7). To a solution of 0.24 g (1.15 mmol) of compound **7** in 8 mL of anhydrous MeOH in argon atmosphere at stirring was added 0.02 g (0.34 mmol) of NH_4Cl and 0.52 g (8.0 mmol) of Zn-Cu couple. The reaction mixture was stirred for 2 h at boiling (TLC monitoring), the precipitate was filtered off, the mother liquor was concentrated, and the residue was chromatographed on a column packed with SiO_2 (eluent petroleum ether–ethyl acetate, 8 : 2). Yield 0.096 g (60%) dechlorinated lactone **14**.

(1a*S*,2a*R*,5a*R*,5b*R*)-5,5-Dichlorohexahydro-4*H*-oxireno[3,4]cyclopenta[1,2-*b*]furan-4-one (*ent*-7). $[\alpha]_D^{20}$ +90.7° (*c* 1.0, CH_2Cl_2).

(1a*S*,2a*R*,5a*R*,5b*R*)-Hexahydro-4*H*-oxireno[3,4]-cyclopenta[1,2-*b*]furan-4-one (*ent*-14). $[\alpha]_D^{20}$ +107.6° (*c* 1.0, CH_2Cl_2).

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