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Synthesis of Enantiomeric (+)- and (–)-6-(1-Methylethylidene)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-1-ones

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Abstract—Baeyer–Villiger oxidation of racemic [2+2]-cycloadduct derived from dichloroketene and dimethylfulvene gave 3,3-dichloro-6-(1-methylidene)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one, and opening of the lactone ring in the latter with (+)-α-methylbenzylamine produced diastereoisomeric amides which can be readily separated by chromatography on silica gel. The subsequent lactonization and reductive dechlorination afforded enantiomeric (–)- and (+)-6-(propan-2-ylidene)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]-furan-1-ones.

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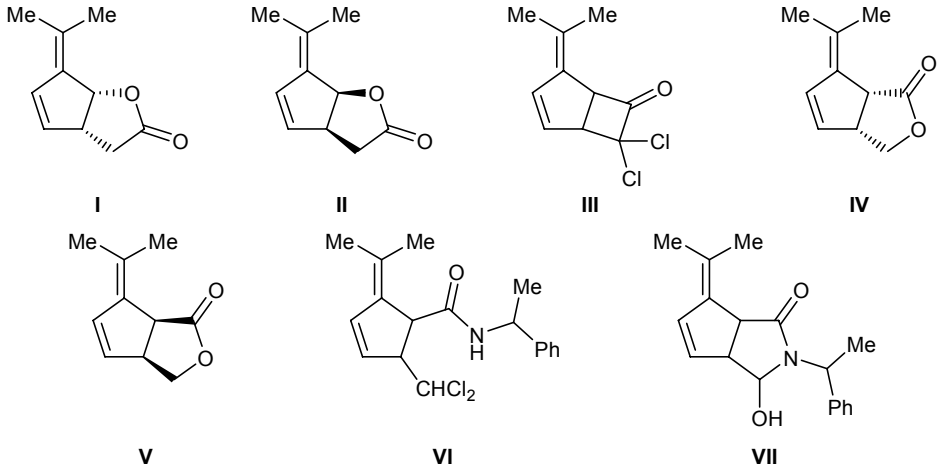
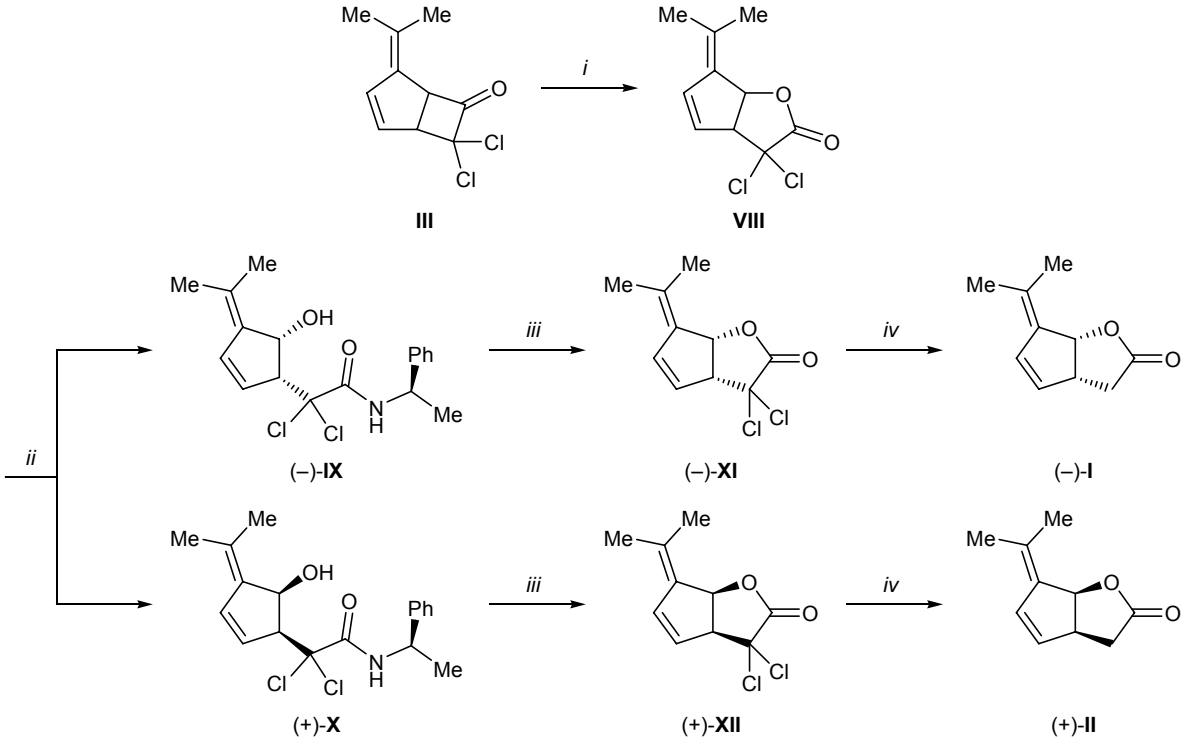
Chiral polyfunctionalized cyclopentan(en)one building blocks are widely used in the synthesis of natural cyclopentanoids and related compounds [1–3]. In the present article we describe the synthesis of enantiomeric orthogonally functionalized cyclopentene γ-lactones **I** and **II** from readily accessible [2+2]-cycloadduct **III** of 6,6-dimethylfulvene and dichloroketene [4]. We previously reported on the synthesis of building blocks **IV** and **V** that are isomeric to **I** and **II** from the same starting compound **III** through diastereoisomeric amides **VI** [5].

In both cases, enantiomeric lactone pairs were obtained with the use of (+)-α-methylbenzylamine as a source of chirality. The key steps leading to lactones **IV** and **V** were facile opening of the dichlorocyclobutane ring in **III** by the action of chiral (+)-α-methylbenzylamine and subsequent transformation of amide **VI** into readily separable (by silica gel column chromatography) diastereomeric cyclic aminals **VII**. The successful synthesis of lactones **I** and **II** was favored by smooth opening of the activated lactone ring in **VIII** with the same chiral amine. Compound **VIII** was



I **II** **III** **IV** **V** **VI** **VII**

Scheme 1.



i: 30% H_2O_2, 10% NaOH, Et_2O; *ii*: (+)-α-Ph(Me)CHNH$_2$, pyridin-2-ol, $CHCl_3$, Δ, 1.5 h; *iii*: 0.5 N H_2SO_4; *iv*: Zn-Cu, NH_4Cl, MeOH, Δ, 2 h.

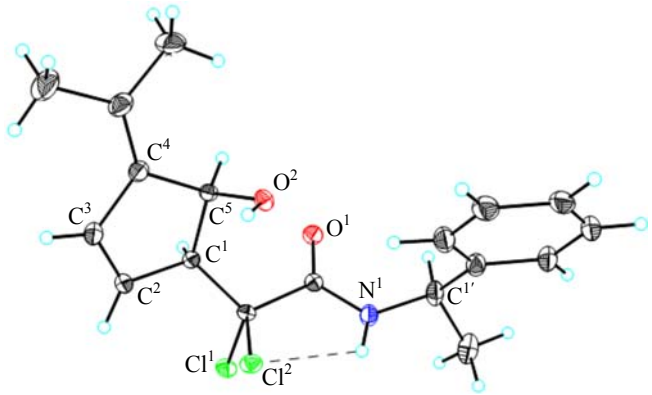
prepared in turn by oxidative ring expansion in racemic adduct **III** according to Baeyer–Villiger. Unlike amides **VI**, we succeeded in isolating pure diastereoisomeric amides **IX** and **X** by silica gel column chromatography.

Lactone **VIII** readily reacted with (+)-α-methylbenzylamine in boiling chloroform in the presence of pyridin-2-ol [6] to produce a mixture of diastereoisomeric amides (–)-**IX** and (+)-**X** at a ratio of 1 : 1 (according to the ^{1}H NMR data). The subsequent acid-catalyzed lactonization of (–)-**IX** and (+)-**X** and reductive dechlorination smoothly afforded enantiomeric lactones (–)-**I** and (+)-**II** (Scheme 1).

The structure of the isolated compounds was proved by spectral methods. In the ^{1}H NMR spectra of (–)-**I** and (+)-**II** the vicinal coupling constant for the 3a-H and 6a-H protons in the bridgehead positions [^3J = 6.8 Hz for (–)-**IX** and ^3J = 6.7 Hz for (+)-**X**] confirmed *cis* junction of the five-membered rings.

Despite almost identical synthesis and isolation conditions, the absolute optical rotation values of (–)-lactones **XI** and **I** were somewhat lower than the corresponding values of enantiomeric dextrorotatory lactones, which is difficult to interpret.

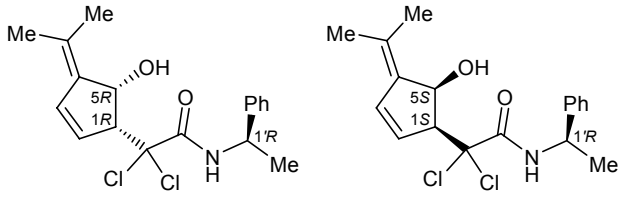
The configuration of amides (–)-**IX** and (+)-**X** and lactones (–)-**I** and (+)-**II** was unambiguously determined by X-ray analysis of a single crystal of (+)-**X** [stereoisomeric amide (–)-**IX** was isolated as an oily material]. Crystals of (+)-**X** suitable for X-ray analysis were obtained by slow crystallization from petroleum ether–chloroform (5 : 1). According to the X-ray diffraction data (see figure), the five-membered ring in molecule (+)-**X** has a flattened *envelope* conformation



Structure of the molecule of 2,2-dichloro-2-[(1*S*,5*S*)-5-hydroxy-4-(propan-2-ylidene)cyclopent-2-en-1-yl]-*N*-[(1*R*)-1-phenylethyl]acetamide (+)-(**X**) according to the X-ray diffraction data.

with the C^1 atom deviating by 0.288 Å from the plane formed by the other ring atoms. Both substituents on the five-membered ring (OH and CCl_2R) are oriented toward one side, the torsion angle $O^2C^5C^1CCl^2$ being –21.23(13)°. The presence of chlorine atoms in molecule (+)-**X** allowed us to determine its absolute configuration. Hydrogen atoms of both NH and OH groups are involved in intra- and intermolecular hydrogen bonds. The NH groups form weak intramolecular hydrogen bond $N^1–H^1\cdots Cl^2$ [N···Cl 2.9342(11), H···Cl 2.38 Å, ∠NHCl 120°], whereas relatively strong intermolecular hydrogen bonds $O^2–H^2\cdots O^1$ [O···O 2.8297(12), H···O 1.98 Å, ∠OHO 173°] give rise to chains of molecules along the *a* crystallographic axis. The chains are additionally stabilized via shortened intermolecular contacts $Cl^1\cdots Cl^2$ with a distance of 3.5629(4) Å.

Taking into account the X-ray diffraction data and *R* configuration of initial α-methylbenzylamine, amide (+)-**X** was assigned (1*S*,5*S*,1′*R*)-configuration of the chiral centers. Correspondingly, diastereoisomeric amide (–)-**IX** has (1*R*,5*R*,1′*R*) configuration.



(–)-**IX** (+)-**X**

Chiral building blocks **I** and **II**, as well as isomeric compounds **IV** and **V** described previously [5], are characterized by specific functionalization pattern and synthetic potential, and they can find versatile applications in target-oriented organic syntheses.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu IR Prestige-21 spectrometer from samples prepared as thin films or dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer at 300.13 and 75.47 MHz, respectively, using $CDCl_3$ as solvent and reference ($CHCl_3$, δ 7.27 ppm; $CDCl_3$, δ_C 77.00 ppm). The optical rotations were measured on a Perkin Elmer 241 MC polarimeter. The mass spectra (electron impact, 70 eV) were obtained on a ThermoFinnigan MAT 95XP instrument (ion source temperature 200°C). HPLC analyses were carried out using a Shimadzu instrument equipped with a 25-m glass column packed with OV-101. The progress of reactions was monitored by TLC on Sorbfil plates; spots were visualized by treatment with a 10% solution of 4-methoxybenzaldehyde in ethanol acidified wit sulfuric acid [6].

3,3-Dichloro-6-(propan-2-ylidene)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (VIII). A solution of 0.11 g (2.70 mmol) of sodium hydroxide in 1 mL of water was added under stirring to a solution of 0.49 g (2.25 mmol) of compound **III** in 10 mL of diethyl ether, the mixture was cooled to 0°C, and 0.83 mL (7.90 mmol) of 30% hydrogen peroxide was added dropwise. The mixture was stirred for 1.5 h at 0°C (TLC), and the product was extracted into diethyl ether (3×40 mL). The extracts were combined, washed with a 10% solution of Na_2SO_3 and saturated solutions of ammonium chloride and sodium chloride, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (95:5) as eluent. Yield 0.53 g (90%), R_f 0.76 (petroleum ether–ethyl acetate, 7:3). IR spectrum, ν, cm^{-1}: 1789 (C=O). ^1H NMR spectrum, δ, ppm: 1.83 s and 1.93 s (3H each, Me), 4.14 m (1H, 3a-H), 5.65 d (1H, 6a-H, $^3J_{6a,3a}$ = 5.5 Hz), 5.88 d (1H, 5-H, $^3J_{5,4}$ = 5.6 Hz), 6.52 d (1H, 4-H, $^3J_{4,5}$ = 5.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.34 and 21.43 (Me), 61.42 (C^{3a}), 79.75 (C^3), 79.89 (C^{6a}), 127.64 (C^5), 133.73 (C^4), 134.79 ($C^{1'}$), 136.33 (C^6), 167.87 (C^2). Found, %: C 51.29; H 4.19; Cl 30.14. $C_{10}H_{10}Cl_2O_2$. Calculated, %: C 51.53; H 4.32; Cl 30.42.

Reaction of compound VIII with (+)-α-methylbenzylamine. Compound **VIII**, 0.5 g (2.2 mmol), was dissolved in 10 mL of anhydrous chloroform, 0.001 g (0.011 mmol) of pyridin-2-ol and 0.55 mL (4.3 mmol) of (+)-α-methylbenzylamine were added in succession under stirring at 20°C in an argon atmosphere, and the mixture was heated for 1.5 h under reflux with stirring until the reaction was complete (TLC, petroleum ether–ethyl acetate, 9:1; triple elution). The mixture was concentrated under reduced pressure, and the residue was subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (20:1) as eluent to isolate 0.26 g (30%) of compound **IX** and 0.26 g (30%) of stereoisomer **X**.

2,2-Dichloro-2-[(1*R*,5*R*)-5-hydroxy-4-(propan-2-ylidene)cyclopent-2-en-1-yl]-*N*-[(1*R*)-1-phenylethyl]acetamide (IX). Yellow oily substance, R_f 0.25 (petroleum ether–ethyl acetate, 9:1, triple elution), $[\alpha]_D^{20}$ = –54.5° (*c* = 1.0, $CHCl_3$). ^1H NMR spectrum, δ,

ppm: 1.56 d (3H, 1″-Me, ^3J = 6.6 Hz), 1.67 d (1H, OH, ^3J = 7.0 Hz), 1.81 s and 1.85 s (3H each, Me), 4.04 d.d (1H, 1-H, $^3J_{1,2}$ = 3.0, $^3J_{1,5}$ = 6.0 Hz), 4.96 d.d (1H, 5-H, $^3J_{5,1}$ = 6.0, $^3J_{5,OH}$ = 7.0 Hz), 5.08 d.q (1H, 1″-H, $^3J_{1'',Me}$ = 6.6, $^3J_{1'',NH}$ = 7.0 Hz), 6.07 d (1H, 3-H, $^3J_{3,2}$ = 5.9 Hz), 6.54 d.d (1H, 2-H, $^3J_{2,1}$ = 3.0, $^3J_{2,3}$ = 5.9 Hz), 7.03 d (1H, NH, $^3J_{NH,1''}$ = 7.0 Hz), 7.27–7.37 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 21.00 (Me), 21.30 (1″-Me), 50.04 ($C^{1''}$), 61.00 (C^1), 76.65 (C^5), 86.65 ($C^{1'}$), 126.03 (C^m), 127.59 (C^p), 128.80 (C^o), 130.18 (**C**Me$_2$), 130.26 (C^3), 131.89 (C^2), 140.51 (C^4), 142.19 (C^i), 165.80 ($C^{2'}$). Found, %: C 61.12; H 5.99; Cl 20.11; N 3.99. $C_{18}H_{21}Cl_2NO_2$. Calculated, %: C 61.02; H 5.97; Cl 20.01; N 3.95.

2,2-Dichloro-2-[(1*S*,5*S*)-5-hydroxy-4-(propan-2-ylidene)cyclopent-2-en-1-yl]-*N*-[(1*R*)-1-phenylethyl]acetamide (X). Colorless crystals, mp 104°C, R_f 0.30 (petroleum ether–ethyl acetate, 8:2), $[\alpha]_D^{20}$ = +232° (*c* = 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3458 (OH), 3415 (NH), 1693 (C=O), 1552 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.56 d (3H, 1″-Me, ^3J = 6.6 Hz), 1.70 d (1H, OH, ^3J = 8.5 Hz), 1.81 s and 1.82 s (3H each, Me), 4.03 d.d (1H, 1-H, $^3J_{1,2}$ = 2.5, $^3J_{1,5}$ = 6.0 Hz), 4.92 d.d (1H, 5-H, $^3J_{5,1}$ = 6.0, $^3J_{OH,5}$ = 8.5 Hz), 5.13 d.q (1H, 1″-H, $^3J_{1'',Me}$ = 6.6, $^3J_{1'',NH}$ = 7.0 Hz), 6.08 d (1H, 3-H, $^3J_{3,2}$ = 5.9 Hz), 6.54 d.d (1H, 2-H, $^3J_{2,1}$ = 2.5, $^3J_{2,3}$ = 5.9, Hz), 7.06 d (1H, NH, $^3J_{NH,1''}$ = 7.0 Hz), 7.27–7.37 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 20.27 (1″-Me), 20.70 and 21.27 (Me), 49.96 ($C^{1''}$), 67.00 (C^1), 71.57 (C^5), 86.03 ($C^{1'}$), 126.03 (C^m), 126.28 (C^3), 127.59 (C^p), 128.72 (C^2), 128.77 (C^o), 130.08 (**C**Me$_2$), 140.39 (C^4), 142.10 (C^i), 167.35 ($C^{2'}$). Found, %: C 61.13, H 5.91; Cl 20.00; N 3.91. $C_{18}H_{21}Cl_2NO_2$. Calculated, %: C 61.02; H 5.97; Cl 20.01; N 3.95.

X-Ray diffraction data for compound (+)-X. Colorless crystals. $C_{18}H_{21}Cl_2NO_2$. *M* 354.26. Orthorhombic crystal system, space group $P2_12_12_1$; unit cell parameters (100 K): *a* = 5.6722(3), *b* = 15.0425(8), *c* = 20.5905(11) Å; *V* = 1756.9(2) Å^3; *Z* = 4; d_{calc} = 1.339 g/cm^3; μ = 0.378 mm^{-1}. Total of 21563 reflection intensities were measured on a Bruker Smart Apex II CCD diffractometer. The structure was solved by the direct method and was refined by the full-matrix least-squares procedure in anisotropic approximation from 6120 independent reflections (R_{int} = 0.0320). The final divergence factors were wR_2 = 0.0707 (against F_{hkl}^2 for all independent reflections) and R_1 = 0.0296 [against F_{hkl} for 5732 reflections with $I > 2\sigma(I)$]; goodness of fit 1.032. The crystallographic data for compound (+)-**X** were deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 893073) and are available at *www.ccdc.cam.ac.uk/data_request/cif*.

(3a*S*,6a*S*)-3,3-Dichloro-6-(propan-2-ylidene)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (XI). Amide **IX**, 0.26 g (0.77 mmol), was dissolved in 5 mL of dioxane, 7.8 mL of 0.5 N H_2SO_4 was added dropwise under stirring, and the mixture was heated for 1 h under reflux with stirring. When the reaction was complete, the mixture was diluted with chloroform, washed with a saturated solution of sodium hydrogen carbonate to pH 5, and the product was extracted into $CHCl_3$ (3×50 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated, and the residue was subjected to silica gel column chromatography using petroleum ether–ethyl acetate (20:1) as eluent. Yield 0.15 g (87%), colorless crystals, mp 68°C, R_f 0.66 (petroleum ether–ethyl acetate, 7:3), $[\alpha]_D^{20}$ = –55° (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.85 s and 1.95 s (3H each, Me), 4.11 br.s (1H, 3a-H), 5.61 d (1H, 6a-H, $^3J_{3a,6a}$ = 5.2 Hz), 5.86 d (1H, 5-H, $^3J_{5,4}$ = 5.8 Hz), 6.53 d (1H, 4-H, $^3J_{4,5}$ = 5.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.36 and 21.44 (Me), 61.48 (C^{3a}), 79.73 (C^3), 79.86 (C^{6a}), 127.68 (C^5), 133.74 (C^4), 134.78 ($C^{1'}$), 136.35 (C^6), 167.83 (C^1). Found, %: C 51.59; H 4.33; Cl 30.29. $C_{10}H_{10}Cl_2O_2$. Calculated, %: C 51.53; H 4.32; Cl 30.42.

(3a*R*,6a*R*)-3,3-Dichloro-6-(propan-2-ylidene)-3,3a,6,6a-tetraydro-2*H*-cyclopenta[*b*]furan-2-one (XII) was synthesized in a similar way from 0.26 g (0.77 mmol) of amide **X**. Yield 0.15 g (87%), colorless crystals, mp 76°C, R_f 0.66 (petroleum ether–ethyl acetate, 7:3), $[\alpha]_D^{20}$ = +173° (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.85 s and 1.95 s (3H each, Me), 4.11 br.s (1H, 3a-H), 5.61 d (1H, 6a-H, $^3J_{6a,3a}$ = 5.2 Hz), 5.86 d (1H, 5-H, $^3J_{5,4}$ = 5.8 Hz), 6.53 d (1H, 4-H, $^3J_{4,3}$ = 5.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.36 and 21.44 (Me), 61.48 (C^{3a}), 79.73 (C^3), 79.86 (C^{6a}), 127.68 (C^5), 133.74 (C^4), 134.78 ($C^{1'}$), 136.35 (C^6), 167.83 (C^1). Found, %: C 51.61; H 4.36; Cl 30.45. $C_{10}H_{10}Cl_2O_2$. Calculated, %: C 51.53; H 4.32; Cl 30.42.

(3a*S*,6a*S*)-6-(Propan-2-ylidene)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (I). Ammonium chloride, 0.01 g (0.19 mmol), and zinc–copper couple, 0.25 g (4 mmol), were added under stirring in an argon atmosphere to a solution of 0.15 g (0.64 mmol) of compound **XI** in 15 mL of anhydrous methanol. The mixture was stirred for 2 h on heating under reflux (TLC), the precipitate was filtered off, the filtrate was concentrated, the residue was dissolved in 20 mL of

methylene chloride, the solution was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by flash chromatography using petroleum ether–ethyl acetate (20:1) as eluent. Yield 0.1 g (91%), white crystals, mp 80°C, R_f 0.25 (petroleum ether–ethyl acetate, 7:3; double elution), $[\alpha]_D^{20}$ = –180° (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.87 s and 1.94 s (3H each, Me), 2.49 d.d (1H, 3-H$_A$, $^4J_{3A,4}$ = 2.2, ^2J = 18.2 Hz), 2.84 d.d (1H, 3-H$_B$, $^3J_{3B,3a}$ = 10.5, ^2J = 18.2 Hz), 3.62 m (1H, 3a-H), 5.54 d (1H, 6a-H, $^3J_{6a,3a}$ = 6.5 Hz), 5.80 d (1H, 5-H, $^3J_{5,4}$ = 4.9 Hz), 6.44 d.d (1H, 4-H, $^4J_{4,3A}$ = 2.2, $^3J_{5,4}$ = 4.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.23 and 21.44 (Me), 33.36 (C^3), 43.72 (C^{3a}), 82.21 (C^{6a}), 131.20 (C^5), 133.37 (C^4), 132.53 ($C^{1'}$), 136.85 (C^6), 177.13 (C^1). Found, %: C 73.19; H 7.35. $C_{10}H_{12}O_2$. Calculated, %: C 73.15; N 7.37.

(3a*R*,6a*R*)-6-(Propan-2-ylidene)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (II) was synthesized in a similar way from 0.15 g (0.64 mmol) of compound **XII**. Yield 0.1 g (91%), white crystals, mp 85°C, R_f 0.25 (petroleum ether–ethyl acetate, 7:3; double elution), $[\alpha]_D^{20}$ = +295° (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.85 s and 1.91 s (3H each, Me), 2.45 d.d (1H, 3-H$_A$, $^4J_{3A,4}$ = 2.5, ^2J = 18.3 Hz), 2.82 d.d (1H, 3-H$_B$, $^3J_{3B,3a}$ = 10.5, ^2J = 18.3 Hz), 3.59 m (1H, 3a-H), 5.51 d (1H, 6a-H, $^3J_{6a,3a}$ = 6.5 Hz), 5.77 d (1H, 5-H, $^3J_{5,4}$ = 4.9 Hz), 6.40 d.d (1H, 4-H, $^4J_{4,3A}$ = 2.5, $^3J_{4,5}$ = 4.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.23 and 21.44 (Me), 33.36 (C^3), 43.71 (C^{3a}), 82.21 (C^{6a}), 131.21 (C^5), 132.54 ($C^{1'}$), 133.36 (C^4), 136.84 (C^6), 177.14 (C^1). Found, %: C 73.21; H 7.30. $C_{10}H_{12}O_2$. Calculated, %: C 73.15; N 7.37.

REFERENCES

1. Johnson, C.R. and Chen, Y.F., *J. Org. Chem*., 1991, vol. 56, p. 3344.
2. Ferrier, R.Y., *Chem. Rev*., 1993, vol. 93, p. 2779.
3. Moon, H.R., Choi, W.J., and Kim, H.O., *Tetrahedron: Asymmetry*, 2002, vol. 13, p. 1189.
4. Greene, A.E. and Depres, J.-P., *J. Am. Chem. Soc*., 1979, vol. 101, p. 4003.
5. Valiullina, Z.R., Akhmetdinova, N.P., Ivanova, N.A., Shitikova, O.V., and Miftakhov, M.S., *Russ. J. Org. Chem*., 2011, vol. 47, p. 180.
6. Edwards, M.P., Ley, S.V., Lister, S.G., Palmer, B.D., and Williams, D.J., *J. Org. Chem*., 1984, vol. 49, p. 3503.
7. Kirchner, J.G., *Thin-Layer Chromatography*, Perry, E.S., Ed., New York: Wiley, 1978, 2nd ed. Translated under the title *Tonkosloinaya khromatografiya*, Moscow: Mir, 1981, vol. 1, p. 228.