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Cyclization of Nitrospirobenzopyrans to Bridged Benzoxazepino[3,2-*a*]indoles

Neringa Kleizienė[1], **Virginė Amankavičienė**[1], **Ulf Berg**[2], **Carsten Schicktanz**[3], **Klaus Schlothauer**[3], and **Algirdas Šačkus**[1,*]

[1] Department of Organic Chemistry, Kaunas University of Technology, Kaunas, Lithuania
[2] Organic Chemistry 1, Department of Chemistry, Lund University, Lund, Sweden
[3] Faculty of Informatics and Nature Sciences, University of Applied Nature Sciences, Merseburg, Germany

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Summary. Condensation of 1-substituted 1,2,3,9a-tetrahydro-9*H*-imidazo[1,2-*a*]indol-2-ones with 5-nitrosalicylaldehyde afforded 1′-[(N-monosubstituted carbamoyl)methyl]indoline nitrospirobenzopyrans. Treatment of the latter with strong base led to the formation of a mixture of *cis*/*trans*-5a,13-methano-1,3-benzoxazepino[3,2-*a*]indoles. Results of semiempirical calculations gave evidence that such a transformation of nitrospirobenzopyrans to bicyclic indole derivatives could proceed *via* a single transition state, where the negatively charged carbon atom attacks the vinylic double bond of the spiropyran system.

Keywords. Heterocycles; Indoles; Nitrospiropyrans; Carbanions; 5a,13-Methano-1,3-benzoxazepino[3,2-*a*]indoles.

Introduction

Indoline spirobenzopyrans constitute a very interesting class of cyanine dyes due to their photochromic behaviour [1]. The performance of such systems is based on a reversible heterolytic cleavage of a carbon-oxygen bond of the spiro form, to generate a colored ring-open merocyanine form. The interconversion of these forms is strongly influenced by the substituents attached to both sides of the spiro molecule. The presence of such a strong electron-withdrawing group as the nitro one at the benzopyran moiety stabilizes the merocyanine form [2]. In the last decade, a considerable number of structurally modified spirobenzopyrans have been prepared and examined for use in various practical applications [3].

The most common route for the synthesis of spiropyrans is based on condensation of 1-substituted 2,3,3-trimethyl-3*H*-indolium salts or the corresponding

* Corresponding author. E-mail: algirdas.sackus@ktu.lt

methylene bases with *ortho*-hydroxy-substituted aromatic aldehydes [1]. This synthesis protocol was applied to prepare various functionalized spirobenzopyrans, which were often employed for further chemical transformations. For example, indoline iodospirobenzopyrans obtained by condensation of *Fisher's* base with iodosalicylaldehydes were used in *Suzuki* palladium catalysed cross-coupling reactions [4], while 1′-(2-carboxyethyl)indoline spirobenzopyrans underwent esterification [5] and coupling with amines [6].

Recently, we have demonstrated that indoline spirobenzopyrans and spironaphthopyrans bearing an (*N*-monosubstituted carbamoyl)methyl moiety at the indoline ring nitrogen atom underwent cyclization to the bridged 1,3-benzoxazepino[3,2-*a*]indole derivatives on treatment with base [7]. The latter found application in the preparation of imprinted polymer stationary phases [8].

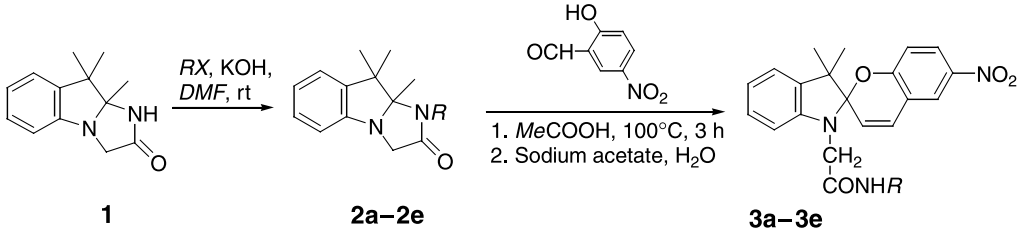
In continuation of our investigations on chemical behaviours of functionalized spirobenzopyrans, we wish to report here the synthesis of 1′-[(*N*-monosubstituted carbamoyl)methyl]indoline 6-nitrospirobenzopyrans and their base induced rearrangement to bicyclic indole derivatives. The nitrospirobenzopyrans of the relevant structure are known as fatigue resistant photochromes [9].

Results and Discussion

The starting 9,9,9a-trimethyl-1,2,3,9a-tetrahydro-9*H*-imidazo[1,2-*a*]indol-2-one (**1**) was prepared by the reaction of 2,3,3-trimethyl-3*H*-indole with α-chloroacetamide [10]. Alkylation of **1** with haloalkanes afforded 1-substituted imidazo[1,2-*a*]indol-2-ones **2a**–**2e** [11]. The structure of the new compounds **2b** and **2d** was confirmed by spectral investigations.

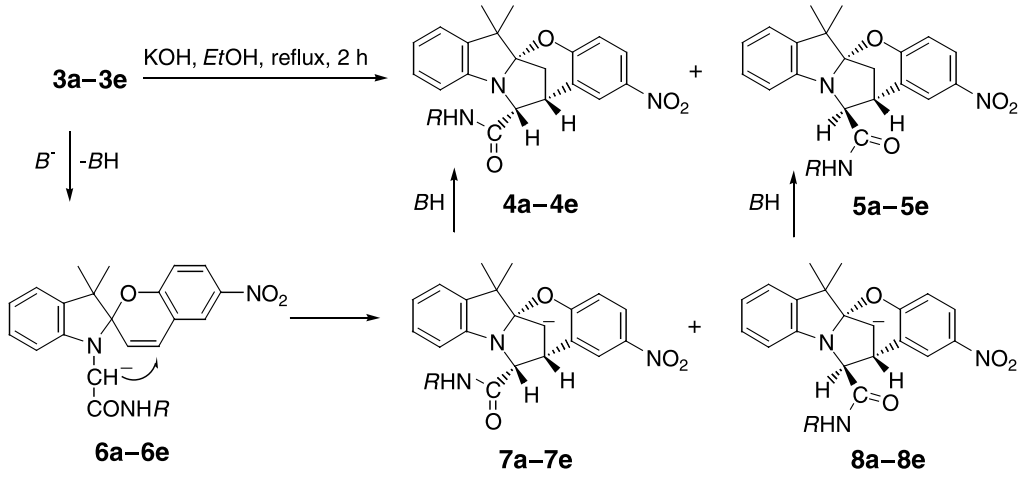
Condensation of 1-substituted imidazo[1,2-*a*]indol-2-ones **2a**–**2e** with 5-nitrosalicylaldehyde was carried out in acetic acid. Work-up of the reaction mixture with sodium acetate gave 6-nitrospirobenzopyrans **3a**–**3e**. The ^{1}H NMR spectra of **3a**–**3e** contained a characteristic doublet of the methine proton in the area of 5.54–6.03 ppm with vicinal $^3J_{3,4} = 10.2$–10.5 Hz, which evidences a *cis*-allocation of vinylic protons in the spiropyran system [12].

When **3a**–**3e** were treated with sodium hydroxide in boiling ethanol, formation of a mixture of the diastereomeric *cis*/*trans*-5a,13-methano-1,3-benzoxazepino[3,2-*a*]indoles **4a**–**4e** and **5a**–**5e** took place, from which the target products were isolated in moderate yields of 40–48 and 13–26%. Assignment



2, **3a** *R* = ethyl, **b** *R* = isobutyl, **c** *R* = benzyl, **d** *R* = *o*-chlorobenzyl, **e** *R* = 1-naphthyl

Scheme 1



4–8a R = ethyl, **b** R = isobutyl, **c** R = benzyl, **d** R = *o*-chlorobenzyl, **e** R = 1-naphthyl

Scheme 2

of *cis*/*trans* configuration to **4a**–**4e** and **5a**–**5e** was based on comparisons with the ^{1}H NMR spectra of the relevant structure compounds [7] and results of MM3* calculations. For example, experimental value of a vicinal coupling constant between protons 12-H and 13-H ($^3J_{12,13}$) is 4.9 Hz for *cis*-**4c** and 0 Hz for *trans*-**5c**. Monte Carlo conformational searches using the MM3* force field of the optimized structures followed by energy minimizations gave for the dihedral angle H–$C_{(12)}$–$C_{(13)}$–H of the optimized structures of *cis*-**4c** and *trans*-**5c** 39.56 and 87.06°. In such case, $^3J_{12,13}$ calculated by the *Karplus* equation [13] is 7.18 Hz for *cis*-**4c** and 1.98 Hz for *trans*-**5c**, and agrees satisfactorily with the experimental values.

In our previous work [7b] it was assumed that the mechanism of transformation of 1′-[(*N*-monosubstituted carbamoyl)methyl]indoline spiropyrans includes ring opening of the spiropyran system and generation of an intermediate azomethine ylide. Results of recent semiempirical calculations gave evidence that transformation of the nitrospiropyran **3c** to the diastereomers **4c** and **5c** could proceed *via* one transition state, where the negatively charged carbon atom attacks the double vinylic bond of the spiropyran system. Therefore, the mechanism depicted in Scheme 2 of the cyclization reaction includes presence of intermediate carbanions **6a**–**6e** that undergo further transformation to **7a**–**7e** and **8a**–**8e**. Protonation of the latter affords the final products **4a**–**4e** and **5a**–**5e**.

The proton transfer to a hydroxide ion is calculated to be an equi-energetic process with negligible activation energy in the gas phase and the ring closure was calculated to proceed with a higher activation barrier for **4c** than for **5c** by 13.8 kJ mol^{-1}. The calculated heat of formation is also higher for **7c** than for **8c** by 11.7 kJ mol^{-1}. The transition structures are shown in Fig. 1. The $C_{(19)}$–$C_{(12)}$ distances of the bond to be formed are 2.043 Å for both transition structures and the $N_{(1)}$–$C_{(10)}$ and the $C_{(10)}$–$O_{(1)}$ bonds are considerably lengthened to 1.55 and

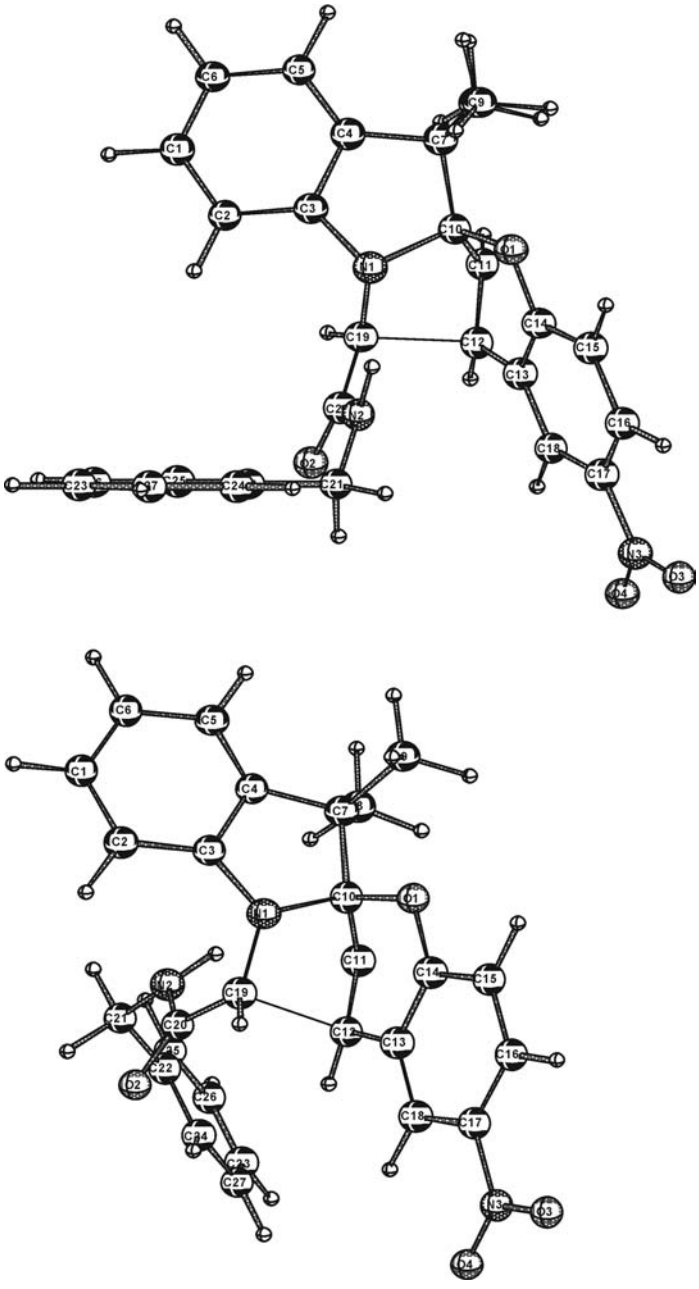


Fig. 1. Transition structures of the ring closure step of **4c** (above) and **5c** (below) using the AM1 *Hamiltonian* for the gas phase reaction

1.47 Å. Attempts to localize transition states for the initial $C_{(10)}$–$O_{(1)}$ bond cleavage were unsuccessful.

Experimental

Melting points were determined on a *Kleinfeld* melting point apparatus. IR spectra were obtained on a Perkin Elmer Spectrum BXII spectrophotometer in KBr pellets. ^{1}H NMR spectra were recorded at

300 MHz and ^{13}C NMR spectra were recorded at 75 MHz on a Varian Gemini 2000 instrument. TMS was used as the internal standard. For TLC analyses, Merck precoated TLC plates (silica gel 60 F_{254}) were used. Separations by flash chromatography were performed on silica gel Merck, 9385, 230–400 mesh. Microanalyses were performed by the Institute of Organic Chemistry, Martin Luther University, Halle-Wittenberg, Germany, and the Laboratory of Microanalyses, Department of Organic Chemistry, Kaunas University of Technology, Lithuania. These results agreed favourably with the calculated values.

Semiempirical calculations were carried out using the AM1 *Hamiltonian* in the AMPAC v.7.0 program [14]. Transition states were localized by the CHAIN algorithm for the parent molecule stripped from substituents in the gas phase. After addition of the proper substituents new transition states were localized and characterized. The molecular mechanics calculations were performed using the MM3* force fields of the Macromodel program version 6.5, using default parameters [15]. The calculations were carried out on a Silicon Graphics O2 workstation. The *Polak-Ribiere* conjugate gradient algorithm was applied in all minimizations with 300 iterations limit and a cut-off of 12 Å was used for the non-bonded interactions and energy convergence criterion of 0.05 kJ/mol.

1-Isobutyl-1,2,3,9a-tetrahydro-9,9,9a-trimethyl-9H-imidazo[1,2-a]indol-2-one (**2b**, $C_{17}H_{24}N_2O$)
1,2,3,9a-Tetrahydro-9,9,9a-trimethyl-9*H*-imidazo[1,2-*a*]indol-2-one (**1**, 1.50 g, 6.9 mmol) was dissolved in 8 cm^3 *DMF*, and 0.79 g finely powdered KOH (17.3 mmol) was added. Isobutyl bromide (1.89 g, 1.50 cm^3, 13.8 mmol) was added dropwise to the solution, and the mixture was stirred for 2 h at room temperature. Then the reaction mixture was poured into 100 cm^3 H_2O and extracted with ether (3×50 cm^3). The combined organic layers were washed with 20 cm^3 H_2O and dried ($CaCl_2$). Most of the solvent was distilled off and the residue kept at 4°C overnight. The precipitated colourless crystals were collected by filtration, washed with a small amount of ether, and recrystallized from ethanol to afford 1.13 g (60%) **2b**. Mp 93–95°C; ^1H NMR ($CDCl_3$): $\delta = 7.26$–6.75 (m, Ar-H), 3.90 (AB-q, $J = 15.0$ Hz, CH_2CO), 3.58 (dd, $J = 8.8 + 13.7$ Hz, ½ CH_2CH), 2.77 (dd, $J = 7.0 + 13.7$ Hz, ½ CH_2CH), 2.55–2.02 (m, CH_2CH), 1.47 (s, 9a-CH_3), 1.45 (s, 9-CH_3), 0.99 (d, $J = 6.7$ Hz, CH_3CH), 0.98 (s, 9-CH_3), 0.97 (d, $J = 6.6$, CH_3CH) ppm; IR: $\bar{\nu} = 1710$ (C=O) cm^{-1}.

1-(2-Chlorobenzyl)-1,2,3,9a-tetrahydro-9,9,9a-trimethyl-9H-imidazo[1,2-a]indol-2-one
(**2d**, $C_{20}H_{21}N_2OCl$)
Compound **2d** was obtained from 1.52 g **1** (7.0 mmol) and 2.23 g 2-chlorobenzyl chloride (1.43 cm^3, 13.9 mmol) as described above. Yield 1.68 g (70%); mp 112–113°C (from ethanol); ^1H NMR ($CDCl_3$): $\delta = 7.32$–6.79 (m, Ar-H), 4.63 (AB-q, $J = 16.5$ Hz, $CH_2C_6H_5$), 4.01 (AB-q, $J = 15.6$ Hz, CH_2CO), 1.39 (s, 9a-CH_3), 1.36 (s, 9-CH_3), 1.09 (s, 9-CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 172.52$ (C=O), 148.79 (C), 140.57 (C), 134.66 (C), 132.06 (C), 129.20 (CH), 128.61 (CH), 128.35 (CH), 128.20 (CH), 127.05 (CH), 122.50 (CH), 122.01 (CH), 113.91 (CH), 93.09 (C-9a), 54.57 (C-3), 49.27 (C-9), 42.51 (CH_2), 26.77 (9a-CH_3), 24.10 (9-CH_3), 22.15 (9-CH_3) ppm; IR: $\bar{\nu} = 1700$ (C=O) cm^{-1}.

1′-[(N-Ethylcarbamoyl)methyl]-1′,3′-dihydro-3′,3′-dimethyl-6-nitrospiro[1-benzopyran-2,2′-indole] (**3a**, $C_{22}H_{23}N_3O_4$)
A mixture of 1.27 g **2a** (5.0 mmol) and 0.92 g 2-hydroxy-5-nitrobenzaldehyde (5.5 mmol) in 10 cm^3 acetic acid was heated at 100°C for 3 h. Then the mixture was poured into 100 cm^3 5% sodium acetate solution and extracted with ether (2×15 cm^3). The combined organic layers were washed with 20 cm^3 H_2O, dried ($MgSO_4$), the solvent was evaporated *in vacuo*, and the residue crystallized from ethanol to afford 1.43 g (73%) of yellowish crystals. Mp 169–170°C (from ethanol); ^1H NMR ($CDCl_3$): $\delta =$ 8.09–6.46 (m, Ar-H, CH=C*H*, NH), 5.86 (d, $J = 10.2$ Hz, C*H*=CH), 3.80 (AB-q, $J = 17.8$ Hz, CH_2CO), 3.26–3.37 (m, CH_2CH_3), 1.36 (s, 3′-CH_3), 1.28 (s, 3′-CH_3), 1.10 (t, $J = 7.2$ Hz, CH_2CH_3) ppm; IR: $\bar{\nu} = 3395$ (N–H), 1660 (C=O), 1520 (amide II), 1480, 1345 (NO_2) cm^{-1}.

1′,3′-Dihydro-1′-[(N-isobutylcarbamoyl)methyl]-3′,3′-dimethyl-6-nitrospiro[1-benzopyran-2,2′-indole] (**3b**, $C_{24}H_{27}N_3O_4$)

Compound **3b** was synthesized from 1.36 g **2b** (5.0 mmol) and 0.92 g 2-hydroxy-5-nitrobenzaldehyde (5.5 mmol) by a similar method as described for **3a**. Yield 0.88 g (42%); mp 131–132°C (from ethanol); ^{1}H NMR ($CDCl_3$): $\delta = 8.04$–6.52 (m, Ar-H, CH=C*H*, NH), 5.83 (d, $J = 10.5$ Hz, 1H, C*H*=CH), 3.79 (AB-q, $J = 17.7$ Hz, CH_2CO), 3.01–3.16 (m, NHC*H*$_2$), 1.67–1.75 (m, CH_2CH), 1.33 (s, 3′-CH_3), 1.25 (s, 3′-CH_3), 0.83 (d, $J = 6.6$ Hz, 2×CHC*H*$_3$) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 169.64$ (C=O), 159.25, 146.44, 142.16, 136.53, 129.94, 128.75, 126.79, 123.56, 122.70, 121.97, 121.05, 118.89, 116.16, 108.45 (14 × $C_{(Ar,\ vinyl)}$), 106.74 (C-2′), 53.27 (1′-CH_2), 48.86 (C-3′), 47.16 (*C*H$_2$CH), 29.13 (CH_2*C*H), 26.72 (3′-CH_3), 20.72 (3′-CH_3), 20.61 (CH*C*H$_3$), 20.59 (CH*C*H$_3$) ppm; IR: $\bar{\nu} = 3380$ (N–H), 1660 (C=O), 1523 (amide II), 1475, 1338 (NO_2) cm^{-1}.

1′-[(N-Benzylcarbamoyl)methyl]-1′,3′-dihydro-3′,3′-dimethyl-6-nitrospiro[1-benzopyran-2,2′-indole] (**3c**, $C_{27}H_{25}N_3O_4$)

Compound **3c** was synthesized from 1.5 g **2c** (4.9 mmol) and 0.9 g 2-hydroxy-5-nitrobenzaldehyde (5.4 mmol) by a similar method as described for **3a**. Yield 0.87 g (39%); mp 124–125°C (from ethanol); ^{1}H NMR (*DMSO*-d_6): $\delta = 6.48$–8.22 (m, Ar-H, CH=C*H*, NH), 6.03 (d, $J = 10.2$ Hz, C*H*=CH), 4.22–4.92 (m, C*H*$_2$C$_6$H$_5$), 3.71 (AB-q, $J = 18.8$ Hz, CH_2CO), 1.27 (s, 3′-CH_3), 1.25 (s, 3′-CH_3) ppm; IR: $\bar{\nu} = 3378$ (N–H), 1655 (C=O), 1520 (amide II), 1460, 1340 (NO_2) cm^{-1}.

1′-[[N-(2-Chlorobenzylcarbamoyl]methyl]-1′,3′-dihydro-3′,3′-dimethyl-6-nitrospiro[1-benzopyran-2,2′-indole] (**3d**, $C_{27}H_{24}N_3O_4Cl$)

Compound **3d** was synthesized from 1.02 g **2d** (3.0 mmol) and 0.55 g 2-hydroxy-5-nitrobenzaldehyde (3.3 mmol) by a similar method as described for **3a**. Yield 0.71 g (48%); mp 89–91°C (from ethanol); ^{1}H NMR ($CDCl_3$): $\delta = 6.47$–8.00 (m, Ar-H, CH=C*H*, NH), 5.83 (d, $J = 10.2$ Hz, C*H*=CH), 4.53 (d, $J = 5.4$ Hz, 2H, C*H*$_2$C$_6$H$_4$Cl), 3.85 (AB-q, $J = 17.6$ Hz, CH_2CO), 1.34 (s, 3H, 3′-CH_3), 1.25 (s, 3H, 3′-CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.36$ (C=O), 158.64, 145.79, 141.54, 135.94, 130.38, 129.66, 129.32, 129.21, 129.45, 128.45, 128.17, 127.24, 126.19, 122.99, 122.15, 121.39, 120.59, 118.33, 115.56, 107.80 (20 × $C_{(Ar,\ vinyl)}$), 106.20 (C-2′), 52.80 (1′-CH_2), 48.28 (C-3′), 41.60 (NHCH_2), 26.10 (CH_3), 20.20 (CH_3) ppm; IR: $\bar{\nu} = 3365$ (N–H), 1670 (C=O), 1520 (amide II), 1480, 1350 (NO_2) cm^{-1}.

1′,3′-Dihydro-3′,3′-dimethyl-1′-[[N-(1-naphthylmethyl)carbamoyl]methyl]-6-nitrospiro[1-benzopyran-2,2′-indole] (**3e**, $C_{31}H_{27}N_3O_4$)

Compound **3e** was synthesized from 1.43 g **2e** (4.0 mmol) and 0.74 g 2-hydroxy-5-nitrobenzaldehyde (4.4 mmol) by a similar method as described for **3a**. Yield 1.22 g (60%); mp 99–100°C (from ethanol); ^{1}H NMR ($CDCl_3$): $\delta = 6.03$–7.89 (m, Ar-H, CH=C*H*, NH), 5.54 (d, $J = 10.3$ Hz, C*H*=CH), 4.36 (dd, $J = 5.7 + 14.4$ Hz, ½ NHC*H*$_2$), 4.79 (dd, $J = 5.1$, 14.4 Hz, ½ NHC*H*$_2$), 3.91 (AB-q, $J = 17.8$ Hz, CH_2CO), 1.18 (s, 3H, 3′-CH_3), 0.99 (s, 3H, 3′-CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 168.83$ (C=O), 157.96, 145.27, 141.12, 135.45, 133.73, 132.89, 131.04, 128.94, 128.63, 128.61, 127.95, 126.56, 126.42, 125.85, 125.78, 125.17, 123.62, 122.55, 121.91, 120.91, 120.25, 117.87, 114.84, 107.25 (24 × $C_{(Ar,\ vinyl)}$), 105.89 (C′-2), 52.71 (*C*H$_2$CO), 47.79 (C′-3), 41.62 (*C*H$_2$C$_{10}$H$_7$), 25.74 (CH_3), 19.82 (CH_3) ppm; IR: $\bar{\nu} = 3250$ (N–H), 1660 (C=O), 1520 (amide II), 1480, 1330 (NO_2) cm^{-1}.

(5aR,12S*,13S*)-12,13-Dihydro-5a,13-methano-6,6-dimethyl-2-nitro-6H-1,3-benzoxazepino[3,2-a]indole-12-(N-ethylcarboxamide)* (*cis*-**4a**, $C_{22}H_{23}N_3O_4$) *and (5aR*,12R*,13S*)-Isomer* (*trans*-**5a**, $C_{22}H_{23}N_3O_4$)

To a solution of 1.43 g **3a** (3.6 mmol) in 8 cm^3 ethanol 0.6 g fine powdered KOH (10.7 mmol) were added, the mixture was refluxed for 2 h and then most of the solvent was distilled off. The concentrated solution was poured into 20 cm^3 H_2O, the precipitated crystalline material was collected by filtration, and washed with 5 cm^3 H_2O. The obtained product mixture was recrystallized two times from ethanol

to afford 0.57 g (40%) *cis*-**4a**. The combined ethanol filtrate was concentrated *in vacuo* and the residue purified by column chromatography (silica gel, eluent: acetone/*n*-hexane = 1/3) to give 0.26 g (18%) *trans*-**5a**.

cis-**4a**: Mp 218–220°C; ^{1}H NMR (*DMSO*-d_6): $\delta = 6.43$–8.14 (m, Ar-H, NH), 3.91 (d, $J = 4.8$ Hz, 12-H), 3.85–3.88 (m, 13-H), 3.01–3.14 (m, ½ CH_3CH_2), 2.78–2.66 (m, ½ CH_3CH_2), 2.31 (dd, $J = 3.9 + 11.7$ Hz, 14-H), 2.17 (d, $J = 11.7$ Hz, 14-H), 1.52 (s, 6-CH_3), 1.49 (s, 6-CH_3), 0.47 (t, $J = 7.3$ Hz, CH_2CH_3) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 169.82$ (C=O), 159.92 (C), 149.76 (C), 141.23 (C), 139.63 (C), 129.23 (CH), 127.53, 125.84, 125.35 (2 × CH, C), 123.52 (CH), 122.43 (CH), 117.64 (CH), 111.88 (C-5a), 111.06 (CH), 77.36 (C-12), 45.60 (C-6), 42.63 (C-13), 33.80 (CH_3CH_2), 32.94 (C-14), 27.00 (6-CH_3), 24.35 (6-CH_3), 15.17 (CH_3CH_2) ppm; IR (KBr): $\bar{\nu} = 3370$ (N–H), 1670 (C=O), 1525 (amide II), 1480, 1345 (NO_2) cm^{-1}.

trans-**5a**: Mp 195–197°C (from ethanol); ^{1}H NMR ($CDCl_3$): $\delta = 6.32$–8.17 (m, 7H, Ar-H), 5.96 (s, br., NH), 4.35 (s, 12-H), 3.80 (d, $J = 3.8$ Hz, 13-H), 3.23–3.35 (m, 2H, CH_3CH_2), 2.69 (dd, $J = 3.8 + 11.7$ Hz, 14-H), 2.07 (d, $J = 11.7$ Hz, 14-H), 1.62 (s, 6-CH_3), 1.36 (s, 6-CH_3), 1.09 (t, $J = 7.3$ Hz, 3H, CH_3CH_2) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 168.75$ (C=O), 159.58 (C), 141.29 (C), 141.29 (C), 140.59 (C), 128.43 (C), 127.91 (CH), 124.93 (CH), 123.18 (CH), 122.75 (CH), 120.01 (CH), 117.39 (CH), 108.83 (C-5a), 107.30 (CH), 67.84 (C-12), 46.52 (C-6), 45.00 (C-13), 34.46 (CH_3CH_2), 28.20, 28.57 (6-CH_3, C-14), 20.80 (6-CH_3), 14.80 (CH_3CH_2) ppm; IR (KBr): $\bar{\nu} = 3380$ (N–H), 1680 (C=O), 1520 (amide II), 1490, 1345 (NO_2) cm^{-1}.

(5aR,12S*,13S*)-12,13-Dihydro-5a,13-methano-6,6-dimethyl-2-nitro-6H-1,3-benzoxazepino[3,2-a]indole-12-(N-isobutylcarboxamide)* (*cis*-**4b**, $C_{24}H_{27}N_3O_4$) *and (5aR*,12R*,13S*)-Isomer* (*trans*-**5b**, $C_{24}H_{27}N_3O_4$)

Compounds **4b** and **5b** were synthesized from 0.88 g **3b** (2.1 mmol) by a similar method as described for **4a** and **5a**.

cis-**4b**: Yield 0.33 g (38%); mp 187–188°C (from ethanol); ^{1}H NMR ($CDCl_3$): $\delta = 6.53$–8.11 (m, Ar-H, NH), 3.99 (d, $J = 4.8$ Hz, 12-H), 3.83–3.86 (m, 13-H), 2.97–3.08 (m, ½ $NHCH_2$), 2.61–2.72 (m, ½ $NHCH_2$), 2.15–2.26 (m, 14-H_2), 1.53 (s, 6-CH_3), 1.51 (s, 6-CH_3), 1.29 (m, $NHCH_2CH$), 0.59 (d, $J = 6.4$ Hz, 3H, CH_3CH), 0.53 (d, $J = 6.4$ Hz, 3H, CH_3CH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.30$ (C=O), 158.33 (C), 148.73 (C), 141.48 (C), 138.47 (C), 128.67 (CH), 125.91 (C), 125.26 (CH), 124.81 (CH), 122.79 (CH), 122.64 (CH), 116.43 (CH), 111.05 (C-5a), 110.56 (CH), 77.90 (C-12), 46.35 ($NHCH_2CH$), 45.25 (C-6), 42.07 (C-13), 32.98 (C-14), 28.54 ($NHCH_2CH$), 26.58 (6-CH_3), 23.23 (6-CH_3), 19.85 ($CHCH_3$) 19.85 ($CHCH_3$) ppm; IR: $\bar{\nu} = 3330$ (N–H), 1650 (C=O), 1520 (amide II), 1480, 1340 (NO_2) cm^{-1}.

trans-**5b**: Yield 0.12 g (13%); mp 200–201°C (from ethanol); ^{1}H NMR ($CDCl_3$): $\delta = 8.43$ (s, br., NH), 6.28–8.35 (m, Ar-H), 4.49 (s, 12-H), 3.80 (d, $J = 3.8$ Hz, 13-H), 2.96–3.04 (m, ½ $NHCH_2$), 2.85–2.93 (m, ½ $NHCH_2$), 2.77 (dd, $J = 3.8 + 11.3$ Hz, 14-H), 2.03 (d, $J = 11.3$ Hz, 14-H), 1.72 (m, CH_2CH), 1.58 (s, 6-CH_3), 1.36 (s, 6-CH_3), 0.91 (d, $J = 4.2$ Hz, CH_3CH), 0.89 (d, $J = 3.9$ Hz, CH_3CH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.58$ (C=O), 160.61 (C), 144.05 (C), 142.09 (C), 141.03 (C), 130.57 (CH), 128.43 (C), 125.78 (CH), 124.84 (CH), 123.27 (CH), 119.87 (CH), 118.33 (CH), 109.84 (C-5a), 108.38 (CH), 68.01 (C-12), 47.03 (C-6), 46.71, 45.72 (C-13, $NHCH_2CH$), 29.12, 29.12, 29.02 (6-CH_3, C-14, $NHCH_2CH$), 21.81, 21.04, 21.04 (2 × CH_3CH, 6-CH_3) ppm; IR: $\bar{\nu} = 3370$ (N–H), 1650 (C=O), 1520 (amide II), 1450, 1310 (NO_2) cm^{-1}.

(5aR,12S*,13S*)-12,13-Dihydro-5a,13-methano-6,6-dimethyl-2-nitro-6H-1,3-benzoxazepino[3,2-a]indole-12-(N-benzylcarboxamide)* (*cis*-**4c**, $C_{27}H_{25}N_3O_4$) *and (5aR*,12R*,3S*)-Isomer* (*trans*-**5c**, $C_{27}H_{25}N_3O_4$)

Compounds **4c** and **5c** were synthesized from 0.87 g **3c** (1.9 mmol) by a similar method as described for **4a** and **5a**.

cis-**4c**: Yield 0.33 g (38%); mp 157–158°C (from ethanol); ^{1}H NMR ($CDCl_3$): $\delta = 6.54$–7.98 (m, Ar-H, NH), 4.49 (dd, $J = 8.0 + 14.7$ Hz, ½ $NHCH_2$), 4.02 (d, $J = 4.9$ Hz, 12-H), 3.96 (dd,

$J = 4.7 + 14.7$ Hz, ½ NHCH_2), 3.82–3.85 (m, 13-H), 2.21 (dd, $J = 3.8 + 11.8$ Hz, 14-H), 2.14 (d, $J = 11.8$ Hz, 14-H), 1.49, 1.49 (s, $2 \times$ 6-CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.79$ (C=O), 158.67 (C), 149.14 (C), 141.92 (C), 138.99 (C), 138.21 (C), 129.15 (CH), 129.01 (CH), 128.01 (CH), 127.94, 127.94, 127.94 ($3 \times$CH), 126.04 (C), 125.84 (CH), 125.16 (CH), 123.27 (CH), 123.19 (CH), 116.78 (CH), 111.52 (C-5a), 111.09 (CH), 78.30 (C-12), 45.81 (C-6), 43.47 ($NHCH_2$), 42.69 (C-13), 33.60 (C-14), 27.10 (6-CH_3), 23.84 (6-CH_3) ppm; IR: $\bar{\nu} = 3320$ (N–H), 1650 (C=O), 1510 (amide II), 1475, 1345 (NO_2) cm^{-1}.

trans-**5c**: Yield 0.23 g (26%); mp 132–134°C (from ethanol); ^{1}H NMR (*DMSO*-d_6): $\delta = 8.86$ (s, br., NH), 6.28–8.31 (m, Ar-H), 4.52 (s, 12-H), 4.35 (dd, $J = 5.9 + 15.2$ Hz, ½ NHCH_2), 4.28 (dd, $J = 5.6 + 15.2$ Hz, ½ NHCH_2), 3.83 (d, $J = 3.6$ Hz, 13-H), 2.75 (dd, $J = 3.6 + 11.5$ Hz, 14-H), 2.02 (d, $J = 11.5$ Hz, 14-H), 1.55 (s, 6-CH_3), 1.34 (s, 6-CH_3) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 168.9$ (C=O), 159.8 (C), 143.2 (C), 141.3 (C), 140.3 (C), 139.3 (C), 129.8 (C), 128.7, 128.7 ($2 \times$CH), 127.7 (CH), 127.6, 127.6 ($2 \times$CH), 127.3 (CH), 125. (CH), 124.1 (CH), 122.5 (CH), 119.20 (CH), 117.6 (CH), 109.1 (C-5a), 107.8 (CH), 67.4 (C-12), 46.0 (C-6), 45.1 (C-13), 42.6 ($NHCH_2$), 28.6 (C-14), 28.4 (6-CH_3,), 21.3 (6-CH_3) ppm; IR (KBr): $\bar{\nu} = 3300$ (N–H), 1660 (C=O), 1525 (amide II), 1480, 1340 (NO_2) cm^{-1}.

(5aR,12S*,13S*)-12,13-Dihydro-5a,13-methano-6,6-dimethyl-2-nitro-6H-1,3-benzoxazepino [3,2-a]indole-12-[N-(2-chlorobenzyl)carboxamide]* (*cis*-**4d**, $C_{27}H_{24}N_3O_4Cl$)
and (7aR,12R*,13S*)-Isomer* (*trans*-**5d**, $C_{27}H_{24}N_3O_4Cl$)

Compounds **4d** and **5d** were synthesized from 0.71 g **3d** (1.4 mmol) by a similar method as described for **4a** and **5a**.

cis-**4d**: Yield 0.34 g (48%); mp 185–187°C (from ethanol); ^{1}H NMR ($CDCl_3$): $\delta = 6.55$–7.75 (m, Ar-H, NH), 4.53 (dd, $J = 8.4 + 14.4$, ½ NHCH_2), 4.01 (dd, $J = 4.5 + 14.4$, ½ NHCH_2), 3.97 (d, $J = 4.8$ Hz, 12-H), 3.72–3.75 (m, 13-H), 2.16 (dd, $J = 3.9 + 12.0$ Hz, 14-H), 2.09 (dd, $J = 0.6 + 12.0$ Hz, 14-H), 1.51 (s, CH_3), 1.47 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.70$ (C=O), 158.32 (C), 148.99 (C), 141.09 (C), 138.70 (C), 135.30 (C), 133.64 (C), 130.97 (CH), 129.56 (CH), 129.37 (CH), 128.90 (CH), 127.14 (CH), 125.52 (CH), 125.29 (C), 124.58 (CH), 123.00 (CH), 122.90 (CH), 116.42 (CH), 111.24 (C-5a), 110.91 (CH), 77.73 (C-12), 45.49 (C-6), 42.34 (C-13), 41.35 ($NHCH_2$), 33.15 (C-14), 26.84 (CH_3), 23.30 (CH_3) ppm; IR: $\bar{\nu} = 3410$ (N–H), 1670 (C=O), 1505 (amide II), 1575, 1330 (NO_2) cm^{-1}.

trans-**5d**: Yield 0.11 g (15%); mp 157–159°C (from ethanol); ^{1}H NMR ($CDCl_3$): $\delta = 6.27$–8.14 (m, Ar-H, NH), 4.53 (dd, $J = 6.0 + 14.6$ Hz, ½ NHCH_2), 4.47 (dd, $J = 5.8 + 14.6$ Hz, ½ NHCH_2), 4.39 (s, 12-H), 3.81 (d, $J = 3.9$ Hz, 13-H), 2.61 (dd, $J = 3.9 + 11.8$ Hz, 14-H), 2.06 (d, $J = 11.8$ Hz, 14-H), 1.60 (s, 6-CH_3), 1.27 (s, 6-CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 168.80$ (C=O), 159.36 (C), 141.27 (C), 140.97 (C), 140.71 (C), 134.86 (C), 133.66 (C), 130.40 (CH), 129.57 (CH), 129.27 (CH), 128.22 (C), 127.93 (CH), 127.15 (CH), 124.91 (CH), 123.09 (CH), 122.79 (CH), 120.15 (CH), 117.33 (CH), 108.76 (C-5a), 107.43 (CH), 67.88 (C-12), 46.50 (C-6), 45.01 (C-13), 41.78 ($NHCH_2$), 28.73, 28.08 (6-CH_3, C-14), 20.89 (6-CH_3) ppm; IR (KBr): $\bar{\nu} = 3375$ (N–H), 1670 (C=O), 1520 (amide II), 1490, 1345 (NO_2) cm^{-1}.

(5aR,12S*,13S*)-12,13-Dihydro-5a,13-methano-6,6-dimethyl-2-nitro-6H-1,3-benzoxazepino[3,2-a]indole-12-[N-(1-naphthylmethyl)carboxamide]* (*cis*-**4e**, $C_{31}H_{27}N_3O_4$)
and (5aR,12R*,13S*)-Isomer* (trans-**5e**, $C_{31}H_{27}N_3O_4$)

Compounds **4e** and **5e** were synthesized from 1.22 g **3e** (2.4 mmol) by a similar method as described for **4a** and **5a**.

cis-**4e**: Yield 0.52 g (43%); mp 208–209°C (from ethanol); ^{1}H NMR ($CDCl_3$): $\delta = 6.37$–7.86 (m, Ar-H, NH), 4.49 (dd, $J = 7.5 + 14.7$ Hz, ½ NHCH_2), 4.54 (dd, $J = 5.0 + 14.7$ Hz, ½ NHCH_2), 4.01 (d, $J = 5.0$ Hz, 12-H), 3.75–3.79 (m, 13-H), 2.16 (dd, $J = 3.8 + 11.9$ Hz, 14-H), 2.06 (dd, $J = 0.6 + 11.9$ Hz, 14-H), 1.44 (s, $2 \times CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.53$ (C=O), 158.10 (C), 148.88 (C), 141.04 (C), 138.69 (C), 134.12 (C), 133.20 (C), 131.25 (C), 129.28 (CH), 128.89

(CH), 128.81 (CH), 126.75 (CH), 126.68 (CH), 126.13 (C), 125.59 (CH), 125.37 (CH), 125.22 (CH), 124.57 (CH), 123.04 (CH), 123.03 (CH), 122.90 (CH), 115.97 (CH), 111.11 (C-5a), 110.88 (CH), 77.87 (C-12), 45.43 (C-6), 42.32 (C-13), 41.13 ($NHCH_2$), 33.22 (C-14), 26.72 (CH_3), 23.43 (CH_3) ppm; IR: $\bar{\nu} = 3380$ (N–H), 1675 (C=O), 1515 (amide II), 1475, 1340 (NO_2) cm^{-1}.

trans-**5e**: Yield 0.20 g (16%); mp 192–193°C (from ethanol); ^1H NMR ($CDCl_3$): $\delta = 6.72$–8.08 (m, Ar-H), 6.24 (d, $J = 7.8$ Hz, 10-H), 6.17 (m, NH), 5.02 (dd, $J = 5.9 + 14.4$ Hz, ½ $NHCH_2$), 4.70 (dd, $J = 3.6 + 14.4$ Hz, ½ $NHCH_2$), 4.34 (s, 12-H), 3.76 (d, $J = 3.6$ Hz, 13-H), 2.62 (dd, $J = 3.6 + 11.7$ Hz, 14-H), 2.01 (d, $J = 11.7$ Hz, 14-H), 1.55 (s, CH_3), 1.11 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 168.45$ (C=O), 159.34, 141.18, 141.06, 140.65, 133.87, 132.76, 131.08, 128.89, 128.85, 128.17, 127.83, 126.79, 126.74, 126.03, 125.28, 124.89, 123.05, 126.05, 122.70, 120.09, 117.34 ($21C_{(Ar)}$), 108.69 (C-5a), 107.44 (C-10), 67.97 (C-12), 46.60 (C-6), 44.99 (C-13), 41.85 ($NHCH_2$), 28.68 (C-14), 27.86 (CH_3), 20.89 (CH_3) ppm; IR: $\bar{\nu} = 1650$ (C=O), 3410 (N–H), 1650 (C=O), 1510 (amide II), 1475 1330 (NO_2) cm^{-1}.

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