

SYNTHESIS AND REARRANGEMENT OF AMINOALKYL LACTONES TO SPIRO-CYCLIC HYDROXYMETHYL LACTAMS

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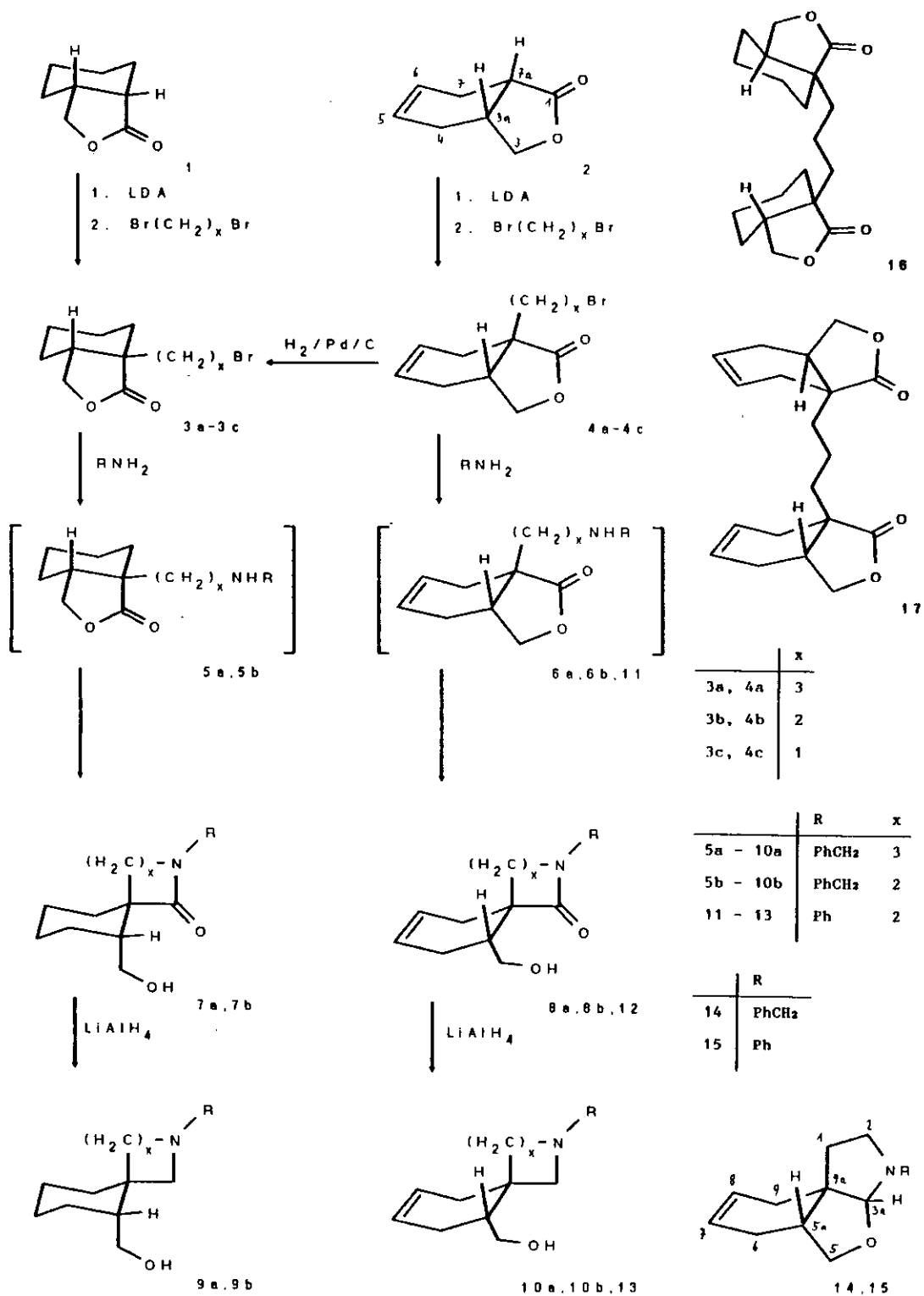
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Abstract - Lithiation of lactones (1) and (2) followed by electrophilic substitution with dibromoalkanes afforded bromoalkyl lactones (3a - 3c) and (4a - 4c). Treatment of 3a, 3b, 4a and 4b with primary amines led to formation of aminoalkyl lactones (5a, 5b, 6a, 6b and 11), which were rearranged to spirocyclic hydroxyalkyl lactams (7a, 7b, 8a, 8b and 12). Spirocyclic lactams (7a, 7b, 8a and 8b) were reduced to spirocyclic amines (9a, 9b, 10a and 10b), whereas reduction of lactam (12) gave a separable mixture of amine (13) and tricyclic aminal (15).

INTRODUCTION

GABA (= γ -aminobutyric acid) is an important inhibitory neurotransmitter in central nervous system^{1,2} and findings that GABA is involved in the development of certain neurological and psychiatric diseases increase interest in GABA analogs.³ GABA can exist in a wide variety of conformations due to comparative freedom of rotation about the single bonds.¹ Information¹ on the active site conformation of GABA has been obtained by studying the activities of molecules in which conformational mobility is reduced. Restrained GABA analogs have been constructed by incorporation of bulky substituents, unsaturation, carbocyclic rings, heterocyclic rings or combination of these.¹⁻³ Our aim was the synthesis of aminoalkylisobenzofuranones, which represent analogs of GABA containing the carboxylic function as part of a heterocyclic ring system. Homologous amino alkyl lactones should be prepared to study the influence of the distance between basic nitrogen and lactone carboxyl group to assumed activity of such compounds.

Scheme 1:



RESULTS AND DISCUSSION

Readily available lactones (1) ⁴ and (2) ⁵ were used as starting compounds, which should be reacted to bromoalkyl lactones by metallation and electrophilic substitution at C-7a. Desired aminoalkyl lactones should be accessible by substitution reaction of bromoalkyl lactones with primary amines.

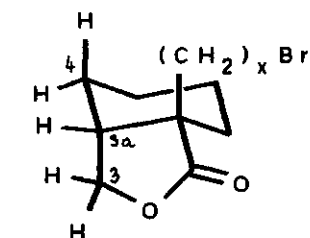
Thus lactones (1) and (2) were lithiated at standard conditions (1.1 equivalent LDA, -78°C, 1 h) ^{6,7} and treated with an excess of dibromoalkanes. Reaction of lithiated lactone (1) (or 2) with 1,3-dibromopropane afforded a mixture of single substitution product (3a) (or 4a) and double substitution product (16) (or 17) in a ratio of 2:1. 3-Bromopropyl lactones (3a) (61%) and (4a) (68%) were separated by distillation in vacuo, whereas dimeric lactones (16) (29%) and (17) (29%) were isolated by crystallization from the distillation residue. Using 1,2-dibromoethane as electrophile led to an equimolar mixture of starting material (1) (or 2) and single substitution product (3b) (or 4b). Obviously main side reaction is the elimination of HBr, which causes high ratio of starting lactones (1) and (2), whereas double substitution products are not formed, because distance between bulky isobenzofuranone skeleton and brominated carbon is distinctly shorter in 2-bromoethyl lactones (3b) and (4b) than in 3-bromopropyl lactones (3a) and (4a).

Removal of starting lactone by vacuum distillation and crystallization of the residue yielded pure (3b) (28%) and (4b) (47%). Treatment of lithiated 1 and 2 with dibromomethane resulted in formation of bromomethyl lactones (3c) (98%) and (4c) (71%) respectively as single products, which were purified by crystallization. Another access to saturated bromoalkyl lactones (3a - 3c) was found to be the catalytic hydrogenation (10% Pd/C, 1 bar) of the double bond in 4a - 4c, which proceeded in high yields (95 - 99%) without hydrogenolytic cleavage of HBr.

Structure of bromoalkyl lactones (3a - 3c) and (4a - 4c) was confirmed by ¹H- and ¹³C-nmr spectroscopic studies (see Tables 1 and 2). Characteristic molecular mass peaks were detected in mass spectra of dimerisation products (16) and (17). Comparison of ¹H-¹H coupling constants which were measured in spectra of 3a - 3c and 4a - 4c indicated that substitution at C-7a proceeded under retention of configuration. This fact was in accordance with results obtained by electrophilic substitution of analogous bicyclic lactones containing an asymmetric center in both α - and β -positions of lactone carboxyl group. ⁶⁻⁸ Chirality at the α -carbon was lost

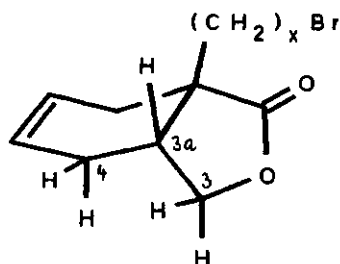
during enolate formation but reproduced by a diastereoselective substitution reaction, mediated by chiral β -carbon.

Table 1: ^1H - ^1H Coupling constants (in Hz) and deduced preferred conformations of bromoalkyl lactones (3a - 3c) and (4a - 4c) in CDCl_3 .



3 a - c

^1H - ^1H	<u>3a</u>	<u>3b</u>	<u>3c</u>	<u>4a</u>	<u>4b</u>	<u>4c</u>
3/1-3a	6.0	6.0	7.4	8.0	9.0	8.0
3/2-3a	6.0	6.0	7.4	9.0	9.0	8.0
3a-4/1	6.0	6.0	7.4	2.0	0	2.0
3a-4/2	6.0	6.0	7.4	8.0	9.0	9.0
x=	3	2	1	3	2	1



4 a - c

Table 2: ^{13}C -Shifts (CDCl_3 , δ in ppm) of starting compounds (1) and (2) in comparison with bromoalkyl lactones (3a - 3c) and (4a - 4c).

	<u>1</u>	<u>3a</u>	<u>3b</u>	<u>3c</u>	<u>2</u>	<u>4a</u>	<u>4b</u>	<u>4c</u>
C-1	178.09	179.99	179.31	177.65	178.49	180.58	180.00	178.33
C-3	71.38	69.14	68.98	68.55	72.24	69.96	69.87	70.31
C-3a	35.03	38.66	38.51	36.35	31.31	36.40	36.36	35.48
C-4	23.07	25.11	24.62	23.21	21.45	22.95	22.58	22.72
C-5	22.19	21.60	21.35	20.98	124.47	124.35	123.90	123.90
C-6	22.57	21.88	21.59	21.11	127.06	124.48	124.54	125.27
C-7	26.83	29.16	28.75	28.77	24.14	28.82	28.14	28.67
C-7a	39.08	44.41	45.39	46.26	36.63	43.04	43.67	45.74
C-8	--	27.12	27.02	35.02	--	27.31	26.97	35.86
C-9	--	33.05	37.58	--	--	33.24	38.45	--
C-10	--	33.52	--	--	--	34.02	--	--

Reaction of bromoalkyl lactones (3a), (3b), (4a) and (4b) with excess benzylamine led to formation of aminoalkyl lactones (5a), (5b), (6a) and (6b), which were rearranged at the substitution conditions (toluene/reflux/16 h) to spirocyclic hydroxymethyl lactams (7a), (7b), (8a) and (8b). Reaction of 4b with aniline resulted in substitution and rearrangement to spiro lactam (12). In contrast to those results steric hindered bromomethyl lactones (3c) and (4c) remained completely unreacted, even if refluxing in excess benzylamine without a solvent. Reacting spiro lactam (8b) and an equimolar amount of p-toluenesulfonic acid in refluxing toluene (24 h) gave aminoalkyl lactone (6b) after basic workup. But 6b was not stable enough to be characterized, because rearrangement to 8b was complete at room temperature within 1 - 2 d or in refluxing toluene within 2 h so that further investigations in preparation of aminoalkyl lactones were omitted.

Structure of spirocyclic lactams was ensured by spectroscopic methods. Signals of carbinol-, N-benzyl- and N-methylene-protons (H-3) in ¹H-nmr spectra of 7a, 7b, 8a and 8b were detected well separated at 400 MHz. Ir absorption bands of δ-lactams (7a) and (8a) (1620 or 1625 cm⁻¹) and γ-lactams (7b) and (8b) (1665 or 1670 cm⁻¹) at low wave numbers indicated the presence of an intramolecular hydrogen bridge bond between lactam carbonyl and hydroxymethyl group.

Reduction of spirocyclic lactams (7a), (7b), (8a) and (8b) led to spirocyclic amines (9a), (9b), (10a) and (10b) respectively using solutions of LiAlH₄ in THF, whereas reaction of 12 gave a mixture of expected amine (13) and tricyclic aminal (15) in a ratio of 1:5, which could be separated by column chromatography. Arylamine (13) was rapidly oxidised to 15, if solutions were in contact with air. Treatment of 8b with a suspension of LiAlH₄ resulted in formation of an equimolar mixture of spirocyclic amine (10b) and tricyclic aminal (14), which was separated by column chromatography. Benzylamine (10b) proved to be inert in presence of air.

Comparing ¹H-nmr spectral data of spiro amines to corresponding spiro lactams showed typical shifts of N-benzyl- and N-methylene protons (H-3) to high field, due to lost of inductive and anisotropic effect of lactam carbonyl group. Large shift increments (≈1.4 ppm) were observed between geminal protons at C-1 in 9a, 9b, 10a and 10b. ¹H-Nmr spectra of tricyclic aminals (14) and (15) showed well separated signals of N- and O-methylene protons (H-2 and H-5) and a typical singlet of aminal proton (H-3a).

Relative configuration of chiral centers C-3a, C-5a and C-9a in 14 and 15 was considered to be coupled, due to rigidity of tricyclic amins. Because reaction sequence from bromoalkyl lactams to tricyclic amins (14) and (15) should proceed without racemisation of present chiral centers, postulated relative configuration at asymmetric carbons of spiro lactams, spirocyclic amines and bromoalkyl lactones was regarded to be ensured.

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EXPERIMENTAL

All melting points were determined on a KOFLER melting point apparatus and are uncorrected. ^1H -Nmr and ^{13}C -nmr spectra were recorded on a BRUKER AC 80 or AM-400 WB, using tetramethylsilane as internal standard. Infrared spectra were recorded on a PERKIN ELMER 298 spectrophotometer. Mass spectra were detected on a MAT CH-7 by A. Nikiforov (Institut für Organische Chemie). Microanalyses were determined by J. Theiner (Institut für Physikalische Chemie).

General procedure A:

A solution of diisopropylamine (30.8 ml, 220 mmol) in dry THF (42.2 ml) was cooled to 0°C followed by addition of n-BuLi (147 ml, 1.5 M in hexane, 220 mmol). This solution was added at -78°C to a solution of freshly distilled starting lactone (200 mmol) dissolved in dry THF (200 ml) and the mixture was stirred at -78°C for 1 h. After addition of appropriate dibromoalkane (1 mol), the cooling bath was removed, the reaction mixture was allowed to warm up to room temperature and stirring was continued for 16 h. The solvent was distilled off at reduced pressure, the residue was dissolved in 2N HCl (100 ml) and extracted with toluene (4x100 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo to yield the raw product, which was purified by vacuum distillation or recrystallization.

General procedure B:

The unsaturated starting lactone (0.1 mol) was dissolved in ethyl acetate (150 ml), the hydrogenation catalyst (10% Pd on charcoal, 1 g) was added and the mixture was stirred in a hydrogen atmosphere (1 bar) until no more hydrogen was absorbed. After removal of the catalyst by filtration and of the solvent by evaporation the residue was purified by distillation or recrystallization.

General procedure C:

The corresponding bromoalkyl lactone (20 mmol) was dissolved in toluene (100 ml), the appropriate amine (100 mmol) was added and the mixture was refluxed for 16 h. The organic layer was washed with 2N HCl (3x100 ml), dried (Na₂SO₄) and the solvent was evaporated at reduced pressure. The residue was purified by recrystallization.

General procedure D:

To the corresponding spiro lactam (20 mmol) dissolved in dry THF (150 ml) was added LiAlH₄ (1M in THF, 50 ml) at 0°C. The mixture was refluxed for 2 h, cooled to 0°C and hydrolysed by addition of H₂O (9 ml). After stirring for 2 h the slurry was filtered off and washed with ethyl acetate (50 ml). Evaporation of the solvent yielded spirocyclic amine (free base). An analytical sample (2 mmol) dissolved in ether (15 ml) was treated with HCl (1M in ether, 2 ml), the solvent was removed at reduced pressure and the residue was recrystallized to yield pure hydrochloride.

(3aRS,7aRS)-7a-(3-Bromopropyl)perhydroisobenzofuranone (3a)

Starting material 1 (28 g, 200 mmol), electrophile 1,3-dibromopropane (102 ml, 1 mol), method A. Distillation gave 3a (31.8 g, 61%, colourless oil), bp 138-140°C/ 0.03 mm Hg. Starting material 4a (25.9 g, 100 mmol), method B. Distillation afforded 3a (24.8 g, 95%, colourless oil), bp 139-140°C/0.03 mm Hg. ¹H-Nmr: (CDCl₃) (δ, ppm) 4.32 (dd, J = 9.0 and 6.0 Hz, 1H, H-3/1), 3.99 (dd, J = 9.0 and 6.0 Hz, 1H, H-3/2), 3.42 (dt, J = 6.0 and 10.0 Hz, 1H, H-10/1), 3.40 (dt, J = 6.0 and 10.0 Hz, 1H, H-10/2), 2.30 (qui, J = 6.0 Hz, 1H, H-3a), 2.01 - 1.31 (m, 12H, aliphatic-H).

Anal. Calcd for C₁₁H₁₅O₂Br: C, 50.58; H, 6.57; Br, 30.59. Found C, 50.36; H, 6.42; Br, 30.81.

(3aRS,7aRS)-7a-(2-Bromoethyl)perhydroisobenzofuranone (3b)

Starting material 1 (28g, 200 mmol), electrophile 1,2-dibromoethane (86 ml, 1 mol), method A. 1 was removed by distillation (bp 78-80°C/0.2 mm Hg). The residue was recrystallized from methanol to afford 3b (13.8 g, 28%, colourless crystals), mp 48°C. Starting material 4b (24.5 g, 100 mmol), method B. Recrystallization from methanol yielded 3b (24.5 g, 99%, colourless crystals), mp 48°C. ¹H-Nmr: (CDCl₃) (δ, ppm) 4.33 (dd, J = 9.0 and 6.0 Hz, 1H, H-3/1), 4.03 (dd, J = 9.0 and 6.0 Hz, 1H, H-3/2), 3.45 (dt, J = 7.0 and 9.0 Hz, 1H, H-9/1), 3.42 (dt, J = 7.0 and 9.0 Hz, 1H, H-9/2), 2.37 (qui, J = 6.0 Hz, 1H, H-3a), 2.27 (ddd, J = 14.0, 9.0 and 7.0 Hz, 1H, H-8/1), 2.19 (ddd, J = 14.0, 9.0 and 7.0 Hz, 1H, H-8/2), 1.90 - 1.70 (m, 2H, aliphatic -H), 1.55 - 1.35 (m, 6H, aliphatic-H). Ir (KBr) 1760 cm⁻¹ (γ-lactone). Ms: m/z 248 (M⁺, ⁸¹Br), 246 (M⁺, ⁷⁹Br), 139 (M⁺-CH₂-CH₂-Br). Anal. Calcd for C₁₀H₁₅O₂Br: C, 48.59; H, 6.13; Br, 32.33. Found C, 48.32; H, 6.14; Br, 32.68.

(3aRS,7aRS)-7a-Bromomethylperhydroisobenzofuranone (3c)

Starting material 1 (28 g, 200 mmol), electrophile dibromomethane (70 ml, 1 mol), method A. Recrystallization from ethyl acetate afforded 3c (45.7 g, 98%, colourless crystals), mp 51-53°C. Starting material 4c (23.1 g, 100 mmol), method B. Recrystallization from ethyl acetate gave 3c (23.1 g, 99%, colourless crystals), mp 52°C. ¹H-Nmr: (CDCl₃) (δ, ppm) 4.31 (dd, J = 8.9 and 7.4 Hz, 1H, H-3/1), 4.02 (dd, J = 8.9 and 7.4 Hz, 1H, H-3/2), 3.67 (d, J = 10.7 Hz, 1H, H-8/1), 3.46 (d, J = 10.7 Hz, 1H, H-8/2), 2.85 (qui, J = 7.4 Hz, 1H, H-3a), 1.76 - 1.46 (m, 8H, aliphatic-H). Ir: (KBr) 1775 cm⁻¹ (γ-lactone). Ms: m/z 234 (M⁺, ⁸¹Br), 232 (M⁺, ⁷⁹Br), 153 (M⁺-Br), 109 (M⁺-Br-CO₂). Anal. Calcd for C₉H₁₃O₂Br: C, 46.37; H, 5.63; Br, 34.27. Found: C, 46.63; H, 5.92; Br, 34.09.

(3aRS,7aSR)-7a-(3-Bromopropyl)-3a,4,7,7a-tetrahydroisobenzofuranone (4a)

Starting material 2 (27.6 g, 200 mmol), electrophile 1,3-dibromopropane (102 ml, 1 mol), method A. Distillation afforded 4a (35.2 g, 68%, colourless oil), bp 135-136°C/0.02 mm Hg. ¹H-Nmr: (CDCl₃) (δ, ppm) 5.80 (m, 2H, H-5, H-6), 4.33 (dd, J = 9.0 and 8.0 Hz, 1H, H-3/1), 3.92 (t, J = 9.0 Hz, 1H, H-3/2), 3.41 (m, 2H, H-10), 2.61 (ddt, J = 9.0, 2.0 and 8.0 Hz, 1H, H-3a), 2.40 - 2.20 (m, 2H, aliphatic-H), 2.09 - 1.64 (m, 6H, aliphatic-H). Anal. Calcd for C₁₁H₁₅O₂Br: C, 50.98; H, 5.85; Br, 30.83. Found: C, 51.12; H, 5.94; Br, 30.62.

(3aRS,7aRS)-7a-(2-Bromoethyl)-3a,4,7,7a-tetrahydroisobenzofuranone (4b)

Starting material 2 (27.6 g, 200 mmol), electrophile 1,2-dibromoethane (86 ml, 1 mol), method A. 2 was removed by distillation (bp 80-83°C/0.3 mm Hg). The residue was recrystallized from methanol to afford 4b (23 g, 47%, colourless crystals), mp 56-57°C. ¹H-Nmr: (CDCl₃) (δ, ppm) 5.78 (m, 2H, H-5, H-6), 4.35 (t, J = 9.0 Hz, 1H, H-3/1), 3.93 (t, J = 9.0 Hz, 1H, H-3/2), 3.48 (dt, J = 6.6 and 10.0 Hz, 1H, H-9/1), 3.40 (dt, J = 6.6 and 10.0 Hz, 1H, H-9/2), 2.69 (qua, J = 9.0 Hz, 1H, H-3a), 2.52 - 1.89 (m, 6H, aliphatic-H). Ir: (KBr) 1775 cm⁻¹ (γ-lactone). Ms: m/z 246 (M⁺, ⁸¹Br), 244 (M⁺, ⁷⁹Br), 137 (M⁺-CH₂-CH₂-Br). Anal. Calcd for C₁₀H₁₃O₂Br: C, 49.00; H, 5.35; Br, 32.60. Found: C, 49.21; H, 5.35; Br, 32.91.

(3aRS,7aRS)-7a-(Bromomethyl)-3a,4,7,7a-tetrahydroisobenzofuranone (4c)

Starting material 2 (27.6 g, 200 mmol), electrophile dibromomethane (70 ml), method A. Recrystallization from methanol afforded 4c (32.8 g, 71%, colourless crystals), mp 47°C. ¹H-Nmr: (CDCl₃) (δ, ppm) 5.80 (m, 2H, H-5, H-6), 4.40 (dd, J = 9.0 and 8.0 Hz, 1H, H-3/1), 3.92 (dd, J = 9.0 and 8.0 Hz, 1H, H-3/2), 3.74 (d, J = 10.0 Hz, 1H, H-8/1), 3.45 (d, J = 10.0 Hz, 1H, H-8/2), 3.11 (ddt, J = 9.0, 2.0 and 8.0 Hz, 1H, H-3a), 2.50 - 2.24 (m, 2H, aliphatic-H), 2.17 - 1.98 (m, 2H, aliphatic-H). Ir: (KBr) 1775 cm⁻¹ (γ-lactone). Ms: m/z 232 (M⁺, ⁸¹Br), 230 (M⁺, ⁷⁹Br), 151 (M⁺-Br), 137 (M⁺-CH₂-Br). Anal. Calcd for C₉H₁₁O₂Br: C, 46.77; H, 4.81; Br, 34.57. Found: C, 47.07; H, 4.84; Br, 34.58.

(6RS,11RS)-2-Benzyl-11-hydroxymethyl-2-azaspiro[5.5]undecanone (7a)

Starting material 3a (5.22 g, 20 mmol) + benzylamine (10.7 g, 100 mmol), method C. Recrystallization from methanol afforded 7a (5.46 g, 95%, colourless crystals), mp 20°C. ¹H-Nmr: (CDCl₃) (δ, ppm) 7.37 - 7.14 (m, 5H, aromatic-H), 4.61 (d, J = 14.0 Hz, 1H, H-1'/1), 4.53 (d, J = 14.0 Hz, 1H, H-1'/2), 3.96 (dd, J = 12.0 and 6.0 Hz, 1H, H-12/1), 3.70 (dd, J = 12.0 and 4.0 Hz, 1H, H-12/2), 3.24 (dt, J = 12.0 and 6.0 Hz, 1H, H-3/1), 3.18 (dt, J = 12.0 and 6.0 Hz, 1H, H-3/2), 2.92 (m, 1H, OH), 2.34 (ddd, J = 13.0, 9.0 and 4.0 Hz, 1H, H-5/1), 2.22 (ddd, J = 13.0, 9.0 and 4.0 Hz, 1H, H-5/2), 2.00 - 1.57 (m, 7H, aliphatic-H), 1.57 - 1.43 (m, 2H, aliphatic-H), 1.37 (m, 1H, aliphatic-H), 1.26 (m, 1H, aliphatic-H). Ir: (KBr) 1625 cm⁻¹ (δ-lactam). Ms: m/z 287 (M⁺), 257 (M⁺-30), 228 (M⁺-59), 91 (PhCH₂⁺, base peak). Anal. Calcd for C₁₈H₂₅NO₂: C, 75.21; H, 8.79; N, 4.87. Found C, 75.31; H, 8.58; N, 4.81.

(5RS,10RS)-2-Benzyl-10-hydroxymethyl-2-azaspiro[4.5]decanone (7b)

Starting material **3b** (4.94 g, 20 mmol) + benzylamine (10.7 g, 100 mmol), method C. Recrystallization from ether/pet. ether afforded **7b** (5.30 g, 97%, colourless crystals), mp 20°C. ¹H-Nmr: (CDCl₃) (δ, ppm) 7.35 - 7.20 (m, 5H, aromatic-H), 4.45 (s, 2H, H-1'), 4.20 (dd, J = 11.0 and 8.0 Hz, 1H, H-11/1), 3.69 (m, 1H, OH), 3.54 (d, J = 11.0 Hz, 1H, H-11/2), 3.22 (ddd, J = 10.0, 8.0 and 6.0 Hz, 1H, H-3/1), 3.16 (ddd, J = 10.0, 8.0 and 6.0 Hz, 1H, H-3/2), 2.04 (ddd, J = 14.0, 8.0 and 6.0 Hz, 1H, H-4/1), 2.01 (m, 1H, aliphatic-H), 1.98 (ddd, J = 14.0, 8.0 and 6.0 Hz, 1H, H-4/2), 1.90 - 1.52 (m, 5H, aliphatic-H), 1.52 - 1.23 (m, 3H, aliphatic-H). Ir: (KBr) 1670 cm⁻¹ (γ-lactam). Ms: m/z 273 (M⁺), 243 (M⁺-30), 214 (M⁺-59), 91 (PhCH₂⁺, base peak). Anal. Calcd for C₁₇H₂₃NO₂: C, 74.68; H, 8.50; N, 5.12. Found C, 74.32; H, 8.92; N, 4.96.

(6RS,11SR)-2-Benzyl-11-hydroxymethyl-2-azaspiro[5.5]undec-8-en-one (8a)

Starting material **4a** (5.18 g, 20 mmol) benzylamine (10.7 g, 100 mmol), method C. Recrystallization from methanol afforded **8a** (3.03 g, 53%, colourless crystals), mp 91-92°C. ¹H-Nmr: (CDCl₃) (δ, ppm) 7.40 - 7.10 (m, 5H, aromatic-H), 5.62 (m, 1H, H-8), 5.58 (m, 1H, H-9), 4.76 (d, J = 14.0 Hz, 1H, H-1'/1), 4.46 (d, J = 14.0 Hz, 1H, H-1'/2), 4.09 (ddd, J = 12.0, 8.0 and 4.0 Hz, 1H, H-12/1), 3.68 (dd, J = 10.0 and 4.0 Hz, 1H, OH), 3.44 (ddd, J = 12.0, 10.0 and 4.0 Hz, 1H, H-12/2), 3.30 (dt, J = 12.0 and 6.0 Hz, 1H, H-3/1), 3.22 (dt, J = 12.0 and 6.0 Hz, 1H, H-3/2), 3.08 (m, 1H, H-7/1), 2.30 (m, 1H, H-10/1), 2.10- 1.60(m, 7H, aliphatic-H). Ir: (KBr) 1620 cm⁻¹ (δ-lactam). Ms: m/z 285 (M⁺), 255 (M⁺-30), 226 (M⁺-59), 91 (PhCH₂⁺). Anal. Calcd for C₁₈H₂₃NO₂: C, 75.74; H, 8.14; N, 4.91. Found C, 75.45; H, 8.51; N, 4.91.

(5RS,10RS)-2-Benzyl-10-hydroxymethyl-2-azaspiro[4.5]dec-7-en-one (8b)

Starting material **4b** (4.9 g, 20 mmol) + benzylamine (10.7 g, 100 mmol), method C. Recrystallization from ether/pet. ether afforded **8b** (4.02 g, 74%, colourless crystals), mp 51°C. ¹H-Nmr: (CDCl₃) (δ, ppm) 7.44 - 7.17 (m, 5H, aromatic-H), 5.67 (m, 1H, H-7), 5.57 (m, 1H, H-8), 5.35 (dd, J = 11.0 and 1.6 Hz, 1H, OH), 4.53 (d, J = 14.5 Hz, 1H, H-1'/1), 4.45 (d, J = 14.5 Hz, 1H, H-1'/2), 4.08 (ddd, J = 12.0, 11.0 and 1.6 Hz, 1H, H-11/1), 3.44 (ddd, J = 12.0, 11.0 and 3.0 Hz, 1H, H-11/2), 3.25 (m, 2H, H-3), 2.57 (m, 1H, H-6/1), 2.28 (m, 1H, H-9/1), 2.06 - 1.78 (m, 5H, aliphatic-H). Ir: (KBr) 1665 cm⁻¹ (γ-lactam). Ms: m/z 271 (M⁺), 241 (M⁺-30), 212 (M⁺-59), 91

(PhCH₂⁺, base peak). Anal. Calcd for C₁₇H₂₁NO₂: C, 75.23; H, 7.82; N, 5.16. Found C, 75.42; H, 7.89; N, 5.02.

(6RS,11RS)-2-Benzyl-11-hydroxymethyl-2-azaspiro[5.5]undecane (9a)

Starting material 7a (5.75 g, 20 mmol), method D, gave 9a (5.09 g, 93%, yellow oil) and 9a.HCl by recrystallization from ether (502 mg, 81%, yellow crystals), mp 40°C. ¹H-Nmr: (free base, CDCl₃) (δ, ppm) 7.36 - 7.22 (m, 5H, aromatic-H), 6.75 (m, 1H, OH), 3.98 (dd, J = 12.0 and 2.0 Hz, 1H, H-12/1), 3.69 (d, J = 13.0 Hz, 1H, H-1'/1), 3.49 (dd, J = 12.0 and 3.0 Hz, 1H, H-12/2), 3.25 (d, J = 13.0 Hz, 1H, H-1'/2), 3.17 (d, J = 12.0 Hz, 1H, H-1/1), 2.82 (m, 1H, H-3/1), 1.90 - 1.53 (m, 7H, aliphatic-H), 1.50 - 1.10 (m, 8H, aliphatic-H). 9a.HCl: Ir: (KBr) 3380 cm⁻¹ (OH, NH). Ms: m/z 273 (M⁺-HCl), 182 (M⁺-HCl-PhCH₂), 91 (PhCH₂⁺, base peak). Anal. Calcd for C₁₈H₂₇NO.HCl: C, 69.75; H, 9.13; N, 4.52; Cl, 11.44. Found C, 69.33; H, 9.00; N, 4.17; Cl, 11.83.

(5RS,10RS)-2-Benzyl-10-hydroxymethyl-2-azaspiro[4.5]decane (9b)

Starting material 7b (5.47 g, 20 mmol), method D, gave 9b (4.67 g, 90%, yellow oil) and 9b.HCl by recrystallization from ethanol (420 mg, 71%, yellow crystals), mp 152-155°C. ¹H-Nmr: (free base, CDCl₃) (δ, ppm) 7.37 - 7.23 (m, 5H, aromatic-H), 6.10 (m, 1H, OH), 3.91 (dd, J = 11.0 and 4.0 Hz, 1H, H-11/1), 3.71 (d, J = 12.0 Hz, 1H, H-1'/1), 3.47 (d, J = 12.0 Hz, 1H, H-1'/2), 3.34 (dd, J = 11.0 and 4.0 Hz, 1H, H-11/2), 3.26 (d, J = 9.0 Hz, 1H, H-1/1), 3.01 (dt, J = 4.0 and 10.0 Hz, 1H, H-3/1), 2.22 (dt, J = 8.0 and 10.0 Hz, 1H, H-3/2), 1.96 (dt, J = 14.0 and 8.0 Hz, 1H, aliphatic-H), 1.96 (d, J = 9.0 Hz, 1H, H-1/2), 1.75 (m, 1H, aliphatic-H), 1.70 - 1.40 (m, 6H, aliphatic-H), 1.33 - 1.10 (m, 3H, aliphatic-H). 9b.HCl: Ir: (KBr) 3040 cm⁻¹ (OH, NH). Ms: m/z 259 (M⁺-HCl), 168 (M⁺-HCl-PhCH₂), 91 (PhCH₂⁺, base peak). Anal. Calcd for C₁₇H₂₅NO.HCl: C, 68.99; H, 8.87; N, 4.73; Cl, 12.00. Found C, 69.06; H, 9.10; N, 4.98; Cl, 11.78.

(6RS,11SR)-2-Benzyl-11-hydroxymethyl-2-azaspiro[5.5]undec-8-ene (10a)

Starting material 8a (5.71 g, 20 mmol), method D, gave 10a (4.07 g, 75%, yellow oil) and 10a.HCl by recrystallization from ether (468 mg, 76%, yellow crystals), mp 54°C. ¹H-Nmr: (free base, CDCl₃) (δ, ppm) 7.40- 7.20(m, 5H, aromatic-H), 7.05 (m, 1H, OH), 5.60 (m, 1H, H-8), 5.48 (m, 1H, H-9), 3.99 (dd, J = 12.0 and 2.0 Hz, 1H, H-12/1), 3.59 (d, J = 12.0 Hz, 1H, H-1'/1), 3.44 (dd, J = 12.0 and 3.0 Hz, 1H, H-12/2), 3.35 (d, J = 12.0 Hz,

1H, H-1'/2), 3.10 (d, $J = 12.0$ Hz, 1H, H-1/1), 2.88 (m, 1H, H-3/1), 2.34 (m, 1H, aliphatic-H), 2.00 - 1.80 (m, 4H, aliphatic-H), 1.75 - 1.55 (m, 4H, aliphatic-H), 1.61 (d, $J = 12.0$ Hz, 1H, H-1/2), 1.27 (m, 1H, aliphatic-H). 10a.HCl: Ir: (KBr) 3370 cm^{-1} (OH, NH), 1655 cm^{-1} (C=C). Ms: m/z 271 ($M^+ - \text{HCl}$), 180 ($M^+ - \text{HCl} - \text{PhCH}_2$), 91 (PhCH_2^+ , base peak). Anal. Calcd for $\text{C}_{18}\text{H}_{25}\text{NO} \cdot \text{HCl}$: C, 70.21; H, 8.53; N, 4.55; Cl, 11.51. Found C, 69.96; H, 8.62; N, 4.24; Cl, 11.01.

(5RS,10RS)-2-Benzyl-10-hydroxymethyl-2-azaspiro[4.5]dec-7-ene (10b)

Starting material 8b (5.43 g, 20 mmol), method D, gave 10b (4.84 g, 94%, yellow oil) and 10b.HCl by recrystallization from ethanol (403 mg, 72%, yellow crystals), mp $180\text{--}182^\circ\text{C}$. $^1\text{H-Nmr}$: (free base, CDCl_3) (δ , ppm) 7.40 - 7.20 (m, 5H, aromatic -H), 5.68 (m, 1H, H-7), 5.59 (m, 1H, H-8), 3.96 (dd, $J = 13.0$ and 2.0 Hz, 1H, H-11/1), 3.75 (d, $J = 12.5$ Hz, 1H, H-1'/1), 3.47 (d, $J = 12.5$ Hz, 1H, H-1'/2), 3.38 (dd, $J = 13.0$ and 2.0 Hz, 1H, H-11/2), 3.11 (d, $J = 10.0$ Hz, 1H, H-1/1), 3.03 (dt, $J = 4.0$ and 9.0 Hz, 1H, H-3/1), 2.51 (m, 1H, aliphatic-H), 2.24 - 1.93 (m, 5H, aliphatic-H), 1.88 (d, $J = 10.0$ Hz, 1H, H-1/2), 1.68 - 1.50 (m, 2H, aliphatic-H). 10b.HCl: Ir: (KBr) 3370 cm^{-1} (OH, NH), 1655 cm^{-1} (C=C). Ms: m/z 257 ($M^+ - \text{HCl}$), 166 ($M^+ - \text{HCl} - \text{PhCH}_2$), 91 (PhCH_2^+ , base peak). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO} \cdot \text{HCl}$: C, 69.48; H, 8.25; N, 4.76; Cl, 12.06. Found C, 69.59; H, 8.31; N, 4.70; Cl, 12.00.

(5RS,10RS)-10-Hydroxymethyl-2-phenyl-2-azaspiro[4.5]dec-7-en-one (12)

Starting material 4b (4.9 g, 20 mmol) + aniline (9.31 g, 100 mmol), method C. Recrystallization from methanol afforded 12 (1.65 g, 32%, colourless crystals), mp $75\text{--}77^\circ\text{C}$. $^1\text{H-Nmr}$: (CDCl_3) (δ , ppm) 7.60 (d, $J = 8.0$ Hz, 2H, H-2', H-6'), 7.39 (t, $J = 8.0$ Hz, 2H, H-3', H-5'), 7.19 (t, $J = 8.0$ Hz, 1H, H-4'), 5.69 (m, 1H, H-7), 5.61 (m, 1H, H-8), 4.75 (m, 1H, OH), 4.09 (dd, $J = 12.0$ and 8.0 Hz, 1H, H-11/1), 3.89 (dt, $J = 10.0$ and 8.0 Hz, 1H, H-3/1), 3.83 (ddd, $J = 10.0$, 8.0 and 4.0 Hz, 1H, H-3/2), 3.45 (d, $J = 12.0$ Hz, 1H, H-11/2), 2.57 (d, $J = 18.0$ Hz, 1H, H-6/1), 2.32 (m, 1H, H-9/1), 2.20 - 1.90 (m, 5H, aliphatic-H). Ir: (KBr) 1670 cm^{-1} (γ -lactam). Ms: m/z 257 (M^+), 227 ($M^+ - 30$), 198 ($M^+ - 59$), 77 (Ph^+ , base peak). Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_2$: C, 74.67; H, 7.46; N, 5.44. Found C, 74.76; H, 7.57; N, 5.53.

(5RS,10RS)-10-Hydroxymethyl-2-phenyl-2-azaspiro[4.5]dec-7-ene (13)

Starting material 12 (5.15 g, 20 mmol), method D, gave 13 + 15 (1:5).

The mixture was separated by column chromatography (silica gel, CH₂Cl₂) to yield 13 (633 mg, 13%, yellow oil). ¹H-Nmr: (free base, CDCl₃) (δ, ppm) 7.23 (t, J = 8.0 Hz, 2H, H-3', H-5'), 6.69 (t, J = 8.0 Hz, 1H, H-4'), 6.58 (d, J = 8.0 Hz, 2H, H-2', H-6'), 5.68 (m, 1H, H-7), 5.63 (m, 1H, H-8), 3.68 (dd, J = 11.0 and 5.0 Hz, 1H, H-11/1), 3.63 (dd, J = 11.0 and 6.0 Hz, 1H, H-11/2), 3.39 (dt, J = 3.0 and 10.0 Hz, 1H, H-3/1), 3.36 (q, J = 10.0 Hz, 1H, H-3/2), 3.31 (d, J = 10.0 Hz, 1H, H-1/1), 3.08 (d, J = 10.0 Hz, 1H, H-1/2), 2.35 - 2.15 (m, 7H, aliphatic-H).

(3aRS,5aSR,9aSR)-3-Benzyl-1,2,3,3a,5,5a,6,9-octahydroisobenzofuro[2,3-b]pyrrole (14)

LiAlH₄ (7.2 g, 190 mmol) was suspended in dry THF (500 ml) followed by addition of 8b (26 g, 95 mmol) dissolved in THF (100 ml) at 0°C. The mixture was refluxed for 2 h, hydrolysed by addition of H₂O (35 ml) and stirred for 2 h at room temperature. The slurry was removed by filtration and washed with ethyl acetate (100 ml). Evaporation of the solvent gave 10b + 14 (1:1). The mixture was separated by column chromatography (silica gel, CH₂Cl₂) to yield 10b (9.05 g, 37%, yellow oil) and 14 (10.68 g, 44%, yellow oil). ¹H-Nmr: (CDCl₃) (δ, ppm) 7.40 - 7.16 (m, 5H, aromatic-H), 5.76 (m, 1H, H-8), 5.68 (m, 1H, H-7), 4.56 (s, 1H, H-3a), 4.00 (d, J = 13.0 Hz, 1H, H-1'/1), 3.95 (dd, J = 8.0 and 4.0 Hz, 1H, H-5/1), 3.76 (d, J = 13.0 Hz, 1H, H-1'/2), 3.57 (dd, J = 8.0 and 2.0 Hz, 1H, H-5/2), 2.87 (dt, J = 3.0 and 9.0 Hz, 1H, H-2/1), 2.68 (q, J = 9.0 Hz, 1H, H-2/2), 2.41 - 1.69 (m, 7H, aliphatic-H).

(3aRS,5aSR,9aSR)-3-Phenyl-1,2,3,3a,5,5a,6,9-octahydroisobenzofuro[2,3-b]pyrrole (15)

Starting material 12 (5.15 g, 20 mmol), method D, gave 13 + 15 (1:5). The mixture was separated by column chromatography (silica gel, CH₂Cl₂) to yield 15 (3.19 g, 66%, yellow oil). ¹H-Nmr: (CDCl₃) (δ, ppm) 7.25 (dd, J = 8.0 and 6.6 Hz, 2H, H-3', H-5'), 6.79 (d, J = 8.0 Hz, 2H, H-2', H-6'), 6.76 (t, J = 6.6 Hz, 1H, H-4'), 5.82 (m, 1H, H-8), 5.73 (m, 1H, H-7), 5.15 (s, 1H, H-3a), 4.19 (dd, J = 9.0 and 5.0 Hz, 1H, H-5/1), 3.64 (dd, J = 9.0 and 3.6 Hz, 1H, H-5/2), 3.52 (dt, J = 4.0 and 8.0 Hz, 1H, H-2/1), 3.47 (q, J = 8.0 Hz, 1H, H-2/2), 2.37 - 2.15 (m, 4H, aliphatic-H), 2.10 (m, 1H, H-9/2), 2.05 (m, 1H, H-6/2), 1.85 (ddd, J = 12.0, 8.0 and 4.0 Hz, 1H, H-1/2).

1,3-Bis(1-oxoperhydroisobenzofuran-7a-yl)propane (16)

Starting material 1 (28 g, 200 mmol), electrophile 1,3-dibromopropane (102 ml, 1 mol), method A. 3a was separated by distillation (bp 138-140°C/0.03 mm Hg). The residue was recrystallized from ethyl acetate to afford 16 (9.35 g, 29%, colourless crystals), mp 118-120°C. Starting material 17 (31.6 g, 100 mmol), method B. Recrystallization from ethyl acetate yielded 16 (31.7 g, 99%, colourless crystals), mp 118-120°C. ¹H-Nmr: (CDCl₃) (δ, ppm) 4.27 (dd, J = 8.0 and 6.0 Hz, 2H, H-3/1, H-3/1'), 3.98 (dd, J = 8.0 and 6.0 Hz, 2H, H-3/2, H-3/2'), 2.32 (qui, J = 6.0 Hz, 2H, H-3a, H-3a'), 1.89 - 1.78 (m, 2H, aliphatic-H), 1.78 - 1.60 (m, 4H, aliphatic-H), 1.59 - 1.25 (m, 16H, aliphatic-H). Ir: (KBr) 1760 cm⁻¹ (γ-lactone). Ms: m/z 320 (M⁺), 181 (M⁺-139), 167 (M⁺-153), 139 (M⁺-181). Anal. Calcd for C₁₉H₂₈O₄: C, 71.20; H, 8.83. Found C, 70.98; H, 9.06.

1,3-Bis(1-oxo-3a,4,7,7a-tetrahydroisobenzofuran-7a-yl)propane (17)

Starting material 2 (27.6 g, 200mmol), electrophile 1,3-dibromopropane (102 ml, 1 mol), method A. 4a was separated by distillation (bp 135-136°C/0.02 mm Hg). The residue was recrystallized from ethyl acetate/ether (1:1) to give 17 (9.2 g, 29%, colourless crystals), mp 93-95°C. ¹H-Nmr: (CDCl₃) (δ, ppm) 5.76 (m, 4H, H-5, H-5', H-6, H-6'), 4.29 (t, J = 9.0 Hz, 2H, H-3/1, H-3/1'), 3.89 (t, J = 9.0 Hz, 2H, H-3/2, H-3/2'), 2.63 (m, 2H, H-3a, H-3a'), 2.40 - 1.20 (m, 14H, aliphatic-H). Ir: (KBr) 1770 cm⁻¹ (γ-lactone). Ms: m/z 316 (M⁺), 179 (M⁺-137), 165 (M⁺-151), 137 (M⁺-179). Anal. Calcd for C₁₉H₂₄O₄: C, 72.11; H, 7.66. Found C, 72.00; H, 7.52.

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