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GABA-ANALOGOUS SPIROCYCLIC AMINO ACID ESTERS, 5. *N*-BENZYL-7-AZASPIRO[4.5]DECANE-1-CARBOXYLATES

Markus Bendl, Michael Eder, Ingo Langhammer, and Ernst Urban*

Institute of Pharmaceutical Chemistry, University of Vienna,
Althanstraße 14, A-1090 Vienna, Austria

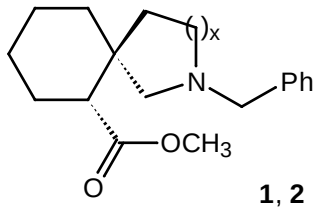
Abstract - *N*-Benzyl-7-azaspiro[4.5]decane-1-carboxylates (**4a** and **4b**) were prepared in a seven step synthesis starting from ethyl cyclopentanonecarboxylate (**5**). Aminolysis of the β-keto ester (**5**) with benzylamine led to the β-keto amide (**9**) which gave the α-substituted β-keto amide (**10**) by addition of acrolein. Reduction of **10** with $LiAlH_4$ resulted in a reductive cyclization yielding a mixture of the epimeric spirocyclic alcohols (**12a** and **12b**, 3:1). Oxidation of the alcohols (**12a** and **12b**) was archieved with $(COCl)_2$/DMSO giving the spirocyclic ketone (**14**). Treatment of **14** with tosylmethyl isocyanide and *tert*-BuOK yielded a mixture of diastereomeric nitriles (**15a** and **15b**, 6:4) which was separated by chromatography. Hydrolysis and esterification of **15a** and **15b** led to the diastereomerically pure amino acid esters (**4a** and **4b**) which represent novel analogs of GABA with restricted conformational flexibility.

INTRODUCTION

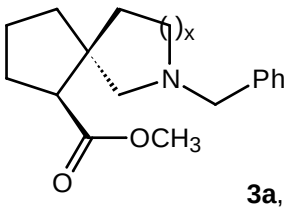
γ-Aminobutyric acid (GABA) is one of the most important inhibitory neurotransmitters involved in the control of neuronal activity in virtually all regions of the mammalian central nervous system.[1-3] GABA uptake inhibitors enhance the concentration of GABA in the synaptic cleft and as a result they potentiate the GABA-ergic neurotransmission. The development of new GABA uptake inhibitors is a valuable objective, because they act as GABA-mimetic drugs where GABA is physiological released. Cyclic amino acids such as nipecotic acid and guvacine have been shown to inhibit GABA uptake. However these small amino acids do not readily cross the blood-brain barrier thus limiting their usefulness for *in vivo* experiments.[4,5] A recent strategy to develop systemically active GABA uptake inhibitors is to attach an arylalkyl group to the nitrogen of a GABA analogous amino acid.[6] Indeed such lipophilic analogs of nipecotic acid and guvacine readily cross the blood-brain barrier and have turned out to be potent inhibitors of GABA uptake *in vitro* and *in vivo*.[7]

In contrast to the literature known GABA uptake inhibitors which are mostly constructed by incorporation of the GABA skeleton into flexible ring systems, our novel spirocyclic amino acids (**1-4**) represent GABA analogues which are based on rather rigid ring systems (see scheme 1).[8-11] For further improvement of the lipophilicity we have decided on synthesis of spirocyclic amino acid esters, instead of their corresponding free amino acids, although we know that the *in vitro* activity of the esters will be rather smaller, because we expect a better biological availability and activity *in vivo*.

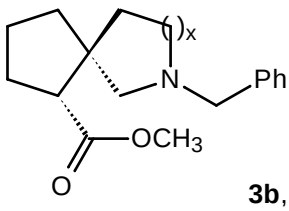
Scheme 1. GABA-analogous amino acid esters based on spirocyclic ring systems.



1, **2**



3a, **4a**



3b, **4b**

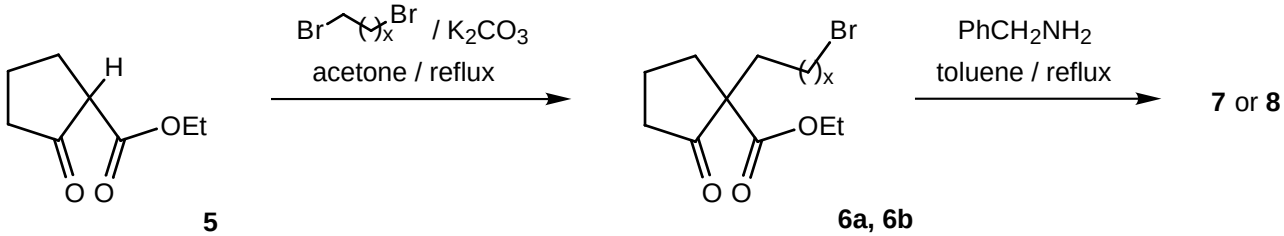
1, **3a**, **3b** x = 1 **2**, **4a**, **4b** x = 2

Recently, we have developed synthetic methods allowing an access to the spirocyclic amino acid esters (**1-3**).[8-11] First biochemical studies on derivatives bearing arylalkyl residues at the nitrogen have revealed a specific activity of such compounds as GABA uptake inhibitors.[10,11] In this paper we want to report on the preparation of *N*-benzyl-7-azaspiro[4.5]decane-1-carboxylates (**4a** and **4b**), which represent analogues of GABA with restricted conformational flexibility.

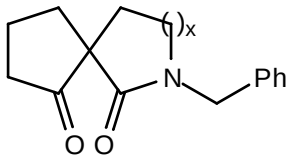
RESULTS AND DISCUSSION

Starting from ethyl cyclopentanonecarboxylate (**5**) we prepared the bromopropyl substituted β-keto ester (**6a**) in good yields (74%) by the procedure of Jarowicki.[12] Treatment of **6a** with benzylamine in refluxing toluene resulted in the substitution of the bromo atom by the benzylamino group, but subsequent cyclization gave in despite of our hopes the bicyclic enamine (**8a**) instead of the desired spirocyclic β-keto lactam (**7a**). This result was in contrast to our previous report[9] on cyclization of the corresponding bromoethyl substituted β-keto ester (**6b**) which exclusively yielded the spirocyclic lactam (**7b**). Obviously the bromoethyl side chain of **6b** was too short for a cyclisation to the bicyclic enamine (**8b**) leading to the fewer constrained spirocyclic lactam (**7b**),[9] while the bromopropyl side chain of **6a** was long enough for the formation of the bicyclic enamine (**8a**).

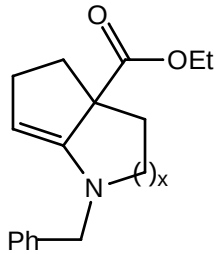
Scheme 2. Cyclization of bromoalkyl substituted β-keto esters (**6a** and **6b**) with benzylamine.



5 **6a, 6b**



7a, 7b



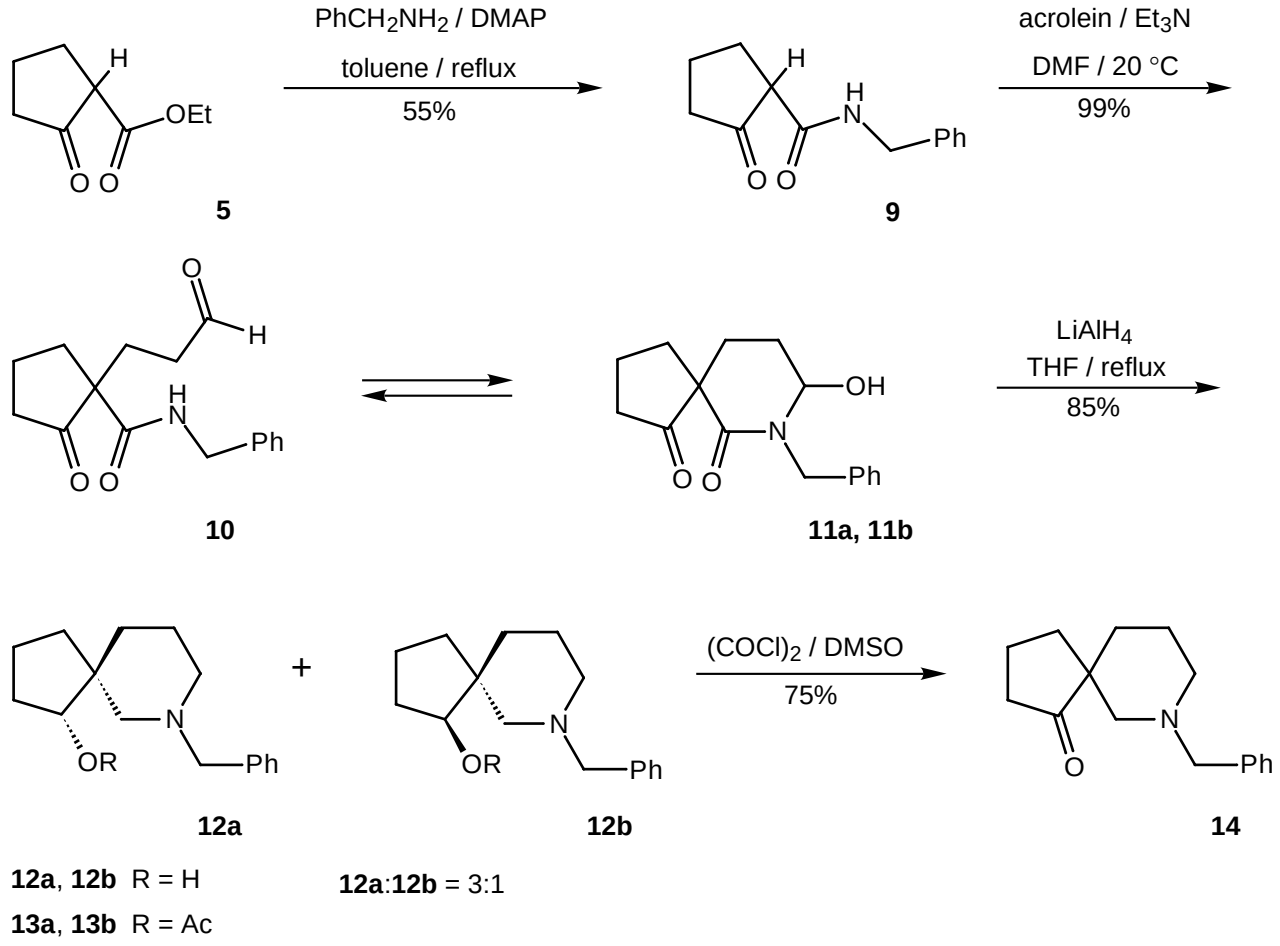
8a, 8b

6a-8a x = 2

6b-8b x = 1

Thus, the first step of our new approach was the aminolysis of the β-keto ester (**5**) to the β-keto amide (**9**) which was archieved by the method of Cossy[13] (see scheme 3). The advantage of this starting step was the fact, that the nitrogen was already fixed in the correct position for the preparation of a spirocyclic lactam. Introduction of the side chain succeeded by conjugate addition of the β-keto amide (**9**) to acrolein leading to the aldehyde (**10**) in excellent yields (99%). However, a complete conversion of **10** to a mixture of the aminals (**11a** and **11b**) occurred by intramolecular addition of the amide to the formyl function on storage for some hours. Reaction of the aldehyde (**10**) or of the mixture of the aminals (**11a** and **11b**) with $LiAlH_4$ resulted in a reductive cyclization yielding a mixture of the spirocyclic alcohols (**12a** and **12b**, 3:1, 85%).

Scheme 3 . Four step synthesis of spirocyclic ketone (**14**) from β-keto ester (**5**).



5 **9** **10** **11a, 11b** **12a** **12b** **14**

12a, **12b** R = H
13a, **13b** R = Ac

12a:**12b** = 3:1

Due to great differences in polarity of the diastereomeric alcohols (**12a** and **12b**), the mixture was well separable by flash chromatography yielding the alcohols (**12a**, 42%; **12b**, 8%) in diastereomerically pure form. The great difference in the chromatographic behavior of **12a** and **12b** allowed to predict the structure of spirocyclic alcohols, because the less polar alcohol should be **12a** fulfilling the sterical demands on formation of an intramolecular hydrogen bridge bond between the nitrogen and the hydroxy group, while the much more polar alcohol should be **12b** bearing this polar groups hindered at an intramolecular interaction by steric circumstances.

A comparison of ^{13}C NMR data (see Table 1) of the alcohols (**12a** and **12b**) and the acetates (**13a** and **13b**) enabled an assignment of carbons, but some ^{13}C NMR resonances of **12a** were slightly ambigous, because we had problems to predict the effect of the intramolecular hydrogen bridge bond to the ^{13}C NMR shifts of **12a**. Finally, we proved the correctness of the assignment by an carbon-carbon correlation spectrum of **12a**.

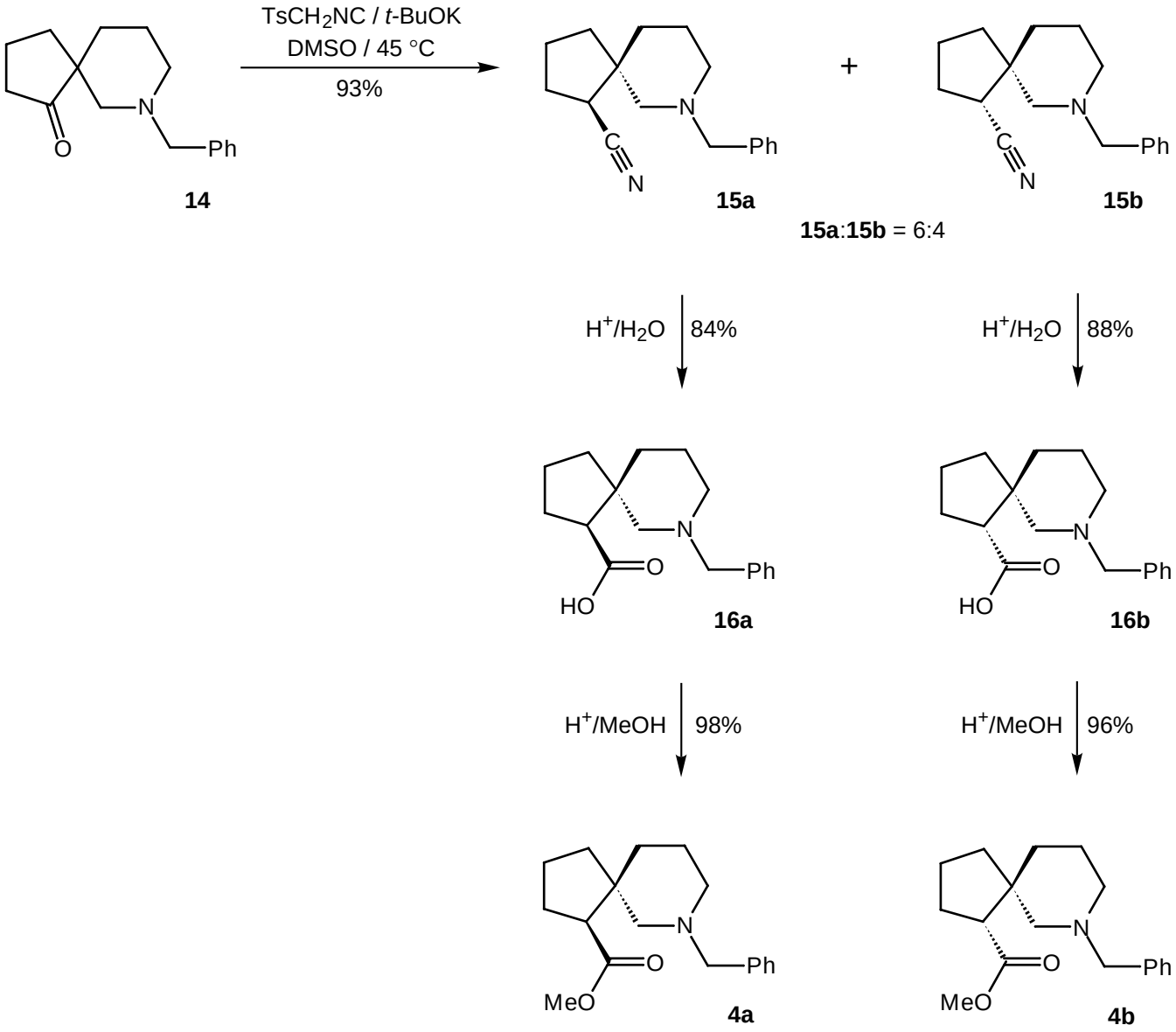
Table 1. ^{13}C NMR Shifts ($CDCl_3$, δ in ppm) of *N*-Benzyl-7-azaspiro[4.5]decanes (**11-14**).

	11a	**11b**	**12a**	**12b**	**13a**	**13b**	**14**
C-1	218.89	216.89	80.39	79.74	80.58	80.31	222.01
C-2	38.86	37.58	35.51	32.05	30.65	30.01	38.06
C-3	19.67	19.46	21.11	19.54	20.33	20.65	18.97
C-4	36.25	36.01	38.26	34.54	34.31	34.30	33.60
C-5	56.70	55.92	42.65	45.29	45.78	46.36	50.22
C-6	170.77	170.64	61.21	63.28	58.14	61.44	57.72
C-8	78.30	78.66	52.86	54.52	54.37	54.35	54.05
C-9	27.61	26.46	22.77	23.22	22.72	23.13	22.16
C-10	24.79	24.66	36.98	29.61	33.62	30.99	30.74
Benzyl-C	46.95	47.33	63.04	63.28	63.46	63.00	62.98
C-1'	137.31	136.84	137.24	138.59	139.10	138.98	138.66
C-2', C-6'	128.48	128.53	128.94	128.69	128.67	128.52	128.59
C-3', C-5'	127.82	127.24	129.24	128.14	127.95	128.03	128.09
C-4'	127.19	127.08	127.16	126.65	126.56	126.68	126.80

Typical shift differences of C-6 and C-10 in ^{13}C NMR spectra of alcohols (**12a** and **12b**) and acetates (**13a** and **13b**) were caused by the γ-gauche effect[14] of the vicinal hydroxy or acetoxy functions either to C-6 in **12a** and **13a** or to C-10 in **12b** and **13b**. Thus, we were able to determine the relative configuration at the asymmetric carbons of **12a** and **13a** (1R*,5S*) and at the chiral centers of **12b** and **13b** (1R*,5R*).

Next we wanted to introduce a cyano group at the C-1 of the spirocyclic ring system. But our attempts to substitute the hydroxy groups of **12a** and **12b** failed, obviously due to neopentyl structure of the alcohols. Thus, we oxidized the mixture of the alcohols (**12a** and **12b**) with $(COCl)_2$/DMSO (see Scheme 3) and obtained the spirocyclic ketone (**14**) in good yields (75%). Then the spirocyclic ketone (**14**) was reacted with tosylmethyl isocyanide/*tert*-BuOK (see Scheme 4) leading to a mixture of diastereomeric nitriles (**15a** and **15b**, 6:4) in 93% yield. After chromatographic separation we isolated the nitriles (**15a**, 47%) and (**15b**, 27%) as pure diastereomers (de > 99%, HPLC). Characteristic shift differences of C-6 and C-10 in ^{13}C NMR spectra of nitriles (**15a** and **15b**), which were caused by the γ-gauche effect[14] of the vicinal cyano group either to C-10 in **15a** or to C-6 in **15b**, allowed an assignment of structure (see Table 2).

Scheme 4 . Conversion of spirocyclic ketone (**14**) to spirocyclic amino acid esters (**4a** and **4b**).



Transformation of the spirocyclic nitriles (**15a** and **15b**) to the corresponding amino acid esters (**4a** and **4b**) required rather drastic reaction conditions. Hence, pinner reaction of the nitriles (**15a** and **15b**) in methanolic hydrochloric acid gave after refluxing for 16 h only 24% of the desired amino acid esters (**4a** and **4b**). More successful was a two step procedure reacting first the nitriles (**15a** and **15b**) to the amino acids (**16a** and **16b**) and secondly to the desired amino acid esters (**4a** and **4b**). Starting from of the mixture of nitriles (**15a** and **15b**, 6:4) we obtained by this procedure a mixture of the desired spirocyclic amino acid esters (**4a** and **4b**, 6:4) in good yield (90%), but in despite of our hopes no chromatograhic resolution of the diastereomeric esters (**4a** and **4b**) was possible due to exceptional similarity of chromatographic properties. Thus, we used the diastereomerically pure nitriles (**15a** and **15b**) and prepared the corresponding amino acids (**16a** and **16b**) by hydrolysis with hydrochloric acid. Subsequent esterification with an excess of sulfuric acid in methanol gave the diastereomerically pure (de > 95%, NMR) amino acid esters (**4a** and **4b**) in an overall yield of 82-84%.

Table 2. ^{13}C NMR Shifts ($CDCl_3$, δ in ppm) of *N*-Benzyl-7-azaspiro[4.5]decanes (**4**, **15** and **16**).

	4a	**4b**	**15a**	**15b**	**16a**	**16b**
C-1	52.09	53.15	36.67	38.19	54.62	54.36
C-2	28.01	28.60	29.28	29.20	26.63	29.86
C-3	22.88	22.84	22.23	22.28	19.40	21.30
C-4	35.61	36.64	35.50	35.06	40.40	39.83
C-5	46.98	46.68	46.29	45.94	43.25	43.84
C-6	63.01	60.03	61.60	60.19	63.02	59.26
C-8	54.36	53.61	54.02	53.32	52.72	50.86
C-9	23.10	23.31	23.11	23.15	20.73	21.39
C-10	32.19	36.78	33.07	35.06	29.75	35.99
Benzyl-C	63.15	63.18	62.69	62.96	61.56	61.25
C-1'	139.17	138.82	138.63	138.61	133.56	132.71
C-2', C-6'	128.54	128.73	128.47	128.74	129.43	129.64
C-3', C-5'	128.06	127.93	128.10	127.97	128.53	128.52
C-4'	126.69	126.62	126.85	126.74	127.99	128.19
CN	-	-	121.83	121.18	-	-
COO	175.78	175.26	-	-	176.35	177.55
OCH_3	51.03	51.05	-	-	-	-

Typical shift differences of C-6 and C-10 in ^{13}C NMR spectra of spirocyclic amino acid esters (**4a**) and (**4b**) were caused by the γ-gauche effect[14] of the vicinal ester function either to C-10 in **4a** or to C-6 in **4b**. Hence, we were able to determine the relative configuration at the asymmetric carbons of **4a** (1R*,5S*) and at the chiral centers of **4b** (1R*,5R*).

ACKNOWLEDGEMENT

M. Bendl thanks the "Bundesministerium für Wissenschaft und Forschung" for a scholarship.

EXPERIMENTAL

The melting points were determined with a KOFLER melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance DPx200 or a Varian unity plus 300 spectrometer, using TMS as an internal standard. A carbon-carbon correlation spectrum of **12a** was detected by Richter using the INADEQUATE pulse sequence.[15] The HPLC system consisted of a Shimadzu pump (LC-10AD), a Reodyne injection valve (20 µl), a Merck column (250×5 mm, LiChrospher Si 60, 5 µm), a Shimadzu UV/VIS detector (SPD-10A, 262 nm), and a Borwin integration system (software version 1.21). The MPLC system was composed of a Büchi pump (B-688), a gradient former (B-687) a Büchi injection valve (20 mL), a Büchi column (460×36 mm, LiChrospher Si 60, 15-25 µm), a Knauer UV/VIS detector (K-2000, 254 nm), a Knauer Refractometer (A0301), a Büchi fraction collector (B-684) and a Borwin integration system. Microanalyses were determined by Theiner (Institute of Physical Chemistry).

(1R*,5S*)-Methyl *N*-benzyl-7-azaspiro[4.5]decane-1-carboxylate (4a)

In the teflone tube of an autoclave the amino acid (**16a**, 4.42 g, 16.2 mmol) was dissolved in methanol (100 mL), sulfuric acid (96%, 6.61 g, 64.7 mmol) was added and the mixture was heated to 110 °C for 16 h. Then the solvent was distilled off *in vacuo*, the residue was dissolved in CH_2Cl_2 (100 mL), the organic layer was washed with aqueous solution of NH_3 (2N, 150 mL) and the aqueous layer was extracted with CH_2Cl_2 (4×100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent distilled off *in vacuo* to yield of **4a** (4.56 g, 98%, colorless oil). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.39 - 7.16 (m, 5H, aromatic H), 3.66 (s, 3H, OCH_3), 3.50 (d, J = 13.8 Hz, 1H, benzyl-H), 3.41 (d, J = 13.8 Hz, 1H, benzyl-H), 2.65 - 2.47 (m, 2H), 2.25 - 1.97 (m, 3H), 1.97 - 1.30 (m, 9H), 1.20 (m_c, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ see Table 2. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found C, 75.04; H, 8.58; N, 4.73.

(1R*,5R*)-Methyl *N*-benzyl-7-azaspiro[4.5]decane-1-carboxylate (4b)

In the teflone tube of an autoclave the amino acid (**16b**, 3.50 g, 12.8 mmol) was dissolved in methanol (100 mL), sulfuric acid (96%, 5.23 g, 51.2 mmol) was added and the mixture was heated to 110 °C for 16 h. Then the solvent was distilled off *in vacuo*, the residue was dissolved in CH_2Cl_2 (100 mL), the organic layer was washed with aqueous solution of NH_3 (2N, 150 mL) and the aqueous layer was extracted with CH_2Cl_2 (4×100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent distilled off *in vacuo* to yield of **4b** (3.53 g, 96%, colorless oil). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.39 - 7.15 (m, 5H, aromatic H), 3.62 (s, 3H, OCH_3), 3.48 (d, J = 13.3 Hz, 1H, benzyl-H), 3.34 (d, J = 13.3 Hz, 1H, benzyl-H), 2.46 (t, J = 8.3 Hz, 2H, H-8), 2.30 (d, J = 11.0 Hz, 1H, H-6), 2.20 - 1.27 (m, 12H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ see Table 2. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found C, 75.07; H, 8.64; N, 4.69.

Ethyl *N*-benzyl-2,3,4,4a,5,6-hexahydro-1*H*-1-pyrindine-4a-carboxylate (8a)

A solution of **6a**[12] (500 mg, 1.8 mmol) and benzylamine (580 mg, 5.4 mmol) in toluene (20 mL) was refluxed for 16 h. Then HCl (2 M, 20 mL) was added and the mixture was stirred at 20 °C for 1 h. The organic layer was separated and washed with HCl (2 M). The combined aqueous layers were basified with NH_3 (2 M) and extracted with ether. The ether layer was washed with a solution of NH_4Cl (5%), dried (Na_2SO_4) and the solvent was evaporated to give **8a** (397 mg, 77%, colorless oil). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 - 7.15 (m, 5H, aromatic H), 4.59 (m_c, 1H, H-7), 4.25 (d, J =14.5 Hz, 1H, benzyl-H), 4.18 (q, J = 7.1 Hz, 2H, OCH_2), 3.70 (d, J = 14.5 Hz, 1H, benzyl-H), 2.88 (dddd, J = 10.4, 3.4, 2.4 and 1.3 Hz, 1H), 2.55 (dt, J = 12.9 and 3.2 Hz, 1H), 2.44 - 2.27 (m, 2H), 2.23 - 2.11 (m, 2H), 1.86 - 1.54 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H, CH_3), 1.22 (dt, J = 3.8 and 13.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.70 (COO), 149.75 (C-7a), 138.63 (C-1'), 128.02 (C-2' , C-6'), 127.78 (C-3' , C-5'), 126.58 (C-4'), 101.62 (C-7), 60.34 (OCH_2), 57.24 (benzyl C), 54.92 (C-4a), 51.20 (C-2), 37.43 (C-6), 34.79 (C-5), 27.97 (C-3), 22.80 (C-4), 14.23 (CH_3). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found C, 75.51; H, 7.99; N, 4.78.

Conjugate addition of 9 to acrolein:

A solution of **9**[13] (12.28g, 56.5 mmol), acrolein (3.49 g, 62.2 mmol) and triethylamine (573 mg, 5.7 mmol) in DMF (300 mL) was stirred at 20 °C for 3 h. Then the solvent was removed *in vacuo* to give **10** (15.30 g, 99%, colorless oil).

***N*-Benzyl-2-oxo-1-(3-oxopropyl)cyclopentanecarboxamide (10)**

^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.70 (s, 1H, formyl H), 7.50 - 7.00 (m, 6H, NH, aromatic H), 4.50 (dd, J = 16.0 and 5.3 Hz, 1H, benzyl H), 4.30 (dd, J = 16.0 and 5.3 Hz, 1H, benzyl H), 3.00 - 1.60 (m, 10H).

After storage for some hours, a complete conversion of **10** to a mixture of the diastereomeric aminals (**11a** and **11b**) occurred. For analytical purposes the mixture of diastereomers (1 g) was separated by flash chromatography (silica gel, 100 g; hexane:EtOAc = 1:1) to yield **11a** (171 mg, 17%, colorless crystals, mp 123 °C, R_f = 0.28) and **11b** (313 mg, 31%, colorless crystals, mp 113 °C, R_f = 0.22).

***N*-Benzyl-8-hydroxy-7-azaspiro[4.5]decane-1,6-dione (11a)**

^{1}H-NMR (300 MHz, $CDCl_3$, 300 MHz): δ 7.36 - 7.20 (m, 5H, aromatic H), 5.11 (d, J = 15.0 Hz, 1H, benzyl H), 4.86 (m_c, 1H, H-8), 4.26 (d, J = 15.0 Hz, 1H, benzyl H), 3.72 (d, J = 8.8 Hz, 1H, OH), 2.70 - 2.47 (m, 2H), 2.45 - 2.19 (m, 3H), 2.06 - 1.82 (m, 4H), 1.57 (dt, J = 13.7 and 4.7 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) see Table 1. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found C, 70.02; H, 6.96; N, 5.10.

***N*-Benzyl-8-hydroxy-7-azaspiro[4.5]decane-1,6-dione (11b)**

^{1}H-NMR (300 MHz, $CDCl_3$, 300 MHz): δ 7.37 - 7.21 (m, 5H, aromatic H), 5.08 (d, J = 15.2 Hz, 1H, benzyl H), 4.94 (m_c, 1H, H-8), 4.35 (d, J = 15.2 Hz, 1H, benzyl H), 2.89 (d, J = 5.8 Hz, 1H, OH), 2.82 (m_c, 1H), 2.41 (m_c, 2H), 2.37 - 2.11 (m, 2H), 2.00 - 1.81 (m, 3H), 1.78 - 1.66 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) see Table 1. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found C, 70.19; H, 7.30; N, 5.06.

Reduction of 10 to alcohols (12a) and (12b):

In an argon atmosphere **10** (15.30 g, 56.0 mmol) was dissolved in dry THF (300 mL), the solution was cooled to 0 °C and $LiAlH_4$ (220 mL, 1M in THF, 220 mmol) was added. After the reaction mixture was refluxed for 2 h, water (16 mL) was added dropwise and stirring was continued for 1 h. Then the precipitate was filtered off and washed with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a mixture of **12a** and **12b** (3:1, 11.7 g, 85%, colorless oil). For analytical purposes the mixture of diastereomers (1 g) was separated by flash chromatography (silica gel, 100 g, hexane:EtOAc:Et_3N = 85:10:5) to yield **12a** (512 mg, 42%, colorless oil, R_f = 0.56) and **12b** (100 mg, 8%, colorless oil, R_f = 0.39).

(1R*,5S*)-*N*-Benzyl-7-azaspiro[4.5]decan-1-ol (12a)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46 - 7.09 (m, 5H, aromatic H), 6.02 (br s, 1H, OH), 3.90 (t, J = 6.6 Hz, 1H, H-1), 3.53 (d, J = 12.9 Hz, 1H, benzyl H), 3.33 (d, J = 12.9 Hz, 1H, benzyl H), 3.00 (d, J = 11.2 Hz, 1H, H-6), 2.85 (m_c, 1H, H-8), 2.03 (m_c, 1H, H-8), 1.92 (d, J = 11.2 Hz, 1H, H-6), 1.90 - 1.77 (m, 2H), 1.68 - 1.40 (m, 5H), 1.39 - 1.20 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 1. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found C, 78.33; H, 9.59; N, 5.63.

(1R*,5R*)-*N*-Benzyl-7-azaspiro[4.5]decan-1-ol (12b)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33 - 7.19 (m, 5H, aromatic H), 3.94 (t, J = 5.9 Hz, 1H, H-1), 3.48 (d, J = 13.3 Hz, 1H, benzyl H), 3.41 (d, J = 13.3 Hz, 1H, benzyl H), 2.53 (m_c, 1H, H-8), 2.29 (m_c, 1H, H-8), 2.23 (d, J = 10.8 Hz, 1H, H-6), 2.04 (d, J = 10.8 Hz, 1H, H-6), 1.98 - 1.38 (m, 10H), 1.25 (m_c, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 1. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found C, 78.02; H, 9.63; N, 5.55.

(1R*,5S*)-1-Acetoxy-*N*-benzyl-7-azaspiro[4.5]decane (13a)

A solution of **12a** (491 mg, 2 mmol) and DMAP (293 mg, 2.4 mmol) in acetic anhydride (5 mL, 53 mmol) was stirred at 20 °C for 16 h. Then the excess acetic anhydride was distilled off *in vacuo*. The residue was dissolved in CH_2Cl_2, the organic layer was washed with $NaHCO_3$ (5%), dried (Na_2SO_4) and the solvent distilled off at reduced pressure. Purification of the crude product by flash chromatography (silica gel, 50 g, hexane:EtOAc:Et_3N = 80:15:5) gave **13a** (410 mg, 71%, colorless oil, R_f = 0.67). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33 - 7.18 (m, 5H, aromatic H), 4.96 (m_c, 1H, H-1), 3.44 (d, J = 13.4 Hz, 1H, benzyl H), 3.39 (d, J = 13.4 Hz, 1H, benzyl H), 2.44 - 2.25 (m, 3H, H-6, H-8), 2.19 (d, J = 10.7 Hz, 1H, H-6), 2.01 (m_c, 1H), 1.88 (s, 3H, CH_3), 1.82 - 1.54 (m, 6H), 1.50 - 1.34 (m, 2H), 1.23 (m_c, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.55 (COO), 21.05 (CH_3); for further signals see Table 1. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found C, 75.46; H, 9.00; N, 4.80.

(1R*,5R*)-1-Acetoxy-*N*-benzyl-7-azaspiro[4.5]decane (13b)

A solution of **12b** (491 mg, 2 mmol) and DMAP (293 mg, 2.4 mmol) in acetic anhydride (5 mL, 53 mmol) was stirred at 20 °C for 16 h. Then the excess acetic anhydride was distilled off *in vacuo*. The residue was dissolved in CH_2Cl_2, the organic layer was washed with $NaHCO_3$ (5%), dried (Na_2SO_4) and the solvent distilled off at reduced pressure. Purification of the crude product by flash chromatography (silica gel, 50 g, hexane:EtOAc:Et_3N = 90:5:5) gave **13b** (320 mg, 56%, colorless oil, R_f = 0.52). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34 - 7.19 (m, 5H, aromatic H), 5.07 (m_c, 1H, H-1), 3.44 (s, 2H, benzyl H), 2.36 (m_c, 1H, H-8), 2.10 (d, J = 10.9 Hz, 1H, H-6), 2.04 (s, 3H, CH_3), 2.00 (d, J = 10.9 Hz, 1H, H-6), 1.86 (m_c, 1H), 1.78 - 1.40 (m, 8H), 1.30 (m_c, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.63 (COO), 21.17 (CH_3); for further signals see Table 1. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found C, 75.44; H, 8.60; N, 4.78.

***N*-Benzyl-7-azaspiro[4.5]decan-1-one (14)**

A solution of $(COCl)_2$ (4.79 g, 54.9 mmol) in CH_2Cl_2 (120 mL) was cooled to -60 °C, a solution of DMSO (8.91 g, 114 mmol) in CH_2Cl_2 (6 mL) was added and the mixture was stirred at -60 °C for 10 min. Then a mixture of the diastereomeric alcohols (**12a**:**12b** = 3:1, 11.7 g, 47.8 mmol) dissolved in CH_2Cl_2 (40 mL) was added and the mixture was stirred at -60 °C for 15 min. After Et_3N (33.1 mL, 239 mmol) was added, the mixture was allowed to warm up to 20 °C, a solution of NaOH (240 mL, 2 M) was added and the reaction mixture was extracted with CH_2Cl_2 (3×70 mL). The organic layer was dried (Na_2SO_4) and the solvent distilled off at reduced pressure. Purification by flash chromatography (silica gel 800 g, hexane:Et_3N = 95:5) gave **14** (8.72 g, 75%, colorless oil, R_f = 0.32). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35 - 7.17 (m, 5H, aromatic H), 3.55 (d, J = 13.3 Hz, 1H, benzyl H), 3.37 (d, J = 13.3 Hz, 1H, benzyl H), 2.82 (m_c, 1H, H-8), 2.40 (d, J = 11.0 Hz, 1H, H-6), 2.30 - 2.15 (m, 3H), 2.04 (m_c, 1H),1.93 (d, J = 11.0 Hz, 1H, H-6), 1.90 - 1.17 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 1. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found C, 78.74; H, 9.00; N, 5.53.

Conversion of ketone (14) to nitriles (15a) and (15b):

In an argon atmosphere a solution of tosylmethyl isocyanide (21.92 g, 112 mmol) in dry DMSO (130 mL) was cooled to 0 °C, reacted with *tert*-BuOK (26.86 g, 239 mmol) and stirred at 20 °C for 10 min. Then methanol (9.8 mL) and a solution of **14** (11.58 g, 47.6 mmol) in dry DMSO (16 mL) were added and the resulting mixture was heated to 45 °C for 5 d. After addition of a solution of $NaHCO_3$ (5%, 190 mL) the mixture was extracted with ether (3×300 mL). The combined organic layers were washed with a solution of $NaHCO_3$ (5%, 3×200 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a mixture of **15a** and **15b** (6:4, 11.20 g, 93%).

In four sequential runs the mixture of diastereomers was separated by MPLC (petroleum ether:Et_3N = 97:3) to yield **15a** (5.65 g, 47%, colorless oil) and **15b** (3.31 g, 27%, colorless oil) with a diastereomeric excess of >99%. The purity of the chromatographic fractions was determined by HPLC (solvent petroleum ether:Et_3N = 97:3, flow 2 mL/min, **15a** R_t = 4.68 min, **15b** R_t = 5.85 min).

(1R*,5S*)-*N*-Benzyl-7-azaspiro[4.5]decane-1-carbonitrile (15a)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33 - 7.20 (m, 5H, aromatic H), 3.49 (d, J = 13.2 Hz, 1H, benzyl H), 3.42 (d, J = 13.2 Hz, 1H, benzyl H), 2.98 (m_c, 1H), 2.54 (m_c, 1H), 2.30 (m_c, 1H), 2.20 (d, J = 11.2 Hz, 1H, H-6), 2.00 - 1.60 (m, 11H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ see Table 2. Anal. Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found C, 80.22; H, 8.63; N, 10.98.

(1R*,5R*)-*N*-Benzyl-7-azaspiro[4.5]decane-1-carbonitrile (15b)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 - 7.20 (m, 5H, aromatic H), 3.62 (d, J = 13.3 Hz, 1H, benzyl H), 3.40 (d, J = 13.3 Hz, 1H, benzyl H), 2.58 (t, J = 7.8 Hz, 1H, H-1), 2.48 (m_c, 1H, H-8), 2.40 (s, 2H, H-6), 2.25 (m_c, 1H, H-8), 2.10 - 1.25 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ see Table 2. Anal. Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found C, 80.07; H, 8.89; N, 10.99.

(1R*,5S*)-*N*-Benzyl-7-azaspiro[4.5]decane-1-carboxylic acid (16a)

The nitrile (**15a**, 1.00 g, 3.93 mmol) was dissolved in hydrochloric acid (12N, 50 mL) and the mixture was refluxed for 6 h. After cooling to 20 °C the mixture was basified with NH_3 (6N, 110 mL) and extracted with CH_2Cl_2 (4×100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent distilled off *in vacuo* to yield a mixture of **15a** and **16a** (15:85, 1.05 g, 99%). The residue was dissolved in CH_2Cl_2 (20 mL), washed with NaOH (1N, 2×30 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent distilled off *in vacuo* to yield unreacted nitrile (**15a**, 150 mg, 15%), colorless oil. The aqueous layer was acidified with hydrochloric acid (6N, 15 mL), basified with an aqueous solution of NH_3 (6N, 15 mL) and then extracted with CH_2Cl_2 (5×100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent distilled off *in vacuo* to yield **16a** (900 mg, 84%, **16a:16b** = 94:6, colorless oil). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 13.32 (s, 1H, COOH), 7.35 (s, 5H, aromatic H), 3.70 (s, 2H, benzyl-H), 3.05 (m_c, 1H, H-8), 2.79 (d, J = 11.7 Hz, 1H, H-6), 2.41 (m_c, 1H, H-1), 2.40 (d, J = 11.7 Hz, 1H, H-6), 2.29 - 1.83 (m, 5H), 1.80 - 1.36 (m, 5H), 1.13 (m_c, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ see Table 2. Potentiometric tiration: pK_1 = 3.69, pK_2 = 9.29, pH_i = 6.49. Anal. Calcd for $C_{17}H_{23}NO_2 \cdot H_2O$: C, 70.07; H, 8.65; N, 4.81. Found C, 70.18; H, 8.35; N, 4.72.

(1R*,5R*)-*N*-Benzyl-7-azaspiro[4.5]decane-1-carboxylic acid (16b)

The nitrile (**15b**, 1.00 g, 3.93 mmol) was dissolved in hydrochloric acid (12N, 50 mL) and the mixture was refluxed for 6 h. After cooling to 20 °C the mixture was basified with NH_3 (6N, 110 mL) and extracted with CH_2Cl_2 (4×100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent distilled off *in vacuo* to yield a mixture of **15b** and **16b** (11:89, 1.05 g, 99%). The residue was dissolved in CH_2Cl_2 (20 mL), washed with NaOH (2N, 2×30 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent distilled off *in vacuo* to yield unreacted nitrile (**15b**, 110 mg, 11%), colorless oil. The aqueous layer was acidified with hydrochloric acid (6N, 15 mL), basified with an aqueous solution of NH_3 (6N, 15 mL) and then extracted with CH_2Cl_2 (5×100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent distilled off *in vacuo* to yield **16b** (940 mg, 88%, **16b:16a** = 94:6, colorless oil). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 12.25 (s, 1H, COOH), 7.36 (s, 5H, aromatic H), 3.91 (d, J = 12.7 Hz, 1H, benzyl-H), 3.44 (d, J = 12.7 Hz, 1H, benzyl-H), 3.07 (d, J = 12.0 Hz, 1H, H-6), 3.01 (m_c, 1H, H-8), 2.68 (t, J = 9.0 Hz, 1H, H-1), 2.26 (d, J = 12.0 Hz, 1H, H-6), 2.21 - 2.04 (m, 3H), 1.88 (m_c, 1H), 1.77 - 1.35 (m, 7H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ see Table 2. Potentiometric tiration: pK_1 = 3.41, pK_2 = 9.13, pH_i = 6.27. Anal. Calcd for $C_{17}H_{23}NO_2 \cdot H_2O$: C, 70.07; H, 8.65; N, 4.81. Found C, 70.06; H, 8.33; N, 4.79.

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