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Synthesis of conformationally restricted glutamic acid analogs based on the spiro[3.3]heptane scaffold

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ABSTRACT

A library of isomeric glutamic acid analogs based on the spiro[3.3]heptane skeleton is designed. Two members of the library, (*R*)- and (*S*)-2-amino-spiro[3.3]heptane-2,6-dicarboxylic acid hydrochlorides, were synthesized. The stereochemistry of the synthesized amino acids was determined using ^{1}H–^{1}H-NOESY of their diastereomeric derivatives. The aminocarboxylate moiety and the carboxylic group in the synthesized glutamic acid analogs are 'fixed' in space relative to each other due to the rigid spirocyclic scaffold and therefore, they can be used to probe topologies of different glutamate receptors.

1. Introduction

Design and synthesis of series of isomeric organic compounds that possess functional groups mounted on a conformationally restricted or rigid scaffold are of interest in medicinal chemistry for structure–activity relationship (SAR) studies.[1] Functional groups in different compounds within such series (libraries) have different rigidly fixed dispositions in space. This can be used for mapping active sites of biological targets, or in the search for the most efficient ligands for them. The rigidity of the scaffold might be beneficial for the biological activity: if the fragments in a conformationally restricted ligand are fixed in space exactly as needed for efficient interaction with a receptor or enzyme, the efficiency of the interaction (due to decreasing of the entropy barrier) can be markedly higher than that for the analogous conformationally flexible ligands.[1]

An example of such libraries is a set of spiro[2.2]pentane derivatives (±)-**1**-(±)-**4** (Fig. 1).[2] Compounds (±)-**1**-(±)-**4** are stereoisomers; therefore, the whole set was called a 'stereolibrary'. All the compounds (±)-**1**-(±)-**4** mimic glutamic acid—an excitatory neurotransmitter in the central nervous system. The spiro[2.2]pentane scaffold fixes the C–C bonds between the functional groups in different conformations; therefore, (±)-**1**-(±)-**4** were expected to interact selectively with different types of glutamate receptors. In fact, compounds (±)-**1**-(±)-**4** showed only modest or no activity at ionotropic and metabotropic glutamate receptors, presumably, because the mutual orientation of the aminocarboxylate moiety and the carboxylic group was unfavorable for the interaction with the receptors.

This library illustrates the importance of scaffold in the design of the libraries, in particular, the ability of the scaffold to accommodate functional groups at different mutual orientations. The spiro[2.2]pentane skeleton allows only a limited number of spatial arrangements of the functional groups, and as a consequence, compounds with high biological activity are missing in the set.

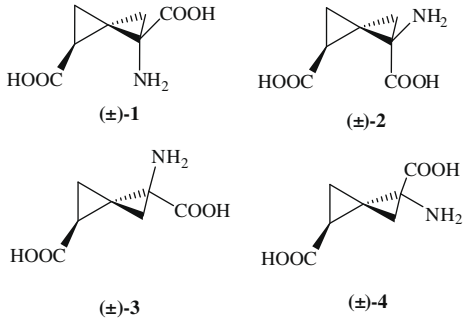

Figure 1. 'Stereolibrary' of glutamic acid analogs composed of spiro[2.2]pentane derivatives (only one enantiomer is shown for each diastereomer).

A more diverse library, based on the norbornane skeleton, was reported;[3] the library is shown in Figure 2 (compounds (±)-**5**-(±)-**12**). Though all these compounds are less active than glutamic acid at the glutamate receptor studied, the authors demonstrated that some of the library members show receptor subtype selectivity. Important conclusions regarding biologically active conformations of the glutamic acid interacting with different subtypes of receptors were drawn on the basis of this study.

2. Results and discussion

In designing a new library of glutamic acid analogs, we focused our attention on the spiro[3.3]heptane skeleton, which allows one

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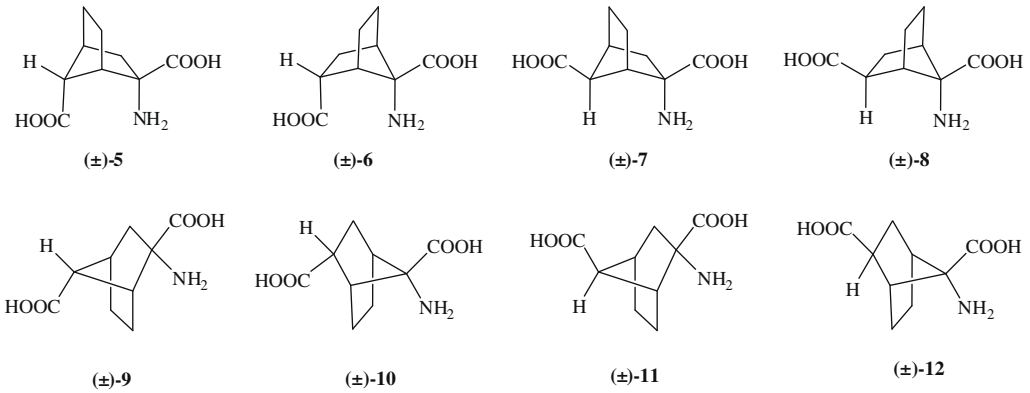


Figure 2. Norbornane-based library of glutamic acid analogs (one enantiomer is shown for each diastereomer).

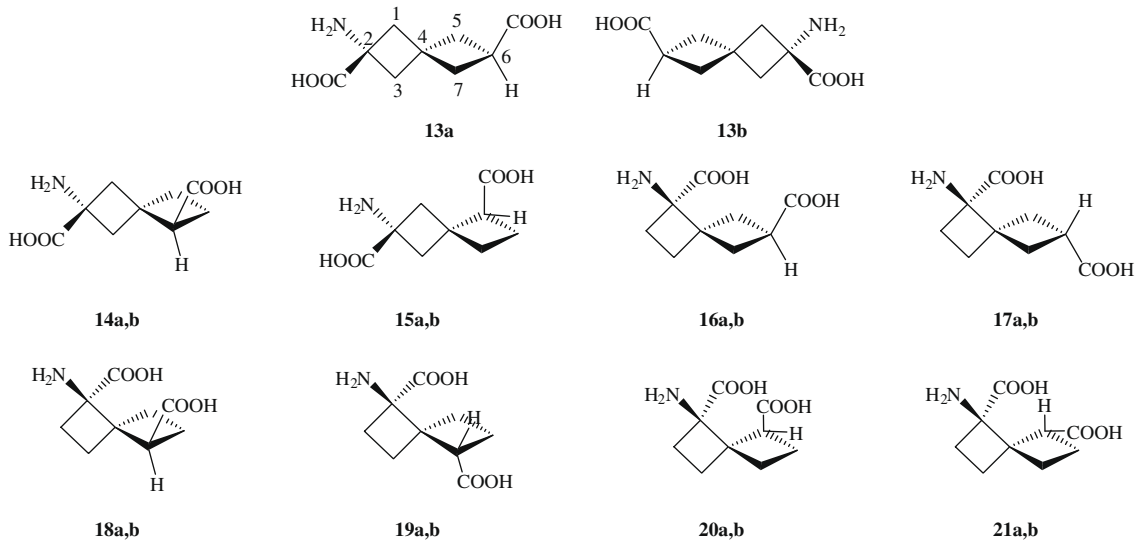


Figure 3. Library of glutamic acid analogs composed of spiro[3.3]heptane derivatives. Only one enantiomer is shown for compounds **14**–**21**.

to synthesize a larger library of isomeric glutamic acid analogs than the known scaffolds. While the above described spiro[2.2]pentane skeleton provides the possibility for synthesis of eight isomeric glutamic acid analogs (four pairs of enantiomers), the spiro[3.3]heptane scaffold, being still sufficiently conformationally restricted, gives rise to 18 isomers **13a,b**–**21a,b** (nine pairs of enantiomers, Fig. 3). Molecular models showed that spatial disposition of the aminocarboxylate moiety and the carboxylic group, essential for the biological activity, is very diverse in the spiro[3.3]heptane series. It should be noted that to the best of our knowledge, the spiro[3.3]heptane scaffold has not been used previously in construction of glutamic acid analogs.

Herein, we report both non-stereoselective and stereoselective syntheses of the first two members of the library, namely, compounds **13a** and **13b**, the molecules of which possess axial dissymmetry. It is appropriate to note here that axially dissymmetric spiro[3.3]heptane derivatives, for example, Fecht's acid (spiro [3.3]heptane-2,6-dicarboxylic acid), captured interest of chemists long ago.[4–6]

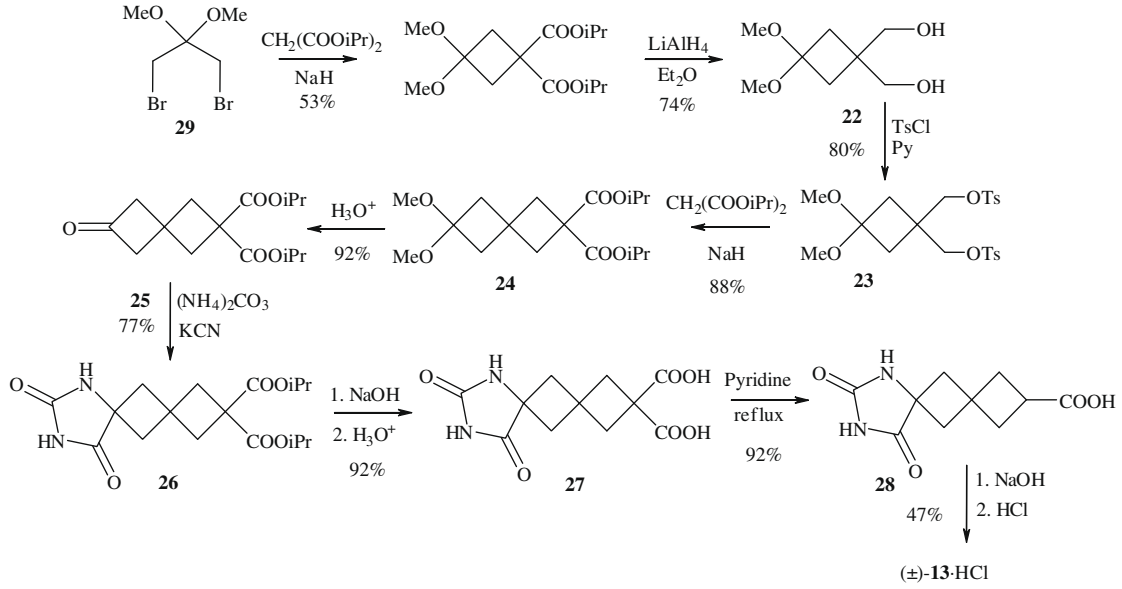
In our syntheses, the construction of the cyclobutane rings was based on malonate chemistry reported more than 100 years ago.[7,8]

Synthesis of the racemic mixture (±)-**13** was performed first in order to find optimal conditions for the formation of the spiro[3.3]heptane scaffold and isolation of the target amino acid (Scheme 1). Compound **22**, which has been described in the literature,[9] was transformed into its (bis)tosyl derivative **23**, which, in turn, was then used to alkylate the diisopropylmalonate in order to form compound **24** possessing the spiro[3.3]heptane core. The following ketal hydrolysis, hydantoine formation, decarboxylation, and hydrolysis led to the target (±)-**13**. The overall yield of the synthesis (calculated on the starting compound **29**) is 8%.

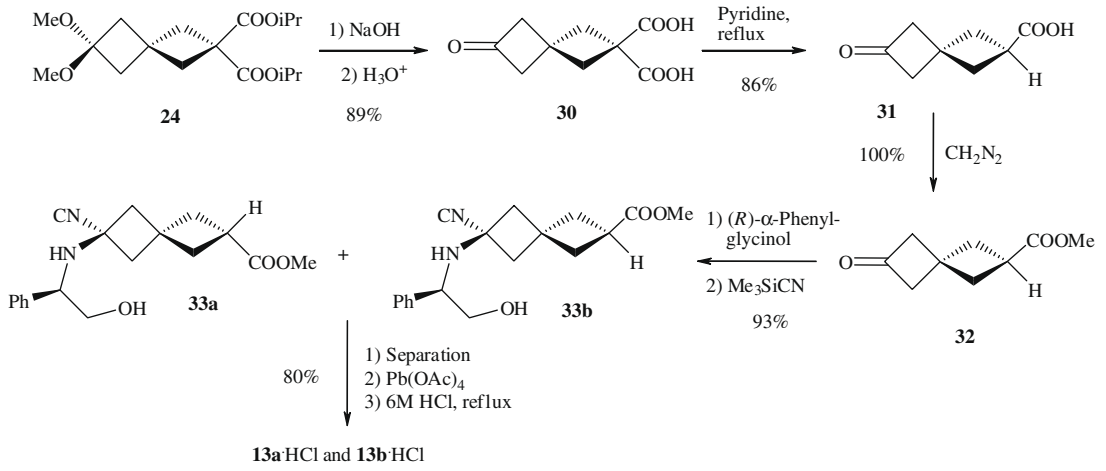
The enantioselective synthesis of **13a** and **13b** was based on the separation of diastereomeric derivatives, as shown in Scheme 2. It commenced from the diester **24,** which was used in the non-stereoselective synthesis. Exhaustive hydrolysis gave the keto-dicarboxylic acid **30**, which was then subjected to the decarboxylation and esterification of the remaining carboxylic group. The resulting keto-ester **32** smoothly underwent the asymmetric Strecker reaction.[10–13]

Diastereoselectivity of the Strecker reaction was very low, but the chiral auxiliary, (*R*)-α -phenylglycinol, allowed chromatographic separation of the ~1:1 mixture of diastereomers **33a** and **33b** on a silica gel column. Removal of the chiral auxiliary completed the synthesis.

The hydrolysis of the nitrile and ester groups in **33a** and **33b** was carried out by prolonged reflux in 6 N HCl, which could cause epimerization at the carbon atom bearing the distal carboxylic group. We suspected this when measuring the specific rotation of the final amino acids **13a**·HCl and **13b**·HCl: it turned out to be surprisingly low for both enantiomers, $[\alpha]_D^{20} = -2$ and +2 corre-



Scheme 1. Synthesis of racemic glutamate analog (±)-**13**·HCl.



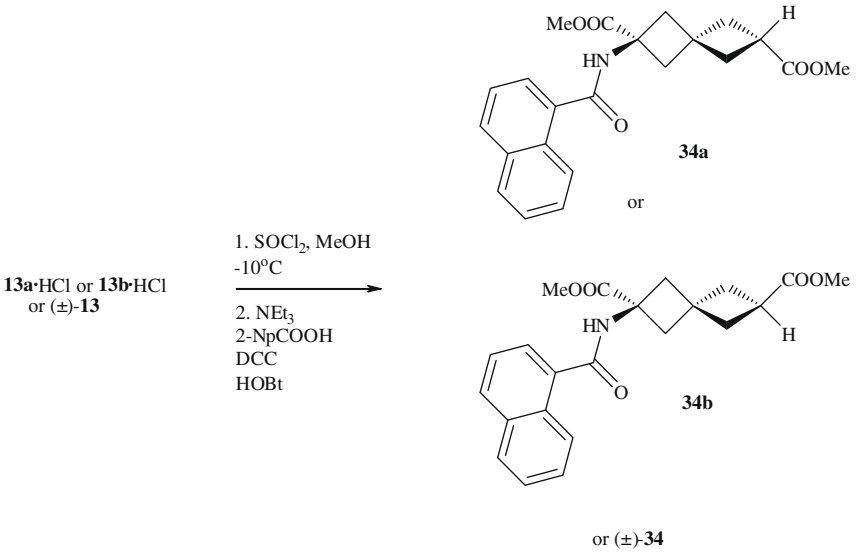
Scheme 2. Synthesis of individual enantiomers **13a**·HCl and **13b**·HCl.

spondingly (*c* 0.78, H_2O). The literature data show that the optical activity for similar compounds can be low indeed;[14] nevertheless, we decided to check the enantiomeric purity of **13a**·HCl and **13b**·HCl (non-crystallized). In order to do this, we transformed the amino acids into the corresponding β-naphthylamide dimethyl esters **34a**,**b** under mild conditions (Scheme 3). Racemic (±)-**34** was synthesized from (±)-**13**·HCl to find optimal conditions for chiral HPLC analysis of the derivatives **34a** and **34b**.

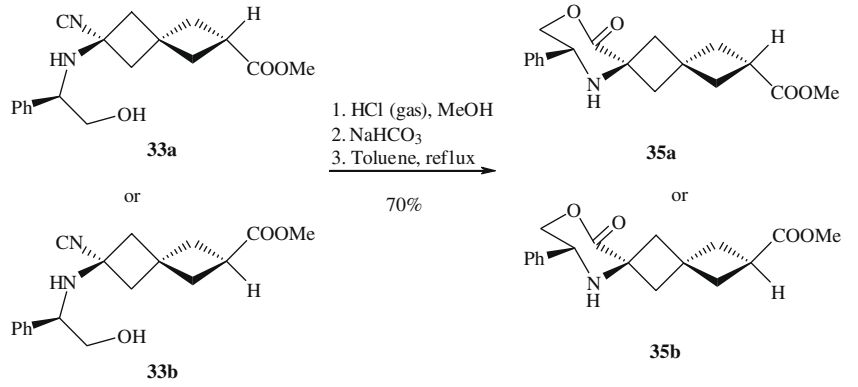
Good separation of enantiomers of the racemic mixture (±)-**34** was achieved on a ChiralPack IB® column. Analysis of the **34a** and **34b** under the same conditions showed that they are not racemic. Moreover, the enantiomeric purity of each compound (~86 ee) was essentially the same as the de of the aminonitriles **33a** and **33b** (determined by the analysis of their ^{1}H NMR spectra). Thus, racemization did not occur at all under the drastic conditions of the last steps of the **13a**·HCl and **13b**·HCl synthesis.

To address the question of absolute stereochemistry, we synthesized cyclic derivatives **35a** and **35b** (Scheme 4) and analyzed them by NMR spectroscopy. As the absolute configuration of the stereogenic carbon center bearing phenyl substituent (C(8)) is known (we used (*R*)-α-phenylglycinol), it was possible to assign stereoisomers based on the correlation patterns in their H,H-NOESY spectra (assignment of the signals in the ^{1}H NMR spectra of **35a,b** was done using DQF-COSY, Long-Range COSY, and HSQC experiments).

For one of the diastereomers, **35a**, there is a continuous path of strong NOE correlations from H(8) to H(2) signals as shown in Figure 4, which proves the configuration shown. Another convincing proof of the stereochemistry of **35a** is the NOE correlation peak H(2)–H(5a) (marked by a red arrow in Fig. 4), possible only for this diastereomer. For the other compound, **35b**, the strong NOE correlation paths from H(8) and from H(2) are not convergent. These facts allow the conclusion that the amino acid **13a** possesses the (a*S*)-configuration, and **13b**—(a*R*). Of course, for the above hypotheses on the stereochemistry of **35a,b** and **13a**,**b** to be correct, one should be sure that the six-membered rings in **35a** and **35b** are in the (flattened) chair conformations, in which the phenyl substituent adopts equatorial position. This assumption is verified by the vicinal coupling constants between H(8) and H(9) in both the **35a** and **35b** ^{1}H NMR spectra. The constants are markedly different (10.5 and 3.5 Hz in **35a**; 10.5 and 2.5 Hz in **35b**) and are characteristic for axial-axial and axial-equatorial couplings, which should be expected for the conformation shown in Figure 4.



Scheme 3.



Scheme 4.

3. Experimental

General: Solvents were purified according to the standard procedures.[15] Compound **29** has been synthesized from acetone following the procedure described in the literature.[16] All other materials were purchased from Acros, Merck, and Fluka. Melting points are uncorrected. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Kieselgel Merck 60 (230-400 mesh) as the stationary phase. ^{1}H-, ^{13}C NMR, and all 2D NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 499.9 MHz for protons, 124.9 MHz for carbon-13). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. HPLC-MS analyses were done on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)). Elemental analysis: Analytical Laboratory of Institute of Organic Chemistry of NAS, Ukraine. Optical rotation values were measured on a PerkinElmer 341 Polarimeter. Chiral HPLC analysis was done at 20 °C on an Agilent 1100 instrument equipped with CHIRALPAK IB® column (4.6*250 mm, 5 mkm), using UV detection (215 nm); eluent—hexane/2-propanol 80:20, flow rate—1.3 mL/min.

3.1. (1-Hydroxymethyl-3,3-dimethoxycyclobutyl)methanol 22

A solution of diisopropyl 3,3-dimethoxycyclobutane-1,1-dicarboxy-late[9] (51 g, 176.9 mmol) in diethyl ether (500 ml) was slowly added to a suspension of $LiAlH_4$ (13.6 g, 358.4 mmol) in diethyl ether (1000 ml) under stirring. After the addition, the mixture was refluxed for 2 h. The excess of the lithium alanate was slowly quenched by water (26.3 ml) (*CAUTION*! Exothermic reaction, use external cooling). The precipitate was filtered off, washed by ether, the filtrate was dried by $MgSO_4$ and evaporated. The resulting diol **22** (23 g, 74%) was sufficiently pure (HPLC-MS analysis) for the next step. ^{1}H NMR ($CDCl_3$), δ: 1.94 (s, 4H, CCH_2C), 3.12 (s, 6H, OCH_3), 3.29 (s, 2H, O*H*), 3.70 (s, 4H, CH_2OH). ^{13}C NMR ($CDCl_3$), δ: 34.15 ((CH$_2$)$_2$C(CH$_2$OH)$_2$), 36.51 (C(*C*H$_2$)$_2$C), 48.23 (O*C*H$_3$), 69.06 (*C*H$_2$OH), 99.41 (*C*(OCH$_3$)$_2$).

3.2. (1-Hydroxymethyl-3,3-dimethoxycyclobutyl)methanol bis-*p*-toluenesulfonate 23

The diol 22 (21.4 g, 121.4 mmol) was dissolved in dry pyridine (200 ml) and cooled by an ice bath. *p*-Toluenesulfonyl chloride (69.2 g, 364.2 mmol) was added in small portions to the cooled solution under stirring in a dry atmosphere. The mixture was left standing overnight. The precipitate was filtered off, the filtrate was carefully poured into water (1000 ml), and the product was extracted with CH_2Cl_2. The extract was washed with 3 N HCl and water, dried by K_2CO_3/$MgSO_4$, and was evaporated to dryness. The product **23** (47 g, 80%) was sufficiently pure (HPLC-MS analysis) for the next step. Mp 110 °C. ^{1}H NMR ($CDCl_3$, δ): 1.92 (s, 4H,

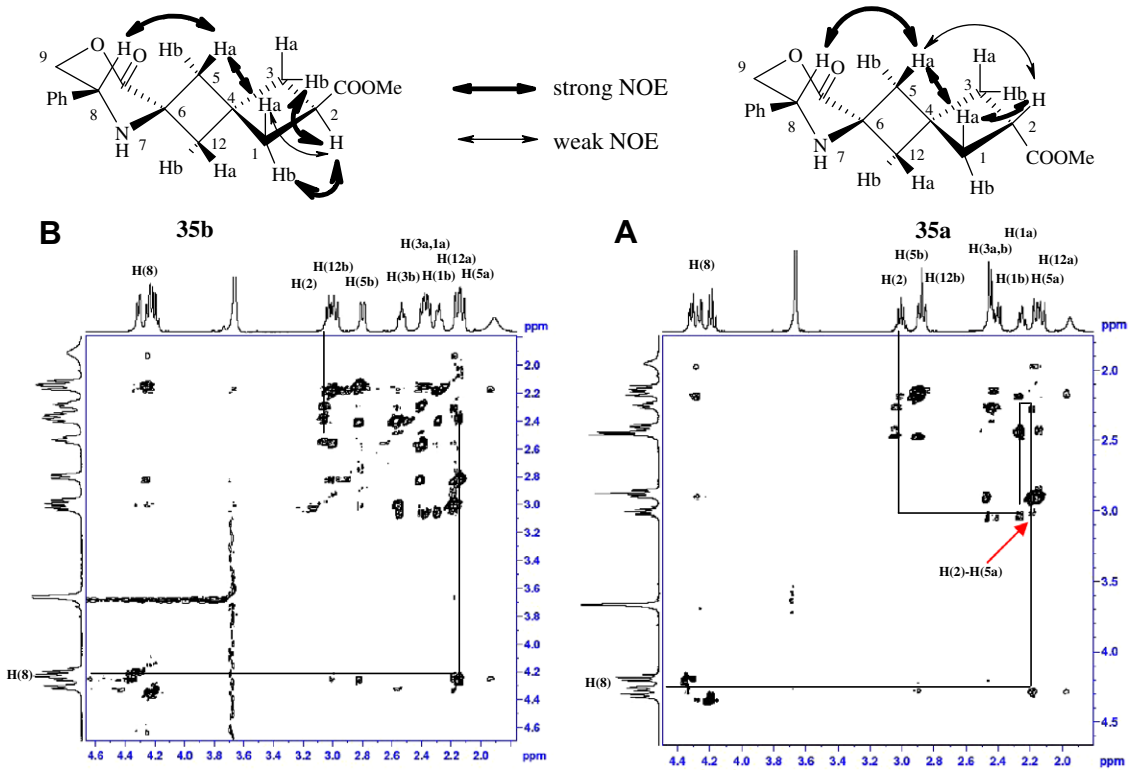


Figure 4. Determination of absolute stereochemistry of **35a** and **35b** by H,H-NOESY experiments, **A** for **35a** and **B** for **35b**.

CH2), 2.46 (s, 6H, Ar-CH_3), 3.01 (s, 6H, OCH_3), 3.99 (s, 4H, CH_2OTs), 7.35 (d, J = 8 Hz, 4H, CH), 7.74 (d, J = 8 Hz, 4H, CH). ^{13}C NMR ($CDCl_3$), δ: 21.67 (Ar-CH_3), 32.42 (C(CH_2)$_4$), 36.53 (cyclic-CH_2), 48.28 (OCH_3), 71.45 (CH_2OTs), 98.31 ((CH_2)$_2$$C(OMe)_2$), 127.93, 129.99, 132.50 (CH_2OSO_2C), 145.09 (CCH_3).

3.3. 6,6-Dimethoxy-spiro[3.3]heptane-2,2-dicarboxylic acid diisopropyl ester 24

Diisopropylmalonate (19.34 g, 103 mmol) was slowly added to a suspension of NaH (60% suspension in mineral oil) (4.94 g, 113 mmol) in dry DMF (120 ml) under stirring at such a rate that the temperature was maintained below 70 °C. The ditosylate **23** (24.9 g, 51 mmol) and KI (0.86 g, 5.1 mmol) were added to the mixture in one portion. The mixture was then stirred at 140 °C for 12 h. Then, it was cooled, poured into saturated aqueous solution of NH_4Cl, and the products were extracted with hexanes. The extract was dried with $MgSO_4$ and evaporated. The residue was distilled in vacuum. The unreacted diisopropylmalonate was distilled off first (64 °C/2 mm), followed by **24** as a colorless oil (125–127 °C/2 mm). The yield was 14.91 g (88%). ^{1}H NMR ($CDCl_3$, δ): 1.22 (d, J = 6.5 Hz, 12H, CH(CH_3)$_2$), 2.20 (s, 4H), 2.57 (s, 4H), 3.11 (s, 6H, OCH_3), 5.04 (septet, J = 6.5 Hz, 2H, CH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$), δ: 21.51 (CH(CH_3)$_2$), 28.94 (C(CH_2)$_4$), 41.13, 44.72, 48.51, 48.97, 68.64 (CH(CH_3)$_2$), 99.57 (C(OMe)$_2$), 171.22 ($COOCH$(CH_3)$_2$).

3.4. 6-Oxo-spiro[3.3]heptane-2,2-dicarboxylic acid diiso-propyl ester 25

Compound **24** (6.32 g, 19.2 mmol) was stirred in 3 M aqueous HCl (63 ml) for 8 h. The precipitate formed was filtered to yield 5 g (92%) of white crystals. Mp 72 °C. ^{1}H NMR ($CDCl_3$, δ): 1.24 (d, J = 6.4 Hz, 12H, CH(CH_3)$_2$), 2.78 (s, 4H, 1-CH_2 and 3-CH_2), 3.14 (s, 4H, 5-CH_2 and 7-CH_2), 5.07 (septet, J = 6.4 Hz, 2H, CH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$), δ: 21.55 (CH(CH)$_3$), 28.06 (CH(CH_3)$_2$), 40.31, 48.62, 59.49, 69.10 (CH(CH_3)$_2$), 170.82 ($COOCH$(CH_3)$_2$), 206.11 (C=O).

3.5. 8,10-Dioxo-7,9-diaza-dispiro[3.1.4.1]undecane-2,2-dicarboxylic acid diisopropyl ester 26

Keto-ester **25** (5 g, 17.7 mmol) was dissolved in a mixture of ethanol (50 ml) and water (20 ml). Potassium cyanide (1.72 g, 26.4 mmol mmol) and ammonium carbonate (7.08 g, 86.3 mmol) were added to the solution. The resulting mixture was stirred at 60 °C for 20 h. Then, pH of the mixture was adjusted to 3 by 3 N HCl. The precipitate of **26** formed was filtered, washed with water, and dried. White powder, 4.82 g (77%). ^{1}H NMR ($CDCl_3$), δ: 1.22 (d, J = 6 Hz, 12H, OCH(CH_3)$_2$), 2.38 (d, J = 13.5 Hz, 2H, NH(CO)C(CH)$_2$), 2.59 (s, 2H, (CH_2)(CH_2)C(COOi-Pr)$_2$), 2.72 (d, J = 13.5 Hz, 2H, NH(CO)C(CH)$_2$), 2.78 (s, 2H, (CH_2)(CH_2)C(COOi-Pr)$_2$), 5.03 (septet, J = 6 Hz, 2H, OCH(CH_3)$_2$), 6.48 (s, 1H, (CH_2)$_2$CNHCO), 8.45 (s, 1H, CONHCO). ^{13}C NMR ($CDCl_3$), δ: 21.55 (CH(CH_3)$_2$), 30.64, 40.83, 40.99, 45.04, 48.22, 58.67, 68.96, 156.15 (NH–CO–NH), 171.15 (CCOOH), 176.98 (10-C).

3.6. 8,10-Dioxo-7,9-diaza-dispiro[3.1.4.1]undecane-2,2-dicarboxylic acid 27

The hydantoine **26** (4,59 g, 13 mmol mmol) was dissolved in 2 M aqueous NaOH (52 ml) and the resulting solution was maintained at ambient temperature overnight. The solution was then acidified by 3 N HCl to pH 3 and was left at ~5 °C for several hours to allow the dicarboxylic acid **27** to precipitate completely. The precipitate was filtered, washed with 1 N HCl, and dried. White needles, 3.18 g (92%). ^{1}H NMR (CD_3OD), δ: 2.39 (dd, J = 11 Hz and J = 3 Hz, 2H, 5-CHH and 11-CHH), 2.59 (s, 2H, 1-CH_2), 2.61 (dd, J = 11 and 3 Hz, 2H, 5-CHH and 11-CHH), 2.76 (s, 2H, 3-CH_2). ^{13}C NMR (CD_3OD), δ: 30.07 (C(CH_2)$_4$), 41.09 (1-CH_2), 41.33 (3-CH_2), 44.33 (5-CH_2 and 11-CH_2), 47.91 ((CH_2)$_2$$C$(COOH)$_2$), 58.09 (6-$C$),

157.24 (NH–*C*O–NH), 173.81 (*C*COOH), 179.09 (10-*C*). Anal. Calcd for $C_{11}H_{12}N_2O_6$: C, 49.26; H, 4.51; N, 10.44. Found: C, 49.22; H, 4.56; N, 10.40.

3.7. 8,10-Dioxo-7,9-diaza-dispiro[3.1.4.1]undecane-2-carboxylic acid 28

The dicarboxylic acid **27** (2.78 g, 10.4 mmol) was dissolved in pyridine (20 ml), and the solution was refluxed for 20 h. The mixture was then evaporated, the residue triturated by concd HCl. White crystals of the acid **28** were filtered, washed with cold water, and dried. White crystals, 2.14 g (92% yield). ^{1}H NMR (CD_3OD, δ): 2.75 (s, 2H), 2.96 (quintet, J = 8.8 Hz, 1H), 2,65 (dd, J = 8.8 Hz and 3 Hz, 1H), 2,52 (m, 2H), 2.2–2.4 (m, 5H). ^{13}C NMR (CD_3OD), δ: 179.59, 177.33, 159.66, 66.10, 40.05, 37.79, 33.78, 32.99.

3.8. 2-Amino-spiro[3.3]heptane-2,6-dicarboxylic acid hydrochloride (±)-13·HCl

The hydantoine **28** (1 g, 4.5 mmol) and NaOH (1.8 g, 45 mmol) were dissolved in water, and were heated in an autoclave at 150 °C for 20 h. The solution was evaporated in order to remove ammonia, acidified with 3 M HCl, evaporated, and dried in vacuum. **(±)-13**·HCl was extracted from the residue by methanol. White crystals, 0.49 g (47%). Mp > 240 °C (decomp.). ^{1}HNMR (CD_3OD), δ: 2.28–2.60 (m, 6H), 2.71 (dd, J = 13.2 Hz and 2.4 Hz, 1H), 2.81 (dd, J = 13.6 Hz and 3.2 Hz, 1H), 3.05 (quintet, J = 8 Hz, 1H, C*H*COOH). ^{13}C NMR (CD_3OD), δ: 33.89, 34.57, 39.16, 39.61, 43.46, 43.82, 54.17 (2-*C*), 173.76 (2-C*C*OOH), 177.74 (6-CH*C*OOH). Anal. Calcd for $C_9H_{14}ClNO_4$: C, 45.87; H, 5.99; N, 5.94. Found: C, 45.88; H, 5.95; N, 5.91.

3.9. 6-Oxo-spiro[3.3]heptane-2,2-dicarboxylic acid 30

Compound **24** (13.5 g, 41.1 mmol) was refluxed in a solution of NaOH (9.1 g, 0.225 mol) in ethanol (150 ml) for 3 h. The solvent was evaporated, the residue was triturated by 6 M aqueous HCl (100 ml), stirred for 30 min. Then, the solution was evaporated, dissolved in water, and evaporated again. This procedure was repeated three times in order to remove the residual HCl. The ketodicarboxylic acid **30** was extracted from the dried residue by ethanol. The extract was evaporated. White crystals, 7.6 g (89% yield), ^{1}H NMR (DMSO-D_6), δ: 2.66 (s, 4H, CH_2), 3.08 (s, 4H, CH_2). ^{13}C NMR (DMSO-D_6), δ: 27.84, 40.04, 48.35, 59.34 (CO*C*H$_2$), 173.16 (*C*OOH), 207.41 (*C*=O).

3.10. 6-Oxo-spiro[3.3]heptane-2-carboxylic acid 31

The dicarboxylic acid **30** (7.6 g, 38.3 mmol) was dissolved in pyridine (300 ml), and the resulting solution was refluxed for 5 h. Pyridine was distilled off on a rotary evaporator; the residue was combined with 6 N aqueous HCl, and was evaporated again. Compound **31** was extracted from the residue by diethyl ether (10 × 20 ml), the extract was dried over $MgSO_4$, evaporated. White solid, 5.1 g (86%). ^{1}H NMR ($CDCl_3$), δ: 3.15 (m 3H), 3.01 (m, 2H). 2.55 (m, 2H), 2.42 (m, 2H). ^{13}C NMR ($CDCl_3$), δ: 29.69 ((CH$_2$)$_4$*C*), 35.49, 36.87, 58.83 (CO*C*H$_2$), 59.19 (CO*C*H$_2$), 181.57 (*C*OOH), 206.11 (*C*=O).

3.11. 6-Oxo-spiro[3.3]heptane-2-carboxylic acid methyl ester 32

A mixture of diethyl ether (20 ml) and 40% aqueous KOH solution (4.5 ml) was cooled in an ice bath. *N*-nitroso-*N*-methylurea (1.46 g, 14.2 mmol) was added carefully to the cooled mixture under stirring. The temperature of the reaction mixture was maintained below 5 °C. The yellow solution of the diazomethane formed was decanted. The ketoacid **31** (1 g, 6.5 mmol) was added to the solution under stirring, the ice bath was removed, and the stirring continued for 8 h. The solution was evaporated to yield yellow oil, 1.1 g (100% yield). ^{1}H NMR ($CDCl_3$), δ: 2.45 (dt, J = 9 and 2 Hz, 2H), 2.57 (m, 2H), 3.09 (m, 2H, CH_2), 3.15 (m, 3H, CH_2 and C*H*COOMe), 3.70 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 29.87 ((CH$_2$)$_4$*C*), 32.97, 36.95, 51.87 (*C*H$_3$), 58.81 (CO*C*H$_2$), 59.24 (CO*C*H$_2$), 175.24 (*C*OOMe), 206.62 (*C*=O).

3.12. (a*S*)-6-Cyano-6-((1*R*)-2-hydroxy-1-phenyl-ethylamino)-spiro[3.3]heptane-2-carboxylic acid methyl ester 33a

3.13. (a*R*)-6-Cyano-6-((1*R*)-2-hydroxy-1-phenyl-ethylamino)-spiro[3.3]heptane-2-carboxylic acid methyl ester 33b

(*R*)-phenylglycinol (0.9 g, 6.5 mmol) was added to the solution of **32** (1 g, 6 mmol) in benzene (15 ml), and the resulting mixture was stirred for 2 h. Benzene was evaporated; the residue was dissolved in MeOH (15 ml). Trimethylsilylcyanide (1.5 ml, 12 mmol) was added to this solution at 0 °C. The solution was stirred overnight at ambient temperature and evaporated to give a crude mixture of two diastereomers at 1:1 ratio. Both isomers were obtained in pure form by column chromatography on silica gel (Hexane/EtOAc, 3:2 was used as an eluent). The chromatographic separation yielded 300 mg (16%) of (a*S*,1*R*)-isomer **33a** (eluted first) and 340 mg (18%) of (a*R*,1*R*)-isomer **33b** as well as 1.1 g (59%) of mixed fractions, which can be subjected for further separation. Yellow viscous oil. Spectral data for **33a**: $[\alpha]_D^{20} = -42$ (*c* 0.13, MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.81 (d, J = 11.5 Hz, 1H), 2.08 (dd, J = 12 and 4 Hz, 1H), 2.16 (m, 2H), 2.26 (d, J = 12.5 Hz, 1H), 2.32 (m, 2H), 2.39 (d, J = 8 Hz, 1H), 2.62 (dd, J = 12 and 4 Hz, 2H), 2.90 (quintet, J = 8.5 Hz, 1H, C*H*COOMe), 3.57–3.75 (m, 6H), 3.97 (dd, J = 8.5 and 4 Hz, 1H, CH*H*OH), 7.36 (m, 5H, C$_6H_5$). ^{13}C NMR ($CDCl_3$), δ: 175.45 (C=O), 139.68, 128.62, 128.22, 128.01, 122.24 (CN), 66.66 (CH_2OH), 62.35 (CHNH), 51.76, 49.63, 46.66, 46.26, 37.76, 37.40, 34.93, 33.05. **33b**: $[\alpha]_D^{20} = -68$ (*c* 0.72, MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.76 (d, J = 12.5 Hz, 1H), 2.04 (dd, J = 12.5 and 3 Hz, 1H), 2.25 (d, J = 8 Hz, 2H), 2.30–2.45 (m, 4H), 2.70 (dd, J = 12.5 Hz and 3.5 Hz, 1H), 3.00 (quintet, J = 8 Hz, 1H, C*H*COOMe), 3.65 (m, 4H), 3.74 (dd, J = 4 and 11 Hz, 1H), 3.96 (dd, J = 8 and 4 Hz, 1H, CH*H*OH), 7.36 (m, 5H, C$_6H_5$); ^{13}C NMR ($CDCl_3$), δ: 175.31 (C=O), 139.62, 128.63, 128.23, 127.91, 122.23 (CN), 66.67 (CH_2OH), 62.30 (CHNH), 49.63, 46.67, 46.13, 37.76, 37.54, 34.93, 33.06.

The aminonitriles **33a** and **33b** underwent retro-Shtrecker reaction on standing: their NMR spectra showed appearance of ketone **32** upon storage at ambient temperature in several hours**.** Therefore, the chromatographic separation and deprotection should be performed immediately after obtaining the **33a** and **33b**.

3.14. (a*S*)-2-Amino-spiro[3.3]heptane-2,6-dicarboxylic acid hydrochloride 13a·HCl

3.15. (a*R*)-2-Amino-spiro[3.3]heptane-2,6-dicarboxylic acid hydrochloride 13b·HCl

Compound **33a** (150 mg, 0.5 mmol) was dissolved in 1:1 mixture of CH_2Cl_2–MeOH (30 ml). The resulting solution was cooled to 0 °C, and $Pb(OAc)_4$ was added rapidly. After 5 min at 0 °C, a saturated solution of $NaHCO_3$ (7 ml) was added. The precipitate was filtered and washed by CH_2Cl_2 (15 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic extracts were dried over $MgSO_4$ and evaporated. The residue was dissolved in 5 N aqueous HCl (30 ml) and refluxed for 2 h, then washed with Et_2O (3 × 15 ml) and evaporated to give 90 mg (80%) of **13a.** Mp **>** 250 °C (decomp.). $[\alpha]_D^{20} = -2$ (*c* 0.78, H_2O). ^{1}H NMR (CD_3OD),

δ: 2.28–2.60 (m, 6H), 2.71 (dd, J = 13.2 and 2.4 Hz, 1H), 2.81 (dd, J = 13.6 and 3.2 Hz, 1H), 3.05 (quintet, 1H, *CH*COOH). ^{13}C NMR (CD_3OD), δ: 33.89, 34.57, 39.16, 39.61, 43.46, 43.82, 54.17 (2-*C*), 173.76 (2-CCOOH), 177.74 (6-CHCOOH). Anal. Calcd for $C_9H_{14}ClNO_4$: C, 45.87; H, 5.99; N, 5.94. Found: C, 45.83; H, 5.97; N, 5.90.

Compound **13b**·HCl was obtained analogously to **13a**·HCl from **33b**. Mp > 250α°C (decomp.). $[\alpha]_D^{20} = +2$ (c 0.78, H_2O). The NMR spectral data were identical to that for **13a**·HCl.

3.16. (a*S*)-dimethyl 2-(1-naphthoylamino)spiro[3.3]hepta-ne-2,6-dicarboxylate 34a

3.17. (a*R*)-dimethyl 2-(1-naphthoylamino)spiro[3.3]hepta-ne-2,6-dicarboxylate 34b

Compound **(±)-13**·HCl, **13a**·HCl, or **13b**·HCl (200 mg, 0.85 mmol) was dissolved in dry methanol (5 ml), the solution was cooled to −10 °C. Thionyl chloride (107 mg, 0.9 mmol) was added to the stirred solution; the stirring continued for 5 h, then the reaction mixture was refluxed for 1 h. The solvent was distilled off, the residue was dissolved in methanol again, and evaporated to dryness. The dimethyl ester of **13** thus obtained was sufficiently pure for the next synthetic operation. It was suspended in CH_2Cl_2 (200 mg, 0.76 mmol in 5 ml) and combined with triethylamine (116 μL, 1.52 mmol), 2-hydroxybenzotriazole (112 mg, 0.82 mmol), 1-naphthoic acid (130 mg, 0.76 mmol), and then—*N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (160 mg, 0.83 mmol). The mixture was left stirring for 18 h. Dichloromethane (50 ml) was added, the solution was washed with saturated aqueous $NaHCO_3$ solution, then with water, dried over $MgSO_4$, and evaporated. The product obtained was subjected to chiral HPLC analysis without recrystallization. ^{1}H NMR ($CDCl_3$), δ: 8.28 (d, J = 8 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 7.48 (m, 2H), 7.36 (t, J = 8 Hz, 1H), 6.88 (s, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 2.97 (quintet, J = 9 Hz, 1H), 2.83 (d, J = 13 Hz, 1H), 2.71 (d, J = 13 Hz, 1H), 2.51 (d, J = 13 Hz, 1H), 2.42 (d, J = 13 Hz, 1H), 2.36 (m, 4H). ^{13}C NMR ($CDCl_3$), δ: 175.75, 173.68, 169.45, 133.75, 133.59, 130.69, 130.23, 128.23, 127.11, 126.40, 125.40, 125.17, 124.60, 54.95, 52.68, 51.73, 44.09, 43.69, 38.58, 37.88, 34.52, 32.82.

3.18. (a*S*,8*R*)-11-Oxo-8-phenyl-10-oxa-7-aza-dispiro[3.1.5.1]-dodecane-2-carboxylic acid methyl ester 35a

Compound **33a** (215 mg, 0.7 mmol) was dissolved in CH_2Cl_2 (20 ml) and saturated with gaseous HCl for 15 min at 0 °C. MeOH (5 ml) was added, and the resulting mixture was saturated with HCl for another 15 min. The reaction mixture was stirred overnight at ambient temperature, and then evaporated. The residue was treated by CH_2Cl_2 (20 ml). The resulting solution was washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4 Then, the solvent was evaporated, the residue was dissolved in toluene and refluxed for 12 h. The mixture was evaporated, and the solid residue recrystallized from a mixture of hexane-ethyl acetate to give 150 mg (70%) of **35a**. $[\alpha]_D^{20} = -23$ (c 0.75, MeOH). Mp 115 °C. ^{1}H NMR ($CDCl_3$), δ: 1.92 (br s, 1H, NH), 2.12 (d, J = 12 Hz, 1H, 12a-H), 2.16 (d, J = 12 Hz, 1H, 5a-H), 2.25 (pt, J = 8 Hz, 1H, 1a-H), 2.40 (dd, J = 8 and 10 Hz, 1b-H), 2.45 (two d, J = 8 Hz, 2H, 3a,b-H), 2.86 (d, J = 12 Hz, 1H, 12b-H), 2.88 (d, J = 12 Hz, 1H, 5b-H), 3.00 (quintet, J = 8 Hz, 1H, 2-H), 3.67 (s, 3H, OCH_3), 4.18 (pt, J = 10.5 Hz, 1H, 9-H), 4.26 (dd, J = 3.5 and 10.5 Hz, 1H, 8-H), 4.31 (dd, J = 3.5 and 10.5 Hz, 1H, 9-H),7.25–7.35 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$), δ: 32.83 (CH), 33.46 (C), 38.14 (CH_2), 38.78 (CH_2), 45.90 (CH_2), 48.46 (CH_2), 51.71 (CH_3), 54.26 (CH), 56.45 (C), 73.65 (OCH_2), 127.00 (CH), 128.56 (CH), 128.92 (CH), 138.23 (C), 172.59 (C=O), 175.55 (C=O).

Compound **35b** was obtained analogously from **33b**: $[\alpha]_D^{20} = -72$ (c 0.6, MeOH). Mp 136 °C. ^{1}H NMR ($CDCl_3$), δ:1.91 (br s, 1H, NH), 2.12 (d, J = 13 Hz, 1H, 5a-H), 2.16 (d, J = 13 Hz, 1H, 12a-H), 2.28 (pt, J = 8 Hz, 1H, 1b-H), 2.36 (pt, J = 13 Hz, 1H, 1a-H), 2.38 (pt, J = 13 Hz, 1H, 3a-H), 2.54 (pt, J = 8 Hz, 1H, 3b-H), 2.80 (d, J = 12 Hz, 1H, 5b-H), 2.97 (d, J = 12 Hz, 1H, 12b-H), 3.03 (quintet, J = 8 Hz, 1H, 2-H), 3.67 (s, 3H, OCH_3), 4.20 (pt, J = 10.5 Hz, 1H, 9-H), 4.24 (dd, J = 10.5 and 2.5 Hz, 1H, 8-H), 4.31 (dd, J = 10.5 and 2.5 Hz, 1H, 9-H), 7.30–7.50 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$), δ: 32.90 (CH), 33.51 (C), 38.35 (CH_2), 38.95 (CH_2), 46.26 (CH_2), 48.22 (CH_2), 51.71 (CH_3), 54.14 (CH), 56.39 (C), 74.19 (OCH_2), 127.04 (CH), 128.58 (CH), 128.92 (CH), 138.10 (C), 172.10 (C=O), 175.70 (C=O).

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