Tetrahedron: *Asymmetry* 20 (2009) 1500–1505

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of isatins with a chiral substituent at the nitrogen atom

Alexander V. Kurkin *, Anna A. Bernovskaya, Marina A. Yurovskaya

Chemical Department of M.V. Lomonosov, Moscow State University, Moscow 119899, Russia

ARTICLE INFO

Article history:
Received 30 April 2009
Accepted 12 May 2009
Available online 26 June 2009

ABSTRACT

(*R*)-Ethyl 2-(isatin-1-yl)propanoates **8a–c** were prepared from the corresponding (*R*)-arylalanines by Sandmeyer's method in high yield and good enantioselectivity (up to 99%). The key step of the process is the Mitsunobu reaction.

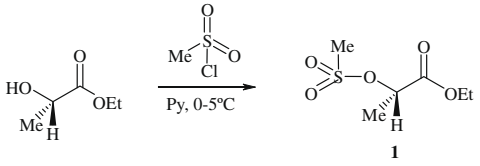
1. Introduction

Isatin and its derivatives are widely used for the synthesis of different heterocyclic compounds, amongst which a great number of drugs and drug candidates have been found. The variety of useful applications of isatin derivatives is due to their extremely wide range of biological activities. They demonstrate antibacterial, antiprotozoal, antifungal, antiviral, anti-HIV, anticonvulsant, and antihelminthic activities; influence CNS; participate in metabolism; and stimulate the growth of plants.[1] There is a tendency nowadays to use pure or practically pure enantiomers of heterocyclic compounds instead of their racemic mixtures as starting materials in the preparation of pharmaceuticals.[2] It is true for the derivatives of isatin. In this context the purpose of our study is the development of a synthetic approach to new isatin derivatives with a chiral C-atom adjacent to the N-atom of the heterocycle.

During our investigation, we found a new approach to the derivatives of isatin, chiral (*R*)-2-methyl-2-indolyl-propanoates of high enantiomeric purity. To the best of our knowledge, these compounds have not been described. The method makes it possible to prepare different chiral substances as a result of modification of both five-membered and benzene rings (e.g., in some cross-coupling reactions).

2. Results and discussion

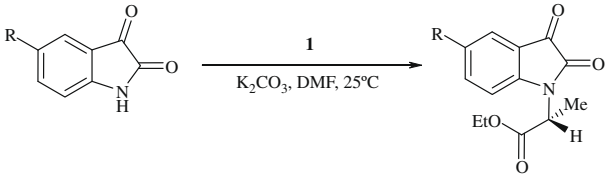
Our synthetic plan includes an alkylation of the corresponding NH-isatins under Mitsunobu reaction conditions. However, our attempts to alkylate (time of reaction, temperature, and ratio of reagents) isatins under different conditions did not give alkylated products. This is most likely due to the insufficient nucleophilicity of substrate because of the negative charge at the N-atom of the isatin molecule, which delocalizes between the O-atom and the N-atom. An alternative method for the preparation of optically active isatins is the direct alkylation of the corresponding NH-isatins by ethyl (*S*)-2-hydroxypropionate. The use of such a hydroxyester as an alkylating agent requires its preliminary activation, which is why we have synthesized the corresponding methanesulfonyl derivative of the hydroxyester (Scheme 1). There is no loss in the enantiomeric purity of compound **1** during the transformation.[3,4]



1

Scheme 1. Synthesis of methanesulfonyl derivative of hydroxyester **1**.

For the alkylation of the isatins, we used equimolar amounts of the starting reagents. However, the starting isatins remained in the reaction mixture for 12 h after the beginning of the process. Only after the addition of 15% molar excess of an optically active methanesulfonyl derivative of hydroxyester, were the isatins consumed during the nucleophilic substitution (Scheme 2).



2a, R = Me, $[\alpha]_D^{20}$ = -1.3, 30% *ee*
2b, R = Br, (*rac*)

Scheme 2. Alkylation of isatins by methanesulfonyl derivative of hydroxyester **1**.

However in this case, the process is accompanied by racemization. The enantiomeric purity of compound **2a** determined by HPLC with a chiral stationary phase did not exceed 30% ee, while isatin **2b** was obtained as a racemate. The racemization over the course

* Corresponding author. Tel./fax: +7 495 939 22 88.
E-mail address: kurkin@direction.chem.msu.ru (A.V. Kurkin).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.05.015

of alkylation may be explained by giving an example of esters by effect of bases (alcoholates of alkaline and alkaline-earth metals, e.g., K_2CO_3). Similar to its chemical nature, racemization has been observed during the alkaline hydrolysis of esters of α-aminoacids.[5] Thus, the alkylation of isatins by a methanesulfonyl derivative of (*S*)-2-hydroxypropionic acid is accompanied by a partial loss of enantiomeric purity because of high CH-acidity of the α-carbon atom in **1**. This does not allow us to apply the direct alkylation of isatins for the preparation of optically active isatins of the above type.

As a result we suggested a sequence of conversions in which the key step is construction of the isatin molecule with a chiral substituent at the nitrogen atom from an optically active aniline.

It should be noted that Liu et al.[6] recently proposed a synthetic method for optically active anilines, for example, **7b**, with enantioselectivities up to 98% ee. This method is based on using of complexes of Cu(I) with chiral spirobisoxazolynic ligands as catalysts. However, our variant has considerable advantages in its being inexpensive as well as the availability of the starting materials and the simplicity of the experimental work.

We used the Mitsunobu reaction for the synthesis of optically active anilines **6a–c**, alkylation of the NH-acid substances by an optically active alcohol in the presence of a redox-system, triphenylphosphine/diisopropyl azadicarboxylate. The Mitsunobu reaction has frequently been used as a reliable method for the alkylation of moderately acidic heteroatoms ($pK_a \leqslant 11$). Anilines have low NH-acidity, hence it is necessary to introduce an activating group in order to increase the NH-acidity of the aniline (Scheme 3).

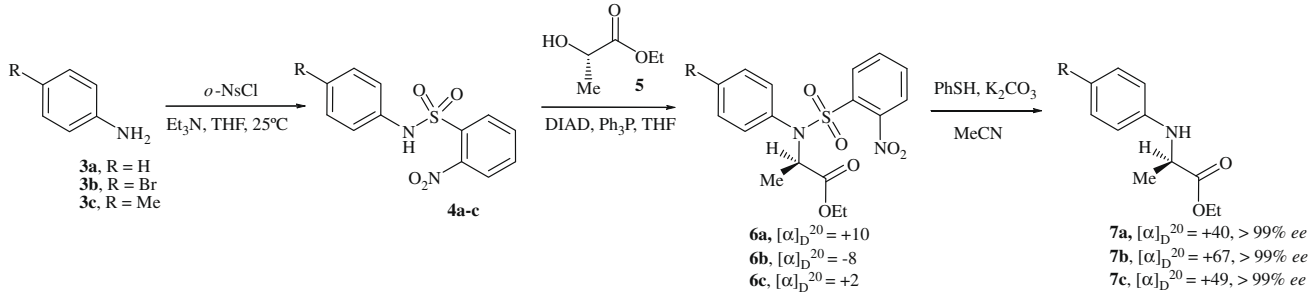
We chose the activating group by taking into account two factors. First, the activating group should increase NH-acidity of aniline to such an extent, that the Mitsunobu reaction becomes possible. Second, such an activating group should be easily removed to give the product of alkylation. As an activating group, we used the 2-nitrophenylsulfonyl (*o*-nosyl). The use of this powerful electron-withdrawing group has been reported recently. The Ns-group could be readily removed under mild conditions, giving secondary amines in high yields and without losing enantiomeric purity.[7,8] *N*-Aryl-2-nitrobenzenesulfonamides **4a–c**, prepared from anilines **3a–c** and 2-nitrobenzenesulfonyl chloride in 72–90% yield, were efficiently alkylated under the Mitsunobu conditions[9] with commercially available ethyl (*S*)-2-hydroxypropionate **5** to give N,N-disubstituted 2-nitrobenzenesulfonamides **6a–c** in 68–75% yield. Triphenylphosphine/diisopropyl azadicarboxylate (DIAD) was chosen as a redox system.

It is known that the Mitsunobu reaction is accompanied by complete inversion of the configuration under the formation of the alkylated product.[9,10] Edwards et al.[11] performed some transformations to demonstrate that the Mitsunobu reaction proceeded with inversion of configuration and that the reductive removal of the activating group (Tf-group) did not result in a loss of enantiopurity. The authors compared the specific rotation of the materials prepared by well-known methods with predicted results and with that of the materials prepared by the Mitsunobu reaction and following removal of the activating group. Samples prepared by these methods gave similar values of $[\alpha]_D^{20}$ and proved an inversion of the configuration under the Mitsunobu conditions and retention of chirality after removal of the activating group.

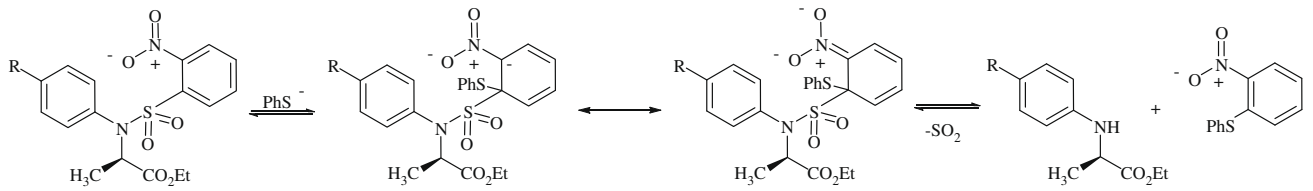
The deprotection of secondary amines with the 2-nitrophenylsulfonyl group under extremely mild conditions could be carried out by two alternative methods: upon treatment with PhSH/K_2CO_3/DMF at 23 °C,[7] or with $HSCH_2CO_2H$/LiOH/DMF at the same temperature.[8] As a rule, both methods give similar results. The reaction, presumably, proceeds via the formation of the Meisenheimer complex[8] (Scheme 4).

In our experiments we used PhSH/K_2CO_3/DMF system with satisfactory results: optically active ethyl (*R*)-2-(*N*-aryl)aminopropanoates **7a–c** were prepared in 73–78% yield and in >99% ee.

The enantiomeric purity of ester (*R*)-*N*-arylalanine was determined by ^{1}H NMR analysis (spectrum) for (*R*)-**7b** and substance (*R,S*)-**7b** with equimolar amounts of chiral solvating agent (*S*)-1,1′-binaphthyl-2.2′-diol. There were two doublet signals (J = 6.8, 2.9 Hz) of the –CH*CH*$_3$ group in a 1:1 ratio of integral intensities in the spectrum of substance (*R,S*)-**7b** (B) in the range 1.13–1.16 ppm (Fig. 1A). In the spectrum of substance (*R*)-**7b** (A) only one doublet signal of the protons of the aforementioned group was obtained (Fig. 1A). The configuration of the multiplet signal of the *CH*$_2$CH$_3$ group (Fig. 1B) indicated the excellent enantioselectivity of substance (*R*)-**7b** (A) which was obtained under alkylation by ethyl (*S*)-lactate under Mitsunobu reaction conditions.



Scheme 3. Synthesis of optically active anilines **7a–c**.



Scheme 4. Mechanism of 2-nitrophenylsulfonyl group deprotection.

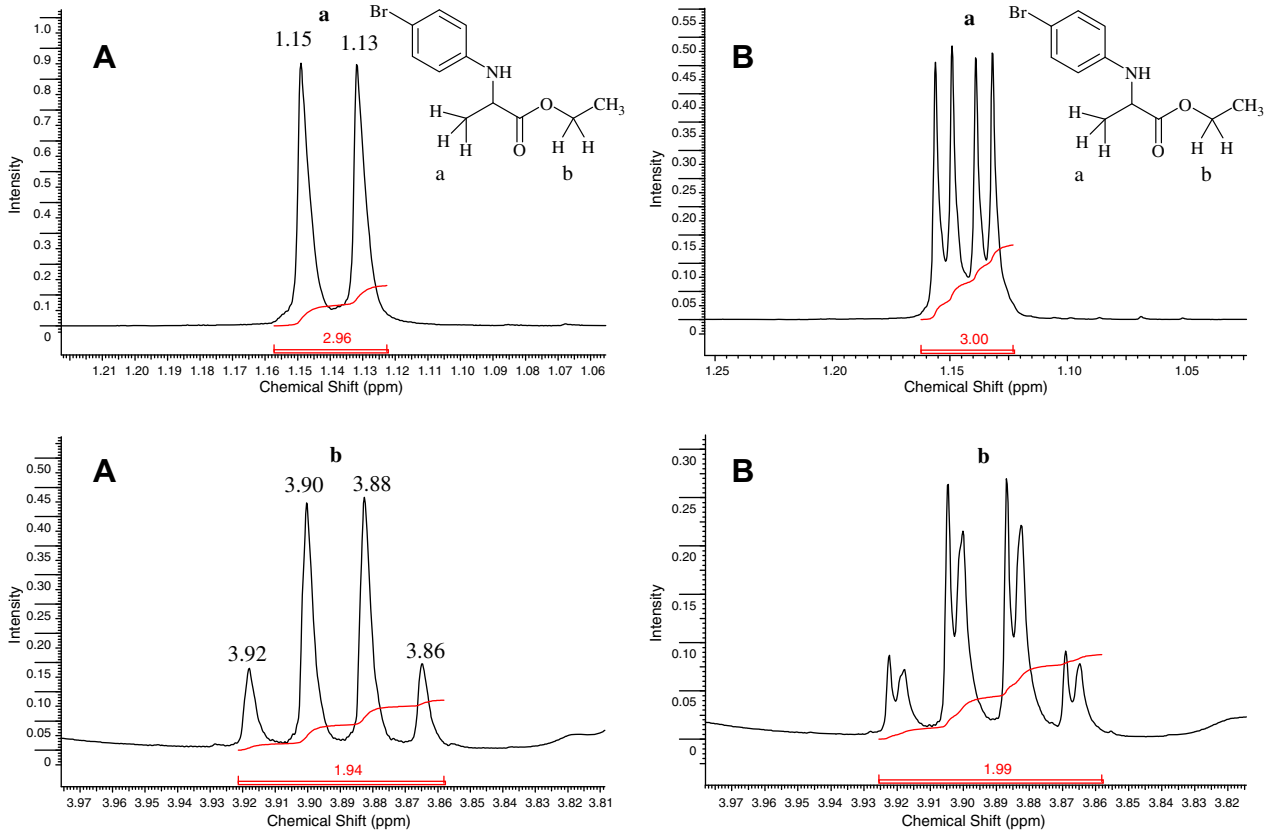
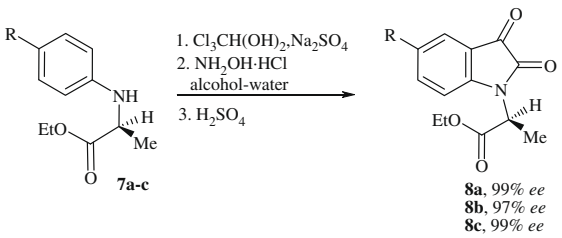


Figure 1. Fragments of spectrum (range of aliphatic protons) of ethyl esters (*R*)-**7b** (A) and (*R*,*S*)-**7b** (B) with (*S*)-1,1′-binaphthyl-2.2′-diol in C_6D_6.

We synthesized isatins **8a–c** from optically active anilines **7a–c** by Sandmeyer's method (Scheme 5). In addition we used ethanol as a solvent in order to increase the aniline solubility. Isatins **8a–c** were purified by column chromatography and their enantiomeric purities that were achieved were 97–99% ee, which were determined by HPLC with a chiral stationary phase. Since Sandmeyer's method has sufficiently harsh reaction conditions (concd H_2SO_4), we attempted to synthesize N-alkylated isatin by Stolle's method (oxalyl chloride/$AlCl_3$ in CH_2Cl_2). However, we did not obtain the chiral isatin. This method seems applicable for N-unsubstituted anilines, while Sandmeyer's method makes it possible to prepare optically active isatins **8a–c** in high yield with good enantioselectivity. We determined the absolute configuration to be (*R*) for isatin **8b** by X-ray structure analysis.[12]



Scheme 5. Synthesis of isatins **8a–c**.

3. Conclusion

In conclusion, we not only have developed a synthetic method for isatins with a chiral substituent on the nitrogen atom but have also revealed that under these conditions racemization did not occur when using active substrates. Thus, we have reported a method which may be used for obtaining chiral isatins with high enantioselectivity.

4. Experimental

4.1. General

HRMS spectra were recorded on Carlo Erba/Kratos Fractovap Series 4200 gas–liquid chromatograph, column Ultra-1, Hewlett Packard, 25 m × 0.2 mm, thickness of phase layer 0.33 mkm, carrier gas—helium (1 ml/min), flow divider 1:10, temperature of evaporator 280 °C, gradient of temperature from 150 °C to 280 °C (5 °C/min). Mass spectral detector ITD-700 (Finnigan MAT), EU, with ionizing electrons of energy 70 eV, and range of mass *m/z* 45–400 was used. NMR spectra were recorded with a Bruker AMX-400 spectrometer at 400.13 (^{1}H NMR) and at 100.61(^{13}C NMR) MHz with $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are reported in parts per million downfield from internal Me_4Si. Optical rotations were measured using a Jasco DIP-360 (589 nm) polarimeter. Melting points were measured in an open capillary, and are uncorrected. IR spectra were recorded on a Thermo Nicolet 200 IR spectrometer. Reaction control and control of products purity were carried out by thin-layer chromatography on slices of Silufol UV-254 and by gas chromatography with mass spectral detector. Enantiomeric purities were tested using HPLC with chiral stationary phase: Chiralpak AD-RH 4.6 × 150 mm 5 mkm, eluent: H_2O + CF_3COOH/CH_3CN 50:50 flow: 1.0 ml/min, rt, and 250 nm.

4.2. Ethyl-*O*-methanesulfonyl-(*S*)-2-hydroxypropanoate 1

Methanesulfonyl chloride (5.82 g, 0.05 mol) was added to a solution of ethyl ester (*S*)-2-hydroxypropionic acid (5 g, 0.04 mol) in pyridine (40 ml) and stirred at 0–5 °C for 3 h. The reaction

mixture was kept overnight at 0–5 °C. The resulting mixture was diluted with water (300 ml) and ice, and extracted with Et_2O (50 ml) five times. The extract was washed with diluted hydrochloric acid (50 ml) four times, and with a saturated solution of $NaHSO_4$ (100 ml) and a saturated solution of NaCl (100 ml), and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure to afford a red oil (79%), $[\alpha]_D^{20} = -65$ (*c* 1, $CHCl_3$). This substance was used in further transformations without extra purification. ^{1}H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 1.30 (t, *J* = 7.2, 3H, –CH_2–CH_3), 1.60 (d, *J* = 7.0, 3H, –CH–CH_3), 3.14 (s, 3H, –SO_2CH_3), 4.25 (q, *J* = 7.2, 2H, –CH_2–CH_3), 5.11 (q, *J* = 7.0, 1H, –CH–CH_3).

4.2.1. Ethyl 2-(5-methylisatin-1-yl)propanoate 2a

At first K_2CO_3 (1.28 g, 0.009 mol) was added to a solution of 5-methylisatin (1 g, 0.006 mol) in DMF (5 ml). The reaction mixture was stirred until the complete dissolution of isatin. After 30 min, the solution became bright red in color, after which (*S*)-ethyl 2-(methanesulfonyl)propanoate (1.6 ml, 0.01 mol) was added dropwise to the reaction mixture. This was stirred at rt for 12–14 h. The resulting mixture was diluted with water, extracted with CH_2Cl_2, washed with water, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent—ethyl acetate/petroleum ether = 10:1) to afford **2a** (1.08 g, 67%) as a red solid, $[\alpha]_D^{20} = -1.3$ (*c* 3.8, $CHCl_3$), 30% ee, Mp 63 °C. ^{1}H NMR (DMSO-d_6), δ, ppm, *J* (Hz): 1.14 (t, *J* = 7.0, 3H, –CH_2–CH_3), 1.55 (d, *J* = 7.3, 3H, –CH–CH_3), 2.29 (s, 3H, 5-CH_3), 4.14 (q, *J* = 7.0, 2H, –CH_2–CH_3), 5.12 (q, *J* = 7.3, 1H, –CH–CH_3), 7.03 (d, *J* = 8.1, 1H, 7-H), 7.43 (s, 1H, 4-H), 7.49 (d, *J* = 8.1, 1H, 6-H). ^{13}C NMR (DMSO-d_6), δ, ppm: 14.34 (CH_3), 16.53 (CH_3), 20.44 (CH_3), 49.46 (CH), 61.81 (CH_2), 111.59 (CH), 118.08 *I*, 125.49 (CH), 133.38 *I*, 139.10 (CH), 148.01 *I*, 158.18 (CO), 169.91 (CO), 183.37 (CO). Mass-spectroscopy, *m/z* (*I*, %): 261 [M^+], 188 [M^+–CO_2Et], 160 [M^+–CH_3CHCO_2Et], 117 (34), 91 (50), 43 (60). Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.32; H, 5.92; N, 5.23.

4.2.2. Ethyl 2-(5-bromisatin-1-yl)propanoate 2b

Compound **2b** was obtained as a red solid (57%, mp 125 °C, petroleum ether/ethyl acetate) due to the same method. ^{1}H NMR (DMSO-d_6), δ, ppm, *J* (Hz): 1.15 (t, *J* = 6.4, 3H, –CH_2–CH_3), 1.54 (d, *J* = 6.3, 3H, –CH–CH_3), 4.09–4.21 (m, 2H, –CH_2–CH_3), 5.11–5.21 (m, 1H, –CH–CH_3), 7.13 (d, *J* = 7.7, 1H, 7-H), 7.78 (s, 1H, 4-H), 7.85 (d, *J* = 7.7, 1H, 6-H). Mass-spectroscopy, *m/z* (*I*, %): 224 [M^+–CH_3CHCO_2Et], 145 [M^+–CH_3CHCO_2Et, –Br], 117 (8), 106 (5), 91 (36), 57 (100), 41 (39).

4.2.3. *N*-(4-Bromophenyl)-2-nitrobenzenesulfonamide 4b

Triethylamine (4.2 ml, 0.03 mol) was added to a stirred solution of *p*-bromaniline (5 g, 0.03 mol) in THF (35 ml). The mixture was kept in an ice-bath for 15 min, and then the solution of 2-nitrobenzenesulfonyl chloride (6.4 g, 0.03 mol) in THF (15 ml) was added dropwise. The mixture was stirred at rt for 6 h and was then concentrated under reduced pressure up to 15 ml. The residue was diluted with water (50 ml) and extracted with chloroform (50 ml) four times. The combined extracts were washed with dilute hydrochloric acid and water (50 ml) twice and were then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. Purification of the residue by recrystallization from ethanol afforded **4b** as a pale yellow solid (7.71 g, 72%, mp 105 °C). ^{1}H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 7.11 (d, *J* = 8.8, 2H, H-2, H-6), 7.42 (d, *J* = 8.8, 2H, 3-H, 5-H), 7.63 (t, *J* = 7.8, 1H, 5′-H), 7.72 (br s, 1H, NH), 7.74 (t, *J* = 7.8, 1H, 4′-H), 7.85 (d, *J* = 7.8, 1H, 3′-H), 7.89 (d, *J* = 7.8, 1H, 6′-H). ^{13}C NMR ($CDCl_3$), δ, ppm: 120.13 (C), 124.86 (2C, CH), 125.45 (CH), 131.83 (CH), 132.60 (2C, CH), 132.79 (C), 134.26 (CH), 134.61 (C), 148.17 (C).

4.2.4. *N*-(4-Phenyl)-2-nitrobenzenesulfonamide 4a

Compound **4a** was obtained as a white solid (90%, mp 120 °C, ethanol).^{1}H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 7.18–7.23 (m, 3H, 2-H, 6-H, NH), 7.28–7.32 (m, 3H, 3-H, 4-H, 5-H), 7.59 (t, *J* = 7.8, 1H, 5′-H), 7.71 (t, *J* = 7.8, 1H, 4′-H), 7.84 (d, *J* = 7.8, 1H, 3′-H), 7.87 (d, *J* = 7.8, 1H, 6′-H). ^{13}C NMR ($CDCl_3$), δ, ppm: 123.27 (2C, CH), 125.32 (CH), 126.66 (CH), 129.50 (2C, CH), 131.80 (CH), 132.08 (C), 132.61 (CH), 134.07 (CH), 135.47 (C), 148.18 (C).

4.2.5. *N*-(4-Methylphenyl)-2-nitrobenzenesulfonamide 4c

Compound **4c** was obtained as a yellow solid (88%, mp 110 °C, ethanol). ^{1}H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 2.27 (s, 3H, 4-CH_3), 7.05 (br s, 4H, 2-H, 3-H, 5-H, 6-H), 7.16 (br s, 1H, NH), 7.56 (t, *J* = 7.8, 1H, 5′-H), 7.68 (t, *J* = 7.8, 1H, 4′-H), 7.78 (d, *J* = 7.8, 1H, 3′-H), 7.84 (d, *J* = 7.8, 1H, 6′-H). ^{13}C NMR ($CDCl_3$), δ, ppm: 20.92 (CH_3), 123.72 (2C, CH), 125.26 (CH), 130.04 (2C, CH), 131.86 (CH), 132.19 (C), 132.56 (CH), 132.72 (C), 133.95 (CH), 136.74 (C), 148.20 (C).

4.2.6. Ethyl-(*R*)-*N*-(2-nitrophenylsulfonyl)-*N*-(4-bromophenyl)-2-aminopropanoate 6b

Diisopropyl azadicarboxylate (3.54 ml, 0.018 mol) was added dropwise to a solution of *N*-(2-nitrophenylsulfonyl)aniline **5** (0.017 mol), triphenylphosphine (4.72 g, 0.018 mol), and ethyl (*S*)-2-hydroxypropionate **6** (2.04 ml, 0.018 mol) in dry THF (50 ml) and stirred with ice-bath cooling under argon for 12 h. The reaction mixture was then stirred at rt for 12 h and then concentrated under reduced pressure. The residue was dissolved in Et_2O at 0–5 °C, the precipitated triphenylphosphine oxide was filtered off, and CH_2Cl_2 was added to an ether solution (Et_2O/CH_2Cl_2 = 3:1), which was washed with water, 10% hydrochloric acid, and saturated solution of $NaHSO_4$. The ether extract was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent—ethyl acetate/petroleum ether) to give **6b** as a white solid (68%, mp 89 °C), $[\alpha]_D^{20} = -8.4$ (*c* 3.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 1.29 (t, *J* = 7.0, 3H, –CH_2–CH_3), 1.33 (d, *J* = 7.4, 3H, –CH–CH_3), 4.16–4.27 (m, 2H, –CH_2–CH_3), 5.16 (q, *J* = 7.4, 1H, –CH–CH_3), 7.22 (d, *J* = 8.6, 2H, 2-H, 6-H), 7.47 (d, *J* = 8.6, 2H, 3-H, 5-H), 7.55–7.60 (m, 1H, 5′-H), 7.65–7.74 (m, 3H, 3′-H, 4′-H, 6′-H). ^{13}C NMR ($CDCl_3$), δ, ppm: 14.10 (CH_3), 16.69 (CH_3), 57.46 (CH_2), 61.71 (CH), 123.92 (CH), 124.11 (CH), 131.41 (CH), 132.07 (CH), 132.36 (2C, CH), 132.88 (C), 133.76 (C), 133.83 (CH), 134.36 (2C, CH), 147.82 (C), 171.69 (CO). IR (KBr) *v*: 3103, 2976, 1734 (CO), 1547 (NO_2), 1485, 1371, 1360, 1165, 1101, 1011, 592, 565 cm^{-1}. Mass-spectroscopy, *m/z* (*I*, %): 456 [M^+], 383 [M^+–CO_2Et], 199 [M^+–CO_2Et, –Ns], 186 [M^+–Ns], 155 (32), 77 (18), 76 (43). Calcd for $C_{17}H_{17}BrN_2O_6S$: C, 44.65; H, 3.75; N, 6.13. Found: C, 44.61; H, 3.74; N, 6.08.

4.2.7. Ethyl-(*R*)-*N*-(2-nitrophenylsulfonyl)-*N*-(4-phenyl)-2-aminopropanoate 6a

Compound **6a** was obtained as a white solid (71%, mp 123 °C, petroleum ether/ethyl acetate), $[\alpha]_D^{20} = +10.1$ (*c* 3.27, $CHCl_3$). ^{1}H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 1.27–1.36 (m, 6H, –CH_2–CH_3, –CH–CH_3), 4.16–4.28 (m, 2H, –CH_2–CH_3), 5.17 (q, *J* = 7.4, 1H, –CH–CH_3), 7.27–7.42 (m, 5H, 2-H, 3-H, 4-H, 5-H, 6-H), 7.50–7.56 (m, 1H, 5′-H), 7.63–7.72 (m, 3H, 3′-H, 4′-H, 6′-H). ^{13}C NMR ($CDCl_3$), δ, ppm: 14.10 (CH_3), 16.62 (CH_3), 57.50 (CH_2), 61.59 (CH), 123.96 (CH), 129.06 (2C, CH), 129.44 (CH), 131.22 (CH), 132.13 (CH), 132.67 (2C, CH), 133.21 (C), 133.57 (CH), 134.65 (C), 147.85 (C), 171.78 (CO). IR (KBr) *v*: 3099, 2991, 1745 (CO), 1545 (NO_2), 1375, 1351, 1205, 1165, 592, 557 cm^{-1}. Mass-spectroscopy, *m/z* (*I*, %): 378 [M^+], 305 [M^+–CO_2Et], 186 [M^+–Ns], 119 [M^+–CO_2Et, –Ns], 104 (67), 77 (67), 51 (21). Calcd for $C_{17}H_{18}N_2O_6S$: C, 53.96; H, 4.79; N, 7.40. Found: C, 53.94; H, 4.83; N, 7.49.

4.2.8. Ethyl (*R*)-*N*-(2-nitrophenylsulfonyl)-*N*-(4-methylphenyl)-2-aminopropanoate 6c

Compound **6c** was obtained as a white solid (77%, mp 82 °C, petroleum ether/ethyl acetate), $[\alpha]_D^{20} = +2.1$ (*c* 3.27, $CHCl_3$). ^1H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 1.28 (t, *J* = 7.2, 3H, $-CH_2-CH_3$), 1.32 (d, *J* = 7.4, 3H, $-CH-CH_3$), 2.35 (s, 3H, 4-CH_3), 4.14–4.27 (m, 2H, $-CH_2-CH_3$), 5.14 (q, *J* = 7.4, 1H, $-CH-CH_3$), 7.08–7.19 (m, 4H, 2-H, 3-H, 5-H, 6-H), 7.50–7.57 (m, 1H, 5′-H), 7.61–7.73 (m, 3H, 3′-H, 4′-H, 6′-H).^{13}C NMR ($CDCl_3$), δ, ppm: 14.09 (CH_3), 16.58 (CH_3), 21.18 (CH_3), 57.42 (CH_2), 61.53 (CH), 123.94 (CH), 129.74 (2C, CH), 131.26 (CH), 131.82 (C), 132.11 (CH), 132.30 (2C, CH), 133.24 (C), 133.58 (CH), 139.58 (C), 147.79 (C), 171.80 (CO). IR (KBr) *v*: 3078, 2993, 1745 (CO), 1543 (NO_2), 1373, 1346, 1205, 1174, 1103, 596, 573 cm^{-1}. Mass-spectroscopy, *m/z* (*I*, %): 392 [M^+], 319 [M^+-CO_2Et], 186 [M^+-Ns], 133 [$M^+ -CO_2Et$, −Ns], 118 (41), 91 (31), 65 (10). Calcd for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14. Found: C, 55.08; H, 5.11; N, 7.35.

4.2.9. Ethyl (*R*)-*N*-(4-bromophenylamino)-propanoate 7b

Potassium carbonate (3.2 g, 0.023 mol) and thiophenol (1.8 ml, 0.017 mol) were added to a solution of *o*-nitrophenylsulfonylaniline **7** (2.28 g, 0.006 mol) in DMF (100 ml) and stirred at rt for 6 h. The reaction mixture was diluted with water, extracted with Et_2O/CH_2Cl_2 = 3:1, and washed with water twice. The extract was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent—ethyl acetate/petroleum ether) to give **7b** (73%) as a yellow oil, $[\alpha]_D^{20} = +67$ (*c* 3.37, $CHCl_3$). ^1H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 1.28 (t, *J* = 7.1, 3H, $-CH_2-CH_3$), 1.48 (d, *J* = 6.9, 3H, $-CH-CH_3$), 4.09 (q, *J* = 6.9, 1H, $-CH-CH_3$), 4.21 (q, *J* = 7.1, 2H, $-CH_2-CH_3$), 6.50 (d, *J* = 8.9, 2H, 2-H, 6-H), 7.27 (d, *J* = 8.9, 2H, 3-H, 5-H). ^{13}C NMR ($CDCl_3$), δ, ppm: 14.20 (CH_3), 18.75 (CH_3), 52.00 (CH), 61.27 (CH_2), 109.94 (C), 114.98 (2C, CH), 132.04 (2C, CH), 145.64 (C), 174.24 (CO). IR (KBr) *v*: 3388 (NH), 2981, 1734 (CO), 1595, 1500, 1315, 1161, 816 cm^{-1}. Mass-spectroscopy, *m/z* (*I*, %): 271 [M^+], 198 [M^+-CO_2Et], 155 (12), 118 [M^+-CO_2Et, −Br], 91 (30), 76 (34), 50 (34). Calcd for $C_{11}H_{14}NO_2$: C, 48.55; H, 5.19; N, 5.15. Found: C, 48.71; H, 5.27; N, 5.27.

4.2.10. Ethyl-(*R*)-*N*-(4-phenylamino)-propanoate 7a

Compound **7a** was obtained as a yellow oil, 70%, $[\alpha]_D^{20} = +40$ (*c* 2.71, $CHCl_3$). ^1H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 1.29 (t, *J* = 7.1, 3H, $-CH_2-CH_3$), 1.51 (d, *J* = 6.6, 3H, $-CH-CH_3$), 4.12–4.27 (m, 3H, $-CH-CH_3$, $-CH_2-CH_3$), 6.66 (d, *J* = 8.4, 2H, 2-H, 6-H), 6.75–6.82 (m, 1H, 4-H), 7.17–7.27 (m, 2H, 3-H, 5-H). ^{13}C NMR ($CDCl_3$), δ, ppm: 14.19 (CH_3), 18.94 (CH_3), 52.03 (CH), 61.13 (CH_2), 113.42 (2C, CH), 118.27 (CH), 129.32 (2C, CH), 146.63 (C), 174.62 (CO). IR (KBr) *v*: 3396 (NH), 2981, 1736 (CO), 1605, 1508, 1315, 1161, 750, 694 cm^{-1}. Mass-spectroscopy, *m/z* (*I*, %): 193 [M^+], 120 [M^+-CO_2Et], 104 (4), 91 (4), 77 [$M^+-NHCH(CH_3)CO_2Et$], 65 (8), 42 (2). Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.07; H, 7.69; N, 7.36.

4.2.11. Ethyl-(*R*)-*N*-(4-methylphenylamino)-propanoate 7c

Compound **7c** was obtained as a yellow oil, 75%, $[\alpha]_D^{20} = +49$ (*c* 3.30, $CHCl_3$). ^1H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 1.29 (t, *J* = 7.1, 3H, $-CH_2-CH_3$), 1.50 (d, *J* = 6.9, 3H, $-CH-CH_3$), 2.28 (s, 3H, 4-CH_3), 3.95 (br s, 1H, NH), 4.15 (q, *J* = 6.9, 1H, $-CH-CH_3$), 4.22 (q, *J* = 7.1, 2H, $-CH_2-CH_3$), 6.59 (d, *J* = 8.2, 2H, 2-H, 6-H), 7.03 (d, *J* = 8.2, 2H, 3-H, 5-H). ^{13}C NMR ($CDCl_3$), δ, ppm: 14.22 (CH_3), 18.98 (CH_3), 20.41 (CH_3), 52.41 (CH), 61.04 (CH_2), 113.69 (2C, CH), 127.55 (C), 129.82 (2C, CH), 144.38 (C), 174.81 (CO). IR (KBr) *v*: 3390 (NH), 2981, 1734 (CO), 1620, 1522, 1304, 1159, 810 cm^{-1}. Mass-spectroscopy, *m/z* (*I*, %): 207 [M^+], 134 [M^+-CO_2Et], 118 (9), 91 (19), 77 [$M^+-NHCH(CH_3)CO_2Et$], 57 (22), 43 (34). Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.53; H, 8.40; N, 6.77.

4.2.12. (*R*)-Ethyl-2-(5-bromisatin-1-yl)propanoate 8b

A mixture of chloralhydrate (0.003 mol) in water (5.1 ml), a solution of aniline **7b** (0.0018 mol) in water (1.23 ml) with concentrated hydrochloric acid (0.26 g), a solution of hydroxylamine hydrochloride (0.0061 mol) in water (1.03 ml) and Na_2SO_4 (0.42 g), was stirred at reflux for 1–2 min. In addition we used ethanol as a solvent to increase the aniline solubility. The reaction mixture was cooled to rt, extracted with CH_2Cl_2, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford isonitroso substance as a brown oil (83%). The isonitroso substance (0.0015 mol) was added to concentrated sulfuric acid (1.46 g) at 50 °C so that the temperature of the reaction mixture did not exceed 70 °C. The reaction mixture was stirred at 80 °C for 10–15 min. The resulting mixture was cooled to rt, diluted with cold water, extracted with CH_2Cl_2, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent—ethyl acetate/petroleum ether = 10:1) to afford **8b** as an orange solid (57%, 97% ee, mp 124–125 °C, petroleum ether/ethyl acetate). ^1H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 1.15 (t, *J* = 7.0, 3H, $-CH_2-CH_3$), 1.53 (d, *J* = 7.1, 3H, $-CH-CH_3$), 4.08–4.21 (m, 2H, $-CH_2-CH_3$), 5.15 (q, *J* = 7.1, 1H, $-CH-CH_3$), 7.12 (d, *J* = 8.5, 1H, 7-H), 7.77 (s, 1H, 4-H), 7.85 (d, *J* = 8.1, 1H, 6-H). ^{13}C NMR (DMSO-d_6), δ, ppm: 14.19 (CH_3), 14.42 (CH_3), 49.55 (CH), 61.89 (CH_2), 113.94 (CH), 115.71 (C), 119.92 (C), 127.52 (CH), 140.41 (CH), 148.95 (C), 157.70 (CO), 169.73 (CO), 181.87 (CO). IR (KBr) *v*: 3086, 2989, 1736 (CO), 1604, 1469, 1439, 1242, 841, 719, 474 cm^{-1}. Mass-spectroscopy, *m/z* (*I*, %): 224 [$M^+-CH_3CHCO_2Et$], 145 [M^+-Br], 117 (8), 91 (36), 41 (39). Calcd for $C_{13}H_{12}BrNO_4$: C, 47.88; H, 3.71; N, 4.29. Found: C, 47.78; H, 3.64; N, 4.46.

4.2.13. (*R*)-Ethyl-2-(isatin-1-yl)propanoate 8a

Compound **8a** was obtained as an orange solid (52%, >99% ee, mp 69 °C, petroleum ether/ethyl acetate).^1H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 1.22 (t, *J* = 7.2, 3H, $-CH_2-CH_3$), 1.69 (d, *J* = 7.4, 3H, $-CH-CH_3$), 4.23 (q, *J* = 7.2, 2H, $-CH_2-CH_3$), 5.16 (q, *J* = 7.4, 1H, $-CH-CH_3$), 6.85 (d, *J* = 7.1, 1H, 7-H), 7.15 (t, *J* = 7.1, 1H, 5-H), 7.57 (t, *J* = 7.1, 1H, 6-H), 7.65 (d, *J* = 7.1, 1H, 4-H). ^{13}C NMR (DMSO-d_6), δ, ppm: 14.08 (CH_3), 14.27 (CH_3), 49.18 (CH), 62.16 (CH_2), 111.46 (CH), 117.89 (C), 123.89 (CH), 125.64 (CH), 138.19 (CH), 149.45 (C), 157.69 (CO), 169.43 (CO), 182.70 (CO). IR (KBr) *v*: 3467, 2993, 1739 (CO), 1608, 1468, 1367, 1309, 1246, 1113, 750, 476 cm^{-1}. Mass-spectroscopy, *m/z* (*I*, %): 247 [M^+], 174 [M^+-CO_2Et], 146 [$M^+-CH_3CHCO_2Et$], 128 (1), 117 (6), 91 (12), 77 (26), 51 (9). Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.26; H, 5.42; N, 5.78.

4.2.14. (*R*)-Ethyl-2-(5-methylisatin-1-yl)propanoate 8c

Compound **8c** was obtained as a red solid (67%, >99% ee, mp 64 °C, petroleum ether/ethyl acetate).^1H NMR ($CDCl_3$), δ, ppm, *J* (Hz): 1.23 (t, *J* = 7.1, 3H, $-CH_2-CH_3$), 1.68 (d, *J* = 7.3, 3H, $-CH-CH_3$), 2.90 (s, 3H, 5-CH_3), 4.23 (q, *J* = 7.1, 2H, $-CH_2-CH_3$), 5.17 (q, *J* = 7.3, 1H, $-CH-CH_3$), 6.74 (d, *J* = 8.1, 1H, 7-H), 7.37 (d, *J* = 8.1, 1H, 6-H), 7.48 (s, 1H, 4-H). ^{13}C NMR (DMSO-d_6), δ, ppm: 14.09 (CH_3), 14.28 (CH_3), 20.62 (CH_3), 49.12 (CH), 62.10 (CH_2), 111.27 (CH), 121.42 (C), 125.96 (CH), 133.74 (C), 138.57 (CH), 152.92 (C), 157.83 (CO), 169.57 (CO), 178.89 (CO). IR (KBr) *v*: 3456, 2989, 1739 (CO), 1622, 1597, 1491, 1309, 1227, 1107, 837, 478 cm^{-1}. Mass-spectroscopy, *m/z* (*I*, %): 261 [M^+], 188 [M^+-CO_2Et], 160 [$M^+-CH_3CHCO_2Et$], 130 (11), 117 (33), 91 (40), 65 (44), 51 (20). Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.22; H, 5.56; N, 5.70.

References

1. (a) Silva, J. F.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273; (b) Natarajan, A.; Fan, Y. H.; Chen, H.; Guo, Y.; Iyasere, J.; Harbinski, F.; Christ, W. J.; Aktas, H.; Halperin, J. A. *J. Med. Chem.* **2004**, *47*, 1882; (c) Sassatelli, M.; Bouchikhi, F.; Messaoudi, S.; Anizon, F.; Debiton, E.; Barthomeuf, C.; Prudhomme, M.; Moreau, P. *Eur. J. Med. Chem.* **2006**, *41*, 88.
2. Farinam, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 7. 2734.
3. Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1986**, *51*, 3664.
4. Stephenson, L. M.; Speth, D. R. *J. Org. Chem.* **1979**, *44*, 4683.
5. Kurkin, A. V.; Nesterov, A. V.; Karchava, A. B.; Yurovskaya, M. A. *Khim. Get. Soed.* **2003**, *39*, 1466.
6. Liu, B.; Zhu, S.-F.; Zhang, W.; Chen, C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 5834.
7. Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253.
8. Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.
9. Mitsunobu, O. *Synthesis* **1981**, *1*, 1.
10. Hughes, D. L. *Org. React.* **1992**, *42*, 335.
11. Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 3417.
12. Kurkin, A. V.; Bernovskaya, A. A.; Yurovskaya, M. A.; Rybakov, V. B. *Acta Crystallogr., Sect. E* **2008**, *64*, 1448.