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tert-BUTYL (2*S*)-(*p*-TOLYLSULFONYLOXY)-PROPIONATE – A SUITABLE REAGENT FOR THE DIRECT ALKYLATION OF INDOLE DERIVATIVES*

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A new method is proposed for the synthesis of indole derivatives containing a chiral substituent at the nitrogen atom, which includes the direct alkylation of indole derivatives with tert-butyl (2S)-(p-tolyl-sulfonyloxy)propionate, obtained from commercial ethyl (S)-lactate with subsequent conversion to the corresponding p-toluenesulfonyloxy derivative by hydrolysis, and esterification.

Keywords: *tert*-butyl (2*S*)-(*p*-tolylsulfonyloxy)propionate, isatins, nonracemic N-substituted indoles, 1,2,3,4-tetrahydrocarbazoles and γ-carbolines, ethyl (*S*)-lactate.

The leading role of derivatives of indole derivatives among physiologically active compounds of both natural and synthetic sources is well known. A considerable number of indole derivatives have been synthesized with the objective of developing new biologically active compounds and medicinals. The results of investigations associated with the synthesis of derivatives of esters of N-(1H-indolyl)alanines were recently patented and the possibility of using them for the treatment of diabetes, obesity, hyperlipidemia, and atherosclerosis has been demonstrated. The authors paid particular attention to the development of the synthesis of enantiomerically pure compounds, since the optical purity of the substrates determines the biological activity and permits, for example, the use of such derivatives of indole for the combination therapy of diabetes [1]. In this connection especial value is attached to the development of methods for the synthesis of derivatives of indole with chiral substituents in particular, at the nitrogen atom of indole. However the authors of the patent [1] used, in place of asymmetric synthesis to prepare the required chiral structures, the separation of racemic substrates using chromatography on columns with a chiral stationary phase.

In our view the use of asymmetric synthesis has considerably greater promise for the preparation of derivatives of indole with chiral substituents at the nitrogen atom. In principle, there are two methods to solve the problem of the synthesis of derivatives of indole with a chiral substituent at the nitrogen atom. The first method – synthesis from a chiral predecessor – was developed by us in detail previously [2]. The second method – introduction of a chiral substituent at the nitrogen atom of an available indole structure – is the subject of this paper. The standard route for the N-alkylation of indole structures is connected with the preliminary generation of an N-anion under basic conditions and its interaction with activated alkylating agents.

* Dedicated to Academician B. A. Trofimov on his 70th birthday.

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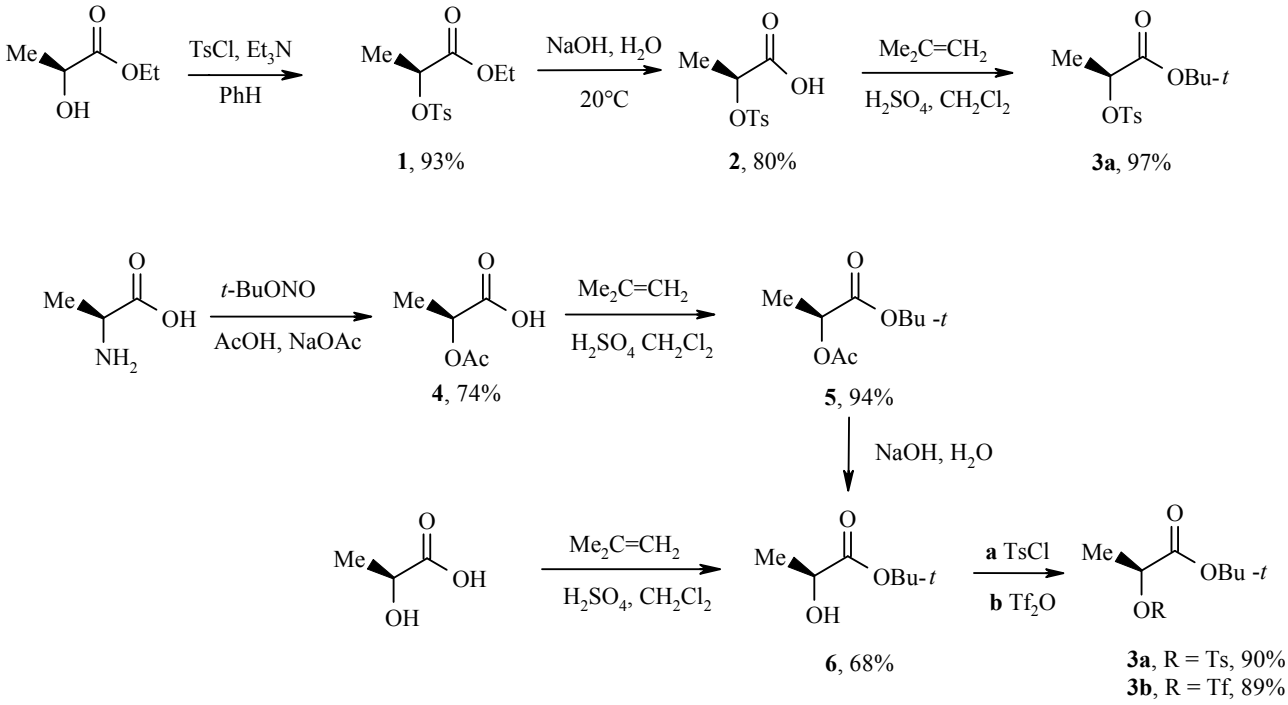
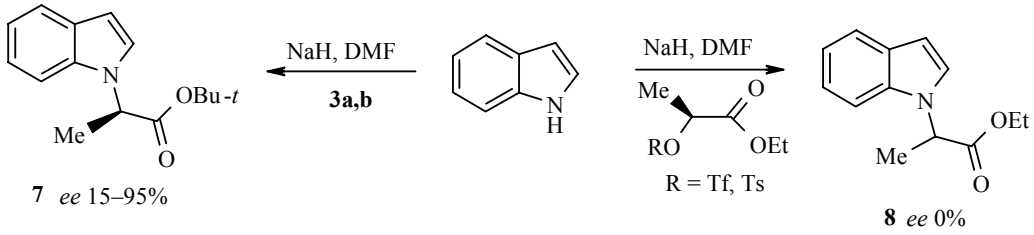


We used as the alkylating agent commercially available ethyl (*S*)-lactate, converted into an activated derivative (triflate, mesylate, tosylate, or acetate). Alkylation was carried out in the presence of sodium hydride in DMF. However variation of the reaction conditions and of the activating group did not lead to the chiral products of alkylation. The process of alkylation in the chosen conditions is accompanied by complete racemisation, resulting from enolisation of the substrates in the presence of strong bases. Analogous results were obtained on alkylation of various substituted isatins even in the presence of much weaker bases (e.g., K_2CO_3).

It is known [3] that *tert*-butyl esters of amino acids are favored in comparison with the generally used methyl and ethyl esters, and are used in peptide synthesis. In particular, they are more stable in basic media, and the effect of bases on substrates with a chiral carbon atom in the α-position to the *tert*-butoxycarbonyl group does not lead to racemisation, whereas this *tert*-butyl group is easily removed under mild conditions under the influence of an acid, and, in distinction from benzyl esters, it is stable to hydrogenation in the presence of catalysts. The absence of racemisation is evidently determined by spatial effects.

Based on literature data [3], we decided to use *tert*-butyl (*S*)-lactate as an alkylating agent to obtain derivatives of indole with a chiral substitutent at the nitrogen atom. For the synthesis of the chiral alkylating agent, we tested the three different routes shown in the scheme.



All three of the developed routes easily lead to the production in good yields of the *tert*-butyl ester, using as starting materials (*S*)-lactic acid, its ethyl ester, or alanine. We used the synthesized alkylating agents to introduce a chiral substituent at the nitrogen atom of indole (Table 1).

Table 1. Alkylation of Indole with Derivatives of *tert*-Butyl (*S*)-Lactate

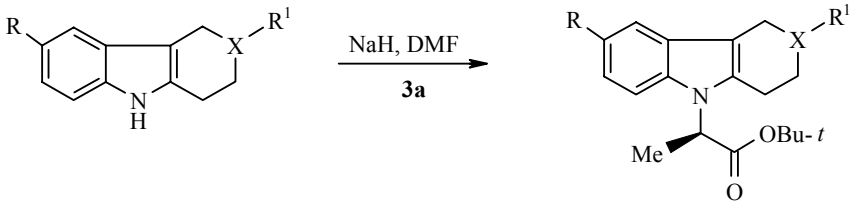
Com-pound	Reaction condition	Yield, %	*ee*, %*
3a	DMF, NaH 1.1 equiv., ~20°C, 2 h	25	0
3a	DMF, NaH 0.9 equiv., ~20°C, 2 h	20	95
3a	DMF, NaH 0.9 equiv., 80°C, 1 h	37	15
3b	DMF, NaH 1.1 equiv., ~80°C, 2 h	27	0
3b	DMF, NaH 0.9 equiv., ~20°C, 2 h	31	91
3b	DMF, NaH 0.9 equiv., 80°C, 1 h	38	20

* In all cases the enantiometric purity of the compounds obtained was determined via ^{1}H NMR spectra recorded in the presence of chiral ligands.

Although the corresponding product of alkylation, ester **7**, was produced in the chosen conditions of alkylation in yields no greater than 38%, nevertheless we succeeded in obtaining optimal conditions for obtaining indoles with a chiral substituent at the nitrogen atom with an optical purity of the product greater than 95% *ee*.

Experiments on the optimization of the alkylation conditions showed that an increase in the amount of base (1.1 equiv in place of 0.9 equiv) and also an increase of the reaction temperature to 80°C led to a decrease in the enantiometric excess of the reaction product, apparently as a result of the ease of racemisation of the reagent under these conditions. The best result (*ee*, 95%) was obtained using the tosyl activating group, 0.9 equiv of base at a temperature of ~ 20°C.

The method was universal, for example, it was successfully extended to tricyclic structures of the indole series, including the known variously physiologically active 1,2,3,4-tetrahydro-γ-carbolines, which creates the prospect of success among such structures of new biologically active compounds:

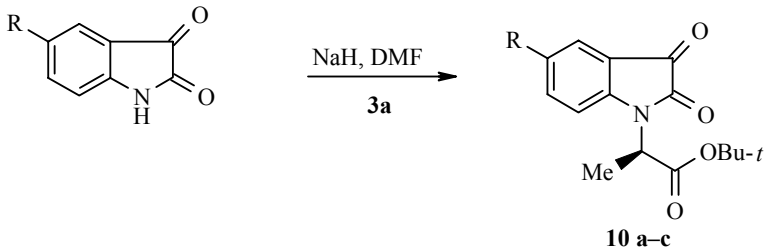


9a–c

9 a,b X = CH, R^1 = H; **a** R = H, **b** R = Me, **c** X = N, R = R^1 = Me

By HPLC analysis with a chiral carrier we observed from compound **9a** made by this method that the process was stereoselective (*ee* 95%).

Substituted isatins were also used as substrates for alkylation:



10 a–c

10 a R = H, **b** R = Br, **c** R = Me

There was virtually no racemisation in the case of the isatins: the enantiometric excess reached 90-97%.

Thus the demonstrated effectiveness of the proposed reagents for the preparation of different chiral derivatives of indole (with further optimization of the preparative yields) permits the hope for its wide use to obtain derivatives also of other NH-acid heterocycles with chiral substituent on the nitrogen atom.

EXPERIMENTAL

The chromato-mass spectroscopic studies of the reaction mixtures and the isolated compounds were carried out using a Carlo Erba/Kratos Fractovap Series 4200 chromatograph with a 25 m×0.2 mm Hewlett Packard Ultra-1 column, with an 0.33 mm thick phase, helium carrier gas (1 ml/min); 1:10 divided flow, evaporator temperature 280°C, and a temperature gradient from 150 to 280° C (5°C/min). The mass spectroscopic detector ITD-700 (Finnigan MAT); EI ionization, 70 eV, mass range 39-400 *m/z*. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance-400 (400 and 100 MHz respectively) with TMS as internal standard. Specific rotations were measured with a Jasco DIP-360 polarimeter (589 nm). Melting points were measured in a open capillary and were not corrected. The course of the reactions and the purity of the products were measured by TLC on Silufol UV-254 plates and gas chromatography with a mass spectroscopic detector.

Ethyl (2*S*)-2-(*p*-Tolylsulfonyloxy)propanoate (1). A solution of ethyl 2-(*S*)-lactate (30 g, 254 mmol) and *p*-toluenesulfonyl chloride (58.1 g, 304 mmol) in benzene (130 ml) was stirred for 15 min at ~ 20°C. Triethylamine (53.4 ml, 380 mmol) was added dropwise with vigrous stirring and cooling. The reaction mixture was stirred for 4 h (monitored by TLC), filtered, and the filtrate was washed with water, dried over anhydrous Na_2SO_4, and evaporated in vacuum. The residue was recrystallized from a 3:2 ether–petroleum ether mixture (100 ml) to give ester **1** (64.3 g, 93%); mp 33-33.5°C, $[\alpha]_D^{25}$ = -36.7°C (1% solution in chloroform). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.23 (3H, t, *J* = 7.1, $C\underline{H}_3CH_2$); 1.53 (3H, d, *J* = 6.95, $C\underline{H}_3CH$); 2.47 (3H, s, CH_3 tosyl); 4.12 (2H, q, *J* = 7.1, $CH_3C\underline{H}_2$); 4.96 (1H, q, *J* = 6.95, $C\underline{H}CH_3$); 7.36 (2H, d, *J* = 8.2, Ar); 7.84 (2H, d, *J* = 8.2, Ar). Found, %: C 52.91; H 5.98. $C_{12}H_{16}O_5S$. Calculated, %: C 52.93; H 5.92.

(2*S*)-2-(*p*-Tolylsulfonyloxy)propanoic Acid (2). Compound **1** (12 g, 44 mmol) was added to a solution of sodium hydroxide (2.1 g, 52.5 mmol) in a mixture of water (18 ml) and ethanol (12 ml) and stirred for 5 h at ~20°C, diluted with water, extracted with methylene chloride (2×50 ml); the aqueous phase was acidified with 6 N HCl to pH 4 and extracted with methylene chloride (3×50 ml). The extract was dried over anhydrous Na_2SO_4, and evaporated in vacuum. The residue crystallized on standing to give compound **2** (10.3 g, 80 %); mp 120-121°C. $[\alpha]_D^{25}$ = -34.9° (1% solution in chloroform). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.57 (3H, d, *J* = 7.0, $C\underline{H}_3CH$); 2.48 (3H, s, CH_3 tosyl); 4.99 (1H, q, *J* = 7.0, $C\underline{H}CH_3$); 7.38 (2H, d, *J* = 8.2, Ar); 7.84 (2H, d, *J* = 8.2, Ar); 7.52-8.63 (1H, br. s, CO_2H). Found, %: C 49.19; H 5.00. $C_{10}H_{12}O_5S$. Calculated, %: C 49.17; H 4.95.

***tert*-Butyl (2*S*)-2-(*p*-Tolylsulfonyloxy)propanoate (3a).** Conc. H_2SO_4 (1.8 ml) was added to a solution of compound **2** (26.2 g, 107 mmol) in methylene chloride (180 ml); the mixture was cooled to -15°C, and liquefied isobutene (90 ml) was added in one portion. The temperature was raised to room temperature and the mixture was stirred for 3 days. The mixture was washed with 1 N sodium hydroxide until alkaline. The organic layer was separated, dried with anhydrous Na_2SO_4, and evaporated in vacuum to give compound **3a** (31.2 g, 97%); R_f 0.91 (3:1 ether–petroleum ether), mp 105-107°C, $[\alpha]_D^{25}$ = -50.1° (1% solution in chloroform).^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.40 (9H, s, $(CH_3)_3C$); 1.54 (3H, d, *J* = 6.9, $C\underline{H}_3CH$); 2.47 (3H, s, CH_3 tosyl); 4.96 (1H, q, *J* = 6.9, $CH_3C\underline{H}$); 7.36 (2H, d, *J* = 8.2, Ar); 7.84 (2H, d, *J* = 8.2, Ar). Found, %: C 55.94, H 6.78. $C_{14}H_{10}O_5S$. Calculated, %: C 55.98; H 6.71.

O-Acetyl-(*S*)-lactic Acid (4) [4], ***tert*-Butyl O-Acetyl-(*S*)-lactate (5)** [5], ***tert*-Butyl (*S*)-Lactate (6)** [5], and ***tert*-Butyl (2*S*)-(Trifluoromethylsulfonyloxy)propionate (3b)** [6] were prepared by known methods. Their melting points , specific rotations, and spectral characteristics agreed with literature values.

Alkylation of Derivatives of Indole with *tert*-Butyl (2*S*)-(*p*-Tolylsulfonyloxylactate (General Method). A solution of a derivative of indole (0.9 mmol) in DMF (25 ml) was added to a suspension of sodium hydride (0.7 mmol) in DMF (50 ml) and stirred for 30 min. Then compound **3a** (1 mmol) was added in small portions and the mixture was stirred for 1 day. The reaction mixture was poured into water and extracted with methylene chloride (3×50 ml). The organic layers were combined, dried with anhydrous Na_2SO_4, and the solvent evaporated in vacuum. The residue was purified by chromatography on a silica gel column in a 10:1 system of petroleum ether–methylene chloride.

***tert*-Butyl 2-(Indolyl-1)propanoate (7).** Yield 20%. Viscous liquid. Mass spectrum, *m/z* (I_{rel}, %): 245 [M^+] (15); 189 [M^+–$C(CH_3)_3$] (24); 144 [M^+–CO_2–*t*-Bu] (100); 115 [M^+–CH_3CHCO_2–*t*-Bu] (9); 89 (9); 57 (90); 43 (68); 39 (56). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.41 (9H, s, $C(CH_3)_3$); 1.80 (3H, d, *J* = 7.3, $C\underline{H}_3CH$); 5.06 (1H, q, *J* = 7.3, $C\underline{H}CH_3$); 6.56 (1H, d, *J* = 2.8, H-3 indole); 7.13 (1H, t, *J* = 7.1, Ar); 7.23 (1H, t, *J* = 8.3, Ar); 7.28 (1H, d, *J* = 3.5, Ar); 7.35 (1H, d, *J* =8.3, Ar); 7.65 (1H, d, *J* = 7.8, Ar). Found, %: C 73.49, H 7.90, N 5.75. $C_{15}H_{19}NO_2$. Calculated, %: C 73.44; H 7.81; N 7.71.

Ethyl 2-(Indolyl-1-)propanoate (8). Yield 41%. Viscous liquid. ^{1}H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 0.71 (3H, t, *J* = 7.0, $C\underline{H}_3CH_2$); 1.24 (3H, d, *J* = 6.9, $C\underline{H}_3CH$); 3.78 (2H, q, *J* = 7.0, $CH_3C\underline{H}_2$); 4.76 (1H, q, *J* = 7.0, $C\underline{H}CH_3$); 6.62 (1H, d, *J* = 3.1, H-3 indole); 7.13 (1H, d, *J* = 3.1, H-2 indole); 7.18 (1H, t, *J* = 7.8, Ar); 7.24-7.32 (2H, m, Ar); 7.69 (1H, d, *J* = 7.8, Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.03 (CH_3CH_2); 19.27 (CH_3); 59.34 (CH); 63.68 (CH_2); 102.81 (CH); 110.91 (CH); 120.13 (2C, CH); 122.25 (CH); 124.81 (CH); 129.21 (C); 136.52 (C); 173.68 (C=O). Found, %: C 71.89; H 6.95; N 6.45. $C_{13}H_{15}NO_2$. Calculated, %,: C 71.87; H 6.96; N 6.45.

***tert*-Butyl (2*R*)-2-(1,2,3,4-Tetrahydro-9H-carbazol-9-yl)propanoate (9a).** Yield 30%. Viscous liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.40 (9H, s, $(CH_3)_3C$); 1.71 (3H, d, *J* = 7.3, CH_3); 1.80-1.98 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$); 2.67-2.79 (4H, m, $C\underline{H}_2CH_2CH_2C\underline{H}_2$); 4.96 (1H, q, *J* = 7,3, CH); 7.16 (1H, t, *J* = 7.1, Ar); 7.25 (1H, t, *J* = 8.3, Ar); 7.34 (1H, d, *J* = 8.3, Ar); 7.16 (1H, d, *J* = 7.8, Ar). Found, %: C 76.26; H 8.47; N 4.68. $C_{19}H_{25}NO_2$. Calculated, %: C 76.22; H 8.42; N 4.68.

***tert*-Butyl (2*R*)-2-(6-Methyl-1,2,3,4-tetrahydro-9H-carbazol-9-yl)propanoate (9b).** Yield 25%. Viscous liquid. Mass spectrum, *m/z* (I_{rel}, %): 313 [M^+] (5); 257 [M^+ - $C(CH_3)_3$] (20); 212 [M^+–CO_2– *t*-Bu] (32); 184 [M^+–CH_3CHCO_2–*t*-Bu] (18); 168 (9); 128 (7); 97 (11); 57 (100), 43 (77); 39 (40). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.39 (9H, s, $(CH_3)_3C$); 1.69 (3H, d, *J* = 7.3, CH_3); 1.83-2.00 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$); 2.45 (3H, s, Ar–$CH_3$); 2.65-2.77 (4H, m, $C\underline{H}_2CH_2CH_2C\underline{H}_2$), 4.92 (1H, q, *J* = 7.3, CH); 6.94 (1H, d, *J* = 8.4, Ar); 7.17 (1H, d, *J* = 8.4, Ar); 7.26 (1H, s, Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.59 (CH_3); 21.08 (C-4); 21.36 (CH_3-Ar); 22.81 (C-3); 23.11 (C-2); 23.45 (C-1); 27.89 ((CH_3)$_3$); 53.01 (CH); 81.78 ($\underline{C}(CH_3)_3$); 109.67 (C-8); 112.88 (C-4a); 117.65 (C-7); 121.97 (C-5); 125.93 (C-6); 127.90 (C-4b); 133.84 (C-9a); 145.13 (C-8a); 170.43 ($\underline{C}O$). Found, %: C 76.66; H 8.67; N 4.48. $C_{20}H_{27}NO_2$. Calculated, %: C 76.64; H 8.68; N 4.47.

***tert*-Butyl (2*R*)-2-(2,8-Dimethyl-1,2,3,4-tetrahydro-γ-carbolin-5-yl)propanoate (9c).** Yield 18%. Viscous liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.41 (9H, s, $(CH_3)_3C$); 1.73 (3H, d, *J* = 7.3, CH_3); 2.44 (3H, s, 8-CH_3); 2.60 (3H, s, 2-CH_3); 2.80-2.85 (4H, m, CH_2CH_2); 3.68 (2H, s, H-1); 4.95 (1H, q, *J* = 7.3, CH); 7.24 (1H, m, Ar); 7.34 (1H, d, *J* = 8.4, Ar); 7.62 (1H, d, *J* = 7.8, Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.59 (CH_3); 21.42 (1C, 4-CH_2); 22.95 (8-CH_3); 27.89 ((CH_3)$_3$); 45.35 (2-CH_3); 46.35 (2-CH_3); 51.72 (3-CH_2); 53.01 (CH); 81.78 ($\underline{C}(CH_3)_3$); 108.10 (6-CH); 108.66 (C-9b); 117.86 (7-CH_3); 122.71 (9-CH); 126.23 (8-$CH_3\underline{C}$); 128.66 (C-9a); 133.40 (C-4a); 135.18 (C-5a); 169.39 (C=O). Found, %: C 73.16; H 8.57; N 8.58. $C_{20}H_{28}N_2O_2$. Calculated, %: C 73.14; H 8.59; N 8.53.

***tert*-Butyl (2*R*)-2-(Isatin-1-yl)propanoate (10a).** Yield 15%, *ee* 97%. Viscous liquid. ^{1}H NMR spectrum ($CDCl_3$); δ, ppm (*J*, Hz): 1.44 (9H, s, $(CH_3)_3C$); 1.64 (3H, d, *J* = 7.3, CH_3); 5.15 (1H, q, *J* = 7.3, CH); 7.14 (1H, d, *J* = 8.2, H-7); 7.17 (1H, t, *J* = 8.2, H-6); 7.62 (1H, d, *J* = 8.1, H-4); 7.68 (1H, t, *J* = 8.1, H-5). ^{13}C NMR spectrum ($CDCl_3$); δ, ppm: 16.60 (CH_3); 27.90 ((CH_3)$_3$); 52.98 (CH); 81.81 ($\underline{C}(CH_3)_3$); 111.70 (CH); 118.12 (C); 123.93 (CH); 125.31 (CH); 138.80 (CH); 150.14 (C); 158.11 (C=O); 169.86 (C=O); 183.14 (C=O). Found, %: C 65.38; H 6.29; N 5.01. $C_{15}H_{17}NO_4$. Calculated, %: C 65.44; H 6.22; N 5.09.

***tert*-Butyl (2*R*)-2-(5-Bromisatin-1-yl)propanoate (10b).** Yield 36%, *ee* 95%. Viscous liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.44 (9H, s, $(CH_3)_3C$); 1.64 (3H, d, *J* = 7.3, CH_3); 5.08 (1H, q, *J* = 7.3, CH); 6.78 (1H, d, *J* = 8.6, Ar); 7.68 (1H, dd, *J* = 8.3, *J* = 1.8, Ar); 7.76 (1H, d, *J* = 1.8, Ar). Found, %: C 50.82; H 4.61; N 3.90. $C_{15}H_{16}BrNO_4$. Calculated, %: C 50.87; H 4.55; N 3.95.

***tert*-Butyl (2*R*)-2-(5-Methylisatin-1-yl)propanoate (10c).** Yield 28%, *ee* 95%. Viscous liquid. Mass spectrum, *m/z* (I_{rel}, %): 289 [M^+] (25); 160 [M^+–CH_3CHCO_2–*t*-Bu] (100); 168 (9); 128 (7); 97 (11); 117 (34); 91 (50); 57 (80); 43 (77). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.43 (9H, s, $(CH_3)_3C$); 1.64 (3H, d, *J* = 7.3, CH_3); 2.44 (3H, s, CH_3, isatin); 5.01 (1H, q, *J* = 7.3, CH); 6.68 (1H, d, *J* = 8.3, Ar); 7.61 (1H, d, *J* = 8.3, Ar); 7.71 (1H, s, Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.60 (CH_3); 23.02 (CH_3, isatin); 27.92 (($CH_3)_3$); 53.05 (CH); 81.82 ($\underline{C}(CH_3)_3$); 111.59 (CH); 118.08 (C); 125.49 (CH); 133.38 (C); 139.10 (CH); 148.01 (C); 158.18 (CO); 169.91 (CO); 183.37 (CO). Found, %: C 66.51; H 6.69; N 4.86. $C_{16}H_{19}NO_4$. Calculated, %: C 66.42; H 6.62; N 4.84.

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