*Chemistry of Heterocyclic Compounds, Vol. 41, No. 10, 2005*

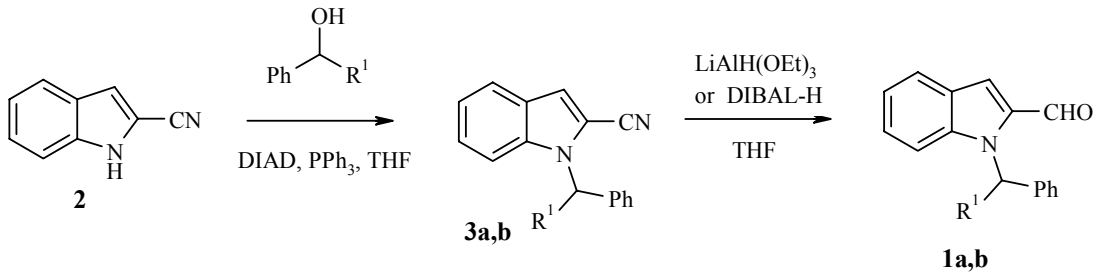
# CHIRALLY N-SUBSTITUTED INDOLE-2-CARBALDEHYDES. PREPARATION AND USE IN ASYMMETRIC SYNTHESIS

**N. E. Golantsov[1], A. V. Karchava[1], Z. A. Starikova[2], F. M. Dolgushin[2], and M. A. Yurovskaya[1]**

*A simple method is proposed for the synthesis of optically active indole-2-carbaldehydes via alkylation of 2-cyanoindole by optically active secondary alcohols and subsequent reduction of the cyano group to an aldehyde. Reaction of the aldehydes obtained with aromatic amines gave imines whose reaction with the Danishefsky diene was studied. The structure of the major diastereomer of (2R')-1-phenyl-2-[1-((1R')-1-phenylethyl)indol-2-yl]-1,2,3,4-tetrahydropyridine-4-one and minor diastereomer (2S)-2-[1-((1S)-2-methoxy-1-phenylethyl)indol-2-yl]-1-phenyl-1,2,3,4-tetrahydropyridine-4-one respectively were established by X-ray analysis.*

**Keywords:** N-substituted indoles, chiral aldehydes, 2-cyanoindole, aza Diels–Alder reaction, asymmetric synthesis, Mitsunobu reaction.

The preparation of optically active indole derivatives remains an important problem for synthetic chemists [1]. At this time a large number of examples of the asymmetric synthesis involving chiral indole derivatives have been reported [1-3] but instances of the use in asymmetric synthesis of indole derivatives containing a chiral substituent on the nitrogen atom are rare [4, 5]. We propose a simple method for preparing chiral N-substituted indole-2-carbaldehydes (**1a,b**) and have studied their potential use in asymmetric synthesis in the case of the aza Diels–Alder reaction.




**1, 3 a** $R^1$ = Me, **b** $R^1$ = $CH_2OMe$

The starting compound was 2-cyanoindole (**2**). We have previously shown the possibility of alkylating the nitrile **2** with ethyl (*S*)-2-hydroxypropionate under Mitsunobu reaction conditions in the presence of the classical oxidative-reductive system $PPh_3$-azodicarboxylate [7]. The Mitsunobu reaction occurs in mild

[1] M. V. Lomonosov State University, Moscow 119234, Russia; e-mail: yumar@org.chem.msu.ru.
[2] A. N. Nesmeyanov Institute of Organoelement Compounds, Moscow 119991, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1540-1550, October, 2005. Original article submitted June 14, 2005.

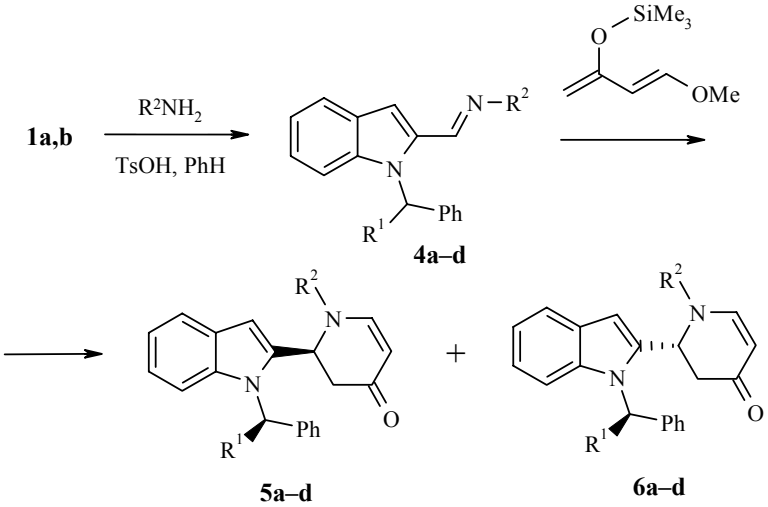
conditions with complete inversion of configuration [7]. For this work racemic 1-phenylethanol and optically active (*R*)-2-methoxy-1-phenylethanol ($[\alpha]_D^{25}$ -32.1° (*c* 1.4, $CH_2Cl_2$), enantiomeric excess 63%) [8, 9]) were used for alkylating 2-cyanoindole in the presence of $PPh_3$ and diisopropyl azodicarboxylate (DIAD). The alkylation products **3a,b** were obtained in high yields. For compound **3b** it was particularly important to carry out the Mitsunobu reaction at 0-5°C because a concurrent elimination takes place even at room temperature and the yield of the alkylation product does not exceed 50%.

$LiAlH(OEt)_3$ [10] was used for reduction of the cyano group of compound **3a** to an aldehyde but for nitrile **3b** the given reduction surprisingly proved ineffective and variation of the reaction conditions did not lead to a positive result. Diisobutyl aluminum hydride (DIBAL-H) [11] was used to reduce **3b** and the aldehyde **1b** was obtained in high yield.

The aldehydes **1a,b** were converted to the imines **4a-d** by reaction with aromatic amines. The aza Diels–Alder reaction involving imines is widely used in the asymmetric synthesis of nitrogen-containing heterocyclic systems [12]. Electron-excessive siloxidenes [13, 14] are often used as dienes. The reaction of the imines with such dienes can occur together or in stages including a tandem sequence of Mannich and Michael reactions [12, 14, 15]. The Danishefsky diene (1-methoxy-3-trimethylsiloxybuta-1,3-diene) has proved particularly efficient [13] and leads to substituted 1,2,3,4-tetrahydropyridin-4-ones. An indole fragment containing a piperidine substituent in position 2 occurs in the composition of a whole series of alkaloids and biologically active materials and the synthesis of such compounds is of significant interest [2, 3].

We have studied the reaction of the prepared imines **4a-d** with the Danishefsky diene. The imines **4a** and **4b** were tried out under different reaction conditions and catalysts. Diastereomer products of cycloaddition **5a,b** and **6a,b** were observed in different ratios and with yields from low to high. The results of the investigation are summarized in Table 1.

The best results were obtained using anhydrous $ZnCl_2$ (1.1 equivalents) as catalyst and methylene chloride as solvent. The yield of the major isomer for imine **4b** with the reaction carried out at -60°C was 70%. A significant difference in the ratio of diastereomers for imines **4a** and **4b** was not observed.




**4-6 a** $R^1$ = Me, **b-d** $R^1$ = $MeOCH_2$; **a**, **b** $R^2$ = Ph, **c** $R^2$ = *o*-$MeOC_6H_4$, **d** $R^2$ = *o*-$FC_6H_4$

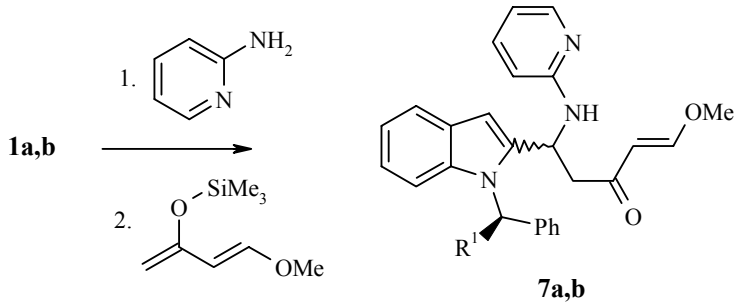
Increase in the amount of catalyst for the imine **4b** led to a small decrease in the yield and the diastereoselectivity. When the reaction was carried out in $LiClO_4$ solution in ether (0.5 molar) [16] the yield was close to quantitative but the diastereoselectivity was markedly lower. The use of a proton acid in aqueous-organic medium as catalyst [17] did not proved effective.

TABLE 1. Reaction of Imines **4a-d** with the Danishefsky Diene under Varying Conditions

| No | Imine | Catalyst | Reaction conditions | | Yield **5**+**6**, % | **5** : **6** |
|---|---|---|---|---|---|---|
| | | | Solvent | T, °C | | |
| 1 | **4a** | $ZnCl_2$, 1.1 eq. | THF | -60 | 25 | 35 : 65 |
| 2 | **4a** | $ZnCl_2$, 1.1 eq. | $CH_2Cl_2$ | -20 | 68 | 34 : 66 |
| 3 | **4a** | $ZnCl_2$, 1.1 eq. | $CH_2Cl_2$ | -60 | 72 | 25 : 75 |
| 4 | **4b** | $ZnCl_2$, 1.1 eq. | $CH_2Cl_2$ | -60 | 90 | 22 : 78 |
| 5 | **4b** | $ZnCl_2$, 2.1 eq. | $CH_2Cl_2$ | -60 | 85 | 25 : 75 |
| 6 | **4b** | TFA, 0.1 eq. | MeCN–$H_2O$ | -50 | 30 | 23 : 77 |
| 7 | **4b** | 0.5 mol/l $LiClO_4$ | $Et_2O$ | 20 | 95 | 37 : 63 |
| 8 | **4b** | 0.5 mol/l $LiClO_4$ | THF | -60 | 53 | 24 : 76 |
| 9 | **4c** | $ZnCl_2$, 1.1 eq. | $CH_2Cl_2$, | -60 | 79 | 16 : 84 |
| 10 | **4d** | $ZnCl_2$, 1.1 eq. | $CH_2Cl_2$, | -60 | 23 | 19 : 81 |

The cycloaddition products with good diastereoselectivity were obtained in the reaction of the Danishefsky diene with the imines **4c** and **4d** using methylene chloride at -60°C in the presence of anhydrous $ZnCl_2$. The yield for the imine **4d** prepared from *o*-fluoroaniline was moderate.

Attempts to carry out the aza Diels–Alder reaction with imines obtained from the aldehydes **1a,b** and 2-aminopyridine under similar conditions did not give the corresponding cycloaddition products but the Mannich reaction products **7a** and **7b** were produced in high yield as a mixture of diastereomers. The ratio of diastereomers was 1:2 in both cases which is significantly lower that in the case of the cycloaddition.




**7a,b**

**7 a** $R^1$ = Me; **b** $R^1$ = $MeOCH_2$

The diastereomers **5** and **6** have a marked difference in $R_f$ when chromatographed on silica gel and can be separated quite readily in the pure state by preparative column chromatography.

The structure of the major diastereomer **6a** and the minor isomer **5b** were determined by X-ray analysis of their single crystals (Figs. 1 and 2). The structure of **6a** contains two crystallographically independent molecules, differing in the rotation about the Ph-rings.

The molecules have similar structures with the exception of the orientation of the phenyl ring C(22)-C(27). The indole ring, atoms C(9) and C(20) form a planar fragment (plane 1), relative to which the 1,2,3,4-tetrahydropyridin-4-one ring is positioned orthogonally, the dihedral angle between plane 1 and the mean square plane of the 1,2,3,4-tetrahydropyridin-4-one ring (plane 2) being 79.7° (**5b**) and 88.7° and 90.2° (in the individual molecules of **6a**). The ring has a *twist* conformation, atoms C(9) and C(10) deviating from the plane of atoms C(11), C(12), C(13), and N(2) to different sides. In both molecules of **6a** they are symmetrical with an average of 0.32 Å whereas in **5b** they are 0.18 and 0.43 Å. The phenyl ring C(14)-C(19) is twisted relative to plane 2 by about the same in all of the molecules (the corresponding dihedral angle being 31.5° (**5b**)

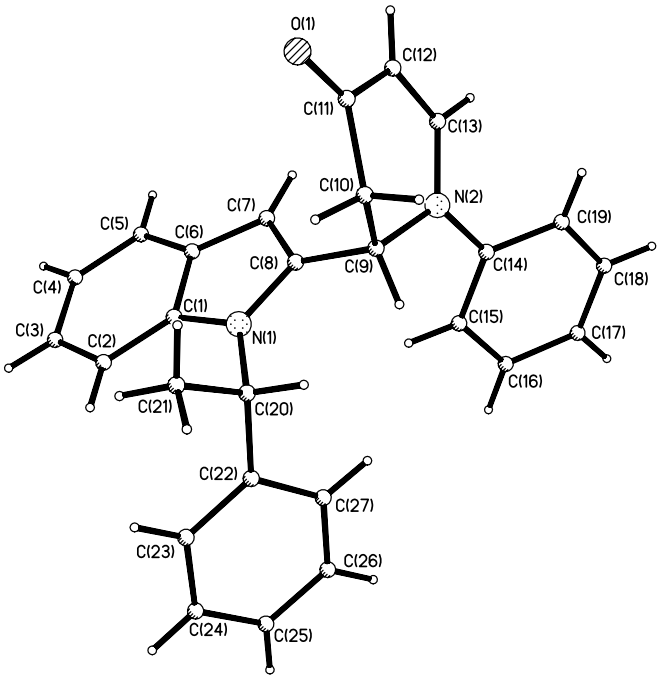



Fig. 1. Structure of molecule **6a**.

and 35.4 and 41.0° (**6a**)). The orientations of the Ph-ring C(22)-C(27) relative to the 1,2,3,4-tetrahydropyridin-4-one ring in molecules **6a** and **5b** are different, the torsional angles C(8)–N(1)–C(20)–C(21) and C(8)–N(1)–C(20)–C(22) being 106.0, 114.6 and -115.7, -125.3° respectively in **6a** and 130.6, -101.5° in **5b**.

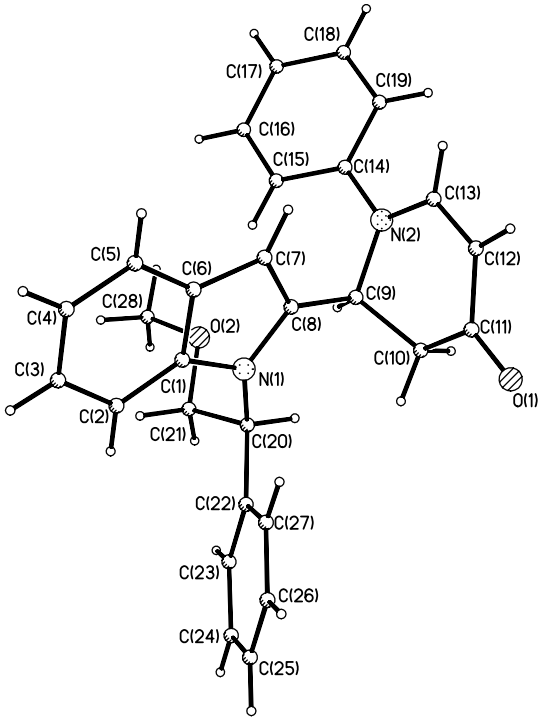



Fig. 2. Structure of molecule **5b**.

TABLE 2. Some Bond Lengths (*d*) in the Molecule **5b** and the Two Independent Molecules of **6a**

| Bond | *d*, Å | | |
|---|---|---|---|
| | **5b** | **6a** | |
| N(1)–C(8) | 1.389(2) | 1.378(6) | 1.386(5) |
| N(1)–C(1) | 1.390(2) | 1.393(5) | 1.380(5) |
| C(8)–C(9) | 1.511(2) | 1.500(6) | 1.507(5) |
| C(9)–C(10) | 1.535(2) | 1.533(6) | 1.523(6) |
| C(10)–C(11) | 1.519(2) | 1.513(7) | 1.517(7) |
| C(11)–O(1) | 1.223(2) | 1.232(6) | 1.222(5) |
| C(11)–C(12) | 1.435(2) | 1.417(8) | 1.417(7) |
| C(12)–C(13) | 1.356(2) | 1.347(7) | 1.338(7) |
| C(13)–N(2) | 1.361(2) | 1.348(6) | 1.359(6) |
| N(2)–C(9) | 1.473(2) | 1.477(6) | 1.477(6) |
| N(2)–C(14) | 1.423(2) | 1.417(6) | 1.411(6) |

The geometric parameters for the molecules are identical. Several bond lengths are given in Table 2.

On the basis of the X-ray data it can be deduced that the diastereomers of **6a** and **5b** have the (*R*',*R*')-configuration, i.e. the major diastereomer of **6a** is (2*R*')-1-phenyl-2-[(1-((1*R*')-1-phenylethyl)indol-2-yl]-1,2,3,4-tetrahydropyridin-4-one and the major diastereomer of **6b** obtained from optically active (*R*)-2-methoxy-1-phenylethanol is (2*R*)-2-[1-((1*S*)-2-methoxy-1-phenylethyl)indol-2-yl)]-1-phenyl-1,2,3,4-tetrahydropyridin-4-one.

Hence we have shown that the aza Diels–Alder reaction of the Danishefsky diene with enamines prepared from indole-2-carbaldehydes containing a chiral substituent on the nitrogen atom occurs with good diastereoselectivity and with yields from moderate to high.

## EXPERIMENTAL

**X-ray Structural Investigation of 6a and 5b**. Crystals of **6a** were prepared by crystallization from a 1:1 mixture of ethyl acetate and petroleum ether and crystals of **5b** from a 1:2 mixture of methylene chloride and petroleum ether. The crystallographic parameters, experimental details, and structural refinement data are given in Table 3.

The structures were solved by a direct method in which all of the non hydrogen atoms were localized in electron density difference synthesis with $F^2_{hkl}$ refinement in the anisotropic approximation. All of the hydrogen atoms were placed in the geometrically calculated positions and refined using the "riding" model with $U(H) = 1.2\ U(C)$ where $U(C)$ is the equivalent temperature factor for the carbon atom with which the corresponding H atom is bonded. Treatment of the experimental data, calculations, and illustrations were performed using the programs [18-22]. Atomic coordinates and temperature factors have been deposited in the Cambridge structural data bank.

IR spectra were obtained on a UR-20 instrument for suspensions in vaseline oil or for the pure compounds. The specific rotation was measured on a Jasco DIP-360 polarimeter (589 nm). $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance-400 instrument (400 and 100 MHz respectively) for solutions in DMSO-$d_6$ (unless another solvent is quoted) and the internal standard was TMS. UPT experiments were carried out for compounds **5a,b** and **6a-d**.

TABLE 3. Crystallographic Data and Refinement Parameters for Compounds **6a** and **5b**

| Parameter | **6a** | **5b** |
|---|---|---|
| Empirical formula | $C_{27}H_{24}N_2O$ | $C_{28}H_{26}N_2O_2$ |
| Mol. weight | 392.48 | 422.51 |
| Space group, *Z* | *Cc*, 8 | $P2_1/n$, 4 |
| Temperature, K | 293(2) | 100(2) |
| Crystal lattice parameters, Å | | |
| *a* | 21.68(2) | 8.7334(4) |
| *b* | 10.462(6) | 17.2868(8) |
| *c* | 18.51(1) | 14.4271(7) |
| β, deg | 99.52(5) | 90.272(1) |
| Unit cell volume, *V,* Å$^3$ | 4140(14) | 2178.1(2) |
| $D_{calc}$, g·cm$^{-3}$ | 1.340 | 1.288 |
| Color and crystal form | Colorless needle | Light yellow prism |
| Size, mm | 0.40 × 0.35 × 0.25 | 0.40 × 0.30 × 0.08 |
| Diffractometer | CAD4 Enraf-Nonius | Bruker SMART |
| Irradiation | MoKα (λ = 0.71073 Å) | |
| μ, cm$^{-1}$ | 0.77 | 0.81 |
| Scanning mode | θ –5/3θ | ϕ/ω |
| $2\theta_{max}$, deg | 46.0 | 58.74 |
| Total reflections | 3118 | 23332 |
| Number of independent reflections ($R_{int}$) | 2947 (0.0314) | 6007 (0.0389) |
| $R_1$ (from *F* for reflections with $I > 2\sigma(I)$) | 0.0406 (2654 refl.) | 0.0583 (4796 refl.) |
| $wR_2$ (from $F^2$ for all reflections) | 0.1041 | 0.1331 |
| Number of refinement parameters | 541 | 289 |
| Weighting scheme | $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, where $P = 1/3(F_o^2+2F_c^2)$ | |
| *A* | 0.0653 | 0.0609 |
| *B* | 2.5501 | 0.7565 |
| *GOOF* | 1.003 | 1.075 |
| *F*(000) | 1664 | 896 |

Assignment of the signals in the $^1$H NMR spectra for compounds **7a,b** were made on the basis of double resonance experiments. Melting points were measured in open capillaries and values given are not corrected. Monitoring of the reaction course and the purity of the compounds obtained was carried out by TLC on Silufol UV-254 and Merck Silica gel 60 $F_{254}$ plates. Solvents were dehydrated by standard methods [23].

**Mitsunobu Reaction (General Method).** The alcohol (26 mmol) and then dropwise a solution of diisopropyl azodicarboxylate (5.1 ml, 26 mmol) in THF (10 ml) were added to a solution of 2-cyanoindole (2.5 g, 17.5 mmol) and triphenylphosphine (6.8 g, 26 mmol) in THF (50 ml) at 0-5°C. The mixture was stirred at this temperature for 1 h and left for 24 h. Solvent was removed in vacuo and the residue was chromatographed on silica gel with elution using a mixture of petroleum ether and ethyl acetate.

**2-Cyano-1-(2-phenylethyl)indole (3a)**. Yield 95%. Viscous liquid. IR spectrum, ν, cm$^{-1}$: 710 ($C_6H_5$), 750, 760, 2235 (CN). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.02 (3H, d, *J* = 7.1, $CH_3$); 6.15 (1H, q, *J* = 7.1, C<u>H</u>$CH_3$); 7.16-7.23 (3H, m, H arom.); 7.27-7.39 (4H, m, H arom.); 7.52 (1H, s, C(3)H); [7.60 (1H, d, *J* = 8.5); 7.71 (1H, d, *J* = 7.9); H-4 and H-7]. Mass spectrum, *m/z* (*I*, %): 246 $[M]^+$ (22), 142 (35), 105 (100), 77 (17). Found, %: C 82.62; H 5.70; N 11.18. $C_{17}H_{14}N_2$. Calculated, %: C 82.90; H 5.73; N 11.37.

**(*S*)-2-Cyano-1-(2-methoxy-1-phenylethyl)indole (3b)**. Yield 91%; mp 76-78°C (ethyl acetate–hexane). $[\alpha]_D^{25}$ 34.8 (*c* 5.3, $CH_2Cl_2$). IR spectrum, ν, cm$^{-1}$: 705 ($C_6H_5$); 720, 755, 770, 2230 (CN). $^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.43 (3H, s, $OCH_3$); 4.34 (1H, dd, *J* = 10.1, *J* = 5.6, C<u>H$_a$</u>H$_b$); 4.42 (1H, t, *J* = 10.1, CH$_a$<u>H$_b$</u>); 6.03 (1H, dd, *J* = 10.1, *J* = 5.6, C<u>H</u>$C_6H_5$); 7.30-7.85 (9H, m, H arom.); 7.69 (1H, d, *J* = 8.0, H arom.). Found, %: C 77.99; H 5.76; N 10.22. $C_{18}H_{16}N_2O$. Calculated, %: C 78.24; H 5.84; N 10.14.

**2-Formyl-1-(1-phenylethyl)indole (1a)**. A mixture of ethyl acetate (1.2 ml, 12 mmol) and THF (1 ml) was added to a suspension of lithium aluminum hydride (0.3 g, 8 mmol) in THF (2.5 ml) at 0-10°C under an argon atmosphere. The mixture was cooled to 0°C, stirred at this temperature for 30 min, and a solution of compound **3a** (1 g, 4 mmol) in THF (1.5 ml) was added. The reaction mixture was stirred for 1 h at 0-5°C, $H_2SO_4$ (5N, 20 ml) was added, the product was stirred for 5 min, and extracted with ether (3 × 30 ml). The extract was washed with saturated NaCl solution and dried over anhydrous sodium sulfate. Solvent was evaporated off in vacuo and the residue was chromatographed on silica gel eluting with a mixture of petroleum ether and ethyl acetate (100:6) to give 0.76 g (76%) of compound **1a**; mp 48-49°C (ethyl acetate–hexane). IR spectrum, ν, $cm^{-1}$: 720 ($C_6H_5$), 750, 765, 780, 1680 (C=O). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.92 (3H, d, *J* = 7.1, $CH_3$); 6.92 (1H, q, *J* = 7.1, C<u>H</u>$CH_3$); 7.10 (1H, dd, *J* = 8.1, *J* = 6.1, H arom.); 7.16-7.39 (7H, m, H arom.); 7.57 (1H, s, C(3)H); 7.60 (1H, d, *J* = 8.1, H arom.); 9.94 (1H, s, CHO). Found, %: C 82.20; H 6.16; N 5.47. $C_{17}H_{15}NO$. Calculated, %: C 81.90; H 6.06; N 5.62.

**(*S*)-2-Formyl-1-(2-methoxy-1-phenylethyl)indole (1b)**. A solution of DIBAL-H (1 molar, 6.6 ml) in hexane (~ 6.6 mmol) was added to a solution of compound **3b** (0.9 g) in a mixture of hexane (15 ml) and THF (15 ml) at -70°C under an argon atmosphere. The reaction mixture was stirred at the same temperature for 1 h letting the mixture warm to room temperature and stirred for a further 1 h. A saturated solution of $NH_4Cl$ (50 ml) was added and the product was stirred for 20 min, dilute $H_2SO_4$ (1:5, 15 ml) was added followed by extraction with ethyl acetate (3 × 30 ml). The extract was washed with a saturated solution of $NaHCO_3$, saturated NaCl solution, and dried over anhydrous sodium sulfate. Solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with a mixture of petroleum ether and ethyl acetate (100:6). Yield 0.78 g (85%). Viscous liquid. $[\alpha]_D^{25}$ 28.2 (*c* 5.3, $CH_2Cl_2$). IR spectrum, ν , $cm^{-1}$: 710 ($C_6H_5$), 750, 770, 1675 (C=O). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.24 (3H, s, $CH_3$); 4.27-4.37 (2H, m, $CH_2$); 6.96 (1H, t, *J* = 6.6, C<u>H</u>$C_6H_5$); 7.12 (1H, dd, *J* = 7.9, *J* = 6.9, H arom.); 7.20-7.35 (7H, m, H arom.); 7.58 (1H, s, H-3); 7.79 (1H, d, *J* = 8.0, H arom.); 9.91 (1H, s, CHO). Found, %: C 77.56; H 5.95; N 5.30. $C_{18}H_{17}NO_2$. Calculated, %: C 77.40; H 6.13; N 5.01.

**Synthesis of Imines. (General Method).** A catalytic amount of *p*-toluenesulfonic acid was added to a solution of the aldehyde (6.8 mmol) and the amine (7.1 mmol) in benzene (7 ml) and the product was refluxed for 2 h in a Dean and Stark apparatus filled with molecular sieve (4 Å). The course of the reaction was monitored by TLC. The solvent was evaporated in vacuo and the product was used without further purification.

**Aza Diels–Alder Reaction of Imines with the Danishefsky Diene. (General Method).** Anhydrous $ZnCl_2$ (0.1 g, 7.5 mmol) was added to a solution of the imine (6.8 mmol) in $CH_2Cl_2$ (7 ml) at -60°C. The product was stirred for 10 min, the Danishefsky diene [24] (0.2 ml, 10.2 mmol) was added, and stirring was continued at the same temperature for 6 h. Decomposition was brought about by the addition of HCl (1 molar, 10 ml) to the reaction mixture. Product was let to heat to room temperature. The organic layer was separated and the aqueous layer extracted with $CH_2Cl_2$ (3 × 10 ml). The extract was washed with a saturated solution of $NaHCO_3$ and then saturated NaCl solution and dried over anhydrous sodium sulfate. Solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with a mixture of petroleum ether and ethyl acetate.

Compounds **5a** and **6a** were prepared from 2-formyl-1-(1-phenylethyl)indole (**1a**) and aniline.

**(2*R*')-1-Phenyl-2-[1-((1*S*')-1-phenylethyl)indol-2-yl]-1,2,3,4-tetrahydropyridin-4-one (5a)** (minor diastereomer). Yield 18%; mp 228-229°C (ethyl acetate–hexane). IR spectrum, ν, $cm^{-1}$: 710 ($C_6H_5$), 780, 1650 (C=O). $^1$H NMR spectrum, ($CDCl_3$), δ, ppm (*J*, Hz): 1.93 (3H, d, *J* = 7.1, $CH_3$); 2.85 (1H, dd, *J* = 16.4, *J* = 2.9, C<u>H</u>$_a$H$_b$); 3.31 (1H, dd, *J* = 16.4, *J* = 7.1, CH$_a$<u>H</u>$_b$); 5.38 (1H, d, *J* = 7.8, NCH=C<u>H</u>CO); 5.53 (1H, dd, *J* = 7.1, *J* = 2.9, C<u>H</u>CH$_a$H$_b$); 5.67 (1H, q, *J* = 7.1, C<u>H</u>$CH_3$); 6.64 (1H, s, C(3)H); 6.86 (1H, d, *J* = 8.4, H arom.); 6.98 (1H, t, *J* = 7.6, H arom.); [7.03-7.10 (3H, m), 7.13-7.23 (3H, m), 7.26-7.40 (5H, m), 7.55 (1H, d, *J* = 7.8), 7.66 (1H, d, *J* = 8.0), H arom. and NC<u>H</u>=CHCO]. $^{13}$C NMR spectrum, δ, ppm: 19.35 ($CH_3$); 42.55 ($CH_2$); 52.77 (CH); 54.80 (CH); 101.26 (CH); 101.52 (CH); 113.02 (CH); 118.89 (2CH); 119.81 (CH); 120.90 (CH); 121.35 (CH); 124.40 (CH); 126.39 (2CH); 127.70 (CH); 128.45 (C); 129.17 (2CH); 129.93 (2CH); 135.97 (C); 136.95

(C); 141.18 (C); 144.53 (C); 149.38 (CH); 189.45 (C=O). Found, %: C 82.47; H 6.08; N 7.18. $C_{27}H_{24}N_2O$. Calculated, %: C 82.62; H 6.16; N 7.14.

**(2*R*')-1-Phenyl-2-[1-((1R')-1-phenylethyl)indol-2-yl]-1,2,3,4-tetrahydropyridin-4-one (6a)** (major diastereomer). Yield 54%; mp 219-220°C (ethyl acetate–hexane). IR spectrum, ν, $cm^{-1}$: 710 ($C_6H_5$), 770, 1660 (C=O). $^1$H NMR spectrum, ($CDCl_3$), δ, ppm (*J*, Hz): 1.96 (3H, d, *J* = 7.1, $CH_3$); 2.69 (1H, dd, *J* = 16.4, *J* = 4.0, C$\underline{H}_a$H$_b$); 3.20 (1H, dd, *J* = 16.4, *J* = 7.1, CH$_a\underline{H}_b$); 5.36 (1H, d, *J* = 7.6, NCH=C$\underline{H}$CO); 5.51 (1H, dd, *J* = 7.1, *J* = 4.0, C$\underline{H}$CH$_a$CH$_b$); 5.64 (1H, q, *J* = 7.1, C$\underline{H}$CH$_3$); 6.63 (1H, s, C(3)H); [6.97-7.13 (8H, m), 7.20-7.34 (5H, m), 7.51 (1H, d, *J* = 8.0), 7.63 (1H, d, *J* = 7.8), H arom. and NC$\underline{H}$=CHCO]. $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 19.44 ($CH_3$); 42.16 ($CH_2$); 53.48 (CH); 56.25 (CH); 102.04 (CH); 102.65 (CH); 112.61 (CH); 119.84 (3CH); 120.92 (CH); 121.60 (CH); 125.07 (CH); 126.09 (2CH); 127.56 (CH); 128.31 (C); 128.86 (2CH); 129.53 (2CH); 135.60 (C); 136.14 (C); 140.72 (C); 144.63 (C); 149.60 (CH); 189.62 (C=O). Found, %: C 82.50; H 6.10; N 7.25. $C_{27}H_{24}N_2O$. Calculated, %: C 82.62; H 6.16; N 7.14.

Compounds **5b** and **6b** were prepared similarly from (*S*)-2-formyl-1-(2-methoxy-1-phenylethyl)indole (**1b**) and aniline.

**(2*S*)-2-[1-((1*S*)-2-Methoxy-1-phenylethyl)indol-2-yl]-1-phenyl-1,2,3,4-tetrahydropyridin-4-one (5b)** (minor diastereomer). Yield 20%; mp 181-182°C (ethyl acetate–hexane). $[\alpha]_D^{25}$ 24.0 (*c* 2.0, $CH_2Cl_2$). IR spectrum, ν, $cm^{-1}$: 710 ($C_6H_5$), 770, 1650 (C=O). $^1$H NMR spectrum, ($CDCl_3$), δ, ppm (*J*, Hz): 2.77 (1H, d, *J* = 16.3, C$\underline{H}_a$H$_b$C=O); 3.32 (1H, dd, *J* = 16.3, *J* = 7.1, CH$_a\underline{H}_b$C=O); 3.38 (3H, s, $OCH_3$); 4.26 (1H, t, *J* = 9.3, C$\underline{H}_a$H$_b$OCH$_3$); 4.41 (1H, dd, *J* = 9. 3, *J* = 3.9, CH$_a\underline{H}_b$OCH$_3$); 5.38 (1H, d, *J* = 7.9, NCH=C$\underline{H}$CO); 5.67 (1H, dd, *J* = 9.3, *J* = 3.9, C$\underline{H}$CH$_a$H$_b$OCH$_3$); 5.78 (1H, d, *J* = 7.1, C$\underline{H}$CH$_a$H$_b$C=O); 6.50 (1H, s, C(3)H); [6.72 (1H, d, *J* = 8.4); 6.93 (1H, t, *J* = 7.8); 7.04 (1H, t, *J* = 7.4); 7.14 (1H, t, *J* = 6.8); 7.22-7.44 (9H, m), 7.52 (1H, d, *J* = 7.6), 7.79 (1H, d, *J* = 8.0), H arom. and NC$\underline{H}$=CHCO]. $^{13}$C NMR spectrum, δ, ppm: 42.40 ($CH_2$); [55.31, 57.28, 59.16, 2CH + $CH_3$]; 71.59 ($CH_2$); 100.98 (CH); 101.82 (CH); 112.85 (CH); 117.89 (2CH); 119.81 (CH); 120.86 (CH); 121.19 (CH); 123.90 (CH); 126.48 (2CH); 128.12 (CH); 128.46 (C); 129.32 (2CH); 129.68 (2CH); 136.12 (C); 137.52 (C); 137.90 (C); 144.41 (C); 148.93 (CH); 189.56 (C=O). Found, %: C 79.74; H 6.14; N 6.26. $C_{28}H_{26}N_2O_2$. Calculated, %: C 79.59; H 6.20; N 6.63.

**(2*R*)-2-[1-((1*S*)-2-Methoxy-1-phenylethyl)indol-2-yl]-1-phenyl-1,2,3,4-tetrahydropyridin-4-one (6b)** (major diastereomer). Yield 70%. Glassy material. $[\alpha]_D^{25}$ -94.1 (*c* 4.8, $CH_2Cl_2$). IR spectrum, ν, $cm^{-1}$: 705 ($C_6H_5$), 745, 760, 1645 (C=O). $^1$H NMR spectrum, ($CDCl_3$), δ, ppm (*J*, Hz): 2.97 (1H, d, *J* = 16.3, C$\underline{H}_a$H$_b$C=O); 3.25 (1H, dd, *J* = 16.3, *J* = 7.1, CH$_a\underline{H}_b$C=O); 3.34 (3H, s, $OCH_3$); 4.10 (1H, dd, *J* = 9.6, *J* = 7.1, C$\underline{H}_a$H$_b$OCH$_3$); 4.40 (1H, dd, *J* = 9.6, *J* = 5.9, CH$_a\underline{H}_b$OCH$_3$); 5.37 (1H, d, *J* = 8.1, NCH=C$\underline{H}$CO); 5.54 (1H, dd, *J* = 7.1, *J* = 5.9, C$\underline{H}$CH$_a$H$_b$OCH$_3$); 5.65 (1H, t, *J* = 7.1, C$\underline{H}$CH$_a$H$_b$C=O); 6.72 (1H, s, C(3)H); [6.94-7.12 (8H, m), 7.21 (2H, t, *J* = 8.0), 7.27-7.34 (3H, m), 7.54 (1H, d, *J* = 7.8), 7.62 (1H, d, *J* = 7.8), H arom. and NC$\underline{H}$=CHCO]. $^{13}$C NMR spectrum, δ, ppm: 42.04 ($CH_2$); [54.68, 57.69, 59.00, 2CH + $CH_3$]; 72.24 ($CH_2$); 101.08 (CH); 101.25 (CH); 112.97 (CH); 119.51 (2CH); 119.87 (CH); 120.79 (CH); 121.49 (CH); 124.51 (CH); 127.10 (2CH); 127.99 (CH); 128.30 (C); 128.95 (2CH); 129.71 (2CH); 136.09 (C); 138.31 (C); 138.37 (C); 144.55 (C); 149.59 (CH); 189.70 (C=O). Found, %: C 82.50; H 6.10; N 7.25. $C_{27}H_{24}N_2O$. Calculated, %: C 82.62; H 6.16; N 7.14.

**(2*R*)-1-(2-Methoxyphenyl)-2-[(1-((1*S*)-2-methoxy-1-phenylethyl)indol-2-yl]-1,2,3,4-tetrahydro-pyridin-4-one (6c)** (major diastereomer) was prepared from compound **1b** and *o*-methoxyaniline. Yield 66%. $[\alpha]_D^{25}$ -93.3 (*c* 2.4, $CH_2Cl_2$). Glassy material. IR spectrum, ν, $cm^{-1}$: 715 ($C_6H_5$), 770, 1645 (C=O). $^1$H NMR spectrum, ($CDCl_3$), δ, ppm (*J*, Hz): 2.85 (1H, d, *J* = 16.7, C$\underline{H}_a$H$_b$C=O); 3.12 (1H, dd, *J* = 16.7, *J* = 6.2, CH$_a\underline{H}_b$C=O); 3.22 (3H, s, $OCH_3$); 3.69 (3H, s, $OCH_3$); 3.85 (1H, t, *J* = 9.1, C$\underline{H}_a$H$_b$OCH$_3$); 4.25 (1H, dd, *J* = 9.1, *J* = 5.5, CH$_a\underline{H}_b$OCH$_3$); 5.29 (1H, d, *J* = 7.8, NCH=C$\underline{H}$CO); 5.59-5.69 (2H, m, C$\underline{H}$CH$_a$H$_b$C=O + C$\underline{H}$CH$_a$H$_b$OCH$_3$); 6.68-6.81 (5H, m, H arom.); 6.85 (1H, s, C(3)H); 6.91 (1H, t, *J* = 7.6); [7.02 (1H, t, *J* = 7.5), 7.07 (1H, dd, *J* = 7.7, *J* = 1.4), 7.11-7.27 (5H, m), 7.56 (1H, d, *J* = 7.8), H arom. and NC$\underline{H}$=CHCO]. $^{13}$C NMR spectrum, δ, ppm: 42.58 ($CH_2$); [54.86, 56.27, 56.87, 58.94, 2CH + 2$CH_3$]; 71.82 ($CH_2$); 99.21 (CH); 100.92 (CH); 112.49 (CH); 113.16 (CH); 119.78 (CH); 120.79 (CH); 121.25 (CH); 121.30 (CH); 126.94 (2CH); 127.33

(CH); 127.88 (CH); 128.26 (C); 128.52 (CH); 128.82 (2CH); 133.23 (C); 135.30 (C); 138.04 (C); 139.49 (C); 153.84 (C); 153.94 (CH); 189.36 (C=O). Found, %: C 76.69; H 6.18; N 6.00. $C_{29}H_{28}N_2O_3$. Calculated, %: C 76.97; H 6.24; N 6.19.

**(2*R*)-1-(2-Fluorophenyl)-2-[1-((1*S*)-2-methoxy-1-phenylethyl)indol-2-yl]-1,2,3,4-tetrahydropyridin-4-one (6d)** (major diastereomer) was prepared from (*S*)- 2-formyl-1-(2-methoxy-1-phenylethyl)-indole (**1b**) and *o*-fluoroaniline. Yield 19%. Glassy material. $[\alpha]_D^{25}$ -133.7(*c* 2.1, $CH_2Cl_2$). IR spectrum, ν, $cm^{-1}$: 710 ($C_6H_5$), 770, 800, 1505, 1590, 1660 (C=O). $^1$H NMR spectrum, ($CDCl_3$) δ, ppm (*J*, Hz): 2.87 (1H, d, *J* = 16.0, C$\underline{H}_a$H$_b$C=O); 3.18 (1H, dd, *J* = 16.0, *J* = 6.9, CH$_a\underline{H}_b$C=O); 3.24 (3H, s, $OCH_3$); 3.93 (1H, t, *J* = 9.6, C$\underline{H}_a$H$_b$OCH$_3$); 4.29 (1H, dd, *J* = 9.6, *J* = 5.5, CH$_a\underline{H}_b$OCH$_3$); 5.36 (1H, d, *J* = 8.0, NCH=C$\underline{H}$CO); 5.54-5.66 (2H, m, C$\underline{H}$CH$_a$H$_b$C=O + C$\underline{H}$CH$_a$H$_b$OCH$_3$); 6.75-6.90 (4H, m, H arom.); [6.91-7.07 (4H, m), 7.10-7.17 (2H, m), 7.19-7.27 (3H, m), 7.31 (1H, dd, *J* = 7.9, *J* = 1.2); 7.57 (1H, d, *J* = 7.8), H arom. and NC$\underline{H}$=CHCO]. $^{13}$C NMR spectrum, δ, ppm: 42.72 ($CH_2$); 55.79 (d, *J* = 2.0, CH); [57.56, 59.18, CH + $CH_3$]; 72.97 ($CH_2$); 101.55 (CH); 102.26 (CH); 112.27 (CH); 116.96 (d, *J* = 20.0, CH); 119.86 (CH); 121.03 (CH); 121.51 (CH); 125.00 (d, *J* = 4.0, CH); 126.34 (2CH); 127.11 (CH); 127.67 (CH); 128.28 (C); 128.36 (CH); 128.68 (2CH); 132.40 (d, *J* = 11.0, C); 135.46 (C); 137.34 (C); 138.29 (C); 151.93 (CH); 156.84 (d, *J* = 249.0, C); 190.79 (C=O). Found, %: C 76.03; H 5.70; N 6.26. $C_{28}H_{25}FN_2O_2$. Calculated, %: C 76.34; H 5.72; N 6.36.

**2-[5-Methoxy-3-oxo-2-(2-pyridylamino)pent-4-enyl]-1-(1-phenylethyl)indole (7a).** Anhydrous $ZnCl_2$ (0.18 g, 13.2 mmol) was added to a solution of the imine prepared from compound **1a** (0.15 g, 0.6 mmol) and 2-aminopyridine (62 mg, 0.66 mmol) in $CH_2Cl_2$ (7 ml) at -60°C. The product was stirred for 10 min, the Danishefsky diene (0.18 ml, 9 mmol) was added, and stirring was continued for 6 h at the same temperature. Decomposition was brought about by the addition of HCl (1 molar, 20 ml), the product was let to heat to room temperature. A solution of concentrated ammonia solution was added to pH ~ 12, the organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 ml). The extract was washed with water and then saturated NaCl solution and dried over anhydrous sodium sulfate. Solvent was removed in vacuo and the residue was chromatographed on silica gel eluting with a mixture of petroleum ether and ethyl acetate (1:2). Yield 0.19 g (81%) as a white crystalline material. IR spectrum, ν, $cm^{-1}$; 710, 750, 760, 785, 1470, 1600, 1645, 1680, 3350 (br, NH). $^1$H NMR spectrum, ($CDCl_3$), (1:2 mixture of diastereomers), δ, ppm (*J*, Hz): 1.89 and 1.99 (3H, 2d, *J* = 7.0 and *J* = 7.1, respectively, CHC$\underline{H}_3$); 3.13-3.37 (2H, m, $CH_2$); 3.69 and 3.71 (3H, 2c, $OCH_3$); 4.89 and 4.97 (1H, 2d, *J* = 8.4 each, NH); 5.64 and 5.67 (1H, 2d, *J* = 12.5 and *J* = 12.6, respectively, C$\underline{H}$=CHOCH$_3$); 5.88-6.04 (2H, m, C$\underline{H}$NH+C$\underline{H}$CH$_3$); 6.29 and 6.39 (1H, 2d, *J* = 8.4 and *J* = 8.2, respectively, H arom.); 6.51-6.65 (2H, m, H arom.); 6.89-7.07 (3H, m, H arom.); 7.18-7.43 (6H, m, H arom.); 7.57 (1H, d, *J* = 7.6, H arom.); 7.70 and 7.71 (1H, 2d, *J* = 12.5 and *J* = 12.6, respectively, CH=C$\underline{H}$OCH$_3$); 8.07 and 8.11 (1H, 2d, *J* = 3.9 each, H arom.). Found, %: C 75.81; H 6.34; N 9.31. $C_{27}H_{27}N_3O_2$. Calculated, %: C 76.21; H 6.40; N 9.87.

**2-[5-Methoxy-3-oxo-2-(2-pyridylamino)pent-4-enyl]-1-(2-methoxy-1-phenylethyl)indole (7b)** was prepared similarly to compound **7a**. Yield 83%. White crystalline material. IR spectrum, ν, $cm^{-1}$: 710, 750, 790, 1475, 1505, 1600, 1645, 1680, 3330 (br, NH). $^1$H NMR spectrum, ($CDCl_3$) (1: 2 mixture of isomers), δ, ppm (*J*, Hz): [3.10-3.55 (m), 3.28 (c), 3.36 (c), 5H overall, C$\underline{H}_3$OCH$_2$+C$\underline{H}_2$C=O]; 3.68 and 3.69 (3H, 2c, CHOC$\underline{H}_3$); 4.18-4.31 (1H, m, C$\underline{H}_a$H$_b$OCH$_3$); 4.38-4.52 (1H, m, CH$_a\underline{H}_b$OCH$_3$); 5.31 (1H, d, *J* = 8.1, NH); 5.64 and 5.66 (1H, 2d, *J* = 12.7 and *J* = 12.5, respectively, C$\underline{H}$=CHOCH$_3$); [5.76-5.84 (m), 5.86-5.96 (m), 6.04 (t, *J* = 6.7), 2H overall, C$\underline{H}$NH+C$\underline{H}$C$_6$H$_5$]; 6.33 and 6.40 (1H, 2d, *J* = 8.4 and *J* = 7.8, respectively, H arom.); 6.50-6.64 (2H, m, H arom.); 6.90-7.08 (3H, m, H arom.); 7.20-7.42 (6H, m, H arom.); 7.55 and 7.57 (1H, 2d, *J* = 7.9 each, H arom.); 7.74 and 7.75 (1H, 2d, *J* = 12.7 and *J* = 12.5, respectively, CH=C$\underline{H}$OCH$_3$); 8.06 and 8.13 (1H, 2d, *J* = 3.9 each, H arom.). Found, %: C 73.45; H 6.30; N 9.01. $C_{28}H_{29}N_3O_3$. Calculated, %: C 73.82; H 6.42; N 9.22.

**REFERENCES**


1. J. Leonard, *Nat. Prod. Rep.*, **16**, 319 (1999).
2. H. Waldmann, M. Braun, M. Weymann, and M. Gewehr, *Tetrahedron*, **49**, 397 (1993).
3. J. T. Kuethe, I. W. Davies, P. G. Dormer, R. A. Reamer, D. J. Mathre, and P. J. Reider, *Tetrahedron Lett.*, **43**, 29 (2002).
4. A. V. Karchava, M. A. Yurovskaya, T. R. Wagner, B. L. Zybailov, and Y. G. Bundel, *Tetrahedron: Asymmetry*, **6**, 2895 (1995).
5. T. Itoh, M. Miyazaki, S. Ikeda, K. Nagata, M. Yokoya, Y. Matsuya, Y. Enomoto, and A. Ohsawa, *Tetrahedron*, **59**, 3527 (2003).
6. N. E. Golantsov, A. V. Karchava, V. M. Nosova, and M. A. Yurovskaya, *Izv. Akad. Nauk, Ser. Khim.*, 226 (2005).
7. O. Mitsunobu, *Synthesis*, 1 (1981).
8. M. Yatagai and T. Ohnuki, *J. Chem. Soc., Perkin Trans. 1*, **6**, 1826 (1990).
9. H. Brunner and T. Rückert, *Monatsh. Chem.*, **129**, 339 (1998).
10. G. Hesse and R. Schrödel, *Angew. Chem.*, **68**, 438 (1956).
11. K. Watanabe, S. Kuroda, A. Yokoi, K. Ito, and S. Itsuno, *J. Organomet. Chem.*, **581**, 103 (1999).
12. P. Buonora, J.-C. Olsen, and T. Oh, *Tetrahedron*, **57**, 6099 (2001).
13. J. F. Kerwin, J. Danishefsky, and S. Danishefsky, *Tetrahedron Lett.*, **23**, 3739 (1982).
14. L. Le Coz, L. Wartski, and J. Seyden-Penne, *Tetrahedron Lett.*, **30**, 2795 (1989).
15. H. Waldmann and M. Braun, *J. Org. Chem.*, **57**, 4444 (1992).
16. P. A. Grieco, *Tetrahedron Lett.*, **34**, 5567 (1993).
17. T. Akiyama, J. Takaya, and H. Kagoshima, *Tetrahedron Lett.*, **40**, 7831 (1999).
18. K. Harms, *XCAD4; Program for the LP-Correction of CADC4 / Mach 3 Diffractometer Data,* University of Marburg, Germany (1996).
19. SAINTPlus. Data Reduction and Correction Program v. 6.01, Bruker AXS, Madison, Wisconsin, USA (1998).
20. SMART. Bruker Molecular Analysis Research Tool, v. 5.059, Bruker AXS, Madison, Wisconsin, USA (1998).
21. G. M. Sheldrick, *SHELXTL V. 5.10. Structure Determination Software Suite,* Bruker AXS, Madison, Wisconsin, USA (1998).
22. Enraf-Nonius, *Enraf-Nonius Delft*, Scientific Instrument Division, Netherlands (1984).
23. *Organikum. Laboratory Manual for Organic Chemistry* [Translated from the German], Vol. 2, Mir, Moscow (1979), p. 355.
24. S. Danishefsky, *J. Am. Chem. Soc.*, **96**, 7808 (1974).