Stereoselective Halogenation in Friedel–Crafts Acylation of 1-Acetylindoline with Chiral 2-(Methanesulfonyloxy)propionyl Chlorides

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The Friedel–Crafts acylation of 1-acetylindoline with (*S*)-2- or (*R*)-2-(methanesulfonyloxy)propionyl chloride, and aluminum chloride in dichloromethane at room temperature did not afford the expected (*S*)- or (*R*)-1-acetyl-5-[2-(methanesulfonyloxy)propionyl]indoline, but gave optically pure (*R*)- or (*S*)-1-acetyl-5-(2-chloropropionyl)indoline, whose stereochemistry at the asymmetric carbon was inverted during the reaction. Similar reaction of 1-acetylindoline with the same chiral acylating agents in the presence of aluminum bromide gave mainly the corresponding 2-bromopropionyl derivatives, but as stereo mixtures.

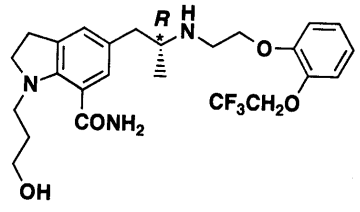
Key words halogenation; Friedel–Crafts acylation; 1-acetylindoline; chiral propionyl chloride

Friedel–Crafts acylation is a very useful and convenient method for introducing a variety of acyl side chains on aromatic rings, and is also important for introducing various alkyl side chains because of the ease of reduction of the acyl group and the unfavorable polyalkylations that occur in normal Friedel–Crafts alkylation. Recently, a new synthetic application, in which chiral acyl halides are used, has been developed for the preparation of some chiral compounds.[1)] In the course of our development of selective inhibitors of adrenaline α_{1A} receptor, we found KMD-3213 **1** (Fig. 1),[2)] which has a 2-(*R*)-(substituted amino)propyl group at the 5-position on the indoline nucleus, and to assist in its further evaluation, we required a more efficient synthetic sequence. Friedel–Crafts acylation between an indoline derivative and chiral acyl halides was considered, and we found that the reaction of 2-acetylindoline with (*S*)-2-(methanesulfonyloxy)propionyl chloride[3)] proceeded smoothly in the presence of excess aluminum chloride in dichloromethane at room temperature. However, the only product was (*R*)-1-acetyl-5-(2-chloropropionyl)indoline instead of the expected (*S*)-1-acetyl-5-[2-(methanesulfonyloxy)propionyl]indoline. Such stereospecific halogenation during Friedel–Crafts acylation is rare. In this paper we describe this abnormal halogenation in the Friedel–Crafts acylation of 1-acetylindoline with (*S*)- or (*R*)-2-(methanesulfonyloxy)-propionyl chloride[3)] and we discuss the reaction mechanism.

Results and Discussion

Friedel–Crafts Acylation of 1-Acetylindoline with Some Chiral Acylating Agents Since the Friedel–Crafts acylation of indoline itself (**2a**) with (*S*)-2-(methanesulfonyloxy)propionyl chloride (**3a**) in the presence of various Lewis acid catalysts did not give any significant products, the reaction of the *N*-protected indoline was investigated. The Friedel–Crafts reaction of 1-acetylindoline (**2b**) with **3a** was first examined in the presence of a weaker Lewis acid catalyst such as ferric chloride, as indicated by Tsuchihashi and co-workers,[1c)] but the reaction did not proceed. We then tried a stronger catalyst, aluminum chloride (**4a**). When a mixture of 1-acetylindoline (**2b**), a small excess of (*S*)-2-(methanesulfonyloxy)propionyl chloride (**3a**), and 4.6 eq of aluminum chloride (**4a**)[4)] was stirred in dichloromethane at room temperature for 3 h, **5b**, mp 146—147 °C, was obtained in 74.2% yield as pale yellow prisms. Similarly, the reaction of **2b** and (*R*)-2-(methanesulfonyloxy)propionyl chloride (**3b**) under the same conditions gave **5c**, mp 146—147 °C, in 72.4% yield (Chart 1).

These products **5b, c** were optically active and the values of their optical rotations were almost the same, but their signs were opposite ($[\alpha]_D^{23}$ −81.07° (c=1.03, $CHCl_3$) for **5b** and $[\alpha]_D^{25}$ +83.22° (c=1.03, $CHCl_3$) for **5c**). Elemental analyses for **5b, c** gave the same composition ($C_{13}H_{14}ClNO_2$), which was different from that ($C_{14}H_{17}NO_5S$) expected for (*S*)- (**6b**) or (*R*)-1-acetyl-5-[2-(methanesulfonyloxy)propionyl]indoline (**6c**). The proton NMR (^{1}H-NMR) spectra of **5b, c** were identical, showing characteristic proton signals at δ 1.73 (3H, d, J=6.7 Hz, COCH(Cl)C<u>H</u>$_3$), 2.27 (3H, s, COC<u>H</u>$_3$), 3.26 (2H, t, J=8.5 Hz, 3-H), 4.14 (2H, t, J=8.5 Hz, 2-H), 5.22 (1H, q, J=6.7 Hz, COC<u>H</u>(Cl)CH$_3$), 7.87 (1H, s, 4-H), 7.89 (1H, d, J=8.6 Hz, 6-H), and 8.27 (1H, d, J=8.6 Hz, 7-H), but no signal due to methyl protons of the methanesulfonyloxy group. Furthermore, the ^{1}H-NMR spectra (see Experimental) using a chiral shift reagent, tris-[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III) [(+)-Eu(hfc)$_3$], indicated that **5b, c** were each almost optically pure, (*R*)-1-acetyl-5-(2-chloropropionyl)indoline and its (*S*)-enantiomer, or *vice versa*, respectively. The structures of **5b, c** were finally decided



1(KMD-3213)

Fig. 1

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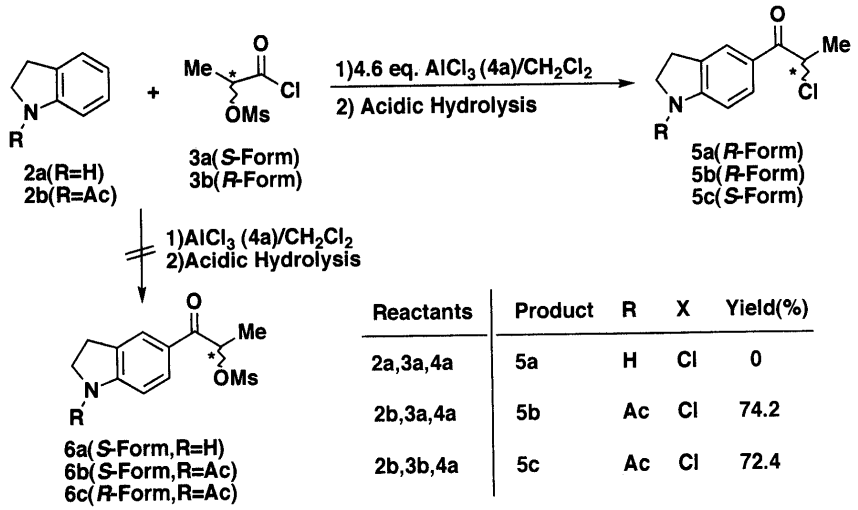


Reactants	Product	R	X	Yield(%)
2a,3a,4a	5a	H	Cl	0
2b,3a,4a	5b	Ac	Cl	74.2
2b,3b,4a	5c	Ac	Cl	72.4

Chart 1

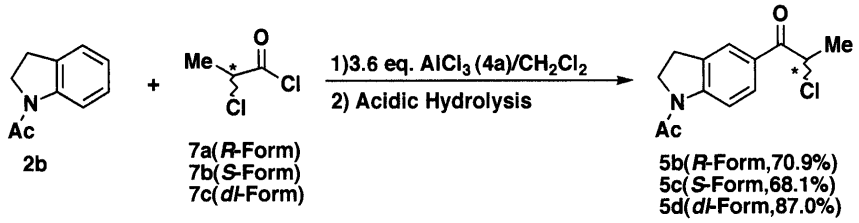
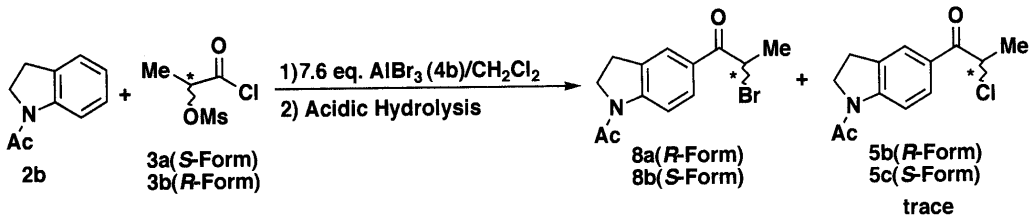


Chart 2



Reactants	Products	Yield(%)
2b,3a,4b	8a+8b+5b[a)]	43.8
2b,3b,4b	8a+8b+5c[b)]	44.6

a) The ratio of 8a to 8b is ca. 1.7:1.
b) The ratio of 8a to 8b is ca. 1:1.5.

Chart 3

based on (+)-Eu(hfc)$_3$-shifted ^{1}H-NMR spectral comparisons of (*R*)-(**5b**), (*S*)-(**5c**), and *dl*-1-acetyl-5-(2-chloropropionyl)indoline (**5d**), synthesized independently by means of Friedel–Crafts acylations of 1-acetylindoline (**2b**) with (*R*)-(**7a**), (*S*)-(**7b**), and racemic 2-chloropropionyl chloride (**7c**)[5] in the presence of aluminum chloride (**4a**) (Chart 2).

With regard to the origin of the chlorine atom in the above products **5b**, **c**, we assumed the participation of the catalyst **4a**. As might be expected, we found that a change of the catalyst from aluminum chloride (**4a**) to aluminum bromide (**4b**) in these reactions at 5 °C gave mainly the corresponding 1-acetyl-5-(2-bromopropionyl)-indolines **8a**, **b**, together with a small amount of the 2-chloropropionyl derivative **5b** or **5c**. However, larger amounts of the catalyst (**4b**, 7.6 eq) were necessary to complete these reactions and the yields were not high (Chart 3). From the inspection of the (+)-Eu(hfc)$_3$-shifted ^{1}H-NMR spectra, moreover, these products were not optically pure, but were stereo mixtures of **8a**, **b** (the ratios of **8a** to **8b** were *ca.* 1.7 : 1 for **3a** and 1 : 1.5 for **3b**, respectively).[6]

Possible mechanisms for the reactions of **2b**, **3a**, and **4a**, **b** are shown in Chart 4. Since the retention of the configuration at the asymmetric center of the chiral acyl halide during Friedel–Crafts acylation is well documented,[1] the reaction of **2b** and **3a** in the presence of excess catalyst **4a** or **4b** should proceed with retention of the configuration to provide a complex **9** ((*S*)-1-acetyl-5-[2-(methanesulfonyloxy)propionyl]indoline (**6b**)–AlX_3). This complex has a good leaving group (AlX_3^-–MsO^+) and an adjacent electron-withdrawing carbonyl group on the asymmetric carbon, so that this position is very electrophilic. The *S*N2 reaction of halide ion, generated *in*

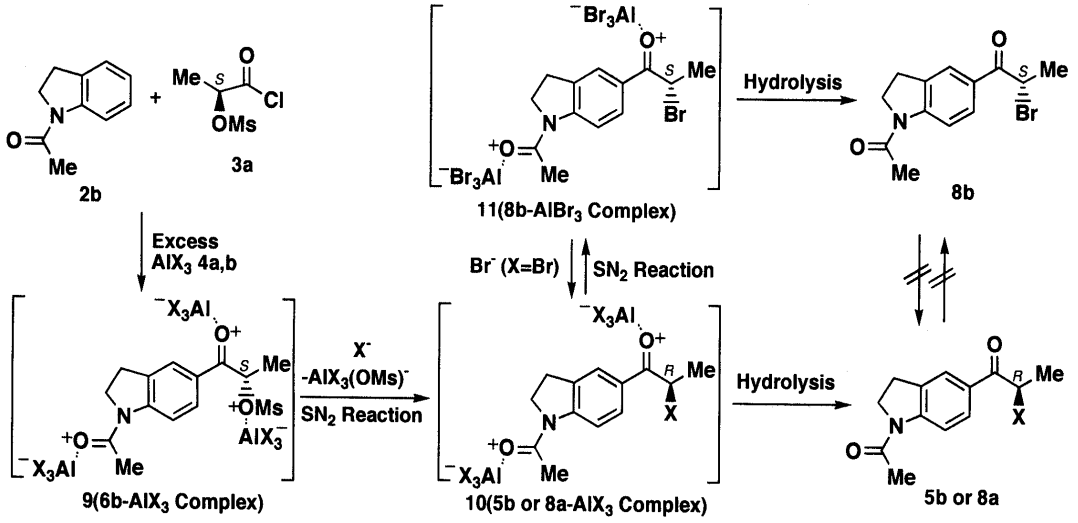


Chart 4

situ from the catalyst **4a** or **4b**, at the chiral center should give rise to a new AlX_3-complex **10**. The complex **10** (X=Cl) can then be hydrolyzed to give optically pure **5b**. On the other hand, the formation of a mixture of the bromo derivatives **8a, b** can be interpreted by considering further S_N2 bromination of the complex **10**. The racemization of **8** is unlikely because the ratios of the mixtures **8a, b** obtained from both reactions were unchanged during prolonged storage at room temperature and in chloroform solution. On the other hand, the stereospecific formation of a small amount of the 2-chloropropionyl derivative **5b** or **5c** may be rationalized in terms of S_N2 chlorination of **3a** or its precursor by thionyl chloride.

The reason why the Friedel–Crafts acylations of **2a** with **3a, b** in the presence of aluminum chloride (**4a**) gave rise to a stereospecific chlorination and those in the presence of aluminum bromide (**4b**) showed stereoselective bromination is unclear, but the higher nucleophilicity of bromide ion and the use of an excess of catalyst **4b** may be significant.

Experimental

The melting points were measured with a Yanagimoto micromelting point apparatus and were not corrected. Microanalyses were carried out on a Perkin–Elmer 2400 elemental analyzer. The ^{1}H-NMR spectra were determined with a Bruker AMX-400 spectrometer (400 MHz) in deuteriochloroform with tetramethylsilane as an internal standard; the chemical shifts are expressed in δ values. The IR spectra were taken with a Nicolet 510 FT-IR spectrophotometer. The optical rotations were measured with a JASCO DIP-370 digital polarimeter and refer to $CHCl_3$ solution and 589 nm.

Friedel–Crafts Acylation of 1-Acetylindoline with (*S*)- or (*R*)-2-(Methanesulfonyloxy)propionyl Chloride. General Procedure A dichloromethane solution (1 ml) of (*S*)- (**3a**) or (*R*)-2- (methanesulfonyloxy)propionyl chloride (**3b**), was fleshly prepared by the treatment of (*S*)- or (*R*)-2-(methanesulfonyloxy)propionic acid (0.500 g, 2.97 mmol) with thionyl chloride (0.5 ml, 6.85 mmol) in the presence of 3 drops of pyridine followed by the evaporation of excess thionyl chloride. This solution was added dropwise to a solution of aluminum chloride (**4a**) (1.31 g, 9.82 mmol) or aluminum bromide (**4b**) (4.32 g, 16.19 mmol) in dichloromethane (1 ml) at 5 °C. After 0.5 h a solution of 1-acetylindoline (**2b**) (0.343 g, 2.13 mmol) in dichloromethane (1 ml) was added under stirring at 5 °C and the resulting mixture was allowed to react for an additional 3 h at room temperature in the case of **4a** or at 5 °C for **4b**. The reaction mixture was treated with chilled 10% hydrochloric acid (30 ml) to hydrolyze the product–aluminum halide complex and then extracted three times with ethyl acetate (20 ml). The combined ethyl acetate solution was washed with water (30 ml), saturated sodium hydrogen carbonate solution (30 ml), and water (30 ml), and dried over magnesium sulfate. Filtration of the solution, concentration of the filtrate under reduced pressure, and recrystallization of the residue from ethyl acetate gave the corresponding (*R*)- or (*S*)-1-acetyl-5-(2-halopropionyl)-indoline (**5** or **8**) as light yellow prisms. Some data for these products **5b—d** and **8a, b** are as follows:

(*R*)-1-Acetyl-5-(2-chloropropionyl)indoline (**5b**), 74.2% from **2b**, **3a** and **4a**, mp 146—147 °C, $[\alpha]_D^{23}$ −81.07° (*c*=1.03, $CHCl_3$). IR (KBr): 1662, 1597 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.73 (3H, d, *J*=6.7 Hz, $COCH(Cl)C\underline{H}_3$), 2.27 (3H, s, $COC\underline{H}_3$), 3.26 (2H, t, *J*=8.5 Hz, 3-H), 4.14 (2H, t, *J*=8.5 Hz, 2-H), 5.22 (1H, q, *J*=6.7 Hz, $COC\underline{H}(Cl)CH_3$), 7.87 (1H, s, 4-H), 7.89 (1H, d, *J*=8.6 Hz, 6-H), 8.27 (1H, d, *J*=8.6 Hz, 7-H). *Anal.* Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61;N, 5.56. Found: C, 62.03; H, 5.73; N, 5.39.

(*S*)-1-Acetyl-5-(2-chloropropionyl)indoline (**5c**), 72.4% from **2b**, **3b** and **4a**, mp 146—147 °C, $[\alpha]_D^{25}$ +83.22° (*c*=1.03, $CHCl_3$). IR (KBr): 1662, 1597 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) see those for **5b**. *Anal.* Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56. Found: C; 62.00; H, 5.71; N, 5.37.

(*R*)- **8a** and (*S*)-1-acetyl-5-(2-bromopropionyl)indoline (**8b**), 43.8% (as a 1.7 : 1 mixture of **8a** and **8b** containing a small amount of **5b** from **2b**, **3a**, and **4b**, mp 143.5—145 °C, $[\alpha]_D^{24}$ −32.30° (*c*=1.07, $CHCl_3$). IR (KBr): 1665, 1597 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.89 (3H, d, *J*=6.6 Hz, $COCH(Br)C\underline{H}_3$), 2.27 (3H, s, $COC\underline{H}_3$), 3.26 (2H, t, *J*=8.6 Hz, 3-H), 4.14 (2H, t, *J*=8.6 Hz, 2-H), 5.27 (1H, q, *J*=6.6 Hz, $COC\underline{H}(Br)CH_3$), 7.87 (1H, s, 4-H), 7.89 (1H, d, *J*=8.4 Hz, 6-H), 8.26 (1H, d, *J*=8.4 Hz, 7-H). *Anal.* Calcd for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.76; N, 4.73. Found: C, 52.87; H, 4.77; N, 4.56.

(*R*)- **8a** and (*S*)-1-acetyl-5-(2-bromopropionyl)indoline (**8b**), 44.6% (as a 1 : 1.5 mixture of **8a** and **8b** containing a small amount of **5c** from **2b**, **3b**, and **4b**, mp 142—144 °C, $[\alpha]_D^{24}$ +23.94° (*c*=1.04, $CHCl_3$). IR (KBr): 1665, 1597 cm^{-1} (CO). *Anal.* Calcd for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.76; N, 4.73. Found: C, 52.83; H, 4.78; N, 4.61.

Independent Syntheses of (*R*)-, (*S*)-, and *dl*-1-Acetyl-5-(2-chloropropionyl)indolines These products **5b—d** were prepared in 70.9, 68.1, and 87.0% yields by using (*R*)-(**7a**) , (*S*)-(**7b**), and racemic 2-chloropropionyl chloride (**7c**)[5] in place of (*S*)- (**3a**) or (*R*)-2-(methanesulfonyloxy)propionyl chloride (**3b**) in the presence of 3.6 eq of aluminum chloride (**4a**) in the procedure described above. Some data for these products **5b—d** are as follows:

5b, mp 146.5—147.5 °C, 70.9%, $[\alpha]_D^{25}$ −81.40° (*c*=1.00, $CHCl_3$). *Anal.* Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56. Found: C, 62.06; H, 5.56; N, 5.61.

5c, mp 145—146.5 °C, 68.1%, $[\alpha]_D^{25}$ +77.51° (*c*=1.05, $CHCl_3$). *Anal.* Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56. Found: C, 61.91; H, 5.43; N, 5.49.

5d, mp 134.5—135.5 °C, 87.0%. *Anal.* Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56. Found: C, 62.09; H, 5.59; N, 5.39.

Determination of Absolute Structures of (*R*)- and (*S*)-1-Acetyl-5-(2-halopropionyl)indolines The absolute structures of products **5b, c** and **8a, b** were decided by the inspection of their ^{1}H-NMR spectra in the presence of a chiral shift reagent ((+)-Eu(hfc)$_3$). First, the (*R*)-isomer **5b** (2.6 mg), and racemic mixture **5d** (2.6 mg), which were independently prepared through the reactions of 1-acetylindoline (**2b**) and (*R*)-(**7a**) and racemic 2-chloropropionyl chloride (**7c**) in the presence of aluminum chloride (**4a**), were dissolved in C_6D_6 solutions (0.6 ml) including the shift reagent (22 mg) and the ^{1}H-NMR spectra were measured. Two separated singlet peaks with different magnitude for the 4-proton appeared in the range of δ 8.0—8.4, and the stronger singlet peak corresponding to the 4-proton of (*R*)-isomer **7a** was at higher magnetic field. On the other hand, the inverse relation for the 4-proton was observed in the ^{1}H-NMR spectrum of the (*S*)-isomer **5c** (2.6 mg), racemic isomer **5d** (2.6 mg), and (+)-Eu(hfc)$_3$ (22 mg) in C_6D_6 (0.6 ml). Next, the ^{1}H-NMR spectrum of a C_6D_6 solution (0.6 ml) of (*R*)-**5b** (5.2 mg) or (*S*)-isomer **5c** (5.2 mg), obtained from the reactions of 2-acetylindoline (**2a**) and (*S*)-(**3a**) or (*R*)-2-(methanesulfonyloxy)propionyl chloride (**3b**) in the presence of aluminum chloride (**4a**), and (+)-Eu(hfc)$_3$ (22 mg) was measured, and the absolute structure was confirmed from the signal positions for the 4-proton singlet.

The structures and the formation ratios for the 2-bromopropionyl derivatives **8a, b** were evaluated mainly by (+)-Eu(hfc)$_3$-shifted ^{1}H-NMR spectral comparisons with **5b—d** and by the inspection of peak areas for the 4-protons. Attempts to quantitate the products, including **8a, b** and **5b** or **5c**, by high pressure liquid chromatography with several chiral packed columns were unsuccessful.

References and Notes

1) *a*) Buckley T. F., III, Rapoport H., *J. Am. Chem. Soc.*, **103**, 6157—6163 (1981); *b*) McClure D. E., Arison B. H., Jones J. H., Baldwin J. J., *J. Org. Chem.*, **46**, 2431—2433 (1981); *c*) Tsuchihashi G., Mitamura S., Kitajima K., Jpn. Kokai Tokkyo Koho, JP10525 (1983) [*Chem. Abstr.*, 178945 (1983)]; *d*) McClure D. E., Lumma P. K., Arison B. H., Jones J. H., Baldwin J. J., *J. Org. Chem.*, **48**, 2675—2679 (1983); *e*) Nordlander J. E., Payne M. J., Njoroge F. G., Balk M. A., Laikos G. D., Vishwanath V. M., *ibid.*, **49**, 4107—4111 (1984); *f*) Nordlander J. E., Njoroge F. G., Payne M. J., Warman D., *ibid.*, **50**, 3481—3484 (1985); *g*) Yamauchi T., Hattori K., Nakao K., Tamaki K., *Bull. Chem. Soc. Jpn.*, **60**, 4015—4018 (1987); *h*) Piccolo O., Spreafico F., Visentin G., *J. Org. Chem.*, **52**, 10—14 (1987); *i*) Effenberger F., Steegmüller D., *Chem. Ber.*, **121**, 117—123 (1988); *j*) Itoh O., Honnami T., Amano A., Murata K., Koichi Y., Sugita T., *J. Org. Chem.*, **57**, 7334—7338 (1992).

2) Kitazawa M., Ban M., Okazaki K., Ozawa M., Yazaki T., Yamagishi R., EP 600675A1 (1994) [*Chem. Abstr.*, 358647 (1995)].

3) These chiral acyl chlorides, 2-(*S*)-(**3a**) and 2-(*R*)-(methanesulfonyloxy)propionyl chloride (**3b**) were prepared in 4 steps starting from the corresponding (*R*)- and (*S*)-lactic acids according to the reported method (see ref. 1*c*, *g*).

4) By thin layer chromatographic monitoring of the reaction, we found that 1-acetylindoline (**2b**) was completely consumed when more than 4.6 eq of aluminum chloride (**4a**) was used.

5) Fu S.-C. J., Birnbaum S. M., Greenstein J. P., *J. Am. Chem. Soc.*, **76**, 6054—6058 (1954).

6) The products which were obtained from the reactions without cooling showed no optical rotation.