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Nucleophilic Substitution of Chiral Amine *N,N*-Ditosylderivatives

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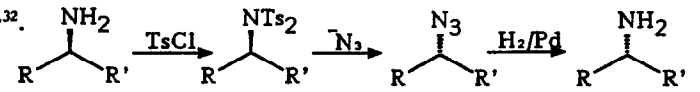
Abstract: The chiral transformation of the optically active amine **10** to the corresponding alcohol **2** with opposite configuration is reported. The transformation is carried out via an S_N2 type reaction of the *N,N*-ditosylimide, -NTs_2, by nucleophilic attack of the hydroxide, acetate or benzoate ion to give an inversion degree of 85-100%. 0-34% stereoselectivity was obtained in the corresponding chloride nucleophilic substitutions. Separation parameters for the chromatographic enantioseparations of the amines **10-12**, the chlorides **4, 7, 9** and the alcohol **2** using a chemically bonded cyclodextrin GLC column are discussed.

INTRODUCTION: For the preparation of homochiral substances it is important to have access to a set of synthetic methods which make use of already existing stereogenic centres in available starting material such as natural products or other low price compounds. It is essential that synthetic transformations which involve such stereogenic centres proceed with complete stereoselectivity, either by full inversion of configuration or by retention of the stereochemistry. By development of a number of chiral transformation reactions a variety of functional groups can be transformed to different functions with defined stereochemistry and a lot of target molecules can be synthesized. For some substance groups there exist convenient chiral transformation methods based on nucleophilic substitution reactions for the preparation of compounds with new functionality; Chiral alcohols have been transformed to a variety of new compounds with inverted stereochemistry by the Mitsunobu reaction[1]. In the recent years many new and creative applications of this reaction have been published[2-11]. Nucleophilic attack on alcohols[12] and sulphonates[13-15] give inversion of configuration. Epoxides can be regio- and stereoselectively opened by different nucleophiles[16-19] while other oxygen-heterocycles have been opened[20] by an S_N2 mechanism by alkyl lithium reagents. Halides are substituted by inversion of the stereochemistry by azide[21-25] and by silyl reagents[12]. Amino acids can be transformed to α-hydroxy- or α-bromo-carboxylic acids via their diazonium salts with retention of configuration[26-30].

It is evident from this recent literature summary that chiral transformations now are used over a braod synthetic spectrum. In contrast to the above mentioned groups, there are few known methods for the transformation of optically active amines to products with new functionality and specific stereochemistry. For that purpose there is a need for the development of stereoselective transformation reactions for amines. We have previously shown[31,32] that the stereochemistry of optically active amines can be completely inverted in a three-step synthesis. The inversion was carried out with an S_N2 type reaction of the *N,N*-ditosylimide, NTs_2, by nucleophilic attack of the azide ion. The azide product was reduced by hydrogenolysis to give the inverted amine, see Scheme 1.

Scheme 1.

Inversion of optically active amines[31,32].

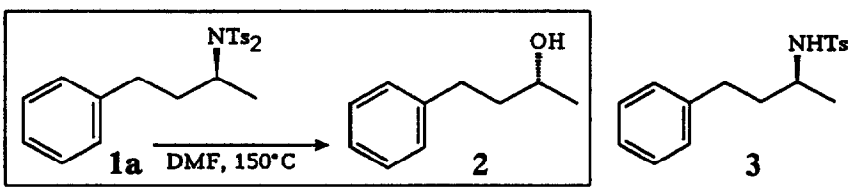


Based on our experience from the inversion of optically active amines we wanted to test the *N,N*-ditosylimides as key intermediates for nucleophilic substitution by other nucleophiles. In the present study we report the results from nucleophilic attack on *N,N*-ditosylimides by oxygen- and halide-nucleophiles for the preparation of the respective alcohol and alkylhalides, see Scheme 2 and 3.

RESULTS AND DISCUSSION.

Starting with the *(S)-N,N*-ditosylimide **1a**, the nucleophilic attack was accomplished utilizing hydroxide, acetate and benzoate as oxygen-nucleophiles (Scheme 2). The *R*-alcohol **2** was obtained in 67 % yield when hydroxide was used as a nucleophile. Even though the alcohol products from a series of reactions had completely inverted stereochemistry, several different experiments including varying *R*- or *S*-substrate (**1a**, **1b**) concentration, nucleophile concentration and reaction temperature, showed that the inversion degree for this reaction generally was between 85-100 %. As a result of the competing hydrolysis of the *N,N*-ditosylimide, the *N*-tosylamide (**3**) biproduct also was expected from the potassium hydroxide reaction. The sulfonamide (**3**) was isolated and identified in 20 % yield using the reported reaction conditions. The hydrolysis product (**3**) was however dominating when DMF was replaced by DMSO as a solvent.

Scheme 2.



i) 6 equiv.KOH, 20h → 85-100% inversion

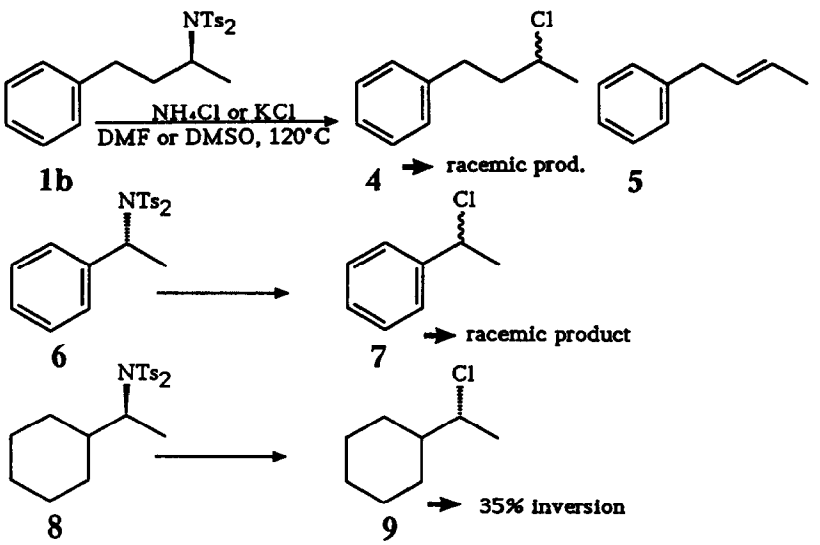
ii) 6 equiv. NH_4OAc, 40h → 90-100% inversion

iii) 6 equiv. NH_4OBz, 30h → 100% inversion

Since it is reported[16,18] that ammonium as a counterion to a series of nucleophiles has a positive effect on nucleophilic substitution reactions, ammonium acetate and ammonium benzoate were used as reagents for the nucleophilic attack of acetate and benzoate, respectively. Surprisingly no trace of the expected acetate or benzoate ester products could be observed whereas the *R*-alcohol (**2**) was isolated directly. Chiral analysis indicated a stereoselectivity of 90-100 % in these substitution reactions. A combination of high reaction temperature and not pre-dried solvents are supposed to be sufficient for the spontaneous hydrolysis of the ester intermediates to the alcohol **2**.

The results of the nucleophilic substitution of three *N,N*-ditosylimides (**1b**, **6** and **8**) by chloride, either with ammonium or potassium as a counterion, in DMF or DMSO are presented in Scheme 3. From all the experiments including the *(S)*-1-methyl-3-phenyl-propylamine derivative (**1b**) and the *(S)*-1-phenylethylamine derivative (**6**) racemic chloride substitution products (**4**,**7**) were obtained. The *(R)*-1-cyclohexylethylamine analogue (**8**) was substituted by chloride to give a 67:33 isomer mixture of the chloride product (**9**) presumably indicating 34 % inversion in this substitution reaction. For substrate **1b** the competing elimination reaction afforded 1-phenyl-3-butene (**5**) as a biproduct. Preliminary studies for nucleophilic attack on substrate **1b** by bromide or iodide indicated similar racemic results for these nucleophiles. Since the *N,N*-ditosylimide **1b** give inverted stereochemistry using other nucleophiles (azide[31,32], hydroxide, acetate and benzoate), it is not known whether the halide substitution reactions proceed either via the elimination product or an ionic mechanism and thus can explain the racemic products, or if the racemization is caused by the combination of the halide both as a nucleophile and a good leaving group. Halide used as nucleophiles on amino acid diazonium salts are however known to give complete stereoselectivity[26-30].

Scheme 3.



Chiral analysis, enantiomeric separations.

In a synthetic study of optically active compounds the chiral analysis is essential. In some cases enantiomers can be indirectly separated after derivatization; the diastereomeric derivatives often separate on conventional nonchiral stationary phases (GLC or HPLC). An absolute requirement for the chiral compound to be analysed by the indirect method, is the presence of a functional group suitable for derivatization. Classical compounds analysed by this method are primary amines, alcohols and carboxylic acids. A variety of chiral derivatizing agents are available. This indirect method, however, generally suffers from a number of disadvantages and limitations. When the analyte in addition has no suitable "handle" for derivatization, direct analytical methods based on chiral stationary phases are required for the chromatographic enantioseparation.

In this report we hereby present the analytical enantiomeric resolution of the chlorides **4**, **7** and **9**, the alcohol **2** and the amines **11** and **12** on a chemically bonded cyclodextrin capillary GLC column. The amine **10** could not be separated on this column. The isomer elution sequence of the compounds **2** and **9-12** are reported as well. Increased resolution and selectivity were expected to be obtained using this chemically bonded column compared to previous commercially available cyclodextrin columns. Prolonged column life time caused by less column bleeding combined with regeneration possibilities are advantages as well. Several different inlet carrier gas pressures giving the respective linear gas velocities were tested to optimize the column efficiency, see Table 2. The maximum column efficiency (71000 theoretical plates) was obtained using a carrier gas inlet pressure at 4.0 p.s.i., giving a linear gas velocity of 28 cm/sec. This is about 25 % higher velocity than recommended by the producer and allows a corresponding favourable reduction of the analysis time.

Table 1. Chromatographic separation parameters for the *(R)/(S)* enantioseparations of the chlorides **4**, **7**, **9**, the alcohol **2** and the amines **10-12** using a capillary GLC cyclodextrin column.

Substance	Column temperature	k'	α	R_S
(3-chlorobutyl)benzene (**4**)	120°C (iso)	6.99 7.13	1.02	1.06
(1-chloroethyl)benzene (**7**)	120°C (iso)	2.33 2.44	1.05	2.03
(1-chloroethyl)cyclohexane (**9**)	120°C (iso)	2.38 *(S)* 2.45 *(R)*	1.03	1.37
1-Phenyl-3-butanol (**2**)*	100°C(1min)- 150°C(2°/min)	12.96 *(S)* 13.30 *(R)*	1.03	2.75
1-Methyl-3-phenylpropylamine (**10**)*	70°C(5min)- 150°C(3°/min)	17.3	appr. 1.00	appr. 0
1-Phenylethylamine (**11**)*	70°C(5min)- 150°C(3°/min)	12.03 *(R)* 12.26 *(S)*	1.02	1.57
1-Cyclohexylethylamine (**12**)*	70°C(5min)- 150°C(3°/min)	12.21 *(R)* 12.29 *(S)*	1.01	0.62

* For the alcohol (**2**) and the amines (**10-11**) corresponding analyses were achieved by the indirect method by separation of the diasteromeric derivatives on a CP-Sil 5CB column after derivatization with (-)-camphanic acid chloride and *(S)*-α-methoxyphenylacetyl chloride, respectively.

To our knowledge there are hardly any published reports regarding the chromatographic enantioseparation of chiral alkylchlorides. Separation parameters from the chiral analyses of the chlorides **4**, **7** ,**9**, the alcohol **2** and the amines **10-12** listed in Table 1 demonstrate that this chemically bonded cyclodextrin column is able to give complete base line separations ($R_S > 1.2$) of the *(R)-/(S)*-isomers of two of the three chlorides (**7** and **9**) and for many purposes sufficient separation of the last chloride (**4**). The isomer resolution of the chlorides increases going from the chlorinated butylbenzene, ethylcyclohexane to ethylbenzene ($R_{S,chloride}$: $4 < 9 < 7$). Cyclodextrin columns are known to be well suited for the enantioseparation of chiral alcohols which is also confirmed by these results ($R_S = 2.75$ for the alcohol **2**). The indirect analysis method for the separation of the diastereomeric alcohol (**2**) (-)-camphanic acid derivatives is more time consuming but convenient as well. Supplementary data for the analysis of the amines **10-12** show that this column gives base line separation of the benzylic amine **11**, less separation of the cyclohexyl analogue **12** and hardly any separation of the amine **10** ($R_{S,amine}$: $10 < 12 < 11$). This is the identical effect as observed for the corresponding chloride substances even if the resolutions of the amines are much lower. Regarding the optically active amines, we find that these substances are rapidly and more conveniently separated by the indirect chiral analysis method. For all the amines (**10-12**) increased resolutions and more reliable results were obtained by separation of the diastereomeric amides after derivatization with *(S)*-α-methoxyphenylacetyl chloride.

In many cases it is important to know the isomer elution sequence for identification purposes. For the alcohol **2** and the chloride **9** the isomer elution sequence is the same; the (*S*)-isomer is eluted before the *(R)*-isomer, see Table 1. However for the two amines separated (**11** and **12**) the opposite elution order was observed. The isomer identifications reported here follow from the synthetic preparations and are also based on correlation with optical rotational data.

In conclusion, the *N,N*-ditosylimides are promising intermediates for the chiral transformation of optically active amines to chiral alcohols with opposite configurations using hydroxide, acetate or benzoate as nucleophiles. 85-100 % inversion of configuration was obtained for the transformation of amine **10** to alcohol **2**. The preparation of chlorides from homochiral amines via their *N,N*-ditosylimides seems however to proceed with almost complete racemization of the stereogenic centre demonstrated here by the synthesis of the chlorides **4**, **7**, **9** (0-34% stereoselektivity) from the amines **10-12**. Regarding chiral analysis the chemically bonded cyclodextrin GLC column gives base line enantioseparations ($R_S > 1.2$) of the chiral chlorides (**4**, **7**, **9**), the alcohol (**2**) and the benzylic amine (**11**). Our data illustrate that the best resolutions are obtained for the compounds having an aromatic substituent connected directly to the chiral center and that the resolutions are dramatically decreasing going from an alcohol to the corresponding chloride to the amine substances. The indirect chiral analysis of diastereomeric derivatives are recommended for amines in general.

EXPERIMENTAL

Chemicals: *(S)*- and *(R)*-*N,N*-Di-(*p*-toluenesulfonyl)-1-methyl-3-phenylpropylamine (**1a** and **1b**) and *(R)*-*N,N*-Di-(*p*-toluenesulfonyl)-1-methylbenzylamine (**6**) were prepared from the respective primary amines (**10** and

11) as described elsewhere[31,32]. *(S)*-1-cyclohexylethylamine (12), *p*-toluenesulfonyl chloride, ammonium acetate, ammonium benzoate, Fluka (*purum*); ammonium chloride, potassium chloride, Merck *p.a.*; (-)-camphanic acid chloride and *(S)*-α-methoxyphenylacetyl chloride from *(S)*-α-methoxyphenylacetic acid (Fluka, *purum*). Solvents: *p.a.* quality. M.p.: uncorrected, apparatus from Büchi. TLC: DC-Fertigplatten Kieselgel 60 F_{254} (0.25 mm). Detection: UV light at 254 nm or preferentially by 5 % alcoholic molybdatophosphoric acid and heating. Flash chromatography: Kieselgel 60 (230-400 mesh) Merck. GLC: Carlo Erba Model 8130; injector: split (100 ml/min, T = 300°C), hydrogen, detector: FID (T = 270°C), column: Chrompack CP-SIL 5CB fused silica WCOT (25 m, carrier gas velocity 40 cm/sec.). Chiral GLC analysis: Chrompack CP-CHIRASIL-DEX-CB fused silica WCOT (25 m x 0.32 mm; 0.32 μm), carrier gas pressure 0.27 bar, 4 p.s.i., carrier gas linear velocity 28 cm/sec., concentration 0.2 % of each isomer and compound in diethylether. ^{1}H NMR: Jeol FX-100 100 MHz NMR spectrometer, chemical shifts are reported in ppm downfield from TMS. MS: AEI MS-902. IR: Nicolet 20SXC FT-IR spectrometer. $[\alpha]_D$: Perkin Elmer 241 polarimeter (10 cm cell with a total volume of 1 ml).

***(R)*-4-phenyl-2-butanol (2) from *(S)*-*N,N*-Di-(*p*-toluenesulfonyl)-1-methyl-3-phenylpropylamine (1a) with KOH.** A solution of the *(S)*-*N,N*-ditosylimide (**1a**, 46 % ee, 1.0 g, 2.19 mmol) and KOH (0.74 g, 13.14 mmol, 6 equiv.) in DMF (20 ml) was stirred and heated to 150 °C. The reaction was followed by TLC. After complete conversion of the imide (about 20 h), the product was extracted with ether after addition of water. Purification of the the crude product, a pale yellow oil, by flash chromatography afforded 0.22 g (67 %) of 2 as a colourless liquid. MS [m/z (% rel. int.)]: 150 (*M*, 26), 132 (59), 117 (96), 105 (18), 91 (100), 77 (15), 45 (35). IR (film, cm^{-1}): 3368 (br s), 3062 (w), 3026 (m), 2988 (s), 2967 (s), 2928 (s), 1603 (w), 1496 (s), 1454 (s), 1374 (m), 1218 (m), 1128 (m), 1055 (m), 755 (s), 699 (s). ^{1}H NMR ($CDCl_3$): δ 1.23 (d, 3H, J=6.34 Hz), 1.44 (br 1H), 1.80 (m, 2H), 2.6 (dt, 2H), 3.83 (m, 1H), 7.25 (m, 5H). The alcohol 2 had an optical purity of 46 % ee of the *(R)*-isomer, indicating an inversion degree of 100 %. However, the results from twelve experiments starting with either the *(S)*-isomer (**1a**, 46 % ee) as described above or the *(R)*-isomer (**1b**, 92 % ee) where the substrate and nucleophile concentrations and reaction temperature were varied, showed that the stereoselectivity for this reaction generally was 85-100 %. From the *(R)*-isomer (**1b**) experiments optical rotation of the *(S)*-alcohol product (78 % ee) was $[\alpha]_D$ +10.4 (c=1, $CHCl_3$) (Lit.[33] +15.8 , 97 % ee). Chiral analysis of the alcohol (2) was carried out both by GLC of the diastereomeric esters after derivatization with (-)-camphanic acid chloride and by GLC on a chiral cyclodextrin column. Separation parameters and chromatographic conditions for the separations on the chiral stationary phase are given in Table 1. Enantiomeric excesses of the *N,N*-ditosylimides are based on GLC analysis of the of the primary amine after derivatization with *(S)*-α-methoxyphenylacetyl chloride to the diastereomeric amides. The hydrolysis biproduct ***(S)*-*N*-(*p*-toluenesulfonyl)-1-methyl-3-phenylpropylamine** (3, 0.13 g, 20 %) could also be isolated from this reaction. Characterization data (m.p., TLC, $[\alpha]_D$, ^{1}H NMR, IR, MS) of the *N*-tosylamide (3) were in accordance with data presented elsewhere[31].

***(R)*-4-phenyl-2-butanol (2) from *(S)*-*N,N*-Di-(*p*-toluenesulfonyl)-1-methyl-3-phenylpropylamine (1a) with ammonium acetate and ammonium benzoate.** Except for replacing the KOH (6 equiv.) by respectively ammonium acetate (6 equiv.) and ammonium benzoate (6 equiv.), the identical reaction conditions were used as described above. After 30-40 h reaction time, work-up and chromatographic purification, about 50 % of the alcohol **2** could be isolated. No ester products could be observed. Chiral analyses of several alcohol products prepared by using either ammonium acetate or ammonium benzoate indicated an inversion degree of 90-100 % in these reactions.

1-Methyl-3-phenylpropylchloride (4) from *(R)*-*N,N*-Di-(*p*-toluenesulfonyl)-1-methyl-3-phenylpropylamine (1b). A solution of the *(R)*-*N,N*-ditosylimide (**1b**, 92 % ee, 3.41 g, 7.46 mmol) and NH_4Cl (2.0 g, 37.5 mmol, 5 equiv.) in DMF (40 ml) was stirred and heated to 120 °C. The reaction was followed by TLC. After 40 h the product was extracted with ether after addition of water. Purification of the the crude product (1.2 g, 95 %) by flash chromatography yielded 0.76 g (61 %) of **4** as a colourless liquid with a characteristic odour. MS [m/z (% rel. int.)]: 170/168 (*M*, 8/23), 132 (27), 117 (45), 105 (9), 91 (100), 77 (7), 51 (10). IR (film, cm^{-1}): 3028 (m), 2971 (m), 2927 (m), 1603 (w), 1496 (m), 1454 (m), 1379 (m), 1274 (w), 1030 (w), 748 (m), 699 (s). ^1H NMR ($CDCl_3$): δ 1.45 (d, 3H, J=6.84 Hz), 1.95 (m, 2H), 2.75 (dt, 2H), 3.87 (m, 1H), 7.0 (m, 5H). $[\alpha]_D$ = 0. Chiral GLC-analysis (see Table 1 for separation parameters) showed a 1:1 mixture of the *(R)*- and *(S)*-chloride product (**4**). Several experiments using either i) DMSO as solvent, ii) KCl as nucleophile, iii) 100 °C as reaction temperature or iv) 2.5 equivalents of the nucleophile were carried out, all of which gave a complete racemization of the substitution product. The less polar elimination biproduct, **1-phenyl-2-butene** (**5**, 0.1 g, 10 %), was isolated and characterized; MS [m/z (% rel. int.)]: 132 (*M*, 47), 131 (107), 117 (15), 115 (21), 105 (75), 103 (71), 91 (75), 77 (58), 51 (46), 43 (59). IR (film, cm^{-1}): 3063 (w), 3027 (m), 2967 (w), 2916 (m), 2855 (w), 1603 (w), 1494 (m), 1453 (m), 1030 (w), 967 (s), 746 (s), 698 (s). ^1H NMR ($CDCl_3$): δ 1.62 (d, 3H), 3.23 (t, 2H), 5.34-5.48 (m, 2H), 7.03 (m, 5H).

1-phenylethylchloride (7) from *(R)*-*N,N*-Di-(*p*-toluenesulfonyl)-1-phenylethylamine (6). The same procedure as described for the preparation of the chloride **4** above except for more careful reaction conditions (80 °C in 18h) was used. MS [m/z (% rel. int.)]: 142/140 (*M*, 0.5/1), 105 (100), 104 (41), 91 (12), 77 (22), 51 (10). IR (film, cm^{-1}): 3265 (m), 2930 (s), 2860 (m), 1495 (m), 1455 (m), 1370 (m), 1265 (m), 1170 (m), 1090 (s), 1035 (m), 800 (m). ^1H NMR ($CDCl_3$): δ 1.86 (d, 3H, J=6.83 Hz), 5.10 (q, 1H), 7.36 (m, 5H). Chiral GLC-analysis (see Table 1 for separation parameters); a 1:1 mixture of the *(R)*- and *(S)*-chloride product (**7**).

***(S)*-*N,N*-Di-(*p*-toluenesulfonyl)-1-cyclohexylethylamine (8) was prepared from *(S)*-cyclohexylethylamine (12)** by a procedure described elsewhere[32]. m.p. 148-150 °C. MS [m/z (% rel. int.)]: 435 (*M*, 0.3), 420 (0.5), 354 (9), 353 (17), 352 (83), 280 (0.5), 198 (3), 157 (5), 156 (9), 155 (100), 91 (67). IR (film, cm^{-1}): 2933 (s), 2852 (m), 1922 (w), 1598 (m), 1494 (w), 1450 (m), 1369 (s), 1346 (s), 1187 (w), 1171 (s), 1083 (s), 1041 (w), 963 (s), 858 (s), 813 (s), 712 (m), 663 (s), 536 (s). ^1H NMR ($CDCl_3$): δ 1.26 (d, 3H, J=6.83 Hz), 1.58-1.9 (m, 11H), 2.47 (s, 6H), 3.85 (m, 1H), 7.34 (d, 4H, J=8.3 Hz), 7.93 (d, 4H, J=8.3 Hz). $[\alpha]_D$ +55.8 (c=1, $CHCl_3$).

1-cyclohexylethylchloride (9) from *(S)-N,N*-Di-(*p*-toluenesulfonyl)-1-cyclohexylethylamine (8). The same procedure as described for the preparation of the chloride 4 above was used. MS [m/z (% rel. int.)]: 148/146 (*M*, 0.5/1.5), 111 (3), 110 (26), 95 (2), 84 (7), 83 (100), 82 (41), 81 (13), 67 (12), 55 (50), 44 (44). IR (film, cm^{-1}): 2924 (s), 2853 (m), 1736 (w), 1462 (m), 1365 (w), 1166 (w), 759 (m). ^1H NMR ($CDCl_3$): δ 1.47 (d, 3H, J = 6.83 Hz), 1.5-1.9 (m, 11H), 3.93 (m, 1H). Chiral GLC-analysis (see Table 1 for separation parameters) showed a 67:33 isomer-mixture of the chloride product (9). $[\alpha]_D$ -5.01 (c = 0.2, $CHCl_3$).

Table 2. Optimalization of chromatographic conditions, carrier gas pressure (test component *n*-tridecane).

Carrier gas inlet pressure (psi/bar)	Linear gas velocity (cm/sec.)	Number of theoretical plates, N
2.9/0.20	21	63600
3.5/0.24	25	68400
4.0/0.27	28	71000
4.5/0.31	31	70700

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