Supporting Information

Efficient, Stereodivergent Access to 3-Piperidinols by Traceless $P(OEt)_3$ Cyclodehydration

P. H. Huy,* A. M. P. Koskinen*

Aalto University, School of Chemical Technology, Laboratory of Organic Chemistry, Kemistintie 1, 00076 Aalto, Finland

Ari.Koskinen@aalto.fi

Peter.huy@uni-koeln.de

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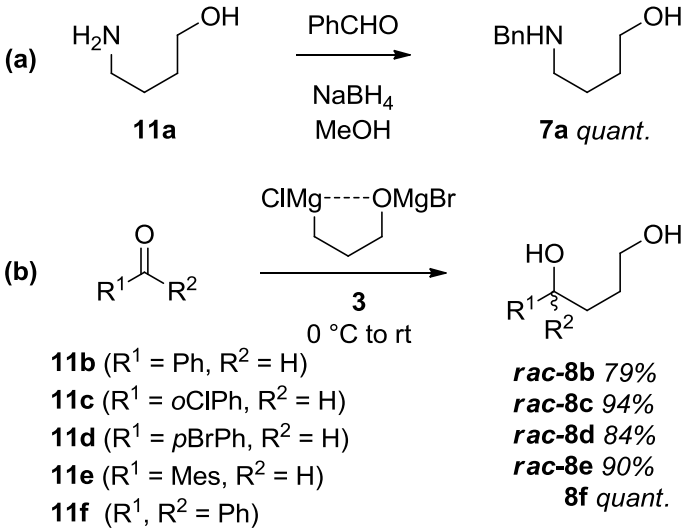
1 Additional Information

1.1 Synthesis of Substrates 7 for the I_2/P(OEt)$_3$ Cyclisation Studies (Table 1)

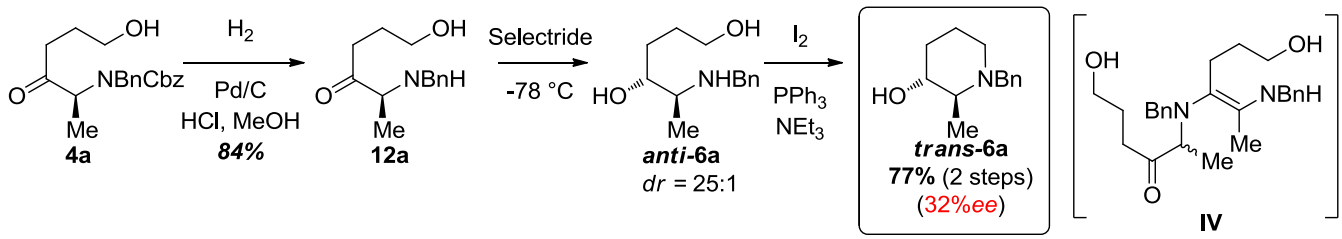
The substrates for the cyclisation study (see Table 1) were synthesized either by reductive amination of the commercial amino alcohol **11a** (Scheme S1 (a)), or by addition of the *Grignard* reagent **3** to the carbonyl compounds **11b-f** (Scheme S1 (b)):



Scheme S1: Synthesis of the amino alcohols and diols **8**.

1.2 Synthesis of *trans*-Piperidinol 7athrough *Appel* reaction (not shown in Scheme 3)

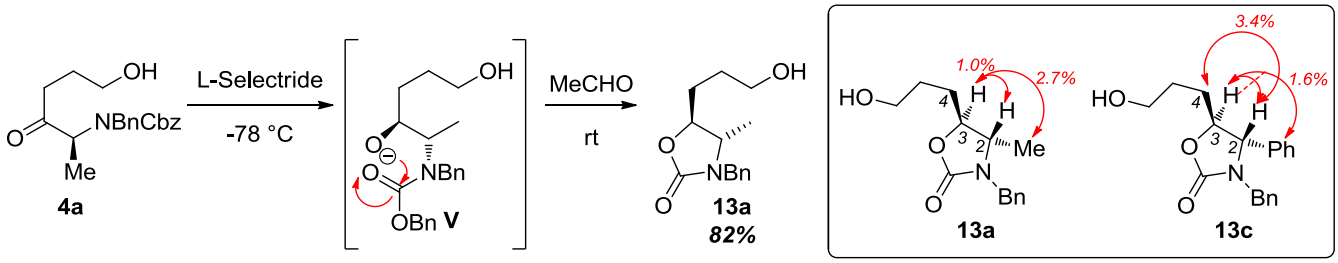
In our first attempt to obtain piperidinol ***trans*-6a** in a high optical purity, the Cbz-moiety of hydroxy ketone **4a**was cleaved with H_2 and Pd/C (Scheme S2). Next, Selectride reduction provided the amino alcohol ***anti*-6a** in an excellent diastereoselectivity of ≥25:1 (according to crude^{1}H-NMR). Unfortunately, subsequent *Appel*-cyclisation delivered ***trans*-6a** in only 32%*ee*, which might be explained through an intermolecular enamine formation as indicated in intermediate **IV**.



Scheme S2: Synthesis of the *trans*-configured piperidinol **7a** through *Appel* reaction.

1.3 Determination of the relative configuration of Piperidinols 6

After L-Selectride reduction of the hydroxyl ketone **4a** and quenching with acetaldehyde the oxazolidinone **13a** was isolated as the major product in 82% yield (Scheme S3). This cyclic carbamate resulted most probably from reaction of the alcoholate moiety with the Cbz-group in the intermediate **III** at higher temperatures.



Scheme S3: Synthesis of the oxazolidinone 1**3a** and observed NOE effects demonstrating the *trans*-configuration.

The relative *trans*-configuration of the oxazolidinones **13a** was demonstrated by NOE-spectroscopy (Scheme S2): The NOE between H-3 and the methyl group (2.7%) were significantly stronger than for H-2 and H-3 (1.0%).[1] As the reduction conditions are identical with those of diol **5a** (the precursor of ***cis*-6a**, see Scheme 3), the hydroxy piperidine **6a** must be *cis*-configured. Additionally, the oxazolidinone **13c** was isolated as a side product in the reduction of carbamate **4c** (see Scheme 2), most likely resulting from the same type of cyclisation. Again a relative *trans*-configuration was clearly established by strong NOE effects between the protons of the phenyl moiety and H-3 (1.6%) and H-2 and the first CH_2 group of the hydroxypropyl side chain (H-4) of 3.4%.

The relative *cis*-configuration of the piperidines **6a-c** was additionally validated through NOE-NMR-spectroscopy (Figure S1): While a clear NOE was observed between H-2 and H-3 (1.2-3.5%), no (**6b**) or only a week NOE occurred between H-3 and the thus *trans*-oriented Me- (**6a**) and CH-protons of the neighboring Ph substituent (**6c**), respectively (0.5-0.9%).

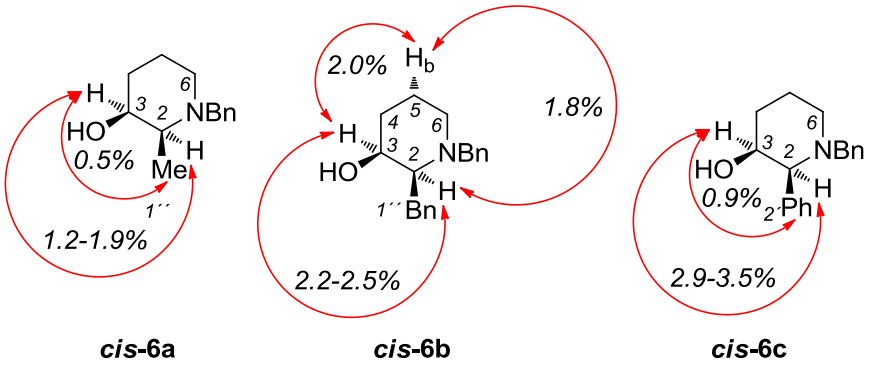


Figure S1: Proof of the relative *cis* configuration of**6a-c** through NOE-NMR spectroscopy.

1 The NOEs were extracted from NOESY-spectra, which are depicted in the experimental descriptions.

Furthermore, in derivative **6b** the *cis*-configuration is also shown by a clear NOE (1.8-2.0%) between H-2 and H-3-, respectively, and the same proton of the CH_2-group on the opposite site of the piperidine ring system (H-4_b). In Figure S2 to S4 the ^{1}H-NMR-spectra and the NOE-spectra with irradiation on the multiplets of H-2 and H-3 (in the order top to bottom) of piperidines ***cis*-6a-c** are shown:

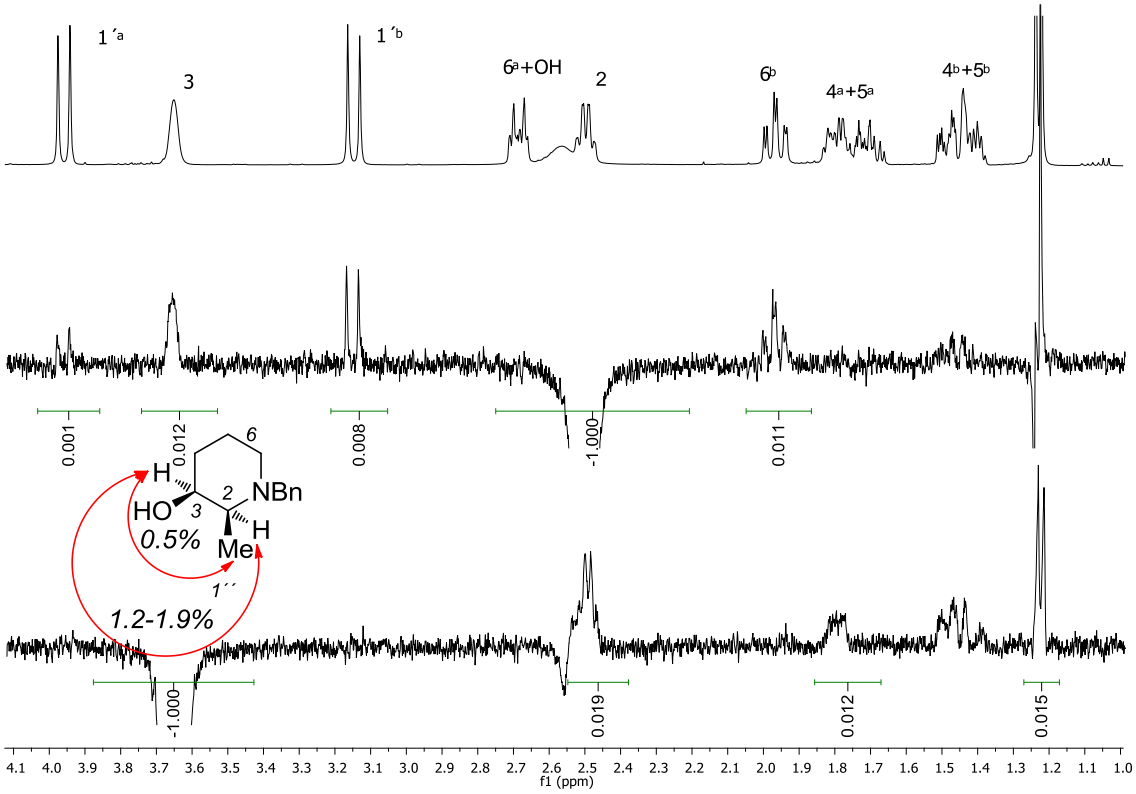


Figure S2: ^{1}H-NMR-spectra and the NOE-spectra with irradiation on the multiplets of H-2 and H-3 (in the order top to bottom) of piperidine ***cis*-6a**.

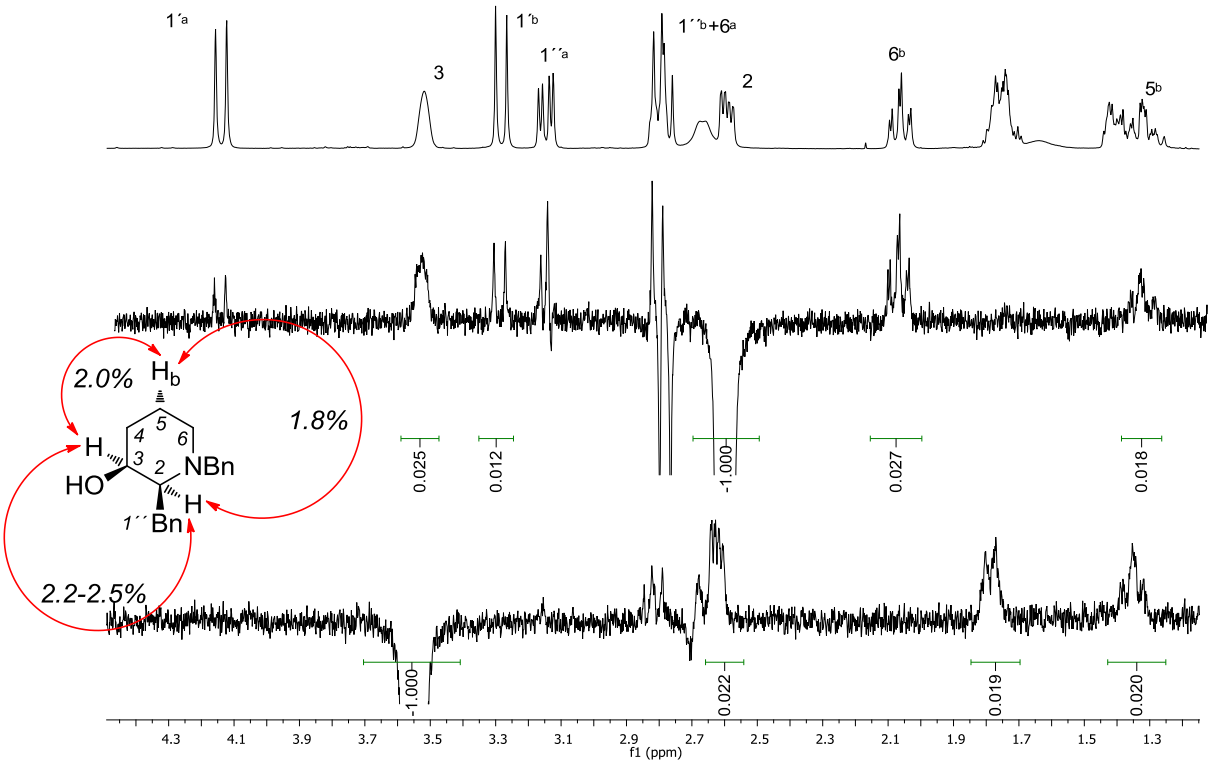


Figure S3: [1]H-NMR-spectra and the NOE-spectra with irradiation on the multiplets of H-2 and H-3 (in the order top to bottom) of piperidine ***cis*-6b**.

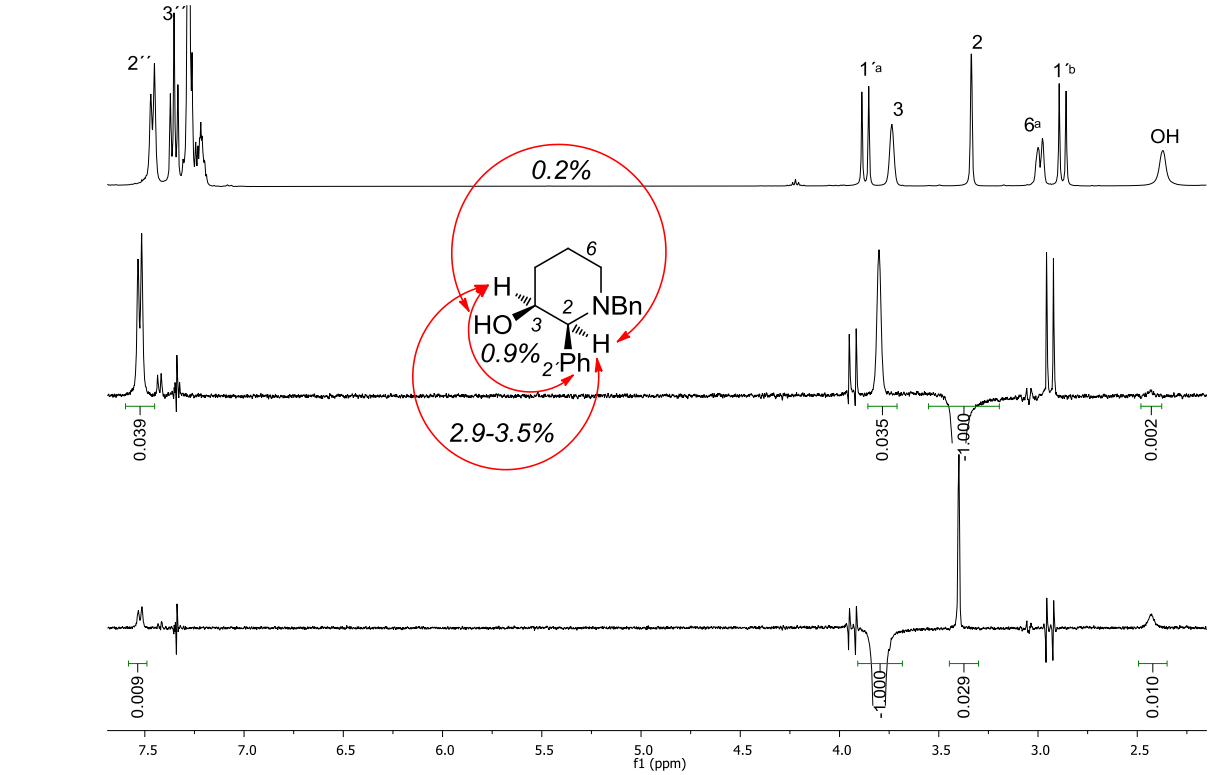


Figure S4: [1]H-NMR-spectra and the NOE-spectra with irradiation on the multiplets of H-2 and H-3 (in the order top to bottom) of piperidine ***cis*-6c**.

The relative configuration of the major and the minor Boc-protected piperidinol epimers **10** (prepared as given in Scheme 4) derived from the piperidinol **6c** were elucidated by NOE-spectroscopy to be *cis* and *trans*, respectively (Figure S5). In the major epimer of **10** a stronger NOE (5.3-5.9% compared to 3.3-4.4%) between H-2 and H-3 proofs the *cis*-orientation. Additionally, H-3 shows in the minor epimer of **10** a clear NOE (7.2%) with the protons of the phenyl moiety, while in the other diastereomer only a very week NOE occurred between the same protons (0.6%), demonstrating a *trans*-configuration.

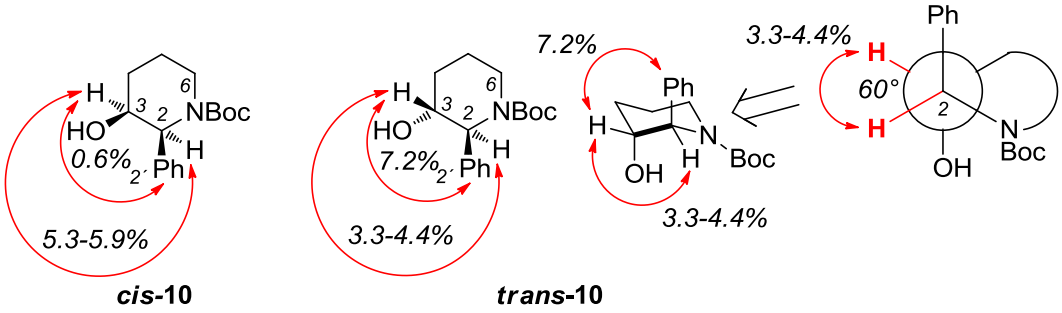


Figure S5: Relative configuration of piperidinols **10**.

The surprisingly strong NOE between H-2 and H-3 of ***trans*-10** (but still weaker than in the *cis*-isomer) can be rationalized by the chair conformer depicted in Figure S5: The phenyl substituent might be forced in an axial position through the sterically demanding Boc-group on the neighboring nitrogen atom. Thus both hydrogen atoms, H-2 and H-3, would end up in equatorial orientations providing a very small dihedral angle (H-2 – C-2 – C-3 – H-3) of approximately 60°). In Figure S6 and S7 the ^{1}H-NMR-spectra and the NOE-spectra with irradiation on the multiplets of H-2 and H-3 (in the order top to bottom) of piperidines ***cis*-** and ***trans*-10** are given:

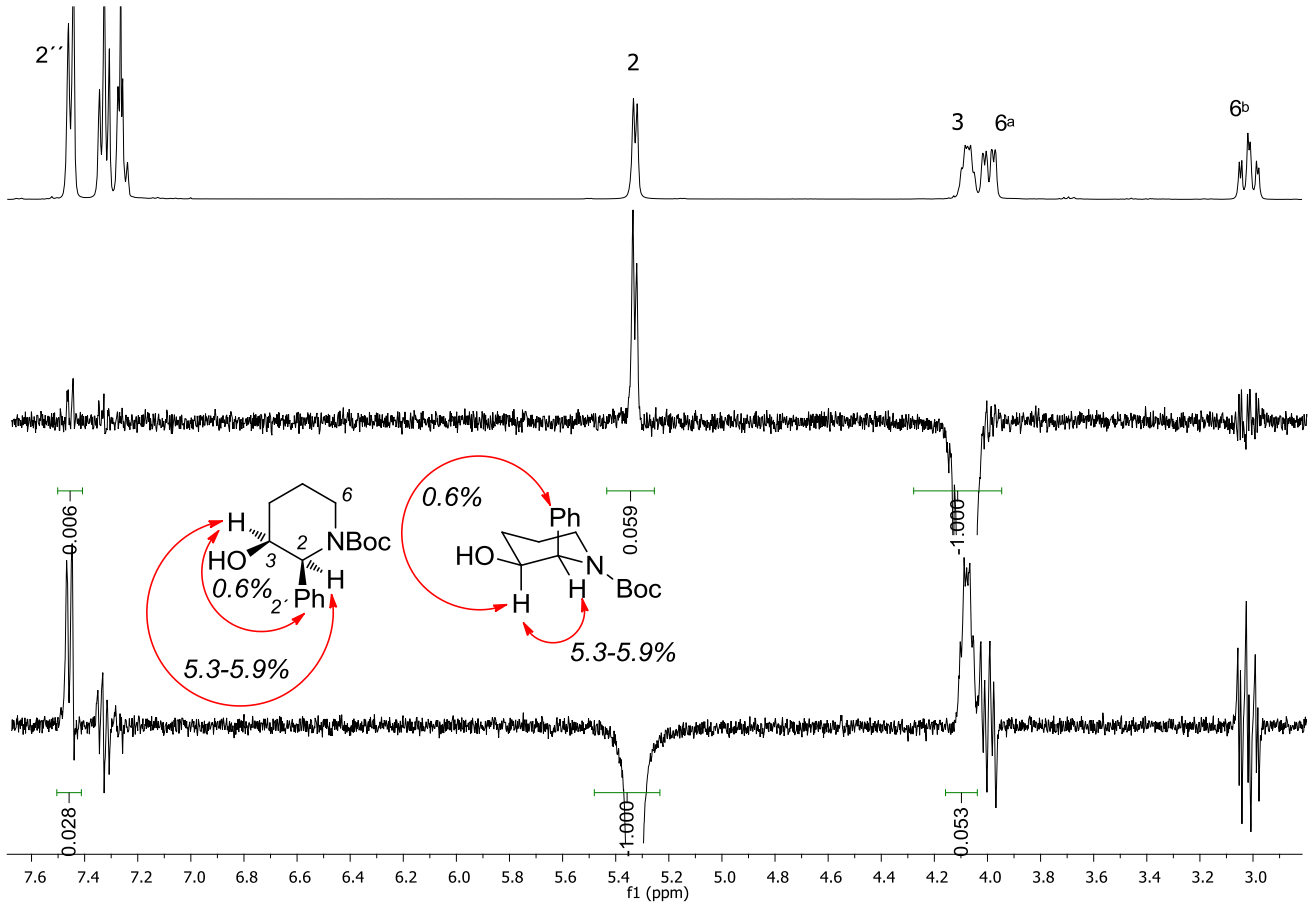


Figure S6: ^{1}H-NMR-spectra and the NOE-spectra with irradiation on the multiplets of H-2 and H-3 (in the order top to bottom) of piperidine ***cis*-10**.

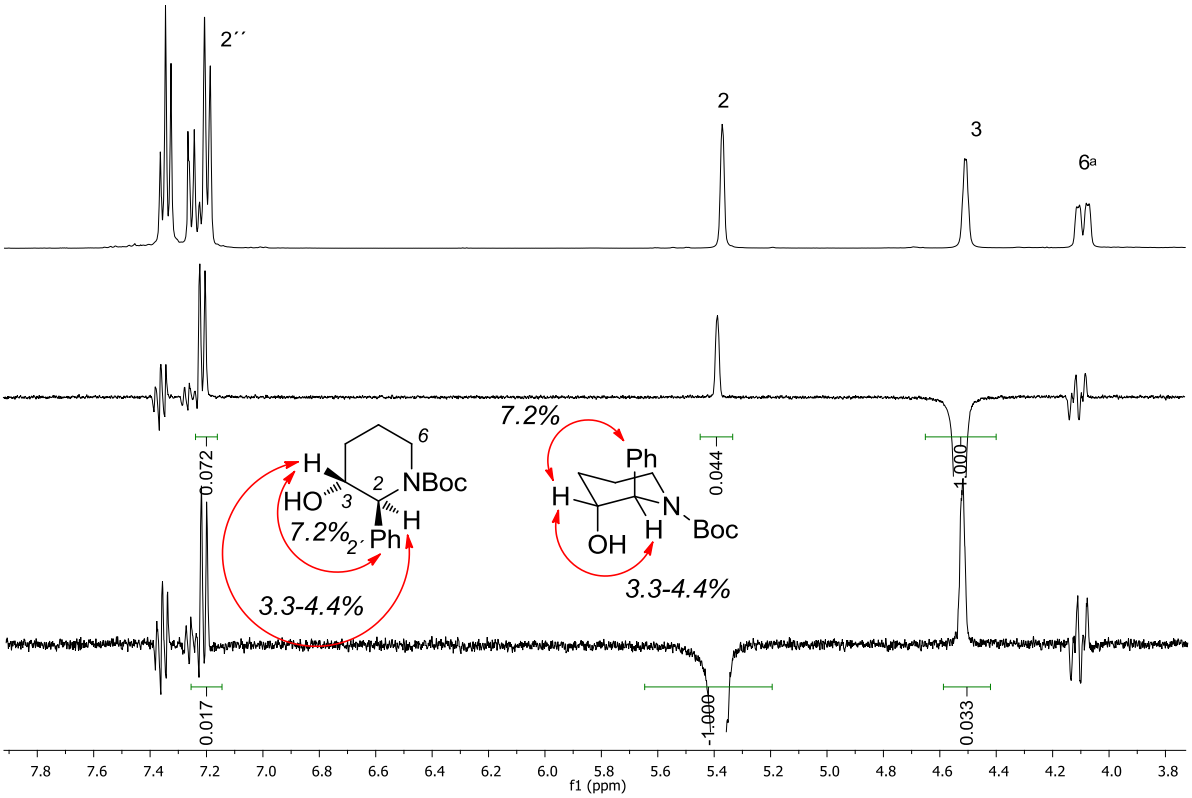
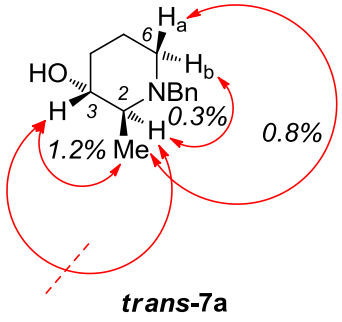


Figure S7: ^{1}H-NMR-spectra and the NOE-spectra with irradiation on the multiplets of H-2 and H-3 (in the order top to bottom) of piperidine ***trans*-10**.

The *trans*-configuration of **6a**, synthesized as shown on Scheme 4, was proven by NOE-NMR-spectroscopy (Figure S8): While a definite NOE (1.2%) between H-3 and the Me-group was observed, no NOE occurred with H-2.[2]



***trans*-7a**

Figure S8: Determination of the relative *trans*-configuration of hydroxyl piperidine **6a** via NOE-spectroscopy.

Furthermore, the *trans*-configuration is further established by NOEs between H-2 and H-6$_b$, and H-3 and H-6$_b$, respectively: Thus H-2 and H-3 show interactions to opposite protons of this CH_2-group. Also in *L-733,060-HCl* a clear evidence for a *cis*-orientation is delivered by a strong NOE between H-2 and H-3 (2.6-6.6%) as depicted in Figure S9:

2 The NOEs were extracted from NOESY-spectra, which are depicted in the experimental descriptions.

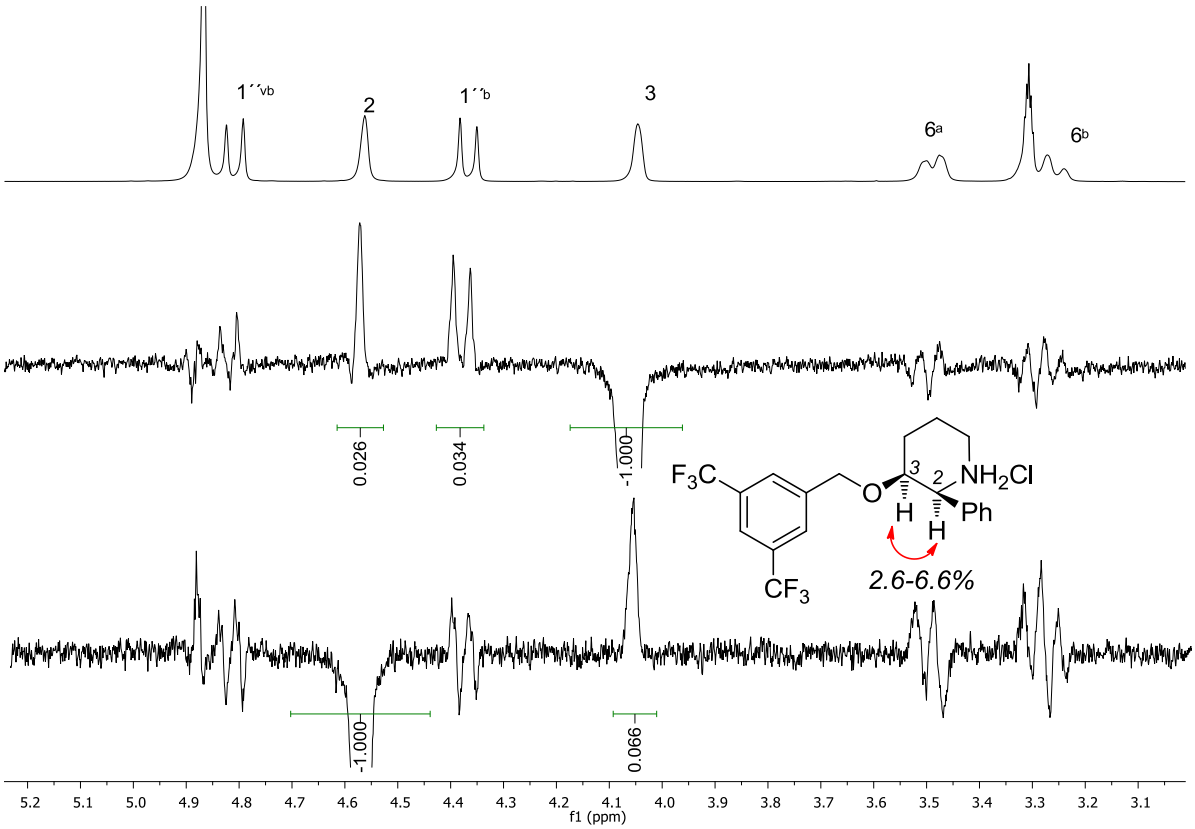


Figure S9: ^{1}H-NMR-spectra and the NOE-spectra with irradiation on the multiplets of H-2 and H-3 (in the order top to bottom) of ***L-733,060-HCl***.

2 Experimental Part

2.1 General experimental conditions

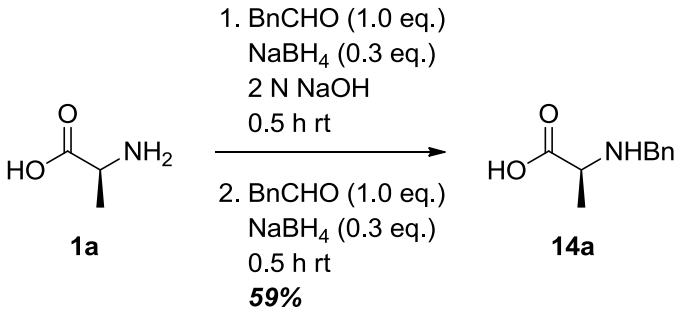
Unless otherwise stated all ^{1}H and ^{13}C NMR spectra were recorded at room temp. on a *Bruker Avance* 400 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS) using the residual solvent resonance or TMS as the internal standard ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). IR spectra were recorded on *Perkin–Elmer* Spectrum One instrument at room temperature. Relative intensities of the signals are given as very strong (vs), strong (s), medium (m), weak (w) and broad (br). Mass spectra were recorded on Micro Mass LCT Premier Spectrometer from *Waters*. Optical rotations were determined on a *Perkin Elmer* polarimeter 343. Melting points (uncorrected) were determined on a *Gallenkamp* melting point apparatus MFB 595. CHN analyses were recorded on a *Perkin–Elmer* Elemental Analyzer 2400 CHN. Analytical TLC was carried out using precoated silica gel plates (*Merck* TLC plates silica gel 60 F_{254}).TLC plates were visualized under UV irradiation (254 nm) or with $KMnO_4$-solution. Flash column chromatography was performed using silica *Merck* silica gel 60 (0.040-0.063 mm). All water sensitive reactions were carried out in flame dried glassware under an argon atmosphere. Chemicals were purchased from *Sigma-Aldrich* or *Acros* and used without further purification. Grignard reagents were titrated with I_2/LiCl,[3] lithium organyls with *N*-benzyl benzamide before application.[4]Solvents were dried as follows: THF and Et_2O were distilled over Na/benzophenone, DCM and MeCN were distilled over CaH_2.

3 A. Krasovskiy, P. Knochel, *Synthesis***2006**, *5*, 890–891; In contrast to the authors the saturated LiCl solution in THF was not prepared in prior (stirring overnight). Instead an excess of LiCl (>100 mg) and an exactly weighed amount of Iodine (30-350 mg, depending on the concentration of the Grignard reagent) were stirred in 5 mL of dry THF for a few minutes before titration.

4 A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281-283.

2.2 Synthesis of Hydroxy Ketones 4 (Scheme 1)

2.2.1 Synthesis of *S*-2-(benzylamino) propionic acid (14a)[5]



In a 250 mL one necked round bottom flask with a strong stir bar L-alanine (5.00 g, 56.1 mmol, 1.0 equiv) was dissolved 2 N NaOH solution in water (28 mL, 56 mmol, 1.0 equiv). Then benzaldehyde (5.7 mL, 56.1 mmol, 1.0 equiv) was added in one portion and the resulting heterogeneous mixture was stirred vigorously at ambient temperature for ¼ h, whereby a clear solution was obtained. Thereafter the mixture was cooled to 0 °C, $NaBH_4$ (640 mg, 16.8 mmol. 0.3 equiv) was added in three portions over 5 min (H_2-evolution), the cooling bath was removed and the mixture was allowed to stir at room temperature for 0.5 h. Again benzaldehyde (5.7 mL) was added and after ¼ h at ambient temperature the clear solution was treated with further $NaBH_4$ (640 mg) under cooling in an ice bath and stirred for 0.5 h at room temperature.

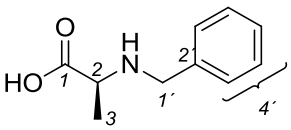
Next the heterogeneous reaction mixture (pH = 12) was diluted with water (10 mL), washed with three 15 mL portions of MTBE,[6] whereupon it resulted in a clear solution, and cooled to 0 °C. Then aqueous 3 N HCl-solution (7 mL) was added dropwise, until the product started to precipitate.[7]Next, aqueous 1 N HCl-solution (43 mL in total) was added dropwise through a dropping funnel to the mixture. When the mixture became impossible to stir (due to the precipitating product **14a**), the precipitate was collected through filtration through a sintered funnel. The filtrate was returned to the reaction flask and further neutralized with 1 N HCl solution. This process was repeated until pH = 7 was reached (two more times). Thereby the same sintered funnel (containing the precipitate collected from earlier filtrations) and collection flask were used. Finally, the combined precipitates were washed with an ice cold 2:1 acetone/water mixture (30 mL) and acetone (60 mL). The collected precipitates were transferred to a 100 mL NS 29 flask, dried in high vacuum (18 h) and broken (remaining in the flask)

5 (a) Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta***1963**, *46*, 327-333; b) Lelais, G.; Seebach, D.*Helv. Chim. Acta***2003**, *86,* 4152-4168.(c) Reeve, T. B.; Cros, J.-P.; Gennari, C.; Piarulli, U.; de Vries, J. G.*Angew. Chem. Int. Ed.***2006**, *45*, 2449 –2453.

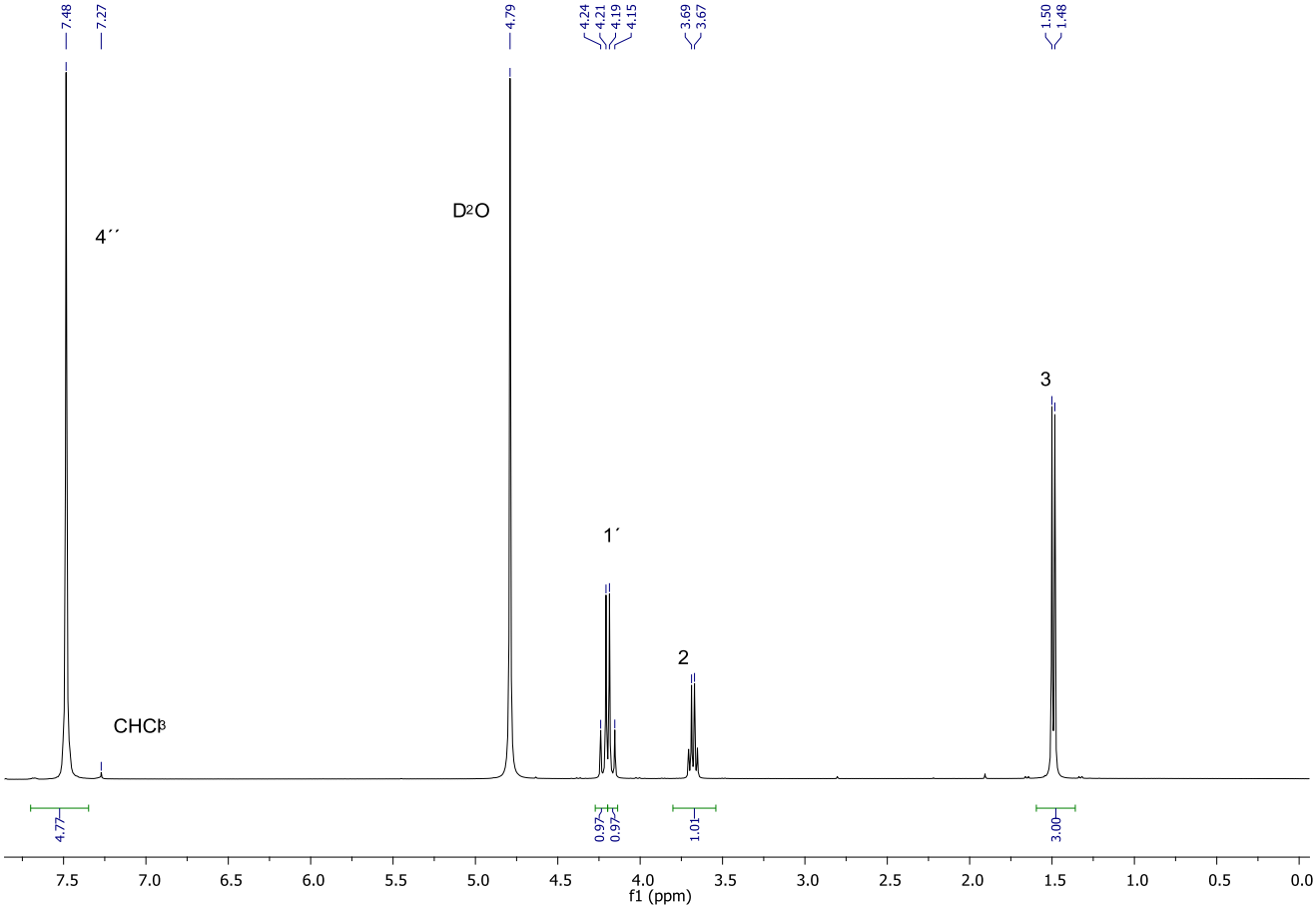
6 The slow phase seperation can be accelerated by carefully heating with a heatgun.

7 In the beginning a gas evolution was observed (through hydrolyses of remaining $NaBH_4$).

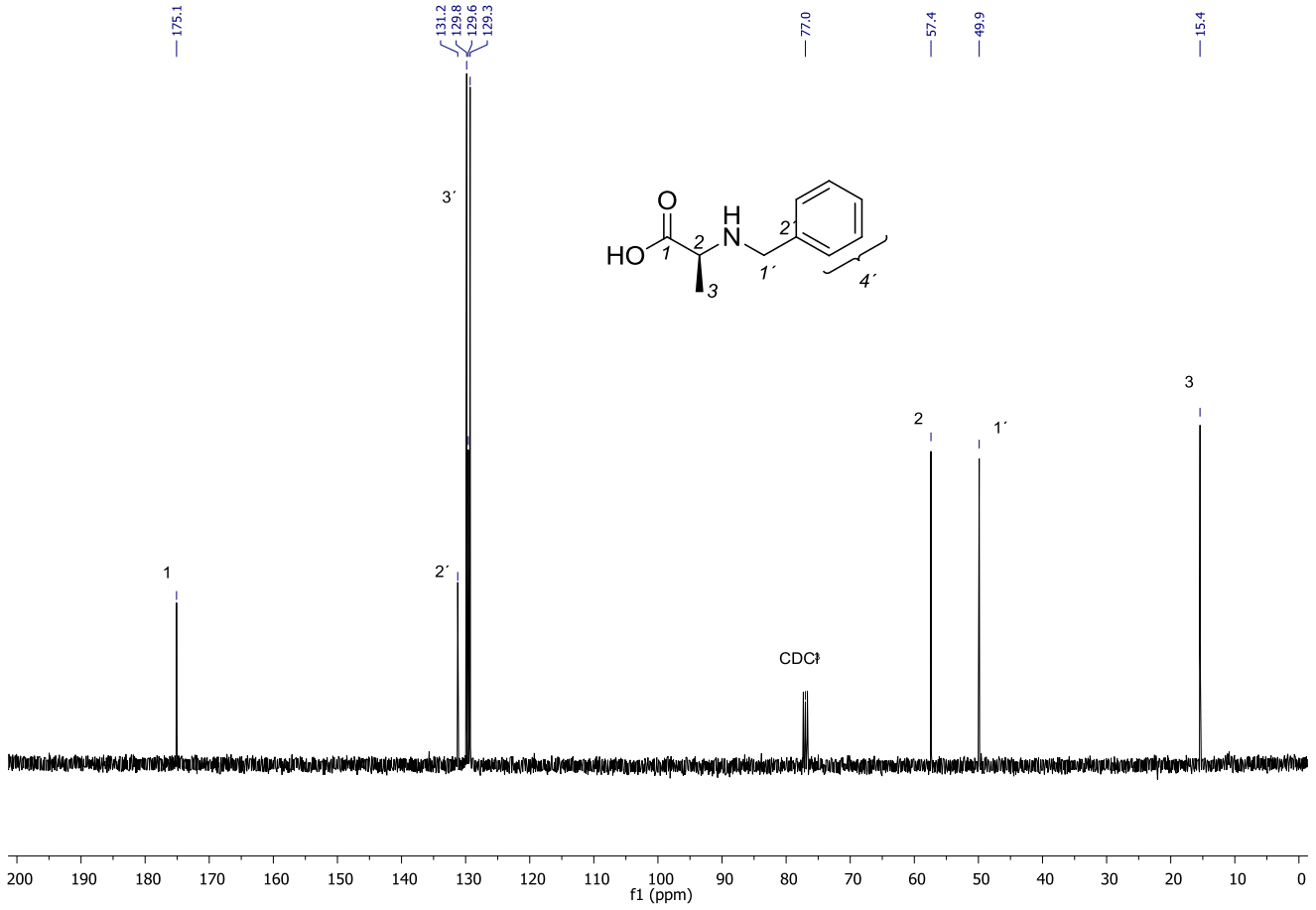
several times with a magnetic stir bar retriever, until the product was obtained as a fine powdered solid. Finally, the amine **14a** was isolated as a colorless solid (5.96 g, 33.3 mmol, 59%).



M ($C_{10}H_{13}NO_2$) = 179.22 g/mol; **mp.** 255 °C (decomposition), lit.: 255 °C (decomposition);5[a] **^{1}H-NMR** (400 MHz, D_2O) δ ppm = 7.48 (s, 5H, H-3´), 4.23 (d, 1H, H-1´$_a$, *J* = 13.1 Hz), 4.17 (d, 1H, H-1´$_b$, *J* = 12.8 Hz), 3.68 (q, 1H, H-2, *J* = 7.2 Hz), 1.49 (d, 3H, H-3, *J* = 7.2 Hz); **^{13}C-NMR** (100 MHz, D_2O, capillary with $CDCl_3$ as standard) δ ppm = 175.1 (C-1), 131.2 (C-2´), 129.8/129.6/129.3 (C-3´), 57.4 (C-2), 50.0 (C-1´), 15.4 (C-3); **IR** (KBr) ν cm^{-1} = 3685 (w), 3031 (m), 2983 (m), 2847 (m), 2756 (m), 2684 (w), 2595 (w), 2381 (w), 1957 (w), 1816 (w), 1621 (vs), 1614 (vs), 1499 (w), 1457 (m), 1384 (s), 1361 (vs), 1344 (m), 1291 (w), 1224 (w), 1140 (w), 1095 (w), 1084 (w), 1057 (w), 1006 (w), 929 (w), 909 (w), 867 (w), 825 (w), 776 (w), 755 (s), 698 (s), 645 (w), 607 (w), 536 (m), 498 (s); **α_D** (c = 0.460 g/100 mL, H_2O, T = 21 °C) = +3.6, lit.: **α_D** (c = 1 g/100 mL, H_2O, T = 24 °C) = +3.9.5[a]

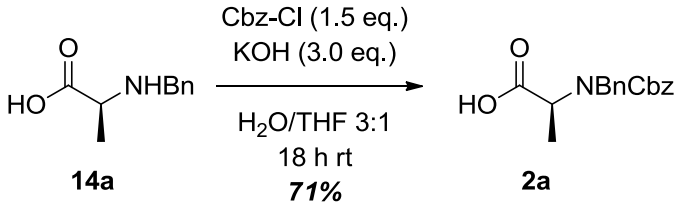


[1]H-NMR-spectra of the benzylamine **14a** in D_2O with a $CDCl_3$ filled capillary as internal standard (400 MHz).



^{13}C-NMR-spectrumof the benzylamine **14a** in D_2O with a $CDCl_3$ filled capillary as internal standard (100 MHz).

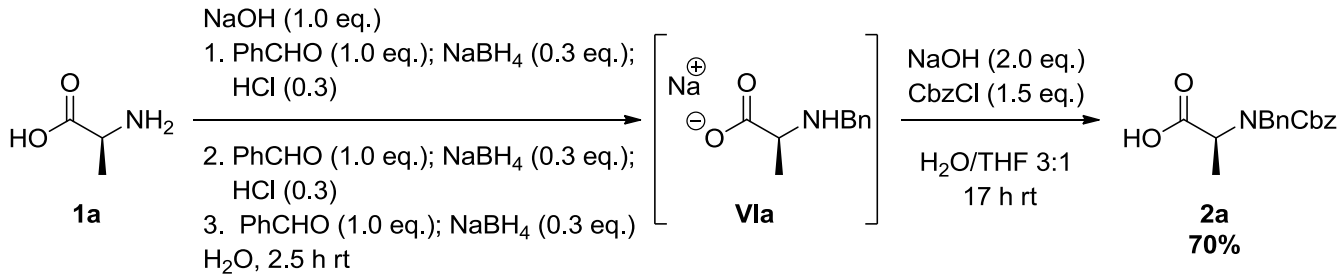
2.2.2 Synthesis of *S*-2-(benzyl-(benzyloxycarbonyl)-amino)-propanoic acid (2a)



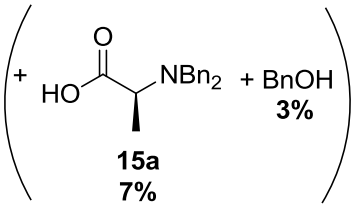
The alanine derivative **14a** (1.00 g, 5.58 mmol, 1.0 equiv) and KOH (0.94 g, 16.7 mmol, 3.0 equiv) were dissolved in water (10 mL, **14a** = 0.6 mol/L) and cooled to 0 °C. Then a solution of of Cbz-Cl (1.19 mL, 8.37 mmol, 1.5 equiv) in THF (3 mL) was added dropwise (10 min), the cooling bath was removed and the reaction solution allowed to stir at ambient temperature for 18 h.

Next THF was removed under reduced pressure in a rotatory evaporator, the residue (pH = 10) was washed with MTBE (3x5 mL), cooled in an ice bath and acidified to pH ≤ 0 through successive addition of aqueous 3 N HCl solution (3 mL) and 1 N HCl solution (5 mL), whereby the acid **2a** precipitated partly. The aqueous phase was extracted with EtOAc (3x15 mL), the combined EtOAc-phases were dried over $MgSO_4$, concentrated under reduced pressure and dried in high vacuum under stirring and

heating to 60 °C for 15 h. The product **2a** (1.236 g, 3.94 mmol) was isolated in 71% yield as a colorless, viscous oil.



L-alanine (**1a**, 15.00 g, 168.4 mmol, 1.0 equiv) and NaOH (168.4 mmol, 6.74 g 1.0 equiv) were dissolved in H_2O (85 mL, **1a** = 2 mol/L, 5 min of stirring, pH = 13) in a 1 L flask. Benzaldehyde[8] (17.2 mL, 168.4 mmol, 1.0 equiv) was added in one portion and the resulting emulsion was stirred for 15 min at room temperature. Thereby a clear solution was obtained after 5 min of stirring indicating imine formation of the starting amine **1a** with benzaldehyde. The reaction mixture was cooled in an ice bath, $NaBH_4$ (1.91 g, 50.5 mmol, 0.3 equiv) was added in three portions over 5 min (a weak H_2-evolution was observed) and the mixture was allowed to stir for 5 min at 0 °C and 30 min at room temperature. Subsequently, a 6 N HCl solution in water (8.4 mL, 50.5 mmol, 0.3 equiv) was added dropwise (pH = 10) accompanied by a solid precipitation.



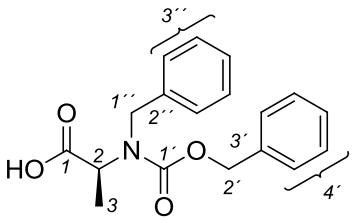
Further PhCHO (17.2 mL), $NaBH_4$ (1.91 g) and 6 N HCl-solution (0.3 equiv, 50.5 mmol, 8.4 mL) in water were added to the reaction suspension following the above described procedure. In order to achieve a quantitative benzylation of the starting material **1a**, to the reaction suspension was added benzaldehyde (17.2 mL) and 15 min later under cooling to 0 °C $NaBH_4$ (1.91 g) again. After stirring for 5 min at 0 °C, the mixture was allowed to stir for 30 min at ambient temperature.[9]

Subsequently, water (110 mL, **Ia** = 0.8 mol/L) and NaOH (13.47 g, 336.8 mmol, 2.0 equiv) were added and the mixture was stirred for 5 min at ambient temperature (pH 10 →>14) to from a clear solution. After cooling to0 °C a solution of Cbz-Cl (36 mL, 252.6 mmol, 1.5 equiv) in THF (70 mL, water/THF 3:1) was added dropwise within 30 min through a dropping funnel. After stirring for 15 min at 0 °C, the cooling bath was removed and the reaction mixture was stirred for 17 h at room temperature.

´´8 To remove BzOH 20 mL of benzaldhyde were diluted with 2 mL of Et_2O (in order to improve the phase separation), washed successively with three 10 mL portions of saturated $NaHCO_3$ and 10 mL of brine and dried over $MgSO_4$. After concentration under reduced pressure at the rotatory evaporator only small amounts of Et_2O remained (2-3mol% according to ^{1}H-NMR).

9 With adding two (instead of three) portions of PhCHO/$NaBH_4$ the product **2a** was isolated in an about 15% diminished yield. As no trace of *N*-Cbz alanine was detectable in both cases in the isolated product, Cbz protected alanine (resulting from inquantitative benzylation of **1a** and acylation of **1a** with Cbz-Cl) is supposebly poorly soluble in Et_2O and therefore is not coextracted with the less polar product **2a.**

Thereafter the reaction suspension (pH = 11) was cooled in an ice bath and acidified to pH ≤ 0 through the dropwise (10 min) addition of aqueous6 N HCl solution (60 mL)through the same dropping funnel. Subsequently, the mixture was extracted with three 140 mL portions of Et_2O (H_2O/Et_2O 2:1), the collected Et_2O phases were dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture of the product **2a** and BnOH (98.64 g of a pale yellow oil). Next the crude product was dissolved in Et_2O (170 mL, **2a** = 1 mol/L), a small spatula tip of phenolphthalein was added, the solution was cooled in an ice bath and a 1.0 N LiOH solution in water (170 mL) was added dropwise (10 min) through a dropping funnel, until a color change (colorless → violet) was observed (pH = 10).[10]The phases were separated (volume of the separated organic phase was 140 mL), the aqueous phase was washed with 90 mL of Et_2O (H_2O/Et_2O 2:1, 100 mL of organic phase separated), 160 mL of EtOAc (H_2O/EtOAc 1:1, 140 mL of organic phase separated), two 90 mL portions of EtOAc (90 and 110 mL, respectively,of organic phase separated) and 90 mL of Et_2O (100 mL separated). After addition of 100 mL of Et_2O (H_2O after HCl addition/Et_2O 2:1) and cooling in an ice bath, the mixture was acidified to pH ≤0 by the dropwise addition of 6 N HCl-solution in water (26 mL).[11]Next, the organic phase was separated, the aqueous phase was extracted with two further 100 mL portions of Et_2O, the combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. After drying in high vacuum under stirring at 60 °C for 14 h,the acid **2a** (39.412 g, 125.8 mmol, 75%) was isolated as a colorless, highly viscous oil. ^{1}H-NMR indicated 3% of residual BnOH, less than 1% of BzOH and 7% of *N,N*-Bn_2 alanine **15a**.[12] Considering residual BnOH and dibenzyl alanine the product **2** was isolated in a yield of 70% (117.5 mmol).



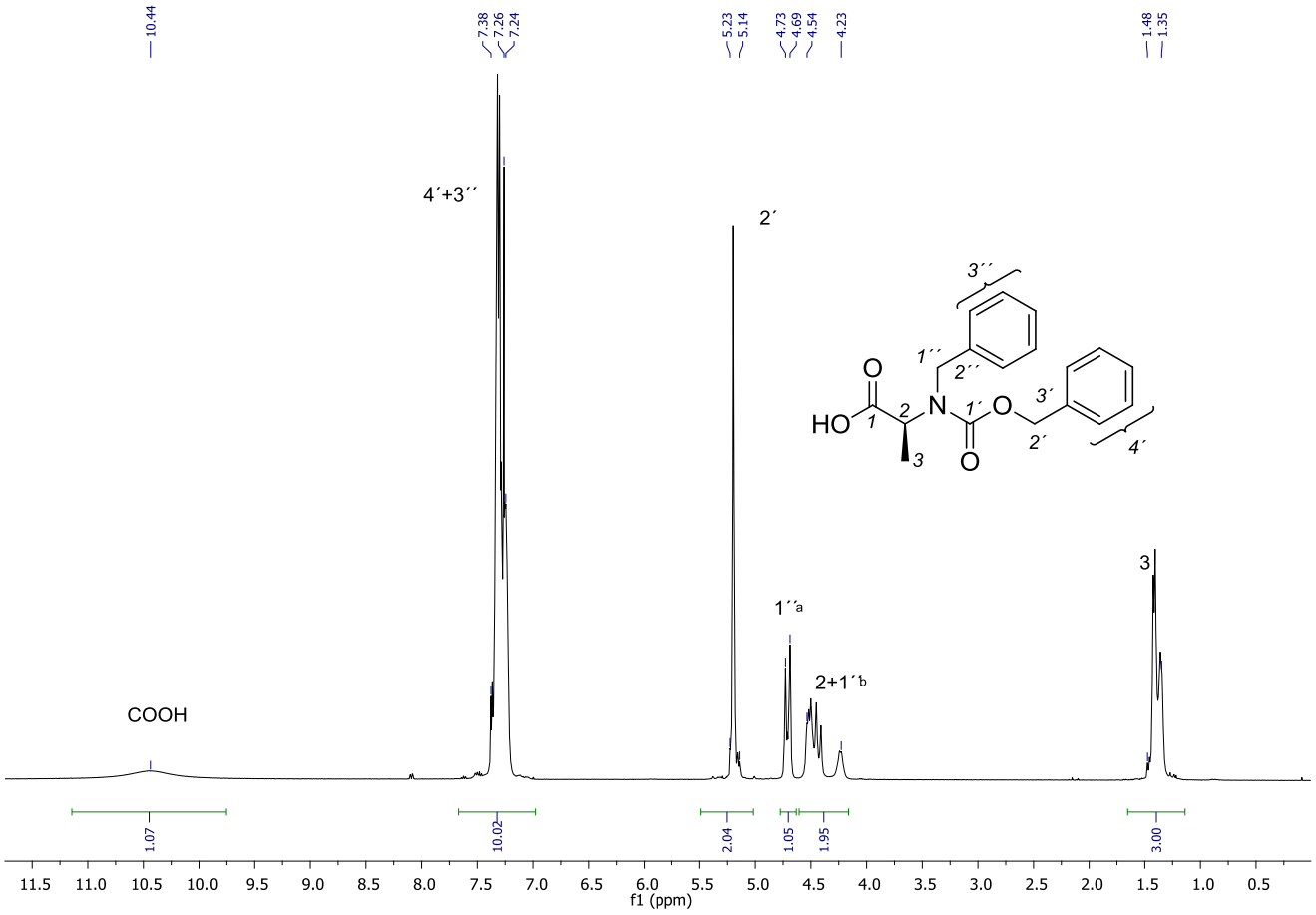
M ($C_{18}H_{19}NO_4$) = 313.35 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 10.44 (s, 1H, CO_2H), 7.38-7.24 (m, 10H, H-4´, H-3´´), 5.23-5.14 (m, 2H, H-2´), 4.73-4.69 (m, 1H, H-1´$_a$), 4.54-4.23 (m, 2H, H-2, H-1´´$_b$), 1.48-1.35 (m, 3H, H-3´); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 177.3 (C-1), 156.5 (C-1´), 137.9 (C-2´´), 136.1 (C-3´), 128.6/128.5/128.4/128.2/128.0/127.8/127.6/127.3/127.1/127.0 (C-4´, C-3´´), 67.7/65.3 (C-2´), 55.5/55.0 (C-2), 51.1/50.1 (C-1´´), 15.8/15.1 (C-3); **IR** (film) ν cm^{-1} = 3407 (w), 3147 (w), 3089 (m), 3064 (m), 3033 (s), 2993 (m), 2947 (m), 2607 (w), 1954 (w), 1878 (w), 1811 (w), 1740 (s), 1698 (vs), 1682 (vs), 1607 (w), 1587 (w), 1497 (w), 1471 (m), 1454 (s), 1417 (m), 1367 (w), 1307 (w), 1250 (m), 1213 (m), 1144 (w), 1098 (w), 1069 (m), 1015 (m), 975 (w), 911 (w), 823 (w), 771 (w), 735 (m), 698 (s), 629 (w); **HR-MS** (ESI, $C_{18}H_{20}NO_4^+$) calc. 314.1392 u, found 314.1386 u, (ESI, $C_{18}H_{19}NO_4Na^+$) calc. 336.1212 u, found 336.1225 u; α_D (c = 0.954 g/100 mL, $CHCl_3$, T = 21.0 °C) = -33.5, α_D of **2a** synthesized according

10 Without adjusting the pH carefully to 9-10, the isolated product **2a** contained residual HOAc (resulting from saponification during EtOAc washings).

11 Thereby the product **2a** precipitated and dissolved in the etheral phase again.

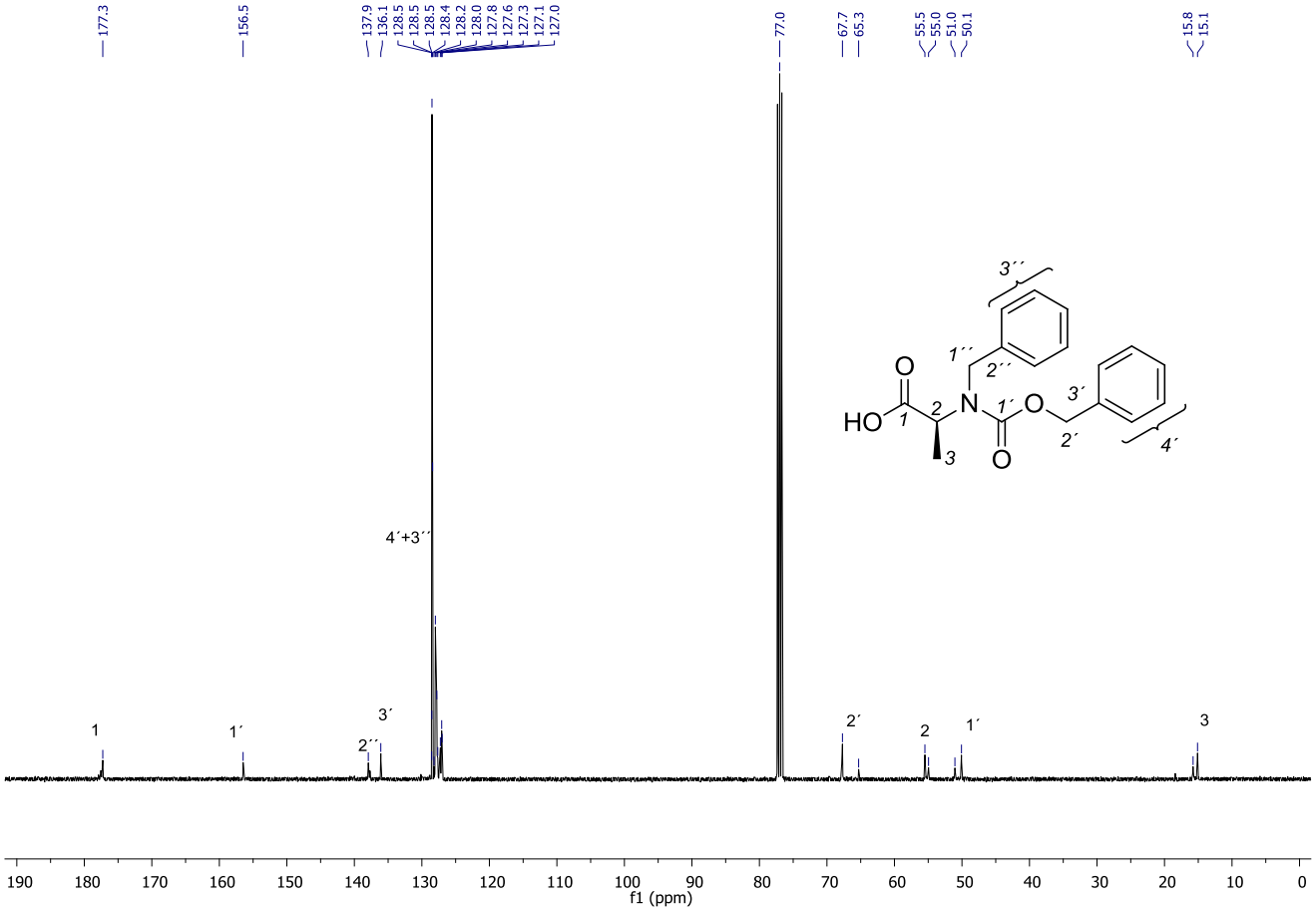
12 Further drying overnight did not reduce the amount of BnOH.

to the one-pot procedure given (c = 0.910 g/100 mL, $CHCl_3$, T = 20.5 °C) = -31.0, lit.: α_D (c = 0.68 g/100 mL, DCM, T = 20 °C) = -29.2.[13]



^{1}H-NMR-spectrumof acid **2a** in $CDCl_3$ (400 MHz).

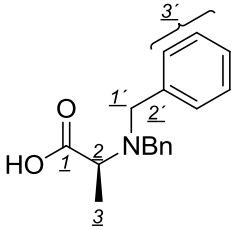
13 A. B. Hughes, B. E. Sleebs, *Synth. Comm.***2009**, *39*, 48-60.

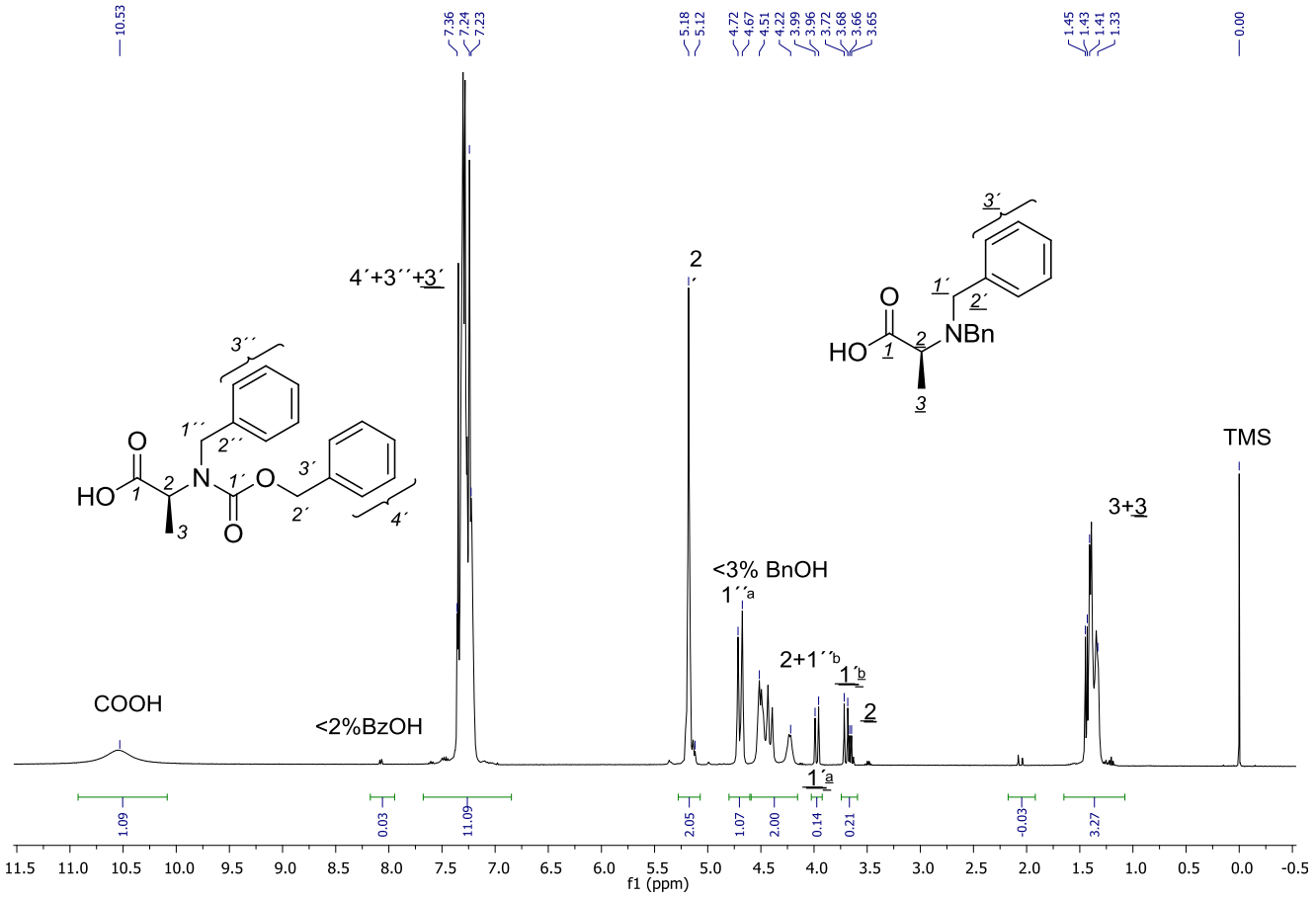


^{13}C-NMR-spectrumof acid **2a** in $CDCl_3$ (100 MHz).

S-2-(dibenzyl amino)-propanoic acid (15a, in mixture with the major product 2a)

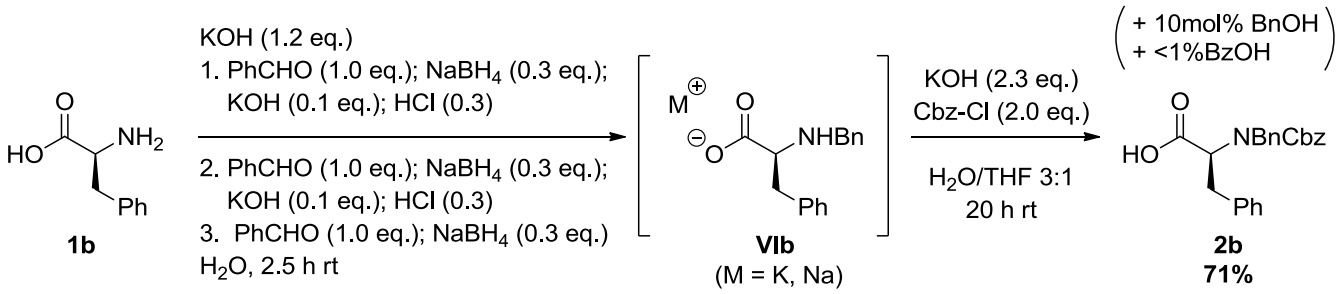
M ($C_{17}H_{19}NO_2$) = 269.338 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers, 7mol% **15a**) δ ppm = 10.53 (s, 1H, CO_2H), 7.36-7.23 (m, 20H, H-4´, H-3´´, H-3´), 5.18-5.12 (m, 2H, H-2´), 4.70 (d, 1H, H-1´´$_a$), 4.51-4.22 (m, 2H, H-2, H-1´´$_b$), 3.97 (d, 2H, H-1´$_a$, *J* = 13.3 Hz, 7 mol% **3**), 3.70 (d, 2H, H-1´$_b$, *J* = 13.6 Hz, 7mol% **3**), 3.66 (q, 1H, H-2, *J* = 7.3 Hz, 7mol% **3**), 1.45-1.33 (m, 6H, H-3, H-3; amongst at 1.44 ppm, d, H-3, *J* = 7.3 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of rotamers, only **15a** according to HMBC and HMQC,) δ ppm = 175.3 (C-1), 135.6 (C-2´), 129.6 (C-3´) 58.8 (C-2), 54.9 (C-1´´), 11.2 (C-3); **HR-MS** (ESI, $C_{17}H_{20}NO_2^+$) calc. 270.1494 u, found 270.1498 u.





^{1}H-NMR-spectrumof a mixture of the acid **2a** and the benzyl amine **16a** prepared according to the large scale one-pot procedure in $CDCl_3$ (400 MHz).

2.2.3 Synthesis of *S*-2-(Benzyl-(benzyloxycarbonyl)-amino)-3-phenyl propanoic acid (2b)



L-Phenylalanine (**1b**, 5.00 g, 30.27 mmol, 1.0 equiv) and KOH (2.04 g, 36.3 mmol, 1.2 equiv)[14] were dissolved water (50 mL, **1b** = 0.6 mol/L) at ambient temperature (pH = 11). This solution was treated

14 With NaOH after the first acidification a precipitate was formed, which could only be dissolved by adding further NaOH and heating with a heatgun. An incomplete benzylation resulted from the basic conditions.

with benzaldehyde[15] (3.1 mL, 30.27 mmol, 1.0 equiv) and stirred for 15 min at room temperature. A clear solution was obtained after 5 min of stirring indicating imine formation. The reaction mixture was then cooled in an ice bath, $NaBH_4$ (340 mg, 9.08 mmol, 0.3 equiv) was added in one portion (a weak H_2-evolution was observed) and the mixture was allowed to stir for 5 min at 0 °C and 30 min at room temperature. As a colorless solid precipitated, a thick, viscous slurry was formed (pH = 11). In order to dissolve the precipitate, one KOH pellet (190 mg, 3.4 mmol, 0.1 equiv) was added and to the resulting clear solution was added 3 N aq. HCl (2.0 mL, 6.0 mmol, 0.2 equiv, pH 12 → 11) dropwise. A solid precipitated again, but formed bigger aggregates, therefore keeping the mixture stirrable.[16]

Next the reaction mixture was treated again with benzaldehyde (3.1 mL, 30.27 mmol, 1.0 equiv), stirred for 15 min at ambient temperature and under cooling with an ice bath, $NaBH_4$ was added (340 mg, 9.08 mmol, 0.3 equiv). After further 5 min of stirring at 0 °C, the cooling bath was removed and the mixture was allowed to stir for 30 min at room temperature. Due to a solid precipitated, one KOH pellet (220 mg, 3.92 mmol, 0.13 equiv) was added, and to the resulting clear solution 3 N aq. HCl (2.0 mL, 6.0 mmol, 0.2 equiv; pH 12 → 11) was added. To ensure complete conversion of the amine **1a** to the benzyl amine **VIb**, treatment with benzaldehyde and $NaBH_4$ was repeated for a third time as described above. After stirring for 5 min at 0 °C, the mixture was allowed to stir for 30 min at ambient temperature, KOH (3.91 g, 60.54 mmol, 2.3 equiv) was added, the reaction mixture was stirred until KOH had dissolved (5 min) and cooled in an ice bath. A solution of Cbz-Cl (8.6 mL, 60.5 mmol, 2.0 equiv) in THF (17 mL, water/THF 3:1) was added dropwise through a dropping funnel within 10 min. After stirring for 15 min at 0 °C, the cooling bath was removed and the reaction mixture was allowed to stir for 20 h at room temperature.

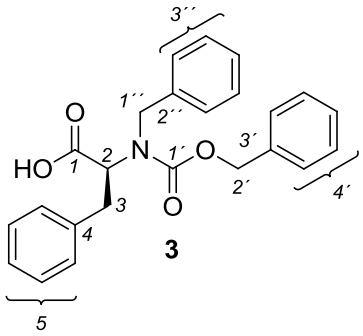
The reaction suspension (pH = 10-11) was cooled in an ice bath and acidified by dropwise addition of 17 mL of 3 N HCl solution (pH →≤ 0). The mixture was diluted with 40 mL of Et_2O and the remaining precipitate was separated through filtration (sintered funnel). In order to improve phase separation the filtrate was diluted with 20 mL of Et_2O and the phases were separated. The precipitate was rinsed with 40 mL of Et_2O, the ether phase was separated through filtration and used for the extraction of the

15 To remove BzOH 20 mL of benzaldehyde were diluted with 2 mL of Et_2O (in order to improve the phase separation), washed successively with three 10 mL portions of saturated $NaHCO_3$ and 10 mL of brine and dried over $MgSO_4$. After concentration under reduced pressure at the rotatory evaporator only small amounts of Et_2O (2-3mol% according to ^{1}H-NMR).

16 Without the careful adjustment of the pH-value to 11, the reductive amination was not quantitative. Thus, the isolated product **3** contained 5-10 mol% of the undesired Cbz-protected phenylalanine. However, the addition of more than 0.2 equiv of HCl increased the viscosity of the reaction mixture (due precipitation), so that stirring with a magnetic stir bar became impossible.

aqueous phase. After repeating this procedure with a further 40 mL of Et_2O the collected organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.[17]

The mixture of the acid **2b** and BnOH (21.05 g, 180%, colorless oil) obtained was dissolved in 15 mL of Et_2O, a small spatula tip of phenolphthalein was added, the mixture was cooled in an ice bath and a 1.0 N LiOH solution in water (28 mL) was added dropwise until a color change (colorless → violet) was observed (pH = 9-10).[18] To the clear solution (one phase!) 15 mL of *c*Hex was added, the resulting upper organic phase was separated. The aqueous phase was washed with 20 mL of Et_2O, three 20 mL portions of Et_2O/EtOAc 1:1[19] (pH → 9)[20] and 20 mL of Et_2O.[21] After addition of 25 mL of Et_2O and cooling in an ice bath, the mixture was acidified to pH ≤ 0 by dropwise addition of 8 mL of 3 N HCl.[22] The aqueous phase was separated, extracted with two 20 mL portions of Et_2O,[23] the combined extraction phases were dried over $MgSO_4$ and concentrated under reduced pressure. After drying in high vacuum with stirring at 60 °C for 3 h the acid **2a** (8.561 g, 22.00 mmol, 73%) was isolated as a colorless highly viscous oil. Taking 10% residual BnOH indicated by ^{1}H-NMR into account, the product **3** was obtained in a yield of 71% (21.39 mmol).[24]



M ($C_{24}H_{23}NO_4$) = 389.444 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 10.72 (s, 1H, CO_2H), 7.36-6.95 (m, 15H, H-5, H-4´, H-3´´), 5.29 (d, 1H, H-2´$_a$, *J* = 12.7 Hz), 5.20-5.15 (m, 1H, H-2´$_b$), 4.66/4.52 (2xd, 1H, H-1´´$_a$, *J* = 15.3/15.7 Hz, ratio 1:1.4), 4.21-4.10 (m, 1H, H-2), 3.79/3.74 (2xd, 1H, H-1´´$_b$, *J* = 15.7/15.0 Hz), 3.33-3.04 (m, 2H, H-2); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 176.3/175.7 (C-1), 156.3 (C-1´), 137.5/136.5/136.2 (C-4, C-3´, C-2´´), 129.2/128.7/2x128.5/128.4/128.3/128.01/127.9/127.5/127.4/126.7 (C-5, C-4´, C-3´´), 67.9/67.7 (C-2´), 62.1/60.8 (C-2), 52.4 (C-1´´), 36.3/35.1 (C-3); **IR** (film) ν cm^{-1} =3144 (br), 3109 (w), 3088 (w), 3064 (m), 3031 (m), 3007 (w),

17 Additional extraction with EtOAc (40 mL) did not deliver any further product **3**. Thus the extraction with Et_2O (x3) allows a quantitative separation of **3**.

18 Without adjusting the pH carefully to 9-10, the isolated product **2b** contained residual HOAc (resulting from saponification during EtOAc washings).

19 After addition of 10 mL EtOAc alone, no phase separation was observed.

20 The weak pH-change may be attributed to minimal saponification of EtOAc. Also the intensity of the violet color decreased during the EtOAc-washings.

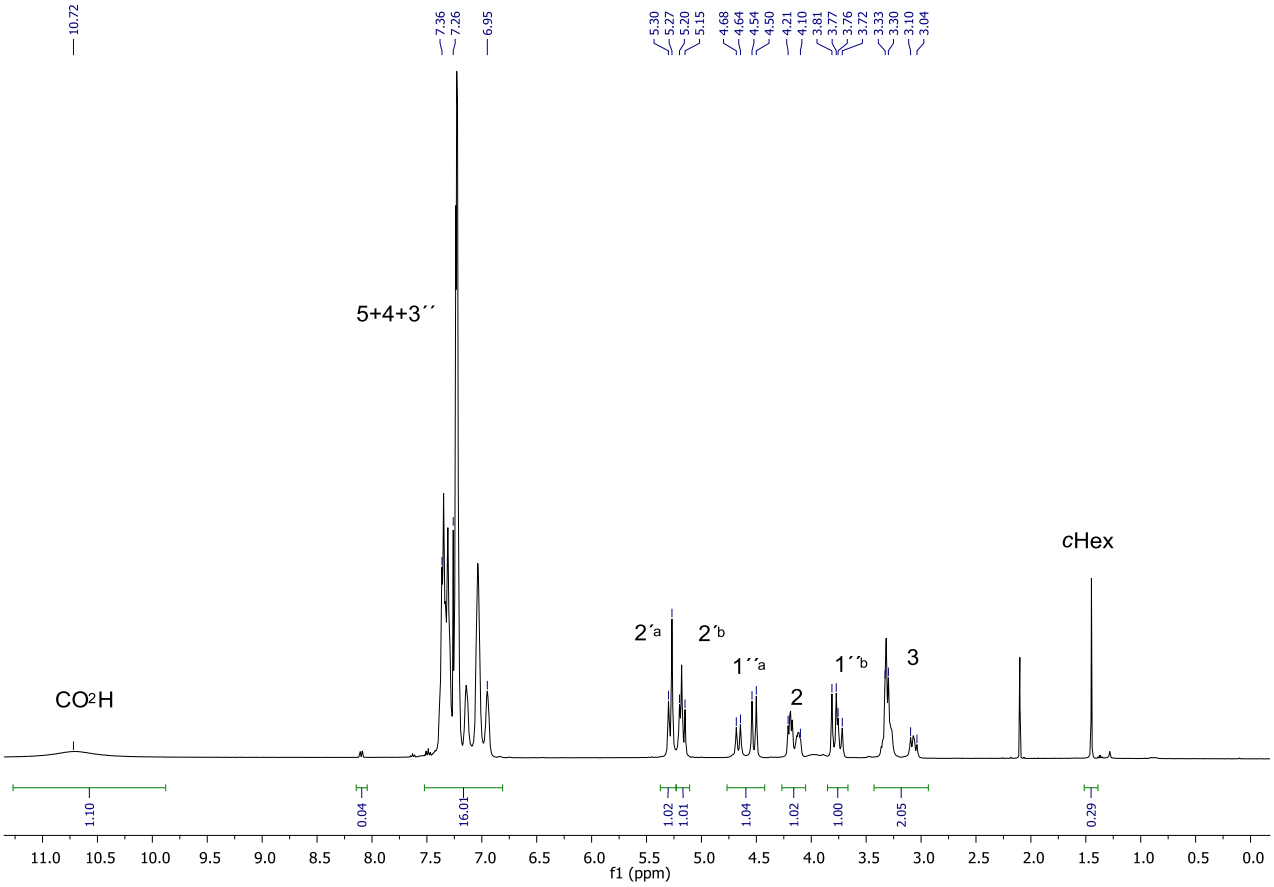
21 During the EtOAc/Et_2O washings the aqueous phase increases in volume due to absorption of organic solvent. The final Et_2O washing removes most of the organic solvent from the aqueous phase. After washing with Et_2O/cHex 1:1 and three portions of Et_2O the acid **2b** was isolated containing around 30 mol% of BnOH. Hence washing with EtOAc (/Et_2O is essential to remove BnOH.

22 Thereby the product **2b** precipitated and dissolved in the ethereal phase again.

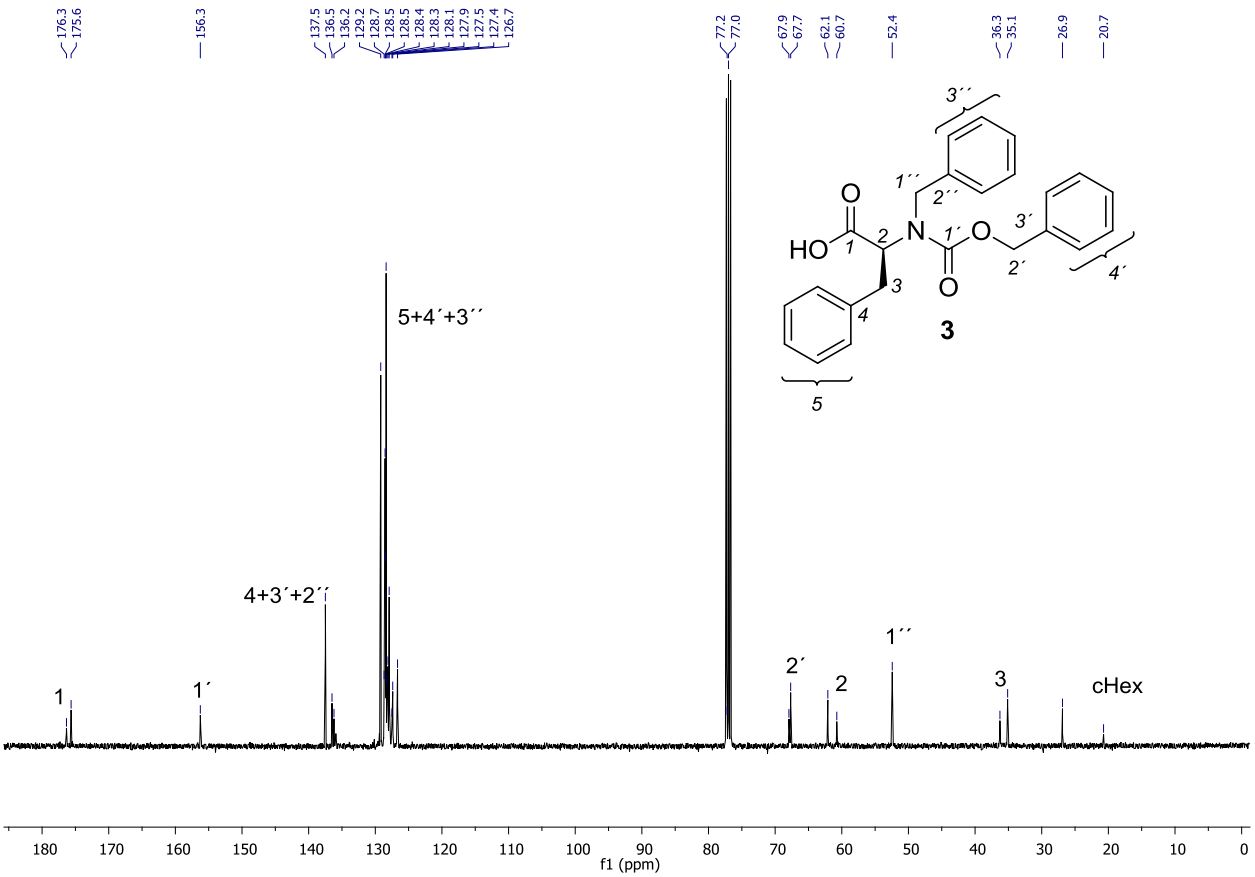
23 Additional extraction with EtOAc (40 mL) did not deliver any further product **2b**. Thus the extraction with Et_2O (x3) allows a quantitative separation of **2b**.

24 Further drying overnight did not reduce the amount of BnOH.

2946 (w), 2607 (w), 1952 (w), 1877 (w), 1810 (w), 1738 (m), 1713 (vs), 1704 (vs), 1682 (m), 1605 (w), 1586 (w), 1496 (m), 1455 (s), 1423 (m), 1366 (w), 1307 (w), 1239 (s), 1179 (m), 1124 (m), 1079 (w), 1029 (w), 986 (w), 911 (w), 821 (w), 769 (m), 750 (m), 735 (m), 698 (s), 645 (w), 565 (w), 492 (w); **HR-MS** (ESI, $C_{24}H_{24}NO_4^+$) calc. 390.1705 u, found 390.1714 u; (ESI, $C_{24}H_{23}NO_4Na^+$) calc. 412.1525 u, found 412.1533 u; α_D (c = 0.804 g/100 mL, $CHCl_3$, T = 22.2 °C) = -118.9.

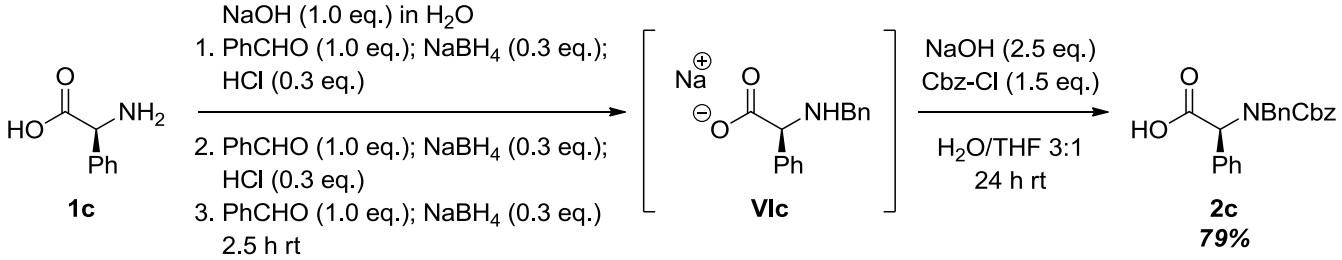


^{1}H-NMR-spectrum of the acid **2b** in $CDCl_3$ (400 MHz).



^{13}C-NMR-spectrum of the acid **2a** in $CDCl_3$ (100 MHz).

2.2.4 Synthesis of *S*-2-(Benzyl-(benzyloxycarbonyl)-amino)-2-phenyl ethanoic acid (2c)



L-Phenylglycine (**1c**, 10.00 g, 66.09 mmol, 1.0 equiv) was dissolved under stirring (for 10 min) in a 2 N NaOH solution in water (33 mL, 66.0 mmol, 1.0 equiv).This solution (pH = 12) was treated with benzaldehyde[25] (6.7 mL, 66.09 mmol, 1.0 equiv) and stirred for 15 min at room temperature. A clear solution was obtained after 5 min of stirring, indicating quantitative imine formation. The reaction mixture was then cooled in an ice bath, $NaBH_4$ (750 mg, 19.8 mmol, 0.3 equiv) was added in two portions over 5 min (a weak H_2-evolution was observed) and the mixture was allowed to stir for 5 min at

25 To remove BzOH 20 mL of benzaldehyde were diluted with 2 mL of Et_2O (in order to improve the phase separation), washed successively with three 10 mL portions of saturated $NaHCO_3$ and 10 mL of brine and dried over $MgSO_4$. After concentration under reduced pressure at the rotatory evaporator only small amounts of Et_2O (2-3mol% according to ^{1}H-NMR).

0 °C and 30 min at room temperature. Subsequently, to the clear reaction solution 3 N HCl solution (aq., 6.6 mL, 19.8 mmol, 0.3 equiv) was added dropwise, whereby a colorless solid precipitated (pH 11 → 10).

The reaction mixture was treated again with benzaldehyde (6.7 mL, 66.09 mmol, 1.0 equiv), stirred for 15 min at ambient temperature, cooled in an ice bath and $NaBH_4$ (750 mg, 19.8 mmol, 0.3 equiv) was added in two portions over 5 min. After further 5 min of stirring at 0 °C, the cooling bath was removed, the mixture was allowed to stir for 30 min at room temperature and 3 N HCl solution (aq., 6.6 mL, 19.8 mmol, 0.3 equiv) was added dropwise (pH = 9). As magnetic stirring became impossible due to a precipitated solid, 2 N NaOH solution (0.5 mL, 1 mmol, pH → 10) was added, until the viscosity of the reaction slurry decreased enough to allow magnetic stirring again. Then PhCHO (6.7 mL, 66.09 mmol, 1.0 equiv) and $NaBH_4$ (750 mg, 19.8 mmol, 0.3 equiv) were added for a third time as described above.

Thereafter the reaction suspension was diluted with 2 N NaOH solution in water (66 mL, 132.2 mmol, 2.0 equiv; **2c** = 0.6 mol/L), cooled in an ice bath anda solution of Cbz-Cl (14 mL, 99.2 mmol, 1.5 equiv) in 35 mL of THF (water/THF 3:1) was added dropwise through a dropping funnel within 30 min. After stirring for 15 min at 0 °C, the cooling bath was removed and the reaction mixture was stirred for 24 h at room temperature.

The reaction suspension (pH = 11) was cooled in an ice bath and was acidified to pH = 0 through the slow addition of a 3 N HCl solution in water (55 mL) over 20 min (through a dropping funnel). Then the mixture was extracted with three 80 mL portions of Et_2O (H_2O/Et_2O 2:1), the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

The residue (59.70 g, 240%, pale yellow oil) was dissolved in Et_2O (70 mL, **2c** = 1 mol/L), a small spatula tip of phenolphthalein was added, the mixture was cooled in an ice bath and a 1.0 N LiOH solution in water (70 mL) was added dropwise (within 10 min) until a color change (colorless → violet) was observed (pH = 10).[26]The phases were separated (volume of separated organic phase was 45 mL), the aqueous phase was washed with one further 40 mL portion of Et_2O (H_2O/Et_2O ca. 2:1, 55 mL organic phase separated), 70 mL of EtOAc (H_2O/EtOAc 1:1, 50 mL separated) H_2O/EtOAc 1:1), two 40 mL portions of EtOAc (H_2O/EtOAc ca. 2:1, 2x40 mL separated) and 40 mL of Et_2O again (60 mL separated).

After addition of 50 mL of Et_2O (H_2O after HCl addition/Et_2O 2:1) and cooling in an ice bath, the mixture was acidified to pH ≤ 0 by dropwise addition of 24 mL of 3 N HCl.[27] The organic phase was separated, the aqueous phase was extracted with two more 50 mL portions of Et_2O, the combined extraction phases were dried over $MgSO_4$ and concentrated under reduced pressure. After drying in

26 Without adjusting the pH carefully to 9-10, the isolated product **2c** contained residual HOAc (resulting from saponification during EtOAc washings).

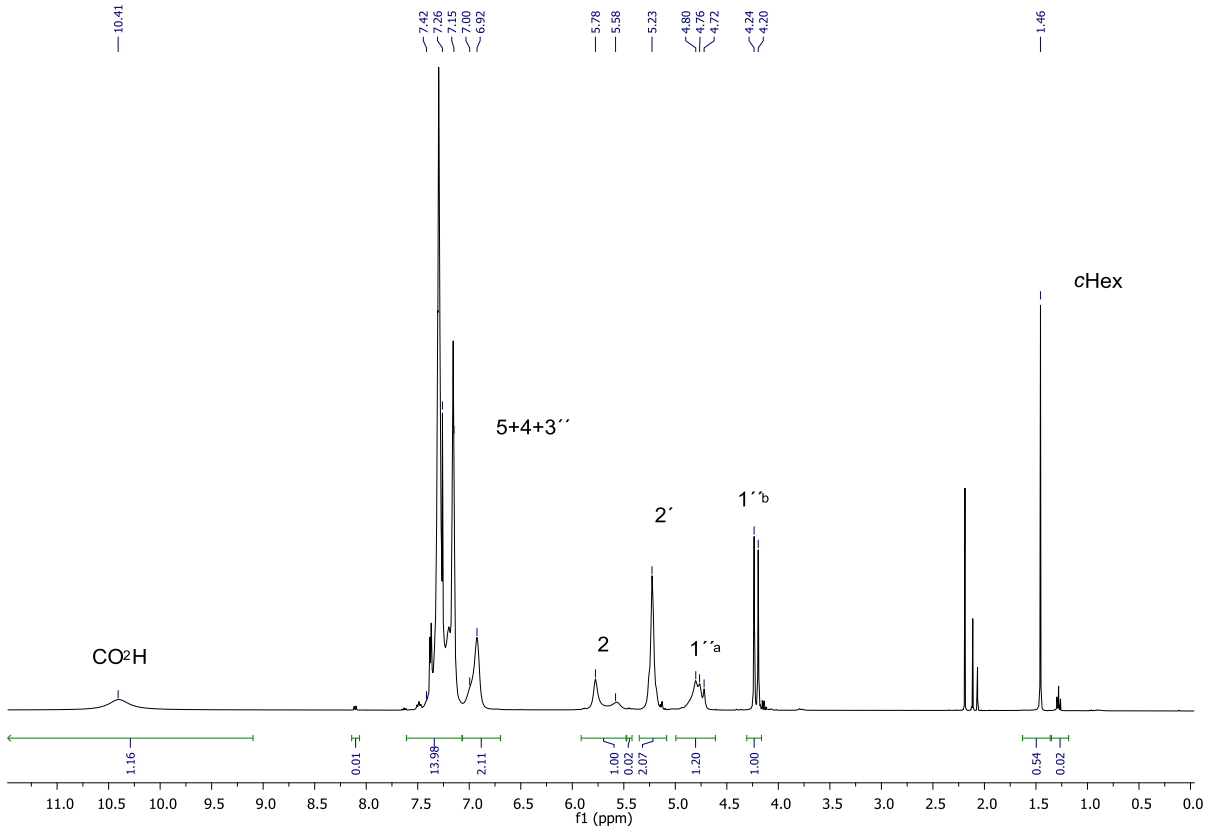
27 Thereby the product **2c** precipitated and dissolved in the ethereal phase again.

high vacuum under stirring at 60 °C for 1 h the acid **2c** (20.84 g, 55.5 mmol, 84%) was isolated as a colorless, highly viscous oil. ^{1}H-NMR indicated 10% residual BnOH, 8% of EtOAc and 2% of presumably *N,N*-Bn,Bn-phenyl glycine. Accounting these residual impurities, the carbamate **2c**was obtained in a yield of 79% (52.1 mmol).

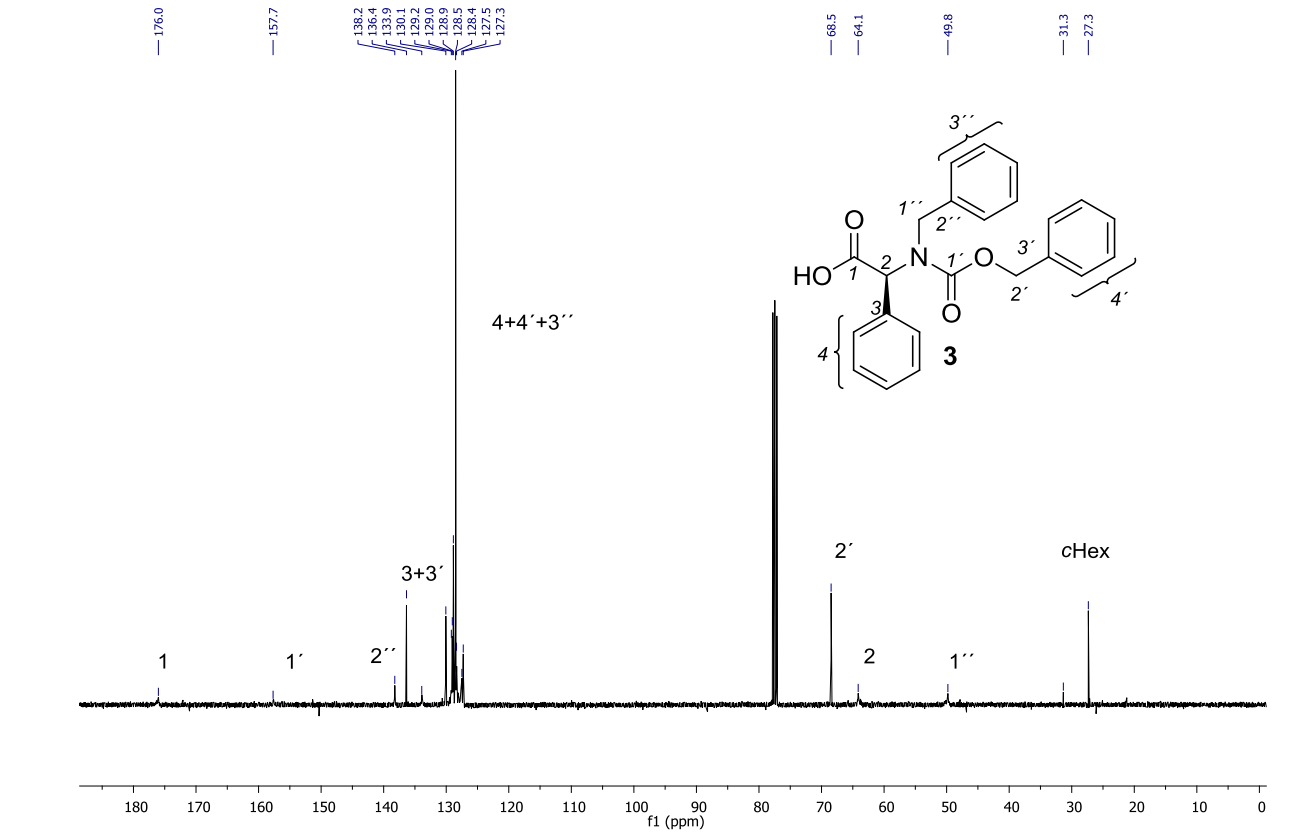
M ($C_{23}H_{21}NO_4$) = 375.417 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 10.41 (s, 1H, CO_2H), 7.42-7.15 (m, 13H, H-4, H-4´, H-3´), 7.00-6.92 (m, 2H, H-3´´), 5.78/5.58 (2xs, 1H, H-2), 5.23 (s, 2H, H-2´), 4.78 (d, 1H, H-1´´$_a$, *J* = 15.2 Hz), 4.22 (d, 1H, H´´$_b$, *J* = 16.2 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 176.0 (C-1), 157.7 (C-1), 138.22 (C-2´´), 136.4/133.9 (C-3, C-3´), 130.1/129.2/129.0/128.9/128.5/128.4/127.50/ 127.3 (C-4, C-4´, C-3´´), 68.5 (C-2´), 64.1 (C-2), 49.8 (C-1´´); **IR** (film) ν cm^{-1}= 3148 (w), 3109 (w), 3089 (m), 3064 (m), 3032 (s), 2955 (m), 2608 (w), 1954 (w), 1881 (w), 1810 (w), 1745 (s), 1702 (vs), 1605 (w), 1586 (w), 1497 (m), 1454 (s), 1412 (s), 1365 (w), 1259 (s), 1209 (m), 1171, (m) 1118 (w), 1078 (w), 1029 (w), 1003 (w), 965 (w), 912 (m), 867 (w), 823 (w), 768 (w), 735 (s), 697 (vs), 634 (w), 616 (w), 596 (w), 569 (w); **HR-MS** (ESI, $C_{23}H_{22}NO_4^+$) found 376.1549 u calc. 376.1553 u; α_D (c = 1.134 g/100 mL, $CHCl_3$, T = 21.5 °C) = +58.9.

***S*-2-(Dibenzyl amino)-2-phenyl ethanoic acid**

M ($C_{22}H_{21}NO_2$) = 331.4 g/mol; **HR-MS** (ESI, $C_{22}H_{22}NO_2^+$) found 332.1478 u calc. 332.1651.

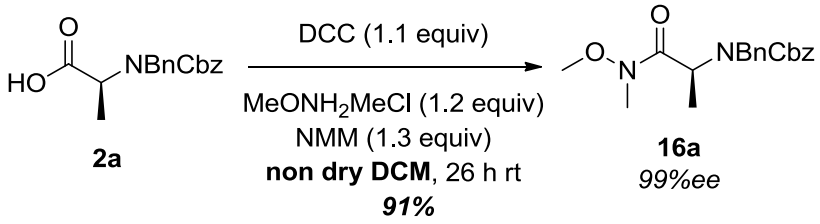


^{1}H-NMR-spectrumof the acid **2c** in $CDCl_3$ (400 MHz).



^{13}C-NMR-spectrumof the acid **2c** in $CDCl_3$ (100 MHz).

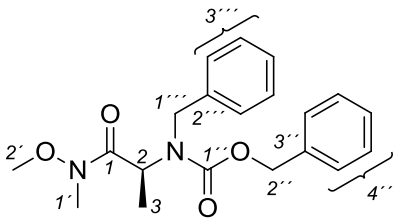
2.2.5 Synthesis of *S*-*N*-methyl-*N*-methoxy-2-(benzyl-(benzyloxycarbonyl)-amino)-propanoic amide (16a)



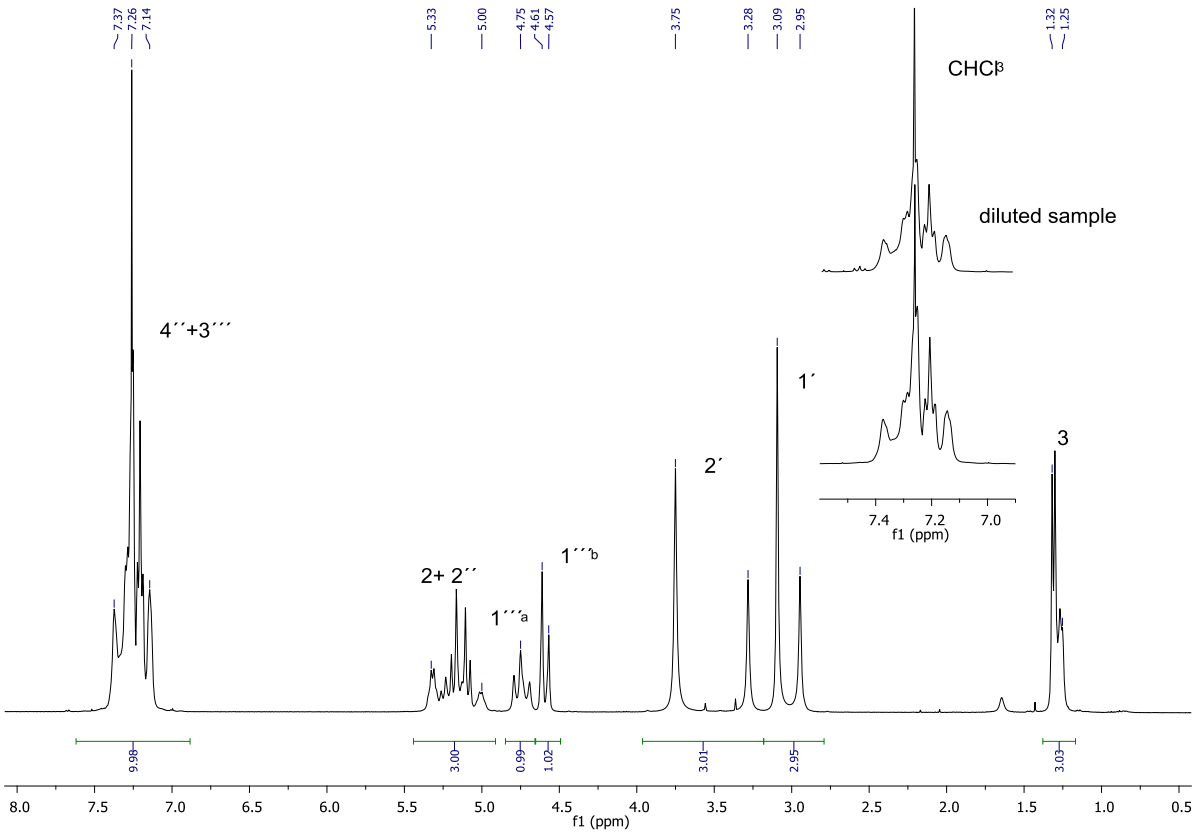
The acid **2a** (44.35 g, 141.5 mmol, 1.0 equiv) was dissolved in DCM (430 mL, reagent grade, non-dry, **2a** = 0.3 mol/l) in a 1 L flask, the mixture was cooled in an ice bath and NMM (18.7 mL, 184.0 mmol, 1.3 equiv) and $MeNOH_2MeCl$ (16.57 g, 169.8 mmol, 1.2 equiv) were added successively. After stirring for 5 min, DCC (32.11 g, 155.7 mmol, 1.1 equiv) was added to the reaction suspension in one portion and the mixture was allowed to stir for 30 min at 0 °C and for 26 h at ambient temperature.

DCM was evaporated under reduced pressure, the residue was partitioned between 1 N HCl solution in water (100 mL) and EtOAc (200 mL), stirred for 5 min at room temperature to hydrolyse excess DCC, and filtered through a sintered funnel. The residue (urea) was washed with two 100 mL portions of EtOAc, from the combined filtrates the organic phase was separated, washed successively with one 100 mL portion of 1 N HCl solution, one 100 mL portion of saturated $NaHCO_3$-solution in

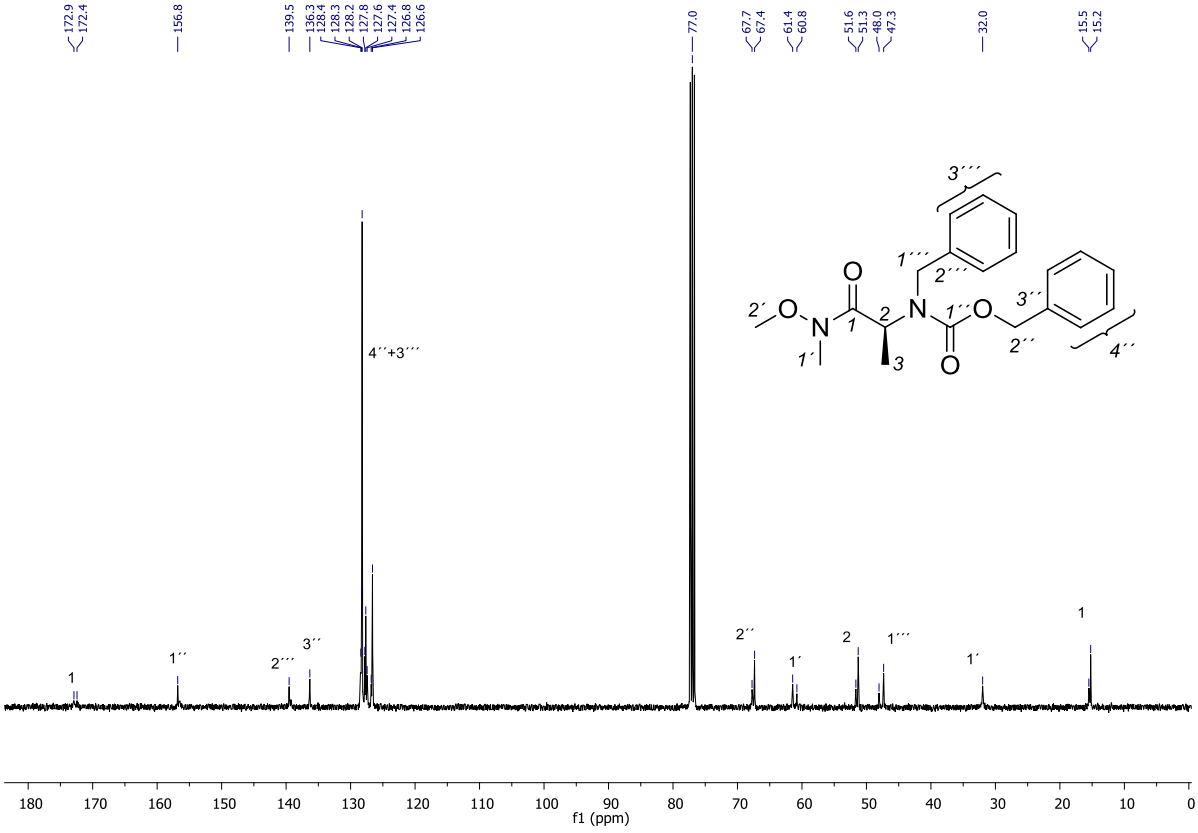
water and 100 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure. To remove remaining *N,N´*-dicyclohexyl urea the residue was dissolved in *c*Hex (140 mL, **16a** = 1 mol/L) and filtered, the precipitated urea was washed with 30 mL of *c*Hex and the combined filtrates were concentrated *in vacuo*. After drying in high vacuum for 14 h under stirring and heating to 40 °C, the amide **16a** (45.64 g, 128.05 mmol, 91%) was isolated as a pale yellow oil in an *ee* of 99%.



M ($C_{20}H_{24}N_2O_4$) = 356.42 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex) = 0.73 (1:1), 0.24 (1:3); **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 7.37-7.14 (m, 10H, H-4´´, H-3´´´), 5.33-5.00 (m, 2H, H-2, H-2´), 4.79-4.69 (m, 1H, H-1´´´$_a$), 4.59 (d, 1H, H-1´´´$_b$, *J* = 17.3 Hz), 3.75/3.28 (2xs, 3H, H-2´), 3.09/2.95 (2xs, 3H, H-1´), 1.32-1.25 (m, 3H, H-3); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 172.9/172.4 (C-1), 156.8 (C-1´´), 139.5/136.3 (C-2´´´), 128.4/128.3 (C-3´´), 128.2/127.8/127.7/127.4/126.8/126.6 (C-4´´/C-3´´´), 67.7/67.4 (C-2´´), 61.4/60.8 (C-1´), 51.6/51.3 (C-2), 48.1/47.3 (C-1´´´), 32.0 (C-1´), 15.5/15.2 (C-3); **IR** (film) ν cm^{-1} = 3374 (br), 3091 (w), 3065 (w), 3033 (w), 2961 (vs), 2932 (s), 2905 (m), 2871 (m), 2254 (w), 1713 (vs), 1600 (m), 1516 (s), 1503 (m), 1455 (m), 1426 (w), 1373 (m), 1345 (s), 1297 (w), 1244 (s), 1194 (w), 1177 (vs), 1106 (w), 1072 (m), 1040 (m), 1025 (m), 974 (m), 915 (m), 884 (w), 845 (w), 809 (w), 778 (w), 738 (s), 698 (m), 665 (m), 623 (w), 581 (m), 562 (m), 478 (w), 457 (w); **HR-MS** (ESI, $C_{20}H_{25}N_2O_4^+$) calc. 357.1814 u, found 357.1812 u, (ESI, $C_{20}H_{24}N_2O_4Na^+$) calc. 379.1634 u, found 379.1619 u; α_D (c = 1.306 g/100 mL, $CHCl_3$, T = 21.0 °C) = -29.2; α_D of unpurified amide according to the given procedure: (c = 1.654 g/100 mL, $CHCl_3$, 20.5 °C) = -28.2

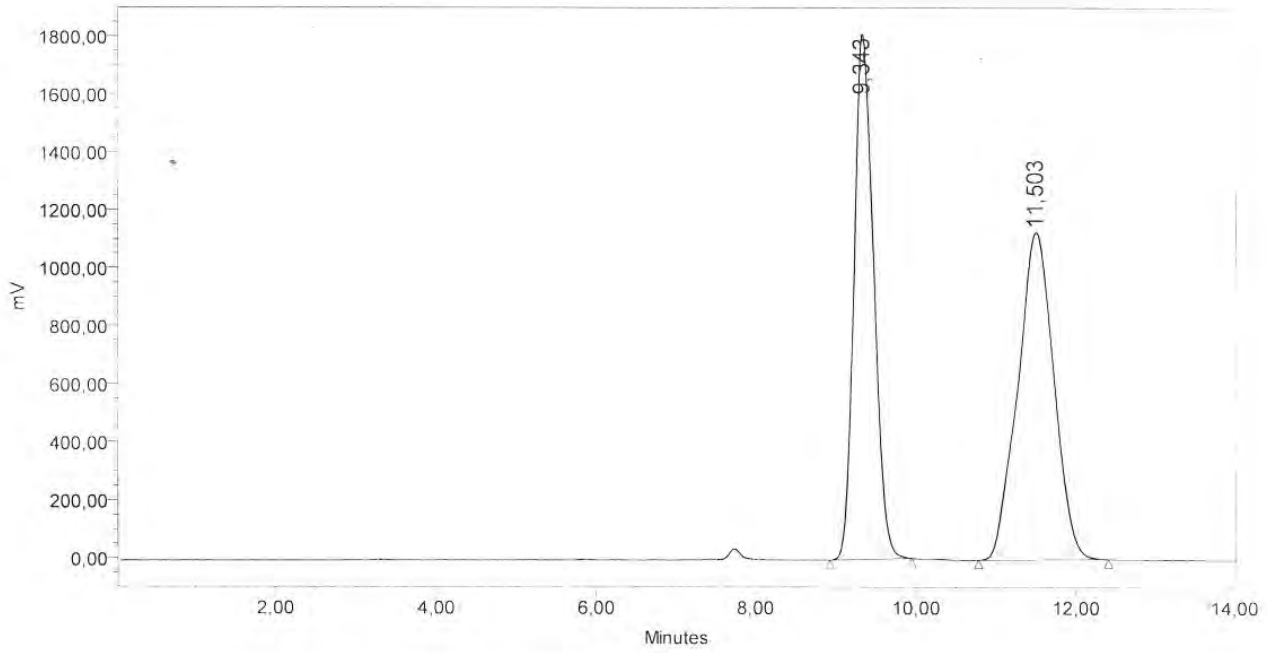


^{1}H-NMR-spectrumof the amide **16a** in $CDCl_3$ (400 MHz).

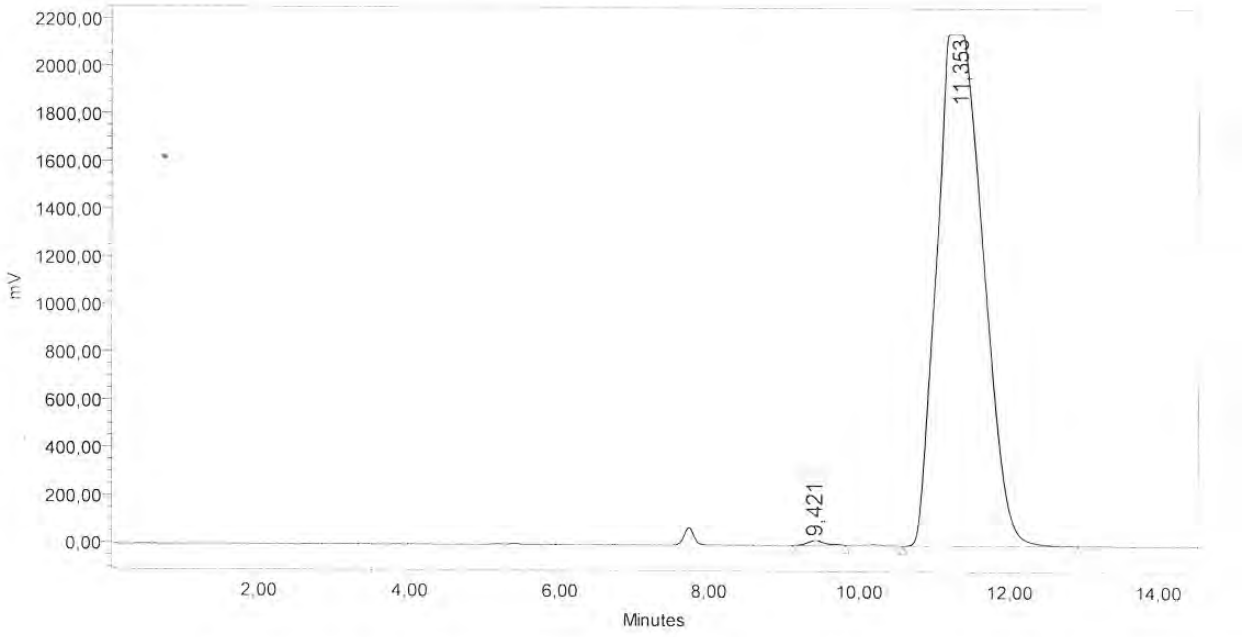


^{13}C-NMR-spectrumof the amide **16a** in $CDCl_3$ (100 MHz).

HPLC-chromatograms of the racemate and enantioenriched amide **16a** (separation conditions: column Chiralpak AI from Daicel Industries, flow 1 ml/min, eluent EtOH/*n*Hex 1:9, detected at wave length 220 nm):

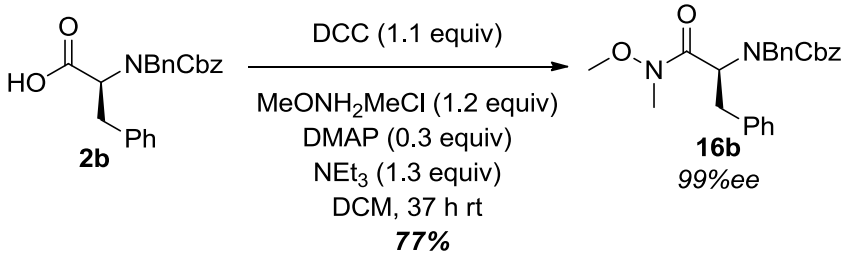


	RT	Area	% Area	Height
1	9,343	30592771	46,28	1818788
2	11,503	35512081	53,72	1127387



	RT	Area	% Area	Height
1	9,421	337218	0,37	20876
2	11,353	91660487	99,63	2150123

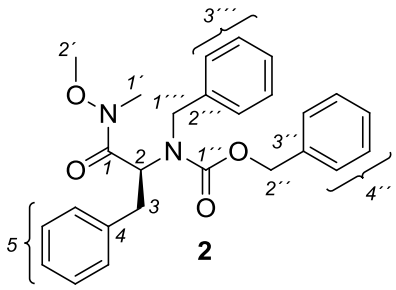
2.2.6 Synthesis of *S*-*N*-Methyl-*N*-methoxy-2-(benzyl-(benzyloxycarbonyl)-amino)-3-phenyl propanoic amide (16b)



The carboxylic acid **2b** (5.363 g+8.424 g = 13.787 g, containing 10 mol% of residual BnOH, 35.41 mmol, 1.0 equiv) was dissolved in DCM (90 mL reagent grade, non-dry, **2b** = 0.4 mol/l) and cooled in an ice bath. NEt_3 (6.4 mL, 46.0 mmol, 1.3 equiv), $MeONH_2MeCl$ (4.14 g, 42.5 mmol, 1.2 equiv) and DMAP (1.30 g, 10.62 mmol, 0.3 equiv) were added successively. After stirring for 5 min, DCC (8.02 g, 39.0 mmol, 1.1 equiv) was added in one portion. Subsequently, the mixture was stirred at 0 °C for 15 min, the cooling bath was removed and the mixture was allowed to stir at ambient temperature for 37 h.

DCM was evaporated *in vacuo*, the residue (colorless solid) was suspended in 1 N HCl solution (aq., 40 mL) and Et_2O (40 mL, 1 mL H_2O/1 mmol) and stirred for 5 min at room temperature to hydrolyse excess DCC. The precipitated urea was separated by filtration through a sintered funnel.The filter cake was washed with two 20 mL portions of Et_2O. From the collected filtrates (H_2O/Et_2O 1:2) the

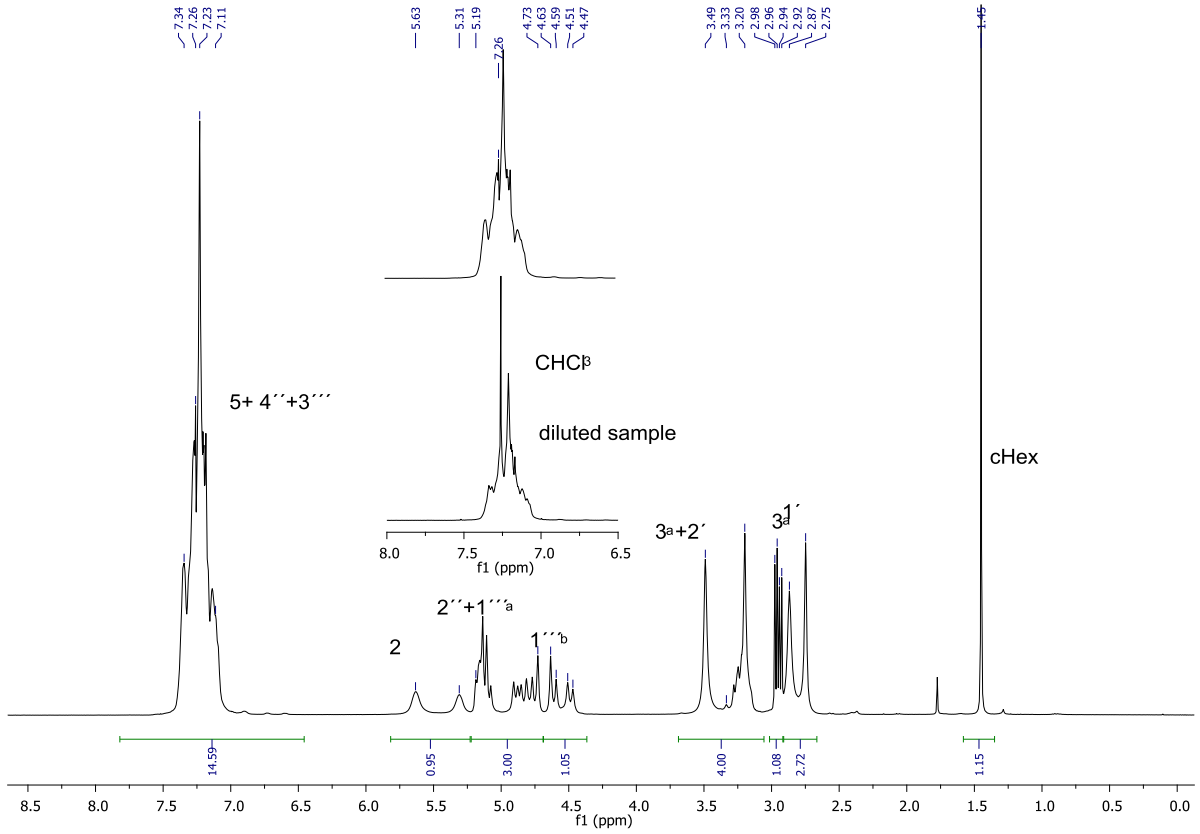
organic phase was separated, washed with 1 N HCl solution (aq.), saturated $NaHCO_3$ solution (aq.) and brine (40 mL each). After drying over $MgSO_4$, concentration under reduced pressure and drying in high vacuum for 2 h at 40 °C under stirring, the crude amide **16b** (14.723 g, 96%) was isolated as a pale yellow oil.[28] The crude product was dissolved in 15 mL EtOAc/*n*Hex 2:7 and purified with flash chromatography on silica (210 g, 14:1 SiO_2/crude **16b**) with EtOAc/*n*Hex 2:7. After dissolution of the amide **16b** in 15 mL *c*Hex and concentration under reduced pressure to remove EtOAc (x2) and drying in high vacuum at 40 °C under stirring for 14 h, the amide **16b** (11.798 g, 27.28 mmol, 77%) was obtained as a colorless oil in an *ee* of 99% according to HPLC.



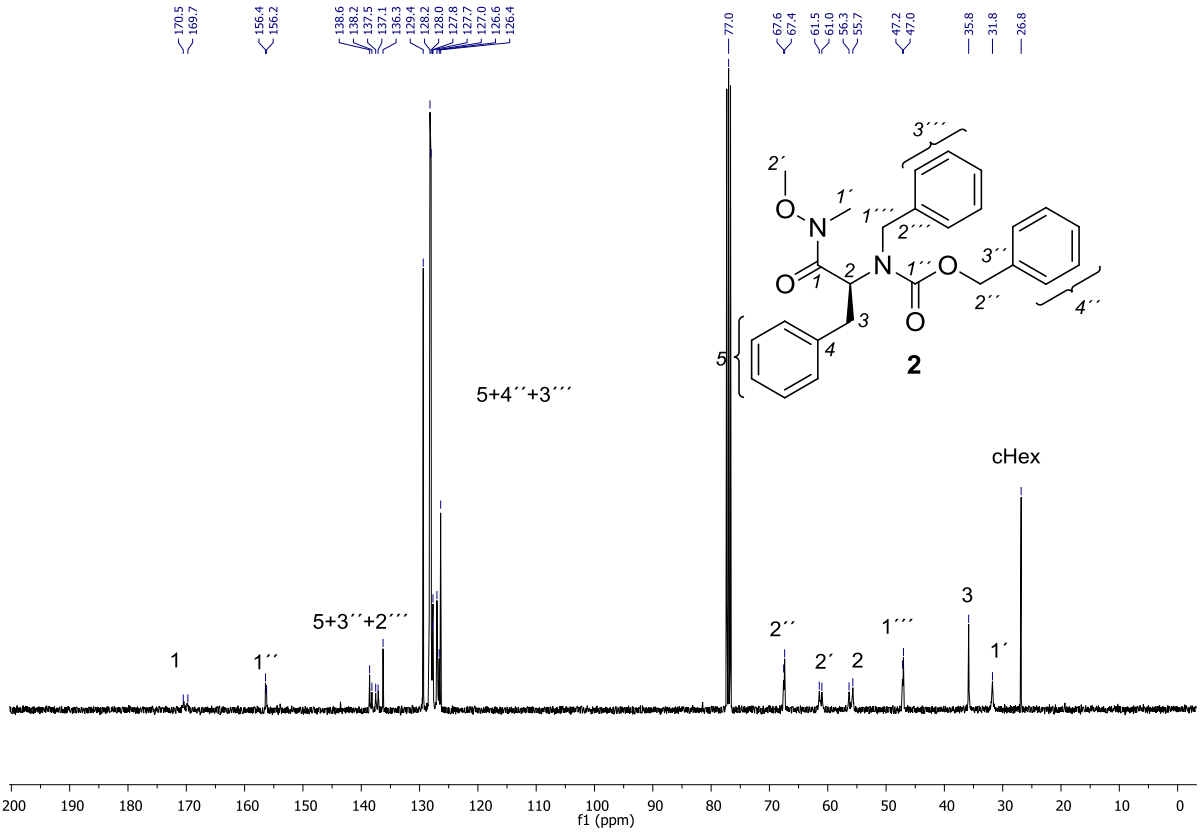
2

M ($C_{26}H_{28}N_2O_4$) = 432.512 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex) = 0.43 (1:3), 0.29 (2:7), 0.24 (1:4); **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 7.34-7.11 (m, 15H, H-5, H-4´´, H-3´´), 5.63/5.31 (2xs, 1H, H-2), 5.19-4.73 (m, 3H, H-2´´, H-1´´´$_a$), 4.61/4.49 (2xd, 1H, H-2´´´$_b$, *J* = 16.3/15.3 Hz) 3.49-3.20 (m, 4H, H-3$_a$, H-2´), 2.95 (dd, 1H, H-3$_b$, *J* = 13.7, 7.0 Hz), 2.87/2.75 (2xd, 3H, H-1´); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 170.5/169.7 (C-1), 156.4/156.2 (C-1´´), 138.6/138.2/137.5/137.1/136.3 (C-4, C-3´´, C-4´´´), 129.4/128.2/128.0/ 127.8/127.7/127.0/126.6/126.4 (C-5, C-4´´, C-3´´´), 67.6/67.4 (C-2´´), 61.5/61.0 (C-2´), 56.4/55.7 (C-2), 47.2/47.0 (C-2´´´), 35.8 (C-3), 31.8 (C-1´); **IR** (film) ν cm^{-1} =3087 (w), 3063 (m), 3030 (s), 3005 (w), 2958 (m), 2937 (s), 2819 (w), 1954 (w), 1882 (w), 1810 (w), 1700 (vs), 1667 (vs), 1604 (w), 1585 (w), 1496 (m), 1453 (s), 1409 (s), 1388 (w), 1368 (w), 1305 (m), 1251 (s), 1209 (w), 1178 (w), 1113 (m), 1074 (w), 1029 (w), 995 (m), 943 (w), 913 (w), 861 (w), 742 (s), 698 (vs), 636 (w), 595 (w), 568 (w), 551 (w), 534 (w), 487 (w); **HR-MS** (ESI, $C_{26}H_{29}N_2O_4^+$) found 433.2147 u calc. 433.2127 u;(ESI, $C_{26}H_{28}N_2O_4Na^+$) found 455.1955 u calc. 455.1947 u; α_D (c = 1.112 g/100 mL, $CHCl_3$, T = 20.5 C) = -52.5.

28 The crude product contained ca 10% of an impurity according to ^{1}H-NMR (most probably *N,N*-Bn,Cbz-Phe-OBn resulting from the condensation of the starting material **16b** with residual BnOH).

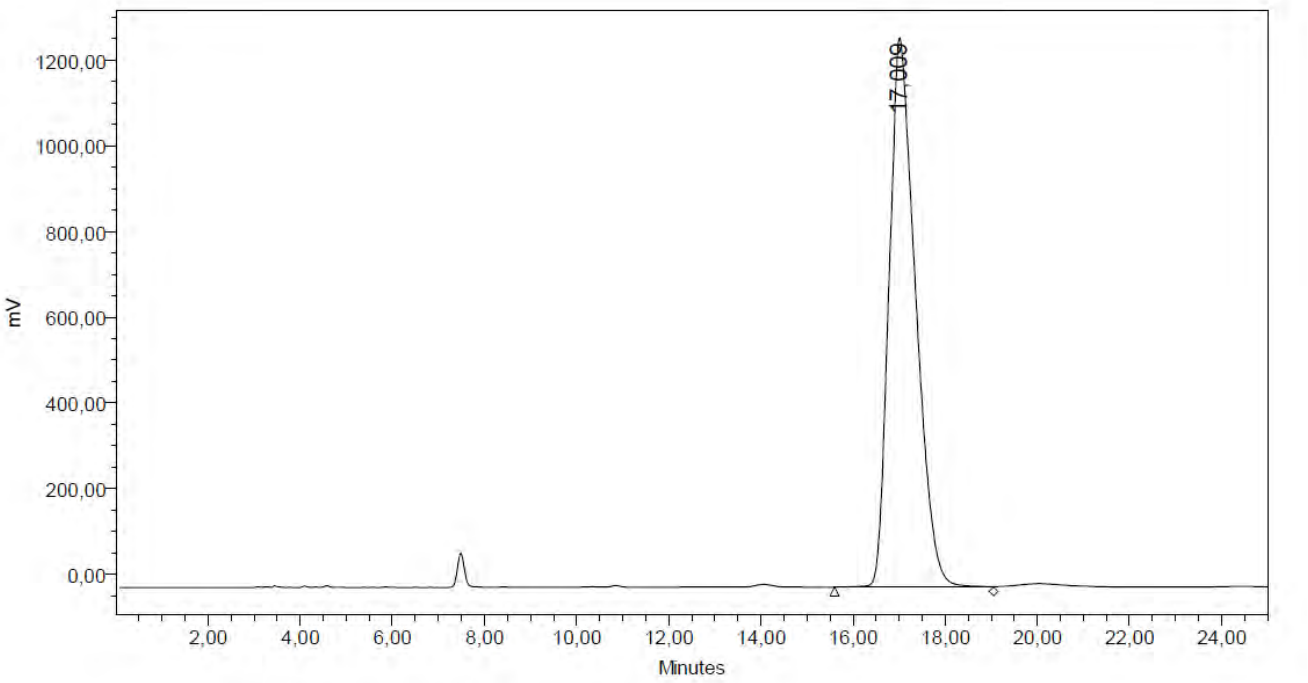


^{1}H-NMR-spectrumof the amide **16b** in $CDCl_3$ (400 MHz).



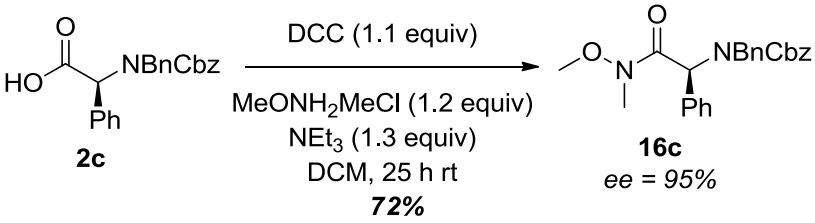
^{13}C-NMR-spectrumof the amide **16b** in $CDCl_3$ (100 MHz).

HPLC-chromatograms of the enantioenriched amide **16b** under the same conditions as for amides **16a+c** (separation conditions: column Chiralpak AI from Daicel Industries, flow 1 ml/min, eluent EtOH/*n*Hex 1:9, detected at wave length 220 nm):



	RT	Area	% Area	Height
1	17,009	51062410	100,00	1281825

2.2.7 Synthesis of *S*-*N*-Methyl-*N*-methoxy-2-(benzyl-(benzyloxycarbonyl)-amino)-2-phenyl ethanoic amide (16c)



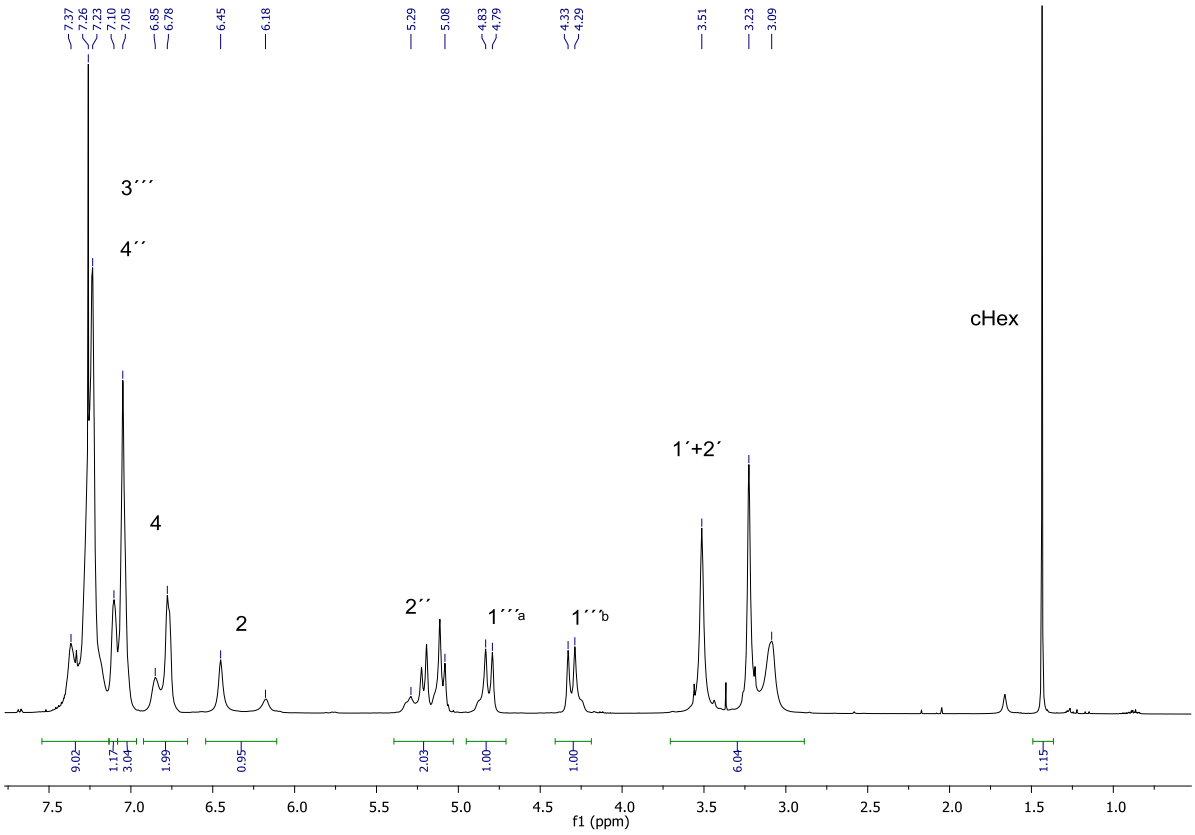
The carboxylic acid **2c** (20.64 g, 54.98 mmol, 1.0 equiv, containing less than 10% of BnOH and 8% of EtOAc) was dissolved in 140 mL DCM (reagent grade, non-dry, **2c** = 0.4 mol/l). Successively, NMM (7.9 mL, 71.5 mmol, 1.3 equiv) and $MeONH_2MeCl$ (6.44 g, 66.0 mmol, 1.2 equiv). After stirring for 5 min, the reaction suspension was cooled in an ice bath and DCC (12.46 g, 60.5 mmol, 1.1 equiv) was added in one portion. Subsequently, the mixture was stirred at 0 °C for 45 min, the cooling bath was removed and the mixture allowed to stir at ambient temperature for 25 h.

DCM was evaporated *in vacuo*, the residue (colorless solid) was up taken in 1 N HCl solution (60 mL, aq.) and Et_2O (60 mL, 1 mL H_2O/1 mmol) and stirred for 5 min at room temperature to hydrolyse excess DCC. The mixture was passed through a sintered funnel and the collected precipitated (urea) was rinsed with Et_2O (2x30 mL). From the combined filtrates (H_2O/Et_2O 1:2) the organic phase was separated, washed with 1 N HCl solution (aq., 60 mL), saturated $NaHCO_3$ solution (aq., 60 mL) and brine (60 mL). After drying over $MgSO_4$ and concentration under reduced pressure, the crude amide **16c** (23.25 g, 101%)[29] was isolated as a yellow oil. The crude product was dissolved in EtOAc/*c*Hex 4:9 (15 mL) and purified with flash chromatography on silica (170 g, 7:1 SiO_2/crude **16c**) with EtOAc/*n*Hex 2:5 → 4:9. After dissolution of the amide **16c** in *c*Hex (20 mL) and concentration under reduced pressure to remove EtOAc (x2) and drying in high vacuum at 40 °C under stirring for 2 h, the amide **16c** (16.594 g) was obtained as a colorless oil in an *ee* of 95% according to HPLC. Accounting 4mol% of residual *c*Hex the enentioenriched product was isolated in a yield of 72% (39.33 mmol).[30]

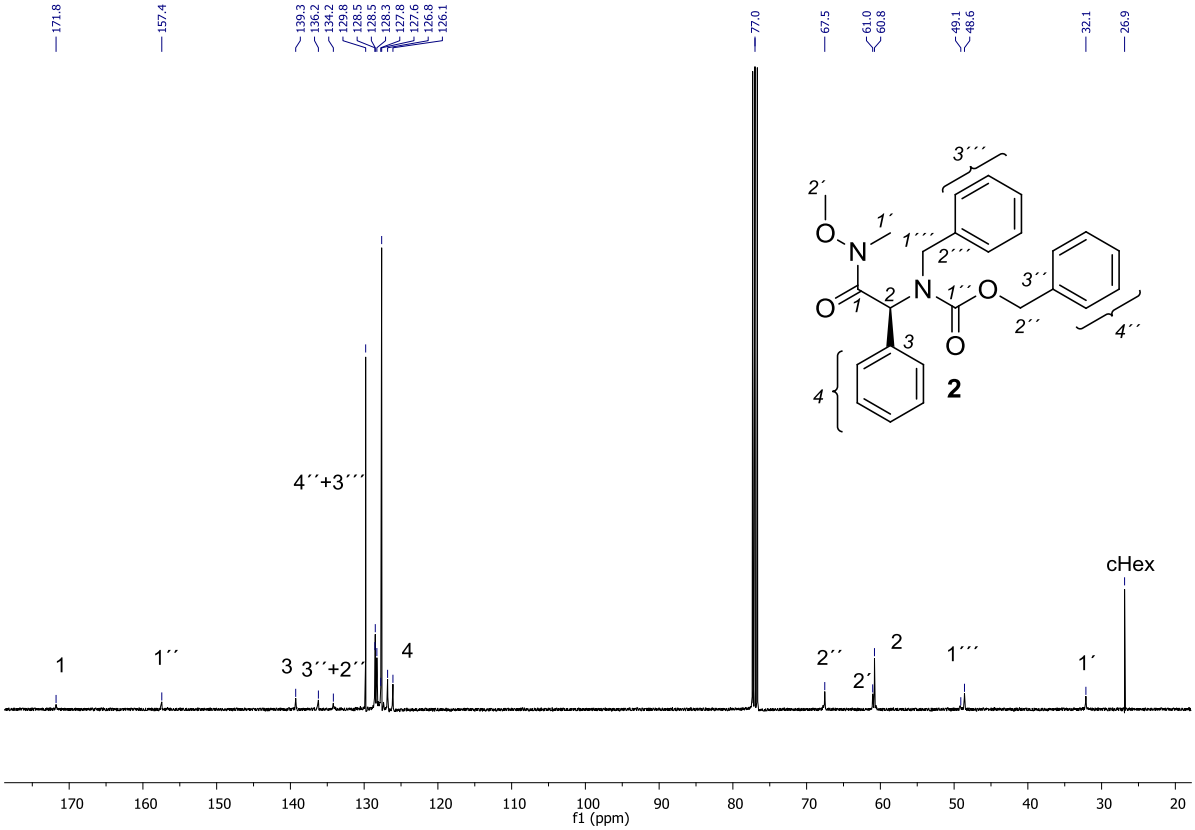
M ($C_{25}H_{26}N_2O_4$) = 418.485 g/mol;**r_f** (SiO_2, EtOAc/*n*Hex) = 0.76 (1:1), 0.34 (1:2), 0.28 (4:9), 0.24 (2:5); **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ ppm =7.37-7.23 (m, 9H, H-4´´, H-3´´´), 7.10 (s, 1H, H-4´´or H-3´´´), 7.05 (s, 3H, H-4), 6.85/6.78 (2xs, 2H, H-4), 6.45/6.18 (2xs, 1H, H-2), 5.29-5.08 (m, 2H, H-2´´), 4.81 (d, 1H, H-1´´´$_a$, *J* = 16.6 Hz), 4.31 (d, 1H, H-1´´´$_a$, *J* = 16.4 Hz), 3.51/3.23/3.09 (3xs, 6H, H-1´, H-2´); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 171.8 (C-1), 157.4 (C-1´´), 139.3 (C-3), 2x136.2 (C-3´´, C-2´´´), 129.8/ 2x128.5/128.3/127.8 (C-4´´, C-3´´´), 127.6/126.8/126.1 (C-4), 67.5 (C-2´´), 61.0 (C-2´), 60.8 (C-2), 49.1/48.6 (C-1´´´), 32.1 (C-1´); **IR** (film) ν cm^{-1} = 3088 (w), 3063 (w), 3031 (w), 3005 (w), 2969 (w), 2939 (w), 2899 (w), 1954 (w), 1883 (w), 1807 (w), 1699 (vs), 1670 (vs), 1605 (w), 1585 (w), 1496 (w), 1454 (m), 1404 (s), 1365 (w), 1282 (m), 1255 (s), 1210 (m), 1175 (w), 1111 (m), 1075 (w), 1029 (w), 999 (m), 957 (w), 936 (w), 915 (w), 843 (w), 768 (m), 736 (m), 697 (vs), 643 (w), 626 (w), 611 (w), 559 (w); **GC-MS** (EI, 70 eV): m/z (%) = 358 (5), 330 (5), 286 (10), 240 (10), 194 (10), 179 (10), 132 (15), 118 (10), 91 (100, Bn^+), 77 (10, Ph^+), 65 (15, Cp^+), 51 (5); **HR-MS** (ESI, $C_{25}H_{27}N_2O_4^+$) found 419.1966 u calc. 419.1971 u, ESI, $C_{25}H_{26}N_2O_4Na^+$) found 441.1788 u calc. 441.1790 u; **α_D** (c = 1.624 g/100 mL, $CHCl_3$, T = 20.0 °C, *ee*> 95%) = +120.5.

29 The major impurities in crude **16c** are 43% Et_2O, traces of urea and 3mol% of presumably *N,N*.-Bn,Cbz phenyl glycine Weinreb amide.

30 In a 5 mmol scale we achieved a yield of 81% under exactly the same conditions.

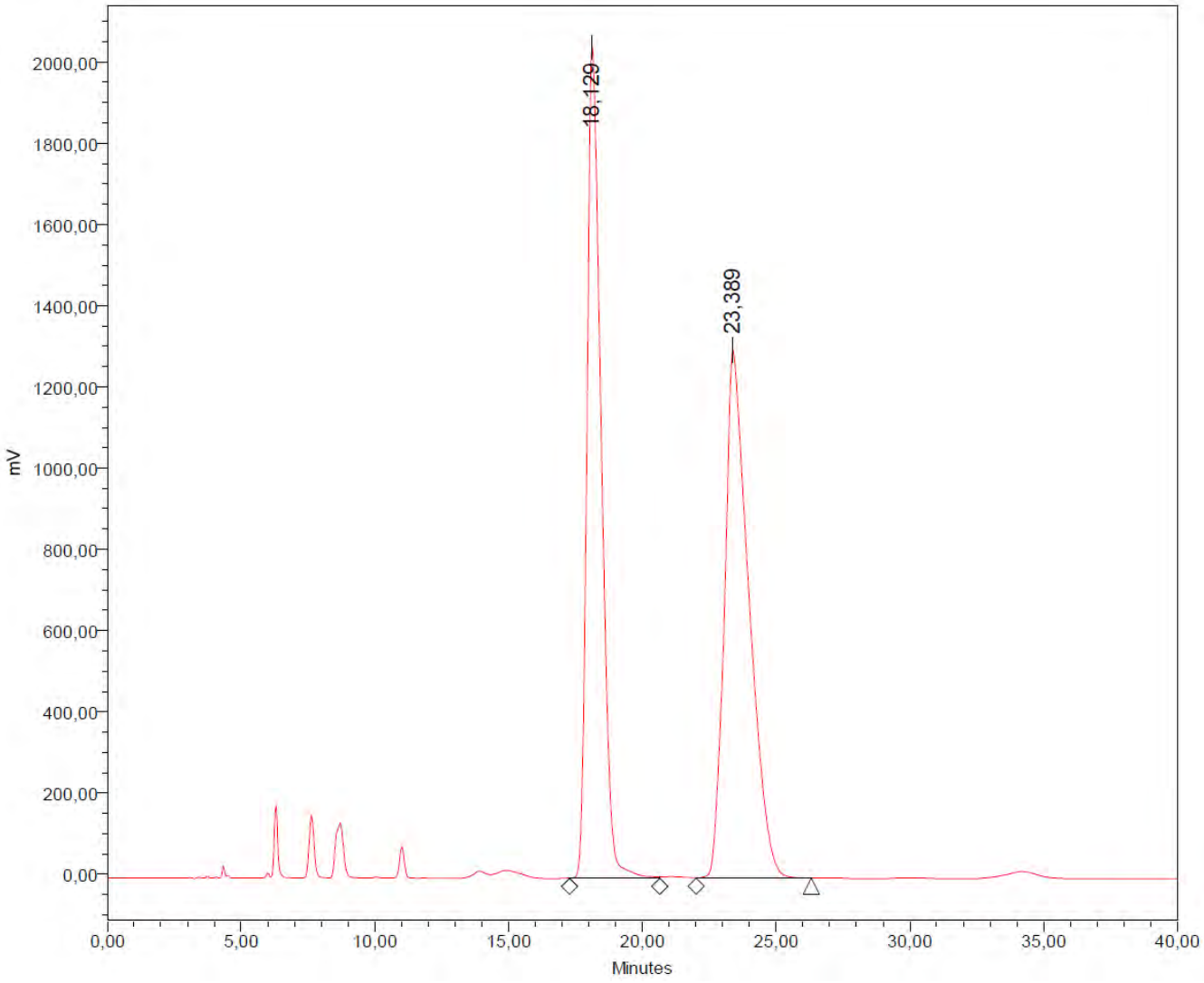


^{1}H-NMR-spectrumof the amide **16c** in $CDCl_3$ (400 MHz).



^{13}C-NMR-spectrumof the amide **16c** in $CDCl_3$ (100 MHz).

HPLC-chromatograms of the racemic and enantioenriched amide **16c** (separation conditions: column Chiralpak AI from Daicel Industries, flow 1 ml/min, eluent EtOH/*n*Hex 1:9, detected at wave length 220 nm):



Retention Time (min)	Area	% Area
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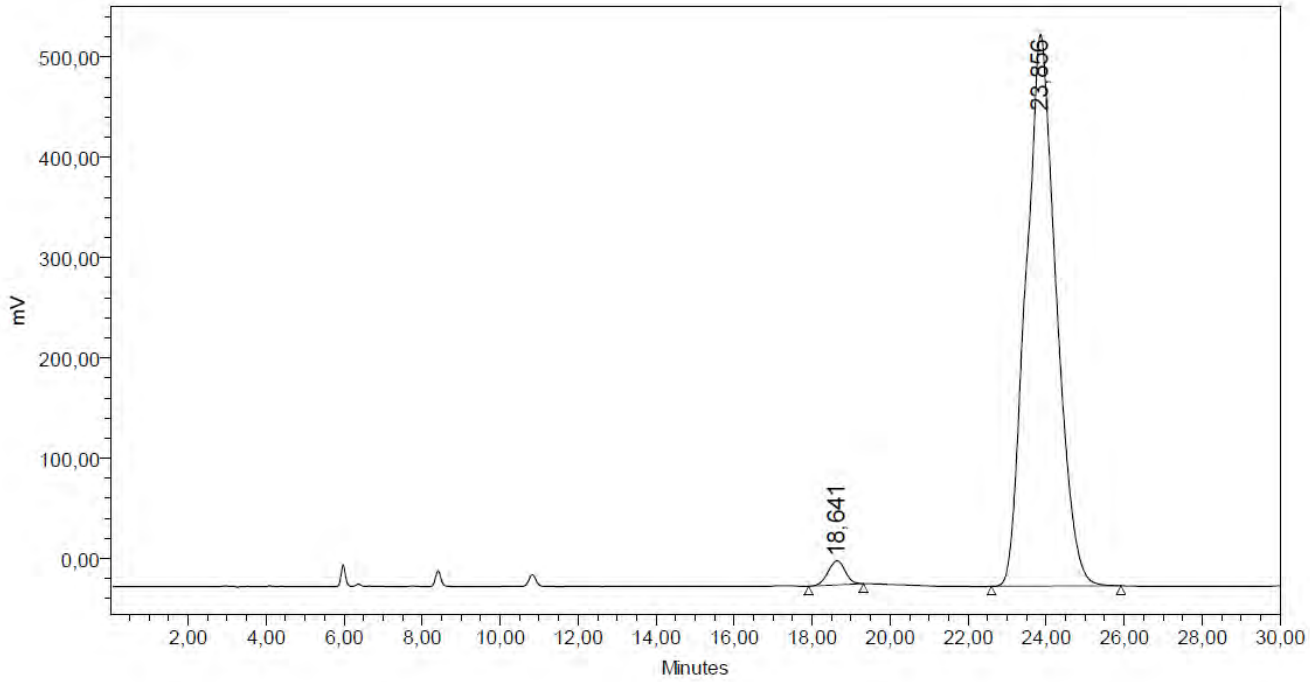
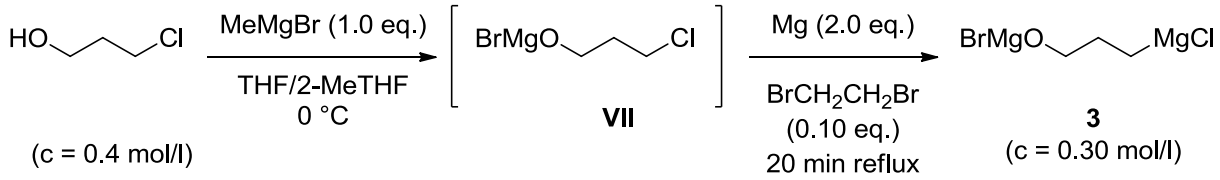
23,389	82530591	52,20



	RT	Area	% Area	Height
1	18,641	726333	2,39	23904
2	23,856	29702126	97,61	550385

2.2.8 Synthesis the 3-Chloropropanol derived Grignard reagent3



Under an atmosphereof argon (balloon) a flame dried 250 mL three necked flask equipped with reflux condenser and a rubber septum was charged with dry THF (64 mL) and 3-chloro propanol (2.5 mL, 30.0 mmol, 1.0 equiv) and cooled to 0 °C. Then a commercial, dark brown 2.75 N MeMgBr solution in 2-MeTHF (11.5 mL, 31.6 mmol, 1.05 equiv) was added dropwise over 5 min (CH_4-evolution, **VII** = 0.4 mol/L). An excess of MeMgBr was indicated by a color change from colorless to pale yellow at the end of the MeMgBr addition. The cooling bath was removed and the reaction solution was allowed to warm to ambient temperature (over 5 min). Furthermore Mg (1.96 g, 60.6 mmol, 2.0 equiv) and 1,2-dibromoethane (0.26 mL, 3.0 mmol, 0.1 equiv) were added and the mixture was allowed to stir 15 min at ambient temperature. During this time an oil bath was preheated to 90 °C.

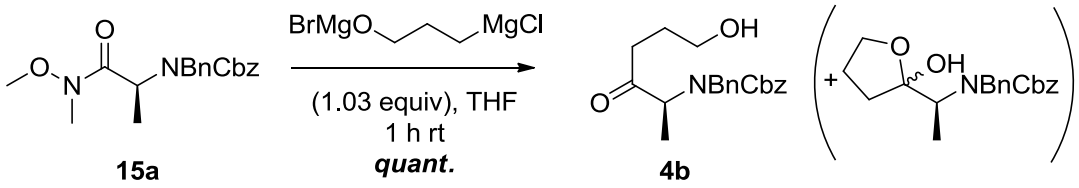
Subsequently, the mixture was heated in an oil bath (90 °C), until it started to reflux, then the mixture was allowed to stir at ambient temperature, whereby it continued to reflux due to the exothermic *Grignard*-formation for 5 min. Titration in the following showed a concentration of 0.23 mol/L

of **3**. After heating to reflux for 15 min the concentration of the resulting dark grey *Grignard*-solution increased to 0.30 mol/L. The freshly prepared reagent **3** was used further within 1 d after preparation.

Large Scale Preparation: Under an atmosphere of argon (balloon) 3-chloro propanol (14.2 mL, 217 mmol, 1.0 equiv) was dissolved in dry THF (530 mL) in a flame dried three necked 1 L flask equipped with a reflux condenser, a dropping funnel with pressure balance and a volumetric scale and a rubber septum and cooled in an ice bath.[31]Subsequently, a commercial, dark brown 3.2 N solution of MeMgBr in 2-MeTHF (72 mL, 228 mmol, 1.05 equiv,*Sigma-Aldrich*) was transferred through a cannula to the dropping funnel und a positive pressure of argon and added dropwise to the reaction solution under CH_4 evolution (over 20 min).[32] An excess of MeMgBr was indicated through a color change from colorless to pale yellow at the end of the addition. Then the ice bath was removed and the mixture was allowed to stir for further 15 min at ambient temperature.

Next, Mg (10.6 g, 434 mmol, 2.0 equiv) and 1,2-dibromoethane (1.9 mL, 21.7 mmol, 0.1 equiv) were added to the reaction solution and the mixture was stirred for 50 min at ambient temperature (during this time an oil bath was preheated to 90 °C). After 20 min of stirring the mixture started to reflux due to the exothermic *Grignard*-reagent formation for 10 min, Titration after 50 min of stirring at ambient temperature showed a concentration of 0.21 mol/L. Subsequently, the mixture was heated to reflux for 15 min. A final titration indicated a concentration of the dark grey *Grignard* solution of 0.22 mol/l.

2.2.9 Synthesis of *S*-2-(Benzyl-(benzyloxycarbonyl)amino)-6-hydroxy-3-hexanone (4a)



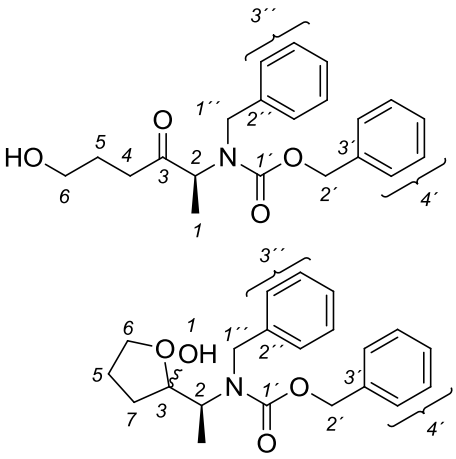
15a **4b**

Under an atmosphere of argon the Weinrebamide **15a** (45.61 g, 127.8 mmol, 1.0 equiv) was dissolved in dry THF (70 mL, **15a** = 2 mol/l) in a one necked 2 L flask and cooled in an ice bath. Under a positive argon pressure a freshly prepared 0.22 N solution of ClMg*n*PrOMgBr (600 mL, 1.02 equiv, 130.2 mmol) was transferred slowly through a cannula to the stirred solution of **15a** (within 1 h). Thereafter the cooling bath was removed and the reaction solution was stirred for 1 h at ambient temperature.

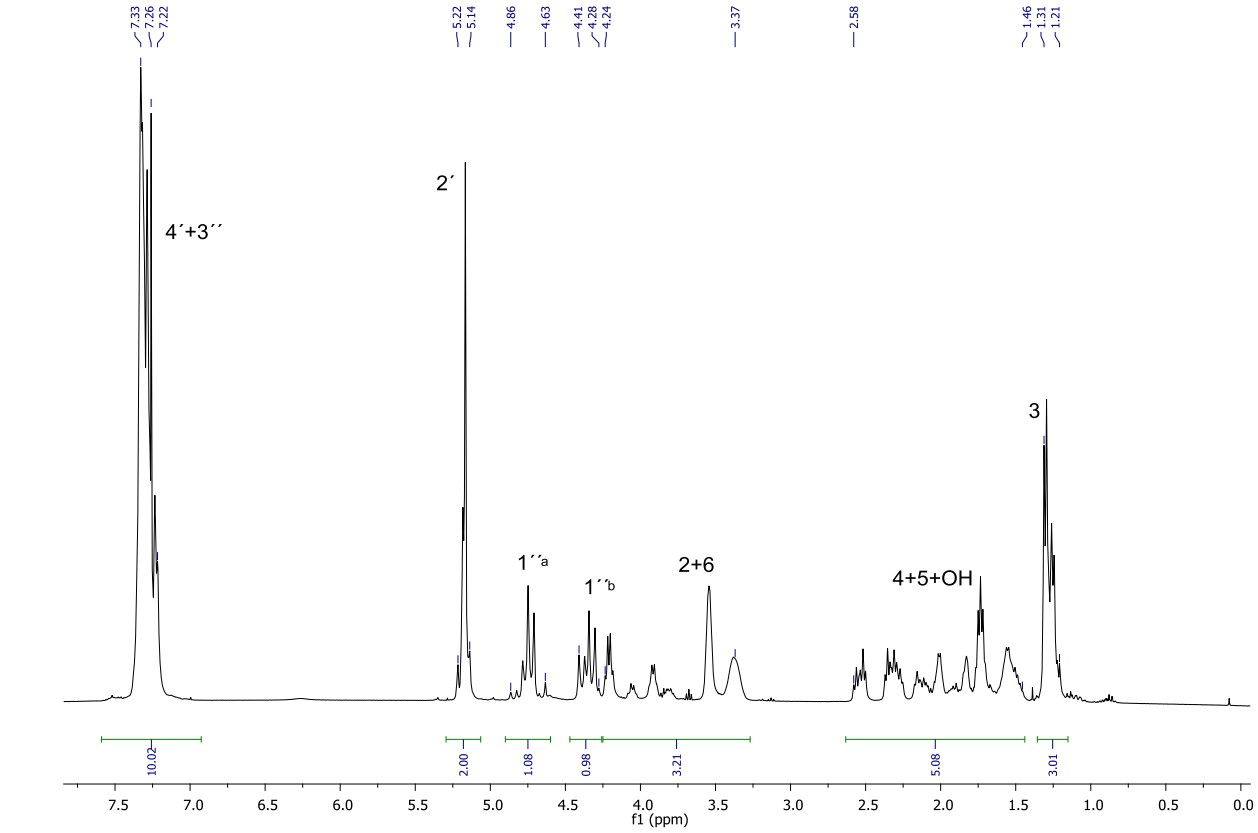
31 In order to determine the amount of THF, the whole apparatus (equipped with an argon balloon) was weight. Then dry THF was transferred through cannula to the reaction vessel under positive argon pressure and the apparatus was weight again.

32 After 10 min CH_4-pressure was released through a cannula.

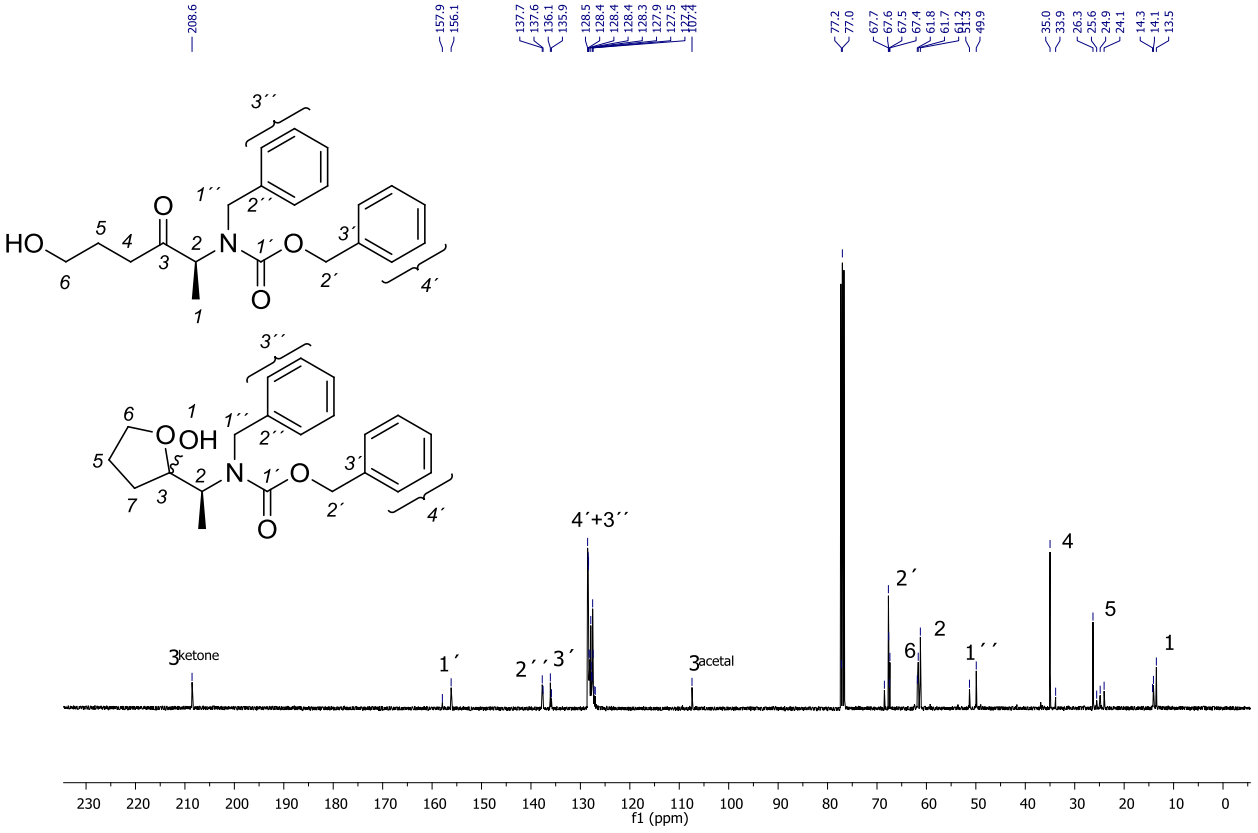
Then a mixture of saturated aq. NH_4Cl (260 mL, 1 mmol **4**/2 mL NH_4Cl (aq.)) and 6 N HCl solution in water (60 mL, pH of the mixture≤ 0, in a 2 L one necked flask) was cooled to 0 °C and the reaction mixture was poured at once into this mixture under stirring. After evaporation of THF/MeTHF under reduced pressure, the residue was diluted with water (80 mL, to dissolve precipitated solid) and 200 mL of Et_2O (H_2O/Et_2O, 2:1, pH of the mixture = 4). Subsequently, the phases were separated (in a 1 L extraction funnel), the organic phase was extracted with two further 200 mL portions of Et_2O, the collected Et_2O-phases were dried over $MgSO_4$ and concentrated under reduced pressure. After drying in high vacuum under stirring and heating to 40 °C for 2.5 h, 46.68 g (quant. yield) of the hydroxyketone **4a** were isolated as pale yellow oil and were further converted without any purification to the diol ***syn*-5a** in 85% yield over two steps.



M ($C_{21}H_{25}NO_4$) = 355.43 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex) = 0.35 (1:1), 0.27 (4:5); **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 7.33-7.22 (m, 10H, H-4´, H-3´´), 5.22-5.14 (m, 2H, H-2´), 4.86-4.63 (m, 1H, H-1´´$_a$), 4.41-4.28 (m, 1H, H-1´´$_b$), 4.24-3.37 (m, 3H, H-2, H-6), 2.58-1.46 (m, 5H, H-4, H-5, OH) 1.31-1.21 (m, 3H, H-1); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 208.6 (C-3$_{ketone}$), 157.9/156.2 (C-1´), 137.7/137.6 (C-2´´), 136.1/135.9 (C-3´), 128.5/3x128.4/128.3/128.1/127.9/127.8/127.8/127.7/127.5/127.4/127.2/127.0 (C-4´, C-3´´), 107.4 (C-3$_{acetal}$), 68.5/67.7/67.63/ 67.5/67.4 (C-2´), 61.9/61.7 (C-6), 61.2 (C-2), 51.3/49.9 (C-1´´), 35.0/33.9 (C-4), 26.3/25.6/ 24.9/24.0 (C-5), 14.3/14.1, 13.5 (C-1); **IR** (film) ν cm^{-1} = 3444 (br), 3111 (w), 3089 (w), 3064 (w), 3032 (w), 2983 (m), 2943 (m), 2883 (m), 1956 (w), 1883 (w), 1812 (w), 1722 (s), 1704 (s), 1694 (vs), 1682 (s), 1606 (w), 1586 (w), 1540 (w), 1496 (m), 1470 (m), 1463 (m), 1455 (s), 1437 (m), 1416 (m), 1367 (w), 1310 (w), 1293 (w), 1240 (m), 1186 (w), 1133 (w), 1051 (s), 1029 (m), 1002 (m), 911 (w), 861 (w), 821 (w), 770 (m), 736 (s), 699 (s), 616 (w), 589 (w), 492 (w), 457 (w); **HR-MS** (ESI, $C_{21}H_{25}NO_4Na^+$) calc. 378.1681 u, found 378.1705 u; α_D (c = 1.108 g/100 mL, $CHCl_3$, T = 21.5 °C) = -45.0.

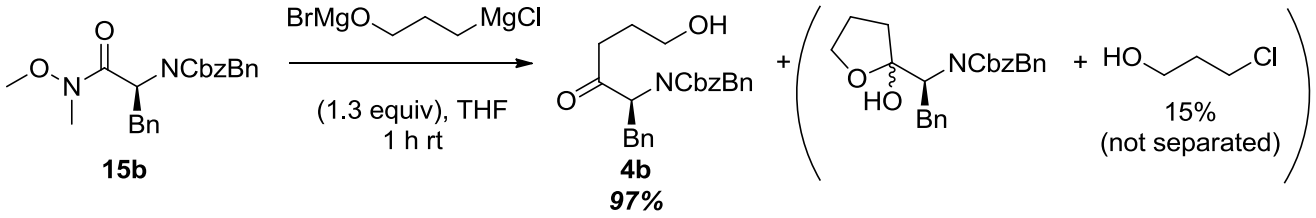


^{1}H-NMR-spectrumof the hydroxy ketone **4a** in $CDCl_3$ (400 MHz).



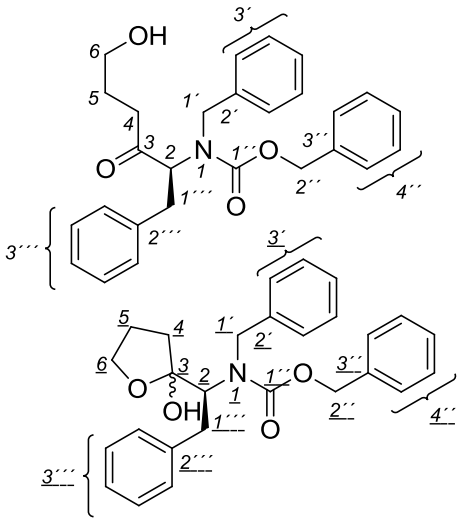
^{13}C-NMR-spectrumof the hydroxy ketone **4a** in $CDCl_3$ (100 MHz).

2.2.10 Synthesis of *S*-2-(Benzyl-(benzyloxycarbonyl)-amino)-6-hydroxy-1-phenyl-3-hexanone (4b)



Under an atmosphere of argon the amide **15b** (3.686 g, 8.52 mmol) was dissolved in dry THF (10 mL, **15b** = 1 mol/L) in a 250 mL flask equipped with a 100 mL dropping funnel with volumetric scale (only the dropping funnel was flame dried in prior) and cooled to 0 °C. Then a 0.24 N solution of ClMg*n*PrOMgBr in THF/MeTHF (46 mL, 11.1 mmol, 1.3 equiv), prepared like described above,were transferred through a cannula under a positive argon pressure to the dropping funnel andwas added dropwise within 10 min to the reaction solution. Then the ice bath was removed and the reaction solution was allowed to stir at room temperature for 1 h.[33]

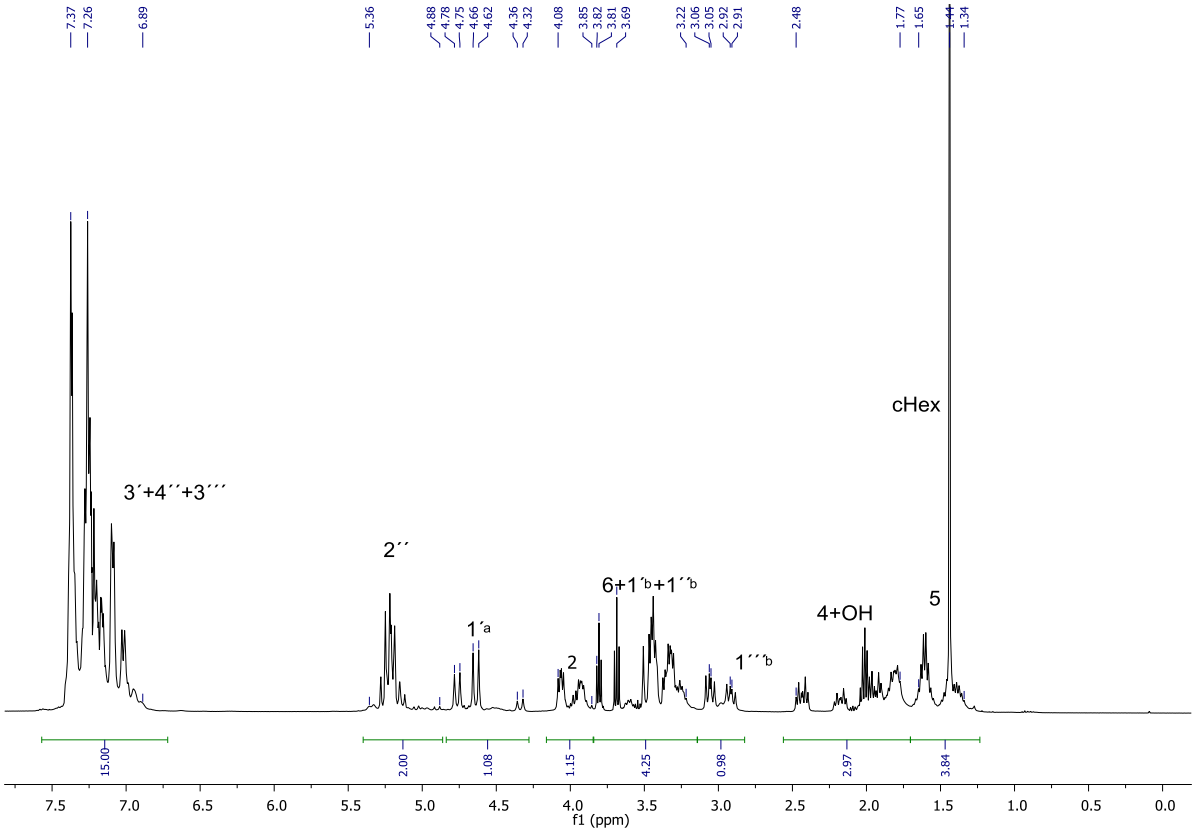
Next the reaction suspension was cooled in an ice bath again and a saturated, aqueous NH_4Cl-solution was added (30 mL, 2 mL NH_4Cl solution/1 mmol *Grignard* reagent). Then THF/MeTHF was evaporated under reduced pressure at the rotatory evaporator, water(10 mL, in order to dissolve precipitated NH_4Cl) and EtOAc (60 mL, pH = 10) were added, the organic phase was separated and washed with brine (30 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. After concentration of the product**4b** with two 5 mL portions of *c*Hex at the rotatory evaporator and drying in high vacuum (0.1 mbar) under stirring for 13 h, the ketone/hemiactale mixture **4b** was isolated as a colorless oil (3.705 g). As the mixture contained 1mol% of *c*Hex and 15mol% of 3-chloro propanol according to ^{1}H-NMR, the ketone**4b** was isolated in a yield of 97% (8.28 mmol).



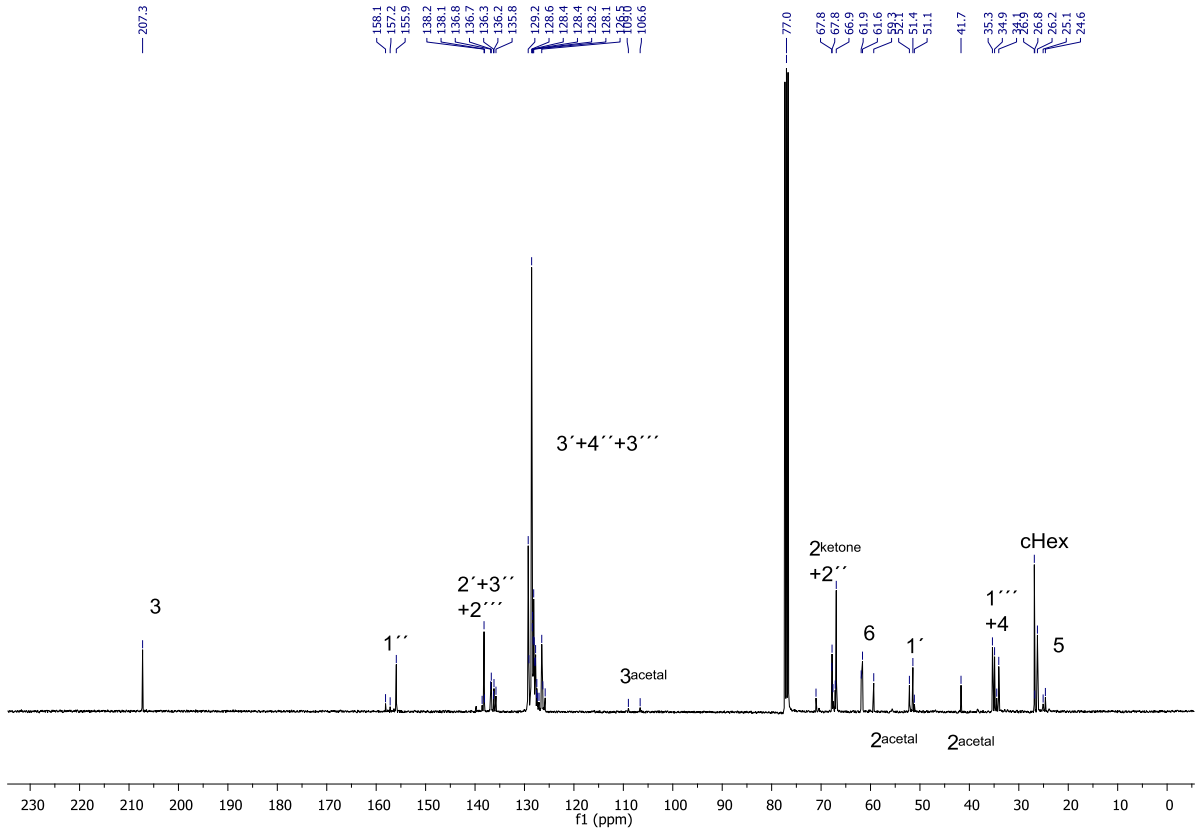
M ($C_{27}H_{29}NO_4$) = 431.524 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex) = 0.28 (4:5); **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 7.37-6.89 (m, 15H, H-3´, H-4´´, H-3´´´), 5.36-4.88 (m, 2H, H-2´´), 4.78-4.32 (m, 1H, H-1´$_a$; amongst 2xd at 4.77 (*J* = 14.7 Hz) and 4.64 (*J* = 15.5 Hz)), 4.08-3.85 (m, 1H, H-2), 3.82-3.22 (m, 4H, H-6, H-1´$_b$, H-1´´´$_a$; amongst 2xt at 3.81 (*J* = 5.9 Hz) and 3.69 (*J* = 6.3 Hz))3.06/2.92 (2xd, 1H, H-1´´´$_b$, *J* = 13.8, 9.4/14.0, 9.1 Hz), 2.48-1.77 (m, 3H, H-4, OH), 1.65-1.34 (m, 2H, H-5); ^{13}C-

33 Micro work up (ca. 0.1 mL of the reaction mixture) with aqueous saturated NH_4Cl-solution and EtOAc and TLC-control (EtOAc/*n*Hex 1:1) indicated full conversion.

NMR(100 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 207.2 (C-3_{ketone}), 158.1/157.2/155.9 (C-1´´), 138.6/138.2/138.1/136.8/136.7/136.23/136.2/135.8 (C-2´, C-3´´, C-2´´´), 129.3/129.1/128.6/2x128.4/128.2/128.1/128.0/127.9/2x127.8/127.6/127.5/127.3/127.1/126.5/126.3/125.8 (C-3´, C-4´´, C-3´´´), 109.0/106.6 (C-3_{acetal}), 71.0/2x67.8/67.6/67.1/66.9 (C-2_{ketone}, C-2´´), 61.9/61.6 (C-6), 59.4 (C-2_{acetal}), 52.1/51.4/51.1 (C-1´), 41.7 (C-2_{acetal}), 35.3/34.9/34.534.1 (C-4, C-1´´´), 26.8/26.2/25.1/24.6 (C-5); **IR** (film) ν cm^{-1} = 3451 (br), 3086 (w), 3063 (w), 3030 (m), 3003 (w), 2948 (m), 2882 (w), 1953 (w), 1882 (w), 1810 (w), 1697 (vs), 1604 (w), 1585 (w), 1496 (m), 1454 (s), 1426 (m), 1364 (w), 1311 (m), 1235 (s), 1177 (w), 1123 (m), 1061 (m), 1029 (m), 1002 (m), 968 (w), 912 (w), 849 (w), 822 (w), 748 (s), 699 (vs), 651 (w), 564 (w), 539 (w); **GC-MS** (EI, 70 eV) m/z % = 344 (20), 300 (25), 232 (5), 207 (5), 188 (20), 91 (100, Bn^+), 65 (10, Cp^+); **HR-MS** (ESI, $C_{27}H_{29}NO_4Na^+$) found 454.2007 u calc. 454.1994 u; α_D (c = 1.236 g/100 mL, $CHCl_3$, T = 22.5 °C) = -132.5.

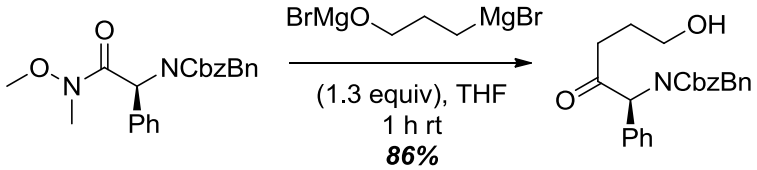


^{1}H-NMR-spectrum of the hydroxy ketone **4b** in $CDCl_3$ (400 MHz).



^{13}C-NMR-spectrum of the hydroxy ketone **4b** in $CDCl_3$ (100 MHz).

2.2.11 Synthesis of *S*-1-(Benzyl-(benzyloxycarbonyl)-amino)-5-hydroxy-1-phenyl-2-penatanone (15c)

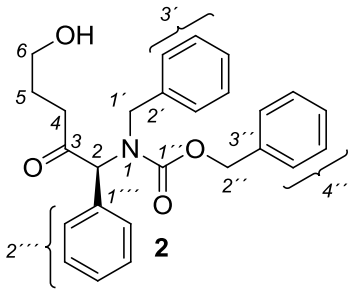


15c **4c**

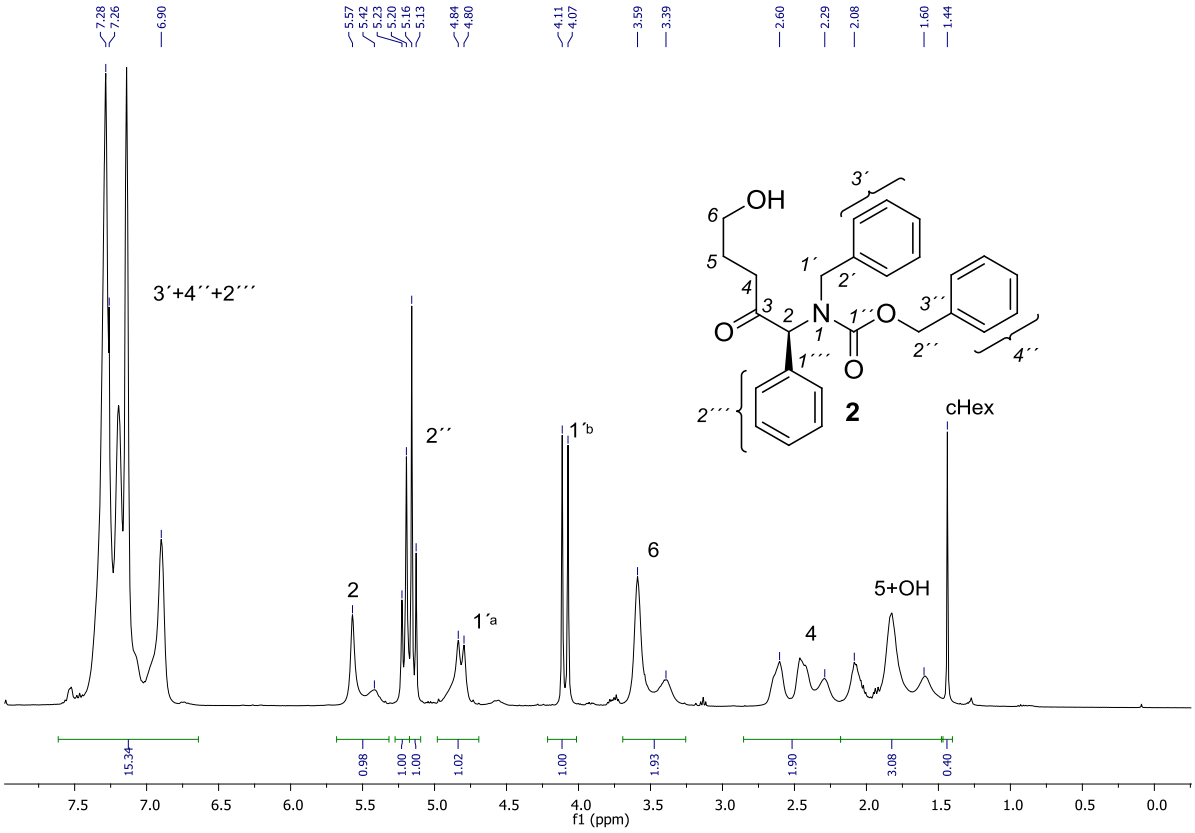
Under an atmosphere of argon the amide **15c** (11.61 g, 27.51 mmol taking 4mol% of residual *c*Hex into account, 1.0 equiv, *ee* = 95%) was dissolved in dry THF (28 mL; **15c** = 1.0 mol/l) in a 500 mL flask and a 0.22 N solution of ClMg*n*PrOMgBr in THF/MeTHF (160 mL, 39.75 mmol, 1.3 equiv) cooled to 0 °C within 1 h under stirring. After removing of the ice bath and stirring for 0.25 h at ambient temperature micro work of a small aliquot (ca. 100 μL) with aqueous 1 N HCl-solution and Et_2O indicated full conversion of the staring material **15c**. Saturated NH_4Cl solution (aq., 70 mL, 2 mL/1 mmol **15c**) and HOAc (10 mL, 1 mL/4 mmol **15c**) were added consecutively under cooling to 0 °C.

The THF/MeTHF were evaporated under reduced pressure (→ 300 mbar), the residue was diluted with 30 mL of H_2O (to dissolve precipitated NH_4OAc) and 60 mL of MTBE (H_2O/MTBE 3:2, pH = 6), the aqueous phase was separated and extracted with two further 60 mL portions of MTBE, the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to givethe crude

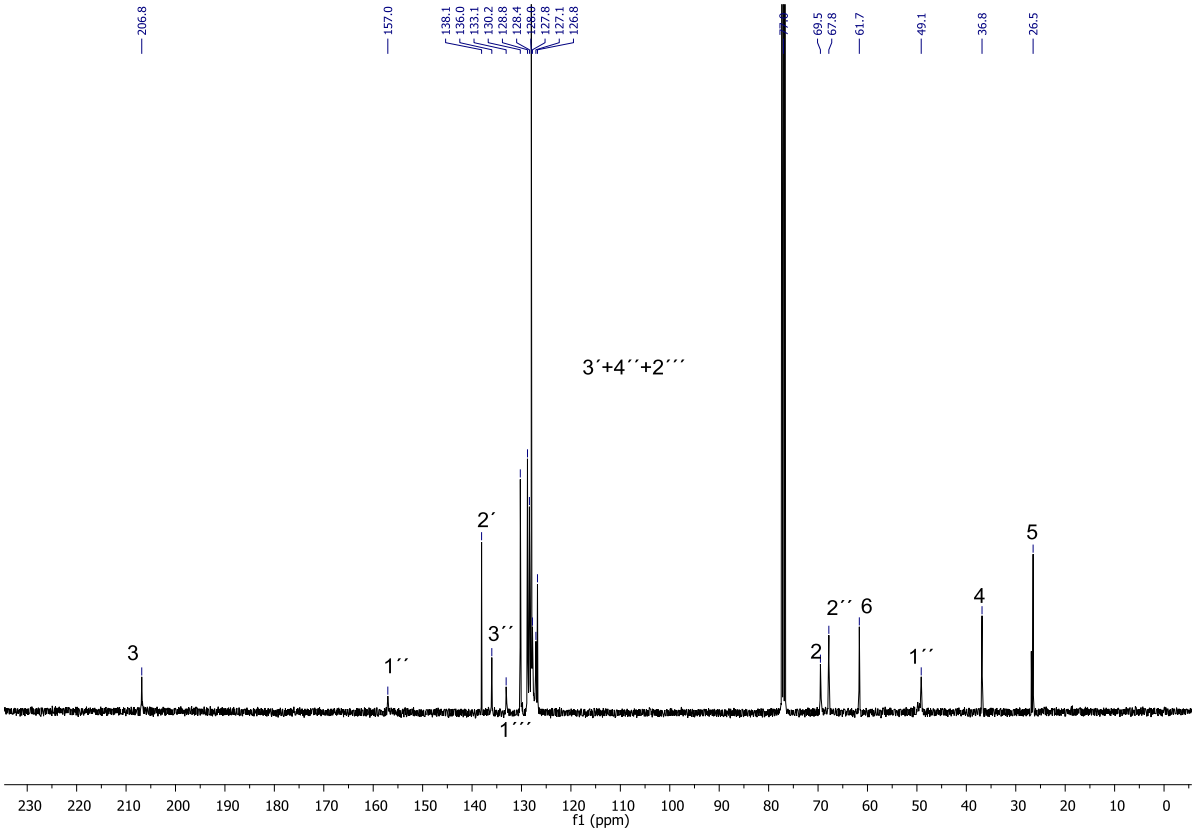
ketone **4c** as a pale yellow oil (12.52 g, 110%). The crude alcohol **4c** was dissolved in 10 mL EtOAc/*c*Hex 4:5 and subjected to column chromatographic purification on silica gel (130 g) with EtOAc/*n*Hex 4:5 as eluent system. After dissolution of the ketone **4c** in 5 mL *c*Hex and concentration under reduced pressure (x 2) to remove EtOAc and drying in high vacuum for 2.5 h under stirring, the product **4c** (10.26 g) was isolated as a pale yellow viscous oil. Taking 5mol% of residual *c*Hex and 14mol% of Cl*n*PrOH into account, the hydroxy ketone **4c** was obtained in a yield of 86% (23.6 mmol).



M ($C_{26}H_{27}NO_4$) = 417.497 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex) = 0.33 (4:5), 0.23 (2:3); **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 7.28-6.90 (m, 15H, H-3´, H-4´´, H-2´´´), 5.57/5.42 (2xs, H-2), 5.22 (d, 1H, H-2´´$_a$, *J* = 12.3 Hz), 5.15 (d, 1H, H-2´´$_b$, *J* = 12.3 Hz), 4.82 (d, 1H, H-1´$_a$, *J* = 15.6 Hz), 4.09 (d, 1H, H-1´$_b$, *J* = 16.0 Hz) 3.59-3.39 (m, 2H, H-6), 2.60-2.29 (m, 2H, H-4), 2.08-1.60 (m, 3H, H-5, OH); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 206.8 (C-3), 157.1 (C-1´´), 138.1 (C-2´), 136.0 (C-3´´), 133.1 (C-1´´´), 130.2/128.8/128.4/128.0/127.8/127.1/126.8 (C-3´, C-4´´, C-2´´´), 69.5 (C-2), 67.8 (C-2´´), 61.7 (C-6), 49.1 (C-1´), 36.8 (C-4), 26.5 (C-5); **IR** (film) ν cm^{-1} = 3445 (br), 3088 (w), 3063 (w), 3031 (m), 3007 (w), 2949 (m), 2884 (m), 2248 (w), 1956 (w), 1886 (w), 1811 (w), 1724 (s), 1694 (vs), 1605 (w), 1585 (w), 1541 (w), 1496 (m), 1454 (s), 1408 (s), 1364 (m), 1330 (w), 1254 (s), 1213 (m), 1179 (w), 1113 (m), 1056 (w), 1029 (w), 1003 (w), 974 (w), 951 (w), 913 (w), 845 (w), 822 (w), 737 (m), 699 (s), 641 (w), 612 (w), 590 (w), 564 (w); **HR-MS** (ESI, $C_{26}H_{27}NO_4Na^+$) found 440.1847 u calc. 440.1838 u; α_D (c = 0.996 g/100 mL, $CHCl_3$, T = 20.5 °C, *ee* = 90%) = +76.0.

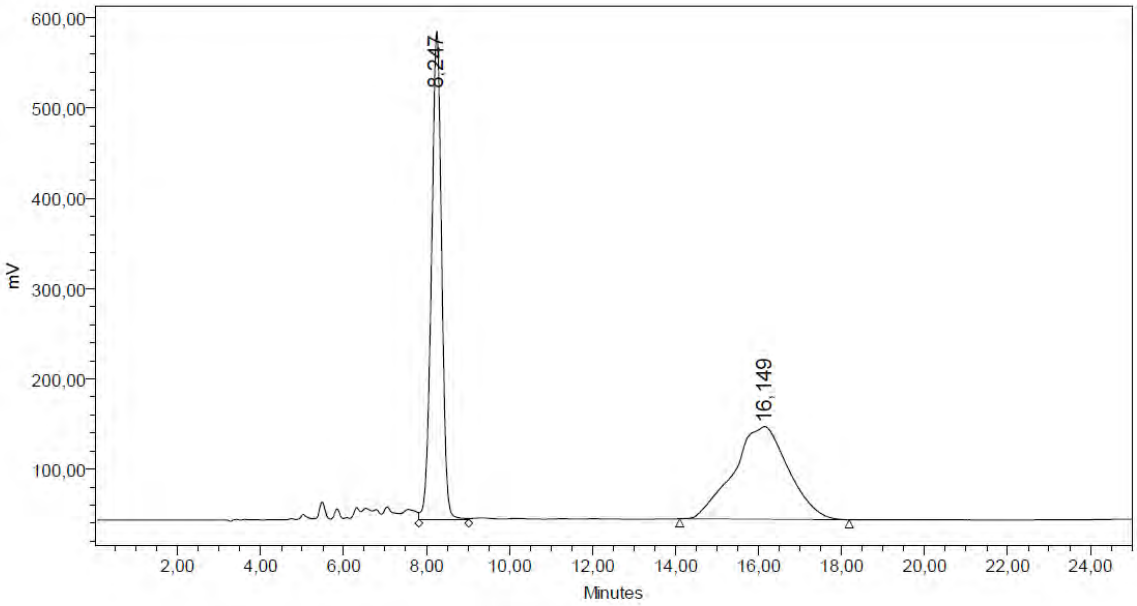


^{1}H-NMR-spectrum of the hydroxy ketone **4c** in $CDCl_3$ (400 MHz).

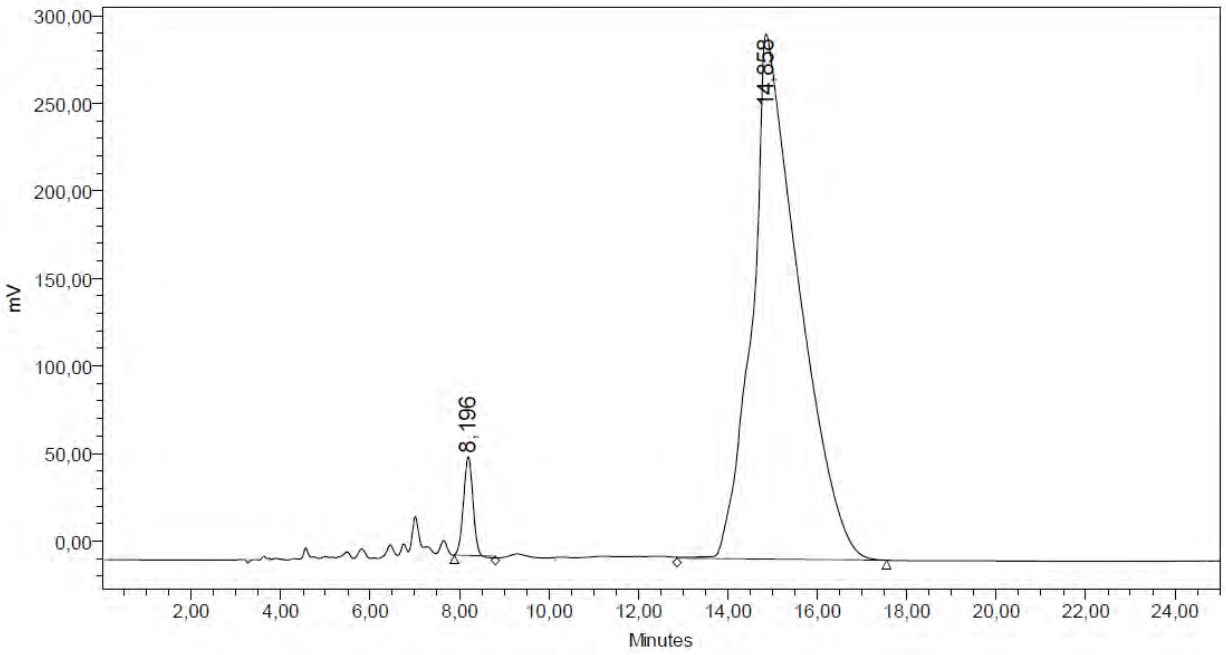


^{13}C-NMR-spectrum of the hydroxy ketone **4c** in $CDCl_3$ (100 MHz).

HPLC-chromatograms of the racemic and enantioenriched ketone**4c** (separation conditions: column *Chiralpak* AI from *Daicel Industries*, flow 1 ml/min, eluent EtOH/*n*Hex 1:3, detected at wave length 220 nm):



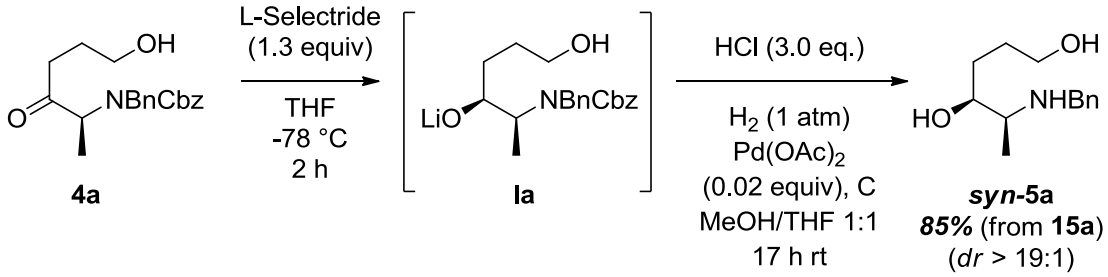
	RT	Area	% Area	Height
1	8,247	9210114	49,41	541370
2	16,149	9431633	50,59	102596



	RT	Area	% Area	Height
1	8,196	835658	3,68	56348
2	14,858	21859762	96,32	300082

2.3 Synthesis of *cis*-Configured Piperidinols 6 (Scheme 2)

2.3.1 Synthesis of (*2S,3S*)-2-(Benzylamino)-3,6-hexandiol (*syn*-5a)



Ketone **4a** (46.68 g, 127.8 mmol) was dissolved in dry THF (**4a** = 2 mol/L, 70 mL) under an atmosphere of argon in a 1 L one necked flask equipped with a dropping funnel with a volumetric scale (dried overnight in an oven at 120 °C) and cooled in a dry ice acetone bath to -78 °C. Under a positive argon pressure a 1.0 N L-Selectride solution in THF (170 mL, 166.1 mmol, 1.3 equiv) was transferred to the dropping funnel and added slowly (within 1.5 h) to the reaction mixture (only a weak H_2 evolution was observed). After 0.5 h of stirring at -78 °C a small aliquot of the reaction (ca. 100 µl) was quenched through fast addition to 1 mL of 1 HCl-solution (aq.)/1 mL EtOAc. TLC control indicated full conversion of the ketone **4a** (r_f = 0.69 in EtOAc) to the intermediate **Ia** (as the diol, r_f = 0.41 in EtOAc).

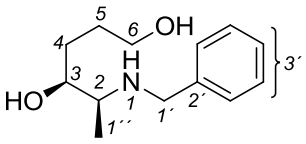
Subsequently, concentrated HCl-solution (32% in water, 38 mL, 383.4 mmol, 3.0 equiv) was added dropwise through the dropping funnel (H_2 evolution) and the cooling bath was removed.

During the addition of the L-Selectride solution to the substrate **4a**, a mixture of $Pd(OAc)_2$ (580 mg, 2.56 mmol, 0.02 equiv) and of MeOH (160 mL) was stirred for 45 min in a separate 500 mL flask resulting in a brown solution (some of Pd-salt remained undissolved). Then activated charcoal (5.2 g) was added, the mixture was degassed in high vacuum and flushed with 1 atm of H_2 (3x) and the suspension was stirred for 30 min at ambient temperature (under 1 atm of H_2).

Directly after the cooling bath was removed after quenching with HCl-solution, the Pd/C suspension in MeOH was added, the flask, in which Pd/C had been prepared, was rinsed with two 40 mL portions of MeOH (in total THF/MeOH 1:1) and the resulting reaction suspension was degassed in high vacuum/subjected to 1 atm of H_2 (6 x times). After stirring overnight (17 h) at room temperature under 1 atm of H_2 (balloon), TLC control showed full conversion of the carbamate **Ia** (as neutral diol) to the amine **5a**.[34,35]

To remove Pd/C, the mixture was passed through a layer of celite (ca. 1 cm, in a sintered funnel), the residue was washed with two 50 mL portions of MeOH and the solvent was removed under reduced pressure in a rotatory evaporator. The residue was dissolved in H_2O (130 mL, **5a** = 1 mol/L) and Et_2O (60 mL, H_2O/Et_2O 2:1, pH of the mixture = 1), the aqueous phase was separated and washed with Et_2O (2x60 mL). Then the H_2O-phase was cooled in an ice bath, neat NaOH (20.5 g, 511 mmol, 20.5 g) was added under stirring and the resulting emulsion was stirred at 0 °C, until NaOH had dissolved completely (10 min, pH ≥ 14). After addition of 60 mL of DCM a poor phase separation was observed. Therefore the mixture was diluted with further 60 mL of water and 30 mL of DCM (H_2O/DCM 2:1), the aqueous phase was separated and extracted with two further 90 mL portions of DCM. After drying of the collected DCM-phases over $MgSO_4$, concentration under reduced pressure and drying in high vacuum for 18 h under stirring, the diol **5a** (24.18 g, 108.4 mmol, 85% over 2 steps from Weinreb amide **15a**) were isolated as a pale yellow oil in a purity of ≥90% and a dr of >19:1 (the second diastereomer was not detectable) according to ^{1}H-NMR.[36]

M ($C_{13}H_{21}NO_2$) = 223.311 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc) = 0.00; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.35-7.24 (m, 5H, H-3´), 3.93 (d, 1H, H-1´$_a$, J = 13.1 Hz), 3.72-3.61 (m, 3H, H-6, H-1´$_b$; beneath at 3.68 ppm, d, H-1´$_b$, J = 13.1 Hz),

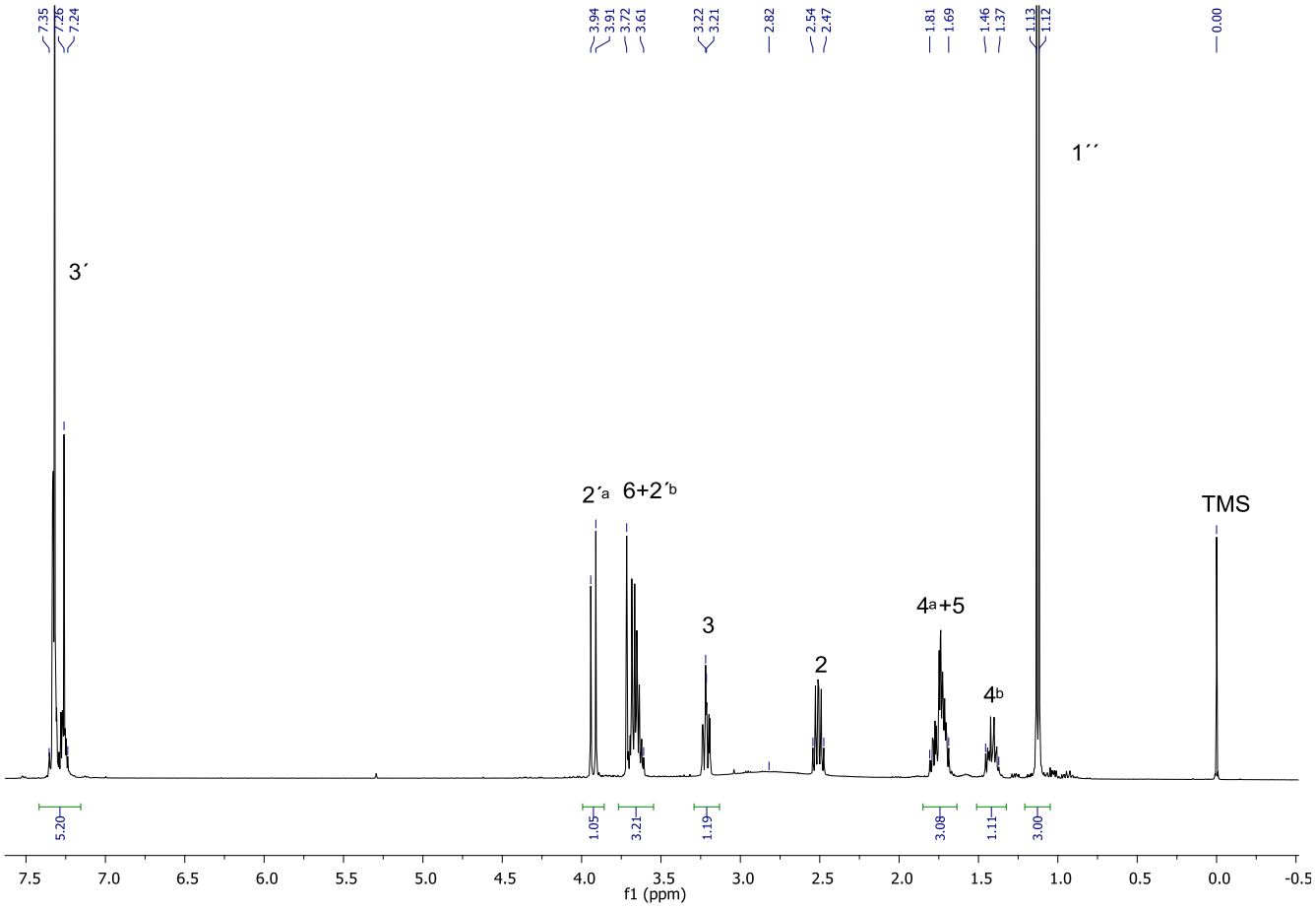


34 After 4 h of stirring under H_2 atmosphere, TLC control still showed traces of **IIa** (r_f of the amine **6a** as hydrochloride salt = 0.00 in EtOAc).

35 In a smaller scale (≤10 mmol) a quantitative hydrogenolysis of the Cbz-group was achieved in ≤ 3 h with an active commercial Pd/C bach or with *insitu* generated Pd/C as described above.

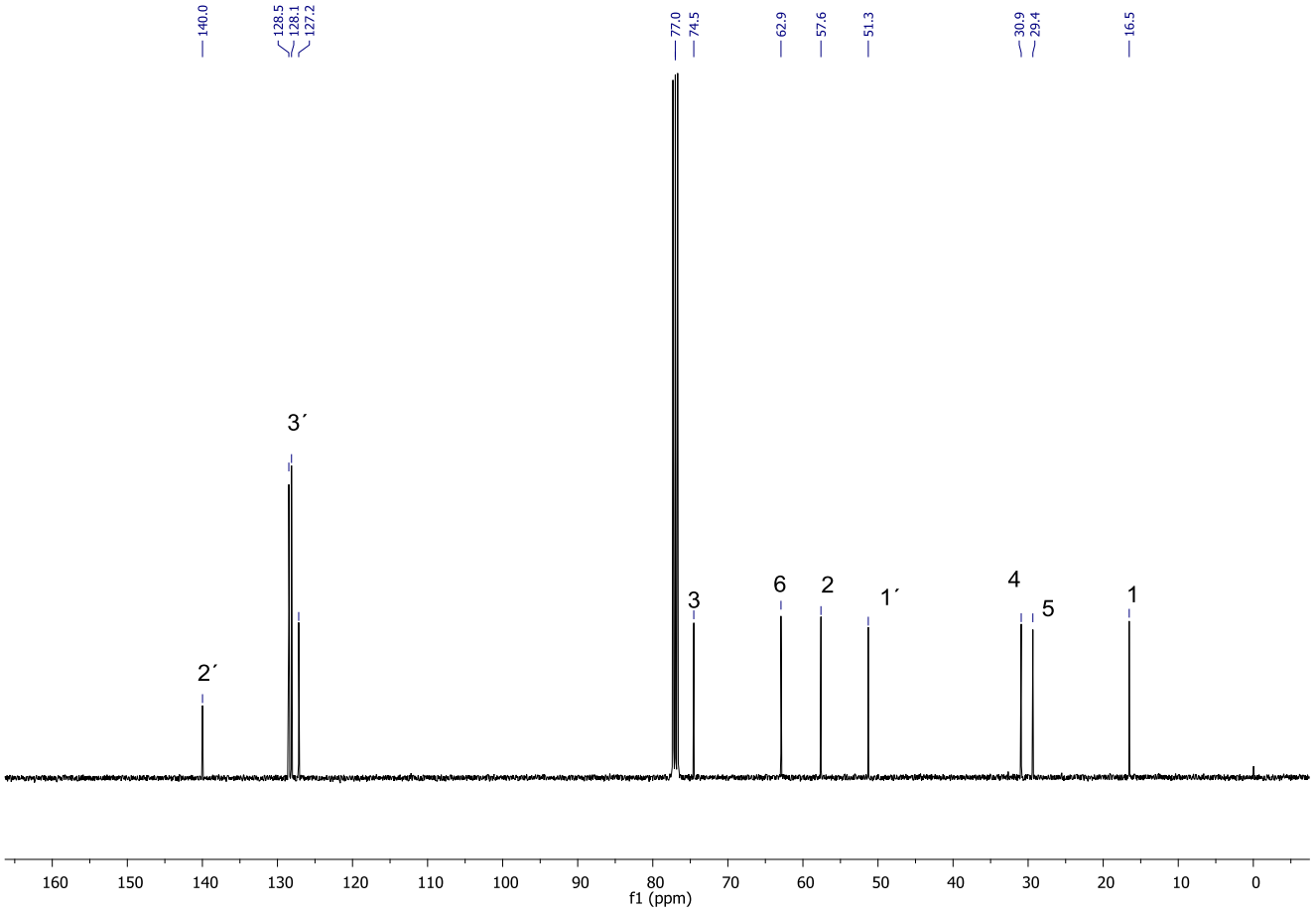
36 Diol ***syn*-5a** was obtained in a ≤10 mmol scale in 91-93% yield (referred to ketone **4a**).

3.22 (td, 1H, H-3, *J* = 8.5, 2.7 Hz), 2.82 (s, 2H, NH, OH),[37] 2.54-2.47 (m, 1H, H-2), 1.81-1.69 (m, 3H, H-4_a, H-5), 1.46-1.37 (m, 1H, H-4_b), 1.12 (d, 3H, H-1´´, *J* = 6.4 Hz); ^{13}C-**NMR** (100 MHz, $CDCl_3$) δ ppm = 140.0 (C-2´), 128.5/128.1/127.2 (C-3´), 74.5 (C-3), 62.9 (C-5), 57.6 (C-2), 51.3 (C -1´), 30.9 (C-4), 29.4 (C-5), 16.5 (C-1); **IR** (film) ν cm^{-1} = 3391 (br), 3090 (w), 3065 (w), 3029 (w), 2945 (m), 2873 (w), 1645 (m), 1606 (w), 1495 (w), 1453 (s), 1380 (m), 1331 (w), 1145 (w), 1060 (m), 1028 (w), 1009 (w), 912 (w), 746 (s), 699 (s); **GC-MS** (EI, 70 eV) m/z u = 224 (10%, $M+H^+$), 204 (5%), 177 (5%), 136 (5%), 120 (5%), 91 (50%, Bn^+), 77 (10%, Ph^+), 57 (35%), 50 (40%), 39 (100%); **HR-MS** (ESI, $C_{13}H_{22}NO_3^+$) calc. 224.1651 u, found 224.1645 u; α_D (c = 1.228 g/100 mL, $CHCl_3$, T = 21.5 °C) = +49.8.



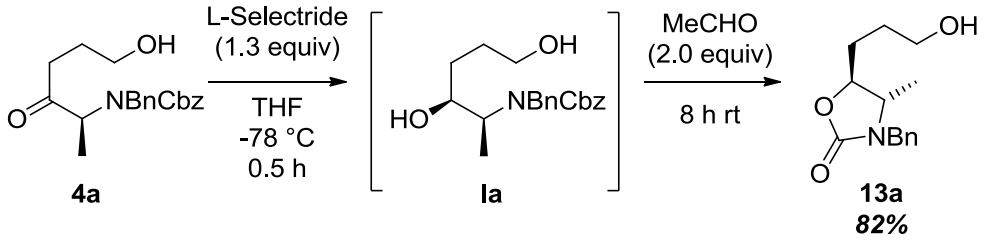
[1]H-NMR-spectrum of the diol ***syn*-5a** in $CDCl_3$ (400 MHz).

37 The third heteroatomic proton is missing.



^{13}C-NMR-spectrum of the diol ***syn*-5a** in $CDCl_3$ (100 MHz).

2.3.2 Synthesis of (2*S*,*S*)-1-Benzyl-4-(3-hydroxypropyl)-5-methyl-2-oxazolidinone (13a)

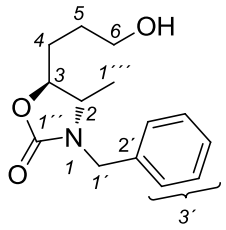


Under an atmosphere of argon the ketone **4a** (468 mg, 1.29 mmol, 1.0 equiv) was dissolved in dry THF (1.3 mL, **4a** = 1.0 mol/L) and cooled to -78 °C. Subsequently, 1.0 N L-Selectride solution in THF (1.70 mL, 1.67 mmol, 1.3 equiv) was added dropwise within 5 min. After stirring at -78 °C for 0.5 h, an excess of reducing agent was quenched through the addition of acetaldehyde (0.15 mL, 2.58 mmol, 2.0 equiv). Finally, the cooling bath was removed and the mixture was allowed to stir to 8 h at ambient temperature.

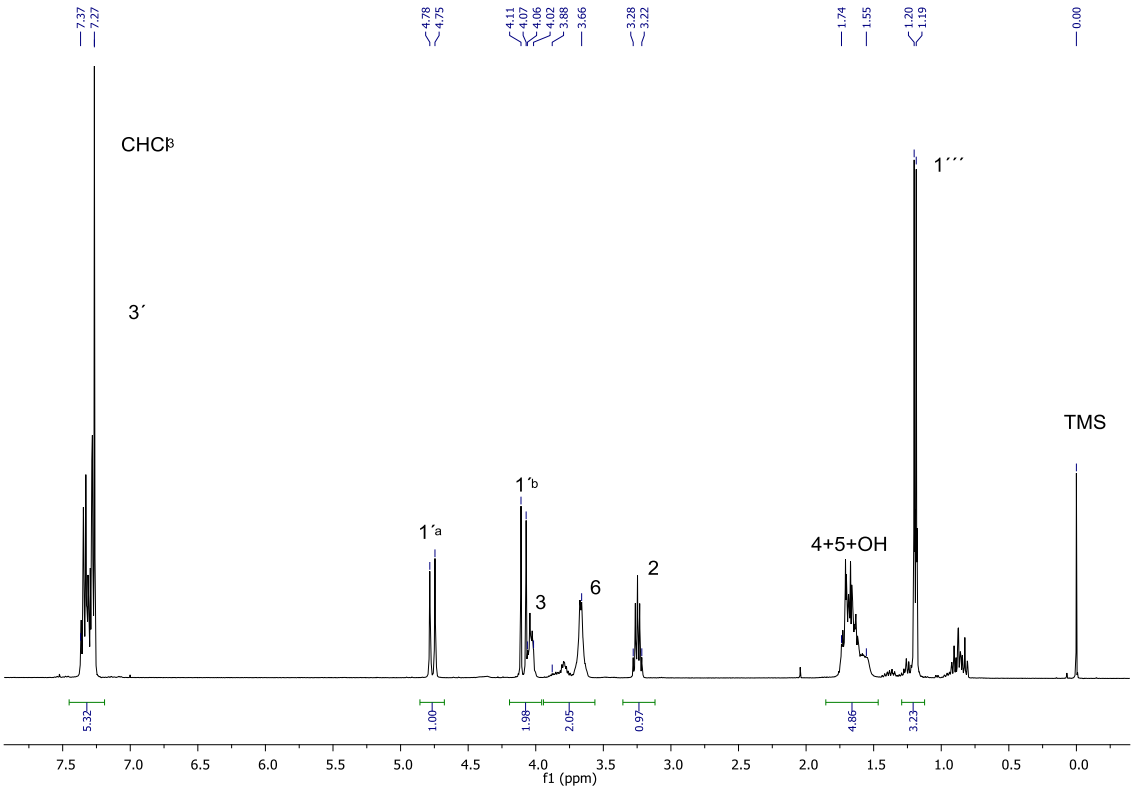
Then to the brown reaction solution was added 1 N HCl solution in water (6 mL), whereby a color change to yellow was observed. The mixture was extracted with three 6 mL portions of Et_2O, the

combined extraction phases were dried over $MgSO_4$ and concentrated under reduced pressure to result in the crude oxazolidinone**13a** as a pale yellow oil (923 mg).

The crude product was dissolved in ca. 0.5 mL of EtOAc/*n*Hex 1:2 and purified with column chromatography on silica gel with EtOAc/*n*Hex 1:2. After dissolution in 2 mL of chloroform and concentration in vacuum (2x) and drying in high vacuum for 12 h, the oxazolidinone **13a** (264 mg, 1.06 mmol, 82%,) was isolated as a colorless oil.

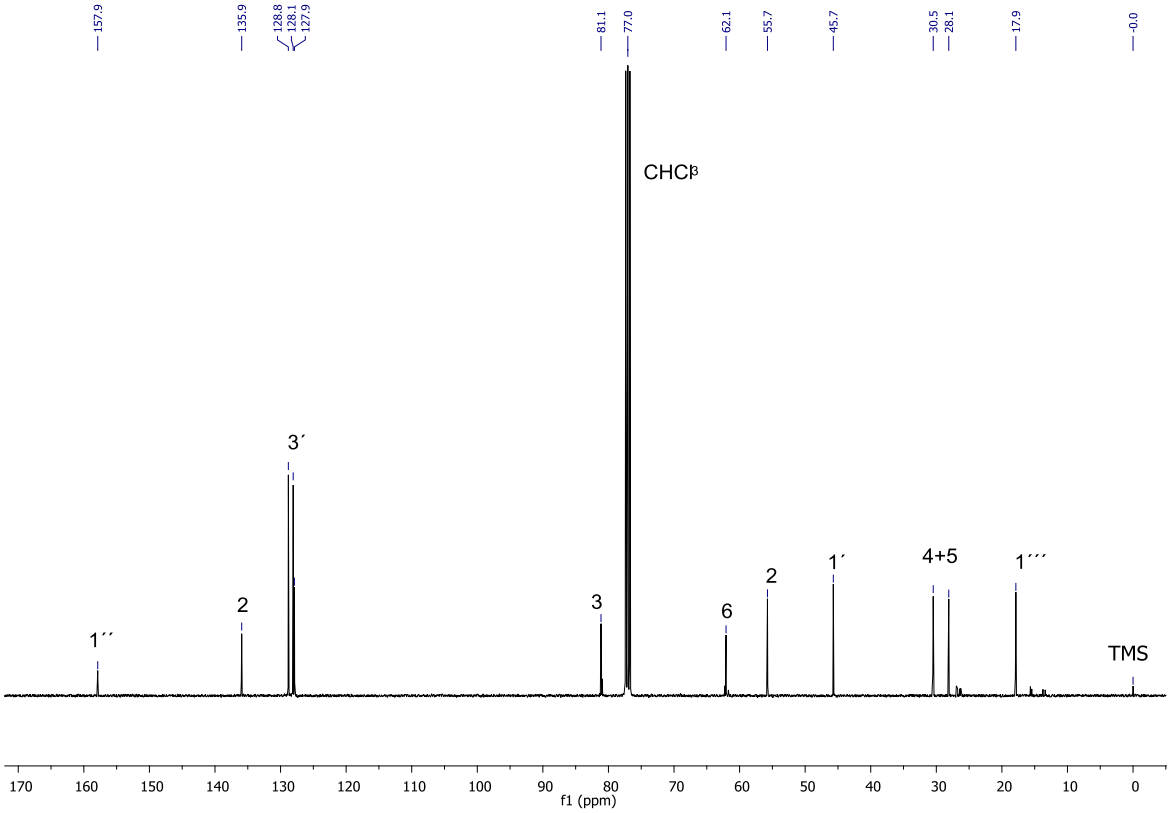


M ($C_{14}H_{19}NO_3$) = 249.306 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex) = 0.31 (4:1), 0.19 (2:1); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.37-7.27 (m, 5H, H-3´), 4.77 (d, 1H, H-1´´$_a$, *J* = 14.9 Hz), 4.09 (d, 1H, H-1´´$_b$, *J* = 15.2 Hz), 4.06-4.02 (m, 1H, H-3), 3.88-3.66 (m, 2H, H-6), 3.28-3.22 (m, 1H, H-2), 1.74-1.55 (m, 5H, H-4, H-5, OH), 1.20 (d, 3H, H-1´´´, *J* = 6.3 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 157.9 (C-1´´), 135.9 (C-2´), 128.8/128.1/127.9 (C-3´), 81.1 (C-3), 62.1 (C-6), 55.8 (C-2), 45.7 (C-1´), 30.5/28.1 (C-4, C-5), 17.9 (C-1´´´); **IR** (film) ν cm^{-1} = 3428 (br), 3091 (w), 3065 (w), 3033 (w), 2945 (m), 2871 (w), 1729 (s), 1645 (m), 1496 (w), 1439 (m), 1421 (m), 1383 (w), 1360 (w), 1333 (w), 1249 (w), 1204 (w), 1115 (w), 1061 (m), 971 (w), 764 (w), 736 (w), 702 (m), 679 (w); **HR-MS** (ESI, $C_{14}H_{29}NO_3Na^+$) calc. 272.1263 u, found. 272.1253 u; $\boldsymbol{\alpha_D}$ (c = 1.084 g/100 mL, $CHCl_3$, T = 21.0 C) = +80.8 (lit.: +87.85 (c = 1.045 g/100 mL, $CHCl_3$, 20 °C)).[38]

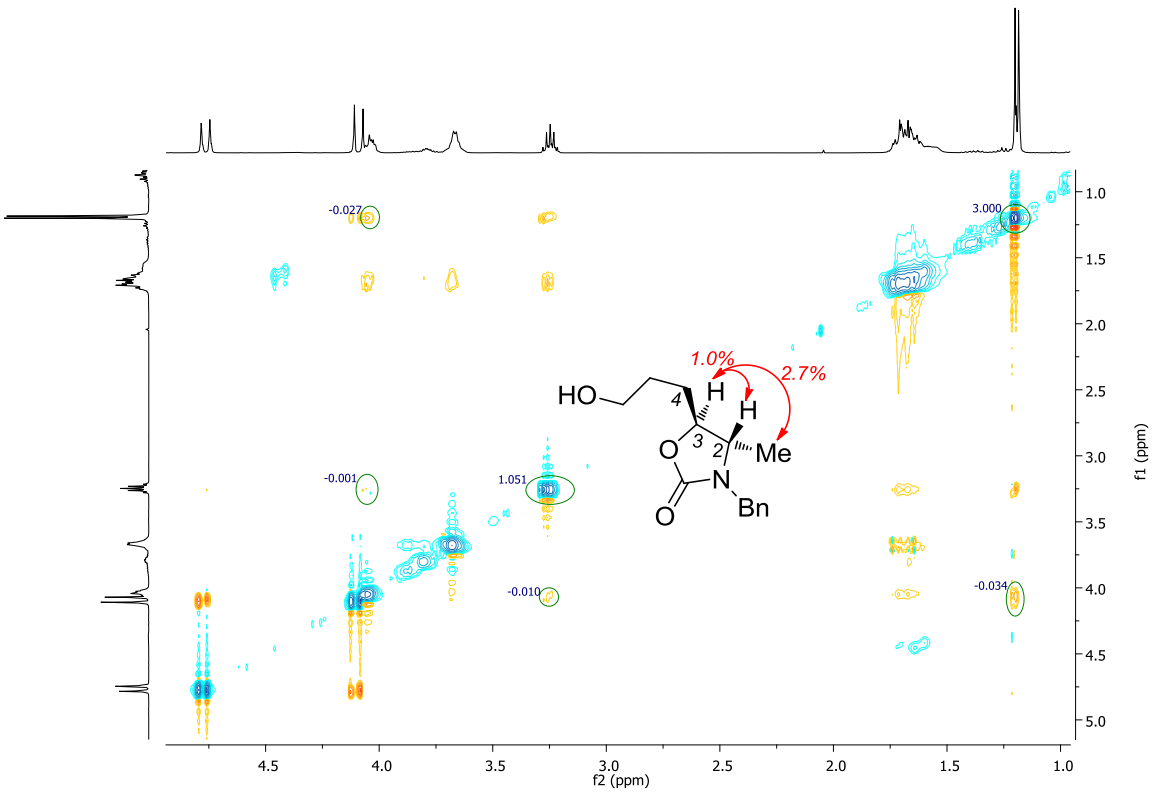


^{1}H-NMR-spectrum of the oxazolidinone **13a** in $CDCl_3$ (400 MHz).

38 A. Pahl, J. Oetting, J. Holzkamp, H. H. Meyer, H. H. *Tetrahedron* **1997**, *53*, 7255-7266.

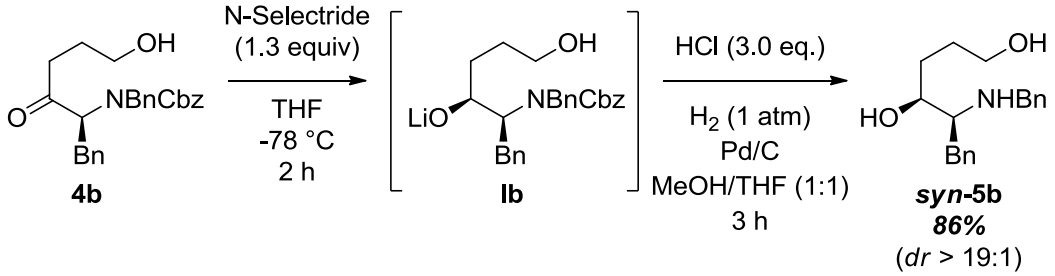


^{13}C-NMR-spectrum of the oxazolidinone **13a** in $CDCl_3$ (100 MHz).



NOESY-spectrum of oxazolidinone **13a** (400 MHz).

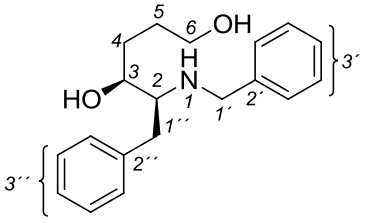
2.3.3 Synthesis of (2S)-2-(Benzylamino)-1-phenyl-3,6-hexandiol (*syn*-5b)



4b **Ib** ***syn*-5b** ***86%*** (*dr* > 19:1)

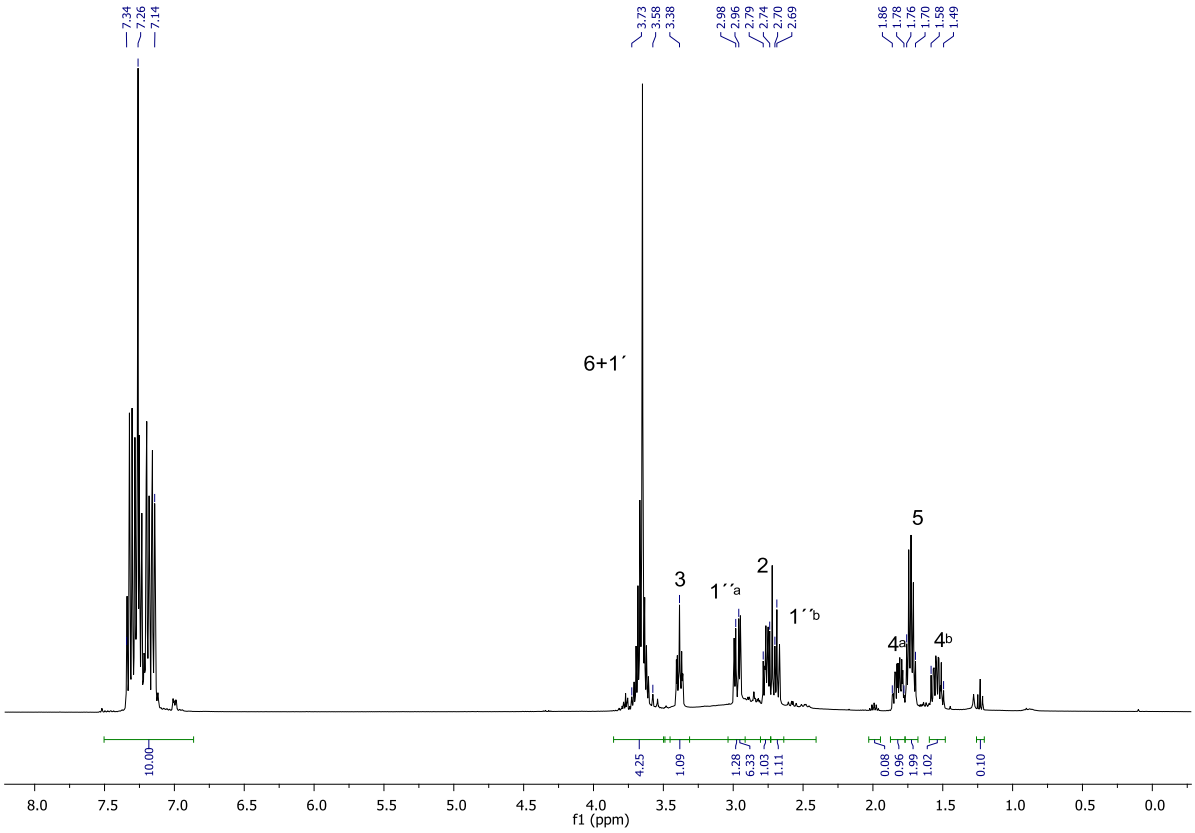
Under an atmosphere of argon the ketone **4b** (3.092 g, 7.17 mmol considering 7% of Cl*n*PrOH, 1.0 equiv) was dissolved in dry THF (7 mL, **4b** = 1.0 mol/l) in a 250 mL round bottom flask and cooled to -78 °C. Then a 1.0 N N-Selectride solution in THF (9.3 mL, 9.3 mmol, 1.3 equiv) was added slowly through a syringe pump over 2 h. Micro work up of a small aliquot of the reaction mixture (ca. 100 μL) with 1 N HCl (aq)/EtOAc and TLC control after 1 h of stirring at -78 °C indicated full conversion to the diol **Ib** (r_f (**Ib** as the neutral diol) = 0.20 (1:1 EtOAc/*n*Hex)). Subsequently, 37% HCl solution in water was added (1.80 mL, 21.5 mmol, 3.0 equiv), whereby a hydrogen evolution was observed, the cooling bath was removed, MeOH was added (16 mL, THF/MeOH 1:1) and the mixture was degassed in high vacuum for three times to remove H_2. After addition of Pd/C (300 mg, 2.87 mmol, 0.04 equiv), degassing in high vacuum/purged with 1 atm of H_2 (3x) and stirring for 3 h under 1 atm of hydrogen (balloon), TLC control showed complete conversion of the carbamate **Ib** (as diol) to the amine **5b** (r_f (**Ib** as diol) = 0.49 (2:1 EtOAc/*n*Hex), r_f (**5b-HCl**) = 0.00 (2.1), r_f($BsBu_3$) = 0.90 (2:1, non UV active).

Pd/C was removed through filtration through a thin layer of celite (sintered funnel), the remaining Pd/C and celite were washed with two 5 mL portions of MeOH and the solvent was removed under reduced pressure. The residue was dissolved in 8 mL of water and 4 mL of Et_2O (pH ≤ 0), the aqueous phase was separated and washed with two further 4 mL portions of Et_2O. Subsequently, the H_2O-phase was treated portionwise with KOH (1.61 g, 28.7 mmol, 4.0 equiv) under stirring (pH ≥ 14), the resulting emulsion was extracted with four 6 ml portions of Et_2O, the combined Et_2O-extraction phases were dried over $MgSO_4$ and concentrated under reduced pressure. After drying in high vacuum for 2 h under heating to 40 C and stirring, the diol ***syn*-5b** (1.837 g, 6.14 mmol, 86%) was isolated as a pale yellow, viscous oil. The *dr* was determined to be >19:1 after the following cyclisation to ***cis*-6b**.

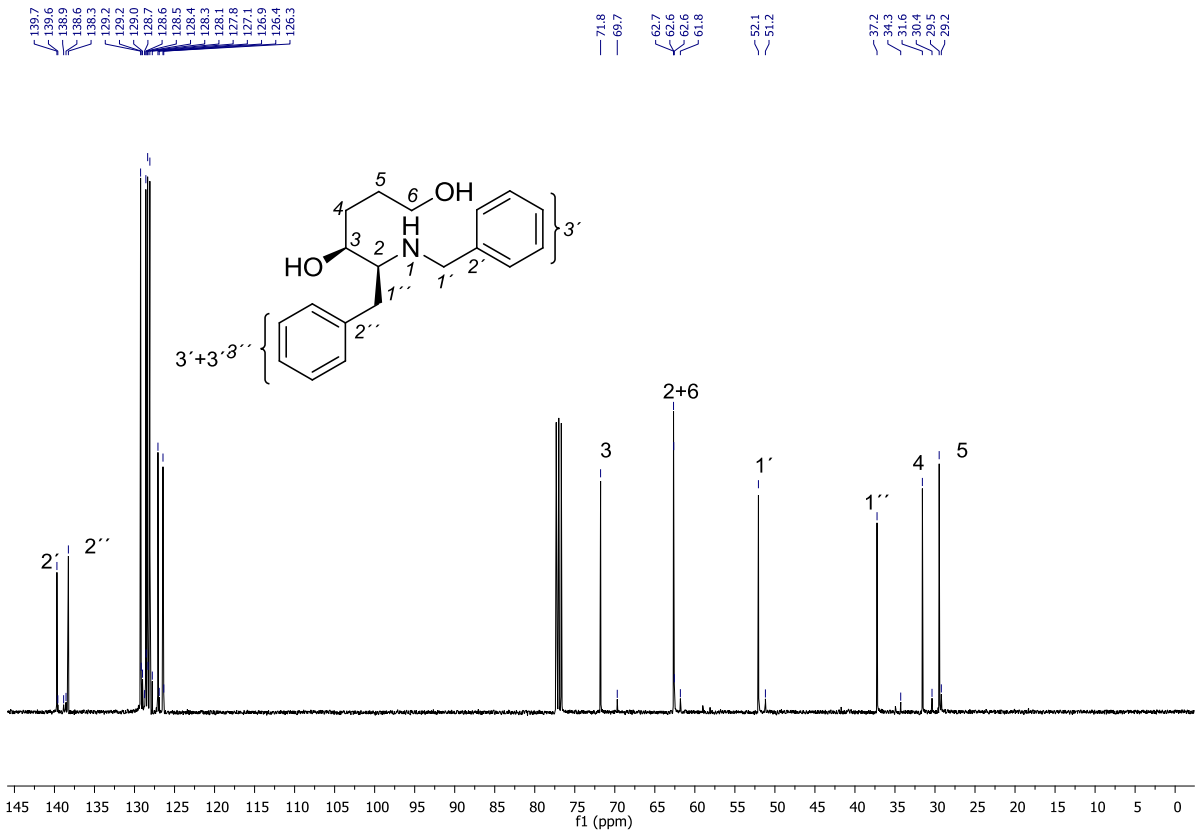


M ($C_{19}H_{25}NO_2$) = 299.407 g/mol; **r_f** (SiO_2) = 0.45 (MeOH/EtOAc 1:10); **^{1}H-NMR** (400 MHz, $CDCl_3$,) δ ppm = 7.34-7.14 (m, 10H, H-3´, H-3´´), 3.73-3.58 (m, 4H, H-1´, H-6), 3.38 (ddd, 1H, H-3, *J* = 9.0, 6.3, 2.5 Hz), 2.97 (dd, 1H, H-1´´$_a$, *J* = 13.2, 4.6 Hz; amongst broad s, 2H, 2xOH), 2.79-2.74 (m, 1H, H-2), 2.70 (dd, 1H, H-1´´$_b$, *J* = 12.8, 8.0 Hz), 1.86-1.78 (m, 1H, H-4$_a$), 1.76-1.70 (m, 2H, H-5), 1.58-1.49 (m, 1H, H-4$_b$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 139.7 (C-2´), 138.3 (C-2´´), 2x129.2/129.0/128.7/128.6/128.5/128.4/128.3/128.1/127.8127.1/126.9/2x126.4

(C-3´, C-3´´), 71.8 (C-3), 62.7/62.6 (C-6, C-1´), 52.1 (C-1´), 37.2 (C-1´´), 31.6 (C-4), 29.5 (C-5); **IR** (film) ν cm^{-1} = 3338 (br), 3084 (w), 3061 (w), 3026 (w), 2930 (m), 2864 (m), 1949 (w), 1879 (w), 1809 (w), 1602 (w), 1585 (w), 1494 (m), 1453 (s), 1331 (w), 1179 (w), 1156 (w), 1055 (m), 1029 (m), 1012 (w), 913 (w), 743 (s), 699 (vs); **GC-MS** (EI, 70 eV) m/z % = 240 (2), 210 (35), 190 (10), 118 (5), 104 (5), 91 (100, Bn^+), 77 (5), 65 (10, Cp^+), 51 (5); **HR-MS** (ESI, $C_{19}H_{26}NO_2^+$) calc. 300.1964 u, found 300.1967 u; α_D (c = 0.640 g/100 mL, $CHCl_3$, T = 21.0 °C) = -8.0.

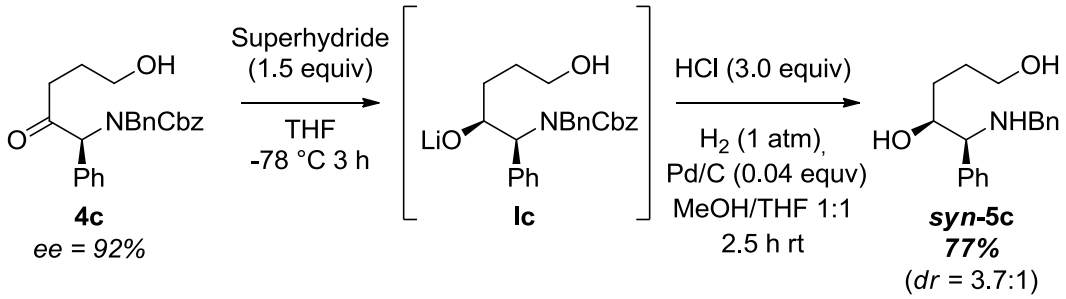


^{1}H-NMR-spectrum of the diol ***syn*-6b** in $CDCl_3$ (400 MHz).



^{13}C-NMR-spectrum of the diol ***syn*-5b** in $CDCl_3$ (100 MHz).

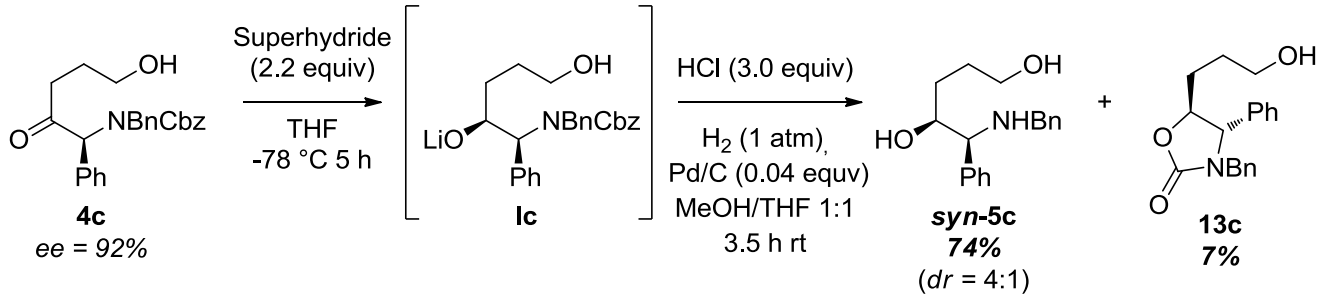
2.3.4 Synthesis of (*2S*,*3S*)-1-(Benzylamino)-1-phenyl-2,5-pentandiol (5c)



Ketone **4c** (2.948 g, 7.06 mmol, 1.0 equiv, *ee* = 92%,) was dissolved under an atmosphere of argon in 7 mL of dry THF (**4c** = 1 mol/L) in a one necked, round bottom 100 ml flask and cooled to -78 °C. Subsequently, a 1.0 N solution of Superhydride in THF (9.2 mL, 9.18 mmol, 1.3 equiv) was added very slowly (syringe pump, 50 min). After stirring for 1.5 h at -78 °C, quenching of a small aliquot of the reaction mixture (ca. 100 μL) by fast addition to a mixture of 1 mL of 1 N HCl solution (aq.)/1 mL EtOAc and TLC control indicated incomplete conversion of the starting ketone **4c**. Therefore Superhydride solution (0.2 equiv, 1.41 mmol, 1.4 mL) was added dropwise to the reaction solution and the mixture was stirred for further 30 min at -78 °C, whereupon micro work up as described above and TLC control showed full conversion of **4c**.

Subsequently, 32% aq. HCl solution (2.1 mL, 21.2 mmol, 3.0 equiv) was added dropwise (H_2-evolution), the cooling bath was removed, MeOH (17 mL, THF/MeOH 1:1) was added and the mixture was degassed in high vacuum/purged with air for three times (to remove H_2). Then 10% Pd/C (300 mg, 0.282 mmol, 0.04 equiv) was added and the reaction suspension was degassed in high vacuum/purged with hydrogen (1 atm, balloon, 3 x times). After 2.5 h of stirring under 1 atm H_2, TLC-control indicated complete conversion of the carbamate **Ic** (as diol) to the amine **5c**.

The mixture was passed through a thin layer of Celite (sintered funnel), rinsed with two 5 mL portions of MeOH, and the solvent was removed under reduced pressure. The residue was dissolved in H_2O (14 mL, **5a** = 0.5 mol/L) and Et_2O (7 mL, H_2O/Et_2O 2:1, pH of the mixture ≤ 0), the phases were separated and the aqueous phase was washed with three further 7 mL of Et_2O. Subsequently, the aqueous phase was treated portionwise with K_2CO_3 (2.93 g, 21.2 mmol, 3.0 equiv) under stirring (CO_2 evolution), the resulting emulsion (pH = 10) was extracted with three 10 mL portions of Et_2O, the combined Et_2O-extraction phases were dried over $MgSO_4$ and concentrated under reduced pressure. After drying in high vacuum under stirring and heating to 40 °C for 2 h, the diol ***syn*-5a** (1.552 g, 5.44 mmol, 77%) were isolated as a pale yellow oil in an *dr* of 3.7:1*syn/anti*.



Ketone **4c** (9.288 g, 22.25 mmol, 1.0 equiv, *ee* = 92%) was dissolved under an atmosphere of argon in dry THF (23 mL, **4c** = 1 mol/L) in a one necked, round bottom 500 ml flask and cooled to -78 °C. Subsequently, a 1.0 N solution of Superhydride[39] in THF (33 mL, 33.4 mmol, 1.5 equiv) was added very slowly through a syringe pump (3.25 h). After stirring for 0.5 h at -78 °C, quenching of a small aliquot of the reaction mixture (ca. 100 μL) by fast addition into a mixture of 1 mL of 1 N HCl solution (aq.)/1 mL EtOAc and TLC control indicated incomplete conversion of the starting ketone **4c**.[40] Therefore further Superhydride solution (9.0 mL, 8.9 mmol, 0.4 equiv) was added dropwise. As micro work und TLC-control like describer above still showed remaining traces of the starting material **4c**, more Superhydride solution (6.0 mL, 5.6 mmol, 0.25 equiv) was added again.

Subsequently, 37% aq. HCl solution (5.6 mL, 66.8 mmol, 3.0 equiv) was added dropwise (H_2-evolution), the cooling bath was removed, MeOH (70 mL, THF/MeOH 1:1) was added and the mixture was degassed in high vacuum/ventilated with air three times (to remove H_2). Then 10% Pd/C (470 mg,

39 The utilized Superhydride batch was at least two years old.

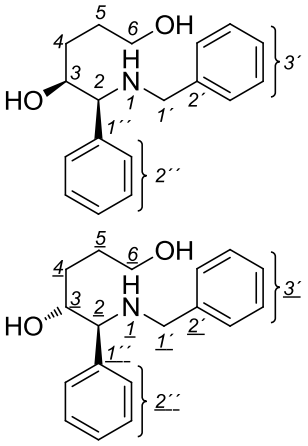
40 r_f (**Ic** as neutral diol, SiO_2) = 0.42+0.33 (EtOAc/nHex 2:1), r_f (**4c**, SiO_2) = 0.58 (EtOAc/nHex 2:1).

0.445 mmol, 0.02 equiv) was added and the reaction suspension was degassed in high vacuum/purged with hydrogen (1 atm, balloon, 3 x times). After 3.5 h of stirring under 1 atm of H_2, TLC-control indicated complete conversion of the carbamate **Ic** (as the diol) to the amine **5c**.

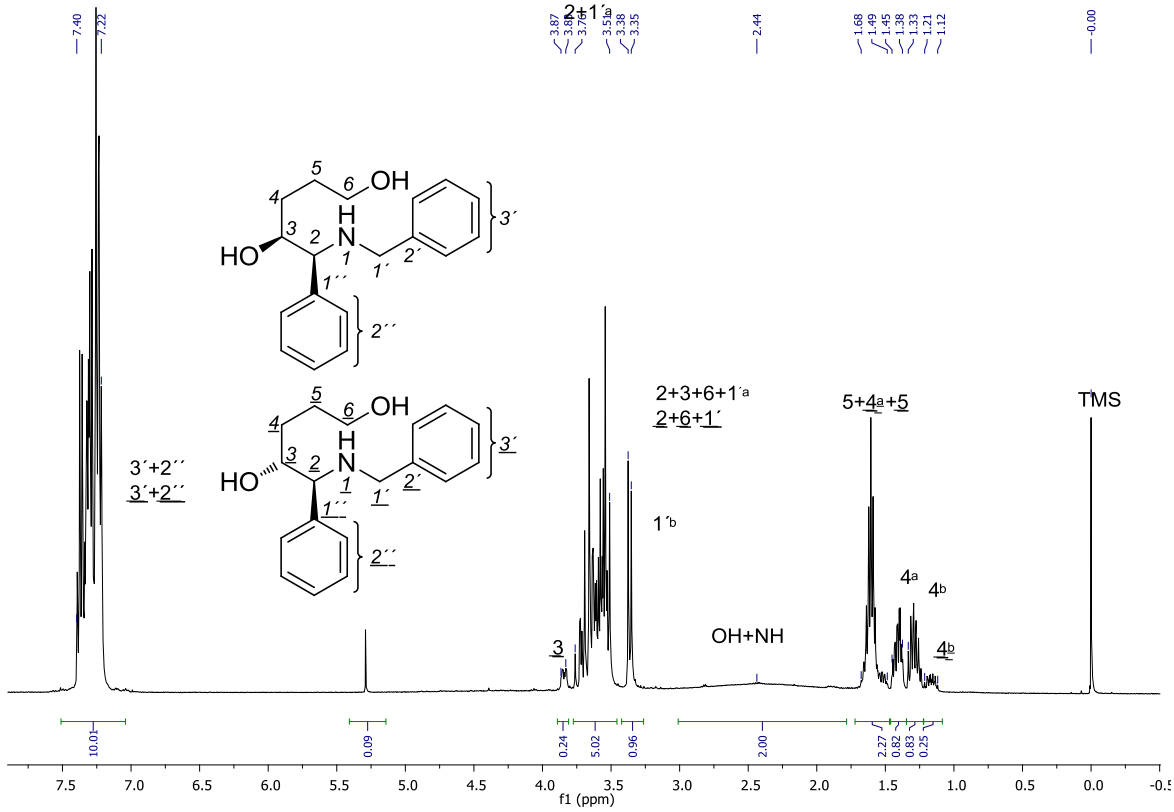
The mixture was passed through a thin layer of Celite (sintered funnel), the residual Pd/C and Celite were washed with two 30 mL portions of MeOH, and the collected filtrates were concentrated under reduced pressure (→ 100 mbar). The residue was dissolved in H_2O (50 mL, **5c** = 0.5 mol/L) and 20 ml of Et_2O (Et_2O, ca. H_2O/Et_2O 2:1, pH of the mixture ≤ 0), the aqueous phase was separated and washed with two further 20 mL of Et_2O. Subsequently, the aqueous phase was cooled in an ice bath and treated portion wise with KOH (4.98 g, 89.0 mmol, 4.0 equiv) under stirring, the resulting emulsion (pH = 13) was extracted with Et_2O (3x40 mL), the combined Et_2O-extraction phases were dried over $MgSO_4$ and concentrated under reduced pressure. After concentration with DCM (10 mL x2) and drying in high vacuum under stirring and heating to 40 C for 3 h, the diol **5c** (4.72 g, 16.54 mmol, 74%) was isolated as a yellow oil in an *dr* of 4:1.

The combined Et_2O washing phases (see above) were dried over $MgSO_4$ and concentrated under reduced pressure to give 942 mg (*dr* = 9:1) of the crude oxazolidinones **13a**. After chromatographic purification on silica gel (31 g) with EtOAc/*c*Hex 1:1, concentration with chloroform under reduced pressure (2x2 mL) and drying in high vacuum for 2 h, the oxazolidinone **13a** was obtained as a pale yellow oil (514 mg, 1.61 mmol, 7%, *dr*> 19:1).

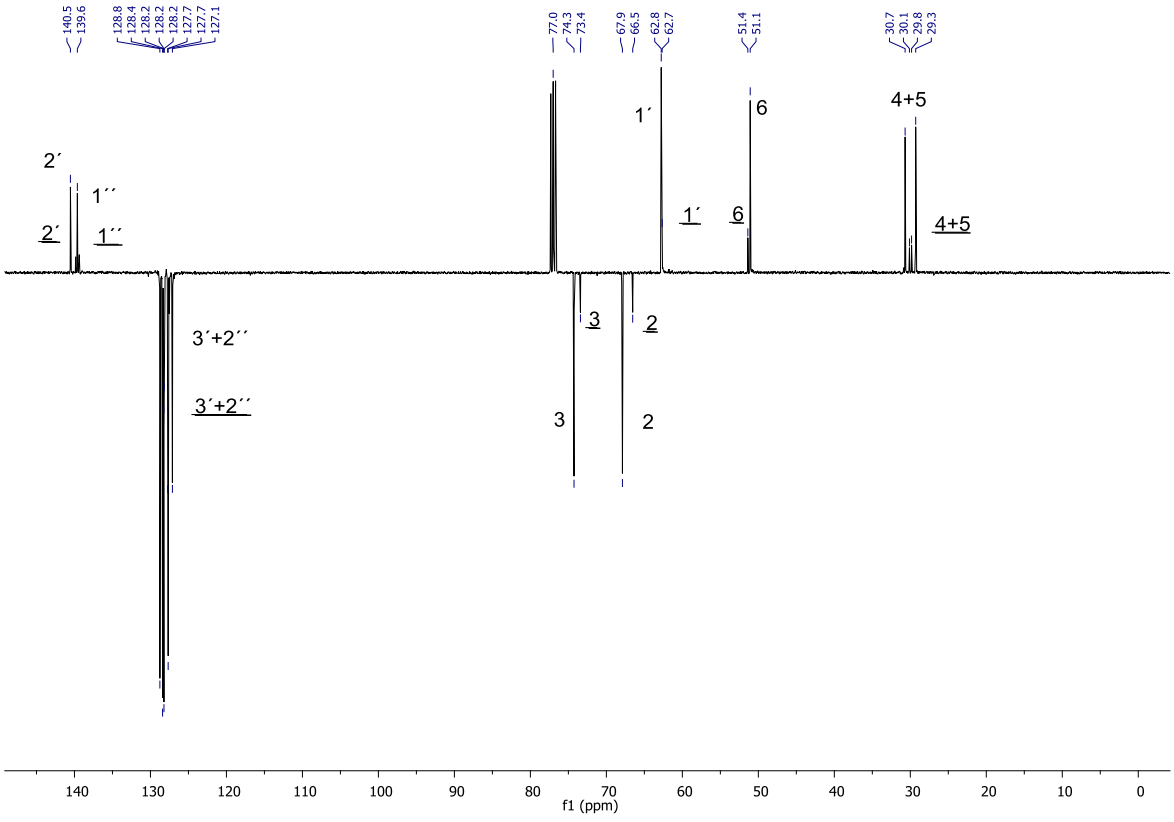
(*2S*,*3S*) and (*2S,3R*)-1-(Benzylamino)-1-phenyl-2,5-pentandiol(*syn*-5c)



M ($C_{18}H_{23}NO_2$) = 285.381 g/mol; $\mathbf{r_f}$ (SiO_2) = 0.51+0.42 (MeOH/EtOAc 1:10; **^{1}H-NMR** (400 MHz, $CDCl_3$, *dr* = 4.0:1) δ ppm = 7.40-7.22 (m, 20H, H-3´, H-2´´, H-3´), 3.87-3.83 (m, 1H, H-3, *dr* = 1:4.0), 3.76-3.51 (m, 10H, H-2, H-3, H-6, H-1´$_b$, H-2, H-6, H-1´), 3.37 (d, 1H, H-1´$_b$, *J* = 9.3 Hz, *J* = 4.0:1), 2.44 (s (broad), 4H, OH, NH, OH, NH), 1.68-1.49 (m, 5H, H-5, H-4$_a$, H-5), 1.45-1.38 (m, 1H, H-4$_a$), 1.33-1.24 (m, 1H, H-4$_b$) 1.21-1.12 (m, 1H, H-4$_b$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm =140.5 (C-2´), 139.6 (C-2´), 128.8 (C-1´´), 128.4 (C-1´´), 3x128.2/2x127.74/127.1 (C-3´, C-2´´, C-3´, C-2´´), 74.3 (C-3), 73.4 (C-3), 67.9 (C-2), 66.5 (C-2), 62.8 (C-1´), 62.7 (C-1´), 51.4 (C-6), 51.1 (C-6), 30.7/30.1/29.8/29.3 (C-4, C-5, C-4, C-5); **IR** (ATR) ν cm^{-1} = 3304 (br), 3082 (w), 2060 (w), 3025 (w), 2914 (m), 2940 (m), 2866 (m), 1950 (w), 1878 (w), 1809 (w), 1600 (w), 1582 (w), 1493 (m), 1452 (s), 1347 (w), 1303 (w), 1199 (w), 1056 (s), 1026 (s), 1004 (s), 907 (vs); **GC-MS** (EI, 70 eV) m/z % = 226 (1, M-*n*PrOH$^+$), 196 (100, PhCH=NHBn$^+$), 165 (2), 129 (4), 117 (5), 105 (10), 91 (80, Bn$^+$), 77 (10, Ph$^+$), 65 (10, Cp$^+$), 51 (9); **HR-MS** (ESI, $C_{18}H_{24}NO_2^+$) calc. 286.1807 u, found 286.1805 u; α_D (c = 1.154 g/100 mL, $CHCl_3$, T = 20.5 °C) = +58.5.

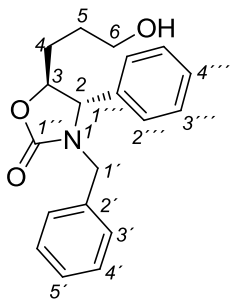


^{1}H-NMR-spectrum of the diol ***syn*-5c** in $CDCl_3$ (400 MHz).

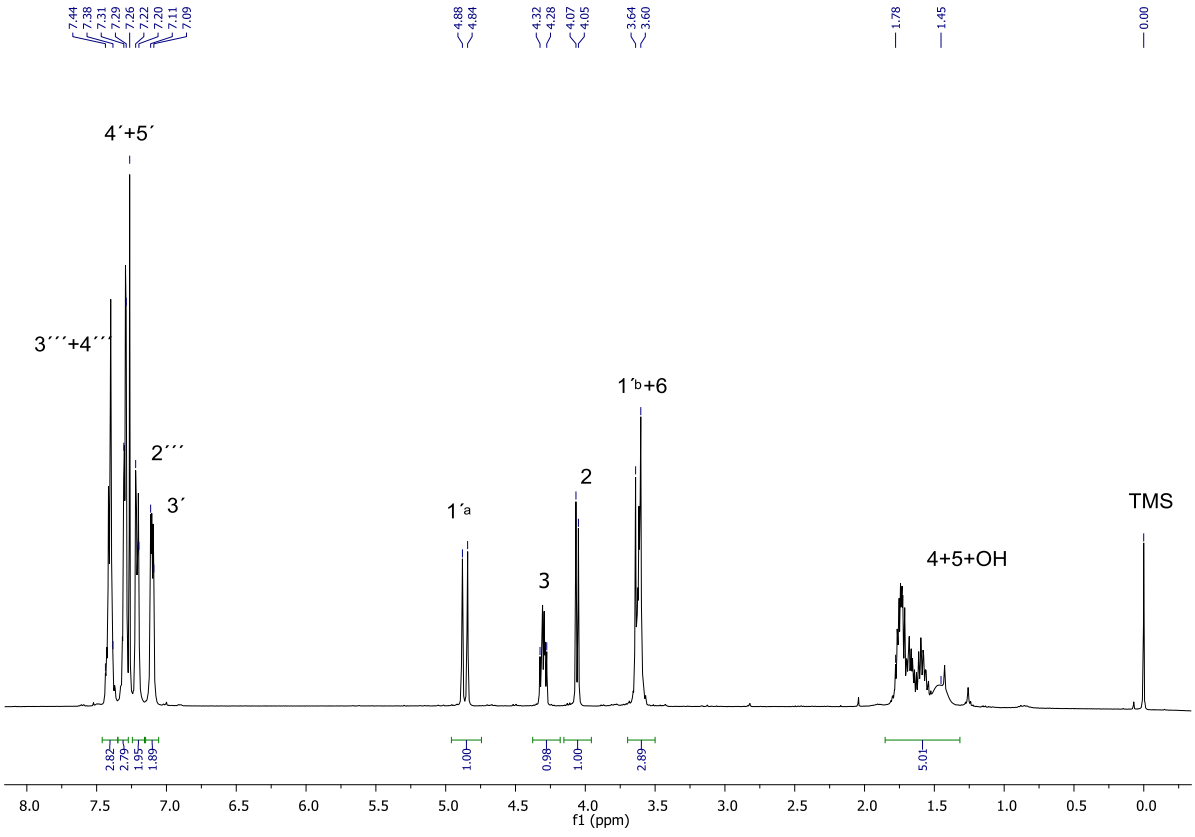


DEPT-135 spectrum of the diol ***syn*-5c** in $CDCl_3$ (100 MHz).

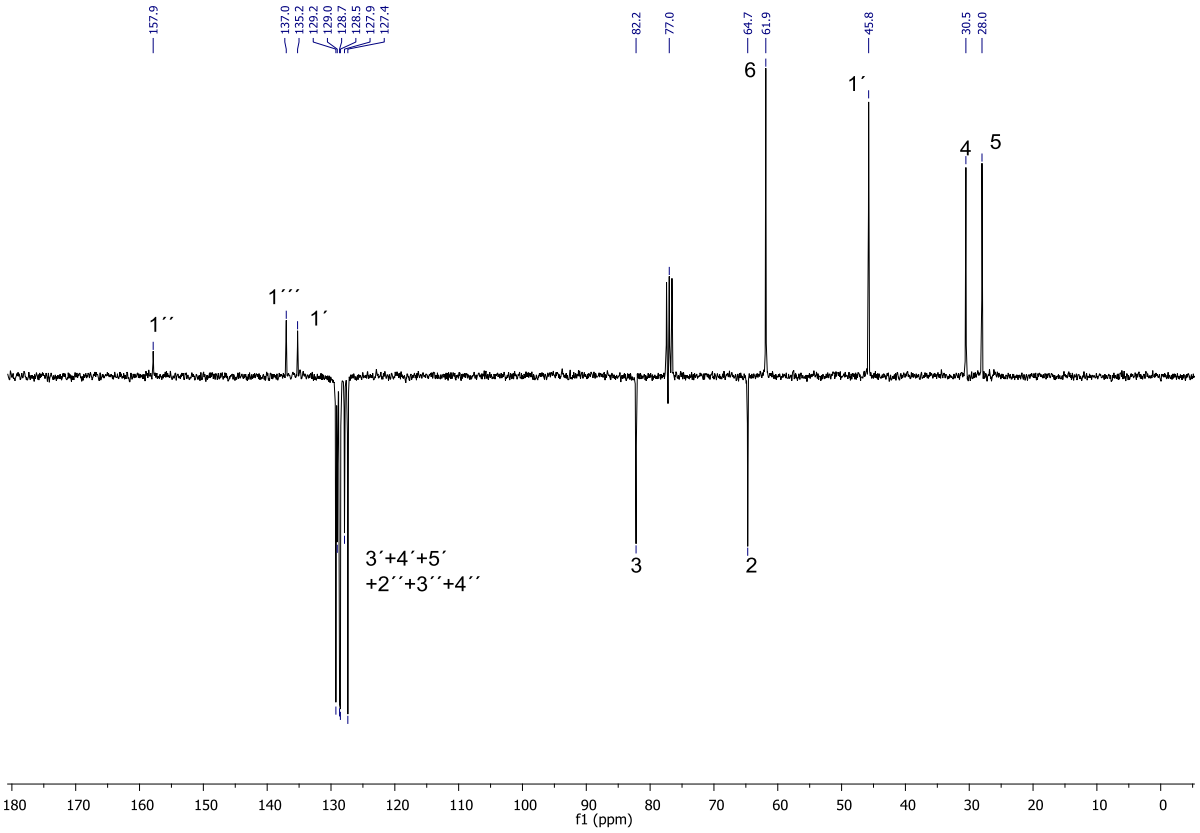
1-Benzyl-(3-hydroxypropyl)-phenyl-2-oxazolidinone (*syn*-13a)



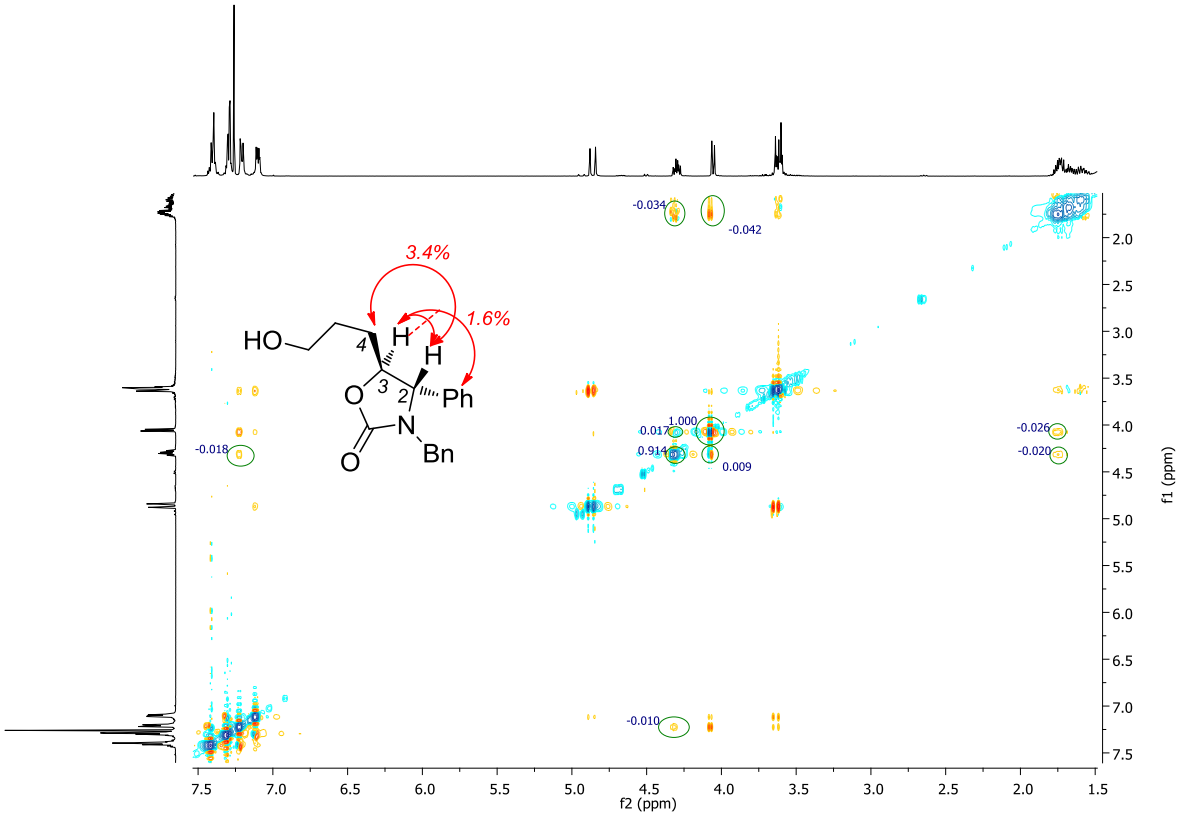
M ($C_{19}H_{21}NO_3$) = 311.375 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.44-7.38 (m, 3H, H-3´´´, H-4´´´), 7.31-7.29 (m, 3H, H-4´, H-5´), 7.22-7.20 (m, 2H, H-2´´´), 7.11-7.09 (m, 2H, H-3´), 4.86 (d, 1H, H-2´$_a$, *J* = 15.2 Hz), 4.30 (td, 1H, H-3, *J* = 7.0, 5.2 Hz), 4.06 (d, 1H, H-7.0 Hz), 3.64-3.60 (m, 3H, H-6, H-1´$_b$), 1.78-1.45 (m, 5H, H-4, H-5, OH); **^{13}C-NMR** (100 MHz, $CDCl_3$)δ ppm = 157.9 (C-1´´), 137.0 (C-1´´´), 135.2 (C-1´), 129.2/129.0/128.7/128.5/127.9/127.4 (C-3´, C-4´, C-5´, C-2´´´, C-3´´´, C-4´´´), 82.2 (C-3), 64.7 (C-2), 61.9 (C-6), 45.8 (C-1´), 30.5 (C-4), 28.0 (C-5); **IR** (ATR) ν cm^{-1} = 3422 (br), 3085 (w), 3061 (w), 3029 (w), 2926 (m), 2870 (w), 1955 (w), 1884 (w), 1730 (vs), 1602 (w), 1602 (w), 1585 (w), 1494 (w), 1454 (m), 1415 (s), 1272 (m), 1235 (m), 1209 (m), 1170 (m), 1060 (s), 1029 (m), 954 (m), 910 (m), 855 (w), 821 (w), 759 (s), 729 (s), 697 (vs); **GC-MS** (EI, 70 eV) m/z % = 261 (5), 246 (10), 233 (10), 218 (20), 206 (5), 190 (65), 146 (50), 91 (100, Bn^+), 57 (50); **HR-MS** (ESI, $C_{19}H_{22}NO_3^+$) calc. 312.1600 u, found 312.1607 u;



^{1}H-NMR-spectrum of the oxazolidinone **13a** in $CDCl_3$ (400 MHz).

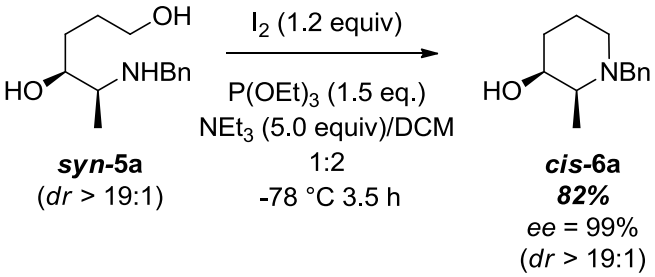


DEPT-135 spectrum of the oxazolidinone **13a** in $CDCl_3$ (100 MHz).



NOESY spectrum of the diol **13a** in $CDCl_3$ (100 MHz).

2.3.5 Synthesis of (*2S,3S*)-1-Benzyl-2-methyl-3-piperidinol (*cis*-6a)



***syn*-5a**
(*dr* > 19:1)

***cis*-6a**
82%
ee = 99%
(*dr* > 19:1)

Under a positive pressure of argon the amino alcohol ***syn*-5a** (18.46 g, 82.7 mmol, 1.0 equiv, *dr*>19:1) was dissolved in dry DCM (115 mL, DCM/NEt_3 2:1) and NEt_3 (57 mL, 5.0 equiv, 414 mmol) in a flame dried three necked flask equipped with a mechanical overhead stirrer, cooled to -78 °C and treated with triethyl phosphite (21.5 mL, 124.1 mmol, 1.5 equiv). Then iodine (25.20 g, 99.3 mmol, 1.2 equiv) was added in one portion and the mixture was stirred for 3.5 h at -78 °C. After 15 min, a colorless solid started to precipitate and after 2.25 h of stirring iodine had dissolved completely. Micro work up with 1 N NaOH solution in water and Et_2O after 2.5 h of stirring showed full conversion of the amino alcohol ***syn*-5a**.

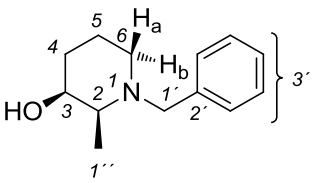
To quench the reaction, 4 N KOH solution in MeOH was added next (83 mL, 3.31 mmol, 4.0 equiv) within 10 min through a dropping funnel at -78 °C, the cooling bath was removed and the mixture was concentrated under reduced pressure. Then further methanolic 4 N KOH solution (124 mL, 49.6 mmol, 6.0 equiv)[41] and MeOH (83 mL) were added and the reaction suspension was stirred for 5 h at ambient temperature. Then the solvent was removed *in vacuo* (→50 mbar), the residue was dissolved in water (280 mL, ***cis*-6a** = 0.3 mol/L) and 190 mL of Et_2O (190 mL, H_2O/Et_2O 2:1), the aqueous phase was separated and extracted with further two 190 mL portions of Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give crude **6a** (19.53 g) as an orange oil containing 25mol% or $O{=}P(OEt)_3$ (according to ^{1}H-NMR).

In order to hydrolyse the remaining phosphate, 4 N KOH-solution in MeOH was added (105 mL, 414 mmol, 5.0 equiv) and the mixture was stirred for 4 h at ambient temperature. To remove colored impurities $NaBH_4$ (300 mg) was added to the reaction mixture and after 15 min of stirring at ambient temperature (whereby a color change from orange to yellow was observable) the mixture was concentrated under reduced pressure. The residue was dissolved in water (190 mL, **6a** = 0.5 mol/L) and *c*Hex (100 mL, H_2O/*c*Hex ca. 2:1), the aqueous phase was separated and extracted with two further 100 mL portions of *c*Hex. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give crude **6** (15.24 g) as a yellow oil (90%, NMR showed no remaining phosphate).

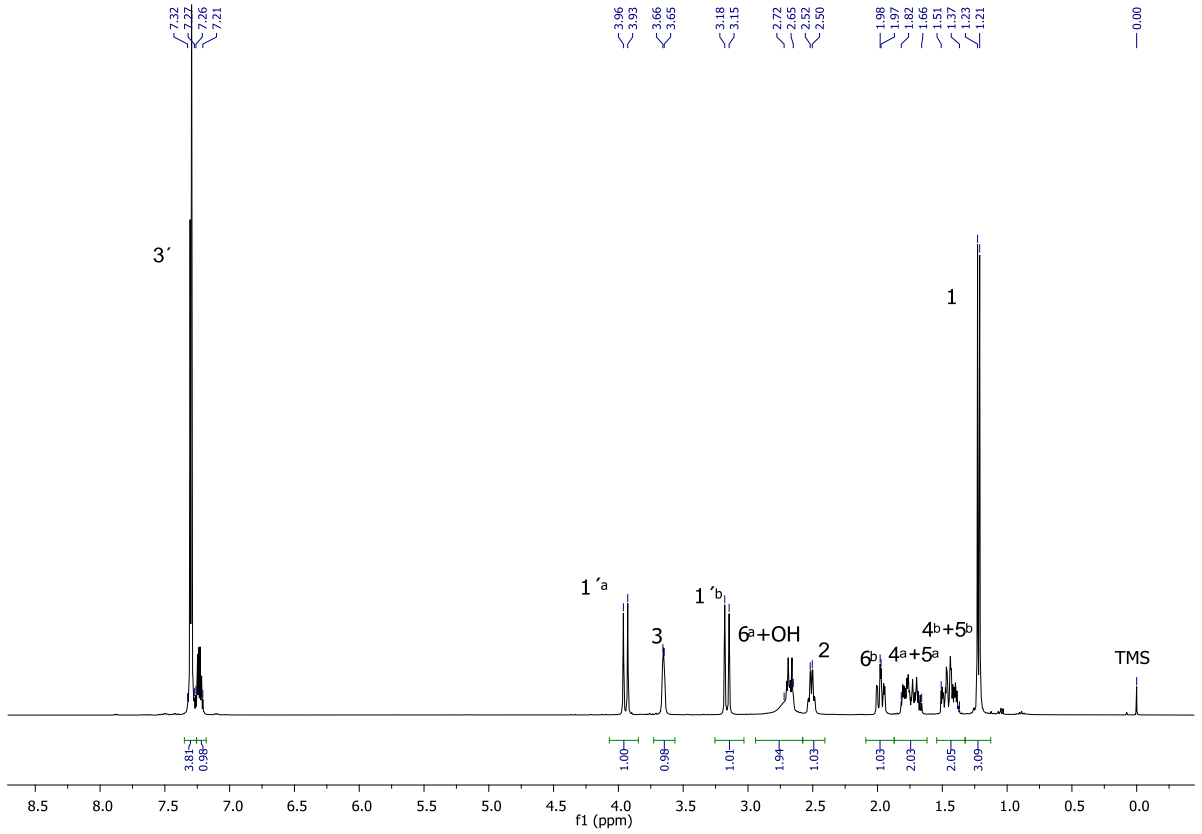
41 Due to the limited volume of the reaction vessel (500 mL) the methanolic KOH-solution was added in two portions.

Next, crude **6** was dissolved in ca. 10 mL of *i*PrOH/*c*Hex/NEt_3 2.5:100:0.8 and purified with chromatographic on silica gel (310 g, column diameter 8 cm, height of silica layer 14 cm) with *i*PrOH/*c*Hex/NEt_3 2.5:100:0.8 (2 L) → 2.5:100:1.2 (2 L). Thereby, the product began to elute after 1.2 L of the solvent mixture. The first fractions (ca. 250 mL), containing piperidine**6a** in a low concentration according to the coloring intensity of the TLC-plates with $KMnO_4$ were collected and concentrated to give **6a** (252 mg) in approximately 80% purity. In the following 1.2 L of eluent were collected, concentrated *in vacuo*, concentrated with DCM (10 mLx2) to get rid of NEt_3 and dried in high vacuum under stirring until gas evolution ceased (0.5 h), which delivered the product ***cis*-6a** (13.38 g, 65.3 mmol, 79%) as a pale yellow oil in analytical purity and an *ee*≥ 99% according to HPLC, which crystallized upon storage in the fridge. The next eluted fractions, showing a low concentration of **6a** again (ca. 0.5 L) were concentrated to give the heterocycle **6a** (419 mg) in ca. 70% purity.

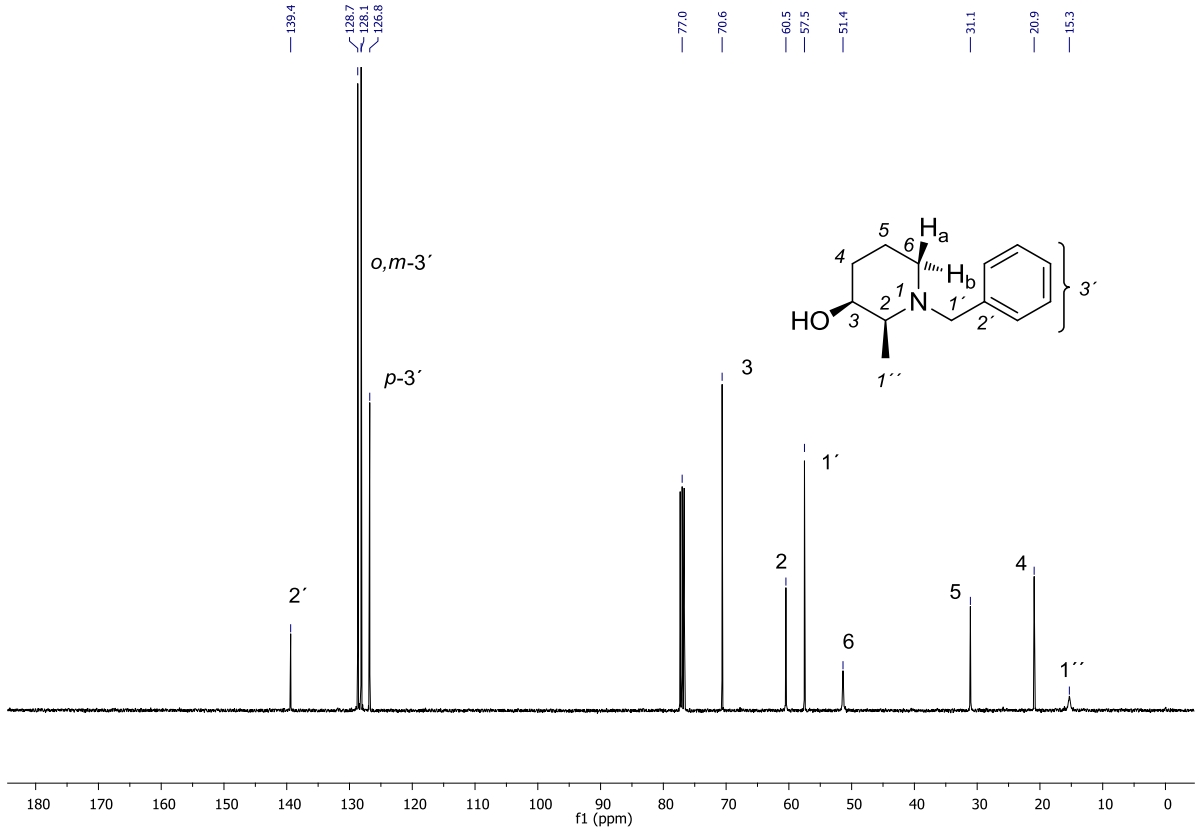
The two batches of piperidine ***cis*-6a** of a lower purity (early and late fractions of the first column) were combined and purified through chromatography on silica gel (18 g) with *i*PrOH/*c*Hex/NEt_3 2.5:100:0.8. After concentration with DCM *in vacuo* (2x2 mL) and drying in high vacuum further heterocycle **6a** (513 mg, 2.50 mmol, 3% *dr*> 19:1) was isolated as a pale yellow oil (purity ≥95% according to NMR).



M ($C_{13}H_{19}NO$) = 205.296 g/mol; **mp.** = 43-44 °C; $\mathbf{r_f}$ (SiO_2, tailing) = 0.36 (MeOH/DCM 1:12), 0.24 (*i*PrOH/*n*Hex 1:5), 0.08 (*i*PrOH/*n*Hex 1:40+1% NEt_3); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.32-7.27 (m, 4H, *o,m*-H-3´), 7.26-7.21 (m, 1H, *p*-H-3´) 3.95 (d, 1H, H-1´$_a$, *J* = 13.4 Hz), 3.66-3.65 (m, 1H, H-3), 3.17 (d, 1H, H-1´$_b$, *J* = 13.4 Hz), 2.72-2.65 (m, 1H, H-6_a), 2.50 (qd, 1H, H-2, *J* = 6.5, 1.6 Hz), 1.98 (td, 1H, H-6_b, *J* = 11.4, 2.8 Hz), 1.82-1.66 (m, 2H, H-4_a, H-5_a), 1.51-1.37 (m, 2H, H-4_b, H-5_b), 1.22 (d, 3H, H-1´´$_{cis}$, *J* = 6.6 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 139.4 (C-2´), 128.7/128.1 (*o,m*-C-3´), 126.8 (*p*-C-3´), 70.6 (C-3), 60.5 (C-2), 57.5 (C-1´), 51.4 (C-6), 31.1 (C-5), 20.9 (C-4), 15.3 (C-1´´); **IR** (film) ν cm^{-1} = 3380 (br), 3085 (w), 3061 (w), 3027 (w), 2967 (w), 2935 (vs), 2867 (w), 2799 (m), 2756 (w), 2716 (w), 1949 (w), 1875 (w), 1811 (w), 1732 (w), 1651 (w), 1603 (w), 1494 (m), 1451 (s), 1370 (m), 1344 (w), 1327 (w), 1276 (w), 1224 (w), 1137 (s), 1107 (m), 1072 (s), 1040 (m), 1026 (m), 994 (m), 967 (m), 922 (w), 911 (w), 857 (w), 810 (w), 768 (w), 737 (vs), 698 (vs); **GC-MS** (EI, 70 eV) m/z u = 205 (5%, M^+, 190 (60%, M-Me^+), 160 (5%), 148 (3%), 132 (5%), 114 (10%), 91 (Bn^+), 65 (10%, Cp^+); **HR-MS** (ESI, $C_{13}H_{20}NO^+$) calc. 206.1545 u, found 206.1538 u; **CHN-Analysis** calc. C: 76.06% H: 9.33% N: 6.83% found C: 75.92% H: 9.41 N: 6.73%; α_D (c = 1.555 g/100 mL, $CHCl_3$, 20 °C) = +85.2.

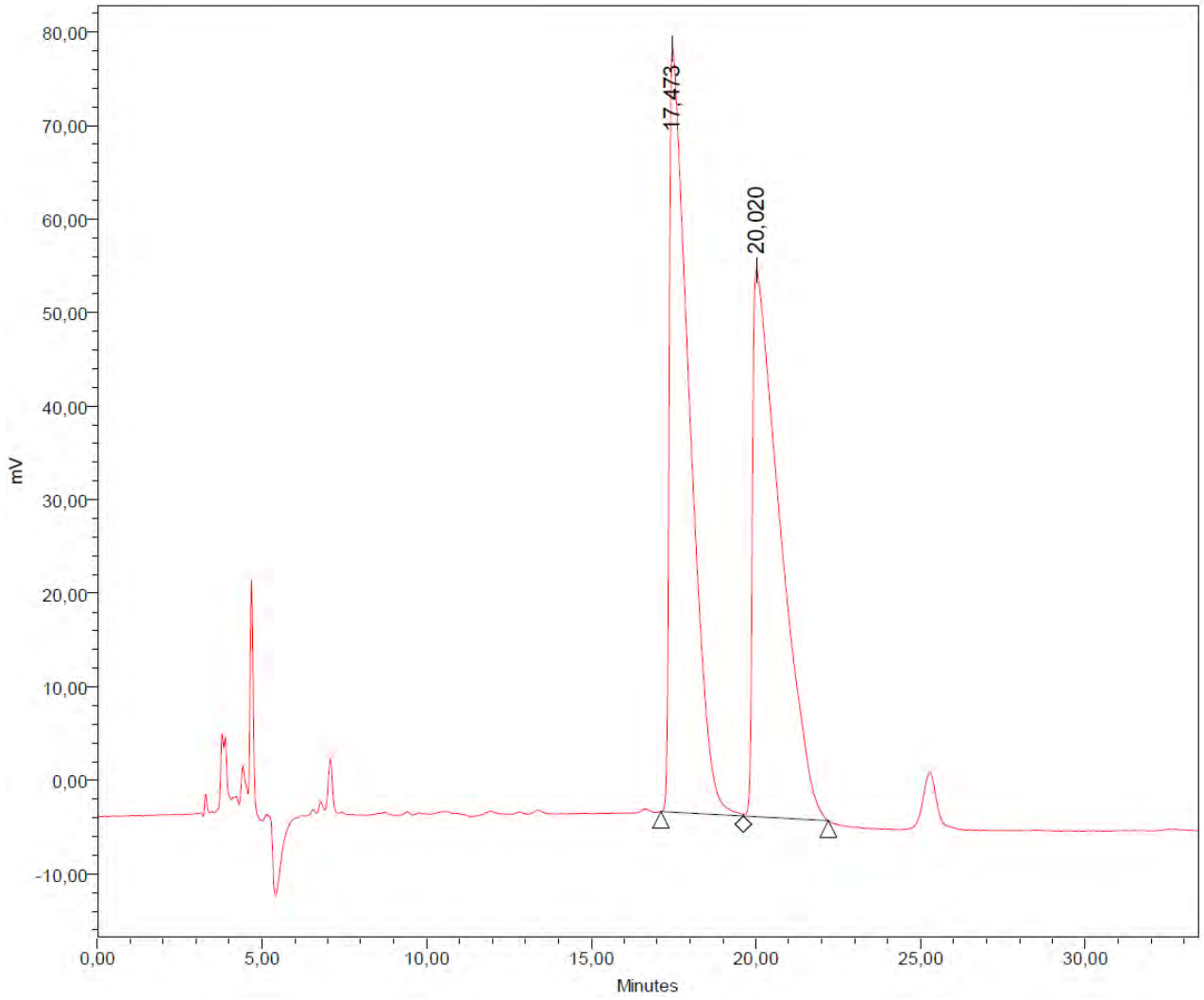


^{1}H-NMR-spectrum of piperidinol ***cis*-6a** in $CDCl_3$ (400 MHz).

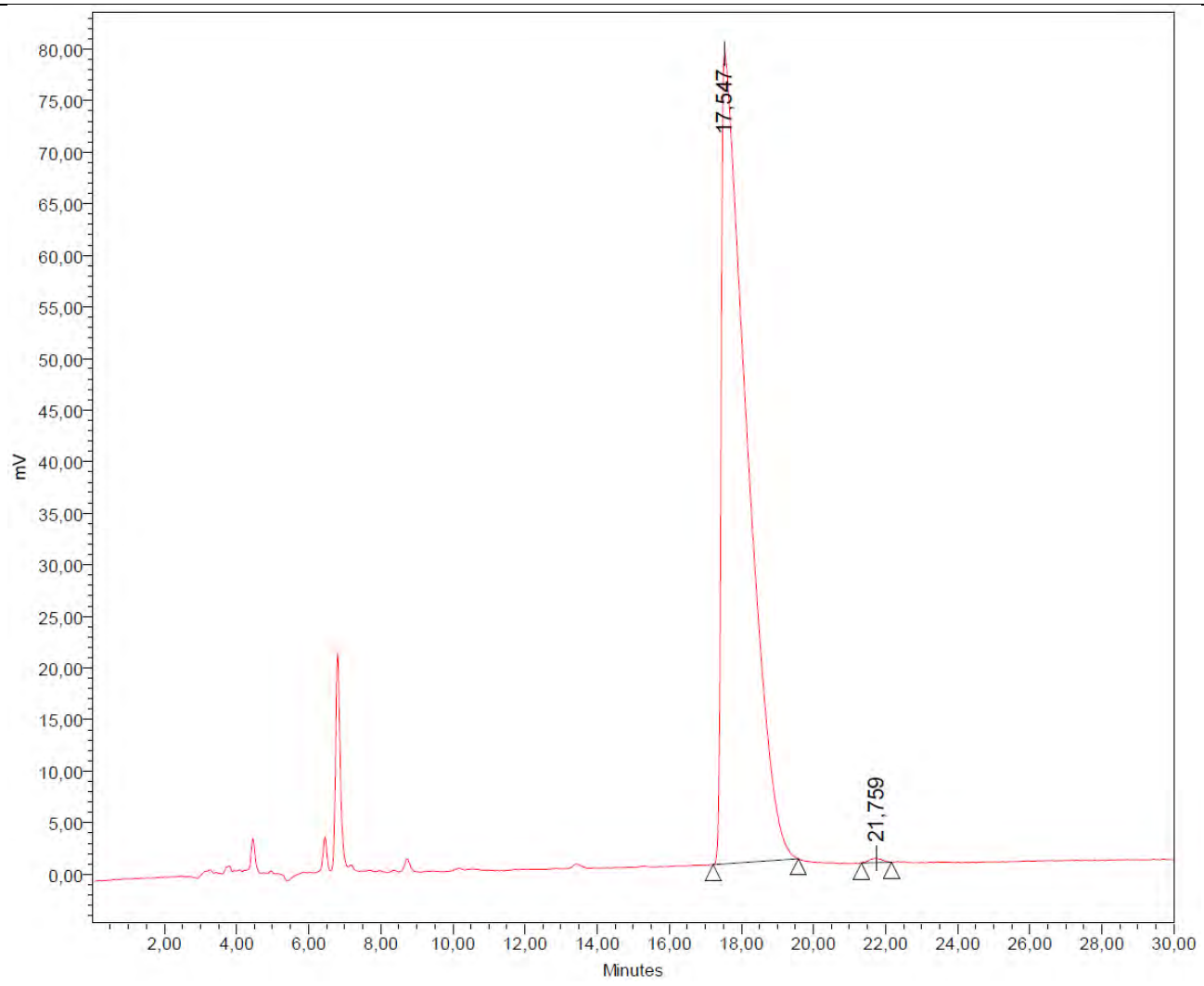


^{13}C-NMR-spectrum of piperidine **6a** in $CDCl_3$ (100 MHz).

HPLC-chromatograms of the racemic and enantioenriched piperidine ***cis*-6a** (separation conditions: column Chiralpak AI from Daicel Industries, flow 1 ml/min, eluent EtOH/*n*Hex/NEt_3 1:100:0.1, detected wavelength 254 nm):

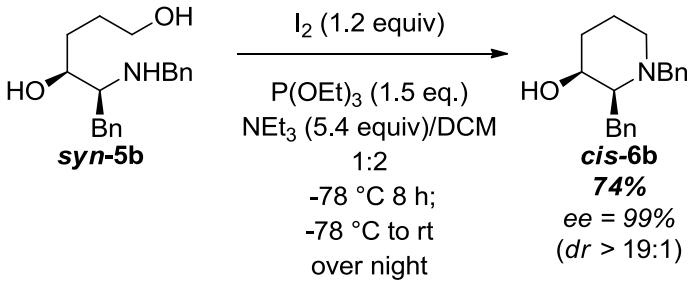


Retention Time (min)	Area	% Area
17,473	3468495	50,50
20,020	3399590	49,50



Retention Time (min)	Area	% Area
17,547	3852853	99,72
21,759	10980	0,28

2.3.6 Synthesis of (*2S,3S*)-1,2-Dibenzyl-3-piperidinol (*cis*-6b)

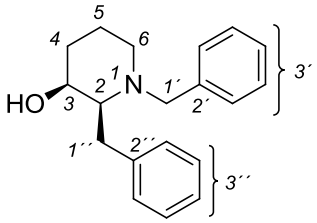


Under an atmosphere of argon the amino alcohol **5b** (1.75 g, 6.85 mmol, 1.0 equiv) was dissolved in dry DCM (8.2 mL, DCM/NEt_3 2:1) and NEt_3 (4.1 mL, 29.2 mmol, 5.0 equiv), cooled to -78 °C and treated with triethyl phosphite (1.50 mL, 8.78 mmol, 1.5 equiv). Then in one portion iodine (1.78 g,

7.02 mol, 1.2 equiv) was added. As magnetically stirring became hampered after 2 h at -78 °C due to a solid precipitate, further dry DCM (0.8 mL) and NEt_3 (0.40 mL, 0.29 mmol, 0.4 equiv) were added dropwise (NEt_3/DCM 1:2) and the mixture was continued to stir at -78 °C for 6 h (I_2 dissolved completely after 1.25 h). Then the reaction suspension was allowed to warm to room temperature overnight (12 h) remaining in the cooling bath and 4 N KOH solution in MeOH (15 mL, 58.5 mmol, 10.0 equiv,) was added.

Next, the mixture was concentrated under reduced pressure (→ 50 mbar),[42] 15 mL of MeOH were added and the resulting suspension was kept in a rotatory evaporator (800 mbar) for 2.5 h at 40 °C. After evaporation of the solvent *in vacuo* (→50 mbar), the residue was dissolved in water (12 mL, **6b** = 0.5 mmol/ml) and Et_2O (H_2O/Et_2O 2:1), the aqueous phase was separated and extracted with further two 8 mL portions of Et_2O.[43] The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give crude **6b** as a yellow oil (1.623 g).

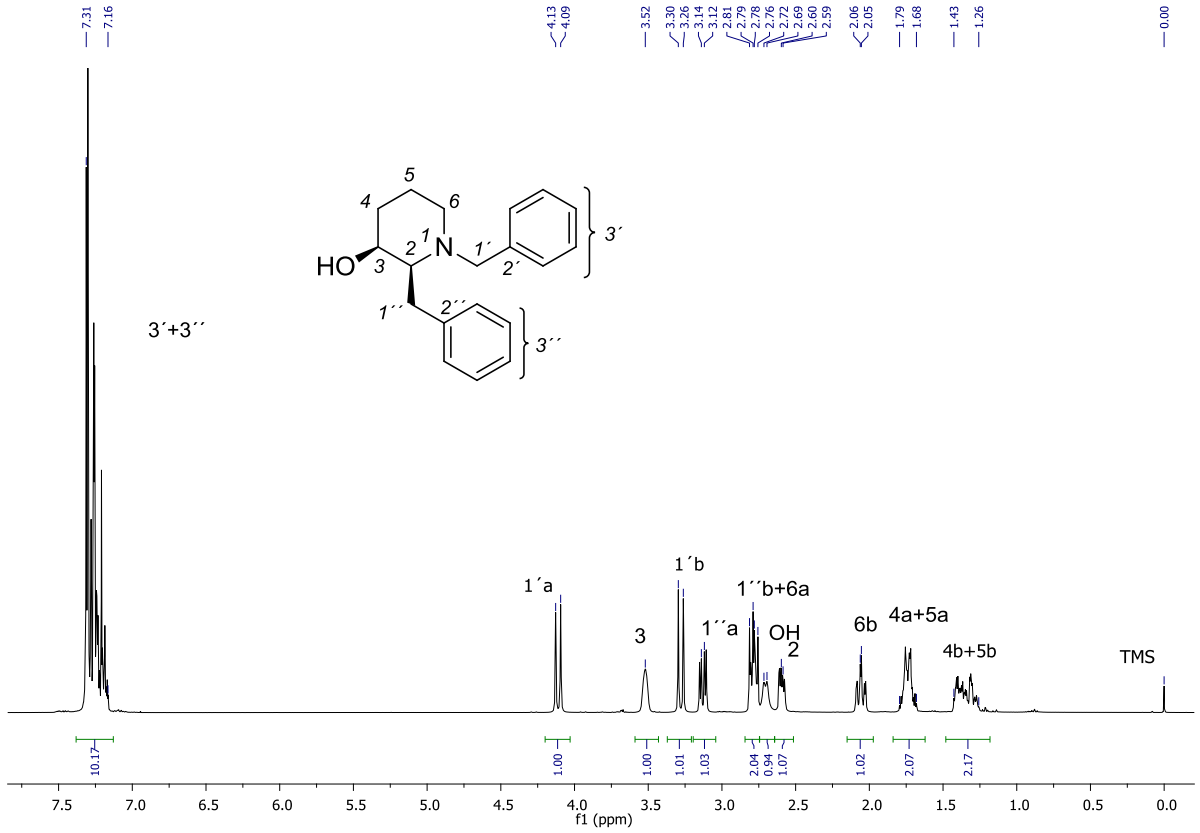
Chromatographic purification on silica gel (40 g; crude **6a** was dissolved in the eluent) with *i*PrOH/*c*Hex/NEt_3 1:100:3 delivered after concentration with DCM (2x2 mL) to remove NEt_3 and drying in high vacuum under stirring at 40 °C for 3 h, piperidine **6a** (1.21 g, 4.30 mmol, 74%, *dr*>19:1) as a yellow oil in analytical purity and an *ee* of >99% according to HPLC.



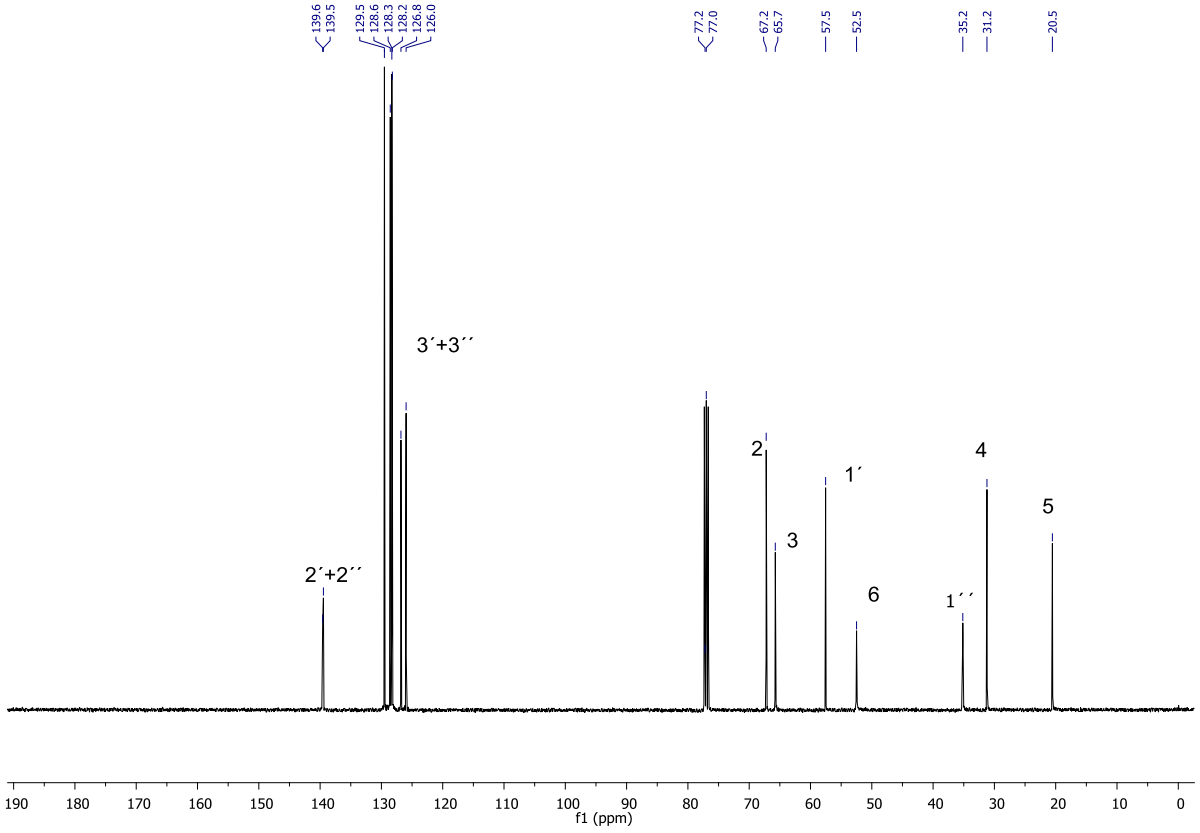
M ($C_{19}H_{23}NO$) = 281.392 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex) = 0.29 (1:2), 0.21 (1:3), (*i*PrOH/*n*Hex) = 0.36 (1:10); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.31-7.16 (m, 10H, H-3´, H-3´´), 4.11 (d, 1H, H-2´$_a$, *J* = 13.6 Hz), 3.52 (app. broad s, 1H, H-3), 3.28 (d, 1H, H-1´$_b$, *J* = 13.6 Hz), 3.13 (dd, 1H, H-1´´$_a$, *J* = 13.3, 4.6 Hz), 2.81-2.76 (m, 2H, H-6$_a$, H-1´´$_b$), 2.70 (d, 1H, OH, *J* = 8.5 Hz), 2.60 (dd, 1H, H-2, *J* = 9.5, 4.7 Hz), 2.06 (td, 1H, H-6$_b$, *J* = 11.7, 2.7 Hz), 1.79-1.68 (m, 2H, H-4$_a$, H-5$_a$), 1.43-1.26 (m, 2H, H-4$_b$, H-5$_b$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 139.6/39.5 (C-2´, C-2´´), 129.5/128.6/128.3/128.2/126.8/126.0 (C-3´, C-3´´), 67.2 (C-2), 65.7 (C-3), 57.5 (C-1´), 52.5 (C-6), 35.2 (C-1´´), 31.2 (C-4), 20.5 (C-5); **IR** (film) ν cm^{-1} = 3462 (br), 3108 (w), 3087 (w), 3064 (w), 3030 (w), 2979 (m), 2938 (m), 2897 (m), 1958 (w), 1888 (w), 1750 (vs), 1605 (w), 1586 (w), 1496 (w), 1454 (m), 1438 (m), 1416 (s), 1384 (w), 1354 (m), 1339 (m), 1268 (m), 1238 (w), 1182 (w), 1169 (w), 1138 (w), 1084 (s), 1046 (m), 1019 (m), 959 (w), 914 (m), 861 (m), 761 (m), 734 (m), 701 (s), 671 (m), 584 (w), 508 (w); **GC-MS** (EI, 70 eV) m/z % = 190 (100, M-Bn^+), 172 (2), 130 (2), 117 (3), 104 (3), 91 (100, Bn^+), 77 (5, Ph^+), 65 (15, Cp^+), 51 (5); **CHN-Analysis** calc. C: 81.10% H: 8.24% N: 4.98% found C: 81.00/81.06% H: 8.26/8.41% N: 4.94/4.90%; **HR-MS** (ESI, $C_{19}H_{24}NO^+$) calc. 282.1858 u, found 282.1855 u; α_D (c = 1.355 g/100 ml, $CHCl_3$, 20 °C) = +44.6.

42 If only DCM is evaporated (→600 mbar), approximately 20mol% of $O=P(OEt)_3$ remained in the crude.

43 Piperidinol **6** was not quantitatively extracted with three portions of *c*Hex.

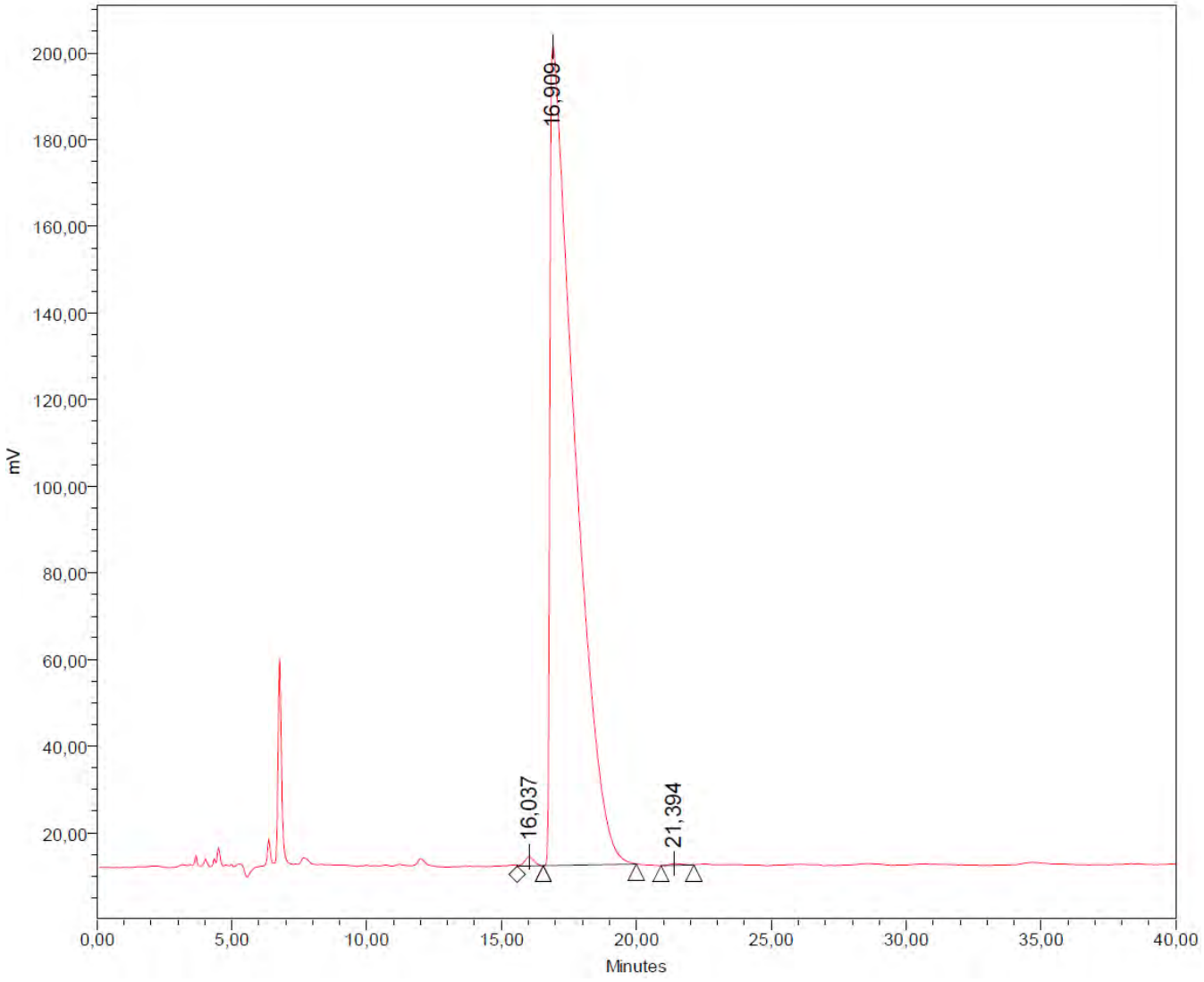


^{1}H-NMR-spectrum of piperidine **6b** in $CDCl_3$ (400 MHz).



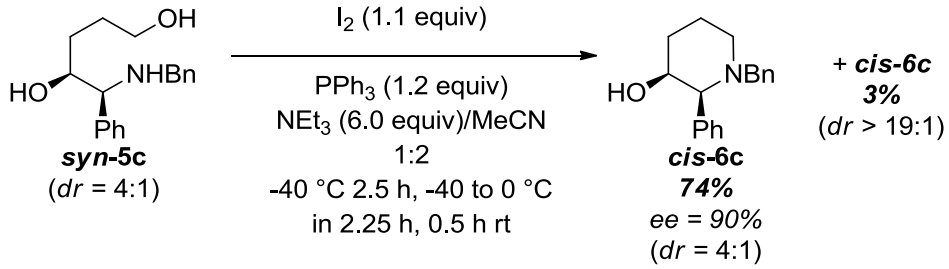
^{13}C-NMR-spectrum of piperidine **6b** in $CDCl_3$ (100 MHz).

HPLC-chromatograms of the enantioenriched piperidine ***cis*-6b** under the same separation conditions as for piperinols ***cis*-6a+c** (separation conditions: column Chiralpak AI from Daicel Industries, flow 1 ml/min, eluent EtOH/*n*Hex/NEt_3 1:100:0.1, detected wavelength 254 nm):



Retention Time (min)	Area	% Area
16,037	50114	0,42
16,909	11977526	99,49
21,394	11169	0,09

2.3.7 Synthesis of (*2S,3S*) 1-Benzyl-2-phenyl-3-piperidinol (*cis*-6c)



Under an atmosphere of argon the amino alcohol ***syn*-5c** (3.226 g, 11.30 mmol, *dr* = 4:1) was dissolved in dry MeCN (19 mL), and NEt_3 (9.5 mL, 67.8 mmol, 6.0 equiv, reagent grade, MeCN/NEt_3 2:1) and PPh_3 (3.40 g, 13.0 mmol, 1.2 equiv) were added and the mixture was stirred at ambient temperature, until PPh_3 had dissolved completely (5 min). Then the reaction solution was cooled in an acetone/dry ice bath to -78 °C and iodine (3.15 g, 12.4 mmol, 1.1 equiv) was added to the clear solution in one portion. The resulting reaction suspension (a colorless precipitate formed after iodine addition) was stirred at -40 °C until complete dissolution of iodine (2.5 h). Then the mixture was allowed to warm to 0 °C within 2.25 h, the cooling bath was removed and stirring was continued for 0.5 h at ambient temperature.[44]

Subsequently, silica gel (22.6 g, **5c**/SiO_2 1:7) was slowly added to the reaction solution under stirring[45] and the solvent was evaporated under reduced pressure. Next, the residue was suspended in *c*Hex (50 mL), the solvent was removed again *in vacuo* (to eliminate traces of MeCN) and the resulting fine powder was dried in high vacuum for 0.5 h.[46] After chromatographic purification on silica gel (160 g, **6a**/SiO_2 1:50) with *i*PrOH/*c*Hex/NEt_3 0.25:100:2 (1 L) → 0.5:100:2 (1 L) 1:100:3 (1 L) → 1:100:4 (0.5 L) → 1:100:5 (0.5 L), 2.065 g of piperidine**6c**in a purity of ≥90% according to ^{1}H-NMR (containing 15mol% of residual DCM) as a yellow oil and 438 mg contaminated with side products (yellow oil, 0.3 L of the early **6c** containing fractions eluted after 1.5 L of the eluent) were isolated. The side product containing fractions (dissolved in the eluent) were purified with a second chromatography on silica (23 g) with *i*PrOH/*c*Hex/NEt_3 0.5→1:100:2. After combination of the product from the first and second column, concentration with DCM under reduced pressure (2x10 mL) and drying in high vacuum under stirring and heating to 40 °C for 0.5 (until the product crystallized) piperidine **7c** was obtained (2.26 g)

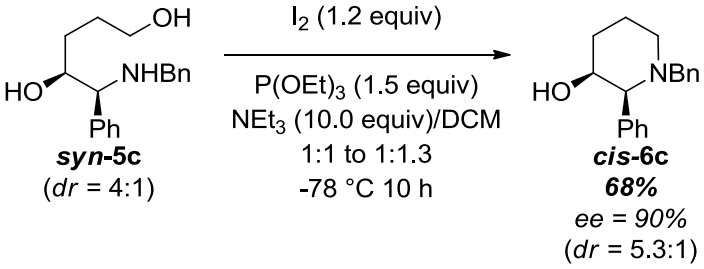
44 After warming to -30 °C, micro work up of a small aliquot of the reaction solution (ca. 50 μL) with 1 N NaOH (aq.)/Et_2O and GC-MS demonstrated full conversion of the starting diol **5a**: Only signals for both stereoisomers of **6c**, PPh_3 and $OPPh_3$ were detected.

45 We recommend a dilution of the reaction mixture with 19 mL of MeCN prior to the addition of SiO_2 to absorb the mixture more homogenously on silica.

46 The mixture was concentrated with the stir bar remaining in the reaction flask, because the stir bar effected milling of the silica gel and prevented “sloshing”, and was removed before chromatographic purification.

as a yellow, waxy solid. Considering 5mol% of residual DCM, the product **6c** was isolated in a yield of 74% (8.31 mmol, *dr* = 4.0:1 *cis/trans*, *ee* = 90% according to HPLC).

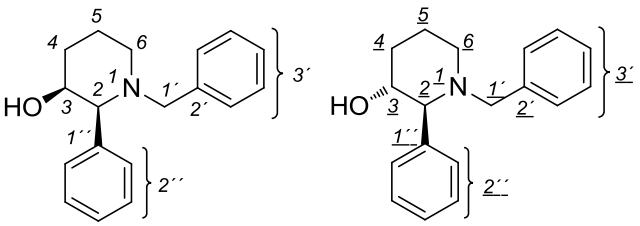
After the second column 154 mg of piperidine **6a** in mixture with side products (early eluted fractions) were isolated, too. Additional chromatographic purification with *i*PrOH/*c*Hex/NEt_3 0.25:100:2 →0.5:100:3, concentration with chloroform (2x2 mL) and drying in high vacuum for 2 h gave of the pure *trans*-isomer of **6a** (79 mg, 0.295 mmol, 3%) as a pale yellow oil.



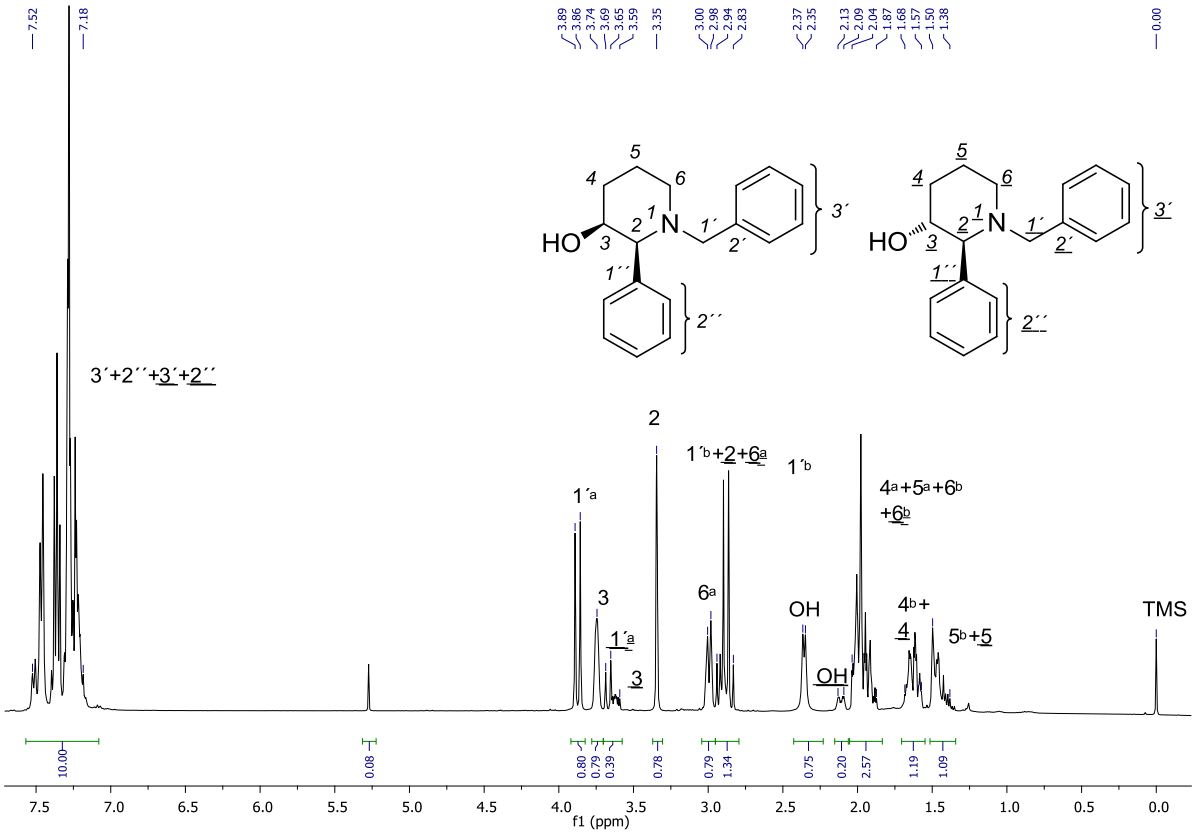
Under an atmosphere of argon the amino alcohol **5c** (190 mg, 0.665 mmol, 1.0 equiv, *dr* = 4:1) was dissolved in dry DCM (0.92 mL, DCM/NEt_3 1:1) and NEt_3 (0.92 mL, 6.65 mmol, 10.0 equiv), cooled to -78 °C and treated with triethyl phosphite (0.17 mL, 0.998 mmol, 1.5 equiv). Then iodine (202 mg, 0.798 mmol, 1.2 equiv) was added in one portion and the reaction mixture was stirred for 4.5 h at -78 °C, whereby a colorless precipitate started to form after 0.5 h of stirring. As iodine had still not completely dissolved, the reaction suspension was diluted with dry DCM (0.2 mL, NEt_3/DCM 1:1.2) and stirred for further 5 h at -78 °C. Then further dry DCM (0.1 equiv, NEt_3/DCM 1:1.3) was added and after 0.5 h iodine had dissolved completely. Thereafter the reaction was quenched by the addition of 4 N KOH solution in MeOH (1.7 mL, 6.65 mmol, 10.0 equiv) at -78 °C. Subsequently, the solvent was removed under reduced pressure (→ 50 mbar), the residue was diluted with 1.7 mL of MeOH and kept in the rotatory evaporator (800 mbar) for 0.5 h at 40 °C. After evaporation of the solvent, the mixture was dissolved in H_2O (4 mL) and Et_2O (4 mL), the aqueous phase was separated and extracted with two further 4 mL portions of Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give crude **6c** as a yellow oil (185 mg). Chromatographic purification on silica gel (10 g; crude **6c** was dissolved in the eluent) with *i*PrOH/*c*Hex/NEt_3 0:100:3 → 0.5:100:2 → 1:100:3 and concentration with DCM (2x2 mL) delivered he crude piperdine **6c** (136.9 mg, *dr* = 4.8:1) and furan **19c** in a ratio of 85:15.

Piperidine **6c** was separated from the furan side product **19c** (eluted in earlier fractions than **6c**) through two consecutive chromatographic purifications (with the second column from the first column remaining mixture of **6c**/**19c** was separated) with *i*PrOH/*c*Hex/NEt_3 0.25:100:3→1:100:3 on silica. After concentration with DCM and drying in high vacuum for 3 h, the desired piperidine **6c** (122.9 mg, *dr* = 5.3:1) were isolated as a pale yellow oil. Considering 7mol% of residual DCM, **6c** was obtained in a yield of 68% (0.450 mmol).

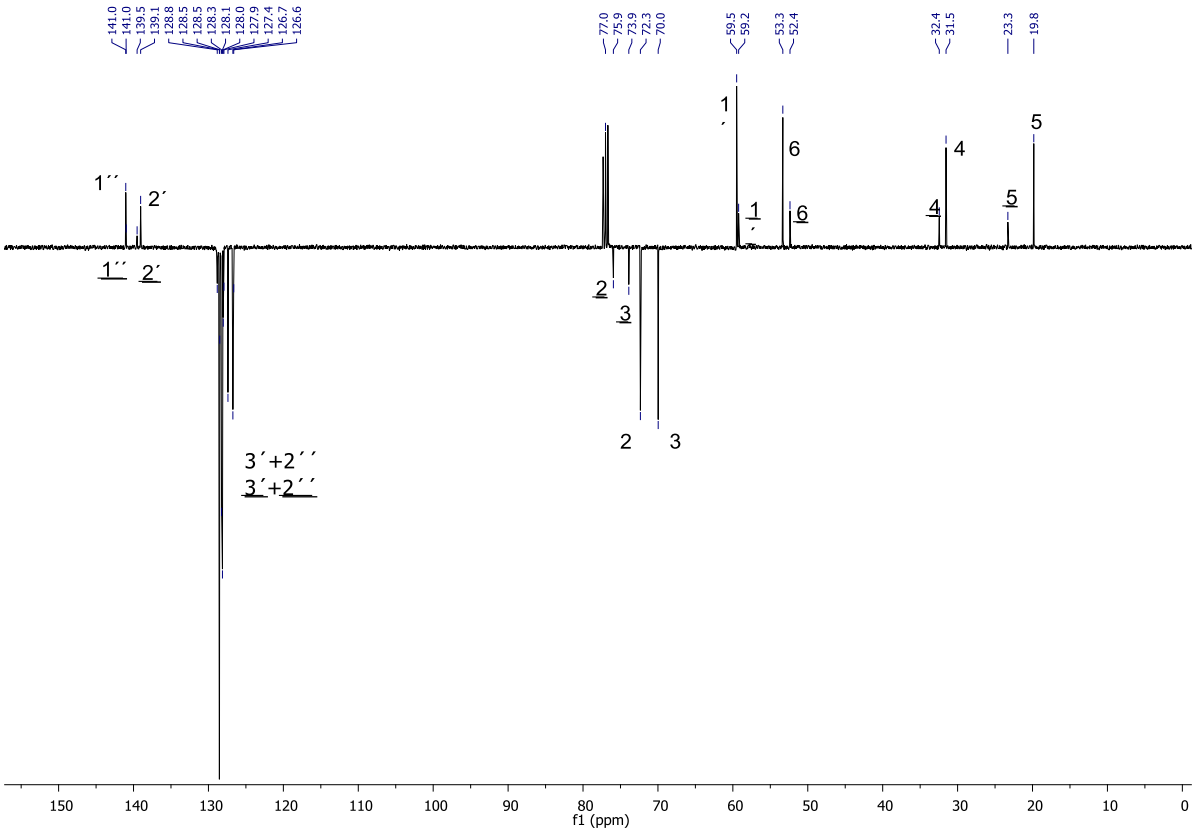
(*2S,3S*) and (*2S,3R*)-1-Benzyl-3-hydroxy-2-phenylpiperidin (6c)



M ($C_{16}H_{21}NO$) = 267.365 g/mol; $\mathbf{r_f}$ (SiO_2) = 0.25 (EtOAc/*n*Hex 1:3), 0.45 (*i*PrOH/*n*Hex 1:10), 0.42 (1:8 *i*PrOH/*c*Hex), 0.06 (*i*PrOH/*n*Hex 1:80 + 1% NEt_3), 0.06, 0.50 (*i*PrOH/*c*Hex 1:6), 0.26 (*i*PrOH/*c*Hex/NEt_3 1:100:3); **^{1}H-NMR** (400 MHz, $CDCl_3$, *dr* = 4:1 *cis/trans*) δ ppm = 7.52-7.18 (m, 20H, H-3´, H-2´´, H-3´, H-2´´), 3.88 (d, 1H, H-1´$_a$, *J* = 13.4 Hz), 3.74 (app. broad s, 1H, H-2), 3.67/3.65-3.59 (d/m, 2H, H-2, H-1´$_a$, *J* = 13.2 Hz), 3.35 (app. broad s, 1H, H-3), 2.99 (d, 1H, H-6$_a$, *J* = 9.1 Hz), 2.94-2.83 (m, 3H, H-1´$_b$, H-3, H-6$_a$), 2.36 (d, 1H, OH, *J* = 6.5 Hz), 2.13-2.09 (m, 1H, OH), 2.04-1.87 (m, 4H, H-4$_a$, H-5$_a$, H-6$_b$, H-6$_b$), 1.68-1.57 (m, 2H, H-4$_b$, H-4$_b$), 1.50-1.38 (m, 2H, H-5$_b$, H-5$_b$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 141.0 (C-1´´), 141.0 (C-1´´), 139.5 (C-2´), 139.1 (C-2´), 128.8/2x128.54/128.3/128.1/128.0/127.9/127.4/126.7/ 126.6 (C-3´, C-2´´, C-3´, C-3´´), 76.0 (C-2), 73.9 (C-3), 72.3 (C-2), 70.0 (C-3), 59.5 (C-1´), 59.2 (C-1´), 53.3 (C-6), 52.4 (C-6´), 32.4 (C-4), 31.5 (C-4), 23.3 (C-5), 19.83 (C-5); **IR** (film) ν cm^{-1} = 3555 (br), 3446 (br), 3085 (w), 3060 (m), 3027 (m), 2939 (s), 2857 (w), 2791 (s), 2751 (w), 2718 (w), 1951 (w), 1884 (w), 1812 (w), 1601 (w), 1584 (w), 1493 (s), 1451 (s), 1384 (m), 1369 (m), 1356 (w), 1309 (w), 1263 (w), 1220 (w), 1182 (w), 1119 (m), 1069 (m), 1028 (m), 1014 (s), 971 (m), 912 (w), 899 (w), 837 (w), 750 (vs), 701 (vs), 533 (s); **HR-MS** (ESI, $C_{18}H_{22}NO^+$) calc. 268.1701 u, found 268.1700 u, (ESI, $C_{18}H_{22}NO^+$) calc. 268.1701 u found 286.1700 u; **GC-MS** (EI, 70 eV) m/z u = 268 (<1%, M+H$^+$), 118 (<5%), 103 (<5%), 91 (100%, Bn$^+$), 77 (10%, Ph$^+$), 65 (20%, Cp$^+$), 57 (10%), 44 (15%); α_D (c = 1.612 g/mol, $CHCl_3$, 21.0 °C) = +29.6.



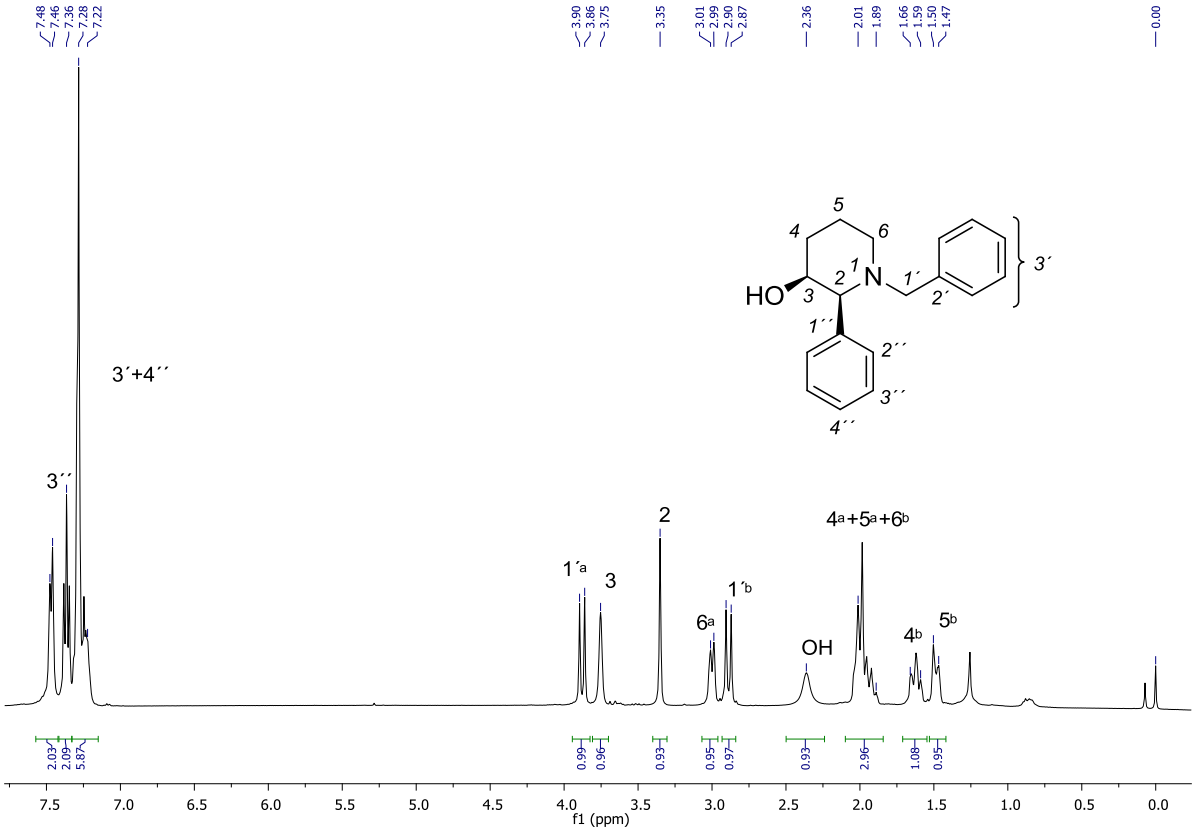
^{1}H-NMR-spectrum of piperidine **6c** in $CDCl_3$ (*dr* = 4:1, 400 MHz).



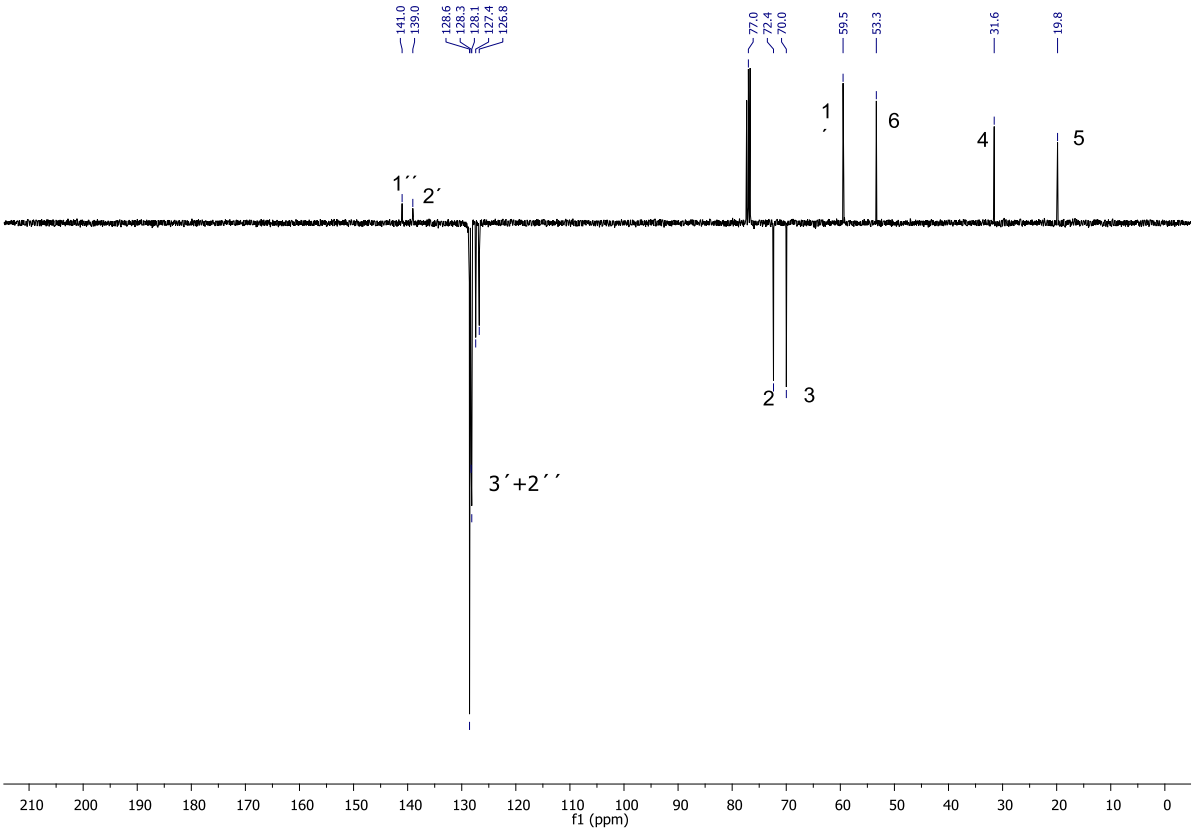
DEPT-135 spectrum of piperidine **6c** in $CDCl_3$ (*dr* = 4:1 100 MHz).

(*2S,3S*)-1-Benzyl-3-hydroxy-2-phenylpiperidin (*cis*-6c)

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm = 7.47 (d, 1H, H-4´´, *J* = 7.3 Hz), 7.36 (t, 2H, H-3´´, *J* = 7.6 Hz), 7.28-7.22 (m, 7H, H-3´), 3.88 (d, 1H, H-1´$_a$, *J* = 13.6 Hz), 3.75 (app. broad s, 1H, H-3), 3.35 (app. broad s, 1H, H-2), 3.00 (d, 1H, H-6$_a$, *J* = 9.0 Hz), 2.89 (d, 1H, H-1´$_b$, *J* = 13.8 Hz), 2.36 (s, 1H, OH), 2.01-1.89 (m, 3H, H-4$_a$, H-5$_a$, H-6$_b$), 1.66-1.59 (m, 1H, H-4$_b$) 1.50-1.47 (m, 1H, H-5$_b$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 141.0 (C-1´´), 139.1 (C-2´), 128.6/128.3/128.2/127.4/126.8 (C-3´, C-3´´, C-4´´), 72.4 (C-2), 67.0 (C-3), 59.5 (C-1´), 53.3 (C-6), 31.6 (C-4), 19.8 (C-5); α_D (c = 1.095 g/100 mL, $CHCl_3$, 20 °C) = +30.2.

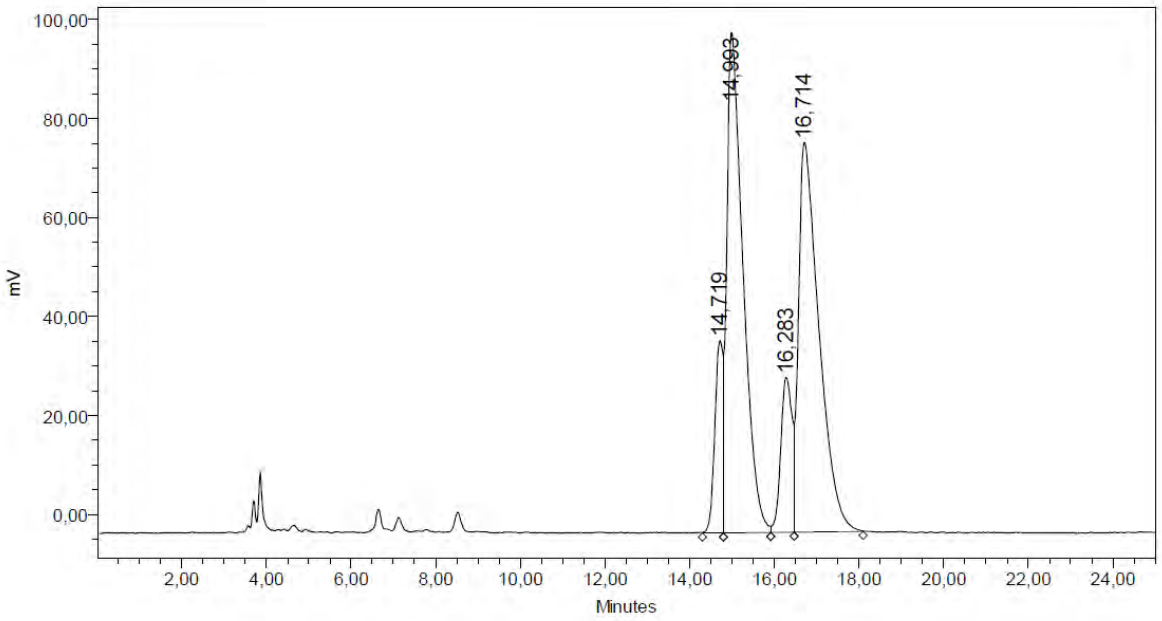


^{1}H-NMR-spectrum of piperidine ***cis*-6c** in $CDCl_3$ (400 MHz).

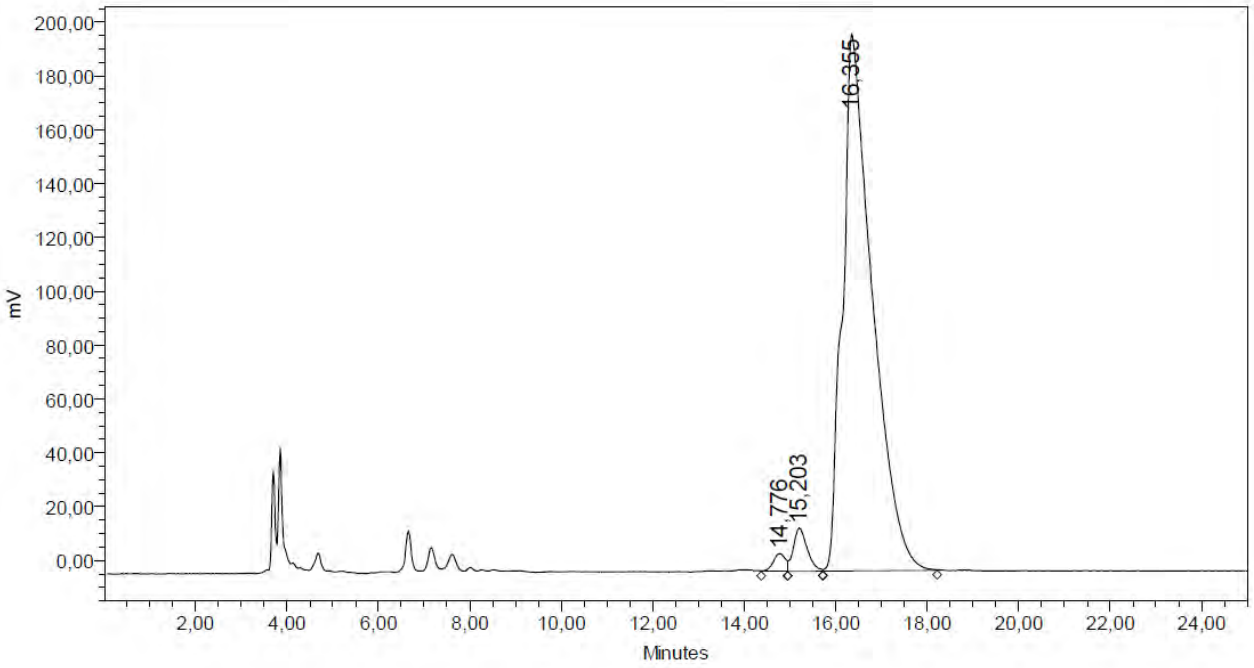


DEPT-135 spectrum of piperidine ***cis*-6c** in $CDCl_3$ (100 MHz).

HPLC-chromatograms of the racemic and enantioenriched piperidine **6c** (*dr* = 4:1 *cis/trans*; separation conditions: column Chiralpak AI from Daicel Industries, flow 1 ml/min, eluent EtOH/*n*Hex/NEt_3 1:100:0.1, detected wavelength 254 nm):



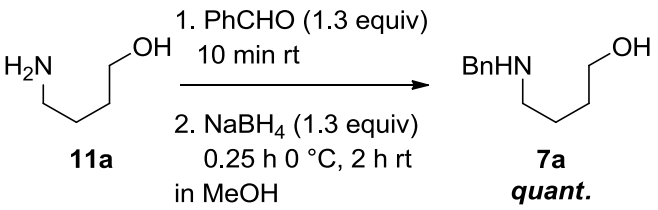
	RT	Area	% Area	Height
1	14,719	513206	7,97	38850
2	14,993	2704344	41,97	101281
3	16,283	577562	8,96	31294
4	16,714	2648133	41,10	78734



	RT	Area	% Area	Height
1	14,776	121666	1,28	6608
2	15,203	338203	3,57	15996
3	16,355	9021406	95,15	199464

2.4 Synthesis of Heterocycles 8 (Table 1)

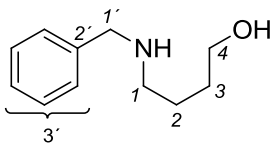
2.4.1 Synthesis of 4-(Benzylamino)-1-butanol (7a)



11a **7a** ***quant.***

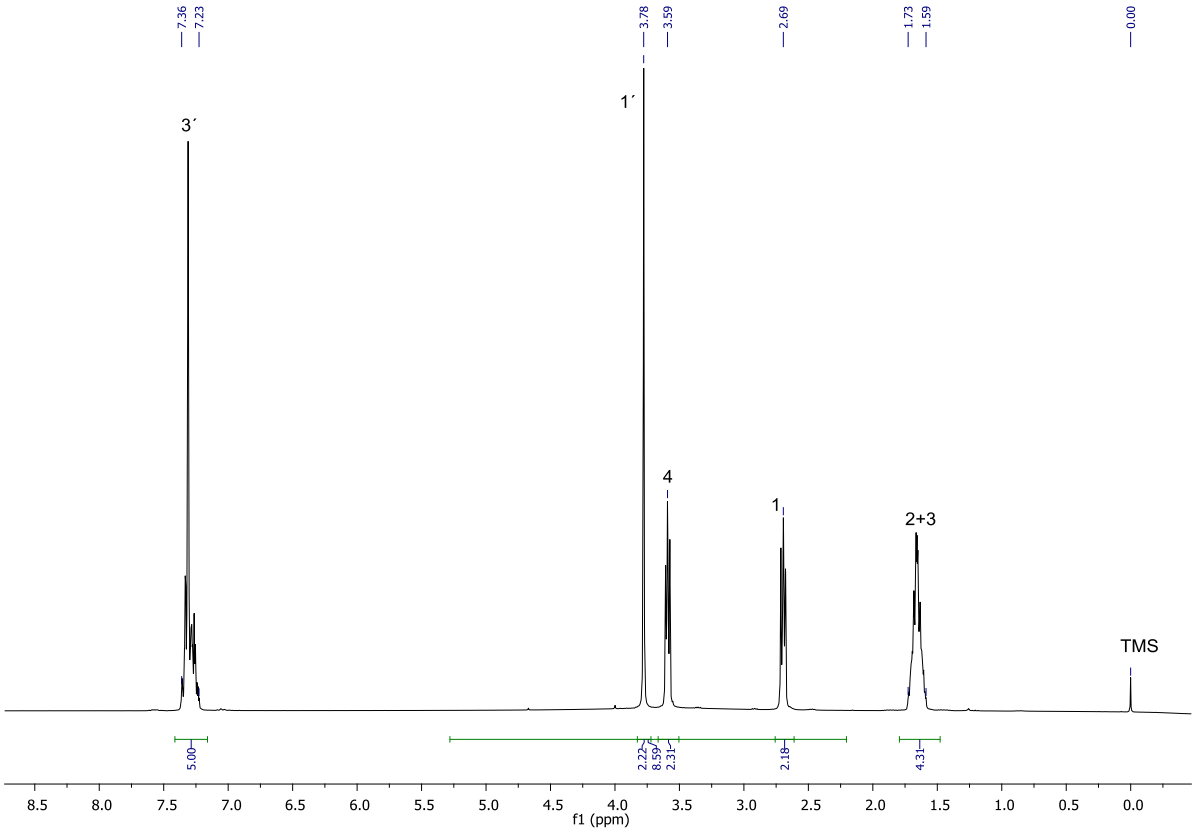
Amino alcohol **11a** (0.30 mL, 2.87 mmol, 1.0 equiv) was dissolved in MeOH (6 mL, **11a** = 0.5 mol/L), then benzaldehyde[47] (0.38 mL, 3.73 mmol, 1.3 equiv) was added and the mixture was allowed to stir for 10 min at room temperature. Subsequently, the reaction was cooled in an ice bath, $NaBH_4$ (140 mg, 3.73 mmol, 1.3 equiv) was added in two portions within 5 min, the mixture was stirred for 0.25 h at 0 °C and 2 h at ambient temperature.

Next, the reaction suspension was cooled again to 0 °C, 37% HCl-solution in water (0.70 mL, 8.61 mmol, 3.0 equiv) was added dropwise and MeOH was removed under reduced pressure (→ 100 mbar). The residue was diluted with water (6 mL) and Et_2O (4 mL; pH of the mixture ≤ 0), the phases were separated and the aqueous phase was washed with two further 4 mL portions of Et_2O. In the following, the aqueous phase was cooled in an ice bath, KOH (380 mg, 6.8 mmol, 2.5 equiv) was added and dissolved under stirring, whereby an oil separated. The basic mixture (pH = 13) was extracted with three 4 mL portions of Et_2O, the combined extraction phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude benzyl amine **7a**was dissolved in 1 mL of chloroform and concentrated under reduced pressure (x2) to remove residual Et_2O and dried in high vacuum for 0.5 h under stirring (until the gas evolution ceased). The product **7a** (541 mg, 3.01 mmol, *quant*.) was obtained as a colorless oil.

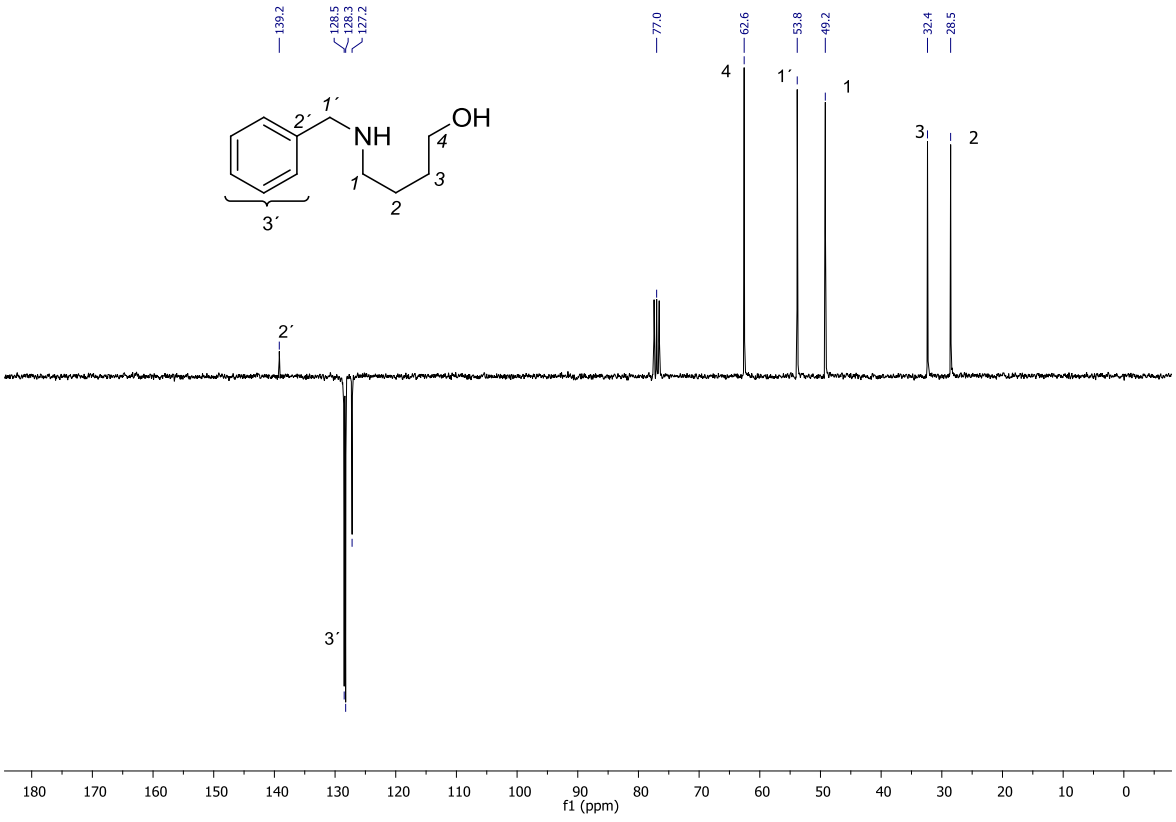


M ($C_{11}H_{17}NO$) = 179.259 g/mol; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ ppm = 7.36-7.23 (m, 5H, H-3´), 3.78 (s) (2H, H-1´), 3.70 (s, very broad, 2H, OH, NH) 3.59 (t, 2H, H-4, *J* = 5.0 Hz), 2.69 (t, 2H, H-1, *J* = 5.5 Hz), 1.73-1.59 (m, 4H, H-2, H-3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 139.2 (C-2´), 128.5/128.3/127.2 (C-3´), 62.6 (C-4), 53.8 (C-4), 49.2 (C-1), 32.4 (C-3), 28.6 (C-4); **IR** (ATR) ν cm^{-1} = 3274 (br), 3082 (w), 3058 (w), 3024 (w), 2926 (m), 2855 (m), 1950 (w), 1873 (w), 1811 (w), 1603 (w), 1493 (m), 1451 (s), 1366 (w), 1309 (w), 1176 (w), 1104 (m), 1056 (s), 1027 (s), 910 (w), 731 (vs), 695 (vs); **GC-MS** (EI, 70 eV) m/z u = 175 (1, M^+), 120 (35, M-*n*$PrOH^+$), 106 (15, M-*n*$BuOH^+$) 91 (100, Bn^+), 77 (5, Ph^+), 65 (15, Cp^+), 51 (5), 39 (10).

47 Benzaldehyde (10 mL) was diluted with 1 mL of Et_2O (so improve phase separation in the following washing), washed with three 5 mL portions of saturated $NaHCO_3$-solution in water and brine (5 mL) and dried over $MgSO_4$. Finally, Et_2O was removed under reduced pressure.

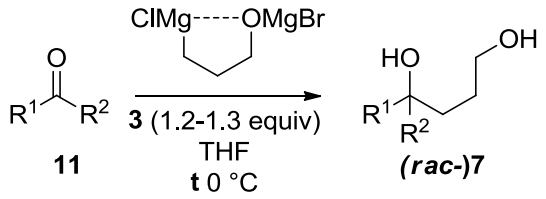


^{1}H-NMR-spectrum of amino alcohol **7a** in $CDCl_3$ (300 MHz).



DEPT-135 spectrum of amino alcohol **7a** in $CDCl_3$ (75 MHz).

2.4.2 General Procedure for the Addition of *Grignard*-reagent 3 with Carbonyl Compounds 7b-f

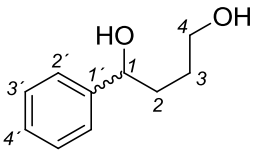


Under an atmosphere of argon the carbonyl compound **11** (1.0 equiv, 3-5 mmol) was dissolved in dry THF (**1** = 1 mol/L) and cooled to 0 °C. Then a 0.30 N solution of ClMg*n*PrOMgBr in THF/MeTHF (1.2 equiv) was added dropwise within 10-20 min. After stirring for a time period **t** at 0 °C, the reaction was quenched through the addition of saturated NH_4Cl-solution in water (2 mL/1 mmol **3**).

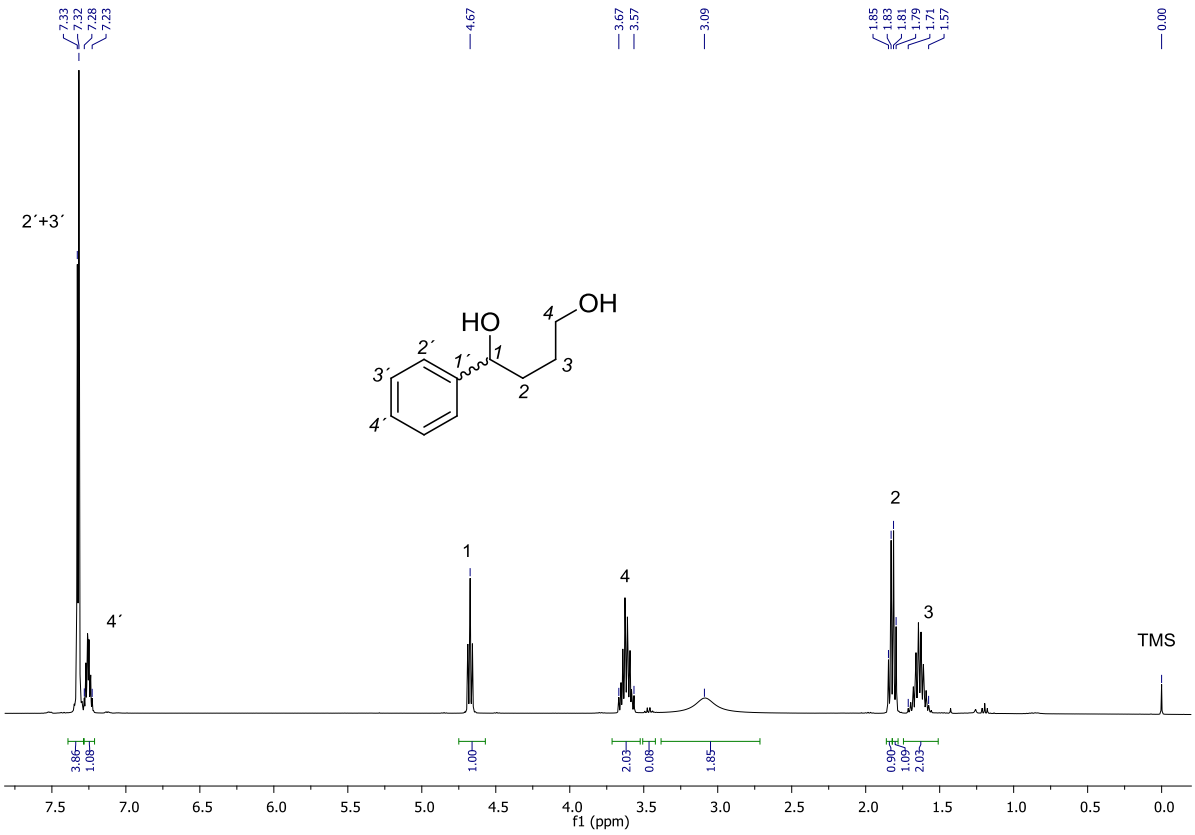
The THF/MeTHF was evaporated under reduced pressure (→200 mbar), the remaining mixture was diluted with water to dissolve precipitated NH_4Cl (usually 1/3 to 1/4 of the volume of the NH_4Cl solution) and DCM (aq. Phase/DCM 2:1). If a precipitate still remained after adding water (up to 1/3), the mixture was neutralized to pH = 6-8 with conc. HOAc. Then the aqueous phase was separated and extracted with two further portions of DCM. The combined DCM-phases were dried over $MgSO_4$ and concentrated under reduced pressure. Finally the crude diol **7** was purified through column chromatography on silica (SiO_2/**8** 30-20:1) with EtOAc/*c*Hex as eluent mixtures, concentrated *in vacuo* with chloroform (x2) and dried in high vacuum with stirring for a couple of hours.

2.4.3 Analytical data of 1-phenyl-1,4-butandiol (R^1 = Ph, R^2 = H; *rac*-7b)

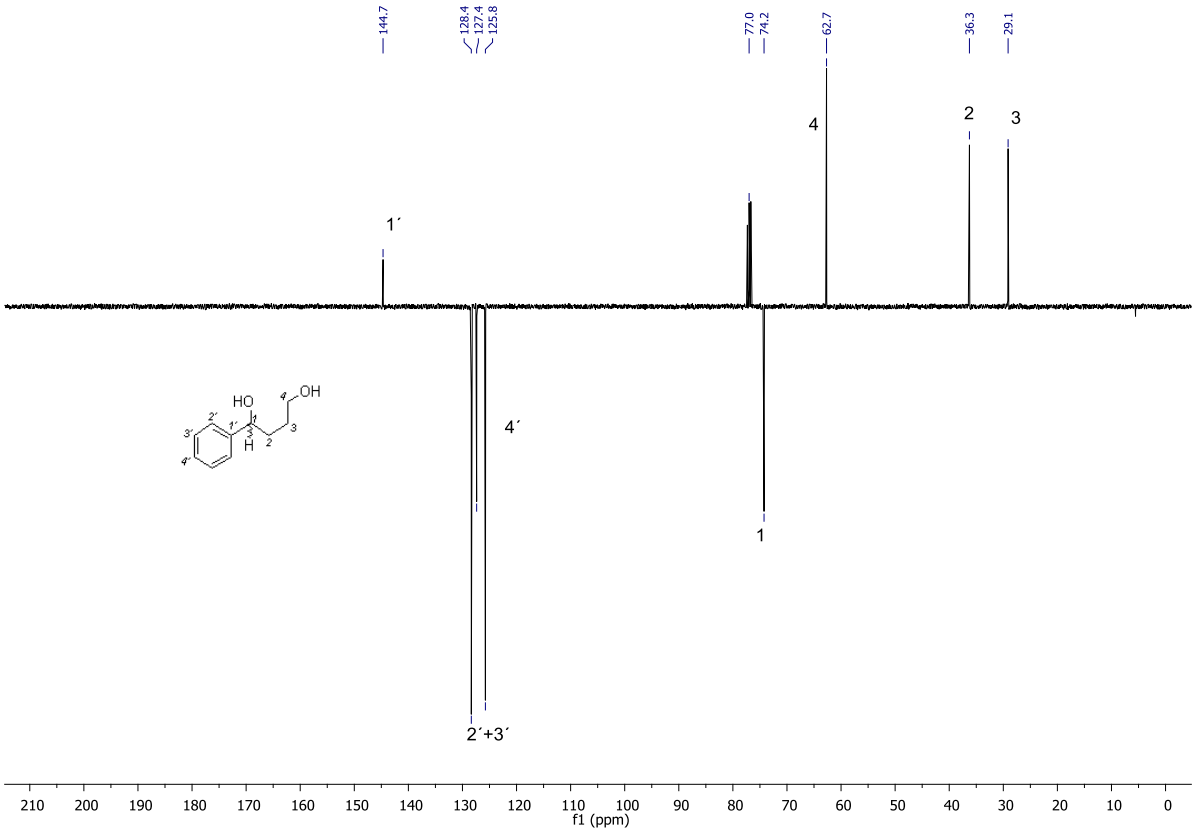
t: 5 min; **eluent:** EtOAc/*c*Hex 3:1 (crude dissolved in eluent); **yield:** 79% (655 mg, 3.94 mmol, colorless oil)



M ($C_{10}H_{14}O_2$) = 166.217 g/ml; **mp.** = 64-65 °C; $\mathbf{r_f}$(SiO_2) = 0.50 (EtOAc), 0.29 (EtOAc/*c*Hex 3:1); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.33/7.32 (2xs, 4H, H-2´, H-3´), 7.28-7.23 (m, 1H, H-4´), 4.67 (t, 1H, H-1, *J* = 6.4 Hz), 3.67-3.57 (m, 2H, H-4), 3.09 (s, 2H, OH), 1.84 (d, 1H, H-2_a, *J* = 7.1 Hz), 1.80 (d, 1H, H-2_b, *J* = 7.0 Hz), 1.71-1.57 (m, 2H, H-3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 144.7 (C-1´), 128.4 (C-2´ or C-3´), 127.4 (C-4´), 125.8 (C-2´ or C-3´), 74.2 (C-1), 62.7 (C-4), 36.3 (C-2), 29.1 (C-3); **IR** (ATR) ν cm^{-1} = 3303 (br), 3083 (w), 3059 (w), 3026 (w), 2939 (m), 2867 (m), 1950 (w), 1883 (w), 1810 (w), 1760 (w), 1601 (w), 1492 (m), 1450 (s), 1331 (w), 1200 (w), 1048 (s), 1026 (s), 1006 (s), 975 (w), 956 (w), 913 (w), 762 (s), 608 (vs); **GC-MS** (EI, 70 eV): m/z % = 166 (10, M^+), 147 (15, M-H_2O-H^+), 115 (10), 107 (100, $PhCHOH^+$), 105 (40, $PhCO^+$), 91 (15, Bn^+), 79 (90), 77 (75, Ph^+), 51 (20), 39 (10).



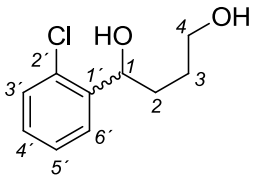
^{1}H-NMR-spectrum of diol ***rac-7a*** in $CDCl_3$ (400 MHz).



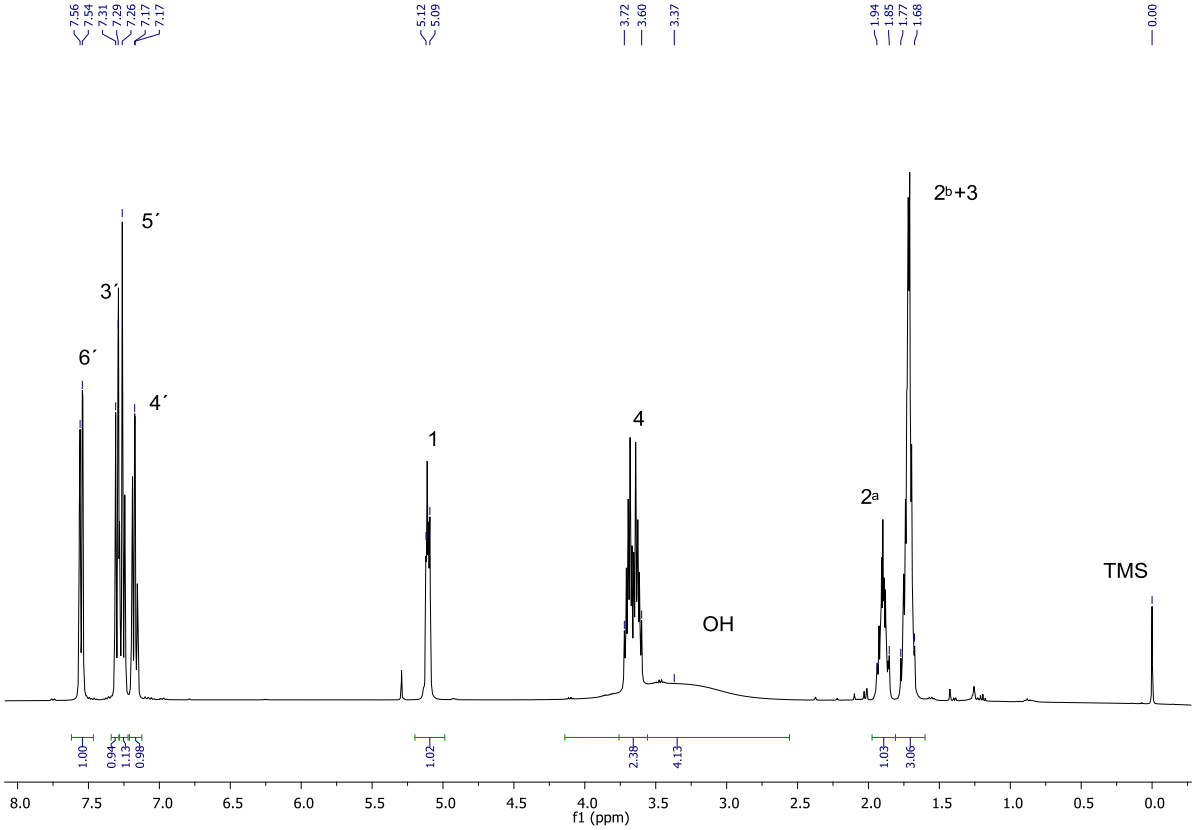
DEPT-135 spectrum of diol ***rac-7b*** in $CDCl_3$ (100 MHz).

2.4.4 Analytical Data of *rac*-1-(2-Chlorophenyl)-1,4-butandiol (R^1 = *o*ClPh, R^2 = H; *rac*-7c)

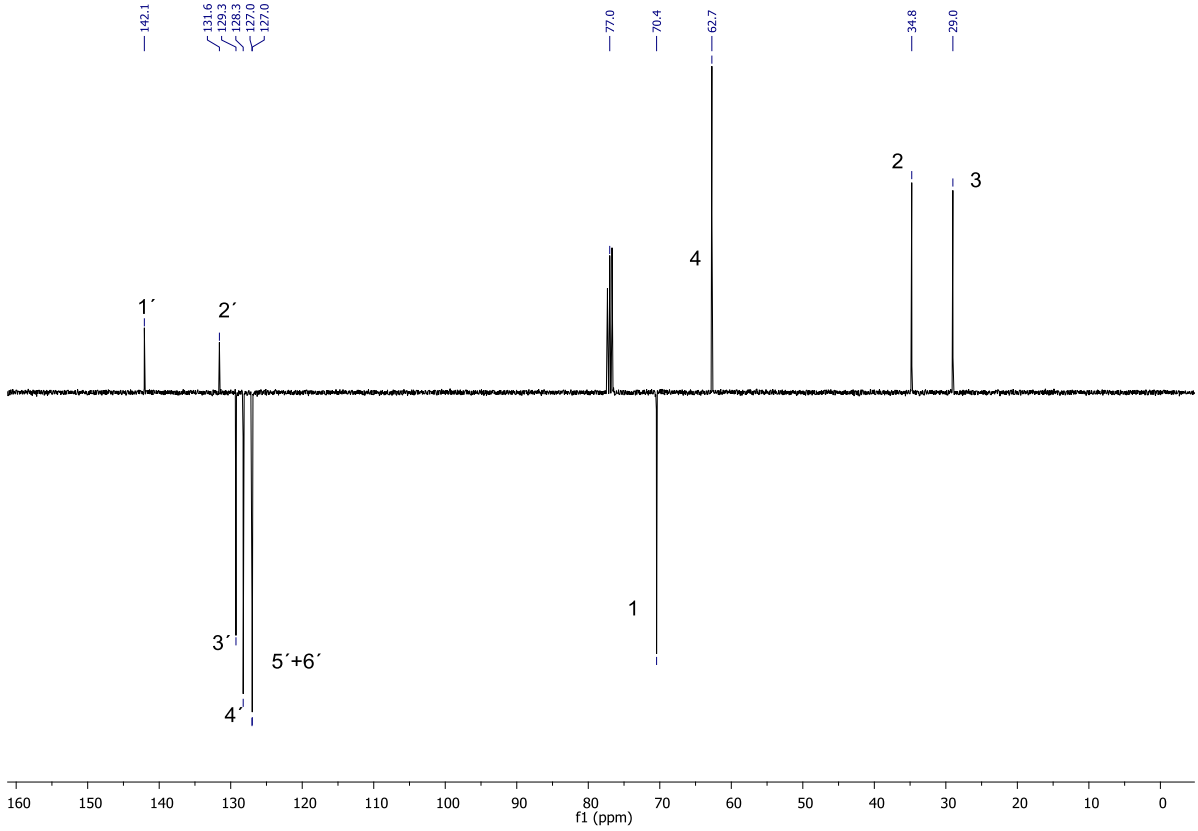
t: 30 min; **eluent**: EtOAc/*c*Hex 1:1→3:2 (crude **7c** was dissolved in the eluent); **yield**: 94% (668 mg, 3.35 mmol, colorless oil).



M ($C_{10}H_{13}ClO_2$) = 200.662 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*c*Hex) = 0.23 (1:1), 0.27 (3:2), 0.45 (2:1); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.55 (dd, 1H, H-6´, *J* = 7.8, 1.3 Hz), 7.30 (dd, 1H, H-3´, *J* = 7.9, 1.0 Hz), 7.26 (t, 1H, H-5´, *J* = 7.3 Hz), 7.17 (td, 1H, H-4´, *J* = 7.7, 1.5 Hz), 5.12-5.09 (m, 1H, H-1), 3.72-3.60 (m, 2H, H-4), 3.37 (s (broad), 2H, 2xOH), 1.94-1.85 (m, 1H, H-2_a), 1.77-1.68 (m, 3H, H-2_b, H-3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 142.1 (C-1´), 131.6 (C-2´), 129.3 (C-3´), 128.3 (C-4´), 2x127.0 (C-5´, C-6´), 70.5 (C-1), 62.7 (C-4), 34.8 (C-2), 29.0 (C-3); **GC-MS** (EI, 70 eV) m/z u = 200 (2, M^+), 181 (5), 165 (5), 147 (15), 143 (20, M(^{37}Cl)-*n*PrOH$^+$), 141 (100, M-*n*PrOH$^+$), 139 (20, M-H_2-*n*PrOH$^+$), 115 (20), 105 (10, $PhCO^+$), 89 (10), 77 (70, Ph^+), 63 (5), 51 (20), 39 (20); **IR** (ATR) ν cm^{-1} = 3312 (br), 3065 (w), 2940 (m), 2870 (w), 2922 (w), 1805 (w), 1593 (w), 1571 (w), 1471 (m), 1436 (s), 1342 (w), 1262 (w), 1197 (w), 1157 (w), 1128 (w), 1047 (vs), 1033 (vs), 1011 (vs), 957 (m), 750 (vs), 702 (s).



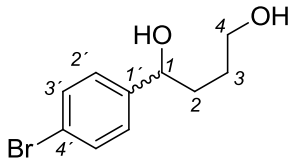
^{1}H-NMR-spectrum of diol ***rac*-7c** in $CDCl_3$ (400 MHz).



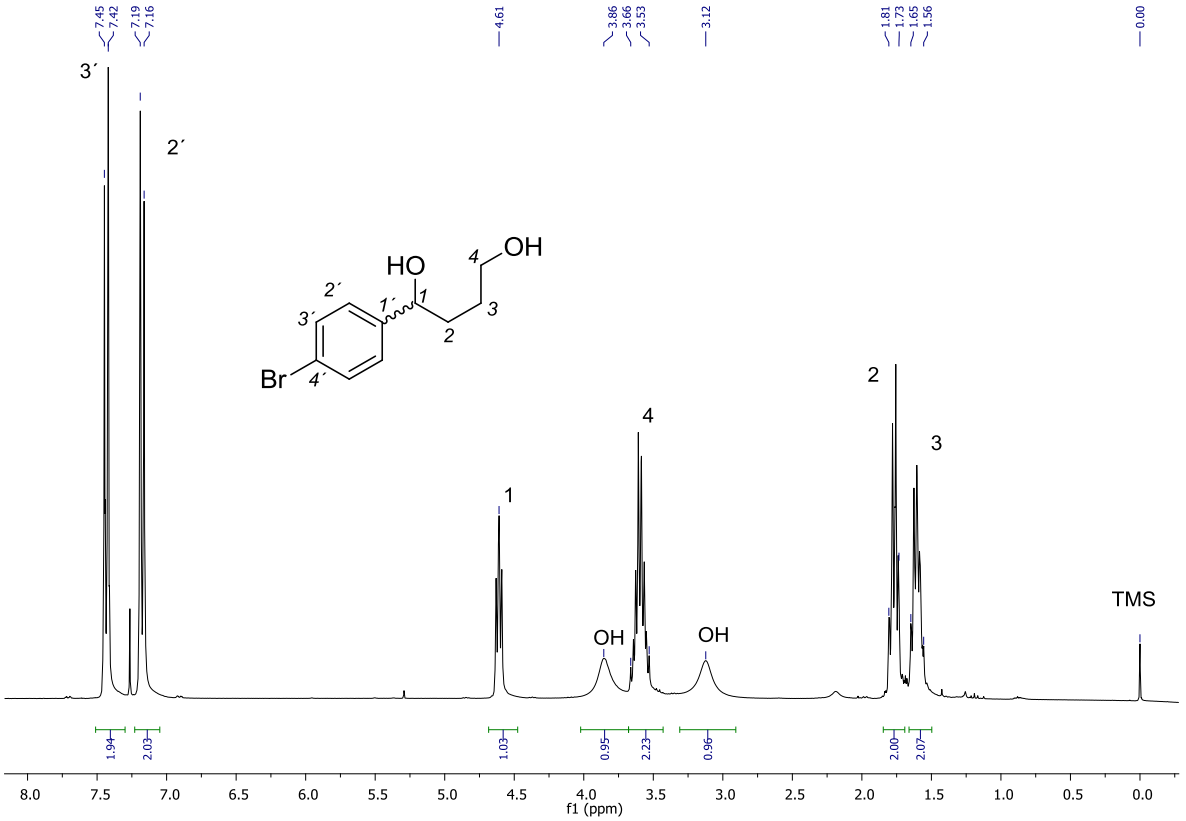
DEPT-135 spectrum of the diol ***rac*-7c** in $CDCl_3$ (100 MHz).

2.4.5 Analytical Data of *rac*-1-(4-Bromophenyl)-1,4-butandiol (R^1 = *p*BrPh, R^2 = H; *rac*-8d)

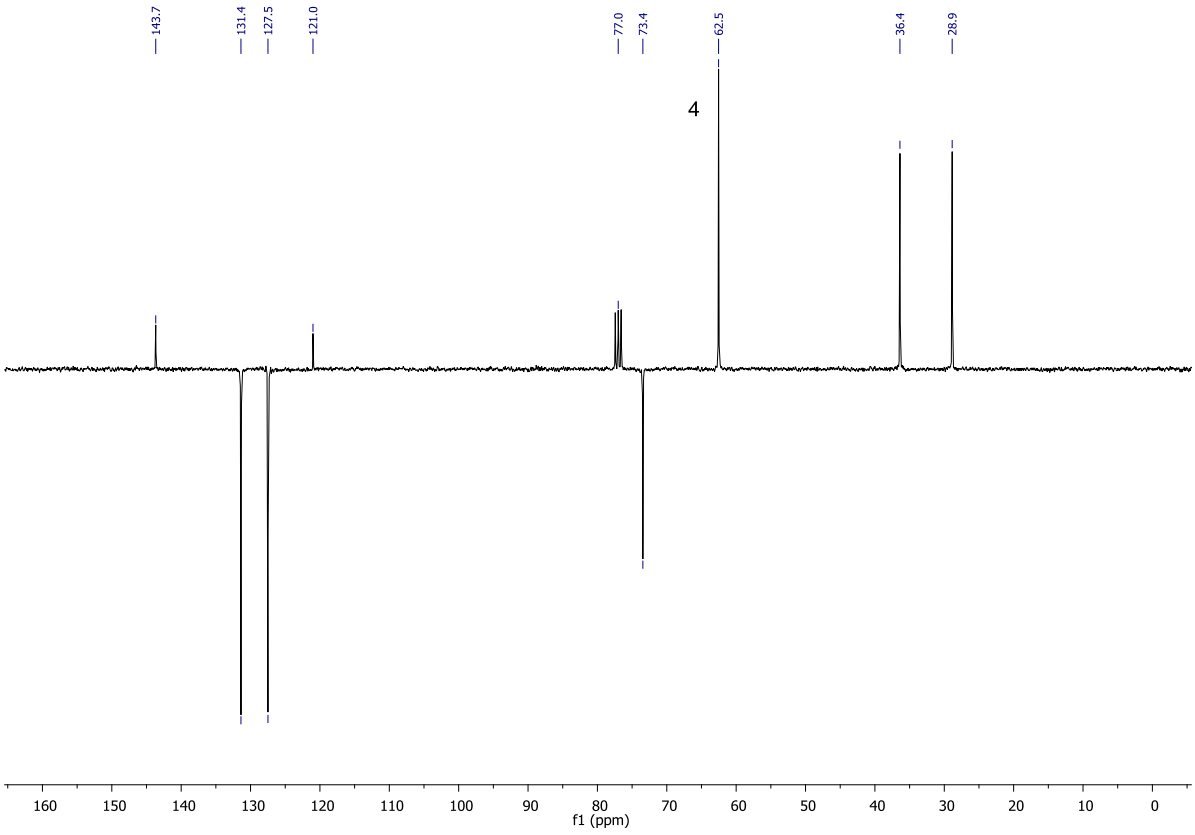
t: 20 min; **eluent**: EtOAc/*c*Hex 2:1→5:2 (crude **7d** was dissolved in DCM under heating); **yield:** 84% (982 mg, 4.01 mmol, colorless solid).



M ($C_{10}H_{13}BrO_2$) = 245.113 g/mol; **mp.** = 77-78 °C; $\mathbf{r_f}$(SiO_2, EtOAc/*c*Hex)= 0.16 (3:2), 0.23 (5:2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ ppm = 7.44 (d, 2H, H-3´, *J* = 8.3 Hz), 7.18 (d, 2H, H-2´, *J* = 8.3 Hz), 4.61 (t, 1H, H-1, *J* = 6.1 Hz), 3.86 (s, 1H, OH), 3.66-3.53 (m, 2H, H-4), 3.12 (s, 1H, OH), 1.81-1.73 (m, 2H, H-2), 1.65-1.56 (m, 2H, H-3); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ ppm = 143.7 (C-1´), 131.4 (C-3´), 127.5 (C-2´), 121.0 (C-4´), 73.5 (C-1), 62.5 (C-4), 36.4 (C-2), 28.9 (C-3); **IR** (ATR) ν cm^{-1} = 3307 (br), 2939 (m), 2869 (m), 1900 (w), 1784 (w), 1590 (w), 1484 (s), 1402 (m), 1334 (w), 1197 (w), 1069 (s), 1008 (vs), 958 (w), 825 (s); **GC-MS** (EI, 70 eV), m/z u = 246 (5, M(^{81}Br)$^+$), 244 (5, M(^{79}Br)$^+$), 187 (80), 185 (100), 159 (5) 157 (15), 147 (35, M-Br-H_2O^+), 128 (5), 115 (15), 105 (20, $PhCO^+$), 91 (5, Bn^+), 77 (65, Ph^+), 51 (15); **HR-MS** (ESI, $C_{13}H_{13}ClO_2$+Na^+) calc. 223.0496 u found 223.0496 u.



^{1}H-NMR-spectrum of diol ***rac*-7d** in $CDCl_3$ (300 MHz).

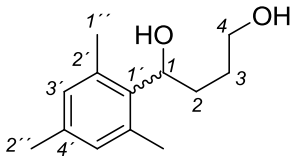


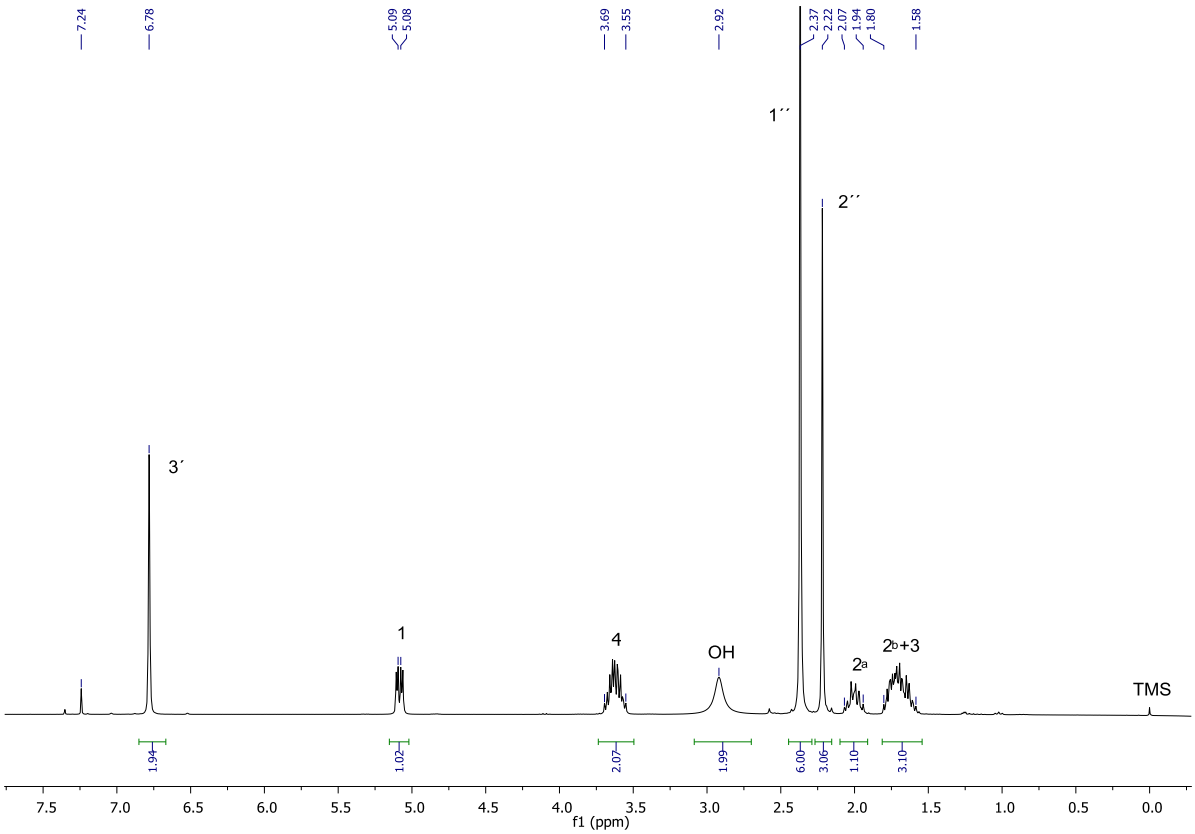
DEPT-135 spectrum of the diol ***rac*-7d** in $CDCl_3$ (75 MHz).

2.4.6 Analytical Data of *rac*-1-(2,4,6-Trimethylphenyl)-1,4-butandiol (R^1 = 2,4,6-Me_3Ph, R^2 = H; *rac*-7e)

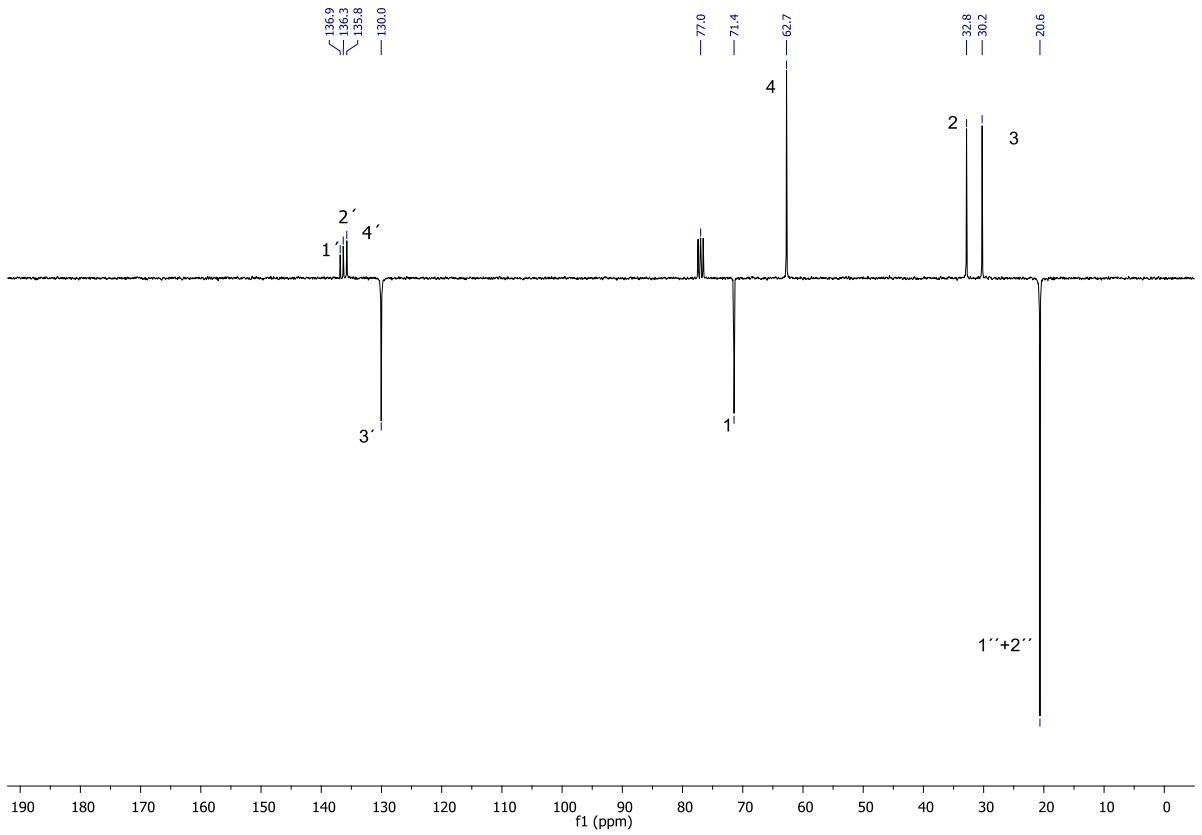
t: 1 h; **eluent**: EtOAc/*c*Hex 3:2 (crude **7e** was dissolved in the eluent); **yield**: 90% (631 mg, 3.03 mmol, colorless solid).

M ($C_{13}H_{20}O_2$) = 208.297 g/mol; **mp.** = 82-84 °C; $\mathbf{r_f}$(SiO_2) = 0.44 (EtOAc/*c*Hex 2:1), 0.29 (EtOAc/*c*Hex 3:2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ ppm = 6.78 (s, 2H, H-3´), 5.09 (dd, 1H, H-1, *J* = 9.6, 4.0 Hz), 3.69-3.55 (m, 2H, H-4), 2.92 (s, 2H, OH), 2.37 (s, 6H, H-1´´), 2.22 (s, 3H, H-2´´), 2.07-1.94 (m, 1H, H-2_a), 1.80-1.58 (m, 3H, H-2_b, H-3); **^{13}C-NMR** (75 MHz, $CDCl_3$,) δ ppm = 136.9 (C-1´), 136.4 (C-2´), 135.8 (C-4´), 130.0 (C-3´), 71.5 (C-1), 62.7 (C-4), 32.8 (C-2), 30.3 (C-3), 20.7 (C-1´´, C-2´´); **IR** (ATR) ν cm^{-1} = 3324 (br), 3003 (w), 2943 (s), 2917 (s), 2864 (m), 1734 (w), 1609 (m), 1573 (w), 1445 (s), 1376 (m), 1315 (w), 1205 (w), 1166 (w), 1142 (w), 1038 (vs), 1000 (vs), 907 (s), 849 (s), 728 (vs); **GC-MS** (EI, 70 eV) m/z u = 190 (30, M-H_2O^+), 175 (15, M-H_2O-Me^+), 159 (30), 149 (100, M-*n*$PrOH^+$), 147 (30, M-H_2-*n*$PrOH^+$) 121 (30), 105 (30), 91 (25, Bn^+), 77 (10, Ph^+), 41 (10, allyl$^+$).





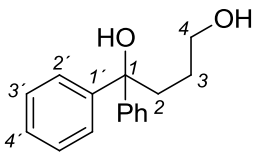
^{1}H-NMR-spectrum of diol ***rac*-7e** in $CDCl_3$ (300 MHz).



DEPT-135 spectrum of the diol ***rac*-7d** in $CDCl_3$ (75 MHz).

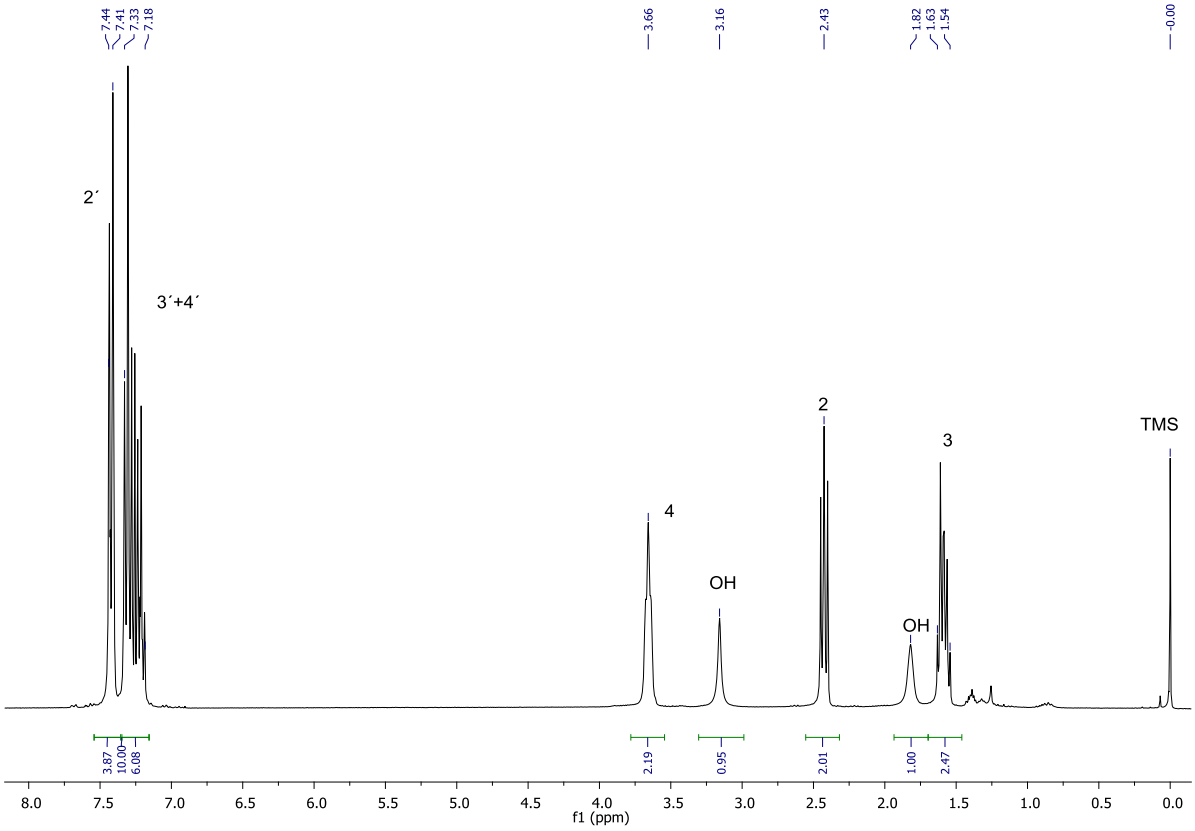
2.4.7 Analytical Data of 1,1-diphenyl-1,4-butandiol (R^1, R^2 = Ph 7f)

t: 1.5 h; **eluent**: no chromatographic purification necessary; **yield**: *quant*. (1.276 g, 5.27 mmol, colorless solid).

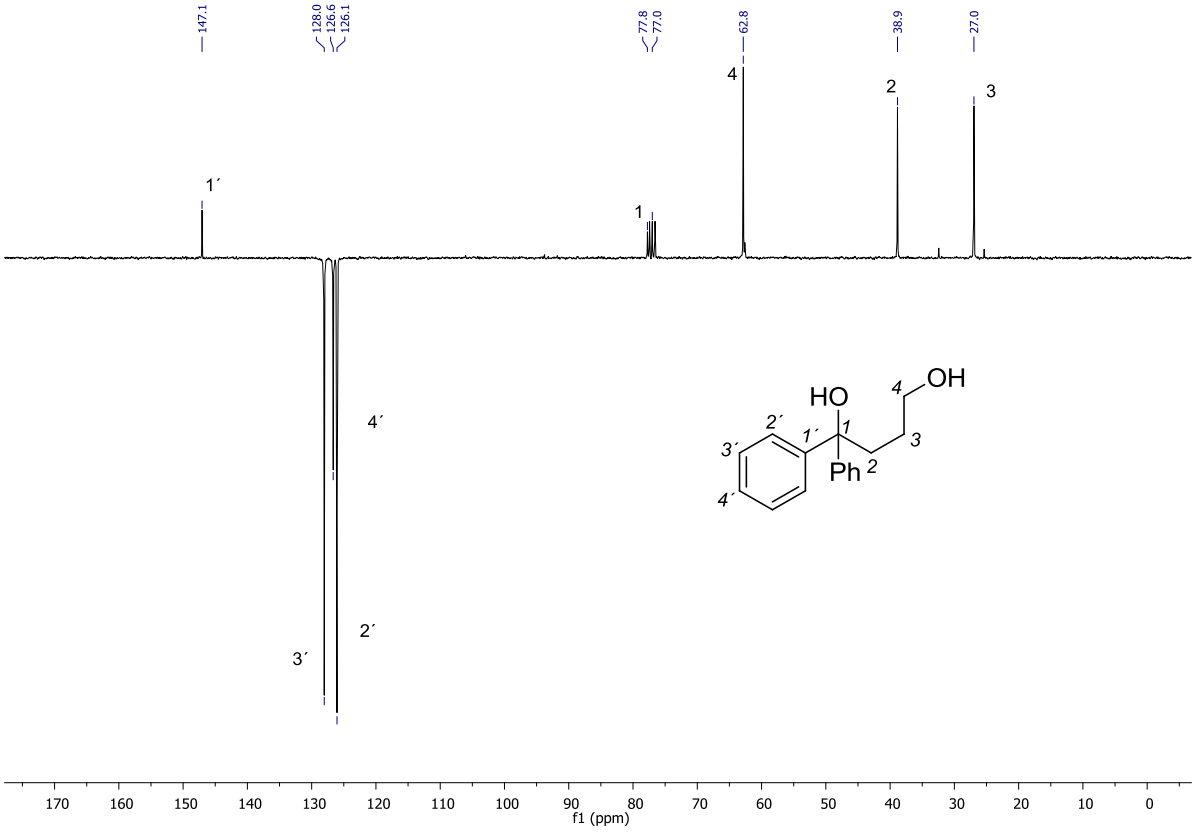


M ($C_{16}H_{18}O_2$) = 242.313 g/mol; **mp.** = 99-100 °C (lit.: 108 °C);[481] **^{1}H-NMR** (300 MHz, $CDCl_3$) δ ppm = 7.44-7.41 (m, 4H, H-2´), 7.33-7.18 (m, 6H, H-3´, H-2´), 3.66 (t, 2H, H-4 *J* = 5.5 Hz), 3.16, (s, 1H, C-1-OH), 2.43 (t, 2H, H-2, *J* = 7.3 Hz), 1.82 (s, 1H, C-4-OH), 1.63-1.54 (m, 2H, H-3); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ ppm = 147.1 (C-1´), 128.0 (C-3´), 126.7 (C-4´), 126.1 (C-2´), 77.8 (C-1), 62.8 (C-4), 38.9 (C-2), 27.0 (C-3); **IR** (ATR) ν cm^{-1} = 3351 (br), 3084 (w), 3056 (w), 3024 (w), 2951 (m), 2929 (m), 2871 (w), 1954 (w), 1886 (w), 1807 (w), 1597 (w), 1489 (m), 1445 (s), 1385 (m), 1238 (w), 1204 (m), 1124 (w), 1050 (m), 1031 (s), 975 (s), 924 (m), 909 (m), 874 (w), 851 (w), 746 (vs), 693 (vs); **GC-MS** (EI, 70 eV): m/z % = 242 (<1, M^+) 224 (15, M-H_2O^+), 206 (5), 193 (5), 183 (100, PhC(=OH)Ph^+), 165 (15, M-Ph^+), 147 (40, M-H_2O-Ph^+), 115 (15), 105 (100, $PhCO^+$), 91 (10, Bn^+), 77 (60, Ph^+), 51 (15), 39 (5).

48 C. Weizmann, F. Bergmann, *J. Am. Chem. Soc.***1938**, 60, 2647-2649.

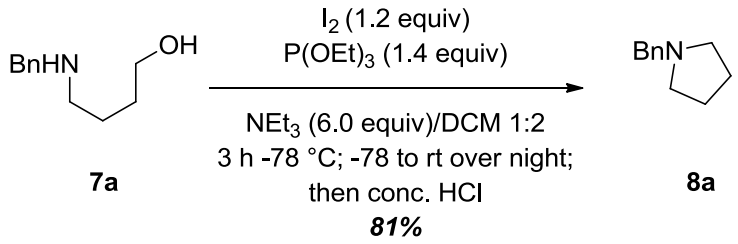


^{1}H-NMR-spectrum of diol **7f** in $CDCl_3$ (300 MHz).



DEPT-135 spectrum of the diol **7f** in $CDCl_3$ (75 MHz).

2.4.8 Synthesis of *N*-Benzyl-pyrrolidine (8a)

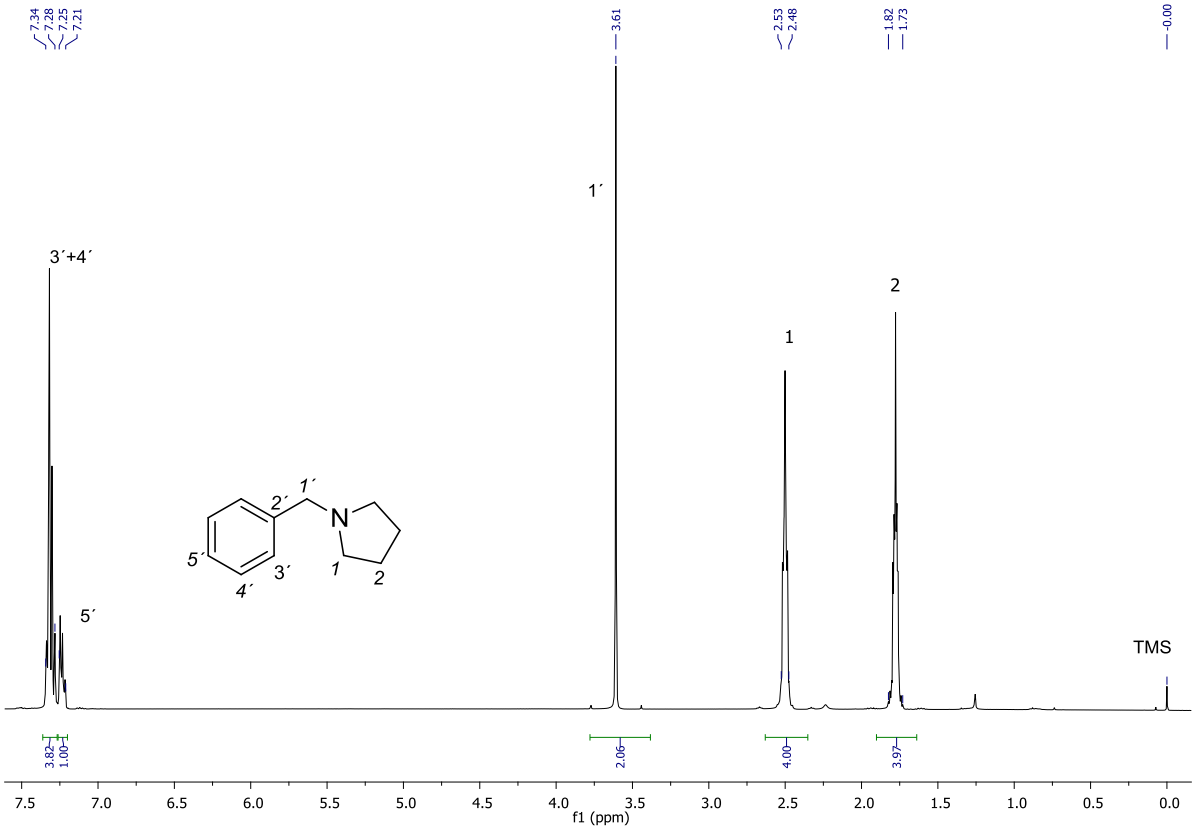


Under an atmosphere of argon amino alcohol **7a** (298 mg, 1.67 mmol, 1.0 equiv) was dissolved in NEt_3 (1.4 mL, 9.99 mmol, 6.0 equiv) and dry DCM (2.8 mL, DCM/NEt_3 2:1) and cooled to -78 °C. Successively, $P(OEt)_3$ (0.40 mL, 2.34 mmol 1.4 equiv) and iodine (510 mg, 2.00 mmol, 1.2 equiv, added in one portion) were added and the mixture was stirred at -78 °C, until I_2 had dissolved completely (3 h), whereby a colorless precipitation formed. The mixture was then allowed to warm to room temperature overnight (12 h) remaining in the cooling bath.

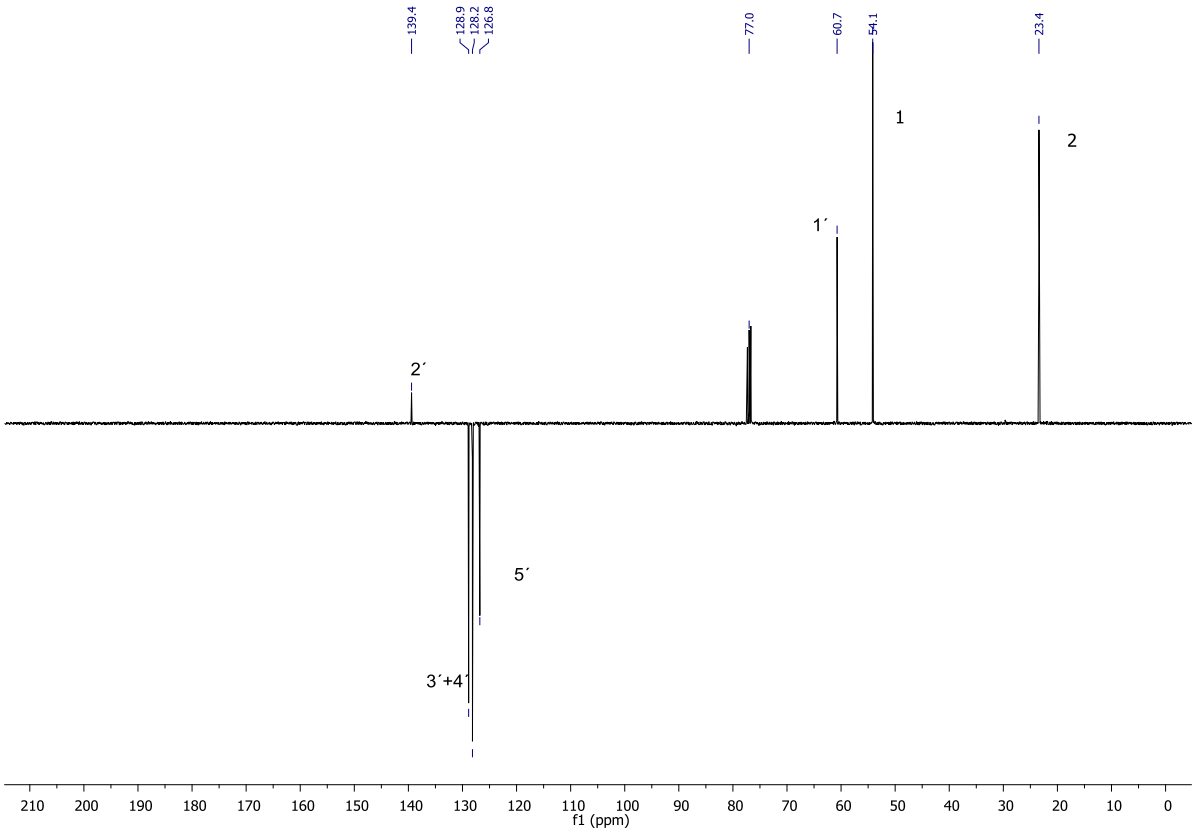
The brown suspension was cooled in an ice bath, conc. HCl-solution in water (37%, 1.1 mL, 13.4 mmol, 8.0 equiv) was added dropwise and the resulting brown solution was concentrated under reduced pressure (→20 mbar). The residue was diluted with H_2O (4 mL, **8a** = 0.5 mol/L, pH of the mixture ≤ 0) and washed with five 5 ml portions of EtOAc.[49] The aqueous phase was cooled again to 0 °C, 0.85 g of K_2CO_3 were added carefully (CO_2 evolution), whereby an oil precipitated. Finally, the basic (pH = 10-11) mixture was extracted with *n*Pen (3x5 mL), the collected *n*Pen-phases were dried over $MgSO_4$ and concentrated *in vacuo* (→10 mbar). The residue was diluted with 2 mL of *n*Pen and concentrated again under reduced pressure (→10 mbar, repeated one more time) to remove residual NEt_3 yielding amine **8a** (219 mg, 1.36 mmol, 81%) as a pale yellow, thin oil.

M ($C_{11}H_{15}N$) = 161.244 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.34-7.28 (m, 4H, H-3´, H-4´), 7.25-7.21 (m, 1H, H-5´), 3.61 (s, 2H, H-1´), 2.53-2.48 (m, 4H, H-1), 1.82-1.73 (quint., 4H, H-2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 139.4 (C-2´), 128.9/128.2 (C-3´, C-4´), 126.8 (C-5´), 60.7 (C-1´), 54.2 (C-1), 23.4 (C-1); **IR** (ATR) ν cm^{-1} = 3083 (w), 3059 (w), 3024 (w), 2961 (m), 2908 (w), 2871 (w), 2779 (s), 2729 (w), 1944 (w), 1871 (w), 1806 (w), 1602 (w), 1583 (w), 1491 (s), 1451 (s), 1373 (s), 1346 (s), 1327 (w), 1290 (s), 1253 (w), 1200 (w), 1141 (m), 1124 (s), 1073 (m), 1027 (s), 991 (w), 994 (w), 908 (m), 875 (m), 735 (vs), 696 (vs).

49 After washing with three portions of EtOAc, neutralisation with K_2CO_3 and extraction with *n*Pen approximately 5mol% of $OP(OEt)_3$ (referred to the product **9a** according to ^{1}H-NMR) remained in crude **9a**. While Et_2O is a too poor washing solvent to remove triethyl phosphate, with DCM some of the product **9a** is coextracted.



^{1}H-NMR-spectrum of pyrrolidine **8a** in $CDCl_3$ (400 MHz).



DEPT-135 spectrum of pyrrolidine **8a** in $CDCl_3$ (75 MHz).

2.4.9 General Procedure for the Synthesis of Furans *rac*-8b-f

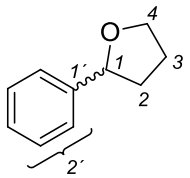
Under an atmosphere of argon the diol (***rac*-**)**7** (1.0 equiv, 1-2 mmol) was dissolved in NEt_3 (6.0 equiv) and dry DCM (NEt_3/DCM 1:2), the mixture was cooled to -78 °C in an acetone/dry ice bath and treated with $P(OEt)_3$ (1.4 equiv). Subsequently, iodine (1.2 equiv) was added in one portion and the mixture was stirred at -78 °C until complete dissolution of iodine (2.5-5 h). Then the cooling bath was removed and the clear reaction solution was allowed to stir at ambient temperature for 0.5 h.[50]

In order to quench the reaction 4 N KOH-solution in MeOH (5.0 equiv) was added to the reaction suspension, the solvent was removed *in vacuo* (→ 50 mbar) and the residue was dried under reduced pressure (50 mbar) in a rotatory evaporator for 5-10 min. The residue was dissolved in 3 mL of H_2O and 2 mL of *n*Pen, the organic phase was separated, the aqueous phase was extracted with two further 2 mL portions of *n*Pen. To remove remaining traces of $O=P(OEt)_3$,[51] the combined organic phases were washed with five 2 mL portions of H_2O, dried over $MgSO_4$, concentrated under reduced pressure (→ 10 mbar) to deliver the (usually volatile) desired furan (***rac*-**)**8.**For the work up, a 20 mL syringe rather than an extraction funnel was utilized.

2.4.10 Analytical Data of *rac*-2-Phenyl-tetrahydrofuran (*rac*-8b)

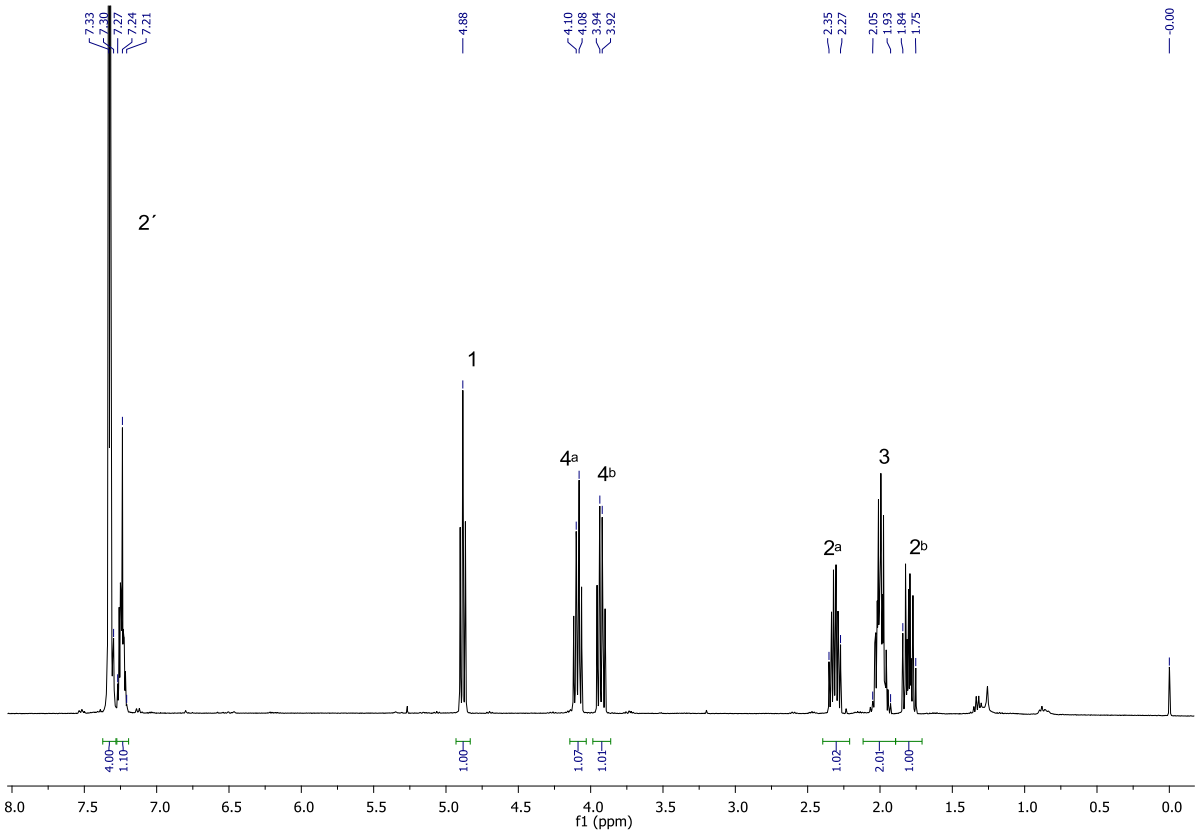
yield: 138.6 mg (0.935, 92%, pale yellow oil).

M ($C_{10}H_{12}O$) = 148.202 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.33-7.21 (m, 5H, H-2´), 4.88 (t, 1H, H-1, *J* = 7.2 Hz), 4.09 (dd, 1H, H-4_a, *J* = 14.4, 7.4 Hz), 3.93 (dd, 1H, H-4_b, *J* = 7.3, 14.4 Hz), 2.35-2.27 (m, 1H, H-2_a), 2.05-1.93 (m, 2H, H-3), 1.84-1.75 (m, 1H, H-2_b); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 143.4 (C-1´), 128.2/127.1/125.6 (C-2´), 80.6 (C-1), 68.6 (C-4), 34.6 (C-2), 26.0 (C-3); **IR** (ATR) ν cm^{-1} = 3082 (w), 3059 (w), 3025 (w), 2970 (m), 2946 (m), 2864 (m), 1945 (w), 1877 (w), 1806 (w), 1602 (m), 1491 (s), 1450 (s), 1363 (m), 1347 (w), 1305 (w), 1286 (w), 1210 (w), 1174 (w), 1078 (s), 1055 (vs), 1026 (s), 964 (w), 919 (m), 751 (s), 697 (vs); **GC-MS** (EI, 70 eV): m/z % = 148 (95, M^+), 147 (100, M-H^+), 115 (15), 105 (100, $PhCO^+$), 91 (35, Bn^+), 77 (55, Ph^+), 51 (25), 39 (25); **HR-MS** (EI, $[C_{10}H_{12}O]^+$) calc. 148.089 u found 148.088 u.

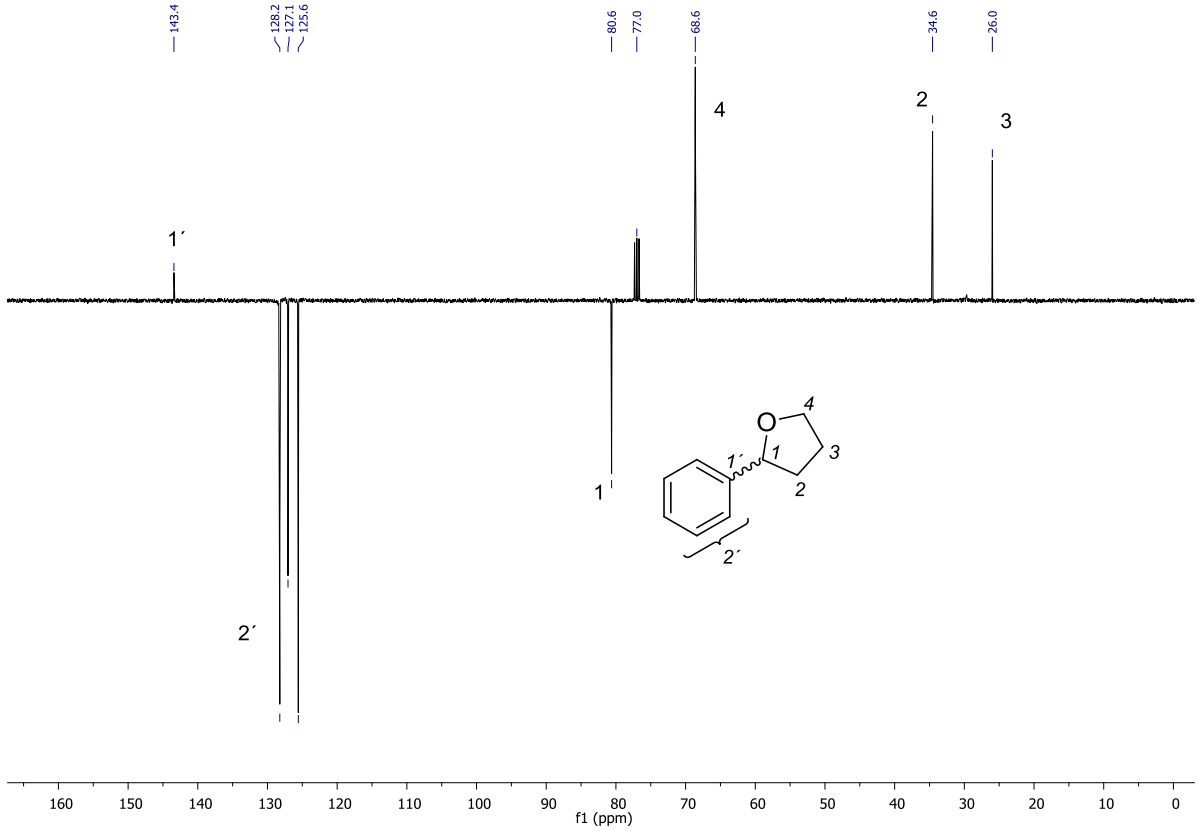


50 Except of substrate **7f** a quantitative conversion to the furans **8** was achieved by slowly warming to reaction mixture from -78 °C to -40/-30 °C. However, by removing the cooling bath and stirring at ambient temperature as indicated the desired furans **9** were isolated in essentially the same yields and purities, as by allowing the reaction mixture to warm to -40/-30 °C slowly.

51 After saponification crude **8** contained approximately 10-20mol% of $O=P(OEt)_3$.



^{1}H-NMR-spectrum of furan***rac*-8b** in $CDCl_3$ (400 MHz).

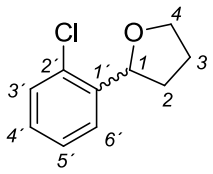


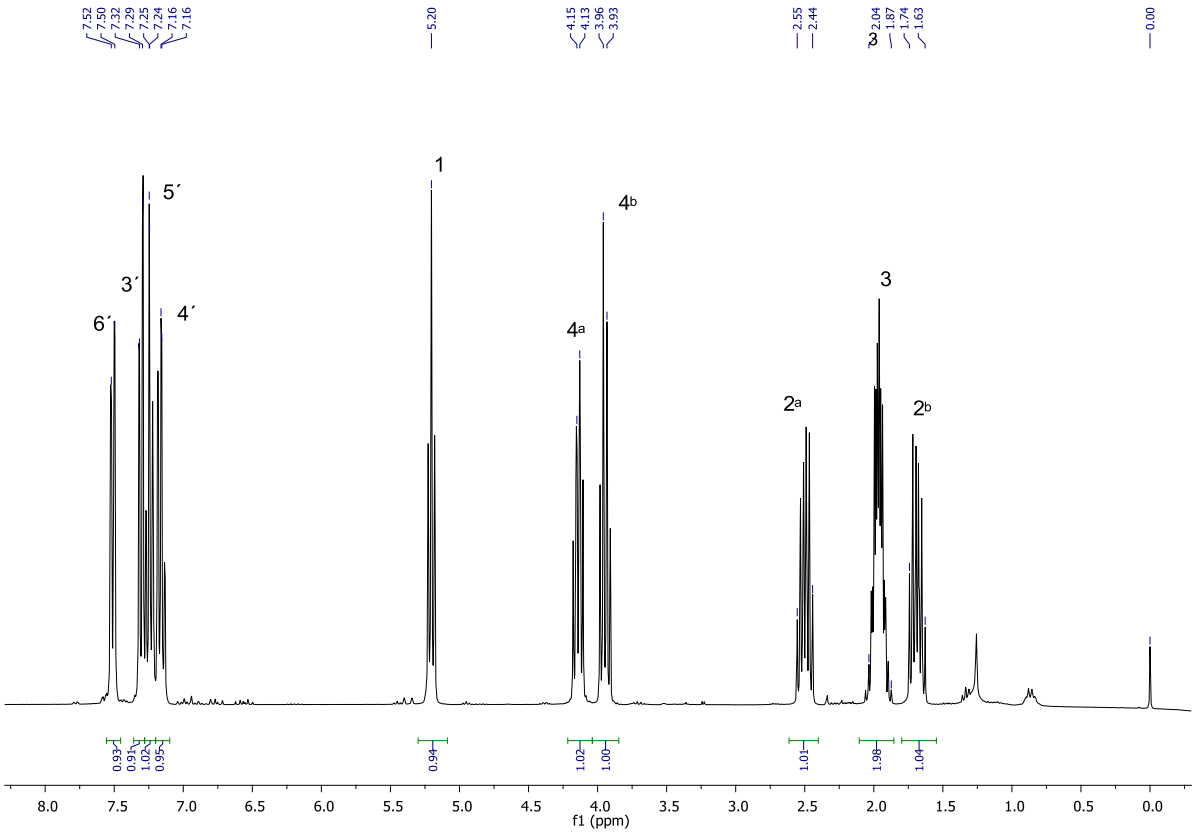
DEPT-135 spectrum of furan ***rac*-8b** in $CDCl_3$ (100 MHz).

2.4.11 Analytical Data of *rac*-1-(2-Chlorophenyl))-tetrahydrofuran (*rac*-8c)

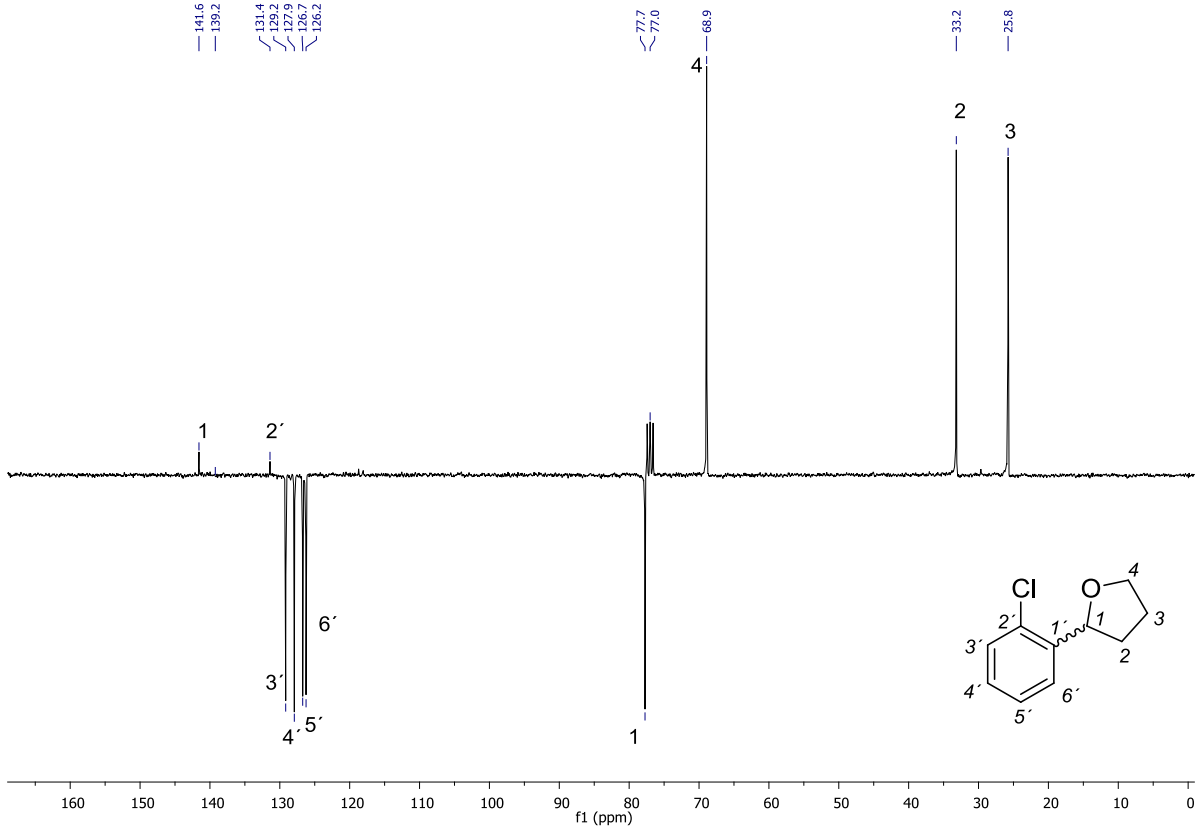
yield: 189.5 mg (1.04 mmol, 85%, pale yellow oil).

M ($C_{10}H_{11}ClO$) = 182.647 g/mol; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ ppm = 7.51 (dd, 1H, H-6´, *J* = 7.5, 1.4 Hz), 7.31 (dd, 1H, H-3´, *J* = 7.7, 1.3 Hz), 7.25 (td, 1H, H-5´, *J* = 7.5, 1.2 Hz), 7.16 (td, 1H, H-4´, *J* = 7.6, 1.7 Hz), 5.20 (t, 1H, H-1, *J* = 6.7 Hz), 4.14 (dd, 1H, H-4_a, *J* = 14.2, 6.9 Hz), 3.95 (dd, 1H, H-4_b, *J* = 15.3, 6.9 Hz), 2.55-2.44 (m, 1H, H-2_a), 2.04-1.87 (m, 2H, H-3), 1.7-1.63 (m, 1H, H-3_a); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ ppm = 141.6 (C-1´), 131.4 (C-2´), 129.2 (C-3´), 127.9 (C-4´), 126.7 (C-5´), 126.2 (C-6´), 77.7 (C-1), 68.9 (C-4), 33.2 (C-2), 25.8 (C-3); **IR** (ATR) ν cm^{-1} = 3065 (w), 2974 (m), 2946 (m), 2865 (m), 1807 (w), 1593 (w), 1572 (m), 1468 (s), 1441 (s), 1360 (w), 1344 (w), 1267 (w), 1206 (w), 1173 (w), 1124 (m), 1067 (vs), 1046 (vs), 1031 (vs), 925 (m), 749 (vs), 702 (m); **GC-MS** (EI, 70 eV) m/z u = 182 (10, M^+), 181 (20, M-H^+), 147 (100, M-Cl^+), 139 (95, M-$MeCO^+$), 125 (10), 115 (25), 105 (15, $PhCO^+$), 89 (15), 77 (20, Ph^+), 63 (10), 51 (10), 42 (20); **HR-MS** (EI, $[C_{10}H_{11}ClO]^+$) calc. 183.050 u found 182.048 u.





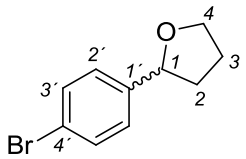
^{1}H-NMR-spectrum of furan ***rac*-8c** in $CDCl_3$ (400 MHz).



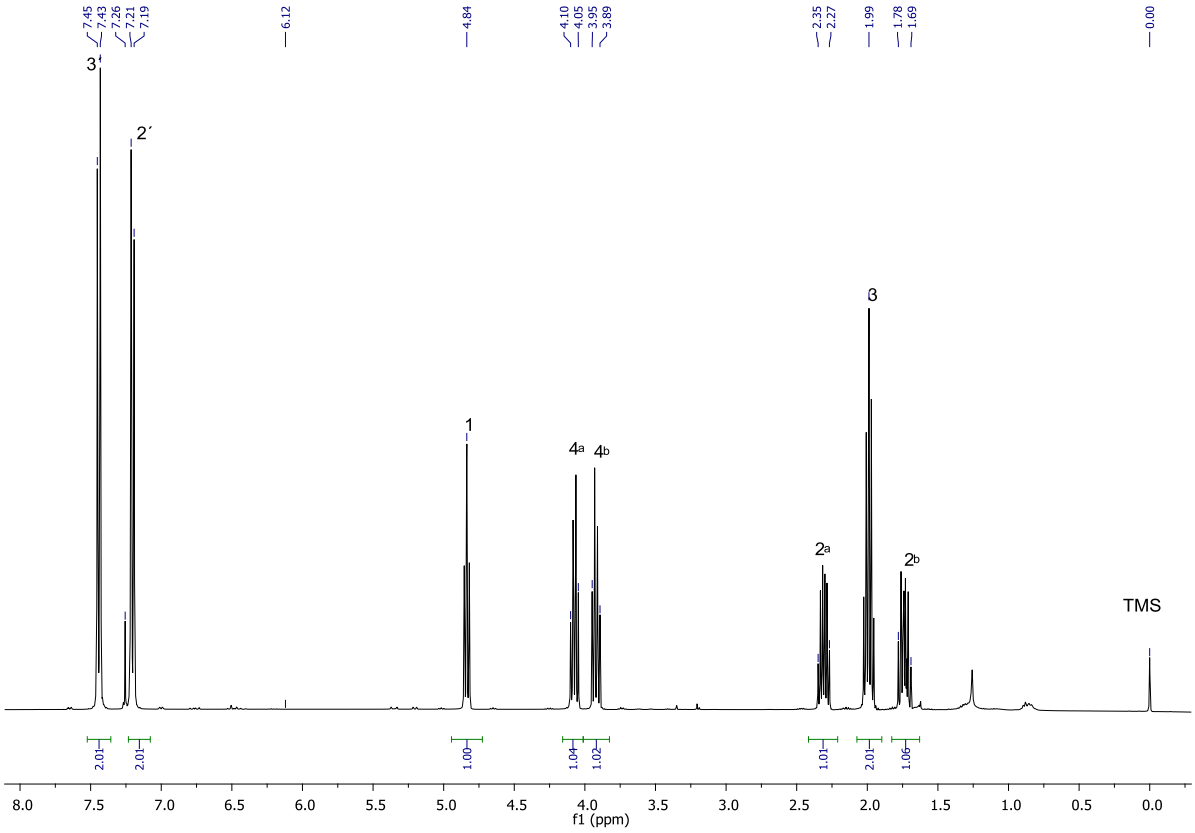
DEPT-135 spectrum of furan ***rac*-8c** in $CDCl_3$ (100 MHz).

2.4.12 Analytical Data of *rac*-1-(4-Bromophenyl)-tetrahydrofuran (*rac*-8d)

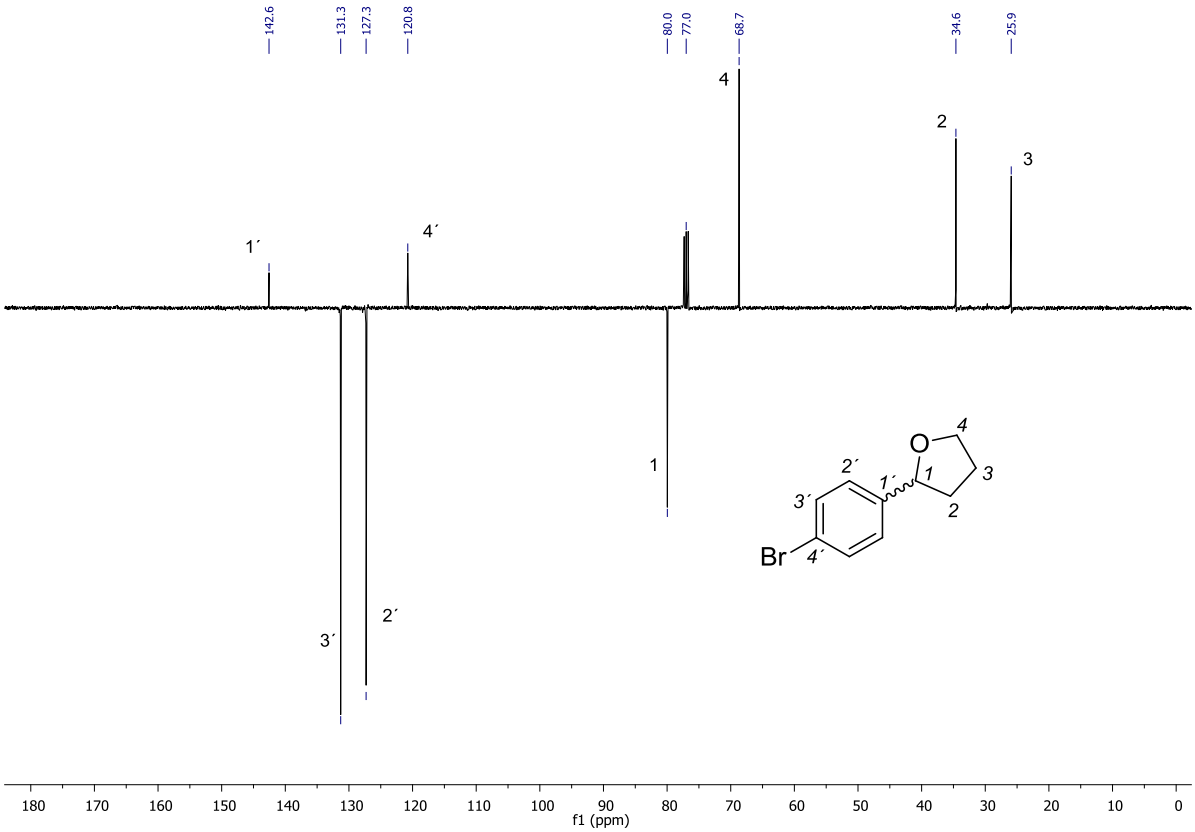
yield: 206.8 mg (0.91 mmol, 83%, pale yellow oil).



M ($C_{10}H_{11}BrO$) = 227.098 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.44 (d, 2H, H-3´, *J* = 8.3 Hz), 7.20 (d, 2H, H-2´, *J* = 8.7 Hz), 4.84 (t, 1H, H-1, *J* = 7.5 Hz), 4.10-4.05 (m, 1H, H-4), 3.95-3.89 (m, 1H, H-4_b), 2.35-2.27 (m, 1H, H-2_a), 1.99 (quint, 2H, H-3, *J* = 7.2 Hz), 1.78-1.69 (m, 1H, H-2_b); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 142.6 (C-1´), 131.3 (C-3´), 127.3 (C-2´), 120.8 (C-4´), 78.0 (C-1), 68.7 (C-4), 34.6 (C-2), 25.9 (C-3); **IR** (ATR) ν cm^{-1} = 3044 (w), 3022 (w), 2969 (s), 2945 (m), 2865 (s), 1899 (w), 1750 (w), 1790 (w), 1484 (s), 1457 (w), 1443 (w), 1399 (m), 1360 (w), 1350 (w), 1293 (w), 1173 (w), 1101 (w), 1059 (vs), 1008 (vs), 918 (m), 818 (s), 712 (m); **GC-MS** (EI, 70 eV) m/z u = 228 (10, M(^{81}Br)$^+$), 227 (15, M(^{81}Br)-H$^+$), 226 (10, M(^{79}Br)$^+$), 225 (15, M(^{79}Br)-H$^+$), 186 (10, M(^{81}Br)-H_2C=C=O$^+$), 185 (50, M(^{81}Br)-H-H_2C=C=O$^+$), 184 (10 M(^{79}Br)- H_2C=C=O$^+$), 183 (50, M(^{79}Br)-H- H_2C=C=O$^+$), 157 (10), 147 (100, M-Br$^+$), 115 (10), 105 (25, PhCO$^+$), 89 (10), 77 (15, Ph$^+$), 63 (5), 42 (15, MeCO$^+$).



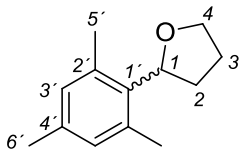
^{1}H-NMR-spectrum of furan ***rac*-8d** in $CDCl_3$ (400 MHz).



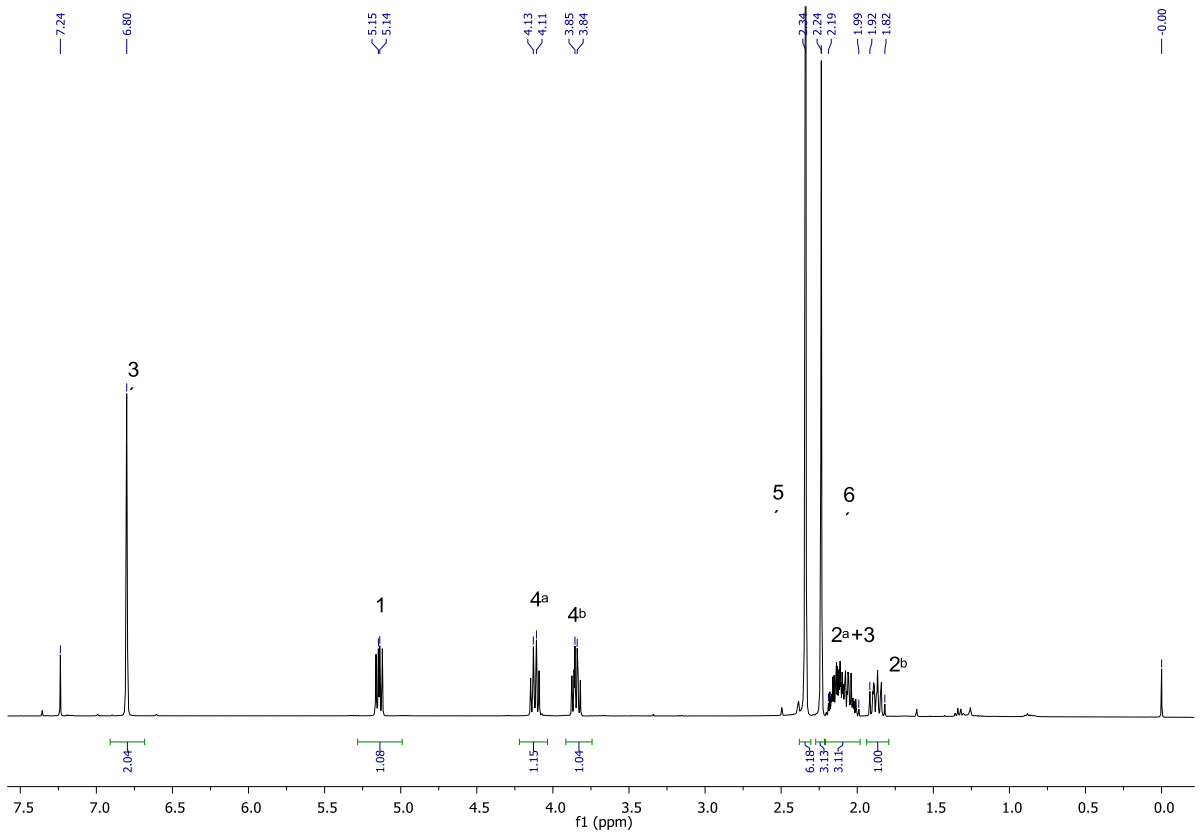
DEPT-135 spectrum of furan ***rac*-8d** in $CDCl_3$ (100 MHz).

2.4.13 Analytical Data of *rac*-(2,4,6-Trimethylphenyl)-tetrahydrofuran(*rac*-8e)

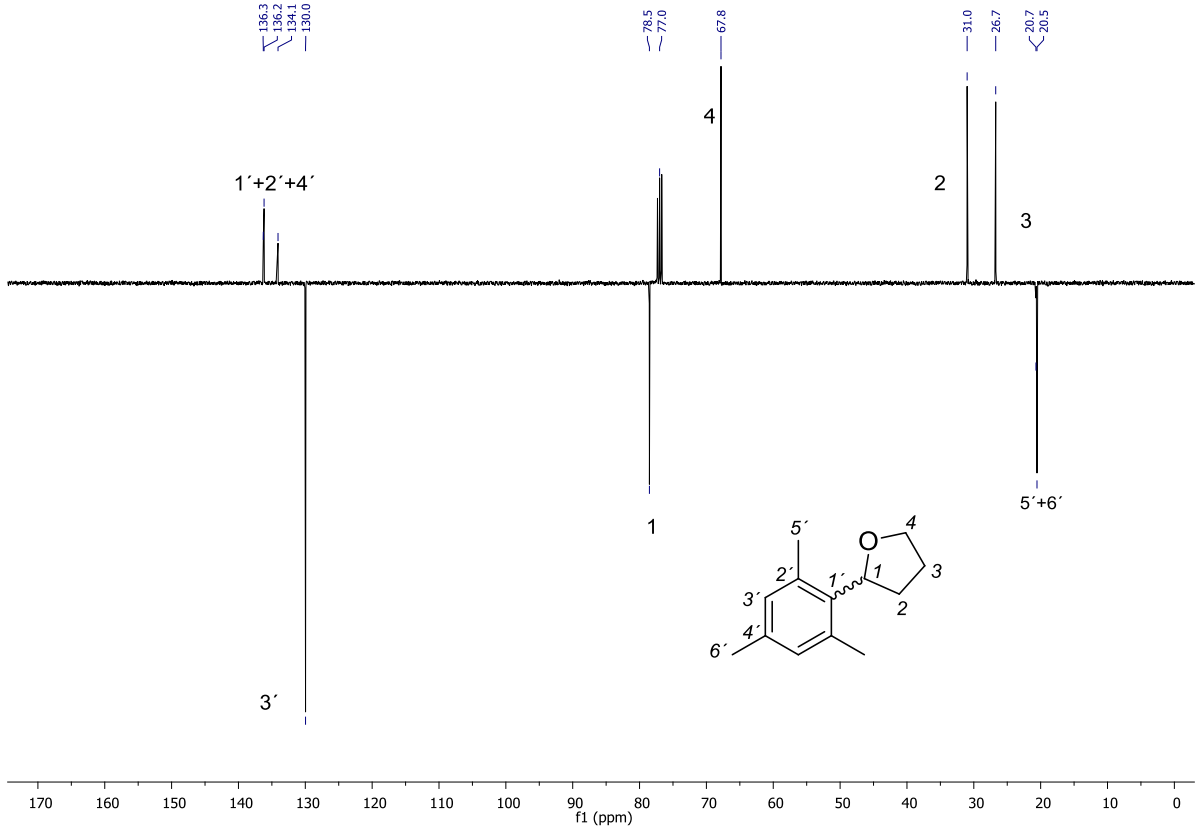
yield: 316 mg (1.66 mmol, 84%, yellow oil).



M ($C_{13}H_{18}O$) = 190.281 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 6.80 (s, 2H, H-3´), 5.15 (dd, 1H, H-1, *J* = 10.3, 6.4 Hz), 4.12 (dd, 1H, H-4_a, *J* = 15.0, 6.7 Hz), 3.85 (td, 1H, H-4_b, *J* = 8.0, 5.7 Hz), 2.34 (s, 6H, H-5´), 2.24 (s, 3H, H-6´), 2.19-1.99 (m, 3H, H-2_a, H-3), 1.92-1.82 (m, 1H, H-2_b); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 136.3/136.2/134.1 (C-1´, C-2´, C-4´), 130.0 (C-3´), 78.5 (C-1), 67.8 (C-2), 31.0 (C-3), 26.7 (C-4), 20.7/20.6 (C-5´, C-6´); **IR** (ATR) ν cm^{-1} = 2965 (s), 2916 (s), 2860 (m), 2726 (w), 1611 (m), 1575 (w), 1481 (m), 1459 (s), 1446 (s), 1371 (m), 1349 (w), 1322 (w), 1277 (w), 1214 (w), 1172 (w), 1058 (vs), 1035 (vs), 964 (m), 913 (m), 847 (vs), 780 (w), 733 (m); **GC-MS** (70 eV, EI) m/z u = 190 (35, M^+), 175 (40, M-Me^+), 159 (100), 147 (80, $MesCO^+$), 133 (30), 119 (35, Mes^+), 105 (25, Me_2Ph^+), 91 (30, Bn^+), 77 (15, Ph^+), 65 (10, Cp^+); **HR-MS** (ESI, $C_{13}H_{20}O_2$+Na^+) calc. 213.1250 u found 213.1250 u.



^{1}H-NMR-spectrum of furan ***rac*-8e** in $CDCl_3$ (400 MHz).



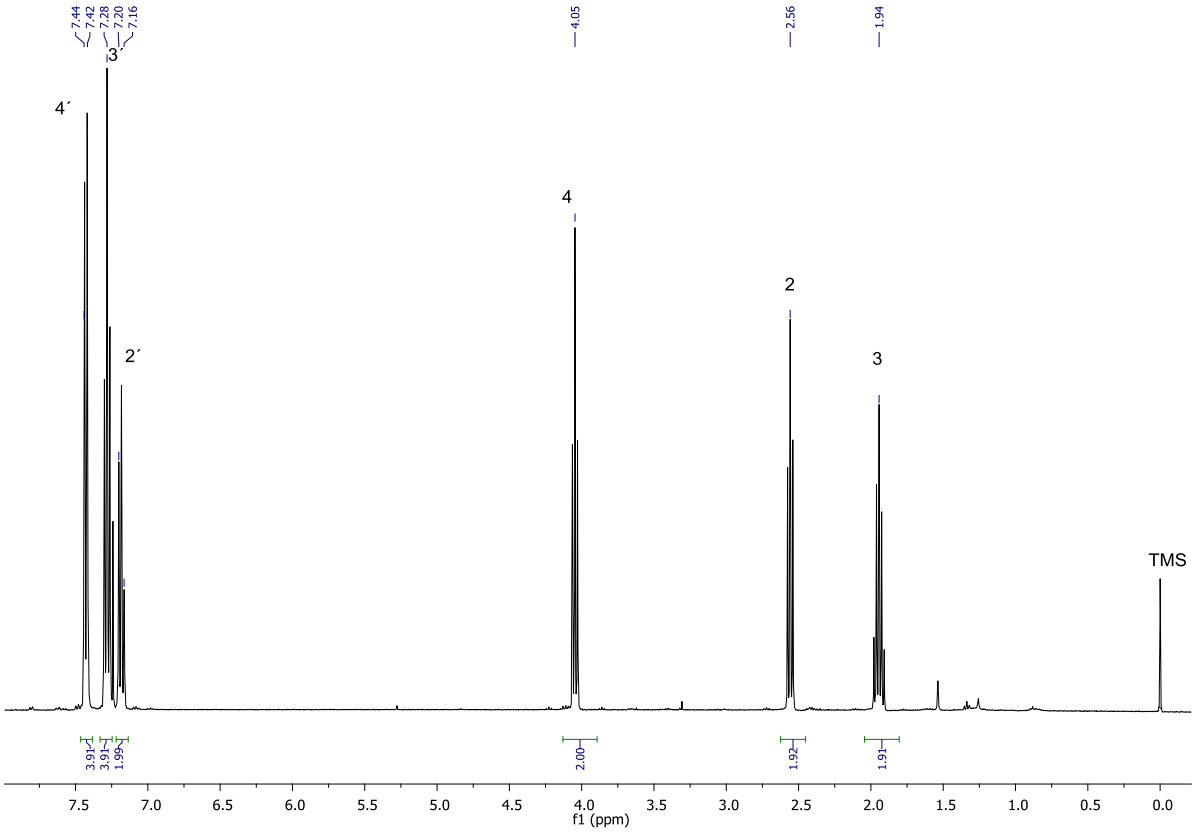
DEPT-135 spectrum of furan ***rac*-8e** in $CDCl_3$ (100 MHz).

2.4.14 Analytical Data of 2,2-Diphenyltetrahydrofuran (8f)

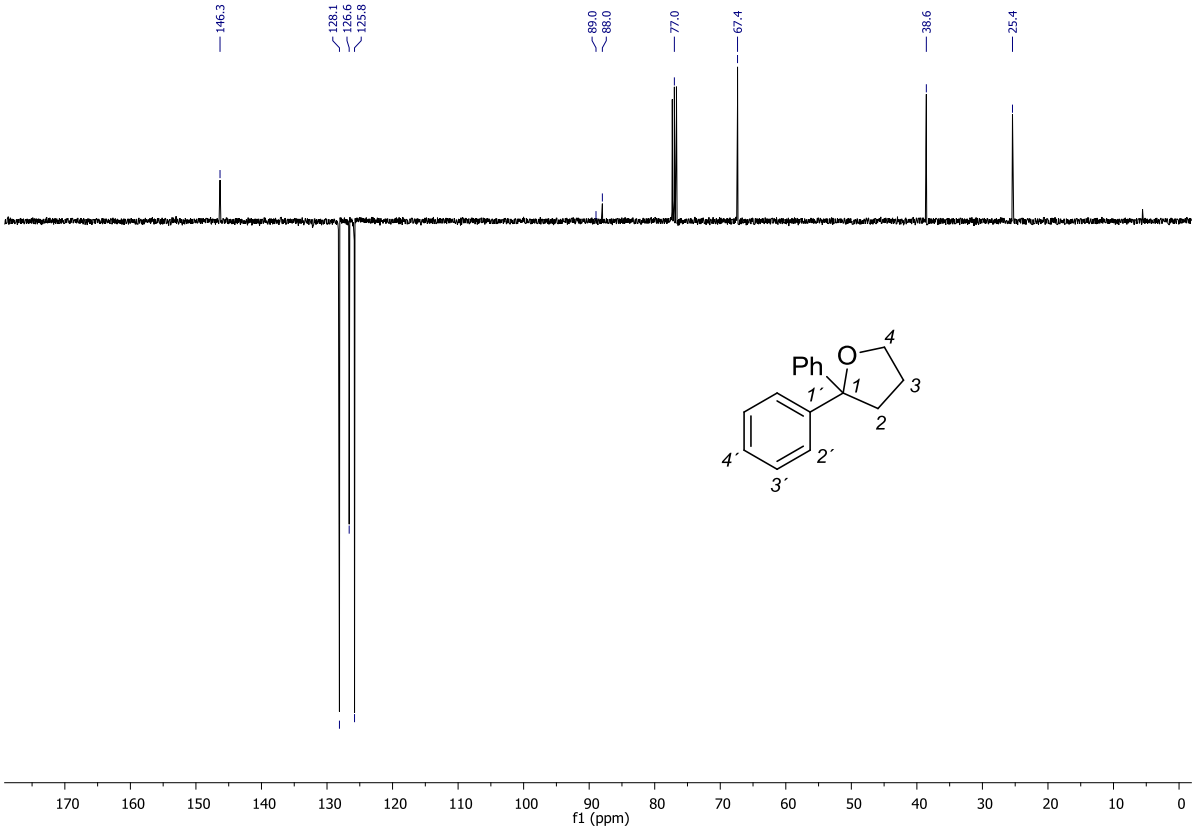
yield: 211.7 mg (0.94 mmol, 82%, colorless solid).

M ($C_{11}H_{14}O$) = 224.298 g/mol; **mp.** = 65-66 °C (lit.: 65.5 °C);[521] **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.44-7.42 (m, 4H, H-2´), 7.28 (dd, 4H, H-3´, *J* = 7.5 Hz), 7.18 (tt, 2H, H-4´, *J* = 7.3, 1.7 Hz), 4.05 (t, 2H, H-4, *J* = 7.5 Hz), 2.56 (t, 2H, H-2, *J* = 7.2 Hz), 1.94 (quint., 2H, H-3, *J* = 7.3 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 146.3 (C-1´), 128.1 (C-3´), 126.5 (C-4´), 125.8 (C-2´), 88.0 (C-1), 67.4 (C-4), 38.6 (C-2), 25.4 (C-3); **IR**(ATR) ν cm-1 = 3080 (w), 3049 (w), 3019 (w), 2977 (s), 2941 (m), 2924 (m), 2872 (s), 1968 (w), 1951 (w), 1886 (w), 1807 (w), 1660 (w), 1593 (m), 1488 (s), 1445 (vs), 1315 (m), 1295 (m), 1241 (m), 1210 (m), 1191 (m), 1156 (m), 1063 (w), 1050 (vs), 1026 (s), 1001 (m), 988 (m), 953 (s), 935 (m), 912 (m), 866 (w), 772 (s), 745 (m), 721 (m), 701 (vs); **GC-MS** (EI, 70 eV): m/z % = 224 (30, M^+), 165 (10), 147 (100, M-Ph^+), 115 (10), 105 (80, $PhCO^+$), 91 (10, Bn^+), 77 (60, Ph^+), 51 (15), 39 (5).

52 P. Mirosevic-Sorgo, B. C. Saunders, *Tetrahedron***1959**, *5*, 38-42.



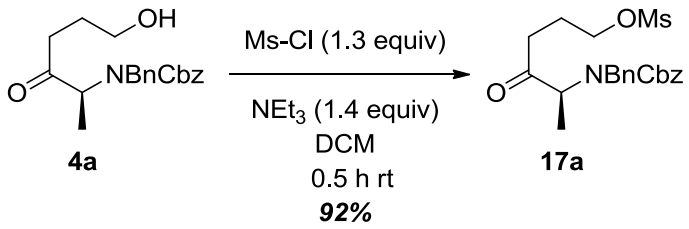
^{1}H-NMR-spectrum of furan **8f** in $CDCl_3$ (400 MHz).



DEPT-135 spectrum of furan **8f** in $CDCl_3$ (100 MHz).

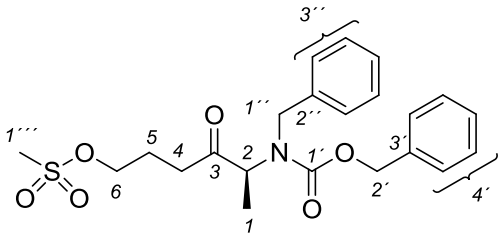
2.5 Synthesis of *trans*-Configured Piperidinol 6a (Scheme 3)

2.5.1 Synthesis of *S*-5-(benzyl(benzyloxycarbonyl)amino)-4-oxohexyl methyl sulfonate (17a)



Under an atmosphere of argon hydroxy ketone **4a** (4.907 g, 13.60 mmol considering 6mol% of residual $Cl(CH_2)_3OH$, 1.0 equiv) was dissolved in dry DCM (28 mL, **4a** = 0.5 mol/mL), treated with NEt_3 (2.6 mL, 19.0 mmol, 1.4 equiv) and cooled to 0 °C. Then, MsCl (1.4 mL, 17.7 mmol, 1.3 equiv) was added dropwise within 20 min through a syringe pump, whereby $HNEt_3Cl$ precipitated. The ice bath was removed and the reaction suspension was allowed to stir for 0.5 h at ambient temperature, whereupon TLC control indicated full conversion of **4a**.

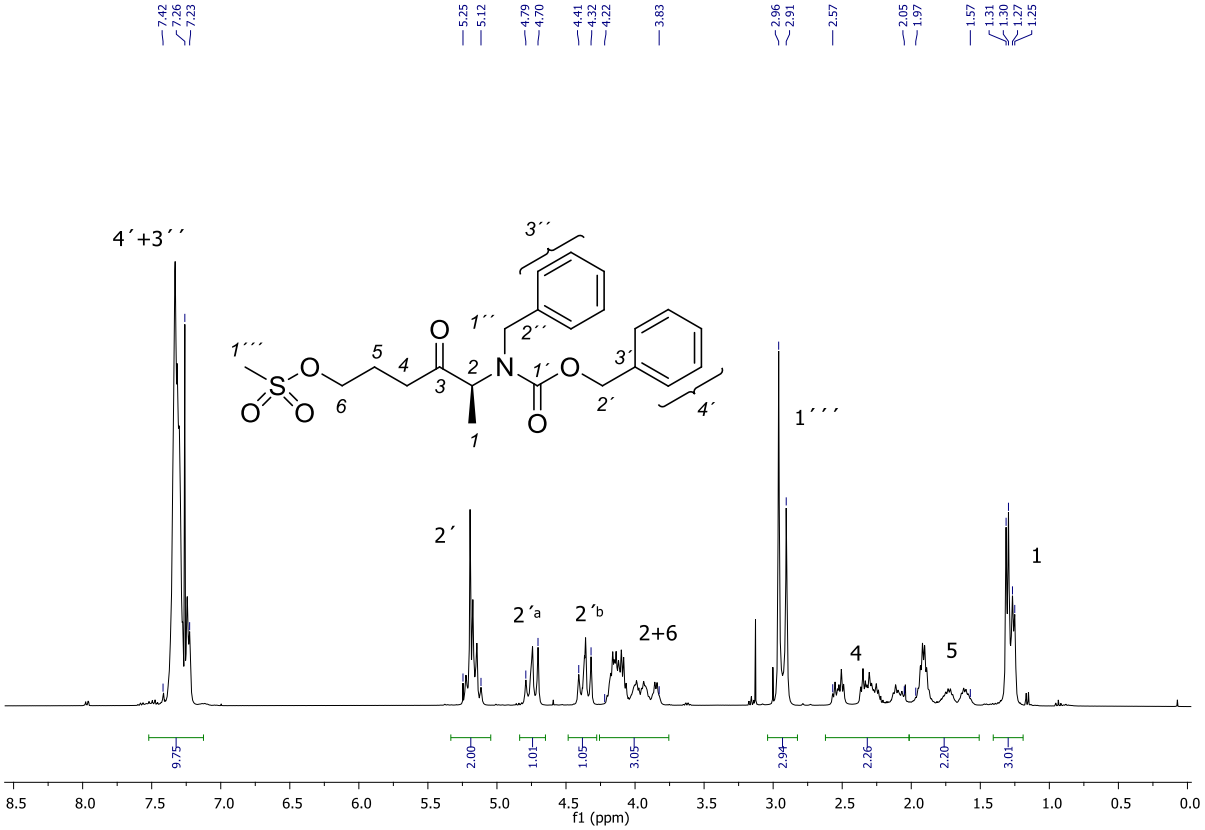
Under ice bath cooling 15 mL of a 1 N HCl solution in water were added, the organic phase was separated, washed with 15 mL of saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The residue (6.23 g of a pale yellow oil) was dissolved in DCM (ca. 10 mL) and subjected to column chromatographic purification on silica with EtOAc/*n*-hexane 4:7. After concentration of the isolated mesylate with two 10 mL portions of $CHCl_3$ under reduced pressure (to remove EtOAc) and drying in high vacuum for 1 h under stirring at ambient temperature,[53] the mesylate **17a** (5.441 g, 12.55 mmol) were isolated as a colorless oil in a yield of 92%.



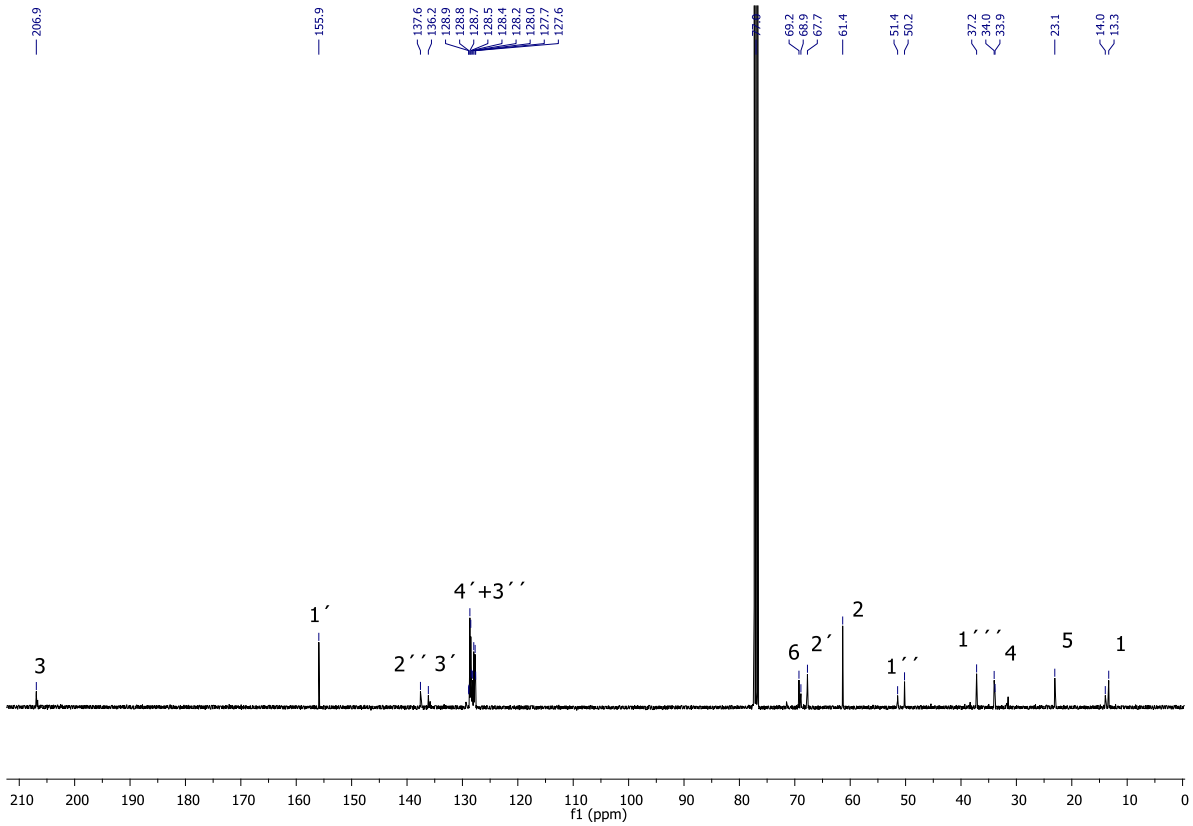
M ($C_{22}H_{27}NO_6S$) = 433.518 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex) = 0.60 (1:1), 0.31 (4:7), 0.22 (1:2); **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 7.42-7.23 (m, 10H, H-4´, H-3´´), 5.25-5.12 (m, 2H, H-2´), 4.79-4.70 (m, 1H, H-1´´$_a$), 4.41-4.32 (m, 1H, H-1´´$_b$), 4.22-3.83 (m, 3H, H-2, H-6), 2.96/2.91 (2xs, 3H, H-1´´´), 2.57-2.05 (m, 2H, H-4), 1.97-1.57 (m, 2H, H-5), 1.31/1.26 (2xd, 3H, H-1, *J* = 7.0/6.5 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of rotamers) δ ppm = 206.9 (C-3), 155.9 (C-1´), 137.6 (C-2´´), 136.2 (C-3´), 128.9/128.8/128.7/128.5/128.4/128.2 /128.0/127.7/127.6 (C-4´, C-3´´), 69.3/68.9 (C-6), 67.7 (C-2´), 61.4 (C-2), 51.4/50.2 (C-1´´), 37.2/34.0 (C-1´´´), 33.9 (C-4), 23.1 (C-5), 14.0/13.3 (C-1); **IR** (film) ν cm^{-1} = 3088 (w), 3063 (w), 3030 (w), 2984 (w), 2939 (w), 2903 (w), 1958 (w), 1890 (w), 1813

53Drying under heating (40 °C) lead to decomposition of **10a**.

(w), 1721 (m), 1694 (vs), 1605 (w), 1586 (w), 1496 (w), 1464 (m), 1454 (m), 1425 (m), 1352 (vs), 1334 (s), 1238 (vs), 1173 (vs), 1132 (w), 1080 (w), 1052 (w), 1027 (w), 971 (m), 923 (m), 821 (w), 771 (m), 737 (w), 700 (m), 528 (m), 463 (w); **HR-MS** (ESI, $C_{22}H_{28}NO_6S^+$) calc. 434.1637 u found: 434.1630 u; (ESI, $C_{22}H_{27}NO_6SNa^+$) calc.: 456.1457 u found: 456.1448 u; α_D (c = 1.380 g/100 ml, $CHCl_3$, T = 21.5 °C) = -47.1 (589 nm).

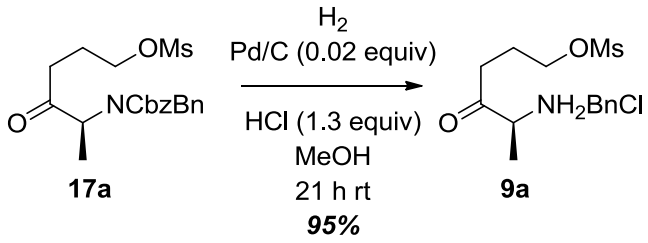


^{1}H-NMR-spectrum of mesylate **17a** in $CDCl_3$ (400 MHz).



^{13}C-NMR-spectrum of mesylate **17a** in $CDCl_3$ (400 MHz).

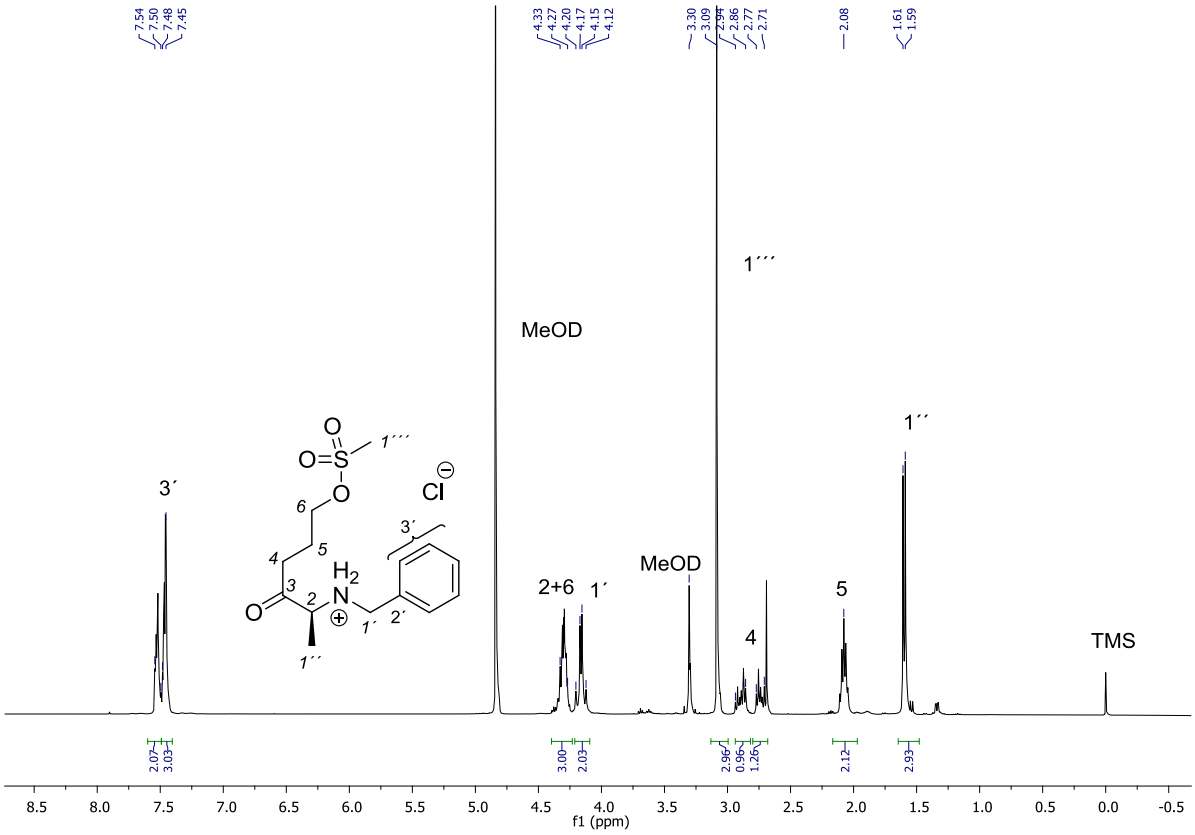
2.5.2 Synthesis of *S*-5-(benzylamino)-4-oxohexyl methane sulfonate hydrochloride (9a)



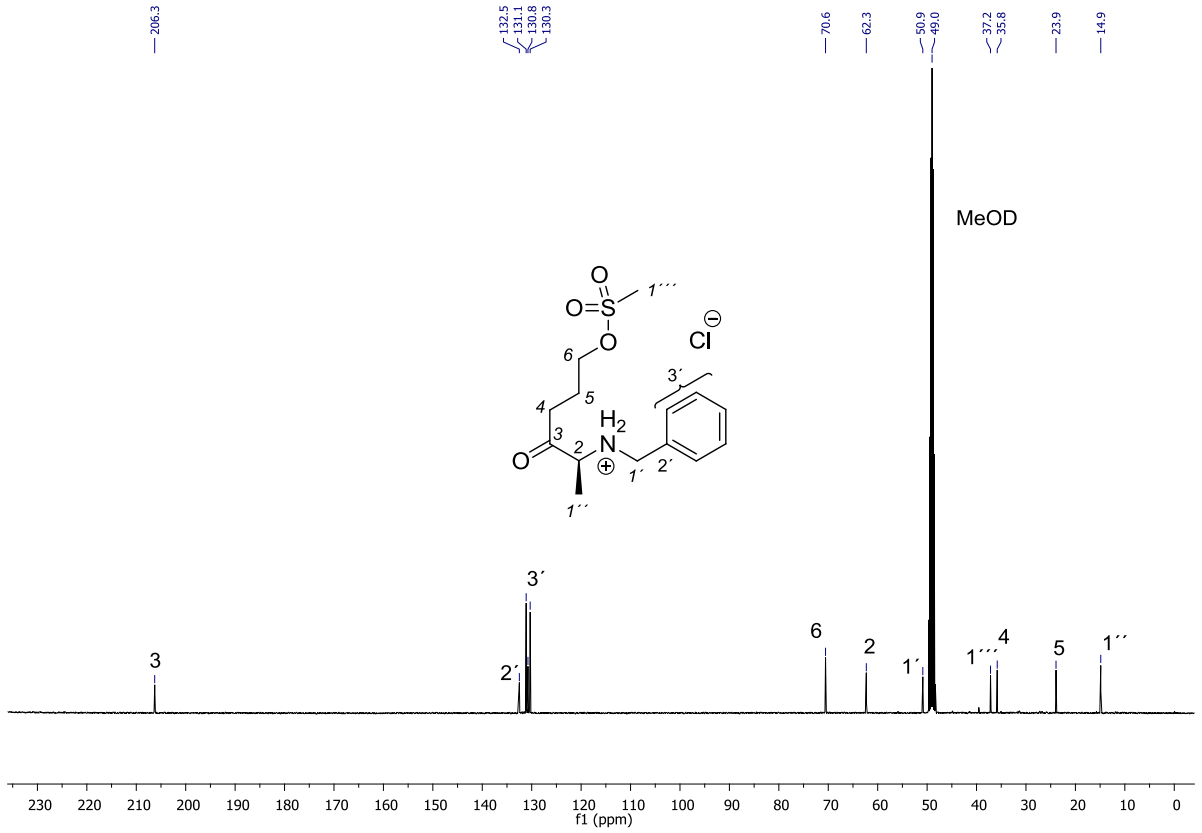
Mesylate **10a** (625 mg, 1.44 mmol, 1.0 equiv) was dissolved in MeOH (3 mL, **17a** = 0.5 mol/l), 32% HCl solution in water (019 mL, 1.87 mmol, 1.3 equiv) and 10% Pd/C (31 mg, 0.029 mmol, 0.02 equiv) were added and the reaction suspension was stirred for 21 h under 1 atm of H_2. Subsequently, the mixture was diluted with 5 mL of MeOH, passed through a thin layer of celite, the celite cake was washed with two 5 mL portions of MeOH and the collected filtrates were concentrated under reduced pressure. In order to remove remaining water, the residue was dissolved in 2 mL of $CHCl_3$ and concentrated under reduced pressure (2x). After 8 h of drying in high vacuum the ammonium salt **17a** (457 mg, 1.36 mmol, 95%) was isolated as a colorless solid.

M ($C_{14}H_{22}ClNO_4S$) = 335.847 g/mol; **solubility:** water, MeOH: good; EtOH: moderate; DCM, $CHCl_3$: insoluble; **mp.** 102.5-103.5 °C; **^{1}H-NMR** (400 MHz, MeOH-d_4) δ ppm = 7.54-7.45 (m, 5H, H-3´), 4.33-4.27 (m, 3H, H-2, H-6), 4.19 (d, 1H, H-1´$_a$, *J* = 12.7 Hz), 4.14 (d, 1H, H-1´$_b$, *J* = 13.0 Hz) 3.30 (s, 3H,

H-1´´´), 3.09-2.94 (m, 1H, H-4_a), 2.86-2.77 (m, 1H, H-4_b), 2.08 (p, 2H, H-5, J = 6.4 Hz), 1.60 (d, 3H, J = 7.3 Hz); **^{13}C-NMR** (100 MHz, MeOH-d_4) δ ppm = 206.3 (C-3), 132.5 (C-2´), 131.1/130.8/130.3 (C-3´), 70.6 (C-6), 62.3 (C-2), 50.9 (C-1´), 37.2 (C-1´´´), 35.8 (C-4), 23.9 (C-5), 14.9 (C-1´´); **HR-MS** (ESI, $C_{14}H_{22}NO_4S^+$) calc. 300.127 u found 300.1265 u; α_D (c = 0.588 g/100 ml, MeOH, 21.0 °C) = +34.4.

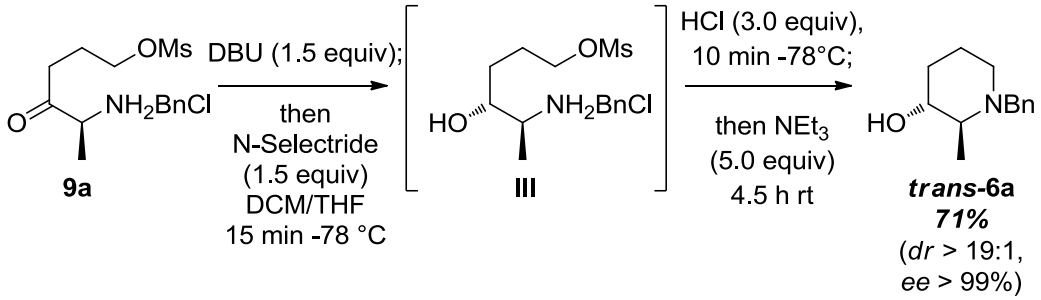


^{1}H-NMR-spectrum of hydrochloride **9a** in MeOH-d_4 (400 MHz).



^{13}C-NMR-spectrum of hydrochloride **9a** in MeOH-d_4 (100 MHz).

2.5.3 Synthesis of (*2S,3R*)-1-Benzyl-2-methyl-3-piperidinol (*trans*-6a)



The hydrochloride salt **9a** (103.5 mg, 0.308 mmol, 1.0 equiv) was suspended in dry DCM (1 mL, **9a** = 0.3 mol/l) under an atmosphere of argon. Upon cooling to -78°C, DBU (70 µl, 0.47 mmol, 1.5 equiv) was added dropwise in order to ensure the complete dissolution of the starting material as neutral amino ketone. Subsequently, of 1.0 N N-Selectride solution in THF (0.46 ml, 0.462 mmol, 1.5 equiv) was added dropwise (no H_2 evolution was observed). After 15 min of stirring at -78 °C, 32% HCl-solution in water (90 µl, 0.924 mmol, 3.0 equiv) was added,[54] whereupon an H_2 evolution and the formation of a solid precipitation occurred. After 10 min NEt_3 (0.21 mL, 1.54 mmol, 5.0 equiv) was

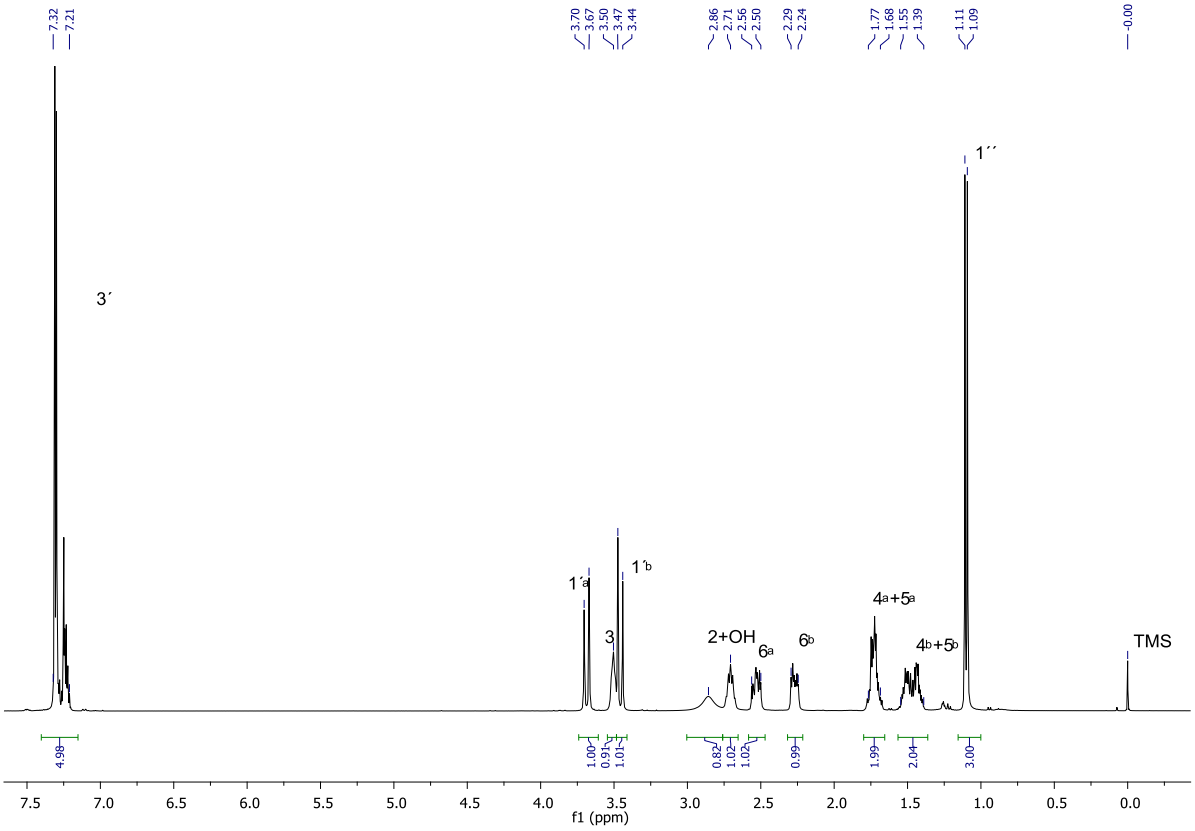
54 After quenching with HOAc (instead of HCl) a gel like mixture formed. A few droplets of water decreased the viscosity dramatically. However, to avoid these hassles, HCl was preferred for quenching an excess of reducing agent.

added, the cooling bath was removed and the reaction suspension was stirred for 4.5 h at room temperature.

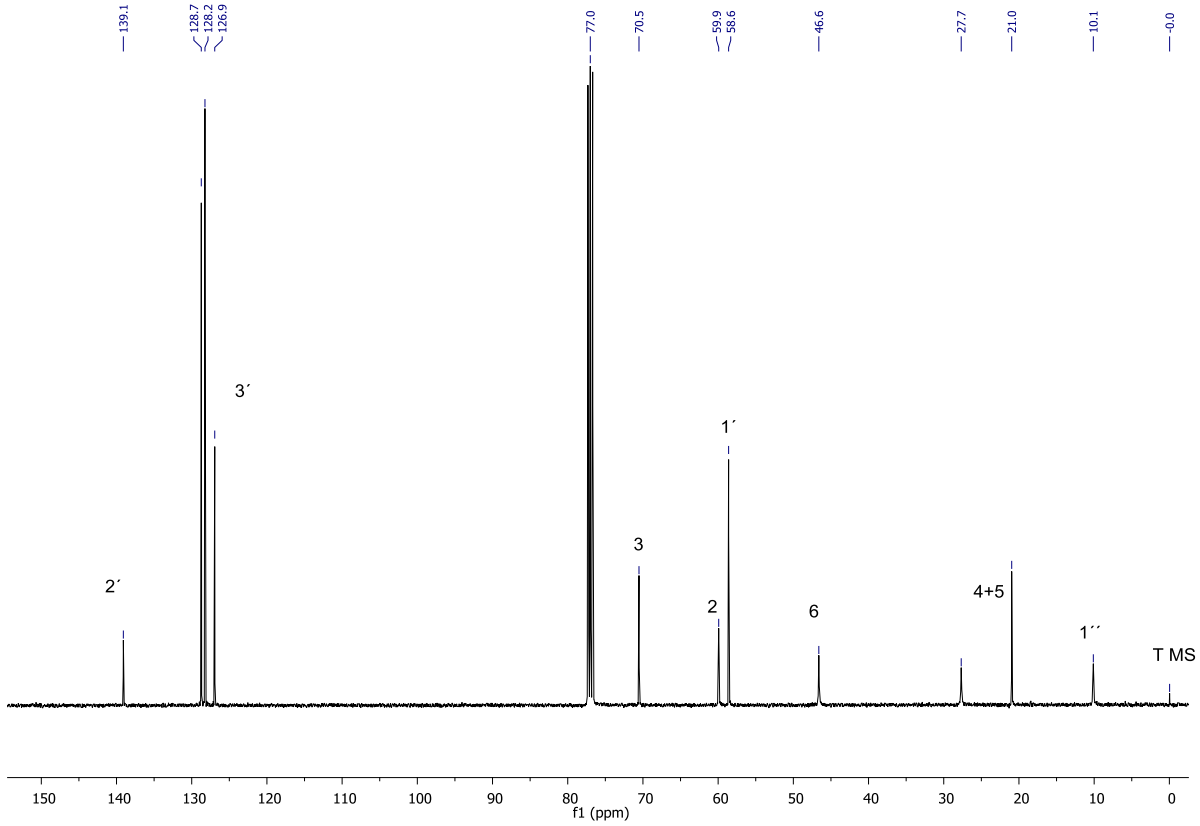
Next, 2 N NaOH solution in water (4 mL) was added, the mixture was extracted with three 4 mL portions of Et_2O,[55] the combined Et_2O-phases were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product **6a** (119 mg, pale yellow oil, one stereoisomer according to ^{1}H-NMR) was purified through column chromatography on silica gel with *i*PrOH/*n*Hex/NEt_3 2.5:100:1.2 as eluent (the crude piperidine **6a** was dissolved in 0.5 ml of the eluent prior to the purification). For further purification the isolated product **6a** was dissolved in 1 N HCl-solution in water (4 mL), washed with Et_2O (3x4 mL), 550 mg (4.0 mmol) K_2CO_3 where added (CO_2-evolution) and the resulting emulsion (pH = 11) was extracted with of Et_2O (3x4 mL). Drying of the collected extraction phases over $MgSO_4$, evaporation of the solvent under reduced pressure and drying in high vacuum for 1 h delivered the piperidine derivative ***trans*-6a** (45.0 mg, 0.219 mmol, 71%) as a colorless oil, a pure stereoisomer (according to ^{1}H-NMR) and a pure enantiomer (according to HPLC on a chiral stationary phase).

M ($C_{13}H_{19}NO$) = 205.296 g/mol; $\mathbf{r_f}$ (SiO_2, *i*PrOH/*n*Hex, tailing) = 0.24 (1:5, tailing), 0.08 (2.5:100:1 (NEt_3)); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.32-7.21 (m, 5H, H-3´), 3.69 (d, 1H, H-1´$_a$, *J* = 12.9 Hz), 3.50 (app. broad s, 1H, H-3), 3.46 (d, 2H, H-1´$_b$, *J* = 13.9 Hz), 2.86 (s, 1H, OH), 2.71 (p, 1H, H-2, *J* = 5.7 Hz), 2.56-2.50 (m, 1H, H-6$_a$), 2.29-2.24 (m, 1H, H-6$_b$), 1.77-1.68 (m, 2H, H-4$_a$, H-5$_a$), 1.55-1.39 (m, 2H, H-4$_b$, H-5$_b$), 1.10 (d, 3H, H-1´´, *J* = 6.6 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 140.0 (C-2´), 128.7/128.2/126.9 (C-3´), 70.5 (C-3), 59.9 (C-2), 58.6 (C-1´), 46.6 (C-6), 27.7/21.0 (C-5), 10.11 (C-1´´); **IR** (film) ν cm^{-1} = 3379 (br), 3106 (w), 3085 (w), 3062 (w), 3027 (w), 2977 (m), 2936 (vs), 2858 (m), 2791 (s), 2715 (w), 1947 (w), 1875 (w), 1809 (w), 1602 (w), 1494 (m), 1452 (s), 1369 (m), 1321 (w), 1272 (w), 1226 (w), 1188 (w), 1156 (w), 1141 (m), 1113 (s), 1069 (s), 1029 (m), 1016 (m), 963 (w), 897 (w), 863 (w), 792 (w), 742 (s), 699 (vs), 638 (w), 577 (w), 541 (w); **HR-MS** (ESI, $C_{13}H_{20}NO^+$) calc. 206.1544 u, found 206.1545; α_D (c = 0.900 g/100 ml, $CHCl_3$, 21.0 °C, *ee*>99%) = +38.7.

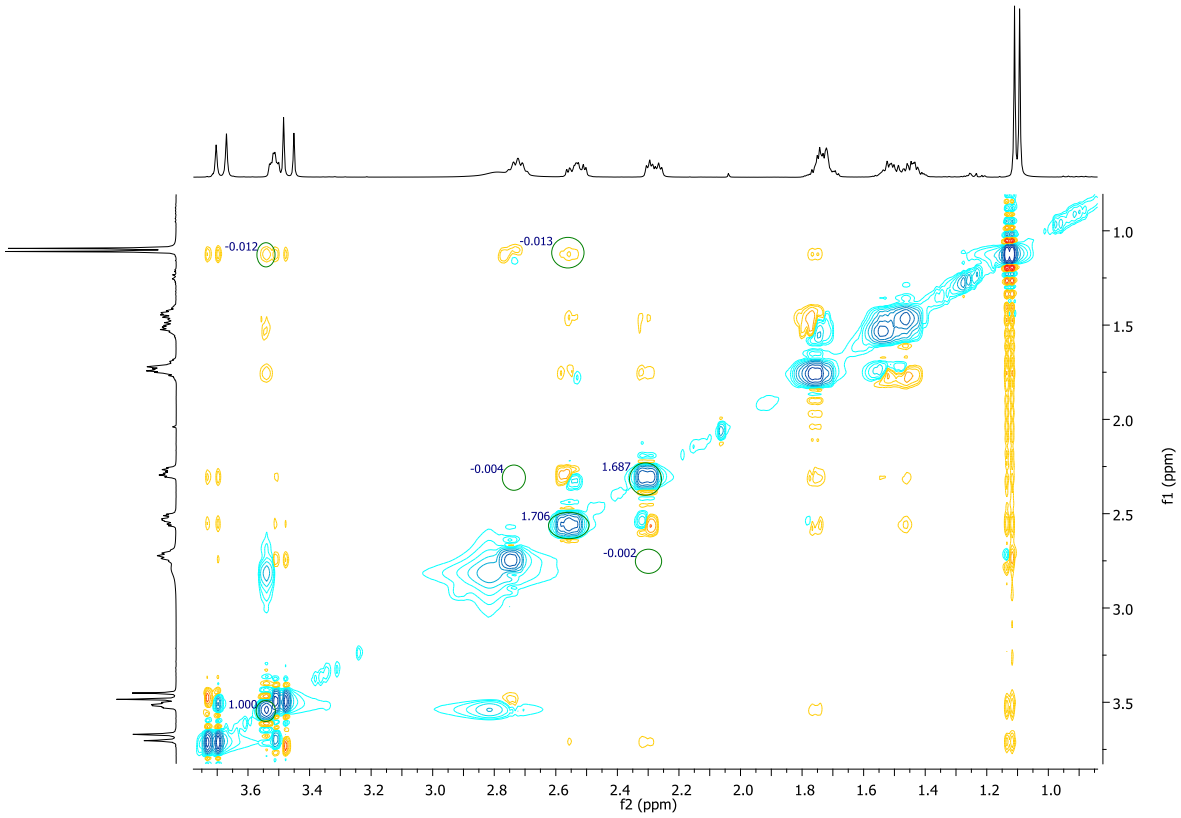
55 A 20 ml syringe was utilized instead of an extraction funnel for the work up.



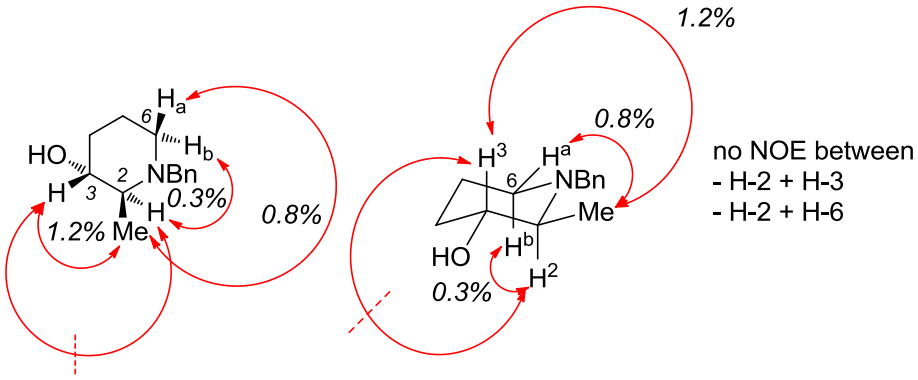
^{1}H-NMR-spectrum of piperidinol ***trans*-6a** in $CDCl_3$ (400 MHz).



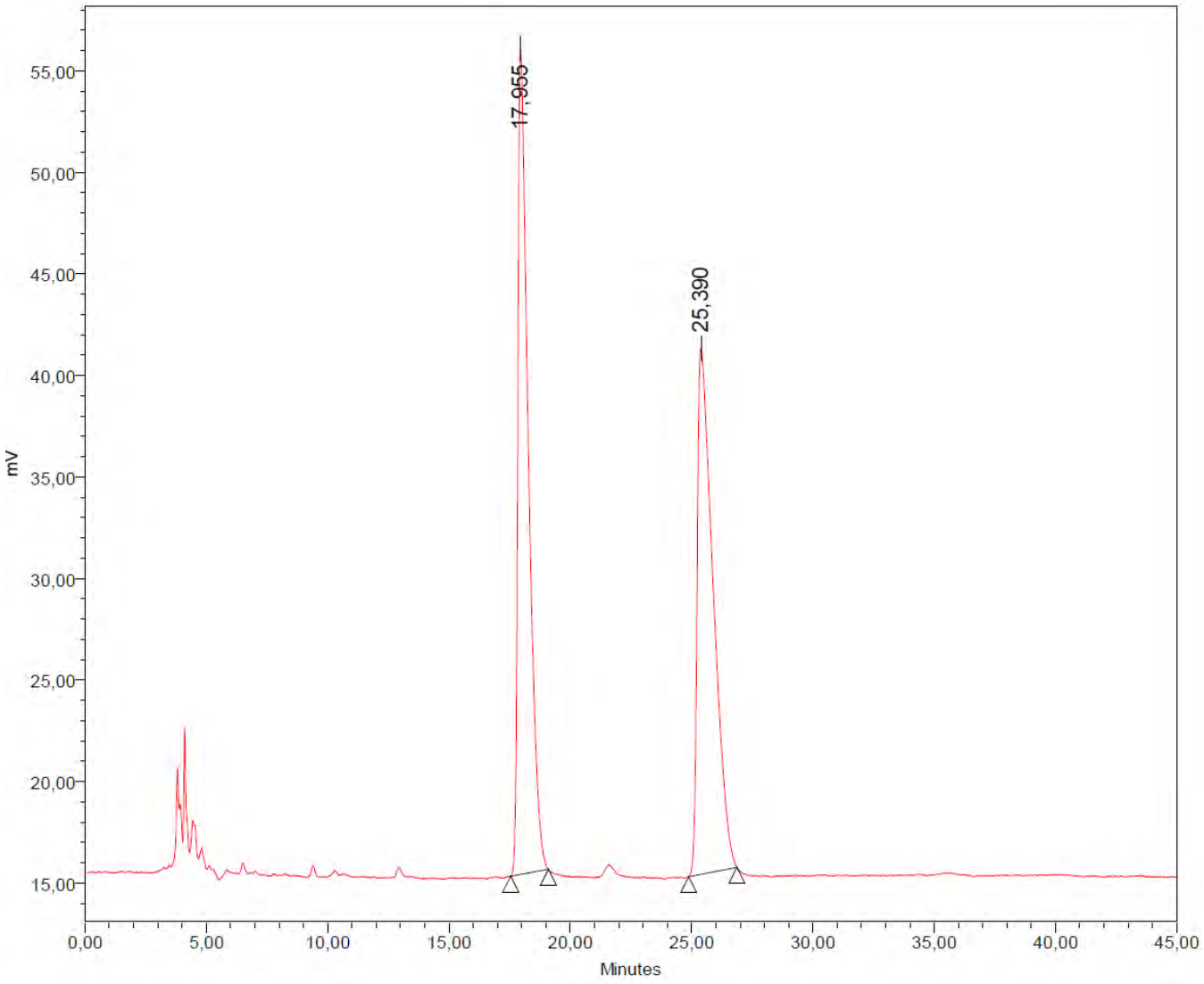
^{13}C-NMR-spectrum of piperidinol **6a** in $CDCl_3$ (100 MHz).



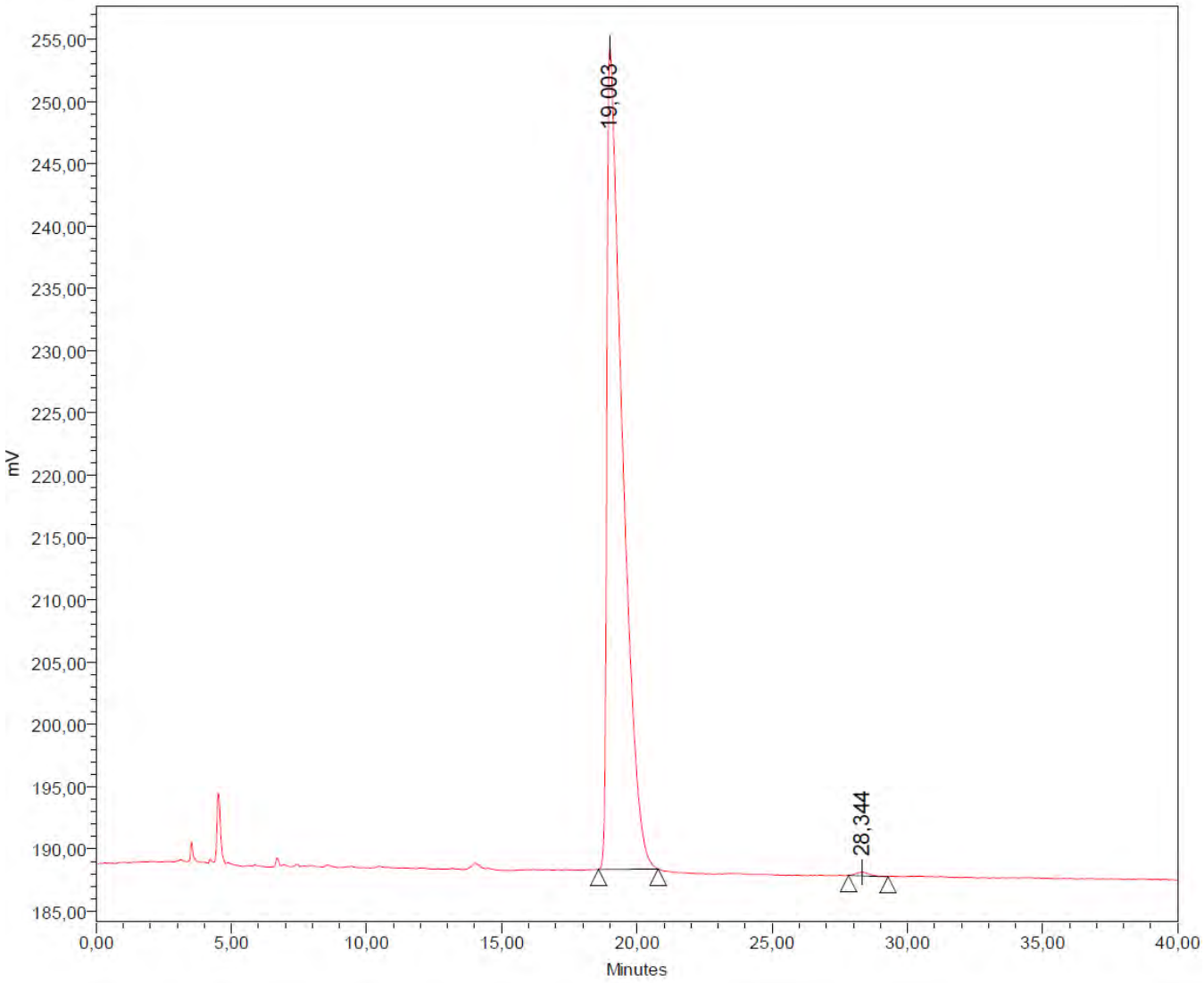
NOESY-spectrum of piperidine ***trans*-6a** in $CDCl_3$ (400 MHz).



HPLC-chromatograms of the racemic and enantioenriched piperidine ***trans*-6a** (*dr* = 4:1 *cis*/*trans*; separation conditions: column Chiralpak AI from Daicel Industries, flow 1 ml/min, eluent EtOH/*n*Hex/NEt_3 1:100:0.1, detected wavelength 254 nm):



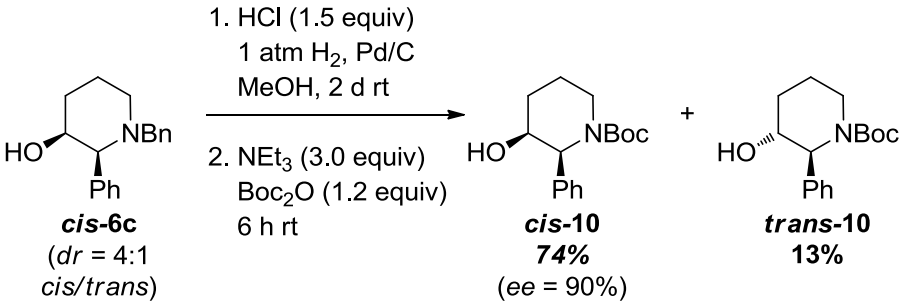
Retention Time (min)	Area	% Area
17,955	1207064	50,54
25,390	1181087	49,46



Retention Time (min)	Area	% Area
19,003	2640422	99,63
28,344	9764	0,37

2.6 Synthesis of *L-733,060* (Scheme 3)

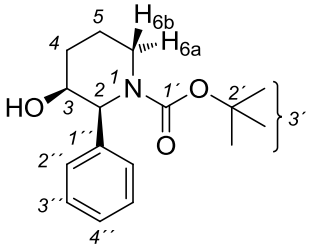
2.6.1 Synthesis of (*2S,3S*)-*N*-(*tert*-Butyloxycarbonyl)-2-phenyl-3-piperidinol (*cis*-10)



The benzyl amine **6c** (304 mg, 1.14 mmol, 1 equiv, *dr* = 4:1 *cis/trans*, *ee* = 90%) was dissolved in MeOH (2.5 mL, **6c** = 0.5 ml/L), cooled to 0 °C and 37% HCl solution in water (0.14 mL, 1.71 mmol, 1.5 equiv) and 10% Pd/C (50 mg, 0.046mmol, 4mol%) were added. The mixture was degassed in vacuum/purged with 1 atm of hydrogen (x6), the cooling bath was removed and the reaction suspension was allowed to stir for 2 d under 1 atm of hydrogen.[56]The reaction mixture was cooled in an ice bath again, neutralized with NEt_3 (0.47 mL, 3.42 mmol, 3.0 equiv) and treated with Boc_2O (0.32 mL, 1.48 mmol, 1.3 equiv). After 15 min of stirring the cooling bath was removed and the mixture was allowed to stir for 6 h at ambient temperature.

Then the reaction suspension was diluted with MeOH (5 mL), passed through a thin layer of celite, the celite cake was washed with MeOH (2x2 mL) and the collected filtrates were concentrated *in vacuo* (→ 100 mbar). The residue was dissolved in 1 N HCl-solution in water (2 mL) and DCM (2 mL), the aqueous phase was separated, and extracted with further two 2 mL portions of DCM, the combined DCM-phases were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude carbamate **10** as a yellow oil (341 mg).[57] Purification on silica gel with EtOAc/*c*Hex 1:3 → 1:2, concentration with chloroform under reduced pressure (2x2 mL) and drying in high vacuum for 12 h delivered the *cis*-epimer of **10** (233 mg, 0.841 mmol, 74%) as a pale yellow oil and the *trans*-diastereomer of **10** (41.6 mg, 0.150 mmol, 13%) as a colorless oil.

(*2S,3S*)-*N*-(*tert*-Butyloxycarbonyl)-2-phenyl-3-piperidinol (*cis*-10)

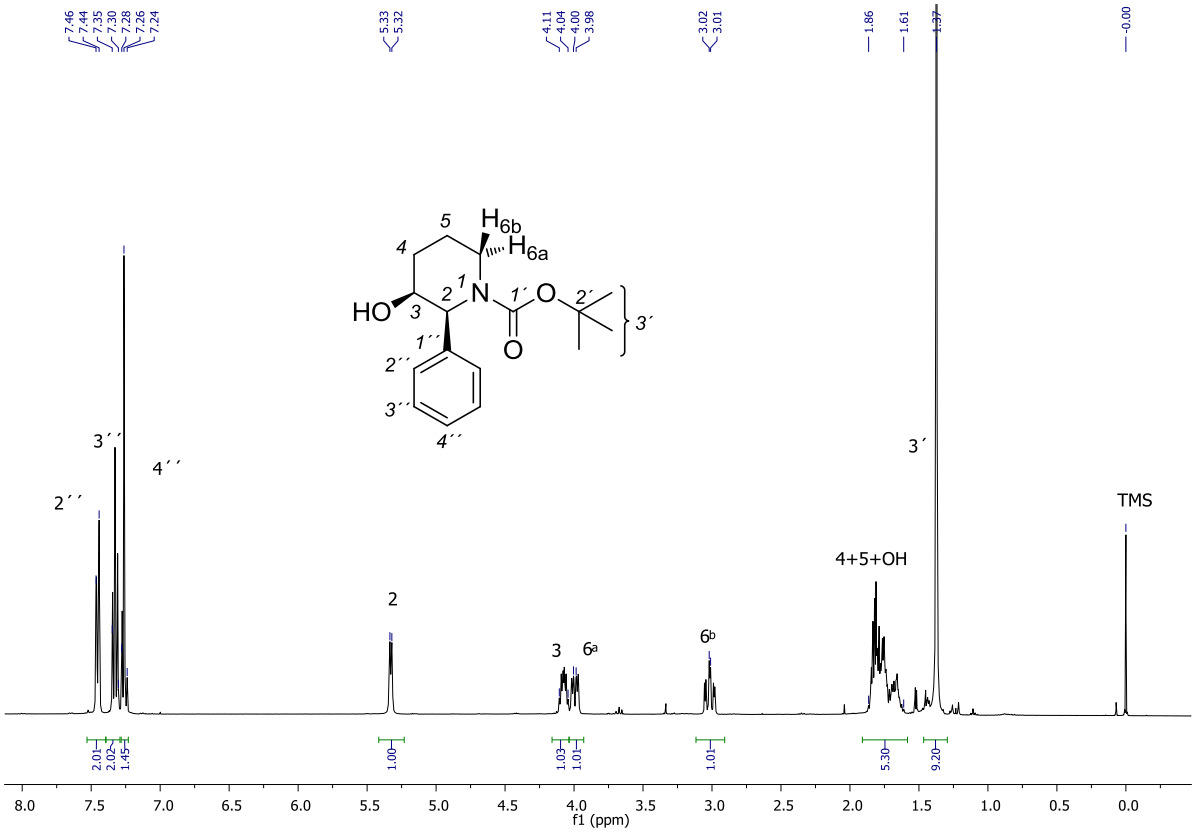


M ($C_{16}H_{23}N_3O$) = 277.359 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex) = 0.23 (2:7), 0.31 (1:3), 0.45 (1:2); r_f (SiO_2, EtOAc/*c*Hex) = 0.27 (1:3); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.46-7.44 (m, 2H, H-2´´), 7.35-7.30 (m, 2H, H-3´´), 7.28-7.24 (m, 2H, H-4´´), 5.33 (d, 1H, H-2, *J* = 5.4 Hz), 4.11-4.04 (m, 1H, H-3), 3.99 (dd, 1H, H-6_a, *J* = 13.4, 5.4 Hz), 3.02 (td, 1H, H-6_b, 13.4, 3.8 Hz), 1.86-1.61 (m, 5H, H-4, H-5, OH), 1.37 (s,

56 Micro work up with 1 N NaOH solution in water and Et_2O after 1.5 d of reaction time and TLC control indicated almost full conversion of the starting material **1**.

57 Instead of an extraction funnel a 20 mL syringe was applied in the work up.

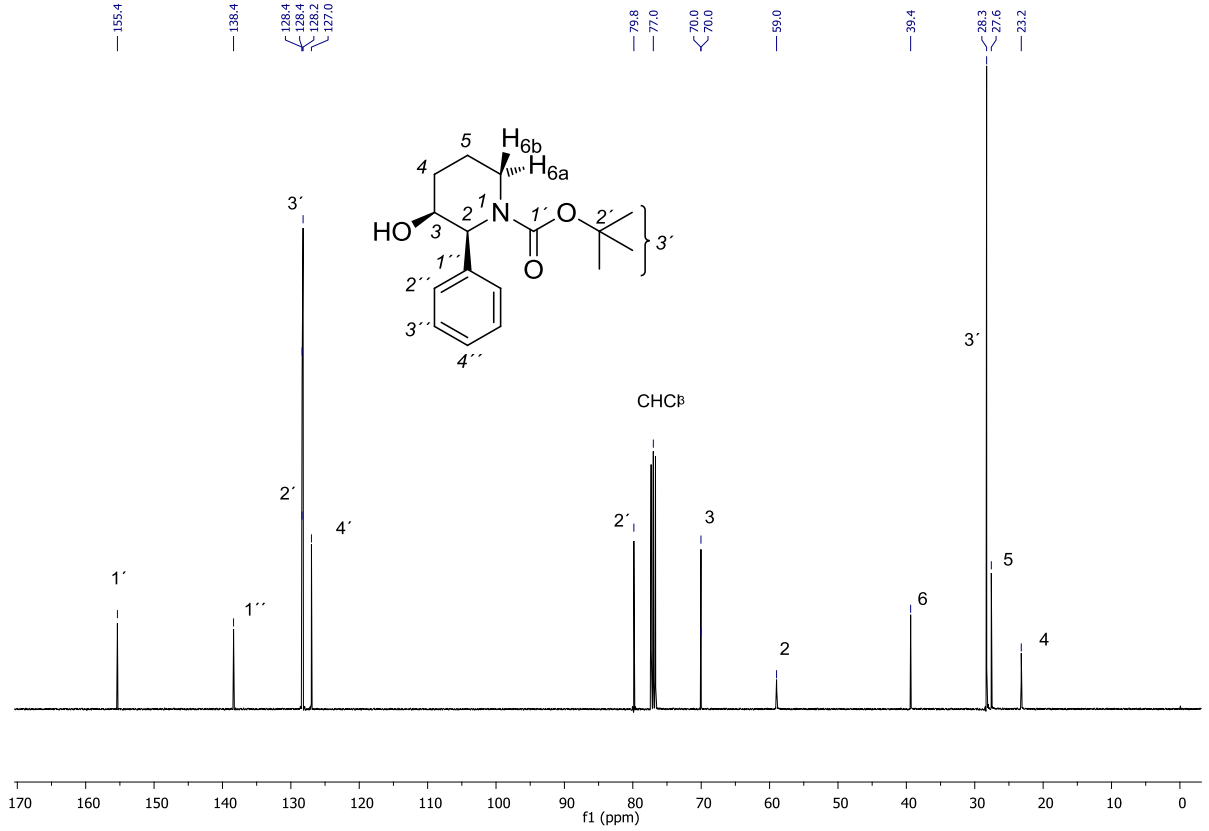
9H, H-3´); ^{13}C**-NMR** (100 MHz, $CDCl_3$) δ ppm = 155.4 (C-1´), 138.4 (C-1´´), 128.4 (C-2´´), 128.2 (C-3´), 127.0 (C-4´), 79.9 (C-2´), 70.1 (C-3), 59.0 (C-2), 39.4 (C-6), 28.3 (C-3´), 27.6 (C-4), 23.20 (C-5); **IR** (film) ν cm^{-1} = 3428 (br), 3092 (w), 3060 (w), 3028 (w), 3004 (w), 2976 (s), 2942 (s), 2870 (m), 1955 (w), 1895 (w), 1816 (w), 1693 (vs), 1667 (vs), 1603 (w), 1581 (w), 1495 (w), 1452 (m), 1416 (s), 1392 (w), 1366 (s), 1345 (w), 1296 (w), 1269 (m), 1253 (m), 1172 (s), 1147 (vs), 1082 (m), 1032 (w), 964 (m), 912 (w), 880 (w), 792 (w), 732 (m), 700 (m), 662 (w), 585 (w), 566 (w); **GC-MS** (EI, 70 eV) m/z u = 259 (5, M-H_2O^+), 221 (10, M-H_2C=$C(CH_3)_2^+$), 203 (100, M-H_2O-H_2C=$C(CH_3)_2^+$), 176 (95, M-CO_2*t*Bu^+), 158 (15), 146 (10), 132 (25), 118 (20), 104 (30), 91 (80, Bn^+), 77 (20, Ph^+), 57 (100, *t*Bu^+), 41 (70, allyl$^+$); **HR-MS** (ESI, $C_{16}H_{23}NO_3Na^+$) calc. 300.1576 u, found 300.1564 u; α_D (c = 1.33 g/100 mL, $CHCl_3$, 20.0 °C) = +46.2 (highest lit.: +56.7 (c = 1.3 g/100 mL, $CHCl_3$, 22 °C),[58] lowest lit: +33.17 (c = 0.5 g/100 mL, $CHCl_3$, 25.7 °C)[59]).



^{1}H-NMR-spectrum of piperidinol ***cis*-10** in $CDCl_3$ (400 MHz).

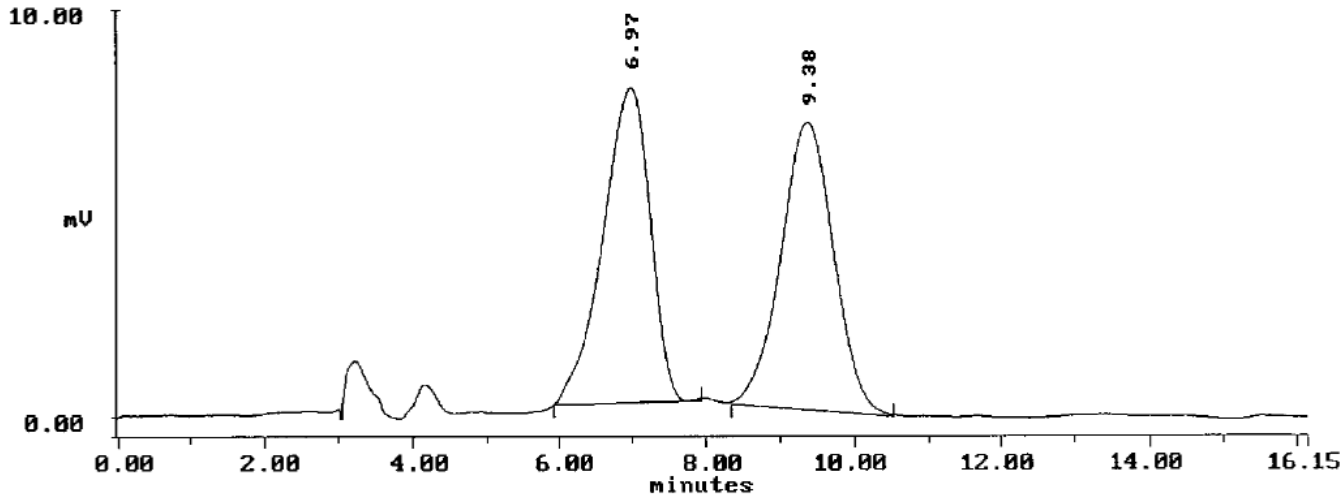
58 Oshitari, T. Mandai, T. *Synlett* **2006**, *20*, 3395-3398.

59 Li, G.-L.; Zhao, G.*Org. Lett.* **2006**, *8*, 633-636.

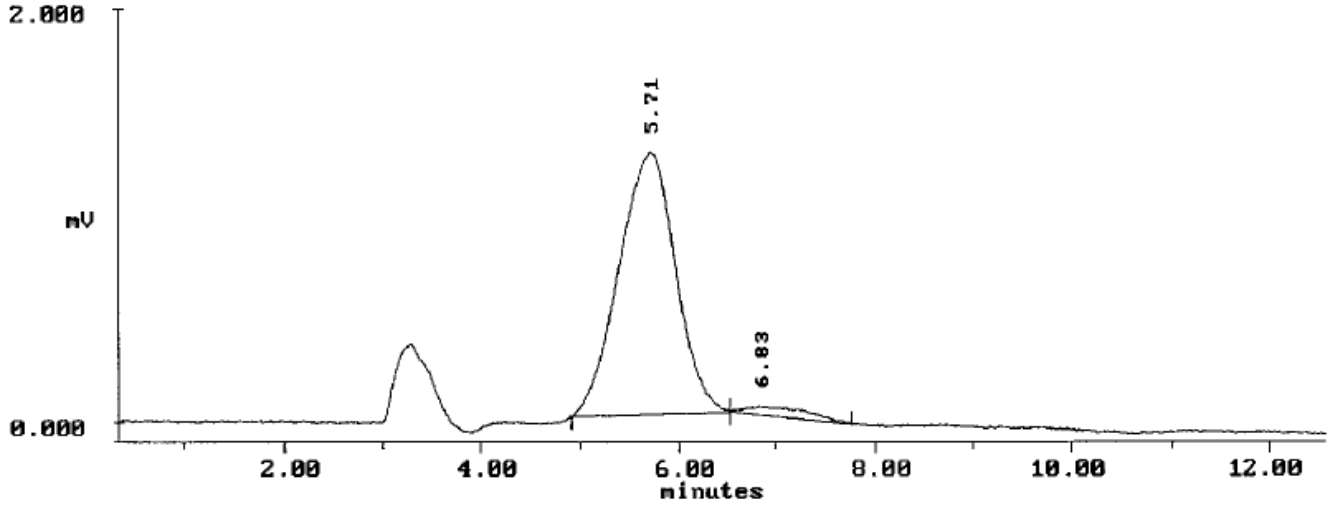


^{13}C-NMR-spectrum of piperidinol ***cis*-10** in $CDCl_3$ (100 MHz).

HPLC-chromatograms of the racemic and enantioenriched piperidine ***cis*-10** (separation conditions: column *Chiracel* OJ from *Daicel Industries*, flow 1 ml/min, eluent *i*PrOH/*n*Hex 1:19, detected wavelength 254 nm):



NO	RT	AREA		BC
1	6.97	340774	49.567	BB
2	9.38	346731	50.433	BB

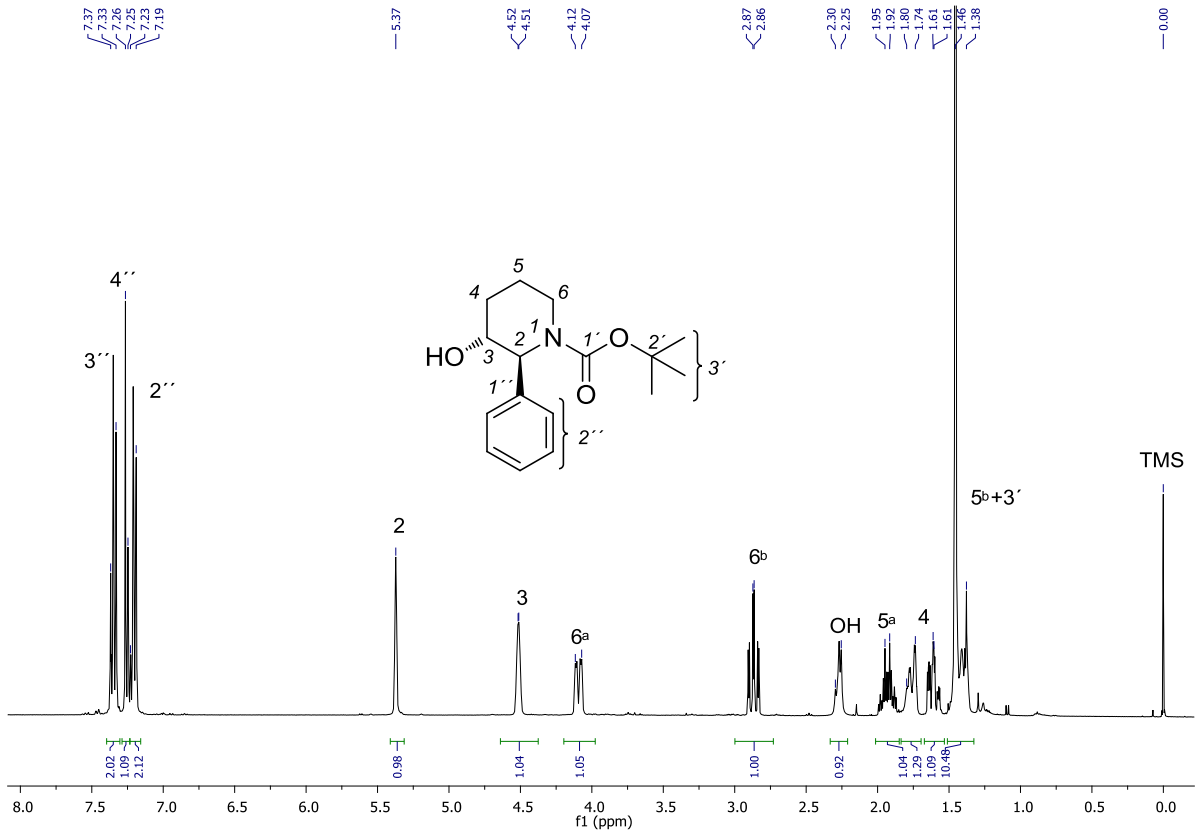


NO	RT	AREA		BC
1	5.71	50404	96.143	BB
2	6.83	2021	3.857	BB

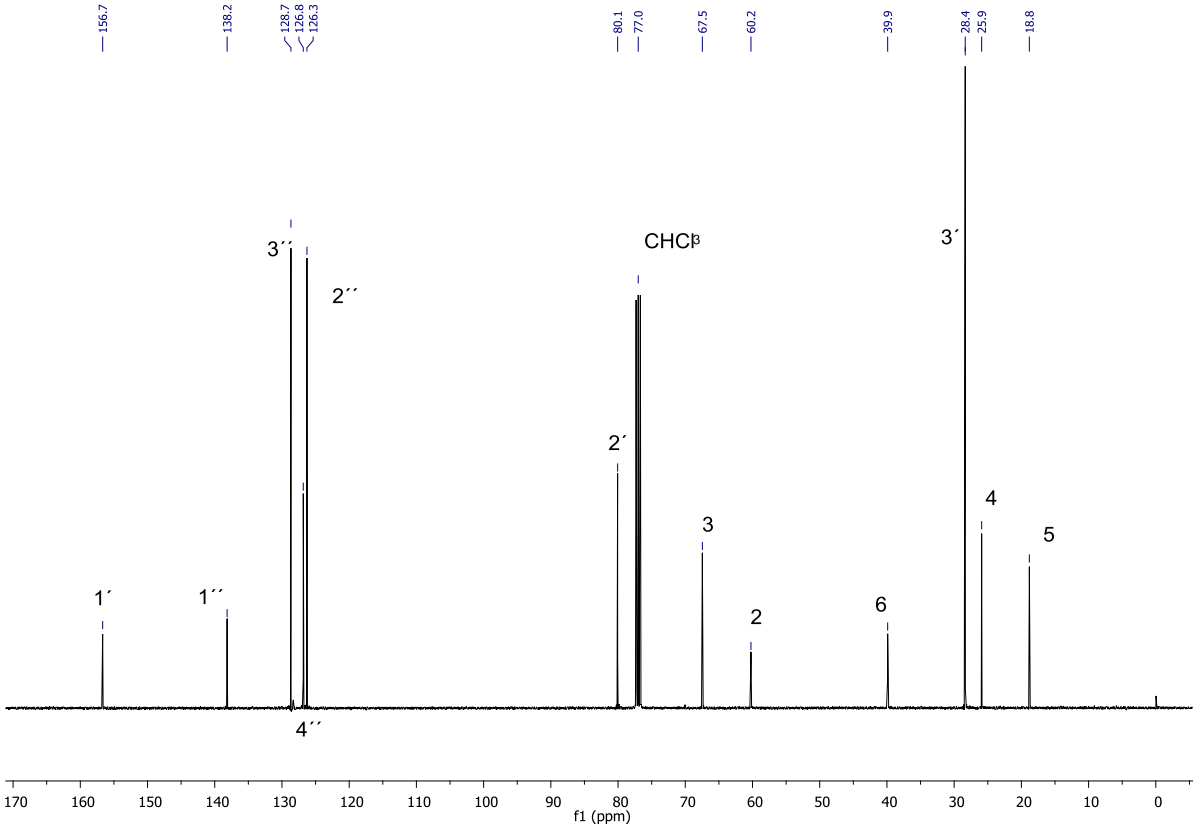
(*2S,3R*)-*N*-(*tert*-Butyloxycarbonyl)-2-phenyl-3-piperidinol (*trans*-10)

M ($C_{16}H_{23}NO_3$) = 277.359 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex) = 0.20 (1:3), 0.12 (1:4); r_f (SiO_2, EtOAc/*c*Hex) = 0.17 (1:3), 0.31 (2:3); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.37-7.33 (m, 3H, H-3´´), 7.26-7.25 (m, 1H, H-4´´), 7.23-7.19 (m, 2H, H-2´´), 5.37 (app. broad s, 1H, H-2), 4.52 (d, 1H, H-3, *J* = 2.2 Hz), 4.12-4.07 (m, 1H, H-6_a), 2.87 (td, 1H, H-6_b, *J* = 13.0, 3.2 Hz), 2.30-2.25 (m, 1H, OH), 1.94 (qt, 1H, H-5_a, *J* = 13.3, 4.6 Hz), 1.80-1.74 (m, 1H, H-4_a), 1.61 (qdd, 1H, H-4_b, *J* = 13.5, 4.6, 2.5 Hz), 1.46-1.38 (m, 10H, H-5_b, H-3´); ^{13}C-**NMR** (100 MHz, $CDCl_3$) δ ppm = 156.7 (C-1´), 138.2 (C-1´´), 128.7 (C-3´´), 126.8 (C-4´´), 126.3 (C-2´´), 80.1 (C-2´), 67.5 (C-3), 60.2 (C-2), 39.9 (C-6), 28.4 (C-3´), 25.9 (C-4), 18.8 (C-5); **IR** (film) ν cm^{-1} = 3434 (br), 3061 (w), 3089 (w), 3028 (w), 3004 (w), 2975 (m), 2933 (m), 2867 (w), 1689 (s), 1667 (vs), 1603 (w), 1495 (w), 1477 (w), 1449 (m), 1419 (s), 1366 (s), 1347 (w), 1324 (w), 1276 (m), 1254 (m), 1170 (s), 1138 (s), 1129 (s), 1078 (w), 1031 (w), 986 (s), 914 (w), 878 (m), 852 (w), 809 (w), 752 (w), 740 (w), 707 (m), 697 (m), 664 (w), 624 (w), 546 (w); **GC-MS** (EI, 70 eV) m/z u = 259 (2, M-H_2O^+), 221 (5, M-$H_2C{=}C(CH_3)_2^+$), 203 (35, M-H_2O-$H_2C{=}C(CH_3)_2^+$), 176 (40, M-CO_2tBu$^+$), 158 (10), 146 (5), 132 (10), 118 (15), 104 (20), 91 (45, Bn$^+$), 77 (20, Ph$^+$), 57 (100, *t*Bu$^+$), 41 (50, allyl$^+$); **HR-MS** (ESI, $C_{16}H_{23}NO_3Na^+$) calc. 300.1576 u found 300.1562 u; α_D (c = 1.33 g/100 mL, $CHCl_3$, 20.0 °C) +49.4 (lit: +64.1 (c = 0.96 g/100 mL, $CHCl_3$, T= 22 °C)).[60]

60 B. Helal, F. Ferreira, C. Botuha, F. Chemla, A. Perez-Luna, *Synlett***2009**, *19*, 3115-3118.

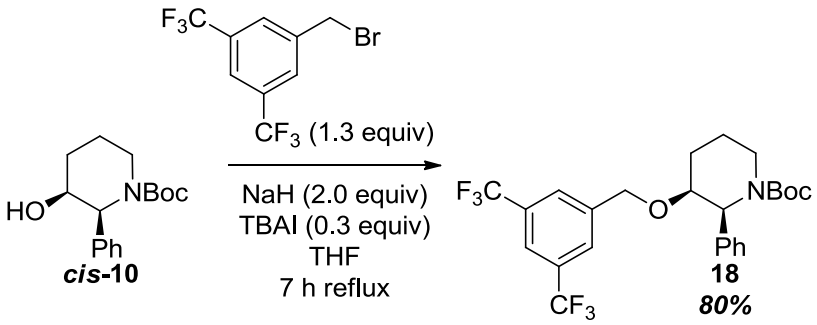


^{1}H-NMR-spectrum of piperidinol ***trans*-10** in $CDCl_3$ (400 MHz).



^{13}C-NMR-spectrum of piperidinol ***trans*-10** in $CDCl_3$ (100 MHz).

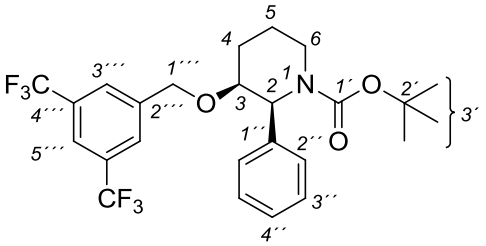
2.6.2 Synthesis of (*2S,3S*)-*N*-(*tert*-Butyloxycarbonyl)-3-(bis(3,5-trifluoromethyl)-benzyloxy)-2-phenyl piperidine (18)



Under an atmosphere of argon NaH (60%, 65 mg, 1.56 mmol, 2 equiv) was washed with two 0.5 mL portions of *n*Hex, the residual solvent was removed in high vacuum, the washed NaH was suspended in dry THF (1.6 mL, "NaH" = 1 mol/L) and cooled in an ice bath. Next, a solution of the alcohol ***cis*-10** (220 mg, 0.793 mmol, 1.0 equiv, *ee* = 90%) in dry THF (2 mL), TBAI (90 mg, 0.240 mmol, 0.3 equiv) and the benzyl bromide (190 μL, 1.03 mmol, 1.3 equiv) were added successively. Then the reaction solution was heated to reflux, whereby gas evolution was observed, and maintained at reflux temperature for 7 h.

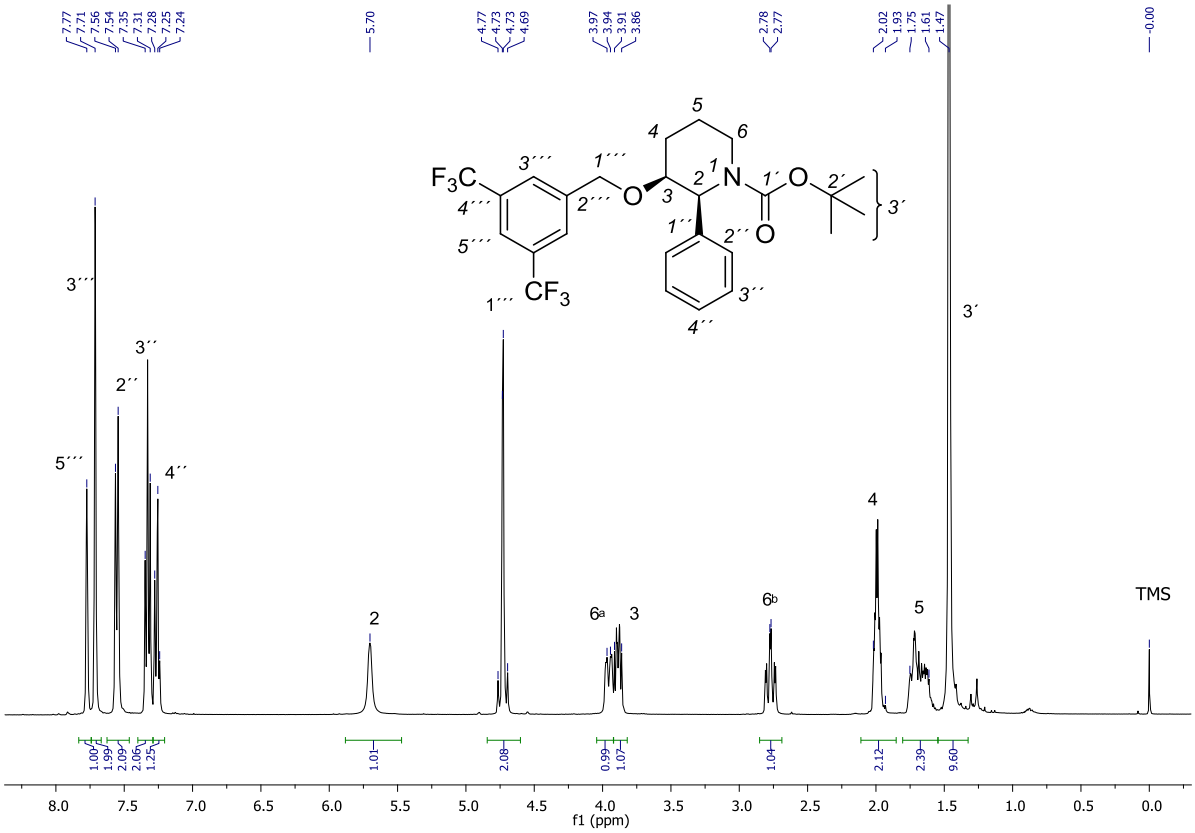
After cooling to ambient temperature, the brown suspension was cooled in an ice bath and 5 mL of 1 N HCl-solution in water were added dropwise (accompanied by a gas evolution). The mixture was extracted with three 3 mL portions of Et_2O, the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting black oily crude ether **18** (430 mg) was dissolved in ca. 1 mL of EtOAc/*c*Hex 1:10 and purified with column chromatography on silica (24 g) with the same solvent mixture. After concentration with chloroform (1 mLx2) and drying in high vacuum for 5 h, the ether **18** (319 mg, 0.633 mmol, 80%) was obtained as a pale yellow oil.

(*2S,3S*)-*N*-(*tert*-Butyloxycarbonyl)-3-(bis(3,5-trifluoromethyl)-benzyloxy)-2-phenyl piperidine (18)



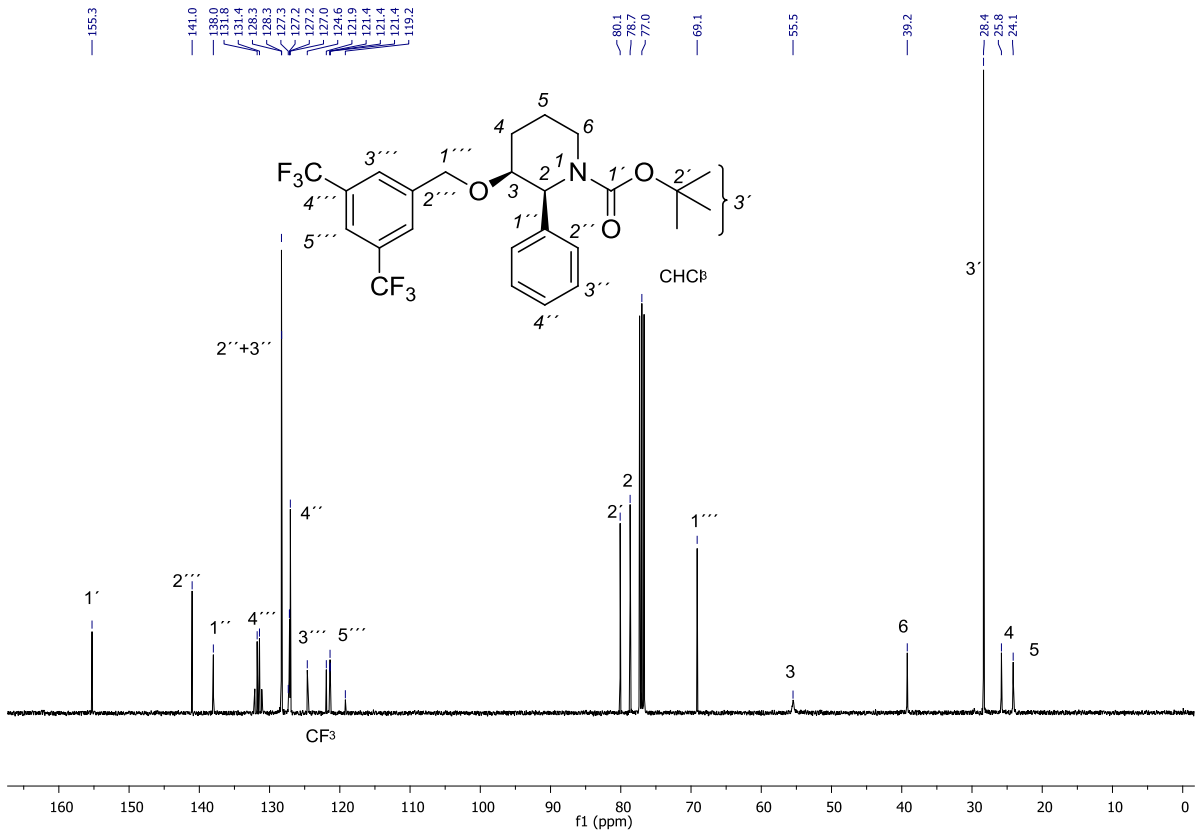
M ($C_{25}H_{27}F_6NO_3$) = 503.477 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex) = 0.25 (1:10), 0.41 (1:5); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm = 7.77 (s, 1H, H-5´´´), 7.71 (s, 2H, H-3´´´), 7.55 (d, 2H, H-2´´, *J* = 8.1 Hz), 7.35-7.31 (m, 2H, H-3´´), 7.28-7.24 (m, 1H, H-4´´), 5.70 (s, 1H, H-2), 4.75 (d, 1H, H-1´´´$_a$, *J* = 13.0 Hz), 4.71 (d, 1H, H-1´´´$_b$, *J* =12.3 Hz), 3.96 (dd, 1H, H-6$_a$, *J* = 13.6, 3.9 Hz), 3.91-3.86 (m, 1H, H-3), 2.78 (td, 1H, H-6$_b$, *J* = 13.1, 3.4 Hz), 2.02-1.93 (m, 2H, H-4), 1.75-1.61 (m, 2H, H-5), 1.47 (s, 9H, H-3´); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm = 155.3 (C-1´), 141.0 (C-2´´´), 138.0 (C-1´´), 131.6 (q, C-4´´´, *J* = 33 Hz), 2x128.3 (C-2´´, C-3´´), 127.2 (d, C-3´´´, *J* = 3 Hz), 127.0 (C-4´´´), 123.3 (q, CF_3, *J* = 271 Hz), 121.4 (p, C-5´´´, *J* = 4.0 Hz), 80.1 (C-2´), 78.7 (C-3), 69.1 (C-1´´´), 55.5 (C-2), 39.2 (C-6), 28.4 (C-3´), 25.8 (C-4), 24.1 (C-5); **IR** (film) ν cm^{-1} = 3441 (br), 3094 (w), 3062 (w), 3032 (w), 3005 (w), 2977

(s), 2944 (s), 2871 (m), 1953 (w), 1810 (w), 1689 (vs), 1624 (w), 1604 (w), 1496 (w), 1462 (m), 1413 (s), 1393 (w), 1366 (s), 1279 (vs), 1253 (s), 1175 (vs), 1135 (vs), 1095 (s), 1034 (w), 1002 (w), 956 (m), 885 (s), 843 (m), 795 (w), 767 (w), 731 (m), 704 (s), 682 (s), 648 (w), 585 (w); **HR-MS** (ESI, $C_{25}H_{28}NO_3F_6^+$) calc. 504.1973 u, found 504.1978 u; α_D (c = 1.685 g/100 mL, $CHCl_3$, 20.0 °C) +41.8 (highest lit.: +43.3 (c = 1.60 g/100 mL, $CHCl_3$, 23 °C)[58]; lowest lit.: +30.38 (c = 1.55 g/100 mL, $CHCl_3$, 25 °C))[61].



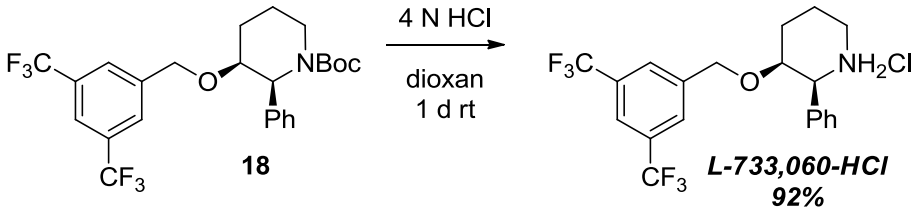
^{1}H-NMR-spectrum of benzyl ether **18** in $CDCl_3$ (400 MHz).

61 Bhaskar, G.; Rao, V. B.*Tetrahedron Letters***2003**, *44*, 915-918.



^{13}C-NMR-spectrum of benzyl ether **18** in $CDCl_3$ (100 MHz).

2.6.3 Synthesis of (*2S,3S*)-3-(bis(3,5-trifluoromethyl)-benzyloxy)-2-phenyl piperidine hydrochloride (*L-733,060-HCl*)

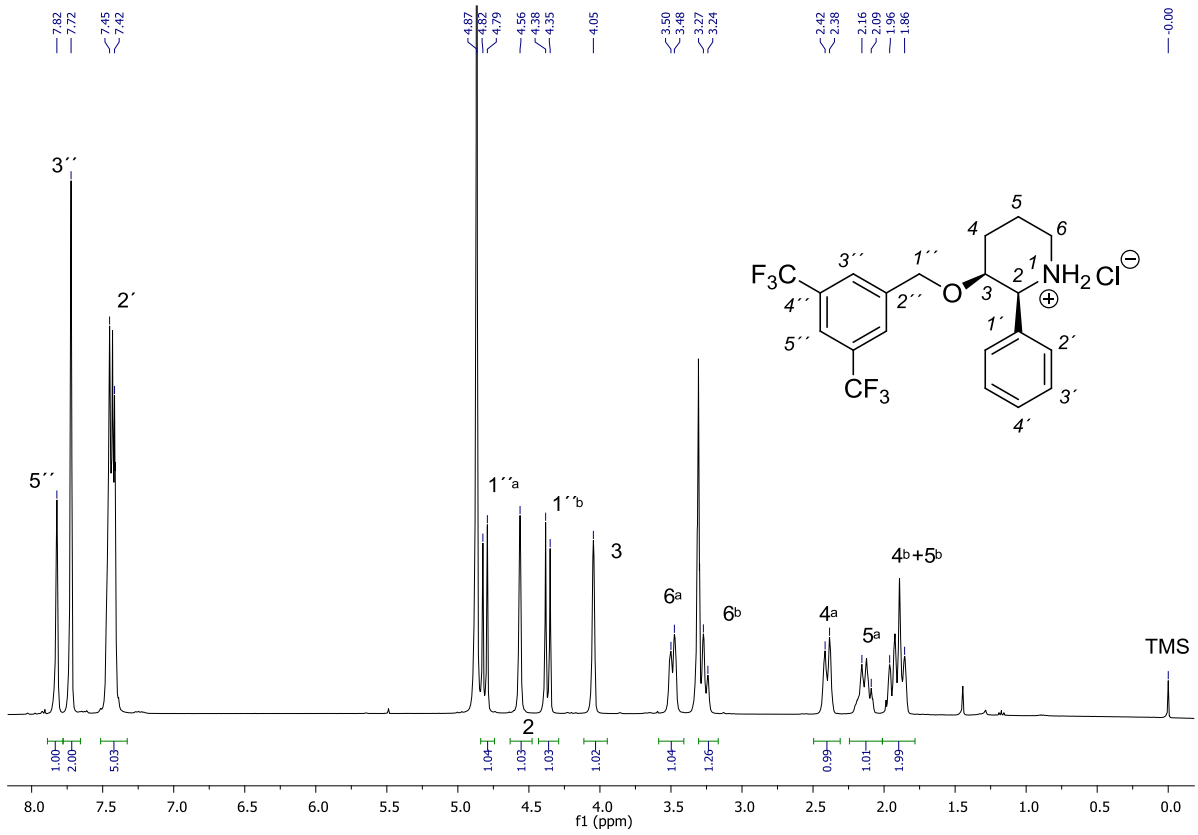


Carbamate **18** (315 mg, 0.626 mmol, 1.0 equiv) was dissolved in dioxane (0.8 mL), cooled to 0 °C and 37% HCl solution in water was added dropwise (0.4 mL, → 4 N HCl in dioxane, **18** = 0.5 mol/L). The reaction solution was stirred for 0.25 h at 0 °C and 24 h at ambient temperature, whereupon TLC control indicated full conversion (r_f (***L-733,060-HCl***) = 0.00 in EtOAc).

Dioxane was removed under reduced pressure (→ 60 mbar), the residue was diluted with 2 mL of water and extracted EtOAc (5x2 mL),[62] the combined EtOAc phases were dried over $MgSO_4$ and concentrated under reduced pressure. To remove dioxane and EtOAc the colorless residue was dissolved in 1 mL of chloroform and concentrated *in vacuo* (x2). The resulting colorless solid was concentrated *in vacuo* with 2 mL of Et_2O and dried in high vacuum for 3 h to give the ammonium salt ***L-733,060-HCl*** (253 mg. 0.575 mmol, 92%) as a pale yellow solid.

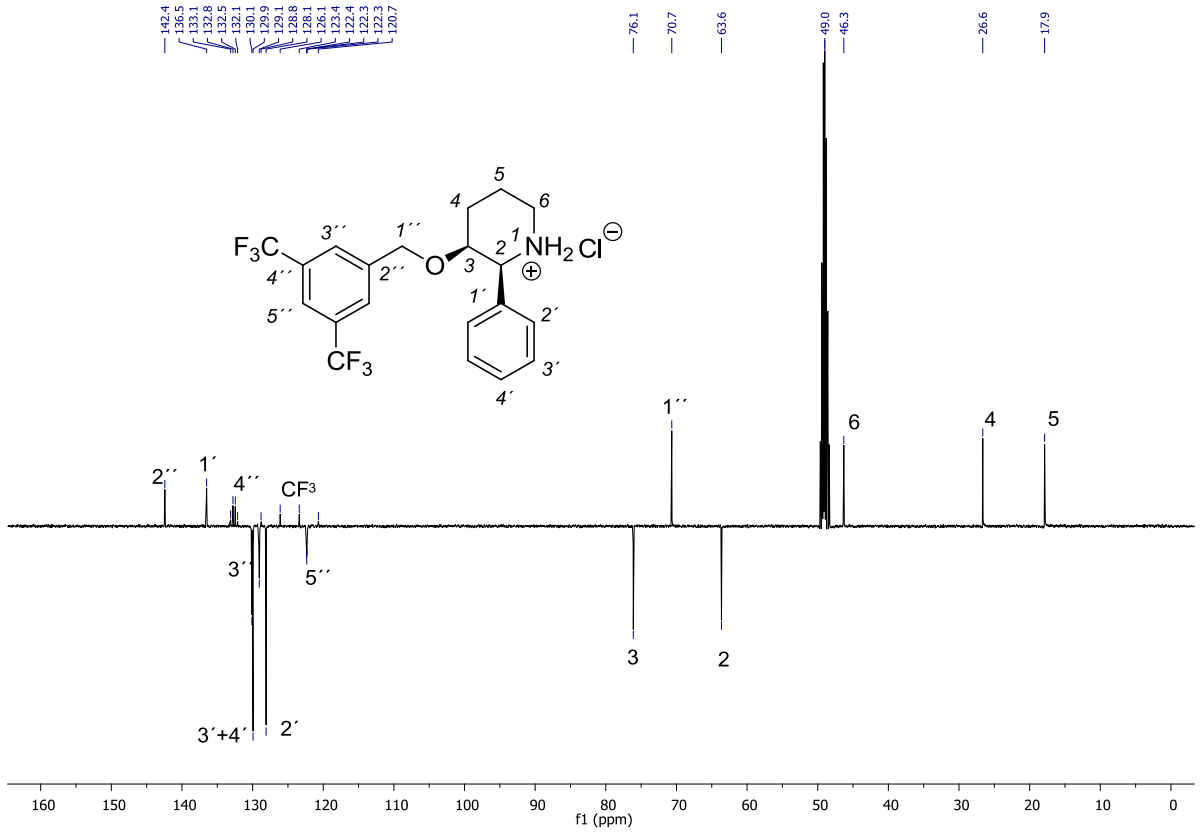
62A 10 mL syringe was used for the extraction rather than an extraction funnel.

M ($C_{20}H_{20}F_6NOCl$) = 439.822 g/mol; **mp.** = 200-203 °C (lit.: 215-217 °C)[63]; **^{1}H-NMR** (400 MHz, MeOH-d_4) δ ppm = 7.82 (s, 1H, H-5´´), 7.72 (s, 2H, H-3´´), 7.45-7.42 (m, 5H, H-2´, H-3´, H-4´), 4.81 (d, 1H, H-1´´$_a$, *J* = 13.0 Hz), 4.56 (s, 1H, H-2), 4.37 (d, 1H, H-1´´$_b$, *J* = 12.4 Hz), 4.05 (s, 1H, H-3), 3.49 (d, 1H, H-6$_b$, *J* = 9.9 Hz), 3.27-3.25 (m, 1H, H-6$_b$), 2.42-2.38 (d, 1H, H-4$_a$, *J* = 12.2 Hz), 2.16-2.09 (m, 1H, H-5$_a$), 1.96-1.86 (m, 2H, H-4$_b$, H-5$_b$); ^{13}C**-NMR** (100 MHz, MeOH-d_4) δ ppm = 142.4 (C-2´´), 136.5 (C-1´), 132.7 (q, C-4´´, *J* = 33 Hz), 130.1 (C-4´), 129.9 (C-3´), 129.1 (C-3´´), 128.1 (C-2´), 124.8 (q, CF_3, *J* = 270 Hz), 122.30 (quint., C-5´´, *J* = 4 Hz), (C-3), 70.7 (C-1´´), 63.6 (C-2), 46.3 (C-6), 26.6 (C-4), 17.9 (C-5); **IR** (film) ν cm^{-1} = 3419 (br), 2608 (w), 2103 (w), 1644 (s), 1457 (w), 1374 (w), 1276 (m), 1178 (w), 1123 (m), 890 (w), 841 (w), 763 (s), 750 (s), 701 (m), 681 (m); **HR-MS** (ESI, $C_{20}H_{20}NOF_6^+$) calc. 404.1449 u, found 404.1454 u; **α_D** (c = 0.925 g/100 ml, MeOH, 20 °C, MeOH) = +80.9, (c = 0.630 g/100 mL, $CHCl_3$, 20 °C) = +58.4 (lit.: +87.5 (c = 0.74 g/100 mL, MeOH, T = 23 °C)).[63]



^{1}H-NMR-spectrum of ***L-733,060-HCl*** in MeOH-d_4 (400 MHz).

63 Liu, R. H. Fang, K.; Wang, B.; Xu, M.-H.; Lin, G.-Q.*J. Org. Chem.* **2008**, *73*, 3307-3310.



^{13}C-NMR-spectrum of ***L-733,060-HCl*** in MeOH-d_4 (100 MHz).