Chemical Communications

SUPPORTING INFORMATION

Highly Enantioselective Synthesis of α-Azido-β-Hydroxy Methyl Ketones Catalyzed by a Cooperative Proline/Guanidinium Salt System

Ángel Martínez-Castañeda, Kinga Kędziora, Iván Lavandera, Humberto Rodríguez-Solla, Carmen Concellón* and Vicente del Amo*

Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo, C/ Julián Claveria 8, 33006, Oviedo, Spain

ccf@uniovi.es; vdelamo@uniovi.es

General

All commercially available reagents and solvents were used without further purification unless otherwise stated. Liquid aldehydes were in all cases distilled under reduced pressure before use. LBADH from *Lactobacillus brevis* was obtained from Codexis. ADH from *Rhodococcus ruber* (ADH-A) was obtained from Prof. Wolfgang Kroutil at the University of Graz (Austria) and has been overexpressed on *E. coli* following the methodology previously described.[1] Flash chromatography of reaction products was carried out using Silica 60A, particle size 230-400 micron (Merck). Analytical thin layer chromatography (TLC) was performed on DC-Alufolien Kieselgel $60F_{254}$ 0.2 mm plates (Merck) and compounds were visualised by UV fluorescence or 5% phosphomolybdic acid in methanol. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 or a Bruker DPX-300 spectrometer, using deuterated solvents and were referenced internally to the residual solvent peak (δ_H = 7.26 ppm, δ_C = 77.36 ppm) signal.[2] Coupling constants (*J*-values) are given in hertz (Hz). The DEPT 135 technique was used to assign methylene (CH_2) signals. Chemical shifts are reported as follows: value (number of protons, description of absorption, coupling constant(s) where applicable, assignment). NMR spectra assignation was aided by comparison with literature values for similar compounds. In this experimental section only clear identifiable peaks are assigned. HPLC analyses on chiral stationary phases were performed on an Agilent 1100 Series apparatus.

[1] K. Edegger, C. C. Gruber, T. M. Poessl, S. R. Wallner, I. Lavandera, K. Faber, F. Niehaus, J. Eck, R. Oehrlein, A. Hafner, W. Kroutil, *Chem. Commun.* **2006**, 2402-2404.
[2] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512-7515.

Synthesis of α-azidoacetone 5 (1-azido-2-propanone).

Sodium azide (2.60 g, 40 mmol) was poured onto a solution of chloroacetone (1.85 g, 1.6 mL, 20 mmol) in dry acetone (50 mL). The heterogeneous reaction mixture was vigorously stirred at room temperature for 24 h before it was filtered and the filtrate was washed with acetone. The mother liquors were concentrated under pressure and the resulting oil was diluted with Et_2O (50 mL) and washed with distilled water (2 x 15 mL). The organic layer was dried ($MgSO_4$), and the solvent and volatiles were removed in vacuum, affording the title compound **5** (1.90 g, 96%) as a pale-yellow oil.

Standard procedure for the synthesis of α-azido-β-hydroxy ketones 7a-i (SP1).

Tetraphenylborate guanidinium salt **6** (13.8 mg, 0.03 mmol), (*S*)-proline (2.3 mg, 0.02 mmol), aldehyde **4a-i** (0.2 mmol), and azidoacetone **5** (198 mg, 2.0 mmol) were weighed together inside a screw-capped test tube in the indicated order. The resulting suspension was stirred for 120 h at -10 ºC. Then, it was quenched with NH_4Cl (aq. sat.), extracted with DCM (2 x 15 mL) and the organic liquors dried ($MgSO_4$). Solvents and excess of azidoacetone **5** were eliminated under reduced pressure. Flash chromatography of silica gel afforded pure α-azido-β-hydroxy ketones **7**.

General protocols for the ADH-catalyzed synthesis of alcohols 11d and 12d

Effect of the pH and cofactor recycling system on the stability of *anti*-7d in aqueous media

Blank reactions without enzyme were performed in the presence of *anti*-**7d** (1.5 mg) dissolved in Tris-HCl buffer (0.5 mL, 50 mM) at pH 6.5 and 7.5 with the addition of isopropanol (25 µL, 5% v/v) or glucose (50 mM). The reaction tubes were shaken horizontally under orbital agitation at 30 ºC for 24 h and 150 rpm. After that time, the mixture was extracted with EtOAc (3 x 0.5 mL). The organic layers were separated by centrifugation (1.5 min, 13000 rpm) and dried over anhydrous Na_2SO_4. Finally, supernatant was transferred to a fresh vial and the organic solvent was evaporated with a N_2 flow. The substrate stability was determined by HPLC analysis. It was observed that at pH 7.5 and in the absence of 2-PrOH the substrate suffered from slight epimerization at C*H*-N3 and C*H*-OH positions, therefore the bioreductions were done at pH 6.5 using 2-PrOH as hydrogen donor.

Bioreduction of ketone *anti*-7d with *E. coli*/ADH-A (SP2)

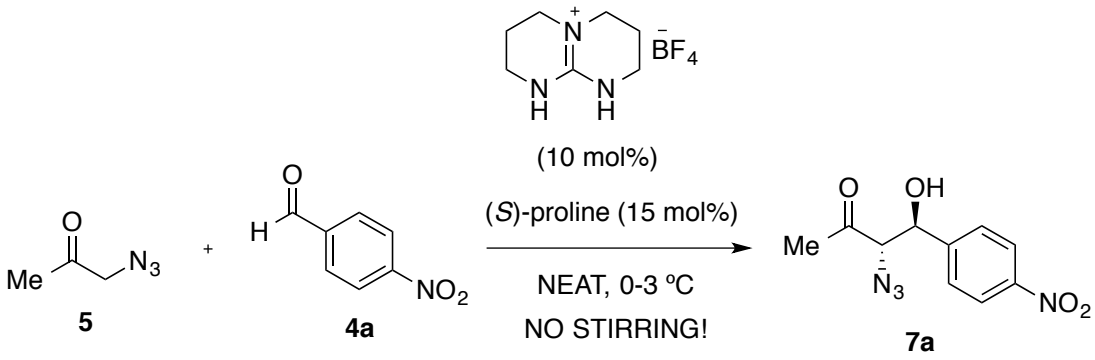
To 20 mg of overexpressed *E. coli*/ADH-A (lyophilised cells) in an Eppendorf vial (1.5 mL), 510 µL of Tris-HCl buffer (50 mM, pH 6.5), NADH (60 µL of a 10 mM solution, final concentration: 1 mM), 2-propanol (30 µL, 5% v/v) and substrate *anti*-**7d** (3.7 mg,

30 mM) were added. The reaction was set up in duplicate and the microtubes were shaken horizontally at 30 ºC under orbital agitation for 24 h and 150 rpm. After that time, the reaction products were extracted with EtOAc (3 x 0.5 mL). The organic layers were separated by centrifugation (1.5 min, 13000 rpm) and dried over anhydrous Na_2SO_4. Supernatant from both tubes was transferred to the same fresh vial and the organic solvent was evaporated with a N_2 flow. Finally, the crude was dried under high vacuum. The conversion rate and absolute configuration were determined by ^{1}H-NMR spectroscopy.

Bioreduction of ketone *anti*-7d with LBADH (SP3)

In an Eppendorf vial (1.5 mL), LBADH (10 µL, 3 U) was added to 450 µL of Tris-HCl buffer (50 mM, pH 6.5), followed by NADPH (60 µL of a 10 mM solution, final concentration: 1 mM), $MgCl_2$ (60 µL of a 10 mM solution, final concentration: 1 mM), 2-propanol (30 µL, 5% v/v) and substrate *anti*-**7d** (3.7 mg, 30 mM). The reaction was set up in duplicate and the microtubes were shaken horizontally at 30 ºC for 24 h and 150 rpm. After that time, the reaction products were extracted with EtOAc (3 x 0.5 mL). The organic layers were separated by centrifugation (1.5 min, 13000 rpm) and dried over anhydrous Na_2SO_4. Supernatant from both tubes was transferred to the same fresh vial and organic solvent was evaporated with a N_2 flow. Finally, the crude was dried under high vacuum. Conversion rate and absolute configuration were determined by ^{1}H-NMR spectroscopy.

Table S1. Screening of reaction time and stoichiometry (ratio aldehyde **4a**/azidoacetone **5**) in the (*S*)-proline/tetrafluoroborate guanidinium salt co-catalyzed reaction.[a]



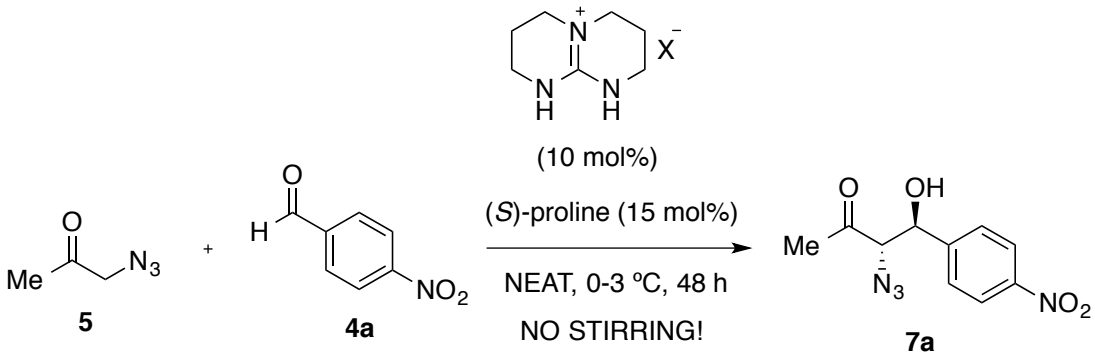
Entry	Time (h)	Equiv. **5**[b]	Conversion (%)[c]	d.r.[d]	*ee* (%)[e]
1	96	1.7	83	74:26	79
2	96	5	>99	75:25	87
3	96	10	>99	83:17	91
4	48	10	>99	75:25	91
5	24	10	99	72:28	88
6[f]	6	10	>99	65:35	79

[a] Reaction conditions: azidoacetone **5** (amount stated in the table), **4a** (0.2 mmol), (*S*)-proline (15 mol%), tetrafluoroborate guanidinium salt (10 mol%), no solvent. The reaction mixture was left to stand the indicate time inside a standard laboratory fridge (0-3 ºC) with no stirring. [b] Number of equivalents of azidoacetone **5** used, respect to aldehyde **4a**. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. Conversion of aldehyde **4a** (limiting reagent) into α-azido-β-hydroxy ketone **7a**. [d] Diastereoisomeric ratio of *anti*- to *syn*-**7a** determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [e] Enantiomeric excess of α-azido-β-hydroxy ketones *anti*-**7a** as determined by HPLC analysis on chiral stationary phases of the crude reaction mixtures. [f] Reaction stirred at 25 ºC.

We started to explore reaction conditions, which proved to be successful in related transformations disclosed by our group,[3] employing a tetrafluoroborate guanidinium salt. 10 equivalents of azidocetone **5**, respect to aldehyde **4a**, were necessary to optimise d.r. values (Table S1, entry 3).

[3] a) A. Martínez-Castañeda, B. Poladura, H. Rodríguez-Solla, C. Concellón, V. del Amo, *Org. Lett.* **2011**, *13*, 3032-3035. b) A. Martínez-Castañeda, B. Poladura, H. Rodríguez-Solla, C. Concellón, V. del Amo, *Chem. Eur. J.* **2012**, *18*, 5188-5190.

Table S2. Screening of different guanidinium salt's anions in the (*S*)-proline/guanidinium salt co-catalyzed reaction.[a]



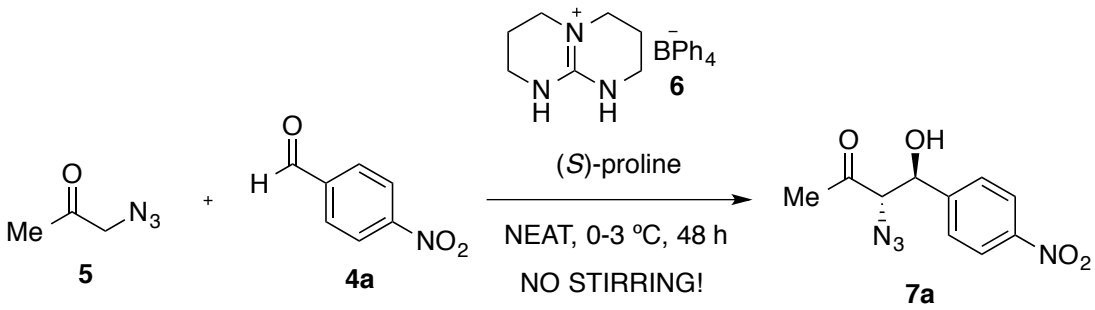
Entry	X^-	Conversion (%)[b]	d.r.[c]	*ee* (%)[d]
1	BF_4	>99	75:25	91
2	BPh_4	>99	85:15	95
3	$B(4\text{-}ClC_6H_4)_4$	>99	70:30	84
4	Cl	>99	60:40	84
5	NTf_2	99	75:25	85

[a] Reaction conditions: azidoacetone **5** (2.0 mmol), **4a** (0.2 mmol), (*S*)-proline (15 mol%), guanidinium salt (10 mol%), no solvent. The reaction mixture was left to stand for 48 h inside a standard laboratory fridge (0-3 ºC) with no stirring. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. Conversion of aldehyde **4a** (limiting reagent) into α-azido-β-hydroxy ketone **7a**. [c] Diastereoisomeric ratio of *anti*- to *syn*-**7a** determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [d] Enantiomeric excess of α-azido-β-hydroxy ketones *anti*-**7a** as determined by HPLC analysis on chiral stationary phases of the crude reaction mixtures.

As we have previously demonstrated, the nature of the anion accompanying the guanidinium salt core in (*S*)-proline/guanidinium salt co-catalytic systems is of central relevance.[4] The results from Table S2 evidence that guanidinium salt **6** is the most advantageous for this transformation (Table S2, entry 2).

[4]A. Martínez-Castañeda, H. Rodríguez-Solla, C. Concellón, V. del Amo, *J. Org. Chem.* **2012**, *77*, 10375-10381.

Table S3. Screening of different stoichiometries in the (*S*)-proline/guanidinium salt **6** co-catalyzed reaction.[a]

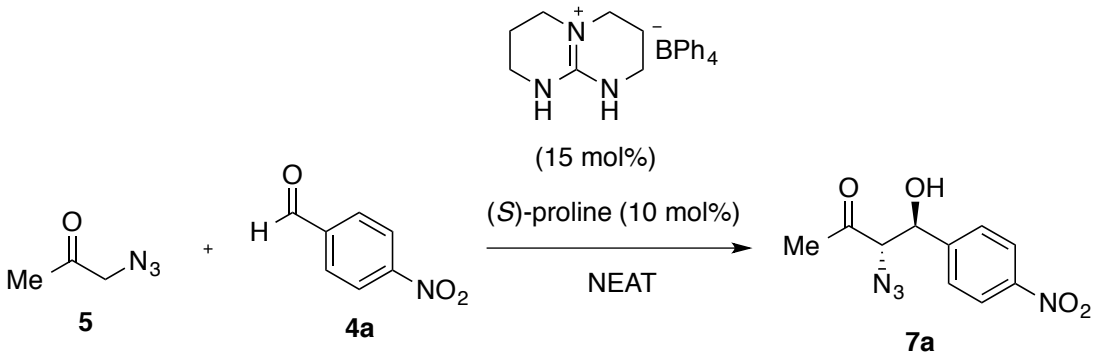


Entry	(*S*)-proline (mol %)	**6** (mol %)	Conversion (%)[b]	d.r.[c]	*ee* (%)[d]
1	15	10	>99	85:15	95
2	5	5	>99	84:16	95
3	10	10	>99	85:15	96
4	10	15	>99	85:15	97
5	3	3	>99	73:27	93
6	2	2	97	73:27	n.d.
7	5	15	>99	81:19	97
8	5	10	>99	83:17	97
9	10	20	>99	83:17	98
10	15	20	>99	81:19	97

[a] Reaction conditions: azidoacetone **5** (2.0 mmol), **4a** (0.2 mmol), (*S*)-proline and guanidinium salt **6** (amounts stated in the table), no solvent. The reaction mixture was left to stand for 48 h inside a standard laboratory fridge (0-3 ºC) with no stirring. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. Conversion of aldehyde **4a** (limiting reagent) into α-azido-β-hydroxy ketone **7a**. [c] Diastereoisomeric ratio of *anti*- to *syn*-**7a** determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [d] Enantiomeric excess of α-azido-β-hydroxy ketones *anti*-**7a** as determined by HPLC analysis on chiral stationary phases of the crude reaction mixtures.

Considering this set of experiments, the best conditions (Table S3, entry 4) were adopted in further optimisation screenings.

Table S4. Screening of reaction time and temperatures in the (*S*)-proline/guanidinium salt **6** co-catalyzed reaction.[a]

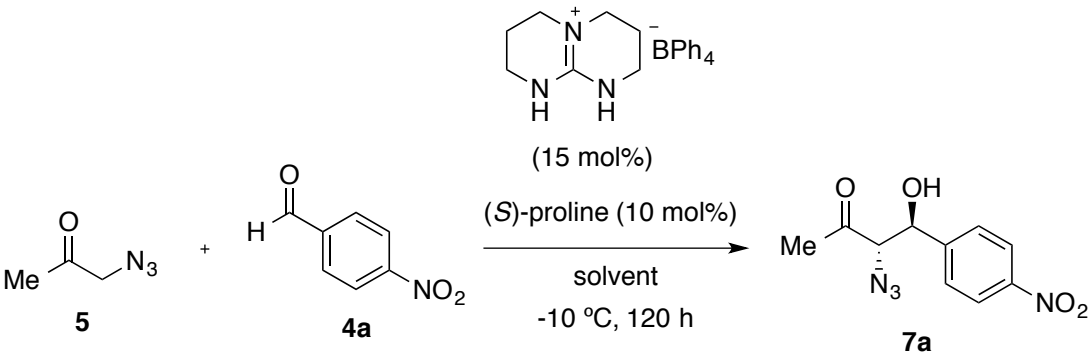


Entry	Time (h)	Temp. (ºC)	Conversion (%)[b]	d.r.[c]	*ee* (%)[d]
1	72	-5	>99	86:14	97
2	72	-10	87	91:9	97
3	120	-10	>99	90:10	97
4	144	-20	40	90:10	n.d.

[a] Reaction conditions: azidoacetone **5** (2.0 mmol), **4a** (0.2 mmol), (*S*)-proline (10 mol%), guanidinium salt **6** (15 mol%), no solvent. The reaction mixture was stirred the indicated time at the temperature stated in the table. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. Conversion of aldehyde **4a** (limiting reagent) into α-azido-β-hydroxy ketone **7a**. [c] Diastereoisomeric ratio of *anti*- to *syn*-**7a** determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [d] Enantiomeric excess of α-azido-β-hydroxy ketones *anti*-**7a** as determined by HPLC on chiral stationary phases of the crude reaction mixtures.

The finest reaction conditions for our transformation were found in Table S4, entry 3.

Table S5. Screening of standard organic solvents in the (*S*)-proline/guanidinium salt **6** co-catalyzed reaction.[a]

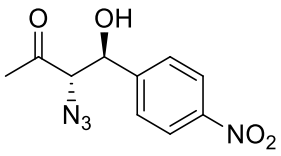


Entry	Solvent	Conversion (%)[b]	d.r.[c]	*ee* (%)[d]
1	CH_2Cl_2	59	87:13	n.d.[e]
2	Toluene	0	-	-
3	DMSO	>99	89:11	99

[a] Reaction conditions: azidoacetone **5** (2.0 mmol), **4a** (0.2 mmol), (*S*)-proline (10 mol%), guanidinium salt **6** (15 mol%), solvent (1 mL). The reaction mixture was stirred for 120 h at -10 ºC. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. Conversion of aldehyde **4a** (limiting reagent) into α-azido-β-hydroxy ketone **7a**. [c] Diastereoisomeric ratio of *anti*- to *syn*-**7a** determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [d] Enantiomeric excess of α-azido-β-hydroxy ketones *anti*-**7a** as determined by HPLC on chiral stationary phases of the crude reaction mixtures. [e] The enantiomeric excess of the product was not determined as a consequence of the moderate conversion.

Table S5 outcasts the results of the (*S*)-proline/guanidinium salt **6** co-catalyzed reaction performed in the presence of typical organic solvents. For comparison with optimal reaction conditions (Table S4, entry 3) in all the experiments a 10-fold excess of azidoacetone **5** respect to aldehyde **4a** was used. Reactions carried out in toluene do not occur to any extent. CH_2Cl_2, when used as the solvent, affords product **7a** with moderate conversion. Reactions carried out in DMSO render the desired product *anti*-**7a** with good d.r. and excellent *ee*. As DMSO is frozen at the temperature of the experiment (-10 ºC), thus there is no observed agitation in the reaction mixture, Table S5, entry 3, was somehow hard to reproduce.

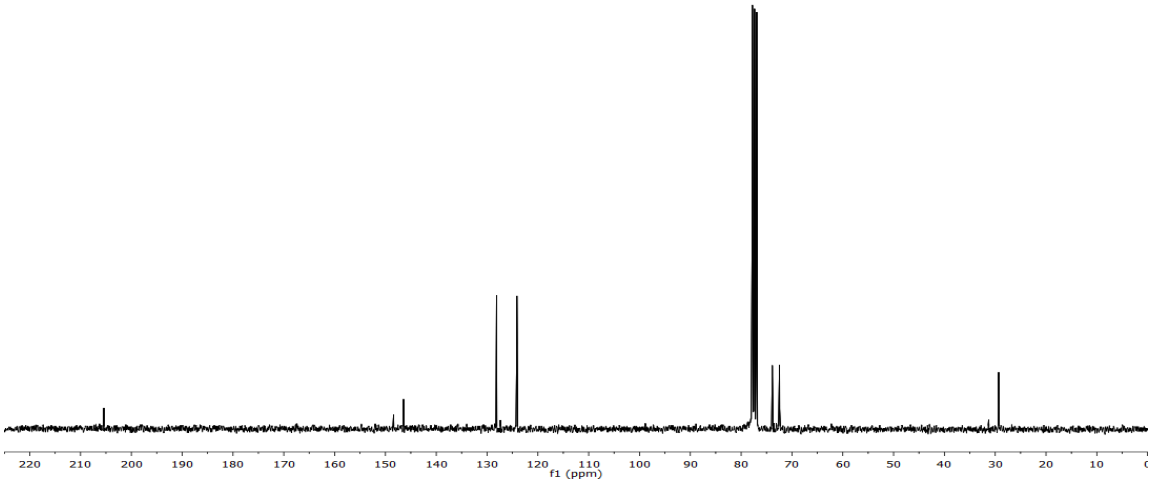
Synthesis of (3*S*,4*S*)-3-azido-4-hydroxy-4-(4-nitrophenyl)butan-2-one (7a)



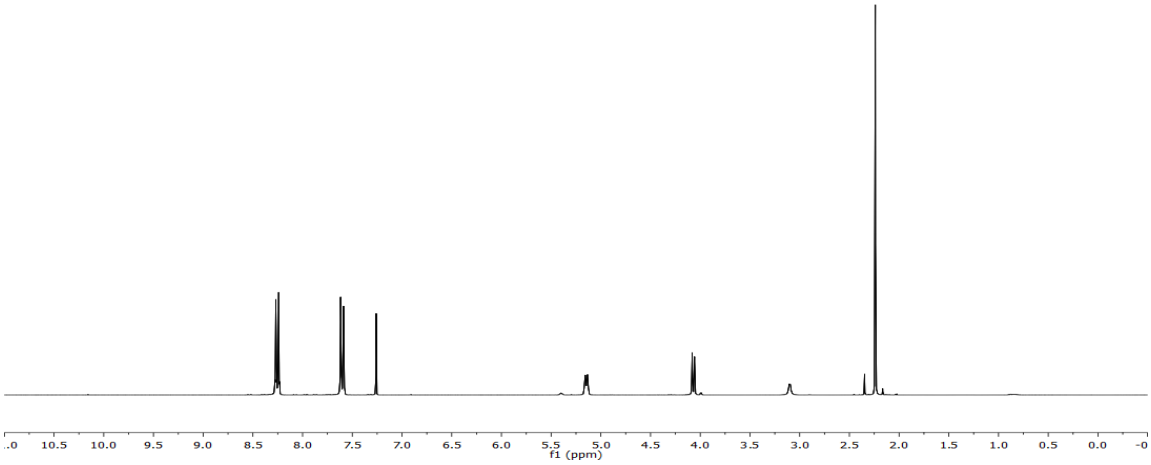
Prepared in 90% yield according to procedure **SP1**. Orangish solid. Purified by flash chromatography (Hex/EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.60 (2H, d, *J* = 8.7 Hz, Ar*H*), 5.15 (1H, dd, *J* = 6.9, 2.6 Hz, C*H*OH), 4.07 (1H, d, *J* = 6.9 Hz, C*H*N_3), 3.10 (1H, d, *J* = 3.7 Hz, O*H*), 2.23 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.4 (*C*=O), 148.4 (Ar*C*), 146.4 (Ar*C*), 128.1 (2 x Ar*C*H), 124.1 (2 x Ar*C*H), 73.9 (*C*HOH), 72.4 (*C*HN_3), 29.3 (*C*H_3); MS (ES^+) *m/z* (%) = 251 (100); HRMS (ES^+): *m/z* calcd. for $[M+H]^+$ $[C_{10}H_{11}N_4O_4]^+$ 251.0780, found 251.0791.

^{13}C NMR (75 MHz, $CDCl_3$)

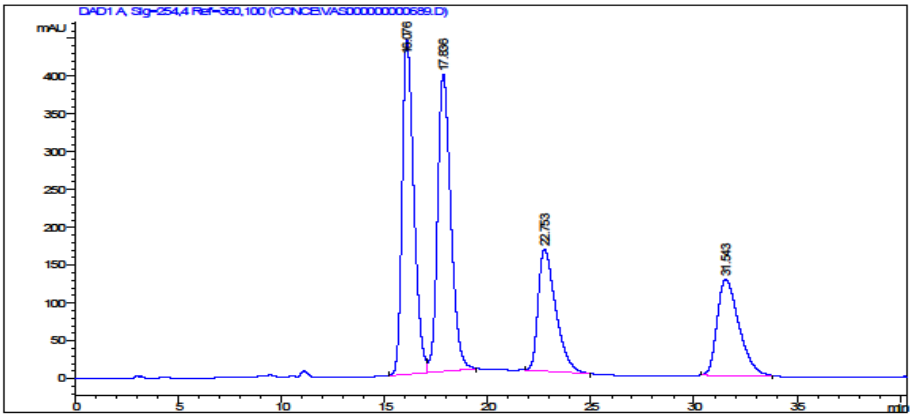


^{1}H NMR (300 MHz, $CDCl_3$)

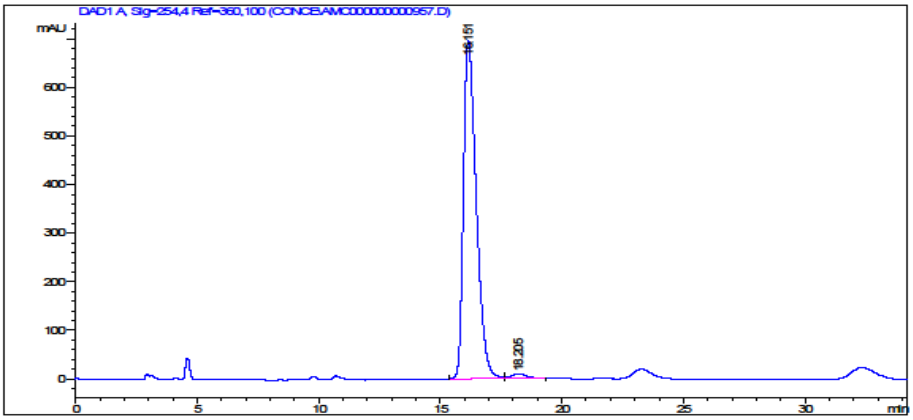


Compound *anti*-**7a** was obtained in a maximum of 97% *ee*, from crude reaction mixtures, and in 94% *ee* as an isolated pure product. The optical purity was determined by HPLC on a chiralpak OD-H column (hexane/2-propanol 90:10), flow rate 1.0 mL/min, λ 254 nm.

HPLC chromatogram of racemic *syn*- and *anti*-**7a**



HPLC chromatogram of crude product **7a**



Area Percent Report

Sorted By : Signal
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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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2	18.205	BB	0.6127	406.87152	9.11707	1.5751
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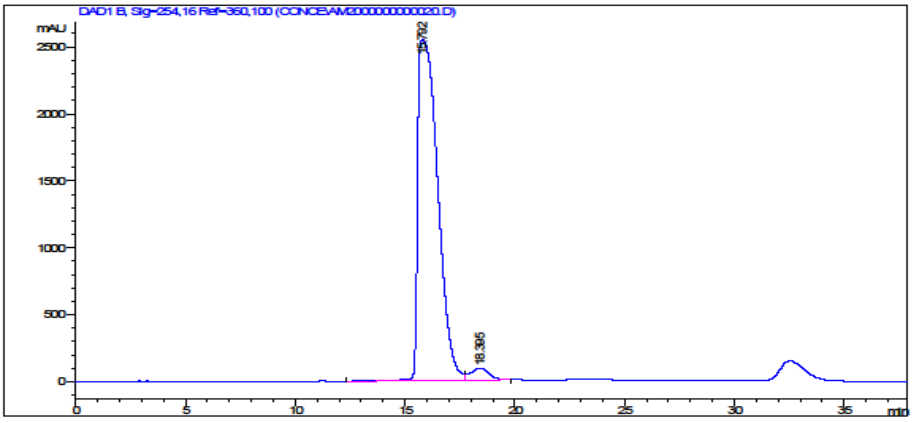
*** End of Report ***

HPLC chromatogram of pure product *anti*-**7a**.



Area Percent Report

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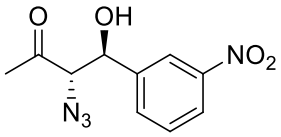
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.792	BV	0.7549	1.61122e5	2543.97534	97.0006
2	18.395	VB	0.8403	4982.05273	88.83852	2.9994
Totals :				1.66104e5	2632.81387	

*** End of Report ***

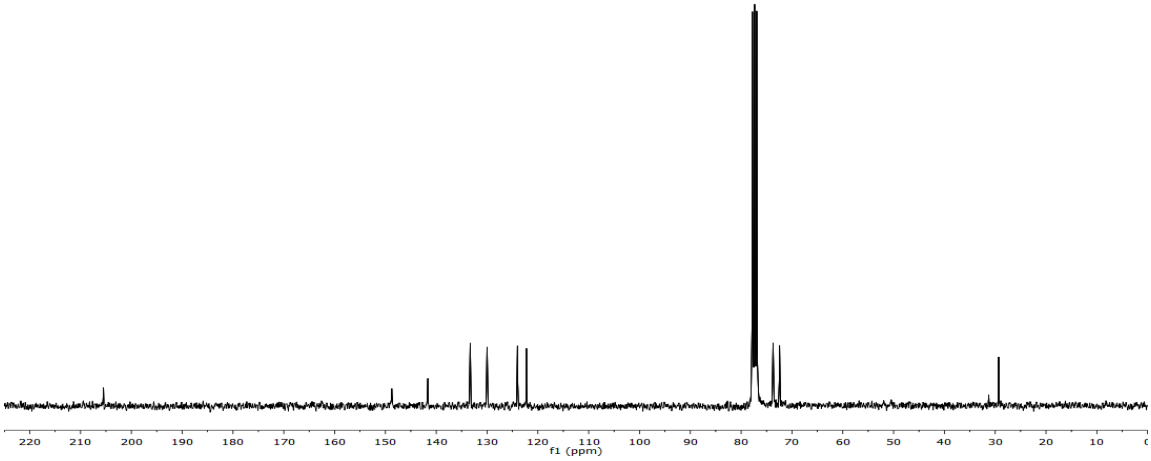
Synthesis of (3*S*,4*S*)-3-azido-4-hydroxy-4-(3-nitrophenyl)butan-2-one (7b)



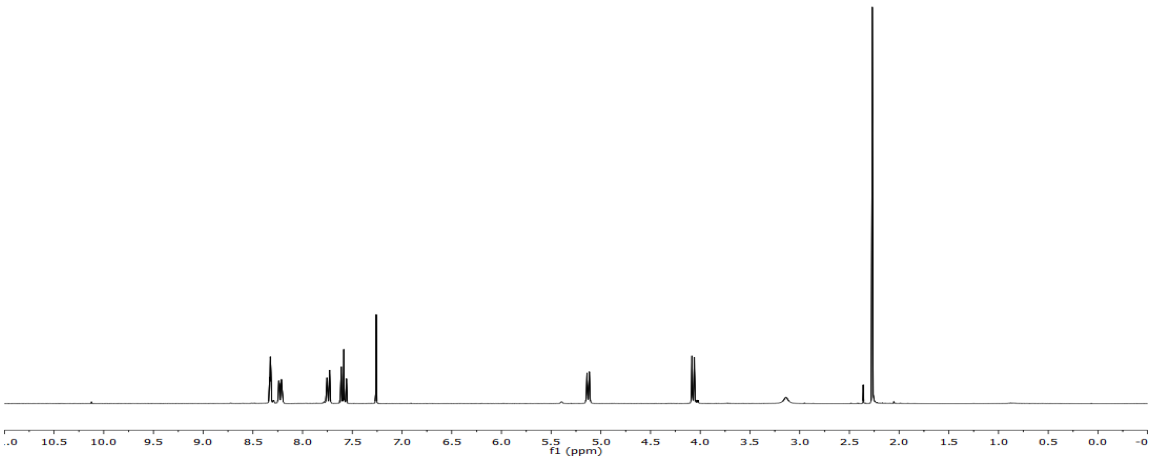
Prepared in 91% yield according to procedure **SP1**. Orangish oil. Purified by flash chromatography (Hex/EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (1H, t, *J* = 2.0 Hz, Ar*H*), 8.22 (1H, ddd, *J* = 8.2, 2.4, 1.2 Hz, Ar*H*), 7.74 (1H, dt, *J* = 7.7, 1.5 Hz, Ar*H*), 7.58 (1H, t, *J* = 7.9 Hz, Ar*H*), 5.13 (1H, d, *J* = 7.1 Hz, C*H*OH), 4.07 (1H, d, *J* = 7.2 Hz, C*H*N_3), 3.14 (1H, broad s, O*H*), 2.27 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.5 (*C*=O), 148.7 (Ar*C*), 141.6 (Ar*C*), 133.3 (Ar*C*H), 130.0 (Ar*C*H), 124.0 (Ar*C*H), 122.3 (Ar*C*H), 73.7 (*C*HOH), 72.4 (*C*HN_3), 29.3 (CH_3); MS (ES^+) *m/z* (%) = 251 (100); HRMS (ES^+): *m/z* calcd. for $[M+H]^+$ $[C_{10}H_{11}N_4O_4]^+$ 251.0780, found 251.0788.

^{13}C NMR (75 MHz, $CDCl_3$)

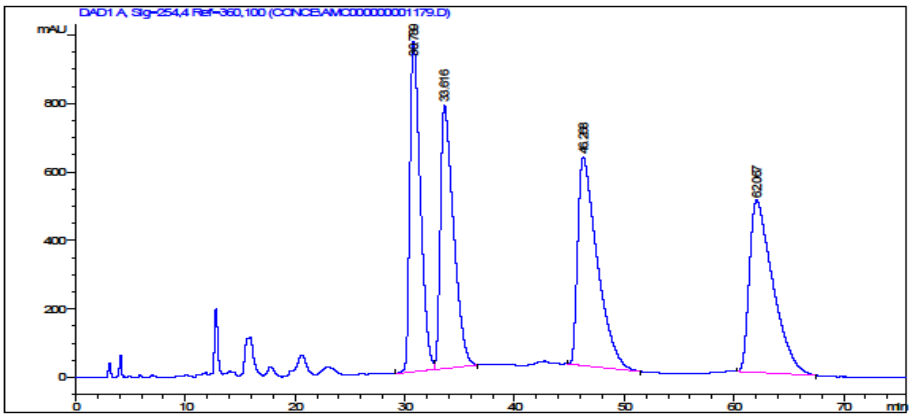


^{1}H NMR (300 MHz, $CDCl_3$)

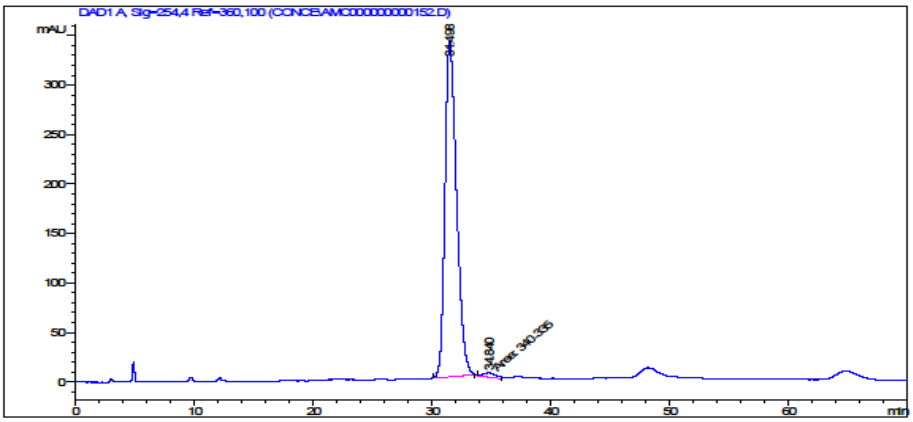


Compound *anti*-**7b** was obtained in a maximum of 97% *ee*, from crude reaction mixtures, and in 95% *ee* as an isolated pure product. The optical purity was determined by HPLC on a chiralpak OD-H column (hexane/2-propanol 95:5), flow rate 1.0 mL/min, λ 254 nm.

HPLC chromatogram of racemic *syn*- and *anti*-**7b**



HPLC chromatogram of crude product **7b**



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

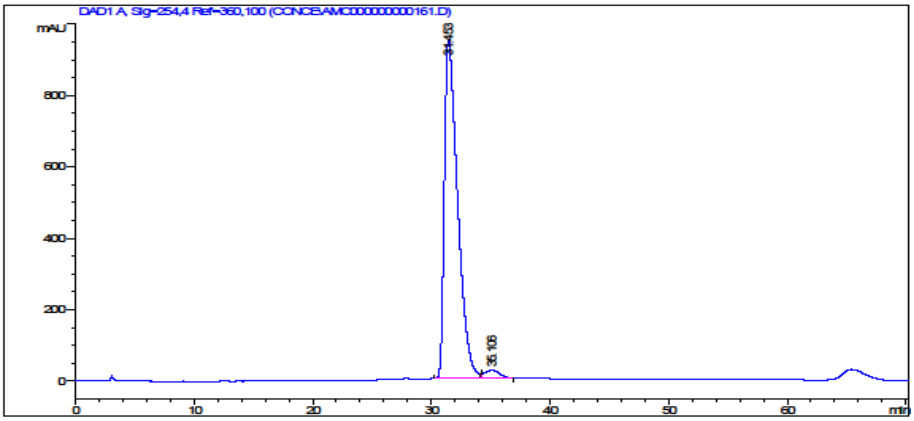
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.498	BB	1.0469	2.29184e4	338.94775	98.5367
2	34.840	MM	1.3038	340.33450	4.35043	1.4633

Totals : 2.32587e4 343.29818

*** End of Report ***

HPLC chromatogram of pure product *anti*-**7b**



Area Percent Report

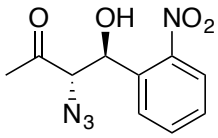
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.453	BB	1.1392	7.34910e4	947.17621	97.5597
2	35.106	BB	1.0308	1838.22644	21.68974	2.4403
Totals :				7.53293e4	968.86595	

*** End of Report ***

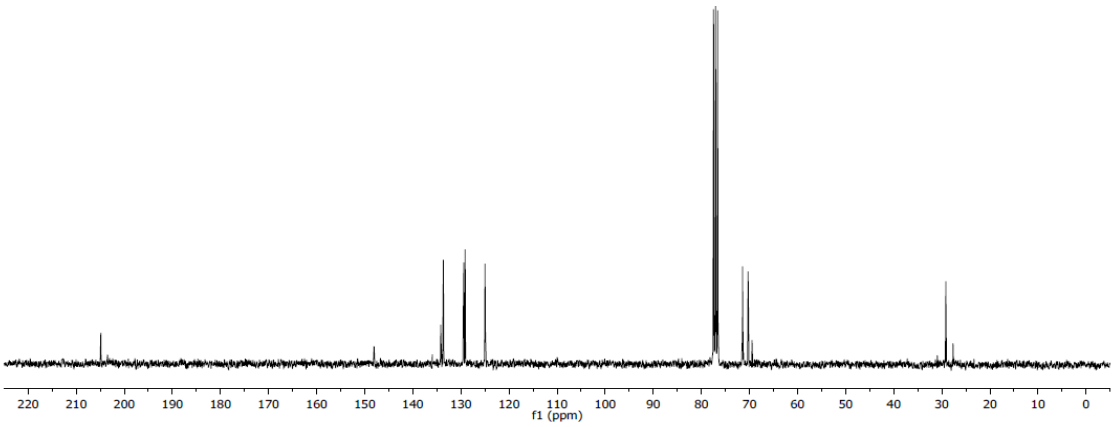
Synthesis of (3*S*,4*S*)-3-azido-4-hydroxy-4-(2-nitrophenyl)butan-2-one (7c)



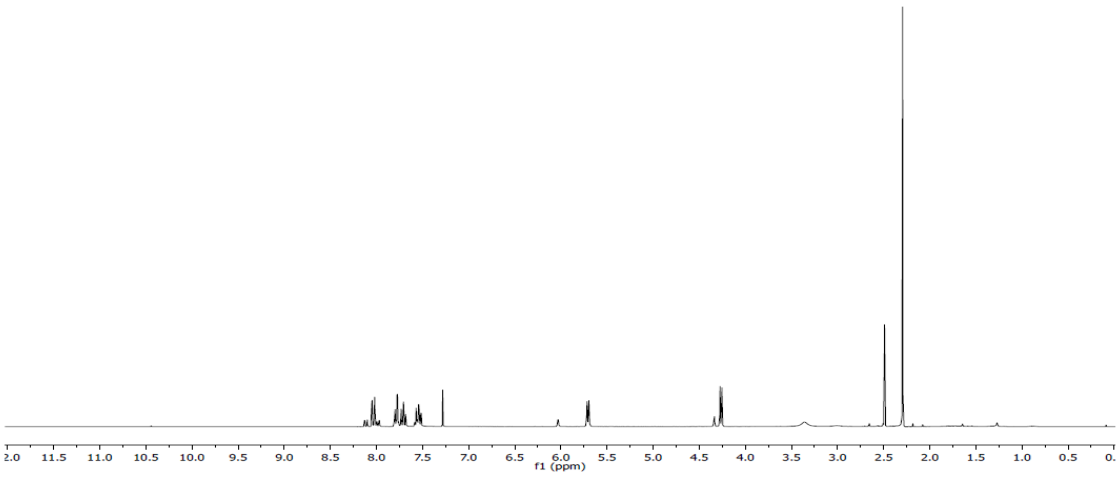
Prepared in 97% yield (crude yield) according to procedure **SP1**. Isolated as orangish oil. Stereoisomers *syn*- and *anti*-**7c** could not be separated by flash chromatography.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti* diastereoisomer) = 8.01 (1H, dd, *J* = 8.2, 1.3 Hz, Ar*H*), 7.79-7.75 (1H, m, Ar*H*), 7.69 (1H, td, *J* = 7.6, 1.3 Hz, Ar*H*), 7.56-7.49 (1H, m, Ar*H*), 5.68 (1H, d, *J* = 6.0 Hz, C*H*OH), 4.24 (1H, d, *J* = 6.0 Hz, C*H*N_3), 3.33 (1H, broad s, O*H*), 2.27 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti* diastereoisomer) = 205.2 (*C*=O), 148.4 (Ar*C*), 134.0 (Ar*C*H), 129.7 (Ar*C*H), 129.5 (Ar*C*H), 125.3 (Ar*C*H), 71.8 (*C*HOH), 70.6 (*C*HN_3), 29.5 (*C*H_3); MS (ES^+) *m/z* (%) = 251 (100); HRMS (ES^+): *m/z* calcd. for $[M+H]^+$ $[C_{10}H_{11}N_4O_4]^+$ 251.0780, found 251.0791.

^{13}C NMR (75 MHz, $CDCl_3$)

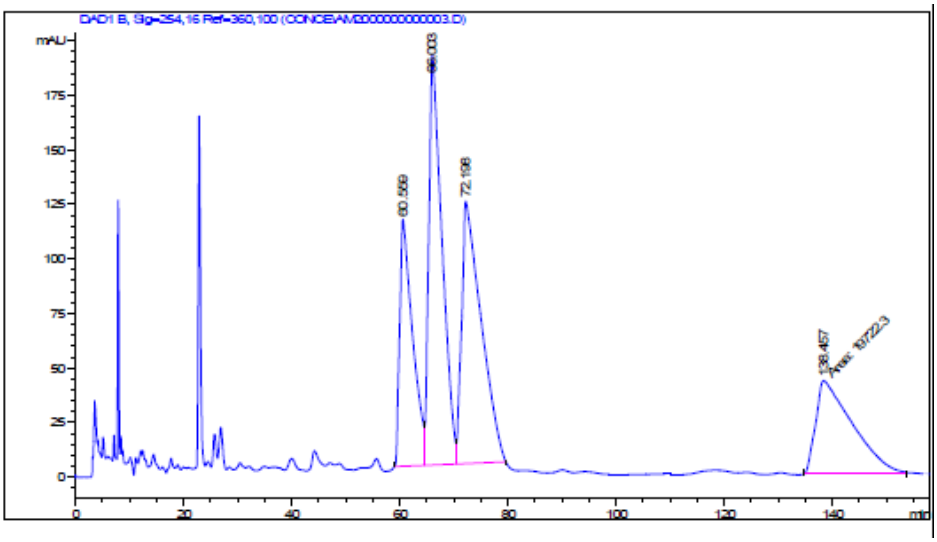


^{1}H NMR (300 MHz, $CDCl_3$)

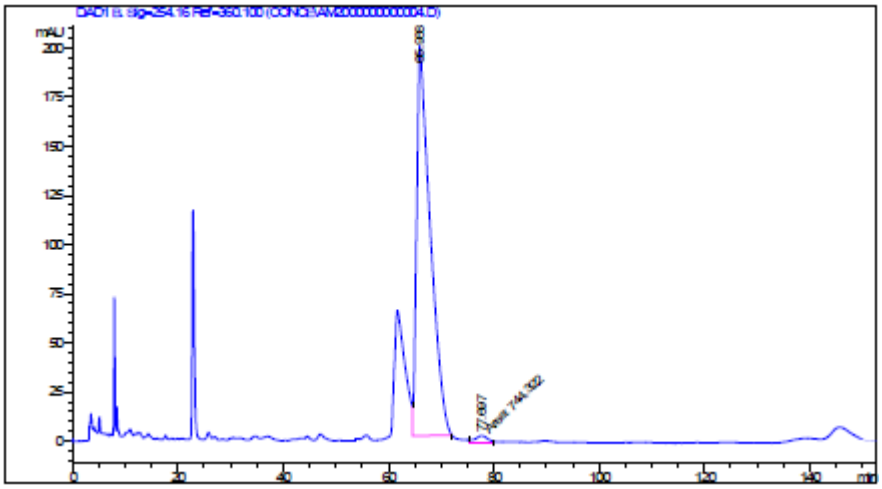


Compound *anti*-**7c** was obtained in a maximum of 96% *ee*, from crude reaction mixtures. The optical purity was determined by HPLC on a chiralpak OJ-H column (hexane/2-propanol 95:5), flow rate 1.0 mL/min, λ 254 nm.

HPLC chromatogram of racemic *syn*- and *anti*-**7c**



HPLC chromatogram of crude product **7c**



Area Percent Report

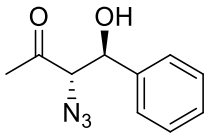
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	65.968	VB	2.2427	3.55134e4	198.36687	97.9471
2	77.697	MM	3.0297	744.32239	4.09464	2.0529
Totals :				3.62577e4	202.46150	

*** End of Report ***

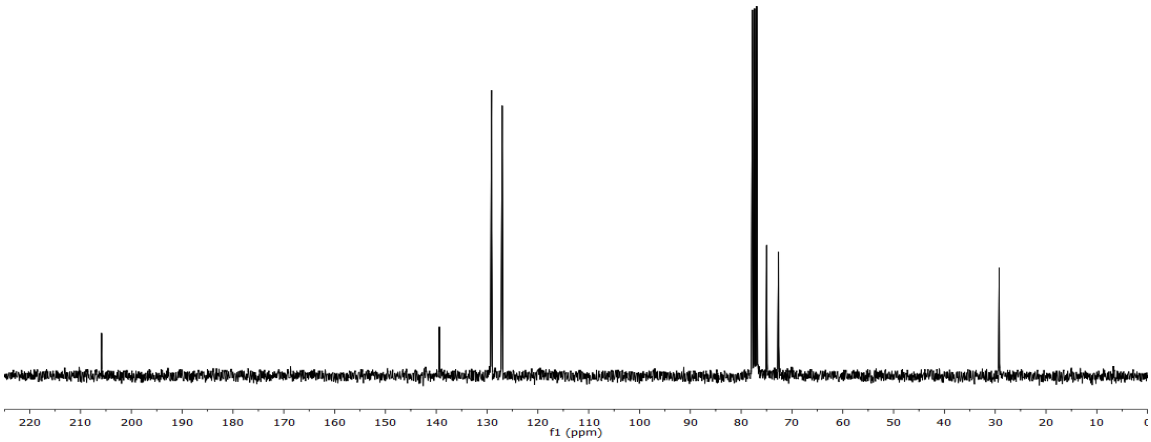
(3*S*,4*S*)-3-azido-4-hydroxy-4-phenylbutan-2-one (7d)



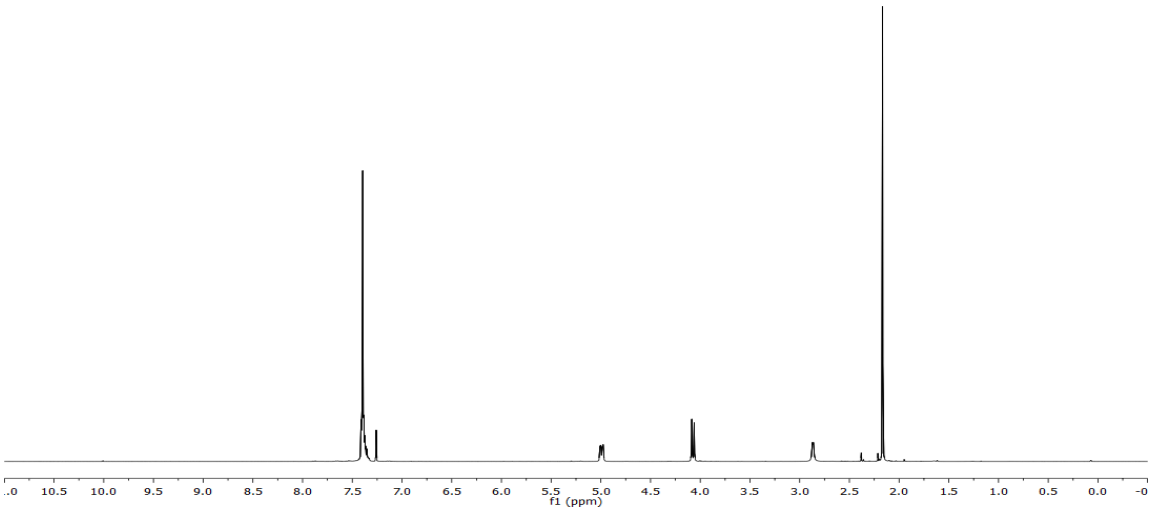
Prepared in 84% yield according to procedure **SP1**. Yellow oil. Purified by flash chromatography (Hex/EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42-7.34 (5H, m, Ar*H*), 4.99 (1H, dd, *J* = 7.0, 2.4 Hz, C*H*OH), 4.07 (1H, d, *J* = 7.0 Hz, C*H*N_3), 2.87 (1H, d, *J* = 3.1 Hz, O*H*), 2.17 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9 (*C*=O), 139.4 (Ar*C*), 129.2 (Ar*C*H), 129.1 (2 x Ar*C*H), 127.0 (2 x Ar*C*H), 75.0 (*C*HOH), 72.6 (*C*HN_3), 29.2 (*C*H_3); MS (ES^+) *m/z* (%) = 206 (100); HRMS (ES^+): *m/z* calcd. for $[M+H]^+$ $[C_{10}H_{12}N_3O_2]^+$ 206.0930, found 206.0939.

^{13}C NMR (75 MHz, $CDCl_3$)

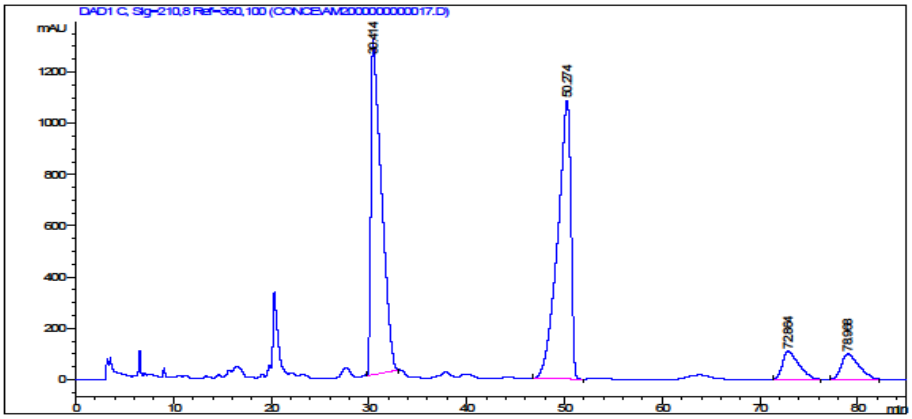


^{1}H NMR (300 MHz, $CDCl_3$)

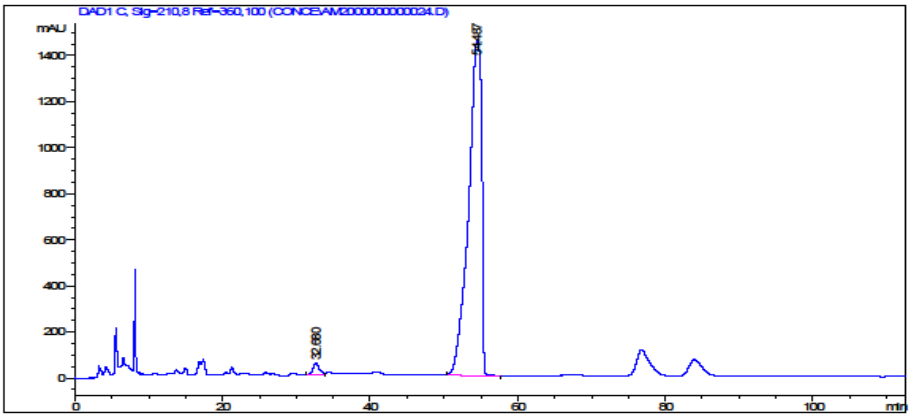


Compound *anti*-**7d** was obtained in a maximum of 97% *ee*, from crude reaction mixtures, and in 95% *ee* as an isolated pure product. The optical purity was determined by HPLC on a chiralpak OJ-H column (hexane/2-propanol 90:10), flow rate 1.0 mL/min, λ 210 nm.

HPLC chromatogram of racemic *syn*- and *anti*-**7d**



HPLC chromatogram of crude product **7d**



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

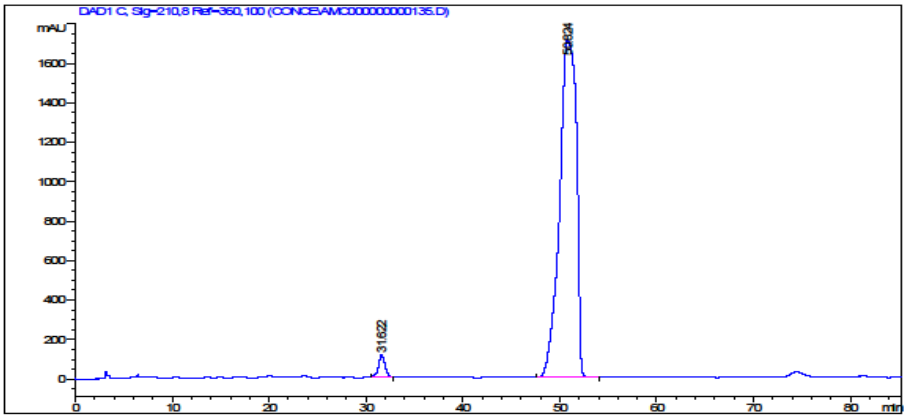
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.680	BV	0.8466	3003.05981	50.58567	1.6482
2	54.487	BB	1.4522	1.79196e5	1455.66052	98.3518

Totals : 1.82199e5 1506.24620

*** End of Report ***

HPLC chromatogram of pure product *anti*-**7d**



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

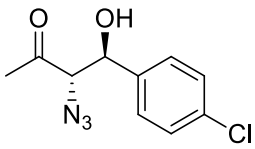
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.622	BB	0.7194	5419.04199	112.60907	2.5404
2	50.824	BB	1.4345	2.07897e5	1709.86316	97.4596

Totals : 2.13316e5 1822.47223

*** End of Report ***

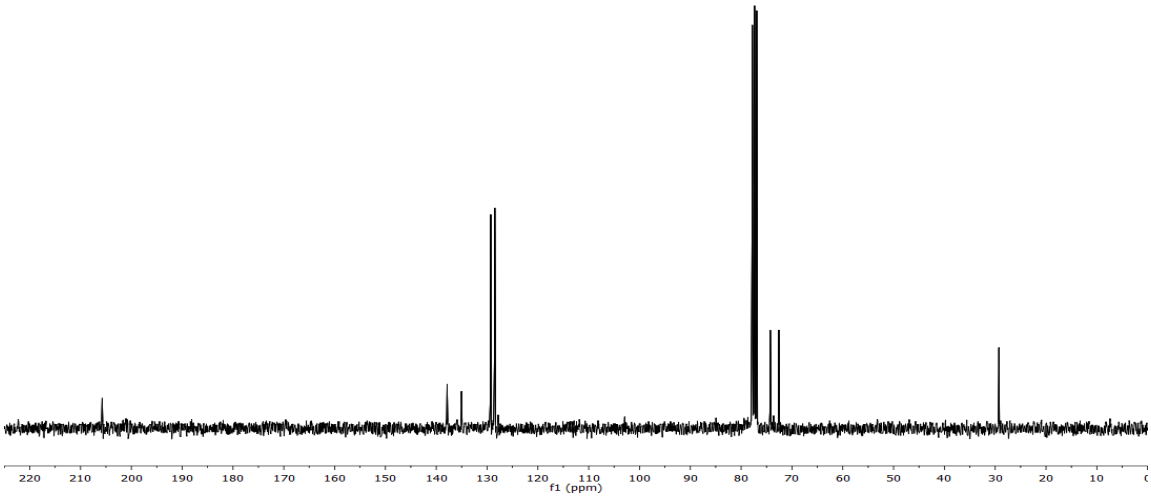
Synthesis of (3*S*,4*S*)-3-azido-4-(4-chlorophenyl)-4-hydroxybutan-2-one (7e)



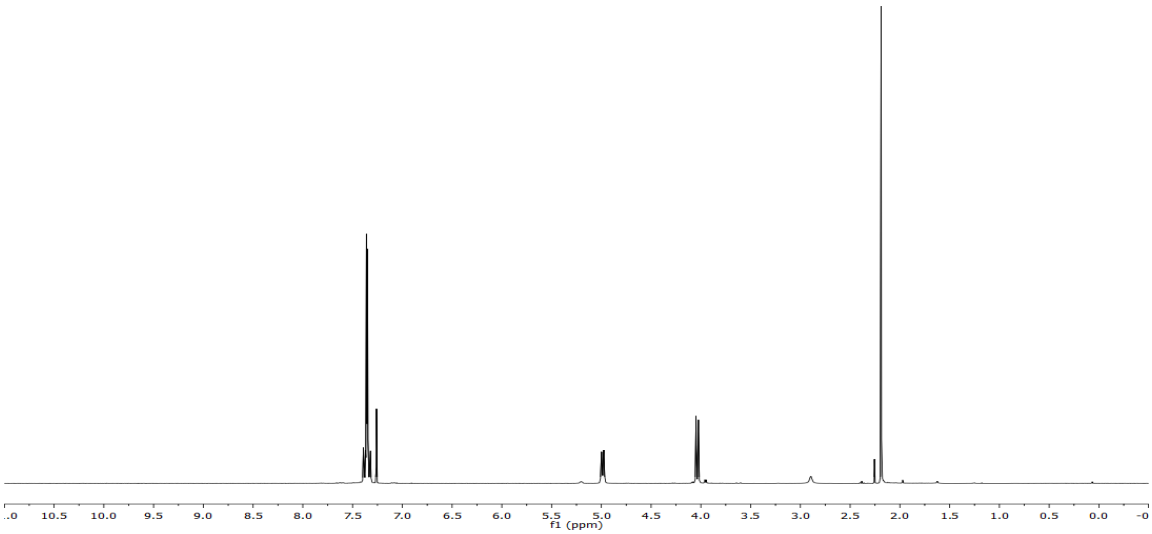
Prepared in 85% yield according to procedure **SP1**. Orangish oil. Purified by flash chromatography (Hex/EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42-7.29 (4H, m, Ar*H*), 4.99 (1H, d, *J* = 7.0 Hz, C*H*OH), 4.04 (1H, d, *J* = 7.0 Hz, C*H*N_3), 2.90 (1H, broad s, O*H*), 2.19 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.7 (*C*=O), 137.9 (Ar*C*), 135.0 (Ar*C*), 129.3 (2 x Ar*C*H), 128.5 (2 x Ar*C*H), 74.6 (*C*HOH), 72.6 (*C*HN_3), 29.3 (*C*H_3).

^{13}C NMR (75 MHz, $CDCl_3$)

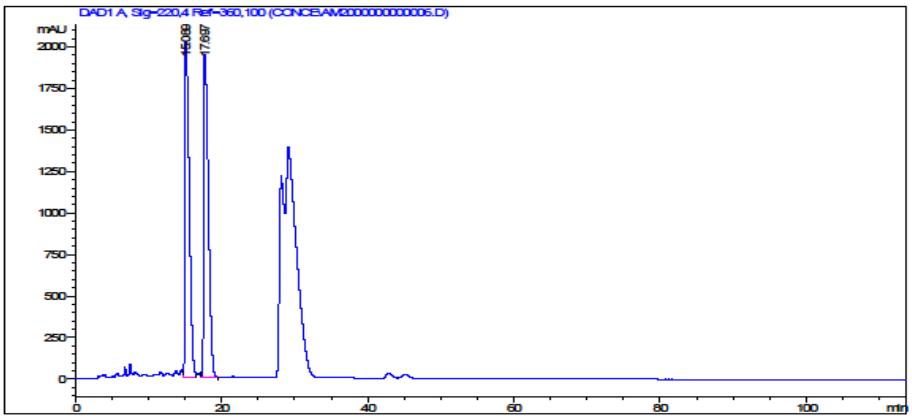


^{1}H NMR (300 MHz, $CDCl_3$)

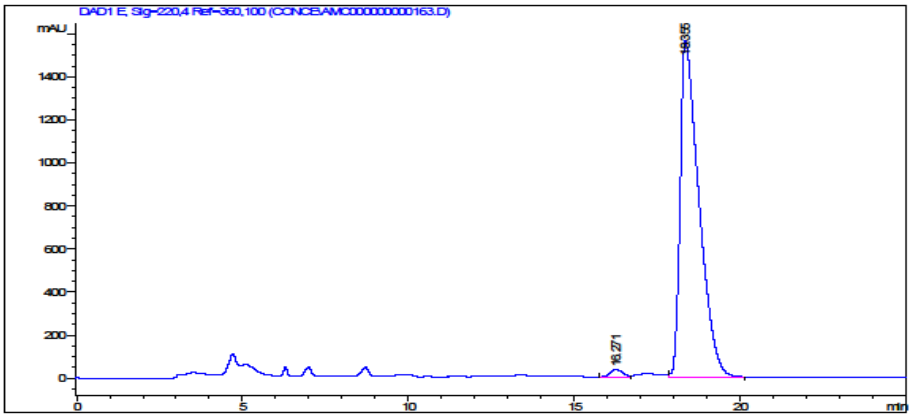


Compound *anti*-**7e** was obtained in a maximum of 97% *ee*, from crude reaction mixtures, and in 94% *ee* as an isolated pure product. The optical purity was determined by HPLC on a chiralpak OJ-H column (hexane/2-propanol 90:10), flow rate 1.0 mL/min, λ 220 nm.

HPLC chromatogram of racemic *syn*- and *anti*-**7e**



HPLC chromatogram of crude product **7e**



Area Percent Report

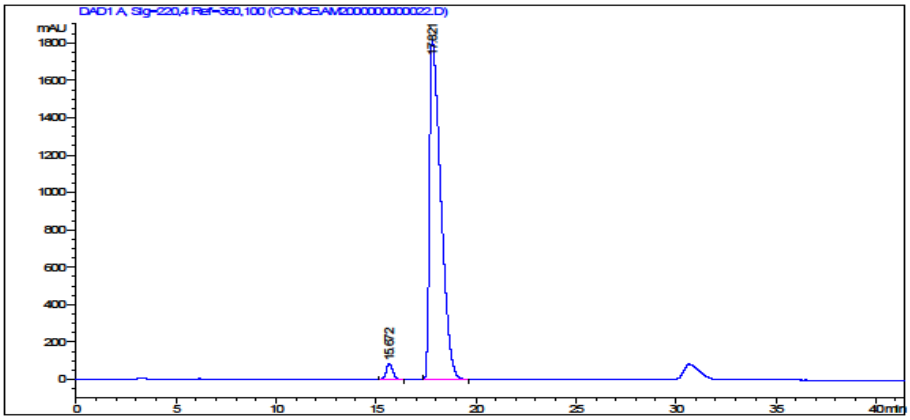
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 E, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.271	BV	0.3910	878.43213	34.51132	1.4103
2	18.355	BB	0.5735	6.14104e4	1565.93262	98.5897
Totals :				6.22888e4	1600.44394	

*** End of Report ***

HPLC chromatogram of pure product *anti*-**7e**



Area Percent Report

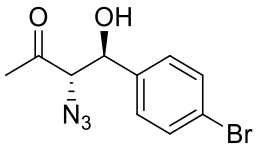
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.672	BB	0.3663	2039.65649	85.51816	2.7746
2	17.821	BB	0.5954	7.14723e4	1814.96411	97.2254
Totals :				7.35120e4	1900.48227	

*** End of Report ***

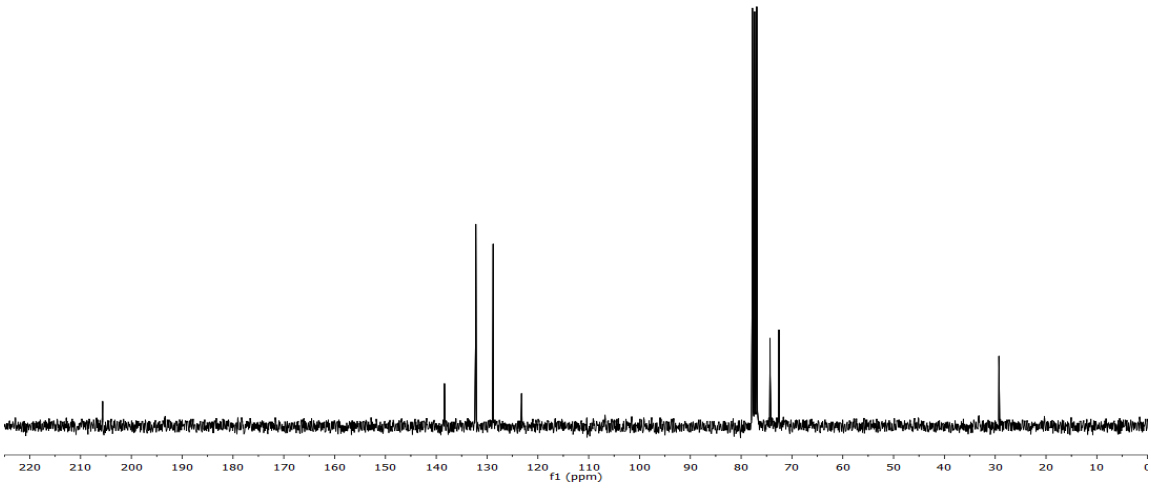
Synthesis of (3*S*,4*S*)-3-azido-4-(4-bromophenyl)-4-hydroxybutan-2-one (7f)



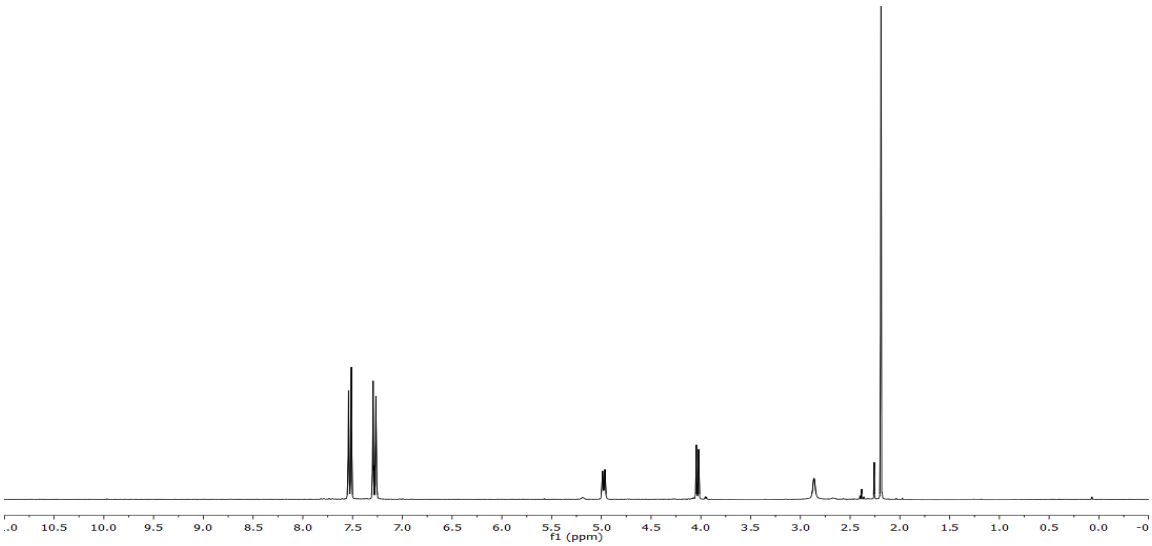
Prepared in 84% yield according to procedure **SP1**. Orangish oil. Purified by flash chromatography (Hex/EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.28 (2H, d, *J* = 8.5 Hz, Ar*H*), 4.98 (1H, d, *J* = 6.9 Hz, C*H*OH), 4.03 (1H, d, *J* = 7.0 Hz, C*H*N_3), 2.83 (1H, broad s, O*H*), 2.19 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.7 (*C*=O), 138.4 (Ar*C*), 132.2 (2 x Ar*C*H), 128.8 (2 x Ar*C*H), 123.2 (Ar*C*), 74.3 (*C*HOH), 72.5 (*C*HN_3), 29.3 (*C*H_3).

^{13}C NMR (75 MHz, $CDCl_3$)

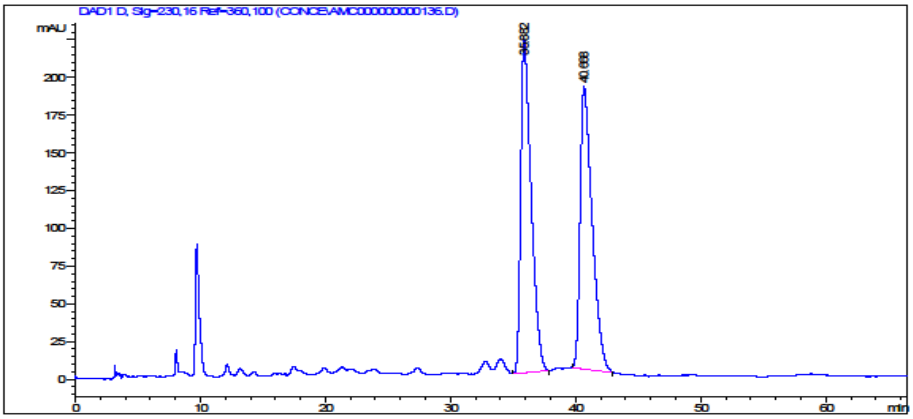


^{1}H NMR (300 MHz, $CDCl_3$)

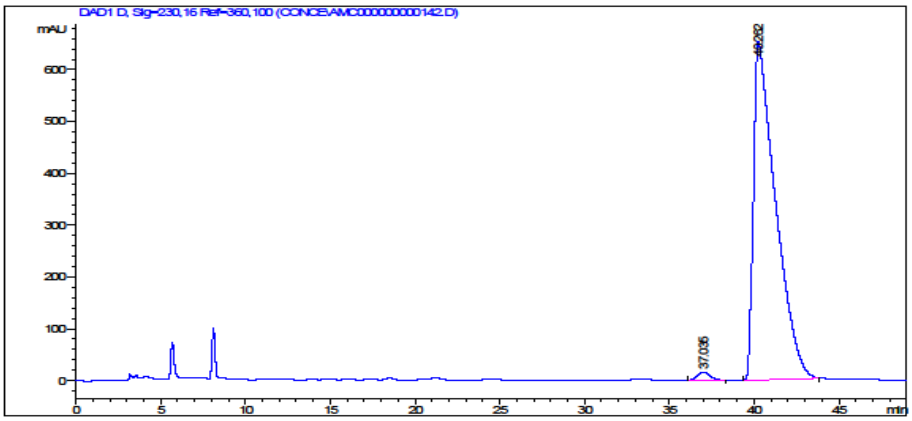


Compound *anti*-**4f** was obtained in a maximum of 97% *ee*, from crude reaction mixtures, and in 95% *ee* as an isolated pure product. The optical purity was determined by HPLC on a chiralpak OJ-H column (hexane/2-propanol 95:5), flow rate 1.0 mL/min, λ 230 nm.

HPLC chromatogram of racemic *anti*-**7f**



HPLC chromatogram of crude product **7f**



Area Percent Report

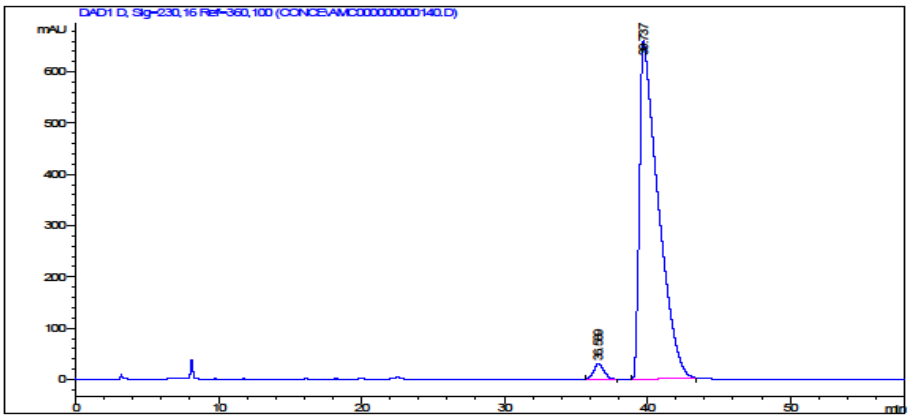
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.035	BB	0.7069	772.01105	15.61259	1.2921
2	40.262	BB	1.1885	5.89767e4	653.72040	98.7079
Totals :				5.97487e4	669.33299	

*** End of Report ***

HPLC chromatogram of pure product *anti*-**7f**



Area Percent Report

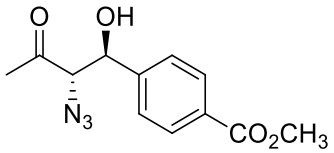
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.589	BB	0.7446	1509.32385	29.71323	2.4518
2	39.737	BB	1.2040	6.00495e4	659.68744	97.5482
Totals :				6.15588e4	689.40067	

*** End of Report ***

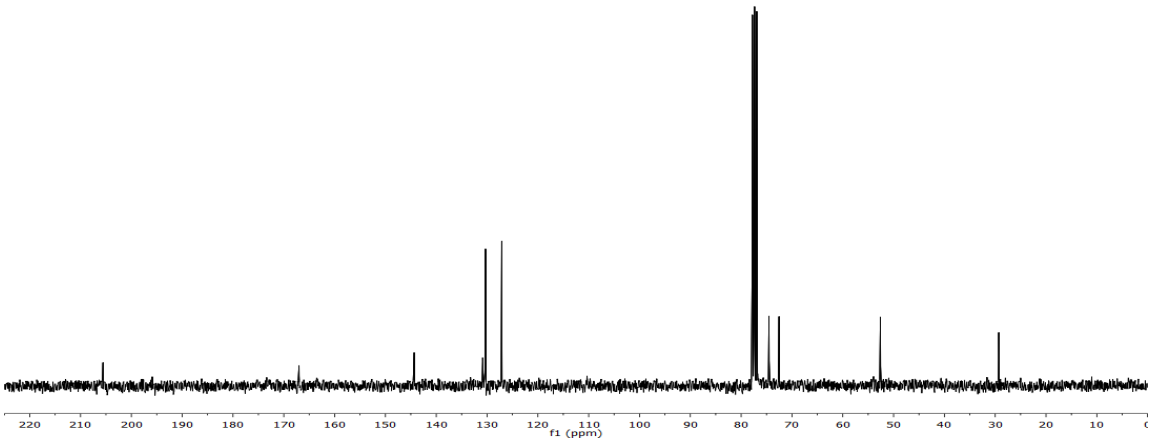
Synthesis of (3*S*,4*S*)-3-azido-4-hydroxy-4-(4-methoxycarbonylphenyl)butan-2-one (7g)



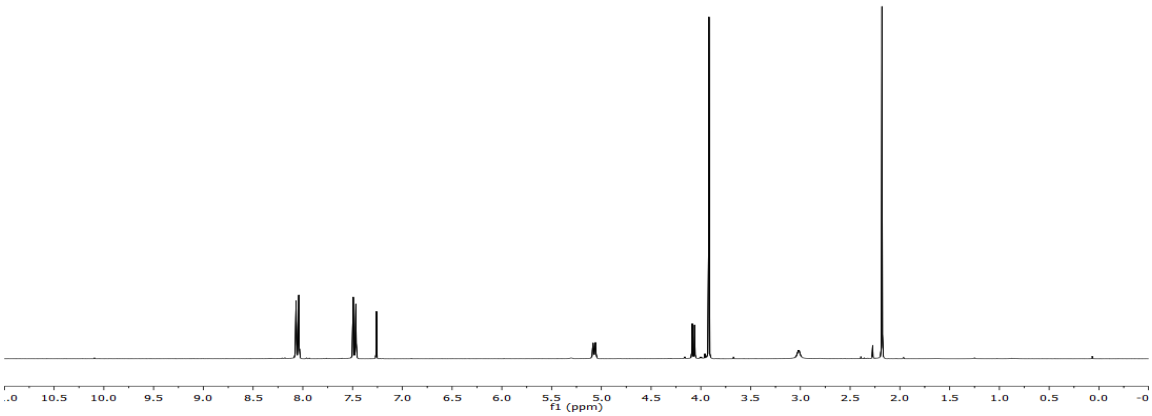
Prepared in 83% yield according to procedure **SP1**. Orangish oil. Purified by flash chromatography (Hex/EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.48 (2H, d, *J* = 8.2 Hz, Ar*H*), 5.07 (1H, d, *J* = 6.9 Hz, C*H*OH), 4.07 (1H, d, *J* = 6.9 Hz, C*H*N_3), 3.92 (3H, s, CO_2CH_3); 3.02 (1H, broad s, O*H*), 2.18 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.6 (*C*=O), 167.0 (*C*O_2), 144.3 (Ar*C*), 130.8 (Ar*C*), 130.3 (2 x Ar*C*H), 127.1 (2 x Ar*C*H), 74.5 (*C*HOH), 72.5 (*C*HN_3), 52.6 (O*C*H_3), 29.3 (*C*H_3); MS (ES^+) *m/z* (%) = 264 (100); HRMS (ES^+): *m/z* calcd. for $[M+H]^+$ $[C_{12}H_{14}N_3O_4]^+$ 264.0984, found 264.0979.

^{13}C NMR (75 MHz, $CDCl_3$)

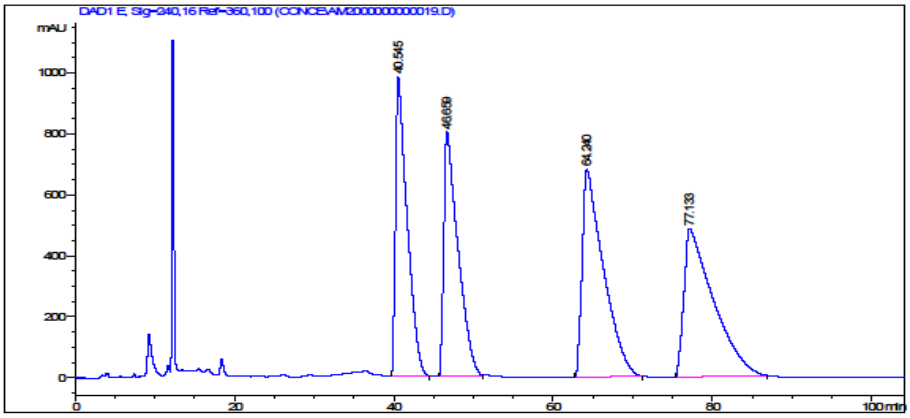


^{1}H NMR (300 MHz, $CDCl_3$)

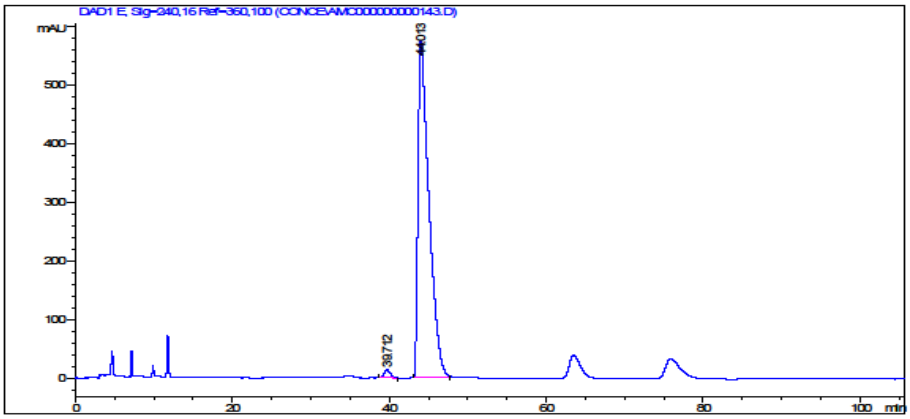


Compound *anti*-**7g** was obtained in a maximum of 97% *ee*, from crude reaction mixtures, and in 95% *ee* as an isolated pure product. The optical purity was determined by HPLC on a chiralpak OJ-H column (hexane/2-propanol 90:10), flow rate 1.0 mL/min, λ 240 nm.

HPLC chromatogram of racemic *syn*- and *anti*-**7g**



HPLC chromatogram of crude product **7g**



Area Percent Report

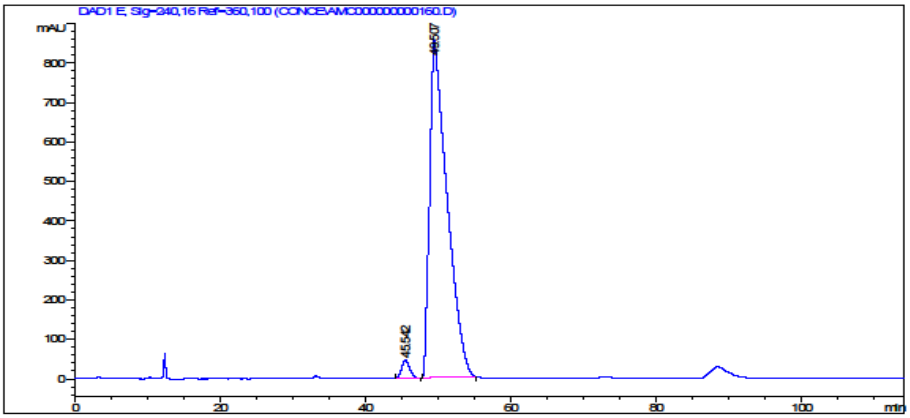
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 E, Sig=240,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	39.712	BB	0.7877	787.03961	13.54938	1.4011
2	44.013	BB	1.3418	5.53876e4	576.04773	98.5989
Totals :				5.61746e4	589.59711	

*** End of Report ***

HPLC chromatogram of pure product *anti*-**7g**



Area Percent Report

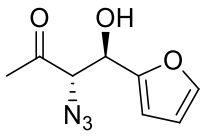
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 E, Sig=240,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	45.542	BB	1.1021	3428.98120	44.64417	2.3483
2	49.507	BB	2.1678	1.42590e5	854.93225	97.6517
Totals :				1.46019e5	899.57642	

*** End of Report ***

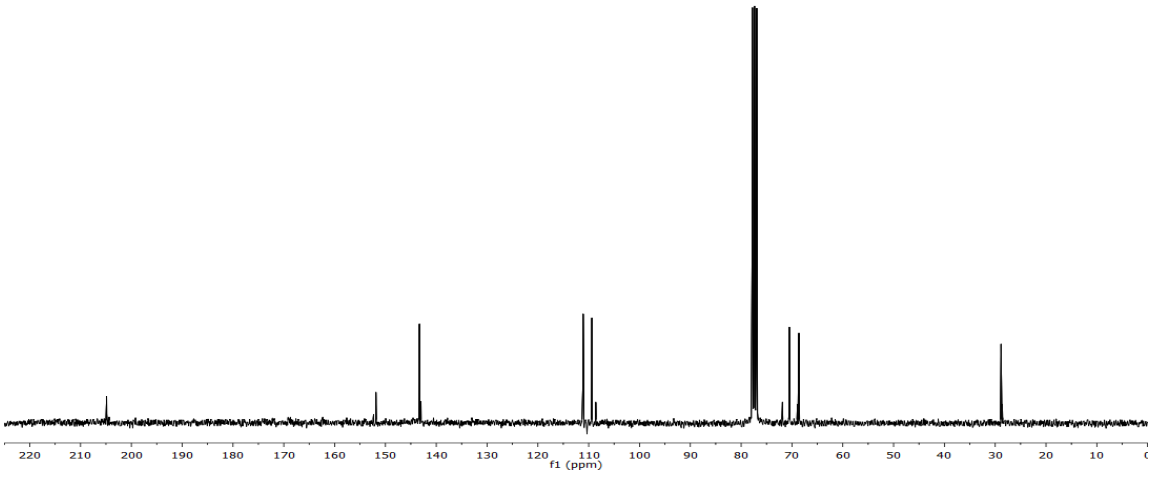
Synthesis of (3*S*,4*R*)-3-azido-4-(furan-2-yl)-4-hydroxybutan-2-one (7h)



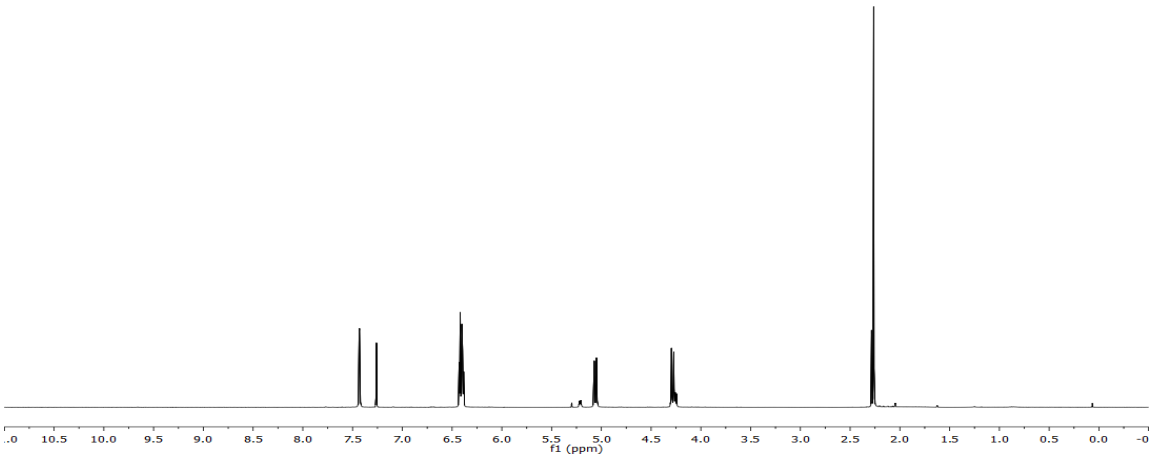
Prepared in 78% yield according to procedure **SP1**. Orangish oil. Purified by flash chromatography (Hex/EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44-7.42 (1H, m, Ar*H*), 6.43-6.38 (2H, m, Ar*H*), 5.06 (1H, d, *J* = 6.8 Hz, C*H*OH), 4.28 (1H, d, *J* = 6.8 Hz, C*H*N_3), 2.26 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.8 (*C*=O), 151.9 (Ar*C*), 143.3 (Ar*C*H), 111.1 (Ar*C*H), 109.4 (Ar*C*H), 70.5 (*C*HOH), 68.6 (*C*HN_3), 28.8 (*C*H_3); MS (ES^+) *m/z* (%) = 196 (100); HRMS (ES^+): *m/z* calcd. for $[M+H]^+$ $[C_8H_{10}N_3O_3]^+$ 196.0722, found 196.0728.

^{13}C NMR (75 MHz, $CDCl_3$)

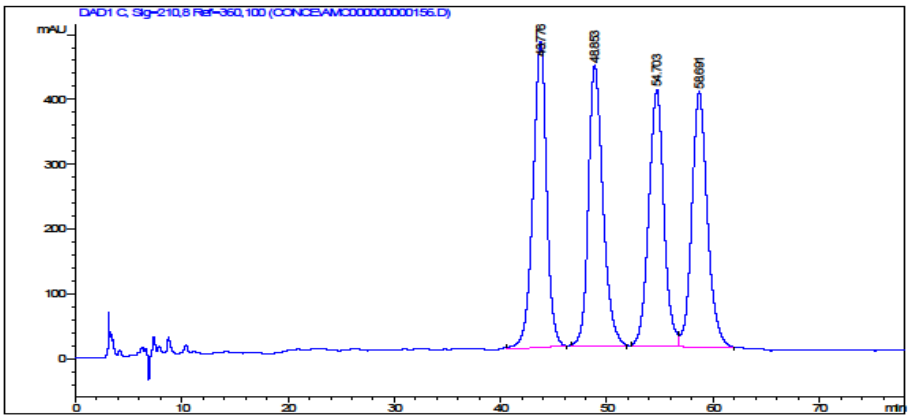


^{1}H NMR (300 MHz, $CDCl_3$)

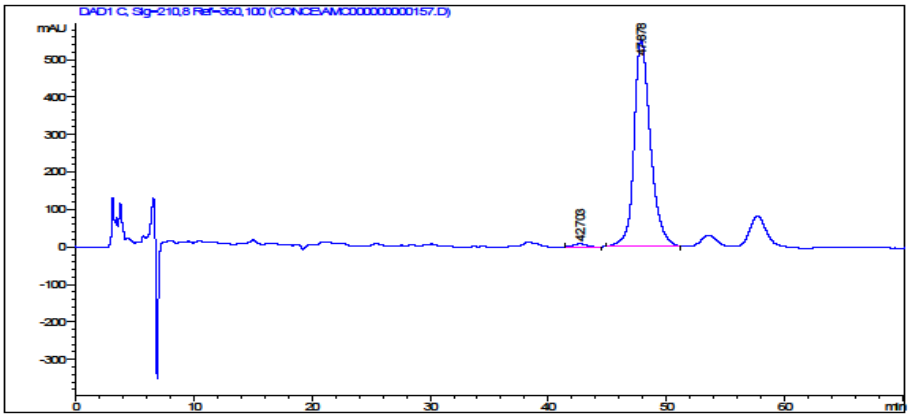


Product *anti*-**4h** was obtained in a maximum of 98% *ee*, from crude reaction mixtures, and in 93% *ee* as an isolated pure product. The optical purity was determined by HPLC on a chiralpak AD-H column (hexane/2-propanol 98:2), flow rate 1.0 mL/min, λ 210 nm.

HPLC chromatogram of racemic *syn*- and *anti*-**7h**



HPLC chromatogram of crude product **7h**



Area Percent Report

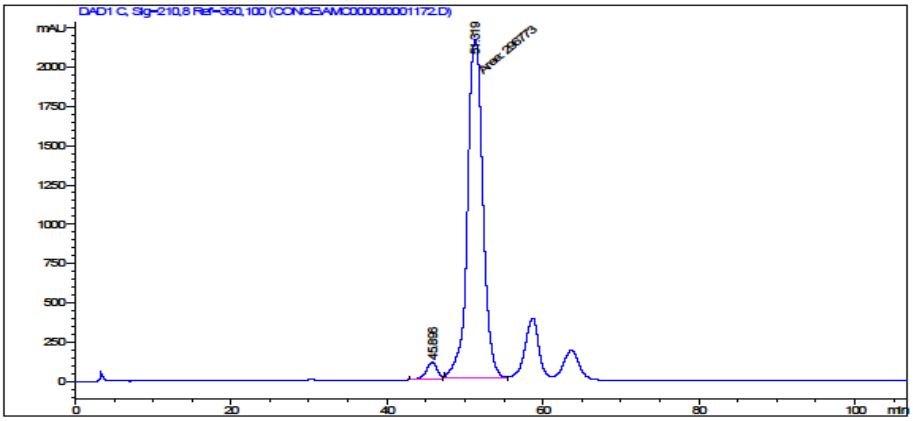
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.703	BB	0.8448	617.32544	8.58573	1.1502
2	47.878	BB	1.4332	5.30560e4	550.13257	98.8498
Totals :				5.36733e4	558.71830	

*** End of Report ***

HPLC chromatogram of pure product *anti*-**7h**



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

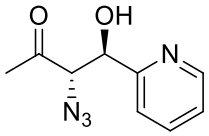
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	45.896	BV	1.3244	1.04228e4	106.25777	3.3929
2	51.319	MM	2.2989	2.96773e5	2151.60107	96.6071

Totals : 3.07196e5 2257.85885

*** End of Report ***

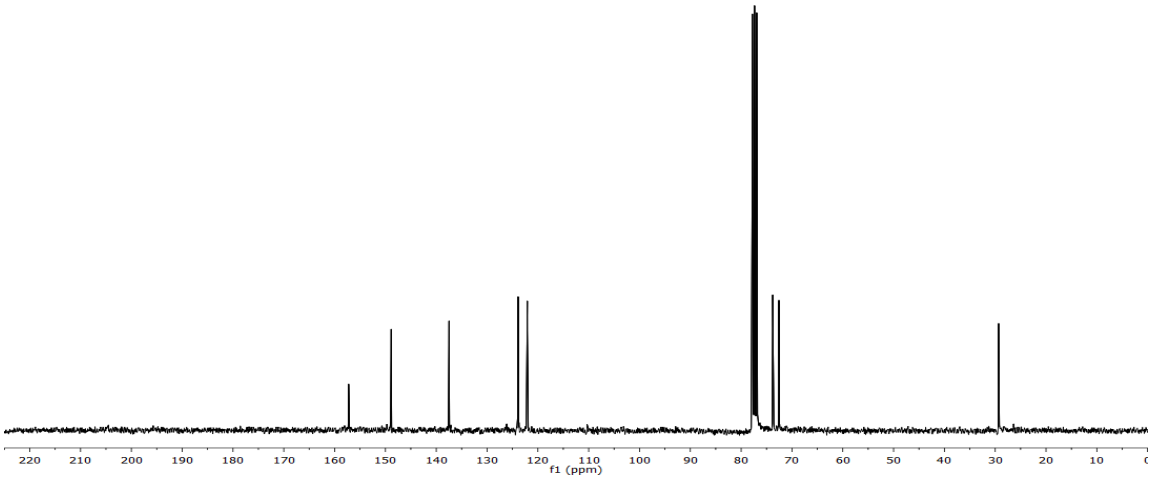
Synthesis of (3*S*,4*R*)-3-azido-4-hydroxy-4-(pyridin-2-yl)butan-2-one (7i)



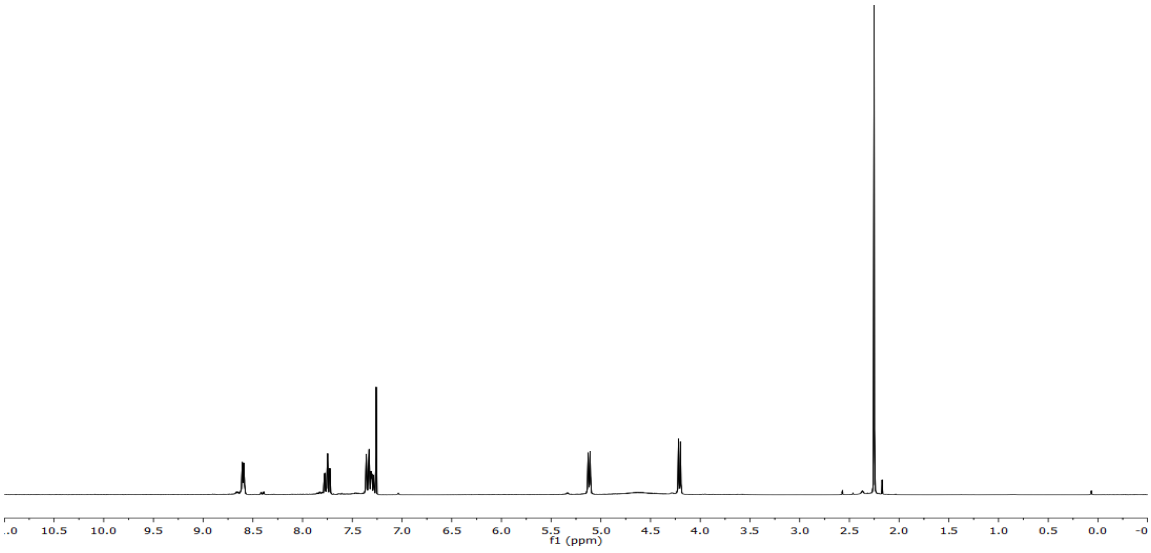
Prepared in 80% yield according to procedure **SP1**. Orangish solid. Purified by flash chromatography (Hex/EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61-8.59 (1H, m, Ar*H*), 7.75 (1H, td, *J* = 7.7, 1.7 Hz, Ar*H*), 7.36-7.28 (2H, m, Ar*H*), 5.12 (1H, d, *J* = 5.9 Hz, C*H*OH), 4.21 (1H, d, *J* = 5.9 Hz, C*H*N_3), 2.25 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.6 (*C*=O), 157.1 (Ar*C*), 148.8 (Ar*C*H), 137.5 (Ar*C*H), 123.9 (Ar*C*H), 122.1 (Ar*C*H), 73.7 (*C*HOH), 72.5 (*C*HN_3), 29.4 (*C*H_3). MS (ES^+) *m/z* (%) = 207 (100); HRMS (ES^+): *m/z* calcd. for $[M+H]^+$ $[C_9H_{11}N_4O_2]^+$ 207.0882, found 207.0880.

^{13}C NMR (75 MHz, $CDCl_3$)

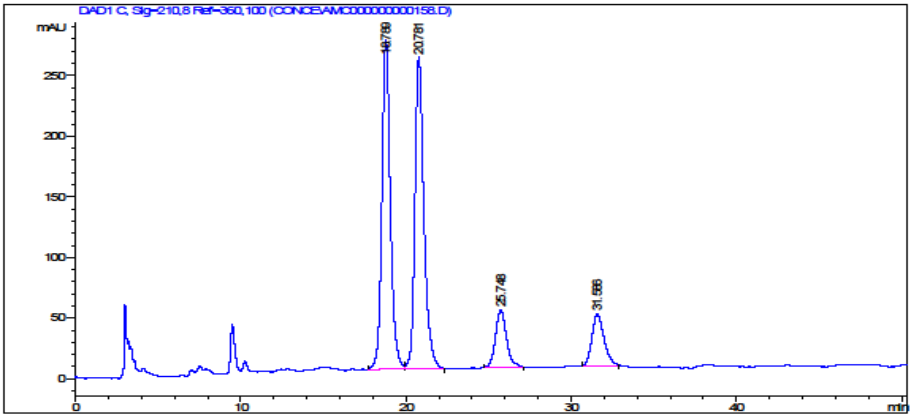


^{1}H NMR (300 MHz, $CDCl_3$)

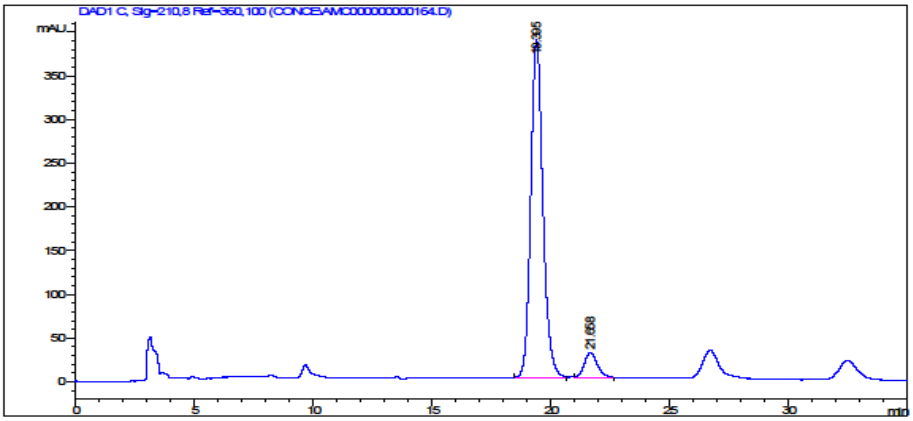


Compound *anti*-**7i** was obtained in a maximum of 86% *ee*, from crude reaction mixtures, and in 88% *ee* as an isolated pure product. The optical purity was determined by HPLC on a chiralpak AD-H column (hexane/2-propanol 95:5), flow rate 1.0 mL/min, λ 210 nm.

HPLC chromatogram of racemic *syn*- and *anti*-**7i**



HPLC chromatogram of crude product **7i**



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

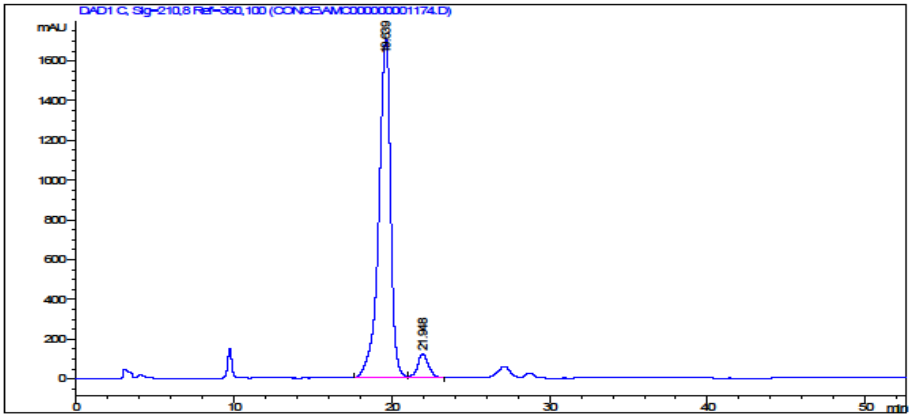
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.395	BB	0.5478	1.37009e4	386.26968	92.8711
2	21.658	BB	0.5601	1051.69714	28.13656	7.1289

Totals : 1.47526e4 414.40625

*** End of Report ***

HPLC chromatogram of pure product *anti*-**7i**



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

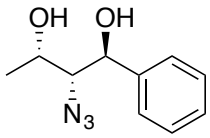
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.639	BB	0.7972	8.86831e4	1704.00793	93.8553
2	21.948	BB	0.7348	5806.05371	120.36617	6.1447

Totals : 9.44892e4 1824.37410

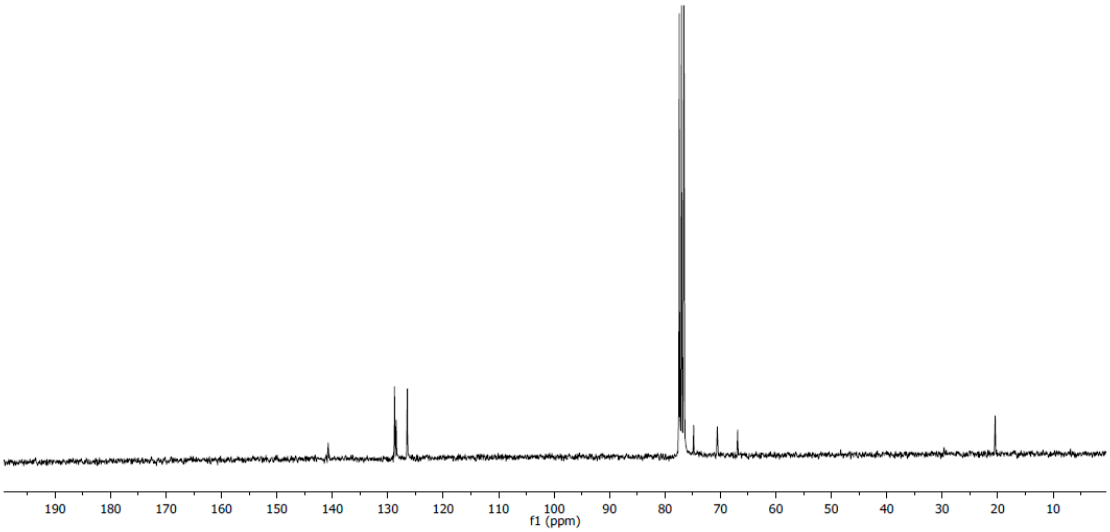
*** End of Report ***

Synthesis of (1*S*,2*R*,3*S*)-2-azido-1-phenylbutane-1,3-diol (11d)

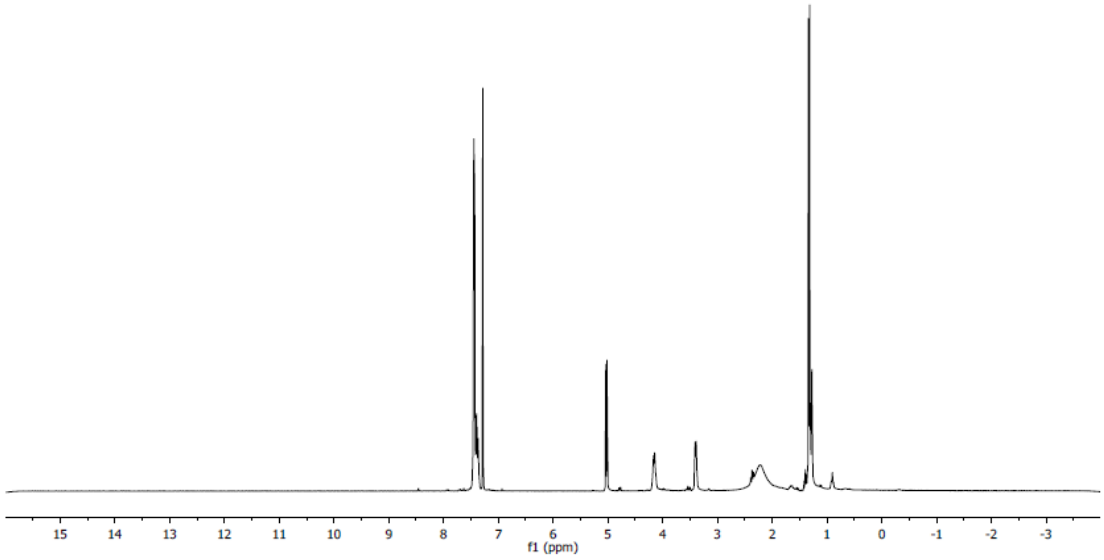


Prepared according to procedure **SP2**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H = 7.44-7.32 (5H, m, ArC*H*), 5.00 (1H, d, *J* = 6.5 Hz, C*H*OH), 4.17-4.11 (1H, m, C*H*OH), 3.37 (1H, dd, *J* = 6.5, 2.6 Hz, C*H*N_3), 2.18 (2H, broad s, 2 x O*H*), 1.31 (3H, d, *J* = 6.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C = 141.1 (Ar*C*), 129.1 (2 x Ar*C*H), 128.8 (Ar*C*H), 126.8 (2 x Ar*C*H), 75.2 (*C*HOH), 70.9 (*C*HOH), 67.2 (*C*HN_3), 20.8 (*C*H_3).

^{13}C NMR (75 MHz, $CDCl_3$)

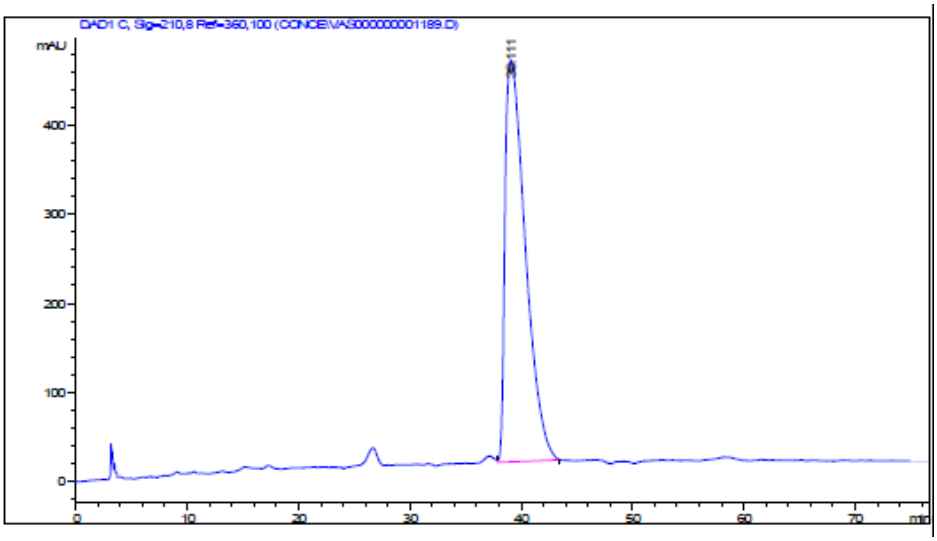


^{1}H NMR (300 MHz, $CDCl_3$)



HPLC (chiralpak OJ-H column, hexane/2-propanol 95:5, flow rate 1 mL/min, λ = 210 nm) t_r = 39.1 min.

HPLC chromatogram of crude product **11d**



Area Percent Report

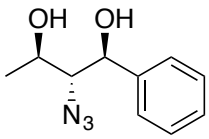
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	39.111	VB	1.5980	5.73666e4	451.60193	100.0000
Totals :				5.73666e4	451.60193	

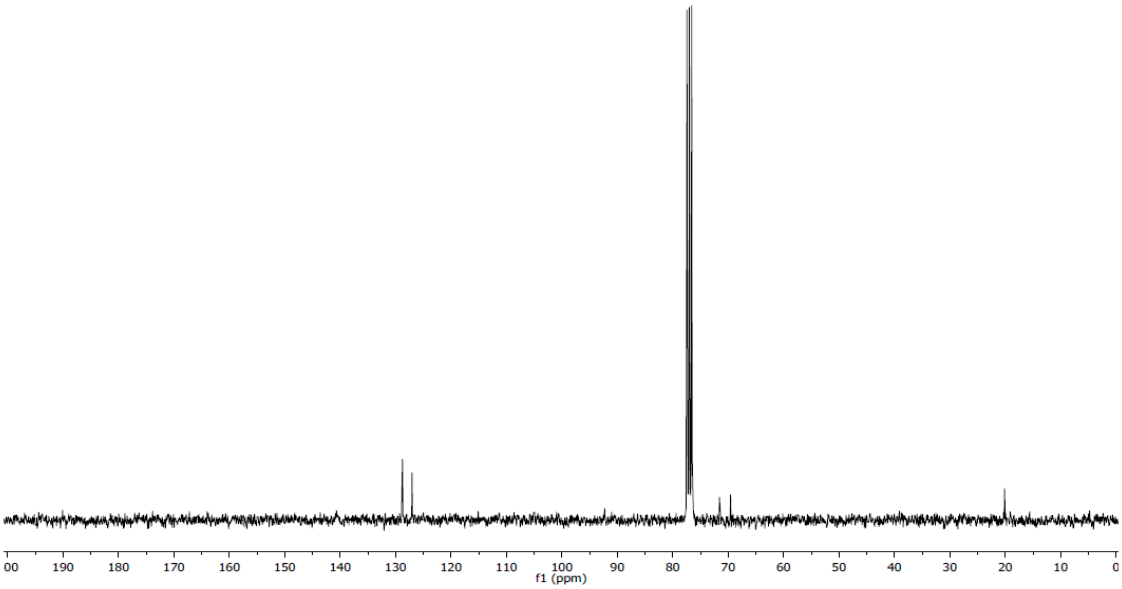
*** End of Report ***

Synthesis of (1*S*,2*R*,3*R*)-2-azido-1-phenylbutane-1,3-diol (12d)

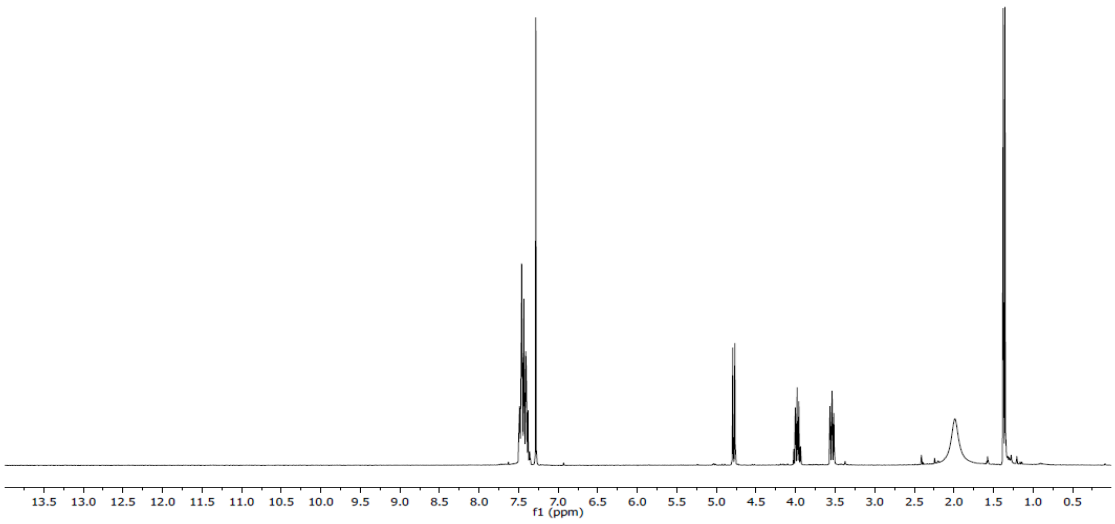


Prepared according to procedure **SP3**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H = 7.47-7.34 (5H, m, ArC*H*), 4.76 (1H, d, *J* = 7.9 Hz, C*H*OH), 3.96 (1H, quintet, *J* = 6.5 Hz, C*H*OH), 3.52 (1H, dd, *J* = 7.9, 6.9 Hz, C*H*N_3), 1.96 (2H, broad s, 2 x O*H*), 1.34 (3H, d, *J* = 6.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C = 141.2 (Ar*C*), 129.1 (2 x Ar*C*H + Ar*C*H), 127.4 (2 x Ar*C*H), 76.8 (*C*HOH), 71.9 (*C*HOH), 69.9 (*C*HN_3), 20.5 (*C*H_3).

^{13}C NMR (75 MHz, $CDCl_3$)

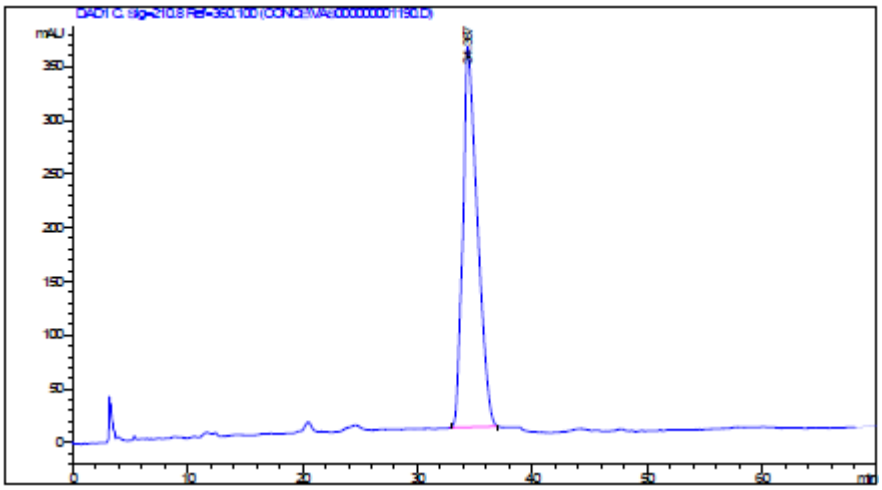


^{1}H NMR (300 MHz, $CDCl_3$)



HPLC (chiralpak OJ-H column, hexane/2-propanol 95:5, flow rate 1 mL/min, λ = 210 nm) t_r = 34.4 min.

HPLC chromatogram of crude product **12d**



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.387	BB	1.1685	3.13049e4	354.40350	100.0000
Totals :				3.13049e4	354.40350	

*** End of Report ***