A Detailed Study of the Diastereoselective Catalytic Hydrogenation of 6-Hydroxytetrahydroisoquinoline-(3*R*)-carboxylic Ester Intermediates

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Supporting information

General Procedure

All catalysts used in this study were purchased from Strem Chemicals and used as such.

Three different hydrogenation reactors were used in this study:

1. Premex 96-Multi Reactor [1] : parallel hydrogenation reactor, up to 96 vessels, total volume = 2.5 mL, maximum pressure = 100 bar, magnetic stirrer.
2. Endeavor™ Reactor [2] : 8 parallel autoclaves, total volume = 5 mL, max pressure = 30 bar, mechanical stirrer up to 500 rpm..
3. Premex Twister Reactor [3] : single autoclave, total volume = 50 mL, max pressure = 100 bar, mechanical stirrer up to 1300 rpm.

It was verified that the different reactors gave very similar results for the hydrogenation of **2**. GC analysis was performed on gas chromatograph HP6890 equipped with FID detector.

Typical procedure for hydrogenation in the Endeavour reactor.

The general procedure consists of having 50 mg of the heterogeneous catalyst (50% wet) and 125 mg of the substrate placed in each vessel/port of the Endeavour reactor. Then 5 mL of solvent is added and the reactor is closed. Each autoclave is pressurized/depressurized 5 times with 3 bar of nitrogen followed by 5 times with 25 bar of hydrogen, then put under the desired pressure of hydrogen. The reaction mixtures are then warmed to the desired temperature and stirred for 16 h at 300 rpm. After hydrogenation, the catalyst is filtered and the reaction mixtures analyzed by GC.

Typical procedure for hydrogenation in the Premex Twister reactor.

The same general procedure as in the Endeavour reactor except 500 mg of the catalyst (50% wet), 1250 mg of substrate, and 60 mL of solvent are used with a stirring speed set at 1300 rpm.

Typical procedure for hydrogenation in the Premex A96 reactor.

The same general procedure as in the Endeavour reactor except 50 mg of the catalyst (50% wet), 50 mg of substrate, and 2 mL of solvent are used.

Pd Catalysts screening results.

A total of 25 Pd/C catalysts were tested for the hydrogenation of substrate **2** at 3 different wt% of catalyst loading using the Premex A96 parallel reactor – i.e. a total of 75 hydrogenation experiments were performed at the same time. The screening conditions were the following: Cat amount = 5 mg, 10 mg or 20 mg (as is) for Pd loading of 5% or less; 2.5 mg, 5 mg, 10 mg for Pd loading of 10% or 20% (M112, 116, 117, 125); 50 mg of substrate **2**, 2 mL EtOAc, 100 °C, 25 bar H_2, 16 h, 300 rpm (magnetic stirrer).

List of catalysts included in the screen

DSM #	Strem #	Catalyst	Escat #	d50 (µm)	% Pd	%H2O
M106	46-1904	Palladium, 5% on activated wood carbon, unreduced, 50% water wet paste	1471	18	5	50
M108	46-1907	Palladium, 3% on activated carbon, reduced, 50% water wet paste	1911	38	3	50
M109	46-1908	Palladium, 5% on activated carbon, reduced, 50% water wet paste	1941	38	5	57.22
M110	46-1909	Palladium, 5% on activated carbon, reduced, 50% water wet paste	1961	20	5	50
M111	46-1911	Palladium, 5% on activated carbon, reduced, 50% water wet paste	1971	27	5	51.38
M112	46-1707	Palladium, 20% on activated carbon, unreduced, 50% water wet paste	1951	24	20	50
M113	46-1901	Palladium, 5% on activated peat carbon, reduced, 50% water wet paste	1621	15	5	50
M114	46-1902	Palladium, 5% on activated wood carbon, reduced, dry	1431	18	5	0
M115	46-1903	Palladium, 5% on activated wood carbon, reduced, 50% water wet paste	1421	18	5	50
M116	46-1905	Palladium, 10% on activated wood carbon, reduced, 50% water wet	1931	38	10	50
M117	46-1906	Palladium, 10% on activated wood carbon, unreduced, 50% water wet	1921	38	10	59.7
M118	46-2022	Palladium, 5% on calcium carbonate, unreduced, dry	1371	3	5	0
M121	46-1710	Palladium, 0.6% on activated carbon, 50% water-wet paste (NanoSelect LF 100)		25	0.6	47.57
M122	46-1711	Palladium, 0.5% on titanium silicate, 50% water-wet paste (NanoSelect LF 200)			0.5	18.42
M123	46-1700	Palladium, 5% on activated carbon (50-70% wetted powder)	E3		5	60.09
M124	46-1703	Palladium, 5% on activated carbon (50-70% wetted powder)	E5		5	56
M125	46-1706	Palladium, 10% on activated carbon, Pearlman (50-70% wetted powder)	E4		10	50-70
M126	46-1709	Palladium, 5% on activated carbon (50-70% wetted powder)	E1		5	50
M127	46-1712	Palladium, 5% on activated carbon (50-70% wetted powder)	E2			58.84
M128	46-1970	Palladium, 5% on barium carbonate			5	0
M129	46-1989	Palladium, 5% on barium sulfate, reduced			5	0
M130	JM	5% Pd/C	A102023-5		5	52.49
M131	JM	5% Pd/C	A105023-5		5	57.12
M132	JM	4.5/0.5 Pd/Rh mixed metal/C	F101023		4.5	62.79
M133	JM	4.5/0.5 Pd/Rh mixed metal/C	F101038		4.5	62.87

Screening Results: Reported as relative area% SM (**2**), % ketone (**3**+**6**), % alcohols (**10**+**11**), and facial selectivity (ratio **10**/(**10**+**11**))

	10 wt% as is (5 wt% for 112, 116,117,125)				20 wt% as is (10 wt% for 112, 116,117,125)				40 wt% as is (20 wt% for 112, 116,117,125)			
DSM #	% SM	% alcohol	% ketone	facial sel	% SM	% alcohol	% ketone	facial sel	% SM	% alcohol	% ketone	facial sel
M106	79	8	13	96	11	52	34	96	0	92	5	94
M108	85	3	11	96	43	24	31	96	0	84	13	94
M109	92	2	6	96	19	42	36	97	0	84	13	96
M110	95	1	3	93	75	10	13	97	13	54	26	97
M111	96	1	3	96	83	5	11	96	12	54	29	97
M112	74	7	19	95	29	25	44	96	0	90	8	94
M113	85	6	8	96	34	34	28	97	0	82	12	97
M114	42	26	30	96	0	85	12	95	0	95	2	93
M115	78	8	13	95	11	54	32	96	0	91	6	95
M116	98	0	2	nd	65	20	14	96	0	69	28	96
M117	82	3	14	94	48	15	36	95	0	83	11	93
M118	89	1	9	93	71	5	22	94	33	21	31	95
M121	100	0	0	nd	100	0	0	nd	99	0	0	nd
M122	100	0	0	nd	100	0	0	nd	99	0	0	nd
M123	91	2	7	96	71	8	20	95	11	42	45	95
M124	92	3	5	94	29	29	39	96	0	87	6	96
M125	95	1	4	91	86	3	11	92	24	28	40	95
M126	67	10	21	96	5	46	46	97	0	88	8	96
M127	87	3	9	93	27	24	46	96	1	58	37	96
M128	100	0	0	nd	99	0	1	nd	98	0	1	nd
M129	100	0	0	nd	100	0	0	nd	97	2	1	96
M130	65	12	22	95	11	48	39	96	0	91	6	95
M131	89	5	5	98	38	50	4	96	6	75	11	97
M132	99	0	1	nd	94	3	3	91	70	10	19	92
M133	95	1	3	93	84	7	8	94	7	72	17	93

Large scale hydrogenation of **2** (Data used in Fig. 1)

Time (min)	**2 (%)**	**10 (%)**	**11 (%)**	**3 (%)**	**6 (%)**	**Ratio 10:11**	**Ratio 3:6**
17	93	0	0.5	0.3	2.2	100:0	88:12
39	81	0	1	1	12	100:0	91:9
100	49	0.2	7	4	35	97:3	91:9
143	32	0.4	12	5	45	97:3	91:9
225	12	0.6	24	6	51	97:3	90:10
280	5	0.9	33	6	48	97:3	89:11
280	5	0.9	33	6	48	97:3	89:11
345	2	1.1	42	6	42	97:3	88:12
425	0	1.5	53	6	32	97:3	85:15
485	0	1.8	62	5	24	97:3	82:18

1440	0	4.7	85	2	1	95:5	18:82

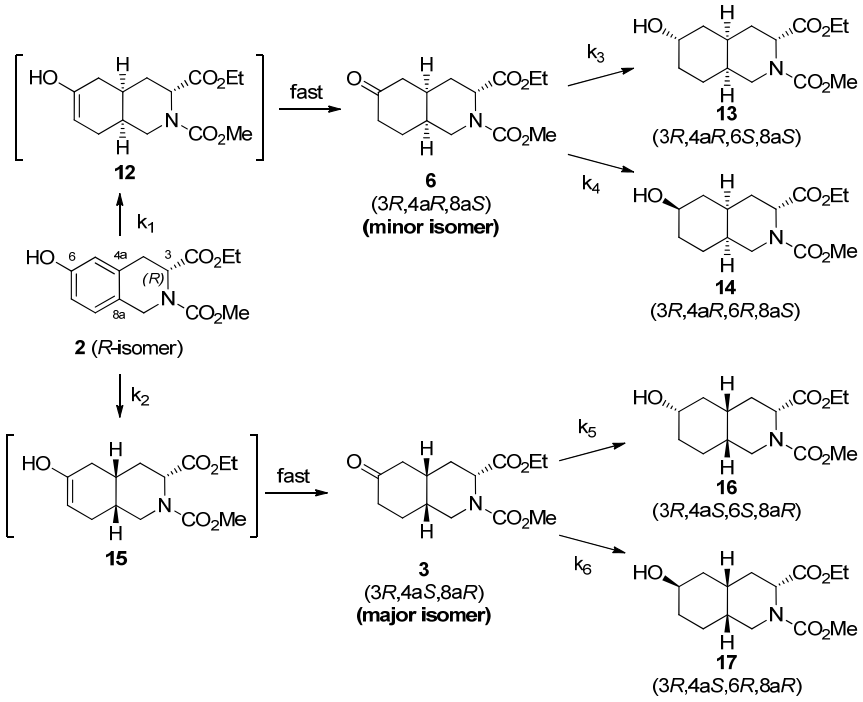
Catalyst amount = 250 mg of Pd/C (Escat 1471, 50% wet), 1250 mg of substrate **2**, 60 mL EtOAc, 100 °C, 25 bar H_2, 16 h, 1300 rpm (mechanical stirrer).

Large scale hydrogenation of **18** (Data used in Fig 2.)

Time (min)	**18 (%)**	**19 (%)**	**20 (%)**	**21 (%)**	**22 (%)**	**Ratio (21+22):(19+20)**
30	97	0.4	0.2	1.5	0.6	77
65	91	0.7	0.6	5.4	2.1	86
95	87	0.7	0.9	8.5	3.3	88
120	81	0.6	1.2	12.2	4.6	90
150	75	0.6	1.6	16.0	5.9	91
210	64	0.7	2.3	23.2	8.6	91
265	55	0.6	2.9	29.0	10.7	92
325	44	0.4	3.6	35.6	13.0	92
385	36	0.3	4.2	41.1	15.0	93
445	28	0.4	4.7	46.1	16.8	93
1320	2	0.4	6.3	63.5	22.5	93

Catalyst amount = 250 mg of Pd/C (Evonik E1, 50% wet), 1250 mg of substrate **18**, 60 mL EtOAc, 100 °C, 25 bar H_2, 16 h, 1300 rpm (mechanical stirrer).

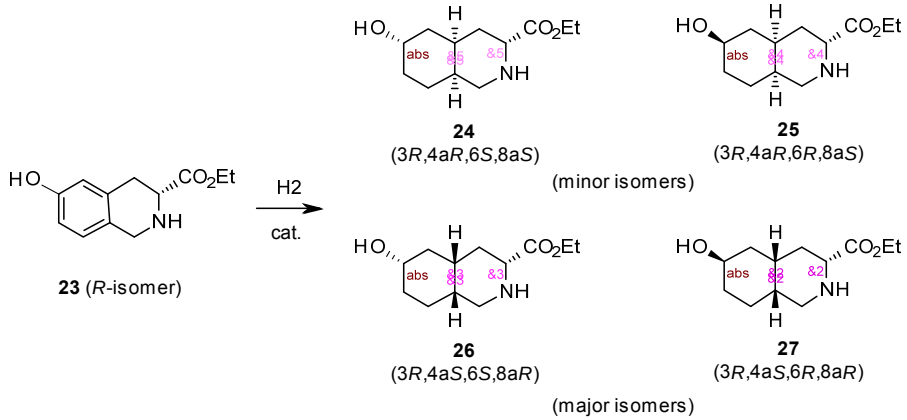
Equations used for the kinetic model



d[**2**]/dt = $[\mathbf{2}]_0 - (k_1 + k_2)$ [**2**]; d[**3**]/dt = k_2 [**2**] – $(k_5 + k_6)$ [**3**]; d[**6**]/dt = k_1 [**2**] – $(k_3 + k_4)$ [**6**]

d[**13**]/dt = k_3 [**6**]; d[**14**]/dt = k_4 [**6**]; d[**16**]/dt = k_5 [**3**]; d[**17**]/dt = k_6 [**3**].

Hydrogenation of substrate **23**.



Entry	1	2	3	4	5	6	7
Catalyst	**Pd/C**	**RuO2**	**RuO2**	**RuO2**	**RuO2**	**RuO2**	**RuO2**

T (°C)	100	60	60	60	100	100	100
Solvent	EtOAc	EtOH	EtOAc	Heptane	EtOH	EtOAc	Heptane
Area % alcohol (**24** + **25** + **26** + **27**)	1	16	2		98	94	
*Major (**26, 27**):minor (**24, 25**)*	*n.d.*	*83:17*	*81:19*		*38:62*	*86:14*	
Distibution **24:25:26:27**	n.d.	4:13:72:11			4:58:28:10	4:10:75:11	
Area % ketone	0	0.3	0.1		1	2	
*Area % **23***	*76*	*82*	*94*	*100*	*0*	*0*	*100*
Area % unknown	23	2	4		1	3	

Reaction conditions: Catalyst = **Pd/C**: Pd, 5% on activated carbon, 50-70% water-wet paste (Evonik E1), 25 mg wet or **RuO_2**: Ru(IV) oxide hydrate, **4**: 125 mg, 25 bar, 5 mL solvent, 300 rpm.

Distribution of the alcohol diastereomers obtained after hydrogenation of **2, 18,** and **23.**

Substrate	**2**	**18**	**23**
(3*R*, 4a*R*, 6*S*, 8a*S*)-**13** or -**19** or **-24**	0.7	0.4	4
(3*R*, 4a*R*, 6*R*, 8a*S*)-**14** or -**20** or **-25**	5	7	10
(3*R*, 4a*S*, 6*S*, 8a*R*)-**16** or -**21** or **-26**	68	69	75
(3*R*, 4a*S*, 6*R*, 8a*R*)-**17** or -**22** or **-27**	27	24	11

Catalyst amount = 250 mg of Pd/C (50% wet), 1250 mg of substrate **2** or **18** or **23**, 60 mL EtOAc, 100 °C, 25 bar H_2, 16 h, 1300 rpm (mechanical stirrer).

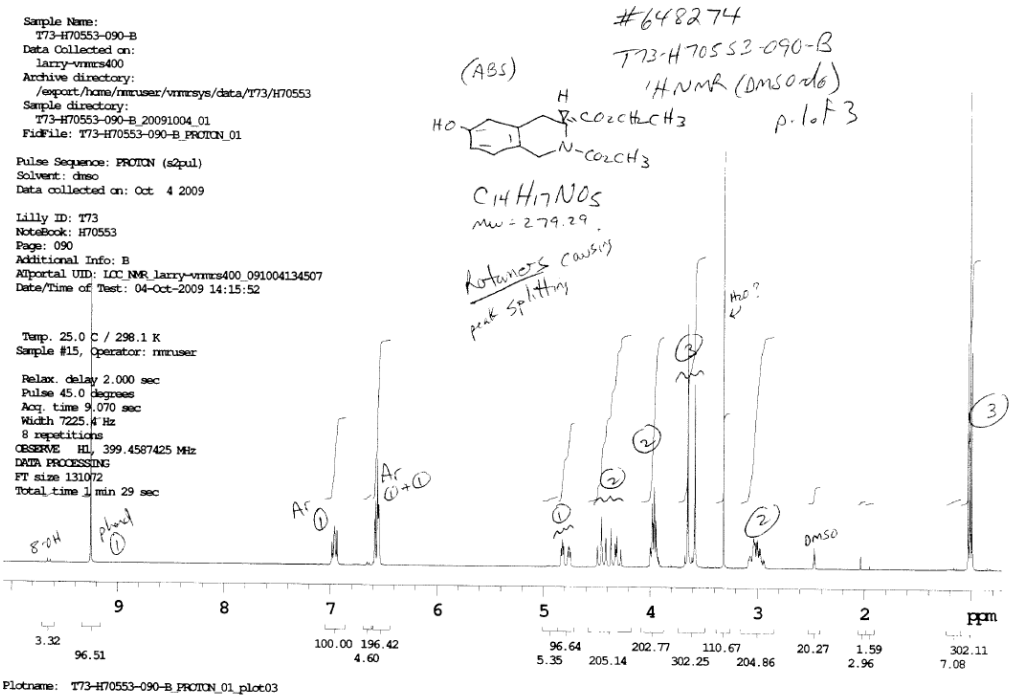
Preparation of Ethyl 6-Hydroxy-2-(methoxycarbonyl)-1,2,3,4-tetrahydro-isoquinoline-(3*R*)-carboxylate (2). *Pictet-Spengler reaction:* D-*m*-tyrosine (20 g, 103 mmol, commercially available), water (200 mL), and conc. HCl (0.76 mL, 8.9 mmol) were charged to a 500 mL 3-

necked round-bottomed flask and heated to 60 °C. Formaldehyde (13.5 g, 154 mmol) was added slowly over 1.5 hour. The resulting white slurry was slowly allowed to cool to room temperature and solid product filtered on a Buchner funnel, washed with water (2x20 mL) and acetone (2x20 mL), and dried to give the desired P-S reaction product 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3*R*)-carboxylic acid in 82% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.8 and 9.4 (br,1H), 7.0 (m, 1H), 6.6 (m, 2H), 4.0 (m, 1H), 3.4 (m, 2H), 3.0 (m, 1 H), 2.8 (m, 1H); 100 %*ee* (HPLC Chiral method conditions: Chirobiotic T2 (250 x 4.6 mm x 5 um) @ 20 °C; 20/80 MeOH /NH_4OAc (pH 4.0 w/HOAc); Flow:1.0 mL/min, Inj Vol:10 uL; UV Det @ 280 nm, retention time *R*-enantiomer = 7 minutes).

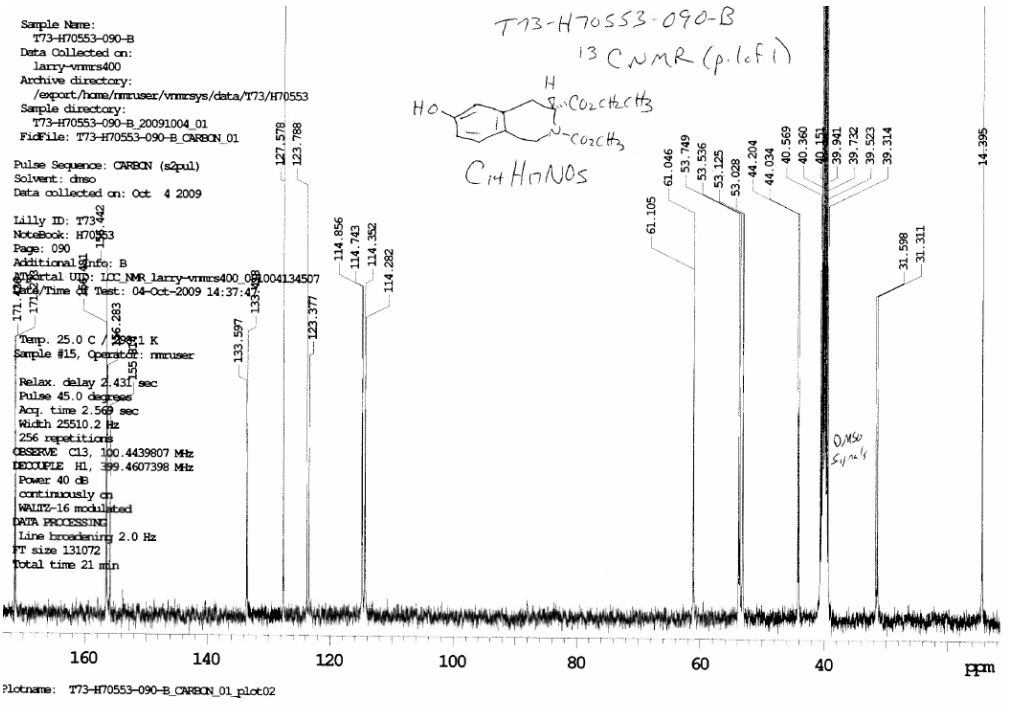
Esterification: The Pictet-Spengler product (75 g, 288 mmoles) and ethanol (450 mL) were charged to a 1-L flask equipped with a scrubber (for HCl/SO_2 gases, used 100 mL of 5N NaOH). The resulting white slurry was heated to 45-55 °C and thionyl chloride (45 mL, 617 mmoles) was added at 45-55 °C over approximately 1 hour via syringe pump and remained heated for an additional 3 hours. Once the reaction was completed, the slurry was placed in an ice-water bath to cool to 0-2 °C, where it was allowed to stir for approx 1 hour before solid product was collected and dried under vacuum at 60 °C to constant weight. This gave 65 g (78%) of an off-white solid ethyl 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3*R*)-carboxylate (compound **23**) . ^{1}H NMR (500 MHz, DMSO-d_6): δ10.1 (s, 1H), 9.66 (s, 1H), 7.01-7.03 (m, 1 H), 6.64-6.70 (m, 2H), 4.43-4.46 (m,1H), 4.13-4.26 (m, 4H), 3.06-3.20 (m, 2H), 1.23-1.26 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168, 158, 132, 128, 119, 115, 115, 62, 53, 44, 29, 14.

Carbamate group protection: The ethyl ester product (36.98 g, 117.6 mmol), ethyl acetate (136 mL), water (75 mL), and potassium carbonate (32.52 g, 235.3 mmol) were charged to a 500 mL 3-necked round-bottomed flask at room temperature. Methyl chloroformate (9.11 mL, 117.68 mmol) was added over 1.5 hours under a nitrogen atmosphere then contents allowed to stir for an additional 5 hours until the reaction was completed by LC (<2% amino ethyl ester remaining). The lower aqueous phase was removed and product phase washed with water (45 mL) and removed. Silica gel (7.6 g) was added to the reaction, stirred for 1 hour then removed by filtration. To the filtrate was added water (190 mL) and ethanol (48 mL), concentrated the solution under vacuum (101 torr, 77 °C) until no more distillate was removed having a cloudy solution of approximately 260 mL remaining. Contents were allowed to cool to room temperature and crystallize. Product isolated was 27.5 g (98.6 mmol) of compound **2**. MS (*m/z* = 279); ^{1}H NMR (DMSO-d_6): (doubling due to amide rotamers) δ 9.25 (s, 1 H), 6.95 (m, 1H), 6.55 (m, 2 H), 4.81 and 4.75 (multiplet of rotamers, 1H), 4.40 and 4.33 (quartet rotamers, 2H), 3.95 (m, 2H), 3.65 and 3.58 (singlet of rotamers, 3H), 3.00 (m, 2H), 1.02 (t, 3H). ^{13}C NMR (DMSO-d_6): δ 171, 156, 134, 128, 124, 123, 115, 114, 61, 54, 53, 44, 32, 14.

^{1}H NMR Spectrum of 2.



^{13}C NMR spectrum of 2



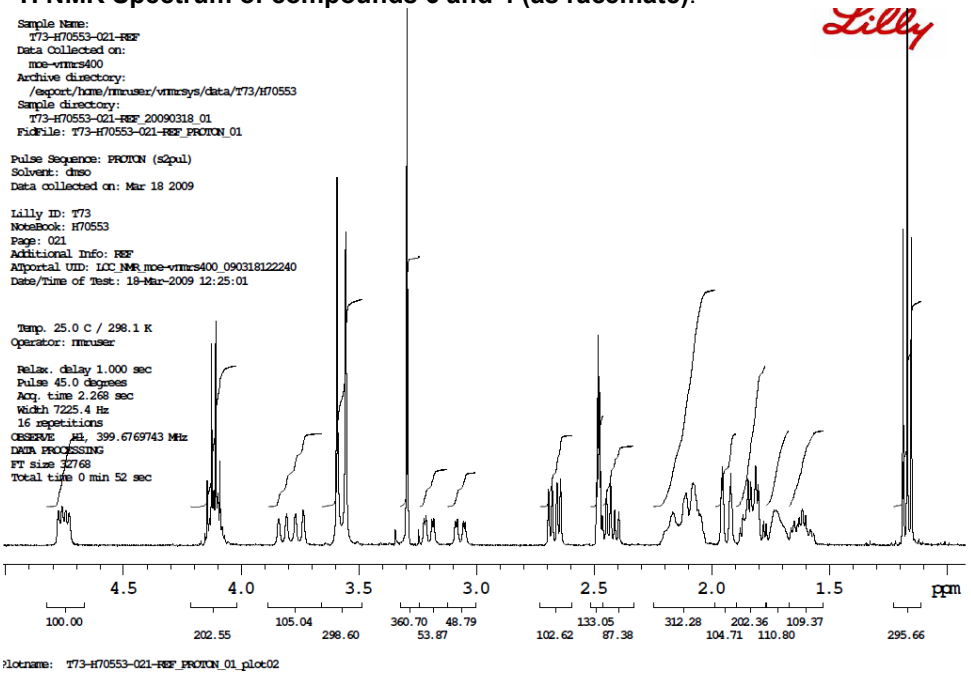
Enantiomers **3** and **7** (as racemate):

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.46 (br s, 1H), 4.14-4.00 (m, 2H), 3.72 (br, 1H), 3.57 (br, 3H), 3.27 (br s, 1H), 2.36-2.28 (m, 1H), 2.36-2.22 (m, 2H), 2.19-1.85 (m, 5H), 1.79-1.73 (m, 2H), 1.15 (t, J = 7.06 Hz, 3H).
^{13}C NMR (100 MHz, DMSO-d_6): δ 210.63, 172.42, 156.44, 61.32, 53.01, 52.35, 42.04, 37.28, 33.23, 32.57, 30.39, 27.04, 14.38.

Enantiomers **6** and **4** (as racemate):

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.73 (dd, J = 13.2 Hz, 6.0 Hz, 1H), 4.12-4.05 (m, 2H), 3.80 + 3.73 (d x 2, J = 13.2 Hz, combined 1H), 3.57 + 3.54 (s x 2, combined 3H), 3.18 and 3.05 (both d, J = 13.2 Hz, 3.6 Hz, combined 1H), 2.66 and 2.63 (both d, J = 6.0 Hz, combined 1H), 2.45-2.37 (m, 1H), 2.20-2.05 (m, 3H), 1.94 and 1.90 (br s x 2, 1H), 1.86-1.55 (m, 4H), 1.15 (t, J = 7.2 Hz, 3H) ppm.
^{13}C NMR (100 MHz, DMSO-d_6): δ 210.39 and 210.32, 171.12, 156.97 and 156.52, 61.42 and 61.35, 54.24 and 54.05, 53.13 and 53.04, 46.17, 45.79 and 45.67, 33.27, 32.81, 27.04 and 26.95, 24.61, 14.48.

^{1}H NMR Spectrum of compounds 6 and 4 (as racemate).



Preparation of reference materials 13 (as its enantiomer) and 14 (as its enantiomer).

To a solution of ketone **4** (same as the enantiomer of **6**) (5 g, 17.7 mmol), cerium III chloride heptahydrate (6.6g, 26.8 mmol), and ethanol (100 mL) in a 250 mL flask at -70 °C was added sodium borohydride (1.36g, 36 mmol) in 50 mL ethanol dropwise to the cold solution over 1 hour keeping the pot temperature less than -65 °C. The resulting slurry was stirred for an additional 1 hour, and then allowed to warm to -50 °C. The reaction was quenched by dropwise addition of aq. ammonium chloride solution (20 mL) with control of the resulting exotherm and eventual rise to room temperature. The reaction was concentrated to remove the ethanol and leave a solid

product. This solid was suspended in water and ethyl acetate, lower aqueous phase separated, ethyl acetate phase washed again with water, then concentrated to an oil. Products were separated on a silica gel column chromatography (1:1 heptane:ethyl acetate), Rf 0.23 starting material, 0.17 **14-ent** (14% yield), 0.10 **13-ent** (46% yield).

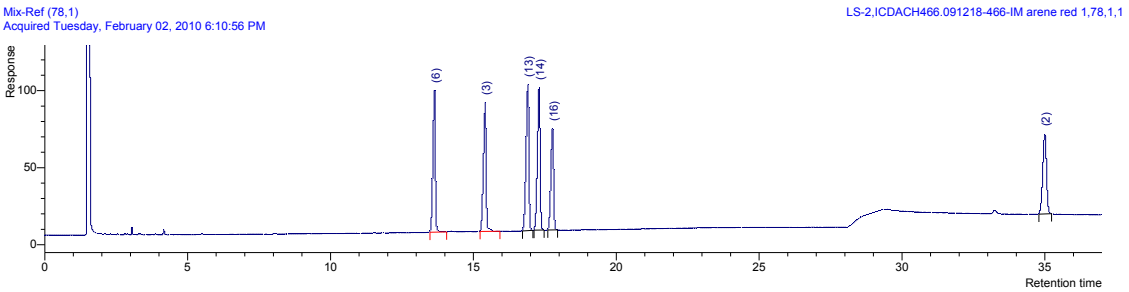
13-enantiomer: MS (*m/z* = 285); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.77 (dd, 1H), 4.39 (m, 1H), 4.11 (m, 2H), 3.70 (dd, 1H), 3.57 (s, rotamers,3H), 3.50 (m, 1H), 3.02(ddd, 1H), 1.94 (m, 1H), 1.82-1.40 (m, 6H), 1.35-1.02 (m, 6H).

14-enantiomer: MS (*m/z* = 285); ^{1}H NMR (400 MHz, DMSO-d_6): δ4.68 (m, 1H), 4.35 (m, 1H), 4.10 (q, 2H), 3.78 (m, 1H), 3.70-3.55 (m, 4H), 3.15-2.90 (m, 1H), 1.82-1.36 (m, 8H), 1.23-1.05 (m, 5H).

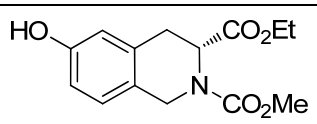
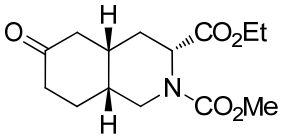
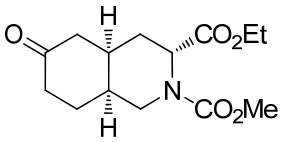
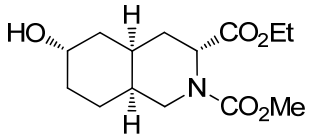
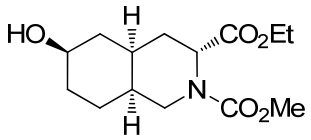
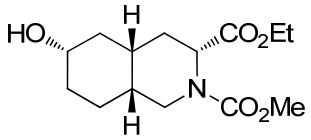
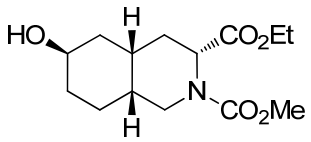
GC Analytical Method for the Hydrogenation Products of Compound **2**

- Column: DB-WAX from Agilent/J&W (30m * 0.32mm, d_f = 0.25 µm)
- Injection: 1 µl, split 1:10
- Ramped flow : 1.6 ml/min (28 min.) → 4 ml/min → 6.9 ml/min (21 min.),
- Temp. gradient: 230 °C (2.5 min) → 1 °C/min → 250 °C (14.5 min)
- Run time: 37 min.
- Injection temp.: 250 °C
- Detection temp.: 260 °C
- We observe unstable retention times from one day to the other. Therefore during each analysis run a reference mixture is injected for peak assignment.

Fig. 1. Chromatogram obtained for a reference mixture containing compound 2, 3, 6, 13, 14, 16.

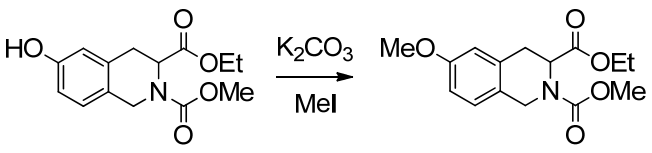


Compound	Structure	Retention Time (min)

2		35.5
3[a]		15.4
6[a]		13.6
13[b]		16.8
14[b]		17.3
16[b]		17.8
17[c]		18.1

a) Racemate used in method development. b) Enantiomer used in method development. c) No pure reference material was available for compound 17. Its retention time was determined from the mixture obtained during a hydrogenation experiment.

Preparation of compound 18



2 **18**

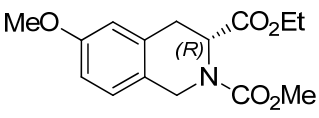
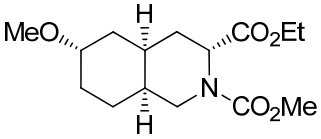
Compound **2** (10 g, 35.8 mmol) was dissolved into 150 mL of acetone then K_2CO_3 (15 g, 108.7mmol) was added followed by addition of methyl iodide (25 g, 176.1mmol). The solution was heated to 60 °C and stirred at this temperature overnight. GC analysis shows that the formation of the desired product with 96 area%. The solids were filtered away and the acetone filtrate concentrated to an oil residue. The remaining oil was dissolved into 150 mL EtOAc and extracted twice with 50 mL H_2O. After drying over Na_2SO_4 and removal of the solvent under vacuum, 11.5 g of red-orange oil product was obtained. Purity by GC analysis = 98 area %. 5.5 g of this material was further purified by column chromatography (silica: 90 g, eluent = heptane:EtOAc: 75/25, flow = 20 mL/min) leading to a material with 99.8 area% purity by GC. Correct mass of the compound was confirmed by GC-MS.

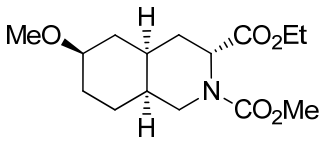
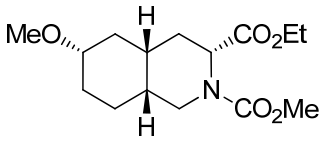
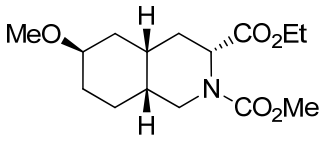
Preparation of Reference Standards for the Hydrogenation Products of 18

Treatment of pure sample of each of compounds **13**, **14**, and **16** with MeI (4 equiv.) in the presence of NaH (1/3 equiv.) provided the methoxy-protected compounds as reference samples **19**, **20** and **21** respectively.

GC Analytical Method for the Hydrogenation of 18

- Column: DB-WAX from Agilent/J&W (30m * 0.32mm, d_f = 0.25 µm)
- Injection: 1 µl, split 1:10
- Ramped flow : 1.6 ml/min (28 min.) → 4 ml/min → 6.9 ml/min (21 min.),
- Temp. gradient: 230 °C (2.5 min) → 1 °C/min → 250 °C (14.5 min)
- Run time: 37 min.
- Injection temp.: 250 °C
- Detection temp.: 260 °C
- We observe unstable retention times from one day to the other. Therefore during each analysis run a reference mixture is injected for peak assignment.

Compound	Structure	Retention Time (min)
18		16.7
19 (minor)		9.9

20 (minor)		9.2
21 (major alcohol)		10.3
22 (major alcohol)		9.7

*(Same analytical method as the one used for **2** and its products).*

Preparation of 23

Compound 23: Synthesized as an intermediate toward **2**.

Preparation of Reference Standards for the Hydrogenation Products of 23

The products from the hydrogenation of **23** (i.e. **24**, **25**, **26**, and **27**) were derivatized into their respective N-carbomethoxy derivatives. These derivatives are, in fact, compounds **13**, **14**, **16**, and **17,** the products from the hydrogenation of **2**. Therefore, the analytical method for **2** and its respective hydrogenation products was used. The derivatization procedure is the following: A sample (0.5 mL, approximately 0.046 mmol of substrate) of reaction mixture in EtOH is concentrated to a residue then EtOAc (2 mL) was added with 50 μL Et_3N and $ClCO_2Me$ (0.3-0.5 equiv) with stirring for 30 minutes.

GC Analytical Method for the Hydrogenation of 23 : (same as that for compound 2)

LCMS Analytical Method for the Hydrogenation Products of 23

- Column: Thermo Hypercarb 4.6 x 100 mm, 3 μm particle
- Mobile Phase A: 0.1% trifluoroacetic acid in water
- Mobile Phase B: 0.1% trifluoroacetic acid in acetonitrile
- Flow Rate: 1.5 mL/min
- Gradient:

Time	%A	%B
0	98	2
20	50	50

20.1	98	2
28	98	2

- Injection: 5 µL of ~0.5 mg/mL sample dissolved in mobile phase A
- Column Temperature: 35 C
- UV Detection: 205 nm (4 nm bandwidth)
- MS Detection: Electrospray in positive mode; 2:1 split ratio; Scanning Mass Range: 10-1000 AMU; Fragmentor = 150; Gain = 2; Threshold = 50; Capillary Voltage = 3500 V.

[1] This reactor was developed by Premex in cooperation with DSM. See: www.premex-reactorag.ch/e/spezialloesungen/produkteneuheiten/

[2] For additional information on the Endeavor™ Catalyst Screening System, see the Biotage website : http://www.biotage.com.

[3] This reactor is commercially available from Premex. See: www.premex-reactorag.ch/index.php?page=472