Acid Promoted Ir-P^N Complexes Catalyzed Hydrogenation of Heavily Hindered 3,4-Diphenyl-1,2-dihydronaphthalenes: Asymmetric Synthesis of Lasofoxifene Tartrate

Antonio Zanotti-Gerosa,[a] Ivana Gazić Smilović[b] and Zdenko Časar[b,c*]

[a] Johnson Matthey, Unit 28, Cambridge Science Park, Milton Road, Cambridge CB4 0FP, UK

[b] Lek Pharmaceuticals, d.d., Sandoz Development Center Slovenia, Verovškova ulica 57, 1526 Ljubljana, Slovenia

[c] Faculty of Pharmacy, University of Ljubljana, Aškerčeva cesta 7, 1000 Ljubljana, Slovenia

* Corresponding author. Tel.: + 386 1 5802079; fax: + 386 1 5683517; e-mail: zdenko.casar@sandoz.com

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1. Screening of asymmetric hydrogenation of 3,4-diphenyl-1,2-dihydronaphthalenes with Ir-P^N-complexes

1.1. Screening of hydrogenation of 3,4-diphenyl-1,2-dihydronaphthalene 12 with Ir-P^N complexes

The first set of hydrogenation screening experiments on substrate **12** (not presented in tables) was performed at 50 °C and 30 bar in CH_2Cl_2 and at a molar substrate to catalyst ratio S/C of 15 with catalysts based on ligands **3a**, **3d**, **3e**, **4e**, **5**, **7**, **8b** and **9**. Disappointingly, we could only detect up to ca. 3% of desired product **13** at best. The increase of temperature to 70 °C in toluene did not improve the performance of these catalysts. A third set of experiments was performed with catalysts based on **2c** and **10c** in a temperature range from 30-75 °C, at 10-30 bar with S/C = 15 in various solvents like dichloroethane (DCE) and *i*-PrOH. The catalyst containing **10c**, which was also one of the best performing in Pfaltz´s report,[20a] provided up to 6% of racemic **13** at 30 bar and 3% of product **13** with 20% *ee* at 10 bar.

More forcing conditions with increased catalyst loading (S/C = 10/1) were applied in the next set of experiments conducted in DCE at 60 °C and 30 bar of H_2 with an extended list of catalysts (Table S1, entries 1-19). This conditions finally led to some noticeable conversion with catalysts bearing ligands **3a** (entry 3) and **6a** (entry 10). Under the same conditions (DCE, 60 °C, 30 bar of H_2) but increasing substrate concentration, both ligands **3a** and **10c** also gave some conversion at S/C = 20/1 (entries 16 and 18) although conversion was reduced under 5 bar H_2 (entries 17 and 19).

Table S1. Screening of hydrogenation of 3,4-diphenyl-1,2-dihydronaphthalene **12** with Ir-P^N complexes.[a]

Entry	[Ir(**L**)(COD)]BAr_F	**12** [%]	**13** [%]	Others [%]	*ee* [%]
1	(*R*,*R*)-**2a**	99	-	1	-
2	(*R*,*R*)-**2b**	>99	-	-	-
3	(*S*)-**3a**	74	25	1	15 (e1)
4	(*S*)-**3c**	98	-	2	-
5	(*S*)-**3f**	97	2	1	-
6	(*S*)-**4a**	95	3	2	7 (e2)
7	(*S*)-**4b**	98	-	2	-
8	(*S*)-**4c**	>99	-	-	-
9	(*S*)-**4d**	98	-	2	-
10	(*S*)-**6a**	85	11	4	7 (e1)
11	(*S*)-**6b**	96	1	3	-
12	(*S*)-**8a**	98	2	-	10 (e1)
13	(*S*)-**10a**	98	2	-	9 (e1)
14	(*S*)-**10b**	90	6	4	9 (e1)
15	(*S*,*S*)-**11**	99	1	-	-
16[b]	(*R*)-**3a**	74	23	3	50 (e2)
17[b,c]	(*R*)-**3a**	90	6	3	33 (e2)
18[b]	(*S*)-**10c**	70	27	3	3 (e1)
19[b,c]	(*S*)-**10c**	82	14	4	7 (e1)

[a] A stock solution of **12** (16 mg in 2 mL DCE, C = ~ 8 mg/mL) was added to the Ir-complex, S/C = 10/1. The reaction was purged with nitrogen and hydrogen and run for 16 hours at 60 °C, 30 bar H_2. HPLC analysis: Halo C18 2 micron column, 15 × 0.46 cm; eluent: H_2O/MeCN + 0.1% TFA from 90/10 to 10/90 over 20 min, hold for 3 min; flow: 1 mL/min; T: 30 °C; detection at 280 nm. Elution times: **12**: 17.6 min; *cis*-**13**: 17.3 min. Chiralpak IC column, 25 × 0.46 cm; *n*-hexane/*i*-PrOH = 95/5; 1 mL/min; 30 °C; 280 nm. Elution times: e1 = *cis*-(*1R*,*2S*)-**13** (9.5 min); e2 = *cis*-(*1S*,*2R*)-**13** (12.6 min). [b] S/C = 20/1 and [**12**] = ~ 32 mg/mL. [c] 5 bar H_2 pressure was used.

ref. 20a of the manuscript: M. G. Schrems, E. Neumann and A. Pfaltz, *Angew. Chem. Int. Ed.*, 2007, **46**, 8274.

1.2. Screening of additives and *in situ* formed catalysts in hydrogenation of 3,4-diphenyl-1,2-dihydronaphthalene 12 with Ir-P^N complexes

Besides Brønsted acids, a variety of other additives were tested in the presence of [Ir(**3a**)(COD)]BAr_F including various Zn, Cu, Cs, Fe salts. Under the conditions of Table S1, the addition of 0.5 to 1 equivalent of ZnI_2, $Zn(acac)_2 \cdot H_2O$, $Zn(BF_4)_2 \cdot (H_2O)_n$, $Zn(OTf)_2$ (in the presence of H_3PO_4), CF_3CO_2Na, Cs_2CO_3, $Cu(OAc)_2$, CuCl, $Fe(acac)_3$, $MgBr_2 \cdot OEt_2$, NaI, KPF_6 gave <10% conversion to **13**. $Zn(OTf)_2$ gave 72-87% *ee* (0.5 to 1 equivalent) with only 13-18% conversion to **13**.

The addition of potential ancillary ligands (in an effort to stabilize catalysts intermediates or to modify the active species) were also included, such as cyclooctadiene, stilbene, cinnamate and Ph_3P but the results were negative or inconclusive.

Encouraged by the results of Table 1, we also undertook another broad screen of [Ir(**L**)(COD)]BAr_F catalysts in the presence of H_3PO_4. Surprisingly, [Ir(**3a**)(COD)]BAr_F remained the only viable option for the desired transformation. Under the conditions of Table S1, catalysts bearing ligands **2a-c**, **3c-e**, **7, 8a**, **9**, **10b-c** gave <15% conversion to **13** and <20% *ee*.

This additional screen, conducted under the conditions of Table S1, also included some catalysts formed *in situ* from $[Ir(COD)Cl]_2$ and chiral phosphine ligands BoPhoz, Phanephos and PPhos: no conversion was obtained.[29]

In addition, we tentatively looked at the use of ligand **3a** with various Ir precursors in the presence of H_3PO_4, but again, no improvement was observed. For this purpose ligand (*R*)-**3a** was mixed in DCE with $[Ir(COD)Cl]_2$, $[Ir(Cp^*)Cl_2]_2$, [Ir(COD)(acac)], [Ir(COD)$_2$]BAr_F and the complexes so obtained were tested under the conditions of Table S1 without further characterization. Pre-treatment of the complexes from [Ir(COD)(acac)] and $[Ir(COD)Cl]_2$ with NaH_2PO_4 or H_3PO_4 also led to catalytically inactive compounds.

***General procedure for screening experiments for hydrogenation of 4-(6-methoxy-2-phenyl-3,4-dihydronaphthalen-1-yl)phenol 12 with additives*.**

A stock solution of **12** (66-603 mg, 0.2-1.84 mmol in 2.5-6.0 mL DCE, ~ 26-201 mg/mL) was added to catalyst [Ir(**L**)(COD)]BAr_F (S/C = 5/1 to 50/1) and the solid additive that had been pre-weighted in the vials. The glass vials were placed in a multi-well autoclave with overhead stirring and computer controlled gas feed, which was closed, purged with nitrogen three times and with hydrogen three times under stirring before being heated and pressurized to the values indicated in the Tables 1-2. After competition of the set reaction time, the reactor was programmed to cool down to 30 °C and automatically release pressure. The reactor was opened and a sample of each reaction was diluted in hexane/EtOH = 1/1 and analyzed by HPLC. Et_3N was added to the reaction crude mixture, if the reaction had been carried out in the presence of acidic additives. HPLC analysis reverse phase method: halo C18 2 micron column, 15 × 0.46 cm; eluent: water/MeCN + 0.1% TFA from 90/10 to 10/90 over 20 min, hold for 3 min; flow: 1 mL/min; temperature: 30 °C; detection at 280 nm. Elution times: **12**: 17.6 min; *cis*-**13**: 17.3 min. HPLC analysis chiral method: Chiralpak IC, 25 × 0.46 cm; eluent: hexane/*i*-PrOH = 95/5; flow: 1 mL/min; temperature: 30 °C; detection at 280 nm. Elution times: **12**: 6.5 min; *cis*-(1*R*,2*S*)-**13**: 9.5 min; *cis*-(1*S*,2*R*)-**13**: 12.6 min.

ref. 29 of the manuscript: (a) N. W. Boaz, S. D. Debenham, E. B. Mackenzie and S. E. Large, *Org. Lett*. 2002, **4**, 2421; (b) P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante and P. J. Reider, *J. Am. Chem. Soc*., 1997, **119**, 6207; (c) C.-C. Pai, C.-W. Lin, C.-C. Lin, C.-C. Chen, A. S. C. Chan and W. T. Wong, *J. Am. Chem. Soc*., 2000, **122**, 11513.

1.3. Screening of hydrogenation of nafoxidine 14 in the presence of $BF_3 \cdot OEt_2$ with various Ir-P^N complexes

Contrary to the case of substrate **12**, where the reaction conditions worked uniquely for catalyst [Ir(**3a**)(COD)]BAr_F, the addition of $BF_3 \cdot OEt_2$ generally produced moderate to high levels of conversion to product **15** (e.g. catalysts bearing ligands **4e** and **7** gave respectively 97% and 88% conversion) but in all cases the enatioselectivity was lower than 25% *ee*. [Ir(**3a**)(COD)]BAr_F, with 42% *ee* (Table 3, entry 8), stood out again as the best candidate for further development.

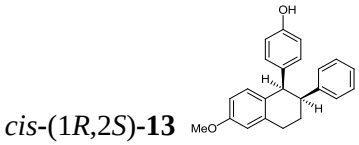
Table S2. Screening of hydrogenation of nafoxidine **14** with Ir-P^N complexes in the presence of $BF_3 \cdot OEt_2$.[a]

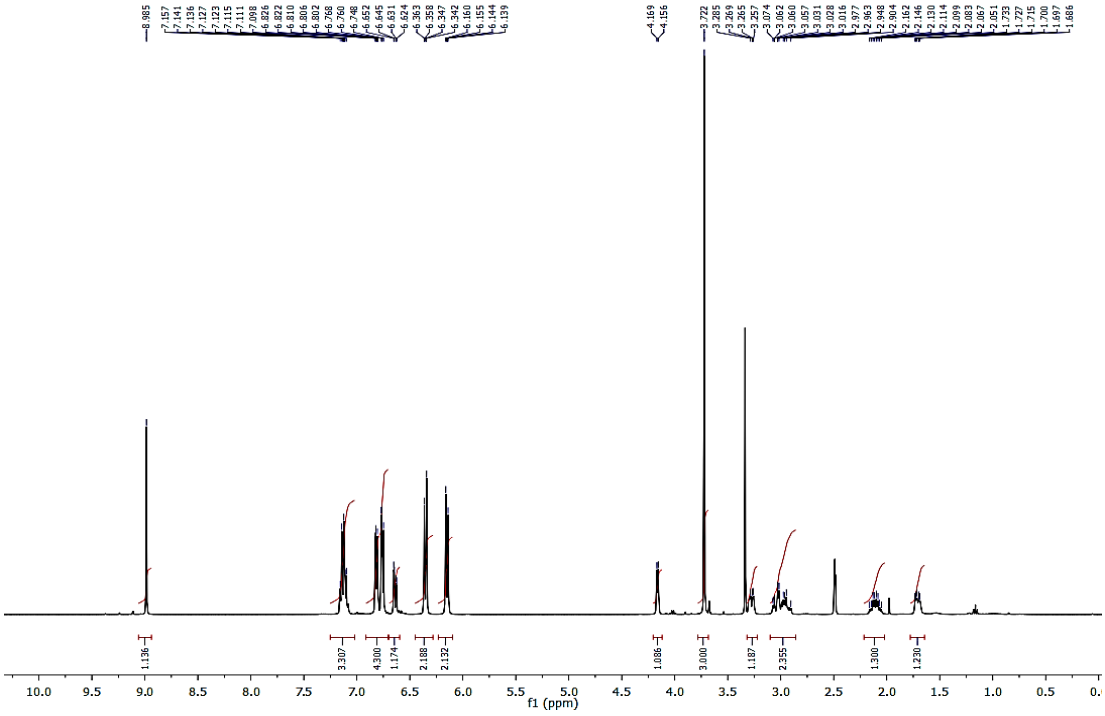
Entry	[Ir(**L**)(COD)]BAr_F	**14** [%]	**15** [%]	Others [%]	*ee* [%]
1	(*R*,*R*)-**2a**	84	15	1	7 (e2)
2	(*R*,*R*)-**2b**	87	11	2	-
3	(*S*)-**2c**	24	59	17	8 (e2)
4	(*S*)-**3b**	72	23	5	9 (e1)
5	(*S*)-**3c**	46	53	1	7 (e2)
6	(*S*)-**3d**	87	9	4	22 (e2)
7	(*S*)-**3e**	74	23	3	17 (e2)
8	(*S*)-**3f**	22	67	1	27 (e2)
9	(*S*)-**4b**	57	35	8	7 (e2)
10	(*S*)-**4d**	89	9	2	17 (e2)
11	(*S*)-**4e**	1	97	2	15 (e2)
12	(*S*)-**5**	40	57	3	5 (e2)
13	(*S*)-**7**	11	88	1	16 (e2)
14	(*S*)-**8b**	48	48	4	*rac*
15	(*R*)-**9**	20	70	10	15 (e1)
16	(*S*,*S*)-**11**	86	11	3	4 (e2)

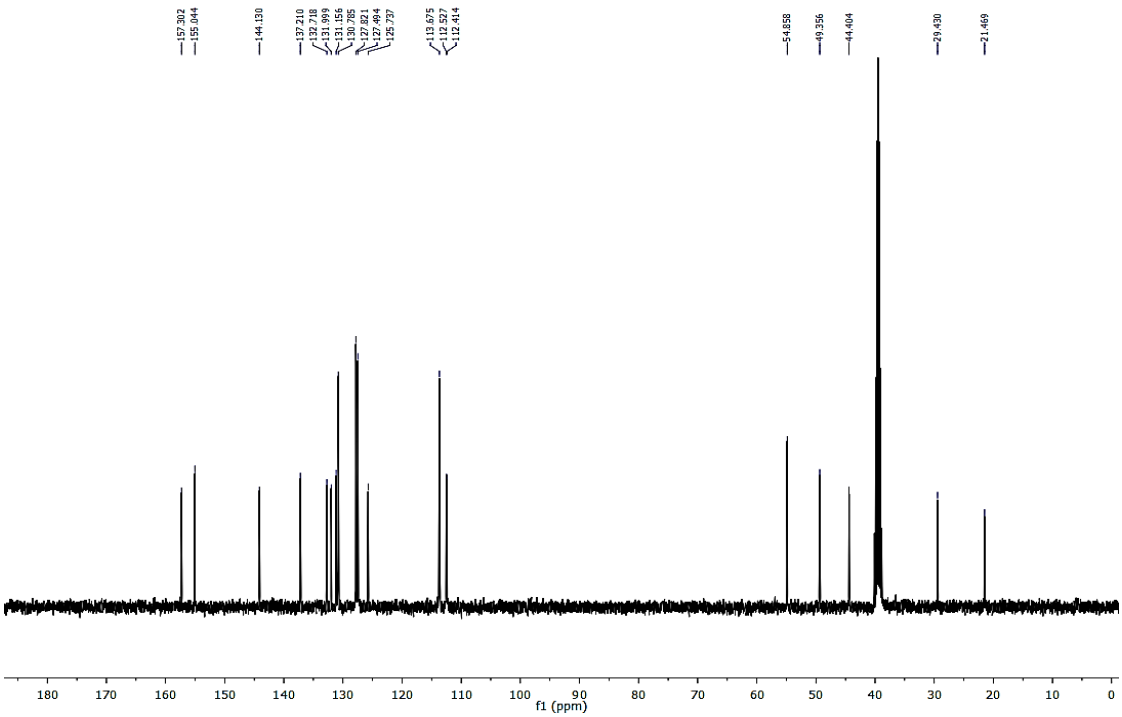
[a] A stock solution of **14** (120 mg in 2.5 mL DCE, C = ~ 50 mg/mL) and $BF_3 \cdot OEt_2$ (0.1 mL, ~ 2.5 equivalent to **14**) was added to the Ir-complex, S/C = 30/1. The reaction was purged with nitrogen and hydrogen and run for 64 hours at 60 °C, 30 bar H_2. HPLC analysis as in Table 3. Uncorrected HPLC areas reported

2. Copies of ^{1}H NMR and ^{13}C NMR spectra:

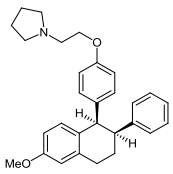
cis-(1*R*,2*S*)-**13**

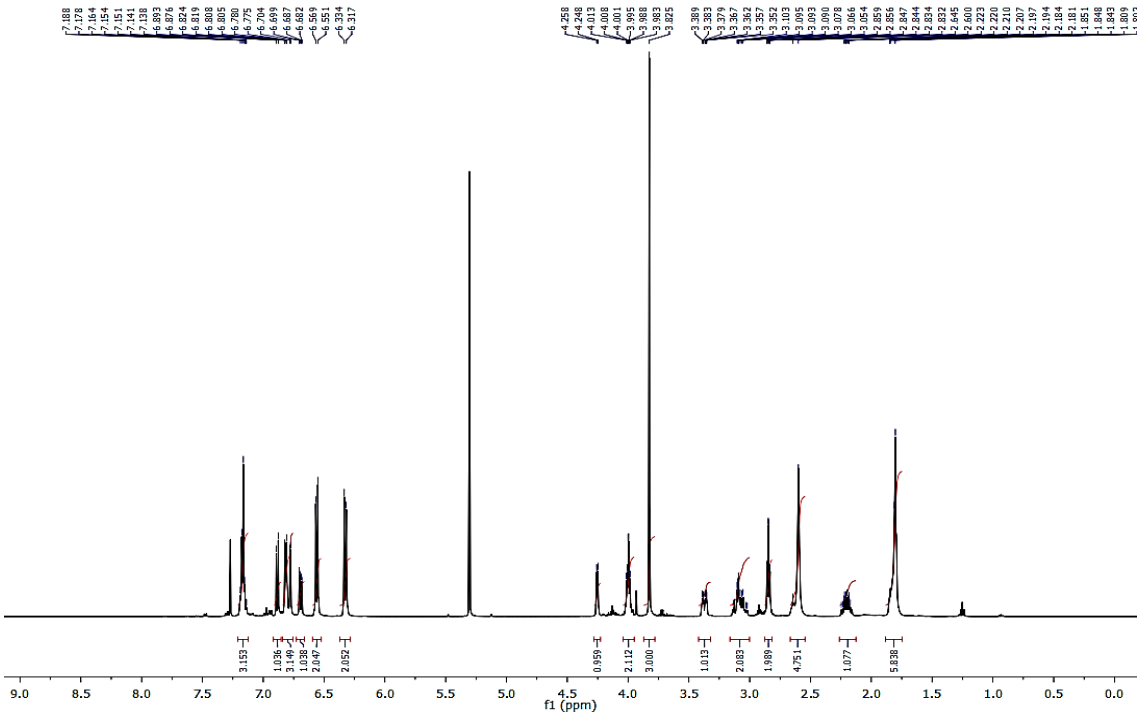


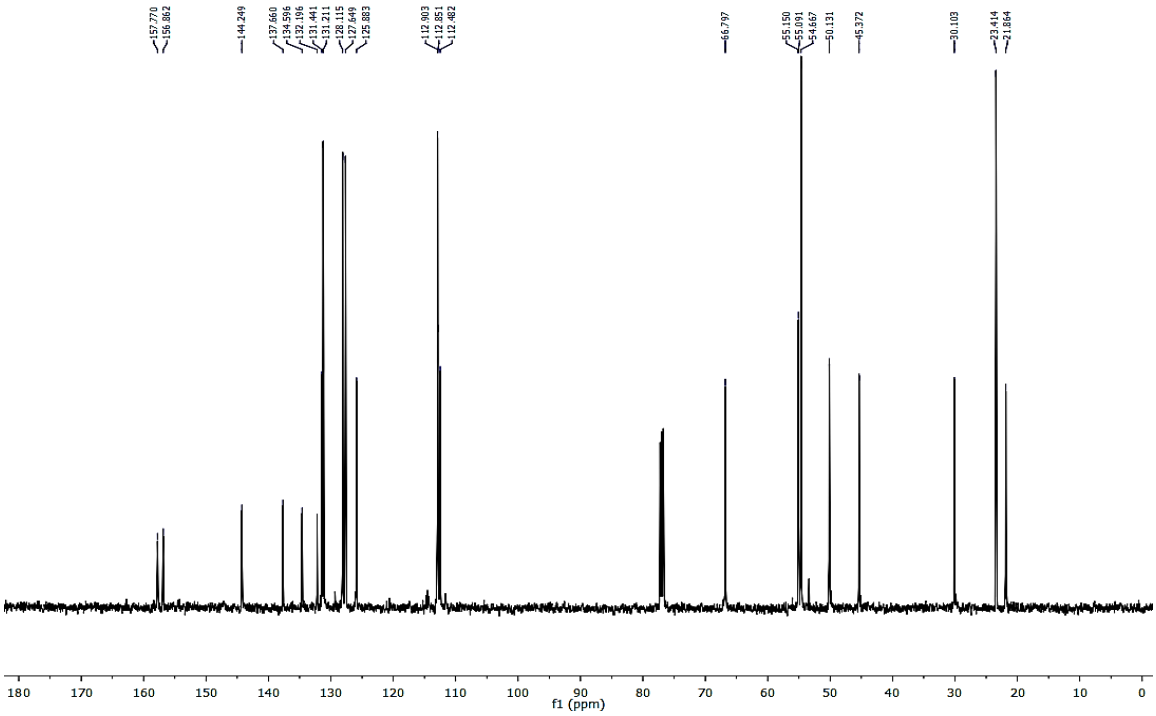




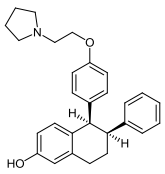
cis-(1*R*,2*S*)-**15**

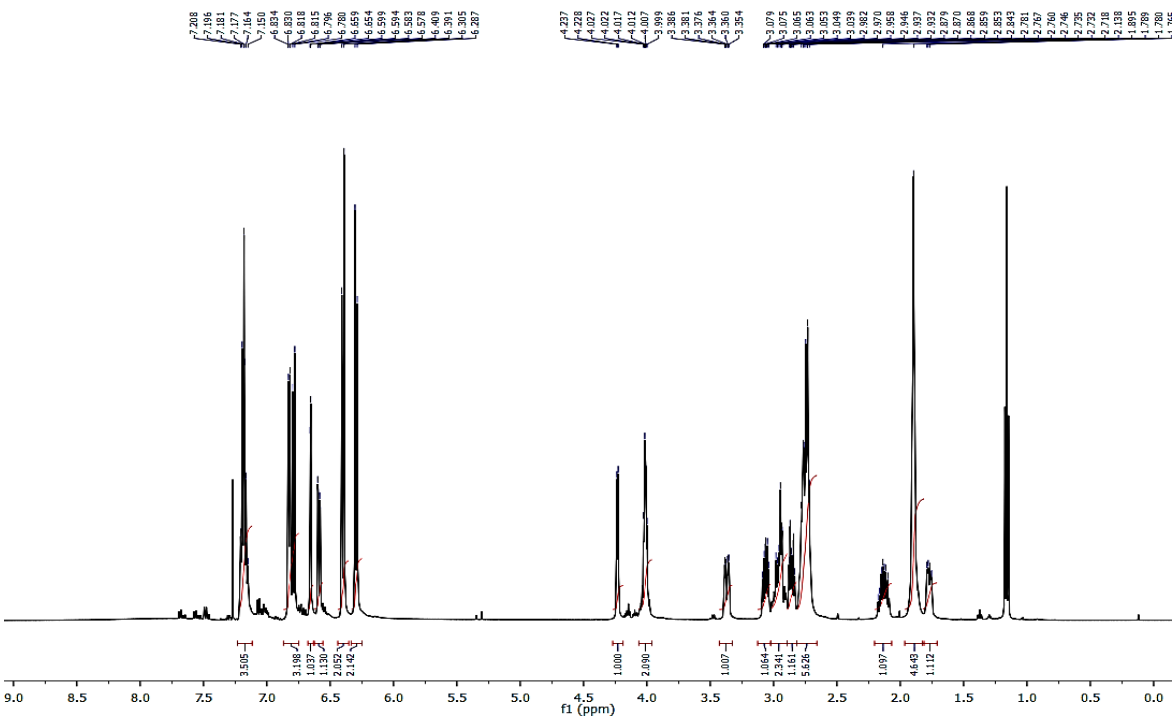


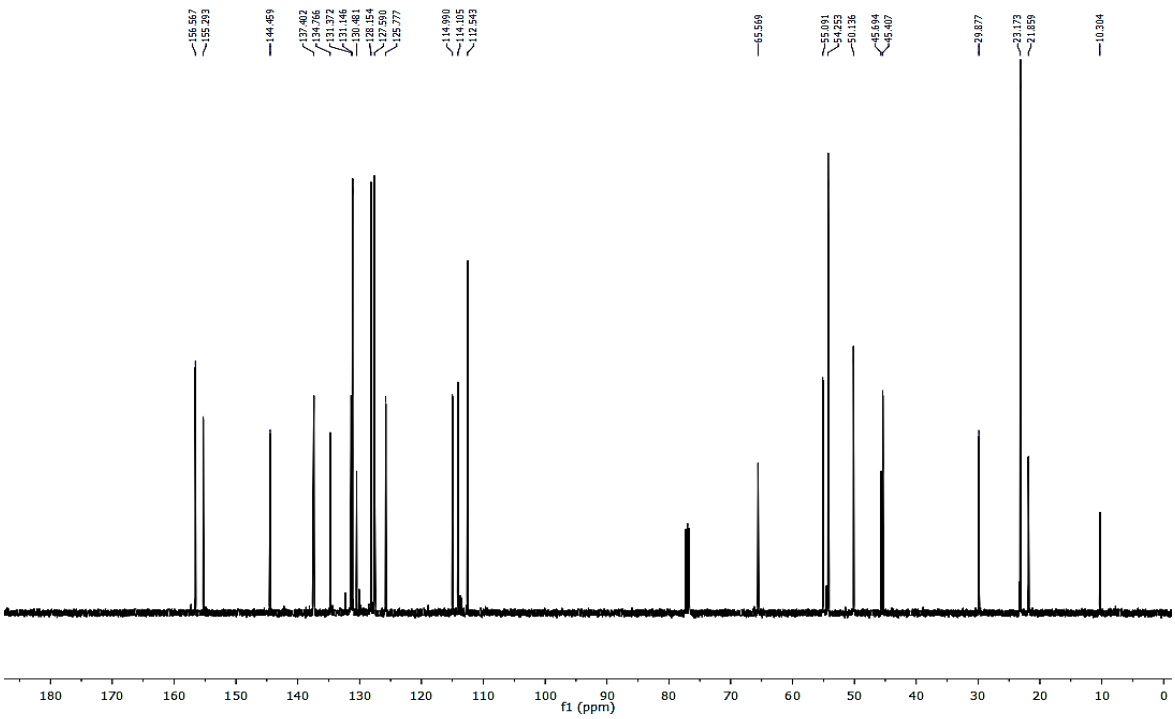




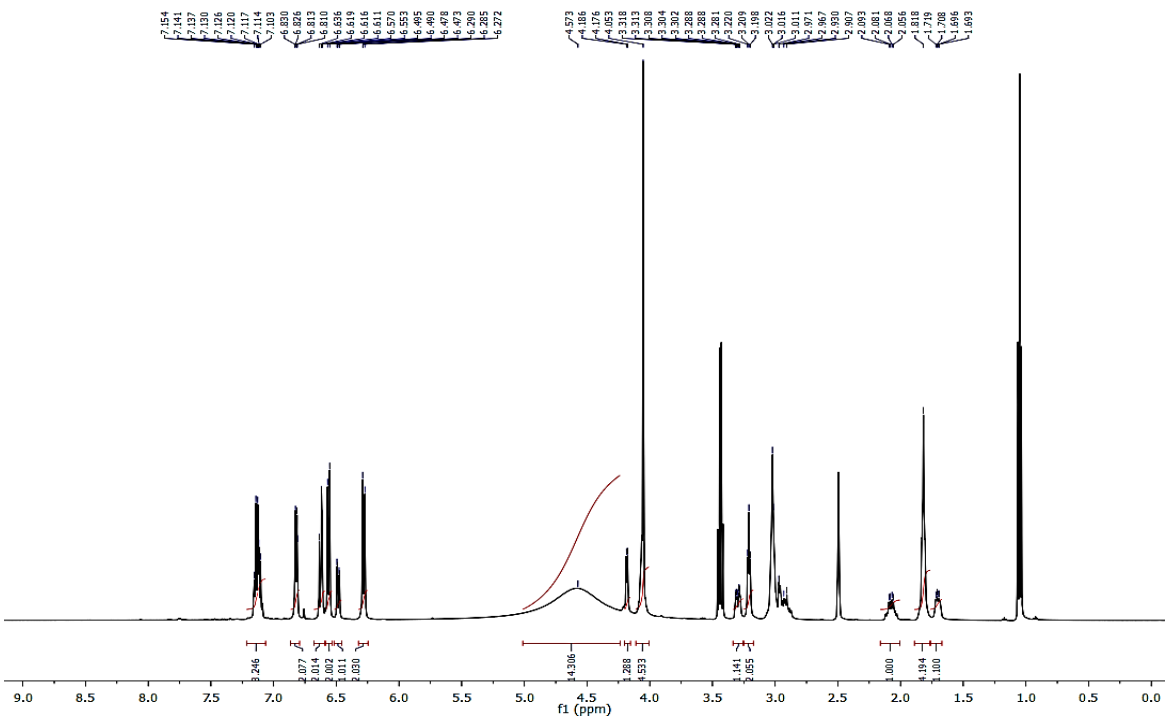
cis-(5*R*,6*S*)-**16**

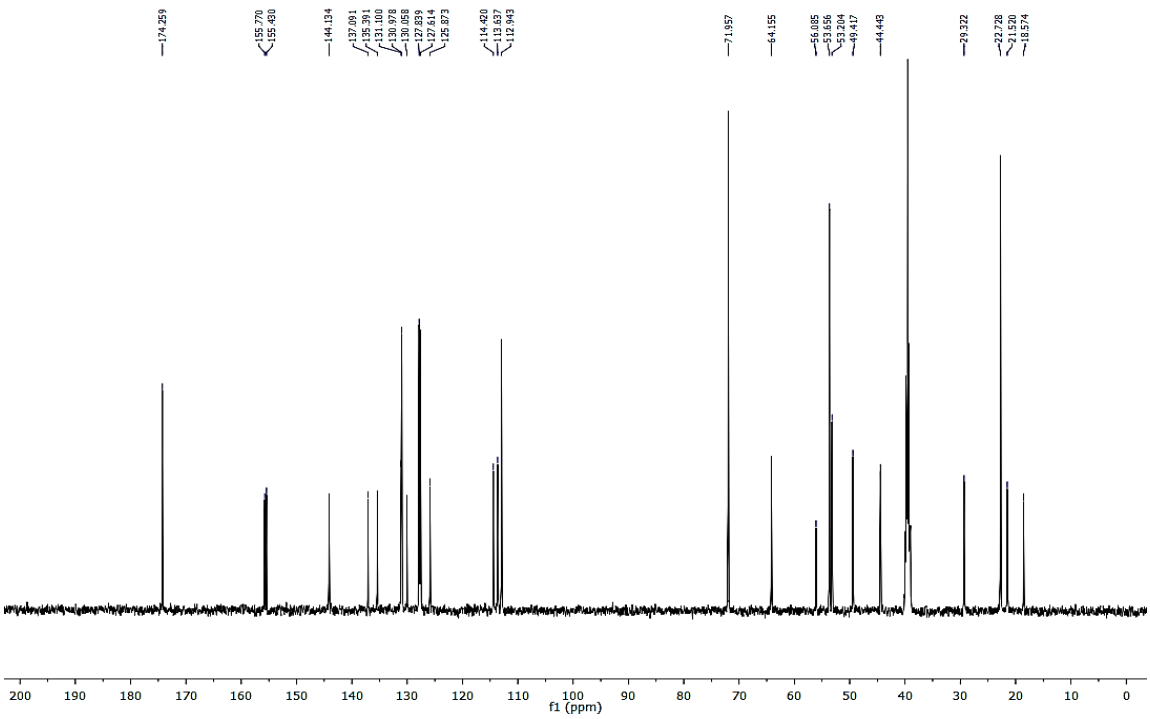






cis-(5*R*,6*S*)-**1**



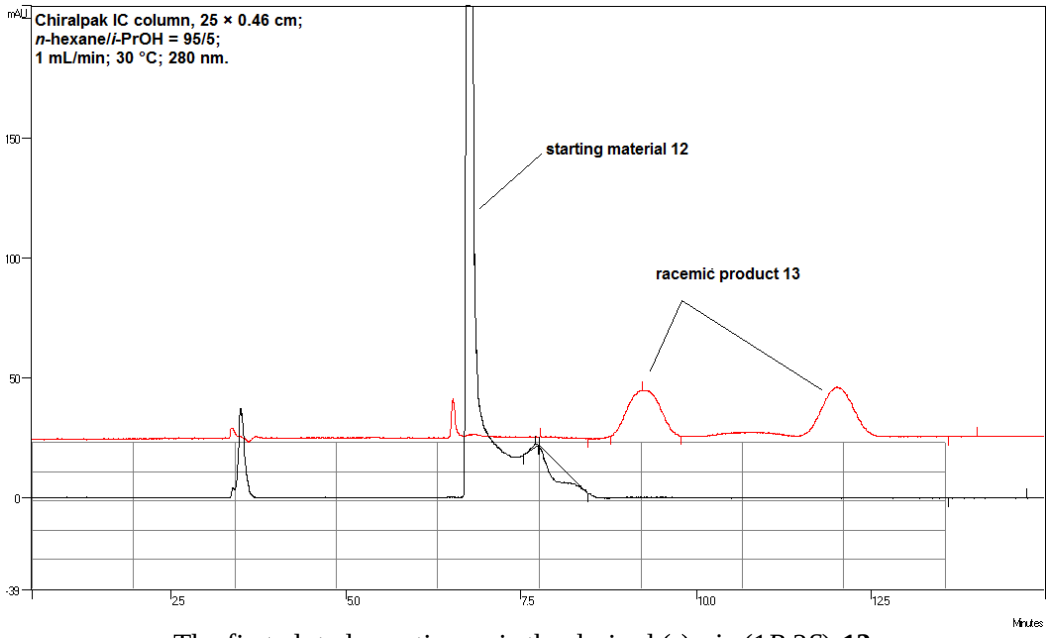


3. Copies of HPLC chromatograms.

3.1. HPLC chromatograms for conversion of 12 to 13 and 13 to 15.

3.1.1. A chiral HPLC method for the analysis of the hydrogenation of 12 to 13.

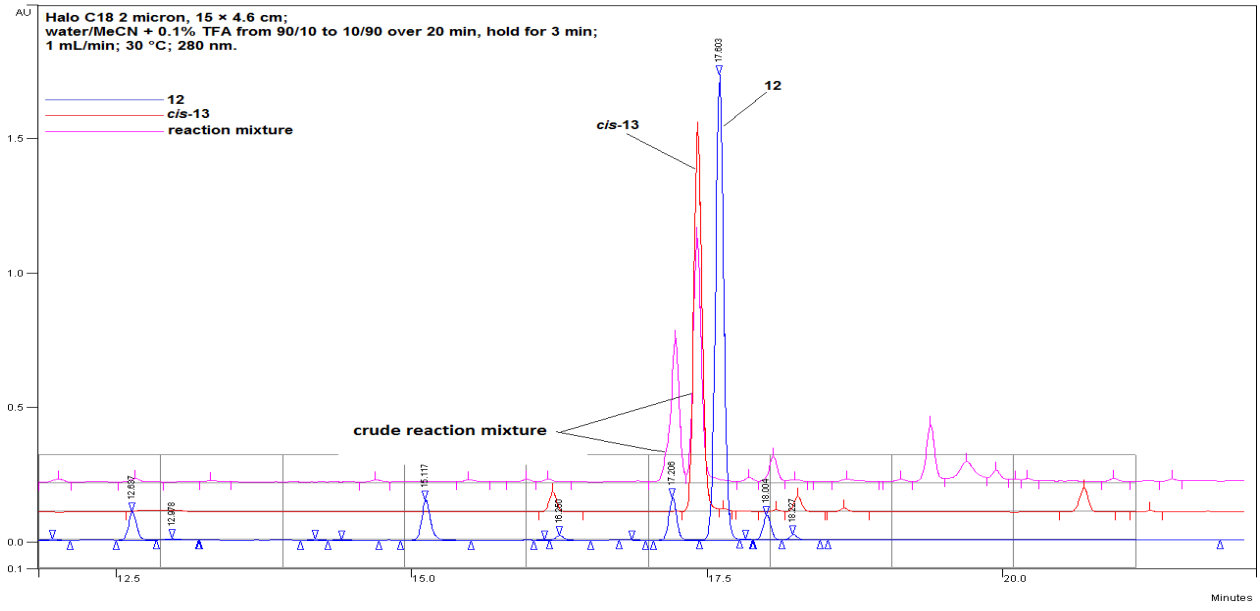
Chiralpak IC column, 25 × 0.46 cm, *n*-hexane/*i*-PrOH = 95/5, 1 mL/min, 30 °C, 280 nm.



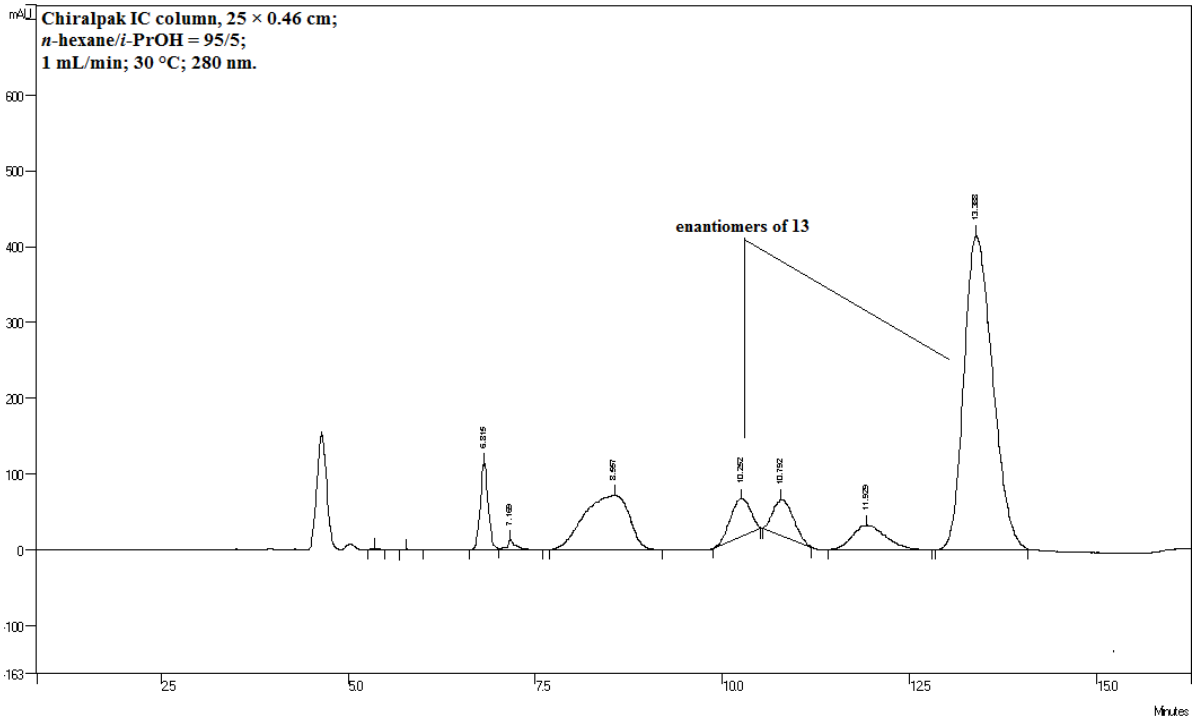
The first eluted enantiomer is the desired (-)-*cis*-(1*R*,2*S*)-**13**.

3.1.2. A reverse phase LC method for the analysis of the hydrogenation of 12 to 13.

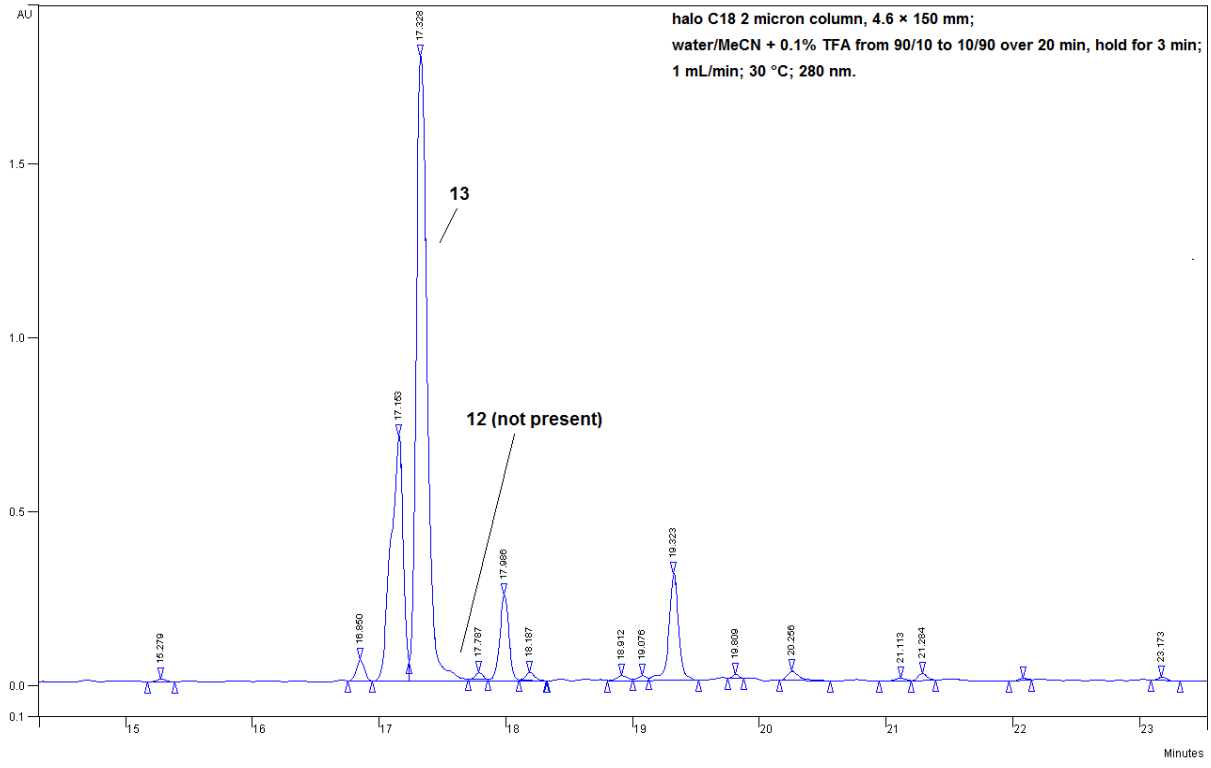
Column: halo C18 2 micron, 15 × 4.6 cm; **Eluent**: water/MeCN + 0.1% TFA from 90/10 to 10/90 over 20 min, hold for 3 min; **Flow:** 1 mL/min; **temperature**: 30 °C; **detection** at 280 nm



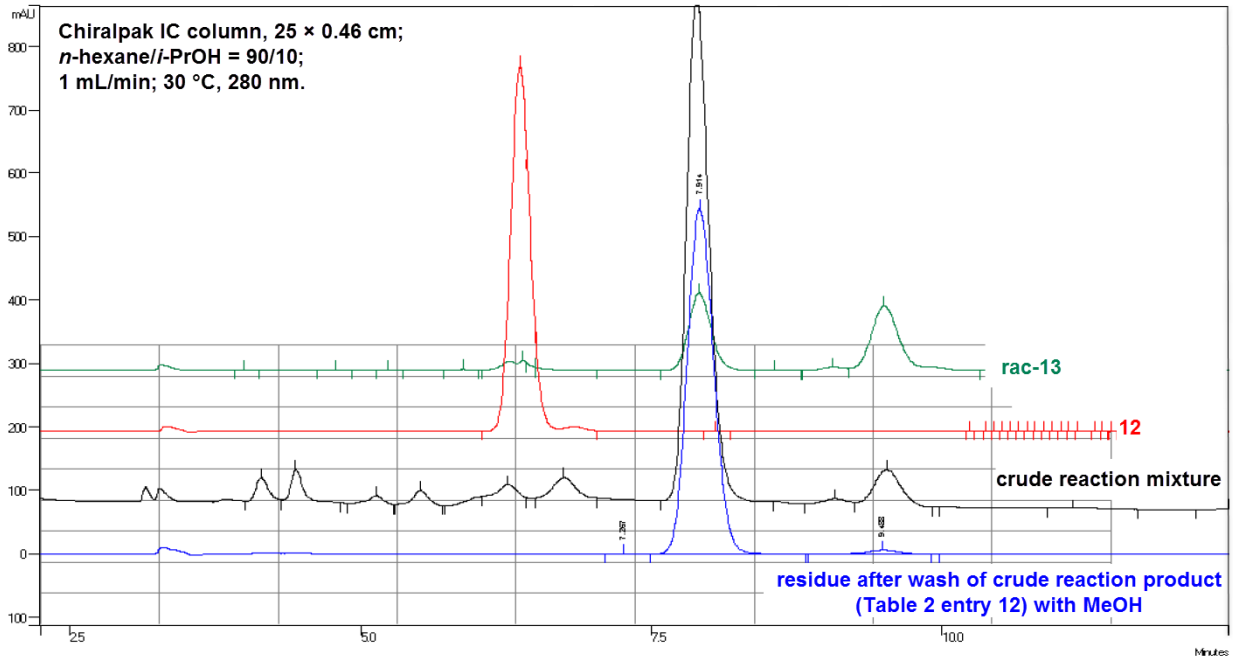
3.1.3. Hydrogenation of 12 to 13; reaction Table 2, entry 8; crude mixture (chiral HPLC method).



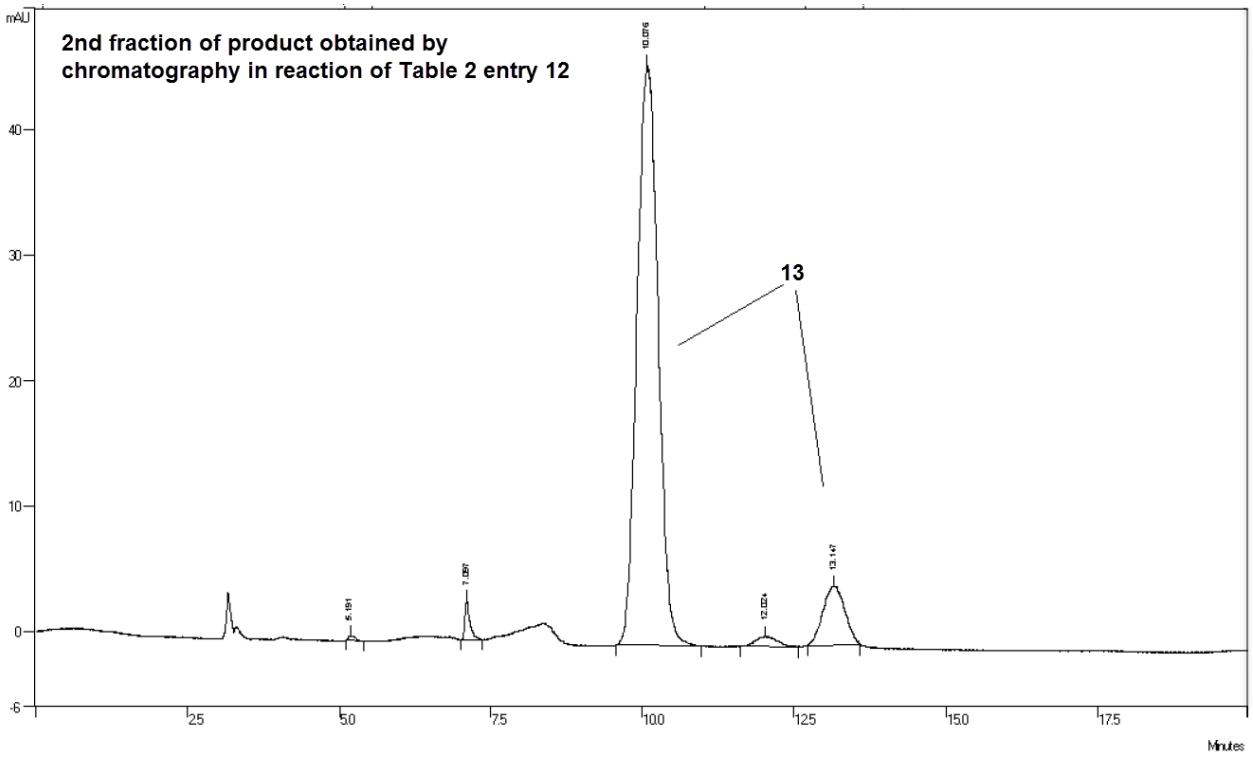
3.1.4. Hydrogenation of 12 to 13; reaction Table 2, entry 8; crude mixture (reverse phase HPLC method).



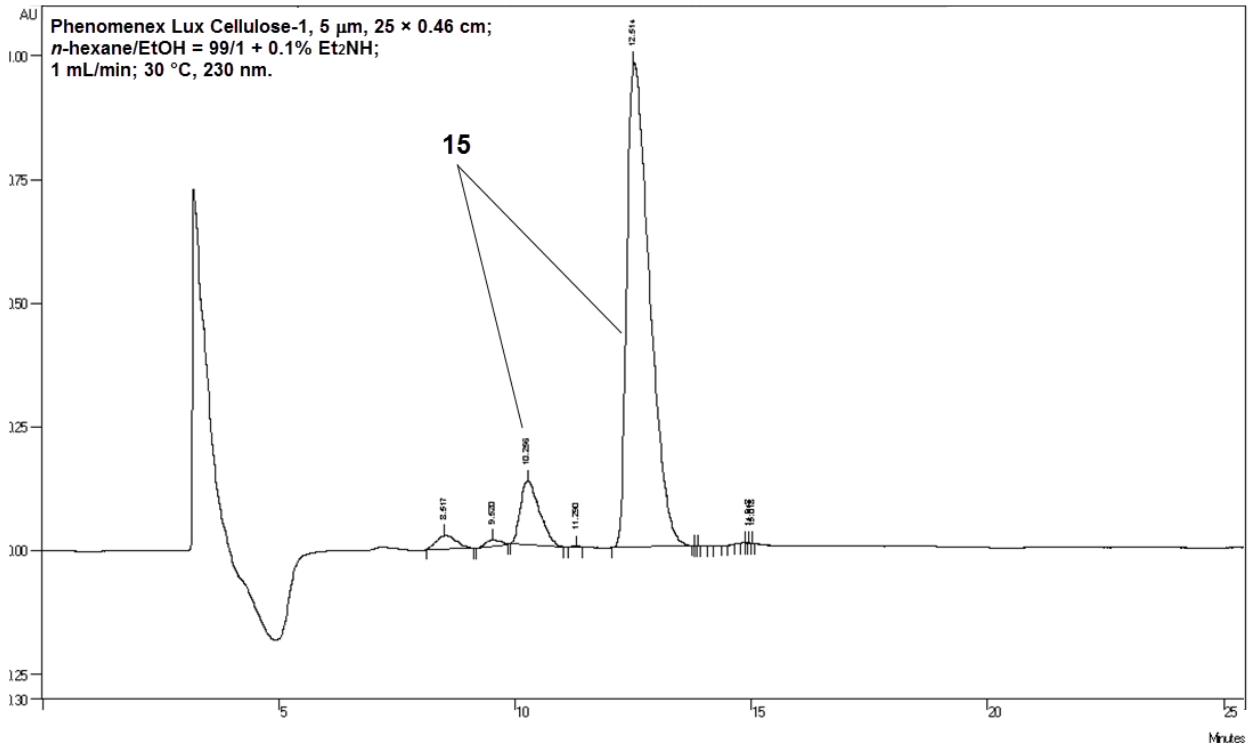
3.1.5. Hydrogenation of 12 to 13; reaction Table 2, entry 12; crude mixture and isolated product by MeOH wash (chiral HPLC method).



3.1.6. Hydrogenation of 12 to 13; reaction Table 2, entry 12; isolated product by chromatography (chiral HPLC method).



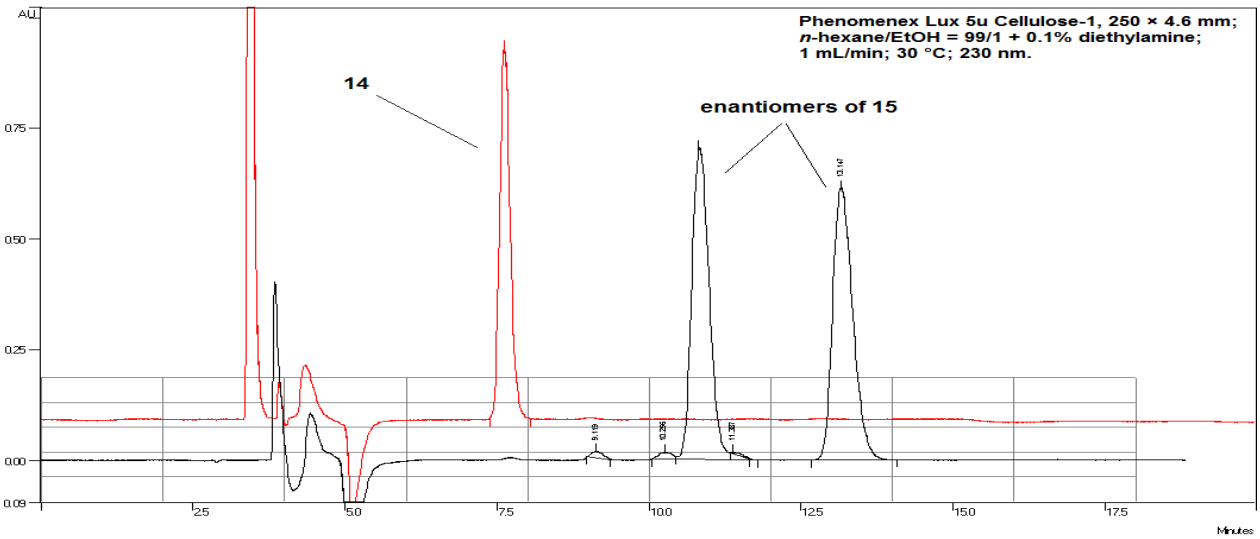
3.1.7. Alkylation of 13 to 15 (chiral HPLC method).



3.2. HPLC chromatograms for conversion of 14 to 15 and 15 to 1.

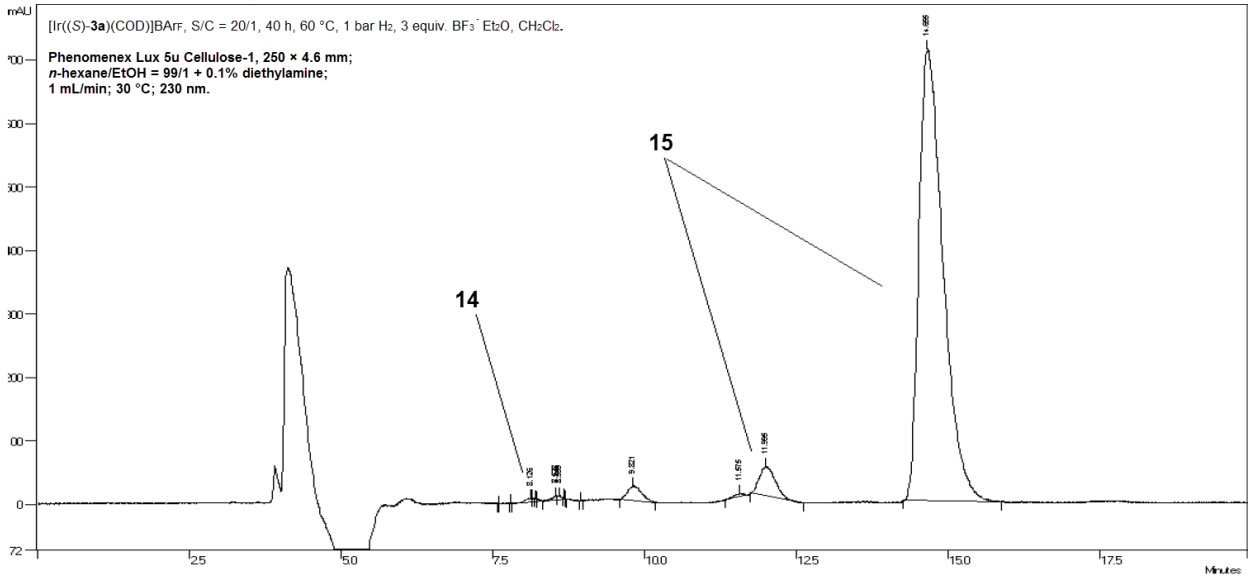
3.2.1. HPLC method for the analysis of the hydrogenation of 14 to 15.

Column: Phenomenex Lux 5u Cellulose-1, 250 × 4.6 mm; **Eluent:** *n*-hexane/EtOH = 99/1 + 0.1% diethylamine; **Flow:** 1 mL/min; **temperature**: 30 °C; **detection** at 230 nm.

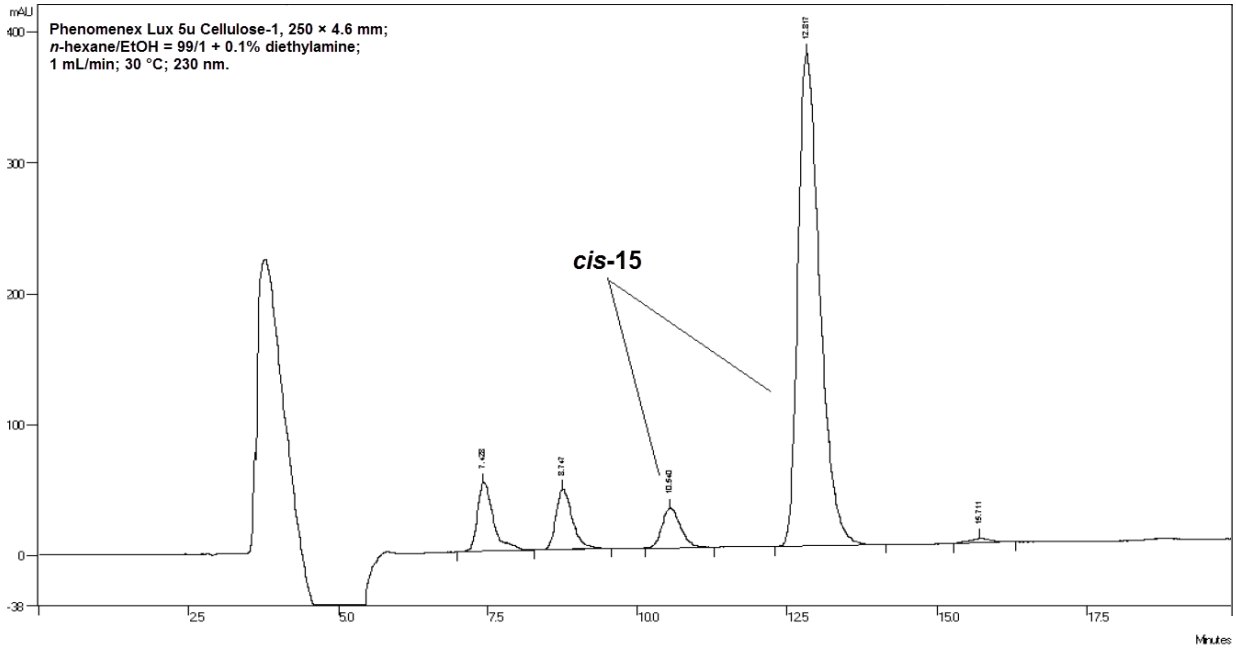


The target compound (-)-**15** corresponds to the second eluted enantiomer.

3.2.2. Hydrogenation of 14 to 15; reaction Table 4, entry 12; crude mixture.

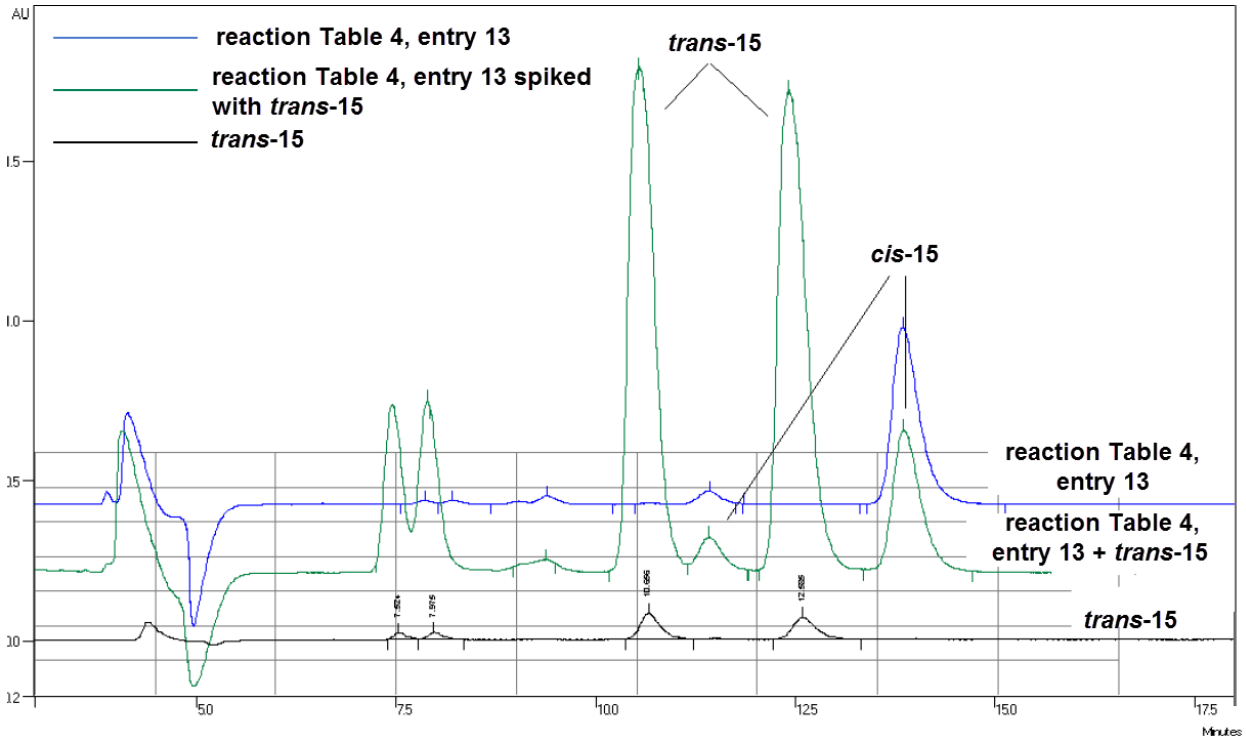


3.2.3. Hydrogenation of 14 to 15 on a ¾ gram scale; reaction Table 4, entry 14 after extractive workup (CH_2Cl_2/ 2M NaOH).



3.2.4. Determination of *trans*-15 in the reaction mixture in hydrogenation of 14 to 15.

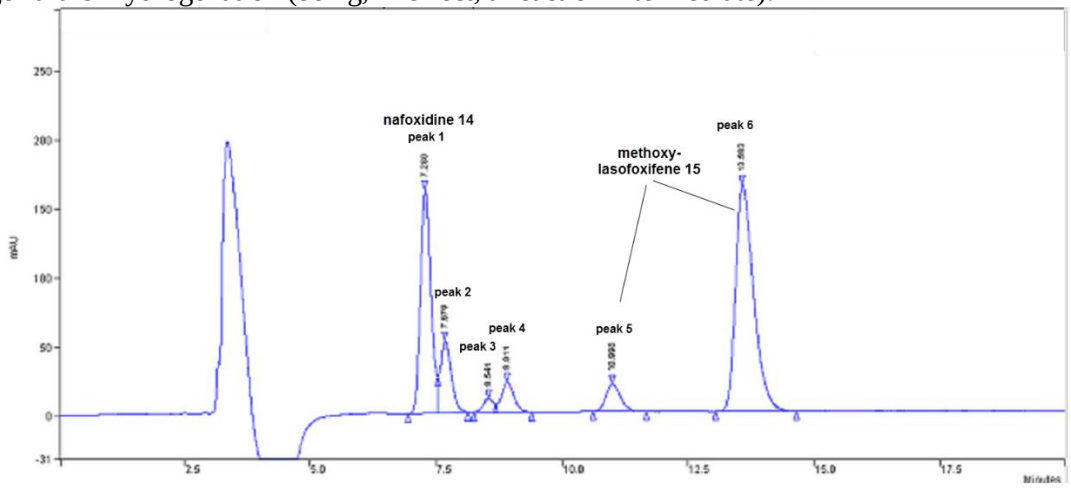
An authentic sample of *trans*-1**5** was prepared according to Lednicer[32a] and Lustig *et al*.[32b] and co-injected with the crude reaction mixture of reaction Table 4, entry 13. This confirmed the assignment of *trans*-**15** peaks. Authentic sample of *trans*-**15** contained ~20% of impurities which elute before *trans*-**15**.



The *trans*-**15** was prepared according to **ref. 32** of the manuscript: (a) Lednicer, D. *Compounds and process for preparing the same*. *U.S. Pat. Appl.* US1976/3947520 A, March 30, 1976; *Chem. Abstr*. **1976**, *85*, 32692. (b) Lustig, P.; Hejtmankova, L. *Method for asymmetric preparation of lasofoxifene*. *PCT Int. Appl.* WO 2008/145075 A2, December 4, 2008; *Chem. Abstr*. **2008**, *150*, 19991.

3.2.5. LC/MS analysis of reaction mixture after hydrogenation of 14 to 15.

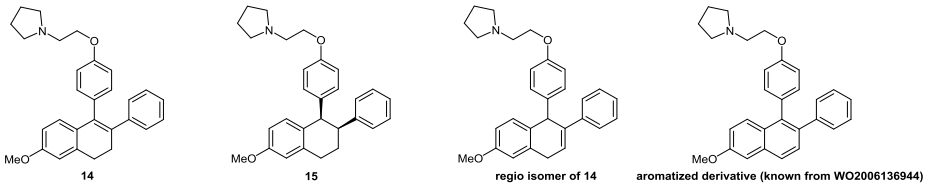
LC/MS analysis of the crude mixture obtained in hydrogenation of **14** with [Ir((*S*)-**3a**)(COD)]BAr_F (reaction conditions: S/C = 30, C = 0.11 M, 60 °C, 5 bar, 16 h, 6.5 equiv. $BF_3{\cdot}Et_2O$) has allowed us to recognize the molecular ions of methoxy-lasofoxifene **15**, nafoxidine **14** and of the two main by-products (see picture below). The mass of peak **1** corresponds to nafoxidine **14**, the mass of peaks **5** and **6** corresponds to methoxy-lasofoxifene **15**. The mass of peaks **3** and **4** correspond to the mass of aromatized product, which can be expected based on literature data.[10c] At this stage it is difficult to conclude why two peaks correspond to the molecule mass of the aromatized product. The mass of peak **2** (eluted soon after nafoxidine **14**) is the same as the mass of nafoxidine **14**, which could suggest an isomerization of the C=C bond. It is impossible to know, at the current stage, if the side-product formed by C=C bond isomerization is racemic or if it can undergo further hydrogenation (being, in effect, a reaction intermediate).



Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		28.7872	7.280	0.000	23371176	BV	13.5	
2		9.5662	7.679	0.000	7766383	VB	16.6	
3		1.6904	8.541	0.000	1372335	BV	13.8	
4		4.5113	8.911	0.000	3662577	VB	15.8	
5		4.9181	10.998	0.000	3992792	BB	18.6	
6		50.5268	13.583	0.000	41020612	BB	22.7	
	Totals:	100.0000		0.000	81185875			

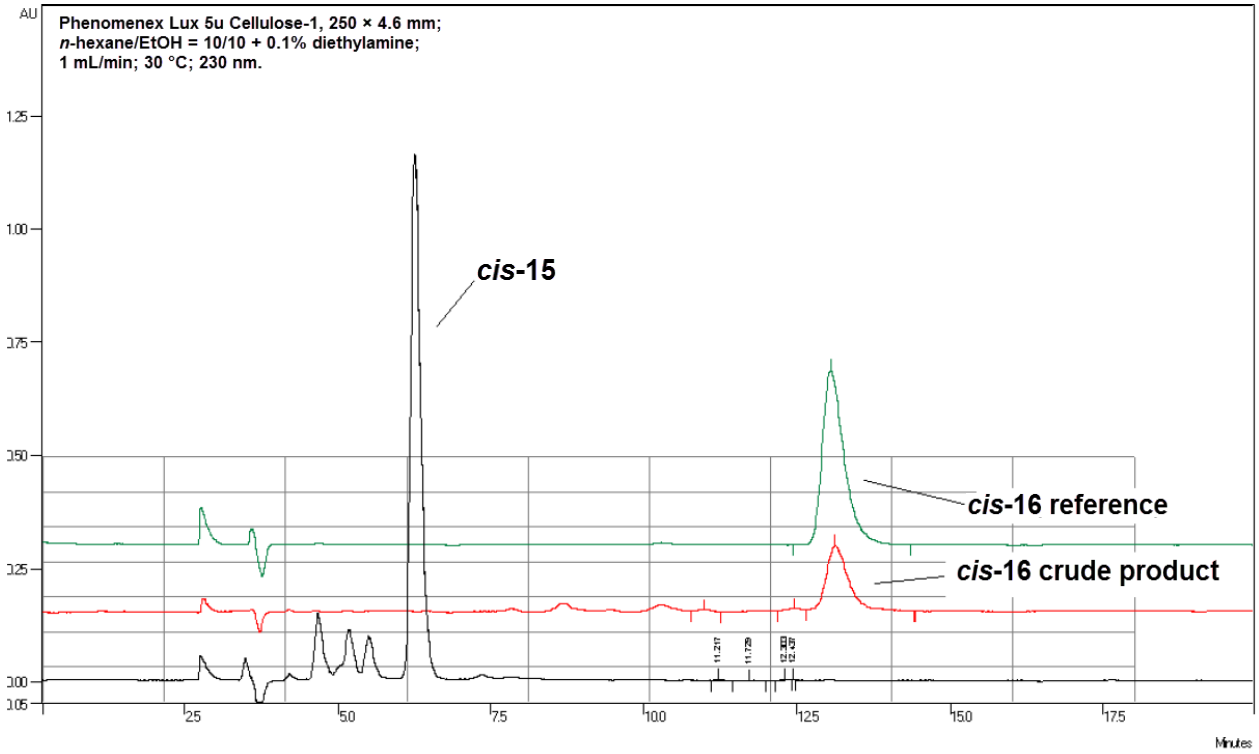
LCMS results
APCI+, Capillary voltage 80, Rf loading 80, mass 80-1000

Peak	[M+H]+	Mass
1	426.4	425.4
2	426.6	425.6
3	424.4	423.4
4	424.5	423.5
5	428.5	427.5
6	428.4	427.4



Aromatized side product of the hydrogenation is reported in the **ref**. **10c** of the manuscript: Lehner, R. S.; Taber, G. P. *Process for preparation of cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-2-methoxy-5,6,7,8-tetrahydronaphthalene hydrochloride via stereoselective hydrogenation of nafoxidine hydrochloride*. *PCT Int. Appl*. WO/2006/136944 A1, December 28, 2006; *Chem. Abstr*. **2006**, *146*, 100553.

3.2.6. Demethylation of 15 to 16.



3.2.7. Formation of 1 from 16.