Supporting Information for

Practical isolation of the (1*R*,2*R*)-enantiomer from a racemic *cis/trans* mixture of 2-methyl-1-cyclohexanamine

Markus Furegati, Sandro Nocito*

Synthesis & Technologies Group, Global Discovery Chemistry, Novartis Institutes for Biomedical Research, Klybeckstrasse 141, 4057 Basel, Switzerland

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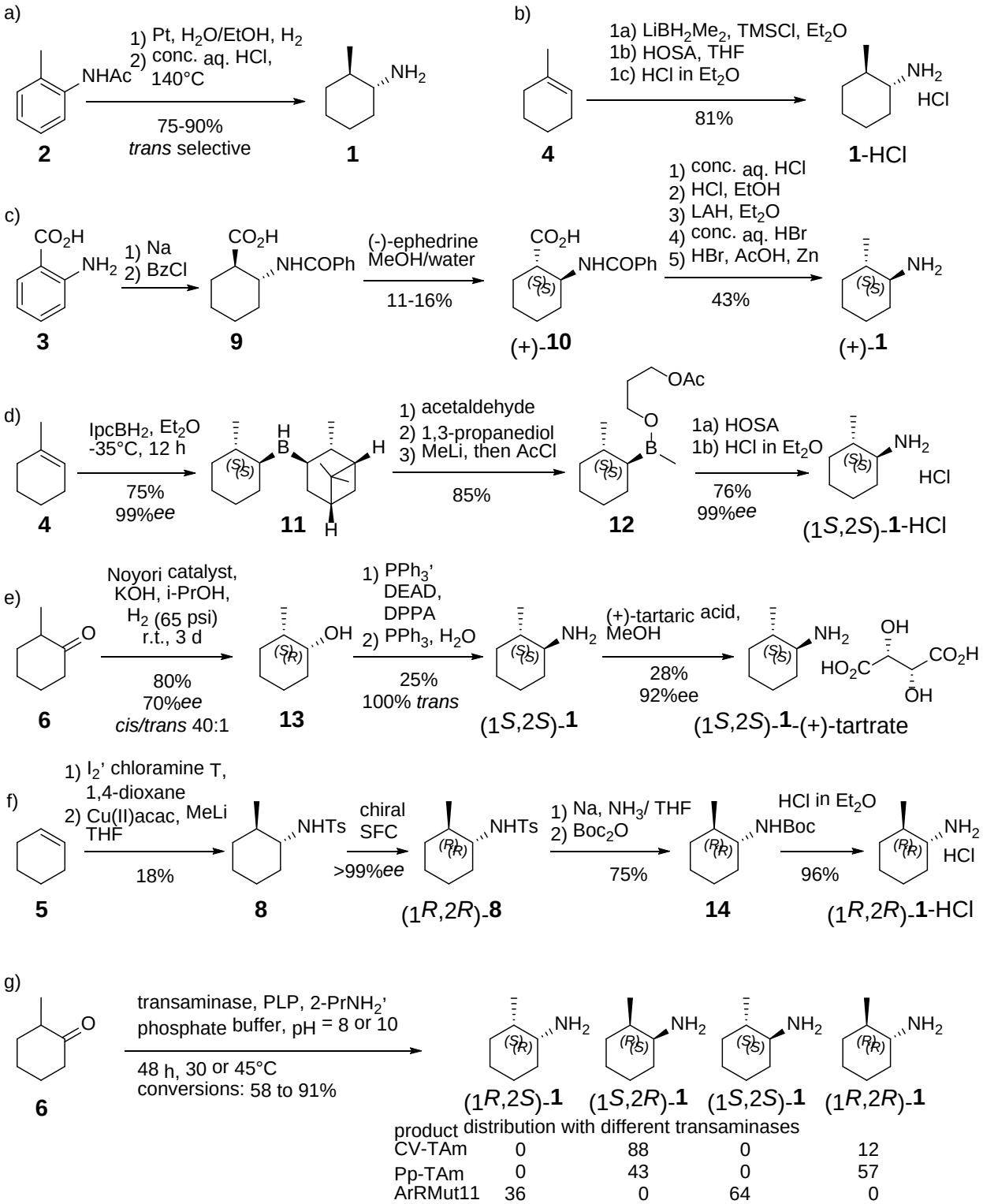
Seven syntheses to racemic or enantiopure *trans*-2-methylcyclohexan-1-amine (**1**) and salts thereof are described in the literature and discussed in the following section. Hydrogenation of 2-acetotoluidine with colloidal platinum in neutral aquous solution (3 atm. of hydrogen) followed by acidic hydrolysis yielded in 75-90% **1** (Scheme S1a).[1] Hydroboration of 1-methyl-cyclohexene (**4**) with $NaBH_4$ and BF_3-etherate in diglyme followed by amination with hydroxylamine-*O*-sulfonic acid (HOSA) resulted in 45% of pure racemic **1**;[2] an improvement in yield (81%) was obtained by the same authors using $LiBH_2Me_2$/TMSCl followed by HOSA and precipitation of the product **1** as its HCl salt (Scheme S1b).[3] Resolution of the *N*-benzoylcarboxylic acid **9** derived from anthranilic acid **3** via diastereomeric salt formation using (–)-ephedrine resulted in (+)-**10** in 11-16% yield. 5 more steps were necessary to deprotect the amine and convert the carboxylic acid into a methyl group (Scheme S1c).[4] The assignment of the absolute stereochemistry was tentatively and based on the algebraic sign of the optical rotation in Et_2O compared to an optical rotation measured earlier in EtOH.[5] The first enantioselective synthesis was accomplished two decades later again by *Brown et al*. Hydroboration of **4** with monoisopinocamphenylborane ($IpcBH_2$) resulted in enantiopure dialkylborane **11**. Several additional transformations were necessary because only the borinic ester **12** reacted with HOSA in the known manner to form (1*S*,2*S*)-**1** in 48% overall yield with an *ee* of >99% (Scheme S1d).[6, 7] Another method applying enantioselective transfer hydrogenation of 2-methylcyclohexanone (**6**) using *Noyori*'s ruthenium catalyst was described (Scheme S1e). The alcohol **13** was obtained as a 40:1 *cis*/*trans* mixture with an *ee* of 70%. The hydroxy group was replaced by an azide under inversion of the stereocenter in a *Mitsunobu* reaction followed by *Staudinger* reaction. The *ee* was increased to 92% by crystallization with (+)-tartaric acid from methanol, the overall yield was 5.6%; one factor that led to this low yield was attributed to the volatility of the free amine

and the lack of a chromophore that made isolation difficult.[8] The enantioselective hydrogen transfer reductive amination of **6** is another option to directly obtain **1** in a single step.[9] However, a 1:2 *cis/trans* mixture was obtained with a *ee* of the *trans* isomer of 64%. The next synthesis started with the aziridination of cyclohexene (**5**) with iodine and chloramine T followed by the stereoselective ring opening using Cu(II) and MeLi to yield the racemic *trans*-*N*-tosyl-2-methylcyclohexan-1-amine (**8**). The resolution into the enantiomers was accomplished by chromatography using supercritical carbon dioxide (SFC) on a chiral stationary phase (*Chiralpak AD*). Deprotection of the tosyl group with sodium in liquid ammonia and re-protection allowed the isolation of *trans*-*N*-boc-2-methylcyclohexan-1-amine (**14**). The HCl salt of (1*R*,2*R*)-**1** was obtained by filtration after deprotection from HCl/Et_2O solution in 6.5% overall yield (Scheme S1f).[10] The most recent advance is the succesfull application of various transaminases for the synthesis of **1** with excellent *ee* >99% (Scheme S1g). All four isomers were obtained, however, *cis*- and *trans*-isomers always as mixtures.[11]

Scheme S1. Literature procedures for the synthesis of racemic or enantiopure *trans*-2-methyl-1-cyclohexanamine.



HOSA: hydroxylamine-*O*-sulfonic acid; DEAD: diethyl azodicarboxylate; DPPA: diphenylphosphoryl azide; SFC: supercritical fluid chromatography; PLP: pyridoxalphosphate

1. Skita, A., Über die Stereochemie der Hexahydro-toluidine. *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1923,** *56*, 1014-1023.
2. Rathke, M. W.; Inoue, N.; Varma, K. R.; Brown, H. C., Stereospecific synthesis of alicyclic and bicyclic amines via hydroboration. *J. Am. Chem. Soc.* **1966,** *88*, 2870-1.
3. Brown, H. C.; Kim, K. W.; Srebnik, M.; Singaram, B., Organoboranes for synthesis. 7. An improved general synthesis of primary amines from alkenes via hydroboration-organoborane chemistry. *Tetrahedron* **1987,** *43*, 4071-8.
4. Nohira, H.; Ehara, K.; Miyashita, A., Resolution and rotations of trans-2-aminocyclohexanecarboxylic acids and derivatives. *Bull. Chem. Soc. Jap.* **1970,** *43*, 2230-3.
5. Mousseron, M.; Winternitz, F.; Granger, R.; Claret, J.; Trinquier, M.; Combes, G., Alicyclic series. XV. Ketones. *Bull. Soc. Chim. Fr.* **1947**, 598-605.
6. Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V., Organoboranes. 46. New procedures for the homologation of boronic esters. A critical examination of the available procedures to achieve convenient homologation of boronic esters. *J. Org. Chem.* **1986,** *51*, 3150-5.
7. Brown, H. C.; Kim, K. W.; Cole, T. E.; Singaram, B., Chiral synthesis via organoboranes. 8. Synthetic utility of boronic esters of essentially 100% optical purity. Synthesis of primary amines of very high enantiomeric purities. *J. Am. Chem. Soc.* **1986,** *108*, 6761-4.
8. Marino, S. T.; Stachurska-Buczek, D.; Huggins, D. A.; Krywult, B. M.; Sheehan, C. S.; Nguyen, T.; Choi, N.; Parsons, J. G.; Griffiths, P. G.; James, I. W.; Bray, A. M.; White, J. M.; Boyce, R. S., Synthesis of chiral building blocks for use in drug discovery. *Molecules* **2004,** *9*, 405-426.
9. Kadyrov, R.; Riermeier, T. H., Highly enantioselective hydrogen-transfer reductive amination: catalytic asymmetric synthesis of primary amines. *Angew. Chem., Int. Ed.* **2003,** *42*, 5472-5474.
10. Hachtel, S.; Wohlfart, P.; Weston, J.; Mueller, M.; Defossa, E.; Mertsch, K.; Weng, J.-H.; Binnie, R. A.; Abdul-Latif, F.; Bock, W. J.; Walser, A. Preparation of benzimidazolecarboxylic acid amino acid amides as apelin receptor modulators. WO2014044738A1, 2014.
11. Richter, N.; Simon, R. C.; Lechner, H.; Kroutil, W.; Ward, J. M.; Hailes, H. C., ω-Transaminases for the amination of functionalised cyclic ketones. *Org. Biomol. Chem.* **2015,** *13*, 8843-8851.

	GC peak area of (S)-mosheramides (pA*s)								
at Rt=	43.99 min cis-1	44.15 min cis-2	44.70 min trans-1	45.03 min trans-2	yield (%)	cis : trans	ee (cis)	ee (trans)	S
SM	216.5	227.4	758.0	752.3		23 : 77	-2	0	
A3	442.7	493.6	1697.7	1594.5	53.0	22 : 78	-5	3	0.04
A4	549.2	595.5	2143.7	2062.0	62.0	21 : 79	-4	2	0.03
A5	330.8	371.4	1006.0	1177.6	32.0	24 : 76	-6	-8	0.07
A14	430.8	448.9	1829.2	1833.8	49.0	19 : 81	-2	0	0.00
C2	37.1	38.7	122.7	119.8	61.0	24 : 76	-2	1	0.02
C3	62.6	63.3	151.4	158.8	49.0	29 : 71	-1	-2	0.03
C4	101.0	101.7	247.3	256.8	36.0	29 : 71	0	-2	0.02
C13	56.5	57.2	155.0	158.4	52.0	27 : 73	-1	-1	0.01
D2	36.0	37.0	100.8	88.1	60.0	28 : 72	-1	7	0.10
D5	11.2	11.9	45.6	36.1	23.0	22 : 78	-3	12	0.07
D13	50.0	49.3	168.7	164.7	50.0	23 : 77	1	1	0.02
E6	274.8	710.9	1455.4	1568.4	39.0	25 : 75	-44	-4	0.04
E7	275.0	533.2	1319.1	1406.1	54.0	23 : 77	-32	-3	0.04
E8	589.4	722.6	2569.0	2619.5	64.0	20 : 80	-10	-1	0.02
E10	624.2	734.1	2399.8	2552.5	62.0	22 : 78	-8	-3	0.05
E11	317.2	437.9	1257.5	1243.3	44.0	23 : 77	-16	1	0.01
E12	684.6	805.6	2325.8	2399.6	50.0	24 : 76	-8	-2	0.02
E15	476.4	527.4	1506.0	1663.4	54.0	24 : 76	-5	-5	0.07
G3	302.9	305.6	1426.1	741.2	18.0	22 : 78	0	32	0.15
G4	212.0	213.2	883.2	721.4	32.0	21 : 79	0	10	0.08
G6	364.1	367.1	1579.1	1150.2	47.0	21 : 79	0	16	0.19
G14	370.9	378.6	1430.0	1435.1	38.0	21 : 79	-1	0	0.00
H3	224.6	243.4	869.1	906.9	27.0	21 : 79	-4	-2	0.01
H4	137.9	145.9	529.7	549.7	26.0	21 : 79	-3	-2	0.01
H6	546.5	574.7	2173.8	2248.9	48.0	20 : 80	-3	-2	0.02
I6	281.3	300.1	1270.7	923.4	35.0	21 : 79	-3	16	0.14
I10	591.6	645.4	2846.1	1747.5	51.0	21 : 79	-4	24	0.32
K9	259.8	287.0	1169.3	1127.6	20.0	19 : 81	-5	2	0.01
K10	658.9	728.7	3046.8	2637.2	39.0	20 : 80	-5	7	0.07
K12	337.6	367.2	1470.1	1373.2	36.0	20 : 80	-4	3	0.03
L2	52.4	43.7	1645.6	976.6	22.0	4 : 96	9	26	0.15
N8	163.3	154.5	409.0	633.6	42.0	23 : 77	3	-22	0.24
N14	122.4	110.3	254.6	496.1	48.0	24 : 76	5	-32	0.40
P11	1.3	1.4	8.6	5.6	36.0	16 : 84	-5	21	0.20
Q9	186.1	146.4	705.7	985.8	19.0	16 : 84	12	-17	0.08
R14	242.6	302.8	406.3	588.8	18.0	35 : 65	-11	-18	0.09
S7	657.6	643.4	1376.9	1464.4	35.0	31 : 69	1	-3	0.03
S8	315.7	346.7	587.1	698.4	37.0	34 : 66	-5	-9	0.08
S12	130.9	147.6	279.0	322.6	46.0	32 : 68	-6	-7	0.09
T2	72.1	82.9	267.0	173.6	40.0	26 : 74	-7	21	0.22
T3	259.8	299.1	987.3	627.0	23.0	26 : 74	-7	22	0.13
T4	326.0	370.5	1272.2	829.1	35.0	25 : 75	-6	21	0.19
T13	14.2	14.9	42.2	28.0	36.0	29 : 71	-2	20	0.19
T14	284.4	330.1	1154.5	731.0	45.0	25 : 75	-7	22	0.26

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Additional Info  : Peak(s) manually integrated
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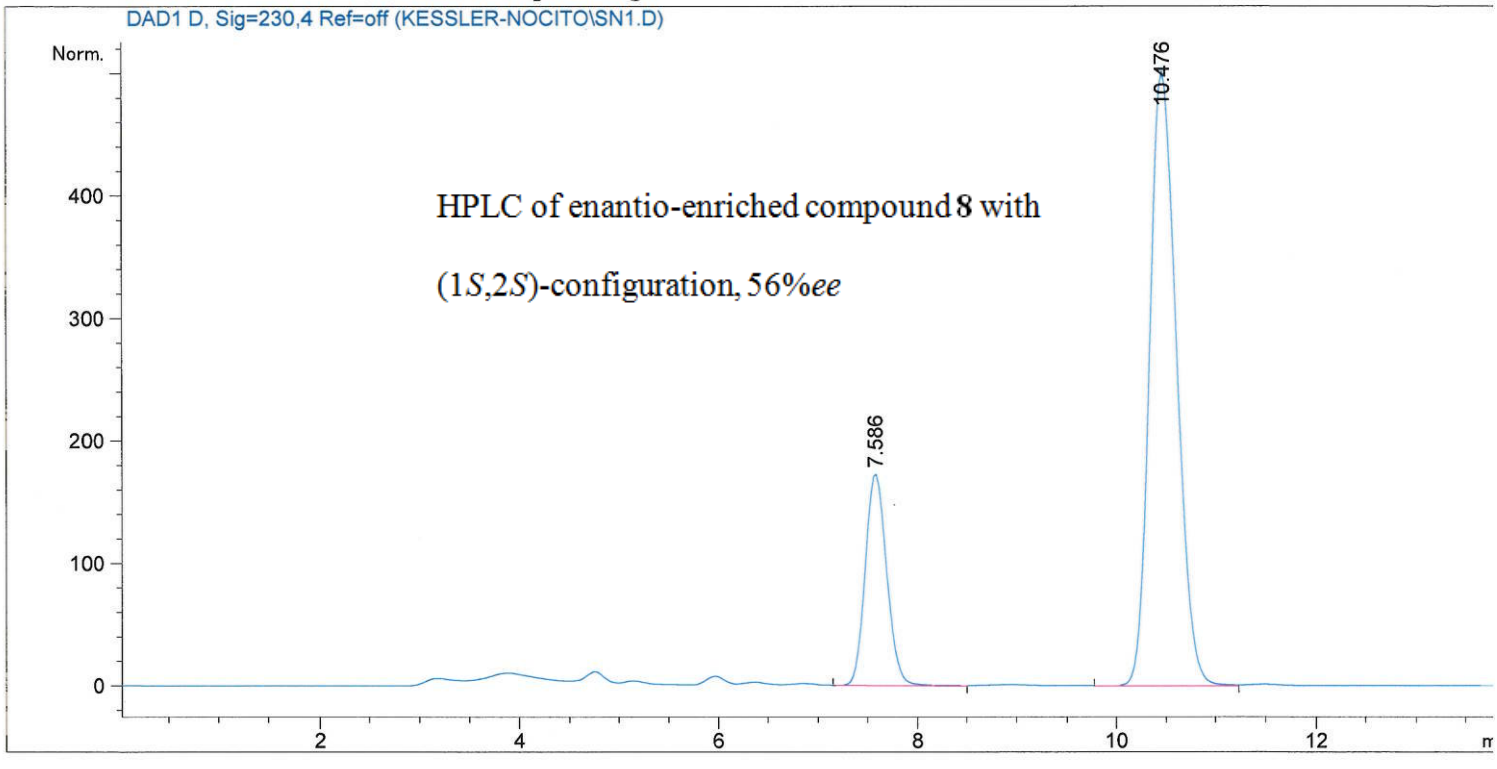


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Do not use Multiplier & Dilution Factor with ISTDs


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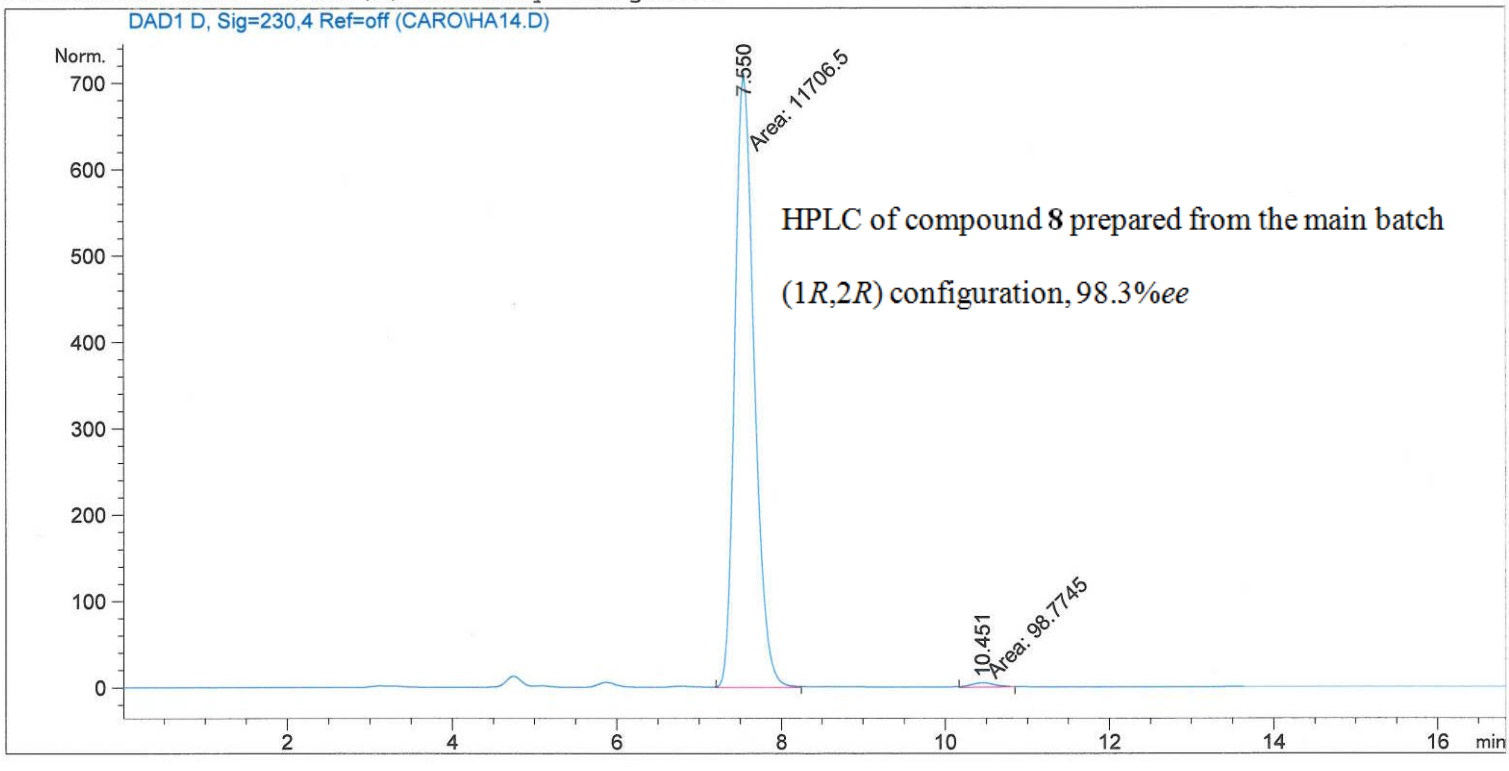

HPLC of compound **8** prepared from the main batch

(1*R*,2*R*) configuration, 98.3%*ee*

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                  derivatized with mosher`s chloride
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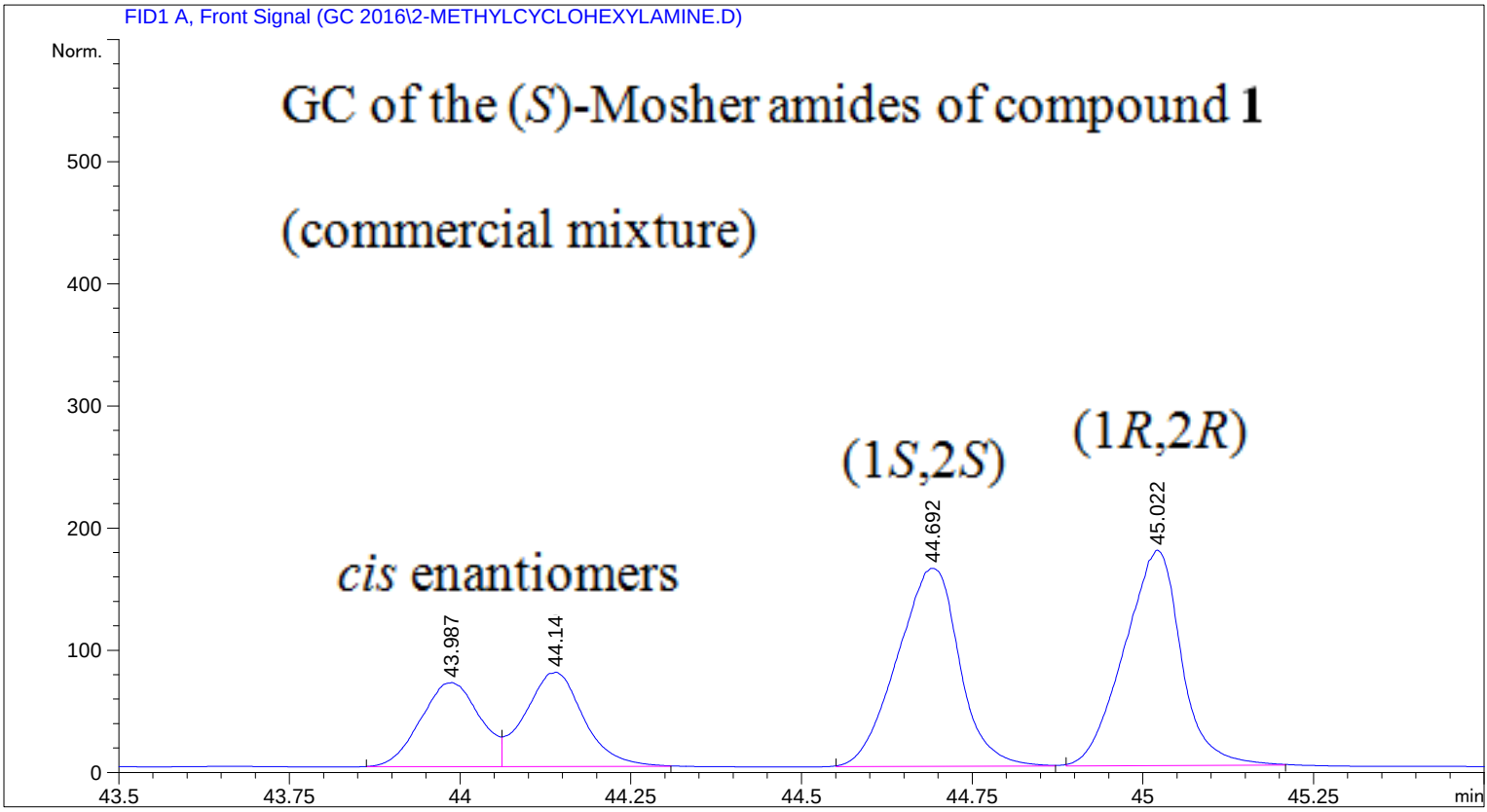


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Use Multiplier & Dilution Factor with ISTDs

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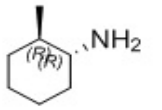

as (S)-(+)-1,1`-binaphtyl-2,2`-phosphoric acid salt

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.05 (dd, J = 18.5, 8.5 Hz, 4H), 7.88 (s, 3H), 7.51 – 7.39 (m, 4H), 7.31 (ddd, J = 8.1, 6.6, 1.3 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 2.45 (td, J = 10.8, 3.8 Hz, 1H), 1.83 (dt, J = 13.3, 3.4 Hz, 1H), 1.57 (dq, J = 12.7, 2.9 Hz, 1H), 1.52 – 1.43 (m, 2H), 1.32 – 1.22 (m, 1H), 1.21 – 1.05 (m, 2H), 1.00 (dddd, J = 15.6, 12.3, 8.2, 3.6 Hz, 1H), 0.86 – 0.82 (m, 1H), 0.84 (d, J = 6.5 Hz, 3H).