

SUPPORTING INFORMATION

Corey-Itsuno reduction of ketones: A development of safe and inexpensive process for synthesis of some API intermediates

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1. Preparation of (*R*)-3-(1-naphthalenyloxy)-1-phenyl-propanol (9)

To the concentrated solution of **8** in toluene, solution of α -naphthol (5.58 kg, 38.75 mol) in DMF (12 L) followed by solution of sodium hydroxide (1.8 kg, 45 mol) in water (1.8 L) was added. Reaction mass was heated and maintained at 90 to 95°C for 2 h and reaction was monitored by HPLC for **8** (0.62%). Reaction mass was cooled to 27 0°C, water (30 L), toluene (24 L) was added, and stir for 30 min. Toluene layer was separated and washed with solution of sodium hydroxide (0.6 kg) in water (12 L) followed with water (12 L). The toluene layer was concentrate up to 12 L volume under vacuum at below 55°C, n-heptane (42 L) was added to the reaction mass, cooled to 5 to 10°C and stirred for 2 h at same temperature. Reaction mass was filtered, washed the cake with n-heptane (12 L) at 5 to 10°C and dried under vacuum at 30 to 45°C for 10 h to obtained solid powder of **9** (6.7 kg) with 67.2% yield from **8** and 97.96% HPLC purity. ^1H NMR (400 MHz, CDCl_3): δ 8.25-6.79 (m, 12H, Ar-H), 5.11 (t, 1H, HO-CH), 4.32-4.18 (dd, 2H, CH_2), 2.44 (d, 1H, -OH), 2.37-2.29 (m, 2H, CH_2), ^{13}C NMR (100 MHz, CDCl_3): δ 154.36, 144.06, 134.42, 134.42, 128.48, 127.57, 127.46, 126.32, 125.81, 125.75, 125.51, 125.18, 121.77, 120.31, 104.74, 71.79, 65.22, 38.34.

2. Preparation of dapoxetine hydrochloride (1)

A methanesulfonyl chloride (4 kg, 34.91 mol) was slowly added to the stirred solution of **9** (6.68 kg, 24 mol) and triethylamine (4.87 kg, 448.17 mol) in methyl-*t*-butyl-ether (33.4

L) at 5 to 10°C and stirred for 6 h at same temperature. A dimethylamine gas (10 kg, 222 mol) purged through the reaction mass at 5 to 10°C and stirred for 18 h at 25 to 30°C. Water (33.4 L) was added and stirred for 30 min, methyl-*t*-butyl-ether thus obtained was separated and washed with water (13.36 L). To the methyl-*t*-butyl-ether layer, solution of hydrochloric acid (6.68 L), DMF (6.68 L) in water (26.72 L) was added and stirred for 30 min. An aqueous layer was separated, pH of aqueous layer adjusted to 10.8 using aqueous solution of sodium hydroxide, extracted in toluene (33.4 L), and washed with water (13.36 L). The toluene layer was concentrated to obtained 6.7 L volume, 2-butanone (33.4 L) was added, hydrogen chloride gas was purged in to the reaction mass till pH 1.5, stirred for 1 h at 10 to 15°C, filtered the product, washed with 2-butanone (13.36 L) and dried under vacuum to obtained **1** (4.8 kg) with chiral purity 99.92% ee, HPLC purity 99.91% and 58.9% yield from **8**. $[\alpha]^{25}_D = +135.5^\circ$ (c = 2.18 in methanol), the obtained SOR is in confirmity with literature.¹ Enantiomeric excess was determined by chiral HPLC on a chiralcel OJ-H (4.6 X 250 mm, 5 μ) column eluting with n-hexane: ethanol (95:5) and 2 mL of diethyl amine at 1.0 mL min⁻¹ flow rate and $\lambda=290$ nm. Retention time was 10.28 and 14.16 min for (*S*) and (*R*) enantiomer respectively. ¹H NMR (400 MHz, CDCl₃): δ 11.13 (brs, 1H, HCl), 8.07-6.73 (m, 12H, Ar), 4.70 (m, 1H, N-CH), 3.67 (m, 2H, O-CH₂), 2.84-2.5 (m, 2H), 2.74 (s, 3H, CH₂), 2.49 (s, 3H), ¹³C NMR (100 MHz, DMSO): δ 153.52, 133.88, 132.58, 129.77, 129.49, 128.9, 127.28, 126.39, 126.0, 125.14, 124.67, 121.68, 120.05, 104.84, 67.05, 64.36, 41.32, 40.12, 39.91, 39.70, 39.50, 39.29, 39.08, 38.87, 29.51, ESI-MS: 306.4 [M + H]⁺.

3. Preparation of 3-naphthoxy propiophenone (**13**)

To a solution of 3-naphthalen-1-yloxy)-1-phenyl-propan-1-ol (40 gm, 0.143 mol) in dichloromethane (400 ml), pyridinium chlorochromate (73.3 gm, 0.34 mol) was added at 25 to 30°C. Reaction mass was stirred for 12 h and quenched in water (400 ml), washed with water (200 ml) three times and concentrated to get residue. The residue was crystallized from isopropyl alcohol (4000 ml) and dried to get 30 gm white solid of **13**. (75% yield). ¹H NMR (400 MHz, CDCl₃): δ 8.15-6.89 (m, 12H, Ar), 4.63-4.60 (t, 2H, CH₂) 3.63-3.60 (t, 2H, CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 197.74, 154.3, 136.78, 134.4, 133.33, 128.64, 128.14, 127.37, 126.29, 125.81, 125.5, 125.06, 121.89, 120.4, 104.8, 63.62, 38.08. ESI-MS: 277 [M + H]⁺, 298.9 [M + Na]⁺. 3-Naphthalen-1-yloxy)-1-phenyl-propan-1-ol was prepared as per reported procedure.²

4. Preparation of (*R*)-3-naphthalen-1-yloxy)-1-phenyl-propan-1-ol (9)

Similar procedure of **8** was performed for asymmetric reduction of **13** (1 gm, 3.62 mmol) using DME (4 ml) sodium borohydride (0.123 gm, 3.26 mmol), solution of **10** (0.614 gm, 3.325 mmol) in dichloromethane (1.5 ml), and **11** (0.05 gm, 0.2 mmol). After concentration of toluene layer, n-heptane (7 ml) was added, filtered and dried to obtain solid of **9** (0.8 gm) with 80% yield and 97.76% ee. $[\alpha]^{25}_D = -61.3^\circ$ (c = 1 in methanol), the sign of obtained SOR is in confirmity with literature.³ Enantiomeric excess was determined by chiral HPLC on an OD-H column (Chiralcel) using n-hexane/EtOH/*N,N*-diethylamine (90/10/0.1) as eluent, a flow rate of 1.0 mL min⁻¹ and the detection was performed at 210 nm. Retention time was 9.6 and 11 min for (*R*) and (*S*) enantiomer respectively. ¹H NMR (400 MHz, CDCl₃) & ¹³C NMR (100 MHz, CDCl₃) matched with the example-1 spectra.

5. Preparation of (*R*)-3-(1-hydroxy-ethyl)-phenol (15)

Similar procedure of **8** was performed for asymmetric reduction of **14** (1 gm, 7.34 mmol) using DME (4 ml), sodium borohydride (0.247 gm, 6.53 mmol), solution of **10** (1.23 gm, 6.66 mmol) in dichloromethane (1.5 ml), and **11** (0.1 gm, 0.4 mmol). After concentration of toluene layer, oily residue of **15** (0.9 gm) was obtained with 95% yield and 85.98% ee. Enantiomeric excess was determined by chiral HPLC on an OJ-H column (Chiralcel) using n-hexane/EtOH/ *N,N*-diethylamine (96/4/0.1) as eluent, a flow rate of 2.0 mL min⁻¹ and the detection was performed at 216 nm. Retention time was 21.0 and 24.6 min for (*S*) and (*R*) enantiomer respectively. The absolute configuration of the compound was determined by converting **8** in to the rivastigmine as per reported process.⁴ ¹H NMR (400 MHz, DMSO): δ 9.2 (s, 1H, Ar-OH), 7.1-6.6 (m, 4H, Ar-H) 5.0 (d, 1H, -OH), 4.6 (q, 1H, CH-OH), 1.27 (d, 3H, CH₃). ¹³C NMR (100 MHz, DMSO): δ 157.2, 149.0, 128.9, 116, 113.4, 112.2, 68, 25.9. ESI-MS: 136.9 negative ion mode. The obtained ¹H NMR is in confirmity with literature.⁴

6. Preparation of (*S*)-3-chloro-1-thiophen-2-yl-propan-1-ol (17)

Similar procedure of **8** was performed for asymmetric reduction of **16** (50 gm, 0.286 mol) using DME (200 ml) sodium borohydride (9.63 gm, 0.254 mol), solution of **10** (48.1 gm, 0.26 mol) in dichloromethane (75 ml), and antipode of **11** (3.98 gm, 0.015 mol). After concentration of toluene layer, oily residue of **17** was obtained (45 gm) with 90% yield and 91.28% ee. $[\alpha]^{25}_D = -10.7^\circ$ (c = 2.06 in *i*-PrOH). ¹H NMR (400 MHz, CDCl₃): δ 7.3-

7.0 (m, 3H, Ar-H), 5.24-5.2 (m, 1H, -CH-OH), 3.8-3.56 (dd, 2H, CH₂), 2.38-2.16 (dd, 2H, CH₂), 2.15 (d, 1H, -OH). ¹³C NMR (100 MHz, CDCl₃): δ 147.2, 126.6, 124.7, 123.9, 66.8, 41.3, 41.2. The obtained SOR & ¹H NMR is in confirmity with literature.⁵

7. Preparation of (*R*)-1-(3,5-bis-trifluoromethyl)-phenyl)-ethanol (19)

Similar procedure of **8** was performed for asymmetric reduction of **18** (2.5 gm, 9.76 mmol) using DME (10 ml) sodium borohydride (0.33 gm, 8.6 mmol), solution of **10** (1.63 gm, 8.8 mmol) in dichloromethane (3 ml), and **11** (0.123 gm, 0.48 mmol). After concentration of toluene layer, solid residue of **19** was obtained (2.2 gm) with 88% yield and 84.98% ee. $[\alpha]^{25}_D = +24.42^\circ$ (c = 1 in acetonitrile), Enantiomeric excess was determined by chiral HPLC on an OD-H column (Daicel) using n-hexane/i-PrOH (98/2) as eluent, a flow rate of 0.5 mL min⁻¹ and the detection was performed at 220 nm. Retention time was 15 and 17.2 min for (*S*) and (*R*) enantiomer respectively. The absolute configuration of the compound was determined by comparing the sign of its specific rotation with reported in handbook of fine chemicals, Aldrich, 2009-2010, 371. ¹H NMR (400 MHz, CDCl₃): δ 7.84 (s, 2H, Ar-H), 7.78 (s, 1H, Ar-H), 5.07-5.01 (q, 1H, -CH-OH), 1.97-1.96 (d, 1H, -OH), 1.55-1.54 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 149.2, 132.2, 131.9, 131.6, 131.3, 127.4, 125.6, 125.5, 124.7, 122.0, 121.4, 121.33, 121.3, 121.26, 121.2, 119.3, 69.3, 25.3. ESI-MS: 257 negative ion mode. The obtained SOR⁶ & ¹H NMR⁷ is in confirmity with literature.

8. Preparation of (*R*)-2-bromo-1-[4-(benzyloxy)-3-nitrophenyl] ethanol (21)

Similar procedure of **8** was performed for asymmetric reduction of **20** (50 gm, 0.286 mol) using DME (200 ml) sodium borohydride (9.63 gm, 0.254 mol), solution of **10** (48.1 gm, 0.26 mol) in dichloromethane (75 ml), and **11** (3.98 gm, 0.015 mol). After concentration of toluene layer, solid residue of **21** was obtained with 11.9% ee. Incomplete conversion observed on TLC.

9. Preparation of 10, 11-dihydro-5H-dibenzo[b,f]azepin-10-ol (23)

Similar procedure of **8** was performed for asymmetric reduction of **22** (50 gm, 0.286 mol) using DME (200 ml) sodium borohydride (9.63 gm, 0.254 mol), solution of **10** (48.1 gm, 0.26 mol) in dichloromethane (75 ml), and **11** (3.98 gm, 0.015 mol). After concentration of toluene layer, solid residue of **23** was obtained with 16.72% ee. Incomplete conversion observed on TLC. Enantiomeric excess was determined by chiral HPLC on an AD-H

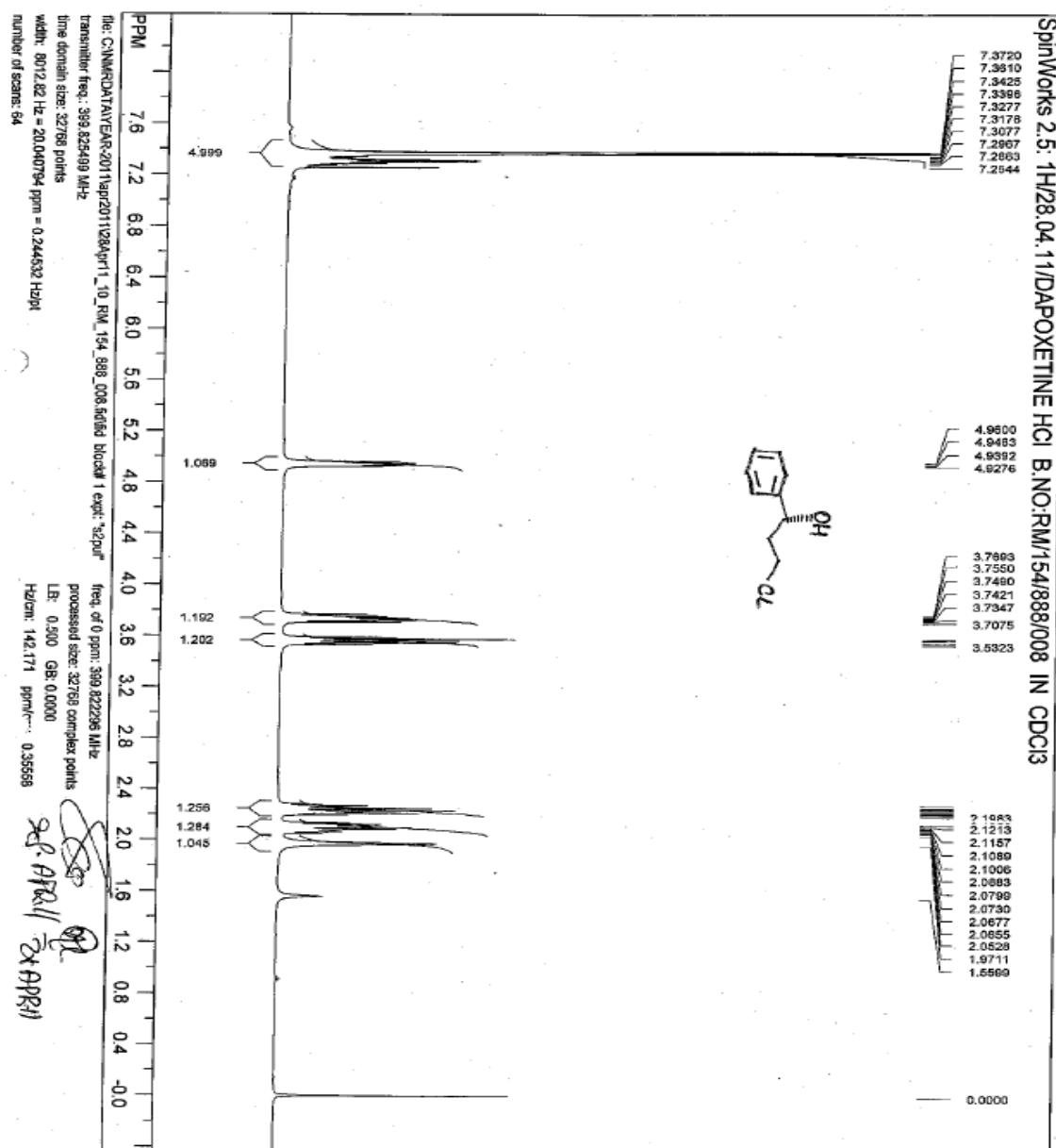
column (Chiralcel) using n-heptane/EtOH/*N,N*-diethylamine (70/30/0.1) as eluent, a flow rate of 1.5 mL min⁻¹ and the detection was performed at 285 nm.

References:

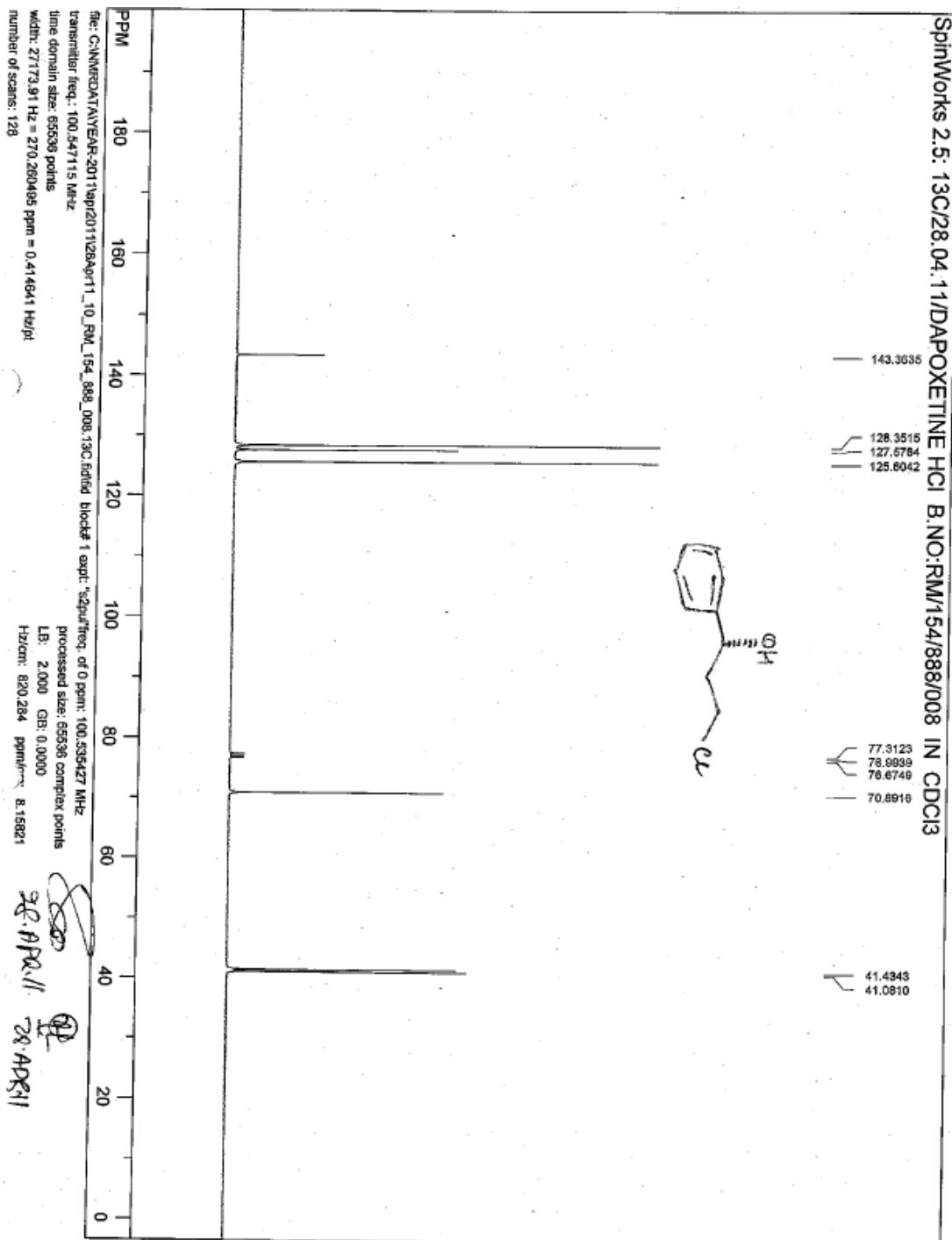
1. Merck Index, 14th edition.
2. Dhar, et al., PCT application, WO 2008/035358 A2.
3. Alt, et al., US patent, 1994/5292962.
4. Mathes, et al., US patent, 2010/0168229 A1.
5. Wheeler, W. J.; Kuo, F. *J. Label Compd. Radiopharm*, 1995, 36, 213-223.
6. *Handbook of fine chemicals*, Aldrich, 2009-2010, 371.
7. Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A.; Zhao, M. M.; Li, J.; Craig, B.; Song, Z. J.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P. G.; Reamer, R. A.; Welch, C. J.; Mathre, D. J.; Tsou, N. N; McNamara, J. M.; Reider, P. J. *J. Am. Chem. Soc.* 2003, 125, 2129-2135.

2.0 SPECTRA

2.1 HNMR of (R)-(+)-3-chloro-1-phenylpropanol (8).



2.2 CNMR of (*R*)-(+)3-chloro-1-phenylpropanol (8).

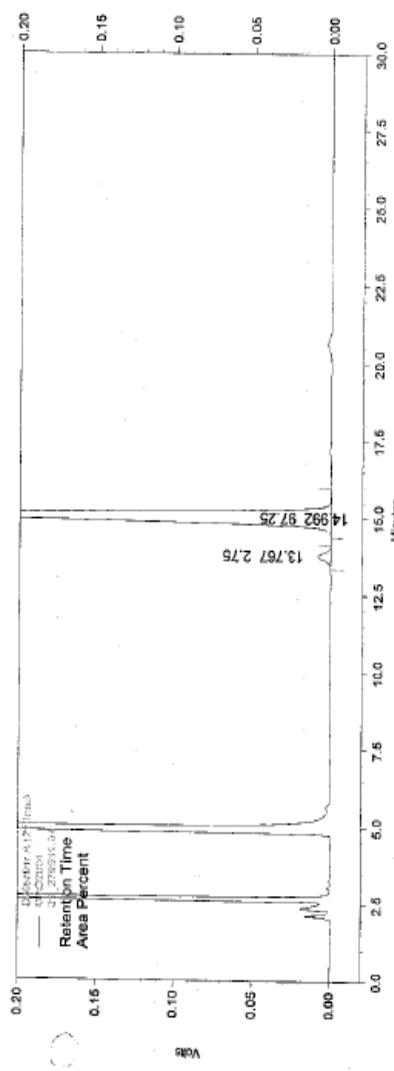


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ANALYTICAL RESEARCH DEVELOPMENT

PROJECT : DAPOXETINE HYDROCHLORIDE
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Analyst : Pranavod

DAO2001



Detector A (210nm)		Retention Time	Area	Area %
Name				
S-ISOMER	13.77	143904	2.75	
R-ISOMER	14.99	5081668	97.25	
Totals		5225572		100.00

94.5 % ee