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Stereoselective Cyclopropanation and Ring-Opening: Application to the Synthesis of Pure *(S)*-2-Methyl-3-arylpropylamines

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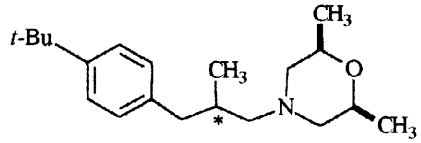
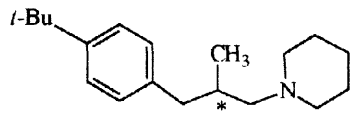
Abstract: Stereoselective catalytic and stoichiometric cyclopropanation of styrenes **3a,3b** was studied; the stoichiometric method turned out superior in the terms of enantioselectivity. The intermediate carboxymethyl cyclopropane **11a,11b**, obtained on reduction of carbethoxy derivatives **4a,4b**, were hydrogenolyzed to *(S)*-1,3-substituted-2-methylpropanes **15a,15b**. The highest conversion and regioselectivity was obtained with 3% Pd/C as the catalyst. The final steps, chlorination of alcohol **15a** into **19a**, and alkylation of cyclic *sec* amines were already demonstrated by us (ref. 2c) to afford *(S)*-(-)-2-(4-*tert*-butylphenyl)-1-*cis*-2,6-dimethylmorpholyl)propane (***S*-1a**) and *(S)*-(-)-2-(4-*tert*-butylphenyl)-1-piperidylpropane (***S*-2a**), the *(S)*-enantiomers of two systemic fungicides presently commercialized as racemates, without any lost of enantiomeric purity.

2-Methyl-3-arylpropylamines constitute an important family of fungicides but, although the *(S)*-enantiomers are biologically more active, their leading representatives **1a** and **2a** are commercialized as racemates under generic names fenpropimorph and fenpropidine.[1]



(±) 1a fenpropimorph



(±) 2a fenpropidine

Continuing our efforts towards stereocontrolled synthesis of the pure *(S)*-enantiomers of these compounds,[2] we envisaged the two approaches to the crucial intermediate ethyl 2-(4-*tert*-butylphenyl)cyclopropane carboxylate (**4a**), shown in the Scheme 1; a catalytic route **A**[3] and a stoichiometric route **B**.[4] Both methods are expected to afford disubstituted cyclopropane **4a** with correct *(S)*-configuration at C(1) with high enantiomeric purity. It is worth nothing that configuration at C(2), *i.e. cis/trans* ratio, does not influence stereocontrol of the over-all process, since on regioselective ring opening between C(1) and methylenic carbon the second chiral center was lost. Therefore *cis/trans* mixtures of cyclopropanes **4a,4b** is acceptable as intermediate provided that their configurations is *(1S)*.

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RESULTS AND DISCUSSION

Cyclopropanation: the catalytic route

The catalytic route **A** is based on the use of catalytic Cu(I) complexes with chiral nitrogen ligands **7-9**, and **10**,[5] the results are given in Table 1. The enantioselectivities with ligands **7-9** were lower than expected according to the literature results,[6] but in accord with the results of Reissig et al, obtained in cyclopropanation of silyl enol ethers.[7] The highest enantioselectivities for both the *cis* and *trans*-isomers of cyclopropane derivative **4a** (respectively 66% and 80% e.e., Table 1, line 2) were obtained with ligand **9**, which is commercially available only under the *(S,S)*-(+)-form which affords the wrong *(1R)*-configuration at C(1) for **4a**.

Scheme 1

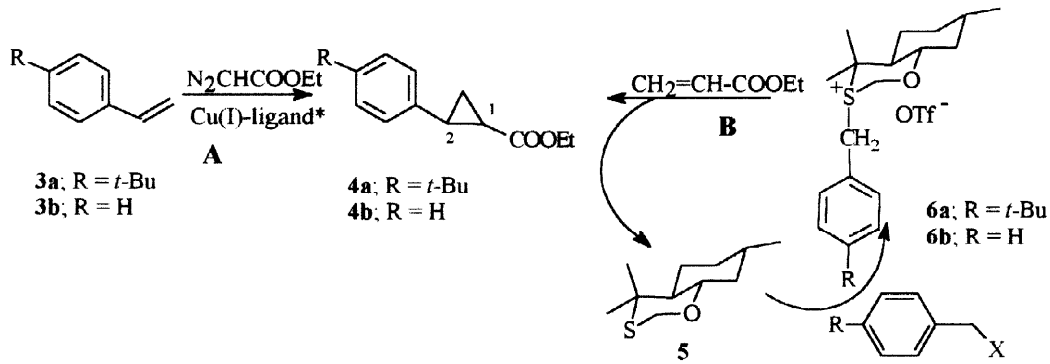
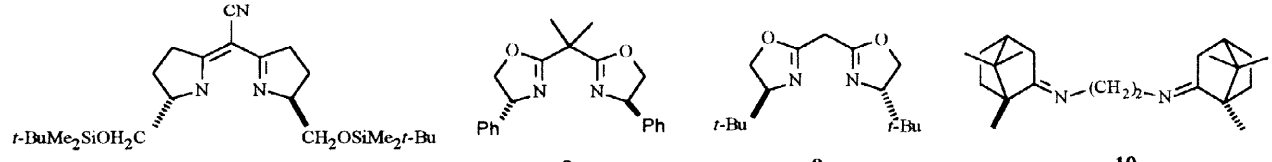


Table 1. Results of Catalytic Cyclopropanation Reaction

Substrate	Ligand	Yield %[a]	*cis/trans* %[b]	e.e. of *cis*-isomer % (abs. confg.)[c]	e.e. of *trans*-isomer % (abs. confg.)[c]
3a	**7**	76	35/65	28 *(1S,2R)*	42 *(1S,2S)*
3a	**9**	87	34/66	66 *(1R,2S)*	80 *(1R,2R)*
3a	**10**	71	40/60	30 *(1R,2S)*	32 *(1R,2R)*
3b	**7**	95	37/63	14 *(1S,2R)*	24 *(1S,2S)*
3b	**8**	90	30/70	42 *(1S,2R)*	40 *(1S,2S)*
3b	**9**	60	38/62	61 *(1R,2S)*	69 *(1R,2R)*
3b	**10**	75	40/60	30 *(1R,2S)*	32 *(1R,2R)*

[a] Isolated and not optimized yields. [b] Determined by GLC. [c] Determined by chiral chromatography.



7 8 9 10

*Cyclopropanation: the stoichiometric route **B***

The stoichiometric route **B** was based on the use of sulfur ylides[8] and, from the chiral Eliel's oxathiane, provided both cyclopropanes in high yields and with the highest enantioselectivities ever obtained (100% and 98.9% e.e.).[9] The use of weak phosphazane base asures complete elimination of triflic acid by preipitation of triflate salt. When the *(S,S,S)*-enantiomer of the oxathiane **5** was used, Table 2, the desired *(1S,2S)*-configuration was obtained for the major (96%) *trans*-isomer, and oxathiane **5** can easily be recycled. However, it must be

noted that, in this case, the minor (4%) *cis*-isomer probably has the undesired *(1R,2S)* configuration, according to the model of approach envisaged until now to rationalize the stereo-course of the reaction.[10] Therefore the *cis*-isomer must be eliminated (from the mixture) unless one can expect the enantiomeric purity of the final compounds to be ~91%.

Table 2. Stoichiometric cyclopropanation

Substrate	Yield %[a]	*cis/trans* %[b]	e.e. of *trans*-isomer % (abs. confg.)[c]
6a	50	4/96	98.9 *(1S,2S)*
6b	83	5/95	100.0 *(1S,2S)*

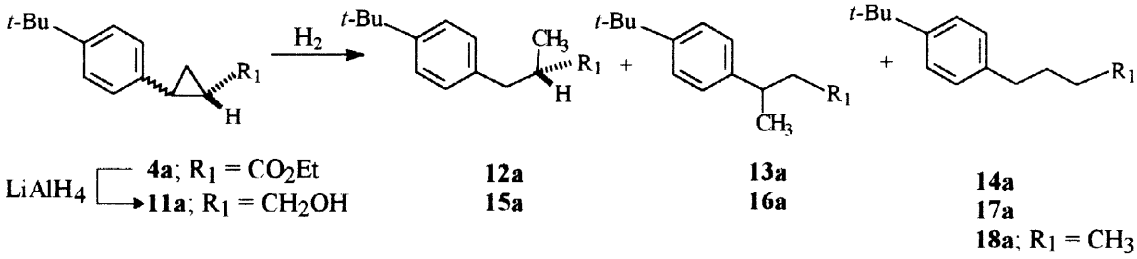
[a] Isolated and not optimized yields. [b] Determined by ^{1}H NMR (200 MHz). [c] Determined by chiral chromatography.

Opening of the cyclopropane ring

The results are collected in Table 3.

The cyclopropane derivative **4a**, submitted to Pd/C catalyzed hydrogenolysis lead, as expected from the literature results,[7a] to a 9:92 mixture of **12a** and **14a**[11] at complete conversion, Scheme 2, Table 3, line 1.

Scheme 2



In an attempt to orientate the ring opening,[12] the 96:4 *trans/cis* mixture of the cyclopropane derivative **4a** obtained by the stoichiometric route with nearly 99% enantiomeric purity was reduced to the corresponding alcohol **11a** which was then submitted to hydrogenolysis. The desired product **15a** was formed in 82% by using 3% Pd/C (Table 3, line 3).

Table 3. Results of Catalytic Hydrogenolysis of **4a** and **11a**

Substrate	*trans/cis* %	Catalyst	Conversion %	12a or 15a %	14a or 17a %	18a %
4a	96/4	10 % Pd/C	100	8	92	-
11a	96/4	10% Pd/C	100	75	17	8
11a	96/4	5 % Pt/C	5	5	-	-
11a	96/4	3% Pd/C	100	82	15	3

It is worth noting that compounds **13a** and/or **16a** were not formed. However, 3 and 8% of the alkane **18a** were obtained upon hydrogenolysis of the alcohol **11a**. Using Pd/C, the desired product is formed with 75% and 82% regioselectivity. It is worth of noting that Pt/C, Lindlar catalyst and homogeneous Wilkinson catalyst [(Ph3)PRhClO4] proved ineffective in hydrogenolysys of cyclopropanes.

Compound **15a** can be converted to the chloro derivative **19a** and subsequent with 2,6-*cis*-dimethylmorpholine or piperidine to ***S*-1a** or ***S*-2a** as we recently reported for **S-15a** obtained by chemoenzymatic route.[2c]

Conclusion

A short (6 steps) synthesis of *(S)*-fenpropimorph (***S*-1a**) and *(S)*-fenpropidine (***S*-2a**) has been achieved. The stoichiometric route **B**, using a chiral ylide derived from oxathiane **5**, proved superior in the terms of enantioselectivity to the catalytic route **A**, using Cu(I) complexes of some established and new chiral nitrogen ligands.

EXPERIMENTAL SECTION

General remarks. IR spectra were obtained for KBr pellets, on a Perkin Elmer M 137 spectrometer ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-GEM 300 or/and on an Bruker AC 200 spectrometer; shifts are given in ppm downfield from TMS as an internal standard. Optical rotations were measured with an Optical Activity AA-10 polarimeter. Melting points were determined with Electrothermal 9100 aparatus. TLC was performed on Merck's DC-alufolien with Kieselgel 60_{254}. GC analyses were performed with Hewlett Packard 5890 Series II gas chromatography instrument. HPLC was performed with a Knauer HPLC pump 64 and Knauer Variable wavelength monitor, equipped with HP 3396A integrator. Analytical chiral columns Chiralcel OJ, Chiralcel OD, Chiralcel OD-H (all 25 cm x 4.6 mm I.D., Daicel, Japan) and Chiral-AGP (10 cm x 4 mm I.D., Chromtech, Sweden) were used. The chiral ligands **7** and **8** have been purchased from Fluka, and **9** from Aldrich.

Catalytic cyclopropanation. To 4-*tert*-butylstyrene (5.5 mL, 30 mmol), Cu(I)triflate (28.0 mg, 0.1 mmol), and *(1S,9S)*-1,9-bis[*tert*-butyldimethylsilyloxy)methyl]-5-cyanosemicorrin (**7**), (10.0 mg, 0.02 mmol) [or: *(R)*-(+)-2,2'-isopropylidene-bis-(4-phenyl-2-oxazoline), (**8**), (7.0 mg, 0.02 mmol; or: *(S,S)*-(+)-2,2'-methylene-bis-(4-*tert*-butyl-2-oxazoline), (**9**), (6.8 mg, 0.02 mmol); or: *(R)*-1,3-(bis-camphoroimino)ethane, (**10**), (36.0 mg, 0.11 mmol)] were added under stirring and nitrogen atmosphere at ambient temperature. Then a solution of ethyl diazoacetate (1.25 mL, 12 mmol) in dichloroethane (12 mL) was added by means of a syringe pump over 5 h. Stirring was continued overnight, whereby the colouration of the reaction mixture changes from deep yellow to green. The excess of 4-*tert*-butylstyrene was separated by flash chromatography with light petroleum as eluent, and *cis/trans* mixture of pure **4a** was then eluted with light petroleum-ethyl acetate (90:10) affording a pale-yellow oil (1.9 g, 76%).

Stoichiometric synthesis of cyclopropanes 4a, 4b. The *(S,S,S)*-oxathiane **5** was prepared from (-)-pulegone following Eliel's method,[13] $[\alpha]_D$ = -12 (c = 2.1, acetone). ^{1}H NMR ($CDCl_3$) δ 5.03 (1H, B part of AB, ^{2}J = 11.0), 4.70 (1H, A part of an AB, ^{2}J = 11.0), 3.35 (1H, td, ^{3}J = 10.0, 10.0, 4.0), 1.42-2.0 (8H, m), 1.43 (3H, s), 1.27 (3H, s), 0.92 (3H, d, ^{3}J = 7.0).

The sulfonium triflates **6a** and **6b** were prepared using the known Vedej's procedure.[14] Only one diastereomer detected by ^{1}H and ^{13}C NMR spectra, and the axial conformation was assigned in both cases from NOESY experiments as described previously.[10] **6a**: ^{1}H NMR ($CDCl_3$) δ 7.45 (4H, bs), 5.62 (1H, d, ^{2}J = 12.0), 4.86 (1H, d, ^{2}J = 12.0), 4.57 (2H, s), 3.80 (1H, td, ^{3}J = 10.0, 10.0, 4.0), 2.01 (1H, m), 1.80 (1H, m), 1.74 (3H, s), 1.68 (3H, s), 1.50 (2H, m), 1.30 (1H, q, ^{3}J = 11.0), 1.28 (9H, s), 1.10 (3H, m), 0.95 (3H, d, ^{3}J = 7.0). ^{13}C NMR ($CDCl_3$) δ 153.4, 130.5, 126.3, 123.4, 120.7 (q, CF_3, ^{1}J = 320), 77.9, 43.0, 30.9, 57.8, 40.0, 36.6, 34.6, 33.7, 31.0, 30.9, 25.9, 23.6, 21.8, 21.0. **6b**: *cf.* ref. 4b,c

To a stirred solution of the desired sulfonium salt, **6a** or **6b**, (1 equiv., 3 mmol) in anhydrous CH_2Cl_2 (10 mL) were succesively added, at –40°C, 1 equiv. of the commercially available phosphazene base EtP_2 and ethyl acrylate (3 equiv.) neat. After stirring for 10 to 15 min the mixture was poured into cold water, the organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (5 x 10 mL). The organic phases were joined dried and concentrated under vacuum. The phosphazene-base salt $EtP_2H^+TfO^-$ was precipitated through addition of ethyl acetate and filtered out. After evaporation the crude cyclopropanes **4a** and **4b** (95% and 85% yields resp.)

were analyzed before purification by ^{1}H NMR and happened to be 96% and 95% *trans* resp. After chromatography no *cis*-isomer was detected in both cases.

4a-*trans*: IR (KBr) ν 1727 (s). ^{1}H NMR ($CDCl_3$) δ 7.30 (2H, d, ^3J = 8.5), 7.03 (2H, d, ^3J = 8.5), 4.16 (2H, q, ^3J = 7.0), 2.49 (1H, ddd, ^3J = 9.5, 7.0, 4.0), 1.88 (1H, ddd, ^3J = 8.5, 5.0, 4.0), 1.58 (1H, ddd, ^2J = 4.0, ^3J = 9.5, 5.0), 1.32 (1H, ddd, ^2J = 4.0, ^3J = 8.5, 7.0), 1.30 (9H, s), 1.26 (3H, t, ^3J =7.0). ^{13}C NMR ($CDCl_3$) δ 173.50, 149.41, 137.06, 125.77 (2C), 125.31 (2C), 60.43, 34.17, 31.09 (3C), 25.62, 23.88, 16.68, 14.01. Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found C, 77.93; H, 9.05.

4a-*cis*: IR (KBr), identical to the *trans*-isomer. ^{1}H NMR ($CDCl_3$) δ 7.30 (2H, d, ^3J = 8.0), 7.21 (2H, d, ^3J = 8.0), 3.81 (2H, AB part of an ABX_3, ^2J = 11.0, ^3J = 7.0), 2.52 (1H, q, ^3J = 8.0), 2.04 (1H, ddd, ^3J = 8.0, 7.0, 5.0), 1.68 (1H, td, ^2J = 5.0, ^3J = 8.0, 5.0), 1.33 (1H, m), 1.28 (9H, s), 0.91 (3H, t, ^3J = 7.0). ^{13}C NMR δ 171.00, 149.27, 133.40, 128.82 (2C), 124.63 (2C), 59.82, 34.09, 31.06 (3C), 24.75, 21,51, 13.59, 10.78. Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found C, 77.87; H, 9.07.

The enantiomeric purity of *trans*-isomer was easily determined by HPLC on Chiralcel OJ but for *cis*-isomer enantiomeric purity was determined by HPLC on Chiralcel OD-H column and by GLC on CP-Chirasil-DEX CB column (25 m x 0.25 mm I.D., Chrompack). *(S)*-Configuration at C(1) atom is ascertained by chemical correlation with ***S*-1a**, for which absolute configuration is determined by X-ray analysis.[1]

***trans-(S,S)*-2-(4-*tert*-Butylphenyl)-1-hydroxymethylcyclopropane (11a)**. A 96/4 *trans/cis* mixture of **4a** (1.0 g, 4.1 mmol) was dissolved in dry ether (25 ml) and added dropwise, under stirring at room temperature, to a suspension of $LiAlH_4$ in dry ether (160 mg in 25 ml). The reaction mixture was then heated under gentle reflux for 3h. After slow addition of water, the resulting precipitate was filtered off. The organic phase was dried over Na_2SO_4 and the solvent evaporated. The crude product was purifed by flash chromatography with dichloromethane-ethyl acetate (98:2) affording 0.82 g (82%) of pure *trans-(1S,2S)*-**11a**.

11a-*trans*: IR (KBr) ν 3360 (s), 3001 (m), 2955 (s), 2866 (m), 1513 (m), 1015 (m). ^{1}H NMR ($CDCl_3$) δ 7.29 (2H, d, ^3J = 8.5), 7.02 (2H, d, ^3J = 8.5), 3.60 (2H, AB of an ABX), 1.80 (1H, ddd, ^3J = 8.0, 5.0, 4.5), 1.54 (1H, bs), 1.43 (1H, m), 1.39 (9H, s), 0.92 (2H, AB of ABMX). ^{13}C NMR ($CDCl_3$) δ 148.44, 139.36, 125.39 (2C), 125.13 (2C), 66.21, 34.06, 31.11 (3C), 24.80, 20.53, 13.44. Anal. Calcd. for $C_{14}H_{20}O$: C, 82.31; H, 9.87. Found C, 82.09; H, 9.91.

Hydrogenolysis of *trans/cis*-ethyl-2-(4-*tert*-butylphenyl)cyclopropane carboxylate (4a). The 96/4 *trans/cis* mixture of ester **4a** (252 mg, 1 mmol) was dissolved in dry THF (10 ml), 10% Pd/C (50 mg) was added, and H_2 was slowly bubbled under stirring. GLC monitoring revealed complete hydrogenolysis after 2 hours. The catalyst was filtered off and the solvent evaporated to give a mixture of ethyl-4-(4-*tert*-butylphenyl)butanoate (**14a**) and ethyl-3-(4-*tert*-butylphenyl)-2-methylpropanoate (**12a**) in the ratio 92/8 as determined by GLC. Separation by flash chromatography (light-petroleum-ethyl acetate 4/1) gave 200 mg (80%) of **14a** as pale-yellow oil, b.p. 85-87 °C (0.04 mmHg) and, as the second fraction, 16 mg (6%) of **12a** identified by comparison with an authentic sample[2c] using GLC. **14a**: IR (KBr) ν 3060 (w), 2962 (s), 1740 (s), 1180 (m). ^{1}H NMR δ 7.31 (2H, d, ^3J = 8.0), 7.11 (2H, d, ^3J = 8.0), 4.12 (2H, q, ^3J = 7.0), 2.62 (2H, t, ^3J = 7.5), 2.32 (2H, t, ^3J = 7.5), 1.95 (2H, tt, ^3J = 7.6, 7.4), 1.31 (9H, s), 1.25 (3H, t, ^3J = 7.0). ^{13}C NMR ($CDCl_3$) δ 173.58, 148.71, 138.32, 128.09 (2C), 125.18 (2C), 60.04, 34.12, 34.38, 33.56, 31.17 (3C), 26.29, 14.00. Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found C, 77.42; H, 9.80.

Hydrogenolysis of *trans-(S,S)*-2-(4-*tert*-butylphenyl)-1-hydroxymethylcyclopropane (11a). The alcohol **11a** (330 mg, 1.6 mmol) was hydrogenated over 3% Pd/C in THF (10 ml) at ambient temperature and atmospheric pressure of hydrogen. GLC monitoring revealed complete hydrogenation after 1 h. The catalyst was filtered off, solvent evaporated and the products separated by flash chromatography. With light-petroleum-ethyl acetate (9/1) **18a** was eluted first as pale-yellow oil, then **15a**, and finally open-chain alcohol **17a**.

18a: IR (KBr) ν 2962 (s), 2930 (s), 2875 (m), 1364 (w), 1269 (w), 828 (w). ^{1}H NMR ($CDCl_3$) δ 7.29 (2H, d, ^3J = 8.0), 7.11 (2H, d, ^3J = 8.0), 2.57 (2H, t, ^3J = 7.5), 1.61 (2H, m), 1.36 (2H, m), 1.31 (9H, s), 0.92 (3H, t, ^3J = 7.0). ^{13}C NMR ($CDCl_3$) δ 148.30, 139.83, 128.02 (2C), 125.07 (2C), 34.93, 34.13, 33.47, 31.24 (3C), 22.27, 13.76. Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found C, 88.20; H, 11.89.

15a: All spectral characteristic correspond to those described for an independently prepared sample.[2c] Enantiomeric purity was determined by HPLC on Chiralcel OD column to be 98.7%. The *(S)*-absolute

configuration was assigned to the major isomer obtained from the X-ray determined configuration of the final products.[1]

17a: IR (KBr) ν 3320 (m), 3050 (m), 1900 (w), 1905 (w). ^{1}H NMR ($CDCl_3$) δ 7.33 (2H, d, ^3J = 8.5), 7.15 (2H, d, ^3J = 8.5), 3.67 (2H, t, ^3J = 6.5), 2.64 (2H, t, ^3J = 7.5), 1.65 (4H, m), 1.34 (9H, s). ^{13}C NMR ($CDCl_3$) δ 148.50, 139.20, 127.99 (3C), 125.12 (2C), 62.66, 34.85, 34.12, 32.17, 31.20 (3C), 27.27. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found C, 81.35; H, 10.95.

Table 4. Relevant Conditions and Parameters for HPLC Analyses on Chiral Columns

Compound	4a-*cis*	4b-*trans*	15a	1a,HCl	2a,HCl
Column	Chiralcel OD-H	Chiralcel OJ	Chiralcel OD	Chiral-AGP	Chiral-AGP
Mobile phase	1% 2-PrOH, 99% hexane	0.5% 2-PrOH, 99.5% hexane	2% 2-PrOH, 98% hexane	1% 2-PrOH, 99% 0.05 M NaH_2PO_4	1% 2-PrOH, 99%, 0.125 M NaH_2PO_4, pH 4.4
Flow (mL/min)	0.5	1.0	0.4	0.7	1.0
k_1'	1.33	3.59	3.83	7.50	6.18
α	1.13	1.25	1.20	1.96	1.22
R_S	4.00	3.44	2.32	2.19	1.03

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