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Stereoselective Synthesis of 2(*S*)-(1,1-Dimethylethylsulfonylmethyl)-3-(1-Naphthyl)-Propionic Acid , Building Block for Protease Inhibitors *via* Asymmetric Hydrogenation

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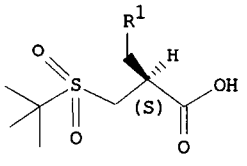
Abstract: *Title compound* **1b** *(purity > 99% , 99.6% ee) is synthesized (100g scale) from commercial 3-bromo-pyruvic acid in six steps with an overall yield of 16% . The sequence is operationally simple and devoid of chromatographic purifications. Key step is the asymmetric hydrogenation of a substrate with sulfur functionality .*

2(*S*)-(*tert*-Butylsulfonylmethyl)-3-aryl-propionic acids **1** are valuable N-terminal components in peptidomimetic protease inhibitors. BBP-OH **1a** is used in activity - optimized inhibitors of human renin [1,2] , DSNP-OH **1b** is the best N-terminal in HIV-protease inhibitors of the phosphinic acid type [3] and in HBY 793 , one of the most potent HIV-protease inhibitors currently known .[4]

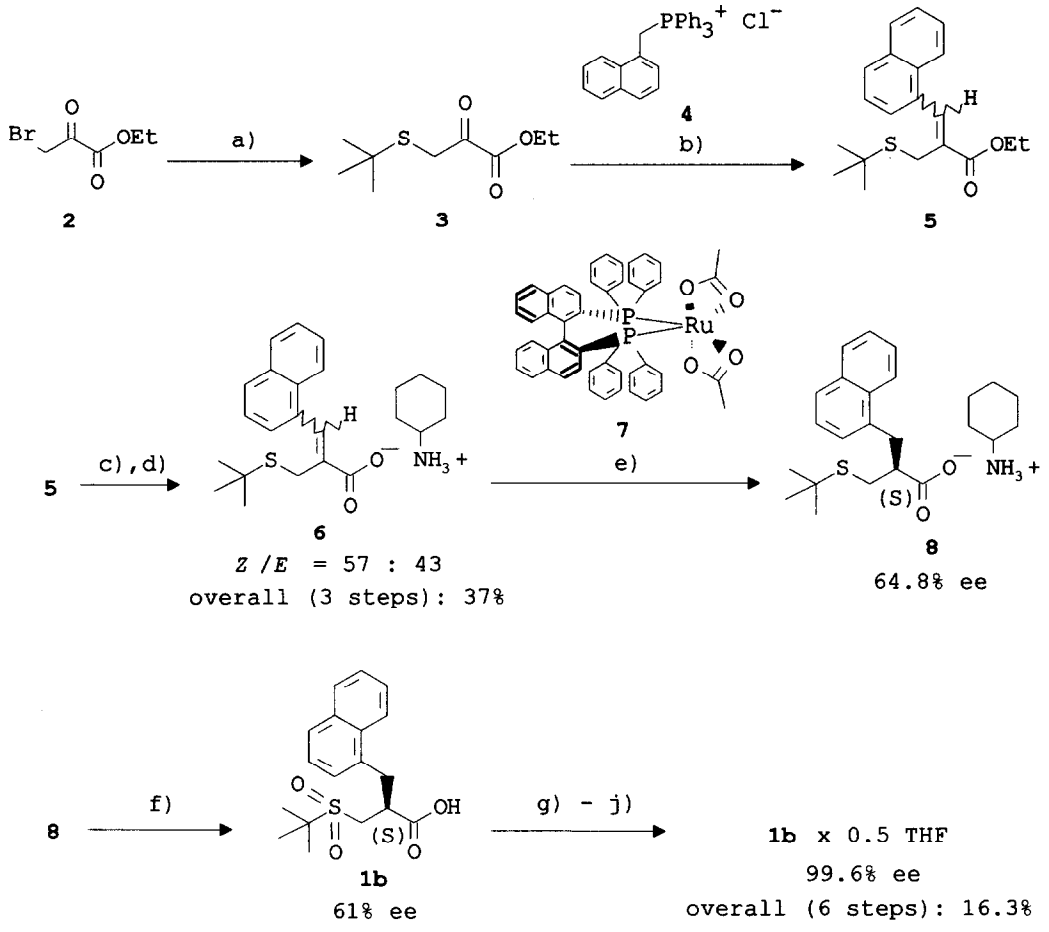


R^1 = Ph	**1a**	"BBP-OH"
R^1 = 1-naphthyl	**1b**	"DSNP-OH"

The only synthesis of **1** reported [1,5] consists of :

1. Preparation of *rac*-**1** in six steps from benzylic chloride R^1CH_2Cl ;
2. formation of diastereomeric amides by reaction of *rac*-**1** with *L*-phenylalaninol ;
3. column chromatographic separation of these diastereomeric amides ;
4. acid - catalyzed hydrolysis of the amide with 2(*S*)-configuration.

We report a synthesis of **1** that is operationally simple , short , devoid of any chromatography , and can thus easily be scaled up. The key step of the sequence is a very rare example of an asymmetric hydrogenation of a substrate with sulfur functionality: The rhodium(I)-catalyzed asymmetric hydrogenation of an N-acetyl-dehydroaminoacid derivative with remote sulfur functionality has been reported.[6] Recently, the enantioselective carbonyl - hydrogenation of β-thiacycloalkanones with cationic iridium-BINAP catalysts was described.[7] Some thioethers are known to be very potent poisons for homogeneous rhodium(I)-diphosphine catalysts.[8]



Reagents and conditions :

a) Me_3CSH (1.0 equiv), $NaHCO_3$ (0.98 equiv), $[MeN(oct)_3]Cl$ (0.05 equiv) / CH_2Cl_2, H_2O, 20°C, 2h.

b) **4** (1.0 equiv), 55% NaH in oil (1.0 equiv) / THF, 20°C, 4h ; then **3** / 35°C, 2h. pH → 6.0 with aq HCl.

c) 2*N* aq NaOH / EtOH, reflux , 5h. Evap. solvent; add ice and EtOAC ; pH → 3.0 with aq HCl / 0°C.

d) Cyclohexylamine (3.0 equiv) / acetone, -10°C, 20h.

e) **7** (0.002 equiv) , 175 bar H_2 / CH_3OH , 100°C , 43h.

f) 35% aq H_2O_2 (8.6 equiv) / AcOH , CH_2Cl_2 (1:3), 0°C, 3h ; add polyphosphoric acid, 85% H_3PO_4 and 35% aq H_2O_2 (4.0 equiv) / 0°C → 20°C, 12 - 24h.

g) (*R*)-(+)-1-Phenylethylamine (1.05 equiv) / acetone, 0°C, 1h ⇒ salt (95.6% ee).

h) Recrystallization from boiling acetone ⇒ salt (99.4% ee).

i) 2*N* aq HCl / *tert*-Bu-OMe, H_2O, 0°C ⇒ **1b** (99.4% ee).

j) Petrol ether, THF (8:1), 25°C, 30 min ⇒ **1b** x 0.5 THF (99.6% ee).

Commercial 3-bromo-pyruvic acid **2** is subjected to a nucleophilic substitution by *tert*-butylmercaptane under phase transfer catalysis .The organic phase is separated and concentrated to give a solution of crude thioether **3**. Phosphonium salt **4** is transformed (NaH , THF) to the deep-red ylide, that is treated with the solution of crude **3**. Work up and removal of triphenylphosphine oxide by filtration gives crude Wittig product **5** as a yellow thick oil (*Z*/*E* ~ 55:45). Saponification of crude ester **5** with aqueous sodium hydroxide in refluxing ethanol , evaporation of the solvent , and adjustment to pH 3 in ethyl acetate / water provides the crude carboxylic acid as a semi-solid. It is dissolved in acetone and the salt **6** (*Z*/*E* = 57 : 43) is precipitated with cyclohexylamine. The overall yield of pure **6** (3 steps) is 37%.

The methanolic solution of salt **6** and (*S*)-binap-ruthenium(II)-diacetate **7** [9] (0.002 equiv) is hydrogenated (100°C , 175 bar H_2) to give the saturated salt **8** (64.8% ee) in 98% yield. [10] Oxidation of sulfide **8** with aqueous hydrogen peroxide in acetic acid / dichloromethane leads to the two diastereomeric sulfoxides, that are further oxidized to sulfone **1b** on addition of polyphosphoric acid , aqueous phosphoric acid, and hydrogen peroxide. Work up provides sulfone **1b** (100% yield , 61% ee) as a solid foam.

Precipitation / recrystallization of its (*R*)-(+)-1-phenylethylammonium salt , followed by acidification gives the target compound **1b** (99.4% ee). Since chemically and optically pure **1b** is a non-crystalline solid foam, we found it advantageous to form its highly crystalline solvate **1b** x 0.5 THF (99.6% ee). The overall yield , based on starting material **2**, is 16%.

EXPERIMENTAL

Reagents:

Acetic acid (glacial, 99.8%, Hoechst), acetone (99.5%, Riedel-de Haen), acetonitrile (99%, < 0.3% H_2O, Aldrich), *tert*-butylmercaptane (99%, Aldrich), *tert*-butylmethyl ether (MTB ether) (98%, Riedel-de Haen), 1-chloromethylnaphthalene (98%, Chem. Werke Weil), cyclohexylamine (99%, Riedel-de Haen), dichloromethane (99.8%, Riedel-de Haen), ethanol (99%), ethyl acetate (> 99.5%, Riedel-de Haen), hydrogen peroxide (35% aq. solution, Riedel-de Haen), methanol (99.5%, 0.2% H_2O, Riedel-de Haen), methyl-trioctylammonium chloride (techn. grade, Hoechst), (*R*)-(+)-1-phenylethylamine {98%, $[\alpha]_D^{25}$ +38° (neat), Aldrich}, *ortho*-phosphoric acid (85%, chem. pure, Riedel-de Haen), polyphosphoric acid ($H_{2n}P_nO_{3n+1}$, content P_2O_5 : 84%, Riedel-de Haen), sodium hydride (55% dispersion in mineral oil, Fluka), sodium hydroxide pellets (98%, Riedel-de Haen), tetrahydrofuran (THF) (99.5%, ≤ 0.1% H_2O, Riedel-de Haen), triphenylphosphine (99%, Aldrich) were used as purchased. Ethyl 3-bromo-2-oxo-propionate (> 90%, Fluka) was distilled *in vacuo* immediately before use to give a compound of > 96% content (GC).

Instrumentation:

With the exception of the asymmetric hydrogenation, all reactions were run in dry glass apparatus in a nitrogen or argon atmosphere. The asymmetric hydrogenation was run in a 30L stainless steel autoclave with a concentric agitator shaft carrying three sets of stirrer blades (Uhde, 1969).

Melting points (mp) were determined on a Büchi capillary melting point apparatus (according to Dr. Tottoli) and are uncorrected. HPLC: Kontron 420 Pump with Kontron 425 Gradient Former, Kontron 360 Autosampler (20 µL injection loop), Kontron 432 HPLC UV-Detector and Kontron 450-MT2 Data System or alternatively Spectra Physics SP 4200 Pump / 8750 Organizer (10 µL injection loop) with SP 8700 Solvent Delivery System, Spectra 100 UV-VIS Detector and SP 4100 Computing Integrator. TLC: 5 x 10 cm glass

plates pre-coated with silicagel 60 F-254 (E.Merck) ; spot visualization with Universal UV Lampe Camag (254 nm). ^{1}H-NMR (internal standard TMS): Varian Gemini 200 (200 MHz) and Bruker AM 270 (270 MHz). ^{13}C-NMR (internal standard TMS): Bruker AM 270 (67.93 MHz) and Bruker AM 400 (100.61 MHz). IR: Perkin Elmer 683 spectrometer. UV: Perkin Elmer 554 UV/VIS spectrometer. MS "dissociation chemical ionization" (DCI): Kratos MS 80. Optical rotations were determined on a Perkin-Elmer 241 polarimeter utilizing a 10 cm length micro-cuvette.

Ethyl (3-*tert*-butylthio-2-oxo)propionate (3):

A 6L four-necked flask is fitted with a mechanical stirrer , a pressure-equalized dropping funnel , a nitrogen inlet, and an outlet that leads to a scrubber filled with a chlorine bleach solution. The flask is charged with the solution of sodium bicarbonate (269 g, 3.15 mol) in water (1.6 L), with methyl-trioctylammonium chloride (66.4 g, 0.16 mol) and with *tert*-butylmercaptane (288 g, 3.2 mol). The flask is cooled with ice , and the solution of freshly distilled ethyl 3-bromo-2-oxo-propionate **(2)** (624 g, 3.2 mol) in dichloromethane (2.5 L) is added dropwise with stirring within 30 min, keeping the reaction temperature below 30°C. The mixture is stirred 90 min at 20°C. TLC (cyclohexane / ethyl acetate 7:3) indicates quantitative reaction of **2** (R_f 0.33) to **3** (R_f 0.65). The aqueous layer is separated. The dichloromethane layer is dried ($MgSO_4$) and then concentrated to 1 L *in vacuo*. The content of **3** is estimated by ^{1}H-NMR to be ~ 600g (2.94 mol, yield 92%). The crude solution of **3** is stored at -20°C until it is (soon) used for the next reaction step.

1-Naphthylmethyl-triphenylphosphonium chloride (4):

The solution of 1-chloromethylnaphthaline (782 g, 4.44 mol) in acetonitrile (500 mL) is added dropwise within 15 min to the warm (80°C) solution of triphenylphosphine (1.163 kg, 4.44 mol) in acetonitrile (7 L). The mixture is refluxed for 8 h. The phosphonium salt starts to precipitate after 2 h. The mixture is allowed to cool to 20°C. The solid is suction-filtered, washed with ethyl acetate and dried *in vacuo*. Yield: 1.84 kg (94%) colourless crystals, mp 308 - 310°C. *Anal.* calcd. for $C_{29}H_{24}ClP$: C 79.36; H 5.51; Cl 8.08; P 7.06. Found: C 79.53; H 5.62; Cl 7.89.

Ethyl [3-(1-naphthyl)-2-*tert*-butylthiomethyl]-acrylate (5) (*Z*/*E*)-mixture:

Phosphonium salt **4** (1.84 kg, 4.19 mol) is dried 1 d at 150°C / 0.001 Torr. It is then suspended in dry THF (6.5 L) in a nitrogen atmosphere, and sodium hydride (184 g of a 55% dispersion in oil, 4.2 mol) is added in small portions within 30 min with stirring, keeping the reaction temperature at 15 - 20°C by cooling. The mixture is stirred 4 h at 20°C to give the dark-red solution of the ylide. The crude solution of ester **3** is added dropwise within 1 h, keeping the reaction temperature at 30 - 40°C by cooling. The mixture is stirred 1 h at 30°C and then poured into a stirred mixture of water (2 L), ice (2 kg) and ethyl acetate (5 L). The pH is adjusted to 6.0 with 2*N* hydrochloric acid. The organic layer is separated and dried (Na_2SO_4) at 0°C. Ethyl acetate (~ 4.5 L) is evaporated *in vacuo* (bath < 30°C). The solid (Ph_3PO and Na_2SO_4) is removed by suction-filtration and washed thoroughly with MTB ether (4 L). MTB ether (3 L) is added to the combined filtrate and washings, and the mixture is stirred 3 h at -10°C. The solid (Ph_3PO) is filtered off and washed thoroughly with MTB ether (2 x 1 L). The combined filtrate and washings are evaporated to dryness *in vacuo* (bath < 30°C). The residue is dried in high vacuum to give a yellow, viscous oil (1.18 kg). The content of **5**

(*Z*/*E* = 55:45) is estimated (^{1}H-NMR) to ~800g (2.44 mol, 83% yield). TLC (cyclohexane / ethyl acetate 7:3): R_f **3** (0.65), **5** (0.76), PPh_3O (0.10). This crude product is used in the next step of the synthesis.

Purified sample: ^{1}H-NMR (200 MHz, $CDCl_3$, *Z*/*E* = 55:45): δ 0.74 and 1.42 (t, OEt), 1.28 and 1.43 (s, *t*Bu), 3.58 and 3.73 (s, SC*H*$_2$), 3.90 and 4.38 (q, OEt), 7.25 - 8.0 (m, aryl-*H*, =C*H*), 8.25 (s, =C*H*). MS (DCI) : m/e (rel. intensity) 328 (M, 17), 239 (M - *t*BuS, 100). *Anal.* calcd. for $C_{20}H_{24}SO_2$: C 73.13; H 7.36; O 9.74; S 9.76. Found: C 73.32; H 7.53.

Cyclohexylammonium [3-(1-naphthyl)-2-*tert*-butylthiomethyl]-acrylate (6) (*Z*/*E*-mixture)**:**

2*N* aq. sodium hydroxide (2.86 L) is added to the solution of crude ester **5** (1.18 kg; containing ~ 800g, ~2.44 mol **5**) in ethanol (6 L) and the mixture is refluxed for 5 h. TLC (cyclohexane / ethyl acetate 7:3) indicates quantitative saponification of **5** (R_f 0.76) to the carboxylate (R_f 0.22). A very unpolar by-product (R_f 0.85) and a highly polar by-product (R_f 0.03, residual Ph_3PO of the preceding step) are also detected. The ethanol is evaporated in *vacuo* and ice (800 g) and ethyl acetate (3 L) is added to the residue. The pH is adjusted to 3.0 with 6*N* hydrochloric acid. The organic phase is separated and the aqueous layer is extracted with ethyl acetate (1 L). The combined organic phases are dried (Na_2SO_4), filtered, and the solvent is evaporated *in vacuo* to give the crude carboxylic acid as a semi-solid. It is dissolved in acetone (3.8 L). Cyclohexylamine (400 mL, 3.5 mol) is added dropwise at 0°C with efficient cooling and stirring. Precipitation of the salt starts after 30 min. The mixture is stirred (exclusion of moisture) 10 h at 0°C and 10 h at -10°C. The solid is collected by suction-filtration , re-suspended in cold acetone (4 L), suction-filtered and washed with acetone (2 x 500 mL) to give **6** (470 g, 1.17 mol) as pale-grey (nearly colourless) crystals, mp 146 - 152°C, *Z*/*E*-ratio 57:43. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.16 (s, 9 x 0.57H, *t*Bu of *Z*-**6**), 1.37 (s, 9 x 0.43H, *t*Bu of *E*-**6**), 1.00 - 1.35 and 1.50 - 1.80 (m, 10H, cyclohexyl), 2.80 (m, 1H, C*H*N), 3.52 (s, 2 x 0.57H, SC*H*$_2$ of *Z*-**6**), 3.62 (d, *J* ~ 1 Hz, 2 x 0.43H, SC*H*$_2$ of *E*-**6**), 6.80 (s, 0.43H, =C*H* of *E*-**6**), 7.32 - 8.02 (m, 7.57H, 7 aryl-*H* and =C*H* of *Z*-**6**).

Pure *Z*- and *E*-isomer of the free carboxylic acid can be obtained by acidification of (*Z*/*E*)-**6**, followed by column chromatography (silicagel, cyclohexane / ethyl acetate 9:1).

(*Z*)-carboxylic acid: mp 168°C (from hot cyclohexane) . ^{1}H-NMR (270 MHz, $CDCl_3$): δ 1.31 (s, 9H, *t*Bu), 3.62 (s, 2H, SC*H*$_2$), 7.50 - 7.60 (m, 3H, aryl-*H*), 7.87 - 8.00 (m, 4H, aryl-*H*), 8.46 (s, 1H, =C*H*). In a selective NOE measurement saturation of the =C*H*-resonance does not induce an increase (< 0.2%) of the SC*H*$_2$ resonance. Resonances of naphthyl protons are intensified by 10%. ^{13}C-NMR (67.93 MHz, $CDCl_3$, multiplicity controlled by DEPT): δ 25.88 (SCH$_2$), 30.61 [(*C*H$_3$)$_3$C], 43.44 [(CH$_3$)$_3$*C*], 124.34, 125.28, 126.25, 126.70, 126.98, 128.62, 129.62 (7 x *C*H of naphthyl), 130.07, 131.52, 131.79, 133.44 (3 x *C* of naphthyl and 1x =*C*-CO_2H), 141.23 (=*C*H), 172.31 (*C*O_2H). MS (DCI): m/e (rel. intensity) 301 (M+H, 100), 300 (75), 211 (M+H - *t*BuSH, 73). *Anal.* calcd. for $C_{18}H_{20}SO_2$: C 71.97; H 6.71; O 10.65; S 10.67. Found: C 71.76; H 6.83. **(*E*)-carboxylic acid:** viscous oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 9H, *t*Bu), 3.72 (d, *J* ~ 1 Hz, 2H, SC*H*$_2$), 7.16 - 7.93 (m, 8H, 7 aryl-*H* and 1 =C*H*). **(*E*)-cyclohexylammonium carboxylate (*E*)-6** : mp 189 - 193°C. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.0 - 1.85 (m, 10H, cyclohexyl), 1.37 (s, 9H, *t*Bu), 2.78 (m, 1H, C*H*N), 3.60 (d, *J* ~ 1 Hz, 2H, SC*H*$_2$), 6.82 (s, 1H, =C*H*), 7.37 (t, *J* 7.6 Hz, 1H, aryl-*H*), 7.50 (m, 2H, aryl-H), 7.65 (d, *J* 6.7 Hz, 1H, aryl-*H*), 7.74 (d, *J* 6.7 Hz, 1H, aryl-*H*), 7.87 (m, 1H, aryl-*H*), 7.98 (m, 1H, aryl-*H*). In a selective NOE measurement saturation of the =C*H*-resonance induced an increase of the

SCH_2 resonance by 14% (and *vice versa*). ^{13}C-NMR (100.61 MHz, $CDCl_3$ / DMSO-d_6, multiplicity controlled by DEPT): δ 23.59 (2 x CH_2 of cyclohexyl), 24.07 (1 x CH_2 of cyclohexyl), 30.12 [$(CH_3)_3C$], 31.60 (2 x CH_2 of cyclohexyl), 32.88 (SCH_2), 41.70 [$(CH_3)_3C$], 48.80 (CHN), 123.71, 124.38, 124.52, 124.67, 125.04, 125.68, 127.15 (7 x aryl-CH), 130.60, 132.20, 134.10 (2 x aryl-C and 1 x =C-CO_2^-), 139.79 (=CH). The resonances of one aryl-C and of CO_2^- are too weak, to be unambiguously detected in the noise.

Cyclohexylammonium [3-*tert*-butylthio-2-(1-naphthyl)methyl]-propionate (8) (65% ee of *S*-config.) :

In a 30 L stainless steel autoclave the solution of cyclohexylammonium salt **6** (350g, 0.87 mol) in methanol (20 L) is deoxygenated by pressing in 5 bar of nitrogen , followed by slow release. This procedure is repeated two times. The deoxygenated solution of (*S*)-binap-ruthenium diacetate **7** [9] (1.48 g, 1.76 mmol, 0.002 equiv.) in methanol (50 mL) is transferred into the autoclave by flex-needle with exclusion of oxygen. 3 bar of hydrogen is pressed in, followed by slow release. 135 bar of hydrogen is pressed in , and the mantle-heating of the autoclave is immediately adjusted to 103°C. A reaction temperature of 100°C is reached within 30 min, while the inner pressure increases to 175 bar. The mixture is stirred 43 h at 100 $\pm$ 5°C under 175 $\pm$ 5 bar hydrogen. The autoclave is cooled to 18°C within 40 min and the hydrogen is released to 10 bar of residual pressure. A sample is removed from the autoclave with exclusion of oxygen by shortly opening a drainage-valve. HPLC-analysis indicates quantitative hydrogenation of **6** to **8** [250 x 4.0 mm Nucleosil 100 C18 7µm; det. 220 nm; flow 1.5 mL/min; eluent: 1 L CH_3CN, 1.05 L H_2O, 3.6 g $NH_4H_2PO_4$, with H_3PO_4 adjusted to pH 3.5; *E*-**6** (t_{rel} 14.87 min), *Z*-**6** (18.26 min), **8** (15.93 min)]. The hydrogen is released from the autoclave. Nitrogen (5 bar) is pressed in and released. This procedure is repeated two times. The reaction mixture is drained from the autoclave and the solvent is removed *in vacuo*. The residue is dried in high vacuum to furnish **8** (345g, 0.86 mol, 98% yield) as a colourless powder. The chemical purity is 98.1% according to HPLC, the optical purity is 64.8% ee of the (*S*)-configuration according to HPLC (*vide infra*). The salt is used in the next step (oxidation) without purification. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 0.98 - 1.92 (m, 11H, 5 x CH_2 of cyclohexyl, $CHCO_2^-$), 1.18 (s, 9H, *t*Bu), 2.57 (m, 1H, CHN), 2.63 - 2.90 (m, 2H, CH_2-naphthyl), 3.10 - 3.40 (m, 2H, SCH_2), 7.37 (m, 2H, aryl-*H*), 7.52 (m, 2H, aryl-*H*), 7.73 (m, 1H, aryl-*H*), 7.90 (m, 1H, aryl-*H*), 8.17 (m, 1H, aryl-*H*).

For analytical purpose, the carboxylic acid (solid, colourless foam) is liberated by acidification and extraction. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.26 (s, 9H, *t*Bu), 2.72 (dd, J_{gem} 12.5 Hz, J_{vic} 6 Hz, 1H, CH-naphthyl), 2.87 (d, J_{gem} 12.5 Hz, J_{vic} 6.5 Hz, 1H, CH-naphthyl), 3.09 (qui, J ~ 6.5 Hz, 1H, $CHCO_2H$), 3.40 (dd, J_{gem} 14.5 Hz, J_{vic} 6.5 Hz, 1H, SCH), 3.49 (dd, J_{gem} 14.5 Hz, J_{vic} ~ 7 Hz, 1H, SCH), 7.38 (m, 2H, aryl-*H*), 7.52 (m, 2H, aryl-*H*), 7.76 (m, 1H, aryl-*H*), 7.85 (m, 1H, aryl-*H*), 8.09 (m, 1H, aryl-*H*). IR ($CHCl_3$): 3600 - 2500 (br, CO_2H), 3017 (w, aryl-H), 2965 (m), 1710 (s, C=O) cm^{-1}. UV (CH_3OH): 224 nm (ε = 6.3 x 10^4), 282 nm (ε = 7 x 10^3). MS (DCI): m/e (rel. intensity) 303 (M+H, 100), 302 (68), 247 (M+H - $Me_2C{=}CH_2$, 12), 229 ("247" - H_2O, 13), 141 (α-naphthylmethyl, 11). $[\alpha]_D^{25}$ - 21.3 (c 1.06, CH_3OH). *Anal.* calcd. for $C_{18}H_{22}SO_2$: C 71.49; H 7.33; O 10.58; S 10.60. Found: C 71.63; H 7.42.

[3-*tert*-Butylsulfonyl-2-(1-naphthyl)methyl]-propionic acid (1b) (61% ee of *S*-configuration) :

The solution of crude cyclohexylammonium salt **8** (345 g, 0.86 mol) in glacial acetic acid (170 mL) and dichloromethane (520 mL) is cooled to 0°C 35% aq. hydrogen peroxide (640 mL, 8.6 equiv) is added at

once. The mixture is stirred 3 h at 0°C. HPLC indicates quantitative transformation of **8** to the two diastereomeric sulfoxides and very little sulfone **1b** [HPLC conditions as described for **8** ; sulfoxide diastereomer 1 (t_{ret} 3.32 min), sulfoxide diastereomer 2 (3.52 min), sulfone **1b** (4.42 min), sulfide **8** (15.93 min)]. The suspension of polyphosphoric acid (116 g) in *ortho*-phosphoric acid (116 g) is added to the reaction mixture at 0°C with good cooling (exothermic !), followed by the addition of 35% aq. hydrogen peroxide (300 mL, 4.0 equiv). The mixture is stirred 12 - 24 h at ambient temperature until HPLC indicates the complete oxidation of the intermediary sulfoxides to sulfone **1b.** (Longer reaction times should be avoided since the enantiomeric excess of **1b** seems to deteriorate very slowly under the reaction conditions). The reaction mixture is poured into a stirred mixture of dichloromethane (3.75 L) and water (3.75 L). The organic layer is separated and the aqueous layer is extracted with dichloromethane (3.75 L). The combined organic phases are washed with 2*N* hydrochloric acid (3.75 L) and with 10% aq. sodium bisulfite solution (2 x 2 L). A test strip (Merckoquant^R peroxide test) indicates the disappearance of peroxides. The organic layer is dried ($MgSO_4$) and then evaporated *in vacuo* to give an off-colourless solid foam (288 g, 0.86 mol, 100% crude yield), 61% ee of the (*S*)-configuration according to HPLC (*vide infra*); ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.27 (s, 9H, *t*Bu), 3.00 - 3.18 (m, 1H, C*H*CO_2H), 3.35 - 3.70 (m, 4H, 2 C*H*$_2$), 7.33 - 7.62 (m, 4H, aryl-*H*), 7.82 (ddd, *J* 17.5, 8.5 and 1.5 Hz, 2H, aryl-*H*), 8.13 (d, *J* 8.5 Hz, 1H, aryl-*H*), CO_2H gives a *very broad* signal difficult to locate; $[\alpha]_D^{25}$ + 1.18 (c 1.0, CH_3OH). *Anal.* calcd. for $C_{18}H_{22}SO_4$: C 64.65; H 6.63; O 19.14; S 9.59. Found: C 64.54; H 6.50.

(2*S*)-[3-*tert*-butylsulfonyl-2-(1-naphthyl)methyl]-propionic acid THF-solvate (1b) x 0.5 THF :

The solution of **1b** (288 g, 0.86 mol, 61% ee) in acetone (3.9 L) is cooled to 0°C. (*R*)-(+)-1-phenylethylamine (109 g, 0.90 mol) is added within 5 min and the mixture is vigorously stirred for 1 h at 0°C. Precipitation of the salt starts after 5 - 10 min and leads after 15 min to a thick slurry, that is somewhat difficult to stir. The solid is suction-filtered and washed with acetone (100 mL) and MTB ether (300 mL). It is dried *in vacuo* to give the colourless salt (209.1 g, 0.459 mol, 53% yield relative to the *total amount* of **1b** employed). From a small sample, the free carboxylic acid is obtained by acidification / extraction. Its optical purity is 95.6% ee according to HPLC (*vide infra*).

The salt (209 g, 0.459 mol) is dissolved in refluxing acetone (2 L). It crystallizes while slowly cooling to ambient temperature overnight. The colourless crystals are suction-filtered, washed with cold acetone (100 mL), MTB ether (300 mL), and dried *in vacuo* (167 g, 99.4% ee). From the mother liquor is obtained a second crop of crystals (18 g, 99.5% ee) after standing 10 d at -20°C. Yield: 185 g (0.406 mol, 47% relative to the *total amount* of **1b** employed).

The suspension of the salt (185 g, 0.406 mol) in MTB ether (7 L) is washed with 2*N* hydrochloric acid (3 x 4 L) and with water (4 L). The organic solution is dried ($MgSO_4$) and the solvent is evaporated *in vacuo* to give the free carboxylic acid **1b** (134.4 g, 0.40 mol, 47% yield relative to the *total amount* of **1b** employed) as a colourless solid foam. Its optical purity is 99.4% ee according to HPLC (*vide infra*).

The solution of the free carboxylic acid **1b** (134.3 g, 0.40 mol, 99.4% ee) in THF (700 mL) is evaporated *in vacuo*. The solid residue is stirred in petrol ether / THF (8:1 , 800 mL) for 30 min at ambient temperature. The solid is suction-filtered, washed with petrol ether / THF (8:1, 100 mL) and dried *in vacuo* (10^{-3} Torr) to give colourless crystalline **1b**-THF-solvate (142.8 g), mp 62 - 63°C. According to ^{1}H-NMR it

contains 0.5 mol-equiv THF, *i.e.* 128.9 g (0.385 mol) **1b**. Yield: 45% relative to the *total amount* of **1b** (of 61% ee) employed ; 16.3% overall yield based on **2**. IR (KBr): 2980, 1738 (C=O), 1295, 1115 cm^{-1} ; UV (CH_3OH): 223 nm (ε = 6.69 x 10^4), 281 nm (ε = 7.0 x 10^3) ; MS (DCI, CH_3OH): $C_{18}H_{22}SO_4$ m/e (rel. intensity) 335 (M+H, 100), 334 (96), 317 (M+H - H_2O, 78), 261 ("317" - $Me_2C{=}CH_2$), 195 (M - H_2O - SO_2tBu, 74) ; $[\alpha]_D^{25}$ 1.98 (c +1.09, CH_3OH) . The optical purity is 99.6% ee according to HPLC (*vide infra*).

HPLC - determination of the optical purity of 8 and 1b :

The free carboxylic acid is derivatized with MEPA [11] / (*R*)-(+)-1-phenylethylamine (CH_2Cl_2, 40°C, 3h) in a reactivial, and the resulting solution of diastereomeric amides is analyzed by HPLC (RP LiChrospher 60 Select B cartridge). With **8**: eluent H_2O / CH_3CN 50:50, 1 mL / min, 25°C, det. 220 nm; *R* (t_{ret} 25.9 min), *S* (27.4 min). With **1b**: eluent H_2O / CH_3CN 56:44, 1 mL / min, 40°C, det. 220 nm; *R* (t_{ret} 15.1 min), *S* (17.6 min). It was secured that racemic and optically pure samples of **8** and **1b** do neither show a kinetic resolution nor a partial racemization during derivatization.

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