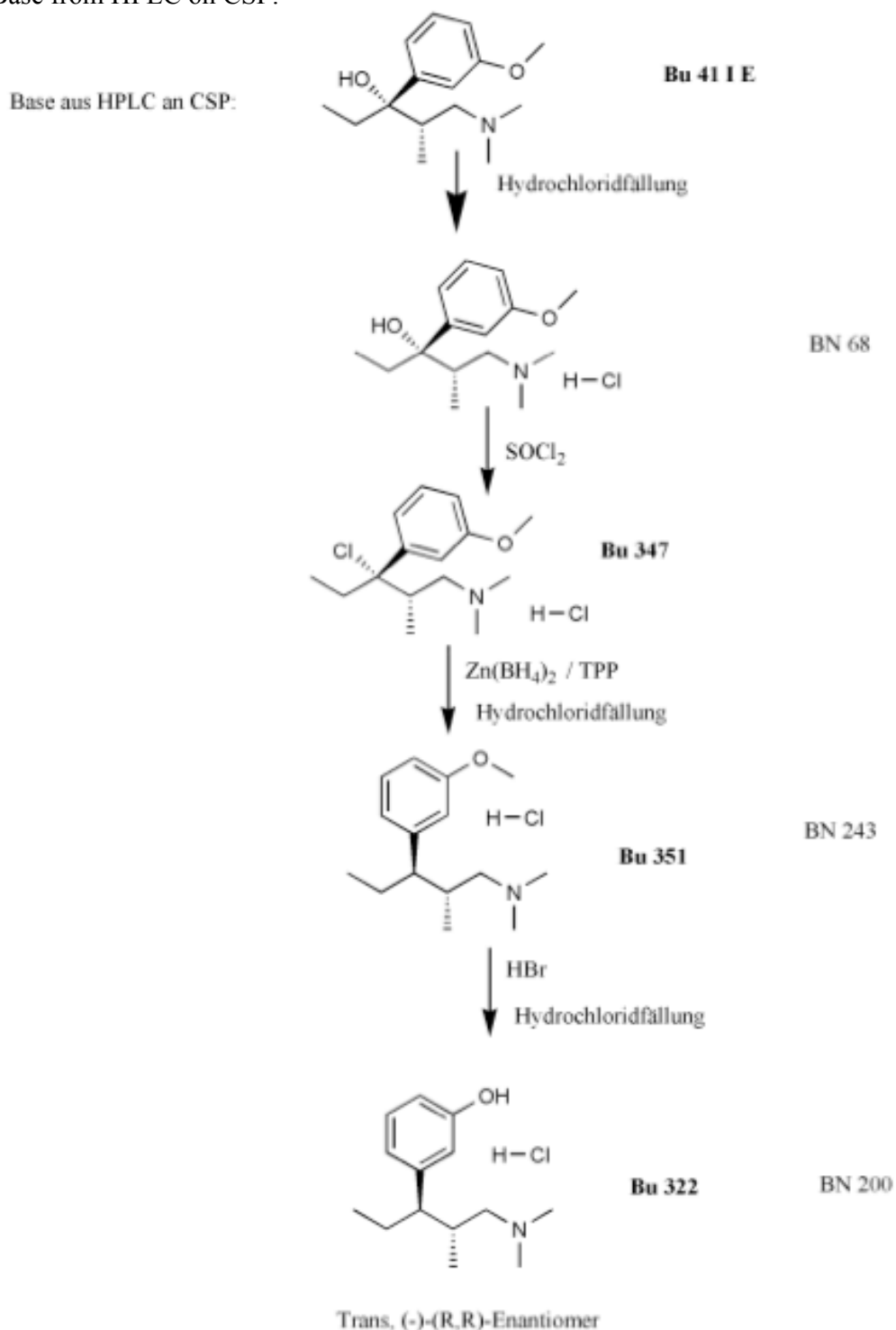


Base from HPLC on CSP:



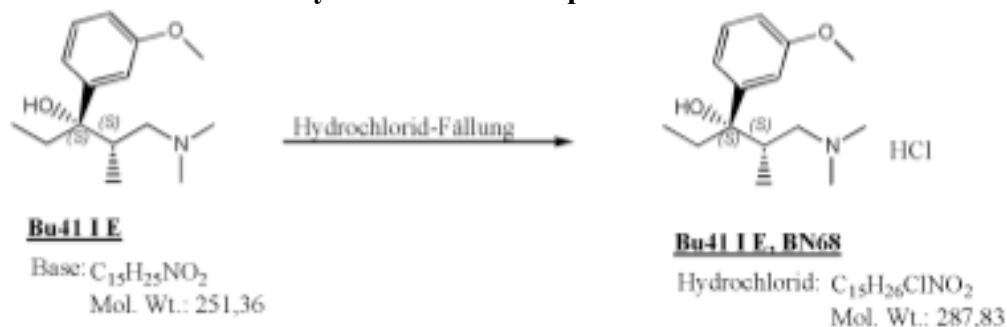
Hydrochloridfällung = hydrochloride precipitation

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GB-Bu41 I E (BN68) Hydrochloride Precipitation



Project Code: FHWF99 Release code: Technician: M. Mueller Date: Aug. 15, 2002

Hydrochloride precipitation	M [g/mol]	m [g]	n [mmol]	V [ml]
Base HPLC-Fr. II	251.36	7.60	30.34	
Methyl ethyl ketone				45.14
Water				0.60
Trimethylchlorosilane			30.24	3.82

Apparatus: 100-ml round flask, magnetic stirrer, dropping funnel, thermometer

Patent specification EP 0 693 475 B1:

The base was released from (1) with dichloromethane/sodium hydroxide solution. After drying the solution, dichloromethane was distilled off under vacuum. The racemate was then separated on the chiral HPLC column. The resulting enantiomers were reacted with trimethylchlorosilane/water in 2-butanone, and the hydrochlorides with a melting point of 150 – 151 °C were obtained.

Execution: Dissolve the base in methyl ethyl ketone and mix while stirring first with water and then with TMCS dropwise. In doing so, the temperature increases to 41 °C. Stir for 30 minutes. No solid precipitates; the solution is clear and colorless.

Remove about half of the solvent on the rotary evaporator. Add 35 ml diethyl ether dropwise while stirring. The hydrochloride will separate as oil. Remove the diethyl ether on the rotary evaporator; in doing so, the hydrochloride precipitates as a solid. Stir for another 30 minutes in the ice bath.

Workup: Filter by suction; wash the solid thoroughly with diethyl ether and suction dry. Concentrate the mother liquor and dry the residue under vacuum. Slurry the remaining solid in diethyl ether, filter by suction and suction dry. Combine with the 1st precipitation. = 8.537 g white solid.

DC: GB-Bu41 I E x HCl Flow agent: ethyl acetate / methanol = 3 / 1

¹H-NMR: Solvent: DMSO
au16.009: GB-Bu41 I E x HCl: OK.

Translated from the German

Ruth Boggs, MA, CT | ATA-Certified Translator (#62196) & Interpreter | rutheboggs@gmail.com



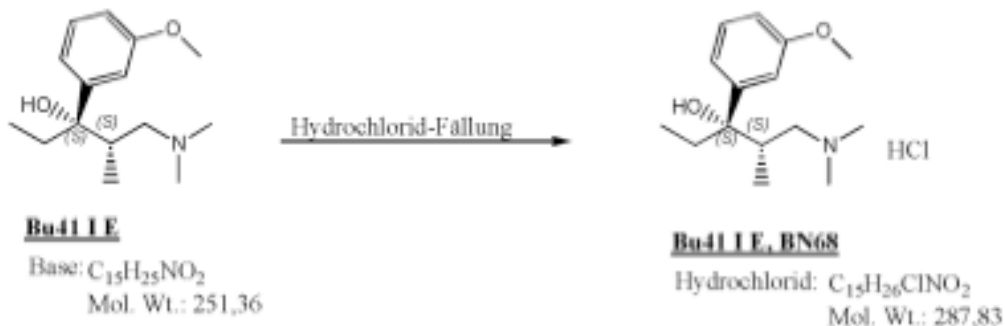
Theoretical yield: 8.70 g hydrochloride

Yield (raw): m = 8.537 g (corresponds to 98.1% of theoretical)

Appearance: white solid

Fusion point: 150 – 152 °C

GB-Bu41 I E (BN68) Hydrochloride Precipitation



Project Code: FHWF99 Release code: Technician: M. Mueller Date: Oct. 7, 2002

Hydrochloride precipitation	M [g/mol]	m [g]	n [mmol]	V [ml]
Base HPLC-Fr. II	251.36	7.60	30.24	
Methyl ethyl ketone				45.14
Water				0.60
Trimethylchlorosilane			30.24	3.82

Apparatus: 100-ml round flask, magnetic stirrer, dropping funnel, thermometer.

Patent specification EP 0 693 475 B1:

The base was released from (1) with dichloromethane/sodium hydroxide solution. After drying the solution, dichloromethane was distilled off under vacuum. The racemate was then separated on the chiral HPLC column. The resulting enantiomers were reacted with trimethylchlorosilane/water in 2-butanone, and the hydrochlorides with a melting point of 150 – 151 °C were obtained.

Execution: Dissolve the base in methyl ethyl ketone and mix while stirring first with water and then with TMCS dropwise. In doing so, the temperature increases to 41 °C. Remove about half of the solvent on the rotary evaporator. Stir for 30 minutes in the ice bath. Add 35 ml diethyl ether dropwise and stir for another 90 minutes in the ice bath.

Workup: Filter by suction; wash the solid thoroughly with diethyl ether and suction dry. Concentrate the mother liquor and dry the residue under vacuum. = 8.07 g white solid. Concentrate the mother liquor, slurry the residue in diethyl ether and stir over night at room temperature. The residue is oily and will be discarded.

¹H-NMR: Solvent: DMSO
dpX022008.003: GB-Bu41 I E x HCl: OK.

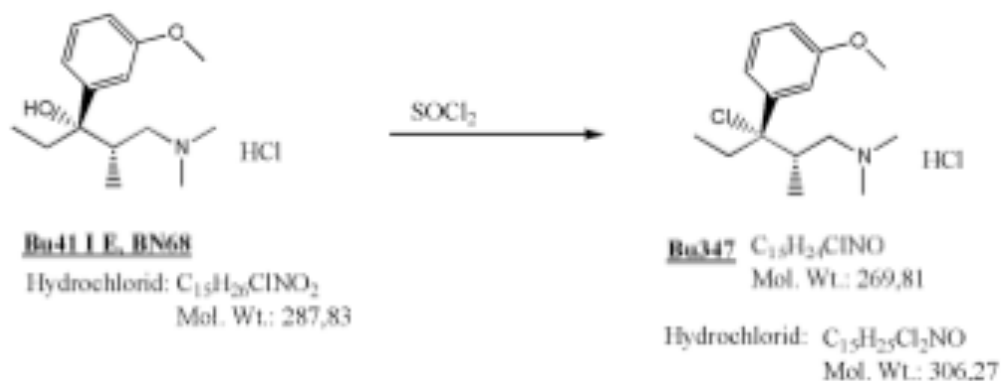
Theoretical yield: 8.70 g hydrochloride

Yield (raw): m = 8.07 g (corresponds to 92.76 % of theoretical)

Appearance: white solid

Fusion point: 148 – 150 °C

GB-Bu347-1-1



Project Code: FHWF99 Release code: Technician: M. Mueller Date: Aug. 19, 2002

Batch size:	M [g/mol]	Density	Factor	n [mmol]	m [g]	V [ml]
GB-Bu41 I E x HCl	287.83		1.0	29.6	8.53	
Thionyl chloride						8.47

Apparatus: 500-ml round flask, magnetic stirrer.**Patent specification EP 0 693 475 B1:****(+)-(2R,3R)-[3-chloro-3-(3-methoxy-phenyl)-2-methyl-pentyl]-dimethylamine, hydrochloride (+22)**

10 g (35 mmol) **(+1)**, prepared according to Example 2, were mixed with 10 ml thionyl chloride at room temperature. To remove excess thionyl chloride, nitrogen was then passed over the reaction mixture for 2 hours. After adding another 10 ml thionyl chloride, the reaction mixture was left to stand for 12 hours, and then excess thionyl chloride was removed again with the help of a stream of nitrogen over 2.5 hours. After drying, the residue was dissolved in 10 ml ice cold 2-butanone and mixed while stirring with 200 ml ether and then with 140 ml diisopropyl ether. The supernatant solvent phase was decanted off and the remaining oil was again taken up in 10 ml 2-butanone. After adding seed crystals, 300 ml diisopropyl ether was added dropwise over 3 hours while stirring vigorously, whereby the hydrochloride crystallized out. 9.8 g (91 % of theoretical) **(22)** were obtained.

Melting point: 120 °C (decomposition)

[α]_D^{RT} = +24.7° (c = 1.01; methanol)

Execution: Mix Bu41 I E x HCl with thionyl chloride and stir for 1 hour at room temperature. Place under nitrogen for 2 hours to remove excess thionyl chloride.
Add another 8.47 ml thionyl chloride and let stand for 16 hours.

Workup: Place again under nitrogen for 2.5 hours while stirring and then dry the residue thoroughly under vacuum.

Hydrochloride precipitation: Dissolve the residue in 8.47 ml ice cooled methyl ethyl ketone and add 169 ml diethyl ether and then 118 ml diisopropyl ether while stirring. Remove the supernatant solvent phase by decanting and take up the remaining oil again in 8.47 ml methyl ethyl ketone. Stirring vigorously, add 254 ml diisopropyl ether dropwise over 3 hours and continue to stir overnight at room temperature.

The product is oily. Remove the solvent and dry the residue **thoroughly** under vacuum.

Dissolve the remaining green oil in methyl ethyl ketone as described above and add diisopropyl ether dropwise over 3 hours. Stir overnight at room temperature.

The product begins to crystallize. Filter by suction and suction dry in air. The solid is strongly hygroscopic; it is removed from the frit with methanol. Remove the solvent and stir the residue overnight in diisopropyl ether.

Completely remove the solvent and dry the residue under vacuum = 8.547g

Immediately continue reaction into Bu351-1-1.

Theoretical yield: 9.076 g hydrochloride**Yield (raw):** m = 8.547 g (corresponds to 94.17 % of theoretical)**Appearance:** gray-green solid

1

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