CEPHALOSPORINS. II
7-(*O*-AMINOMETHYLPHENYLACETAMIDO)CEPHALOSPORANIC ACIDS WITH SIX-MEMBERED HETEROCYCLES IN THE C-3 SIDE CHAIN

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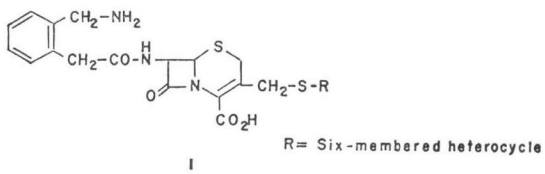
7-(*o*-Aminomethylphenylacetamido)cephalosporanic acids with six-membered heterocycles in the C-3 side chain were prepared by nucleophilic substitution of 7-ACA at the C-3 acetoxy group followed by N-acylation of the 7-amino group. The 7-side chain acid, *o*-aminomethylphenylacetic acid (**5**), was prepared by two new convenient routes, which involved SCHMIDT reaction of indanone (**2**) followed by cleavage of the lactam ring or reduction of *o*-cyanophenylacetic acid (**10**) starting from *o*-nitrotoluene. The antibacterial activity of the cephalosporins in this series depends on the heterocycle in the C-3 side chain. In general pyridazines gave cephalosporin derivatives possessing better activity than those with a pyridine or pyrimidine ring. The most active member of the new cephalosporins was 7-(*o*-aminomethylphenylacetamido)-3-(6-hydroxypyridazin-3-ylthiomethyl)-3-cephem-4-carboxylic acid (BB-S 150) (**1g**) which has *in vitro* antibacterial activity superior to cephalothin and cefazolin against both gram-negative and gram-positive organisms. The *in vitro* activity of BB-S 150 determined in mice was superior to cephalothin and comparable to cefazolin.

The preceding paper[1] described cephaloglycin analogs with six-membered heterocycles in the C-3 side chain. The antibacterial activity varied considerably depending on the azines in the side chain. In general pyridazine and pyridine nuclei gave derivatives with good activity. Recently it has been reported[2] that the phenylglycine residue in the 7-side chain of cephaloglycins may be replaced by *o*-aminomethylphenylacetic acid residue with retention of the antibacterial activity. This paper describes a series of cephalosporins (**1**) which has an *o*-aminomethylphenylacetic acid residue on the 7-amino group and six-membered heterocycles in the C-3 side chain.



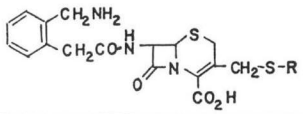
I

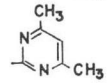
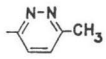
Chemistry

The 7-side chain acid, *o*-aminomethylphenylacetic acid (**5**), was reported by BROWN & REICH[3], but the procedure starting from *o*-ethoxybenzonitrile required rather tedious chemical steps. We investigated the preparation of **5** by two convenient routes as shown in Scheme 1 and Scheme 2.

The first method (Scheme 1) starts with commercially available indene (**2**), which is oxidized with hydrogen peroxide and formic acid[4] to indanone (**3**) in 76% yield. To a suspension of freshly prepared **3** and sodium azide in chloroform was added conc. sulfuric acid at 30~40°C to give the lactam **4** in 87% yield. When sodium azide was added to a solution of **3** in conc. sulfuric acid, the yield of **4** decreased to 30% because of the instability of **3** under acidic conditions. Hydrolysis of **4**

Table 1. 3-Substituted 7-(*o*-aminomethylphenylacetamido) cephalosporins



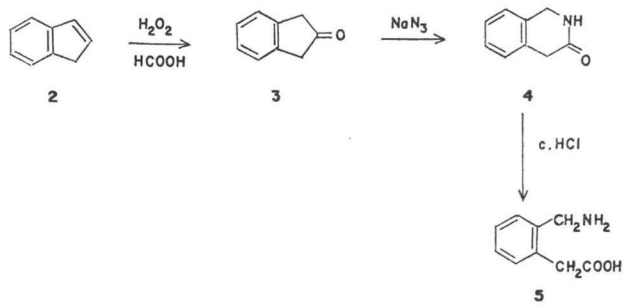
Compound	R	Method[a]	Yield, %	Mp, °C (dec.)	λ_{max}nm(ε)[b]	Formula	Analyses[c]
1a		A	70	222~225	250 (12500) 265 (12500) 290 (sh) (8900)	$C_{22}H_{22}N_4O_4S_2\cdot\frac{1}{2}H_2O$	C, H, N, S
1b		B	30	223~228	238 (30400) 266 (19300) 303 (sh) (4870)	$C_{22}H_{22}N_4O_5S_2\cdot\frac{3}{2}H_2O$	C, H, N, S
1c		A	48	214~218	250 (14000) 265 (14600) 290 (sh)(11100)	$C_{23}H_{24}N_4O_4S_2\cdot\frac{1}{2}H_2O$	C, H, N, S
1d		A	63	250	268 (18500)	$C_{23}H_{25}N_5O_4S_2\cdot\frac{1}{2}H_2O$	C, H, N, S
1e		A	38	260~270	264 (11800)	$C_{21}H_{21}N_5O_4S_2\cdot 2H_2O$	C, H, N, S
1f		A	34	182~184	271 (13900)	$C_{22}H_{23}N_5O_4S_2\cdot 2H_2O$	C, H, N[d]
		A B	67 48	205~210	250 (18000)	$C_{21}H_{21}N_5O_5S_2\cdot 2H_2O$	C, H, N, S

a: A=active ester method, B=mixed anhydride method. b: determined in 1% $NaHCO_3$ solution.
c: Symbols of the elements indicate that analyses are coincident with the calculated value within ±1% deviation unless otherwise states. d: N, calcd, 13.43; found, 12.32.

with conc. hydrochloric acid followed by neutralization with aqueous ammonia gave **5** as colorless needles in 75% yield.

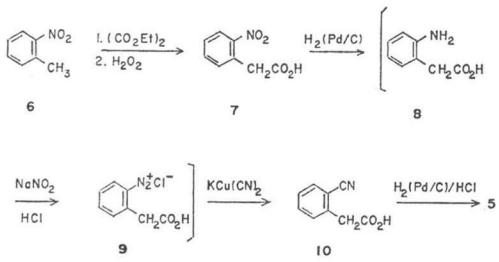
The NMR spectrum of **4** in $CDCl_3$ showed a broad signal at δ8.23 (1 H), a multiplet at δ 4.43 (2 H) and a triplet at δ 3.51 (2 H, J=0.7 Hz). With addition of D_2O the broad signal disappeared and the multiplet changed to a triplet (J=0.7 Hz). Long range coupling between the two sets of methylene protons was confirmed by a decoupling study. This coupling disappeared upon cleavage of the lactam ring of **4** and the NMR of **5** (in $D_2O+K_2CO_3$) gave two singlets due to the corresponding methylenes at δ 3.71 and δ 3.52.

Scheme 1. Preparation of *o*-aminomethylphenylacetic acid (**5**) from indene (**2**)

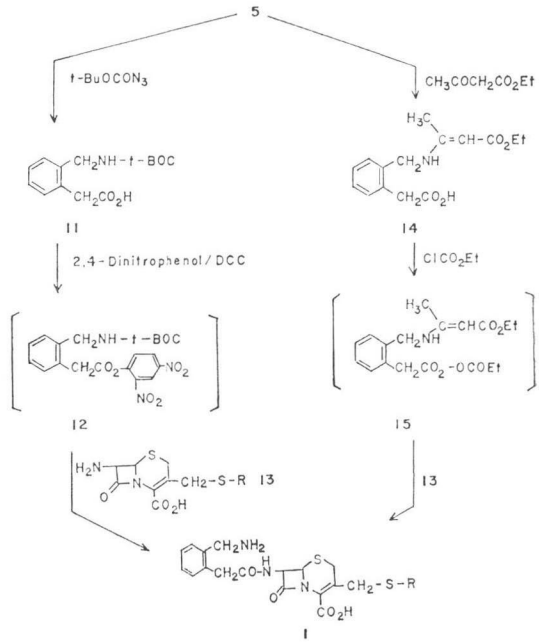


The second route (Scheme 2) is initiated with *o*-nitrotoluene (**6**). According to the procedure of WRIGHT,[5] **6** was treated with diethyl oxalate and then oxidized *in situ* with hydrogen peroxide to afford *o*-nitrophenylacetic acid (**7**) in 45% yield. The nitro acid (**7**) was subjected to catalytic reduction with palladium/charcoal followed by diazotization with sodium nitrite and subsequent cyanation with potassium cuprocyanide to give *o*-cyanophenylacetic acid (**10**)[6] in 77% yield. Hydrogenation of **10** was performed in an acid medium in the presence of palladium/charcoal or platinum oxide to afford

Scheme 2. Preparation of *o*-aminomethylphenylacetic acid (**5**) from *o*-nitrotoluene (**6**)



Schem 3. Preparation of 7-(*o*-aminomethylphenylacetamido)cephalosporanic acids (**1**)



the desired amino acid (**5**) in 75~80% yield, which gave IR and NMR spectra superimposable with those of **5** prepared by the first route.

Derivation to cephalosporins **1** has been carried out by two general methods according to the procedures shown in Scheme 3. Two protective groups were used for protection of the amino function of **5**. Blocking with N-*t*-butoxycarbonyl group (*t*-BOC) was achieved by the reaction of **5** with *t*-butoxycarbonyl azide or *t*-butyl 4,6-dimethylpyrimidin-2-ylthiolcarbonate[7], to give colorless needles **11**. Similar to the procedure of DANE *et al*[8], the reaction of **5** with ethyl acetoacetate gave the N-1-ethoxycarbonyl-1-propen-2-yl derivative (**14**), which was found to be a mixture of *cis* and *trans* isomers by NMR spectrum.

Nucleophilic substitution of the C-3 acetoxy group of 7-ACA was carried out in the usual manner[1] with 6-membered heterocyclic thiols and the resulting 3-substituted 7-ACA's (**13**) were coupled with the N-*t*-butoxycarbonylamino acid (**12**) by the active ester method using 2,4-dinitrophenol and N,N'-dicyclohexylcarbodiimide or with the acetoacetate-protected amino acid (**14**) by the mixed anhydride method using ethyl chloroformate as illustrated in Scheme 3.

The final products **1** were obtained by deblocking of the N-protecting groups with trifluoroacetic acid or formic acid. Table 1 shows the physico-chemical data of **1**.

Antimicrobial Activity

The minimum inhibitory concentration (MIC) of the new series of cephalosporins (**1**) against a variety of gram-positive and gram-negative bacteria were determined by the two-fold serial tube dilution method using nutrient broth (Eiken) and Table 2 shows the results compared with cephalothin (CET) and cefazolin (CEZ).

All of the cephalosporin derivatives **1** in the present study showed antibacterial activity superior to CET and CEZ by one to several tubes against gram-positive test organisms. Differences of the 3-substituent of **1** gave profound differences in the activity against gram-negative bacteria. Three pyridazinylthio derivatives **1e**, **1f** and **1g** were 2~4 fold more active than CEZ and 2~16 fold than CET, whereas the pyridylthio derivatives, **1a**, **1b** and **1c** were nearly equal to or slightly less active than CET and the pyrimidinylthio derivative **1d** was nearly inactive against gram-negative test organisms except *E. coli* NIHJ.

Table 2. *In vitro* activity of 3-substituted-7-(*o*-aminomethylphenylacetamido)cephalosporanic acid derivatives by tube dilution method in nutrient broth

Test organism	MIC (mcg/ml)								
	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	CET	CEZ
S. aureus Smith	0.025	0.2	0.05	0.05	0.1	0.1	0.025	0.4	0.2
S. aureus BX-1633	0.2	0.8	0.1	0.4	0.2	0.4	0.1	0.8	0.4
St. pyogenes A 9604	0.005	0.08	0.005	0.005	<0.0025	0.02	0.02	0.08	0.04
St. pneumoniae	0.005	0.16	0.01	0.01	<0.0025	0.01	0.04	0.16	0.08
E. coli NIHJ	6.3	12.5	0.8	3.1	0.8	1.6	0.8	12.5	3.1
E. coli Juhl A 15119	12.5	6.3	6.3	>100	1.6	1.6	0.8	25	3.1
Kl. pneumoniae A9977	25	3.1	12.5	>100	1.6	1.6	0.8	6.3	1.6
Pr. mirabilis A9900	12.5	12.5	50	>100	3.1	6.3	3.1	6.3	6.3
Salm. enteritidis A9531	12.5	6.3	3.1	100	0.8	1.6	0.8	1.6	1.6

Table 3. Cumulative percentage of 32 test organisms inhibited at indicated antibiotic concentrations

Antibiotic	Minimal inhibitory concentration (mcg/ml)													
	0.025	0.05	0.1	0.2	0.4	0.8	1.6	3.1	6.3	12.5	25	50	100	>100
1f	3.1	3.1	9.4	13	19	41	69	78	78	81	88	91	91	100
1e	3.1	12	16	16	31	56	75	78	84	84	88	91	91	100
1g (BB-S 150)	6.3	9.4	16	16	31	69	75	81	84	84	84	91	94	100
CET	0	0	6.3	12	25	34	38	53	69	69	69	75	78	100
CEZ	0	0	3.1	13	13	44	63	69	75	78	78	78	91	100

Table 4. *In vivo* activity of BB-S 150 (**1g**), cephalothin and cefazolin

Organisms	Route	PD_{50} (mg/kg, mice)		
		BB-S 150	CET	CEZ
S. aureus Smith	sc	0.28	1.9	0.6
E. coli Juhl	sc	4.2	86	2.3
Pr. mirabilis A9554	sc	19	40	19
Pr. vulgaris A9699	sc	29	70	35

The pyridazine derivatives, **1e**, **1f** and **1g** were also evaluated by STEERS' agar dilution method on MUELLER-HINTON agar plates against 4 strains of gram-positive (3 *S. aureus* and 1 *S. faecalis*) and 28 strains of gram-negative bacteria (7 *E. coli*, 4 *K. pneumoniae*, 7 *Proteus* sp., 2 *P. aeruginosa*, 3 *Shigella* sp., 1 *Serratia marcescens*, 1 *Ent. cloacae*, 2 *Salmonella* sp. and 1 *B. anthracis*). The result was compared with CET and CEZ by the cumulative percentage of MIC values (Table 3). These three compounds were more active than both reference antibiotics.

Compound **1g** designated BB-S 150 showed the best *in vitro* activity in this series and was subjected to the comparative *in vivo* evaluation with CET and CEZ. The cephalosporins were administered parenterally to mice infected with *S. aureus* Smith, *E. coli* Juhl, *Pr. mirabilis* A9554 and *Pr. vulgaris* A9699. As shown in Table 4, BB-S 150 was more effective than CET and CEZ against *S. aureus* Smith infection. Against infection caused by the three gram-negative pathogen BB-S 150 was significantly more active than CET and comparable to CEZ.

Experimental

o-Aminomethylphenylacetic acid *δ*-lactam (**4**)

To a chilled suspension of 46 g (0.35 mol) of freshly prepared 2-indanone (**3**)[4] and 27 g (0.42 mol) of sodium azide in 75 ml of $CHCl_3$ was added dropwise 75 ml of conc. H_2SO_4 at such a rate to maintain the temperature at 30~40°C under stirring. After the addition was completed and heat evolution ceased, the stirring was continued for an additional 3 hours. The reaction mixture was poured into 1 kg of crushed ice. The $CHCl_3$ layer was separated and the aqueous layer was extracted with three 200 ml portions of $CHCl_3$. The $CHCl_3$ layer was combined with the $CHCl_3$ extracts, dried over anhydrous Na_2SO_4 and evaporated to dryness to give 44.5 g (87%) of pale yellow prisms **4** melting at 156~159°C.

Anal. Calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52.
Found: C, 73.73; H, 6.08; N, 9.23.

o-Aminomethylphenylacetic acid (**5**)

Preparation from **4**: A mixture of 43.4 g (0.30 mol) of **4** in 140 ml of 6 N HCl was refluxed for 4 hours. The reaction mixture was treated with 1 g of active carbon and evaporated to dryness. The residual oil was triturated with 500 ml of acetone to afford 45 g (75%) of **5** hydrochloride, colorless plates melting at 163~164°C. The hydrochloride was treated with aq. ammonia to give the free amino acid **5**. Colorless plates. M.p. 180~182°C.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48.
Found: C, 65.24; H, 6.47; N, 8.31.

Preparation from **10**: A mixture of 1.6 g (0.01 mol) of *o*-cyanophenylacetic acid (**10**)[6], 25 ml of EtOH and 15 ml of 6 N HCl was hydrogenated with 1 g of 10% Pd on carbon at 50 psi of hydrogen pressure. The theoretical amount of hydrogen was absorbed in 3 hours. The mixture was filtered to removed the catalyst, the filtrate was concentrated to give 1.6 g (80%) of **5** hydrochloride, colorless plates melting at 161~163°C. It was identical with the authentic sample prepared by SCHMIDT rearrangement of 2-indanone (**3**) followed by hydrolysis.

o-(N-BOC-aminomethyl)phenylacetic acid (**11**)

To a solution of 70 g (0.35 mol) of *o*-aminomethylphenylacetic acid hydrochloride (**5**) and 116 g (1.15 mol) of triethylamine in 400 ml of water was added dropwise to a solution of 64 g (0.45 mol) of *t*-butoxycarbonyl azide in 300 ml of THF under stirring at 0°C. After the addition was completed the temperature was allowed to rise to room temperature and the stirring was continued for 20 hours. The THF was distilled off below 40°C and the aqueous solution was washed with 200 ml of ether, layered with 200 ml of ethyl acetate and acidified with dil. HCl to pH 3 under cooling at 0°C. The organic layer was separated and the aqueous layer was extracted with four 200 ml portions of EtOAc. The combined EtOAc solution was washed with 200 ml of water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The concentrate was treated with 500 ml of *n*-hexane to give 87.9 g (95%) of colorless needles **11** melting at 114~116°C.

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28.
Found: C, 63.46; H, 7.11; N, 5.28.

2,4-Dinitrophenyl *o*-(N-BOC-aminomethylphenyl)acetate (**12**)

To an ice-cooled solution of 2.0 g (0.0075 mol) of **11** and 1.38 g (0.0075 mol) of 2,4-dinitrophenol in 16 ml of dry EtOAc was added 1.55 g (0.0075 mol) of DCC with stirring. The reaction mixture was stirred at 5~15°C for 30 minutes and then for an additional 30 minutes at 25°C. The precipitate was removed by filtration and the filtrate was evaporated to dryness under reduced pressure to give 3.8 g of the active ester **12**. IR: ν_{max}^{liq} 3350 (NH), 1780 (CO) cm^{-1}. This ester was employed in the next reaction without further purification.

Sodium *o*-(1-ethoxycarbonyl-1-propen-2-ylaminomethyl)phenylacetate (**14**)

To an ethanolic solution of sodium ethoxide (Na, 0.6 g, 0.026 atom/abs EtOH 50 ml) were added 4.27 g (0.026 mol) of **5** and 3.38 g (0.026 mol) of ethyl acetoacetate and the mixture was refluxed for 6 hours. The mixture was evaporated to dryness and the residue was crystallized from ethanol to

give 6.36 g (82%) of **14**, colorless needles melting at 230~232°C.

IR(KBr): 3320, 1645, 1605, 1470, 1395, 1275, 1180 cm^{-1}.

Anal. Calcd. for $C_{15}H_{18}NO_4Na$: C, 60.20; H, 6.06; N, 4.68.
Found: C, 59.95; H, 5.86; N, 4.67.

7-Amino-3-(pyridin-N-oxido-2-ylthiomethyl)-3-cephem-4-carboxylic acid (**13b**)

To a solution of 9.0 g (0.033 mol) of 7-ACA and 5.6 g (0.066 mol) of sodium bicarbonate in 180 ml of 0.1M SÖRENSEN buffer (pH 6.3) was added in one portion of 4.2 g (0.033 mol) of 2-mercaptopyridine-1-oxide with stirring and the mixture was heated at 75°C for 45 minutes. After cooling, the reaction mixture was acidified with glacial acetic acid to pH 4.0 under cooling at 5°C to give 8.37 g (75%) of **13b**. M.p. 210~230 °C (dec.).

Anal. Calcd. for $C_{13}H_{13}N_3O_4S_2 \cdot \frac{1}{2}H_2O$: C, 44.82; H, 4.05; N, 12.06; S, 18.40.
Found: C, 44.29; H, 3.80; N, 11.87; S, 18.22.

7-(*o*-Aminomethylphenylacetamido)cephalosporanic acid (**1**)

The synthesis of **1a**~**1g** listed in Table 1 has been achieved by two general procedures, the active ester method and the mixed anhydride method. No attempt was made to determine the conditions necessary for optimum yield. The followings are representative procedures for each of the two methods used in this study.

7-(*o*-Aminomethylphenylacetamido)-3-(3-hydroxypyridazin-6-ylthiomethyl)-3-cephem-4-carboxylic acid (**1g**)

(A) Active ester method: To a stirred solution of 1.9 g (3.75 m mol) of **12** in 30 ml of THF was added in one portion a mixture of 7-amino-3-(3-hydroxypyridazin-6-ylthiomethyl)-3-cephem-4-carboxylic acid (**13g**) (1.02 g, 3 m mol), 0.35 ml of triethylamine, 30 ml of THF and 10 ml of water. The reaction mixture was stirred at room temperature for 16 hours and treated with active carbon. The filtrate was diluted with 50 ml of water and washed twice with 100 ml of ether. The aqueous solution was covered with 100 ml of ethyl acetate and acidified to pH 2 with dilute hydrochloric acid under vigorous stirring at 5~10°C. The aqueous layer was extracted twice with 100 ml of ethyl acetate. The organic layer was combined with the ethyl acetate extracts, dried on anhydrous sodium sulfate, treated with active carbon and filtered. Evaporation of the solvent gave a pale yellow oily solid which was triturated with 100 ml of ether to afford 0.95 g of the N-BOC-protected product. A cold mixture of the BOC-protected cephalosporin and 6 ml of trifluoroacetic acid was stirred for 1 hour below 0°C. Ether (100 ml) was added to the reaction mixture and the resulting precipitate was collected. A suspension of the precipitate in 10 ml of water was adjusted to pH 5 with aqueous ammonia. The desired cephalosporin BB-S 150 (**1g**) was collected by filtration, washed with each 5 ml of water and CH_3CN successively, Yield 500 mg (61%). M.p. 205~210°C (dec.).

IR (KBr): 1770, 1665, 1640, 1580, 1395, 1005 cm^{-1}.

NMR ($DO_2 + K_2CO_3$): 3.70 (2H, s, $C\underline{H}_2CO$), 4.15 (2H, s, $C\underline{H}_2$–N), 3.0~4.3 (4H, m, 2–$\underline{H}$ and 3–$C\underline{H}_2$), 4.90 (1H, d, J=4 Hz, 6–$\underline{H}$), 5.45 (1H, d, J=4 Hz, 7–$\underline{H}$), 6.63 (1H, d, J=9 Hz, pyridazine-H), 7.15 (4H, s, phenyl-$\underline{H}$) and 7.20 (1H, d, J=9 Hz, pyridazine-$\underline{H}$).

Anal. Calcd. for $C_{21}H_{21}N_5O_5S_2 \cdot 2H_2O$: C, 48.17; H, 4.81; N, 13.38; S, 12.25.
Found: C, 48.66; H, 4.52; N, 13.04; S, 12.43.

(B) Mixed anhydride method: To a stirred suspension of 0.63 g (2.1 m mol) of **14** in 5 ml of dry CH_3CN containing one drop of N,N-dimethylbenzylamine was added 0.25 g (2.3 m mol) of ethyl chloroformate under stirring at −15°C and the stirring was continued for 20 minutes at −10~−15°C. To the mixture was added in one portion a solution of 0.71 g (2.1 m mol) of **13 g** and 0.21 g (2.1 m mol) of triethylamine in 3 ml of CH_3CN and 3 ml of H_2O, and the mixture was stirred for 1 hour at 0°C. The reaction mixture was treated with a small amount of charcoal. To the filtrate was added 0.5 ml of HCOOH with shaking and the mixture was filtered to remove a small amount of unreacted **13g**. To the filtrate was added 100 ml of CH_3CN and the mixture was allowed to stand for 1 hour at room temperature. The precipitate was filtered and washed with 10 ml of water and dried *in vacuo* to give 0.49 g (48%) of BB-S 150 (**1g**).

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