spectively).

2-[2-Chloroethyl-(*S*)-α-methylbenzylamino]-3-(2-chloroethyl)-2*H*-1,3,2-oxazaphosphorinane 2-Oxide (4). To a solution of **9** (0.41 mmol) and pyridine (0.41 mmol) in benzene (1 mL) was added $SOCl_2$ (1.23 mmol) in an equal volume of the same solvent. The reaction mixture was allowed to stir at 70 °C for 17 h before concentration in vacuo and chromatography of the residue on silica gel ($CHCl_3$/MeOH, 95:5), which gave **4** (R_f 0.75, 35%) as a mixture (44:56) of diastereomers. Separation of the diastereomers of **4** was achieved by multiple-elution (4–5 times) thick-layer (1 mm) chromatography on silica gel using ethyl acetate as eluent. Methanol was used to remove the diastereomers of **4** from the silica gel; however, recovery was low (~60%). For **4A** (faster eluting): ^1H NMR (220 MHz, $CDCl_3$/Me_4Si) δ 7.45–7.25 (m, 5 H, aromatic), 5.07–4.86 (m, 1 H, benzylic), 4.50–4.11 (m, 2 H, CH_2O), 3.80–3.52 and 3.52–3.02 (two m, 10 H), 2.16–1.95 and 1.95–1.80 (two m, 2 H, $CH_2CH_2CH_2$), and 1.56 (d, J_{HH} = 7 Hz, 3 H, CH_3). For **4B** (slower eluting): ^1H NMR δ 7.45–7.27 (m, 5 H, aromatic), 5.14–4.98 (m, 1 H, benzylic), 4.51–4.35 and 4.35–4.14 (two m, 2 H, CH_2O), 3.77–3.57 and 3.48–3.05 (two m, 10 H), 2.18–1.82 (m, 2 H, $CH_2CH_2CH_2$), and 1.58 (d, J_{HH} = 7 Hz, 3 H, CH_3). ^{31}P NMR (40.25 MHz, 4:1 EtOH/H_2O, 25% H_3PO_4 as external reference) (for **4A**) δ 13.92, (for **4B**) δ 14.47.

Hydrogenolysis of 4. A diastereomerically enriched sample of **4A**/**4B** (10:90, 22.4 mg) in EtOH/H_2O (4:1, 5 mL) with 10% Pd–C (134.4 mg) was subjected to a medium-pressure (50 psi) of hydrogen for 3 days at 25 °C. The isophosphamide product (25%) was identified and quantified by direct ^{31}P NMR analysis of the filtered reaction mixture: δ 13.38 (25% H_3PO_4 external reference). Concentration of the reaction mixture, as in the case of **9**, was followed by drying in vacuo over P_2O_5 and gave an oily residue. This material (10 mg) was dissolved in $CDCl_3$ (1.7 mL), and the chiral shift reagent Eu(hfc)$_3$ (2 equiv based on total ^{31}P content) was added in portions for direct assessment of the enantiomeric composition of **1**. Narrow ($\omega_{1/2} \cong 8$ Hz) ^{31}P NMR absorptions were clearly evident for the individual enantiomers of **1** at δ −68.57 and −70.93, and these signals were in a relative abundance of 10 and 90, respectively. There was no problem of overlap between these signals and the further upfield-shifted absorptions of **4A**/**4B** (δ ~−100). Isolation of **1** was accomplished by thin-layer (0.25 mm) chromatography on silica gel (10 × 20 cm plate) using $CHCl_3$/MeOH (9:1) eluent. In this solvent system, Eu(hfc)$_3$ and unreacted **4A**/**4B** travel with the solvent front while **1** has a R_f value of 0.74. Isolation of the area corresponding to R_f ~0.74 followed by desorption with methanol gave material (3 mg) which had a ^1H NMR (220 MHz) spectrum essentially identical with that of authentic **1**.

Oppositely enriched **4A**/**4B** (82:18) starting material under duplicate hydrogenolysis conditions led to a 90 and 10 relative abundance of the ^{31}P signals at δ −68.57 and −70.93, respectively. Chromatographic purification as above likewise gave material (2 mg), which had a ^1H NMR (220 MHz) spectrum essentially identical with that of authentic **1**.

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Registry No.—(+)-**1**, 66849-34-1; (−)-**1**, 66849-33-0; **4A**, 68927-45-7; **4B**, 68927-46-8; **5**, 68927-47-9; **6**, 2627-86-3; **7**, 66921-28-6; **8A**, 68927-48-0; **8B**, 68927-49-1; **9A**, 68927-50-4; **9B**, 68927-51-5; benzyl 2-hydroxyethyl ether, 622-08-2; benzyl 2-chloroethyl ether, 35655-21-1; benzyl 2-iodoethyl ether, 54555-84-9; (*S*)-*N*-(2-hydroxyethyl)-*N*-α-methylbenzylamine, 66849-29-4; (*S*)-*N*-(2-chloroethyl)-*N*-α-methylbenzylamine hydrochloride, 66849-30-7, ethylene glycol, 107-21-1; benzyl bromide, 28807-97-8; 1-amino-3-propanol, 156-87-6; 2-chloroethanol, 107-07-3.

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N^2,N^3-Di-*tert*-butoxycarbonylspermidine. A Synthesis of the Aglycone of the LL-BM123 Antibiotics

Michael Humora and James Quick*[1]

Department of Chemistry, Northeastern University, Boston, Massachusetts 02115

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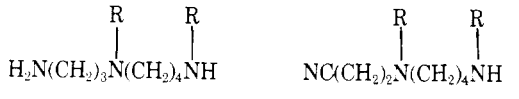
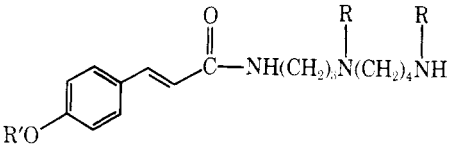
In recent years several alkaloids have been discovered that have spermidine (**1**) incorporated in their structures.[2] As part of our plan to synthesize several of these alkaloids, we required a derivative of spermidine in which the secondary amine and one of the primary amines were blocked by a group that is stable to base and to other vigorous, nonacidic conditions. Because the *tert*-butoxycarbonyl (BOC) group constitutes a base-stable, acid-labile nitrogen protecting group,[3] N^2,N^3-di-*tert*-butoxycarbonylspermidine (**2**) was prepared.[4]

Monoalkylation of 1,4-diaminobutane with acrylonitrile afforded the diaminonitrile **3**.[5] The BOC groups were introduced by treatment of **3** with 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), a reagent previously utilized in peptide chemistry.[6] In nonpeptide applications such as this, the byproduct, 2-hydroxyimino-2-phenylacetonitrile, may be conveniently separated from the product, **4**,

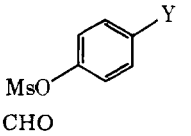


1, R = H
2, R = $(CH_3)_3COC(O)$– (BOC)

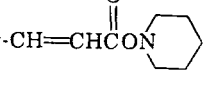
3, R = H
4, R = BOC



5, R = R′ = H
9, R = BOC; R′ = $-SO_2CH_3$ (Ms)
10, R = BOC; R′ = H
11, R = H·HCl; R′ = H



6, Y = CHO
7, Y = *t*-CH=CHCOOH



8, Y = *t*-CH=CHCON

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by washing with base. The nitrile **4** was reduced to the amine **2** by $LiAlH_4$. In contrast to other carbamates,[7] the *tert*-butylcarbamates were unaffected by this reagent. Because of the ease of handling **4** and the expected oxidative instability of **2**, we routinely stored **4** and prepared **2** immediately prior to use.

With the desired spermidine derivative readily available, we first used it in a synthesis of the aglycone **5** of the antibiotics, LL-BM123β, -γ_1, and -γ_2.[8] That the cinnamoyl group was attached to N^1 of spermidine had been deduced from NMR spectra during the structure determination of these antibiotics. A regiospecific synthesis of **5** would be useful in confirming this structure.

The required active ester **8** was prepared from *p*-hydroxybenzaldehyde through its mesylate derivative, **6**, which gave the *trans*-cinnamic acid **7** by a Knovenagel reaction. Treatment of **7** with thionyl chloride followed by *N*-hydroxypiperidine produced **8** in 76% overall yield. The condensation of **8** and **2** afforded **9** in moderate yield. The protecting groups were removed by sequential exposure to base and acid, yielding the dihydrochloride salt **11**. The free aglycone **5** obtained by treatment with ammonium hydroxide had a melting point and an NMR spectrum (270 MHz) essentially identical with those previously reported,[8] confirming the deduced structure.

We are presently studying the versatility of the spermidine derivative **2** in the synthesis of some of the spermidine alkaloids.

Experimental Sections

General. This information is the same as that previously reported[9] with the exception that some of the 60-MHz NMR spectra were recorded with a JOEL FT-60Q spectrometer.

***N,N*-Di-*tert*-butoxycarbonyl-*N*-(2-cyanoethyl)-1,4-diaminobutane (4).** To a solution of 2.0 g (14 mmol) of *N*-(2-cyanoethyl)-1,4-diaminobutane (**3**)[5] and 4.4 g (44 mmol) of triethylamine in 50 mL of a 10% aqueous dioxane solution was added 7.0 g (28 mmol) of BOC-ON.[6] This solution was protected from light and stirred for 3 days at room temperature. After concentration in vacuo, the residue was diluted with ether and washed with 1 N NaOH and brine and the combined ether portions were dried (Na_2SO_4). The ether was removed in vacuo affording an oil. Chromatography on 50 g of silica gel [ether–benzene (2:9)] afforded 3.31 g (70%) of **4**. An analytical sample was obtained by a bulb-to-bulb distillation: IR (film) 3360, 2980, 2200, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.46 (s), 1.48 (s), 1.14–1.63 (m, 22 H), 2.60 (t, J = 7 Hz, 2 H), 3.3 (m, 6 H), and 4.7 (br s, 1 H). Anal. Calcd for $C_{17}H_{31}N_3O_4$: C, 59.80; H, 9.15; N, 12.31. Found: C, 59.78; H, 9.20; N, 12.47.

***N*²,*N*³-Di-*tert*-butoxycarbonylspermidine (2).** To 2.95 g (8.6 mmol) of **4** in 40 mL of anhydrous ether at 0 °C was added 2.00 g (53 mmol) of $LiAlH_4$ in small portions with vigorous stirring. After stirring for 12 h the reaction mixture was quenched by the sequential, dropwise addition of 3 mL of water, 3 mL of 15% aqueous NaOH, and 10 mL of water. The resulting suspension was filtered and the solid was washed three times with 20-mL portions of ether. The combined filtrates were washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo affording 2.08 g (70%) of **2** as an oil: IR (film) 3360, 2980, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.17–1.64 (br, 24 H), 2.7 (t, 2 H), 3.13 (m, 8 H), 4.66 (br s, 1 H).

4-Methanesulfonyloxybenzaldehyde (6). To a 0 °C solution of 12.0 g (98.0 mmol) of *p*-hydroxybenzaldehyde in 40 mL of pyridine was added 15.0 g (130 mmol) of freshly distilled methanesulfonyl chloride. The reaction mixture was allowed to stir for 4 h. The solution was poured into ice-cold aqueous HCl and extracted with ethyl acetate and the combined extracts were washed with saturated sodium bicarbonate and brine and dried ($MgSO_4$). Removal of the solvent in vacuo afforded 19.0 g (96%) of **6** as a yellow solid. An analytical sample of **6** was obtained by two successive bulb-to-bulb distillations: mp 60–61 °C; IR ($CHCl_3$) 3040, 1710, 1605, 1385, 1180, 1160 cm^{-1}; NMR ($CDCl_3$) δ 3.22 (s, 3 H), 7.42 (d, J = 9 Hz, 2 H), 7.93 (d, J = 9 Hz, 2 H), 10.01 (s, 1 H). Anal. Calcd for $C_8H_8O_4S$: C, 47.99; H, 4.03. Found: C, 47.72; H, 3.93.

***trans*-4-Methanesulfonyloxycinnamic Acid (7).** A solution of 8.00 g (40 mmol) of **6**, 6.25 g (60 mmol) of malonic acid, 30 mL of anhydrous pyridine, and 0.5 mL of piperidine was heated on a steam bath for 2.5 h. The cooled reaction was poured into a solution of 50 mL of concentrated hydrochloric acid and 200 g of crushed ice. The precipitate was filtered, washed with 5% hydrochloric acid and water, and air dried, affording 9.38 g (97%) of **7**. Recrystallization from dilute acetic acid afforded analytically pure **7**: mp 211–2 C°; IR (KBr) 3200, 1685, 1505, 1428, 1370, 1215, 1155 cm^{-1}; NMR (acetone-d_6) δ 3.32 (s, 3 H), 6.53 (d, J = 16 Hz, 1 H), 7.3–7.9 (m, 5 H). Anal. Calcd for $C_{10}H_{10}O_5S$: C, 49.58; H, 4.16. Found: C, 49.36; H, 4.18.

1-Piperidyl *trans*-4-Methanesulfonyloxycinnamate (8). A solution of 3.00 g (12.0 mmol) of **7** and 6.00 g (50.4 mmol) of thionyl chloride was heated at reflux for 6 h. The residue obtained after removal of excess thionyl chloride in vacuo was diluted with 10 mL of anhydrous benzene. To this mixture was added 1.50 g (14.8 mmol) of *N*-hydroxypiperidine in 5 mL of anhydrous benzene. This solution was stirred for 3 h at ambient temperature. The benzene was removed in vacuo affording 3.2 g (81%) of an oil that solidified on standing. Recrystallization from benzene–hexane afforded pure **8**: mp 95.6 °C; IR ($CHCl_3$) 1720, 1638, 1500, 1378, 1150 cm^{-1}; NMR ($CDCl_3$) δ 1.8 (br m, 10 H), 3.15 (s, 3 H), 6.35 (d, J = 16 Hz, 1 H), 7.2–7.8 (m, 5 H). Anal. Calcd for $C_{15}H_{19}O_5NS$: C, 55.37; H, 5.89. Found: C, 55.15; H, 5.88.

***N*¹-4-Methanesulfonyloxycinnamoyl-*N*²,*N*³-di-*tert*-butoxycarbonylspermidine (9).** A solution of 1.0 g (3.1 mmol) of ester **8** and 1.0 g (2.9 mmol) of **2** in 20 mL of anhydrous THF was stirred for 6 days at room temperature and protected from light. The THF was removed in vacuo affording 2.02 g of a crude yellow oil. The crude oil was purified by medium pressure liquid chromatography [20 psi; silica gel (0.032–0.063 μm); ethyl acetate–benzene (3:2)] to afford 1.01 g (61%) of pure **9**: IR ($CHCl_3$) 1665, 1505, 1384, 1175, 1155 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.8 (m, 24 H), 2.7–3.5 (m, 11 H), 4.6 (br, 1 H), 6.43 (d, J = 16 Hz, 1 H), 6.8–7.8 (m, 5 H). Anal. Calcd for $C_{27}H_{43}O_8N_3S$: C, 56.92; H, 7.61; N, 7.38. Found: C, 56.76; H, 7.87; N, 7.08.

***N*¹-4-Hydroxycinnamoyl-*N*²,*N*³-di-*tert*-butoxycarbonylspermidine (10).** To a solution of 218 mg (0.383 mmol) of **9** in 75 mL of methanol was added 25 mL of 6 N NaOH solution. The reaction mixture was stirred for 4 h at room temperature. The solution was acidified and extracted with ether (4 × 100 mL) and the combined extracts dried ($MgSO_4$) and concentrated to afford 175 mg (86%) of **10**: IR ($CHCl_3$) 3445, 1660, 1603, 1510, 1210 cm^{-1}; NMR ($CDCl_3$) δ 1.0–1.8 (br, 24 H), 3.14 (m, 8 H), 4.78 (br, 1 H), 6.25 (d, J = 16 Hz, 1 H), 6.6–7.7 (m, 6 H).

***N*¹-4-Hydroxycinnamoylspermidine (5).** A solution of 175 mg (0.36 mmol) of **10** in 14 mL of anhydrous methanol was added dropwise with stirring to methanol saturated with hydrogen chloride. The reaction mixture was stirred for 4 h at room temperature and then concentrated in vacuo to afford 123 mg of **11** as a yellow crystalline solid (mp 228–30 °C).

This salt, **11**, was treated with 10 mL of concentrated ammonium hydroxide for 30 min at room temperature. Concentration of this solution in vacuo afforded a salt mixture which was recrystallized from ethanol to afford 51 mg of **5**: mp 234–5 °C (lit.[8] mp 232–5 °C); IR (KBr) 3315, 2945, 1650, 1605 cm^{-1}; NMR (D_2O) δ 1.83 (m, 4 H), 1.97 (m, 2 H), 3.1 (m, 6 H), 3.36 (t, 2 H), 6.43 (d, J = 16 Hz, 1 H), 6.94 (d, J = 9 Hz, 2 H), 7.40 (d, J = 16 Hz, 1 H), 7.53 (d, J = 16 Hz, 2 H).

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Registry No.—**2,** 68076-39-1; **3,** 4748-73-6; **4,** 68076-41-5; **5,** 67005-74-7; **6,** 69088-97-7; **7,** 69088-98-8; **8,** 69088-99-9; **9,** 69089-00-5; **10,** 69089-01-6; **11,** 69089-02-7; BOC-ON, 58632-95-4; *p*-hydroxybenzaldehyde, 123-08-0; malonic acid, 141-82-2; *N*-hydroxypiperidine, 4801-58-5.

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Ionic Hydrogenations Using $BF_3 \cdot OH_2$. Reductions of Polycyclic Aromatics

John W. Larsen* and Laurence W. Chang

Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830 and Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37916

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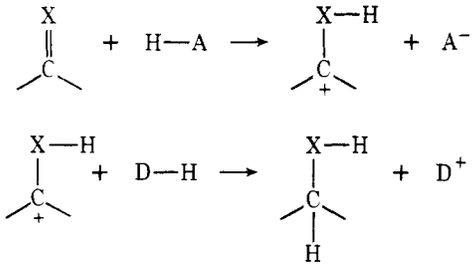
The hydrogenation of organic compounds can be accomplished by protonation to generate a cation followed by hydride abstraction by the cation from some hydride source (eq 1). A variety of acid–hydride donor pairs have been used. The



(1)

most well-developed system is a mixture of CF_3COOH and Et_3SiH,[1] although several other acids have also been used with Et_3SiH.[2-4] Recently, aromatics have been hydrogenated using strong acids such as HF–TaF_5 and molecular hydrogen as the hydride donor.[5] Similar reductions of aliphatic hydrocarbons are also known.[6,7] It has not been possible to use very strong acids with triethylsilane due to reaction of the acids with the silane. Both neat sulfuric and chlorosulfonic acids react with triethylsilane,[8] but aqueous sulfuric acid has been used to carry out reductions.[9] It is clear that the discovery of stronger acids which do not react directly with triethylsilane will increase the scope of this reaction.

The variety of organic compounds which can be reduced by ionic hydrogenation with triethylsilane is not large.[10] Only hydrocarbons giving tertiary or benzylic carbonium ions react with this reagent in protic media. Secondary alcohols have been reduced with BF_3 in methylene chloride[4] and the reduction of carbonyls to methylene has recently been reported.[11] There are no reports of the reduction of aromatics using the CF_3COOH–Et_3SiH pair except for the formation of 9,10-dihydroanthracene from anthracene.[12]

In this paper results obtained using the $F_3B \cdot OH_2$–Et_3SiH pair are reported. Such strong acids as $F_3B \cdot OH_2$ and HF do not react rapidly with triethylsilane, suggesting that the reactions of neat sulfuric and chlorosulfonic acids[8] are due to their high oxidizing power rather than their strength as proton donors. The acid prepared by dissolving BF_3 in water is a fascinating, useful material whose chemistry has not been much explored. The acidity of the monohydrate is comparable to anhydrous sulfuric and hydrofluoric acids.[13] The work described here was carried out in boron trifluoride monohydrate, a stable conducting material (mp 6.0 °C) which has been characterized by Greenwood and Martin.[14] Their work has been summarized together with the most of the known chemistry of the BF_3 hydrates in a good review[15a] and a book[15b] which is out of date. This acid has been little used for organic reactions. Eastham and co-workers studied boron trifluoride hydrate in ethylene dichloride as an initiator for cationic polymerizations.[16] Recently it was shown that it could be used to generate carbonium ions from diphenylethylene in methylene chloride.[17] It has also been used to prepare deuterated aromatics by proton exchange.[18]

Results and Discussion

The following compounds are not reduced by triethylsilane and $F_3B \cdot OH_2$ at 25 °C: naphthalene, phenanthrene, 1-methylnaphthalene, β-naphthalenethiol, phenol, anisole, toluene, and benzene. Compounds reduced and their products are shown in Table I.

Since anthracene is hydrogenated and phenanthrene is not, a carbonium ion stabilized by a pair of phenyls is required for reduction; conjugation with a single ring is not sufficient. The naphthalene nucleus is attacked when strongly activated, but is inert without such activation. As expected,[1] aryl ketones are easily reduced to the hydrocarbons. Some aliphatic ketones can be converted to the corresponding hydrocarbons using this reaction as shown by the formation of adamantane from adamantanone. Reductions of aliphatic ketones to hydrocarbons are quite sensitive to the reaction conditions.

Formally, the mechanism of this reduction is protonation followed by hydride abstraction. In nucleophilic media, a synchronous mechanism involving simultaneous hydride transfer and nucleophilic attack on silicon has been proposed,[19,20] while siliconium ion formation has been proposed in nonnucleophilic media.[21] Earlier we reported that naphthalene, benzene, and activated benzenes readily exchanged hydrogen with $F_3B \cdot OD_2$, presumably by a protonation–deprotonation sequence.[18] These compounds are not reduced by $F_3B \cdot OH_2$–Et_3SiH mixtures. This clearly demonstrates that the second step of the reaction, which is formally a hydride abstraction, must be rate determining. Boron trifluoride monohydrate is the strongest acid known to be compatible with triethylsilane. We hope that the utility of this reducing system with other functional groups will be explored.

Experimental Section

All compounds studied were commercially available and were used without further purification. A 6 ft × 0.125 in. 5% SE-30 on Chromosorb W column was used for GLC work, and decane was used as a GLC internal standard.

Preparation of $BF_3 \cdot H_2O$. A weighed amount of H_2O was cooled in an ice–water bath and BF_3 was bubbled into the liquid until a 1:1 mole ratio was reached as measured by the weight increase. $BF_3 \cdot H_2O$ is a dense fuming liquid and was stored in a polyethylene bottle.

Reduction of Anthracene. To a flask containing 15 g (0.175 mol) of $BF_3 \cdot H_2O$ and cooled in a water bath, 3 g (0.017 mol) of anthracene and 20 mL of methylene chloride were added. The mixture was stirred for 1 min, and 2.5 g (0.022 mol) of triethylsilane was added dropwise. After stirring for 1 h, the reaction mixture was extracted with methylene chloride several times. The methylene chloride extracts were combined, washed with water, and dried ($MgSO_4$). After methylene chloride was evaporated, 2.7 g of 9,10-dihydroanthracene was obtained; mp 108–109 °C; yield 89%; NMR (CCl_4) δ 3.75 (4 H, s), 7.0 (8H, s).

Reduction of Naphthacene. To a flask containing 10 g (0.117 mol) of $BF_3 \cdot H_2O$ and cooled in a water bath, 0.2 g (0.876 m mol) of naphthacene and 10 mL of methylene chloride were added. The mixture was stirred for 5 min followed by the dropwise addition of 1.7 g (14.6 mmol) of triethylsilane. The reaction mixture was stirred for 4 h and was extracted several times with methylene chloride. The methylene chloride extracts were combined, washed with water, dried ($MgSO_4$), and evaporated. The residue was 180 mg of a white solid:

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