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Asymmetric synthesis of *N*-protected chiral 1-aminoalkylphosphonic acids and synthesis of side chain–functionalized depsiphosphonopeptides

HAN LIU, SHUZONG CAI and JIAXI XU*

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

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Abstract: Optically active 1-aminoalkylphosphonic acid derivatives were synthesized in moderate yields and optical purities via Mannich-type reactions of benzyl carbamate, aldehydes, and optically pure chlorophosphites. Side chain–functionalized depsiphosphonopeptides were also prepared in satisfactory yields directly from one-pot reactions of benzyl carbamate, aldehydes, and diethyl (*R,R*)-2-chloro-1,3,2-dioxaphospholane-4,5-dicarboxylate. Copyright © 2005 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: aminoalkylphosphonic acid; asymmetric synthesis; chlorophosphite; depsiphosphonopeptide; peptide; phosphonopeptide

INTRODUCTION

α-Aminoalkylphosphonic acids are a class of very important phosphorus analogues of naturally occurring amino acids that have been discovered in a wide range of living organisms, animals, and even human tissues [1]. Numerous aminoalkylphosphonic acids have been obtained from natural resources and by synthesis previously [1,2]. To date, many methods have been developed for the synthesis of racemic aminoalkylphosphonic acids and derivatives [1–4] and for that of optically active aminoalkylphosphonic acids and derivatives [1,5,6]. The Mannich-type reaction of carbamates, aldehydes, and phosphites is a versatile method for the synthesis of aminoalkylphosphonic acids and derivatives [3–5,7–13]. Herein, we report our results on the asymmetric synthesis of optically active aminoalkylphosphonic acid derivatives and the synthesis of side chain–functionalized depsiphosphonopeptides by using this one-pot three-component condensation reaction.

RESULTS AND DISCUSSION

Mannich-type condensation is one of the important methods of synthesis of α-aminoalkylphosphonic acids and derivatives. Numerous α-aminoalkylphosphonic acids and derivatives have been synthesized by the use of the three-component condensation [3–5], followed by hydrolysis [7–9,13], alcoholysis [11,12], and aminolysis [10]. However, little attention has been paid to the asymmetric synthesis of optically active α-aminoalkylphosphonic acids and derivatives by the use of this reaction [5]. Herein, a one-pot reaction was attempted for preparing optically active aminoalkylphosphonic acid derivatives via simple starting materials, benzyl carbamate, aldehydes, mono- or dichlorophosphites derived from phosphorus trichloride with chiral alcohols (1-phenylethanol, 1,2-diphenyl-1,2-ethanediol, and diethyl L-tartrate) and (*R*)-1,1′-bi-2-naphthol.

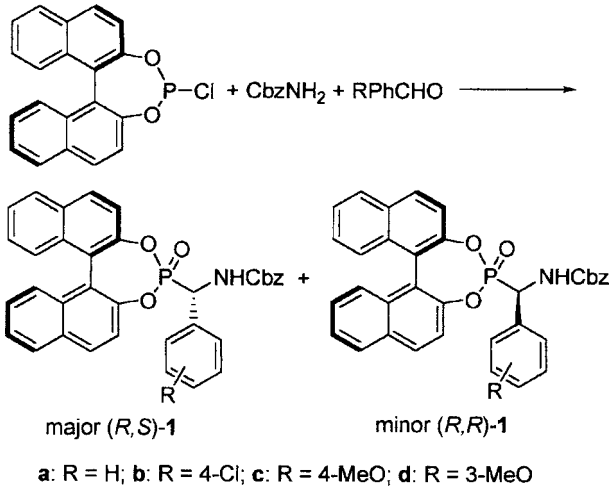
Firstly, optically pure (*R*)-1-phenylethanol and 1,2-diphenyl-1,2-ethanediol were selected as a chiral source. When (*R*)-1-phenylethanol was reacted with phosphorus trichloride to prepare the corresponding chlorophosphite, styrene was obtained instead in high yield because of dehydrolysis of phosphorus trichloride. When the *in situ*–formed 1-phenylethyl dichlorophosphite, prepared via mixing 1-phenylethanol with phosphorus trichloride, was applied in the Mannich reaction with benzaldehyde and benzyl carbamate, 1-(*N*-Cbz-amino)-1-phenylmethylphosphonic acid (**3a**) was obtained in low yield together with styrene. When the *in situ*–formed 2-chloro-4,5-diphenyl-1,3,2-dioxaphospholane, generated from 1,2-diphenyl-1,2-ethanediol and phosphorus trichloride, was applied in the Mannich reaction, electrospray ionization (ESI) and NMR spectra indicated that a mixture of 1-(*N*-Cbz-amino)-1-phenylmethylphosphonic acid (**3a**), 1,2-diphenyl-2-hydroxyethyl 1-(*N*-Cbz-amino)-1-phenylmethylphosphonate and the desired product 1,2-diphenylethylene 1-(*N*-Cbz-amino)-1-phenylmethylphosphonate were obtained in moderate yield.

Secondly, optically pure (*R*)-1,1′-bi-2-naphthol was selected as a chiral source. It was reacted with phosphorus trichloride to afford the corresponding chlorophosphite, (*R*)-4-chloro-dinaphtho[2,1-*d*:1′,2′-*f*]

*Correspondence to: J. Xu, College of Chemistry, Peking University, Beijing 100871, China; e-mail: jxxu@pku.edu.cn

[1,3,2]dioxaphosphepin, according to the method in the literature [14]. The chlorophosphite reacted with benzyl carbamate and aldehyde in anhydrous benzene. The corresponding aminoalkylphosphonate diesters were obtained in satisfactory yields after chromatographic separation (Scheme 1). ^{31}P NMR spectra indicate that the diastereoselective ratios vary from 1.1 : 1 to 1.8 : 1. When we attempted to improve the diastereoselectivity, we found that a similar reaction, in which urethane was used, was published very recently [5]. The reported diastereoselectivities were at the same level as ours. On the basis of the reported results [5], the major isomers of our products were assigned as (*S*)-1-amino-1-arylmethylphosphonic derivatives.

Finally, diethyl (*R*, *R*)-2-chloro-1,3,2-dioxaphospholane-4,5-dicarboxylate was readily prepared from diethyl L-tartrate and phosphorus trichloride according to the method in the literature [15]. It was mixed and stirred with benzyl carbamate and aldehyde in anhydrous benzene. After stirring for 6 h, instead of aminoalkylphosphonate diesters, aminoalkylphosphonate monoesters were obtained in satisfactory yields after crystallization or chromatographic separation (Scheme 2). ^{31}P NMR spectra indicate that the diastereoselective ratios vary from 1.7 : 1 to 2.5 : 1. After saponification of the product **2a**, 1-Cbz-amino-1-phenylmethylphosphonic acid **3a** was obtained with a positive sign of optical rotation. From the literature [16], we can identify that the major isomer of *N*-Cbz-amino phosphonic acid **3a** should be in the *R*-configuration. Although low diastereoselectivity was achieved, the aminoalkylphosphonate monoesters could be considered as a class of phosphonate-linked phosphonopeptides, side chain–functionalized depsiphosphonopeptides. In current cases, depsiphosphonopeptides were straightforwardly synthesized from simple starting materials via the Mannich-type multiple component condensation. In previous synthetic methods, they were obtained by careful selective hydrolysis of phosphonate diester-linkage depsiphosphonopeptides in most cases [17], condensation of phosphonic acid with hydroxy esters [18], oxidation of phosphonous monoester-linkage peptides [19], and the Mannich-type three-component condensation of a carbamate, aldehyde, and chlorophosphite, followed by alcoholysis with an hydroxy ester [20].



Scheme 1 Asymmetric synthesis of aminoalkylphosphonic acids.

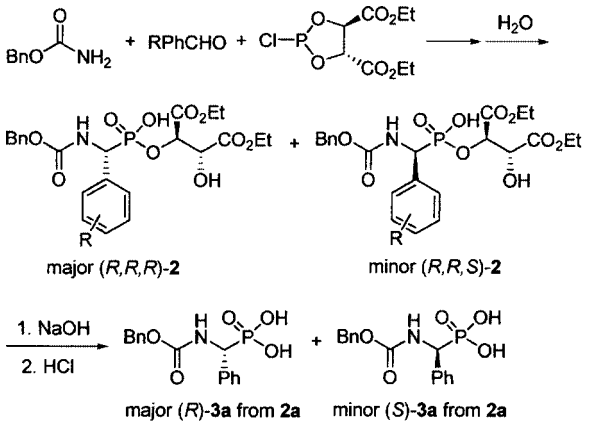
CONCLUSION

In conclusion, optically active 1-aminoalkylphosphonic acid derivatives were synthesized in moderate yields and optical purities via Mannich-type reactions of benzyl carbamate, aldehydes, and optically pure chlorophosphites. A direct method for one-pot preparation of depsiphosphonopeptides was also developed. In the method, side chain–functionalized depsiphosphonopeptides can be conveniently prepared in satisfactory yields directly from benzyl carbamate, aldehydes, and diethyl (*R*,*R*)-2-chloro-1,3,2-dioxaphospholane-4,5-dicarboxylate.

EXPERIMENTAL

General

Melting points were measured on a Yanaco MP-500 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Mercury Plus 300 (300 MHz) spectrometer in $CDCl_3$. ^{31}P NMR spectra were obtained with the use of broadband ^{1}H decoupling; chemical shifts are reported as ppm referenced to 85% phosphoric acid with positive shift downfield. IR spectra were obtained on a Nicolet AVATAR 330 FT-IR spectrometer. Mass spectra were acquired using a Bruker ESQUIRE~LC™ ESI ion trap spectrometer or a VG ZAB-HS mass spectrometer. Optical rotations were measured on a Perkin-Elmer Model 341LC polarimeter with a thermally jacketed 10-cm cell (concentration c given as g/100 ml). TLC



Scheme 2 Synthesis of depsiphosphonopeptides.

separations were performed on silica gel GF_{254} plates with petroleum ether (60–90 °C)/ethyl acetate (1 : 1, v/v). Benzene was refluxed with sodium and freshly distilled prior to use.

Synthesis of 1,1′-bi-2-naphthyl α-Aminoalkylphosphonates (general procedure)

To a stirred solution of benzyl carbamate (0.15 g, 1 mmol) and (*R*)-4-chloro-dinaphtho[2,1-*d*:1′,2′-*f*] [1,3,2]dioxaphosphepin (0.35 g, 1 mmol) in 10 ml of anhydrous benzene cooled in an ice-water bath, aldehyde was added dropwise (1 mmol). After stirring the reaction mixture under a nitrogen atmosphere for another 6 h at 25 °C, the solvent was removed under reduced pressure. The residue was purified on a silica gel column with chloroform as eluent.

(R)-1,1′-Bi-2-naphthyl (S/R)-1-benzyloxycarbonylamino-1-phenylmethylphosphonate (1a). Colorless noncrystalline solid, yield 71%, R_f 0.18 ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 and 5.15 (dd, $J = 12.3$ Hz, 2H, CH_2), 5.34 and 5.61 (dd, $J = 10.2$ Hz, $J_{PH} = 11.7$ Hz, 1H, CHP), 5.94 and 6.71 (d, $J = 9.7$ Hz, 1H, NH), 7.12–7.57 (m, 17H, ArH), 7.74–8.04 (m, 5H, ArH). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 30.53, 31.13 [1.6 : 1.0 for (*R*, *S*) : (*R*, *R*)]. IR (neat) ν 3273 (NH), 1717 (C=O), 1221 (P=O), 1071 and 1027 (P–O–C) cm^{-1}. EI-MS (*m*/*z*): 571 (M^+, 3), 463 (55), 422 (2), 332 (28), 286 (9), 268 (53), 239 (35), 226 (11), 132 (100), 107 (17), 91 (41), 77 (34).

(R)-1,1′-Bi-2-naphthyl (S/R)-1-benzyloxycarbonylamino-1-(4-chlorophenyl)methylphosphonate (1b). Colorless noncrystalline solid, yield 66%, R_f 0.18 ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 and 5.15 (dd, $J = 12.3$ Hz, 2H, CH_2), 5.28 and 5.57 (dd, $J = 9.9$ Hz, $J_{PH} = 11.6$ Hz, 1H, CHP), 5.83 and 6.64 (s, br, 1H, NH), 7.12–7.58 (m, 16H, ArH), 7.74–8.03 (m, 5H, ArH). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 30.23, 30.95 [1.8 : 1.0 for (*R*, *S*) : (*R*, *R*)]. IR (neat) ν 3263 (NH), 1717 (C=O), 1221 (P=O), 1072 (P–O–C) cm^{-1}. EI-MS (*m*/*z*): 605 (M^+, 46), 500 (3), 497 (25), 471 (3), 358 (5), 332 (63), 313 (5), 286 (4), 268 (56), 239 (22), 166 (50), 107 (17), 91 (100).

(R)-1,1′-Bi-2-naphthyl-(S/R)-1-benzyloxycarbonylamino-1-(4-methoxyphenyl)methylphosphonate (1c). Colorless noncrystalline solid, yield 68%, R_f 0.16 ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 and 3.71 (s, 3H, CH_3), 4.89 and 5.07 (dd, $J = 12.3$ Hz, 2H, CH_2), 5.17 and 5.42 (dd, $J = 9.9$ Hz, $J_{PH} = 11.4$ Hz, 1H, CHP), 5.66 and 6.27 (s, br, 1H, NH), 6.72–7.45 (m, 16H, ArH), 7.66–7.94 (m, 5H, ArH). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 31.60, 32.00 [1.4 : 1.0 for (*R*, *S*) : (*R*, *R*)]. IR (neat) ν 3254 (NH), 1717 (C=O), 1221 (P=O), 1070 and 1029 (P–O–C) cm^{-1}. EI-MS (*m*/*z*): 601 (M^+, 3), 493 (13), 452 (2), 332 (18), 317 (1), 268 (14), 239 (10), 224 (2), 162 (100), 135 (7), 107 (6), 91 (30).

(R)-1,1′-Bi-2-naphthyl-(S/R)-1-benzyloxycarbonylamino-1-(3-methoxyphenyl)methylphosphonate (1d). Colorless noncrystalline solid, yield 63%, R_f 0.16 ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 and 3.81 (s, 3H, CH_3), 5.00 and 5.19 (dd, $J = 12.3$ Hz, 2H, CH_2), 5.28 and 5.55 (dd, $J = 9.3$ Hz, $J_{PH} = 10.5$ Hz, 1H, CHP), 5.58 and 6.17 (d, $J = 9.7$ Hz, 1H, NH), 6.84–7.55 (m, 16H, ArH), 7.74–8.04 (m, 5H, ArH). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 30.65, 31.10 [1.1 : 1.0 for (*R*, *S*) : (*R*, *R*)]. IR (neat) ν 3265 (NH), 1716 (C=O), 1221 (P=O), 1070 and 1039 (P–O–C) cm^{-1}. EI-MS (*m*/*z*): 601 (M^+, 4), 493 (49), 332 (67), 317 (6), 268 (49), 239 (34), 226 (9), 224 (7), 162 (100), 134 (12), 107 (19), 91 (54).

Synthesis of Depsiphosphonopeptides (General Procedure)

To a stirred solution of benzyl carbamate (0.51 g, 3 mmol) and aldehyde (3 mmol) in 10 ml of anhydrous benzene cooled in an ice-water bath, diethyl (*R*, *R*)-2-chloro-1,3,2-dioxaphospholane-4,5-dicarboxylate (3 mmol) was added dropwise. After stirring the reaction mixture under a nitrogen atmosphere for another 6 h at below 10 °C, a white solid precipitated thoroughly. The solid was filtered and recrystallized from a mixture of petroleum ether (30–60 °C) and ethyl acetate to afford colorless crystals, or after removal of the solvent, the residue was purified by a silica gel column with a mixture of petroleum ether (30–60 °C) and ethyl acetate (1 : 1, v/v) as eluent.

Diethyl (R,R)-2-hydroxy-3-{(((R/S)-1-benzyloxycarbonylamino-1-phenylmethyl)hydroxyphosphinyl)oxy}succinate (2a). Colorless crystals, m.p. 122–127 °C, yield 40%, R_f 0.14 (hexane : AcOEt 1 : 1, v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.10 (m, 10H, ArH), 6.11 (s, br, 3H, NH and 2OH), 5.30–4.97 (m, 3H, OCH_2 and PCH), 4.68–4.55 (m, 2H, $2CHCO_2$), 4.32 and 3.67 (q, $J = 7.2$ Hz, 2H, OCH_2), 4.28–4.06 (m, 2H, OCH_2), 1.33, 1.26, 1.20 and 1.15 (t, $J = 7.2$ Hz, 6H, $2CH_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 22.51, 21.70 [1.9 : 1.0 for (*RRR*) : (*RRS*)]. IR (neat) ν 3332 (NH), 1736 (C=O), 1240 (P=O), 1030 (P–O–C) cm^{-1}. ESI-MS (*m*/*z*): 510 (MH^+).

Diethyl (R,R)-2-hydroxy-3-{(((R/S)-1-benzyloxycarbonylamino-1-(4-methylphenyl)methyl) hydroxyphosphinyl)oxy}succinate (2b). Colorless crystals, m.p. 106–112 °C, yield 42%, R_f 0.14 (hexane : AcOEt 1 : 1, v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.03 (m, 9H, ArH), 6.50 (s, br, 3H, NH and 2OH), 5.18–4.90 (m, 3H, OCH_2 and PCH), 4.59–4.50 (m, 2H, $2CHCO_2$), 4.30, 4.22 and 3.63 (q, $J = 7.2$ Hz, 4H, $2OCH_2$), 2.28 and 2.25 (s, 3H, CH_3), 1.32, 1.23 and 1.17 (t, $J = 7.2$ Hz, 6H, $2CH_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 22.42, 21.55 [2.0 : 1.0 for (*RRR*) : (*RRS*)]. IR (neat) ν 3332 (NH), 1736 (C=O), 1240 (P=O), 1030 (P–O–C) cm^{-1}. ESI-MS (*m*/*z*): 524 (MH^+).

Diethyl (R,R)-2- hydroxy-3-{(((R/S)-1-benzyloxycarbonylamino-1-(4-chlorophenyl)methyl)hydroxyphosphinyl)oxy}succinate (2c). Colorless crystals, m.p. 120–126 °C, yield 43%, R_f 0.13 (hexane : AcOEt 1 : 1, v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.10 (m, 9H, ArH), 6.18 (s, br, 3H, NH and 2OH), 5.37–4.90 (m, 3H, OCH_2 and PCH), 4.70–4.54 (m, 2H, $2CHCO_2$), 4.34 and 3.68 (q, $J = 7.2$ Hz, 2H, OCH_2), 4.33–4.06 (m, 2H, OCH_2), 1.33, 1.26, 1.20 and 1.16 (t, $J = 7.2$ Hz, 6H, $2CH_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 21.43, 20.38 [2.3 : 1.0 for (*RRR*) : (*RRS*)]. IR (neat) ν 3332 (NH), 1736 (C=O), 1240 (P=O), 1030 (P–O–C) cm^{-1}. ESI-MS (*m*/*z*): 544 (MH^+).

Diethyl (R,R)-2- hydroxy-3-{(((R/S)-1-benzyloxycarbonylamino-1-(4-bromophenyl)methyl)hydroxyphosphinyl)oxy}succinate (2d). Colorless crystals, m.p. 124–129 °C, yield 45%, R_f 0.13 (hexane : AcOEt 1 : 1, v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–6.88 (m, 10H, ArH), 6.33 and 6.03 (s, br, 3H, NH and 2OH), 5.30–5.07 (m, 3H, OCH_2 and PCH), 4.64–4.54 (m, 2H, $2CHCO_2$), 4.38–4.02 (m, 4H, $2OCH_2$), 1.33, 1.27, 1.22 and 1.17 (t, $J = 7.2$ Hz, 6H, $2CH_3$). ^{31}P NMR (121.5 MHz,

$CDCl_3$) δ 21.61, 20.40 [2.4 : 1.0 for (*RRR*) : (*RRS*)]. IR (neat) ν 3332 (NH), 1736 (C=O), 1240 (P=O), 1030 (P–O–C) cm^{-1}. ESI-MS (*m/z*): 588 (MH^+).

Diethyl (R,R)-2- hydroxy-3-{(((R/S)-1-benzyloxycarbonyl-amino-1-(4-nitrophenyl)methyl) hydroxyphosphinyl)oxy} succinate (2e). Colorless crystals, m.p. 138–143 °C, yield 47%, R_f 0.12 (hexane : AcOEt 1 : 1, v/v). ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, $J = 8.1$ Hz, 2H, ArH), 7.58 (d, $J = 8.1$ Hz, 2H, ArH), 7.31 (s, 5H, ArH), 6.61 and 5.64 (s, br, sH, NH and 2OH), 5.47–5.09 (m, 3H, OCH_2 and PCH), 4.73–4.54 (m, 2H, $2CHCO_2$), 4.37–4.09 (m, 4H, $2OCH_2$), 1.29, 1.27, 1.20 and 1.17 (t, $J = 7.2$ Hz, 6H, $2CH_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 20.46, 18.90 [1.7 : 1.0 for (*RRR*) : (*RRS*)]. IR (neat) ν 3332 (NH), 1736 (C=O), 1240 (P=O), 1030 (P–O–C) cm^{-1}. ESI-MS (*m/z*): 555 (MH^+).

Diethyl (R,R)-2-hydroxy-3-{(((R/S)-1-benzyloxycarbonyl-amino-1-(3-chlorophenyl)methyl) hydroxyphosphinyl)oxy} succinate (2f). White solid, yield 39%, m.p. 113–116 °C. R_f 0.13 (hexane : AcOEt 1 : 1, v/v). ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, $J = 7.0$ Hz, 3H, CH_3), 1.27 (t, $J = 7.0$ Hz, 3H, CH_3), 4.14 (q, $J = 7.2$ Hz), 4.28 (q, $J = 7.2$ Hz, CH_2O), 4.64 (s, br, 1H, COH), 5.10–5.38 (m, 3H, CHP and OCH_2), 6.36 (s, 2H, 2CHO), 6.88 (s, br, 1H, NHCO), 7.15–7.45 (m, 9H, ArH). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 21.61, 19.95 [2.5 : 1.0 for (*RRR*) : (*RRS*)]. IR (neat) ν 3342 (NH), 1736 (C=O), 1271 and 1245 (P=O), 1081 and 1020 (P–O–C) cm^{-1}. ESI-MS (*m/z*): 544 (MH^+, 100), 566 (MNa^+, 49).

Saponification of Depsiphosphonopeptide (2a)

Depsiphosphonopeptide **2a** (0.27 g, 0.53 mmol) was dissolved in 5 ml of 2 mol/l NaOH ethanolic solution and the mixture was stirred at room temperature overnight. After neutralizing to pH 2–3 with 2 mol/l HCl, the resulting mixture was extracted with diethyl ether (3 × 50 ml) dried over anhydrous sodium sulfate. After removal of the solvent, the residue was crystallized from chloroform to give colorless crystals of 90 mg with 53% of yield; m.p. 144–146 °C, $[\alpha]_D^{20} = +6.4$ (c 0.5, DMSO), [Lit m.p 142–143 °C, $[\alpha]_D^{20} = -19.4$ (c 2.0, 1M NaOH)].

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