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Preparation of Optically Active 1-Aminoalkylphosphonic Acids from Chiral Carbamates and Chiral Ureas

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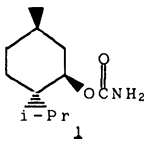
Optically active 1-aminoalkylphosphonic acids were successfully synthesized from chiral carbamate and urea derivatives which were prepared from such chiral substrates as (−)-menthol, (+)-camphor, and (*R*)-(+)- and (*S*)-(−)-(1-phenylethyl)ureas by the actions of aldehydes and triaryl phosphites. 1-Aminoalkylphosphonic acid derivatives, thus prepared, have an (*R*)-(+)- or (*S*)-(−)-configuration, depending on the chiral source via a retention of the configuration; i.e., (+)-products were prepared from chiral (+)-carbamate and (+)-urea derivatives, and (−)-products from chiral (−)-carbamate and (−)-urea derivatives.

Phosphonodipeptides and phosphonotripeptides possess inhibitory biological activities. Especially, 1-aminoethylphosphonic acid is a well-known substance which inhibits the growth of bacteria by interfering with the biosynthesis of peptidoglycan of the bacteria cell walls.[1]

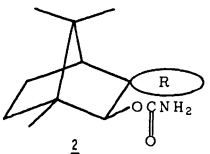
In general, 1-aminoalkylphosphonic acids were derived by several synthetic methods; addition reactions of Schiff bases with dialkyl phosphonates,[2] Mitsunobu reactions of 1-hydroxyalkylphosphonates with phthalimides,[3] condensation of hydrazines with phosphonoacetic esters,[4] catalytic reduction of dimethylhydrazones of 1-oxoalkylphosphonates,[5] reduction of *t*-butyl diazo(diethoxyphosphoryl)acetate,[6] hydrolyses of diethyl 1-(formylamino)alkylphosphonates,[7] and alkylation of 1-(ethoxycarbonylamino)-1-(ethylthio)methylphosphonate.[8] However, only racemic products were afforded by these reported methods. Optically active 1-aminoalkylphosphonic acids have so far been obtained by the optical resolution of racemic 1-aminoalkylphosphonic acids prepared by peptide synthesis.[1] Successful methods known for the asymmetric syntheses of 1-aminoalkylphosphonic acids are enantioselective addition reactions of dialkyl phosphonates with chiral Shiff bases[9,10] and a reaction of chiral (1-phenylethyl)urea with aldehydes and triethyl phosphite.[11] We now wish to report on the useful application of (−)-menthyl carbamate (**1**), 1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-3,2′-indan]-2-yl carbamate (**2**), and (*R*)-(+)- and (*S*)-(+)-(1-phenylethyl)ureas (**3a** and **3b**) to the asymmetric synthesis of 1-aminoalkylphosphonic acids (**7a—d**) according to Oleksyszyn's methods.[12,13] In a previously published paper[11] no definite reaction mechanism for the formation of optically active 1-aminoalkylphosphonic acids from chiral ureas was discussed; therefore, the present paper deals with the further investigation concerning the reaction mechanism for the formation of chiral 1-aminoalkylphosphonic acids starting from both chiral carbamates and ureas.

Results and Discussion

Chiral carbamates **1** and **2** were synthesized[14] from (−)-menthol and 1,7,7-trimethylspiro[bicyclo[2.2.1]-heptane-3,2′-indan]-2-ol,[15] respectively, in the presence of trifluoroacetic acid and sodium cyanate in benzene. Chiral ureas **3a** and **3b** were synthesized according to the reported method.[11] The reaction of aldehydes **4a—d** with (−)-menthyl carbamate **1** and triaryl phosphite **5** in acetic acid led to **6a—d**, which were hydrolyzed without isolation. Optically active 1-aminoalkylphosphonic acid derivatives **7a—d** given by this methods were levorotatory. (+)-Isomenthyl



1



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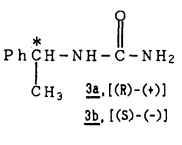
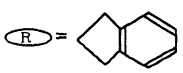
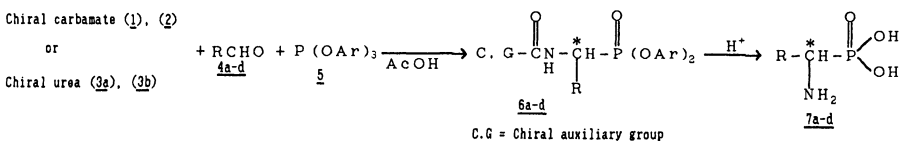


3a, [(R)-(+)]
3b, [(S)-(-)]





carbamate was then used as the chiral source of this reaction so as to clarify the stereoselectivity. (+)-Isomenthyl carbamate gave phosphonic acid with low optical activity (Table 1).

On the other hand, the reaction with chiral carbamate **2** led to dextrotatory 1-aminoalkylphosphonic acids **7**. Levorotatory 1-aminoalkylphosphonic acids are known to be an (*S*)-configuration, while dextrotatory enantiomers are (*R*)-configuration.[1,16] Therefore, 1-aminoalkylphosphonic acids prepared from (−)-menthyl carbamate (**1**) by the present method must be the (*S*)-enantiomer with a retention of the configuration. The stereoselectivity of 1-aminoalkylphosphonic acid produced by the reaction of (*R*)-(+)- and (*S*)-(−)-(1-phenylethyl)urea (**3a** and **3b**, respectively) led to the same conclusion obtained by a method described in the literature[11] where (*R*)-(+)-urea **3a** produced (*R*)-(+)-1-aminoalkylphosphonic acids and (*S*)-(−)-urea **3b** did (*S*)-(−)-1-aminoalkylphosphonic acids (Table 2). Two plausible reaction mechanisms (routes A and B in Scheme 1) may be proposed, based on the stereoselectivity observed in the present reaction, where (*R*)-(+)-urea **3a** and (*S*)-(−)-urea **3b**, afforded 1-aminoalkylphosphonic acid derivatives having (*R*)-(+)- and (*S*)-(−)-configurations, respectively.

Route A: phosphite attacks intermediate **8** in a similar way as that generated [urylenebis(methylene)]-bisphosphonate.[17] Route B: phosphite attacks enantioselectively the iminium ion.[18] In both routes, triaryl phosphite **5** attacks the carbon atom of aldehydes **4** after formation of carbon-nitrogen bond. In route A, optically active (*R*)-(+)- and (*S*)-(−)-(1-phenylethyl)ureas could attack either the *re* or *si* plane of aldehydes, while (*R*)-(+)-urea **3a** predominantly attacks the *si* plane of the aldehyde, leading to intermediate **8**. The intermediate is expected to be thermodynamically stable owing to hydrogen bonding to form a six-membered ring between the oxygen atom of the carbonyl group and the hydrogen atom of the

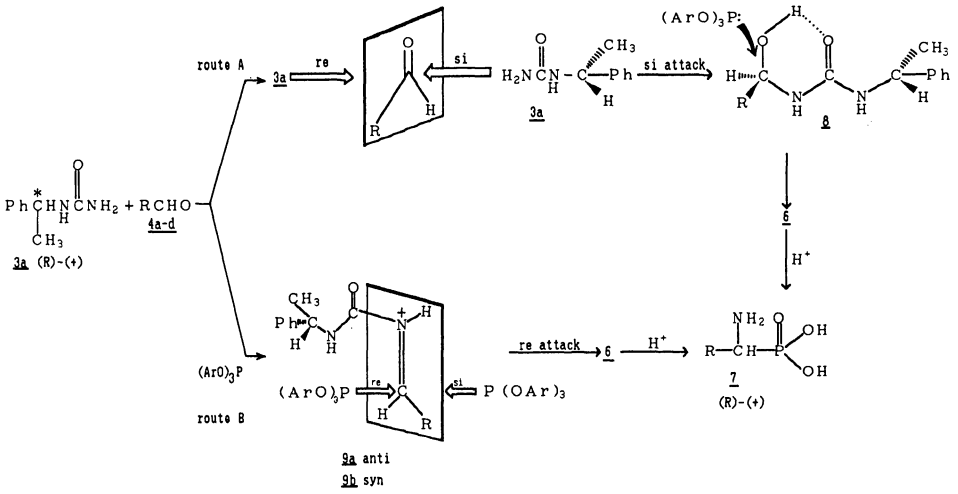
Table 1. Preparation of Optically Active 1-Aminoalkylphosphonic Acids **7** from (−)-Menthyl Carbamate (**1**), Aldehydes, and Phosphite **5**

$P(OAr)_3$, **5** Ar	**7a—d** R	1-Aminoalkylphosphonic acids **7a—d** Mp/°C [lit][a]	C.Y./%	$[\alpha]_D^{17}$ observed	$[\alpha]_D$ lit[a]	O.Y./%	Configuration
Ph	**a** Ph	278—279 [278—279]	47	−7.6° (*c* 1.4, 1 M[b] NaOH)	−18°	42.2	(*S*)
				{−0.6° (*c* 1.0, 1 M NaOH)}[c]		(3.3)	(*S*)
Ph	**b** *i*-Pr	277—278 [277—278]	51	−3.6° (*c* 2.0 1 M NaOH)	−10°	36.0	(*S*)
				{racemic form}[c]		—	—
Ph	**c** CH_3	224—225 [223—224]	52	−1.4° (*c* 1.0, 1 M NaOH)	−16.9°	8.3	(*S*)
Ph	**d** CH_3CH_2	265—266 [264—266]	54	−2.6° (*c* 1.0, 1M NaOH)	—	—	(*S*)
o-Methylphenyl	**a** Ph	278—279	45	−5.7° (*c* 1.0, 1 M NaOH)	−18°	31.7	(*S*)
o-Methylphenyl	**b** *i*-Pr	277—278	49	−3.9° (*c* 1.3, 1 M NaOH)	−10°	39.0	(*S*)
o-Methylphenyl	**d** CH_3	224—225	50	−2.3° (*c* 1.0, 1 M NaOH)	−16.9°	13.6	(*S*)

a) Ref. 16. b) 1 M=1 mol dm^{-3}. c) (+)-Isomenthyl carbamate.

Table 2. Preparation of Optically Active 1-Aminoalkylphosphonic Acids **7a—d** from (*R*)-(+)- and (*S*)-(−)-(1-Phenylethyl)urea (**3a, b**), Aldehydes, and Phosphite **5**

Urea **3a, b** Configuration	$P(OAr)_3$, **5** Ar	**7**, R	1-Aminophosphonic acid **7a—d** C.Y.(%)	$[\alpha]_D^{17}$ observed	O.Y.(%)	Configuration
3a (*R*)	Ph	**a** Ph	55	+6.2° (*c* 0.5, 1M NaOH)	34.3	(*R*)
3b (*S*)	Ph	Ph	56	−5.9° (*c* 1.7, 1M NaOH)	32.6	(*S*)
3a (*R*)	Ph	**b** *i*-Pr	60	+1.4° (*c* 1.0, 1M NaOH)	14.0	(*R*)
3b (*S*)	Ph	*i*-Pr	59	−1.3° (*c* 1.0, 1M NaOH)	13.0	(*S*)
3a (*R*)	Ph	**c** CH_3CH_2	65	+3.2° (*c* 1.2, 1M NaOH)	—	(*R*)
3b (*S*)	Ph	CH_3CH_2	65	−3.3° (*c* 1.1, 1M NaOH)	—	(*S*)
3a (*R*)	Ph	**d** CH_3	54	+1.4° (*c* 1.0, 1M NaOH)	8.3	(*R*)
3b (*S*)	Ph	CH_3	56	−1.5° (*c* 1.0, 1M NaOH)	8.9	(*S*)
3a (*R*)	*o*-Methylphenyl	**a** Ph	49	+5.6° (*c* 1.1, 1M NaOH)	30.8	(*R*)
3b (*S*)	*o*-Methylphenyl	Ph	48	−5.5° (*c* 1.0, 1M NaOH)	30.2	(*S*)
3a (*R*)	*o*-Methylphenyl	**d** CH_3	52	+2.3° (*c* 1.1, 1M NaOH)	13.6	(*R*)
3b (*S*)	*o*-Methylphenyl	CH_3	54	−2.2° (*c* 1.0, 1M NaOH)	13.0	(*S*)



Scheme 1.

Table 3. Preparation of Optically Active 1-Aminoalkylphosphonic Acids **7** from Chiral Carbamate **2**

$P(OAr)_3$ Ar	Produced **7a, b** 7	R	1-Aminoalkylphosphonic acids **7a, b** C.Y.(%)	$[\alpha]_D^{17}$ observed	O.Y. (%)	Configuration
Ph	**a**	Ph	45	+4.6° (*c* 0.8, 1 M NaOH)	25.4	(*R*)
Ph	**b**	CH_3	51	+2.2° (*c* 1.0, 1 M NaOH)	13.0	(*R*)

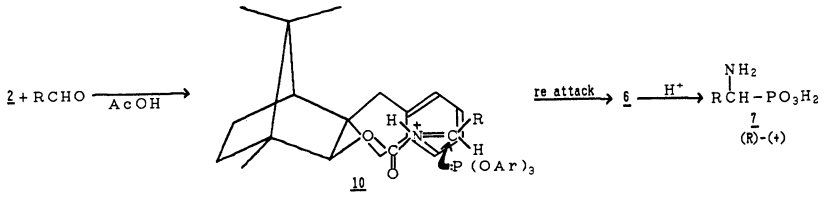
Table 4. ^1H NMR Data of Optically Active 1-Aminoalkylphosphonic Acids **7a—d**

7a—d[a]	^1HNMR, δ (CF_3CO_2H, TMS)
a	3.11—3.75 (m, 1H, P-CH), 7.00 (s, 5H, Ph)
b	0.80 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.81—2.41 (m, 1H, CH), 2.85—3.59 (m, 1H, P-CH)
c	0.80 (t, J=8.0 Hz, 3H, CH_3), 1.45—2.12 (m, 2H, CH_2), 3.04—3.64 (m, 1H, P-CH)
d	1.39 (dd, J_{HH}=7.8 Hz, J_{PCH}=15.6 Hz, 3H, CH_3), 3.09—3.87 (m, 1H, P-CH)

a) Microanalyses agreed satisfactorily with the calculated values.

hydroxyl group (Scheme 1). An attack of triaryl phosphite on intermediary formed **8** should occur at the same side of the hydroxyl group, since the stereochemistry of the product was retained at the chiral center, i.e., dextrotatory 1-aminoalkylphosphonic acids were derived from (*R*)-(+)-urea **3a**, and levorotatory products from (*S*)-(−)-urea **3b**. Generally, it is known that chiral secondary alcohols add to the formed phosphonium salt at the rate-determining step in an Arbuzov reaction of triaryl phosphite with alkyl halide to produce inverted halides from the chiral alcohol.[19] Alternatively, in route B, the intermediate iminium ion **9** could exist as the syn and anti form, where the anti form **9a** is more stable than *syn*-**9b**. Therefore, triaryl phosphite may approach to *anti*-**9a** from the opposite side of the (*R*)-(+)-(1-phenylethyl) group, acting as the chiral source and, hence, the product should be optically active (*R*)-(+)-1-aminoalkylphosphonic acids. In fact, (*R*)-(+)-1-aminoalkylphosphonic acids were derived from (*R*)-(+)-urea **3a** and (*S*)-(−)-1-aminoalkylphosphonic acids from (*S*)-(−)-urea **3b**. Therefore, route B predominantly proceeds over route A in this reaction. The reaction mechanism via the iminium ion intermediate was further supported by the fact that the 1-aminoalkylphosphonic acids obtained from chiral carbamate **2** retained the (*R*)-configuration (see Table 3 and Scheme 2). If molecule **10** forms such an intermediate as **8**, forming a six-membered ring, **8** should offer such a severe steric hindrance that the chemical yield would be suppressed; however, no such low yield result was obtained. Furthermore, reaction of (−)-menthyl carbamate (**1**) afforded (*S*)-(−)-1-aminoalkylphosphonic acid by Cram's rule.

Tris(*o*-methylphenyl) phosphite showed little effect on the improvement of the optical yield in comparison with triphenyl phosphite, probably because of a remote chiral auxiliary from the reaction center. The optical yield was, nevertheless, improved by using tris(*o*-methylphenyl) phosphite in the case of 1-



Scheme 2.

aminoethylphosphonic acid (R=CH_3), which is a ubstance which inhibits the growth of bacteria (alafosfaline[1]).

Experimental

Measurements. Melting poits were measured on a Yanagimoto Seisakusho micro melting-point apparatus. ^1H NHR spectra were recorded on a Hitachi R-24B (60 MHz) spectrometer with TMS as an internal standard, and optical rotations were determined with a JASCO DIP-4 digital and Atago Polax polarimeters, and IR spectra on a JASCO A-3 infrared spectrophotometer.

Preparation of Menthyl Carbamate (1); General Procedure: To a stirred mixture of (−)-menthol 7.8 g (50 mmol) and sodium cyanate 6.5 g (100 mmol) in 30 ml of benzene was added slowly 8.0 ml of trifluoroacetic acid at room temperature; the reaction mixture turned cake immediately. The reaction mixture was heavily stirred for 3 h, and then filtrated. A white crystalline mass was washed with benzene (10 ml×3) and water (50 ml×2); obtained crystalline compound **1** was then dried in desiccator under reduced pressure on standing overnight; yield 67%; mp 156—157 °C; IR (cm^{-1}) 3400 (NH_2), 1720 (C=O); $[\alpha]_D^{17}$ −125° (*c* 0.60, $CHCl_3$).

(+)-Isomenthyl carbamate was synthesized by the same method; yield 57%; mp 61—63 °C; $[\alpha]_D^{19}$+23.7° (*c* 1.1, $CHCl_3$).

Preparation of 1,7,7-Trimethylspiro[bicyclo[2.2.1]heptane-3,2′-indan]-2-yl Carbamate (2). A mixture of camphor 4.4 g (28.7 mmol) and sodium amide 2.5 g (63.2 mmol) in anhydrous toluene (30 ml) was heated at 100—105 °C until evaporation of ammonia gas ceased; a mixture of α,α′-dichloro-*o*-xylene 5.0 g (28.7 mmol) and toluene (20 ml) was then slowly added to the solution. The reaction mixture was refluxed for 3 h, cooled to room temperature, and then added into water (20 ml). The product was extracted with benzene (20 ml×2), and the combined organic layer was dried over anhydrous sodium sulfate; the solvent was evaporated in vacuo. The resulting syrupy products were further subjected to reduced pressure in order to remove unreacted camphor. The separation of products by column chromatography on silica gel (eluent; benzene/hexane=4/1, v/v) afforded the syrupy product; 1,7,7-trimethylspiro[bicyclo-[2.2.1]heptane-3,2′-indan]-2-on in 39% yield, ^1H NMR ($CDCl_3$) δ=0.92 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.55—2.01 (m, 8H, CH_2×4), 3.11 (t, *J*=6.0 Hz, 1H, CH), 7.04 (s, 4H, C_6H_4). To anhydrous tetrahydrofuran (10 ml) solution of 1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-3,2′-indan]-2-on 1.3 g (5.1 mmol) was added slowly lithium aluminium hydride 0.20 g (5.3 mmol) at room temperature; and the mixture was stirred for 2 h. The reaction was quenched by the addition of diluted hydrochloric acid. The product was extracted with ether (30 ml×3), and the combined organic layer was dried over anhydrous magnesium sulfate; the solvent was then evaporated. The residue was separated by thin-layer chromatography on silica gel (eluent; benzene/hexane= 4/1, v/v) to give the syrupy product, 1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-3,2′-indan]-2-ol,[15] in 95% yield; ^1H NMR ($CDCl_3$) δ=0.98 (s, 6H, CH_3×2), 1.31 (s, 3H, CH_3), 1.55—1.79 (m, 8H, CH_2×4), 2.80 (dd, *J*=15.0 Hz, 1H, CH), 3.38 (br s, 1H, OH), 3.52 (s, 1H, CH), 7.09 (s, 4H, C_6H_4). Carbamate **2** was synthesized by the same procedure as that for carbamate **1**. ^1H NMR ($CDCl_3$) δ=0.90 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.61—1.82 (m, 8H, CH_2×4), 3.03—3.18 (m, 2H, CH×2), 4.55 (s, 2H, NH_2), 7.09 (s, 4H, C_6H_4); $[\alpha]_D^{22}$+21.9° (*c* 2.1, EtOH).

Preparation of 1-Aminoalkylphosphonic Acid 7; General Procedure: Mixing of triphenyl phosphite 3.1 g (10 mmol), benzaldehyde 1.6 g (15 mmol), (−)-menthyl carbamate (**1**) 2.0 g (10 mmol), and glacial acetic acid (15 ml) immediately caused a slightly exothermic reaction; the reaction mixture was then stirred for 0.5 h.

The mixture was heated for additional 1 h at 85 °C and hydrolyzed with concentrated hydrochloric acid (15 ml) for 7 h under reflux. The resulting solution was washed with benzene (20 ml×3) in order to remove phenol and menthol; then, the aqueous solution was evaporated in vacuo. The residue was dissolved in methanol (5 ml) and the solution was treated with propylene oxide until pH 6 was reached. The precipitated aminoalkylphosphonic acid **5** was recrystallized from ethanol-water.

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