μL (144 mg, 1.42 mmol) of diisopropylamine in 5 mL of tetrahydrofuran at room temperature). After the addition, the solution was allowed to warm to −50 °C over 1 h, whereupon it was recooled to −78 °C and treated dropwise with a solution of 2.0 mL (4.4 g, 23.2 mmol) of 1,2-dibromoethane in 2.0 mL of hexamethylphosphoric triamide.[3b] The reaction mixture was allowed to warm to −30 °C over 1 h, and was then treated with 1.0 mL of saturated aqueous ammonium chloride solution. The product was isolated with ether in the usual manner and purified by dry-column silica gel chromatography with dichloromethane in pentane to give 12 mg of starting material and 165 mg (82%, 89% based on consumed **5a**) of bromide **5b**: mp 71–75 °C (hexane); $[\alpha]^{22}_D$ −86° (*c* 0.5, chloroform); ^{1}H NMR δ 5.40 (m, 2 H), 4.75 (ddd, *J* = 0.8, 4.8, 10.3 Hz, 1 H), 2.85 (m, 2 H), 2.68 (br q, 9.6 Hz, 1 H), 2.40 (m, 1 H), 2.25–2.00 (m, 3 H), 1.85 (s, 3 H), 1.82 (m, 3 H), 1.71 (d, *J* = 1.4 Hz, 3 H); IR 3050, 3040, 1775, 1195, 950, 880, 810, 800 cm^{-1}; mass spectrum, *m/e* 312, 310 (M^+).

Anal. Calcd for $C_{15}H_{19}BrO_2$: C, 57.89; H, 6.15. Found: C, 57.75; H, 6.13.

(3a*S*,6a*R*,9a*S*,9b*S*)-3a,4,6a,7,9a,9b-Hexahydro-6,9-dimethyl-3-methyleneazuleno[4,5-*b*]furan-2(3*H*)-one (5c). A solution of 354 mg (1.14 mmol) of **5b** and 850 μL (865 mg, 5.68 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 25 mL of toluene was heated at 112 °C (bath) under argon for 1 h.[3b] The crude product was isolated with ether in the usual way and purified by dry-column silica gel chromatography with dichloromethane in pentane to afford 15 mg of starting material and 173 mg (66%, 69% based on consumed **5b**) of triene **5c**: mp 82–84 °C (methanol–water); $[\alpha]^{20}_D$ −210° (*c* 0.5, chloroform); ^{1}H NMR δ 6.19 (d, *J* = 1.6 Hz, 1 H), 5.58 (d, *J* = 1.6 Hz, 1 H), 5.41 (m, 2 H), 4.36 (dd, *J* = 6.2, 10.5 Hz, 1 H), 3.25–3.15 (m, 1 H), 2.97 (br t, 10 Hz, 1 H), 2.70–2.35 (m, 3 H), 2.30–2.15 (m, 1 H), 1.84 (m, 3 H), 1.80 (m, 1 H), 1.71 (m, 3 H); IR 3040, 1750, 1660, 1260, 1145, 995, 960, 810 cm^{-1}; mass spectrum, *m/e* 230 (M^+).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.28; H, 7.93.

(3a*S*,9a*R*,9b*S*)-3a,4,9a,9b-Tetrahydro-6,9-dimethyl-3-methyleneazuleno[4,5-*b*]furan-2,5,7(3*H*)-trione (Oxoisodehydroleucodin, 1). To a rapidly stirred solution of 125 μL (122 mg, 1.55 mmol) of pyridine in 1.5 mL of dichloromethane at 0 °C under argon was added 75 mg (0.75 mmol) of chromium trioxide (dried over phosphorus pentoxide for 12 h under vacuum) and 20 4-Å molecular sieve beads.[9] The burgundy mixture was stirred for 5 min at 0 °C and 30 min at room temperature whereupon a solution of 10.0 mg (0.04 mmol) of **5c** in 1.0 mL of dichloromethane was added. After being stirred for 14 h, the mixture was processed with dichloromethane in the usual manner, and the crude product was purified by dry-column silica gel chromatography with ether in dichloromethane to give 3.2 mg of starting material and 4.0 mg (36%, 52% based on consumed **5c**) of oxoisodehydroleucodin (1):[4] mp 194–195 °C dec (cyclohexane–dichloromethane);[13] $[\alpha]^{20}_D$ −92° (*c* 0.25, methanol); ^{1}H NMR δ 6.41 (d, *J* = 2.0 Hz, 1 H), 6.30 (q, *J* = 1.3 Hz, 1 H), 5.79 (d, *J* = 1.8 Hz, 1 H), 4.41 (dd, *J* = 7.1, 10.4 Hz, 1 H), 3.72 (br d, *J* = 10.4 Hz, 1 H), 3.44–3.34 (m, 1 H), 3.06 (A of AB q, dd, *J* = 13.2, 17.1 Hz, 1 H), 2.76 (B of AB q, dd, *J* = 2.5, 17.1 Hz, 1 H), 2.38–2.35 (m, 6 H); ^{13}C NMR δ 200.09, 195.89, 171.92, 168.42, 141.54, 137.82, 137.01, 135.04, 124.85, 79.78, 50.18, 45.57, 38.50, 19.34, 12.30; IR 3100, 1750, 1685, 1660, 1625, 1600, 1280, 1150, 995, 945, 905 cm^{-1}; UV 267 nm (ε 13 000, methanol); mass spectrum, *m/e* 258 (M^+, 100), 230 (3.1), 212 (34.8), 121 (28), 91 (90.5).

Anal. Calcd for $C_{15}H_{14}O_4$: M_r, 258.0892. Found: M_r (mass spectrum), 258.0951.

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Registry No. 1, 107693-44-7; **2a**, 481-06-1; **2b**, 1618-78-6; **3**, 1618-99-1; **4**, 118172-14-8; **5a**, 118172-15-9; **5b**, 118172-16-0; **5c**, 118332-00-6.

(13) Reported to be an oil.[4]

First Asymmetric Synthesis of Enantiomerically Pure (1*R*,2*S*)-(−)-(1,2-Epoxypropyl)phosphonic Acid (Fosfomycin)

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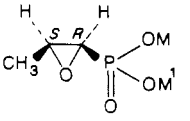
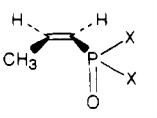
(1*R*,2*S*)-(−)-(1,2-Epoxypropyl)phosphonic acid (**1a**) (fosfomycin) is an antibiotic of unusual structure originally isolated from fermentation broth of *Streptomyces fradiae*.[1] Fosfomycin is present on the pharmaceutical market as the disodium (**1b**),[2] calcium (**1c**),[3] and tris(hydroxymethyl)ammonium (**1d**)[4] salts. Most syntheses of **1a** have





1a: M = M^1 = H
b: M = M^1 = Na
c: M = M^1 = Ca
d: M = H, M^1 = $NH_2[C(CH_2OH)_3]$

2a: X = OH
b: X = Cl

been accomplished by stereospecific cis-epoxidation of (*Z*)-1-propenylphosphonic acid derivatives,[1,5] followed by optical resolution of the racemic epoxide with optically active amines.[1,6,7] Recently, tartaric acid has been shown to be a useful chiral auxiliary for asymmetric functionalization of prochiral olefins such as α,β-unsatured ketones,[8] aldehydes,[9] and enol ethers.[10] We now report the first nonmicrobial[11] asymmetric synthesis of **1a**, based on the use of tartaric acid as a chiral auxiliary in directing an appropriate bifunctionalization of prochiral (*Z*)-1-propenylphosphonic acid (**2a**).

The phosphonic group of **2a** offers the possibility of binding the chiral auxiliary to the (*Z*)-1-propenylphosphonic acid through the formation of its monoesters **5** (Scheme I eq 1). Thus, the reaction of (2*S*,3*S*)-tartaric acid derivatives **3**, such as esters (R = OMe), monoalkyl-

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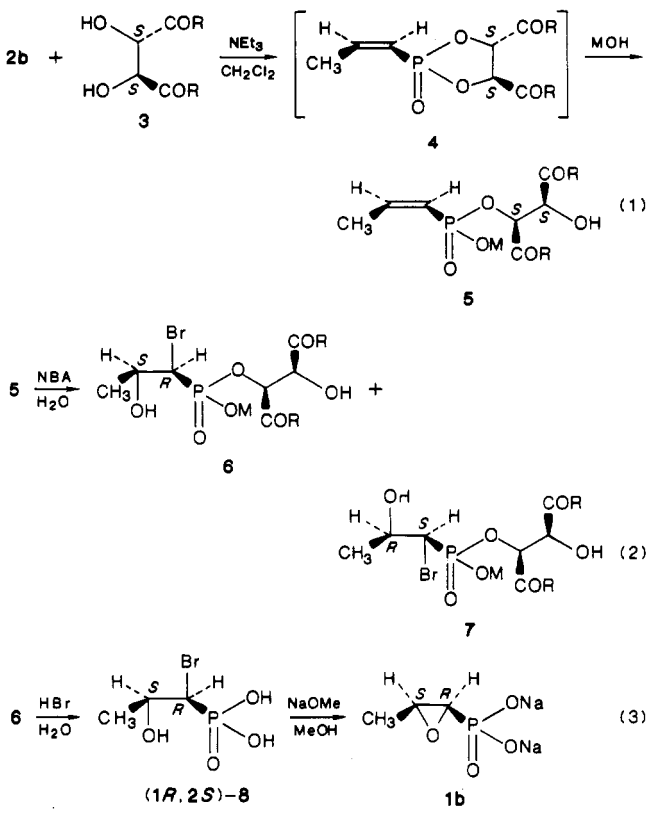
Table I. Yields and Diastereomeric Ratios for the Conversion of 5a–i to 6a/7a–6i/7i in Water at 15 °C

	substrate 5					isolated 6 + 7	
	M	R	reactn time[a]	pH of reactn medium[b]	ratio[c] 6:7	ratio[d] 6:7	yield,[e] %
a	H	OMe	5 min	1.0–1.1	51:49	51:49	94
b	H	NMe_2	5 min	1.0–1.1	60:40	60:40	92
c	Na	NMe_2	20 h	5.9–6.1	60:40	60:40	93
d	H	$\overline{NCH_2CH_2CH_2CH_2}$	5 min	6.0–6.1	60:40	60:40	95
e	H	NHMe	5 min	0.9–1.1	70:30	70:30	90
f	Na	NHMe	24 h	6.2–6.5	70:30	75:25	90
g	H	NHiPr	5 min	0.9–1.1	70:30	70:30	90
						(100:0)	(35)[f]
h	Na	NHiPr	24 h	6.4–6.6	70:30	67:33	90
i	H	$NHCH_2Ph$	2 h	6.4–6.6	70:30		

[a] Reaction time at complete conversion of the starting 5. [b] The pH does not change during the reaction. [c] Determined by ^1H (300 MHz) and ^{31}P NMR (121 MHz) on the solution of the reaction carried out in D_2O. [d] Determined by ^1H (300 MHz) and ^{31}P NMR (121 MHz). [e] Yields refer to the isolated pure product. [f] Yield of pure **6f** obtained after double crystallization from acetone.

Scheme I



amides (R = NHMe, NHiPr), or dialkylamides (R = NMe_2 $-\overline{NCH_2CH_2CH_2CH_2}$) (1 mol) with (*Z*)-1-propenylphosphonic dichloride (**2b**)[12] (1 mol) in the presence of triethylamine (2 mol) in dichloromethane (−10 °C, 3 h) gives rise to the cyclic phosphonates **4** that after aqueous ring opening and crystallization afford the monoesters **5** in yields higher than 70% (Scheme I, eq 1; see Experimental Section).

Bromohydroxylation of **5** was chosen from many bifunctionalizations because bromohydrins are easily converted into epoxides. The bromohydroxylation of **5**, carried out in water at 15 °C under neutral or acidic conditions, with an equimolar amount of *N*-bromoacetamide is highly chemoselective, regiospecific, and stereospecific, providing *threo*-bromohydrins (1*R*,2*S*)-**6** and (1*S*,2*R*)-**7**, in yields higher than 90% (Scheme I, eq 2, Table I; see Experimental Section).

A diastereoselection of 20–40% in favor of the formation of the 1*R*,2*S* isomer **6** and a 2% ds were observed in case of amide and ester derivatives, respectively; a higher diastereoselectivity was observed for monoalkylamide with respect to dialkylamide derivatives. It is worth noting that the monoethyl- and the monoisopropylamide derivatives exhibit similar diastereoselectivities independent of conversions or reaction times. Fortunately, crystallization of the mixture of diastereomeric bromohydrins **6g** and **7g** from acetone provided the preferred **6g** in diastereomerically pure form, thus opening the route to enantiomerically pure fosfomycin. As a matter of fact, fosfomycin **1b** was obtained in 80% yield from **6g**. Thus, **6g** was treated with 23% aqueous HBr (100 °C, 16 h) to provide enantiomerically pure **8**, which in turn was converted to **1b** by reaction with sodium methoxide in methanol (40 °C, 3 h) (Scheme I, eq 3; see Experimental Section). (2*S*,3*S*)-Tartaric acid was recovered from the reaction medium with unchanged optical purity. Following the above procedure, starting from a diastereomeric mixture of **6b**, **7b** (de 20%), **6d**, **7d** (de 20%), **6e**, **7e** (de 40%), **6g**, **7g** (de 40%), and **6i**, **7i** (de 40%), fosfomycin disodium salt (**1b**) was obtained in an enantiomeric excess, which reflects the diastereomeric excess of the mixtures of **6** and **7**. Thus, the present method allows for preparation of the optically active as well as of the enantiomerically pure **1b**. The optical purity of **1b** was determined from the corresponding dimethyl ester by ^1H NMR analysis with the optically active shift reagent $Eu(tfc)_3$.[13]

The diastereomeric bromohydrins **6** and **7** were fully characterized by ^1H, ^{13}C, and ^{31}P NMR, IR, MS, and elemental analyses; the absolute configuration at C_1 and C_2 was assigned on the basis of the absolute configuration of **1b**, taking into account that the configuration at C_1 is inverted in the epoxidation step. The structure of bromohydrin **8** was assigned by comparison with an authentical sample;[7,14] the absolute configuration and the optical purity of **8** was established on the basis of its conversion into **1b**.

The new method represents another meaningful example of the use of tartaric acid as a chiral auxiliary in the functionalization of prochiral olefins. The availability of

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(13) The absolute configuration of **1b** was assigned by comparison of the chiroptical properties of the corresponding dimethyl ester with those of an authentical sample.[7]

(14) The crude **8**, coming from **6g** (see Experimental Section), was converted into the corresponding dimethyl ester by reacting with diazomethane in methanol, which was purified by chromatography: $[\alpha]^{20}_{365}$ −23° (*c* 1, chloroform); ^1H NMR ($CDCl_3$) 1.32 (dd, 3 H, J_{H-CH_3} = 6.2, J_{P-CH_3} = 1.47), 3.83 (d, 3 H, J_{P-OCH_3} = 10), 3.89 (dd, 3 H, J_{P-OCH_3} = 10), 3.88 (dd, 1 H, J_{H-H} = 2.2, J_{P-H} = 12), 4.17 (ddq, 1 H, J_{CH_3-H} = 6.2, J_{H-H} = 2.2, J_{P-H} = 8); ^{31}P NMR ($CDCl_3$, 85% H_3PO_4) 21.88; MS (isobutane) *m/e* 249 (100), 247 (98.74), 169 (92.68), 151 (81.69).

both enantiomers of tartaric acid offers the possibility of preparing bromohydrins, epoxides, and related compounds of opposite configuration.

Experimental Section

^{1}H NMR spectra were taken at 300 MHz. The chemical shifts are expressed in ppm (δ) and are relative to internal tetramethylsilane or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt for solutions in deuteriochloroform or deuterium oxide, respectively. Coupling constants are expressed in hertz. ^{13}C NMR spectra and ^{31}P NMR spectra were run at 80 MHz and 121 MHz, respectively, by using coupled and uncoupled techniques. H_A and H_B are the β and the α hydrogens to the phosphorus, respectively. Optical rotations were measured in a 1-dm cell on a Perkin-Elmer 241 polarimeter. IR spectra were taken on a Perkin-Elmer 1420 instrument; positions of interesting absorptions are quoted to ±2.5 cm^{-1}. HPLC analyses were carried out on a Jasco 880 PV liquid chromatography equipped with an Alltech Nucleosil SB (10 μm; 250 mm × 4.6 mm) column and using a differential refractometer IR Waters 410 as detector (eluent 0.2 M aqueous KH_2PO_4). Analytical TLC analyses were performed by using precoated silica gel 60 F 254 plates supplied by Merck; visualization was accomplished by spraying with a solution of phosphomolybdic acid (5 g) and sulfuric acid (5 mL) in acetic acid (100 mL) and by heating at 120–130 °C. Chromatographic separations were accomplished by flash column chromatography by using silica gel (230–400 mesh) (Merck).

Melting points were measured on a Koefler apparatus and were not corrected. Chemical ionization mass spectra were recorded on a Finnigan MAT 8220 mass system operating at 110 eV, equipped with a Data General Nova 4X data system, with isobutane as ionizing agent. Satisfactory elemental analyses (C ±0.2%; H ±0.2%; Br ±0.3%; N ±0.2%; P ±0.3%) were obtained for all new compounds. All solvents and reagents were commercially available (reagent grade) and were used without further purification.

N,N,N',N'-Tetramethyl-, *N,N'*-dimethyl-, *N,N'*-diisopropyltartaramides were prepared according to known procedures.[15] *cis*-1-Propenylphosphonic acid dichloride was obtained in 70% yield from *cis*-1-propenylphosphonic acid as previously reported.[12]

Preparation of *cis*-1-Propenylphosphonic Acid Monoesters 5 with Tartaric Acid Derivatives: General Procedure. Triethylamine (39 g, 386 mmol) was added dropwise, under nitrogen at −10 °C, to well-stirred mixture of *cis*-1-propenylphosphonic acid dichloride (30 g, 188 mmol), (2*S*,3*S*)-tartaric acid derivative (188 mmol), and dichloromethane (240 mL). The reaction mixture was kept at −10 °C for 3 h, diluted with ethyl acetate (240 mL), and filtered under nitrogen. Evaporation of the solvent under reduced pressure gave the crude **4** as a residue that was dissolved in water (200 mL). The aqueous solution was kept at ambient temperature for 2 h. Evaporation of water under reduced pressure gave a residue that was crystallized to provide **5a,b,d,e,g,i**.

5a (80% yield: mp 76–7 °C (diethyl ether/ethyl acetate); $[\alpha]^{20}_D$ −3.2° (*c* 2, chloroform); IR ($CHCl_3$) 3550 (OH), 1770 (C=O), 1650 (C=C); ^{1}H NMR ($CDCl_3$) 2.06 (ddd, 3 H, $J_{H_A-CH_3}$ = 7.2, $J_{H_B-CH_3}$ = 1.8, J_{P-CH_3} = 3.9), 3.86 (s, 6 H), 4.73 (t, 1 H, J = 2.2), 5.17 (dd, 1 H, J = 2.2, J_{P-H} = 11), 5.68 (ddq, 1 H, $J_{CH_3-H_B}$ = 1.8, $J_{H_A-H_B}$ = 13.5, J_{P-H} = 21.5), 6.61 (ddq, 1 H, $J_{CH_3-H_A}$ = 7.2, $J_{H_B-H_A}$ = 13.5, J_{P-H_A} = 57).

5b (75% yield): oil; $[\alpha]^{20}_{365}$ +20° (*c* 2, water); IR (Nujol mull) 3350 (OH), 1640 (C=O); ^{1}H NMR (D_2O) 1.93 (ddd, 3 H, $J_{H_A-CH_3}$ = 7, $J_{H_B-CH_3}$ = 1.8, J_{P-CH_3} = 3.2), 2.95 (s, 6 H), 3.11 (s, 3 H), 3.17 (s, 3 H), 4.85 (d, 1 H, J = 7), 5.15 (dd, 1 H, J = 7, J_{P-H} = 9), 5.65 (ddq, 1 H, $J_{CH_3-H_B}$ = 1.8, $J_{H_A-H_B}$ = 13, J_{P-H_B} = 22), 6.53 (ddq, 1 H, $J_{CH_3-H_A}$ = 7, $J_{H_B-H_A}$ = 13, J_{P-H_A} = 52).

5d (75% yield): $[\alpha]^{20}_{436}$ +22.3° (*c* 2, water); ^{1}H NMR (D_2O) 1.95 (m, 11 H), 3.50 (m, 8 H), 4.70 (d, 1 H, J = 7.15), 4.95 (dd, 1 H, J = 7.15, J_{P-H} = 8.8), 5.64 (ddq, 1 H, J = 13, J = 1.65, J_{P-H_B} = 21.1), 6.50 (ddq, 1 H, J = 13, J = 7.15, J_{P-H_A} = 51.5).

5e (70% yield): mp 154–6 °C (ethanol); $[\alpha]^{20}_D$ −107.1° (*c* 2, water); IR (Nujol mull) 3440 (NH), 3340 (OH), 1680 (C=O), 1650 cm^{-1} (C=C); ^{1}H NMR (D_2O) 1.92 (ddd, 3 H, $J_{H_A-CH_3}$ = 7.15, $J_{H_B-CH_3}$ = 2.0, J_{P-CH_3} = 3.5), 2.73 (s, 3 H), 2.80 (s, 3 H), 4.48 (d, 1 H, J = 1.8), 4.87 (dd, 1 H, J = 1.8, J_{P-H} = 10.4), 5.52 (ddq, 1 H, $J_{H_A-H_B}$ = 12.8, $J_{CH_3-H_B}$ = 2.0, J_{P-H_B} = 21.2), 6.47 (ddq, 1 H, $J_{H_B-H_A}$ = 12.8, $J_{CH_3-H_A}$ = 7.15, J_{P-H_A} = 52.0).

5g (80% yield): mp 185 °C (2-propanol/acetone); $[\alpha]^{20}_{365}$ −316.8° (*c* 3, water); IR (Nujol mull) 3440 (NH), 3340 (OH), 1680 (C=O), 1650 cm^{-1} (C=C); ^{1}H NMR (D_2O) 1.16 (12 H, CH_3-(CHN)), 1.91 (ddd, 3 H, $J_{H_A-CH_3}$ = 7.1, $J_{H_B-CH_3}$ = 1.7, J_{P-CH_3} = 3.6), 3.90 (heptet, 1 H, J = 6.6), 3.97 (heptet, 1 H, J = 6.6), 4.42 (dd, 1 H, J = 2.2, J_{P-H} = 1.1), 4.80 (dd, 1 H, J = 2.2, J_{P-H} = 15), 5.53 (ddq, 1 H, $J_{H_A-H_B}$ = 13, $J_{CH_3-H_B}$ = 1.7, J_{P-H_B} = 20), 6.41 (ddq, 1 H, $J_{H_B-H_A}$ = 13, $J_{CH_3-H_A}$ = 7.1, J_{P-H_A} = 51.3).

5i (78% yield): mp 150 °C (acetone–water); $[\alpha]^{20}_{365}$ −91.6° (*c* 2, methanol); ^{1}H NMR (CD_3OD) 1.98 (ddd, 3 H, $J_{H_A-CH_3}$ = 7.2, $J_{H_B-CH_3}$ = 1.7, J_{P-CH_3} = 3.7), 4.45 (m, 4 H, CH_2Ph), 4.55 (d, 1 H, J = 2), 5.13 (dd, 1 H, J = 2, J_{P-H} = 10.2), 5.52 (ddq, 1 H, $J_{H_A-H_B}$ = 13.2, $J_{CH_3-H_B}$ = 1.7, J_{P-H_B} = 20.4), 6.45 (ddq, 1 H, $J_{H_B-H_A}$ = 13.2, $J_{CH_3-H_A}$ = 7.2, J_{P-H_A} = 54.4), 7.06–7.37 (m, 10 H, aromatic protons).

The sodium salts (**5c,f,h**) were prepared quantitatively in situ from the corresponding acids by adding an equivalent of aqueous sodium hydroxide. Compound **5c** was isolated in 90% yield by evaporation of water under reduced pressure and by crystallization of the crude from acetone: mp 114–5 °C; $[\alpha]^{20}_D$ +5.9° (*c* 2, water); IR (Nujol mull) 1640, 1660 (C=O), 1650 cm^{-1} (C=C); ^{1}H NMR (D_2O) 1.96 (ddd, 3 H, $J_{H_B-CH_3}$ = 1.8, $J_{H_A-CH_3}$ = 8, J_{P-CH_3} = 3.5), 2.95 (s, 3 H), 2.97 (s, 3 H), 3.18 (s, 3 H), 3.25 (s, 3 H), 4.90 (d, 1 H, J = 7), 5.15 (dd, 1 H, J = 7, J_{P-H} = 9), 5.67 (ddq, 1 H, $J_{CH_3-H_B}$ = 1.8, $J_{H_A-H_B}$ = 14, J_{P-H_B} = 19.5), 6.46 (ddq, 1 H, $J_{H_B-H_A}$ = 14, $J_{CH_3-H_A}$ = 8, J_{P-H_A} = 49.5).

Bromohydroxylation of 5: General Procedure. *N*-Bromoacetamide (15.2 g, 0.11 mol) was added portionwise in 30 min at 15 °C to a solution of **5** (0.1 mol) in water (600 mL). The reaction mixture was kept at 15 °C for the time given in Table I. Evaporation of the solvent under reduced pressure gave a solid residue containing **6**, **7** (in the ratio given in Table I), and acetamide. Ethyl acetate was added at ambient temperature to the residue and the mixture was kept under vigorous stirring for 2 h. The white solid collected by filtration consisted of a diastereomeric mixture of **6** and **7**. ^{1}H NMR: significative resonances of **6** and **7** taken in D_2O. **6a**: 1.27 (d, 3 H, J = 7), 4.14 (m, 1 H), 5.19 (dd, 1 H). **7a**: 1.25 (d, 3 H, J = 7), 4.08 (m, 1 H), 5.16 (dd, 1 H). **6b**: 1.24 (d, 3 H, J = 7), 3.93 (dd, 1 H, J_{H-H} = 3, J_{P-H} = 11.7), 4.13 (m, 1 H, J = 7, J_{H-H} = 3). **7b**: 1.24 (d, 3 H, J = 7), 3.93 (dd, 1 H, J_{H-H} = 3, J_{P-H} = 11.2), 4.11 (m, 1 H, J = 7, J_{H-H} = 3). **6d**: 1.32 (d, 3 H, J = 7), 3.88 (dd, 1 H, J_{H-H} = 3, J_{P-H} = 11.5), 4.20 (m, 1 H, J_{H-H} = 3, J = 7). **7d**: 1.32 (d, 3 H, J = 7), 3.95 (dd, 1 H, J_{H-H} = 3, J_{P-H} = 11.4), 4.18 (m, 1 H). **6e**: 1.27 (dd, 3 H, J_{H-CH_3} = 6.25, J_{P-CH_3} = 1.1), 3.76 (dd, 1 H, J_{H-H} = 3.3, J_{P-H} = 11.5), 4.09 (ddq, 1 H, J_{H-H} = 3.3, J_{CH_3-H} = 6.25, J_{P-H} = 6). **7e**: 1.24 (dd, 3 H, J_{H-CH_3} = 6.6, J_{P-CH_3} = 1.3), 3.77 (dd, 1 H, J_{H-H} = 2.93, J_{P-H} = 8.4), 4.23 (ddq, 1 H, J_{H-H} = 2.93, J_{CH_3-H} = 6.6, J_{P-H} = 11.3). **6g**: see below. **7g**: 1.27 (d, 3 H, J = 7), 3.84 (dd, 1 H, J_{H-H} = 3.3, J_{P-H} = 11.8), 4.07 (ddq, 1 H, J_{H-H} = 3.3, J_{CH_3-H} = 7, J_{P-H} = 17.9). **6i**: 1.12 (d, 3 H, J = 7). **7i**: 1.08 (d, 3 H, J = 7).

Preparation of (1*R*,2*S*)-(1-Hydroxy-2-bromopropyl)-phosphonic Acid, (1*S*,2*S*)-1,2-Bis[(isopropylamino)-carbonyl]-2-hydroxyethyl Ester (6g). Following the typical procedure for the bromination of **5g** and by crystallizing twice the crude from acetone, chemically and diastereomerically pure **6g** was obtained in 35% yield: mp 145–6 °C; $[\alpha]^{20}_{365}$ −258° (*c* 0.5, water); IR (Nujol mull) 3350 (NH), 3250 (OH), 1650 cm^{-1} (C=O); ^{1}H NMR (D_2O) 1.17 (12 H, CH_3(CHN)), 1.30 (d, 3 H, J = 6.4), 3.83 (dd, 1 H, J_{H-H} = 3.3, J_{P-H} = 11.7), 3.96 (m, 2 H, CHN), 4.14 (ddq, 1 H, J_{H-H} = 3.3, J_{CH_3-H} = 6.4, J_{P-H} = 9.3), 4.43 (d, 1 H, J = 2.3), 4.94 (dd, 1 H, J_{H-H} = 2.3, J_{P-H} = 6.7); ^{13}C NMR (D_2O) 21.7 (CH_3), 21.75, 21.96 (CH_3), 42.60 (CHN), 42.7 (CHN), 52 (CH, Br d, J_{P-C} = 14.5), 66.7 (CH(OH)), 72.7 (CH(CO), d, J_{P-C} = 5.66), 76.8 (CH(CO), d, J_{P-C} = 6.49), 170.5 (C=O), 171.5 (C=O).

Preparation of (1*R*,2*S*)-(1,2-Epoxypropyl)phosphonic Acid, Disodium Salt (1b) from 6g. A solution of 46% aqueous HBr (26.5 mL) was added to a solution of **6g** (5.69 g, 13.12 mmol) in water (26.5 mL). The solution was kept at 100 °C for 16 h. The solvent was removed by distillation under reduced pressure. Ethyl acetate (285 mL) was added and the mixture was kept at reflux for 2 h, cooled to ambient temperature, and filtered. Evaporation of the solvent under reduced pressure gave a residue

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that was added to acetone. The precipitate was filtered off. Evaporation of the solvent under reduced pressure gave crude containing (1-bromo-2-hydroxypropyl)phosphonic acid (8) and tartaric acid: ^{1}H NMR (D_2O) 1.34 (dd, 3 H, J_{H-CH_3} = 6, J_{P-CH_3} = 1.2), 3.98 (dd, 1 H, J_{H-H} = 3.6, J_{P-H} = 11.5), 4.20 (ddq, 1 H, J_{H-H} = 3.6, J_{CH_3-H} = 6, J_{P-H} = 9.3), and 4.75 (singlet of tartaric acid).

The crude 8, thus obtained, was dissolved in methanol (50 mL) and the solution was added dropwise at 40 °C under nitrogen to a solution of sodium methoxide in methanol (5.55 M, ca. 15 mL), in such a way as to maintain the pH at 12.5–13. At complete conversion of 8, the reaction mixture was cooled to ambient temperature and filtered. The pH of the solution was brought to pH 9–10 with methanesulfonic acid. The mixture was concentrated under reduced pressure to half volume and filtered. Evaporation of the solvent under reduced pressure gave a residue (3.38 g) containing 63% w/w of **1b** (2.13 g, 11.7 mmol) as determined by HPLC. The residue was dissolved in methanol (18 mL) and added, under stirring at ambient temperature, to 2-propanol (90 mL). Methanesulfonic acid (2.5 g, 26 mmol) was added to the suspension at 15 °C. The mixture was kept at 15 °C for 15 min and filtered. The solution was added at 15 °C to a solution of sodium methoxide in methanol (5.55 M, 4.32 mL) and kept at 15 °C for 2 h. The precipitate was filtered and dried at 50 °C under reduced pressure to yield (1*R*,2*S*)-(epoxypropyl)phosphonic acid, disodium salt (**1b**) (1.91 g, 10.5 mmol): HPLC assay 101.2%; Karl Fisher 2%; $[\alpha]^{20}_{365}$ −19.0° (*c* 10, water); ^{1}H NMR (D_2O) 1.50 (d, 3 H, J = 6), 2.83 (dd, 1 H, J = 5.4, J_{P-H} = 18), 3.27 (ddq, 1 H, J_{CH_3-H} = 6, J_{H-H} = 5.4).

A sample of **1b**, thus obtained, was dissolved in methanol, added to 2 equiv of methanesulfonic acid, and treated with an ethereal solution of diazomethane. Evaporation of the solvent under reduced pressure gave enantiomerically pure dimethyl ester of **1a** as determined by ^{1}H NMR analysis ($CDCl_3$) with the optically active shift reagent Eu(tfc)$_3$.

Registry No. 1 (m = m′ = Me), 25460-63-3; (1*R*,2*S*)-**1b**, 26016-99-9; (1*S*,2*R*)-**1b**, 26017-01-6; **2b**, 25522-46-7; **3a**, 13171-64-7; **3b**, 63126-52-3; **3d**, 102197-56-8; **3e**, 118894-34-1; **3g**, 118894-35-2; **3i**, 108321-43-3; **4a**, 116653-95-3; **4b**, 116653-96-4; **4d**, 118894-36-3; **4e**, 118894-37-4; **4g**, 118894-38-5; **4i**, 118894-39-6; **5a**, 118894-40-9; **5b**, 118894-41-0; **5c**, 118920-32-4; **5d**, 118894-42-1; **5e**, 116654-11-6; **5f**, 118920-33-5; **5g**, 118894-43-2; **5h**, 118920-34-6; **5i**, 118919-65-6; **6a**, 118894-44-3; **6b**, 119007-46-4; **6d**, 118894-45-4; **6e**, 116698-37-4; **6g**, 118894-46-5; **6i**, 118894-47-6; **7a**, 119008-38-7; **7b**, 119008-39-8; **7d**, 119007-47-5; **7e**, 116698-38-5; **7g**, 119007-48-6; **7i**, 119007-49-7; **8**, 119007-50-0; 8 (dimethyl ester), 119007-51-1.

Silylcupration-Mediated Synthesis of 2-Substituted Allylamines

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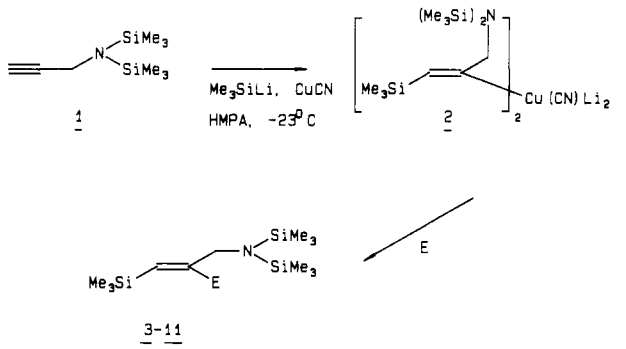
In many instances, the presence in organosilicon compounds of a nitrogen functionality separated from the silicon atom by two or three carbon atoms confers to the molecule various kinds of biological activity.[1]

Scheme I



As part of our current interest[2] in the search for new biologically active organosilicon compounds, we thought it worthwhile to focus our attention on the development of new methods for the synthesis of molecules bearing a SiC≡CCN skeleton.

We report in this paper a new simple one-step procedure for the synthesis of a wide series of 1-silylallylic amines substituted at position 2 from the readily available[3] precursor *N*,*N*-bis(trimethylsilyl)propargylamine (1) by means of a silylcupration followed by in situ reaction with electrophiles, according to Scheme I.

One of the most important aspects of the reaction in Scheme I turns out to be the inversion of regioselectivity in the addition of the reagents to the C≡C bond with respect to that previously reported by Corriu et al.[3] for the carbocupration of 1, which allowed functionalization of the allylic framework only at position 3. The regiochemistry in Scheme I on the other hand fits well with the previous findings of Fleming[4] and does not appear to be affected by replacement of the commonly used $PhMe_2Si$ group with a Me_3Si moiety. Also worth mentioning is the fact that both equivalents of Me_3Si were consumed (see Experimental Section) in the 1,2 addition process, in agreement with the formation of **2** from a $(Me_3Si)_2Cu(CN)Li_2$ mixed organocuprate.[5]

These features prompted us to envisage our reaction as a good entry into the not easily accessible class of 2-substituted allylic amines[6] and the results with a series of electrophiles are summarized in Table I.

In the case of I_2 (entry 2) and of alkyl halides (entries 3–5), the alkenylcuprate reacts easily, while with less reactive electrophiles (entries 6–8) transmetalation into the zinc species is necessary in order to obtain coupling using Pd(0) catalysis.[7] Otherwise reaction with carbon dioxide was performed in the presence of $P(OEt)_3$ as catalyst.[8]

In all cases the final products, isolated in satisfactory to good yields and fully characterized by GC-MS and ^{1}H NMR analyses, showed a stereochemistry coming from syn attack by the trimethylsilyl group and copper to the triple bond, which was maintained in the subsequent coupling step. The coupling constant of 18.6 Hz observed for the

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