Synthesis and Structure–Activity Relationships of 7-(3'-Amino-4'-methoxyppyrrolidin-1'-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids

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A new series of quinolone derivatives 3a–1 bearing 3-amino-4-methoxyppyrrolidines of different configurations and chirality were synthesized and their antibacterial activities as well as some of their toxicological properties were examined. As predicted by our previous quantitative structure–activity relationships (QSAR) analysis of C-7 heterocyclic amine substituted quinolonecarboxylic acid antibacterial agents, these pyrrolidine derivatives showed higher in vitro and in vivo antibacterial activities against both gram-positive and gram-negative bacteria than the analogs bearing various 3-substituted azetidines. Furthermore, the amino and methoxy substituent groups on the pyrrolidine ring exhibited strong configurational and chiral effects on the in vitro and in vivo antibacterial activities of these compounds: (1) cis compounds showed higher antibacterial activities against most of the pathogens examined; (2) N-methylation of the 3-amino group on the pyrrolidine ring lowered in vitro but not in vivo antibacterial activities, particularly leading to superior in vivo anti-pseudomonal activity; (3) the (3'S,4'R)-derivative showed substantially higher activity that the (3'R,4'S)-one. These findings led to the selection of compound 3k for further evaluation as it possessed the highest in vivo antibacterial activity and no cytotoxicity.

Keywords antibacterial agent; quinolonecarboxylic acid; chiral pyrrolidine derivative; optical resolution; QSAR analysis

In the preceding paper,1) we reported a QSAR (quantitative structure–activity relationships) analysis of the quinolone antibacterials 1 possessing various C-3'-substituted azetidinyl groups at the C-7 position of 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid. We expected this versatile synthet to be beneficial in designing useful new derivatives. In that study, the calculated hydrophobic parameters, CLOG P, of these molecules were significantly affected by the C-3' substituents on the azetidine ring. A good parabolic relationship was observed between the CLOG P values and the mean values of relative antibacterial activity indices determined for five gram-negative bacteria, with the CLOG P value for the most potent derivative estimated to be near 2.3. As for antibacterial activity against gram-positive bacteria, it remained rather constant and high regardless of the C-3' substituent on the azetidine group. However, the in vivo antibacterial activities of azetidine derivatives showed somewhat lesser potencies than those of the pyrrolidine derivatives.

Thus, our interest was shifted from azetidine derivatives to the pyrrolidine derivatives: one earlier report2) showed that the pyrrolidine derivative 7-(3'-aminopyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (2) exhibited excellent in vitro as well as in vivo antibacterial activities against both gram-positive and gram-negative bacteria. Interestingly, the CLOG P value of this derivative was 2.11, which was quite close to 2.3, the value predicted for the most potent azetidine derivative. As the development of that pyrrolidine compound as a clinical agent had been abandoned and also because the substituted pyrrolidine derivatives had not been studied much as to their C-7 substituent group, we extended the QSAR information obtained from the 3'-substituted azetidine derivatives to 3'- and/or 4'-substituted pyrrolidine derivatives to find the most promising 3'-amino-4'-methoxyppyrrolidine derivative having a CLOG P value near 2.3.

The main subjects of this work were the synthesis of these new series of quinolone antibacterials 3a–1 having 3'-amino-4'-methoxyppyrrolidine derivatives of different configurations and the evaluation of their antibacterial activities as well as pharmacodynamic and toxicological properties. When our work was almost completed, a similar patented work3) appeared, claiming, in part, the synthesis of the same compound 3a in a racemic form and the evaluation of its in vitro antibacterial activity. However, the work did not described the configurational effects of the amino and methoxy substituent groups on the antibacterial activities, nor did it evaluate the in vivo antibacterial activities. Thus, in our present paper, particular emphasis is given to the following: the in vivo antibacterial activities of these compounds, the geometrical and chiral effects of the two substituent groups on the antibacterial activities, and the pharmacological and toxicological effects of introducing the 5-amino and the 3-methylamino substituent groups. These studies led us to select the new (3'S,4'R)-4'-methoxy-3'-methylaminopyrrolidine derivative 3k for further evaluation of its biological activities.
Results and Discussion

Chemistry  The synthesis schemes for quinolone derivatives 3a and 3c bearing racemic cis- and trans-3-amino-4-methoxypyrrolidines (11) and (16), respectively, are summarized in Chart 1.

The commercially available starting material, 3-pyrrolidine (4), was first treated with di-tert-butyl dicarbonate (Boc₂O) to protect the amino group and then with 3-chloroperbenzoic acid to give the epoxide 6. The epoxide 6 was cleaved with either LiOCH₃ or NaOCH₃ in methanol, providing mono-methyl ether of trans-diol, in excellent yield. The alcohol 7 was converted into mesylate 8 in the usual manner, followed by treatment with NaN₃ in dimethylformamide (DMF) in the presence of tetrabutylammonium bromide, giving the cis-azide 9 with complete inversion of configuration. After reduction of the azide group either with Pd–C catalyzed hydrogenation or with triphenylphosphine, the Boc group was removed by treatment with HCl in methanol to give the desired cis-3-amino-4-methoxypyrrolidine dihydrochloride (11). The other 3-methylamino derivative 12 was also prepared from 10 by treatment with Boc₂O, followed by metatation with NaN₃ and then methylation with CH₃I. Next, to prepare trans-3-amino-4-methoxypyrrolidine dihydrochloride (16), the epoxide 6 was cleaved with NH₃ in aqueous methanol to produce the trans-amino alcohol in good yield. After protection of its amino group as a Schiff base with salicylaldehyde, the resultant alcohol 14 was methylated in the usual manner by successive treatment with NaN₃ and CH₃I, giving 15. Two protective groups, the Schiff base and the Boc group, were simultaneously removed from 15 by treatment with HCl in methanol, producing the desired trans-3-amino-4-methoxypyrrolidine dihydrochloride (16).

![Chart 1](image1)

![Chart 2](image2)
To estimate the effects of chirality on biological activity, optical resolution of racemic cis-3-amino-4-methoxy-pyrrrolidine dihydrochloride (11) was required. Suitable resolution agents \(^7\) were searched for, and the following resolution method was established for the intermediate 10 using L- and D-tartaric acids as resolution agents. The racemate 10 was first treated with 1.5 equimolar amount of natural type L-tartaric acid in methanol and the crystalline precipitates 17 which showed \([\alpha]_D^0 = +34.1^\circ\) were separated in 79% yield. Filtrate 18 was neutralized with \(K_2CO_3\) and the resultant free amine, after isolation, was treated with 1.5 equimolar amount of unnatural type D-tartaric acid, affording, after recrystallization, the crystalline salt 19 with \([\alpha]_D^0 = -33.4^\circ\) in 71% yield.

Both tartaric acid salts 17 and 19 were treated with base to liberate free amines 20 and 21, respectively. They were proven to be optically pure by both NMR spectroscopic measurement and HPLC analysis of the diastereoisomeric ratios of their amide derivatives \(^8\) obtained from the coupling reaction with Mosher’s reagent, \((R)-(+)\)-\(x\)-methoxy-\(x\)-trifluoromethylenylactic acid. Furthermore, the absolute configuration of the crystals 19 was unambiguously determined as \((3S,4R)-(-)-3\)-amino-1-tert-n-butylcarboxy1-4-methoxypyrrolidine D-tartaric acid salt by X-ray crystallographic analysis as shown in Fig. 2.

Thus, our resolution method proved to be very efficient, giving each diastereomer in pure form by a single fractional recrystallization. Removal of the Boc group from 20 and 21 by treatment with HCl in methanol gave the hydrochloric acid slats of the desired optically pure \((3R,4S)-\) and \((3S,4R)-3\)-amino-4-methoxy-pyrrrolidine dihydrochlorides 22 and 23, which showed \([\alpha]_D^0\) values of +54.5\(^\circ\) and -54.4\(^\circ\), respectively. In the same way as described for racemic compound 12, optically pure \((3R,4S)-\) and \((3S,4R)-4\)-methoxy-3-methylaminopyrrrolidine hydrochlorides 26 and 27) were prepared from 20 and 21 via 24 and 25, respectively. All the racemic and chiral pyrrrolidine derivatives heretofore prepared, 11, 12, 16, 22 and 23, were subjected to the well established reaction at the C-7 position of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, \(^9\) giving the desired quinolone derivatives 3a–e as shown in Table I.

To study the effect of introducing the amino group onto the C-5 position of the quinolone skeleton, \(^10\) we prepared the corresponding C-5 amino derivatives, 3f–k, also shown in Table I. In additions, for comparison of antibacterial activity with that of 4’-methoxy-3’-methylaminopyrrrolidine derivative 3g, the 4’-ethoxy-3’-methylaminopyrrrolidine derivative 3l was prepared. These compounds were subjected to biological assay for their antibacterial activities.

**Biological Results**

Tables II and III summarize both in vitro and in vivo antibacterial activities of all the compounds prepared, 3a–l, presenting MIC (minimum inhibitory concentration) and ED\(_{50}\) (median effective doses) values against pathogens examined. The ED\(_{50}\) by the oral route were determined for acute lethal infection in mice. Both in vitro and in vivo assay methods employed in the present work were essentially the same as previously reported (see ref. 11). The characteristic features of the results shown in Tables II and III were as follows. As predicted in our previous work, \(^1\) both pyrrrolidine derivatives 3a and 3c, when compared with azetidine derivatives, showed higher in vitro as well as in vivo antibacterial activities against gram-positive and gram-negative bacteria. Comparison of the MIC and ED\(_{50}\) values of racemic cis- and trans-3’-amino-4’-methoxypyrrrolidine derivatives, 3a and 3c, clearly demonstrated a higher activity for the cis derivative 3a than the trans 3c against all pathogens. Their ED\(_{50}\) values paralleled the MIC values, suggesting similar bioavailability of the two compounds in vivo.

On the other hand, N-methyl compound 3b showed poorer MIC values than 3a against all types of pathogens, revealing that the in vitro antibacterial activity was significantly decreased by N-methylation of the 3-amino group on the pyrrrolidine ring. However, in vivo, 3b and 3a showed almost the same activity, thus suggesting substantially improved bioavailability for the N-methyl compound 3b. Particularly noteworthy was the superiority of the in vivo antibacterial activity of 3b against Pseudomonas aeruginosa SR24. In addition, N-methylation clearly abolished the substantial cytotoxicity observed for the unsubstituted compound 3a. Another noteworthy finding was the fact that introduction of the amino group onto the 5-position of the quinolone skeleton improved the in vitro antibacterial activity against gram-positive bacteria but not the in vivo activity, e.g., 3a versus 3f and 3b versus 3g. Alkyl-chain elongation from the methoxy derivative 3g to the ethoxy one 3i notably diminished both the in vitro and in vivo antibacterial activities against all pathogens examined.

The stereochemical effects of the amino and methoxy substituent groups upon antibacterial activity were examined. First, the activity of the racemic cis compound 3a lacking the 5-amino substituent group on the quinolone skeleton was compared with those of the corresponding chiral \((3'R,4'S)-(+)\)- derivatives, 3d. Surprisingly, no significant differences in activities were noted. However, distinct differences were observed between the corresponding derivatives with the 5-amino substituent, whether or not the 3’-amino group was methylated. Thus, the chiral \((3'S,4'R)(-)\)-derivatives, 3i and 3k, showed substantially higher in vitro antibacterial activities than the corresponding racemates, 3f and 3g, whereas the antipode \((3'R,4'S)(+)-derivatives, 3h and 3j, showed
lower activities than the racemates, 3f and 3g. Interestingly, these chirality effects were stronger on the in vivo activity. The findings from these biological tests showed that compound 3k had the highest in vivo and excellent in vitro antibacterial activity against all pathogens. Furthermore, this compound did not display the cytotoxicity observed with 3a, 3f, 3h and 3l. We therefore selected 3k as our candidate for further evaluation of biological activities.

**Experimental**

All melting points were determined on a Yanagimoto micromelting point apparatus and were not corrected. IR spectra were recorded on a Hitachi 260-10 IR spectrophotometer. The 1H-NMR spectra were taken on a Varian VXR-200 spectrometer for organic and D₂O solutions using tetramethylsilane (TMS) and 3-trimethylsilyl-1-propanesulfonic acid sodium salt (DSS) as an internal standard, respectively, and their chemical shifts were given on a ppm scale. The optical rotations were measured on a Perkin-Elmer model 241 polarimeter. Column chromatography was performed on Merck silica gel 60 (230–400 or 70–230 mesh).

1-tert-Butoxy carbonyl-3,4-epoxy pyrroolidine (6) Into an ice-cooled solution of 3-pyrrole (4) (50.0 g, 0.723 mol) in 300 ml of MeOH was added dropwise di-tert-butyldicarbonate (173.5 g, 0.795 mol) and the reaction mixture was kept at room temperature for 20 h. After evaporation of the solvent, the residue was dissolved in 800 ml of CH₂Cl₂ and then 3-chloroperbenzoic acid (purity of 80%, 250 g, 1.160 mol) was added over a period of 5.0 h at room temperature. After stirring at room temperature for 20 h, the precipitates that appeared were filtered off and the filtrate was successively washed with aqueous NaH₂SO₄, NaHCO₃, and water, dried over MgSO₄, and concentrated in vacuo. The residue was column chromatographed on silica gel using toluene-AcOEt (5:1) as an eluent, giving 6 (109.0 g, 74%) as a colorless oil. 1H-NMR (CDCl₃) δ: 1.40 (9H, s, tert-Bu), 2.87 (2H, dd, J = 13, 2 Hz, C₆H₅-C₆H₅), 3.45–3.83 (4H, m, C₆H₅-C₆H₅). 1-tert-Butoxy carbonyl-trans-3-hydroxy-4-methoxy pyrroolidine (7) The ring opening of epoxide 6 was achieved by stirring the solution of 6 (54.9 g, 0.296 mol) in 2 N LiOMe in MeOH (670 ml, 1.35 mol) for 3 d at room
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<th>No.</th>
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<th>Sa(R)⁰</th>
<th>Sp⁰</th>
<th>Sn⁰</th>
<th>Ec(S)¹</th>
<th>Ec(R)¹</th>
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<td>0.4</td>
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<td>0.8</td>
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</table>

a) MIC (minimum inhibitory concentrations) were determined by the agar dilution method. Inoculation was performed with one loopful of 10⁵ cells per ml.  
b) Staphylococcus aureus Smith.  
c) Staphylococcus aureus C-14.  
d) Streptococcus pneumoniae C-203.  
e) Streptococcus pneumoniae type I.  
f) Escherichia coli EC-14.  
g) Escherichia coli SR73.  
h) Klebsiella pneumoniae 8R1.  
i) Proteus vulgaris CN 2329.  
j) Enterobacter cloacae SR233.  
k) Pseudomonas aeruginosa SR24.

### Table III. In Vivo Antibacterial Activity ED₅₀ (mg/kg)⁶

<table>
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<th>No.</th>
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<th>Ec(S)</th>
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a) Median effective dose. Compounds were administered orally 1 h after intraperitoneal injection of mice. Each value in parenthesis shows MIC from Table II.  
b) Not done.

temperature. After neutralization with AcOH (85 ml) under ice-cocooning, the solvent was evaporated and the residue was dissolved in CH₂Cl₂ and washed with water. The organic layer was dried over MgSO₄, and concentrated. The residue was chromatographed on silica gel using toluene–AcOEt (1:1) as an eluent and crystallized from n-hexane–ether to give 7 (53.3 g, 83%) as colorless prisms, mp 74–75°C. ¹H-NMR (CDCl₃) δ: 1.46 (9H, s, tert-Bu), 2.45 (1H, brs, OH), 3.37 (3H, s, CH₃O), 3.30–3.62 (4H, m, C₂-H, C₃-H), 3.70 (1H, m, C₄-H), 4.24 (1H, m, C₅-H). Anal. Calcd for C₁₀H₁₄NO₂: C, 55.28; H, 8.81; N, 6.54. Found: C, 55.04; H, 8.64; N, 6.38.

1-tert-Butyrocarbonyl-trans-3-methanesulfonyl-4-methoxyproplyridine (8) Methanesulfonyl chloride (14.9 ml, 0.193 mol) was added to a mixed solution of 7 (38.0 g, 0.175 mol) in CH₂Cl₂(200 ml) and pyridine (100 ml) at 0°C. After stirring for 4 h at room temperature, the reaction mixture was washed with water, dried over MgSO₄, and concentrated to give 8 (50.1 g, 97%) as a light brown oil. ¹H-NMR (CDCl₃) δ: 1.47 (9H, s, tert-Bu), 3.08 (3H, s, CH₃O), 3.42 (3H, s, CH₃O), 3.42–3.80 (4H, m, C₂-H, C₃-H), 4.00 (1H, m, C₄-H), 5.05 (1H, m, C₅-H).

1-tert-Butyrocarbonyl-cis-3-azido-4-methoxyproplyridine (9) A mixture of mesylate 8 (50.0 g, 0.169 mol), NaN₃ (22.0 g, 0.338 mol) and tert-butylammonium bromide (2.70 g, 0.008 mol) in DMF (150 ml) was stirred at 100°C for 20 h. The reaction mixture was poured into water and extracted with toluene. The organic layer was washed with water, dried over MgSO₄, and concentrated. The residue was chromatographed on silica gel using toluene–AcOEt (5:1) as an eluent to give 9 (31.1 g, 76%) as a colorless oil. IR (neat): 2100, 1690, 1404 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.46 (9H, s, tert-Bu), 3.46 (3H, s, CH₃O), 3.25–3.58 (4H, m, C₂-H, C₃-H), 3.80–3.95 (2H, m, C₄-H, C₅-H).

1-tert-Butyrocarbonyl-cis-3-arnino-4-methoxyproplyridine (10) Azide 9 (31.0 g, 0.126 mol) was hydrogenated under 4 atm over 10% Pd–C (2.0 g) in MeOH (150 ml) at room temperature. The catalyst was filtered off and the filtrate was concentrated to give 10 (28.2 g, 75%) as a light yellow oil. ¹H-NMR (CDCl₃) δ: 1.46 (9H, s, tert-Bu), 1.64 (2H, brs, NH₂), 3.08 (1H,
m, C=H), 2.40 (3H, s, CH₂O), 3.35—3.55 (4H, m, C=H—C=H), 3.65 (1H, m, C=H—C=H).

cis-3-Amino-4-methoxyphosphoridyl Dibydrochloride (11) Methoxamine 10 (1.00 g, 4.62 mmol) was added to the methanol solution of HCl (1.7 m 20 ml) and the mixture was stirred at room temperature for 18 h. After evaporation of the solvent, the resultant crystals were washed with MeOH, giving 11 (690 mg, 79%) as hygroscopic crystals, mp 220—223 °C (dec.). 1H-NMR (DMSO-d₆) δ: 3.40—3.85 (4H, m, C=H—C=H), 4.19 (1H, m, C=H—C=H), 4.33 (1H, m, C=H—C=H). Anal. Caled for C₅H₇Cl₂N₂O·C₂: 31.76; H, 7.46; Cl, 37.51; N, 14.82. Found: C, 31.47; H, 7.46; N, 14.61.

1-tetra-Butoxycarbonyl-trans-3-amin-4-hydroxyphosphoridyl (13) A solution of epoxide 6 (2.00 g, 10.8 mmol) in a mixture of 28% NH₄OH (20 ml) and MeOH (30 ml) was allowed to stand at room temperature for 7 h. After evaporation of the solvent, the residue was dissolved in ether to give 13 (1.92 g, 88%) as colorless needles, mp 115—117 °C. 1H-NMR (CDCl₃) δ: 1.46 (9H, s, tert-But2), 2.10 (3H, brs, NH₂, OH), 3.12 (1H, m, C=H), 3.30 (2H, m, C=H), 3.66 (2H, m, C=H), 4.00 (1H, m, C=H). Anal. Caled for C₅H₁₀O₃N₂O·C₂: 53.54; H, 8.97; N, 13.85. Found: C, 53.29; H, 8.99; N, 13.90.

1-tetra-Butyloxy-carbonyl-trans-3-‘-hydroxybenzidilenediamino-4-hydroxyphosphoridyl (14) A mixed solution of aminoalcohol 13 (1.50 g, 7.42 mmol) and salicylaldehyde (866 µl, 18.61 mmol) in dry EOH (50 ml) was refluxed for 4 h. After evaporation of the solvent, the residue was crystallized from ether, giving 14 (2.07 g, 91%) as yellow crystals, mp 125—126 °C. 1H-NMR (CDCl₃) δ: 1.47 (9H, s, tert-But2), 3.30—3.55 (2H, m, C=H), 3.65—4.00 (4H, m, C=H—C=H), 4.26 (1H, m, C=H—C=H), 6.85—7.9 (4H, m, aromatic), 8.42 (1H, s, NH—N).

trans-3-Methoxybenzidilenediamino-4-methoxyphosphoridyl (15) Into a stirred solution of imine 14 (1.50 g, 4.89 mmol) in tetrahydrofuran (THF) (50 ml) was added NaH (60% oil dispersion, 468 mg, 11.7 mmol) at 0 °C and the mixture was stirred at room temperature for 2 h. Next, Me₂Sn (3.0 ml) was added to the reaction mixture which was then stirred for 2 h. After evaporation of the solvent, AcOEt and water were added to the residue. The AcOEt layer was separated, dried over MgSO₄ and concentrated in vacuo to give 15 (1.52 g, 93%) as a light yellow oil. 1H-NMR (CDCl₃) δ: 1.47 (9H, s, tert-But2), 3.38 (3H, s, CH₃O), 3.30—3.55 (2H, m, C=H), 3.60—4.02 (4H, m, C=H—C=H), 3.87 (3H, CH₃O—Ar), 6.9—8.0 (4H, aromatic), 8.71 (1H, s, NH—N).

trans-3-Amino-4-methoxyphosphoridyl Dibydrochloride (16) HCl in MeOH (3.0 ml, 3ml) was added to 15 (1.00 g, 3.00 mmol) at 0 °C and the solution was stirred at room temperature for 4 h. During this time, precipitation of crystalline products was completed and resultant crystal was collected by filtration and dried, giving 16 (520 mg, 92%) as colorless prisms, mp 270—275 °C (dec.). 1H-NMR (DMSO-d₆) δ: 3.44 (3H, s, CH₃O), 3.42—4.04 (4H, m, C=H—C=H), 4.12 (1H, m, C=H—C=H), 4.36 (1H, m, C=H—C=H). Anal. Caled for C₆H₁₀O₃N₂O·H₂O·C₂: 51.76; H, 7.46; N, 14.82. Found: C, 51.76; H, 7.5; N, 14.62.

Optical Resolution of 1-tetra-Butyloxy-carbonyl-cis-3-amino-4-methoxyphosphoridyl (10) A mixed solution of cis racemate 10 (10.0 g, 46 mmol) and 30% NaOH (67 ml) in MeOH (50 ml) was allowed to stand at room temperature for 3 h. The resulting crystalline precipitates were collected, washed with MeOH, and recrystallized from MeOH, giving 1-tartaric acid salt 17 (6.12 g). The mother liquid was combined, concentrated in vacuo, and dissolved in water. After neutralization with K₂CO₃, the resultant free amine was extracted with AcOEt, and the AcOEt layer was concentrated in vacuo. The resultant amino residue (6.16 g) was added to a solution of tartaric acid (6.00 g, 40 mmol) in MeOH (40 ml), and the mixture was allowed to stand for 3 h at room temperature. The resultant crystalline precipitates were collected by filtration and recrystallized from MeOH, giving d-tartaric acid salt 19 (5.62 g). The mother liquid was treated again in the manner described, the gave additional l- and d-tartaric acid salts, 17 (0.57 g) and 19 (0.57 g), respectively. l-Tartaric acid salt 17: 79% yield, mp 197—198 °C (dec.). [α]25θ + 34.1° (c = 1.00, MeOH). Anal. Caled for C₅H₇O₃N₂O·C₂: 55.40; H, 7.15; N, 7.65. Found: C, 54.69; H, 6.96; N, 7.63. d-Tartaric acid salt 19: 71% yield, mp 197—198 °C (dec.). [α]25θ —33.4° (c = 1.05, MeOH). Anal. Caled for C₅H₇O₃N₂O·C₂: 54.90; H, 7.15; N, 7.65. Found: C, 54.76; H, 6.89; N, 7.63.

(3R,4S)-(—)-3-Amino-1-tetra-Butyloxy-carbonyl-4-methoxyphosphoridyl (21) A solution of l-tartaric acid salt 17 (16.69 g, 18 mmol) in saturated NaCl (30 ml) was neutralized with K₂CO₃ and extracted with AcOEt. The AcOEt layer was dried over MgSO₄ and concentrated in vacuo, giving 21 (3.80 g, 96%) as colorless oil [α]25θ +28.5° (c = 1.41, MeOH). 1H-NMR (CDCl₃) δ: 1.46 (9H, s, tert-But2), 2.27 (2H, brs, NH₂), 3.10 (1H, m, C=H), 3.28—3.64 (4H, m, C=H—C=H), 3.40 (1H, brs, CH₂O), 3.70 (1H, m, C=H).
corrected for Lorenz and polarization factors, but not for absorption effects. The structure was solved by a direct method, and atomic parameters were refined by a full-matrix least-squares method. The final R value was 0.036 for the 1721 observed reflections [F_o > 3σ(F_o)].

**Supplementary Material Available** Tables of final atomic positional parameters, atomic thermal parameters, and bond length and angles of compound 19 are available. Ordering information is given on the current masthead page.

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**References and Notes**


8) NMR and HPLC of (R) - (+)-Mosher's amide derivatives of 20 and 21. For the derivative of 20: 1H-NMR (CDCl₃): δ: 3.39 (3H, s, MeO of C₆), 3.44 (3H, s, MeO of Mosher's part); HPLC retention time 9.7 min when performed on a Shimadzu SPD-6A spectrometer using a LiChrosorb Si 60 (5 μm) column (4.0 mm i.d. × 250 mm) [mobile phase: n-hexane (95 parts)–isopropanol (5 parts); flow rate 1.0 ml/min, detection 254 nm]. For the derivative of 21: 1H-NMR (CDCl₃): δ: 3.29 (3H, s, MeO of C₆), 3.41 (3H, s, MeO of Mosher's part); HPLC retention time 12.6 min.

