Notes

Novel Syntheses of Hexahydropyrimidines and Tetrahydroquinazolines

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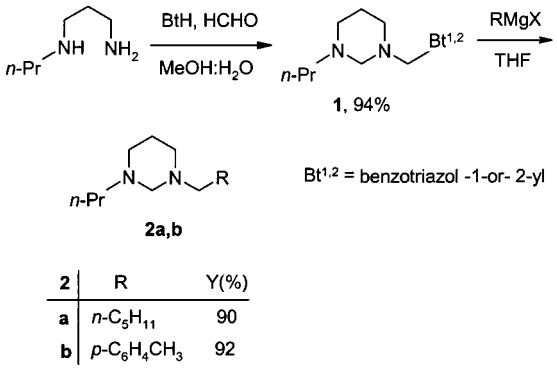
Abstract: 1-Benzotriazolylmethyl-3-propylhexahydropyrimidine (**1**) and 1,3-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-1,2,3,4-tetrahydroquinazoline (**3**) were readily prepared by reactions of *N*-propyl-1,3-propanediamine or 2-aminobenzylamine with benzotriazole and formaldehyde, respectively. Intermediate **1** reacted with alkyl and aryl Grignard reagents to produce *N*,*N*′-unsymmetrically substituted hexahydropyrimidines **2a**,**b** in 90 and 92% yields, respectively. Nucleophilic substitutions of **3** with Grignard reagents, allylsilane, and triethyl phosphite gave *N*,*N*′-disubstituted 1,2,3,4-tetrahydroquinazolines **4a**−**f**, **5**, and **6** in good to excellent yields. Successive treatment of **3** with two different Grignard reagents in one-pot reaction led regiospecifically to *N*,*N*′-unsymmetrically substituted tetrahydroquinazoline derivatives **8a**,**b**.

Hexahydropyrimidines are biologically important. *N*,*N*′-Bisalkylhexahydropyrimidines are effective against Ehrlich carcinoma, LK lymphoma, and *Staphylococcus aureus*.[1] The hexahydropyrimidine skeleton occurs in alkaloids such as verbamethine and verbametrine.[2] *N*-Substituted hexahydropyrimidines are synthetic intermediates for recently discovered spermidine−nitroimidazole drugs for the treatment of A549 lung carcinoma[3] and structural units in new trypanothione reductase inhibiting ligands for the regulation of oxidative stress in parasite cells.[4] Benzo-fused hexahydropyrimidines or 1,2,3,4-tetrahydroquinazolines are potential α-adrenergic blockers[5] and possess antiplatelet activity.[6]

Hexahydropyrimidines are prepared classically by condensations of substituted propane-1,3-diamines with aldehydes and ketones.[7a,b] 1,2,3,4-Tetrahydroquinazolines are accessible by reduction of quinazoline using sodium amalgam[8] or hydride reagents[9] generally in yields of 46−51%.[10]

Scheme 1



2	R	Y(%)
a	n-C_5H_{11}	90
b	p-$C_6H_4CH_3$	92

We now report a simple and efficient access to hexahydropyrimidines and 1,2,3,4-tetrahydroquinazolines in good yields. We have utilized the cyclocondensation property of benzotriazole to construct the hexahydropyrimidine ring system and its good leaving group ability in nucleophilic substitutions,[11] to perform *N*-functionalization.

For the preparation of *N*,*N*′-disubstituted hexahydropyrimidines, the cyclic α-benzotriazolylmethylamine **1** was readily prepared by a Mannich type reaction at room temperature in methanol/water.[12] Condensation of *N*-propyl-1,3-propanediamine with 1 equiv of benzotriazole and 2 equiv of formaldehyde (37% aqueous solution) gave the benzotriazolyl intermediate **1** in 94% yield. ^{1}H NMR spectrum of **1** showed the presence of Bt^1 and Bt^2 isomers in 5:1 ratio. Nucleophilic substitution of the benzotriazolyl group in **1** by representative alkyl and aryl Grignard reagents afforded 1-hexyl-3-propylhexahydropyrimidine (**2a**) in 90% yield and 1-(4-methylbenzyl)-3-propylhexahydropyrimidine (**2b**) in 92% yield (Scheme 1).

Condensation of 2-aminobenzylamine with 2 equiv of benzotriazole and 3 equiv of formaldehyde (37% aqueous solution) gave the unsymmetrical benzotriazolyl intermediate **3** in 88% yield as a sole Bt^1 isomer. Nucleophilic substitution of the benzotriazolyl groups in **3** by alkyl or aryl groups was achieved by treatment of **3** with Grignard reagents in THF at room temperature to furnish the desired *N*,*N*′-bisalkylated 1,2,3,4-tetrahydroquinazolines **4a**−**f** in 81−95% yields. Structures **4a**−**f** are supported by their ^{1}H and ^{13}C NMR spectra and microanalyses or HRMS data. These results illustrate the general applicability of this method for the preparation of *N*,*N*′-disubstituted 1,2,3,4-tetrahydroquinazolines (Scheme 2).

Lewis acid promoted elimination of benzotriazole anion leads to the formation of a planar iminium cation which

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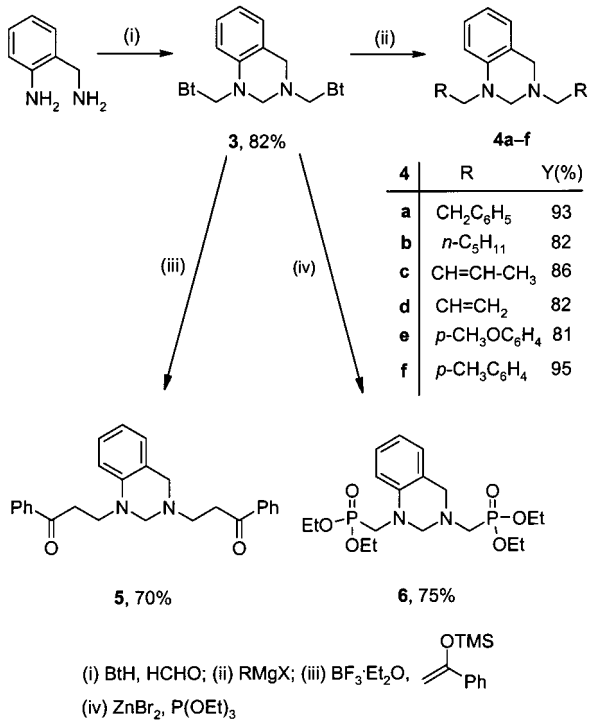
Scheme 2



4	R	Y(%)
a	$CH_2C_6H_5$	93
b	n-C_5H_{11}	82
c	CH=CH-CH_3	86
d	$CH=CH_2$	82
e	p-$CH_3OC_6H_4$	81
f	p-$CH_3C_6H_4$	95

can be attacked by nucleophiles.[13] Treatment of **3** with 2 equiv of 1-phenylvinyl trimethylsilyl ether in the presence of BF_3·Et_2O gave 3-[1-(3-oxo-3-phenylpropyl)-1,4-dihydro-3(2*H*)-quinazolinyl]-1-phenyl-1-propanone (**5**) in 70% yield. Also the reaction of **3** with triethyl phosphite in the presence of $ZnBr_2$ afforded diethyl [1-[(diethoxyphosphoryl)methyl]-1,4-dihydro-3(2*H*)-quinazolinyl]methylphosphonate (**6**) in 75% yield (Scheme 2).

The unsymmetrical structure of **3** prompted us to examine the regioselectivity of this intermediate toward substitution reaction with Grignard nucleophiles. The benzotriazolyl group at N(3) position in **3** is expected to be more reactive as compared to that at N(1) position toward nucleophilic substitution. It was envisioned that first treatment of **3** with 1 equiv of Grignard reagent should give the monosubstituted intermediate **7** which on further treatment with another Grignard reagent will furnish *N*,*N*′-unsymmetrically disubstituted 1,2,3,4-tetrahydroquinazoline. Interestingly, successive treatment of **3** with 1 equiv of *p*-tolylmagnesium bromide and vinylmagnesium bromide gave 1-allyl-3-(4-methylbenzyl)-1,2,3,4-tetrahydroquinazoline (**8a)** in 66% yield. The structure of **8a** was confirmed by NOE experiments. When the allylic proton doublet (3.78 ppm) in **8a** was irradiated, a strong positive NOE effect of the *o*-H of the phenyl ring was observed. Similar treatment of **3** with benzylmagnesium chloride and vinylmagnesium bromide gave 1-allyl-3-phenethyl-1,2,3,4-tetrahydroquinazoline **(8b)** in 61% yield. Thus, a one-pot procedure has been developed for the regiospecific preparation of *N*,*N*′-unsymmetrically disubstituted 1,2,3,4-tetrahydroquinazolines (Scheme 3).

In conclusion, we have introduced a convenient method for the preparation of *N*-substituted hexahydropyrimidines and *N*,*N*′-disubstituted 1,2,3,4-tetrahydroquinazolines via readily available benzotriazolyl intermediates **1** and **3**.

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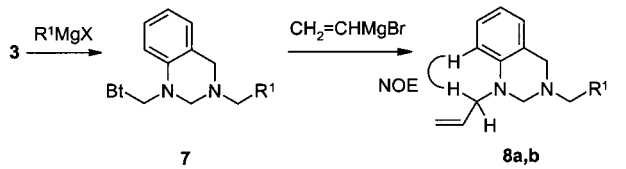
Scheme 3



8	R^1	Y (%)
a	p-$CH_3C_6H_4$	66
b	$C_6H_5CH_2$	61

Experimental Section

Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Gemini 300 NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as the internal reference). Elemental analyses were performed on a Carlo Erba-1106 instrument. HRMS were measured on an AEI-30 mass spectrometer. THF was distilled from sodium/benzophenone prior to use. All of the reactions were carried out under N_2. Column chromatography was performed on silica gel 200−425 mesh.

Procedure for the Preparation of 1-Benzotriazolylmethyl-3-propylhexahydropyrimidine (1). To a solution of *N*-propyl-1,3-propanediamine (1.16 g, 10 mmol) and benzotriazole (1.19 g, 10 mmol) in methanol/water (3/1, 100 mL) was added formaldehyde (37% aqueous solution) (1.49 mL, 20 mmol), and the mixture was stirred overnight at 25 °C. The solvent was evaporated under reduced pressure, and the residue was extracted with ethyl acetate, washed with 2 M NaOH, water, and brine, and dried over $MgSO_4$. Removal of the solvent in vacuo gave **1**, which was used directly for the subsequent reaction.

1-Benzotriazolylmethyl-3-propylhexahydropyrimidine (1): colorless oil; yield, 94%; obtained as Bt^1 and Bt^2 isomers in 5:1 ratio. ^{1}H NMR (Bt^1 isomer) δ 0.89 (t, J = 7.4 Hz, 3H), 1.44−1.56 (m, 2H), 1.72 (t, J = 5.3 Hz, 2H), 2.29 (t, J = 7.6 Hz, 2H), 2.42 (br s, 2H), 2.73 (t, J = 5.3 Hz, 2H), 3.39 (s, 2H), 5.53 (s, 2H), 7.35−7.41 (m, 1H), 7.49 (dd, J = 7.5, 7.5 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H); ^{13}C NMR (Bt^1 isomer) δ 11.4, 19.7, 22.8, 49.1, 51.3, 56.4, 66.9, 72.8, 109.4, 119.3, 123.3, 126.9, 133.1, 145.3. Anal. Calcd for $C_{14}H_{21}N_5$: C, 64.83; H, 8.16. Found: C, 64.59; H, 8.42.

General Procedure for the Nucleophilic Substitution of 1 with Grignard Reagents. To a solution of **1** (0.26 g, 1 mmol) in dry THF (10 mL) at 0 °C was added dropwise a solution of an appropriate Grignard reagent (2 mmol). The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to 25 °C, and stirred overnight. Then, the mixture was successively washed with 2 M NaOH and water. The combined aqueous phase was extracted with EtOAc. The combined organic layer was dried over anhyd Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash column chromatography with hexanes/EtOAc (10:1) as eluent to afford **2a**,**b**.

1-Hexyl-3-propylhexahydropyrimidine (2a): colorless oil; yield, 90%;^{1}H NMR δ 0.86−0.91 (m, 6H), 1.28 (br s, 7H), 1.44−1.56 (m, 4H), 1.67 (t, J = 5.3 Hz, 2H), 2.25−2.33 (m, 4H), 2.46 (br s, 3H), 3.08 (br s, 2H); ^{13}C NMR δ 11.8, 13.8, 20.1, 22.4, 23.5, 27.0, 27.1, 31.6, 52.3, 52.4, 55.3, 57.2, 76.4. Anal. Calcd for $C_{13}H_{28}N_2$: C, 73.52; H, 13.29. Found: C, 73.41; H, 12.97.

Procedure for the Preparation of 1,3-Bis(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-1,2,3,4-tetrahydroquinazoline (3). To a solution of 2-aminobenzylamine (1.22 g, 10 mmol) and benzotriazole (2.38 g, 20 mmol) in methanol/water (3/1, 100 mL) was added formaldehyde (37% aqueous solution) (2.25 mL, 30 mmol), and the mixture was stirred overnight at 25 °C. The white precipitates were filtered and dried to afford **3**, which was used as such for subsequent reactions.

1,3-Bis(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-1,2,3,4-tetrahydroquinazoline (3): white needles (from methanol/hexanes); mp 132−134 °C; yield, 88%; ^{1}H NMR δ 3.90 (s, 2H), 4.37 (s, 2H), 5.49 (s, 2H), 6.14 (s, 2H), 6.84−6.92 (m, 2H), 7.18−7.26 (m, 2H), 7.33−7.43 (m, 4H), 7.51 (dd, J = 7.8, 7.3 Hz, 1H), 7.60 (d, J =

8.4 Hz, 1H), 8.05 (d, J = 4.7 Hz, 1H), 8.07 (d, J = 4.1 Hz, 1H); ^{13}C NMR δ 51.0, 64.3, 65.1, 66.9, 109.6, 109.7, 115.5, 119.8, 120.8, 121.6, 123.9, 124.0, 127.5, 127.6, 127.7, 127.8, 132.6, 133.1, 141.7, 145.9, 146.0. Anal. Calcd for $C_{22}H_{20}N_8$: C, 66.65; H, 5.08; N, 28.26. Found: C, 66.62; H, 5.11; N, 28.42.

General Procedure for the Nucleophilic Substitution of 3 with Grignard Reagents. To a solution of **3** (0.40 g, 1 mmol) in dry THF (10 mL) at 0 °C was added dropwise a solution of an appropriate Grignard reagent (2 mmol) (RMgBr was used except for **4a** using $C_6H_5CH_2MgCl$). The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to 25 °C, and stirred overnight. Then, the mixture was successively washed with 2 M NaOH and water. The combined aqueous phase was extracted with EtOAc. The combined organic layer was dried over anhyd Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash column chromatography with hexanes/EtOAc (10:1) as eluent to afford **4a**−**f**.

For the preparation of **8a**,**b**, after addition of first Grignard reagent (1 mmol) as described above, the reaction mixture was stirred at 25 °C for 5 h and cooled to 0 °C and then the second Grignard reagent (1 mmol) was added. The reaction mixture was allowed to warm to 25 °C, stirred overnight, and then worked up as mentioned above.

1,3-Diphenethyl-1,2,3,4-tetrahydroquinazoline (4a): yellow oil; yield, 93%; ^{1}H NMR δ 2.73−2.88 (m, 6H), 3.44 (t, J = 7.3 Hz, 2H), 3.91 (s, 2H), 4.00 (s, 2H), 6.61−6.67 (m, 2H), 6.89 (d, J = 7.3 Hz, 1H), 7.08−7.30 (m, 11H); ^{13}C NMR δ 33.5, 34.7, 51.6, 53.9, 54.4, 69.9, 110.4, 116.4, 119.2, 126.0, 126.2, 127.2, 127.5, 128.2, 128.4, 128.6, 128.7, 139.5, 140.0, 143.6. Anal. Calcd for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.16; H, 7.75; N, 8.27.

1,3-Dihexyl-1,2,3,4-tetrahydroquinazoline (4b): yellow oil; yield, 82%; ^{1}H NMR δ 0.80−0.96 (m, 6H), 1.31 (br s, 12H), 1.55 (br s, 4H), 2.54 (t, J = 7.5 Hz, 2H), 3.19 (t, J = 7.5 Hz, 2H), 3.86 (s, 2H), 4.04 (s, 2H), 6.59 (t, J = 8.1 Hz, 2H), 6.88 (d, J = 7.3 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H); ^{13}C NMR δ 14.0, 14.0, 22.6, 22.6, 26.9, 27.1, 27.2, 27.7, 31.7, 31.8, 49.7, 52.9, 54.1, 69.5, 110.5, 116.0, 119.2, 127.1, 127.4, 144.1. Anal. Calcd for $C_{20}H_{34}N_2$: C, 79.41; N, 9.26. Found: C, 79.16; N, 9.79; HRMS Calcd for $C_{20}H_{35}N_2$ 303.2800, found 303.2720; GC purity (after column) 91%.

1,3-Bis(4-methylbenzyl)-1,2,3,4-tetrahydroquinazoline (4f): light yellow oil; yield, 95%; ^{1}H NMR δ 2.32 (s, 3H), 2.34 (s, 3H), 3.74 (s, 2H), 3.94 (s, 2H), 4.12 (s, 2H), 4.35 (s, 2H), 6.58−6.67 (m, 2H), 6.89 (d, J = 7.1 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 7.10−7.25 (m, 8H); ^{13}C NMR δ 21.0, 21.1, 53.3, 53.4, 56.8, 69.3, 111.6, 116.9, 119.3, 126.6, 127.1, 127.4, 128.9, 128.9, 129.1, 135.3, 135.8, 136.3, 136.6, 144.6. Anal. Calcd for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.04; H, 7.93; N, 8.19.

1-Allyl-3-(4-methylbenzyl)-1,2,3,4-tetrahydroquinazoline (8a): yellow oil; yield, 66%; ^{1}H NMR δ 2.35 (s, 3H), 3.71 (s, 2H), 3.79 (d, J = 3.8 Hz, 2H), 3.90 (s, 2H), 4.04 (s, 2H), 5.11−5.23 (m, 2H), 5.80−5.90 (m, 1H), 6.56−6.70 (m, 2H), 6.87 (d, J = 6.6 Hz, 1H), 7.01−7.15 (m, 3H), 7.24 (d, J = 5.9 Hz, 2H); ^{13}C NMR δ 21.1, 52.1, 53.5, 56.8, 68.7, 111.4, 116.1, 116.8, 119.4, 127.2, 127.4, 128.9, 129.0, 133.9, 135.3, 136.7, 144.2. Anal. Calcd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.77; H, 8.13; N, 10.29.

1-Allyl-3-phenethyl-1,2,3,4-tetrahydroquinazoline (8b): yellow oil; yield, 61%; ^{1}H NMR δ 2.77 (s, 4H), 3.71 (d, J = 4.9 Hz, 2H), 3.86 (s, 2H), 4.00 (s, 2H), 5.05−5.18 (m, 2H), 5.70−5.83 (m, 1H), 6.49−6.57 (m, 2H), 6.80 (d, J = 7.2 Hz, 1H), 6.97 (t, J = 7.7 Hz, 1H), 7.06−7.20 (m, 5H); ^{13}C NMR δ 34.6, 52.0, 54.0, 54.5, 69.1, 111.4, 116.2, 116.7, 119.4, 126.0, 127.0, 127.4, 128.3, 128.6, 133.9, 140.0, 144.1. Anal. Calcd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.69; H, 8.07; N, 10.23.

Procedure for the Reaction of 3 with 1-Phenyl-1-(trimethylsilyloxy)ethylene. To a solution of **3** (0.40 g, 1 mmol) and 1-phenyl-1-(trimethylsilyloxy)ethylene (0.41 mL, 2 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (0.24 mL, 2 mmol). The reaction mixture was stirred at 0 °C for 3 h, allowed to warm to 25 °C, and stirred for another 3 h. Then, the mixture was successively washed with 5% $NaHCO_3$ and water. The combined aqueous phase was extracted with EtOAc. The combined organic layer was dried over anhyd Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash column chromatography with hexanes/EtOAc (5:1) as eluent to afford **5**.

3-[1-(3-Oxo-3-phenylpropyl)-1,4-dihydro-3(2*H*)-quinazolinyl]-1-phenyl-1-propanone (5): yellow oil; yield, 70%; ^{1}H NMR δ 3.01 (t, J = 6.8 Hz, 2H), 3.21−3.28 (m, 4H), 3.72 (t, J = 6.6 Hz, 2H), 3.92 (s, 2H), 4.19 (s, 2H), 6.66 (dd, J = 7.7, 6.5 Hz, 2H), 6.90 (d, J = 7.5 Hz, 1H), 7.10 (dd, J = 7.7, 7.7 Hz, 1H), 7.38−7.56 (m, 6H), 7.90 (d, J = 7.2 Hz, 2H), 7.95 (d, J = 7.2 Hz, 2H); ^{13}C NMR δ 35.8, 37.1, 44.5, 47.8, 54.3, 70.0, 110.8, 117.0, 119.8, 127.3, 127.7, 128.0, 128.0, 128.6, 128.6, 133.1, 133.2, 136.7, 136.8, 143.4, 198.9, 199.2; HRMS (FAB) Calcd for $C_{26}H_{27}N_2O_2$ 399.2072, found 399.2075.

Procedure for the Reaction of 3 with Triethyl Phosphite. To a solution of **3** (0.40 g, 1 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C was added triethyl phosphite (0.34 mL, 2 mmol) followed by $ZnBr_2$ (0.44 g, 2 mmol). The reaction mixture was stirred at 0 °C for 3 h, allowed to warm to 25 °C, and stirred overnight. The reaction mixture was quenched with 2 M NaOH, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was dried over anhyd Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash column chromatography with hexanes/EtOAc (4:1) as eluent to afford **6**.

Diethyl [1-[(diethoxyphosphoryl)methyl]-1,4-dihydro-3(2*H*)-quinazolinyl]methylphosphonate (6): colorless oil; yield, 75%; ^{1}H NMR δ 1.27−1.36 (m, 12H), 3.03 (d, J = 11.2 Hz, 2H), 3.63 (d, J = 7.6 Hz, 2H), 4.08 (s, 2H), 4.09−4.21 (m, 8H), 4.30 (s, 2H), 6.69 (t, J = 7.2 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 7.2 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H); ^{13}C NMR δ 16.7, 16.8, 46.8 (d, J = 164 Hz), 48.4 (d, J = 168 Hz), 55.5 (d, J = 8.0 Hz), 62.4 (d, J = 6.2 Hz), 62.5 (d, J = 6.3 Hz), 72.2 (d, J = 11.9 Hz), 112.3, 118.2, 119.4, 127.8, 128.0, 144.0. Anal. Calcd for $C_{18}H_{32}N_2O_6P_2$: C, 49.77; H, 7.42; N, 6.45. Found: C, 49.13; H, 7.80; N, 6.57. HRMS Calcd for $C_{18}H_{33}N_2O_6P_2$ 435.1813, found 435.1804.

Supporting Information Available: Characterization data for compounds **2b**, **4c**−**e**. This material is available free of charge via Internet at http://pubs.acs.org.

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