Synthesis of Vinyl Derivatives of Phenanthroline and Bipyridine[1a]

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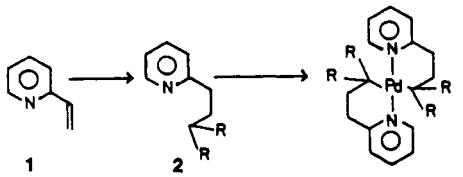
A new series of bipyridine and phenanthroline vinyl heterocycle has been synthesized via the Wittig–Horner reaction. These products arise from the enhanced anion stabilization present in the heterocyclic phosphonate which facilitates β-hydroxy elimination of the intermediate condensation product to generate a vinyl phosphonate. Vinyl phosphonates obtained under these conditions in aqueous methanol undergo facile nucleophilic addition of methoxide with subsequent regeneration of the olefin. In addition, 6,6′-divinyl-2,2′-bipyridine was synthesized under standard Wittig reaction conditions from the corresponding dialdehyde. The ^1H NMR spectral data of these compounds are discussed in detail.

Vinyl heterocycles have received considerable attention as synthetic intermediates because of their propensity for undergoing reactions[2–7] common to olefins, including hydrogenation, reductive coupling, dimerization, oxidation, halogenation, and cycloaddition. Recently we have utilized the known Michael addition of sodiomalonates with 2-vinylpyridine for the synthesis of a model transition metal ligand (**2**).[8] As a result of our interest in the design of new



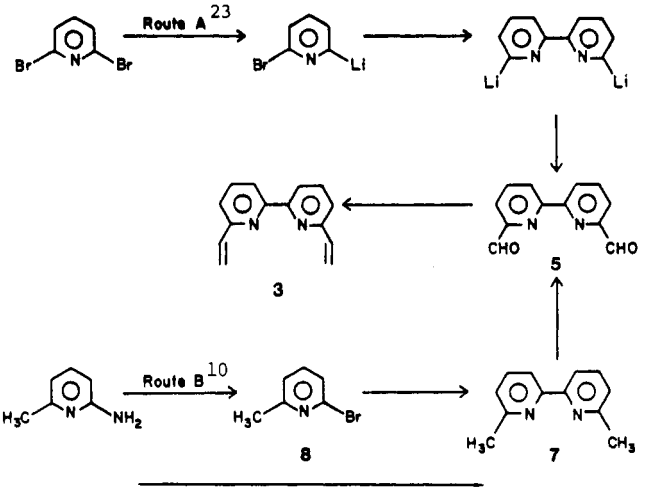
polydonor ligands[9] similar to **2**, we decided to undertake the synthesis of more complex vinyl heterocycles starting from the 2-methyl or 2-chloromethyl precursors.[10–12] Thus, we herein describe the preparation of several novel bipyridine and phenanthroline vinyl derivatives that may serve as useful synthetic intermediates.

Results and Discussion

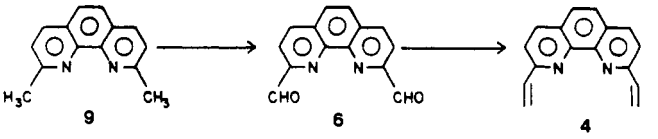
A. Synthetic Aspects. The most obvious approach to 6,6′-divinyl-2,2′-bipyridine (**3**) and 2,9-divinyl-1,10-phenanthroline (**4**) was via the Wittig reaction using methyltriphenylphosphonium bromide and the corresponding dialdehydes **5** and **6**. Thus, a reasonably efficient synthetic route to these aldehydes was a necessary prerequisite (Schemes I and II).

Ultimately, conversion of **7** and **9** into dialdehydes **5** and **6**, respectively, was accomplished via SeO_2 oxidation.[13,14]

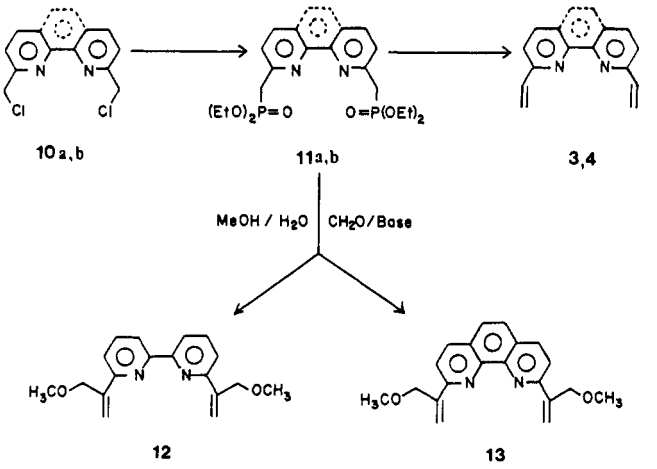
Scheme I



Scheme II



Scheme III



Treatment of **9** with SeO_2 proceeded smoothly in an aqueous 1,4-dioxane solution at 60 °C; however, **7** was resistant to oxidation under these mild conditions and only in refluxing acetic acid (112 °C) did the reaction proceed at a reasonable rate.

(1) (a) Chemistry of Heterocyclic Compounds Series. 110. (b) On leave from the University of Osaka Prefecture, Osaka, Japan, 1983–1984.
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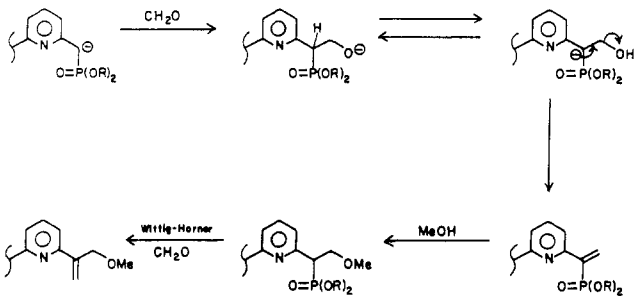
Scheme IV



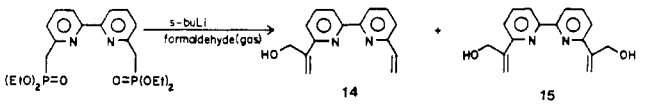
All initial attempts at the Wittig reaction on **5** and **6** in ethereal or hydrocarbon solvents were unsuccessful, due mainly to the limited solubility of the aldehydes at the low reaction temperatures. The use of tetramethylethylenediamine (TMEDA) was found to be the most effective solvent for facilitating the transformation of **5** to **3**. However, even with TMEDA, the olefin was prepared in meager (30%) overall yields.

This obvious general approach was plagued with too many problems to offer a practical route to these olefins. Because of the arduous procedures to the methyl-substituted starting materials, it was necessary to develop a new scheme that would make more efficient use of these intermediates.

Since the α-chloromethyl derivatives **10** obtained by NCS halogenation[10-12] of the dimethyl intermediates **7** and **9** were available, a new synthetic approach was envisioned which would use the Wittig–Horner reaction to obtain **3** and **4** (Scheme III). The phosphonates were easily prepared by refluxing **10** in triethyl phosphite followed by distillation of excess solvent. The phosphonates **11** were then treated with hydroxide in aqueous MeOH, followed by addition of aqueous formaldehyde. The reaction was noticeably exothermic and appeared to be complete in less than 30 min on the basis of a temperature profile.

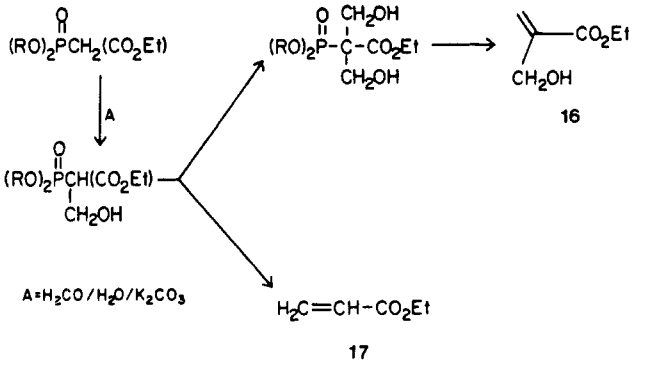
Surprisingly, the isolated products were not the expected divinyl compounds but proved to be the methoxypropenyl derivatives **12** and **13**. These products can be rationalized on the basis of the variety of condensation products that can occur when the phosphonate possesses more than one highly acidic proton.[15-17] In the case of phosphonates **11a** and **11b**, the α-pyridyl moiety substantially increases methylene proton acidity and, thus, causes anomolous olefin formation via dehydration of the intermediate β-hydroxy phosphonate.[17] The intermediate condensation product is then susceptible to nucleophilic attack followed by a second condensation with formaldehyde which culminates in the Wittig–Horner reaction (Scheme IV). Although some evidence supports the validity of this mechanism in alcoholic solvents,[17] other reasonable possibilities can be invoked to explain the products and should not be ruled out. Regardless of the precise mechanistic pathway, it is clear that nucleophilic addition[18] of methoxide is an extremely facile process under these conditions. The related bisolefin **3** was inert to nucleophilic attack by methoxide under identical conditions, even after prolonged reflux. In addition, **3** does *not* undergo a Michael addition with alkyl sodiomalonates.

Scheme V



For comparative purposes, an authentic sample of **15** was prepared (35%) from **11** under anhydrous conditions using *sec*-butyllithium, as base, and dry tetrahydrofuran with formaldehyde gas (Scheme V). The unsymmetric **14** was also isolated (15%) along with unchanged starting material. This reaction indicates that these monosubstituted olefins can be prepared by careful control of electrophile concentration. The reaction course is complicated by the fact that the stoichiometric introduction of formaldehyde is difficult.

To the best of our knowledge, there is only one previous heterocyclic example resembling **15** in which Ivanovski reported the synthesis of 2-(4-pyridyl)-1-propen-3-ol by heating 4-vinylpyridine and formaldehyde at 200 °C in the presence of secondary amines.[19] The similarity arises in starting olefin and product, not in reaction conditions. More recently Villieras and Rambaud reported a nonheterocyclic example whereby ethyl α-(hydroxymethyl)-acrylate **16** and ethyl α-(halomethyl)acrylates were synthesized via the Wittig–Horner reaction in a heterogeneous medium using aqueous formaldehyde and K_2CO_3.[20] They



also found that the formation of ethyl acrylate **17** could be reduced by using a large excess of formaldehyde; thus under optimized reaction conditions, **16** was isolated in 77% yield. The formation of products arising from alkoxide attack, as herein related, was not observed[20] since only aqueous conditions were utilized.

B. NMR Spectral Analysis. The spectral interpretation of the bisolefin **3** was straightforward and similar to styrene.[21] A large trans coupling constant, J_{bx} = 17.4 Hz, and a characteristic geminal, J_{ab} = 1.9 Hz, and cis couplings, J_{ax} = 10.4 Hz (Figure 1) were observed. These spectral data were of utmost importance for subsequent interpretation of complex proton spectra obtained for the unsymmetrical **14**.

For the symmetrical methoxyvinyl-substituted compounds, the methylene protons are split into a doublet of doublets as a result of coupling to the terminal vinyl hydrogens. The methylene proton coupling with H_b (J_{xb} = 1.4 Hz) is greater than with H_a (J_{xa} = 0.9 Hz) as a result of a reasonable planar "W" conformation. Because of the additional coupling, H_b and H_a appear as two six-line patterns at δ 5.60 and 6.11, respectively. In the hydroxyvinyl-substituted **15**, H_b and H_a appear as broad singlets,

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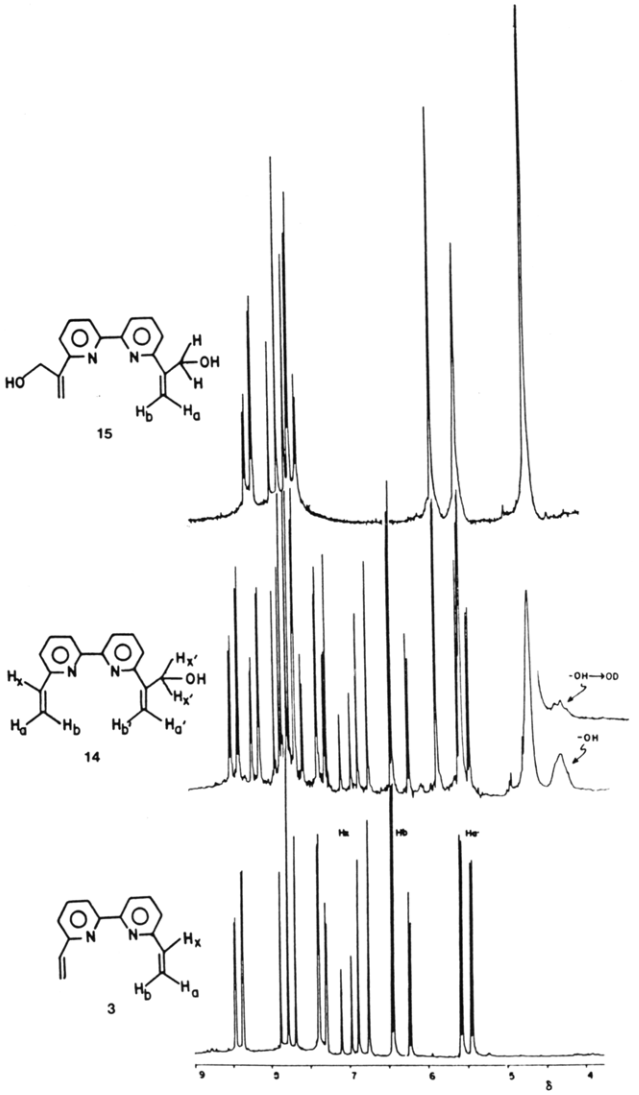

Figure 1. 80-MHz ^1H NMR spectra of **3**, **14**, and **15**.

presumably as a result of hydrogen bonding.

Unsymmetrical **14** displays an extremely complex ^1H NMR spectra with two sets of vinyl protons that are within the aromatic region (Figure 1). Although the spectrum was cumbersome, all signals were well resolved and could be assigned by spectral comparison with the symmetrical vinyl compounds. In addition, the alcohol resonance was confirmed by the addition of D_2O which readily caused H → D exchange as evidenced by the decrease in size of the broad singlet at δ 4.25 and the concomitant sharpening of the methylene resonance (Figure 1, insert).

The ^{13}C NMR of **13** was supportive of its symmetrical nature displaying exactly 10 carbon resonances. The methoxy carbon appears at δ 58.24 with characteristic vinyl resonances at δ 116.91 and 144.57.

Conclusion

The most interesting feature of **12** and **13** is that, in addition to undergoing nucleophilic addition in a manner similar to vinylpyridine, the olefin functionality has been regenerated. This latter point is particularly noteworthy since the olefin is subject to additional chemical modifications to further elaborate the molecular structure. We are currently investigating the scope of this reaction to determine what other nucleophiles can be substituted for methoxide. Ultimately we hope to employ these phosphonates as intermediates for introducing heterocyclic subunits into macrocyclic structures.

Experimental Section

General Comments. All uncorrected melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus. ^1H and ^{13}C NMR spectra were determined on either a Bruker WP-200 or an IBM NR/80 NMR spectrometer by using $CDCl_3$ solutions with Me_4Si (0.01%), as the internal standard. IR spectra were recorded on a Perkin-Elmer 621 grating infrared spectrophotometer. Mass spectral (MS) (70 eV) data [herein reported as (assignment, relative intensity)] were determined by D. Patterson on a Hewlett-Packard HP 5985 gas chromatograph/mass spectrometer in these laboratories.

For preparative thick-layer chromatography (ThLC), 2-mm Brinkmann EM aluminum oxide PF-254 Type E was used. Column chromatography procedures involved either silica gel (Baker, 60–200 mesh) or aluminum oxide (Brinkmann EM, neutral, activity D, 70–230 mesh). Elemental analyses were performed by Mic Anal Organic Microanalysis, Tuscon, AZ.

6,6′-Dimethyl-2,2′-bipyridine (7) was prepared by a known procedure[22] via catalytic coupling of **8**: mp 88–89 °C [lit.[10] mp 89–90 °C].

6,6′-Diformyl-2,2′-bipyridine (5) was prepared by a known procedure[14] via the SeO_2 oxidation of **7** in AcOH: mp 233–237 °C [lit.[23,24] mp 235 °C].

6,6′-Divinyl-2,2′-bipyridine (3). To a stirred dry TMEDA solution (25 mL) of BuLi (0.88 mL, 2.4 M; 2.1 mmol) under nitrogen was added methyltriphenylphosphonium bromide (714 mg, 2.0 mmol). The solution was stirred for 4 h at 25 °C, followed by addition of **5** (212 mg, 1.0 mmol). The mixture was stirred at 65 °C for 17 h, cooled, and filtered. The TMEDA solution was then extracted with Et_2O, followed by washing with water, and drying over anhydrous $MgSO_4$. After concentration in vacuo, the crude residue (288 mg) was chromatographed (ThLC) on Al_2O_3 eluting with C_6H_6 to give (30%) **3**, as white crystals: mp 81–82 °C; ^1H NMR δ 5.49 (dd, H_a, J_{ax} = 10.4 Hz, J_{ab} = 1.9 Hz, 2 H), 6.32 (dd, H_b, J_{bx} = 17.4 Hz, J_{ba} = J_{ab}, 2 H), 6.91 (dd, H_x, J_{xb} = J_{bx}, J_{xa} = J_{ax}, 2 H), 7.31 (dd, 5-py H, J = 7.7, 1.0 Hz, 2 H), 7.76 (t, 4-py H, J = 7.0 Hz, 2 H), 8.40 (dd, 3-py H, J = 7.7, 1.0 Hz, 2 H); IR (KBr) 1550, 1425, 975, 917, 803 cm^{-1}; MS, m/e 208 (M^+, 100), 182 (81), 154 (14). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.77; H, 5.77; N, 13.46. Found: C, 80.81; H, 5.76; N, 13.20.

6,6′-Bis[(diethoxyphosphinyl)methyl]-2,2′-bipyridine (11a). A mixture of 6,6′-bis(chloromethyl)-2,2′-bipyridine (**10a**)[10] (550 mg, 2.2 mmol) and $(EtO)_3P$ (25 mL) was stirred and heated at 120–130 °C for 48 h and cooled, and the excess $(EtO)_3P$ was removed by distillation. The crude product was concentrated in vacuo and passed through a short silica gel column eluting with CH_2Cl_2. After concentration, the product was recrystallized from C_6H_{12} to give (93%) **11a**, as white crystals: mp 95–96 °C; ^1H NMR δ 1.25 (t, CH_3, J = 7.1 Hz, 12 H), 3.49 (d, py CH_2, $^2J_{PH}$ = 21.8 Hz, 4 H), 4.04, 4.14 (2 q, OCH_2, J = 7.1 Hz, 8 H), 7.37 (ddd, 5-py H, J = 7.8, 2.4, 1.2 Hz, 2 H), 7.70, 7.80 (2 dd, 4-py H, J = 7.8, 0.6 Hz, 2 H), 8.30 (ddd, 3-py H, J = 7.8, 2.0, 1.2 Hz, 2 H); IR (KBr) 2950, 1545, 1420, 1370, 1225, 1185, 1010, 945, 820 cm^{-1}; MS, m/e 456 (M^+, 10), 246 (21), 199 (22), 184 (100), 109 (47), 91 (38), 81 (77). Anal. Calcd for $C_{20}H_{30}N_2O_6P_2$: C, 52.58; H, 6.58; N, 6.14. Found: C, 52.19; H, 6.81, N, 6.13.

2,9-Bis[(diethoxyphosphinyl)methyl]-1,10-phenanthroline (11b). The general procedure was the same as described above for **11a**. **11b** was recrystallized from CH_2Cl_2/C_6H_{12} as white crystals (90%): mp 74–76 °C; ^1H NMR δ 1.23 (t, CH_3, J = 7.1 Hz, 12 H), 3.82 (d, py CH_2, $^2J_{PH}$ = 22.1 Hz, 4 H), 4.12, 4.13 (2 q, OCH_2, J = 7.1 Hz, 8 H), 7.74 (s, 5,6-phen H, 2 H), 7.76 (dd, 3,8-phen H, J = 8.2, 1.7 Hz, 2 H), 8.19 (dd, 4,7-phen H, J = 8.2, 0.5 Hz, 2 H); IR (KBr) 2950, 1560, 1425, 1370, 1200 cm^{-1}; MS, m/e 482 (M^+ + 2, 1) 481 (M^+ + 1, 6), 480 (M^+, 20), 479 (2), 344 (51), 209 (19), 208 (99), 207 (100). Anal. Calcd for $C_{22}H_{30}N_2O_6P_2$:

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C, 55.00; H, 6.29; N, 5.83. Found: C, 54.74; H, 6.46; N, 5.55.

6,6′-Bis(3-methoxypropen-2-yl)-2,2′-bipyridine (12). To a MeOH solution (10 mL) of **11a** (400 mg, 0.877 mmol), NaOMe (477 mg, 8.77 mmol) was added. The solution was stirred for 2 h at 25 °C followed by the addition of aqueous HCHO (5 mL, 37% w/v). After being stirred for an additional 48 h at 60 °C, the solution was cooled, MeOH evaporated, and the residue extracted with CH_2Cl_2, followed by an aqueous wash of the organic layer and drying over anhydrous $MgSO_4$. The solvent was evaporated and the residue concentrated in vacuo followed by chromatography (ThLC) on Al_2O_3 eluting with C_6H_6/EtOAc (1:1) to afford (41%) **12**, as white microcrystals: ^1H NMR δ 3.46 (s, CH_3, 6 H), 4.58 (dd, H_x, J_{xb} = 1.4 Hz, J_{xa} = 0.9 Hz, 2 H), 5.60 (dt, H_b, $J_{bx} = J_{xb}$, J_{ba} = 1.5 Hz, 2 H), 6.11 (dt, H_a, $J_{ax} = J_{xa}$, $J_{ab} = J_{ba}$, 2 H), 7.53 (dd, 5-py H, J = 7.8, 1.3 Hz, 2 H), 7.78 (t, 4-py H, J = 7.8 Hz, 2 H), 8.37 (dd, 3-py H, J = 7.8, 1.3 Hz, 2 H); IR (KBr) 1550, 1430, 1085 cm^{-1}; MS, m/e 296 (M^+, 8), 281 (100), 249 (43), 219 (24). Due to the unstable character of this molecule, satisfactory elemental analysis was not possible.

2,9-Bis(3-methoxypropen-2-yl)-1,10-phenanthroline (13). The general procedure was the same as described above for **12**. **13** was recrystallized from petroleum ether as white needles (60%): mp 168–170 °C dec; ^1H NMR δ 3.56 (s, CH_3, 6 H), 4.86 (dd, H_x, J_{xb} = 1.4 Hz, J_{xa} = 0.9 Hz, 2 H), 5.80 (dt, H_b, $J_{bx} = J_{xb}$, J_{ba} = 1.4 Hz, 2 H), 6.30 (dt, H_a, $J_{ax} = J_{xa}$, $J_{ab} = J_{ba}$, 2 H), 7.72 (s, 5,6-phen H, 2 H), 7.92 (d, 3,8-phen H, J = 8.5 Hz, 2 H), 8.19 (d, 4,7-phen H, J = 8.5 Hz, 2 H); ^{13}C NMR δ 58.24 (OCH_3), 72.77 (CH_2), 116.91 (=CH_2), 119.68 (C3), 125.90 (C5), 127.80 (C4a), 136.16 (C4), 144.57 (=CR_2), 145.20 (C10b), 156.03 (C2), IR (CsI) 2900, 1660, 1570, 1470, 1350, 1090, 900 cm^{-1}; MS, m/e 520 (M^+, 10), 305 (100), 275 (41), 273 (32), 205 (34). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.66; H, 6.02; N, 8.55.

General Procedure for Preparation of 14 and 15. To a dry THF solution (30 mL) of **11a** (500 mg, 109 mmol) was added *sec*-BuLi (2.41 mL, 1 M, 2.41 mmol) over a 10-min period under nitrogen atmosphere at −78 °C. The reaction was stirred for 2 h followed by the introduction of formaldehyde gas. After complete disappearance of the red coloration, the mixture was warmed to 25 °C and stirred for an additional 24 h. After concentration in vacuo, the residue was dissolved in CH_2Cl_2, washed with aqueous Na_2CO_3, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude residue was chromatographed (column) on silica gel eluting with CH_2Cl_2/MeOH/$CHCl_3$ (2:1:1), affording two components **14** (first fraction) and **15** (second fraction).

6-Vinyl-6′-(3-hydroxypropen-2-yl)-2,2′-bipyridine (14) was recrystallized from C_6H_{12}, as white crystals (15%): mp 94–95 °C; ^1H NMR δ 4.25 (s, OH, 1 H), 4.67 (m, CH_2, 2 H), 5.52 (dd, H_a, J_{ax} = 10.3 Hz, J_{ab} = 1.9 Hz, 1 H), 5.56 (d, H_b, J = 0.8 Hz, 1 H), 5.87 (d, H_a, J = 0.8 Hz, 1 H), 6.34 (dd, H_b, J_{bx} = 17.4 Hz, $J_{ba} = J_{ab}$, 1 H), 6.92 (dd, H_x, $J_{xb} = J_{bx}$, J_{xa} = 10.3 Hz, 1 H), 7.34 (dd, 5-py H, J = 7.7, 1.3 Hz, 1 H), 7.63 (dd, 5′-py H, J = 7.8, 1.3 Hz, 1 H), 7.77 (t, 4-py H, J = 7.8 Hz, 1 H), 7.84 (t, 4′-py H, J = 7.8 Hz, 1 H), 8.17 (dd, 3′-py H, J = 7.8, 1.3 Hz, 1 H), 8.44 (dd, 3-py H, J = 7.8, 1.3 Hz, 1 H) [see Figure 1]; IR (KBr) 3300 (OH), 1550, 1430 cm^{-1}; MS, m/e 238 (M^+, 87), 237 (100), 210 (26), 209 (99), 208 (72), 207 (66), 185 (57). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.63, H, 5.88; N, 11.76. Found: C, 75.40; H, 5.67; N, 11.50.

6,6′-Bis(3-hydroxypropen-2-yl)-2,2′-bipyridine (15) was recrystallized from C_6H_{12}, as white plates (35%): mp 157–160 °C dec; ^1H NMR δ 4.12 (s, OH, 2 H), 4.68 (m, CH_2, 4 H), 5.58 (d, H_b, J = 0.7 Hz, 2 H), 5.89 (d, H_a, J = 0.7 Hz, 2 H), 7.65 (dd, 5-py H, J = 7.8, 1.5 Hz, 2 H), 7.85 (t, 4-py H, J = 7.8 Hz, 2 H), 8.23 (dd, 3-py H, J = 7.8, 1.5 Hz, 2 H); IR (KBr) 3300 (OH), 1550, 1425, 1025 cm^{-1}; MS, m/e 268 (M^+, 96), 267 (100), 249 (33), 239 (62), 238 (92), 237 (46), 219 (43). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.24; H, 5.70; N, 10.15.

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Stereocontrolled Synthesis of Cis-Fused Hydroisoquinolines by an Intramolecular Diels–Alder Reaction of (*Z*)-Dienes[1]

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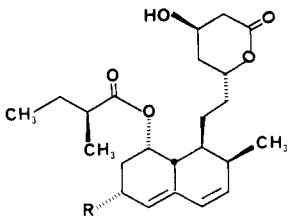
An efficient stereocontrolled synthesis of highly functionalized cis-fused octahydroisoquinolines via an intramolecular Diels–Alder reaction of (*Z*)-dienes is described.

Numerous investigations[2] regarding the use of the intramolecular Diels–Alder reaction as a strategy for stereoselective synthesis of a variety of complex structures have been reported. However, a general method for construction of a substituted cis-fused hydroisoquinoline skeleton with complete stereocontrol via intramolecular cycloaddition has not been published.[3]

In connection with our program concerning structural modifications[4] of the naturally occurring fungal metabolites compactin[5] (**1**, R = H) and mevinolin[6] (**1**, R = CH_3), which



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possess interesting hypocholesterolemic activities,[7] we became interested in the synthesis of an aza analogue **2**

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