Chelation-Controlled Regioselectivity in the Synthesis of Substituted Pyrazolylpyridine Ligands. 3. Unsymmetrically Substituted Tridentates and Ditopic Bis(tridentates) en Route to Singly Stranded Helicates†

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A strategy for the synthesis of helical multinuclear complexes (helicates) of any length is outlined, making use of ditopic ligands to bridge between metals and monotopic ligands to cap the chain's termini. We present the syntheses of both ditopic and monotopic ligands with tridentate binding units for octahedral metals, in liposoluble and functionalized varieties. Of special interest are ligands bearing benzoic acid or toluic acid side-chains which can ionize and serve as counteranions. Several singly *N*(1)-substituted 2,6-bis(4,5,6,7-tetrahydroindazol-3-yl)pyridines were prepared by regioselective, chelation-controlled mono-*N*-alkylation or -arylation of the tautomeric *N*,*N*′-H_2 parent compound. These were then either coupled with CH_2 linkages to provide the ditopic ligands or were further *N*-functionalized to give unsymmetrically substituted capping ligands. The regiochemistry of the *N*-substitutions and the ring-to-ring conformations were ascertained by ^{1}H NMR spectra with and without added complexands (H^+, D^+, Zn^{2+}, and Na^+). The formation of a bis-($ZnBr_2$) adduct confirmed the independence of the metal binding sites while Na^+ formed the 2:2 helicate.

Introduction

Several examples of *helicates*, one-dimensional, oligonuclear metal complexes of helical architecture, have been reported in recent years.[1] Most are formed from polypyridines serving as oligo(bidentates) for tetrahedral metal centers such as Cu^I, and a few examples of oligo-octahedral complexes from oligo(tridentates) are known. The construction of long, doubly stranded helicates uses self-assembly from long, polytopic ligands, wherein the metals glue the intertwined ligand strands. Our approach (Figure 1) obviates the need for long polytopic ligands. Instead, a single strand can be constructed by linking any number of ditopic ligands via the metal centers, with the termini being capped by monotopic ligands. Depending on the length and flexibility of the linker groups (L) chosen, such chains can achieve the same helicity as double strands, especially if interplanar stacking occurs. A greater variety of helicates are accessible and functionality can be introduced at each metal site. Importantly, the ditopic ligands required are much more easily synthesized than those of higher topicity by, as reported herein, a coupling of unsymmetrically substituted monotopic precursors, while monotopic ligands would cap the chains at the terminal metal centers.

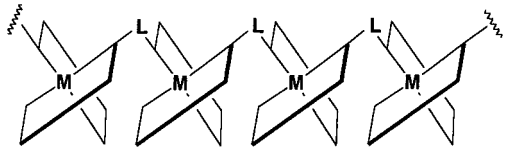

Figure 1. Singly stranded helical polynuclear assembly, where the rectangles depict the binding planes in polytetrahedra or polyoctahedra, and where L represents a linker group.

A suitable class of tridentate building blocks are the 2,6-bis(tetrahydroindazol-3-yl)pyridines **1**. They and their bidentate cousins comprise a class of newly developed ligands for transition metals[2−4] which are readily prepared from commercially available materials by short routes and in good yields. They are lipophilic and readily form stable, organo-soluble Ru(II),[2,5,6] Zn(II),[3] and Co(II)[7] complexes. Unlike the less versatile 2,1(*N*)-linked 2,6-bis(pyrazol-1-yl)pyridines **2**,[8−10] our 2,3(*C*)-linked analogues can be functionalized at N*H* sites, and this facility has been used to prepare pentadentate and macrocyclic

† Part 2: ref 4.

(1) Constable, E. C. *Tetrahedron* **1992**, *48*, 10013. Lehn, J.-M.; Sauvage, J.-P.; Simon, J.; Ziesel, R. *New J. Chem.* **1983**, *7*, 413. Cathey, C. J.; Constable, E. C.; Hannon, M. J.; Tocher, D. A.; Ward, M. D. *J. Chem. Soc., Chem. Commun.* **1990**, 629. Constable, E. C. *Angew. Chem. Intl. Ed. Engl.* **1991**, *30*, 1450. Potts, K. T.; Raiford, K. G. A.; Keshavarz, M.-K. *J. Am. Chem. Soc.* **1993**, *115*, 2793. Cathey, C. J.; Constable, E. C.; Hannon, M. J.; Tocher, D. A.; Ward, M. D. *J. Chem. Soc. Chem. Commun.* **1990**, 621. Buchecker, D. O. C.; Sauvage, J.-P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 189. Piguet, C.; Bernardelli, G.; Williams, A. F. *Inorg. Chem.* **1989**, *28*, 1450. Bell, T. W.; Jousselin, H. *Nature* **1994**, *367*, 441. Koert, U.; Harding, M. M.; Lehn, J.-M. *Nature* **1990**, *346*, 339. Constable, E. C.; Thompson, A. M. W. *Inorg. Chim. Acta* **1994**, *223*, 177. Crane, J. D.; Sauvage, J.-P. *New J. Chem.* **1992**, *16*, 649.

(2) Dash, R.; Potvin, P. G. *Can. J. Chem.* **1992**, *70*, 2249.

(3) Luo, Y.; Potvin, P. G. *J. Org. Chem.* **1994**, *59*, 1761.

(4) van der Valk, P.; Potvin, P. G. *J. Org. Chem.* **1994**, *59*, 1766.

(5) Luo, Y.; Potvin, P. G.; Tse, Y.-H.; Lever, A. B. P. *Inorg. Chem.* **1996**, *35*, 5445.

(6) Zadykowicz, J.; Potvin, P. G. Manuscript in preparation.

(7) Jairam, R., M. Sc. Thesis, York University, 1991. Adorante, J.; Lau, M.; Potvin, P. G. Unpublished work.

(8) Saha, N.; Kar, S. K. *J. Inorg. Nucl. Chem.* **1977**, *39*, 1236. Watson, A. A.; House, D. A.; Steel, P. J. *J. Org. Chem.* **1991**, *56*, 4072. Chabert, N.; Jacquet, L.; Marzin, C.; Tarrago, G. *New J. Chem.* **1995**, *19*, 443.

(9) Jameson, D. L.; Blaho, J. K.; Kruger, K. T.; Goldsby, K. A. *Inorg. Chem.* **1989**, *28*, 4312.

(10) Steel, P. J.; Constable, E. C. *J. Chem. Soc., Dalton Trans.* **1990**, 1389. Downard, A. J.; Honey, G. E.; Steel, P. J. *Inorg. Chem.* **1991**, *30*, 3733.

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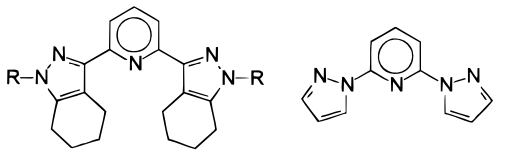
octadentate species[2] as well as ligands bearing acetic or benzoic acid side-chains.[3,4] Ligands bearing peripheral ionizable groups are of particular interest as they provide access to anionic, neutral, or cationic complexes under pH control and we wished to employ this to modulate the interactions between photoexcited Ru^{II} electron donors and cationic electron acceptors such as methylviologen.



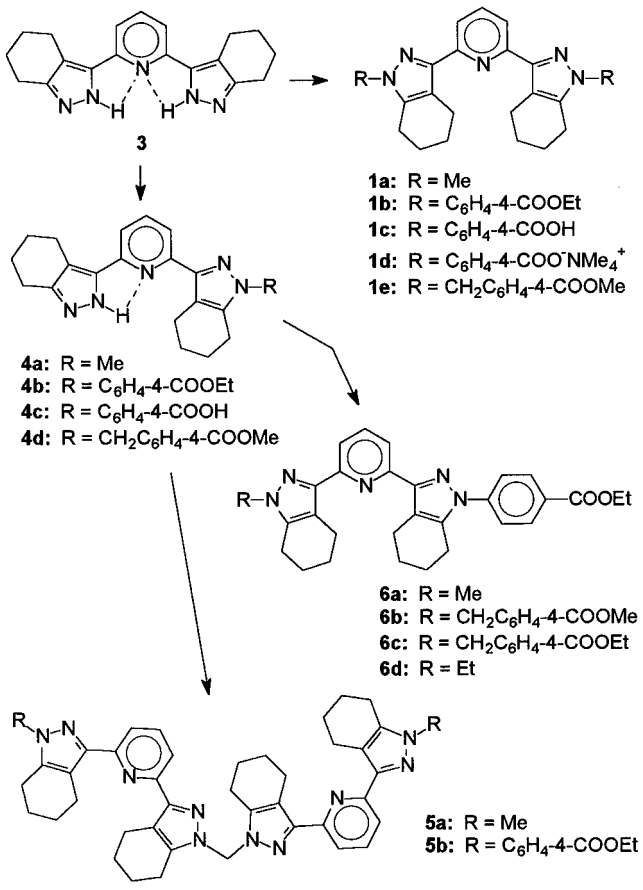
1 **2**

In this paper, we report on the synthesis of unsymmetrical, mono- and disubstituted varieties of **1** as capping ligands and as precursors in the elaboration of ditopic, bis(tridentate) ligands that are suitable for the preparation of helical polynuclear complexes. This calls forth the problem of monofunctionalization of difunctional compounds, and our work includes the first known instance of a monoarylation of a bis(azole).

Results and Discussion

One design consideration in the binding of octahedral metals to a necessarily unsymmetric, ditopic bis(tridentate) ligand is metal-centered chirality and the possible formation of diastereomeric oligonuclear complexes. According to MM2-level calculations, CH_2 spacers allow complexation without undue steric hindrance and favor the *like* (chiral racemic) form of any two-metal fragment of the chain, while aliphatic spacers longer than CH_2-CH_2 present no clear advantage over the shorter ones. In fact, too much length and flexibility enables the formation of *unlike* (or *meso*) fragments, which disrupt helicity. Von Zalewski et al.[11] showed that $(CH_2)_6$-linked bipyridines could even wrap around a single Ru^{II} center. We therefore chose to use CH_2 linkers and targeted the *N*-methyl-capped compound **5a** as the first and simplest example. Elguero et al.[12] used CH_2Cl_2 as a source of CH_2 bridges between pyrazoles under PTC conditions, albeit without regioselectivity. In our experience, a metal ion template in a homogeneous medium should provide the desired selectivity[2−4] in the coupling of two equivalents of monofunctionalized precursors **4**.

It has previously been shown that treatment of bis(pyrazolyl)pyridine **3** with NaH in THF, followed by alkylating agents, leads exclusively to *out,out*- or 1′,1″-disubstituted bis(indazol-3-yl)pyridines.[2,4] Thus, exhaustive methylation of **3** (2.4 equiv of NaH/THF/room temperature/2.3 equiv of CH_3I) produced regiomerically pure **1a** in 60% isolated yield.[4] Metal chelation was apparently critical in directing the regiochemistry and organic bases, such as DBU or Et_3N, generated complicated mixtures of *out,out*, *in,out*, and *in,in* regiomers. With only 1 equiv of CH_3I by the same procedure, however, a nonstatistical product ratio was obtained in which the dialkylated product **1a** dominated, with the balance consisting mostly of the starting material and little of the desired **4a**. Reactions in THF were not homogeneous, containing a suspended white solid which we tentatively identified as the monosodio derivative of **3**. We speculate that the monosodio derivative of **4a** was more soluble and hence more likely to react a second time. The simple replacement of THF by anhydrous DMF led to homogeneous mixtures and produced a reproducible, statistical distribution of products (1:1:2 **3**:**1a**:**4a**) in near-theoretical yields. Chromatography led to a 57% isolated yield of **4a** based on converted **3**, with recycling of unreacted material. The aromatic region of the ^1H NMR spectrum of **4a** showed the expected unsymmetric pattern typical of a *syn,anti* conformer of an *in,out*- (or 2′,1″-) disubstituted product:[3,4] One pyridine doublet lay downfield of the pyridine H-4 triplet and was assigned to the proton on the methylated indazole side, where the indazole is anti to the pyridine, while the other doublet lay upfield of the triplet and was attributed to the pyridine proton on the nonmethylated side, which experiences shielding from the nearby CH_2 group on the unsubstituted indazole, which itself is turned syn with respect to the pyridine by virtue of an internal H-bond involving the *in*- (or 2-)indazole tautomer and the pyridine N. The occurrence of such H-bonding has recently been confirmed in crystal structures,[13] and the postulated shielding in the syn conformation is supported by NOESY experiments.[5,14]

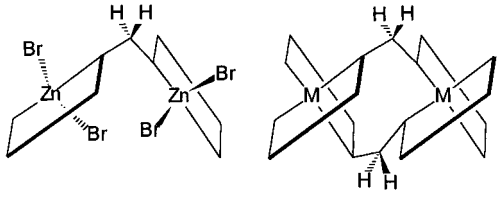


The monofunctional **4a** was converted to the symmetric ditopic **5a** in quantitative yield by a modification (NaH/CH_2Cl_2) of the conditions of Elguero et al.[9] Its structure was determined by $^1H-$ and ^{13}C NMR, MS and elemental

(11) Hayoz, P.; von Zalewski, A.; Evans, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 5111.
(12) Elguero, J.; Ochoa, C. *J. Heterocycl. Chem.* **1960**, *25*, 1797.
(13) Luo, Y.; Potvin, P. G. *J. Coord. Chem.* **1997**, in press. Zadykowicz, J.; Potvin, P. G. Manuscript in preparation.
(14) Luo, Y., Ph.D. Thesis, York University, 1995.

analysis. The presence of a CH_2 bridge was indicated by the appearance of new singlets in the ^{1}H NMR spectrum at 6.26 ppm and in the ^{1}H-decoupled ^{13}C NMR spectrum at 61.07 ppm, both entirely in line with data from similar formaminals.[12] A DEPT experiment confirmed that the one new ^{13}C peak was indeed owing to a CH_2 group. Since the indazoles' CH_2 and CH_3 substituents are similar, the spectra show *pseudo*-symmetry. The two partially overlapping pyridine ^{1}H doublets (H-3 and H-5) were clearly downfield of the H-4 doublet of doublets, signaling anti pyrazole−pyridine bonds. Not surprisingly, **5a** fragmented easily in the mass spectrometer, with two fragment peaks attributable to N−CH_2 bond cleavage.

To help resolve the partial overlaps, a $CDCl_3$ solution of **5a** was treated with an excess of anhydrous $ZnBr_2$. This produced a symmetric spectrum with no overlap of the pyridine doublets. These were upfield of the triplet, the pattern typical of a *syn,syn* conformer, and thus served to prove that the desired *out,out* substitution pattern had been achieved. Although a FAB-MS spectrum of the product was uninformative, we conclude that it was the dinuclear 1:2 species, **5a**$(ZnBr_2)_2$ by elimination of possible alternatives. With a symmetric spectrum, unsymmetric 1:1, 2:3, and higher stoichiometries can be eliminated. Second, the presence of more than one unit of **5a** per metal, such as in the helical 2:2 complex, [(**5a**)-$Zn]_2Br_4$, can be discounted for two reasons. First, Zn^{II} readily forms neutral pentacoordinate species, for instance with terpyridine,[15] whereas the formation of dicationic octahedral centers, such as in $[(\mathbf{5a})Zn]_2^{4+}$, would be disfavored in the solvent used. Second, one would expect the *N*-CH_3 and *N*-CH_2 groups in $[(\mathbf{5a})Zn]_2$-Br_4 to suffer interligand shielding by the ring current of the neighboring ligand on the same metal, and for their signals to therefore migrate upfield relative to the free ligand positions. That phenomenon occurs in complexes with suitable, orthogonally disposed ligands as in, for instance, Ru(bipyridine)$_2L^{2+}$ species[10,16] but not in complexes lacking them such as Ru(terpyridine)$(PMe_3)_2Cl^{+}$[17] and Zn(bidentate)Cl_2 species,[3] where metal induction causing downfield migrations is the dominant effect. This is also true for the *N*-CH_3 signals in Ru$(\mathbf{1a})_2^{2+}$ and related complexes.[5,6] Instead, both the *N*-CH_3 and *N*-CH_2 signals in the present case migrated downfield, consistent with **5a**$(ZnBr_2)_2$. Finally, one might expect diastereotopic CH_2 bridges in the helical $[(\mathbf{5a})Zn]_2Br_4$ due to chirality at the metal centers, but none was evident in the present case.



5a$(ZnBr_2)_2$ [**5a**M]$_2$ M = Zn^{2+} or Na^+

Treatment of **5a** with exactly 1.0 equiv of $ZnBr_2$ led to a mixture of products, including a precipitate that was insoluble even in polar solvents (D_2O, CD_3CN, CD_3-$SOCD_3$, CD_3COCD_3). We presume this to be highly charged, polynuclear material of the type depicted in Figure 1. The ^{1}H NMR spectrum of the supernatant revealed a number of species, including free ligand, and the signals were not in exchange. The FAB-MS spectrum, however, revealed the presence of the 2:2 complex, as the highest mass peaks corresponded to $[(\mathbf{5a})Zn]_2Br_2^+$ and $[(\mathbf{5a})Zn]_2^+$.

Treatment of **5a** in $CDCl_3$ with an excess of anhydrous sodium picrate (NaPic) apparently led to the 2:2 product in a two-stage process. There was an initial, instantaneous uptake of the otherwise insoluble solid, with a strong yellow coloration of the solution and the appearance of a sharp singlet due to Pic^- at 8.7 ppm.[4] Signal integration indicated an initial excess of **5a** over Na^+ but, over the course of about 1 h with vigorous shaking, there was a slower, second stage of uptake that eventually led to a stable ratio of **5a** to bound Na^+ of approximately 1:1. We interpret this two-stage process as an initial formation of $[(\mathbf{5a})_2Na]^+$ while **5a** was in large excess over the dissolved Na^+, followed by further uptake and rearrangement to $[(\mathbf{5a})Na]_2^{2+}$. At all times, there was only one set of pyridine signals, indicating fast ligand exchange, and, as had occurred with $ZnBr_2$, the (partially overlapped) pyridine doublets shifted to positions upfield of the triplet, again indicating rotation to *syn,syn* conformations at the binding sites. The CH_2 signal was broad but there was no clear evidence of diastereotopicity, although the rate of ligand exchange may have disallowed its observation. The FAB-MS spectrum revealed much fragmentation, but a peak corresponding to $[(\mathbf{5a})Na]_n^{n+}$ at *m*/*z* 701 supported our formulation.

N-Arylations of **3** are more difficult. The original reaction[4] with excess ethyl 4-fluorobenzoate and Na_2CO_3 in DMSO (150 °C/2 d) had produced the monoester **4b** as a side-product (20% isolated yield) in the synthesis of **1b** (31% isolated yield). Several alternative procedures were explored in model reactions of 3,5-dimethylpyrazole with ethyl 4-fluorobenzoate, ethyl 4-nitrobenzoate, and ethyl 2,4-dinitrobenzoate. We found that the 4-fluorobenzoate gave the cleanest reactions but the conditions employed by Jameson et al.[9] (K/diglyme/110−130 °C) afforded only a very slow reaction with this reagent. However, replacement of the solvent with DMSO after deprotonation in diglyme gave access to higher temperatures without interference by dimsyl ion and afforded the best yields. By this process, **3** and 2 equiv of ethyl 4-fluorobenzoate produced the di- and monoesters in 66% and 20% isolated yields, respectively, after 4 d at 130−150 °C. By the same procedure with 1 equiv of ethyl 4-fluorobenzoate over 2 d at a more modest temperature (70 °C), we obtained 20% of **1b** and 40% of **4b** after purification. This 2:1 product ratio signals equal rates of reaction at each step, in this homogeneous environment at least.

The hydrolysis of **1b** in TFA/H_2O produced diacid **1c** as the TFA salt in 74% yield, after recrystallization. This was a high melting solid that was difficult to dissolve but which remained soluble upon concentration and so was difficult to recrystallize. The similar TFA/H_2O hydrolysis of monoester **4b** proceeded to give **4c** in 82% isolated yield without salt formation. Hydrolysis of **1b** or neutralization of **1c** with Me_4NOH gave a quantitative crude yield of the H_2O-soluble bis(tetramethylammonium) salt **1d** but all attempts to recrystallize this

(15) Einstein, F. W. B.; Penfold, B. R. *Acta Crystallogr.* **1966**, *20*, 924.

(16) Steel, P. J.; Lahousse, F.; Lerner, D.; Marzin, C. *Inorg. Chem.* **1983**, *22*, 1488. Marzin, C.; Budde, F.; Steel, P. J.; Lerner, D. *New J. Chem.* **1987**, *11*, 33.

(17) Leising, R. A.; Kubow, S. A.; Churchill, M. R.; Buttrey, L. A.; Ziller, J. W.; Takeuchi, K. J. *Inorg. Chem.* **1990**, *29*, 1306.

material provided the H_2O-insoluble free diacid **1c** contaminated with variable amounts of Me_4N^+ salts.

With monoacid **4c** in DMSO-d_6, there was a severe overlap of peaks in the aromatic region but the 2:4:2:8 distribution of aliphatic signals was consistent with the *syn,anti* conformation expected of the nonzwitterionic form of **4c**, and was similar to the pattern with the parent monoester **4b**, also in the *syn,anti* form. Addition of $ZnBr_2$ produced the aromatic pattern typical of the *syn, syn* conformer, just as it had with the diacid **1c**. Treatment with TFA had the same result. ^{1}H NMR analysis of the ammonium salt **1d** indicated the *syn,syn* orientation, just as with the bis(tetramethylammonium) salt of the acetic acid analogue,[4] which we had ascribed to either the enforcement of this conformation by ionic interactions or to the operation of new shielding effects. The ^{1}H NMR spectrum of salt **1c**·TFA in DMSO-d_6 was deceptive as the aromatic pattern indicated an *anti,anti* conformation which is rather expected of the free diacid in nonzwitterionic form. Treatment with CH_3COOD or CF_3COOD caused no change, as expected, but an excess of $ZnBr_2$ did produce the anticipated pattern indicative of complexation of the *syn,syn* conformer.

Compound **4b** was converted in quantitative yield to **5b** using the same conditions that produced **5a**. Unlike with **5a**, there was no overlap of pyridine ^{1}H NMR signals with **5b**. Its ^{1}H NMR, ^{13}C NMR, and mass spectra clearly supported the structural assignment and the melting point was sharp. However, combustion analyses were consistently low for all elements, though the C/N and H/N ratios matched those expected.

In view of the ease of monoalkylation of **3**, compared to its monoarylation, an alternative carboxyl-bearing substituent was sought. Although more mobile than a benzoic acid substituent, which provides a preorganized and entropically advantaged site in diacid **1c** for methylviologen binding, the more flexible *p*-toluic acid group was chosen to possibly adjust and better accommodate the guest in enthalpically favored binding. Further, because we have found in other work[6] that the nature of the side-chain in Ru^{II} complexes of **1** has little effect on the MLCT band positions and the CV oxidation waves, the interposition of a CH_2 group between the tridentate core and the benzoic acid group was not expected to much affect the ligand's electronic properties. Thus, in analogy to the preparation of monobenzoate **4a**, a reaction of **3** with 1 equiv of methyl 4-(bromomethyl)benzoate produced the monotoluate **4d** and the ditoluate **1e** in 47% and 25% isolated yields, respectively. The coproduct **1e** is interesting in its own right as a carboxyl-functionalized ligand.

Because free NH sites are at times undesirable in complexes (for instance, they are slower to complex and strongly decrease the $Ru^{3+/2+}$ oxidation potential[5,6]), the monosubstituted compounds **4** to be used as monotopic ligands were *N*-capped. Thus, monoester **4b** was analogously alkylated with CH_3I and methyl 4-(bromomethyl)benzoate to produce the monoester **6a** and mixed diester **6b**, respectively. However, analysis of the reaction mixtures revealed new ester groups: ethyl ester **6a** was accompanied by a small amount of the corresponding methyl ester while the preparation of the mixed ester **6b** produced a complex mixture presenting some 4-(ethoxycarbonyl)benzyl ester groupings. The crude reaction products were therefore separately subjected to a subsequent transesterification step, using DBU/LiCl in EtOH,[18] to produce the pure monoethyl ester **6a** and pure diethyl ester **6c** in 61% and 71% overall yields, respectively. In terms of flexibility, the mixed diester **6c** presents a compromise between the more rigid **1b** and the looser **1e**.

One possible route to these side-products is the attack of the benzoate ester's ethyl group, in either the starting material or in the desired product, by the X^- (Br^- or I^-) liberated during the alkylations to generate carboxylate ions that then become otherwise *O*-alkylated. This would also generate C_2H_5X species and one would therefore also expect *N*-ethyl groupings in the product mixtures. Such groupings were indeed found in the ^{1}H NMR spectra of the crude reaction products in support of this explanation, but we cannot exclude the intervention of adventitious H_2O, despite the care taken to avoid it, in also producing carboxylate intermediates. To overcome this problem and the necessity for a second operational step in forming an *N*-alkyl monoester such as **6a**, ethyl ester **4b** was also alkylated with C_2H_5Br, leading directly to the *N,O*-diethyl compound **6d** in 92% isolated yield.

Despite the steric bulk of substituents in some cases, many of these ligands have been successfully incorporated into homoleptic and heteroleptic, mononuclear and dinuclear Ru^{II} and Co^{II} complexes, and these will be reported elsewhere.

Experimental Section

THF was distilled over K and benzophenone, and DMSO was dried over CaO, filtered, and distilled over molecular sieves (5 Å) and then was frozen and stored in sealed vials under Ar. All other solvents used were reagent grade and used as such. The petroleum ether (PE) used was the light fraction (bp 30−60 °C). The melting points are not corrected. NMR spectra were obtained on a 400-MHz Bruker instument in $CDCl_3$, unless otherwise indicated. Acetone was used as an internal reference for spectra in D_2O. Mass spectroscopy was carried out by Dr. B. Khouw on a Kratos Profile machine. The microanalyses were perfomed by Guelph Chemical Laboratories Ltd. of Guelph, Ontario, or National Chemical Consulting Inc. of Tenafly, NJ.

2,6-Bis[1-[4-(ethoxycarbonyl)phenyl]-4,5,6,7-tetrahydroindazol-3-yl]pyridine (1b). A mixture of bis(pyrazolyl)-pyridine **3**[4] (0.319 g, 1 mmol) and K metal (0.078 g, 2 mmol) was stirred at 60 °C under Ar for 3 h in anhydrous diglyme. After removal of the solvent, the yellow solid residue was dissolved in dry DMSO, and diethyl 4-fluorobenzoate (0.673 g, 4 mmol) was added. The resulting mixture was stirred for 4 d at 150 °C. After removal of the solvent, the crude product was taken up in $CHCl_3$ and washed with H_2O. The oily residue was purified by column chromatography on alumina, using as eluent AcOEt−PE (50:50). The first fraction (0.406 g, 66%) contained diester **1b**. Subsequent fractions, eluted by EtOAc, contained monoester **4b** (0.093 g, 20%). The spectra and melting points of these materials were identical with those previously reported.[4]

2,6-Bis[1-(4-carboxyphenyl)-4,5,6,7-tetrahydrindazol-3-yl]pyridine (1c). A solution of 0.128 g (0.208 mmol) of diester **1b** in a mixture of CF_3COOH (10 mL) and H_2O (3 mL) was heated to reflux for 24 h. Removal of solvent gave a yellow solid residue, which was washed with water and $CHCl_3$ and then vacuum-dried. Recrystallization from THF gave 0.096 g (66%) of the white solid diacid **1c** as its TFA salt: mp > 300 °C; ^{1}H NMR (DMSO-d_6): δ 1.80 (m, 8H), 2.89 (m, 4H), 2.97 (m, 4H), 7.81 (d, 4H, J = 8.5 Hz), 7.91 (t, 1H, J = 7.9 Hz), 7.97 (d, 2H, J = 7.95 Hz), 8.08 (d, 4H, J = 8.5 Hz); ^{13}C NMR: δ 22.15, 22.35, 22.71, 23.60, 117.64, 120.01, 122.14, 128.66,

(18) Seebach, D.; Thaler, A.; Blaser, D.; Ko, S. Y. *Helv. Chim. Acta* **1991**, *74*, 1102.

130.56, 137.16, 140.35, 142.83, 148. 86, 152. 56, 166.72 ppm; MS *m*/*z* (%) 559 (67, $M^{\bullet+}$), 515 (15, $M^{\bullet+} - CO_2$), 467 (18), 439 (5, $M^{\bullet+} + H - C_6H_4COOH$), 368 (5), 319 (5, $M^{\bullet+} - 2C_6H_4COO^{\bullet}$), 280 (11), 236 (15), 187 (10), 137 (37), 97 (54), 81 (81), 69 (100, C_3H_7CN), 57 (74), 43 (65). Anal. Calcd for $C_{33}H_{29}N_5O_4 \cdot CF_3COOH \cdot H_2O$: C, 60.69; H, 4.80; N, 10.11. Found: C, 60.56; H, 4.92; N, 10.10.

Bis(tetramethylammonium) 2,6-Bis[1-(4-carboxylatophenyl)-4,5,6,7-tetrahydroindazol-3-yl]pyridine (1d). From 1b. A mixture of 0.308 g (0.5 mmol) of diester **1b** and $Me_4NOH \cdot 5H_2O$ (0.181 g, 1 mmol) in EtOH was heated to reflux overnight. The volatiles were removed, and the crude yellow solid was washed with $CHCl_3$ and then vacuum-dried to leave a quantitative yield of salt **1d** in nearly pure form: mp 276−8 °C; ^{1}H NMR (D_2O): δ 1.33 (m, 8H), 2.34 (m, 4H), 2.47 (m, 4H), 3.13 (s, 24H), 7.28 (bd, 4H, J = 8.2 Hz), 7.49 (bd, 2H), 7.52 (bt, 1H), 7.88 (d, 4H) ppm; ^{13}C NMR (D_2O): δ 23.17, 23.40, 23.76, 24.27, 56.32, 117.98, 121.34, 123.60, 131.21, 136.57, 138.32, 141.56, 141.82, 149.73, 152.90, 174.79 ppm; MS *m*/*z* (%) 705 (0.1, $M^{\bullet+}$), 602 (1), 560 (3), 481 (6), 368 (42), 334 (6), 313 (8), 257 (25), 236 (46), 110 (82), 71 (100), 56 (85).

From 1c. An EtOH solution of diacid salt **1c**·$CF_3COOH \cdot H_2O$ (0.063 g, 0.091 mmol) was treated with $Me_4NOH \cdot 5H_2O$ (0.055 g, 0.303 mmol). Workup as above provided nearly pure **1d** (0.060 g, 93%).

2,6-Bis[1-[[4-(methoxycarbonyl)phenyl]methyl]-4,5,6,7-tetrahydroindazol-3-yl]pyridine (1e). Solid NaH (0.053 g, 2.2 mmol) was added to a solution of 0.319 g (1 mmol) of bis(pyrazolyl)pyridine **3** in dry THF. H_2 evolution was immediate, and the solution became milky-white. The mixture was stirred under Ar for 2 h and then treated with methyl 4-(bromomethyl)benzoate (0.504 g, 2.2 mmol). After heating to reflux overnight, THF was removed, and the light yellow solid residue was dissolved in $CHCl_3$ and washed with water. After the removal of $CHCl_3$, the resulting oil was purified by column chromatography on alumina, using EtOAc as eluent, to yield the solid diester **1e** (0.536 g, 87%), mp: 147−149 °C; ^{1}H NMR: δ 1.79 (m, 8H), 2.47 (t, 4H, J = 5.90 Hz), 2.99 (t, 4H, J = 5.75 Hz), 3.90 (s, 6H), 5.35 (s, 4H), 7.20 (d, 4H, J = 8.01 Hz), 7.70 (t, 1H, J = 7.97 Hz), 7.86 (d, 2H, J = 7.85 Hz), 7.98 (d, 4H, J = 8.50 Hz) ppm; ^{13}C NMR: δ 21.73, 22.43, 22.97, 23.23, 52.10, 52.67, 116.47, 119.44, 126.83, 129.49, 130.03, 136.48, 139.83, 142.32, 148.00, 153.33, 166.78 ppm; MS *m*/*z* (%) 616 (10, $M^{\bullet+}$ + H), 524 (5), 466 (5, $M^{\bullet+} - CH_2C_6H_4COOCH_3$), 336 (44), 350 (20), 313 (13), 257 (16), 236 (28), 218 (59), 129 (34), 97 (82), 83 (83), 43 (100). Anal. Calcd for $C_{37}H_{37}N_5O_4$: C, 72.18; H, 6.06; N, 11.37. Found: C, 72.19; H, 6.00; N, 11.29.

2-(1-Methyl-4,5,6,7-tetrahydroindazol-3-yl)-6-(2*H*-4,5,6,7-tetrahydroindazol-3-yl)pyridine (4a). Solid NaH (0.030 g, 1.26 mmol) was added to a solution of 0.190 g (0.6 mmol) of bis(pyrazolyl)pyridine **3** in anhydrous DMF. H_2 evolution was immediate, and the solution became yellow. The mixture was stirred under Ar for 2 h and then treated with CH_3I (0.085 g, 0.6 mmol). After stirring overnight at room temperature, DMF was removed, and the light yellow solid residue was dissolved in $CHCl_3$ and washed with water. After the removal of $CHCl_3$, the resulting oil was purified by column chromatogrsphy on alumina, using EtOAc as eluent. The first fraction was the *N*,*N*′-dimethyl compound **1a** (0.050 g, 24%), whose spectra and melting point were identical with those previously reported.[4] Subsequent fractions, eluted with MeOH:EtOAc (1:99), contained the desired *N*-monomethyl compound **4a** (0.096 g, 48%) and unreacted bis(pyrazolyl)pyridine **3** (0.031 g, 16%). Recrystallization of crude **4a** from EtOAc:PE gave a white solid, mp: 130−132 °C; ^{1}H NMR: δ 1.79 (m, 4H), 1.89 (m, 4H), 2.62 (t, 2H, J = 6.2 Hz), 2.76 (m, 2H), 2.84 (m, 2H), 2.99 (t, 2H, J = 5.75 Hz), 3.81 (s, 3H), 7.38 (d, 1H, J = 7.7 Hz), 7.73 (dd, 1H), 7.83 (d, 1H, J = 7.86 Hz) ppm; ^{13}C NMR: δ 21.69, 22.43, 23.02, 23.16, 23.28, 23.52, 23.70, 35.20, 108.20, 113.53, 116.00, 117.53, 118.96, 136.99, 137.60, 140.28, 147.20, 148.80, 153.80 ppm; MS *m*/*z* (%) 333 (62, $M^{\bullet+}$), 318 (7, $M^{\bullet+} - CH_3$), 304 (13), 279 (16), 256 (14), 241 (14), 213 (14), 185 (14), 149 (42), 129 (84), 111 (30), 81 (63), 69 (100, C_3H_7CN), 57 (39), 43 (23). Anal. Calcd for $C_{20}H_{23}N_5 \cdot 0.5\ H_2O$: C, 70.15; H, 7.06; N, 20.45. Found: C, 70.78; H, 7.39; N, 20.66.

2-[1-[4-(Ethoxycarbonyl)phenyl]-4,5,6,7-tetrahydroindazol-3-yl]-6-(2*H*-4,5,6,7-tetrahydroindazol-3-yl)pyridine (4b). In the same fashion as for diester **1b**, a 2 d arylation in DMSO at 70 °C, using bis(pyrazolyl)pyridine **3** (0.106 g, 0.33 mmol), K metal (0.028 g, 0.716 mmol), and ethyl 4-fluorobenzoate (0.061 g, 0.36 mmol), gave two products. Isolation as before provided diester **1b** (0.040 g, 20%) and the desired monoester **4b** (0.062 g, 40%). The spectra and melting points of these materials were identical with those previously reported.[4]

2-[1-(4-Carboxyphenyl)-4,5,6,7-tetrahydroindazol-3-yl]-6-(2*H*-4,5,6,7-tetrahydroindazol-3-yl)pyridine (4c). As for diacid **1c**, 0.234 g (0.5 mmol) of monoester **4b** gave 0.160 g (73%) of white solid acid **4c**, after recrystallization from THF: mp > 300 °C; ^{1}H NMR (DMSO-d_6); δ 1.78 (m, 8H), 2.65 (m, 2H), 2.89 (m, 4H), 3.10 (m, 2H), 7.80 (m, 3H), 7.90 (m, 2H), 8.09 (d, 2H, J = 8.5 Hz); ^{13}C NMR: δ 20.79, 21.60, 22.38, 22.54, 23.21, 23.63, 113.67, 114.76, 117.81, 119.36, 122.02, 122.29, 124.55, 128.62, 130.472, 130.71, 140.33, 143.82, 148.90, 152.52, 158.59, 166.76 ppm; MS *m*/*z* (%) 439 (100, $M^{\bullet+}$), 410 (20), 395 (10, $M^{\bullet+} - CO_2$), 303 (4), 256 (4), 241 (9), 220 (19), 170 (13), 149 (16), 129 (19), 95 (16), 81 (37), 69 (70, C_3H_7CN), 55 (27, C_2H_5CN), 41 (24). Anal. Calcd for $C_{26}H_{25}N_5O_2$: C, 71.05; H, 5.73; N, 15.93. Found: C, 70.65; H, 6.10; N, 15.52.

2-[1-[[4-(Methoxycarbonyl)phenyl]methyl]- 4,5,6,7-tetrahydroindazol-3-yl]-6-(1*H*-4,5,6,7-tetrahydroindazol-3-yl)pyridine (4d). A mixture of bis(pyrazolyl)pyridine **3** (0.160 g, 0.5 mmol) and NaH (0.014 g, 0.6 mmol) was stirred under Ar in anhydrous DMF at room temperature for 2 h until the solution became clear and the evolution of H_2 had stopped. The mixture was treated with methyl 4-(bromomethyl)benzoate (0.115 g, 0.5 mmol) and allowed to stir under Ar at room temperature for 24 h. The solvent was removed, and the resulting oil was washed with H_2O and extracted into $CHCl_3$. Further purification was carried out by column chromatography on alumina, using MeOH:EtOAc (2:98) as eluent. After liberation from solvents, the first isolated fraction yielded the disubstituted diester **1e** as a white solid (0.080 g, 26%), and the second fraction, a clear oil, was the desired monoester **4d**. This was crystallized from EtOAc:PE to yield a white solid (0.110 g, 47%), mp: 105−107 °C; ^{1}H NMR: δ 1.80 (m, 4H), 1.90 (m, 4H), 2.50 (t, 2H, J = 5.6 Hz), 2.78 (m, 2H), 2.87 (m, 2H), 3.05 (t, 2H, J = 5.4 Hz), 3.92 (s, 3H), 5.38 (s, 2H), 7.22 (d, 2H, J = 7.96 Hz), 7.41 (d, 1H, J = 7.70 Hz), 7.76 (dd, 1H), 7.92 (d, 1H, J = 7.90 Hz), 8.00 (d, 2H, J = 8.05 Hz) ppm; ^{13}C NMR: δ 21.73, 22.36, 22.41, 23.01, 23.10, 23.31, 23.52, 23.69, 52.13, 52.76, 113.61, 116.80, 117.74, 119.27, 126.80, 129.61, 130.10, 137.05, 138.02, 140.38, 142.05, 146.96, 147.96, 150.60, 153.74, 166.72 ppm; MS *m*/*z* (%) 467 (21, $M^{\bullet+}$), 448 (4), 411 (3), 368 (5), 318 (13, $M^{\bullet+} - CH_2C_6H_4COOCH_3$), 301 (3), 284 (5), 249 (23), 2218 (17), 181 (18), 167 (12), 137 (48), 111 (57), 91 (96), 81 (84), 69 (96, C_3H_7CN), 55 (85), 43 (100). Anal. Calcd for $C_{28}H_{29}N_5O_2 \cdot 0.5\ H_2O$: C, 70.57; H, 6.34; N, 14.70. Found: C, 70.45; H, 6.15; N, 14.25.

Bis[3-[2-(1-methyl-4,5,6,7-tetrahydroindazol-3-yl)pyrid-6-yl]-4,5,6,7-tetrahydroindazol-1-yl]methane (5a). A mixture of mono-*N*-methyl derivative **4a** (0.040 g, 0.12 mmol) and NaH (0.009 g, 0.38 mmol) was stirred under Ar in CH_2Cl_2 at room temperature for 2 h until evolution of H_2 stopped. The mixture was heated to reflux overnight and then washed with H_2O. After separation of the organic phase and removal of solvent, the clear oily residue was purified by column chromatography on alumina using EtOAc as the eluent. The white solid residue was subsequently recrystallized from MeOH, yielding 0.038 g (93%) of ditopic ligand **5a** as white solid, mp 238−240 °C; ^{1}H NMR: δ 1.78 (m, 8H), 1.89 (m, 8H), 2.63 (m, 6H), 2.95 (m, 10H), 3.81 (s, 6H), 6.26 (s, 2H), 7.70 (dd, 2H), 7.83 (d, 4H) ppm; ^{13}C NMR: δ 21.72, 21.88, 22.43, 22.52, 22.87, 22.93, 23.11, 23.28, 35.75, 61.07, 115.67, 116.73, 118.93, 119.22, 136.41, 139.78, 140.83, 148.49, 153.00, 153.28, 153.44 ppm; MS *m*/*z* (%) 679 (6, $M^{\bullet+}$), 604 (6), 578 (3), 538 (4), 524 (6), 510 (4), 403 (5), 346 (28, $M^{\bullet+} - C_{20}H_{22}N_5$ (**4a** − H)), 333 (46, $C_{20}H_{22}N_5$ (**4a** − H)), 264 (16), 236 (22), 211 (16), 135(23),

109 (38), 97 (61), 83 (73), 69 (86, C_3H_7CN), 55 (100 C_2H_5CN), 43 (89, C_3H_7). Anal. Calcd for $C_{41}H_{46}N_{10}$: C, 72.54; H, 6.83; N, 20.63. Found: C, 72.06; H, 6.84; N, 20.54.

Bis[3-[2-[1-[4-(ethoxycarbonyl)phenyl]-4,5,6,7-tetrahydroindazol-3-yl]pyrid-6-yl]-4,5,6,7-tetrahydroindazol-1-yl]methane (5b). Using the same procedure as for **5a**, monoester **4b** (0.040 g, 0.086 mmol) and NaH (0.006 g, 0.26 mmol) in CH_2Cl_2 provided ditopic ligand **5b** in a quantitative yield as a white powder, after column chromatography on alumina with 1:1 EtOAc:PE: mp 267−269 °C; ^{1}H NMR: δ 1.44 (t, 6H, J = 7.2 Hz), 1.78 (m, 4H), 2.00 (m, 12H), 2.86 (m, 4H), 2.96 (m, 4H), 3.02 (m, 4H), 3.08 (m, 4H), 4.43 (q, 4H, J = 7.1 Hz), 6.29 (s, 2H), 7.73 (d, 4H, J = 8.6 Hz), 7.78 (t, 2H, J = 7.8 Hz), 7.89 (d, 2H, J = 7.7 Hz), 8.02 (d, 2H, J = 7.7 Hz), 8.17 (d, 4H, J = 8.7 Hz) ppm; ^{13}C NMR: δ 14.36, 21.88, 22.40, 23.03, 23.11, 24.52, 61.00, 61.12, 116.70, 118.55, 119.91, 119.96, 122. 19, 128.20, 130.63, 136.50, 140.02, 140.91, 143.63, 148.42, 149.96, 152.91, 153.10, 166.03 ppm; MS *m*/*z* (%) 798 (0.02, $M^{\bullet+}$ − C_6H_4COOEt), 647 (0.05, $M^{\bullet+}$ − $2C_6H_4COOEt$), 480 (0.4, $M^{\bullet+}$ − $C_{20}H_{22}N_5$ (**4b** − H)), 466 (0.4, $C_{20}H_{22}N_5$ (**4b** − H)), 386 (4), 368 (7), 149 (49, C_6H_4COOEt), 43 (100). Anal. Calcd for $C_{57}H_{58}N_{10}O_4$: C, 72.28; H, 6.17; N, 14.79. Found: C, 60.78; H, 5.09; N, 12.27.

2-(1-Methyl-4,5,6,7-tetrahydroindazol-3-yl)-6-[1-[4-(ethoxycarbonyl)phenyl]-4,5,6,7-tetrahydroindazol-3-yl]-pyridine (6a). From 4b. Solid NaH (0.003 g, 0.128 mmol) was added to a solution of 0.050 g (0.11 mmol) of monoester **4b** in dry THF. H_2 evolution was immediate, and a white precipitate of the Na^+ salt was formed. The mixture was kept under Ar for 2 h and then treated with CH_3I (0.016 g, 0.11 mmol). After stirring overnight at room temperature, THF was removed, and the white solid residue was dissolved in $CHCl_3$ and washed with water. After the removal of $CHCl_3$, the resulting oil was purified by column chromatography on alumina using EtOAc:PE (50:50), but, according to its ^{1}H NMR spectrum, this was an inseparable mixture of methyl and ethyl esters. Retro-transesterification in EtOH with DBU and LiCl[18] was performed. After 24 h reflux, EtOH was removed and the remaining yellow oil was washed with acidified (HCl) H_2O and extracted into $CHCl_3$. Removal of solvent afforded the white solid *N*-methyl monoester **6a** (0.032 g, 60%), mp 166−168 °C; ^{1}H NMR: δ 1.42 (q, 3H, J = 7 Hz), 1.77 (m, 3H), 1.88 (m, 5H), 2.63 (m, 2H), 2.85 (m, 2H), 2.96 (m, 2H), 3.06 (m, 2H), 3.81 (s, 3H), 4.4 (t, 2H, J = 7 Hz), 7.7 (d, 2H, J = 8.7 Hz), 7.74 (d, 1H, J = 7.8 Hz), 7.85 (d, 1H, J = 7.7 Hz), 7.95 (d, 1H J = 7.7 Hz), 8.14 (d, 2H, J = 8.7 Hz) ppm; ^{13}C NMR: δ 14.39, 21.72, 22.50, 22.94, 22.97, 23.02, 23.29, 24.55, 35.77, 61.14, 115.67, 118.54, 119.62, 119.68, 122.18, 128.15, 130.65, 136.54, 139.88, 139.98, 143.66, 147.15, 150.11, 152.77, 153.41, 166.08 ppm; MS *m*/*z* (%) 481 (100, $M^{\bullet+}$), 466 (7, $M\bullet^+$ − CH_3), 452 (23, $M^{\bullet+}$ − CH_2CH_3), 436 (23), 408 (16), 332 (4, $M^{\bullet+}$ − $C_6H_4COOCH_2CH_3$), 318 (7, $M^{\bullet+}$ + H − $C_6H_4COOCH_2CH_3$ − CH_3), 269 (13), 237 (16), 223 (13), 204 (10), 185 (16), 170 (21), 155 (11), 142 (14), 135 (32), 103 (13), 77 (18), 65 (12). Anal. Calcd for $C_{29}H_{31}N_5O_2$: C, 72.31; H, 6.49; N, 14.55. Found: C, 72.37; H, 6.69; N, 14.26.

From 4a. A mixture of mono-*N*-methyl compound **4a** (0.029 g, 0.087 mmol) and K metal (0.004 g, 0.102 mmol) was stirred at 70 °C under Ar for 12 h in anhydrous diglyme. A slow evolution of H_2 was observed, and the white solid K^+ salt was formed. After removal of the solvent, the light yellow, solid residue was dissolved in dry DMSO, and diethyl 4-fluorobenzoate (0.023 g, 0.137 mmol) was added. The resulting mixture was stirred for 4 d at 140 °C. After removal of the solvent, the crude product was taken up in $CHCl_3$ and washed with H_2O/NaCl. The ^{1}H NMR analysis of the crude oil indicated some hydrolysis. Thus, esterification was carried out in refluxing triethyl orthoformate for 24 h. After removal of the volatiles under reduced pressure, the resulting oil was purified as above, and a white powder was obtained (0.013 g, 31%) whose spectra and melting point matched those described.

2-[1-[4-(Ethoxycarbonyl)phenyl]-4,5,6,7-tetrahydroindazol-3-yl]-6-[1-[[4-(ethoxycarbonyl)phenyl]methyl]-4,5,6,7-tetrahydroindazol-3-yl]pyridine (6c). A mixture of monoester **4b** (0.085 g, 0.18 mmol) and NaH (0.008 g, 0.33 mmol) was stirred under Ar in dry THF for 2 h until the solution became milky white from formation of the Na^+ disalt. This mixture was treated with methyl 4-(bromomethyl)-benzoate (0.0.041 g, 0.18 mmol) and stirred overnight. The solvent was removed under reduced pressure, and the oily residue was washed with H_2O and extracted into $CHCl_3$. The ^{1}H NMR spectrum of the crude product showed that undesirable transesterification had occurred. Thus, retro-transesterification was performed in refluxing EtOH with DBU and LiCl.[18] After 16 h, the solvent was removed, and the crude oily residue was washed with dilute HCl solution and extracted into $CHCl_3$. After removal of solvent, the resulting oil was purified by column chromatography on alumina with EtOAc:PE (50:50) as eluent. Recrystallization from EtOAc yielded white crystals of diethyl ester **6c** (0.080 g, 71%), mp 199−201 °C; ^{1}H NMR: δ 1.40 (t, 3H, J = 6.94 Hz), 1.45 (t, 3H, J = 6.96 Hz), 1.78 (m, 3H), 1.90 (m, 5H), 2.51 (m, 2H), 2.81 (m, 2H), 3.02 (m, 2H), 3.10 (m, 2H), 4.39 (q, 2H, J = 6.92 Hz), 4.43 (q, 2H, J = 6.96 Hz), 5.38 (s, 2H), 7.24 (d, 2H, J = 8.09 Hz), 7.74 (d, 2H, J = 8.58 Hz), 7.77 (d, 1H, J = 7.86 Hz), 7.94 (d, 1H, J = 7.71 Hz), 8.00 (m, 3H), 8.17 (d, 2H J = 8.72 Hz) ppm; ^{13}C NMR: δ 14.38, 14.74, 21.74, 22.42, 22.93, 22.98, 23.05, 23.22, 24.17, 24.55, 52.73, 61.02, 61.15, 116.51, 118.52, 119.84, 119.98, 122.21, 126.84, 128.21, 129.87, 130.03, 130.66, 136.65, 139.95, 140.03, 142.10, 143.65, 147.81, 150.08, 152.80, 153.28, 166.06, 166.32 ppm; MS *m*/*z* (%): 629 (31, $M^{\bullet+}$), 509 (48), 481 (100, $M^{\bullet+}$ − $C_6H_4COOCH_2CH_3$), 452 (31, $M^{\bullet+}$ + H − C_6H_4-$COOCH_2CH_3$ − CH_2CH_3), 408 (13, $M^{\bullet+}$ + H − $C_6H_4COOCH_2$-CH_3 − $COOCH_2CH_3$), 353 (33), 313 (34), 239 (54), 213 (48), 185 (37), 135 (61), 96 (81), 69 (89, C_3H_7CN), 56 (76, C_4H_8). Anal. Calcd for $C_{38}H_{39}N_5O_4$:C, 72.48; H, 6.24; N, 11.12. Found: C, 72.25; H, 6.20; N, 10.75.

2-(1-Ethyl-4,5,6,7-tetrahydroindazol-3-yl)-6-[1-[4--(ethoxycarbonyl)phenyl]-4,5,6,7-tetrahydroindazol-3-yl]pyridine (6d). A 0.034 g sample of monoester **4b** (0.073 mmol) was dissolved in 10 mL of C_2H_5Br. Then 0.004 g (0.17 mmol) of NaH was added, and the mixture was stirred at room temperature until the H_2 evolution ceased. Then the solution was refluxed under Ar for 1 h. The solvent was removed, and the resulting oil was washed with H_2O and extracted into $CHCl_3$. The crude oily residue was purified by column chromatography on alumina using EtOAc:PE (50:50) to afford a white solid **6d** (0.033 g, 92%). Further purification was carried out by the diffusion of Et_2O vapor into a $CHCl_3$ solution; this yielded a white powder, mp 152−4 °C; ^{1}H NMR: δ 1.46 (m, 6H), 1.80 (m, 2H), 1.90 (m, 6H), 2.66 (m, 2H), 2.87 (m, 2H), 2.99 (m, 2H), 3.08 (m, 2H), 4.13 (q, 2H, J = 7.4 Hz), 4.43 (q, 2H, J = 7.5 Hz), 7.74 (m, 3H), 7.89 (d, 1H, J = 7.7 Hz), 7.97 (d, 1H, J = 7.7 Hz), 8.16 (d, 2H, J = 8.6 Hz) ppm; ^{13}C NMR: δ 14.38, 15.62, 20.14, 20.67, 21.41, 21.70, 22.57, 22.92, 23.04, 23.40, 24.55, 43.85, 61.14, 115.58, 118.56, 119.54, 119.81, 122.19, 128.15, 130.65, 130.90, 136.51, 138.87, 139.98, 143.68, 147.16, 150.16, 152.74, 153.60, 166.10 ppm; MS *m*/*z* (%) 495 (100, $M^{\bullet+}$), 480 (52, $M^{\bullet+}$ − CH_3), 465 (50, $M^{\bullet+}$ − $2CH_3$), 450 (22, $M^{\bullet+}$ − H − CH_2CH_3 − CH_3), 420 (44), 405 (87), 375 (90), 346 (86, $M^{\bullet+}$ − $C_6H_4COOCH_2CH_3$), 332 (35, $M^{\bullet+}$ + H − C_6H_4-$COOCH_2CH_3$ − CH_3), 318 (7, $M^{\bullet+}$ + H − $C_6H_4COOCH_2CH_3$ − CH_2CH_3), 248 (85), 188 (52), 149 (64, $C_6H_4COOCH_2CH_3$), 124 (68), 111 (69), 98 (59), 85 (68), 71 (73), 57 (87), 44 (51, CO_2). Anal. Calcd for $C_{30}H_{33}N_5O_2$·0.4$CHCl_3$: C, 67.20; H, 6.20; N, 12.89. Found: C, 67.16; H, 6.38; N, 12.69.

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