Metalation of Hantzsch Esters and Mixed Amide Esters: A General Route to C-2 Functionalized 1,4-Dihydropyridines[1]

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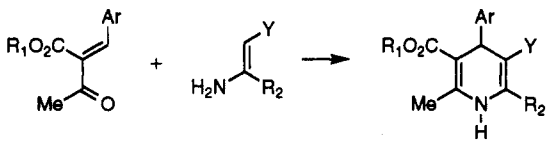
1,4-Dihydropyridine (Hantzsch) diesters **3a–e** readily undergo metalation at the C-2 methyl (vinylogous ester) position on treatment with alkyllithium bases. The resulting anion intermediates can be treated with electrophilic reagents to afford 1,4-dihydropyridine products that have been chemically elaborated at the C-2 methyl position. The methodology permits a variety of electrophilic functionalities to be regiospecifically introduced at the C-2 methyl position of 1,4-dihydropyridines. Deuterium distribution studies with mixed dihydropyridine amide esters **20a** and **20b** having nonequivalent C-2 and C-6 methyl groups indicate specific metalation occurs at the C-2 methyl (vinylogous ester) position. Tri- and tetraanion formation is also possible at both vinylogous methyl and NH positions when the metalation reactions are performed with excess equivalents of *n*-BuLi or *s*-BuLi bases.

1,4-Dihydropyridine esters (Hantzsch esters **3**) represent a potent structural class of therapeutic agents collectively known as calcium antagonists.[2] 1,4-Dihydropyridine esters **3** can be prepared by Hantzsch condensation reactions between various Knoevenagel-derived adducts **1**[3] and aminocrotonates **2** or their β-keto ester precursors.[4] Symmetrical 1,4-dihydropyridine esters **3** (Y = CO_2R_1, R_2 = Me) are generally obtained in high yield using Hantzsch conditions. Unsymmetrical 1,4-dihydropyridine esters, however, are often more difficult to prepare due to the formation of all the possible isomeric Hantzsch condensation products.[5] As a consequence of this, unsymmetrical Hantzsch products are usually obtained in significantly lower yield than their symmetrical counterparts and often require difficult and tedious chromatographic separation to effect their purification.



1 **2** **3**

Routes to prepare unsymmetrical Hantzsch esters (i.e. $R_2 \neq$ Me in **3**) from simple symmetrical precursors have been developed to circumvent this problem.[6] For example, the C-2 methyl position of 1,4-dihydropyridine has been brominated with pyridinium perbromide in CH_2Cl_2 or $CHCl_3$ to give α-bromomethyl intermediates which could be used for further chemical elaboration with various nucleophiles.[6a,b] Additionally, a series of C-2 methyl-substituted dihydropyridines have been obtained from symmetrical starting materials using Mannich type condensation routes.[6c,d]

Utilization of anion chemistry at the C-2 methyl position of Hantzsch dihydropyridine esters has also been explored.[6e] Patterson reported that *N*,2,6-trimethyl-1,4-dihydropyridine derivatives undergo C-2 methyl metalation with lithium diisopropylamide (LDA) at low temperature (−78 °C). After treatment with MeI, he found that these metalated intermediates predominantly gave *N*- and C-3 methylated tetrahydropyridine products as a result of α-alkylation. The expected C-2 methyl, vinylogous γ-alkylation products were only observed in low yield. Others have recently reported similar α-alkylation products from vinylogous metalation of enamines derived from β-keto esters.[7]

Our interest in this area has also focused on the construction of unsymmetrical 1,4-dihydropyridine products via metalation of diester and mixed amide ester precursors. We wish to describe our results on the preparation of C-2 functionalized 1,4-dihydropyridine esters and mixed amide esters via vinylogous metalation methodology.[8]

Results and Discussion

Diester Metalation. We initially examined the metalation of the simple *N*-methyl-1,4-dihydropyridine **3a**. The reactions were carried out at −78 °C with various bases and subsequently quenched at low temperature with MeOD to determine optimal conditions for vinylogous C-2

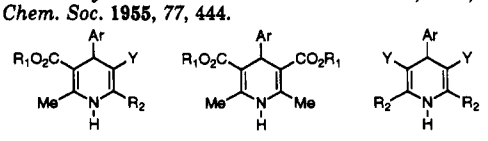
(1) For a preliminary account of this work, see: Poindexter, G. S.; Foley, M. A.; Licause, J. F. *Tetrahedron Lett.* **1989**, *30*, 3393.

(2) (a) Goldmann, S.; Stoltefuss, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1559. (b) Triggle, D. J.; Langs, D. A.; Janis, R. A. *Med. Res. Rev.* **1989**, *9*, 123. (c) Bossert, F.; Vater, W. *Ibid.* **1989**, *9*, 291.

(3) Jones, G. *Org. React.* **1967**, *15*, 204.

(4) (a) Sausins, A., Duburs, G. *Heterocycles* **1988**, *28*, 269. (b) Sausins, A.; Duburs, G. *Ibid.* **1988**, *27*, 291. (c) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. (d) Kuthan, J.; Kurfurst, A. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 191. (e) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1.

(5) Three 1,4-dihydropyridine products **3**, **3'**, and **3''** are possible due to the reversibility of the condensation. See: Berson, J. A.; Brown, E. *J. Am. Chem. Soc.* **1955**, *77*, 444.



3 **3'** **3''**

(6) (a) Sircar, I.; Anderson, K. R.; Bonadies, L. *Tetrahedron Lett.* **1988**, *29*, 6835. (b) Young, S. D. *Synthesis* **1984**, 617. (c) Aritomi, J.; Ueda, S.; Nishimura, H. *Chem. Pharm. Bull.* **1980**, *28*, 3163. (d) Kleinschroth, J.; Mannhardt, K.; Hartenstein, J.; Satzinger, G. *Synthesis* **1986**, 859. (e) Patterson, J. W. *J. Heterocycl. Chem.* **1986**, *23*, 1689.

(7) Hodgson, A.; Marshall, J.; Hallett, P.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2169.

(8) For examples of vinylogous metalation chemistry, see: (a) Adams, A. D.; Schlessinger, R. H.; Tata, J. R.; Venit, J. J. *J. Org. CHem.* **1986**, *51*, 3068. (b) Bryson, T. A.; Gammill, R. B. *Tetrahedron Lett.* **1974**, 3963.

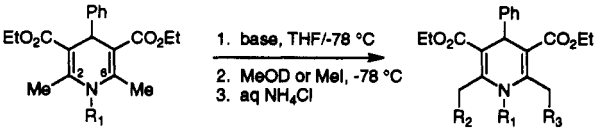
0022-3263/93/1958-3811$04.00/0

Table I. Deuterium Incorporation Studies with Dihydropyridines 3a and 3b

entry	compd	conditions[a] (equiv of base)	product	% yield[b]	deuterium incorp,[c] %
1	3a	1.1 LDA	4a	66	4 at R_2
2	3a	1.1 *n*-BuLi	4a	68	100 at R_2
3	3a	1.1 *s*-BuLi	4a	65	96 at R_2
4	3a	2.1 *s*-BuLi	4a	74	100 at R_2; 83 at R_3
5	3b	1.1 LDA	4b	82	0 at R_2
6	3b	2.1 LDA	4b	76	100 at R_2
7	3b	3.1 LDA	4b	84	100 at R_2
8	3b	2.1 *n*-BuLi	4b	88	100 at R_2
9	3b	3.2 *n*-BuLi	4b	78	100 at R_2; 45 at R_3
10	3b	3.2 *s*-BuLi	4b	84	100 at R_2; 98 at R_3

[a] All metalation reactions carried out at −78 °C in THF for 2 h prior to low temperature MeOD quench. [b] Recrystallized yield. [c] %-d_1.

methyl metalation. Deuterium distribution (%-d_1 incorporation and location) in products **4a** and **4b** was determined by high field ^{1}H and ^{13}C analysis. The results of



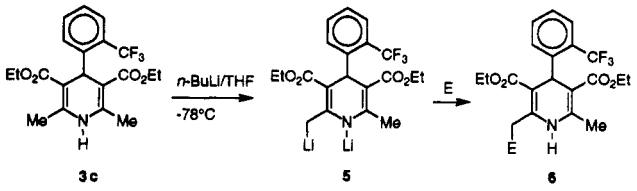
3a, R_1=Me
3b, R_1=H

4a, R_1=Me, R_2, R_3=H or D
4b, R_1=H, R_2, R_3=H or D
4c, R_1, R_2=Me, R_3=H

these studies are summarized in Table I. Treatment of **3a** with 1.1 equiv of LDA in tetrahydrofuran (THF) for 2 h followed by MeOD, workup, and recrystallization gave the starting dihydropyridine **4a** in a 66% yield. NMR analysis of this product indicated little if any metalation with LDA had occurred [4% monodeuterium incorporation at the C-2 methyl position (4%-d_1)]. In contrast, treatment of **3a** with *n*-BuLi under the same conditions (1.1 equiv, entry 2) afforded the deuterium-substituted product **4a** in a 68% yield with 100% monodeuterium incorporation at the C-2 methyl position (100%-d_1). No deuterium incorporation was observed at any other position in the molecule which indicates specific metalation occurred at only the C-2 methyl (vinylogous ester) position of **3a**. Moreover, no addition products resulting from nucleophilic attack at either or both of the ester groups of **3a** were observed.[9] Use of 1.1 equiv of *s*-BuLi as the metalation agent gave similar results (96%-d_1, entry 3). Treatment of **3a** with 2.1 equiv of *s*-BuLi promoted metalation of both *C*-methyl groups (entry 4). In this manner the disubstituted adduct could be prepared with nearly complete monodeuterium incorporation at both the C-2 and C-6 methyl positions (100%-d_1 and 83%-d_1, respectively). Presumably this was the result of the formation of the C,C-dianion intermediate. As above, no carbonyl addition products were observed.

Similar metalation studies were also carried out on the *N*-unsubstituted derivative **3b**. Use of 1.1 equiv of LDA gave no deuterium incorporation in the molecule.[10] Treatment of **3b** with 2.1 or 3.1 equiv of LDA afforded **4b** with 100%-d_1 at the C-2 position. Thus LDA appears to be a sufficiently strong enough base for *N*,*C*-bisdeprotonation but not for N,C,C-trianion formation. Use of 2.1 equiv of *n*-BuLi also afforded **4b** with 100%-d_1 incorporation at the C-2 methyl position. However, incomplete trianion formation resulted when 3.2 equiv of *n*-BuLi was employed (entry 9). Treatment of **3b** with 3.2 equiv of *s*-BuLi afforded complete metalation to give the N,C,C-trianion which on quenching with MeOD gave **4b** with 100%-d_1 and 98%-d_1 incorporation at the C-2 and C-6 methyl positions, respectively. We have found the use of 2.1 equiv of *n*-BuLi in THF is the most convenient method for *N*,*C*-2 methyl bismetalation of *N*-unsubstituted dihydropyridine Hantzsch esters.

Scheme I



We also examined the reaction of metalated **3b** with electrophiles other than deuterium. Treatment of **3b** with 2.1 equiv LDA followed by reaction with MeI gave a complex mixture of products as determined by TLC analysis. Workup and chromatography resulted in the isolated of two major alkylation products **3a** and **4c** in 32 and 25% yields, respectively. Use of *n*-BuLi as base also gave a complex mixture of products. These types of N- and N,C-alkylation products are somewhat analogous to those reported by Patterson using LDA as the base.[6e] We have observed similar results when hard electrophiles such as acid chlorides and chloroformates were employed. No further work with these types of agents was carried out.

We subsequently studied the reaction of metalated Hantzsch esters with other types of electrophiles. As shown in Scheme I, treatment of 1,4-dihydropyridine **3c** with 2.1 equiv of *n*-BuLi in THF at −78 °C yielded the yellow N,C-dianion **5**.[11] After 30 min at −78 °C, a variety of electrophiles (1.25 equiv) were added to the metalation solution and the reaction allowed to warm to room temperature and quenched with saturated aqueous NH_4Cl. Workup and chromatography or recrystallization gave the C-2 methyl adducts **6a–p** in yields ranging from 22–94% (Table II). Alkyl disulfides furnished the highest yields of substituted products in yields of 70–94% (entries 1–4). Other electrophiles, [Me_3SiCN, $(EtO)_2POCl$, Et_2NCOCl, $MeSO_2Cl$, *n*-BuNCO, Me_2NCHO, $(CF_3CO)_2O$, and CO_2], gave lower yields of substituted dihydropyridines (22–87%) due to the formation of secondary substitution products.[12] For example, the bis-substituted derivative **6n** was isolated in 26% yield (vide infra). Ketone **6l** was prepared in 70% yield by treatment of dianion **5** with the Weinreb reagent[14] (entry 11). Use of acetyl chloride to append a ketone moiety at the C-2 methyl position gave a complex mixture of products.

In contrast to compounds **6a–j**, NMR analysis indicated that dihydropyridines **6k–o**, which incorporate aldehyde, ketone, and ester substituents at the C-2 methyl position,

(9) Nucleophilic attack at the C-3 and C-5 ester positions never appears to be competitive with deprotonation of the vinylogous methyl groups in these general types of 2,6-dimethyl-substituted Hantzsch esters. For another example, see: Balasubramanian, T. N.; Natale, N. R. *Tetrahedron Lett.* **1993**, *34*, 1099.

(10) Deuterium incorporation at the NH position was negligible due to rapid proton exchange with water during workup.

(11) Although myriad lithio intermediates can be envisioned, **5** and other metalated intermediates in this manuscript are depicted as the *N*- and C-localized anions for simplicity and clarity.

(12) Sulfone **6i** could be obtained in higher yield (71% total) by oxidation of sulfide **6a** using Oxone.[13]

(13) Trost, B. M.; Curren, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

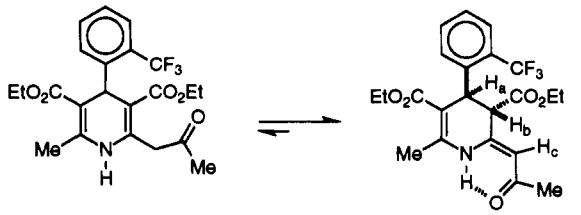
(14) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Table II. Dihydropyridines 6a–p from the Metalation of 3c[a]

entry	electrophile	product, E	% yield[b]	mp °C
1	$(MeS)_2$	**6a**, SMe	83	100–102
2	$(n\text{-BuS})_2$	**6b**, S-*n*-Bu	85	92–93
3	$(PhCH_2S)_2$	**6c**, SCH_2Ph	94	oil
4	**7**[c]	**6d**, $SCH_2CH_2NH_2$	70	oil
5	Me_3SiCN	**6e**, $SiMe_3$[d]	69	145–146
6	$(EtO)_2POCl$	**6g**, $PO(OEt)_2$	87	96–97
7	Et_2NCOCl	**6h**, $CONEt_2$	52	oil
8	$MeSO_2Cl$	**6i**, SO_2Me	29	156–157
9	*n*-BuNCO	**6j**, CONH-*n*-Bu	61	oil
10	$HCONMe_2$	**6k**, CHO[e]	71	82–85
11	MeCON(OMe)Me[f]	**6l**, COMe[e]	70	87–88
12	EtO_2CCN[g]	**6m**, CO_2Et[e,h,i]	30	79–91
13	$(CF_3CO)_2$	**6o**, $COCF_3$[e]	22	oil
14	CO_2	**6p**, CO_2Na[j]	52	154–165

[a] All metalation reactions were carried out as described in the Experimental Section. [b] Isolated yields. [c] STABASE derivative of cystamine, ref 17. [d] The 2,6-bis-TMS derivative **6f** (mp 112–113 °C) was also isolated in 8% yield. [e] Obtained as the 3α,4β-substituted tetrahydropyridine tautomer. [f] Reference 14. [g] Reference 16. [h] Reference 15. [i] The 2,2-bis(carboxyethyl) derivative **6n** (oil) was also isolated in 26% yield. [j] Isolated as the sodium salt after workup. The free carboxylic acid (E = CO_2H) slowly decarboxylated to **3c** on standing at room temperature.

existed as their 3α,4β-6(*Z*)-tetrahydropyridine tautomers. ^1H NMR analysis of **6l**, for example, revealed the NH absorption to be considerably downfield (δ 11.3) from its normal position suggesting its involvement in a hydrogen bonding interaction. The vinylic H_c singlet at δ 5.13 and the H_a and H_b singlets at δ's 4.98 and 3.24, respectively, were also indicative of the tautomeric structure. Expansion of the H_b proton absorption revealed a doublet with



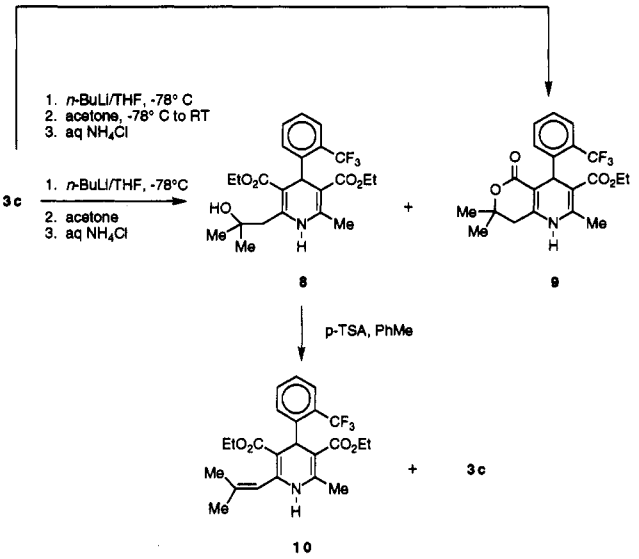
6l **6l'**

a coupling constant of 1.1 Hz which is consistent with a *trans* relationship between the H_a and H_b protons. This type of 1,4-dihydropyridine tautomer has been previously observed by others.[15]

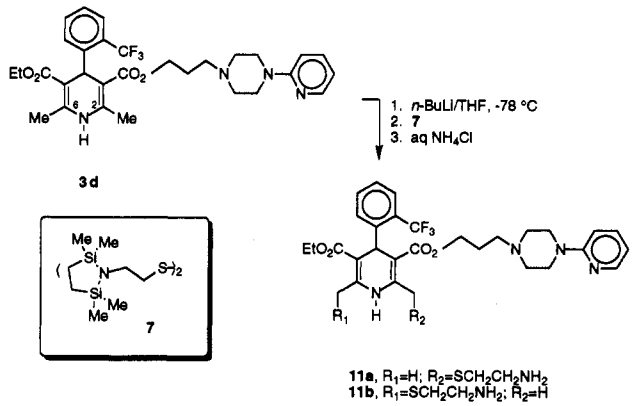
Lithiation of dihydropyridine **3c** at low temperature followed by treatment with acetone gave a 1:1 mixture of hydroxy ester **8** (32%) and lactone **9** (31%) when the reaction was carried out in the usual manner (Scheme II). Attempted conversion of **8** to **9** with *p*-TSA in refluxing toluene afforded two products, olefin **10** (50%) resulting from dehydration of **8**, and starting dihydropyridine **3c** (28%). The latter product was presumably formed via acid-catalyzed cleavage. Higher conversion yields of **3c** to lactone **9** (69%) were subsequently achieved by allowing the reaction mixture to warm to room temperature for several hours prior to the aqueous NH_4Cl quench.

The metalation of the C-3, C-5 unsymmetrical 1,4-dihydropyridine ester **3d** was also examined. We predicted the metalation would preferentially take place at the C-2 methyl position (proximal to the aminoalkyl ester substituent) since this side chain could participate in the

Scheme II



stabilization of approaching base as well as the chelation the resulting dianion.[18] We felt this interaction would preferentially direct metalation to this site since an analogous chelative interaction is not possible at the C-6 methyl position adjacent to the ethyl ester substituent. However, metalation of dihydropyridine **3d** with 2.1 equiv of *n*-BuLi followed by treatment with STABASE adduct **7** yielded a 1:1 mixture of isomeric products. Careful chromatographic separation of this mixture afforded the regioisomeric aminoethyl sulfides **11a** and **11b** in yields of 16 and 18%, respectively, indicating the amino substituent in the piperazine side chain had little or no effect



11a, R_1=H; R_2=$SCH_2CH_2NH_2$
11b, R_1=$SCH_2CH_2NH_2$; R_2=H

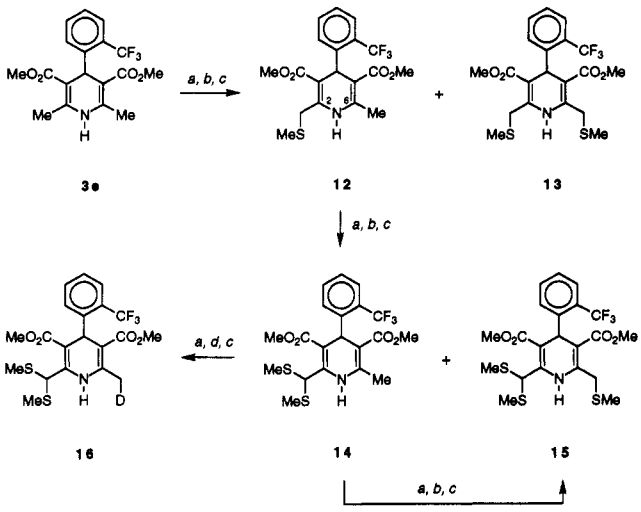
on directing the metalation to the proximal C-2 methyl position. These types of C-3, C-5-dihydropyridines having non-symmetrical ester groups afford equal mixtures of C-2 and C-6 methyl-substituted products when subjected to the these lithiation conditions.

In most of the metalation experiments monosubstituted products were isolated as the major products from the metalation experiments. However, other presumable bis-substituted adducts were also observed by TLC analysis. In two specific instances (entries 5 and 12, Table II) these products were purified by silica gel chromatography and characterized. The symmetrical 2,6-bis[(trimethylsilyl)-methyl] adduct **6f** was obtained in low yield (8%) when

(15) Taylor, M. D.; Badger, E. W.; Steffen, R. P.; Haleen, S. J.; Pugsley, T. A.; Shih, Y. H.; Weishaar, R. E. *J. Med. Chem.* **1988**, *31*, 1659.

(16) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(17) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787.
(18) (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

Scheme III[a]



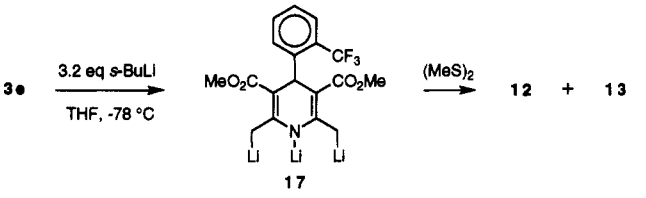
[a] (*a*) 2.1 equiv *n*-BuLi, THF, −78 °C; (*b*) $(MeS)_2$; (*c*) aqueous NH_4Cl; (*d*) MeOD, −78 °C.

Me_3SiCN was used as the electrophile (entry 5). This is a normal primary substitution product which results as a consequence of the formation of the N,C,C-trianion with excess base. On the other hand, the 2,2-bis(carboxyethyl) derivative **6n** was isolated in 26% yield on reaction of **5** with the Mander reagent EtO_2CCN[16] (entry 12). This compound is clearly the result of secondary deprotonation of **6m** at the more acidic C-2 methyl position and followed by subsequent carboxyethylation.

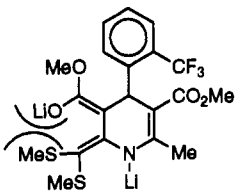
We also wanted to explore the regiochemical outcome of metalation of a C-2, C-6 unsymmetrical dihydropyridine. In order to accomplish this we prepared the C-2 methylthio derivative **12** (81%) from dihydropyridine **3e** using standard conditions (Scheme III). A small amount of the C-2, C-6 symmetrically substituted sulfide **13** was also isolated in low yield (1%). As expected, lithiation of **12** at −78 °C with 2.1 equiv of *n*-BuLi occurred at the more acidic C-2 methyl position adjacent to the methylthio substituent. Subsequent reaction of this intermediate with $(MeS)_2$ furnished the bis-substituted thioacetal **14** (91%) as the major product. A minor product, the asymmetrically substituted methylthio thioacetal **15**, was also observed in low yield (4%). It appears that the methylthio substituent at the C-2 methyl position effectively directs metalation to give the expected thioacetal product.

Interestingly, when thioacetal **14** was subjected to these metalation conditions and treated with $(MeS)_2$, only **15**, the dihydropyridine resulting from lithiation at the unsubstituted C-6 methyl position, was observed (87%). This result was somewhat surprising since we expected the thioacetal group to direct metalation and afford an orthothioester adduct after treatment with $(MeS)_2$. The metalation was repeated using MeOD as the electrophile. After workup, thioacetal **16** incorporating monodeuterium substitution at only the C-6 methyl position was obtained. No deuterium incorporation at the C-2 methyl thioacetal position was observed. Allowing the intermediate metalation solution to warm to 0 °C prior to MeOD addition had no effect on deuterium positioning in this product. It appears that **15** and **16** are the result of preferential kinetic deprotonation at the C-6 methyl position. The resulting anion appears to be stable since warming to 0 °C had no effect on deuterium positioning. Perhaps the relative enhanced kinetic acidity at the C-6 methyl position vs the

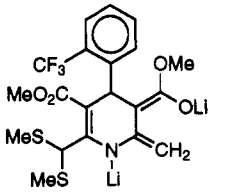
Scheme IV



C-2 methyl position is a consequence of unfavorable steric factors in the latter enolate. Assuming a delocalized, π-coplanar enolate species in **14**, C-2 methyl metalation would result in a dianion enolate species with steric crowding between one of the methylthio substituents and the ester enolate group. This type of unfavorable interaction is not possible in a C-6 methyl-derived enolate, which perhaps explains its formation.



C-2 methyl enolate



C-6 methyl enolate

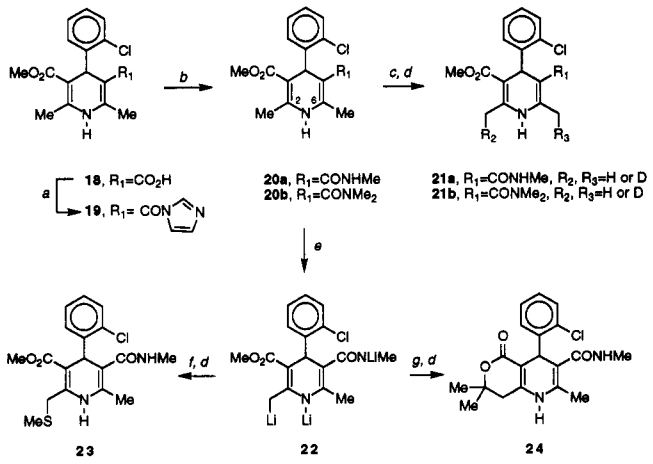
In several examples noted above, we isolated what appeared to be products resulting from N,C,C-trianion formation.[19] For example, the bis(methylthio) adduct **13** in the preparation of the mono adduct **12** and the trisubstituted methylthio product **15** with the disubstituted thioacetal **14** were obtained in yields of 1 and 4%, respectively. These products are presumably the result of excess *n*-BuLi in the reaction mixture and result from the formation of an intermediate N,C,C-trianion rather than sequential metalation of the primary product. In order to provide additional evidence for these types of intermediates, we metalated dihydropyridine **3e** with 3.2 equiv of *s*-BuLi to produce the N,C,C-trianion **17** and subsequently added 2 equiv of $(MeS)_2$. After workup and chromatography, the C-2,C-6-disubstituted methylthio product **13** was obtained in 72% yield along with a smaller amount (17%) of the monosubstituted sulfide **12** (Scheme IV). None of the thioacetal **14** as obtained from the sequential metalation of **12** (vide supra) was observed indicating the intermediacy of the N,C,C-trianion.

Amide Ester Metalation. We were also interested in the metalation of mixed dihydropyridines having amide substituents at the C-5 position on the ring.[20] In comparison to the corresponding dihydropyridine diesters (e.g. **3e**), these mixed amide esters have nonequivalent C-2 methyl (vinylogous ester) and C-6 methyl (vinylogous amide) positions. We were curious whether metalation would take place at the C-2 methyl, the C-6 methyl, or perhaps at both positions to give vinylogous ester and/or vinylogous amide-derived products. Accordingly, we prepared two mixed amide esters in order to study their metalation behavior. The mixed *N*-methyl and *N,N*-dimethyl-1,4-dihydropyridine amide esters **20a** and **20b** were prepared by standard carbonyldiimidazole coupling

(19) For a recent review on C,C-dianion formation, see: Thompson, C. M., Green, D. L. C. *Tetrahedron* **1991**, *47*, 4223.

(20) For an example of this type of mixed dihydropyridine amide ester, see: Lawson, J. E.; Poindexter, G. S.; Owens, D. A.; Cavanagh, R. L.; Goggins, G. D.; Sarmiento, J. G.; Blieberg, B. B.; Weselcouch, E. O. *BioMed. Chem. Lett.* **1993**, *3*, 561.

Scheme V[a]



[a] (*a*) CDI, MeCN; (*b*) $MeNH_2$ or Me_2NH, MeCN; (*c*) Base, MeOD; (*d*) aqueous NH_4Cl; (*e*) *n*-BuLi, THF; (*f*) $(MeS)_2$; (*g*) acetone.

Table III. ^1H and ^{13}C NMR Methyl Shift Assignments for Dihydropyridines 3f, 18, 19, 20a, and 20b[a]

	^1H NMR, ppm		^{13}C NMR, ppm	
compd, R	C-2 Me	C-6 Me	C-2 Me	C-6 Me
3f, R = CO_2Me[b]	2.19	2.19	18.0	18.0
18, R = CO_2H	2.23[c]	2.22[c]	18.1[c]	18.0[c]
19, R = $COC_3H_3N_2$[d]	2.36	1.79	18.4	16.7
20a, R = CONHMe	2.21	1.81	18.6	16.4
20b, R = $CONMe_2$	2.29	1.63	18.8	15.4

[a] All COLOC experiments were carried out in DMSO-d_6 using a Bruker AM 500 spectrometer. [b] **3f**: Ar = 2-ClPh; R_1, R_2 = Me; Y = CO_2Me. [c] Tentative assignment. [d] Acylimidazole.

methods (via acylimidazole **19**) from the corresponding acid **18** (Scheme V). The vinylogous C-2 and C-6 methyl positions of **20a** and **20b** were distinguished through use of NMR COLOC[21] techniques and compared to the 1,4-dihydropyridine dimethyl ester **3f** (Table III). For example, ^1H NMR analysis of **20a** in DMSO-d_6 revealed two vinylogous methyl absorptions at 2.21 and 1.81 ppm. Similarly, ^{13}C NMR analysis showed the two vinylogous methyl absorptions at 18.6 and 16.4 ppm. COLOC experiments confirmed that the lower field ^1H and ^{13}C absorptions were due to the C-2 methyl (vinylogous ester) group while the higher field absorptions were due to the C-6 methyl (vinylogous amide) group. These assignments are consistent for both of these types of ^1H and ^{13}C ester and amide group absorptions.[22]

Metalations of these mixed amide esters were carried out as before (vide supra) and the resulting deuterium distribution ratios determined by NMR. The results of these studies are reported in Table IV. No metalation of **20a** was observed with the use of 3.2 equiv of LDA as base even after the metalation solution was allowed to warm to 0 °C (0%-d_1, entries 1 and 2). However, when 3.2 equiv of *n*-BuLi at −78 °C was used as base and the resulting intermediate quenched with excess MeOD at −78 °C, an 81% yield of **21a** was obtained. ^1H and ^{13}C analysis of the product indicated 61%-d_1 incorporation at the C-2 methyl position. There was no deuterium incorporation noted at any other position in **21a**. The experiment was repeated but the trianion intermediate was now allowed to warm to 0 °C for 30 min prior to MeOD quench. Workup and recrystallization afforded the product **21a** in an 84% yield. ^1H NMR analysis revealed the lower field C-2 methyl singlet now to integrate for only two protons. More importantly, the ^{13}C spectrum corroborated this result by showing that the lower field C-2 methyl absorption to afford a triplet at 18.4 ppm (J = 20.1 Hz) indicating complete monodeuteration incorporation (100%-d_1) at this vinylogous ester position. Even with the use of ^{13}C NMR analysis, no deuterium incorporation could be detected at the C-6 methyl (vinylogous amide) position. These results suggest the vinylogous ester enolate derived from **20a** to be the thermodynamically favored enolate under these metalation conditions. Although the vinylogous ester position is more acidic and hence would be predicted to be the thermodynamic site for deprotonation, we anticipated that the *N*-methylamide group would participate in chelation more effectively than the methyl ester substituent and thus provide additional stabilization for kinetic deprotonation at the C-6 methyl (vinylogous amide) position.[18] However, no C-6 methyl-substituted product was observed under these metalation conditions.

The absence of any vinylogous amide product in the metalation/deuteration sequence of *N*-methylamide **20a** can possibly be explained by a potentially unfavorable charge–charge repulsion between proximal anionic centers (at the C-6 methyl and *N*-methylamide positions). This interaction would tend to disfavor enolate formation at this site relative to the vinylogous methyl position where no such interaction is possible. Accordingly, the *N*,*N*-dimethylamide **20b** was examined in the same metalation/deuteration sequence to determine whether deprotonation could be observed at the vinylogous amide position. Amide **20b** was subjected to similar metalation conditions as **20a** except that 2.1 equiv of *n*-BuLi were employed as base. The dianion intermediate was allowed to warm to 0 °C for 30 min before quenching with MeOD. The product **21b** was isolated in an 83% yield and found to have complete monodeuterium incorporation (100%-d_1) again exclusively at the vinylogous ester (C-2 methyl) position. Amide-directing effects apparently are not a contributing factor for enolate formation in these types of Hantzsch dihydropyridine systems.

Metalation at the C-6 methyl (vinylogous amide) position is possible by N,N,C,C-tetraanion formation with *N*-methylamide **20a** or N,C,C-trianion formation with dimethylamide **20b**. Treatment of **20a** with 4.2 equiv of *n*-BuLi or **20b** with 3.2 equiv of *n*-BuLi (Table IV, entries 5 and 8) at −78 °C and then warming to 0 °C afforded the respective mixed anions. After recooling the anion suspension to −78 °C followed by MeOD quench and workup, the deuterium-substituted derivatives **21a** and **21b** were isolated in good yields. The lower deuterium yield at the C-6 methyl position for **21a** (42%-d_1) in comparison to **21b** (86%-d_1) is probably a consequence of the relative solubilities of the respective di- and trianions to further deprotonation with *n*-BuLi. Allowing the **20a** anion solution to stir at 0 °C for longer periods increased the amount of monodeuterium incorporation at the C-6 methyl position (65%-d_1, entry 6). Thus it appears that the formation of the bis-C-2,C-6-methyl dianion is possible with the mixed 1,4-dihydropyridine amide esters **20** as well as with the diesters **3**, albeit with lower efficiency.

(21) For information on COLOC (Correlated Spectroscopy for Long Range Couplings) techniques, see: Martin, G. E.; Zektzer, A. S. *Two-Dimensional NMR Methods for Establishing Molecular Connectivity*; VCH Publishers: New York, 1988; p 211.

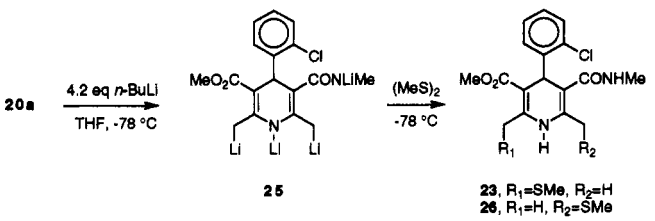
(22) Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T., (Biemann, K., trans.). *Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: New York, 1983.

Table IV. Deuterium Incorporation Studies with the Mixed Dihydropyridine Amide Esters 20a and 20b[a]

entry	compd	conditions[b] (equiv of base)	product, R_1	% yield[c]	deuterium incorp,[d] %
1	**20a**	3.2 LDA, A	**21a**, CONHMe	82	0 at R_2; 0 at R_3
2	**20a**	3.2 LDA, B	**21a**, CONHMe	63	0 at R_2; 0 at R_3
3	**20a**	3.2 *n*-BuLi, A	**21a**, CONHMe	81	61 at R_2; 0 at R_3
4	**20a**	3.2 *n*-BuLi, B	**21a**, CONHMe	84	100 at R_2; 0 at R_3
5	**20a**	4.2 *n*-BuLi. B	**21a**, CONHMe	81	100 at R_2; 42 at R_3
6	**20a**	4.2 *n*-BuLi, B[e]	**21a**, CONHMe	82	100 at R_2; 65 at R_3
7	**20b**	2.1 *n*-BuLi, B	**21b**, $CONMe_2$	83	100 at R_2; 0 at R_3
8	**20b**	3.2 *n*-BuLi, B	**21b**, $CONMe_2$	68	100 at R_2; 86 at R_3

[a] All metalations were carried out as described in the Experimental Section. [b] Method A: stirred at −78 °C for 1 h prior to MeOD quench. Method B: stirred at 0 °C for 30 min prior to recooling to −78 °C and MeOD quench. [c] Recrystallized yields. [d] %-d_1. [e] Stirred at 0 °C for 1.5 h prior to recooling to −78 °C and MeOD quench.

Scheme VI



To further corroborate the regiospecific nature of the metalation with these mixed 1,4-dihydropyridines and to expand the synthetic scope of the reaction with other, non-deuterium electrophiles, several additional experiments were carried out. *N*-Methylamide **20a** was treated at low temperature with 3.1 equiv of *n*-BuLi and then allowed to react with acetone. The resulting bicyclic lactone **24** was isolated in a 64% yield after crystallization from ether. The presence of the *N*-methylamide substituent at the C-5 position in lactone **24** (vs a methyl ester group) unequivocally supports the results of the deuterium labeling experiments above and demonstrates that the intermediate trianion **22** can be captured with electrophiles other than deuterium. In a second experiment $(MeS)_2$ was employed as the electrophile. Lithiation of **20a** in a manner similar to that reported above followed by treatment of the resulting trianion **22** with $(MeS)_2$ gave the C-2 methyl-substituted thioether **23** in an 82% yield. None of the isomeric C-6 methyl-substituted thioether was observed.

In order to determine whether selective C-6 methyl (vinylogous amide) products could be prepared from the these types of mixed amide ester systems, we treated **20a** with 4.2 equiv of *n*-BuLi to form the N,N,C,C-tetraanion **25** (Scheme VI). After allowing the metalation solution to warm to 0 °C and then recooling to −78 °C, 1 equiv of $(MeS)_2$ was added in hopes of preferential reaction at the more reactive C-6 methyl enolate position. After several hours at −78 °C, the reaction was quenched with aqueous NH_4Cl at low temperature and worked up to yield a mixture of three materials. Careful chromatographic separation of the mixture afforded the desired C-6 methyl sulfide **26** (41%), along with the isomeric C-2 methyl sulfide **23** (24%) and some recovered starting dihydropyridine **20a**. This result suggests C-6 methyl (vinylogous amide)-substituted 1,4-dihydropyridines can be prepared via use of the tetraanion **25**. However, it is apparent that selectivity for this methyl position in a practical sense is marginal at best. Incomplete metalation at the C-6 methyl position is probably responsible for the isolation of both vinylogous ester and amide products by way of the tri- and tetralithiated species **22** and **25**, respectively. This result is similar to the partial lithiation observed in the deuterium labeling studies (Table IV, entries 5 and 6).

In summary, 1,4-dihydropyridine Hantzsch esters and mixed amide esters readily undergo vinylogous metalation at the C-2 methyl position with alkyllithium bases. The resulting anion intermediates can be treated with electrophilic reagents to afford 1,4-dihydropyridines which have been chemically elaborated at the C-2 methyl position. Products resulting from alkyllithium addition to the C-3 and C-5 carbonyl positions are never observed even when metalating *N*-alkyldihydropyridines. The methodology permits a variety of electrophilic functionalities to be regiospecifically introduced at the C-2 methyl position of 1,4-dihydropyridines and is complementary to the bromination method described by Sircar and others.[6] Through the intermediacy of N,C,C-trianions and N,N,C,C-tetraanions, it is also possible to prepare disubstituted derivatives at both the C-2 methyl and C-6 methyl positions. Vinylogous ester enolate intermediates derived from mixed 1,4-dihydropyridine amide esters appear to result from a thermodynamically controlled deprotonation process. In these latter examples, amide chelation does not appear to be important or even influence the formation of the vinylogous enolate.

Experimental Section

General. Melting points were determined using a Thomas-Hoover melting point apparatus and are both uncalibrated and uncorrected. The *n*-BuLi and *s*-BuLi used in the metalation experiments were purchased from Aldrich Chemical Co., and the LDA prepared from *N,N*-diisopropylamine and *n*-BuLi in tetrahydrofuran (THF) at 0 °C prior to use. The anhydrous, O_2-free THF was distilled from Na–benzophenone ketyl immediately prior to use or purchased from Aldrich Chemical Co. Unless otherwise indicated, ^1H NMR spectra were determined at 300 MHz and ^{13}C spectra at 75.5 MHz in the indicated solvents. Starting dihydropyridines **3a**[23] (128–129 °C), **3b**[24] (156–158 °C), **3c**[25] (140–141 °C), **3d**[26] (oil), **3e**[25] (mp 146–149 °C), **3f**[6c] (mp 192–193 °C), and **18**[27] (mp 204–205 °C) were prepared according to literature accounts.

(23) Traber, von W.; Karrer, P. *Helv. Chim. Acta.* **1958**, *41*, 2066.
(24) Schiff, R.; Puliti, J. *Chem. Ber.* **1883**, *16*, 1607.
(25) Loev, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E. *J. Med. Chem.* **1974**, *17*, 956.
(26) Poindexter, G. S.; Temple, D. L. *U.S. Patent* 4,755,512, 1988. Dihydropyridine **3d** was isolated as an oil after flash chromatography (SiO_2: MeOH/$CHCl_3$). A small sample of the free base was converted to the HCl salt by treatment with ethereal hydrogen chloride: mp 158–166 °C (sintered with gas evolution); ^1H NMR (DMSO-d_6) δ 11.88 (br s, 1H), 9.29 (s, 1H), 8.13 (d, 1H, *J* = 6.0 Hz), 8.02 (t, 1H, *J* = 7.8 Hz), 7.51 (m, 2H), 7.42 (d, 1H, *J* = 9.0 Hz), 7.33 (t, 1H, *J* = 6.0 Hz), 7.02 (t, 1H, *J* = 6.6 Hz), 5.42 (s, 1H), 4.60 (m, 2H), 4.05 (m, 4H), 3.71 (m, 4H), 3.12 (m, 4H), 2.31 (s, 3H), 2.22 (s, 3H), 2.08 (t, 2H, *J* = 6.6 Hz), 1.07 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 166.7, 153.0, 147.6, 145.6, 144.9, 142.8, 139.4, 132.5, 130.9, 126.6, 125.4, 113.8, 111.8, 102.8, 102.2, 60.4, 58.9, 52.8, 49.8, 43.1, 35.3, 22.8, 18.5, 18.0, 13.9. Anal. Calcd for $C_{30}H_{35}F_3N_4O_4 \cdot 2HCl \cdot 0.75H_2O$: C, 54.69; H, 5.89; N, 8.51; H_2O, 2.05. Found: C, 54.79; H, 5.89; N, 8.53; H_2O, 2.87.
(27) Franckowiak, G.; Thomas, G.; Schramm, M.; Kayser, M.; Gross, R.; Bechem, M. *Ger. Offen.* DE 3,601,397, 1987.

Metalation of *N*-Methyldihydropyridine 3a. To a stirred, N_2-covered solution of **3a** (1.00 g, 2.92 mmol) in 50 mL of THF in a −78 °C cold bath (CO_2/*i*-PrOH) was added the indicated base via syringe over a period of several minutes. The resulting bright yellow solution was allowed to stir at −78 °C for 2 h and then quenched with 1 mL of MeOD. A solution of saturated aqueous NH_4Cl and then water were added, and the solution was warmed to room temperature. The layers were separated and the organic portion then washed with water and brine. After it was dried over anhydrous $MgSO_4$ and filtered, the filtrate was concentrated *in vacuo*. The residue was recrystallized from EtOH to give **4a** in the isolated yields (65–88%) indicated in Table I. Deuterium incorporation (% and location) was determined by NMR analysis. For example, diethyl 2-(monodeuteromethyl)-1,4-dihydro-1,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate (**4a**, Table I, entry 2) was obtained as a yellow solid: mp 123–126 °C; ^{1}H NMR ($CDCl_3$) δ 7.16 (m, 5H), 5.16 (s, 1H), 4.13 (q, 4H, *J* = 7.1 Hz), 3.12 (s, 3H), 2.45 (s, 3H), 2.42 (s, 2H), 1.24 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 167.8, 149.2, 146.2, 128.0, 127.0, 126.0, 106.3, 59.8, 38.4, 34.0, 16.4, 16.2 (t, *J* = 20.4 Hz), 14.3. Anal. Calcd for $C_{20}H_{24}DNO_4$: C, 69.75; H, 7.32; N, 4.07. Found: C, 69.79; H, 7.45; N, 4.11.

Metalation of Dihydropyridine 3b. In a manner similar to that described above, a cold (−78 °C), stirred solution of **3b** (1.66 g, 5 mmol) under N_2 in 100 mL of THF was treated with the indicated base and stirred for 2 h at −78 °C. MeOD (1 mL) was added and the reaction worked up as described above. The product **4b** was recrystallized from EtOH and obtained in the yields shown in Table I. Deuterium results were determined using NMR analysis. For example, diethyl 2,6-bis(monodeuteromethyl)-1,4-dihydro-4-phenyl-3,5-pyridinedicarboxylate (**4b**, Table I, entry 10) was obtained as a pale yellow solid: mp 156–157 °C; ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 5H), 5.75 (br s, 1H), 4.99 (s, 1H), 4.07 (m, 4H), 2.29 (s, 4H), 1.21 (t, 6H, *J* = 7.1 Hz); ^{13}C ($CDCl_3$) δ 167.9, 147.9, 144.6, 127.9, 127.8, 126.1, 103.7, 59.7, 39.7, 18.9 (t, *J* = 19.9 Hz), 14.3. Anal. Calcd for $C_{19}H_{21}D_2NO_4$: C, 68.86; H, 6.99; N, 4.23. Found: C, 68.78; H, 7.02; N, 4.40.

Diethyl 1,4-Dihydro-1,2,6-trimethyl-4-phenyl-3,5-pyridinedicarboxylate (3a) and Diethyl 6-Ethyl-1,4-dihydro-1,2-dimethyl-4-phenyl-3,5-pyridinecarboxylate (4c). In a manner similar to that described above, a 5-mmol THF solution of **3b** was treated with 2.1 equiv of LDA in 20 mL of THF at −78 °C under N_2 and stirred for 2 h. Methyl iodide (0.46 mL, 7.5 mmol) was then added via syringe and the yellow anion solution allowed to warm to room temperature and stir 30 min. The reaction was quenched by the addition of saturated aqueous NH_4-Cl and enough water to dissolve the formed solids. After separation of the layers, the organic portion was washed with water and brine and then dried over $MgSO_4$. Filtration and concentration of the filtrate *in vacuo* gave an orange oil. The oil was purified by flash chromatography (EtOAc/*n*-hex) to give 550 mg (32%) of **3a** and 450 mg (25%) of **4c** as yellow solids. For **4c**: mp 79–80 °C; ^{1}H NMR ($CDCl_3$) δ 7.13 (m, 5H), 5.11 (s, 1H), 4.14 (m, 4H), 3.17 (s, 3H), 2.94 (m, 2H), 2.44 (s, 3H), 1.24 (m, 6H), 1.14 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (DMSO-d_6) δ 166.9, 166.5, 154.7, 149.6, 145.8, 127.8, 126.4, 125.8, 105.3, 103.7, 59.3, 37.5, 33.1, 21.5, 16.0, 14.1, 12.8. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.62; N, 3.92. Found: C, 70.56; H, 7.62; N, 3.69.

General Method for the Preparation of Dihydropyridines 6a–p. To a stirred, low temperature (−78 °C) solution of **3c** (3.97 g, 10.1 mmol) under N_2 in 125 mL of THF was added 8.5 mL (21 mmol) of *n*-BuLi (2.5 *M* in *n*-hexane) via syringe. After the resulting yellow solution was stirred 0.5 h at low temperature, 1.1. equiv of the requisite electrophile was added (Table II) and the solution allowed to warm to room temperature. The reaction was quenched with the addition of saturated aqueous NH_4Cl solution and enough water to dissolve the solids. The layers were separated and the organic portion was washed with water and brine and then dried over anhyd $MgSO_4$. After filtration, the volatiles were removed *in vacuo* and the resulting products purified by either recrystallization or flash chromatography (SiO_2: EtOAc/*n*-hexane). By this method the following dihydropyridines were obtained (yields and melting point information are reported in Table II):

Diethyl 1,4-dihydro-2-methyl-6-[(methylthio)methyl]-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (6a) was isolated as a tan solid after recrystallization from EtOAc/*n*-hex: ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 1H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 7.7 Hz), 7.39 (t, 1H, *J* = 7.7 Hz), 7.22 (t, 1H, *J* = 7.7 Hz), 6.78 (br s, 1H), 4.16 (m, 2H), 4.00 (m, 2H), 3.94 (d, 1H, *J* = 15.3 Hz), 3.85 (d, 1H, *J* = 15.3 Hz), 2.35 (s, 3H), 2.02 (s, 3H), 1.66 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 167.4, 146.7, 144.1, 141.8, 132.0, 131.5, 126.6 (m), 125.1 (q, *J* = 274.8 Hz), 107.5, 104.6, 60.2, 59.8, 36.4, 32.6, 19.3, 14.8, 14.1, 14.0. Anal. Calcd for $C_{21}H_{24}F_3NO_4S$: C, 56.88; H, 5.46; N, 3.16. Found: C, 57.01; H, 5.43; N, 3.11.

Diethyl 2-[(butylthio)methyl]-1,4-dihydro-6-methyl-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (6b) was obtained as a colorless solid after purification by flash chromatography: ^{1}H NMR ($CDCl_3$) δ 7.53 (d, 1H, *J* = 8.0 Hz, 7.48 (d, 1H, *J* = 7.4 Hz), 7.38 (t, 1H, *J* = 7.4 Hz), 7.22 (t, 1H, *J* = 7.6 Hz), 6.89 (br s, 1H), 5.62 (s, 1H), 4.14 (m, 2H), 3.98 (m, 3H), 2.45 (t, 1H, *J* = 7.4 Hz), 2.36 (s, 3H), 1.51 (m, 2H), 1.34 (m, 2H), 1.19 (m, 6H), 0.87 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 167.4, 167.3, 146.7, 144.0, 142.2, 131.9, 131.1, 126.6, 126.3 (m), 107.0, 104.7, 60.1, 59.8, 36.4, 31.5, 31.4, 31.2, 22.0, 19.4, 14.1, 14.0, 13.6. Anal. Calcd for $C_{24}H_{30}F_3NO_4S$: C, 59.37; H, 6.23; N, 2.89. Found: C, 59.75; H, 6.24; N, 3.02.

Diethyl 1,4-dihydro-6-methyl-2-[[(phenylmethyl)thio]methyl]-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (6c) was isolated as a yellow oil after purification by flash chromatography: ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 1H, *J* = 6.7 Hz), 7.37 (t, 1H, *J* = 6.1 Hz), 7.27 (m, 7H), 6.52 (br s, 1H), 5.50 (s, 1H), 4.14 (m, 2H), 3.97 (m, 3H), 3.81 (d, 1H, *J* = 13.3 Hz), 3.66 (s, 2H), 2.23 (s, 3H), 1.15 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 167.1, 167.0, 146.5, 143.5, 141.7, 137.4, 131.7, 131.0, 129.5, 128.6, 128.5, 127.2, 126.4, 126.3, 126.2, 125.1 (q, *J* = 258.2 Hz), 106.7, 104.5, 59.9, 59.5, 36.5, 36.3, 31.4, 19.0, 13.8, 13.7. Anal. Calcd for $C_{27}H_{28}F_3NO_4S$: C, 62.42; H, 5.44; N, 2.70. Found: C, 62.40; H, 5.42; N, 2.66.

Diethyl 2-[[(2-aminoethyl)thio]methyl]-1,4-dihydro-6-methyl-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate monohydrochloride (6d) was obtained as a yellow oil after purification by flash chromatography. A small sample of the oil was converted to the hydrochloride salt by treatment with ethereal HCl and then isolated as a tan solid: mp 95–110 °C (sintered); ^{1}H NMR ($CDCl_3$) δ 8.22 (br s, 3H), 7.99 (br s, 1H), 7.51 (d, 1H, *J* = 8.0 Hz), 7.45 (d, 1H, *J* = 7.9 Hz), 7.35 (t, 1H, *J* = 7.6 Hz), 7.16 (t, 1H, *J* = 7.4 Hz), 5.57 (s, 1H), 4.01 (m, 6H), 3.36 (m, 2H), 2.97 (m, 2H), 2.33 (s, 3H), and 1.13 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 168.1, 167.6, 146.7, 144.7, 144.4, 132.2, 131.0, 126.9, 126.5, 124.8 (q, *J* = 264.1 Hz), 105.9, 104.2, 77.5, 60.5, 59.9, 39.2, 35.8, 29.9, 28.9, 19.0, 14.1, and 13.9. Anal. Calcd for $C_{22}H_{27}F_3N_2O_4S{\cdot}HCl{\cdot}0.34H_2O$: C, 51.30; H, 5.61; N, 5.44; H_2O, 1.19. Found: C, 51.30; H, 5.52; N, 5.36; H_2O, 1.03.

Diethyl 1,4-dihydro-2-methyl-4-[2-(trifluoromethyl)phenyl]-6-[(trimethylsilyl)methyl]-3,5-pyridinedicarboxylate (6e) was obtained as colorless solid after purification by flash chromatography: ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 1H, *J* = 8.0 Hz), 7.46 (d, 1H, *J* = 8.0 Hz), 7.36 (t, 1H, *J* = 7.4 Hz), 7.20 (t, 1H, *J* = 7.6 Hz), 5.60 (br s, 2H), 4.12 (m, 2H), 4.03 (m, 2H), 2.51 (d, 1H, *J* = 12.9 Hz), 2.32 (d, 1H, *J* = 12.8 Hz), 2.28 (s, 3H), 1.16 (m, 6H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.9, 168.7, 148.3, 148.2, 144.5, 132.6, 132.2, 127.3, 106.2, 103.7, 60.8, 60.5, 36.7, 24.9, 20.5, 15.2, 15.1, 00.0. Anal. Calcd for $C_{23}H_{30}F_3NO_4Si$: C, 58.84; H, 6.45; N, 2.99. Found: C, 58.89; H, 6.53; N, 2.94.

Diethyl 1,4-dihydro-4-[2-(trifluoromethyl)phenyl]-2,6-bis[(trimethylsilyl)methyl]-3,5-pyridinedicarboxylate (6f) was isolated as a colorless solid after chromatography: ^{1}H NMR ($CDCl_3$) δ 7.57 (d, 1H, *J* = 8.0 Hz), 7.45 (d, 1H, *J* = 8.0 Hz), 7.36 (t, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 7.6 Hz), 5.63 (br s, 1H), 5.22 (s, 1H), 4.12 (m, 2H), 4.00 (m, 2H), 2.89 (d, 1H, *J* = 12.8 Hz), 1.96 (d, 1H, *J* = 12.8 Hz), 1.15 (t, 6H, *J* = 7.1 Hz), and 0.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 167.7, 147.6, 147.3, 131.3, 131.2, 126.4, 126.3, 102.7, 59.4, 35.4, 24.3, 14.1, and −0.86. Anal. Calcd for $C_{26}H_{38}F_3NO_4Si_2$: C, 57.65; H, 7.08, N, 2.59. Found: C, 57.75; H, 7.18; N, 2.52.

Diethyl 2-[(diethoxyphosphonyl)methyl]-1,4-dihydro-6-methyl-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (6g) was obtained as a creamy white solid after flash chromatography: ^{1}H NMR ($CDCl_3$) δ 7.78 (br s, 1H), 7.58 (d, 1H, *J* = 8.0 Hz), 7.46 (d, 1H, *J* = 7.8 Hz), 7.34 (t, 1H, *J* = 7.4 Hz), 7.23 (t, 1H, *J* = 7.6 Hz), 5.61 (s, 1H), 4.09 (m, 4H), 3.97 (m, 5H),

3.48 (m, 1H), 2.36 (s, 3H), 1.30 (t, 3H, J = 7.0 Hz), 1.15 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 167.8, 167.7, 147.1, 144.6, 138.9, 138.8, 132.1, 131.6, 126.8, 126.5, 106.8, 104.6, 63.0 (d, J = 6.7 Hz), 60.3, 60.0, 36.0, 27.6 (d, J = 132.9 Hz), 19.4, 16.6 (d, J = 5.3 Hz), 16.4 (d, J = 6.8 Hz), 14.4, 14.3. Anal. Calcd for $C_{24}H_{31}F_3NO_7P$: C, 54.03; H, 5.86; N, 2.62. Found: C, 54.41; H, 6.01; N, 2.37.

Diethyl 2-[[(diethylamino)carbonyl]methyl]-1,4-dihydro-6-methyl-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (6h) was obtained as yellow solid after chromatography: ^{1}NMR ($CDCl_3$) δ 8.15 (br s, 1H), 7.57 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 7.7 Hz), 7.38 (t, 1H, J = 7.4 Hz), 7.21 (t, 1H, J = 7.5 Hz), 5.64 (s, 1H), 4.11 (m, 3H), 4.00 (m, 3H), 3.42 (m, 4H), 2.32 (s, 3H), 1.15 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 169.2, 167.7, 167.5, 147.0, 144.0, 141.7, 132.0, 131.2, 126.6, 126.3, 105.1, 104.4, 60.0, 59.7, 42.9, 40.9, 35.8, 32.5, 19.4, 14.5, 14.1, 14.0, 13.0. Anal. Calcd for $C_{25}H_{31}F_3N_2O_5$: C, 60.48; H, 6.30; N, 5.65. Found: C, 60.34; H, 6.27; N, 5.52.

Diethyl 1,4-dihydro-6-methyl-2-[(methylsulfonyl)methyl]-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (6i) was isolated as creamy white solid after flash chromatography: ^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1H, J = 7.9 Hz), 7.52 (d, 1H, J = 8.0 Hz), 7.45 (t, 1H, J = 7.3 Hz), 7.27 (t, 1H, J = 7.4 Hz), 7.21 (br s, 1H), 5.69 (s, 1H), 5.04 (d, 1 H, J = 14.2 Hz), 4.51 (d, 1H, J = 14.2 Hz), 4.22 (m, 2H), 4.05 (m, 2H), 2.90 (s, 3H), 2.21 (s, 3H), 1.21 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 187.3, 187.1, 146.2, 144.1, 135.7, 132.3, 131.1, 127.1, 126.7, 109.1, 104.8, 60.8, 60.1, 55.4, 40.7, 35.9, 18.9, 14.1, 14.0. Anal. Calcd for $C_{21}H_{24}F_3NO_6S$: C, 53.05; H, 53.27; N, 2.95. Found: C, 53.27; H, 5.18; N, 2.88.

Diethyl 2-[[(butylamino)carbonyl]methyl]-1,4-dihydro-6-methyl-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (6j) was obtained as a yellow solid after purification by chromatography: ^{1}H NMR ($CDCl_3$) δ 8.18 (br s, 1H), 7.55 (m, 2H), 7.46 (m, 2H), 7.22 (t, 1H, J = 5.5 Hz), 5.82 (s, 1H), 4.18 (m, 2H), 4.02 (m, 2H), 3.79 (d, 1H, J = 15.1 Hz), 3.54 (d, 2H, J = 15.1 Hz), 3.28 (m, 1H), 3.13 (m, 1H), 2.33 (s, 3H), 1.40 (m, 2H), 1.17 (m, 8H), 0.83 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 169.3, 169.1, 167.5, 147.0, 144.5, 142.9, 130.0, 131.2, 126.7, 126.4, 105.0, 104.6, 60.5, 59.8, 39.5, 39.3, 35.7, 31.5, 20.0, 18.8, 14.1, 14.0, 13.9. Anal. Calcd for $C_{25}H_{31}F_3N_2O_5$: C, 60.48; H, 6.30; N, 5.65. Found: C, 60.64; H, 6.46; N, 5.51.

Diethyl (6*Z*,4,5-*trans*)-1,4-dihydro-2-methyl-6-(2-oxoethylidene)-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (6k) was obtained as a yellow oil after purification by flash chromatography. The oil slowly crystallized to a pale yellow solid on standing at room temperature overnight: ^{1}H NMR ($CDCl_3$) δ 11.28 (s, 1H), 9.23 (d, 1H, J = 1.8 Hz), 7.68 (d, 1H, J = 7.8 Hz), 7.42 (t, 1H, J = 7.8 Hz), 7.33 (t, 1H, J = 7.8 Hz), 7.08 (d, 1H, J = 7.8 Hz), 5.18 (d, 1H, J = 1.8 Hz), 5.04 (s, 1H), 4.21 (m, 2H), 4.00 (m, 2H), 3.31 (s, 1H), 2.55 (s, 3H), 1.26 (t, 3H, J = 7.2 Hz), 1.08 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 100.1, 168.5, 166.0, 149.1, 146.6, 139.6, 132.3, 128.5, 127.4, 126.6, 122.7, 105.7, 103.2, 62.0, 60.1, 50.6, 35.8, 19.5, 14.0, 13.9. Anal. Calcd for $C_{21}H_{22}F_3NO_5$: C, 59.30; H, 5.22; N, 3.30. Found: C, 59.42; H, 5.31; N, 3.18.

Diethyl (6*Z*,4,5-*trans*)-1,4-dihydro-2-methyl-6-(2-oxopropylidene)-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (6l) was isolated as a pale yellow solid after chromatography: ^{1}H NMR ($CDCl_3$) δ 11.3 (s, 1H), 7.66 (d, 1H, J = 7.5 Hz), 7.41 (t, 1H, J = 7.5 Hz), 7.32 (t, 1H, J = 7.5 Hz), 7.06 (d, 1H, J = 7.5 Hz), 5.15 (s, 1H), 5.01 (s, 1H), 4.18 (m, 2H), 4.05 (m, 2H), 3.24 (d, 1H, J = 1.1 Hz), 2.54 (s, 3H), 2.09 (s, 3H), 1.26 (t, 3H, J = 7.2 Hz), 1.07 (t, 3H, J = 7.2 Hz), peak at δ 11.3 disappeared on shaking with CF_3CO_2H and D_2O; ^{13}C NMR ($CDCl_3$) δ 199.1, 168.9, 166.3, 147.5, 147.0, 140.1, 132.2, 128.6, 126.8, 126.6, 126.5, 104.5, 103.3, 61.8, 59.9, 50.8, 35.9, 30.1, 22.7, 14.0, 13.9. Anal. Calcd for $C_{22}H_{24}F_3NO_5$: C, 60.14; H, 5.51; N, 3.19. Found: C, 60.34; H, 5.72; N, 3.17.

Diethyl (6*Z*,4,5-*trans*)-2-[(ethoxycarbonyl)methylene]-1,2,3,4-tetrahydro-6-methyl-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (6m) was isolated as a yellow solid after purification by flash chromatography: ^{1}H NMR ($CDCl_3$) δ 9.97 (br s, 1H), 7.64 (m, 1H), 7.41 (m, 1H), 7.30 (m, 1H), 7.09 (m, 1H), 5.01 (s, 1H), 4.73 (s, 1H), 4.12 (m, 6H), 3.28 (s, 1H), 2.54 (s, 3H), 1.23 (m, 6H), 1.06 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 147.5, 147.1, 140.5, 132.2, 128.7, 126.8, 126.4, 102.5, 94.9, 61.8, 59.8, 51.0, 36.1, 19.9, 14.3, 14.0, 13.9; lit.[15] mp 98–99 °C.

Diethyl (4,5-*trans*)-2-[bis(ethoxycarbonyl)methylene]-1,2,3,4-tetrahydro-6-methyl-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (6n) was isolated as an oil after chromatography: ^{1}H NMR ($CDCl_3$) δ 10.78 (br s, 1H), 7.66 (d, 1H, J = 7.5 Hz), 7.41 (t, 1H, J = 7.4 Hz), 7.31 (t, 1H, J = 7.4 Hz), 7.08 (d, 1H, J = 7.5 Hz), 5.06 (s, 1H), 4.19 (m, 4H), 4.07 (m, 5H), 2.56 (s, 3H), 1.26 (t, 6H, J = 6.9 Hz), 1.10 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 168.3, 167.8, 166.1, 165.4, 150.5, 146.4, 139.1, 132.4, 128.2, 127.3, 126.5, 104.7, 101.8, 61.8, 61.0, 60.9, 60.1, 48.0, 35.9, 19.6, 14.1, 14.0, 13.9, 13.8. Anal. Calcd for $C_{26}H_{30}F_3NO_8$: C, 57.66; H, 5.58; N, 2.59. Found: C, 57.73; H, 5.56; N, 2.73.

Diethyl (6*Z*,4,5-*trans*)-1,4,5,6-tetrahydro-2-methyl-6-(3,3,3-trifluoro-2-oxopropylidene)-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinecarboxylate (6o) was obtained as a yellow oil after chromatography: ^{1}H NMR ($CDCl_3$) δ 11.30 (br s, 1H), 7.70 (d, 1H, J = 7.4 Hz), 7.41 (t, 1H, J = 7.5 Hz), 7.37 (t, 1H, J = 7.6 Hz), 7.04 (d, 1H, J = 7.7 Hz), 5.46 (s, 1H), 5.08 (s, 1H), 4.23 (m, 2H), 4.04 (m, 2H), 3.44 (s, 1H), 2.58 (s, 3H), 1.26 (m, 3H), 1.07 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 180.1, 167.7, 166.5, 155.6, 150.0, 132.5, 128.2, 127.0, 126.3, 108.6, 95.1, 62.4, 60.5, 51.3, 35.7, 19.2, 13.9, 13.8. Anal. Calcd for $C_{22}H_{21}F_6NO_5$: C, 53.56; H, 4.30; N, 2.84. Found: C, 53.78; H, 4.59; N, 2.87.

3,5-Bis(ethoxycarbonyl)-1,4-dihydro-6-methyl-4-[2-(trifluoromethyl)phenyl]-2-pyridineacetic acid sodium salt (6p) was obtained as a pale yellow solid after recrystallization from EtOAc/*n*-hex: ^{1}H NMR (DMSO-d_6) δ 9.47 (br s, 1H), 7.69 (d, 1H, J = 7.9 Hz), 7.46 (m, 2H), 7.28 (t, 1H, J = 7.5 Hz), 5.48 (s, 1H), 3.91 (m, 6H), 2.23 (s, 3H), 1.07 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 174.6, 167.0, 166.8, 147.7, 145.0, 144.9, 132.5, 131.4, 130.9, 126.5, 103.0, 102.3, 59.1, 58.8, 35.3, 18.4, 14.0, 13.9. Anal. Calcd for $C_{21}H_{21}F_3NO_6$·Na: C, 54.44; H, 4.57; N, 3.03. Found: C, 54.12; H, 4.75; N, 2.98.

1,1′-(Dithiodi-2,1-ethanediyl)-bis(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane) (7). Following the general procedure of Magnus,[17] a solution of 1,2-bis(chlorodimethylsilyl)-ethane (6.88 g, 32.0 mmol) in 15 mL of CH_2Cl_2 was slowly added portionwise to a stirred, 0 °C (ice bath) solution of cystamine free base (2.50 g, 16.0 mmol), Et_3N (6.46 g, 64.0 mmol), and 20 mL of CH_2Cl_2 under N_2 (*caution: the addition is very exothermic*!). The resulting white suspension was then allowed to warm to room temperature and stir 30 min. The mixture was washed with H_2O and brine and then dried over anhyd K_2CO_3. After filtration, the filtrate was concentrated *in vacuo* to yield 4.74 g (68%) of **7** as a clear oil: ^{1}H NMR (acetone-d_6) δ 3.64 (m, 2H), 3.18 (m, 2H), 1.02 (s, 4H), 0.58 (m, 12H); ^{13}C NMR (acetone-d_6) δ 42.5, 42.1, 7.9, −0.35.

Diethyl 1,4-Dihydro-2-(2-hydroxy-2-methylpropyl)-6-methyl-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (8) and Ethyl 1,4,7,8-Tetrahydro-2,7,7-trimethyl-5-oxo-4-[2-(trifluoromethyl)phenyl]-5*H*-pyrano[4,3-*b*]pyridine-3-carboxylate (9). In a manner identical to that described above in the metalation of **3c**, dry acetone (0.75 mL, 16 mmol) was added to the dianion **5** and the resulting solution allowed to warm to room temperature and quenched with aqueous NH_4Cl. Workup and chromatography (SiO_2: EtOAc/*n*-hex) furnished 1.44 g (32%) of **8** as a yellow oil and 1.26 g (31%) of **9** as a colorless solid. For **8**: ^{1}H NMR ($CDCl_3$) δ 7.59 (d, 1H, J = 8.0 Hz), 7.46 (d, 1H, J = 8.0 Hz), 7.36 (t, 1H, J = 7.6 Hz), 7.21 (t, 1H, J = 7.7 Hz), 5.60 (s, 1H), 4.14 (m, 2H), 3.99 (m, 2H), 3.04 (d, 1H, J = 14.7 Hz), 2.93 (d, 1H, J = 14.7 Hz), 2.41 (br s, 1H), 2.30 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 1.17 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 168.3, 147.2, 144.7, 144.4, 131.9, 131.2, 126.4, 126.3, 107.1, 103.8, 72.5, 60.1, 59.7, 41.3, 35.9, 30.1, 29.8, 19.7, 19.4, 14.1, 14.0. Anal. Calcd for $C_{23}H_{28}F_3NO_5$: C, 60.65; H, 6.20; N, 3.08. Found: C, 60.29; H, 6.23; N, 3.43. For **9**: mp 194–195 °C, transitional change at 94–95 °C; ^{1}H NMR ($CDCl_3$) δ 8.38 (br s, 1H), 7.58 (d, 1H, J = 7.9 Hz), 7.49 (m, 2H), 7.27 (t, 1H, J = 7.6 Hz), 5.60 (s, 1H), 4.09 (m, 1H), 3.99 (m, 1H), 2.62 (d, 1H, J = 17.2 Hz), 2.51 (d, 1H, J = 17.2 Hz), 2.22 (s, 3H), 1.40 (s, 3H), 1.23 (s, 3H), 1.13 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 167.5, 167.0, 146.4, 146.1, 144.3, 131.8, 131.4, 126.5, 105.9, 100.3, 77.9, 59.8, 36.4, 34.1, 28.6, 26.2, 18.5, 14.0. Anal. Calcd for $C_{21}H_{22}F_3NO_4$: C, 61.61; H, 5.42; N, 3.42. Found: C, 61.57; H, 5.44; N, 3.42.

The metalation was repeated on a 10.0-mmol scale as described above. After the acetone was added, the anion solution was allowed to warm and then stir at room temperature for 60 min

prior to aqueous NH_4Cl quench. In this manner 2.80 g (69%) of **9** could be isolated after chromatography.

Treatment of Hydroxy Ester 8 with Acid. A solution of **8** (0.77 g, 1.7 mmol) and 2 mg of *p*-toluenesulfonic acid in 20 mL of toluene was refluxed 22 h. After removal of the volatiles *in vacuo*, the residue was chromatographed (SiO_2: EtOAc/*n*-hex) to give 0.19 g of **3c** (28%) as a colorless solid (mp 140–141 °C) and 0.37 g (50%) of diethyl 1,4-dihydro-2-(2-methyl-1-propenyl)-6-methyl-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (**10**) as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.62 (d, 1H, J = 7.9 Hz), 7.48 (d, 1H, J = 7.9 Hz), 7.37 (t, 1H, J = 7.9 Hz), 7.20 (t, 1 H, J = 7.9 Hz), 6.17 (s, 1H), 5.77 (br s, 1H), 5.63 (s, 1H), 4.09 (m, 2H), 3.99 (m, 2H), 2.32 (s, 3H), 1.82 (s, 3H), 1.76 (s, 3H), 1.14 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 167.6, 167.0, 147.0, 143.7, 142.5, 139.2, 131.9, 131.3, 126.5, 121.1, 106.1, 104.6, 59.8, 35.9, 25.7, 19.9, 19.4, 14.1. Anal. Calcd for $C_{23}H_{28}F_3NO_4$: C, 63.15; H, 5.99; N, 3.20. Found: C, 62.87; H, 5.99; N, 3.10.

Metalation of Dihydropyridine 3d. In a manner similar to that described above for **3c**, a 5.88-mmol solution **3d** in 80 mL of THF was treated with 2.2 equiv of *n*-BuLi. After stirring at −78 °C for 1 h, a solution of **7** (3.85 g, 8.82 mmol) in 50 mL of THF was added and the resulting solution allowed to warm to ambient temperature. After quenching with aqueous NH_4Cl, the layers were separated and the organic portion washed with H_2O and brine and then dried over anhyd K_2CO_3. The filtrate was concentrated *in vacuo* to give a yellow oil. TLC analysis indicated two major products with similar R_f's. Careful separation of the mixture using flash chromatography (SiO_2: ammoniated MeOH/$CHCl_3$) furnished 0.67 g (18%) of ethyl[5] [3-[4-(2-pyridinyl)-1-piperazinyl]propyl][3] 2-[[(2-aminoethyl)thio]methyl]-1,4-dihydro-6-methyl-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (**11a**) and 0.60 g (16%) of the C-6 methyl isomer, ethyl[3] [3-[4-(2-pyridinyl)-1-piperazinyl]propyl][5] 2-[[(2-aminoethyl)thio]methyl]-1,4-dihydro-6-methyl-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (**11b**).[28] Both products were converted to their HCl salts by treatment with ethereal hydrogen chloride. Isomer **11a** was isolated as a tan solid: mp indistinct; ^1H NMR (DMSO-d_6) δ 11.80 (br s, 1H), 9.64 (s, 1H), 8.36 (br s, 3H), 8.12 (d, 1H, J = 5.5 Hz), 7.94 (t, 1H, J = 8.1 Hz), 7.53 (m, 3H), 7.33 (m, 2H), 6.96 (t, 1H, J = 6.3 Hz), 5.44 (s, 1H), 4.53 (m, 2H), 4.03 (m, 6H), 3.58 (m, 4H), 2.89 (m, 6H), 2.88 (t, 2H, J = 6.9 Hz), 2.34 (s, 3H), 2.07 (t, 2H, J = 6.7 Hz), 1.09 (t, 3H, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6) δ 166.5, 166.3, 153.9, 147.1, 146.2, 145.7, 141.9, 140.8, 132.6, 130.8, 126.8, 126.0, 113.8, 111.0, 103.4, 102.1, 60.5, 59.3, 52.7, 49.9, 42.8, 38.6, 35.2, 29.6, 28.3, 22.8, 18.4, 13.8. Anal. Calcd for $C_{32}H_{40}F_3N_5O_4S \cdot 2.5HCl \cdot 1.25H_2O$: C, 50.48; H, 5.96; N, 9.20; H_2O, 2.96. Found: C, 50.20; H, 6.14; N, 8.99; H_2O, 3.04. Isomer **11b** was isolated as a tan solid: mp indistinct; ^1H NMR (DMSO-d_6) δ 11.85 (br s, 1H), 9.65 (s, 1H), 8.39 (br s, 3H), 8.12 (d, 1H, J = 5.6 Hz), 8.00 (t, 1H, J = 8.0 Hz), 7.56 (m, 3H), 7.45 (m, 2H), 6.99 (t, 1H, J = 6.2 Hz), 5.45 (s, 1H), 4.51 (m, 2H), 3.91 (m, 6H), 3.65 (m, 4H), 3.01 (m, 6H), 2.90 (t, 2H, J = 7.0 Hz), 2.32 (s, 3H), 2.07 (m, 2 H), 1.08 (m, 3 H); ^{13}C NMR (DMSO-d_6) δ 166.5, 166.3, 153.3, 147.1, 146.6, 145.1, 142.5, 139.9, 132.6, 130.8, 126.8, 125.9, 113.8, 111.5, 102.8, 102.6, 60.8, 59.0, 52.7, 49.9, 43.0, 38.6, 35.1, 29.9, 28.4, 22.7, 18.0, 13.9. Anal. Calcd for $C_{32}H_{40}F_3N_5O_4S \cdot 3HCl \cdot 1.0H_2O$: C, 49.59; H, 5.85; N, 9.04; H_2O, 2.31. Found: C, 49.81; H, 6.66; N, 8.64; H_2O, 1.48. HRMS calcd for $C_{32}H_{41}F_3N_5O_4S$ (M + H): 648.2831. Found: 648.2849.

Metalation of Dihydropyridine 3e. Dianion Formation. In a manner similar to that described above, a 25.0-mmol solution of dihydropyridine **3e** in 300 mL of THF was treated under N_2 with 2.1 equiv of *n*-BuLi (21 mL, 53 mmol, 2.5 *M* in *n*-hexane). After stirring at −78 °C for 2 h, methyl disulfide (2.7 mL, 30 mmol) was added and the resulting solution allowed to warm to room temperature and quenched with aqueous NH_4Cl solution. The layers were separated, and the organic portion was washed with 10% aqueous NaOH, H_2O, and brine and then dried over anhyd $MgSO_4$. Removal of the volatiles *in vacuo* and flash chromatography of the residue (SiO_2: EtOAc/*n*-hex) gave 6.65 g (81%) of dimethyl 1,4-dihydro-6-[(methylthio)methyl]-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (**12**) and 0.15 g (1%) of dimethyl 1,4-dihydro-2,6-bis[(methylthio)methyl]-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (**13**) as a pale yellow solids. For **12**: mp 97–99 °C; ^1H NMR ($CDCl_3$) δ 7.52 (d, 1H, J = 8.0 Hz), 7.45 (d, 1H, J = 8.2 Hz), 7.37 (t, 1H, J = 7.6 Hz), 7.21 (t, 1H, J = 7.6 Hz), 6.75 (br s, 1H), 5.56 (s, 1H), 3.99 (d, 1H, J = 15.7 Hz), 3.87 (d, 1H, J = 15.5 Hz), 3.56 (s, 3H), 3.54 (s, 3H), 2.34 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.6, 167.5, 146.8, 144.4, 142.4, 131.8, 130.9, 126.5, 107.1, 104.4, 50.9, 50.7, 36.1, 32.5, 19.3, 14.7. Anal. Calcd for $C_{19}H_{20}F_3NO_4S$: C, 54.94; H, 4.86; N, 3.38. Found: C, 54.92; H, 4.87; N, 3.45. For **13**: mp 86–87 °C; ^1H NMR ($CDCl_3$) δ 7.78 (br s, 1H), 7.53 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 8.1 Hz), 7.39 (t, 1H, J = 7.4 Hz), 7.23 (t, 1H, J = 7.4 Hz), 5.60 (s, 1H), 4.08 (d, 2H, J = 15.7 Hz), 3.95 (d, 2H, J = 15.8 Hz), 3.58 (s, 6H), 2.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.7, 146.5, 143.1, 132.0, 130.8, 126.8, 126.7, 106.6, 51.0, 36.7, 36.6, 32.9, 15.1. Anal. Calcd for $C_{20}H_{22}F_3NO_4S_2$: C, 52.06; H, 4.81; N, 3.04. Found: C, 52.40; H, 4.85; N, 3.04.

Trianion Formation. The metalation of **3e** described above was repeated on a 10-mmol scale in THF except that 3.2 equiv of *s*-BuLi was employed as the base and 2.2 equiv of $(MeS)_2$ was used as the electrophile. Workup and chromatography gave 0.70 g (17%) of **12** and 3.32 g (72%) of **13** as yellow solids (*vide supra*).

Metalation of Dihydropyridine 12. To a stirred, −78 °C (dry ice/2-propanol) solution of **12** (4.15 g, 10.0 mmol) under N_2 in 100 mL of THF was added 2.1 equiv of *n*-BuLi (2.5 *M* in *n*-hexane). The resulting suspension was stirred 1.5 h at −78 °C and then methyl disulfide (1.0 mL, 12 mmol) was added via syringe. The mixture was allowed to warm to room temperature during which time dissolution occurred. The reaction was worked up as usual to give a yellow oil (stench!). The oil was purified by flash chromatography (SiO_2: EtOAc/*n*-hex), to furnish 4.10 g (91%) of dimethyl 1,4-dihydro-2-methyl-6,6-bis[(methylthio)-methyl]-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (**14**) and 0.19 g (4%) of dimethyl 1,4-dihydro-2,2-bis-[(methylthio)methyl]-6-[(methylthio)methyl]-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (**15**) as colorless solids. For **14**: mp 127–128 °C; ^1H NMR ($CDCl_3$) δ 7.51 (d, 1H, J = 8.0 Hz), 7.42 (d, 1H, J = 8.0 Hz), 7.34 (t, 1H, J = 7.5 Hz), 7.18 (t, 1H, J = 7.3 Hz), 6.69 (br s, 1H), 6.21 (s, 1H), 5.58 (s, 1H), 3.55 (s, 3H), 3.51 (s, 3H), 2.32 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.5, 167.3, 146.6, 144.5, 143.7, 132.0, 130.9, 126.8, 107.1, 104.3, 51.1, 50.7, 48.1, 36.1, 19.3, 16.2, 15.9. Anal. Calcd for $C_{20}H_{22}F_3NO_4S_2$: C, 52.06; H, 4.81; N, 3.04. Found: C, 52.11; H, 4.80; N, 2.99. For **15**: mp 108–109 °C; ^1H NMR ($CDCl_3$) δ 7.87 (br s, 1H), 7.50 (d, 1H, J = 7.9 Hz), 7.40 (d, 1H, J = 7.9 Hz), 7.33 (t, 1H, J = 7.5 Hz), 7.17 (t, 1H, J = 7.5 Hz), 6.19 (s, 1H), 5.56 (s, 1H), 4.10 (d, 1H, J = 15.9 Hz), 3.80 (d, 1H, J = 15.9 Hz), 3.60 (s, 3H), 3.57 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.2, 167.1, 146.4, 144.4, 143.3, 132.1, 130.8, 127.1, 106.3, 105.9, 51.2, 51.0, 48.5, 36.8, 36.7, 33.3, 16.2, 15.9, 15.2. Anal. Calcd for $C_{21}H_{24}F_3NO_4S_3$: C, 49.70; H, 4.77; N, 2.76. Found: C, 49.69; H, 4.56; N, 2.73.

Metalation of Dihydropyridine 14. In a manner similar to that described above, a 2.30-mmol solution of thioacetal **14** in 30 mL of THF was treated with 2.1 equiv of *n*-BuLi and stirred at −78 °C for 1 h. Methyl disulfide (2.5 mmol) was added and the gelatinous mixture allowed to warm to ambient temperature and quenched with aqueous NH_4Cl. Workup and trituration from hexane gave 1.02 g (87%) of **15** as a colorless solid.

The metalation of **14** (1.2 mmol) was repeated using the procedure as described above but MeOD was employed as the electrophile. Workup and recrystallization of the crude material from EtOAc/*n*-hex afforded 0.42 g (78%) of dimethyl 2-(monodeuteromethyl)-1,4-dihydro-6-bis[(methylthio)methyl]-4-[2-(trifluoromethyl)phenyl]-3,5-pyridinedicarboxylate (**16**) as a pale yellow solid: mp 122–123 °C; ^1H NMR ($CDCl_3$) same as **14** except the singlet at δ 2.35 integrated for two protons; ^{13}C NMR ($CDCl_3$) same as **14** except the peak at δ 19.3 became a triplet at 19.1 (J = 20.2 Hz). Anal. Calcd for $C_{20}H_{21}DF_3NO_4S_2$: C, 51.94; H, 4.79; N, 3.33. Found: C, 51.84; H, 4.65; N, 2.94.

Allowing the metalation mixture to warm to ice bath temperature (0 °C) and then recooling to −78 °C prior to MeOD quench again gave **16** as the only isolable product.

Methyl 4-(2-Chlorophenyl)-1,4-dihydro-5-(1-imidazolylcarbonyl)-2,6-dimethyl-3-pyridinecarboxylate (19). A sus-

(28) Isomeric assignment of **11a** and **11b** was determined using NOESY (Nuclear Overhauser Effect Spectroscopy) techniques. For an explanation of this type of NMR experiment, see: Freeman, R. A. *Handbook of Nuclear Magnetic Resonance*; John Wiley and Sons: New York, 1988; p 142.

pension of dihydropyridine acid **18** (10.0 g, 30.1 mmol) and carbonyldiimidazole (CDI, 5.10 g, 31.5 mmol) in 125 mL of MeCN was refluxed under N_2 for 2 h and then stirred overnight (18 h) at room temperature. The mixture was poured into water and then extracted with CH_2Cl_2. The combined organic portion was washed with water and brine and then dried over anhyd $MgSO_4$. Filtration and concentration of the filtrate *in vacuo* gave an orange oil. The oil was taken up in hot EtOAc and slowly allowed to crystallize. Filtration gave 6.56 g (59%) of **19** as a pale yellow solid: mp 189–192 °C; ^{1}H NMR (DMSO-d_6) δ 9.11 (br s, 1H), 7.96 (s, 1H), 7.41 (t, 1H, J = 1.4 Hz), 7.26 (d, 1H, J = 3.8 Hz), 7.21 (m, 2H), 7.10 (m, 1H), 7.01 (s, 1H), 5.32 (s, 1H), 3.44 (s, 3H), 2.36 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 167.4, 167.1, 147.8, 144.4, 141.5, 137.5, 130.8, 130.7, 130.5, 129.5, 128.6, 128.3, 117.5, 104.8, 99.5, 50.9, 38.7, 18.4, 16.7. Anal. Calcd for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; N, 11.30. Found: C, 61.25; H, 4.91; N, 11.05.

Methyl 4-(2-Chlorophenyl)-1,4-dihydro-2,6-dimethyl-5-[(methylamino)carbonyl]-3-pyridinecarboxylate (20a). A solution of 30.0 mmol of **19** and 90 mmol of $MeNH_2$ (7.0 g, 40% in water) in 125 mL of MeCN was refluxed 16 h. After cooling to room temperature, the mixture was poured into 500 mL of water and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine and then dried over anhyd $MgSO_4$. After filtration and removal of the volatiles *in vacuo*, the resulting yellow foam was recrystallized from EtOAc/*n*-hex to give 6.53 g (65%) of **20a** as a yellow solid: mp 191–192 °C; ^{1}H NMR (DMSO-d_6) δ 8.31 (br s, 1H), 7.45 (br q, 1H, J = 4.7 Hz), 7.15 (m, 3H), 7.03 (m, 1H), 5.13 (s, 1H), 3.37 (s, 3H), 2.46 (d, 3H, J = 4.6 Hz), 2.21 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 169.1, 167.9, 148.3, 146.4, 133.0, 131.1, 129.1, 127.8, 127.7, 110.0, 98.2, 50.4, 38.4, 25.7, 18.6, 16.4. Anal. Calcd for $C_{17}H_{19}ClN_2O_3$: C, 60.99; H, 5.73; N, 8.37. Found: C, 60.74; H, 5.70; N, 8.26.

Methyl 4-(2-Chlorophenyl)-1,4-dihydro-2,6-dimethyl-5-[(dimethylamino)carbonyl]-3-pyridinedicarboxylate (20b). In a manner similar to that described above, *N*,*N*-dimethylamide **20b** was prepared in 63% yield from **19** using aqueous Me_2NH and isolated as a yellow solid after recrystallization from EtOAc/MeOH: mp 200–204 °C; ^{1}H NMR (DMSO-d_6) δ 8.37 (br s, 1H), 7.20 (m, 3H), 7.07 (m, 1H), 5.04 (s, 1H), 3.35 (s, 3H), 3.00–2.00 (very br s, 3H), 2.69 (br s, 3H), 2.29 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 169.8, 167.8, 149.3, 130.9, 130.6, 129.2, 128.0, 108.2, 96.4, 50.5, 36.8, 33.9, 18.8, 15.4. Anal. Calcd for $C_{18}H_{21}ClN_2O_3$: C, 61.98; H, 6.07; N, 8.04. Found: C, 62.02; H, 6.03; N, 7.95.

Metalation of Dihydropyridines 20a and 20b. Method A. To a stirred solution of **20a** (5 mmol) in 50 mL of THF (N_2 atm, −78 °C cold bath) was added via syringe the indicated base over a period of 5 min (Table IV). The resulting yellow suspension was allowed to stir at −78 °C for 1 h and then it was quenched with 1 mL of MeOD and allowed to warm to room temperature. Saturated aqueous NH_4Cl solution was added, and the layers were separated. The organic portion was washed with water and brine and then dried over anhyd $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo* and the resulting **21a** recrystallized from EtOAc/MeOH/*n*-hexane. Deuterium incorporation (% and location) was determined by NMR analysis and reported in Table IV.

Method B. In a manner identical to that described above, the anion suspension of either **20a** or **20b** was prepared at −78 °C and then allowed to warm to 0 °C (ice bath) for 30 min. After recooling to −78 °C, the electrophile was added and the reaction was worked up and analyzed as described above. For example, methyl 4-(2-chlorophenyl)-2-(monodeuteromethyl)-1,4-dihydro-6-methyl-5-[(methylamino)carbonyl]-3-pyridinecarboxylate (**21a**, Table IV, entry 4) was obtained as a pale yellow solid: mp 191–192 °C; ^{1}H NMR (DMSO-d_6) same as **20a** except that the singlet at δ 2.21 now integrated for two protons; ^{13}C NMR (DMSO-d_6) identical to **20a** except the singlet at δ 18.6 became a triplet at 18.4 (J = 20.1 Hz). Anal. Calcd for $C_{17}H_{18}DClNO_3$: C, 60.81; H, 5.70; N, 8.34. Found: C, 60.65; H, 5.65; N, 8.24.

Methyl 4-(2-Chlorophenyl)-1,4-dihydro-6-methyl-5-[(methylamino)carbonyl]-2-[(methylthio)methyl]-3-pyridinecarboxylate (23). Following method B above, 4.33 mmol of **20a** was metalated with 3.2 equiv of *n*-BuLi and then the suspension was allowed to warm to 0 °C and stir 0.5 h. After recooling to −78 °C, $(MeS)_2$ (0.5 mL, 5.5 mmol) was added and the resulting suspension allowed to warm to room temperature and then quenched with aqueous NH_4Cl. The organic portion was washed with water and brine and then dried over $MgSO_4$. Filtration and removal of the volatiles *in vacuo* afforded a crude material which was subsequently purified by flash chromatography (EtOAc/*n*-hex) to give 1.35 g (82%) of **23** as a yellow solid: mp 171–172 °C; ^{1}H NMR (DMSO-d_6) δ 8.43 (s, 1H), 7.51 (br q, 1H, J = 4.6 Hz), 7.31 (d, 1H, J = 7.8 Hz), 7.20 (t, 2H, J = 7.9 Hz), 7.08 (t, 1H, J = 7.5 Hz), 5.21 (s, 1H), 3.97 (d, 1H, J = 12.9 Hz), 3.66 (d, 1H, J = 12.9 Hz), 3.42 (s, 3H), 2.49 (d, 3H, J = 4.5 Hz), 2.08 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 168.5, 167.2, 148.6, 145.8, 132.9, 130.7, 130.6, 128.8, 127.6, 127.5, 109.3, 98.9, 50.5, 38.3, 31.4, 25.8, 16.5, 14.9. Anal. Calcd for $C_{18}H_{21}ClN_2O_3S{\cdot}0.15H_2O$: C, 56.36; H, 5.60; N, 7.31; H_2O, 0.70. C, 56.11; H, 5.47; N, 7.12; H_2O, 0.64.

4-(2-Chlorophenyl)-1,4,7,8-tetrahydro-*N*,2,7,7-tetramethyl-5-oxo-5*H*-pyrano[4,3-*b*]pyridine-3-carboxamide (24). A solution of **20a** (2.80 g, 8.36 mmol) was taken up in 50 mL of dry, O_2-free THF and cooled in a −78 °C bath under dry N_2. *n*-BuLi (10 mL, 25 mmol) was then added to the cold solution and the resulting yellow suspension warmed to 0 °C and stirred for 45 min. Acetone (1.0 mL, 16 mmol) was then added and the mixture was allowed to warm to ambient temperature and stir an additional 4 h. The resulting homogeneous solution was quenched by the addition of 10 mL of a saturated aqueous ammonium chloride solution. Water (50 mL) and Et_2O (100 mL) were added, and the resulting solid was collected by filtration and washed with ether. The material was then dried to afford 1.93 g (64% yield) of lactone **24** as a colorless white solid: mp >259 °C; ^{1}H NMR (DMSO-d_6) δ 8.79 (s, 1H), 7.54 (br q, 1H, J = 4.5 Hz), 7.25 (m, 3H), 7.09 (m, 1H), 5.23 (s, 1H), 3.34 (s, 2H), 2.45 (q, 3H, J = 4.5 Hz), 1.86 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 168.4, 164.9, 146.7, 144.3, 132.5, 131.6, 131.4, 129.1, 127.6, 127.1, 110.1, 95.7, 76.7, 37.4, 36.0, 28.3, 26.3, 25.7, 16.7. Anal. Calcd for $C_{19}H_{21}ClN_2O_3$: C, 63.25; H, 5.87; N, 7.77. Found: C, 62.96; H, 5.84; N, 7.75.

Metalation of Dihydropyridine 20a. Tetraanion Formation. In a manner similar to that described above, a solution of 9.55 mmol of **20a** (under N_2, −78 °C) in 100 mL of THF was treated with 4.2 equiv of *n*-BuLi (2.5 *M* in *n*-hexane). The resulting orange suspension was warmed to 0 °C in an ice bath for 1.5 h and then recooled to −78 °C. Methyl disulfide (0.95 mL, 10 mmol) was added via a syringe and the resulting suspension was stirred for 2 h at low temperature and then quenched with saturated aqueous NH_4Cl and water. The layers were separated, and the organic layer was washed with water and brine. After drying over $MgSO_4$ and filtration, the filtrate was concentrated *in vacuo* to afford a yellow solid. The solid was carefully purified using flash chromatography (SiO_2: EtOAc/*n*-hex) to furnish 0.83 g (24%) of **23** and 1.49 g (41%) of the C-6 methyl isomer, methyl 4-(2-chlorophenyl)-1,4-dihydro-2-methyl-5-[(methylamino)carbonyl]-6-[(methylthio)methyl]-3-pyridinecarboxylate (**26**) as pale yellow solids. For **26**: mp 168–170 °C; ^{1}H NMR (DMSO-d_6) δ 8.41 (s, 1H), 7.80 (br s, 1H), 7.25 (m, 3H), 7.07 (t, 1H, J = 7.4 Hz), 5.22 (s, 1H), 3.46 (d, 1H, J = 13.7 Hz), 3.41 (s, 3H), 3.24 (d, 1H, J = 13.6 Hz), 2.49 (d, 3H, J = 4.2 Hz), 2.28 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 168.2, 167.2, 148.4, 145.5, 133.4, 130.6, 128.7, 127.6, 127.5, 112.1, 97.6, 64.9, 50.3, 38.7, 30.7, 25.7, 18.7, 14.1. Anal. Calcd for $C_{18}H_{21}ClN_2O_3S$: C, 56.77; H, 5.62; N, 7.36. Found: C, 56.78; H, 5.63; N, 7.21.

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