Conformational Interlocking in Axially Chiral Methyl *N*-(2',4'-Dimethylnicotinoyl)-*N*-methylphenylalaninates

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Axially chiral 2,4-dimethylnicotinamides incorporating a protected *N*-methylphenylalanine moiety (**1**; **2**) have been prepared to serve as NAD^+ model precursors. Starting from L- or D-methyl *N*-methylphenylalaninate hydrochloride ((*S*)- or (*R*)-**4**), the *M*-syn diastereomer **1a** or its *P*-syn enantiomer **2a**, were isolated in fair yield by a combination of rotamerization, helical isomerization, and crystallization. Evidence is presented for a strong conformational preference in solution not only at the amide bond but also at the chiral center (C-2) and at the benzylic carbon (C-3). The conformational interdependence compares well with the spatial arrangement in crystals of analogous axially chiral nicotinamide derivatives. Due to a preferred syn orientation of the amide carbonyl and C-2-H, the phenyl ring of the less polar syn diastereomers resides near the C-2' methyl group either at the α side of the pyridine ring in **1a** or at the β side in **2a**. In these syn diastereomers the *S* chirality in the amino acid residue (i.e., in **1a**) corresponds to a CO UP or *M* helicity, the *R* chirality (i.e., in **2a**) to a CO DOWN or *P* orientation. Conversely, the phenyl ring of the more polar syn diastereomers **1b** (*P* conformer) and **2b** (*M* conformer) resides preferentially in the vicinity of the C-4' methyl group.

Introduction

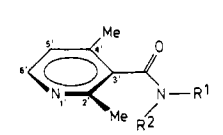
Transient axial chirality induced by out-of-plane rotation of the amide group in NADH-NAD^+ was proposed as a rationale for the high stereoselectivity of the hydride transfer in vivo.[1] NADH Model studies on peralkylated, chiral 3-(aminocarbonyl)-1,4-dihydroquinoline[2] and -pyridine[3] have unambiguously demonstrated that in vitro hydride transfer occurs highly stereoselectively as well as with regard to the NADH model as to the carbonyl substrate. They have given support to the concept of syn orientation of the amide carbonyl dipole and the broken C–H bond during the hydride transfer.

Enzymatic conditions allow the positioning of coenzyme and substrate, presumably owing to the chiral shape of the enzymic cavity and via hydrogen bridge formations with defined amino acid residues. In an attempt to simulate these interactions, the preparation and behavioral study of axially chiral nicotinamide derivatives incorporating an oligopeptide moiety were envisaged. Methyl *N*-methylphenylalaninate was selected as a peptide prototype.

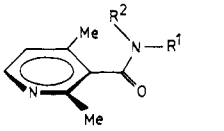
The isolation of axially chiral pyridine derivatives **1a,b** and **2a,b**, which can be considered as immediate precursors for NAD^+ models, is described in this paper. Their spectral characteristics in solution are discussed in terms of conformational interlocking of the pyridine ring, the amide group, the chiral center at C-2, and the phenyl ring at C-3.

Results and Discussion

1. Isolation of 1a,b and 2a,b. Treatment of 2,4-dimethylnicotinoyl chloride hydrochloride (**3**)[4] with methyl *N*-methyl-L-phenylalaninate hydrochloride ((*S*)-**4**)[5] at 0 °C in the presence of an HCl scavenger (Et_3N) gives rise to the formation of four diastereomeric amides **1a–d** as a consequence of two types of conformational isomerism, i.e., the syn–anti rotamerism about the amide bond and the axial chirality around the C-3'–C amide axis.



1a: R^1 = CH(CH_2Ph)CO_2Me (*S*), R^2 = Me
1c: R^1 = Me, R^2 = CH(CH_2Ph)CO_2Me (*S*)
2b: R^1 = CH(CH_2Ph)CO_2Me (*R*), R^2 = Me



1b: R^1 = CH(CH_2Ph)CO_2Me (*S*), R^2 = Me
1d: R^1 = Me, R^2 = CH(CH_2Ph)CO_2Me (*S*)
2a: R^1 = CH(CH_2Ph)CO_2Me (*R*), R^2 = Me

In $CDCl_3$ a ^1H NMR spectrum of the mixture, taken immediately after the reaction, revealed the presence of eight distinct singlets ranging from 1.45 to 2.50 ppm and corresponding to the C-2' and C-4' methyl protons of **1a–d** (Table I). Typical doublet of doublets were observed for C-2-*H*, centered around 5.95 ppm for the two major isomers (~75%, ratio 1:1) and around 4.25 ppm for the minor ones (~25%, ratio 1:1). The latter featured an *N*-methyl proton absorption at lower field (~3.25 ppm) than the former (~2.65 ppm). Interestingly, the signals belonging to the major isomers gradually increased in intensity at the expense of those belonging to the minor conformers, finally reaching a 96:4 ratio at equilibrium. Obviously a relatively slow conformational inversion around the amide C–N bond was responsible for this phenomenon. The preference for the formation of the major isomers **1a,b** was apparently less pronounced than the thermodynamic preference. Taking into account the relative bulkiness of the 1-carbomethoxy-2-phenylethyl group and the behavior of other tertiary nicotinamides (vide infra), an anti → syn transformation (**1c,d** → **1a,b**) was assumed. A ^1H NMR spectrum of a mixture of **1a,b** in $CDCl_3$ featured strikingly selective shieldings exerted on H-5' (δ 6.94 vs 6.82) and on the C-2' and C-4' methyl protons (δ 2.50 and 2.28 vs 1.70 and 1.45). The downfield signals were almost superimposable on those found in the *N,N*-dimethyl analogue **5** (Table I). Fortunately we were able to isolate the less polar diastereomer (R_f 0.17, SiO_2, $CHCl_3$–MeOH, 98:2) by crystallization and demonstrated it to contain considerably shielded C-2' methyl protons (δ 1.70 vs 2.44 for the corresponding protons in **5**). Structure **1a** was assigned to this compound, based on evidence that is described subsequently. The mother liquors were enriched in the more polar diastereomer (R_f 0.12). The relative (vs **5**) shielding of both H-5' (Δ 0.1 ppm) and the C-4' methyl protons (Δ 0.83 ppm) in ^1H NMR offered partial evidence for the assignment of structure **1b** to this compound.

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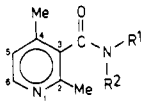
Table I. Relevant ^{1}H NMR Spectral Data of *syn*- and *anti*-2,4-Dimethylnicotinamides[a,b]



entry	R^1 (syn)	R^2 (anti)	C-4 Me	C-2 Me	NCH_x syn	NCH_x anti	H-5	H-6[c]
1a	$CH(CH_2Ph)CO_2Me$ (*S*)	Me	2.28	1.70	5.96	2.65	6.94	8.29
1b	$CH(CH_2Ph)CO_2Me$ (*S*)	Me	1.45	2.50	5.98	2.65	6.82	8.29
1c	Me	$CH(CH_2Ph)CO_2Me$ (*S*)	1.56	2.36	3.27	4.26	6.86	8.34[d]
1d	Me	$CH(CH_2Ph)CO_2Me$ (*S*)	2.18	1.95	3.25	4.23	7.00	8.36
5	Me	Me	2.23	2.44	3.15	2.81	6.92	8.28
6a	$CHMe_2$	Me	2.24	2.46	5.11	2.63	6.99	8.35
6b	Me	$CHMe_2$	2.27	2.48	3.02	3.63	7.00	8.36
7	$CHMe_2$	$CHMe_2$	2.27	2.49	3.56	3.56	6.96	8.30
8	$CHMe_2$	H	2.29	2.50	4.32		6.92	8.29
9	$CH(CH_2Ph)CO_2Me$ (*S*)	H	2.08	2.30	5.15		6.85	8.22

[a] In $CDCl_3$, in ppm. [b] In *N,N*-dimethylacetamide the syn *N*-methyl protons are found at higher field than the corresponding anti protons (2.9 vs 3.1 ppm),[14] while in *N,N*-diisopropylacetamide the same holds for the methine protons (3.52 vs 3.93 ppm). In *N*-methyl-*N*-isopropylacetamide, however, the methine proton of the syn isomer resonates at lower field than that of the anti isomer (4.52 vs 3.92 ppm)![12] [c] In compounds **1a–d** and **9** the protons are numbered: C-2′ and C-4′ Me, H-5′ and H-6′. [d] Structures **1c** and **1d** are assigned tentatively.

Moreover, and comparable to the behavior of optically active **5**,[6a] rotational isomerism around the C-3′–CO bond in the diastereomers **1a** and **1b** took place slowly at room temperature in $CDCl_3$ or C_6D_6 ($t_{1/2} \sim 14$ days). In CF_3CO_2D no appreciable isomerization occurred within a month.[6b] Upon heating at reflux temperature in CD_3CN, however, fast isomerization occurred to afford a ~1:1 mixture of **1a** and **1b** (30 min). On the basis of these observations, a procedure was developed for the high yield conversion of the mixture **1a–d** into pure **1a**. After amide formation, the reaction mixture was taken up in boiling diethyl ether to remove insoluble Et_3N·HCl and to complete concomitantly the anti → syn rotamerization. The resultant 1:1 mixture of **1a** and **1b** was concentrated and subsequently crystallized from diisopropyl ether to afford a solid 9:1 mixture of **1a** and **1b** from which pure **1a** could finally be obtained upon crystallization from diethyl ether at 0 °C. The mother liquors were recycled by using gradually diminishing quantities of diisopropyl ether as solvent. Thus, at a 1-g scale, pure amide **1a** was recovered in more than 60% yield from **3**. With the aid of HPLC also diastereomer **1b** could be isolated in high diastereomeric purity (98:2).

The nicotinamides **2a,b** derived accordingly from (*R*)-**4** and **3**. The next section deals with the conformational analysis of **1a** and its syn stereoisomers in solution.

2. Conformational Analysis of 1a and Its Syn Stereoisomers. Axial Chirality. The severe steric crowding around the C-3′–CO axis forces the pyridine and amide planes in **1** (and **2**) into a perpendicular arrangement and so induces atropisomerism.[7] The syn amides **1a** and **1b** are helical isomers with the CO UP (*M*) and CO DOWN (*P*) conformation, respectively. Judged from ^{1}H NMR data (i.e., relative integrations), in solution no appreciable energy difference exists between conformers **1a** and **1b**.

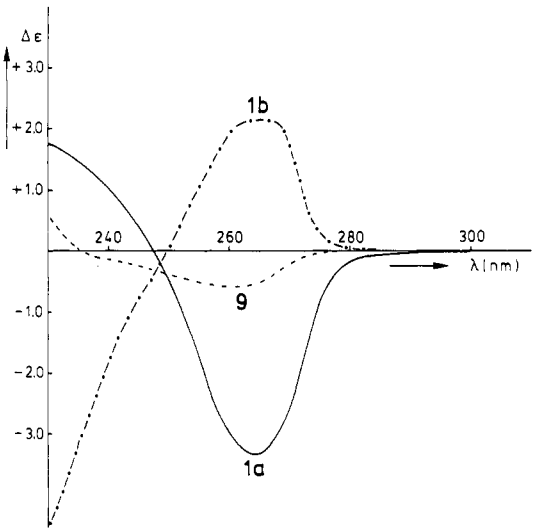


Figure 1. CD spectra of methyl *N*-(2′,4′-dimethylnicotinoyl)-L-phenylalaninates **1a**, **1b** and **9** in MeOH.

However, the former crystallized preferentially and featured the higher melting point and lower polarity. Secondary amide **9** (Table I), lacking the anti *N*-methyl substituent of **1**, by contrast, behaves at room temperature as a single molecule devoid of axial chirality.

The absolute conformation (*M* or *P*) of the amide dipole in **1a** and **1b** was determined by comparison with 2,4-dimethylnicotinamide derivatives of known helicity and containing a common anti *N*-methyl group but differing syn N substituent e.g., **5**, **10**, **11**, **12**.[3,6a,8] A positive Cotton effect was in every case associated with a CO DOWN or *P* conformation, a negative Cotton effect with a CO UP or *M* conformation.[3] Pure, crystalline diastereomer **1a** exhibited a negative Cotton effect [$\Delta\epsilon$ (265 nm) −3.3 (MeOH)], while **1b** featured a positive Cotton effect ($\Delta\epsilon \approx +2.1$). The difference in absolute magnitude of these Cotton effects may be explained by the small contribution to $\Delta\epsilon$ of the *S* chirality at C-2. Indeed, for compound **9** (Table I), lacking stable axial chirality, a $\Delta\epsilon$ (260 nm) ≈ −0.6 was measured (Figure 1). Therefore, amide **1a** was assigned the *M* helicity and its more polar diastereomer

(6) (a) Van Lier, P. M.; Meulendijks, G. H. W. H.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 337. (b) It has been established previously that, at room temperature, optically active **5** undergoes fast racemization in *n*-hexane ($t_{1/2} < 1$ h), while it loses its optical purity only slowly in water ($t_{1/2} > 1$ month) (ref 6a). The more important contribution of the dipolar mesomeric form of the amide in polar solvents lowers the rate of rotamerization (Jackman, L. M.; Kavanagh, T. E.; Haddon, R. C. *Org. Magn. Reson.* **1969**, *1*, 109). This may also diminish the probability for $P \rightleftharpoons M$ interconversion in dimethylnicotinamides **1**, **2**, and **5**, if one assumes—for steric reasons—that the latter is accompanied by rotation around the amide C–N bond. Moreover, the volume of the amide group may be affected in protic solvents by hydrogen bonding. Additional N-1′ protonation in the presence of the strong proton donor CF_3CO_2H may ultimately prevent helical isomerization of **1a,b** (**2a,b**).

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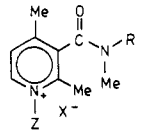
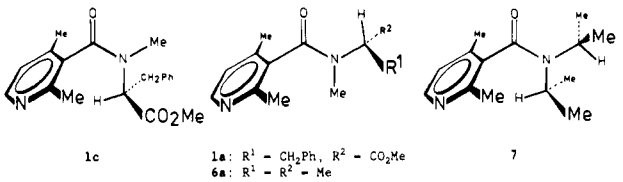
1b the *P* helicity. Evidently **2a**, being enantiomeric to **1a**, exhibited the positive Cotton effect ($\Delta\epsilon \approx +3.3$) required for a CO DOWN or *P* conformation.



10: Z = H, X = Cl, R = CH(Me)Ph
11: Z = Me, X = I, R = Me
12: Z = Me, X = I, R = CH(Me)Ph

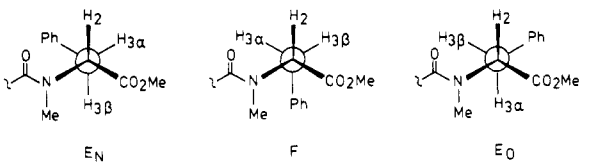
Syn–Anti Rotamerism. Hindered rotation in amides, brought about by the contribution of the dipolar, mesomeric structure, has been studied extensively by ^{1}H NMR spectroscopy.[9] In tertiary 2,4-dimethylnicotinamides (e.g., **1**, **2**, **5**, **6**, **7**), the barrier to rotation about the C–N axis is enhanced by the presence of two locking ortho substituents[10] on the aromatic ring and the absence of cross conjugation between perpendicularly arranged amide and aromatic ring.[9] In the case of nonsymmetric tertiary amides, e.g., **6a,b** (Table I), a complete set of signals for each rotamer becomes visible in ^{1}H NMR. The thermodynamic preference for a particular isomer is —except for formamides—inversely proportional to the degree of steric interaction between the carbonyl substituent and the amide anti N substituent.[9,11] Inspection of the molecular models leaves no doubt that in the anti isomers **1c,d** the 2,4-dimethyl-substituted pyridine ring and the bulky *N*-1-carbomethoxy-2-phenylethyl group suffer from severe van der Waals interactions. As exemplified in Figure 2 for **1c**, the C-2–H bond will be located preferentially parallel to the C-3′–CO bond and any deviation therefrom by rotation around the N–C-2 bond will enhance steric repulsion. This could account for the transformation **1c,d** → **1a,b**. Further proof for the correct attribution of syn or anti conformation in **1a–d** is offered by ^{1}H NMR data concerning N–C-*H* chemical shifts (vide infra).

Rotation around the N–C-2 Axis. It has been established that, due to the anisotropy induced by amide functions and the rotation around the N–C bonds, the relative position of syn and anti N–CH_x protons cannot be used as an a priori criterion for the assignment of the amide conformation.[12] For amidic *N*-methyl protons the δ values observed represent the arithmetic mean of chemical shifts corresponding to the possible conformers; those found for methine protons—as in **1** and **2**—are, however, a weighted mean of shifts corresponding to the relative population of the (staggered) conformers.[9] In the latter case the average dihedral angle between the amide CO and the considered C–H bond is decisive for either a downfield or an upfield shift.[13] Inspection of the ^{1}H NMR data concerning the N substituents of various nicotinamides (Table I, entries 1–9) reveals a seemingly anomalous pattern in the chemical shifts assigned to N–CH_x protons of syn or anti conformers. When, however, these results are compared with those obtained for corresponding acetamides[12,14] and are compensated for the moderate shielding exerted onto the anti N–CH_x protons by the pyridine ring, all results fit. While syn *N*-methyl protons in acetamides are found at higher field than the corresponding anti protons ($\Delta \sim 0.2$ ppm), the reverse is true



1c 1a: R^1 = CH_2Ph, R^2 = CO_2Me 6a: R^1 = R^2 = Me 7

Figure 2. Preferred N–C–H orientations in nicotinamides **1c**, **1a**, **6a**, and **7**.



E_N F E_O

Figure 3. Staggered conformations along the C-2–C-3 axis in **1a**.

in the 2,4-dimethylnicotinamide series (**1a–d**, **5**, **6a,b**). In *N*-methyl-*N*-isopropyl (**6a,b**) or *N*-methyl-*N*-(1-carbomethoxy-2-phenylethyl) derivatives (**1**), the syn isomers have their methine group orientated preferentially syn and coplanar to the amide carbonyl, resulting in a marked deshielding (δ 5.11 and ~5.95, respectively)[15] (Figure 2). In the anti isomers, the methine protons are preferentially directed to the pyridine ring and are therefore subjected to additional shielding (δ 3.63 and ~4.25 in **6b** and **1c,d**, respectively). These considerations explain why the syn and anti *N*-methyl protons are only separated by ~0.35–0.6 ppm while the methine protons differ by ~1.5 and 1.7 ppm in **6a,b** and **1a–d**, respectively. In diisopropyl derivative **7** the conformational preferences for the syn and anti substituents cannot be reconciled and the anti substituent dominates since any deviation from a conformation in which the methine proton is directed to the pyridine ring enhances the van der Waals interaction between the C-2 or C-4 methyl and one of the anti *N*-isopropyl methyl groups. The syn methine proton cannot, therefore, occupy a position similar to that in **6** or **1** without causing two unfavorable syn 1,3-diaxial (eclipsed) interactions. All four methyl groups are accommodated in a 1,3-staggered disposition by turning the syn isopropyl group over 120°. The overall result is that both methine protons in **7** are coinciding at 3.56 ppm.

From all these data it can safely be concluded that the isomers to which we assigned structures **1a** and **1b** are indeed syn rotamers and that in these isomers a strong preference exists for the syn orientation of the C-2–H bond and the amide carbonyl. This has far-reaching consequences for defining the preferred molecular conformation of **1a,b** and **2a,b**.

Conformation around C-3. At last we will discuss the rotational preference around the benzylic carbon C-3, considering three staggered conformers F (folded), E_O (extended to oxygen), and E_N (extended to nitrogen)[16] (Figure 3). The marked nonequivalence of H-3α and H-3β in ^{1}H NMR (Table II, $\Delta\delta$ = 0.57 ppm) and the exceptionally high difference in coupling constant ($^3J_{2,3\alpha}$ = 4.8; $^3J_{2,3\beta}$ = 12.4 Hz) suggest a strong preference for one conformer. The sum of both vicinal coupling constants (17.2 Hz) is indicative for the unimportance of the folded conformer (two gauche couplings). This is presumably due to an unfavorable syn 1,3-diaxial interaction between the phenyl ring and the *N*-methyl group. The diastereoselective synthesis of 3-deuteriophenylalanines (and *N*-

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Table II. Restricted Rotational Freedom around C-3 in Some *syn*-*N*-Acylphenylalanine Derivatives[a]

entry	H-3α	H-3β	Δδ	$J_{2,3\alpha}$	$J_{2,3\beta}$	ΔJ	ΣJ
1a	3.61	3.04	0.57	4.8	12.4	7.6	17.2
1b	3.61	3.03	0.58	4.8	12.4	7.6	17.2
$MeCOCH_2CON(Me)CH(CH_2Ph)CO_2Me$[b] (L)	3.37	3.05	0.32	5.3	11.1	5.8	16.4
9	3.33	3.01	0.32	5.1	9.0	3.9	14.1
$MeCONHCH(CH_2Ph)CO_2Me$[c] (L)	2.97	2.82	0.15	5.9	8.8	2.9	14.7
$CF_3CONHCH(CH_2Ph)CON(Me)CH(Me)CO_2Me$[d] (LL-syn)	3.18	3.02	0.16	6.0	6.9	0.9	12.9
(DL-anti)	3.20	3.06	0.14	6.0	6.9	0.9	12.9

[a] In $CDCl_3$ (^1H NMR data). Chemical shifts are in ppm; J values are in hertz. [b] Reference 21. [c] Reference 22. [d] Reference 16.

Table III. Comparative ASIS Data for 2,4-Dimethylnicotinamides 1a,b and 5[a,b]

entry	solvent		C-2 Me	C-4 Me	Δδ	NMe anti	NCH_x syn	H-5	H-6[c]
1a	$CDCl_3$		1.70	2.28	-0.58	2.65	5.96	6.94	8.29
	C_6D_6		1.95	2.13	-0.18	2.24	5.98	6.47	8.30
		Δδ	-0.25	0.15		0.41	-0.02	0.47	-0.01
1b	$CDCl_3$		2.50	1.45	1.05	2.65	5.98	6.82	8.29
	C_6D_6		2.70	1.35	1.35	2.23	5.98	6.41	8.30
		Δδ	-0.20	0.10		0.42	0.00	0.41	-0.01
5	$CDCl_3$		2.44	2.23	0.21	2.81	3.15	6.92	8.28
	C_6D_6		2.47	1.91	0.56	2.07	2.70	6.41	8.24
		Δδ	-0.03	0.32		0.74	0.45	0.51	0.04

[a] Expressed in ppm. [b] Concentration 0.2 M. [c] In compounds **1a,b** the protons are indicated as C-2′ and C-4′ Me, H-5′, and H-6′.

benzoyl derivatives) allowed the unambiguous assignment of the diastereotopic methylene protons in unlabeled material.[17] In the L isomers the upfield methylene proton (H-3β) corresponds to the *pro-R* proton and features the larger vicinal coupling constant (J = 8 ± 1 Hz vs 5.5 ± 1 Hz for H-3α). This means that the E_N rotamer predominates in solution. All aforementioned data together allow the assignment of the high-field signal in **1a,b** (H-3β) to the *pro-R* proton (large ^3J value) and imply that the E_N rotamer is by far the most abundant staggered conformer. Using various sets of described parameters,[18] consistently a high (>80%) E_N population and a negative F population were calculated. The introduction of slightly enhanced values for J_a (14.43 vs 13.56 Hz) and J_g (2.77 vs 2.60 Hz), as compared to Pachler's parameters,[18a] gave calculated populations of 82, 18, and 0% for the E_N, E_O, and F conformers. The large preference for the E_N conformation can partly be rationalized by assuming some attractive interactions between the amide $N^{\delta+}$ and either the phenyl ring[16] or an ester oxygen or both. In itself it provides a rationale for the relative shielding observed for either the C-2′ methyl protons in **1a** (**2a**) or the C-4′ methyl protons in **1b** (**2b**) (Table I).

3. Molecular Conformation of 1a,b and 2a,b. ^1H NMR Data. On the basis of all preceding conformational data gathered for **1a,b** (**2a,b**), the proposition of a preferred molecular conformation in solution seems to be justified. In these syn amides, a phenyl ring is directed preferentially toward the pyridine ring (Figure 4) and is so responsible for the selective and large shielding effect that either the C-2′ (**1a**, **2a**) or the C-4′ (**1b**, **2b**) methyl protons undergo. As clarified in section 2, in all compounds the proton at the chiral center C-2 is located nearly coplanar and syn with the amide carbonyl dipole. Having determined the conformational preferences at C-2 and C-3, it follows that further proof is given for the absolute helical conformation

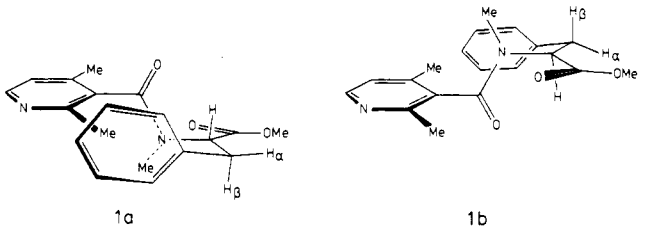

Figure 4. Preferred molecular conformations of **1a** and **1b**.

in **1a,b** and **2a,b** as it was deduced earlier from the sign of the Cotton effect (vide supra). Also ASIS (anisotropic solvent induced shift) measurements in C_6D_6 corroborate the foregoing results. Indeed, as depicted in Table III, the replacement of $CDCl_3$ by C_6D_6 shows that in the *N,N*-dimethyl derivative **5**, only the C-2 methyl protons feature deshielded signals, in accordance with their close vicinity to the negative side of the pyridine dipole. In **1a** the replacement of $CDCl_3$ by C_6D_6 causes the C-4′ and C-2′ methyl proton signals to approach each other (Δδ 0.58 → 0.18 ppm), indicating that the original signal at 1.70 ppm indeed corresponds to the C-2′ methyl group. Conversely in **1b**, the singlets corresponding to the C-2′ and C-4′ methyl groups are more remote in C_6D_6 (Δδ 1.05 → 1.35 ppm), proving that the original signal at 2.50 ppm belongs to the C-2′ methyl protons of **1b**. Interestingly, it was also observed that the C-2-*H* absorptions in **1a,b** (**2a,b**) were barely affected by replacement of $CDCl_3$ through C_6D_6 in contrast to the usual moderate to large shieldings of other amide N substituents (cf. the *N*-methyl groups in Table III).[14] An orientation as proposed by our conformational considerations counterbalances the shielding effect of C_6D_6 by positioning C-2-*H* at the negative side of the carbonyl dipole.

^{13}C NMR Data of 1a and 1b. Also ^{13}C NMR spectra of **1a** and **1b** reveal straightforward differences between both diastereomers. Especially relevant are the relative positions of the signals attributed to the C-2′ and C-4′ methyl carbons: while, with respect to **5**, the C-2′ methyl carbon in **1a** is shielded by 0.8 ppm (δ 21.4 vs 22.2), the same shielding is observed for the C-4′ methyl carbon in **1b** (δ 17.8 vs 18.6). No difference exists between the C-4′ (C-4) methyl carbons of **1a** and **5** or the C-2′ (C-2) methyl carbons of **1b** and **5**. Transmission of the shielding effect

(17) (a) Wightman, R. H.; Staunton, J.; Battersby, A. R.; Hanson, K. R. *J. Chem. Soc., Perkin Trans. I* **1972**, 2355. (b) Kirby, G. W.; Michael, J. *J. Chem. Soc., Perkins Trans. I* **1973**, 115. (c) Trimble, L. A.; Reese, P. B.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *107*, 2175. (d) Matteson, D. S.; Beedle, E. C.; Christenson, E.; Dewey, M. A.; Peterson, M. L. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 675.

(18) (a) Pachler, K. G. R. *Spectrochim. Acta* **1964**, *20*, 581. (b) Kopple, K. D.; Wiley, G. R.; Tauke, R. *Biopolymers* **1973**, *12*, 627. (c) Chu, Y.-H.; Wang, K.-T. *Magn. Reson. Chem.* **1985**, *23*, 450.

to C-2′ and C-4′ is also observed: whereas Δδ C-2–C-4 amounts to 10.2 ppm in **5**, differences of 9.75 ppm in **1a** and 10.4 ppm in **1b** were found for the corresponding signals. The degree of shielding at the methyl carbons is of equal magnitude as that observed in ^{1}H NMR for the corresponding protons.

Difference in Polarity between 1a (2a) and 1b (2b). The difference in polarity between the less polar syn amides **1a** and **2a** (R_f 0.17) and their more polar diastereomers **1b** and **2b** (R_f 0.12) can be correlated with the proposed molecular conformation of these compounds. Indeed, dipoles can be considered directed toward N-1′ in the pyridine ring and toward the ester function in the phenylalanine moiety. It is obvious that these dipoles are opposed in **1a** (**2a**) and parallel in **1b** (**2b**), in full accord with the observed relative polarities.

Interlocking Effect of the Anti *N*-Methyl Group. Finally, the dramatic effect of the presence of an anti *N*-methyl group in **1a,b** and **2a,b** on the molecular conformation will be discussed by comparison with the analogue **9** (Tables I and III) lacking this *N*-methyl group.

Through anti N-methylation, the 2′,4′-dimethylnicotinoyl group is locked, and two stable helical isomers are created. Moreover, it influences the conformations at the chiral center and at the benzylic carbon to a large extent. This is clearly reflected in the selective C-2′ and C-4′ methyl proton shieldings in **1a,b**, when compared with **5**. In **9**, however, no stable axial chirality is present and a small mean shielding (Δ ~0.2 ppm) is exerted on both the C-2′ and C-4′ methyl protons. The relative upfield position of the N-C-*H* proton in **9** (5.15 vs ~5.95 ppm in **1a,b**) and the smaller difference in vicinal coupling constant and δ value of the benzylic protons ($^3J_{2,3\alpha}$ = 5.1, $^3J_{2,3\beta}$ = 9.0 Hz; Δδ = 0.32 ppm) when compared with $^3J_{2,3\alpha}$ = 4.8, $^3J_{2,3\beta}$ = 12.4 Hz and Δδ = 0.57 ppm in **1a,b**, further substantiate the difference in conformational freedom between **1a,b** and **9**. It is certainly not meaningless that crystal structures of a series of *anti*-*N*-methyl-2,4-dimethylnicotinamides, e.g., **10**[8a] and **12**,[3] all display a conformation at the syn N substituent in which the C-H group is nearly coplanar and syn orientated with respect to the amide carbonyl. Therefore, we believe that the conformational behavior of the amides **1a,b** and **2a,b** in solution will closely parallel that in the solid phase.[19]

The effect of *N*-methylation on the structure of peptidic systems has been mentioned previously[16,18c,20] but was never so dramatic as in the case described here.

Concluding Remarks

It has been shown that the *syn*-*N*-(2′,4′-dimethylnicotinoyl)-*N*-methylphenylalaninates **1a,b** and **2a,b** possess at room temperature a strongly preferred molecular conformation in solution and could be obtained as pure, crystalline materials. The behavior of these compounds in solution provides a clear example of the major influence that a small group, e.g., a methyl group, may exert on the spatial structure of a molecule. The aforementioned molecules and analogues therefrom might be useful precursors for appropriate NAD$^+$ or NADH models. The stereo- and regiocontrolled positioning of the phenyl ring and the carbomethoxy group perhaps could be tools in the elaboration of stereo- and regioselective reactions onto the—eventually modified—pyridine ring. For example, after transformation to a pyridinium system, it is not excluded that the isomer derived from **1b**, having located the phenyl ring near C-4′ at the β side of the pyridine ring, behaves differently toward sodium dithionite or other reductants than that derived from **1a**, where the phenyl ring resides in the vicinity of C-2′ and at the α side of the pyridine ring. Ultimately, the design of a NAD$^+$-NADH model, provided with a high, reversible, and stereoselective activity, may be facilitated by taking advantage of restricted conformational freedom in solution.

Experimental Section

General Methods. Column chromatographic separations were performed on silica gel (63–200 μm) and TLC analyses on aluminum sheets precoated with silica gel. Preparative HPLC was realized on a column (120 × 16 mm) loaded with Lichrosorb 5μ and eluted at a rate of 15 mL/min. Melting points are uncorrected.

2,4-Dimethylnicotinoyl Chloride Hydrochloride (3).[4] Acid chloride **3** was obtained from crotonaldehyde and ethyl β-aminocrotonate in four steps.[4b]

Methyl *N*-Methyl-L-phenylalaninate Hydrochloride ((*S*)-4). The title compound was prepared from *N*-methyl-L-phenylalanine according to the description of Warnke and Young[5a] on a 10-mmol scale. The crude reaction mixture was triturated with diethyl ether–2-propanol (9:1, 10 mL) to afford white, solid (*S*)-**4** (1.65 g, 72%). Recrystallization from diisopropyl ether–acetone (1:1, 20 mL) gave analytically pure (*S*)-**4** (1.46 g, 64%): mp 116–117 °C [lit.[5a] mp 86–87 °C (MeOH); lit.[5b] mp 136 °C (acetone)]. $[\alpha]^{20}_D$: +56° (*c* 1, $CHCl_3$) [lit.[5a] +59° ($CHCl_3$); lit.[5b] +19° ($CHCl_3$)]. ^{1}H NMR ($CDCl_3$): δ 2.77 (s, 3 H, NMe), 3.38 (dd, *J* = 13.75 and 9.1 Hz, 1 H, H-3α), 3.68 (dd, *J* = 13.75 and 5.4 Hz, 1 H, H-3β), 3.68 (s, 3 H, CO_2Me), 4.09 (dd, *J* = 5.4 and 9.1 Hz, 1 H, H-2), 7.2–7.35 (m, 5 H, Ar H), 9.9 (bs, 1 H, NH_β), 10.4 (bs, 1 H, NH_α). ^{13}C NMR ($CDCl_3$): δ 31.6 (CH_2), 35.2 (NMe), 52.4 (OMe), 61.9 (CH), 127.1 (C-4′ Ar), 128.3 (C-3′, C-5′ Ar), 128.8 (C-2′, C-6′ Ar), 134.0 (C-1′ Ar), 167.8 (CO). Anal. Calcd for $C_{11}H_{16}ClNO_2$ (MW 229.71): C, 57.52; H, 7.02; N, 6.10. Found: C, 57.8; H, 7.4; N, 6.1.

Methyl *N*-Methyl-D-phenylalaninate Hydrochloride ((*R*)-4). Compound (*R*)-**4** was prepared and purified in the same way as described for its enantiomer (*S*)-**4** (vide supra). Analytically pure (*R*)-**4** was obtained in 62% yield, mp 115–117 °C. $[\alpha]^{20}_D$: −55° (*c* 1, $CHCl_3$). The ^{1}H NMR and ^{13}C NMR spectra were superimposable with those of (*S*)-**4**. Anal. Found for $C_{11}H_{16}ClNO_2$: C, 57.5; H, 6.9; N, 6.1.

Methyl *N*-(2′,4′-Dimethylnicotinoyl)-*N*-methyl-L-phenylalaninates 1a–d. A suspension of (*S*)-**4** (600 mg, 2.61 mmol) in cold dichloromethane (24 mL) was brought to dissolution with triethylamine (1.12 mL, 792 mg, 7.83 mmol). Then, while cooling in an ice bath and stirring, acid chloride **3** (538 mg, 2.61 mmol) was added portionwise. After 2 h of reaction, 3 volumes of ice-cold diethyl ether were added, triethylammonium chloride was removed by extraction with ice–water, and the dried ($MgSO_4$) organic phase was concentrated in vacuo at 0 °C. The residue (0.81 g, 95%) was then subjected to ^{1}H NMR spectroscopy, showing the presence of four components: **1a,b** (syn isomers) and **1c,d** (anti isomers) in a 3:3:1:1 ratio. ^{1}H NMR ($CDCl_3$) (Tables I, II, and III), **1a**: δ 3.84 (s, 3 H, CO_2Me), 7.2–7.45 (m, 5 H, Ar H), $J_{3,3'}$ = 15.0 Hz, $J_{5',6'}$ = 5.1 Hz. **1b**: δ 3.84 (s, 3 H, CO_2Me), 7.2–7.45 (m, 5 H, Ar H), $J_{3,3'}$ = 15.0 Hz, $J_{5',6'}$ = 5.1 Hz. **1c**: δ ~3.05 (H-3β), ~3.60 (H-3α), 3.71 (s, 3 H, CO_2Me), 7.2–7.45 (m, 5 H, Ar H), $J_{5',6'}$ = 5.1 Hz. **1d**: ~3.05 (H-3β), ~3.60 (H-3α), 3.68 (s, 3H, CO_2Me), 7.2–7.45 (m, 5 H, Ar H), $J_{5',6'}$ = 5.1 Hz. H-3α and H-3β in **1c** and **1d** are masked by the equivalent signals of **1a,b**. At

(19) Recent solid-phase ^{13}C NMR data corroborate the results found for **1a** (**2a**) and **1b** (**2b**) in solution. The diastereomers differ markedly in the chemical shifts of their C-2′, C-4′, C-2′ methyl, and C-4′ methyl carbons, respectively. Conversely, secondary amide **9**, which behaves as a single compound in solution, shows axial chirality in the solid phase, as judged from the splitting of both the C-2′ and C-4′ methyl carbon signals.

(20) (a) Tonelli, A. E. *Biopolymers* **1976**, *15*, 1615. (b) Vitoux, B.; Aubry, A.; Cung, M. T.; Marraud, M. *Int. J. Pept. Protein Res.* **1986**, *27*, 617.

(21) Obtained as major (~65%) together with the corresponding enol tautomer (~20%) and the anti keto rotamer (~15%) upon treatment of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one with dehydrochlorinated (*S*)-**4** in xylene at 150 °C (unpublished result).

(22) Nicolai, N.; Tiezzi, E. *J. Phys. Chem.* **1979**, *83*, 3249.

room temperature an anti → syn rotamerization occurred as indicated by the disappearance within a few hours of the NMR signals attributed to **1c** and **1d**. Ultimately a 1:1 mixture of **1a** and **1b** was obtained (0.81 g, 95%).

Methyl (3′*M*)-*syn*-*N*-(2′,4′-Dimethylnicotinoyl)-*N*-methyl-L-phenylalaninate (1a). The mixture of **1a,b** (810 mg, 2.48 mmol, vide supra) was dissolved in boiling diethyl ether (~15 mL) and then allowed to crystallize at 0 °C. Transparent needles (210 mg, 27%, **1a:1b** = 10:1) were isolated. The concentrated mother liquor (**1a:1b** ~ 1:2) was taken up in diisopropyl ether (15 mL) and heated under reflux for 30 min. Upon cooling solid material precipitated (141 mg, 17% **1a:1b** = 9:1). After filtration, the remaining solution was repeatedly subjected to the same procedure with gradually diminishing quantities of diisopropyl ether (12, 9, and 6 mL) to afford more solid material enriched in **1a** (254 mg, 31%, **1a:1b** = 9:1). A final recrystallization of the combined precipitates (614 mg, 76%) from diethyl ether gave analytically pure **1a** (366 mg, 45%, **1a:1b** ≥ 99): mp 132–133 °C. $\Delta\epsilon$ (265 nm, MeOH): −3.34. $[\alpha]^{20}_D$: −84° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$), Tables I–III and foregoing modus; (C_6D_6) (Table III), δ 2.76 (dd, J = 14.8 and 12.3 Hz, 1 H, H-3β), 3.35 (s, 3 H, CO_2Me), 3.38 (dd, J = 14.8 and 4.7 Hz, 1 H, H-3α), 6.9–7.35 (m, 5 H, Ar H), $J_{5',6'}$ = 5.1 Hz. ^{13}C NMR (CD_3CN): δ 18.55 (C-4′ *Me*), 21.4 (C-2′ *Me*), 32.75 (C-3), 34.7 (NMe), 52.9 (OMe), 57.4 (C-2), 123.45 (C-5′), 127.7 (*p*-Ph C), 129.5–130.0 (*o*- and *m*-Ph C), 132.8 (C-3′), 138.2 (ipso Ph C), 144.4 (C-4′), 149.5 (C-6′), 154.15 (C-2′), 170.9 (COO), 171.8 (CON). Anal. Calcd for $C_{19}H_{22}N_2O_3$ (MW 326.40): C, 69.92; H, 6.79; N, 8.58. Found: C, 70.1; H, 7.0; N, 8.8.

Methyl (3′*P*)-*syn*-*N*-(2′,4′-Dimethylnicotinoyl)-*N*-methyl-L-phenylalaninate (1b). The combined mother liquors, obtained from the production of **1a** (444 mg, vide supra, **1a:1b** > 1), were evaporated in vacuo and subsequently heated under reflux in acetonitrile (10 mL) for 30 min to induce $M \rightarrow P$ isomerization. The resultant 1:1 mixture of **1a** and **1b** was then subjected to HPLC (CH_2Cl_2–MeOH, 98:2) to afford **1a** (101 mg, 12%) as the less polar fraction (R_f = 0.165), a mixture **1a,b** (204 mg, 25%), and **1b** (97 mg, 12%) as the more polar fraction (R_f = 0.125). Final trituration of the latter fraction with diisopropyl ether (3 × 1 mL) gave analytically pure **1b** (63 mg, 8%, **1b:1a** ≥ 50): mp 111–113 °C. $\Delta\epsilon$ (265 nm, MeOH): +2.07. $[\alpha]^{20}_D$: −95° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$) Tables I–III and preparation **1a–d** (vide supra); (C_6D_6) (Table III) δ 2.77 (dd, J = 14.8 and 12.3 Hz, 1 H, H-3β), 3.35 (s, 3 H, CO_2Me), 3.38 (dd, J = 14.8 and 4.7 Hz, 1 H, H-3α), 6.9–7.3 (m, 5 H, Ar H), $J_{5',6'}$ = 5.1 Hz. ^{13}C NMR (CD_3CN): δ 17.8 (C-4′ *Me*), 22.15 (C-2′ *Me*), 32.6 (C-3), 34.7 (NMe), 52.9 (OMe), 57.3 (C-2), 123.5 (C-5′), 127.7 (*p*-Ph C), 129.5–130.0 (*o*- and *m*-Ph C), 132.8 (C-3′), 138.2 (ipso Ph C), 144.05 (C-4′), 149.5 (C-6′), 154.45 (C-2′), 170.85 (COO), 171.8 (CON). Anal. Calcd for $C_{19}H_{22}N_2O_3$ (MW 326.40): C, 69.92; H, 6.79; N, 8.58. Found: C, 69.9; H, 6.8; N, 8.5.

Methyl (3′*P*)-*syn*-*N*-(2′,4′-Dimethylnicotinoyl)-*N*-methyl-D-phenylalaninate (2a) and Methyl (3′*M*)-*syn*-*N*-(2′,4′-Dimethylnicotinoyl)-*N*-methyl-D-phenylalaninate (2b). A stirred solution of (*R*)-**4** (345 mg, 1.50 mmol) in dichloromethane (15 mL) was cooled in an ice bath and consecutively treated with triethylamine (0.64 mL, 455 mg, 4.50 mmol) and acid chloride **3** (309 mg, 1.50 mmol). Subsequent reaction at room temperature for 1.5 h, evaporation of the solvent, extraction of the residue with boiling, dry diethyl ether (3 × 20 mL), and concentration of the combined ethereal solutions afforded crude **2a,b** as a 1:1 mixture (^1H NMR) (453 mg, 92.5%). This material was prepurified by column chromatography (SiO_2 20 g; CH_2Cl_2–MeOH, 96:4) and then subjected to preparative HPLC (CH_2Cl_2–MeOH, 98:2) to afford a less polar fraction (R_f = 0.165) containing **2a** (99 mg, 20%), an interfraction (136 mg, 28%), and a more polar fraction containing **2b** (92 mg, 19%). Final trituration of both **2a** and **2b** with diisopropyl ether (3 and 2 mL, respectively) gave analytically pure material (**2a**, 85 mg, 17%; **2b**, 69 mg, 14%). Repeated HPLC separations allowed the recovery of **2a** and **2b** in almost double yield. Compound **2a**: mp 134–135 °C. $\Delta\epsilon$ (265 nm, MeOH): +3.28. $[\alpha]^{20}_D$: +85° (*c* 1, $CHCl_3$). ^1H NMR and ^{13}C NMR: cf. **1a**. Anal. Calcd for $C_{19}H_{22}N_2O_3$ (MW 326.40): C, 69.92; H, 6.79; N, 8.58. Found: C, 69.4; H, 6.75; N, 8.4. Compound **2b**: mp 111–113 °C. $\Delta\epsilon$ (265 nm, MeOH): −2.14. $[\alpha]^{20}_D$ +96° (*c* 1, $CHCl_3$). ^1H NMR and ^{13}C NMR: cf. **1b**. Anal. Found for $C_{19}H_{22}N_2O_3$: C, 69.9; H, 6.8; N, 8.4.

***N,N*,2,4-Tetramethylnicotinamide (5).**[6a,10] Compound **5** was obtained from acid chloride **3** and dimethylamine.[6a] ^1H NMR: Tables I and III. ^{13}C NMR (CD_3CN): δ 18.6 (C-4 *Me*) 22.2 (C-2 *Me*), 34.2 (NMe syn), 37.6 (NMe anti), 123.45 (C-5), 133.5 (C-3), 144.0 (C-4), 149.4 (C-6), 154.25 (C-2), 169.7 (CO).

***syn*- and *anti*-*N*-Isopropyl-*N*,2,4-trimethylnicotinamide (6a and 6b).** A cooled (0 °C) solution of acid chloride **3** (2.58 g, 12.5 mmol) in dichloromethane (20 mL) was treated dropwise in 30 min with a solution of isopropylmethylamine (3.65 g, 50 mmol) in dichloromethane (10 mL). Then, the reaction was continued at room temperature for 3 h, whereafter the solvent and the excess isopropylmethylamine were removed in vacuo. The residue was repeatedly extracted with diethyl ether (3 × 25 mL) and the combined ethereal layers were concentrated to a yellow-brown oily residue (2.55 g, 99%), solidifying upon overnight cooling at 0 °C. Recrystallization from diisopropyl ether furnished pure syn isomer **6a** (1.81 g, 71%), mp 85–87 °C, devoid of anti isomer **6b**. ^1H NMR **6a** ($CDCl_3$): (Table I), δ 1.24 (d, J = 6.8 Hz, 3 H, CH-*Me*β), 1.25 (d, J = 6.8 Hz, 3 H, CH-*Me*α), $^3J_{5,6}$ = 5.1 Hz. ^{13}C NMR (CD_3CN): δ 18.5 (C-4 *Me*), 22.1 (C-2 *Me*), 19.3 (CH-*Me*β), 19.5 (CH-*Me*α), 29.2 (NMe anti), 44.7 (*C*HMe_2), 123.5 (C-5), 134.0 (C-3), 143.7 (C-4), 149.3 (C-6), 154.0 (C-2), 169.2 (CO). Anal. Calcd for $C_{12}H_{18}N_2O$ (MW 206.29): C, 69.87; H, 8.80; N, 13.58. Found: C, 70.1; H, 9.05; N, 13.35. Upon standing at room temperature in $CDCl_3$, new ^1H NMR signals appeared, belonging to anti isomer **6b**. At equilibrium ($t_{1/2} \simeq$ 12 h) a 5:4 ratio of **6a:6b** was attained, as judged from ^1H NMR integrations. ^1H NMR **6b** ($CDCl_3$): (Table I), δ 1.13 (d, J = 6.7 Hz, 3 H, CH-*Me*β), 1.16 (d, J = 6.6 Hz, 3 H, CH-*Me*α), $J_{5,6}$ = 5.1 Hz. ^{13}C NMR (CD_3CN): δ 19.1 (C-4 *Me*), 20.8 (CH-*Me*β), 21.0 (CH-*Me*α), 22.7 (C-2 *Me*), 25.7 (NMe syn), 50.6 (*C*HMe_2), 123.5 (C-5), 133.8 (C-3), 144.1 (C-4), 149.2 (C-6), 154.0 (C-2), 169.2 (CO).

***N,N*-Diisopropyl-2,4-dimethylnicotinamide (7).** Solid acid chloride **3** (4.12 g, 20 mmol) was added portionwise to stirred diisopropylamine (11.4 mL, 8.1 g, 80 mmol) at room temperature. Subsequently the reaction mixture was heated during 2.5 h at 80 °C and then evaporated to dryness. The residue was dissolved in 2 N HCl (60 mL), and the solution was decolorized with charcoal and filtered. Upon basification of the filtrate with ammonia (25%, 30 mL, ~300 mmol), the aqueous phase was extracted with dichloromethane (4 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to leave a brown oily residue. The latter was extracted with boiling hexane to afford—after concentration—pure, slightly yellow **7** (2.59 g, 55%). Analytical material was obtained as a monohydrate (2.19 g, 43%) by recrystallization from a small amount of boiling water: mp 98–99 °C. ^1H NMR (anhydrous **7**) ($CDCl_3$): (Table I), δ 1.15 (d, J = 6.7 Hz, 3 H, CH-*Me* anti β), 1.17 (d, J = 6.7 Hz, 3 H, CH-*Me* anti α), 1.58 (d, J = 6.8 Hz, 3 H, CH-*Me* syn β), 1.59 (d, J = 6.8 Hz, 3 H, CH-*Me* syn α) $J_{5,6}$ = 5.1 Hz. Anal. Calcd for $C_{14}H_{24}N_2O_2$ (MW 252.36): C, 66.63; H, 9.59; N, 11.10. Found: C, 67.0; H, 9.6; N, 11.2.

***N*-Isopropyl-2,4-dimethylnicotinamide (8).** To a stirred, cooled (−10 °C) solution of acid chloride **3** (4.12 g, 20 mmol) in dichloromethane (16 mL) were consecutively added solutions of triethylamine (5.71 mL, 4.04 g, 40 mmol) in dichloromethane (8 mL) and of isopropylamine (2.36 g, 40 mmol) in dichloromethane (8 mL). Then, the reaction was continued at room temperature for 2 h. Evaporation of the reaction mixture under reduced pressure and column chromatography of the residue (CH_2Cl_2–MeOH, 95:5, R_f(**8**) = 0.16) gave a viscous oil, which solidified on standing (3.50 g, 91%). Analytically pure **8** was obtained by crystallization from diethyl ether (3.03 g, 79%), mp 59–61 °C. ^1H NMR ($CDCl_3$): (Table I), δ 1.25 (d, J = 6.6 Hz, 6 H, CHMe_2), 6.13 (d, J = 6.9 Hz, 1 H, NH), $J_{5,6}$ = 5.1 Hz. Anal. Calcd for $C_{11}H_{16}N_2O$ (MW 192.26): C, 68.72; H, 8.39; N, 14.57. Found: C, 68.1; H, 8.6; N, 14.6.

Methyl *syn*-*N*-(2′,4′-Dimethylnicotinoyl)-L-phenylalaninate (9). A cooled (0 °C) suspension of methyl L-phenylalaninate hydrochloride (1.08 g, 5.0 mmol) in dichloromethane (30 mL) was brought to dissolution by adding triethylamine (2.14 mL, 1.51 g, 15 mmol). Subsequently solid acid chloride **3** (1.030 g, 5.00 mmol) was introduced portionwise (15 min) under stirring. The reaction was then continued at room temperature for 1.5 h. The resultant mixture was evaporated to dryness and the residue thoroughly extracted with diethyl ether

(3 × 50 mL). The combined ether fractions were concentrated to afford oily **9** (1.42 g, 91%), which after chromatographic purification (CH_2Cl_2–MeOH, 97:3, R_f = 0.23) gave solid **9** (1.15 g, 74%). Ultimately the material was triturated with diethyl ether: mp 100–101 °C. $\Delta\epsilon$ (260 nm, MeOH): −0.57. $[\alpha]^{20}_D$: +12.5° (*c* = 1, $CHCl_3$). ^1H NMR ($CDCl_3$): (Tables I and II), δ 3.80 (s, 3 H, CO_2Me), 6.70 (d, J = 8.4 Hz, 1 H, NH), 7.0–7.3 (m, 5 H, Ar H), $J_{3\alpha,3\beta}$ = 14.2 Hz, $J_{5',6'}$ = 5.1 Hz. Anal. Calcd for $C_{18}H_{20}N_2O_3$ (MW 312.37): C, 69.21; H, 6.45; N, 8.97. Found: C, 69.4; H, 6.8; N, 9.0.

Registry No. **1**, 129918-83-8; **2**, 129918-88-3; **3**, 67501-00-2; (*S*)-**4**, 19460-86-7; (*R*)-**4**, 130008-09-2; **5**, 55314-19-7; **6**, 129918-87-2; **7**, 129918-84-9; **8**, 129918-85-0; **9**, 129918-86-1; *i*-PrNHMe, 4747-21-1; $(i\text{-Pr})_2NH$, 108-18-9; *i*-$PrNH_2$, 75-31-0; H-Phe-OMe·HCl, 7524-50-7.

Preparation of Chiral Inducers Having the Bicyclo[3.1.1]heptane Framework. Assignment of Diastereomer Configuration by NMR and Comparison of Calculated and Observed Coupling Constants[1]

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Several bicyclo[3.1.1] compounds have been prepared for possible uses in asymmetric synthesis, including 10-phenyl-α-pinene and the diastereomeric (1*S*,2*S*,5*S*)-10-phenylmyrtanols. The geometry and NMR properties of bicyclo[3.1.1] compounds have been investigated by using molecular mechanics and NMR coupling constants.

Among commercially available resolved compounds having the bicyclo[3.1.1] framework, (+)- or (−)-α-pinene (**1a**, X = H) has been of exceptional importance in syntheses of chiral compounds. Its hydroboration product, diisopinocampheylborane, has been developed by Brown's group as a crystalline, readily prepared reagent, which hydroborates some *cis*-alkenes with high enantiomeric excess.[2] Boronate esters of pinanediol, obtained from α-pinene, have been used by Matteson's group to form a wide variety of compounds having one or more chiral centers, often with high stereoselection.[3] We are investigating applications to asymmetric synthesis of other available bicyclo[3.1.1] compounds, including (1*R*)-myrtenol (**1b**, X = OH) and (1*S*,2*S*,5*S*)-myrtanol (**2**). The geometry of these compounds is of interest to us, as is that of isopinocampheol (**3**), which is a compound having the approximate geometry of diisopinocampheylborane and its projected analogues.[4]

Two bicyclo[3.1.1] compounds whose NMR spectra were examined in the course of our synthetic studies showed sufficient separation of NMR peaks at 300 or 500 MHz to permit a preliminary estimate of most of the chemical shifts and coupling constants. Our experience has been that in these systems spectra that have minimal overlap are not often available, even at 500 MHz. Accordingly, we utilized these opportune spectra in conjunction with NMR simulation to provide the first complete assignments of J values in bicyclo[3.1.1] systems, so far as we can determine. In the case of the phenylmyrtanols (to be described), the assignment of chemical shifts permitted an interesting assignment of the configuration of diastereomers without resort to X-ray data.

We were prompted to compare the above-mentioned NMR coupling constants with those calculated by the program PCMODEL.[5] This program utilizes the MM2 force field[6] (or an extended version of it) to calculate energy-minimized structures from structures drawn on an IBM pc screen. In PCMODEL coupling constants are calculated by a complex elaboration of the Karplus relationship developed by Altona et al.[7] Our study provides some indication of the reliability and usefulness of the calculated J values and dihedral angles.

Synthetic Studies

Previous studies from our group have involved the asymmetric hydroboration–oxidation of vinyl ethers with diisopinocampheylborane.[8] When benzyl or diphenylmethyl vinyl ethers were used, the resulting ether–alcohols were readily cleaved to partially resolved 1,2-diols. We wished to prepare analogues of the above-mentioned ethers in which the benzylic moiety is chiral. Preliminary studies[9] showed that addition of phenyllithium or naphthylmagnesium bromide to (1*R*)-(−)-myrtenal gave diastereomeric alcohols of the desired type, which were separable with some difficulty by high performance liquid chromatography (HPLC). Although these alcohols are potentially convertible to vinyl ethers by acylation followed by Tebbe

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