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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-dihydroquinoline² and -pyridine³ 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 (Et₃N) 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.

In CDCl₃ 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 CDCl₃ 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*, 0.17, SiO₂, CHCl₃-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*, 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.

(1) Donkersloot, M. C. A.; Buck, H. M. *J. Am. Chem. Soc.* **1981**, *103*, 6554.

(2) Ohno, A.; Kashiwagi, M.; Ishihara, Y.; Ushida, S.; Oka, S. *Tetrahedron* **1986**, *42*, 961.

(3) De Kok, P. M. T.; Bastiaansen, L. A. M.; van Lier, P. M.; Vekemans, J. A. J. M.; Buck, H. M. *J. Org. Chem.* **1989**, *54*, 1313.

(4) (a) Ohno, A.; Ikeguchi, M.; Kimura, T.; Oka, S. *J. Am. Chem. Soc.* **1979**, *101*, 7036. (b) Van Hooff, H. J. G.; van Lier, P. M.; Bastiaansen, L. A. M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 191.

(5) (a) Warnke, J. G.; Young, G. T. *J. Chem. Soc., Perkin Trans. I* **1980**, 2797. (b) Sarfati, R.; Pais, M.; Jarreau, F. X. *Bull. Soc. Chim. Fr.* **1971**, 255.

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

entry	R ¹ (<i>syn</i>)	R ² (<i>anti</i>)	C-4 Me	C-2 Me	NCH _x <i>syn</i>	NCH _x <i>anti</i>	H-5	H-6 ^c
1a	CH(CH ₂ Ph)CO ₂ Me (<i>S</i>)	Me	2.28	1.70	5.96	2.65	6.94	8.29
1b	CH(CH ₂ Ph)CO ₂ Me (<i>S</i>)	Me	1.45	2.50	5.98	2.65	6.82	8.29
1c	Me	CH(CH ₂ Ph)CO ₂ Me (<i>S</i>)	1.56	2.36	3.27	4.26	6.86	8.34 ^d
1d	Me	CH(CH ₂ Ph)CO ₂ Me (<i>S</i>)	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 ₂ Ph)CO ₂ Me (<i>S</i>)	H	2.08	2.30	5.15		6.85	8.22

^a In CDCl₃, 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 CDCl₃ or C₆D₆ (*t*_{1/2} ~ 14 days). In CF₃–CO₂D no appreciable isomerization occurred within a month.^{6b} Upon heating at reflux temperature in CD₃CN, 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 Et₃N·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 ^1H 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 CF₃CO₂H may ultimately prevent helical isomerization of 1a,b (2a,b).

(7) Ōki, M. *Top. Stereochem.* 1983, 14, 1.

(8) (a) Bastiaansen, L. A. M.; Kanters, J. A.; van der Steen, F. H.; de Graaf, J. A. C.; Buck, H. M. *J. Chem. Soc., Chem. Commun.* 1986, 536. (b) Bastiaansen, L. A. M.; Vermeulen, T. J. M.; Buck, H. M.; Smeets, W. J. J.; Kanters, J. A.; Spek, A. L. *J. Chem. Soc., Chem. Commun.* 1988, 230.

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.

Syn-Anti Rotamerism. Hindered rotation in amides, brought about by the contribution of the dipolar, mesomeric structure, has been studied extensively by ^1H 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 substituents¹⁰ 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 ^1H 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 $\rightarrow$ 1a,b. Further proof for the correct attribution of syn or anti conformation in 1a-d is offered by ^1H 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 ^1H 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

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

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-3 α and H-3 β in ^1H 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*-

(9) Stewart, W. E.; Siddall, T. H., III, *Chem. Rev.* 1970, 70, 517.

(10) Sattler, H. J.; Schunack, W. *Chem. Ber.* 1975, 108, 730.

(11) La Planche, L. A.; Rogers, M. T. *J. Am. Chem. Soc.* 1963, 85, 3728.

(12) Nicolaisen, F. M. *J. Mol. Struct.* 1975, 29, 379.

(13) Paulsen, H.; Todt, K. *Angew. Chem.* 1966, 78, 943.

(14) Hatton, J. V.; Richards, R. E. *Mol. Phys.* 1960, 3, 253; 1962, 5, 139.

(15) Walter, W.; Schaumann, E.; Paulsen, H. *Justus Liebigs Ann. Chem.* 1969, 727, 61.

(16) Zhang, W.; Anteunis, M. J. O.; Borremans, F. A. M. *Int. J. Pept. Protein Res.* 1986, 28, 593.

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

entry	H-3 α	H-3 β	$\Delta\delta$	$J_{2,3\alpha}$	$J_{2,3\beta}$	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 ₂ CON(Me)CH(CH ₂ Ph)CO ₂ Me ^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 ₂ Ph)CO ₂ Me ^c (L)	2.97	2.82	0.15	5.9	8.8	2.9	14.7
CF ₃ CONHCH(CH ₂ Ph)CON(Me)CH(Me)CO ₂ Me ^d (LL- <i>syn</i>)	3.18	3.02	0.16	6.0	6.9	0.9	12.9
(DL- <i>anti</i>)	3.20	3.06	0.14	6.0	6.9	0.9	12.9

^a In CDCl₃ (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	$\Delta\delta$	NMe anti	NCH ₂ syn	H-5	H-6 ^c
1a	CDCl ₃	1.70	2.28	-0.58	2.65	5.96	6.94	8.29
	C ₆ D ₆	1.95	2.13	-0.18	2.24	5.98	6.47	8.30
1b	CDCl ₃	2.50	1.45	1.05	2.65	5.98	6.82	8.29
	C ₆ D ₆	2.70	1.35	1.35	2.23	5.98	6.41	8.30
5	CDCl ₃	2.44	2.23	0.21	0.42	0.00	0.41	-0.01
	C ₆ D ₆	2.47	1.91	0.56	2.81	3.15	6.92	8.28
	CDCl ₃	2.47	1.91	0.56	2.07	2.70	6.41	8.24
	C ₆ D ₆	-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-3 β) corresponds to the *pro-R* proton and features the larger vicinal coupling constant ($J = 8 \pm 1$ Hz vs 5.5 ± 1 Hz for H-3 α). 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-3 β) 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_b (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^{δ+} and either the phenyl ring¹⁶ 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 C₆D₆ corroborate the foregoing results. Indeed, as depicted in Table III, the replacement of CDCl₃ by C₆D₆ 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 CDCl₃ by C₆D₆ causes the C-4' and C-2' methyl proton signals to approach each other ($\Delta\delta$ 0.58 $\rightarrow$ 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 C₆D₆ ($\Delta\delta$ 1.05 $\rightarrow$ 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 CDCl₃ through C₆D₆ 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 C₆D₆ by positioning C-2-H at the negative side of the carbonyl dipole.

¹³C NMR Data of 1a and 1b. Also ¹³C 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. *J. Chem. Soc., Perkin Trans. I* 1973, 115. (c) Trimble, L. A.; Reese, P. B.; Vederas, J. C. *J. Am. Chem. Soc.* 1988, 110, 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 $\Delta\delta$ 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 ^1H 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 ($\Delta \sim 0.2$ 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; $\Delta\delta = 0.32$ ppm) when compared with $^3J_{2,3\alpha} = 4.8$, $^3J_{2,3\beta} = 12.4$ Hz and $\Delta\delta = 0.57$ 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^{16,18,20} 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 $\times$ 16 mm) loaded with Lichrosorb 5 μ 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)]. $[\alpha]_D^{20}$: +56° (c 1, CHCl_3) [lit.^{5a} +59° (CHCl_3); lit.^{5b} +19° (CHCl_3)]. ^1H NMR (CDCl_3): δ 2.77 (s, 3 H, NMe), 3.38 (dd, $J = 13.75$ and 9.1 Hz, 1 H, H-3 α), 3.68 (dd, $J = 13.75$ and 5.4 Hz, 1 H, H-3 β), 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 $\text{C}_{11}\text{H}_{16}\text{ClNO}_2$ (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. $[\alpha]_D^{20}$: –55° (c 1, CHCl_3). The ^1H NMR and ^{13}C NMR spectra were superimposable with those of (S)-4. Anal. Found for $\text{C}_{11}\text{H}_{16}\text{ClNO}_2$: 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 ^1H NMR spectroscopy, showing the presence of four components: **1a,b** (syn isomers) and **1c,d** (anti isomers) in a 3:3:1:1 ratio. ^1H 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, $J_{5,5'} = 5.1$ 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, $J_{5,5'} = 5.1$ Hz. **1c**: δ ~ 3.05 (H-3 β), ~ 3.60 (H-3 α), 3.71 (s, 3 H, CO_2Me), 7.2–7.45 (m, 5 H, Ar H), $J_{5,5'} = 5.1$ Hz. **1d**: ~ 3.05 (H-3 β), ~ 3.60 (H-3 α), 3.68 (s, 3 H, CO_2Me), 7.2–7.45 (m, 5 H, Ar H), $J_{5,5'} = 5.1$ Hz. H-3 α and H-3 β 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 ($\sim 65\%$) together with the corresponding enol tautomer ($\sim 20\%$) and the anti keto rotamer ($\sim 15\%$) upon treatment of 2,2,6-trimethyl-4H-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 $\rightarrow$ 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 $\geq$ 99): mp 132–133 °C. $\Delta\epsilon$ (265 nm, MeOH): -3.34. $[\alpha]_D^{20}$: -84° (c 1, CHCl₃). ¹H NMR (CDCl₃), Tables I–III and foregoing modus; (C₆D₆) (Table III), δ 2.76 (dd, *J* = 14.8 and 12.3 Hz, 1 H, H-3 β), 3.35 (s, 3 H, CO₂Me), 3.38 (dd, *J* = 14.8 and 4.7 Hz, 1 H, H-3 α), 6.9–7.35 (m, 5 H, Ar H), *J*_{5,6} = 5.1 Hz. ¹³C NMR (CD₃CN): 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 C₁₉H₂₂N₂O₃ (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 (CH₂Cl₂-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 $\times$ 1 mL) gave analytically pure 1b (63 mg, 8%, 1b:1a $\geq$ 50): mp 111–113 °C. $\Delta\epsilon$ (265 nm, MeOH): +2.07. $[\alpha]_D^{20}$: -95° (c 1, CHCl₃). ¹H NMR (CDCl₃) Tables I–III and preparation 1a-d (vide supra); (C₆D₆) (Table III) δ 2.77 (dd, *J* = 14.8 and 12.3 Hz, 1 H, H-3 β), 3.35 (s, 3 H, CO₂Me), 3.38 (dd, *J* = 14.8 and 4.7 Hz, 1 H, H-3 α), 6.9–7.3 (m, 5 H, Ar H), *J*_{5,6} = 5.1 Hz. ¹³C NMR (CD₃CN): 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 C₁₉H₂₂N₂O₃ (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, 4.55 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 $\times$ 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 (SiO₂ 20 g; CH₂Cl₂-MeOH, 96:4) and then subjected to preparative HPLC (CH₂Cl₂-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. $[\alpha]_D^{20}$: +85° (c 1, CHCl₃). ¹H NMR and ¹³C NMR: cf. 1a. Anal. Calcd for C₁₉H₂₂N₂O₃ (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. $[\alpha]_D^{20}$: +96° (c 1, CHCl₃). ¹H NMR and ¹³C NMR: cf. 1b. Anal. Found for C₁₉H₂₂N₂O₃: 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. ¹³C NMR (CD₃CN): 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 $\times$ 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 (CDCl₃): (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), *J*_{5,6} = 5.1 Hz. ¹³C NMR (CD₃CN): 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 (CHMe₂), 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 C₁₂H₁₈N₂O (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 CDCl₃, new ¹H NMR signals appeared, belonging to anti isomer 6b. At equilibrium (*t*_{1/2} $\approx$ 12 h) a 5:4 ratio of 6a:6b was attained, as judged from ¹H NMR integrations. ¹H NMR 6b (CDCl₃): (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. ¹³C NMR (CD₃CN): 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 (CHMe₂), 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 $\times$ 40 mL). The combined organic layers were dried (Na₂SO₄) 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) (CDCl₃): (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 C₁₄H₂₄N₂O₂ (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 (CH₂Cl₂-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 (CDCl₃): (Table I), δ 1.25 (d, *J* = 6.6 Hz, 6 H, CHMe₂), 6.13 (d, *J* = 6.9 Hz, 1 H, NH), *J*_{5,6} = 5.1 Hz. Anal. Calcd for C₁₁H₁₆N₂O (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 (CH₂Cl₂-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. Δ_D²⁰ (260 nm, MeOH): -0.57. [α]_D²⁰: +12.5° (*c* = 1, CHCl₃). ¹H NMR (CDCl₃): (Tables I and II), δ 3.80 (s, 3 H, CO₂Me), 6.70 (d, *J* = 8.4 Hz, 1 H, NH), 7.0-7.3 (m, 5 H, Ar H), *J*_{3a,3β} = 14.2 Hz, *J*_{5',6'} = 5.1 Hz. Anal. Calcd for C₁₈H₂₀N₂O₃

(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*-Pr)₂NH, 108-18-9; *i*-PrNH₂, 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 Constants¹

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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-phenylmyrtanol. 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 field⁶ (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 studies⁹ 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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(2) (a) Brown, H. C.; Vara Prasad, J. N. V. *J. Am. Chem. Soc.* 1986, 108, 2050. (b) Brown, H. C.; Singaram, B. *J. Am. Chem. Soc.* 1984, 106, 1797. (c) Brown, H. C.; Bakthian, S. *J. Org. Chem.* 1984, 49, 945. (d) For the first preparation, see: Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* 1977, 99, 5514.

(3) (a) Matteson, D. S. *Acc. Chem. Res.* 1988, 21, 294. (b) For a review of work involving chiral boranes, see: Matteson, D. S. *Synthesis* 1986, 973.

(4) For a molecular mechanics study of mono- and diisopinocampheylboranes, see: Houk, K. N.; Rondan, Y. W.; Metz, J. T.; Padon-Row, M. N. *Tetrahedron* 1984, 40, 2257.

(5) Available from Serena Software, Box 3076, Bloomington, IN.

(6) Allinger, N. L. *J. Am. Chem. Soc.* 1977, 99, 8127.

(7) Haasnoot, C. A. G.; de Leeuw, F. A. M.; Altona, C. *Tetrahedron* 1980, 36, 2783.

(8) (a) Peterson, P. E.; Stepanian, M. *J. Org. Chem.* 1988, 53, 1903. (b) Peterson, P. E.; Stepanian, M. *J. Org. Chem.* 1988, 53, 1907.

(9) Peterson, P. E.; Bedworth, P. Unpublished work.