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Highly Reactive and Stereoselective (*R*)- and (*S*)-3-(*N*,*N*-Dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridines for NADH–NAD$^+$ Mimicry

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NADH model compound 3-(*N*,*N*-dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine, **1**, has been resolved into its enantiomers. Subsequently these hydride donors were brought into reaction with divergent carbonyl substrates, e.g., methyl benzoylformate, methyl pyruvate, acetone-d_6, and DDQ. Significant asymmetric induction was observed in the corresponding axially chiral NAD$^+$ analogue 3-(*N*,*N*-dimethylcarbamoyl)-1,2,4-trimethylpyridinium perchlorate, **2**. The absolute configuration and conformation of optically active **1** and **2** respectively were elucidated. Finally, conditions were developed for the hydride transfer from 1,4-dihydropyridine **1** to methyl benzoylformate affording the corresponding pyridinium derivative **2** and methyl mandelate in optical yields exceeding 95%. In all cases studied, a preferential syn orientation of the amide carbonyl dipole and of the leaving C-4 hydrogen accounts for the observed chirality transfer.

Introduction

Nicotinamide adenine dinucleotide dependent oxido reductases induce reversible and stereoselective transfer of one of the diastereotopic C-4 hydrogens of the dihydronicotinamide moiety to a substrate. According to Benner's theory,[1] the stereospecificity of the redox reaction should rely on the correlation between the geometry of the dehydrogenase and the thermodynamic stability of the substrate. Recent X-ray data obtained for a stable ternary complex NAD$^+$–DMSO–LADH (horse liver alcohol dehydrogenase, A-specific)[2] and for a binary complex consisting of NAD$^+$ and GAPDH (glyceraldehyde-3-phosphate dehydrogenase, B-specific)[3] revealed that the amide carbonyl dipole is syn-orientated with respect to the transferring hydrogen. The possible relevance of the carboxamido group to the dynamics of the enzyme-catalyzed hydride transfer has been suggested first for LADH by Dutler.[4] Quantum chemical calculations of Donkersloot and Buck[5] established the unlikeliness of a permanent axial chirality around the C-3–C-amide axis in NAD$^+$–NADH, but rather suggested that an out-of-plane orientation of the amide group should favor the transfer of H-4 syn, with regard to the carbonyl dipole, primarily due to electrostatic interactions. This would imply that the amide carbonyl dipole is directed to the substrate during hydride transfer, a concept based on the idea that, in the activated complex, fixation of the carboxamido group in an out-of-plane orientation can take place and that by consequence the migration of either H_A or H_B is favored, depending on the type of enzyme.

For more than a decade, efforts have been expended to create model compounds mimicking the activity of the NAD$^+$–NADH redox couple. The introduction of an optically active N-substituent in the amide of 1-alkylated 1,4-dihydronicotinamides, e.g., structures **3a–c** and **4a–c**, induced a minor to moderate chirality transfer toward ethyl benzoylformate.[6,7] Ohno et al. considerably improved the stereoselectivity by the additional introduction of methyl groups at C-2 and C-4 in the NADH model, e.g., structures **5a,b**.[8] The newly created chiral center at C-4 governed the mode of hydride transfer. However, the pyridinium analogue, produced at the same time, did not show stable axial chirality (vide infra). The same group developed a 1,4-dihydroquinoline (**6**)–quinolinium couple[9] combining both reversibility and high enantioselectivity. In the oxidized form, the presence of a second amide N-substituent prevents loss of axial chirality and the annelation of a benzene ring strongly facilitates the selective 1,4-reduction. The observed selectivities toward moderately reactive ketones[9,10] are in support of the proposed syn orientation of the transferred hydrogen and the amide carbonyl dipole in the activated complex (vide supra).[5] One of the few stereoselective reductions of an NAD$^+$ analogue was realized in the sodium dithionite mediated hydride transfer to the strained bicyclic pyridinium derivate **7**.[11] The syn positioning of carbonyl dipole and incoming hydride is in agreement with the aforementioned concept but can also be explained by steric factors. Recently NADH model compounds, containing groups at C-3 other than amides, e.g., **8a,b** and **9a,b**, have been synthesized, and they equally showed asymmetric induction toward methyl benzoylformate.[12,13] Meyers et al. reported the extremely fast and highly enantioselective intramolecular redox reaction of 3-[[(benzoylcarbonyl)oxy]-methyl]-*N*-benzyl-4(*S*)-methyl-1,4-dihydropyridine.[14]

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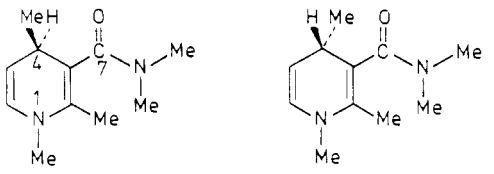
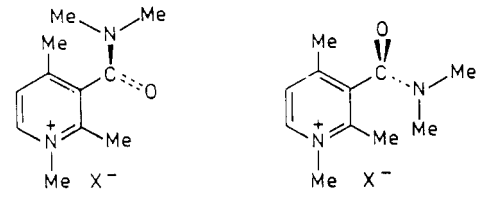
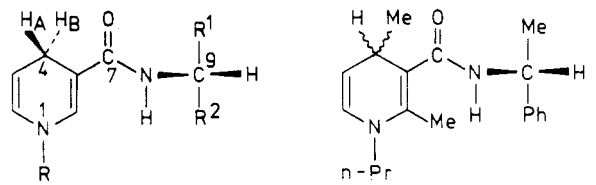


(R)-1 (S)-1

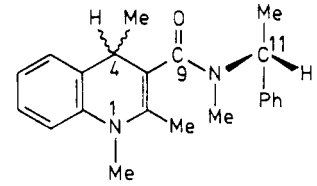


(P)-2 X = ClO_4 (M)-2
(P)-2a X = I (M)-2a

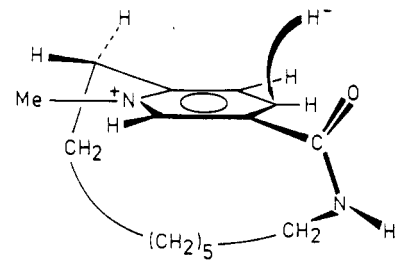


3: R^1 = Me, R^2 = Ph
a: R = n-Pr b: R = CH_2Ph
c: R = 2,6-dichlorobenzyl
4: R = CH_2Ph, R^2 = $CONH_2$
a: R^1 = Me b: R^1 = i-Bu
c: R^1 = CH_2Ph

5a: 4(R)
5b: 4(S)



6a: 4(R)
6b: 4(S)



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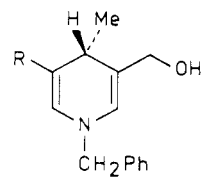
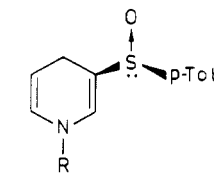


8a: R = H
8b: R = $CONMe_2$



9a: R = n-Pr
9b: R = CH_2Ph

The present paper deals with the preparation and the assignment of the absolute configuration of the novel and very reactive NADH model compounds 4(*R*)- and 4(*S*)-3-(*N*,*N*-dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine, (*R*)-1 and (*S*)-1. The stereoselectivity of their hydride transfer to divergent carbonyl substrates is established, and the performance of these NADH mimics is compared with that of existing model systems. The chirality transfer associated with the redox process is discussed in relation to the concept of preferential out-of-plane orientation of the amide group in the transition state.

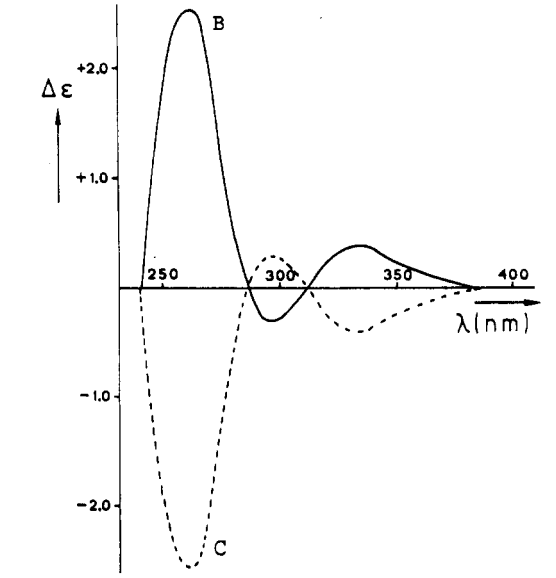


Figure 1. CD spectra of the enantiomers of 1 in *i*-PrOH. The solid line represents enantiomer B, identified as (*R*)-1.

Results and Discussion

Examination of the reactivity of pyridinium cations toward hydride donors revealed that axial chiral stability, which necessitates N,N,2,4-tetrasubstitution of nicotinamide models, apparently is not compatible with 1,4-reducibility.[15] This contrasts with the behavior of the corresponding quinolinium systems,[9] which undergo 1,4-reduction readily[16] and of course do not suffer from alternative reductions (e.g., 1,2 and 1,6). Nevertheless, the synthesis of the structurally simple 1,4-dihydropyridine 1 was pursued in view of its expected strong hydride donor ability.

Synthesis and Resolution of (*R*)-1 and (*S*)-1. The racemic material was readily obtained from the commercially available dimethylacetamide via enamine **10**,[17,18] as outlined in Scheme I. Dihydropyridine 1 is sensitive to air and less stable in concentrated form than in dilute solution. Resolution of crude, racemic 1 was accomplished by chromatography on a column packed with cellulose triacetate[19] upon elution with *i*-PrOH. The mixture was composed of optically inactive impurity A, enantiomer B (R_f ~0.66), and enantiomer C (R_f ~0.55). On repetition of the chromatographic separation, ee values exceeding 95% were reached (vide infra).

Determination of the absolute configuration and the optical purity of components B and C was a prerequisite for a mechanistic evaluation of their hydride transfer reaction. The 4*R*,9*R* configuration of **5a** was proven pre-

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Scheme I

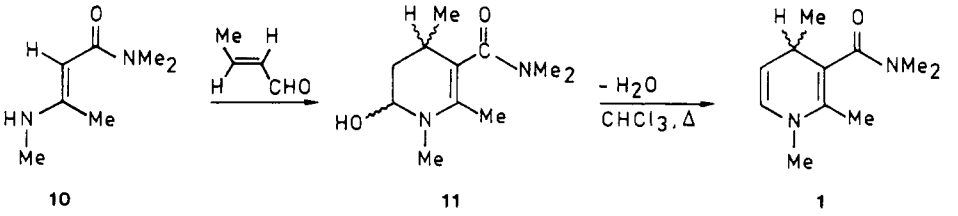

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Table I. Asymmetric Induction during Hydride Transfer from 1,4-Dihydropyridines (*R*)-1 and (*S*)-1[a]

	1			methyl mandelate			2					
entry	confign	% ee	substrate	% ee	confign	opt. yield	% ee	conformn	opt. yield	$Mg(ClO_4)_2$	temp, °C	time, h
1	*R*	91	$PhCOCO_2Me$	60	*R*	66	63	*P*	69	+	25	0.1
2	*S*	84	$PhCOCO_2Me$	54	*S*	64	59	*M*	70	+	25	0.1
3	*R*	91	$PhCOCO_2Me$	7	*R*	8	11	*P*	12	–	25	100
4	*S*	84	CD_3COCD_3[b]				35	*M*	42	+	25	24
5	*S*	69	DDQ				9	*M*	13	–	0→25	0.1
6	*S*	69	$PhCOCO_2Me$	57	*S*	83	60	*M*	87	+	0	0.1
7	*S*	69	$PhCOCO_2Me$	54	*S*	78	57	*M*	83	+	0	0.1[c]
8	*R*	96 ± 2	$PhCOCO_2Me$	91.5	*R*	95 ± 2	93	*P*	97 ± 2	+	−25→0	1
9	*R*	96 ± 2	$MeCOCO_2Me$[d]				91	*P*	95 ± 2	+	−25→0	1
10	*S*	96 ± 2	CD_3CN				62	*M*	65 ± 2	+	−25→25	24

[a] Unless otherwise specified, the reaction was carried out by sequential addition of substrate and $Mg(ClO_4)_2$ to dihydropyridine 1. CD_3CN was used as solvent (concentration ~0.2 M). [b] The substrate was also the solvent. [c] Addition of 1 to a mixture of substrate and $Mg(ClO_4)_2$. [d] Methyl lactate was isolated partially upon distillation, but the ee could not be determined by the chiral shift reagent method.

viously by chemical degradation to dimethyl (*R*)-methylsuccinate, and it was established that the Cotton effect at ~260 nm, associated with the chirality at C-4, was positive.[8] These observations coincided with the X-ray analysis of the same compound,[20] which revealed also, in comparison with the free rotation of its amide group in solution, the out-of-plane orientation of the amide carbonyl dipole by 65° by the B side of the pyridine ring, e.g., the *P* helicity.[21] A CD spectrum of component B showed a maximal, positive Cotton effect at 260 nm, while that of component C exhibited the opposite Cotton effect (Figure 1). The *R* configuration was therefore attributed to component B, while the *S* chirality was assigned to component C.

For quantitative analysis, a concentration-independent method to determine the ee was developed. The addition of (+)-Eu(hfc)$_3$[22] to a solution of 1 in deuterioacetone was found to induce a satisfactory separation of the N-1 methyl proton signals. The (*R*)-1 signal underwent a slightly more upfield shift than that of (*S*)-1 ($\Delta\Delta\delta$ = 0.015 ppm), allowing a relatively accurate ee determination, provided the optical purity was not too high (≤90%).

Hydride Transfer Reactions of 1. With the exception of one intramolecular hydride transfer reaction,[14] all reported enantioselective NADH model mediated reductions of carbonyl substrates take several days or even weeks at room temperature [acetonitrile, 1 equiv of $Mg(ClO_4)_2$ or $Zn(ClO_4)_2$]. However, some very reactive quinones are reduced in the absence of a metal salt.

Qualitative experiments with racemic 1 under standard reaction conditions revealed that methyl benzoylformate, ethyl pyruvate, and benzaldehyde gave rise to the formation of pyridinium compound 2 in less than 5 min at room temperature. The chemical yield of alcohol, as judged from integration of the ^{1}H NMR signals, was almost quantitative with the α-keto esters and good (~2/3) with benzaldehydes. Even the weakly active acetone was able to oxidize 1. A CD_3CN solution of 1 deteriorated completely within 1 day upon addition of $Mg(ClO_4)_2$ to afford pyridinium derivative 2. In the absence of $Mg(ClO_4)_2$, methyl benzoylformate reacted sluggishly (>100 h for completion), but 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) reacted instantaneously.

As compared with NADH model 1, the previously applied enantioselective hydride donors incorporate structure elements stabilizing them either by lacking 2,4-dimethyl substitution (**3**, **4**), or by bearing a secondary instead of a tertiary amide function (**3**–**5**), or by containing a benzene ring annelated onto C-5 and C-6 (**6**). Having shown the high reactivity of racemic 1, attention was focused on the chirality transfer from optically active material to carbonyl substrates and in the pyridinium educt 2.

Initial experiments have been conducted with 1 enriched to a moderate extent either in the *R* (91% ee, entry 1, Table I) or in the *S* configuration (84% ee, entry 2) and with methyl benzoylformate as carbonyl substrate. At room temperature, the addition of equivalent amounts of $Mg(ClO_4)_2$ to an equimolar solution of 1 (0.1 mmol) and methyl benzoylformate in CD_3CN (0.5 mL) induced a reaction, which was complete within a few minutes, as judged from ^{1}H NMR. Separation of the reaction products by extraction afforded methyl mandelate in the organic acid 2 in the aqueous phase. Starting from (*R*)-1, methyl (*R*)-mandelate was obtained in 66% optical yield, as judged from integration and curve fitting (see Experimental Section). Conversely, (*S*)-1 furnished the (*S*)-mandelate in 64% optical yield. As far as the axial chiral pyridinium perchlorate 2 was concerned, it was found that the product originating from (*S*)-1 exerted a Cotton effect at 278 nm, similar to that of the corresponding iodide (+)-**2a**.[23] Upon addition of (+)-Eu(hfc)$_3$ to a solution of 2 in CD_3CN,[24] the syn *N*-methyl ^{1}H NMR signals underwent a strong downfield shift and a significant enantiotopic differentiation. The signal corresponding to the major isomer appeared more upfield than that of the minor one. An entirely similar behavior was observed in iodide **2a** enriched

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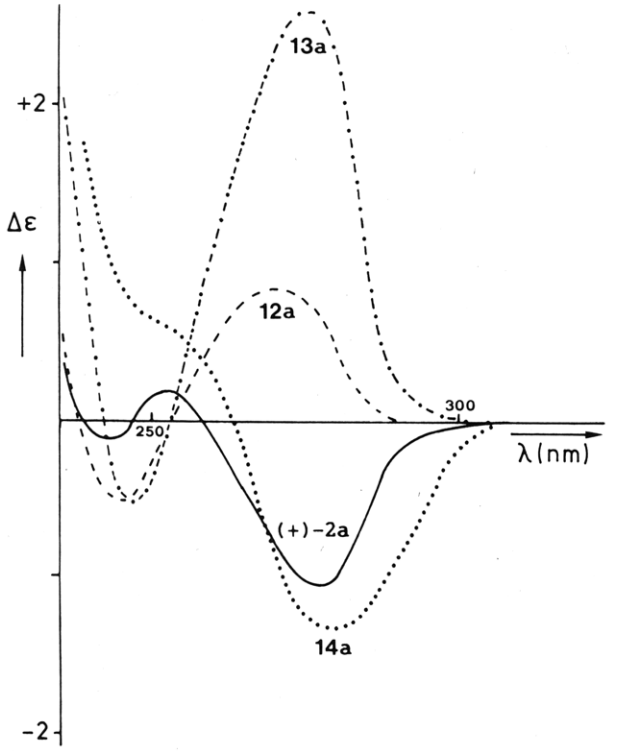


Figure 2. CD spectra of (7*M*)-pyridinium derivatives (+)-**2a** (—), **12a** (– – –), **13a** (–·–·), and **14a** (···) in MeOH.

in the (+) enantiomer. On exhibiting an equally positive sign of optical rotation, the perchlorate derived from (*S*)-**1** is further indicated as (+)-**2**. From integration and curve fitting of several enantiotopic ^{1}H NMR signals, obtained in the presence of (+)-Eu(hfc)$_3$, optical yields of 69% (–)-**2** and 70% (+)-**2** were calculated for the oxidation of (*R*)-**1** and (*S*)-**1** with methyl benzoylformate, respectively. In the next section, it is shown that (–)-**2** corresponds to *P* and (+)-**2** to *M* helicity.

Subsequently, reaction conditions and carbonyl substrates were altered, the results of which are depicted in Table I, entries 3–10. In the presence of Mg(ClO$_4$)$_2$, the chirality transfer is favorably influenced by a high intrinsic reactivity of the carbonyl substrate (entries 1, 2, 4, 6–10); in its absence (entries 3, 5), low optical yields resulted. In all cases studied, the configuration of **1** governs the helicity preference in **2**: (*R*)-**1** corresponds with (*P*)-**2**; (*S*)-**1** with (*M*)-**2**. This contrasts with the behavior of DDQ toward 1,4-dihydroquinoline **6a**.[10] The profound influence of the reaction temperature on the chirality transfer is demonstrated in the methyl benzoylformate case (entries 1, 2, 6–8). On decreasing the reaction temperature from +25 to –25 °C, the asymmetric induction in **2** was enhanced from 70 to 97 ± 2%. A comparable optical yield was recorded for the methyl mandelate obtained concomitantly. The order in which the reactants are brought together seems to have only a minor effect on the optical yields, as evidenced by the results from entries 6 and 7. A blank was performed (entry 10), showing the gradual disappearance of dihydropyridine and the formation of optically active **2**. This observation might suggest the reduction of the nitrile function in the solvent by **1** in the presence of the metal salt and presumably implies that acetonitrile should be replaced by another solvent in reactions with weakly active substrates.[25] Lastly, the chiral stability of optically active **2** at room temperature was

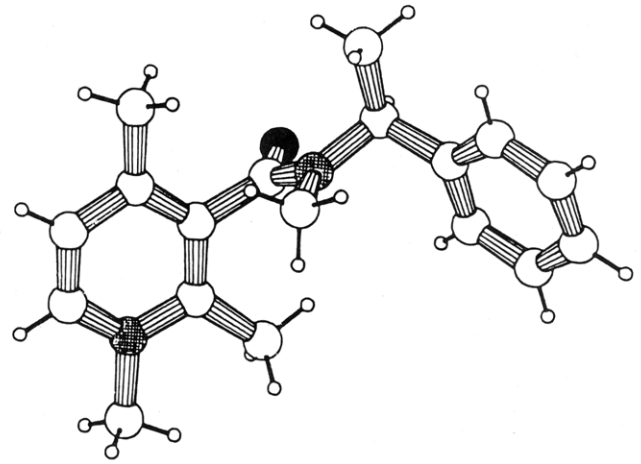
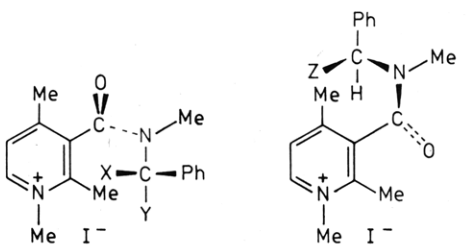


Figure 3. Crystal structure of (7*P*,9*S*)-*syn*-3-[*N*-methyl-*N*-(α-methylbenzyl)carbamoyl]-1,2,4-trimethylpyridinium iodide (**14b**).

monitored. In the absence of chiral shift reagent, a loss of optical purity of ±3%/day was found (CD, CH_3CN), while in the presence of (+)-Eu(hfc)$_3$, an even slower racemization rate was observed ($t_{1/2} \sim 2$ months) (^{1}H NMR, CD_3CN).

The above-mentioned results clearly illustrate the extremely high reactivity of our NADH model compound as well as its very efficient chirality transfer ability, provided the reaction temperature can be kept sufficiently low. The mechanistic implications of our results will be discussed later.

Absolute Conformation of (+)- and (–)-2. The absolute conformation of (+)- or (–)-**2** or -**2a** has not been established previously. Until now, no X-ray analysis of an optically pure 3-(*N*,*N*-dimethylcarbamoyl)pyridinium derivative exists and efforts to obtain crystals of the iodide **2a**, enabling anomalous dispersion, failed. However, the structures of **12a** and **13a** (9*R* configuration) were elucidated by X-ray analysis.[26] They were shown to be anti rotamers with *M* helicity (carbonyl dipole orientated to the A side). CD spectra of crystals of **12a** and **13a** featured a positive Cotton effect at ~275 nm (Figure 2).



12a: X = Y = H [7(*M*)] **12b**: Z = H [7(*P*)]

13a: X = Me, Y = H [7(*M*), 9(*R*)] **13b**: Z = Me [7(*P*), 9(*S*)]

13c: X = H, Y = Me [7(*M*), 9(*S*)]

Additionally, it has been found that syn rotamer **14b** (Figure 3) has the amide carbonyl dipole located at the B side of the pyridinium ring (*P* helicity) and that its mirror image **14a** (9*R* configuration) exhibits a negative Cotton effect ($\Delta\epsilon \sim -1.3$ in MeOH, Figure 2). In the solid state, the side-chain chirality at C-9 governs the helicity associated with the carbonyl dipole. However, the signs of the Cotton effects exerted by syn or anti isomers with the same carbonyl dipole orientation may be opposed to each other. Therefore, in contrast with an earlier suggestion,[15] this sign

(25) As suggested by one of the referees, Mg(ClO$_4$)$_2$-catalyzed autoxidation or oxidation cannot be excluded a priori.

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Table II. (+)-Eu(hfc)$_3$-Induced Separation of Enantiotopic Proton Resonances in Pyridinium Iodides (+)- and (−)-2a, 12a,b, and 13a,b[a]

	H-6	H-5	N-1 Me	C-4 Me	syn *N*-Me
(+)- and (−)-**2a**	(+)	(+)	(+)	(+)	(−)
	+0.06	+0.07	+0.04	+0.02	−0.23
12a,b	*M*	*M*	*M*	*M*	*P*
	+0.05	+0.07	+0.05	+0.07	−0.20
13a,b	*M*	*M*	*M*	*M*	*P*
	+0.08	+0.09	+0.13	+0.11	−0.30

[a] The isomer denoted is the one for which the larger downfield shift is observed for the proton(s) considered. *M* and *P* refer to the helicity, (+) and (−) to the optical rotation. The accompanying figures refer to $\Delta\Delta\delta$ (*M* − *P*) after addition of (+)-Eu(hfc)$_3$ (100 mg) to CD_3CN solutions (0.4 mL) containing (+)-**2a** (4.0 mg) and (−)-**2a** (6.3 mg); **12a** (6.0 mg) and **12b** (3.3 mg); **13a** (1.6 mg) and **13b** (1.1 mg), respectively.

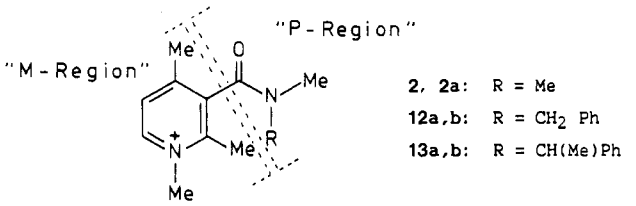

Figure 4. Enantiomeric differentiation of syn *N*-methylpyridinium derivatives **2**, **2a**, **12a,b**, and **13a,b** upon addition of (+)-Eu(hfc)$_3$.

cannot be considered as a reliable measure for the axial chirality in pyridinium compounds of type **2**. Ultimately, the absolute conformation of (+)- and (−)-**2** could be derived from (+)-Eu(hfc)$_3$-induced enantiotopic differentiation of ^{1}H NMR signals in CD_3CN.

As indicated in Table II, the syn *N*-methyl proton signals belonging to (+)-**2a** appeared more upfield than those derived from (−)-**2a**, while the enantiotopic signals assigned to N-1 methyl, C-4 methyl, C-5, and C-6 protons were separated in the opposite sense, albeit to a lower extent. Interestingly, the a forementioned *N*-methyl-*N*-benzyl and *N*-methyl-*N*-α-methylbenzyl derivatives **12a,b** and **13a,b**, differing from **2a** only in their anti N-substituent, show an entirely analogous differentiation pattern. The syn *N*-methyl proton signals belonging to the *P* isomers undergo the larger downfield shift, while the N-1 Me, C-4 Me, C-5, and C-6 proton signals of these isomers are detected at higher field than those of the *M* enantiomers.

This behavior can be rationalized in terms of a (+)-Eu(hfc)$_3$–pyridinium complex in which the amide oxygen atom is binding the shift reagent. The anti *N*-R group (Figure 4), being located at the opposite side of the pyridinium plane, is expected to have only a limited effect while the nearby syn N-substituent (methyl) interacts strongly. The (+) chiral shift reagent will then be positioned in such a way as to exert the larger proton deshielding on the pyridinium part of the *M* enantiomers and—more pronounced—on the amide part of the *P* isomers (particularly the syn *N*-methyl group). Furthermore, on heating of pure anti (*S*)-α-methylbenzyl derivative **13b** in CD_3CN, partial rotamerization and racemization at C-7 occurred, giving rise to a mixture of all four diastereomers. Inspection of the (+)-Eu(hfc)$_3$-mediated ^{1}H NMR spectrum clearly demonstrated that in anti epimer **13c**, which has the carbonyl group directed to the A side of the pyridinium ring, the syn *N*-methyl protons resonate at substantially higher field than in its diastereomeric progenitor **13b** [$\Delta\Delta\delta$ = 0.48 ppm, 50 mg of (+)-Eu(hfc)$_3$].

From all these data it is concluded that in the pyridinium series **2**, **2a**, **12**, and **13** a reliable correlation exists between the helicity and the relative size of the shift induced in enantiotopic signals by Eu(hfc)$_3$. Therefore, (−)-**2** [positive Cotton effect, derived from (*R*)-**1**] must be the enantiomer with the *P* conformation and (+)-**2** [negative Cotton effect, derived from (*S*)-**1**] that with the *M* conformation. The inversion of the sign of the Cotton effect, in going from *N*,*N*-dimethyl derivative **2a** to the anti *N*-benzyl and *N*-α-methylbenzyl analogues **12** and **13** with the same carbonyl dipole orientation (Figure 2), may find its origin in a change in the angle of out-of-plane rotation of the amide group relative to the pyridinium ring. Remarkably, in cases of equal helicity, the syn rotamers **14a,b** and symmetrical amides (+)- and (−)-**2a** produce CD spectra of similar Cotton effect, both in size and in sign. These results can be rationalized by proposing that, in contrast with the chiral shift reagent induced differentiation, not the syn but the anti N-substituent is governing the Cotton effect.

Mechanism of the Hydride Transfer. Recent data concerning the mechanism of the hydride transfer reaction suggest a well-organized transition state.[27] The impact of a multidentate bivalent cation (Mg^{2+} or Zn^{2+}) on both the reactivity and the stereoselectivity is recognized.[28] Whether the hydrogen migration implies a concerted transfer of a hydride entity or a three-step sequence involving two single electron transfers alternated by a proton shift is not yet unequivocally clarified.[29] Both mechanisms can be invoked to explain the enhanced reactivity of **1** when compared with unsubstituted nicotinamide. However, we believe that a concerted hydride transfer mechanism is favored especially at lower temperatures if Mg(ClO$_4$)$_2$ is involved in the transition state.

Ohno et al. rationalized the observed chirality transfer by adopting a ternary complex composed of a Mg^{2+} ion placed in between both reactants.[27] With methyl benzoylformate as substrate, the carbomethoxy group was located syn with respect to the amide function in order to explain the observed configurational preference in the chiral alcohol formed. That group attached to the substrate's carbonyl seems to be positioned preferentially syn to the amide, which bears a free electron pair at two bonds distance from the reactive center.[8] Coordination of the lone pair with Mg^{2+} might well contribute to the organization of the ternary complex and consequently to the high degree of chirality transfer to the carbonyl substrate. However, chelation should imply a planar arrangement of benzoylformate and Mg^{2+} ion.

That Mg(ClO$_4$)$_2$ plays not only the role of activator of the carbonyl substrate is suggested by spectral data recorded in the absence of oxidant. Thus ^{13}C NMR spectra of 1,4-dihydropyridines were significantly affected by the addition of the metal salt,[30] but only at C-3, C-4, and the amide carbon. This implies an interaction of the cation with the amide oxygen, rather than with the dihydropyridine system as was suggested by Ohno et al. previously[27] but which conceivably reduces the hydride transfer ability. Furthermore, the CD spectrum of optically active

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(28) Ohno, A.; Kimura, T.; Yamamoto, H.; Kim, S. G.; Oka, S.; Ohnishi, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1535.
(29) (a) Ohno, A.; Yamamoto, H.; Oka, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3489. (b) Tanner, D. D.; Kharrat, A. *J. Org. Chem.* **1988**, *53*, 1646. (c) Powell, M. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 5834; **1983**, *105*, 7139. (d) Van Laar, A.; van Ramesdonk, H. J.; Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 157. (e) Van der Kerk, S. M.; van Gerresheim, W.; Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 143. (f) Verhoeven, J. W.; van Gerresheim, W.; Martens, F. M.; van der Kerk, S. M. *Tetrahedron* **1986**, *42*, 975. (g) Miller, L. L.; Valentine, J. R. *J. Am. Chem. Soc.* **1988**, *110*, 3982.
(30) Gase, R. A.; Boxhoorn, G.; Pandit, U. K. *Tetrahedron Lett.* **1976**, 2889.

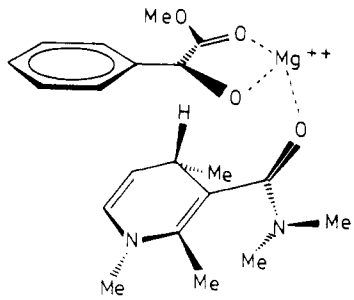

Figure 5. Proposed ternary complex involved in the $Mg(ClO_4)_2$-mediated hydride transfer from (*S*)-**1** to methyl benzoylformate.

1 underwent a very strong hyperchromic effect on the 325-nm peak upon addition of $Mg(ClO_4)_2$. The sign of its Cotton effect was the same as that observed for its progenitor **1** (at 262 nm) and for its axial chiral pyridinium educt **2** (at 278 nm). It is not unreasonable to consider the fixation of the amide group by $Mg(ClO_4)_2$ in an out-of-plane orientation with respect to the dihydropyridine plane as being responsible for this phenomenon.

Recently, Meyers et al.[12] suggested that during the chirality transfer from **8b** to methyl benzoylformate the dimethylcarbamoyl group is rotating out of the dihydropyridine plane, whereby the Mg^{2+} cation should interact with the amide nitrogen atom, despite the higher electron density at the amide oxygen. This hypothesis conflicts with our previous calculations,[5] predicting the preferential syn orientation of the migrating hydride and the amide carbonyl dipole in the transition state. It could not be verified experimentally since the pyridinium educt of **8b** is devoid of stable axial chirality. The assumption that severe nonbonded interactions between the C-4 methyl and the dimethylamino groups prevent the opposite orientation is not necessarily justified, especially if the migrating hydrogen adopts the thermodynamically favored pseudoaxial position. The experiments of Ohno et al. on 1,4-dihydroquinoline **6**[9] and those described here on 1,4-dihydropyridine **1** furnished iminium derivatives with permanent axial chirality and therefore demonstrate which out-of-plane orientation intervenes. The formation of *P* or *M* isomers is unquestionably governed by the *R* and *S* configuration of the NADH models at C-4, respectively, and therefore only a transition state in which H-4 and the amide oxygen are syn orientated can account for the course of the enantioselective hydride transfer. In view of the aforementioned considerations, a transition state is depicted in Figure 5, showing the transformation of (*S*)-**1** into (*M*)-**2** with the concomitant appearance of methyl (*S*)-mandelate. $Mg(ClO_4)_2$ should, for steric reasons, interact preferentially with that side of the dihydropyridine moiety where H-4 is located. It activates both the carbonyl substrate, by Lewis acid complexation, and the dihydropyridine, by preventing the conjugation between the amide group and the π-system of the ring through out-of-plane rotation of the amide carbonyl dipole. During this process the dihedral angle between C-4–H-4 and C-7–O approximates 0°, which facilitates the hydride migration.[5] The orientation of the ketonic oxygen atom to the dihydropyridine ring,[8] together with the complexation of the carbomethoxy group by Mg^{2+}, would then establish the ternary complex accounting for the observed chirality transfer. The proximity of the ketonic oxygen and N-1 may induce an electron flow from the latter to C-4, further accelerating the process.

A comparably organized transition state could also rationalize on steric grounds the exclusive *re* face attack of dihydropyridines **5a** and **5b** (*R* and *S* configuration, respectively) onto the (9*M*)-quinolinium educt of **6**, a vinylogous iminium derivative intrinsically more reactive than many ketones.[31] Presumably the N^+ center is positioning the dihydropyridine system via interaction with the latter's out of plane rotated amide carbonyl dipole, in close analogy to the role of Mg^{2+} in the hydride transfer to ketones. The enormous rate difference between **5a** (slow) and **5b** (fast) probably originates from the obligatory anti and syn orientation of their N-1 with respect to the quinolinium amide group, respectively. In the latter case, the proximity of N-1 and an oxygen atom (here belonging to the quinolinium amide) could facilitate hydride release (vide supra).

Inspection of Table I reveals that the optical purities of the methyl mandelate and of the pyridinium analogue **2** are related and controlled by temperature. This observation might strengthen the idea of two different $Mg(ClO_4)_2$–dihydropyridine complexes being operative. Although a competitive complexation of Mg^{2+} with the amide nitrogen cannot be excluded a priori, it is not clear how such interaction can explain the complete inversion of configuration in the methyl mandelate. Furthermore, no rationale was found for a reversal of the substrate's carbonyl orientation or for interchanging phenyl and carbomethoxy groups. The intermediacy of a competitive mechanism in which free dihydropyridine and Lewis acid activated methyl benzoylformate lead to racemic reaction products seems to offer a more plausible explanation.[32]

For reactions involving very reactive carbonyl substrates, e.g., DDQ, the absence of $Mg(ClO_4)_2$ (or the nonrelevancy of its presence) must be considered. An electron transfer mechanism may well account for the induced configurational preference in the reaction products without the intervention of a well-organized ternary complex. This could lead to the predominant formation of an iminium derivative of opposite helicity as compared with the $Mg(ClO_4)_2$-mediated processes.

Concluding Remarks

NADH model compounds (*R*)- and (*S*)-3-(*N*,*N*-dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine, (*R*)-**1** and (*S*)-**1**, have been shown to combine high reactivity with excellent asymmetric induction. Their redox reaction with methyl benzoylformate in the presence of an equivalent amount of $Mg(ClO_4)_2$ is fast and essentially quantitative. Pyridinium perchlorates (*P*)- and (*M*)-**2** and methyl (*R*)- and (*S*)-mandelate are obtained in ≥95% optical yield. Therefore, a strictly organized transition state is proposed in which the migrating hydride and the amide carbonyl dipole are syn-orientated. The degree of chirality transfer is inversely proportional to the reaction temperature. On incorporation of high reactivity in NADH model **1**, the reversibility is lost. Future studies will focus on the stereoselectivity of (*R*)- and (*S*)-**1** toward other nonsymmetric carbonyl derivatives and to substrates carrying other prochiral functional groups. The design of a readily accessible NADH model compound combining high reactivity and complete stereoselectivity with useful reversibility still remains a challenge.

Experimental Section

General Methods. NMR spectra were run on a Bruker AC200 spectrometer (^1H at 200 MHz and ^{13}C at 50.3 MHz) using TMS

(31) Ohno, A.; Ogawa, M.; Oka, S. *Tetrahedron Lett.* **1988**, *29*, 1951.
(32) The larger affinity of Mg^{2+} to dihydropyridine than to benzoylformate (Ohno, A.; Yamamoto, H.; Okamoto, T.; Oka, S.; Ohnishi, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2385) is not necessarily in conflict with this proposition.

as internal standard. CD spectra were obtained from a Jobin Yvon Dichrograph Mark III-S spectrometer, $[\alpha]_D$ values were measured on an Optical Activity A-10 polarimeter, and a mass spectrum was recorded on a Finnigan 4000 quadrupole GC–MS (EI). Solvents and reagents were reagent grade and were degassed and extensively flushed with argon when 1,4-dihydropyridines were involved.

1,4-Dihydro-*N*,*N*,1,2,4-pentamethylpyridine-3-carboxamide [3-(*N*,*N*-Dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine] (1). To a stirred solution of enamine **10**[17,18] (1.0 g, 7.03 mmol) in methanol (5 mL) were consecutively added piperidine (30 μL, 0.30 mmol) and crotonaldehyde (0.63 g, 9.06 mmol). After additional stirring under an argon atmosphere during 14 h, the solvent was evaporated in vacuo. Chloroform (30 mL) was added, and water was removed azeotropically from the intermediate carbinolamine **11**. Chromatographic purification on aluminum oxide (active basic, type E, Merck 1067, previously degassed and saturated with argon) using chloroform as eluent (R_f ~0.60), treatment of the concentrated product with *n*-hexane, and evaporation of the filtrate afforded syrupy **1** (0.86 g, 63%). This was found to be highly sensitive to air and nondistillable but could be stored at −20 °C when dissolved in nonreducible solvents (e.g., *i*-PrOH, MeOH) $t_{1/2}$, 1% in *i*-PrOH, >1 month). ^{1}H NMR ($CDCl_3$): δ 1.03 (d, J = 7 Hz, 3 H, C-4 Me), 1.77 (s, 3 H, C-2 Me), 2.91 (s, 3 H, N-1 Me), 2.95–3.05 (br s, 6 H, syn and anti *N*-Me), 3.32 (qd, J = 7 and 4 Hz, 1 H, H-4), 4.44 (dd, J = 7.5 and 4 Hz, 1 H, H-5), 5.73 (d, J = 7.5 Hz, 1 H, H-6); (CD_3COCD_3) δ 0.97 (C-4 Me), 1.75 (C-2 Me), 2.96 (N-1 Me), 2.99 (syn and anti *N*-Me), 3.15 (H-4), 4.41 (H-5), 5.80 (H-6). ^{13}C NMR (CD_3COCD_3): δ 16.5 (C-4 Me), 25.7 (C-2 Me), 26.6 (C-4), 32.4 (N-1 Me), 38.5 (*N*-Me_2), 104.8 (C-5), 119.6 (C-3), 133.3 (C-6), 141.3 (C-2), 173.4 (CO). MS: m/z (relative intensity) 195 (5), 194 ($M^{\bullet+}$, 16), 193 (9), 192 (7), 179 (100), 168 (29), 150 (21), 134 (65), 124 (22), 122 (34), 121 (27), 120 (20), 111 (19), 107 (25), 106 (28), 84 (55), 72 (38). The purity of racemic **1** was estimated by ^{1}H NMR using cyclohexane as internal standard and approached 90%, judged from integration.

Generation of an enantiomeric excess was accomplished by chromatography on cellulose triacetate (Merck 16363, 25 × 40 μm). Elution of the column (40 g, 300 mm × 25 mm, 4 bar, 2 mL min^{-1}) loaded with racemic material [150 mg, dissolved in *i*-PrOH (2 mL)] with *i*-PrOH afforded, in order of increasing polarity, component A, containing optically inactive impurities; component B (~60 min) (~40 mg, (*R*)-**1**, 70–80% ee); an interfraction (~40 mg); and component C (~70 min) (~40 mg, (*S*)-**1**, 70–80% ee). On repeating the separation, pure (*R*)-**1** and (*S*)-**1** were obtained (ee >95%) (vide infra). Upon addition of tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III) [(+)-Eu(hfc)$_3$, 60 mg, 0.05 mmol] to a solution of **1** (20 mg, ~0.10 mmol) in CD_3COCD_3 (0.5 mL), the individual N-1 Me signals of the enantiomers could be resolved (δ (*R*)-**1** 3.22, δ (*S*)-**1** 3.24). Integration and curve fitting[33] (rms error ≤ 5%) determined the integrals to be in the ratio of 100:100 ± 1 (0% ee) for racemic material, 100:18 ± 1 (69% ee) for (*S*)-**1** separated once on cellulose triacetate, and 100:4 ± 2 (96% ee) for (*R*)-**1** resolved twice. CD spectra were run (1.25 mg/mL, sensitivity 5 × 10^{-6}, cuvette 0.1 cm), and after correction for the measured ee, Δε values of +2.9 and −2.9 (*i*-PrOH) were calculated for enantiomerically pure (*R*)-**1** and (*S*)-**1** for the maximum at 260 nm. Chemical purities of optically active **1** ranged from 70 to 80% (^{1}H NMR, vide supra).

Hydride Transfer from Optically Active 1: Reaction with Methyl Benzoylformate (Entry 8, Table I). In a typical run, a stirred, cooled (−25 °C) solution of the less polar dihydropyridine enantiomer (*R*)-**1** (96 ± 2% ee, 49 mg, 80% ~0.20 mmol) in CD_3CN (0.5 mL) was treated at once with an equally cold solution of $Mg(ClO_4)_2$ (45 mg, 0.20 mmol) and methyl benzoylformate (33 mg, 0.20 mmol) in CD_3CN (0.4 mL). The reaction mixture was allowed to attain 0 °C within 1 h. A ^{1}H NMR spectrum indicated **1** to be absent. The solvent was removed in vacuo at room temperature, and the residue was partitioned between aqueous NH_4Cl (4 mL, 0.1 M) and dichloromethane (8 mL). The organic phase was washed with water (2 × 1 mL), dried ($MgSO_4$), and concentrated. The solid residue (37 mg) was purified chromatographically (silica gel, 0.063–0.200 mm, Merck 7734, 3 g) via elution with dichloromethane (R_f ~0.12) and furnished methyl mandelate (30 mg, 91%). ^{1}H NMR [10 mg, +25 mg of (+)-Eu(hfc)$_3$, CCl_4–cyclohexane-d_{12}, 95:5]: δ 4.83 [CO_2Me (*R*), 95.5%] and 4.68 [CO_2Me (*S*), 4.5%].[33] $[\alpha]^{20}_D$: −129° (*c* 0.5, H_2O) (lit.[34] $[\alpha]^{20}_D$ −144°). The optical yield was estimated as 95 ± 2%, based on the calculated enantiomeric purity of (*R*)-**1** (96 ± 2%). The combined aqueous layers were evaporated below 30 °C at very low pressure. The residue was suspended in CH_3CN (5 mL), and the filtrate was concentrated to afford **2** (65 mg), contaminated with some inorganic salt. ^{1}H NMR (13 mg, CD_3CN): δ 2.46 (s, 3 H, C-4 Me), 2.59 (s, 3 H, C-2 Me), 2.84 (s, 3 H, anti *N*-Me), 3.14 (s, 3 H, syn *N*-Me), 4.16 (s, 3 H, N-1 Me), 7.71 (d, J = 7.5 Hz, 1 H, H-5), 8.50 (d, J = 7.5 Hz, 1 H, H-6); [**2** + 100 mg of (+)-Eu(hfc)$_3$][35] δ 3.89 [C-4 Me (−)], 3.90 [C-4 Me (+)], 3.99 [C-2 Me (+)], 4.02 [C-2 Me (−)], 4.37 [anti *N*-Me (+)], 4.42 [anti *N*-Me (−)], 4.45 [N-1 Me (−)], 4.48 [N-1 Me (+)], 5.19 [syn *N*-Me (+)], 5.35 [syn *N*-Me (−)], 8.20 [H-5 (−)], 8.26 [H-5 (+)], 8.88 [H-6 (−)], 8.93 [H-6 (+)]. The routine integration and the glinfit[33] method (rms ≤ 4%) established the (−)-**2** conformer to be present in 93 ± 1% ee, which corresponds to an optical yield of 97 ± 2%. ^{13}C NMR (CD_3CN): δ 18.7 (C-2 Me), 20.6 (C-4 Me), 36.1 (anti *N*-Me), 38.7 (syn *N*-Me), 47.3 (N-1 Me), 128.2 (C-5), 137.2 (C-3), 146.8 (C-6), 152.8 (C-2), 156.5 (C-4), 166.2 (CO). $[\alpha]^{20}_D$: −2.0° (*c* 0.5, MeOH) [+2.4° for pure (+)-**2** (vide infra)]. Δε (278 nm, MeOH): +0.8 [−1.0 for pure (+)-**2a** (vide infra)].

Other hydride transfer reactions described in Table I and their analyses were carried out in an analogous manner and on a comparable scale as described for entry 8.

(+)-3-[(*N*,*N*-Dimethylamino)carbonyl]-1,2,4-trimethylpyridinium Perchlorate [(+)-2]. a. From Dihydropyridine (*S*)-1. Vide supra.

b. From Iodide (+)-2a.[15] A solution of pure (+)-**2a** ($[\alpha]_D$ +2.0° (MeOH), 320 mg, 1.00 mmol) in methanol (5 mL) was treated with $AgClO_4$ (207.5 mg, 1.00 mmol), dissolved in methanol (2.5 mL). After centrifugation, the supernatant liquid was isolated and the deposit was washed with methanol (3 × 2 mL). The combined filtrates were adjusted to 15.0 mL for the optical rotation measurement. $[\alpha]^{20}_D$: +2.4° (*c* 1.95, MeOH). Evaporation in vacuo afforded solid material, which was crystallized from ethanol to give analytical **2** as white needles (192 mg, 66%), mp 244–245 °C. Anal. Calcd for $C_{11}H_{17}ClNO_4$ (MW 292.72): C, 45.14; H, 5.85; N, 9.57. Found: C, 45.0; H, 5.4; N, 9.35.

3-[(*N*,*N*-Dimethylamino)carbonyl]-1,2,4-trimethylpyridinium iodide (2a):[15] ^{1}H NMR [4.0 mg of (+)-**2a** + 6.3 mg of (−)-**2a**, CD_3CN] δ 2.46 (s, 3 H, C-4 Me), 2.59 (s, 3 H, C-2 Me), 2.82 (s, 3 H, anti *N*-Me), 3.11 (s, 3 H, syn *N*-Me), 4.15 (s, 3 H, N-1 Me), 7.73 (d, J = 7.5 Hz, 1 H, H-5), 8.58 (d, J = 7.5 Hz, 1 H, H-6); [**2a** + 100 mg of (+)-Eu(hfc)$_3$] δ 4.22 [C-4 Me (−)], 4.24 [C-4 Me (+)], 4.64 [N-1 Me (−)], 4.68 [N-1 Me (+)], 4.79 [anti *N*-Me (+)], 4.84 [anti *N*-Me (−)], 5.65 [syn *N*-Me (+)], 5.88 [syn *N*-Me (−)], 8.38 [H-5 (−)], 8.45 [H-5 (+)], 9.12 [H-6 (−)], 9.18 [H-6 (+)]. Δε (278 nm, MeOH): −1.0 [(+)-**2a**], +1.0 [(−)-**2a**].

(7*M*)- and (7*P*)-*anti*-3-[(*N*-benzyl-*N*-methylamino)carbonyl]-1,2,4-trimethylpyridinium iodide (12a and 12b):[26] ^{1}H NMR [6.0 mg of **12a** (*M*) + 3.3 mg of **12b** (*P*), CD_3CN] δ 2.43 (s, 3 H, C-4 Me), 2.57 (s, 3 H, C-2 Me), 3.11 (s, 3 H, syn *N*-Me), 4.13 (s, 3 H, N-1 Me), 4.32 (d, J = 15 Hz, 1 H, anti *N*-CH_2), 4.53 (d, J = 15 Hz, 1 H, anti *N*-CH_2), 7.67 (d, J = 7.5 Hz, 1 H, H-5), 8.57 (d, J = 7.5 Hz, 1 H, H-6); [**12a,b** + 100 mg of (+)- Eu(hfc)$_3$] δ 4.11 [C-4 Me (*P*)], 4.18 [C-4 Me (*M*)], 4.70 [N-1 Me (*P*)], 4.75 [N-1 Me (*M*)], 5.57 (syn *N*-Me (*M*)], 5.77 [syn *N*-Me (*P*)], 8.47 [H-5 (*P*)], 8.54 [H-5 (*M*)], 9.23 [H-6 (*P*)], 9.28 (H-6 (*M*)]; Δε (270 nm, MeOH), +0.8 [**12a**, (*M*)], −0.8 (**12b**, (*P*)].

(7*M*,9*R*)- and (7*P*,9*S*)-*anti*-3-[[*N*-methyl-*N*-(α-methylbenzyl)amino]carbonyl]-1,2,4-trimethylpyridinium iodide (13a and 13b):[26] ^{1}H NMR [1.6 mg of **13a** (*M*) + 1.1 mg of **13b** (*P*), CD_3CN] δ 1.60 (d, J = 7 Hz, *N*-Me), 4.23 (s, 3 H, N-1 Me), 4.76 (q, J = 7 Hz, 1 H, anti *N*-CH), 7.65 (d, J = 7.5 Hz, 1 H, H-5), 8.57 (d, J = 7.5 Hz, 1 H, H-6); [**13a,b** + 100 mg of (+)-Eu(hfc)$_3$] δ 4.43 [C-4 Me (*P*)], 4.54 [C-4 Me (*M*)], 4.92 [N-1 Me (*P*)], 5.05

(33) Glinfit Program. Copyright Bruker Spectrospin AG, Switzerland.

(34) Clough, G. W. *J. Chem. Soc.* **1925**, 2808.

(35) The exact magnitude of the deshielding effect is very sensitive to the amount of water present. This has, however, no impact on the enantiotopic differentiation pattern.

[N-1 Me (*M*)], 6.45 [syn *N*-Me (*M*)], 6.75 [syn *N*-Me (*P*)], 8.57 [H-5 (*P*)], 8.66 [H-5 (*M*)], 9.36 [H-6 (*P*)], 9.44 [H-6 (*M*)]. $\Delta\epsilon$ (275 nm, MeOH): +2.4 [**13a**, (*M*)], −2.4 [**13b**, (*P*)].

(7*M*,9*S*)-*anti*-3-[[*N*-Methyl-*N*-(α-methylbenzyl)amino]carbonyl]-1,2,4-trimethylpyridinium Iodide (13c). Upon heating of pure **13b** in CD_3CN during several hours at reflux temperature, an equilibrium mixture is produced containing all four diastereoisomers. Compound **13c**, which could not be isolated as a pure substance, is the minor component (<10%). ^1H NMR (CD_3CN): δ 1.56 (d, *J* = 7 Hz, 3 H, α-Me), 2.25 (s, 3 H, C-4 Me), 2.57 (s, 3 H, C-2 Me), 3.09 (s, 3 H, syn *N*-Me), 4.05 (s, 3 H, N-1 Me), 4.61 (q, *J* = 7 Hz, 1 H, *N*-CH), 7.80 (d, *J* = 7.5 Hz, 1 H, H-5), 8.63 (d, *J* = 7.5 Hz, 1 H, H-6); [**13c** + 50 mg of (+)-Eu(hfc)$_3$] δ 3.94 (C-4 Me), 4.65 (N-1 Me), 5.46 (syn *N*-Me), 9.24 (H-6). Compare with the corresponding values for **13b**: δ 3.99 (C-4 Me), 4.78 (N-1 Me), 5.94 (syn *N*-Me), 9.19 (H-6).

(7*P*,9*S*)-*syn*-3-[[*N*-Methyl-*N*-(α-methylbenzyl)amino]carbonyl]-1,2,4-trimethylpyridinium Iodide (14b).[26] **X-ray Data**: $C_{18}H_{23}N_2O^+\cdot I^-$, M_r = 410.30, orthorhombic, $P2_12_12_1$, *a* = 7.0112 (9) Å, *b* = 14.385 (1) Å, *c* = 37.213 (2) Å, *V* = 3753.2 (6) Å^3, *Z* = 8, D_{calcd} = 1.452 g cm^{-3}, Mo Kα, λ = 0.71073 Å, μ = 16.9 cm^{-1}, *F*(000) = 1648, *T* = 294 K, final *R* = 0.0464 for 3213 unique observed reflections. A needle-shaped crystal, 0.9 × 0.13 × 0.03 mm, was used for data collection on an Enraf-Nonius CAD-4 diffractometer with Zr-filtered Mo Kα radiation. Lattice parameters were derived from the angular settings of 25 reflections (6.69° ≤ θ ≤ 13.73°). The intensity data of 4600 reflections were collected, of which 3213 were above the 2.5σ(*I*) level [*h* 0→7, *k* 0→15, *l* −39→39, $2\theta_{max}$ = 44°, ω–2θ scan mode with $\Delta\omega = (0.60 + 0.35 \tan\theta)°$]. The *hkl* and hk$\bar{l}$ Bijvoet pairs were not merged to determine the absolute configuration. Three periodically measured standard reflections (114, 120, 034) showed rms deviations of 1.03, 0.81, and 0.68%, respectively. The structure was solved by Patterson and Fourier methods. H atoms were placed at calculated positions (C–H, 1.00 Å) riding on their carrier atoms with a general temperature factor. Anisotropic, weighted blocked full-matrix refinement of *F*(423 parameters) gave *R* = 0.0464, *wR* = 0.0459 with $w = 1.0550[\sigma^2(F_o) + 0.00269F_o^2]^{-1}$, *S* = 1.13, $(\Delta/\sigma)_{av}$ = 0.012, $(\Delta/\sigma)_{max}$ = 0.051, $(\Delta\rho)_{max}$ = 0.73, $(\Delta\rho)_{min}$ = −0.69 e Å^{-3} (around *I*). The absolute configuration was ascertained by refinement of the inverted model, which resulted in *R* = 0.0495 and *wR* = 0.0536, which established the configuration at C-7 as *S* in accordance with that of its synthetic precursor *N*-methyl-*N*-[(*S*)-α-methylbenzyl]amine. The scattering factors and anomalous-dispersion corrections were taken from *International Tables for X-ray Crystallography* (1974). Calculations were performed with SHELX76[36] (structure determination and refinement) and the EUCLID package[37] (molecular geometry and illustrations) on the CDC-Cyber-855 of the University of Utrecht: ^1H NMR (CD_3CN) δ 1.66 (d, *J* = 7 Hz, 3 H, α-Me), 2.42 (s, 3 H, C-4 Me), 2.52 (s, 3 H, C-2 Me), 2.66 (s, 3 H, anti *N*-Me), 4.19 (s, 3 H, N-1 Me), 6.13 (q, *J* = 7 Hz, 1 H, syn *N*-CH), 7.71 (d, *J* = 7.5 Hz, 1 H, H-5), 8.57 (d, *J* = 7.5 Hz, 1 H, H-6). $\Delta\epsilon$ (280 nm, MeOH): +1.3.

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A Novel Strategy for the Synthesis of Ammonium 3-Deoxy-D-*manno*-2-octulosonate (Ammonium KDO) from Lower Monosaccharides. C–C Bond Construction at C_6 of D-Mannose via Cobaloxime-Mediated Radical Alkyl–Alkenyl Cross Coupling

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Our synthesis of ammonium 3-deoxy-D-*manno*-2-octulosonate (ammonium KDO, **16**) from D-mannose (**3**) proceeds in 10 one-flask operations in 1.5–1.6% overall yield (66% per operation). The strategic reaction is a C–C bond construction at C_6 of D-mannose via photochemically induced radical cross coupling of α-ethoxyacrylonitrile with an alkyl cobaloxime derivative of D-mannose, in aqueous ethanol without protection of carbohydrate hydroxyls. In this paper we provide full experimental details of our KDO synthesis. In addition we provide some observations and insights on vanadium-catalyzed oxidations of α-hydroxy acids to α-keto acids.

Introduction

The eight-carbon monosaccharide 3-deoxy-D-*manno*-2-octulosonic acid, commonly known as KDO (**1**), is an essential component of the outer membrane lipopolysaccharide of all Gram-negative bacteria.[2] KDO is found in the core oligosaccharide, which links lipid A with the O side chain repeating oligosaccharide that protrudes into solution from the cell surface. KDO has also been found in the cell walls of plants.[3] The synthesis of KDO analogues has recently become important for studies aimed at the development of an entirely new class of Gram-negative antibacterials targeting the KDO biosynthetic pathway.[4,5]

We recently communicated a synthesis of ammonium KDO (**16**)[6,7] from D-mannose (**3**) via a novel strategy fea-

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