A Compact Chemical Miniature of a Holoenzyme, Coenzyme NADH Linked Dehydrogenase. Design and Synthesis of Bridged NADH Models and Their Highly Enantioselective Reduction[1]

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Abstract: An L-lactate dehydrogenase that requires coenzyme NADH catalyzes the enantioselective reduction of pyruvate to L-lactate in anaerobic glycolysis. As the first homochiral ansa-type NADH models, we designed the bridged NADH models **10a**−**c** having a parapyridinophane structure for strictly mimicking the stereospecificity of hydrogen transfer in the biological asymmetric reduction with NADH. These models were synthesized in several steps from the corresponding bridged nicotinate **5** prepared by our novel pyridine-formation reaction of formyl-substituted (vinylimino)phosphorane **4** with methyl propiolate. The bridged NADH models **10a**−**c** effected excellent biomimetic reduction at various temperatures in the presence of magnesium ion to achieve both the enantioselective and stereospecific reduction of the pyruvate analogues **12u**−**z** into chiral lactate analogues **13u**−**z** with 88−99% ee. The high enantioselectivity was almost completely dependent on the planar chirality of **10a**−**c** but not on the nature of the substituents of their carbamoyl groups. The biomimetic reduction proceeded with retention of the planar chirality, showing that the bridged NADH models are useful for being recycled. An isotope experiment with the deuterated model (±)-**10d** confirmed the stereospecific hydrogen transfer, which is in good accordance with natural coenzyme characteristics. The model (*S*)-**10c** also exhibited good enantioselectivity for the reduction of activated ketones **14k**−**n** into the corresponding chiral alcohols **15k**−**n** with 79−89% ee. The simple bridged NADH model (*S*)-**10c** having both a primary carbamoyl group and a shielding bridge feigning an enzyme wall suggests a compact chemical miniature of a holoenzyme, coenzyme NADH linked dehydrogenase, in terms of the unique structure, high enantioselectivity, and recyclability.

Introduction

Coenzyme NADH, a cofactor of L-lactate dehydrogenase, functions as an enantioselective agent that reduces pyruvate to L-lactate during anaerobic glycolysis. The environment inside the dehydrogenase achieving the asymmetric reduction satisfies two important elements: (i) stereoselective transfer of one of the diastereotopic C-4 hydrogen atoms in NADH to achiral substrates (H_R specific in L-lactate dehydrogenase)[2] and (ii) activation and well-controlled orientation of the substrates with hydrogen bonds of the amino acid residue[3] (Figure 1). The natural coenzyme NADH contains a simple 1,4-dihydronicotinamide moiety as a recyclable redox center for catalytic use, which has both prochiral unsubstituted hydrogens at its C-4 position and a primary carbamoyl group, and the corresponding

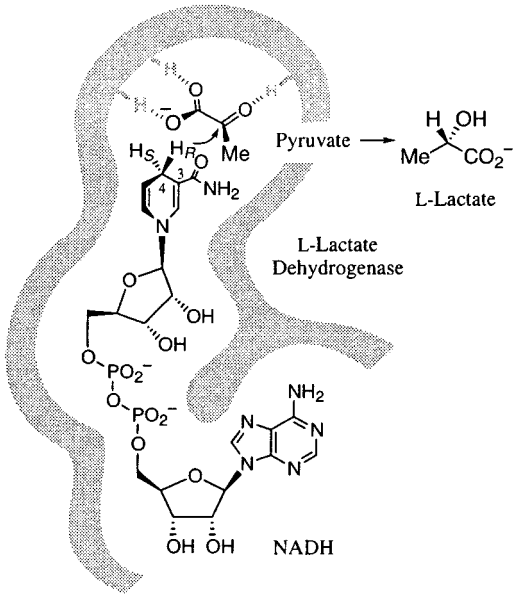

Figure 1. Schematic description of biological reduction with coenzyme NADH in L-lactate dehydrogenase.

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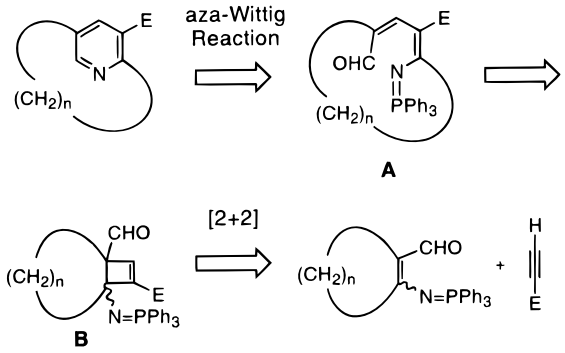
apoenzyme provides a chiral environment for its biological reduction to induce high enantioselectivities toward its substrates. This asymmetric induction has attracted the attention of organic and bioorganic chemists to explore the features of such a stereospecific reduction by challenging its mimicry,[4−10] or the related asymmetric reduction of activated ketones,[8a,c,10b,11] imines,[11b] or enamines[6e] in organic media. However, the conventional strategy to design an artificial NADH is the syntheses of the 1,4-dihydronicotinamides or their analogues having a chiral center at their C-4 positions[5] and/or chiral sidearms on their carbamoyl groups.[6−10] Therefore, the former suffers from loss of chirality at C-4 during the course of the model reactions, and the latter generally requires significant modification of the dihydronicotinamide unit in such a way to introduce a fused ring system, additional chiral auxiliaries, a chiral sulfoxide group, etc. To strictly mimic the stereoselective transfer of the hydrogen atom in recyclable artificial systems, we have designed the novel bridged NADH models **10a**−**c**, which incorporate the oligomethylene bridge feigning an "enzyme wall" to regulate the stereoselective approach of pyruvate analogues for accomplishment of their biomimetic reduction with high enantioselectivity. Especially, the model (*S*)-**10c** incorporating not only the ansa bridge but also a primary carbamoyl group is worth being tested as a compact chemical miniature of lactate dehydrogenase containing coenzyme NADH to probe whether such a simple model compound efficiently works in artificial systems. We now report the detailed results of the synthesis of the bridged NADH models **10a**−**c**, the first homochiral ansa-type NADH models,[12] and their highly enantioselective reduction of pyruvate analogues as well as some activated ketones with good selectivity to demonstrate that stereoselective shielding of a dihydronicotinamide ring is the absolute and the minimally sufficient factor for artificial NADH systems with high enantioselectivity.

Scheme 1[a]



[a] E = an ester group.

Results

Synthesis of Bridged Nicotinate. Scheme 1 outlines our synthetic strategy for bridged nicotinate, a crucial synthetic intermediate for the NADH model compounds. We employed the aza-Wittig reaction as the key step since it seems useful for the syntheses of nicotinates[13] and pyridinophane derivatives.[12b,14] The retrosynthetic cleavage of the C═N double bond in the pyridinophane skeleton reveals the dienal intermediate **A** as the precursor, which is a valence isomer of the corresponding cyclobutene intermediate **B**. The enamine-type [2+2] cycloaddition disassembles **B** to the formyl-substituted (vinylimino)-phosphorane and methyl propiolate.

The actual synthesis of the bridged nicotinate **5** is summarized in Scheme 2. The Vilsmeier−Haack formylation[15] of the readily available cyclododecanone afforded *cis*-2-chloro-1-cyclododecenecarbaldehyde (*cis*-**1**) and its isomer, *trans*-**1**, in 78% and 17% yields, respectively. Compound *cis*-**1** was treated with sodium azide and a catalytic amount of lithium chloride to give *trans*-2-azido-1-cyclododecenecarbaldehyde (*trans*-**2**) and the formyl-substituted cyclododec[*b*]azirinecarbaldehyde (**3**) in a 39/61

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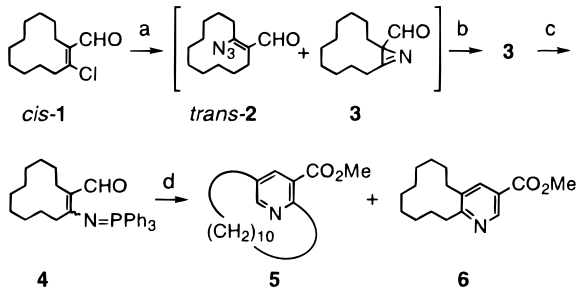
Scheme 2[a]



[a] Reagents: (a) NaN_3, LiCl, THF−H_2O, rt, 5 h. (b) *hν* (Pyrex), $CHCl_3$, rt, 8 h (83% yield for two steps). (c) PPh_3, toluene, reflux, 3 h (91% yield, 3/1 *trans*- and *cis*-**4**). (d) Methyl propiolate, toluene, 140 °C, 12 h (21% and 7% yields for **5** and **6**).

ratio.[16] The following photoirradiation of the mixture in chloroform accomplished the conversion of *trans*-**2** into azirine **3** (83% yield from *cis*-**1**). The thermal ring-opening reaction of **3** with triphenylphosphine proceeded in refluxing toluene to give the iminophosphorane **4** in 91% yield. The ^{1}H NMR spectrum showed that compound **4** is a mixture of *trans*- and *cis*-isomers in a ratio of ca. 3/1 according to their aldehyde signals at δ 9.87 ppm (0.75H) and δ 10.66 ppm[17] (0.25H), respectively. The ^{1}H NMR spectra of **1**, **2**, and **4** were clearly informative for assigning the configuration of C═C double bonds. For the *cis*-isomers, the aliphatic signals of each geminal pair agreed with their symmetric structure, while those of the *trans*-isomers independently appeared according to their substituent groups restricting the free dynamic motion of the decamethylene bridge beyond the C═C double bonds. 3-Methoxycarbonyl[10](2,5)-pyridinophane (**5**) was successfully synthesized from **4** by the novel pyridine-formation reaction with methyl propiolate. The desired bridged nicotinate **5** was obtained in 21% yield as well as its ortho-bridged isomer **6** in 7% yield.[18] The structures of these compounds were deduced on the basis of their ^{1}H and ^{13}C NMR spectra and mass spectra. The ^{1}H NMR spectrum showed that one of the oligomethylene protons of **5** that appeared at δ 0.13 ppm was located in a shielding region above the pyridine ring. Furthermore, every bridge proton is located in a different environment since all the aliphatic signals independently appeared. These findings indicate that compound **5** has a racemic parapyridinophane skeleton and the flipping (jump-rope rotation) of the oligomethylene bridge is frozen on the NMR time scale at room temperature. The structure of **6** was easily assigned since the signals of the oligomethylene protons are half as many as those of **5** due to its symmetric structure.

Synthesis of Bridged NADH Models. Scheme 3 illustrates the synthetic pathways for the bridged NADH models **10a**−**c**. Hydrolysis of the nicotinate **5** with lithium hydroxide afforded the corresponding nicotinic acid (±)-**7**, and the subsequent amide formation with (*S*)-valinol gave the bridged nicotinamides (*S*,*S*)-**8a** and (*R*,*S*)-**8b**. For the synthesis of the primary amide (*S*)-**8c** via the chiral bridged nicotinic acid (*S*)-**7**, the racemic acid (±)-**7** was converted into the homochiral imide derivatives, (*S*,*S*)-**11a** and (*R*,*S*)-**11b**. The compounds **8a**,**b** and **11a**,**b** are quite stable molecules so that flipping of the oligomethylene bridges is frozen and does not disturb the separation from each other at room temperature. This observation is in contrast with the case of 2,8-dithia[10](2,5)pyridinophane racemizing itself.[12h] Heating **8a**,**b** and **11a**,**b** triggered the flipping that is useful to control the planar chirality. The interconversion reached an equilibrium in refluxing toluene after 8 h to give a nearly 1/1 mixture of (*S*,*S*)-**8a** and (*R*,*S*)-**8b** and, more interestingly, a mixture of (*S*,*S*)-**11a** and (*R*,*S*)-**11b** in a ca. 3/2 ratio. The selective preparation of homochiral **8a**,**b** and **11a**,**b** was achieved since repeated "separation and interconversion" could stop the flipping down into either side of the desired planar chirality. This concept is exemplified by preferential synthesis of pure (*S*,*S*)-**11a**, the yield of which increased to 83% (93%, theoretically) after two repeated separations and interconversions.

The structure of (*S*,*S*)-**8a**, colorless plates recrystallized from ethyl acetate, was unequivocally solved by X-ray crystallographic analysis (Figure 2). The interesting feature of the structure is that the oligomethylene bridge significantly blocks the face of the pyridine moiety, and this result agrees with our design that the bridge would function as a bulky shielding wall against substrate approach. The absolute structure of (*S*,*S*)-**11a** was established after hydrolysis; the reaction with lithium hydroperoxide in THF−H_2O (3/1) gave nicotinic acid (*S*)-**7** and nicotinamide (*S*,*S*)-**8a** in 55% and 24% yields, respectively, the latter of which was identical to the authentic specimen. The hydrolysis in DMF−THF−H_2O (3/3/1) allowed the clean removal of the chiral auxiliary[19] to give (*S*)-**7** exclusively in 84% yield. The chiral acid (*S*)-**7** was converted into the corresponding primary amide (*S*)-**8c** in a conventional manner. The N-alkylation of **8a**−**c** with methyl iodide afforded NAD^+ models **9a**−**c** (X = I), in quantitative yields, and the following regioselective 1,4-reduction with aqueous sodium dithionite resulted in the formation of the bridged NADH models **10a**−**c**.[20]

Biomimetic Reduction with Bridged NADH Models. The bridged NADH models **10a**−**c** achieved excellent biomimetic reduction of the pyruvate analogues **12u**−**z** to produce the optically active lactate analogues **13u**−**z** in the presence of magnesium perchlorate in acetonitrile (Table 1). The model (*S*,*S*)-**10a** accomplished the enantioselective hydrogen transfer to methyl benzoylformate (**12u**) to afford (*R*)-methyl mandelate [(*R*)-**13u** (R^1 = Ph)] with 99% ee at room temperature (entry 1). *It is noteworthy that the rate of the reaction was remarkably enhanced as the reaction temperature increased without a significant decrease in enantioselectivity*. The reactions were complete within 24 h at 50 °C and within 6 h at 75 °C to give (*R*)-**13u** with 99% ee and 98% ee, respectively (entries 2 and 3). The planar chirality of the bridged NADH models plays a decisive role in determining the stereochemistry of the products. The diastereomer model (*R*,*S*)-**10b** having the opposite planar chirality behaved as the pseudoenantiomer of (*S*,*S*)-**10a**, the reduction with which resulted in (*S*)-**13u** with 97% ee at room temperature and 98% ee at 75 °C (entries 4 and 5). It is of particular importance to mention that, in each reaction, the homochiral *N*-methylpyridinium perchlorate **9a**,**b** (X = ClO_4)

(16) The ^{1}H NMR spectrum measured immediately after the reaction at 0 °C showed the formation of *cis*-2-azido-1-cyclododecenecarbaldehyde (*cis*-**2**): ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 2H), 2.24 (t, J = 7.5 Hz, 2H), 2.62 (t, J = 7.7 Hz, 2H), 10.1 (s, 1H); the other signals (14H) were overlapped with those of *trans*-**2**. Warming the mixture of *cis*- and *trans*-**2** caused the rapid transformation of *cis*-**2** into azirine **3** even at room temperature.

(17) The aldehyde signal of *cis*-**4** has a chemical shift similar to that of the known cyclohexene analogue with exclusive *cis*-configuration (δ 10.66 in DMSO-d_6). We also prepared this compound and confirmed that the chemical shift in $CDCl_3$ is δ 10.72 ppm: Tabyaoui, B.; Aubert, T.; Farnier, M.; Guilard, R. *Synth. Commun.* **1988**, *18*, 1475−1482.

(18) Our previous communication discusses the reaction pathways for the formation of **5** and **6**. See ref 1. For further synthetic application of formyl-substituted (vinylimino)phosphoranes to highly functional pyridines, see ref 13.

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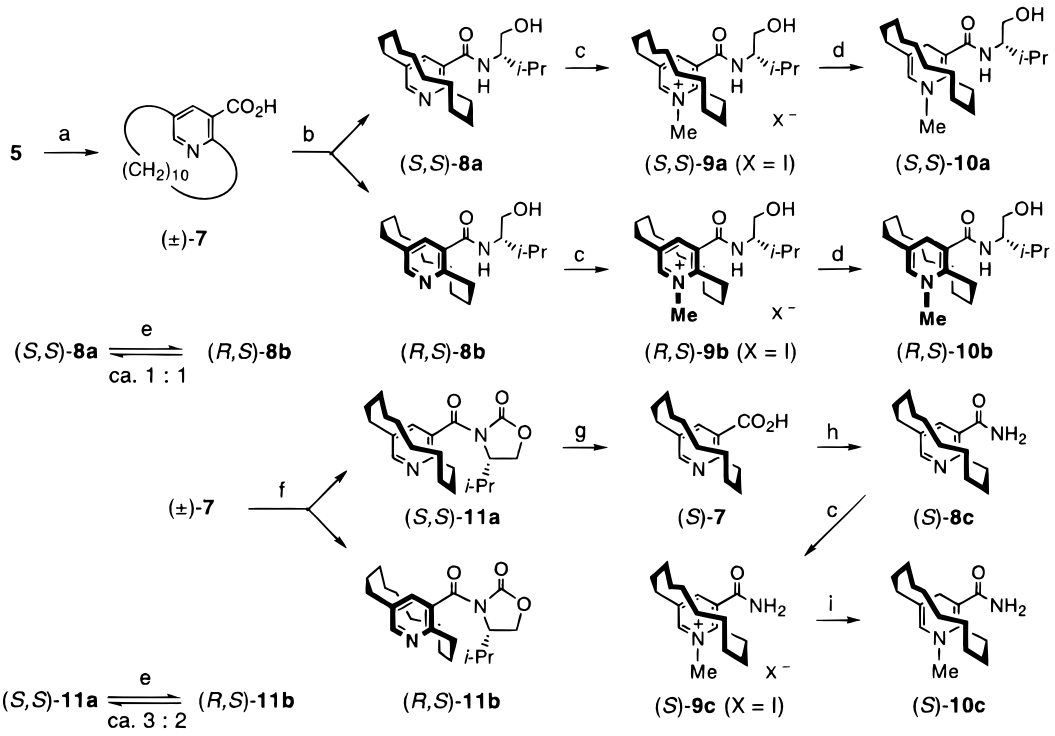
(20) The dihydropyridines **10a**−**c** were used in the next step immediately without further purification. These compounds are apparently sensitive to oxygen.

Scheme 3[a]



[a] Reagents: (a) LiOH, MeOH−H_2O, rt, 12 h (81% yield). (b) $(COCl)_2$, rt, 1 h; (*S*)-valinol, Et_3N, $CHCl_3$, rt, 2 h (48% each). (c) MeI, MeCN, 50 °C, 24 h (quant). (d) $Na_2S_2O_4$, Na_2CO_3, H_2O−CH_2Cl_2, rt, 12 h. (e) Toluene, reflux, 8 h (quant). (f) $(COCl)_2$, rt, 1 h; NaH, (*S*)-4-isopropyloxazolidinone, CH_2Cl_2, rt, 2 h [49% and 48% yields for (*S*,*S*)-**11a** and (*R*,*S*)-**11b**]. (g) LiOH, H_2O_2, DMF−THF−H_2O (3/3/1), 0 °C, 2 h (84% yield). (h) $(COCl)_2$, rt, 1 h; NH_3 (gas), $CHCl_3$, rt, 1 h (96% yield). (i) $Na_2S_2O_4$, Na_2CO_3, H_2O−MeOH−CH_2Cl_2, rt, 14 h (quant).

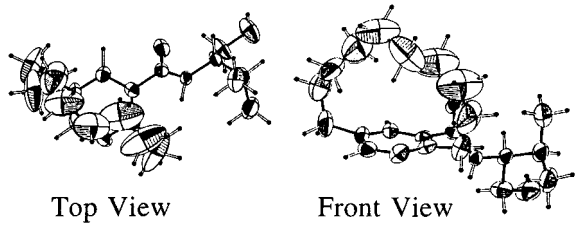


Figure 2. X-ray crystallographic structure of (*S*,*S*)-**8a**.

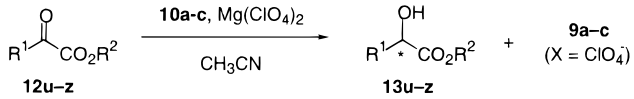
was recovered by chromatography on silica gel in 60−81% yields and that, therefore, the bridged NAD^+/NADH model systems were shown to retain their planar chirality throughout the entire redox processes and were recyclable. The primary amide model (*S*)-**10c** also allowed the excellent enantioselectivity to give (*R*)-**13u** with 98% ee at room temperature and with 97% ee at 75 °C (entries 6 and 7). Pyruvate esters such as *n*-butyl and benzyl pyruvate, **12v**,**w** (R^1 = Me), and the related α-ketoesters such as **12x**,**y** (R^1 = Et and *n*-Bu) were also efficiently reduced with (*S*)-**10c** to afford the corresponding lactates and their analogues (*R*)-**13v**−**y** with 96−98% ee's (entries 8−15). The other analogue **12z** having a slightly bulky alkyl group (R^1 = *i*-Bu) gave (*R*)-**13z** with 82−92% ee's (entries 16 and 17). In each reaction, the (*S*)- or (*R*)-planar chirality of **10a**−**c** resulted in the formation of the (*R*)- or (*S*)-lactate analogues, respectively, with high stereospecificity. The corresponding NAD^+ model (*S*)-**9c** (X = ClO_4) was also obtained in 68−83% isolated yields. These results indicate that the high enantioselectivity with the bridged NADH models **10a**−**c** is fully dependent on their planar chirality of the parapyridinophane moieties, and not on the nature of the carbamoyl sidearms (entries 1−7). When we initially designed the chiral models **10a**,**b**, the chelation sidearms of the hydroxyl groups were introduced to expect the formation of tight ternary complexes in the transition state of the reduction for good asymmetric induction in artificial systems (vide infra).[1] However, it is so surprising that the model (*S*)-**10c** having an unsubstituted carbamoyl group reduced **12u** with remarkably high ee's and achieved the almost identical optical yields of **13u** with slightly higher chemical yields as compared to those of **10a**,**b**.

Scheme 4 summarizes the isotope and related experiments showing the selectivity and the reactivity of the C-4 hydrogens in the bridged NADH model systems. The reduction of (±)-**9c** (X = I) with sodium dithionite in deuterated solvent underwent stereospecific labeling[12c] of the outer C-4 hydrogen of (±)-**10d**; a signal resonating at δ 2.80[21] disappeared in the ^1H NMR spectrum, and the deuterated signal appeared at δ 2.78 in the ^2H NMR spectrum. The deuterium located at the less hindered side of (±)-**10d** was almost exclusively transferred in the successive biomimetic reduction to give the labeled mandelate (±)-**13u**-*d*, with 99% deuterium incorporation. The recovered (±)-**9c** (X = ClO_4) was found not to contain a detectable amount of deuterium. These findings are unambiguous evidence that only one side of the dihydronicotinamide ring is the active face in this redox system. The ternary complex[22] illustrated in Figure 3 rationalizes the enantioselectivity, where magnesium ion exclusively chelates to methyl benzoylformate beneath the bridged NADH model since its top side is protected by the oligomethylene bridge. For further investigation of the reactivity of an inner hydrogen at C-4, we synthesized the 4-methyl-substituted model (±)-**10e**, the hydrogen of which is sandwiched between the methyl group and the bridge (Scheme 4). The

(21) Geminal C-4 protons of **10c** (δ 2.80 and δ 2.89) were unequivocally assigned by the COSY, HMQC, HMBC, and NOE differencial spectra. The NOE enhancement (3%) was observed between the inner proton (δ 2.89) and one of the oligomethylene protons (δ 1.60).

(22) Toyooka, Y.; Matsuzawa, T.; Eguchi, T.; Kakinuma, K. *Tetrahedron* **1995**, *51*, 6459−6474.

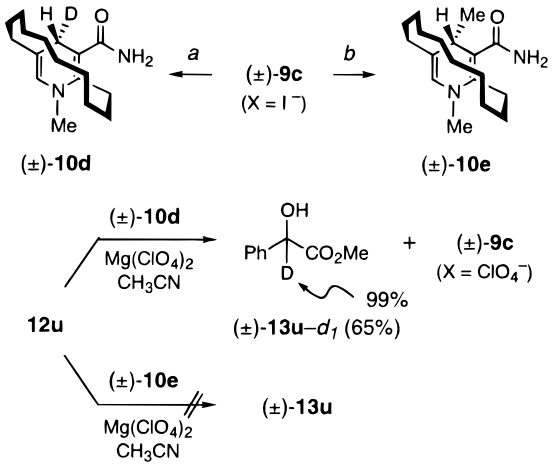
Table 1. Biomimetic Reduction of Pyruvate Analogues **12u−z** with Bridged NADH Models **10a−c**



							13u−z			9a−c
entry	10a−c	12u−z	R^1	R^2	*T*	time	yield (%)[a]	config.	ee (%)[b]	yield (%)[a]
1	**a**	**u**	Ph	Me	rt	5 d	64	*R*	99	66
2	**a**	**u**	Ph	Me	50 °C	24 h	70	*R*	99	81
3	**a**	**u**	Ph	Me	75 °C	6 h	63	*R*	98	65
4	**b**	**u**	Ph	Me	rt	4 d	64	*S*	97	60
5	**b**	**u**	Ph	Me	75 °C	6 h	63	*S*	98	71
6	**c**	**u**	Ph	Me	rt	2 d	84	*R*	98	69
7	**c**	**u**	Ph	Me	75 °C	6 h	78	*R*	97	72
8[c]	**c**	**v**	Me	*n*-Bu	rt	4 d	81[d]	*R*	98	72
9[c]	**c**	**v**	Me	*n*-Bu	75 °C	6 h	78[d]	*R*	97	>99[d]
10	**c**	**w**	Me	Bn	rt	5 d	81	*R*	97	83
11	**c**	**w**	Me	Bn	75 °C	6 h	76	*R*	96	68
12	**c**	**x**	Et	Bn	rt	2 d	80	*R*	98	80
13	**c**	**x**	Et	Bn	75 °C	3 h	71	*R*	98	74
14	**c**	**y**	*n*-Bu	Bn	rt	3 d	85	*R*	96	77
15	**c**	**y**	*n*-Bu	Bn	75 °C	5 h	74	*R*	96	70
16	**c**	**z**	*i*-Bu	Bn	rt	3 d	42	*R*	88	81
17	**c**	**z**	*i*-Bu	Bn	75 °C	6 h	44	*R*	92	71

[a] Isolated yields otherwise specified. [b] Determined by HPLC. [c] The reduction was carried out in CD_3CN. [d] Measured by ^1H NMR spectra using cyclohexanecarboxaldehyde as an internal standard.

Scheme 4[a]



[a] Reagents: (a) (i) $Na_2S_2O_4$, Na_2CO_3, D_2O−MeOD−CH_2Cl_2, rt, 11 h. (b) MeMgBr, THF, −20 °C and then rt, 45 min (36% yield and 32% for its regioisomer).

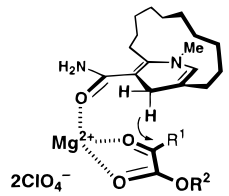
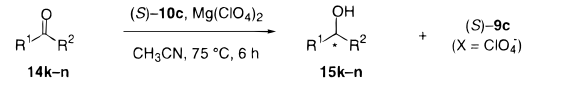


Figure 3. Proposed transition state for the reduction of methyl benzoylformate with NADH models **10c**.

compound (±)-**10e** was fully inert toward **12u** in the presence of magnesium ion even upon heating in acetonitrile at 75 °C for 6 h. This result suggests that the reacting C-4 hydrogen needs to reach its substrate by way of chelation with magnesium ion to form a ternary complex. In the case of (±)-**10e**, a remote interaction between the NADH model and the substrate is apparently insufficient to trigger the reaction.

Asymmetric Reduction of Activated Ketones. Table 2 indicates asymmetric reduction of some activated carbonyl compounds having a trifluoromethyl or 2-pyridyl group with a bridged NADH model compound. As well as the above-mentioned reduction of a series of α-ketoesters including pyruvates, the model (*S*)-**10c** reduced activated ketones such as **14k−n** with reasonably good enantioselectivity in the presence of magnesium ion to give the corresponding chiral alcohols (*R*)-**15k−n** with 79−89% ee. The introduction of the same (*R*)-configuration as in the case of the biomimetic reduction with (*S*)-**10c** suggests that those reactions also proceed through the ternary complex similar to that in Figure 3, in which the coordinating ester group is replaced with either a trifluoromethyl or a 2-pyridyl group.

Table 2. Asymmetric Reduction of **14k−n** with (*S*)-**10c**



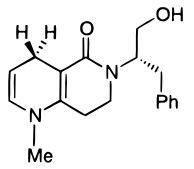
				15k−n			(*S*)-9c
entry	14k−l	R^1	R^2	yield (%)[a]	config.	ee (%)[b]	yield (%)[c]
1	**k**	Ph	CF_3	70	*R*	79	97
2	**l**		CF_3	72	*R*	88	99
3	**m**	CH_3		67	*R*	86	85
4	**n**	Ph		72	*R*	89	78

[a] Obtained on the basis of the formation of (*S*)-**9c**. [b] Determined by HPLC. [c] Isolated yields.

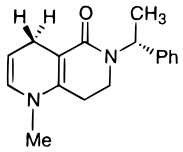
Discussion

Carbamoyl substituents of NADH model compounds are well-known to affect the stereochemistry of the products in coenzyme-mimetic reactions. A series of NADH models having hydroxyl groups exhibited typical sidearm effects;[4c,6,7,22] the model **16** provided 85−94% ee for (*R*)-mandelate, whereas a similar model, **17**,[6b] without a hydroxyl group had only 20% ee. The absolute configuration of the hydroxyl branch is still important for NADH models with competitive chiral auxiliaries. Davies reported NADH models having both a chiral carbamoyl group

and a chiral iron moiety designed for selective shielding of their dihydropyridine rings.[7] However, there seems to be both matched and mismatched combinations between the two auxiliary groups, and although the former achieved 97−98% ee for optically active mandelate, the latter gave only 15−16% ee. On the other hand, all the bridged models **10a**−**c** induced high enantioselectivity, which is strictly subject to the absolute structure of their solid parapyridinophane moieties. Thus, the carbamoyl group derived from (*S*)-valinol does not behave as a "*chirality-inducing group*" in our model systems, and its presence or absence, including the issue of absolute configuration, has almost negligible effects on the selectivity.



16



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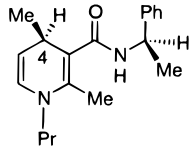

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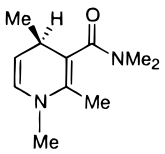

19

Another unique property of **10a**−**c** is the temperature independency of the enantioselectivity during the reduction of **12u**−**y**. Previous studies on the temperature effect of NADH model reactions showed that higher temperatures decreased more or less the enantioselectivity (5−29% decrease of ee's).[5c,6c,8a] The compounds **10a**−**c**, however, demonstrated a temperature independency of ee's though an additional chelation sidearm is missing in the case of **10c**. This means that, in the presence of magnesium ion, the stereoselective blocking of a dihydronicotinamide core is paramount for strictly mimicking the asymmetric reduction with coenzyme NADH and the principle is applicable even at higher temperatures. A striking advantage of bridged NADH models over C-4-substituted models is substantial recyclability, whereas the models such as **18**[5a] and **19**[5c] suffer from a loss of chirality at C-4 in each model reaction. Recyclable NADH models achieving temperature independency of high enantioselectivity should be seriously considered in directing our efforts to catalyze the redox reactions. These classes of NAD^+/NADH models would give us significant discretion to design the reversed course of model reactions ($NAD^+ \rightarrow$ NADH type) at various temperatures to challenge the unprecedented catalytic asymmetric model reactions. The bridged NAD^+/NADH model systems could also correlate with our recent findings of glycolysis-type reactions including the biomimetic oxidation and reduction in aprotic organic media.[23]

Conclusion

The bridged models **10a**−**c**, designed as the first homochiral ansa-type NADH models, successfully functioned in controlling both the direction and the orientation of the substrate approach to the model compounds for inducing high enantioselectivity in their biomimetic and related reactions. In particular, the (*S*)−**10c** model having both a primary carbamoyl group and a shielding bridge feigning an enzyme wall provides a compact chemical miniature of a holoenzyme, coenzyme NADH linked dehydrogenase, in terms of its unique and simple structure, high enantioselectivity, and usefulness for being recycled. In other words, the combination of the stereoselective shielding of a dihydronicotinamide core and the substrate control with magnesium ion satisfies the requirements for the highly enantioselective reduction of pyruvate analogues in the small model system of **10a**−**c**, which is comparable to the chiral environment of a holoenzyme during biological reduction.

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Supporting Information Available: Complete experimental details, including characterization data for *cis*-**1**, *trans*-**1**, *trans*-**2**, **3**−**7**, **8a**−**c**, **9a**−**c** (X = I and ClO_4), **10a**−**e**, and **11a**,**b**, the details of the crystal structure data for (*S*,*S*)-**8a**, and copies of ^{1}H NMR spectra of **10d** and ^{1}H and ^{13}C NMR spectra of *trans*-**1**, *trans*-**2**, **3**, **8b**, **10a**−**c**, **10e**, and **11a**,**b** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992990Y

(23) Kanomata, N.; Suzuki, M.; Yoshida, M.; Nakata, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1410−1412.