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A New Type of NADH Model Compound: Synthesis and Reactions

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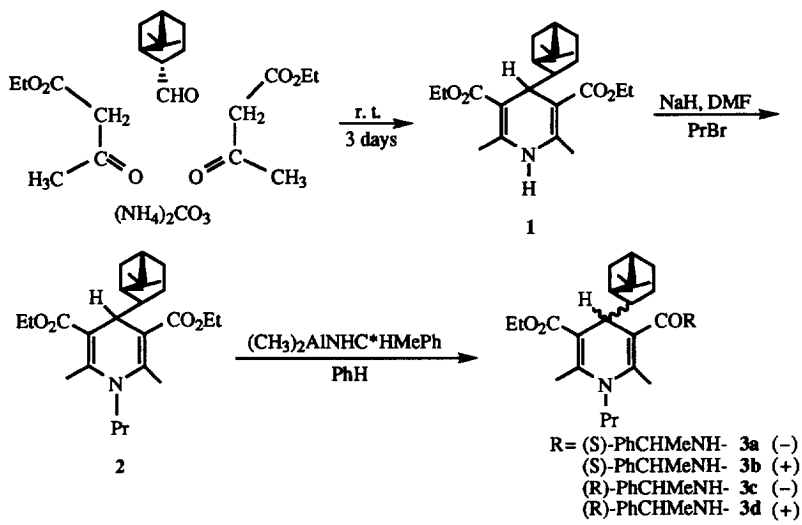
Abstract: Four diastereomeric NADH model compounds were synthesized by the reaction of a pinyl substituted Hantzsch ester with dimethylaluminum amide. The reduction of methyl benzoylformate with these models gave both enantiomers of methyl mandelate.

The design of readily accessible NADH model compounds combining high reactivity and enantioselectivity has ranged through a host of structurally diverse 1,4-dihydropyridines.[2] However, most of the studies on chiral NADH models have been based on modified dihydronicotinamides. Recently, Gelbard et. al. reported the synthesis of a new type of NADH model, a Hantzsch ester with a chiral substituent derived from a sugar at C-4.[3] They showed that the chiral substituent can be incorporated into the C-4 position of the Hantzsch ester easily by a proper choice of a chiral aldehyde as a starting material. Since there are two ester groups in the Hantzsch ester, one would anticipate that a new kind of NADH model would be produced if one of the ester groups was converted to an amide. In this paper, we report the synthesis of four optically active (2,6)-dimethyl-3-ethoxylcarbonyl-5-(N-α-methylbenzylcarbamoyl)-1-N-propyl-4-[(2S)-pinyl]-1,4-dihydropyridines by the reaction of a pinyl substituted Hantzsch esters with dimethylaluminum amide.

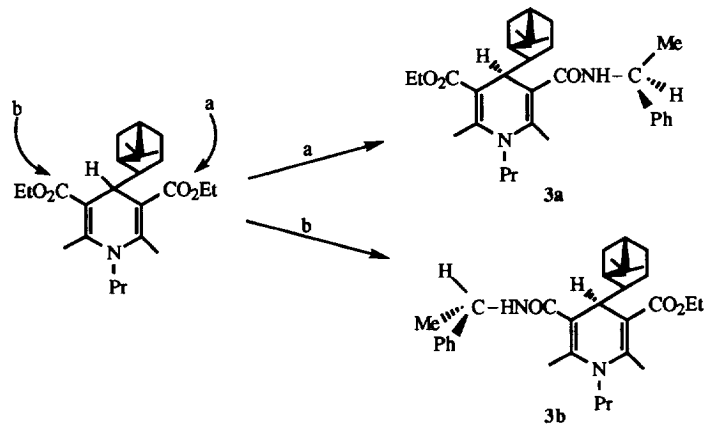
A efficient synthesis of these compounds is outlined in Scheme 1. Commercially available (–)-*trans*-myrtanol was oxidized with PCC to give (+)-*trans*-myrtanal,[4] one-pot condensation of (+)-*trans* myrtanal with ethyl acetoacetate in ammonium carbonate solution produced Hantzsch ester **1** in a 79% yield.[3] Hantzsch ester **1** was treated with sodium hydride in DMF, then allowed to react with 1-bromopropane to give **2**.[4] Treatment of Hantzsch ester **2** with dimethylaluminum amide, derived from (S)-(–)-α-methylbenzylamine, formed a mixture of diastereomeric compounds **3a** and **3b**.[6] A careful chromatographic separation on silica gel gave pure **3a** and **3b** in 44% and 28% yields respectively.[7] Within the detection limits of the ^{1}H NMR, the isolated diastereoisomer **3a** and **3b** were pure. The reaction can be followed by TLC until starting material **2** is completely consumed. Generally, the reaction of **3a** and **3b** was complete in 14 h. When the mixture was heated to reflux for over 20 h with an excess of the amino salt the second ester was slowly converted to a diamide. With the use of (R)-(+)-α-methylbenzylamine, **3c** and **3d** were prepared in 31% and 25% yields respectively.[8]

When the reaction was followed by ^{1}H NMR, the spectra showed the formation of **3a** and **3b** in a ratio of 3:2. As shown in Scheme 2, there are two possible pathways for attack at an ester group by di-methylaluminum amide. It is not unreasonable to assume the attack by dimethylaluminum amide away from

the bridge of the 4-pinyl group (pathway a) proceeds more rapidly than the attack from the bridge side (pathway b). As a result, **3a** is formed as the major product whose configuration can tentatively be assigned to (4S,9S). Accordingly, the configuration of the minor isomer **3b** can be assigned to (4R,9S). To further substantiate these assignments, an MM-2 calculation of the two structures shows that **3a** has the lowest relative energy (**3a**, 75.4 kcal/mol; **3b**, 77.9 kcal/mol). As expected, the bulky pinyl group at C-4 forces the 1,4-dihydropyridine to adopt a flat-boat conformation. This result is consistent with that found for crystal structure of 4-(2-imidazolyl)-1,4-dihydropyridine.[9] However, an attempt to establish the absolute configuration of the diastereomeric isomers (**3a-d**) by x-ray crystallography was not successful. The structural assignments are tentatively made by analogy to the stereochemical relationships established for the reduction reactions of the 2,4-dimethyl substituted chiral amides of dihydronicotinic acid.[10]



Scheme 1. Synthesis of Compounds 3a-d



Scheme 2. Possible Attacks at an Ester by Dimethylaluminum Amide

The reduction of methyl benzoylformate with **3a** or **3c** proceeded quite well in 83% and 61% yields (Table 1). However, the reductions with **3b** and **3d** gave less satisfactory yields. **3a** and **3c** gave S-(+)-methyl mandelate whereas **3b** and **3d** gave R-(–)-methyl mandelate. Both enantiomers of methyl mandelate can be obtained using these NADH models. Although the enantiomeric excess from **3b** or **3d** were not promising, the reduction of methyl benzoylformate with **3a** and **3c** were obtained in moderate to good enantiomeric excess. It appears that the configurations of the reduction products are determined mainly by the configuration of hydrogen at the 4-position of these optically active dihydropyridines.

Table I. The Reduction of Methyl Benzoylformate by Dihydropyridines 3[a]

reaction	model compound	products		
		yield%[b]	ee%[c]	config.
1	**3a**	83	72	(+)-S
2	**3b**	25	31	(–)-R
3	**3c**	61	42	(+)-S
4	**3d**	19	7	(–)-R

[a]Reductions were performed in acetonitrile at 61 °C with 1 eq. of $Mg(ClO_4)_2$ for 20 days. In the absence of $Mg(ClO_4)_2$ no reduction products were observed. [b]The yields given are the average values determined by GC, from duplicate experiments. [c]Based on the optical rotation of pure methyl mandelate, (lit, $[\alpha]_D$=141.4°).[11]

Based on previous models,[10-13] the transition state for the reduction reactions of **3a** can be depicted as resulting from a magnesium complex (Figure 1). One can anticipate that the magnesium is complexed to both the C-3 and the C-5 carbonyl oxygen and to the carbonyl oxygen of methyl benzoylformate. This conformation produces (S)-mandelate as the major enantiomer, see eq. 1.

$$\mathbf{3a} + PhCOCO_2Me \xrightarrow{Mg^{++}} (S)\text{-}PhCH(OH)CO_2Me + \mathbf{3a}^{+}(\text{-H}) \qquad (1)$$

An examination of Dreiding-Stereomodels of the proposed complex indicates that the formation of (R)-mandelate is energetically disfavored due to steric interactions between the benzoyl phenyl and amide group of the model. The high reactivity of **3a** or **3c** and the moderately good e.e.% obtained from these reactions appears to be achieved through a transition state in which chelation of the substrate and the dihydropyridine is efficient. In **3a** the bridge of the pinyl group is away from the hydrogen at C-4, however, in **3b** and **3d**, the hydrogen at C-4 and the bridge of the pinyl group are on the same side. The complex would be forced to adopt a conformation in which the bridge of the pinyl group prevents efficient chelation of the substrate and the dihydropyridine. Both the reactivity of **3b** and **3d** and the %e.e. produced from these reactions are much lower than those from **3a** and **3c**.

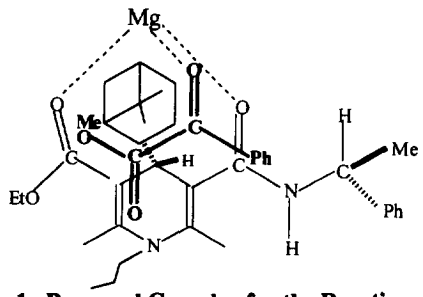


Figure 1. Proposed Complex for the Reaction of Model 3a

References and Notes

1. Taken in part from the M.Sc. thesis of Xianfeng Li, University of Alberta, 1992.
2. For recent reviews see: (a) Burgess,V. A.; Davies, S. G.; Skerlj, R. T. *Tetrahedron: Asymmetry* **1991**, *2*, 299. (b) Ohno, A. Vishida, S. *Lecture Notes in Bioorganic Chemistry;* Springer Verlag: Heideberg, 1986. (c) Kellog, R. M. *Angew. Chem., Int. Ed. Engl.*, **1984**, *23*, 782.
3. (a) Zehani, S.; Lin, J.; Gelbard, G. *Tetrahedron*, **1989**, *45*, 733. (b) Zehani, S.; Gelbard, G. *Bull. Soc. Chim. Fr.* **1988**, 104. (c) Zehani, S.; Gelbard, G. *Reactive Polymer*, **1987**, *6*, 81.
4. Coxon, J. M.; Hydes, G.; Steel, P. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1351.
5. Palecek, J.; Pavlik, M.; Kuthan, J. *Collection Czechoslovak Chem. Commun.* **1983**, *48*, 608.
6. Lipton, M. F.; Basha, A.; Weinreb, S. M. *Organic Synthesis* John Wiley & Sons, Inc. 1980; Vol. 59, p 49.
7. The residue was purified by flash chromatography (ethyl acetate/ether/petroleum ether=1/1/2) to give each diastereomer of **3**. The fast moving product, **3a** (5.5 g, 44%): m.p. 99 °C; $[\alpha]_D^{22}$=-176.8° (EtOH); ^{1}H NMR (300 MH_3, $CDCl_3$) δ: 0.65 (s, 3H), 0.92 (t, 3H) 1.17 (s, 3H), 1.25 (t, 3H), 1.50 (d, 3H), 1.35-2.08 (m, 11H), 2.30 (s, 3H), 2.41 (s, 3H), 3.53 (d, 1H), 3.60 (t, 2H), 4.15 (m, 2H), 5.17 (m, 1H), 5.84 (d,1H), 7.30 (m, 5H); Anal Calcd for $C_{31}H_{44}N_2O_3$: C, 75.57; H 9.00. N, 5.69. Found: C, 75.57; H, 9.14; N, 5.56. The slow moving product, **3b** (3.5 g, 28%): m.p. 78 °C; $[\alpha]_D^{22}$=+149.1° (EtOH); ^{1}H NMR (300 MH_3, $CDCl_3$) δ: 0.59 (s, 3H), 0.90 (t, 3H) 1.10 (s, 3H), 1.23 (t, 3H), 1.49 (d, 3H), 1.35-2.00 (m, 11H), 2.20 (s, 3H), 2.44 (s, 3H), 3.46 (d, 1H), 3.60 (t, 2H), 4.12 (m, 2H), 5.22 (m, 1H), 5.80 (d,1H), 7.33 (m, 5H) Anal Calcd for $C_{31}H_{44}N_2O_3$: C, 75.57; H 9.00; N, 5.69. Found: C, 75.40; H, 9.23; N, 5.58.
8. The fast moving product, **3c** (2.9 g , 31%): m.p. 100 °C; $[\alpha]_D^{22}$=-165.4° (EtOH); ^{1}H NMR (300 MH_3, $CDCl_3$) δ: 0.59 (s, 3H), 0.90 (t, 3H) 1.10 (s, 3H), 1.23 (t, 3H), 1.49 (d, 3H), 1.35-2.00 (m, 11H), 2.20 (s, 3H), 2.44 (s, 3H), 3.46 (d, 1H), 3.60 (t, 2H), 4.12 (m, 2H), 5.22 (m, 1H), 5.80 (d, 1H), 7.33 (m, 5H); Anal Calcd for $C_{31}H_{44}N_2O_3$: C, 75.57; H 9.00; N, 5.69; Found: C, 75.69; H, 9.09; N, 5.64. The slow moving product, **3d** (3.2 g, 25%): m.p. 106 °C; $[\alpha]_D^{22}$=+167.3° (EtOH); ^{1}H NMR (300 MH_3, $CDCl_3$) δ: 0.63 (s, 3H), 0.90 (t, 3H) 1.12 (s, 3H), 1.23 (t, 3H), 1.54 (d, 3H), 1.15-2.01 (m, 11H), 2.17 (s, 3H), 2.42 (s, 3H), 3.53 (d, 1H), 3.60 (t, 2H), 4.10 (m, 2H), 5.20 (m, 1H), 5.78 (d, 1H), 7.36 (m, 5H); Anal Calcd for $C_{31}H_{44}N_2O_3$: C, 75.57; H 9.00; N, 5.69; Found: C, 75.51; H, 9.14; N, 5.68. In addition, and unresolved mixture **3c-d** (2.1 g, 17%) was obtained.
9. Kaptein, B.; Kellogg, R. M. *Recl. Trav. Chim, Pays-Bas*, **1990**, *190*, 388.
10. Tanner, D.D.; Kharrat, A. *J. Am. Chem. Soc.* **1988**, *110*, 2968.
11. Ohno, A; Ikeguchi, M.; Kimura, T.; Oka, S. *J. Am. Chem. Soc.* **1979**, *101*, 7036.
12. (a) Meyers, A. I.; Oppenlaender, T. *J. Am. Chem. Soc.* **1986**, *108*, 1989. (b) Meyers, A. I.; Brown, J. D. *J. Am. Chem. Soc.* **1987**, *109*, 3155.
13. (a) Davies, S. G.; Skerlj, R. T.; Whittaker, M. *Tetrahedron Lett.* **1990**, *31*, 3213. (b) Davies, S. G.; Edwards, A. J.; Skerlj, R. T.; Sutton, K. H.; Whittaker, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1027.

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