Molecules **2007**, *12*, 979-987

molecules

ISSN 1420-3049

www.mdpi.org/molecules

Communication

A New Type of NADH Model Compound: Synthesis and Enantioselective Reduction of Benzoylformates to the Corresponding Mandelates

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Received: 23 March 2007; in revised form: 17 April 2007 / Accepted: 19 April 2007 / Published: 11 May 2007

Abstract: A new type of NADH model compound with good reactivity and enantioselectivity has been synthesized in good yields by an efficient and convenient synthetic method. The structures of these model compounds were confirmed by ^{1}H- and ^{13}C-NMR and MS.

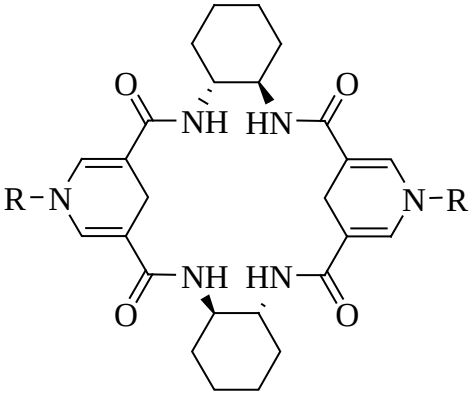
Keywords: NADH model, C_2 symmetry, chirality, synthesis.

Introduction

Since Ohno and coworkers [1] reported the first NADH model compound, a large number of such mimics have been developed [2]. In particular, chiral NADH model compounds have been extensively studied with the aim of developing new enantioselective reducing agents [2]. Generally, highly stereoselective chiral NADH models have been designed by incorporating remote sterically-demanding side chains [3] or a substituent at the reaction centre: the C4 position of the dihydropyridine ring [4]. However, the former approach implies a significant modification of the

dihydropyridine ring and the latter one resulted in a loss of chirality at the C4 position during the course of the model reaction. Recently, several NADH models with specific conformations which could steroselectively reduce pyruvate mimics were reported [5], and a few such models have been studied so far. Herein we report a novel chiral NADH model compounds **1a,b**, possessing a specific C_2-symmetric conformation.

Figure 1. The new NADH model compounds **1a,b**.



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1a: R= -CH_3
1b: R= -CH_2Ph

In our model compounds **1a,b** four chiral carbon centers were introduced by the presence of (1*R*,2*R*)-diaminocyclohexane [6]. Two identical pyridine-3,5-dicarbonyl units were connected by two identical (1*R*,2*R*)-diaminocyclohexane units into a large ring. The C_2-symmetric structure has the following advantages: (i) we can take advantage of an efficient bi-directional synthetic method to prepare **1a,b**; (ii) it simplified the analysis of the reduction reactions using our model compounds **1a,b**.

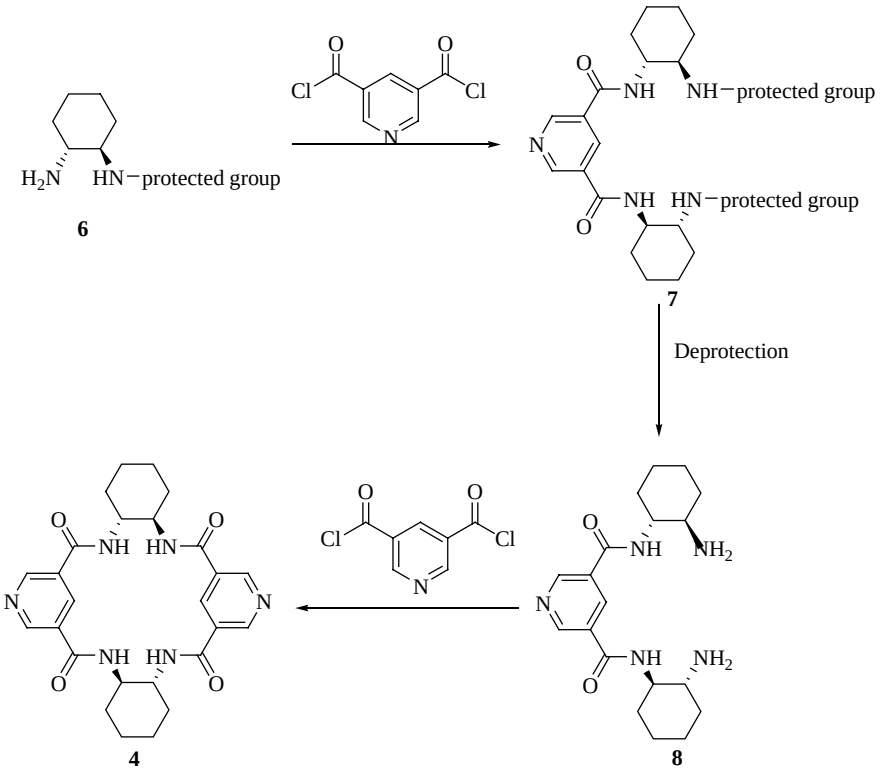
Results and Discussion

Generally, the single-protection method was used to synthesize macrocyclic compounds such as our models **1a,b** (Scheme 1). One of amino groups of (1*R*,2*R*)-diaminocyclohexane was protected and the resulting compound **6** was reacted with pyridine-3,5-dicarbonyl dichloride to obtain compound **7**. After deprotection of **7**, the resulting amide **8** was converted to macrocyclic compound **4** by treatment with another portion of pyridine-3,5-dicarbonyl dichloride. However, this traditional method suffered from low yields and a long synthetic route. Herein, we would like to report a novel practical and efficient method as outlined in Scheme 2.

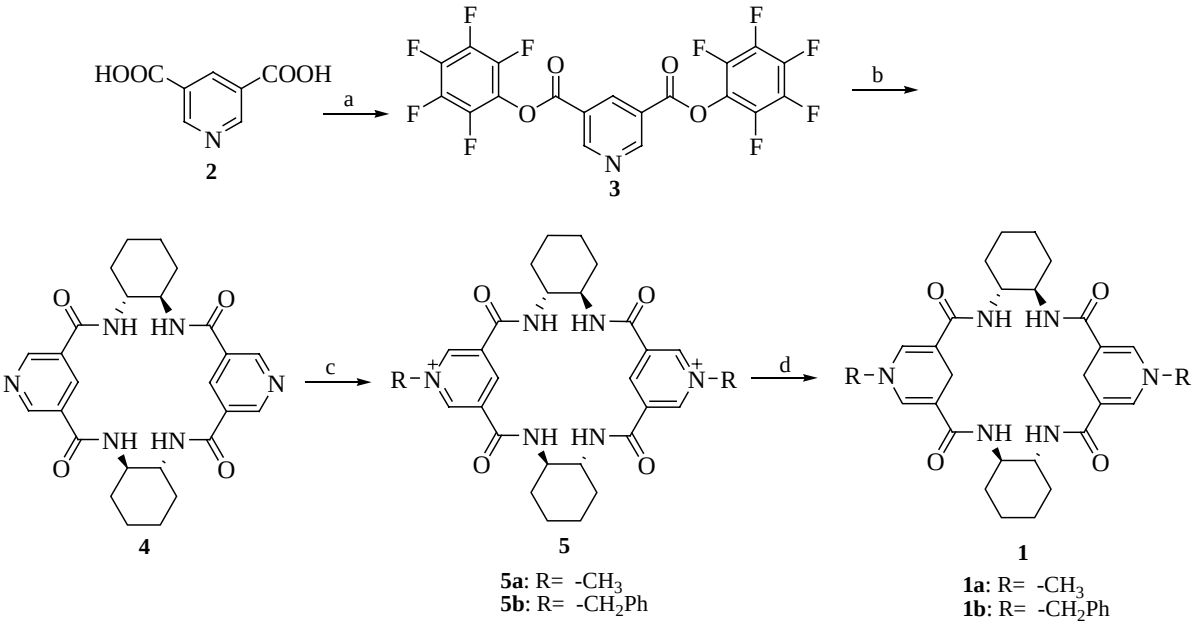
Although the pentafluorophenoxy is a good leaving group, bis(pentafluorophenyl)pyridine-3,5-dicarboxylate (**3**) is not so active as pyridine-3,5-dicarbonyl dichloride in the reaction with (1*R*,2*R*)-diaminocyclohexane. As a result, the key intermediate **4** was obtained conveniently in only one step from (1*R*,2*R*)-diaminocyclohexane, avoiding the complicated single-protected method. When an appropriate halide was added to a DMF solution of **4** and the resulting reaction mixture was heated at 80 $^{\circ}$C ~90 $^{\circ}$C for 12 h, then **5a,b** were obtained. Crude **5a,b**, used directly without further purification,

was reduced by sodium dithionite to afford crude compounds **1a,b**. After separation on Sephadex LH-20 with methanol as the eluent, pure model compounds **1a,b** were obtained.

Scheme 1. Single-protection route to the key intermediate **4**.



Scheme 2. Preparation of NADH model compound **1.**



Reagents and conditions: a) pentafluorophenol, DMF, RT, 6 h, 92%; b) (1*R*,2*R*)-diamino-cyclohexane, THF, RT, 4 h, 62%; c) **5a**: CH_3I, 80 °C ~90 °C, 12 h, 72%; **5b**: $BrCH_2Ph$, 80 °C ~90 °C, 12 h, 64%; d) $Na_2S_2O_4$, Na_2CO_3, H_2O, 12 h, **1a**: 71%, **1b**: 41%

The C_2-symmetric NADH models **1a,b** could enantioselectivly reduce the pyruvate mimic methyl benzoylformate in acetonitrile in the presence of magnesium perchlorate (Scheme 3). The results summarized in Table 1 shows that NADH models **1a** and **1b** are similar as reducing agents. The resulting reduction products were the same enantiomer (*R*-mandelate) and they dispalyed similar enantiomeric excess values, so we believe that the reductibility and the enantioselectivity of model compounds **1a,b** is related to their specific C_2-symmetric conformation, rather than the substituent at the N1 position of the dihydropyridine rings.

Scheme 3. Asymmetric reduction of methyl benzoylformate with **1**.

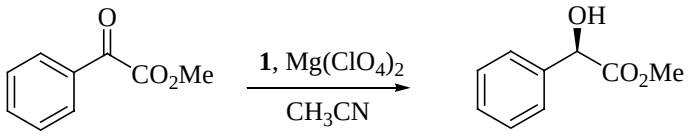


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Table 1 Asymmetric reduction of methyl benzoylformate with **1**.

Entry	T (°C)	t	9		
			Ee (%)[a]	Config.	Yield (%)[b]
1a	RT	3 d	68	R	98
1b	RT	3 d	70	R	96

[a] Determined by HPLC, see Experimental; [b] isolated yields.

Conclusions

In summary, a new type of NADH model compound with good reactivity and enantioselectivity has been synthesized in good yields by an efficient and convenient synthetic method.

Experimental Section

General

All starting materials were commercially available. DMF was dried with $CaSO_4$ and distilled under reduced pressure. THF was distilled from CaH_2. Melting points were measured on an X-4 digital microscope melting point apparatus (Beijing Tech Instrument Co., Ltd.). IR spectra (KBr disks) were recorded on a Perkin-Elmer Nicol FT-50X spectrometer. ^{1}H-NMR and ^{13}C-NMR were recorded on Bruker AC-300 FT or AV-400 FT instruments. The chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane (TMS). Electron impact MS spectra were obtained on a JEOL JMS-HX 100 instrument. High resolution mass spectra (HRMS) were measured in negative ion mode by Electrospray (ESI) on APEX-Qe 94 instrument. Chiralcel OD-H columns were purchased from Daicel Chemical Industries. Column chromatography was carried with silica gel (200-300 mesh), and HF_{254} silica gel for TLC was obtained from Qingdao Marine Chemistry Co. Ltd., Qingdao, China. Sephadex LH-20 (18-110 μm) was provided by H&E Co., Ltd.

bis(Pentafluorophenyl) pyridine-3,5-dicarboxylate (**3**)

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (6.4 g, 33.2 mmol) was added to a solution of pyridine-3,5-dicarboxylic acid (2.8 g, 16.8 mmol) and pentafluorophenol (6.2 g, 33.2 mmol) in 150 mL of dry DMF. The resulting solution was stirred at room temperature for 6 h, water (200 mL) was added and a white precipitate formed. The product was collected by filtration and purified by flash column chromatography (silica gel, eluent CH_2Cl_2) to give compound **3** as a white solid (7.80 g, 93 %); m.p. 154~157 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ=9.20 (s, 1H; pyr-4-C*H*), 9.68 ppm (s, 2H; pyr-2,6-C*H*); IR (KBr): v=3061, 2670, 2465, 1773, 1655, 1602, 1516, 1471, 1430, 1321, 1294, 1223, 1154, 1095, 996, 731 cm^{-1}; EI-MS m/z (%): 316 (100), 260 (23.8), 183 (6.6), 105 (10.8).

(4R,9R,19R,24R)-3,10,14,18,25,29-Hexaazapentacyclo[25.3.1.1^{12,16}.0^{4,9}.0^{19,24}]dotriacontane-1(31),12(32),13,15,27,29-hexaene-2,11,17,26-tetrone (**4**)

A solution of (1*R*,2*R*)-diaminocyclohexane (1.1 g, 9.6 mmol) in tetrahydrofuran (30 mL) was added to a solution of bis(pentafluorophenyl)pyridine-3,5-dicarboxylate (5.0 g, 10.0 mmol) in tetrahydrofuran at 0 ºC (ice bath). Upon complete addition and then the solution was stirred at room temperature for 3 h. The solvent was removed to give the crude product. The product was purified by column chromatography (eluent: 30 % ethyl acetate-hexane) to give **4** as a white solid (1.5 g, yield 62 %); ^{1}H- NMR (400 MHz, $(CD_3)_2SO$): δ=1.25-1.34 (m, 4H; C*H*H'CH_2CHNH), 1.48-1.50 (m, 4H; CH*H'*CH_2CHN-H), 1.71-1.73 (m, 4H; C*H*H'CHNH), 1.84-1.91 (m, 4H; CH*H'*CHNH), 3.94-3.99 (m, 4H; C*H*NH), 8.38 (s, 2H; pyr-4-C*H*), 8.57 (d, *J*=7.76, 4H; N*H*), 8.92 ppm (s, 4H; pyr-2,6-C*H*); ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ=24.9 (*C*$H_2$$CH_2$CHNH), 31.5 (*C*$H_2$CHNH), 53.5 (*C*HNH), 130.3 (pyr-3,5-*C*), 134.8 (pyr-4-*C*H), 150.1 (pyr-2,6-*C*H), 165.0, 165.1 ppm (*C*=O); ESI-MS m/z=491.4 $[M+H]^+$.

(4R,9R,19R,24R)-14,29-Dimethyl-3,10,14,18,25,29-hexaazapentacyclo[25.3.1.1^{12,16}.0^{4,9}.0^{19,24}]-dotriaconane-1(31),12(32),13,15,27,29-hexaene-2,11,17,26-tetrone iodide (**5a**)

Methyl iodide (5 mL) was added to a dry DMF (5 mL) solution of compound **4** (1.0 g, 4.1 mmol). The mixture was stirred under nitrogen at 80 °C ~90 °C for 12 h, then cooled and ether was added. The precipitate formed was collected by filtration and washed with ether to give the crude product **5a** as a yellow solid (1.1 g, yield 72 %), which can be used without further purification.

(4R,9R,19R,24R)-14,29-Dibenzyl-3,10,14,18,25,29-hexaazapentacyclo[25.3.1.1^{12,16}.0^{4,9}.0^{19,24}]dotriacontane-1(31),12(32),13,15,27,29-hexaene-2,11,17,26-tetrone bromide (**5b**)

This preparation was carried out in a similar fashion to that of **5a**, and the product was obtained as a yellow solid (1.1 g, yield 64 %).

(4R,9R,19R,24R)-14,29-Dimethyl-3,10,14,18,25,29-hexaazapentacyclo[25.3.1.1^{12,16}.0^{4,9}.0^{19,24}]dotriacontane-1,12,15,27-tetraene-2,11,17,26-tetrone (**1a**)

An aqueous solution (20 mL) of sodium dithionite (1.8 g, 10.3 mmol) and sodium carbonate (0.68 g, 6.5 mmol) was added dropwise at room temperature under nitrogen to an aqueous solution (10 mL) of compound **5** (0.5 g, 1.3 mmol). The mixture was left to stir over night at room temperature, during which time a yellow precipitate formed. The product was collected by filtration and purified by gel chromatography (Sephadex LH-20, eluent CH_3OH) to give **1a** as a yellow solid (0.24 g, yield 71 %); ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ=1.23-1.25 (m, 8H; C*H*$_2$CH$_2$CHNH), 1.66 (m, 4H; C*H*H'CHNH), 1.88 (m, 4H; CH*H'*CHNH), 2.90 (s, 4H; pyr-4-C*H*), 3.03 (s, 6H; C*H*$_3$N), 3.54 (m, 4H; C*H*NH), 6.80 (s, 4H; pyr-2,6-C*H*), 7.27-7.28 ppm (m, 4H; N*H*); ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ=21.5 (*C*H$_2$CH$_2$CHNH), 24.6 (*C*H$_2$CHNH), 31.8 (*C*H$_3$N), 40.4 (pyr-4-*C*H$_2$), 53.9 (*C*HNH), 104.1 (pyr-3,5-*C*), 136.6 (pyr-2,6-*C*H), 167.1 ppm (*C*=O); ESI-MS m/z=523.5 $[M+H]^+$, 545.5 $[M+Na]^+$.

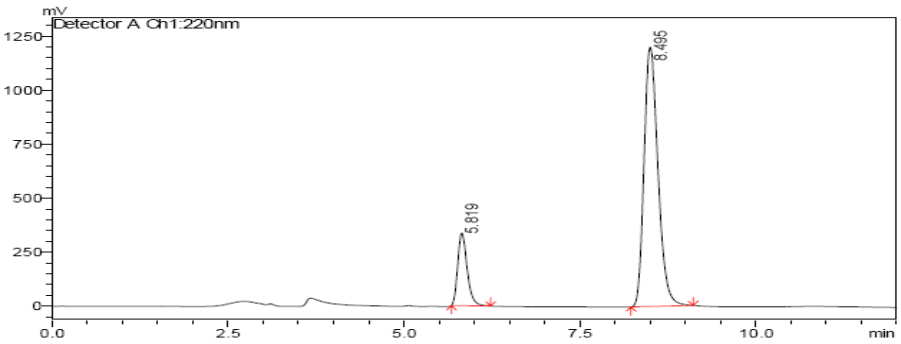
(4R,9R,19R,24R)-14,29-Dibenzyl-3,10,14,18,25,29-hexaazapentacyclo[25.3.1.1^{12,16}.0^{4,9}.0^{19,24}]dotriacontane-1,12,15,27-tetraene -2,11,17,26-tetrone (**1b**)

This preparation was carried out in a similar fashion to that of **6a**. The product was obtained as a yellow solid (0.17g, yield 41 %); ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ=1.24-1.29 (m, 8H; C*H*$_2$CH$_2$CHNH), 1.65 (m, 4H; C*H*H'CHNH), 1.88-1.90 (m, 4H; CH*H'*CHNH), 2.95 (s, 4H; pyr-4-C*H*), 3.54 (m, 4H; C*H*NH), 4.42 (d, *J*=15.66, 2H; ArC*H*H'), 4.58 (d, *J*=15.66, 2H; ArC*H*H'), 6.92 (s, 4H; pyr-2,6-C*H*), 7.27 (m, 4H; N*H*), 7.29-7.39 ppm (m, 10H; C$_6$*H*$_5$); ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ=21.9 (*C*H$_2$CH$_2$CHNH), 24.7 (*C*H$_2$CHNH), 31.8 (pyr-4-*C*H$_2$), 54.0 (*C*HNH), 56.4 (Ar*C*H$_2$), 104.8 (pyr-3,5-*C*), 127.4 (Ar-4-*C*H), 127.7 (Ar-2,6-*C*H), 128.9 (Ar-3,5-*C*H) 138.0 (Ar-1-*C*) 167.2 ppm (*C*=O); HR-MS(ESI) m/z=$[M-H]^-$ calcd. 673.35078, found 673.34907.

General Procedure for the asymmetric reduction of methyl benzoylformate with NADH model compounds **1a-b** [2c]

The NADH model **1a-b** (1 mmol), methyl benzoylformate (2 mmol) and magnesium perchlorate (2 mmol) were dissolved in acetonitrile (5 mL). The resulting solution was stirred in the dark under nitrogen at room temperature for 3 days. Water (0.5 mL) was then added and the product extracted with ether. The organic phase was dried and the solvent evaporated. The crude methyl mandelate was purified by chromatography, using 1:5 ethyl acetate/petroleum ether as eluent, to give a white solid. Product identity and enantiomeric excess were determined by HPLC analysis using a Chiracel OD-H column (0.46 cm I.D. x 25 cm L). Chromatographic conditions: injection: 10 μL; eluent: n-hexane/2-propanol = 85:15; flow rate: 1.0 mL/min; temperature: 35 °C. For **1a** (Figure 2): UV detection: λ= 220 nm; tR = 5.819 min [(S)-enantiomer] and 8.495 min [(R)-enantiomer]. For **1b** (Figure 3): UV detection: λ= 220 nm; t_R = 5.814 min [(S)-enantiomer] and 8.464 min [(R)-enantiomer].

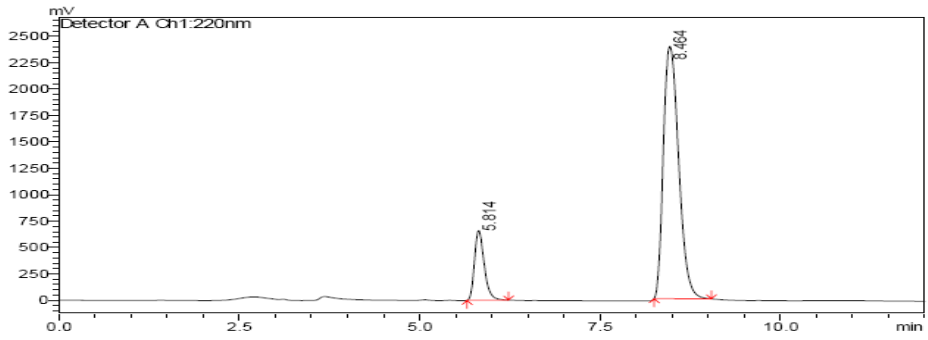
Figure 2. Resolution of methyl mandelate produced with **1a**.



<Column Performance Report>
UV 220 nm

Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	5.819	3131373	15.9021	8674.250	1.367	--
2	8.495	16560247	84.0979	8694.477	1.301	8.713

Figure 3. Resolution of methyl mandelate produced with **1b**.



<Column Performance Report>
UV 220 nm

Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	5.814	6191275	14.9040	8588.810	1.372	--
2	8.464	35349821	85.0960	7665.522	1.366	8.312

Acknowledgements

Support for this research was provided by the Nature Science Foundation of China (grants 20472090 and 10576034).

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Sample Availability: Samples of the compounds described in this paper are available from the authors.