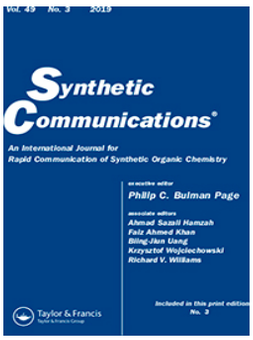

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Design and synthesis of cage-like NADH model molecule intermediate with multi-chiral centers

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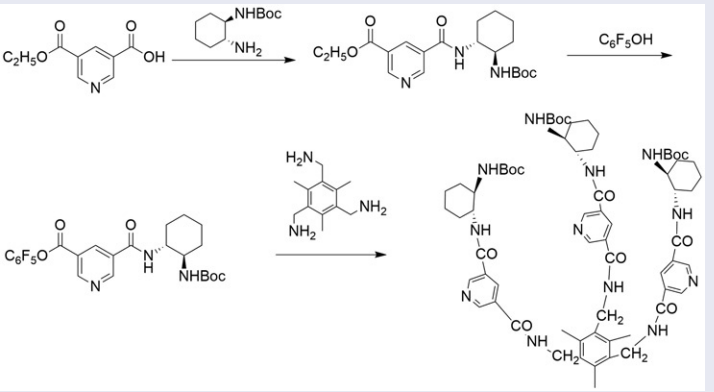
ABSTRACT

Studying NADH molecules is one of the most active areas in biomimetic research. It is important to design novel and efficient chiral NADH model molecules. Herein, a cage-like NADH model with multi-chiral centers was designed, and key intermediates have been synthesized. In this study, we found that pentafluorophenoxy group is an excellent leaving group for our synthetic route.

GRAPHICAL ABSTRACT



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KEYWORDS
Cage-like; multi-chiral centers; NADH; symmetry; intermediate

Introduction

NADH is a very important coenzyme which plays a key role in glycolysis, fatty acid metabolism, amino acid degradation and other metabolic processes. Therefore, studying NADH coenzymes has attracted wide attention of biologists and chemists, and has become one of the most active areas in biomimetic research.[1–8]

In organisms, coenzyme NADH and its oxidation state NAD^+ could reduce or oxidize specific substances by supplying or capturing hydride under the catalysis of related

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enzymes, and provide necessary circular reactions for energy storage and release. Many redox reactions and metabolic processes in organisms could not work without the participation of NADH.[9] Due to the important role of coenzyme NADH in organisms, biomimetic study about NADH is always a hot topic in biochemistry, organic chemistry, physical chemistry and related fields.[10,11] In recent years, some model molecules have been synthesized by biomimetic methods, and dihydropyridine amide group, which is the active group in NADH, has been well investigated. Meanwhile, great progress has been made in the study of hydride and electron transfer between oxidation and reduction states of model molecules.[12–22] Our group has also contributed valuable work and reported several syntheses of novel NADH model molecules.[23,24]

In order to further study the reaction mechanism of chiral NADH model molecules in asymmetric reactions and the catalyzed reactions with enzymes, we designed novel chiral NADH model molecules, and key intermediates were synthesized.

Discussion

Because of the novelty and complexity of the target molecule structure, it is difficult to explore and determine the synthetic route. However, on the basis of our previous work, the synthetic route of target molecules was determined, and the key intermediates have been synthesized (Scheme 1).

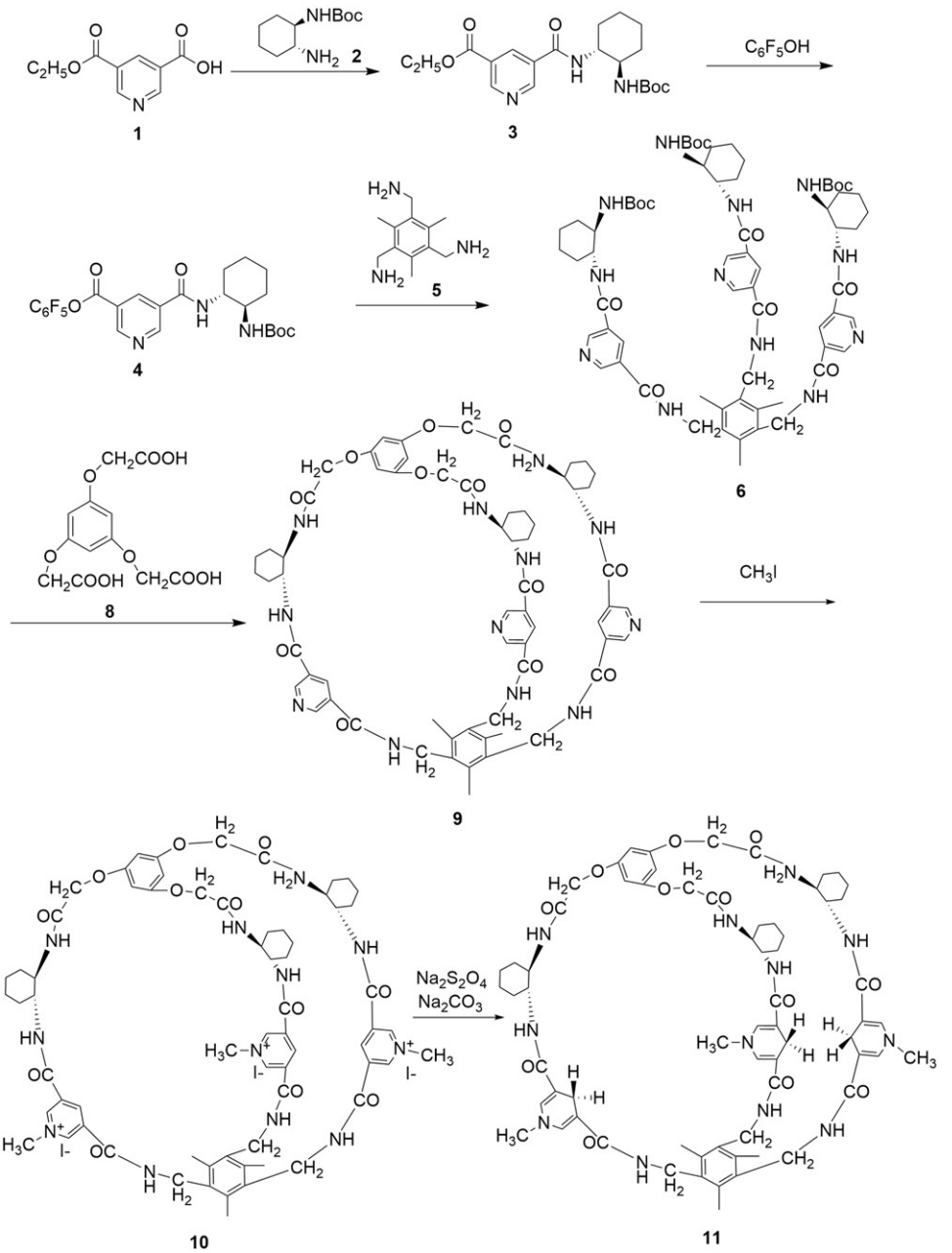
On the basis of our group's previous research work, we improved the synthetic route and replaced some raw materials which are difficult to prepare. The key intermediate compounds **2–8** were synthesized and characterized.

In order to introduce chiral centers into the target molecule, we chose the commercial available cyclohexanediamine as chiral source. With the help of tartaric acid, chiral resolution was achieved and pure chiral cyclohexanediamine was obtained. In order to preserve chiral cyclohexanediamine better, we transformed it to corresponding hydrochloride. $(Boc)_2O$ could selectively protect amino group of cyclohexanediamine under base conditions and generate hydrochloride of compound **2** (Scheme 2).

Through esterification of pyridine 3,5-dicarboxylic acid and unilateral deesterification, pyridine 3,5-dicarboxylic acid by unilateral protection was prepared. Then pyridine 3,5-dicarboxylic acid reacted with compound **2** to provide compound **3**. In order to carry on the macrocyclic ring closure smoothly, we used the pentafluorophenol to react with compound **3**. And compound **4** with pentafluorophenoxy group was synthesized after esterification (Scheme 3).

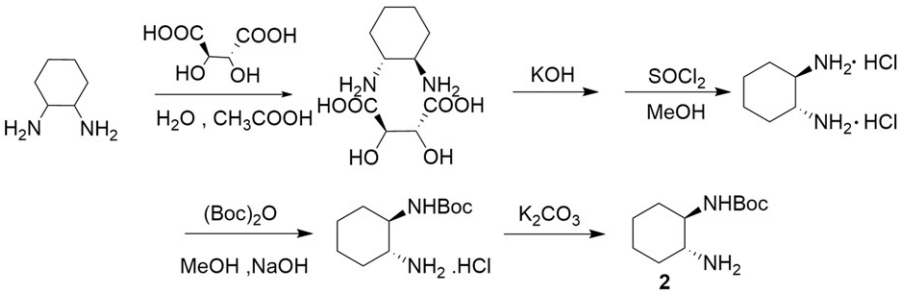
Considering that synthetic conditions of pure tribenzylamine are very harsh and difficult to control, we decide to replace it with trimethyl tribenzylamine as building block, which has high yield. Through bromomethylation, azidation and Staudinger reaction, intermediate **5** was obtained. This synthetic route is efficient and convenient, and the yields of bromomethylation and azidation are very high (Scheme 4).

In this study, we found that pentafluorophenoxy group was an excellent leaving group. Compound **6** should to be synthesized at room temperature to avoid racemization. Initially we tried pyridinecarbonyl chloride to react with compound **5**, but it did not work and pure product could not be obtained. Then we tried methoxy group and ethoxy group as leaving group, and it failed to react with compound **5** at room

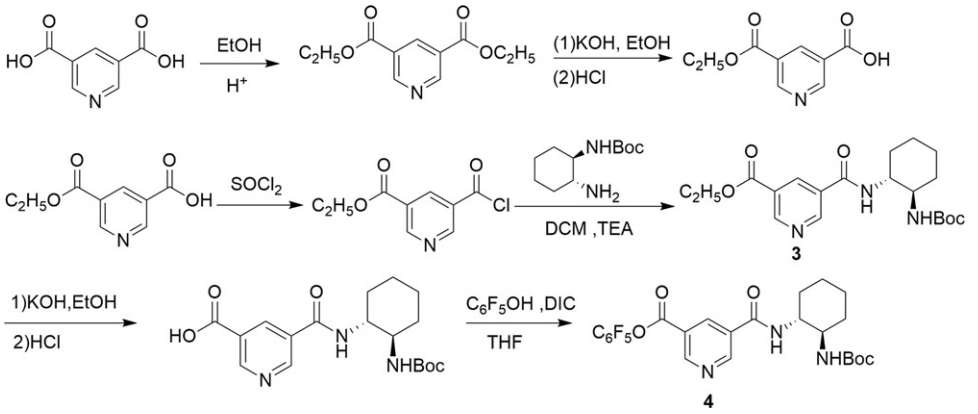


Scheme 1. Proposed synthetic route.

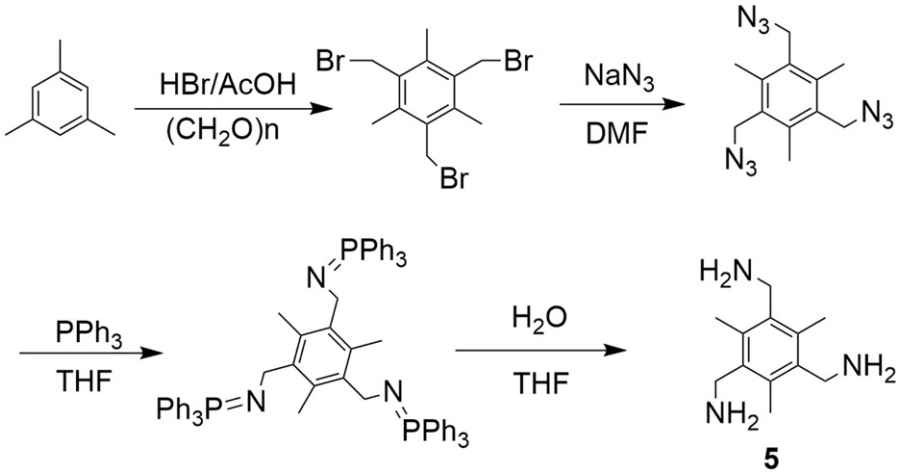
temperature. At last, we found compound **4** could smoothly react with compound **5** with help of leaving group pentafluorophenoxy to obtain key intermediate compound **6**, the key intermediate of the cage-like NADH model molecule which had multiple chiral centers (Scheme 5). In addition, compound **6** could also be transformed to pedal-like NADH model molecule.



Scheme 2. Synthesis of compound **2**.

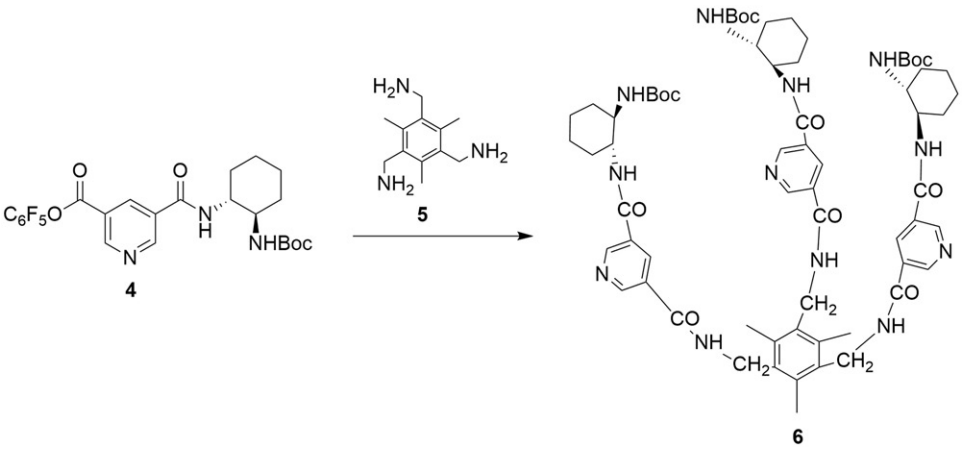


Scheme 3. Synthesis of compound **3** and **4**.

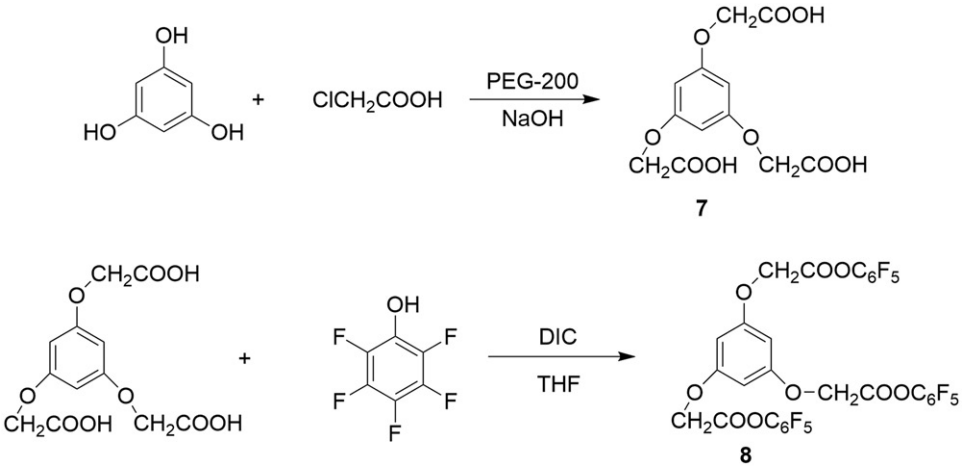


Scheme 4. Synthesis of compound **5**.

According to the synthetic route we designed, intermediate compound **7** is a very important in cyclization step. We used 1,3,5-trihydroxybenzene and chloroacetic acid to react under base condition, and obtained tripod acid with flexible chain in one step. Then compound **8** was synthesized with pentafluorophenyl group as the directing group



Scheme 5. Synthesis of compound **6**.



Scheme 6. Synthesis of compound **7** and **8**.

(Scheme 6). Then we made great efforts for the final macrocyclic ring closure step and spent more than two years, however, it did not work. It might be a bigger entropy decrease and multi reaction cites that inhibited the ring closure, so now we still did not get the desired cage-like model molecule. However, further studies are currently under investigation and will be presented in a due time.

Conclusion

In conclusion, a novel cage-like NADH model with multi-chiral centers was designed, and we have synthesized its key intermediates. In this study, we found that pentafluorophenoxy group was an excellent leaving group. It might be a bigger entropy decrease and multi reaction cites that inhibited the ring closure, so desired cage-like model molecule couldn't be obtained. Further studies are currently under investigation and will be presented in a due time.

Experimental

General considerations: All reagents were commercially available and used without extra purification. ^{1}H and ^{13}C NMR spectra (400 MHz or 100 MHz, respectively) were recorded in $CDCl_3$ with TMS as internal standard. HRMS were recorded by EI (Supplementary material).

Synthesis of compound 6: CH_2Cl_2 solution containing compound 4 (0.57 g, 0.0018 mol) and trimethylamine was slowly adding to CH_2Cl_2 solution containing compound 5 (3.17 g, 0.006 mol). The reactant was stirred at room temperature overnight and monitored by TLC. When the reaction was over, solvent was removed by rotary evaporator and the remaining was purified by column chromatography (CH_2Cl_2/CH_3OH = 10/1) to obtain compound **6** in 35% yield.

Tri-tert-butyl-((1R,1'R,1''R,2R,2'R,2''R)-((5,5',5''-((((2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene))tris(azanediyl)) tris(carbonyl))tris(nicotinoyl))tris(azanediyl))-tris(cyclohexane-2,1-diyl))tricarbamate (compound 6): white solid (0.78 g, 0.00063 mol). ^{1}H NMR (400 MHz, DMSO); δ 9.03–9.01 (d, J = 9.45 Hz, 6H), 8.72 (s, 3H), 8.51 (s, 3H), 8.42–8.40 (d, J = 8.62 Hz, 3H), 6.67–6.65 (d, J = 8.73 Hz, 3H), 4.59 (s, 6H), 3.72–3.70 (d, J = 9.66 Hz, 3H), 3.38–3.36 (d, J = 8.87 Hz, 3H), 2.43 (s, 9H), 1.78 (s, 6H), 1.66 (s, 6H), 1.31–1.19 (m, 41H); ^{13}C NMR (100 MHz, DMSO); δ 164.29, 163.76, 155.61, 150.28, 137.10, 134.13, 132.30, 129.87, 129.56, 129.51, 77.34, 53.73, 53.02, 31.73, 31.55, 28.04, 24.68, 24.45, 16.00; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{66}H_{90}N_{12}O_{12}$ 1265.6693; found, 1265.6691.

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