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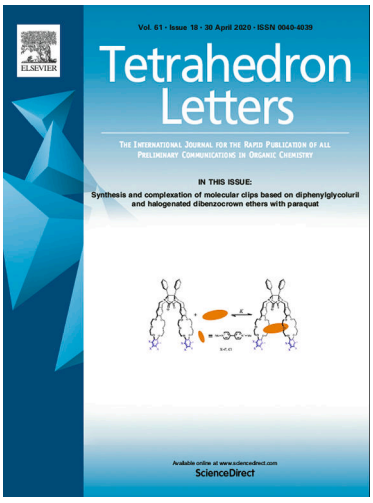

Synthesis of new azapolycyclic scaffolds *via* the domino aminolysis of dicyclopentadiene diepoxide in water

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Synthesis of new azapolycyclic scaffolds *via* the domino aminolysis of dicyclopentadiene diepoxide in water

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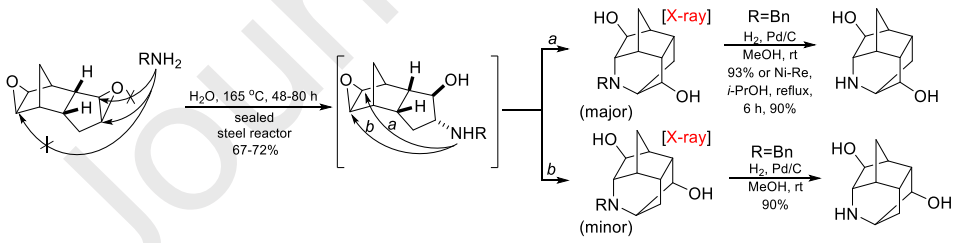
Keywords: 2-Azabicyclo[3.3.1]nonane (morphan), Amino alcohols, Piperidine, Cage-like compounds

Abstract

A convenient method is reported for the multigram scale synthesis of compounds containing the novel octahydro-1*H*-2,5-epimino-4,7-methanoindene azapolycyclic system in good yields. This method involves the domino aminolysis of readily available dicyclopentadiene diepoxide in water at 165 °C. 2D NMR and XRD spectra of the products were studied in detail.

Graphical abstract



Highlights

- First reported synthesis of the octahydro-1*H*-2,5-epimino-4,7-methanoindene azapolycyclic system
- Operationally simple method using water as the solvent
- 2D NMR and XRD spectra of the products were studied in detail

Introduction

Compounds with unusual three-dimensional structures have frequently attracted the attention of chemists as possible synthetic targets because the shape of chemical structures in drug discovery is a crucial component for evoking molecular recognition events with biological targets [1]. Medicinal chemists typically exploit novel conformationally restricted 3D-shaped building blocks with a high fraction of C(sp^3)-hybridized carbons (Fsp^3) [2]. Natural products often contain enhanced three-dimensionality in their structures reflecting the necessary interactions with their biological partners. As many drugs are derived from natural products, creating natural cage-like cores may offer an increased chance of finding bioactive compounds. Moreover, azaheterocyclic cage compounds have received attention from both synthetic and mechanistic considerations for comparing the reactivity pattern of carbon cage compounds with their heteroatom analogs. It is not surprising, therefore, that medicinal chemists are increasingly searching for novel, unique, 3D-shaped, and conformationally restricted building blocks [3].

As part of our drug discovery program, we are interested in developing practical synthetic pathways that allow quick access to alkaloid-like chemical scaffolds that can be used to produce a library of drug-like compounds for bioscreening. Herein, we report the synthesis of the octahydro-1*H*-2,5-epimino-4,7-methanoindene azapolycyclic system **1**. A literature survey of substructures derived from this scaffold emphasizes its unique place among many well-documented bi- and tricyclic analogues (Fig. 1). It is also worth mentioning that core **1** includes the pharmacophore 2-azabicyclononane (2-ABN, Morphan) fragment as a subunit. This fragment is found in more than 300 natural compounds of high biological importance including two of the best-known alkaloids, morphine and strychnine [4]. In addition, a number of similar polycyclic cage structures have already been used as lipophilic scaffolds for neuroactive drugs and antiviral agents [5].

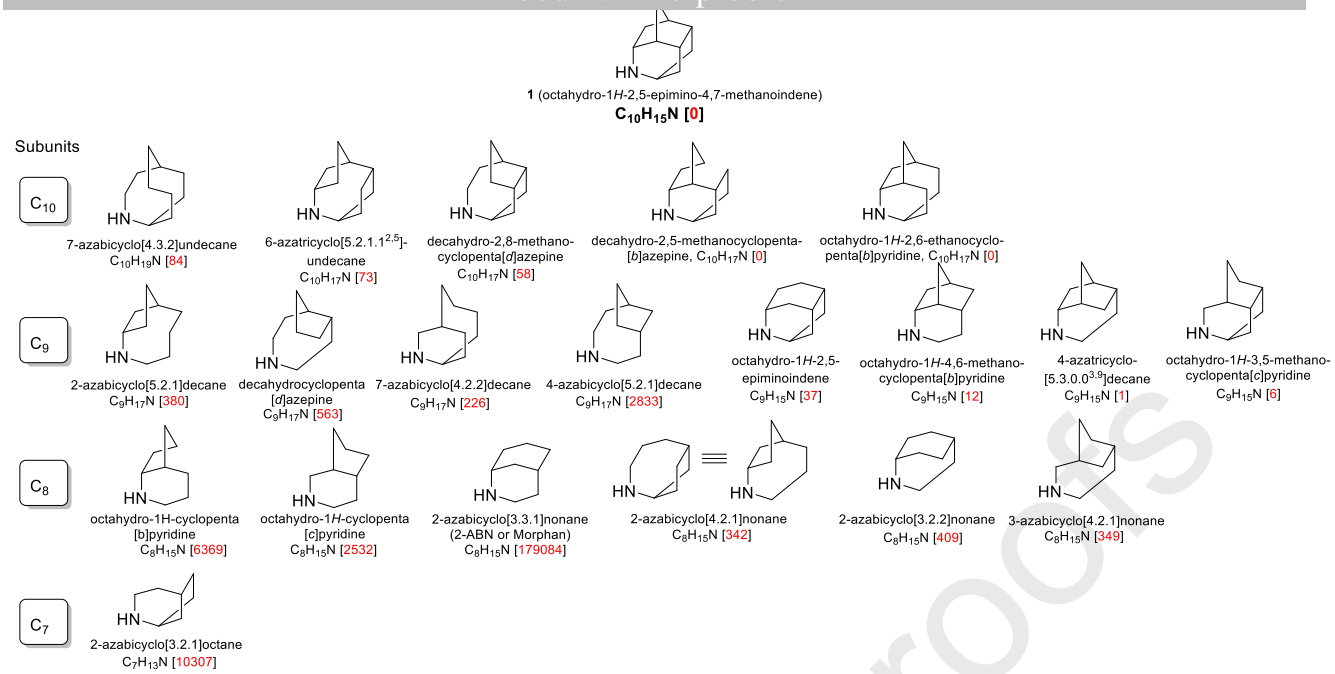
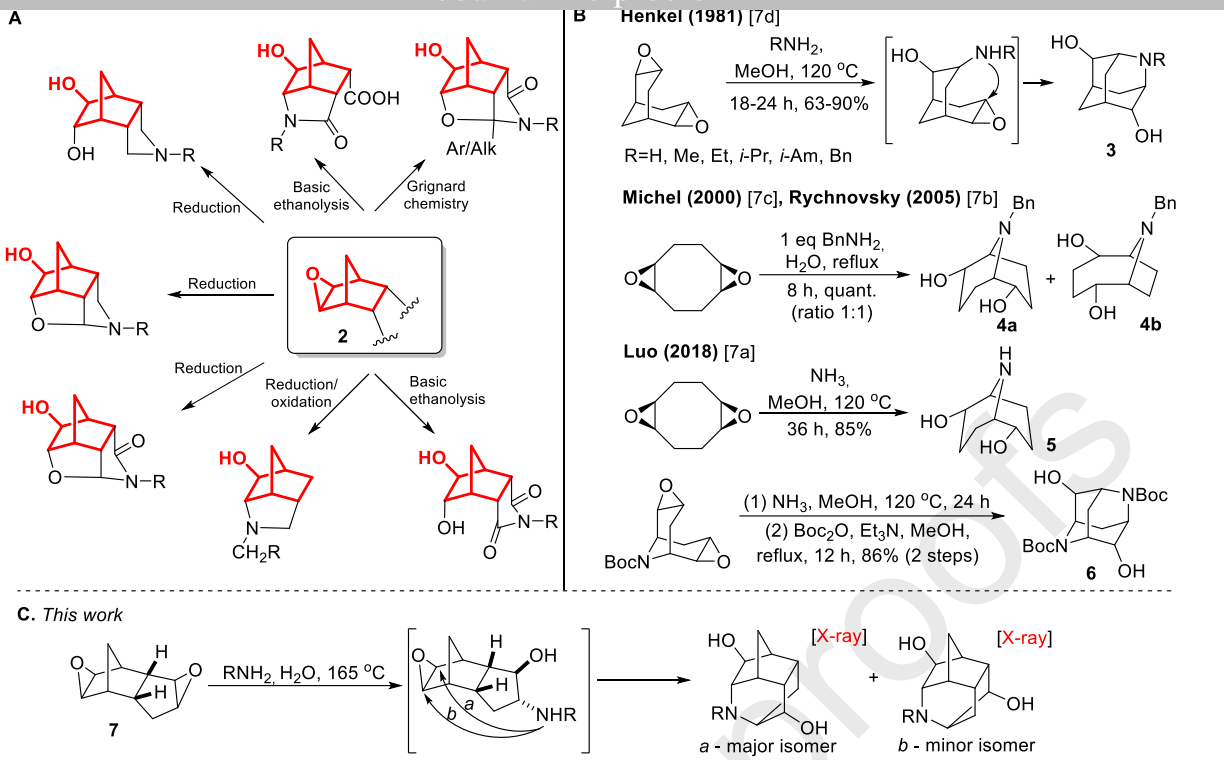


Figure 1. Representative bi- and tricyclic substructures based on the octahydro-1*H*-2,5-epimino-4,7-methanoindene azapolycyclic system **1** and the total number of references (red numbers in brackets) according to the SciFinder database (April, 2020).

Results and Discussion

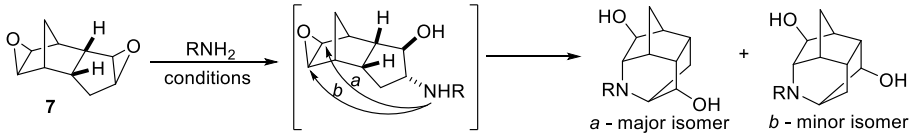
The chemistry of *exo*-epoxynorbornanes **2** has attracted considerable attention from our group as convenient and inexpensive starting compounds for the preparation of cage-like azaheterocycles [6] (Scheme 1A). While searching for a convenient method for the synthesis of new azaheterocycles, we turned our attention to previous work [7a-d] where diepoxides were used for the synthesis of 2-azaadamantanes **3**, 9-azabicyclo[3.3.1]- and [4.2.1]nonanes **4a,b, 5** and 2,6-diazaadamantane **6** (Scheme 1B). Inspired by these results we developed a simple protocol for the synthesis of octahydro-1*H*-2,5-epimino-4,7-methanoindene derivatives by the domino aminolysis of dicyclopentadiene *exo*-diepoxide **7** [7e-g] (Scheme 1C).



Scheme 1. A) Diversity of cage-like azaheterocycles obtained in our laboratory starting from *exo*-epoxynorbornanes **2**. **B**) Diepoxides in the synthesis of cage-like azaheterocycles **3**–**6**. **C**) This work.

To optimize the aminolysis of dicyclopentadiene diepoxide **7**, several amines were evaluated and the results are summarized in Table 1. Our experiments showed that the optimal solvent is water and the reaction temperature needs to be in the range of 160–165 °C (sealed steel reactor). Heating of diepoxide **7** with concentrated aqueous ammonia under microwave irradiation at 100 °C did not lead to the formation of aminolysis products and starting material **7** was recovered quantitatively (Table 1, entry 1). The aminolysis of **7** with benzylamine under various conditions demonstrated the key role of the solvent (water) in the course of this reaction. There is considerable evidence in the literature that the aminolysis of epoxides effectively occurs in aqueous medium [8]. Thus the use of dimethylformamide (DMF), acetonitrile, benzylamine (as solvent) and 2-propanol led to lower conversions of **7** compared to water (Table 1, entries 3, 4, 6–12). Under solvent free conditions the aminolysis of **7** did not occur (Table 1, entry 5). In our experiments aniline was the least reactive amine, and no aminolysis products were isolated in this case (Table 1, entry 13).

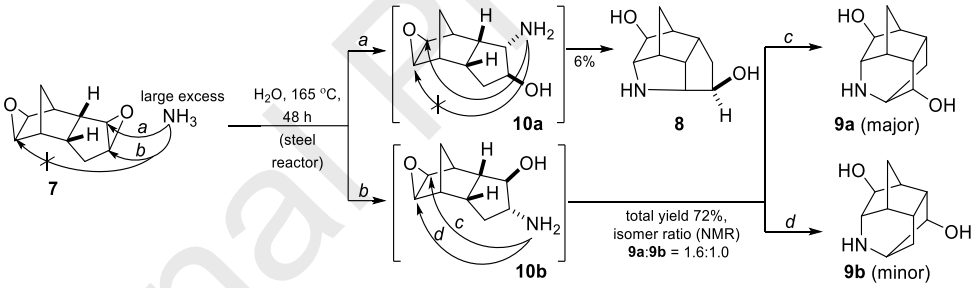
Table 1. Screening of the reaction conditions.



Entry	Reaction conditions	Molar ratio	Temp. (°C)	time	Conversion of the

		7 : amine		(h)	starting epoxide 7 (%, NMR data)
1	Microwave irradiation (800W), H_2O	1 : 480 (NH_3)	100	4	0
2	Sealed steel reactor, H_2O	1 : 27 (NH_3)	165	48	90
3	Reflux, DMF	1 : 2 ($BnNH_2$)	153	60	0
4	$LiClO_4$ (1 equiv.), reflux, dry MeCN	1 : 2 ($BnNH_2$)	85	70	0
5	Sealed steel reactor, solvent free	1 : 2 ($BnNH_2$)	160	70	0
6	Reflux, excess benzylamine	1 : 15 ($BnNH_2$)	185	64	25
7	Sealed steel reactor, *i*-PrOH	1 : 2 ($BnNH_2$)	160	75	30
8	Sealed steel reactor, *i*-PrOH	1 : 2 ($BnNH_2$)	160	200	50
9	Sealed steel reactor, *i*-PrOH	1 : 2 ($BnNH_2$)	160	240	60
10	Sealed steel reactor, *i*-PrOH	1 : 2 ($BnNH_2$)	165	336	80
11	Sealed steel reactor, H_2O	1 : 1.2 ($BnNH_2$)	165	70	90
12	Sealed steel reactor, H_2O	1 : 2 ($BnNH_2$)	165	200	95
13	Sealed steel reactor, *i*-PrOH	1 : 1 ($PhNH_2$)	150	60	0

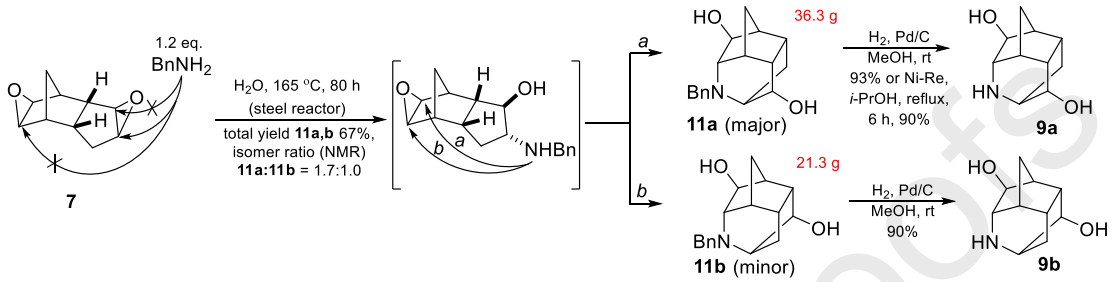
The reaction of diepoxide **7** with ammonia was found to be non-regioselective, thus competing pathways ***a*** and ***b*** led to the formation of all plausible products of aminolysis **8, 9a,b** in different quantities. Clearly the attack *via* pathway ***a*** was more sterically hindered, resulting in a low yield of the product **8** (up to 6%). Path ***b*** has two non-equivalent sites for intramolecular aminolysis of the *exo*-epoxynorbornane fragment – pathways ***c*** and ***d***. These pathways led to a 1.6:1.0 mixture of isomers **9a** and **9b** in 72% total yield (Scheme 2).



Scheme 2. Aminolysis of dicyclopentadiene diepoxide **7** with ammonia.

Thus, we consider the aminolysis of dicyclopentadiene diepoxide **7** as a two-step domino process, where the first (slow) step is chemo-, stereo- and, in the case of ammonia, non-regioselective amine attack (paths ***a, b***, Scheme 2) on the epoxycyclopentane moiety of **7**. The intermediates of this step are the corresponding epoxyaminoalcohols **10a,b**, which were not isolated in any of the reactions. A characteristic feature of intermediates **10a,b** is the placement of the amino group in the *endo*-position of the norbornane fragment, which makes the second (faster) step a non-regioselective attack of the amino group on the carbon atoms of the epoxynorbornane fragment. The reaction of diopexide **7** with a 1.2-fold excess of benzylamine predictably led to the formation of regioisomeric aminodiols **11a,b** in a ratio of 1.7:1.0. The synthesis of compounds **9a,b** was also achieved by reductive debenzylation of aminodiols **11a,b** over a palladium or nickel catalyst in 90–93% yield. Despite the

fact that amino alcohols **9a,b** can be obtained in one step directly from diepoxide **7** and aqueous ammonia (Scheme 2), in practice, it is more expedient to obtain the multigram amounts of these compounds by debenzylation of the pure isomers **11a,b**. The Bn-derivatives **11a,b** (R_f 0.36 (for **11a**) and 0.22 (for **11b**) in ethyl acetate) were much better separated by column chromatography due to the greater difference in R_f compared with the unsubstituted analogs **9a,b** (R_f 0.16 (for **9a**) and 0.08 (for **9b**) in 2-propanol) (Scheme 3).



Scheme 3. Aminolysis of dicyclopentadiene diepoxide **7** with benzylamine.

The structure of the products **8, 9a,b, 11a,b** was studied in detail by 2D NMR techniques and that of isomers **11a,b** was additionally confirmed by X-ray diffraction analysis (Fig. 2, CCDC 1536888 for **11a** and 1536889 for **11b**). For more information and a detailed study of 2D NMR and XRD results see the ESI.

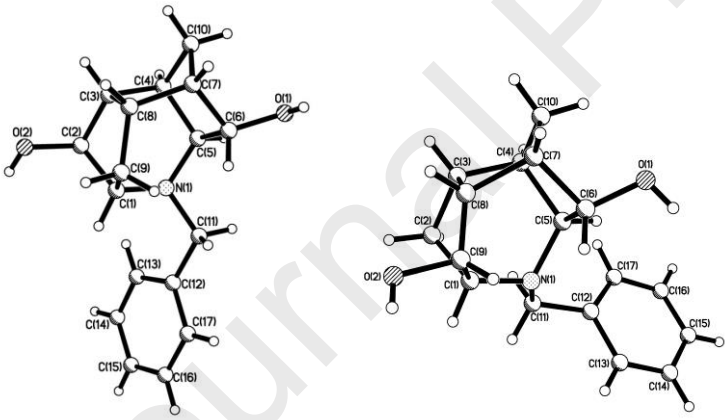
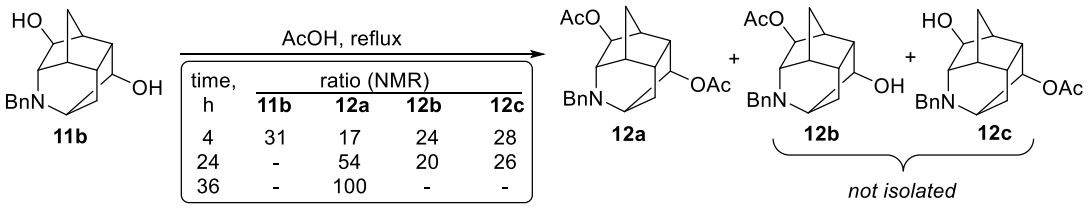


Figure 2. Molecular structure of major-isomer **11a** (*left*, see Fig. S3 in ESI) and minor-isomer **11b** (*right*) according to X-ray diffraction data.

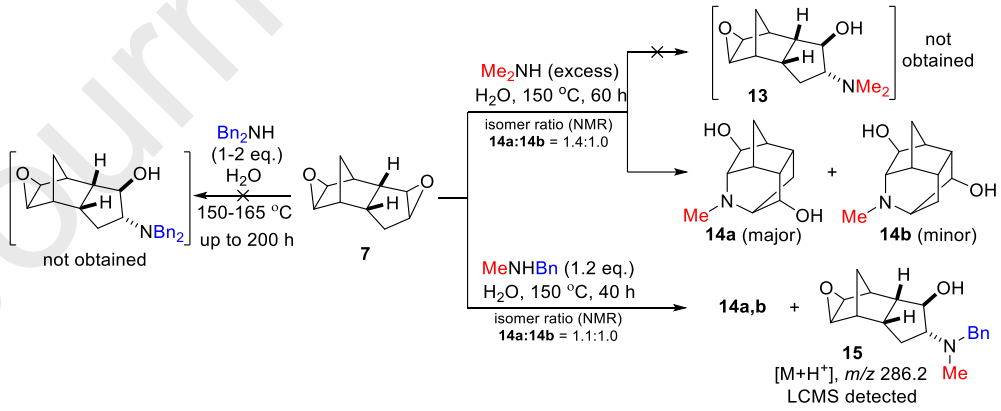
Differently functionalized complex building blocks are in high demand in advanced medicinal chemistry. We hypothesized that the differently oriented hydroxyl groups in aminodiols **11a,b** could be selectively acylated under mild conditions. Thus, we performed the acylation of aminodiol **11b** with acetic acid at reflux according to our previously developed method for protecting hydroxyl groups in cage-like compounds [9]. A mixture of di- and monoacylated products **12a-c** in different ratios was

obtained. According to NMR/LCMS data the reaction was non-regioselective. Prolonged heating in acetic acid at reflux (36 h) led to diacyl derivative **12a** exclusively (Scheme 4).



Scheme 4. Acylation of amino diol **11b**.

Next, we studied the reaction of diepoxide **7** with secondary amines. Unfortunately, under all of the conditions we tested, dibenzylamine did not react with diepoxide **7**. The aminolysis was then carried out with less sterically hindered secondary amines. Interestingly, in the reaction with aqueous dimethylamine, we also failed to obtain the desired epoxyamino alcohol **13**, but the harsh conditions and long reaction time led to demethylation and the formation of a mixture of regioisomeric amino alcohols **14a,b** in a ratio of 1.4:1.0 (NMR). Further confirmation of the formation of a mixture of *N*-monomethyl amino alcohols **14a,b** was obtained from the LCMS trace of the reaction mixture after 60 hours. The chromatogram contained two poorly resolved peaks, each corresponding to the same *m/z* 196.2 ($M+H^+$ of compounds **14a,b**) (see ESI, Fig. S4). The chromatographic separation of this mixture of amino alcohols could not be performed, because they were visualized as a single spot in all of the examined eluents. The most interesting results were obtained in the reaction with methylbenzylamine. The LCMS spectrum of the reaction mixture clearly indicated the formation of, in addition to the mixture of monomethyl derivatives **14a,b**, the corresponding intermediate – epoxyamino alcohol **15** with *m/z* 286.2 [$M+H^+$] (see ESI, Fig. S5) (Scheme 5).



Scheme 5. Aminolysis of dicyclopentadiene diepoxide **7** with secondary amines.

Cage-like polycyclic compounds may interact in a specific way with biological targets. It is known, for example, that the incorporation of a cage-like structure in biologically active compounds

often increases their biological activity [10]. We believe, the newly synthesized compounds are promising for biological applications.

Conclusion

We have developed a one-step multigram scale approach to novel octahydro-1*H*-2,5-epimino-4,7-methanoindene derivatives from inexpensive and readily available dicyclopentadiene diepoxide. To the best of our knowledge, this is the first detailed report of the synthesis of such azatetracyclic cage-like systems. The obtained building blocks can be directly used in drug discovery projects. Given the simplicity and availability of all starting materials, and the efficient synthesis of the products in aqueous medium, we believe that this method will find practical applications in both academia and industry. An investigation of possible ways for the stereoselective functionalization of octahydro-1*H*-2,5-epimino-4,7-methanoindene derivatives is ongoing in our laboratory and will be reported in due course. The chemo-, stereo-, and regiochemical features of the aminolysis of dicyclopentadiene diepoxide established in this work are crucial in planning further syntheses based on it.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data (ESI) to this article can be found online at https://doi.org/10.1016

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Declaration of Interests

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