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Synthesis of enantiomerically pure 2,9-dicycloalkyl substituted perhydro hexaazadibenzotetracenes

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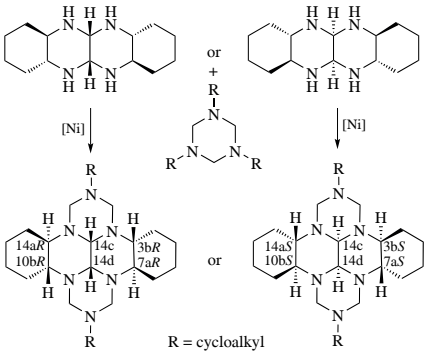
A one-pot synthesis of enantiomerically pure *N*,*N*′-dicycloalkyl substituted octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes has been successfully accomplished *via* the $NiCl_2$-catalyzed reaction between 1,3,5-tricycloalkyl-1,3,5-triazinanes and (*R*,*R*,*R*,*R*)- or (*S*,*S*,*S*,*S*)-perhydro-5,6,11,12-tetraazatetracenes (generated *in situ* from enantiopure *trans*-1,2-diaminocyclohexanes and glyoxal). The transformation may be regarded as the 'trans-aminalization' between cyclic aminals passing toward more stable products.



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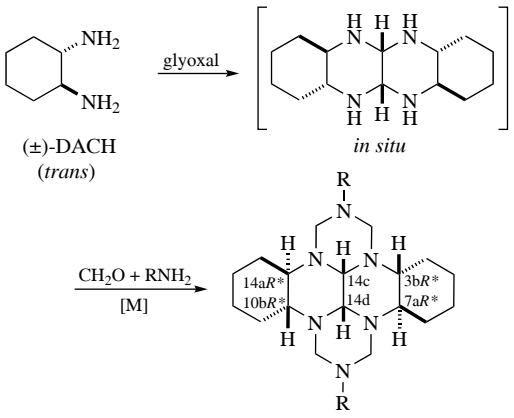
trans-1,2-Diaminocyclohexane[1] (DACH) is a convenient and efficient building block for the synthesis of biologically active molecules. Chiral amino alcohols, potential inhibitors of PTP1B phosphatase and promising drugs for the therapy of type 2 diabetes, were obtained on the basis of enantiopure (*R*,*R*)-DACH.[2] New chiral Mannich adducts, which have antiproliferative activity comparable to that of cisplatin, were synthesized by the reaction of (*R*,*R*)-DACH with aromatic nucleophiles.[3] Structural analogs of oxaliplatin[4–7] are of interest as antitumor agents. (*R*,*R*)-1,2-Diaminocyclohexane is used for the synthesis of chiral piperazine derivatives[8] and optically active polyamine ligands[9] that efficiently cleave DNA and can be used for cancer chemotherapy. (*S*,*S*)-1,2-Diaminocyclohexane finds application in the synthesis of chiral imidazole derivatives[10] that are of interest in medicinal chemistry and in the preparation of ligands for Pd-catalyzed syntheses of a wide range of chiral products.[11] Macrocyclic derivatives with *in vitro* antiproliferative activity against human cancer cell lines (MCF-7, HCT-116, A375)[12] and polycyclic compounds with cytoxic effects against human cancer cell lines (HepG2, HTC-116, SH-SY5Y, MCF-7, A549, Jurkat, THP-1) and *in vitro* antitumor activity against human histiocytic lymphoma cell line (U937)[13,14] were obtained on the basis of racemic (±)-DACH. Multicomponent condensation of (*R*,*R*)/(*S*,*S*)-DACHs with ammonia and formaldehyde yields enantiomerically pure polycyclic aminals[15] that are promising as catalysts for asymmetric synthesis. Cyclocondensation of optically pure and racemic DACH with terephthalic and isophthalic aldehydes leads to highly symmetric polyimine macrocycles such as trianglimines,[16,17] calixalens[18–20] or resorcinsalens[21] that are of interest as catalysts, molecular blocks for supramolecular structures and materials for sequestration of metal ions. Covalent organic frameworks for the separation of enantiomers[22] have been synthesized with involvement of chiral *trans*-1,2-DACH. Some representative structures of useful DACH derivatives are shown in Online Supplementary Materials, Figure S1.

Previously, we used tetraazaperhydrotetracene, which was obtained *in situ* from (±)-DACH, as the starting 'building block' for the synthesis of perhydro hexaazadibenzotetracenes[13,14,23–25] (Scheme 1). As a rule, the synthesis of *N*,*N*′-disubstituted perhydro hexaazadibenzotetratetracenes is performed under the conditions of multicomponent condensation of tetraaza-perhydrotetracene with formaldehyde and primary amines in the presence of salts of rare-earth elements. X-ray diffraction analysis of perhydro hexaazadibenzotetetracenes[13,23] revealed the presence of a second-order symmetry local axis passing through the middle of the C^{14c}–C^{14d} bond of the molecule's

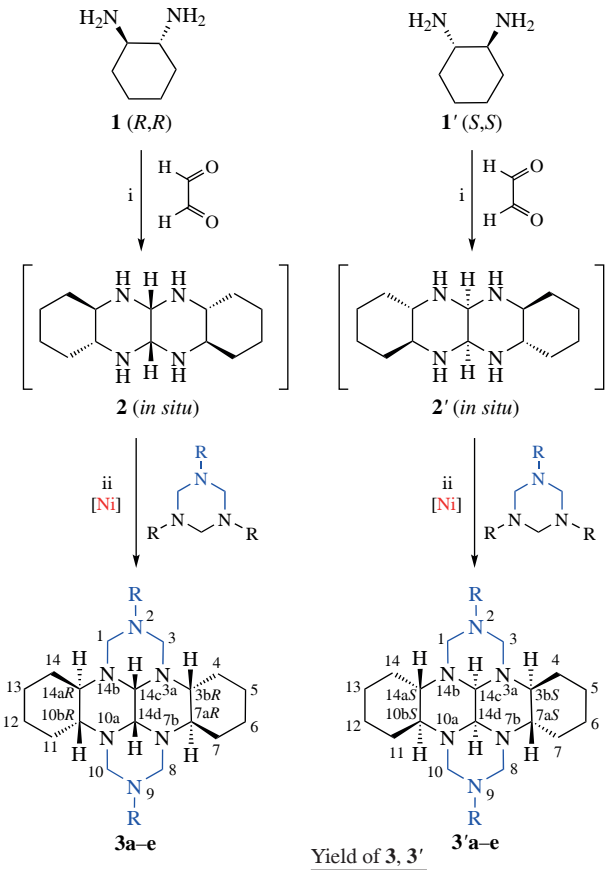


(refs. 13, 14, 23–25)

Scheme 1

polyaza polycyclic backbone. The cyclohexane and piperazine rings in the perhydro tetracene moiety would adopt the *chair* conformation and had the *trans*-configuration. The conformational structure of the compounds determined by X-ray diffraction experiments agrees with two-dimensional NMR correlation spectra. The one-pot catalytic approaches that we developed allow the synthesis of perhydro tetracenes with the *R**,*R**,*R**,*R**-relative configuration of the chiral centers at the C^{3b}, C^{7a}, C^{10b} and C^{14a} carbon atoms and with the *cis*-junction of the piperazine rings along the C^{14c}–C^{14d} bond (see Scheme 1).

To explore the feasibility of synthesizing enantiomerically pure *N*,*N*′-disubstituted perhydro-2,3a,7b,9,10a,14b-hexaazadibenzotetetracenes and to expand the library of potential biologically active polyazapolycycles, we continued studies on the one-pot catalytic heterocyclization of 5,6,11,12-tetraazaperhydrotetracenes prepared *in situ* from enantiopure DACHs, namely, (*R*,*R*)-**1** and (*S*,*S*)-**1′** (Scheme 2). An attempt to synthesize enantiomerically pure disubstituted perhydro hexaazadibenzotetracenes based on tetraazaperhydrotetracenes **2**, **2′** by multicomponent condensation failed. For this reason, we converted primary amines into 1,3,5-trisubstituted 1,3,5-triazinanes known to be efficient cycloaminomethylation reagents.[26] It is known[27,28] that Ni^{II} chloride hexahydrate is widely used in catalytic recyclization reactions since, as an 'intermediate' Lewis acid, it preferably coordinates with the intermediate N-donor ligand.[29,30] Our experiments showed that the reaction of 1,3,5-tricyclopropyl-1,3,5-triazinane with tetraazaperhydrotetracenes **2**, **2′** obtained *in situ* from (*R*,*R*)- or (*S*,*S*)-DACHs **1**, **1′** (5 mol% $NiCl_2 \cdot 6H_2O$, MeOH, 20 °C, 3 h) resulted in the selective formation of enantiopure 2,9-dicyclopropyl substituted octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes **3a**, **3′a** (see Scheme 2). Similar results were obtained if the cyclopropyl moiety at the nitrogen atom of the initial triazinane was replaced by other cycloalkyl substituents, which gave access to homologs **3a–e** and **3′a–e** in 44–60% yields.



	Yield of **3**, **3′**
a R = *c*-C_3H_5	46%, 44%
b R = *c*-C_5H_9	55%, 58%
c R = *c*-C_6H_{11}	50%, 48%
d R = *c*-C_7H_{13}	53%, 52%
e R = *c*-C_8H_{15}	60%, 56%

Scheme 2 *Reagents and conditions*: i, (*R*,*R*)-DACH **1** or (*S*,*S*)-DACH **1′** (2 equiv.), glyoxal (40 wt% aq., 1 equiv.), MeOH, 60 °C, 3 h; ii, 1,3,5-tricycloalkyl-1,3,5-triazinane (2 equiv.), 5 mol% $NiCl_2 \cdot 6H_2O$, MeOH, room temperature, 3 h.

Compounds **3a–e** *vs.* **3′a–e** are mirror images of each other, so their spectral characteristics are identical. The ^1H NMR spectra of the enantiomerically pure perhydro hexaazadibenzotetracenes show a similar spectral pattern typical of the stereochemical features of perhydro hexaazadibenzotetracenes with the *R**,*R**,*R**,*R**-relative configuration of the chiral centers. The characteristic features include the doublet signals of the AB spin system with geminal spin–spin coupling constants $^2J = 8$ and 12.0 Hz that correspond to the methylene protons of the carbon atoms at the $H^{1,8}$ and $H^{3,10}$ positions, respectively. In the ^{13}C NMR spectra, nine framework signals resonate in pairs because compounds **3a–e/3′a–e** represent centrosymmetric structures, with chemical shifts coinciding to within hundredths of a unit. Due to spatial shielding, the signals for the $C^{3,10}$ and $C^{4,11}$ carbon atoms in the ^{13}C NMR spectra are shifted upfield. Downfield shifts of signals are observed for the less spatially shielded $C^{1,8}$ and $C^{7,14}$ carbon atoms. The signals for the $C^{3b,10b}$ carbon atoms are shifted upfield as compared with the signals for the $C^{7a,14a}$ carbon atoms. It should be noted that the **3a–e** and **3′a–e** enantiomers were obtained with preservation of negative or positive values of the polarization plane angles depending on the initial optically pure diamines **1** and **1′**. In view of this, the *R*,*R*,*R*,*R*- or *S*,*S*,*S*,*S*-configuration can be assigned to the chiral centers at the C^{3b}, C^{7a}, C^{10b}, C^{14a} carbon atoms for series **3a–e** and **3′a–e**, respectively.

To conclude, recyclization of 1,3,5-tricycloalkyl substituted 1,3,5-triazinanes with 5,6,11,12-tetraazaperhydrotetracene, obtained from (*R*,*R*)- and (*S*,*S*)-DACHs in the presence of nickel chloride, allows one to perform the selective synthesis of new enantiomerically pure perhydro hexaazadibenzotetracenes that can be of interest as compounds with potential biological activity.

This study was carried out under the research plans of the IPC UFRC RAS [FMRS-2025-0037 (2025–2027), FMRS-2025-0041 (2025–2027)]. The structural studies of the compounds were carried out at the 'Agidel' Center for Collective Use at the Ufa Federal Research Center of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7729.

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