Synthesis of Tryptophan-Flavin-Dyads as Cryptochrome Model Compounds

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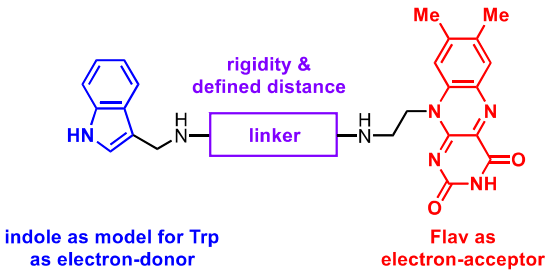
The development of a synthetic route to tryptophan-flavin-dyads as models for cryptochrome proteins which allow birds to detect the Earth's magnetic field is a central goal. These organic models are more stable and available in larger quantities than natural proteins. Herein, we present rigid structures that enhance electron transfer, potentially revealing the quantum mechanisms behind magnetoreception.

Introduction

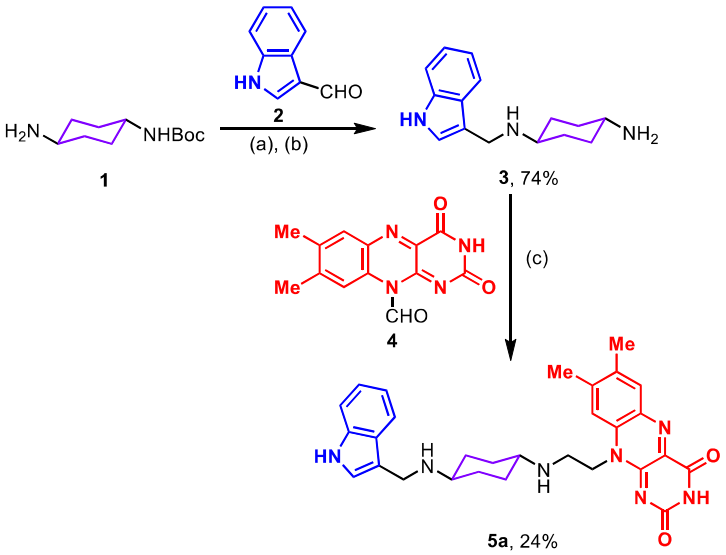
Migratory birds are able to navigate using the Earth's magnetic field, potentially aided by the cryptochrome protein in their eyes. The cryptochromes contain a flavin adenine dinucleotide (FAD) and a chain of up to four tryptophan (Trp) residues in their vicinity. When the FAD is irradiated with blue light, it triggers a series of electron transfers through the nearby Trp residues, resulting in a pair of radical anion and radical cation. This radical pair is thought to play a key role in how birds sense the magnetic field, acting as a spin-chemical compass. Instead of using recombinantly synthesized proteins, we propose the synthesis of organic model compounds. The new models aim for rigid structures with defined distances between the electron donor (indole as model for Trp) and acceptor (flavin, Flav). In our approach to molecular model compounds for cryptochromes we proposed three dyads with rigid linker units.



Scheme 1: Target compounds of our study.

Model Compound with Cyclohexane as Linker

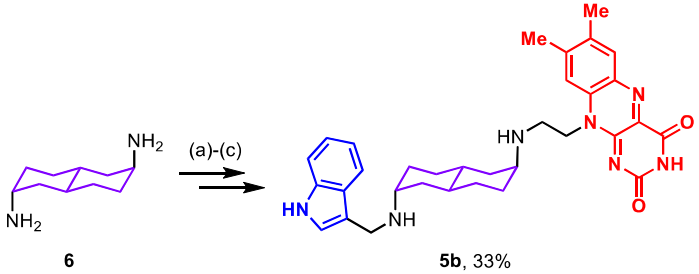
Our first model dyad was synthesized from commercially available *trans*-diaminocyclohexane**,** which was protected with Boc to our starting material **1**. Then, the indole unit was installed using carbaldehyde **2**. After removing the protecting group under acidic conditions, the target compound **5a** was obtained by reductive amination with flavin-funtionalized acetaldehyde **4**.[1]



Scheme 2: (a) 1.0 eq **2**, 2.0 eq $MgSO_4$, CH_2Cl_2, 60°C, 16 h; then 1.0 eq $NaBH_4$, CH_2Cl_2, 23°C, 4 h; (b) TFA, CH_2Cl_2, 23°C, 16 h; (c) 1.5 eq **4**, 1.5 eq $NaBH_3CN$, MeOH, 23°C, 16 h, in the dark.

Model Compound with Decalin as Linker

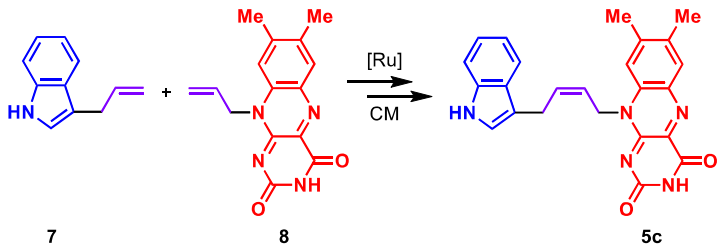
The hitherto unknown 2,6-diaminodecalin (**6**) as linker unit was prepared in four steps from commercially available 2,6-dihydroxynaphthalene as the racemic *ax,ax-trans*-diastereomer. Starting from this extended linker the second model dyad **5b** was synthesized with the same strategy as for the predecessor compound **5a**.[1]



Scheme 3: Reagents and conditions analogue to Scheme 2.

Synthesis of Model Trp-Flav by Cross Metathesis

Since the dyads **5a** and **5b** showed inefficient electron transfer in preliminary spectroscopic investigations presumably due to the too long donor-acceptor distance, we redesigned the structural motif by introducing a (*Z*)-olefinic structure as scaffold (dyad **5c**). The allyl indole **7** and the *N*-allylflavine **8** were each prepared in a few steps. The synthetic assembly of the scaffold **5c** will then be accomplished by olefin cross metathesis (CM) of both units.



Scheme 4: Redesign of a dyad **5c** with minimized donor-acceptor distance.

[1] N. Schröder, M. Schmidtmann, H. Mouritsen, J. Christoffers, *Eur. J. Org. Chem.* **2023**, *26*, e202201327.