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Convergent synthesis of a linker-connected fluorescent ebselen-coumarin heterodimer

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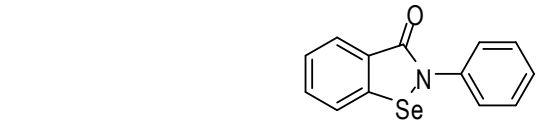
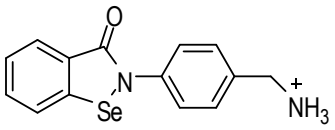
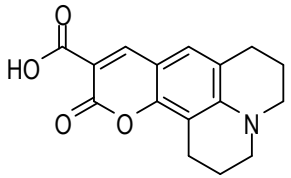


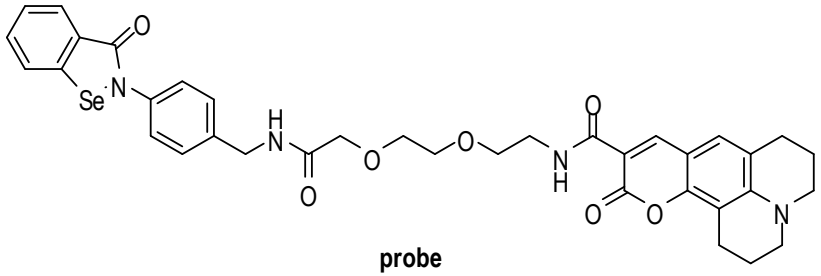
ebselen



1st component



2nd component



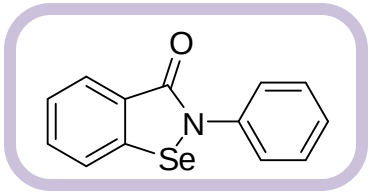
probe

Abstract:
Ebselen is a multifunctional drug with a wide range of pharmacological effects that are predominantly due to its interaction with selenoenzymes, e.g. glutathione peroxidase, thioredoxin reductase. Fluorescence-labeled probes containing ebselen can be suitable for further biological and medicinal studies, to profile enzyme activities, identify target enzymes and characterize their functions.
The synthetic route starts with the conversion of anthranilic acid into a diazonium salt, treatment with disodium diselenide to a 2,2´-diselenobisbenzoate and activation with thionyl chloride. A reaction with an appropriate *para*-substituted aniline derivative and deprotection gave the 1st component. A PEG linker building block was coupled with the 2nd component, the fluorescent coumarin 343. This was synthesized from 8-hydroxyjulolidine-9-carboxaldehyde. After deprotection, the desired probe was assembled from the ebselen and the PEG derivatives.
The new probe will be provided to biochemical and pharmacological studies.

Keywords: ebselen; selenoenzymes; activity-based probe

Introduction

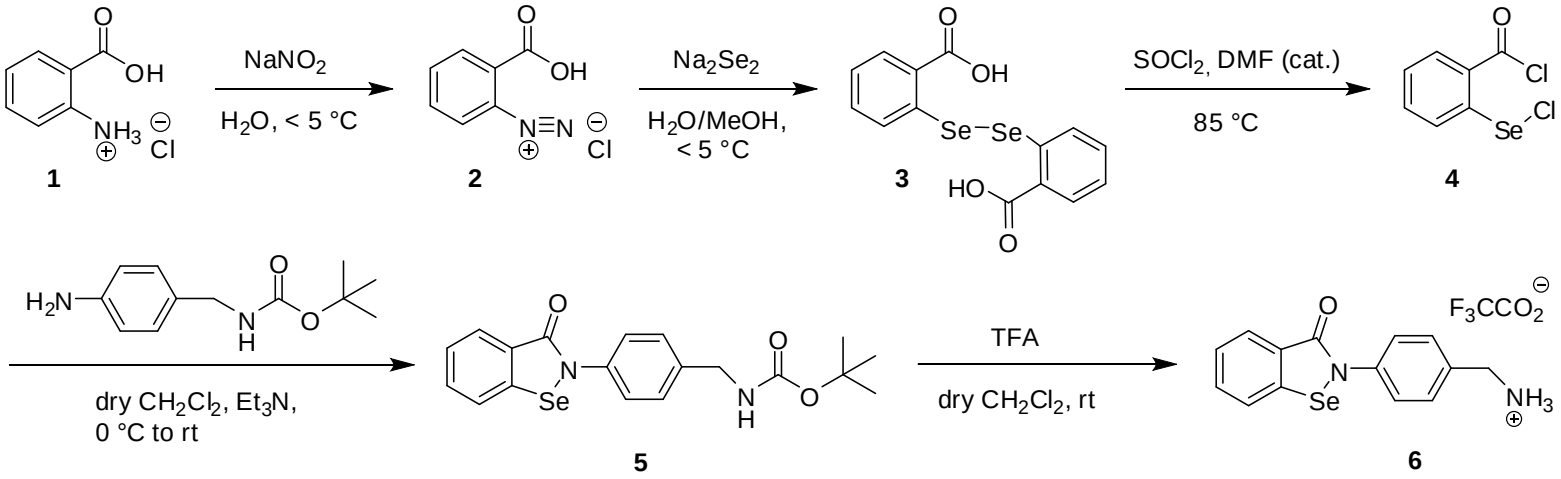
Ebselen is a multifunctional drug with a wide range of pharmacological effects that are predominantly due to its interaction with selenoenzymes, e.g. glutathione peroxidase, thioredoxin reductase [1,2]. Such enzymes play an important role in protecting biomembranes and other cellular components from oxidative stress by catalyzing the reduction of a variety of hydroperoxides [2].



According to its pleiotropic mode of action which is based on its versatile chemical structure, ebselen is currently under clinical trials for the prevention and treatment of different ailments such as cardiovascular diseases, arthritis, stroke, atherosclerosis, and cancer [2]. Fluorescence-labeled probes containing ebselen can be suitable for further biological and medicinal studies, to profile enzyme activities, identify target enzymes and characterize their functions [3].

[1] Stoyanovsky, D. A.; Jiang, J.; Murphy, M. P.; Epperly, M.; Zhang, X.; Li, S.; Greenberger, J.; Kagan, V.; Bayır, H. *ACS Med. Chem. Lett.* **2014**, *5*, 1304-1307.
[2] Azad, G. K.; Tomar, R. S. *Mol. Biol. Rep.* **2014**, *41*, 4865-79.
[3] Xu, K.; Qiang, M.; Gao, W.; Su, R.; Li, N., Gao, Y.; Xie, Y.; Kong, F.; Tang, B. *Chem. Sci.* **2013**, *4*, 1079-1086.

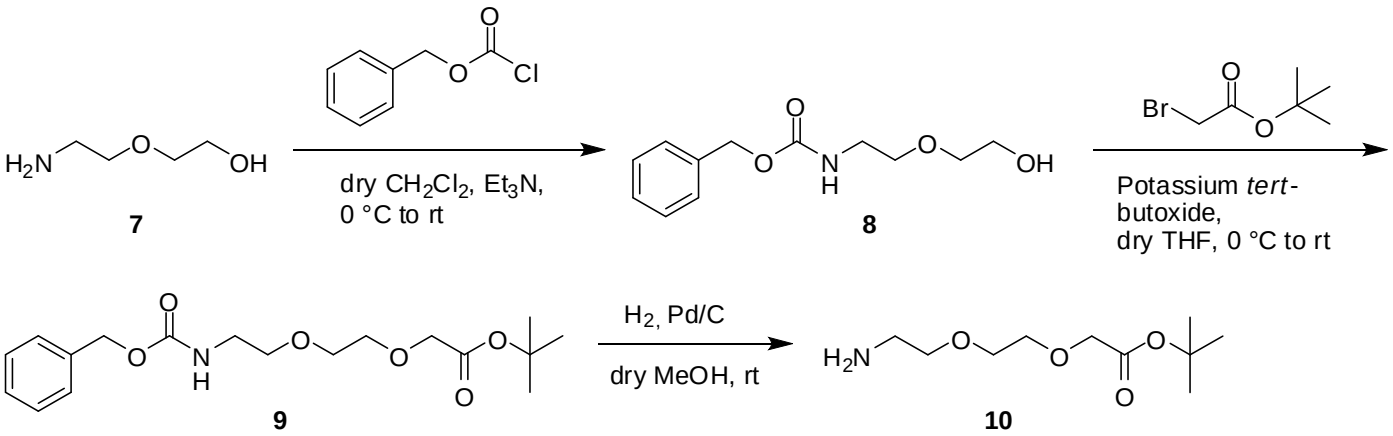
Synthesis



The synthesis starts with the procedure to prepare ebselen [4]. Anthranilic acid hydrochloride (**1**) was converted into a diazonium salt (**2**), which was treated with disodium diselenide to obtain the 2,2'-diselenobisbenzoate (**3**). After treating **3** with thionylchloride, an appropriate *para*-substituted aniline derivative was introduced. Deprotection of **5** led to **6**, the first component for the assembly of the final product **14**.

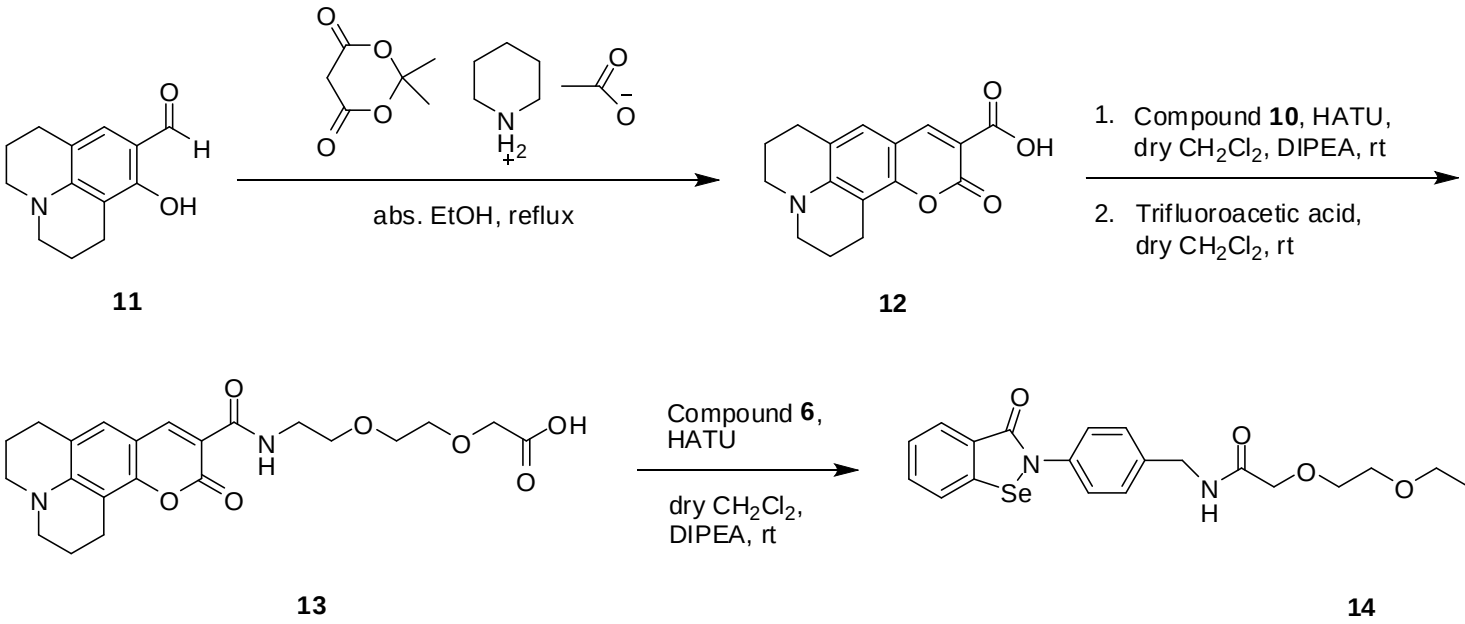
[4] Palus, J.; Młochowski, J.; Juchniewicz, L. *Polish J. Chem.* **1998**, *72*, 1931-1936.

Synthesis



To obtain the PEG linker for the connection of the two components, the amino group of 2-(2-aminoethoxy)ethanol was first Cbz-protected, then alkylated at the hydroxyl group with *tert*-butyl bromoacetate followed by a Cbz deprotection to give compound **10**.

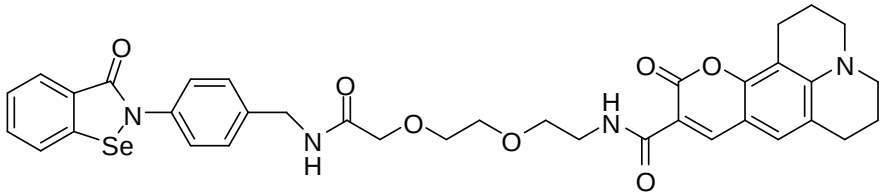
Synthesis



11 **12** **13** **14**

The fluorescent coumarin 343 **12** was synthesized by submitting 8-hydroxyjulolidine-9-carboxaldehyde to a Knoevenagel condensation. This was further coupled with **10** and deprotected to give the PEG-coumarin 343 building block (**13**) which after reaction with the ebselen derivative **6** resulted in the desired probe **14**.

Outlook



14

The new probe was designed to contain the intact ebselen structure, a PEG/two-amide spacer to improve solubility and a rigidified 7-amino coumarin, a type of fluorophore valued for its red shift of absorption and emission, even in aqueous medium [5, 6, 7]. Compound **14** will be provided to biochemical and pharmacological studies.

[5] Murase, T.; Yoshihara, T.; Yamada, K.; Tobita, S. *Bull. Chem. Soc. Jpn.* **2013**, *86*, 510

[6] Mertens, M. D.; Schmitz, J.; Horn, M.; Furtmann, N.; Bajorath, J.; Mareš, M.; Gütschow, M. *ChemBioChem* **2014**, *15*, 955.

[7] Kohl, F.; Schmitz, J.; Furtmann, N.; Schulz-Fincke, A.-C.; Mertens, M. D.; Küppers, J.; Benkhoff, M.; Tobiasch, E.; Bartz, U.; Bajorath, J.; Stirnberg, M.; Gütschow, M. *Org. Biomol. Chem.* **2015**, *13*, 10310-10323.