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Synthesis of (±)-desamino huperzine A

Klemens Högenauer,[a] Karl Baumann[b] and Johann Mulzer[a,*]

[a]*Institut für Organische Chemie, Universität Wien, Währingerstrasse 38, A-1090 Wien, Austria*
[b]*Novartis Forschungsinstitut, Brunner Strasse 59, A-1235 Wien, Austria*

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Abstract

The first synthesis of desamino huperzine A **2** is described. Key steps are a double Michael addition into benzoquinone monoketal **4**, a regiocontrolled double bond isomerisation and a novel pyridone synthesis involving a Michael addition of a β-keto ester into acrylonitrile.

Keywords: alkaloids; acetylcholinesterase inhibitor; Michael addition; pyridone synthesis.

The natural product huperzine A (**1**)[1] is an alkaloid of the *Lycopodium* family and has been shown to be an excellent selective and reversible inhibitor of acetylcholinesterase. Bearing this profile, huperzine A is perceived to be a promising lead structure in the therapy of senile dementia of the Alzheimer type.[2] So far, only two groups have achieved total syntheses[3,4] and the approach by the Kozikowski group has been improved several times, both in number of steps[5] and stereocontrol.[6,7] The discovery that 10-(*S*)-methyl huperzine A is more potent than the natural product itself[8] demonstrates the potential of synthetic derivatives and justifies development of alternative synthetic strategies. In particular, it appears to be of importance whether the bridgehead amino function is essential for the biological activity.

We describe the first synthesis of desamino huperzine A **2** which is based on the construction of the bicyclo[3.3.1]nonane skeleton by a double Michael addition of an α,α′-dianion equivalent of acetone into symmetric benzoquinone monoketal **4** (Scheme 1). One of the keto functionalities in the bicyclic intermediate **3** was then planned to serve as a pyridone precursor, whereas the remaining ketone and the ketal should function as double bond precursors.

Initially, we prepared ketones **6** and **7** as previously reported[9] (Scheme 2), using dimethyl 1,3-acetone dicarboxylate as the double Michael donor. Unfortunately, neither **6** nor **7** could be directly transformed to the pyridone by a sealed tube reaction with methyl propiolate and ammonia in methanol[10] to give **8** or **9**, respectively.

* Corresponding author. Fax: +43-1-4277-52189; e-mail: johann.mulzer@univie.ac.at

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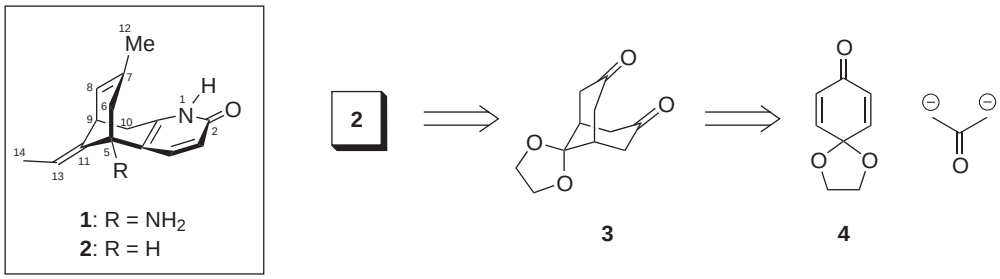
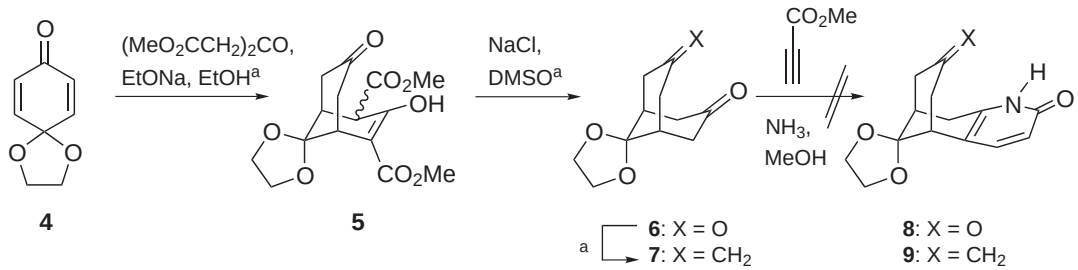


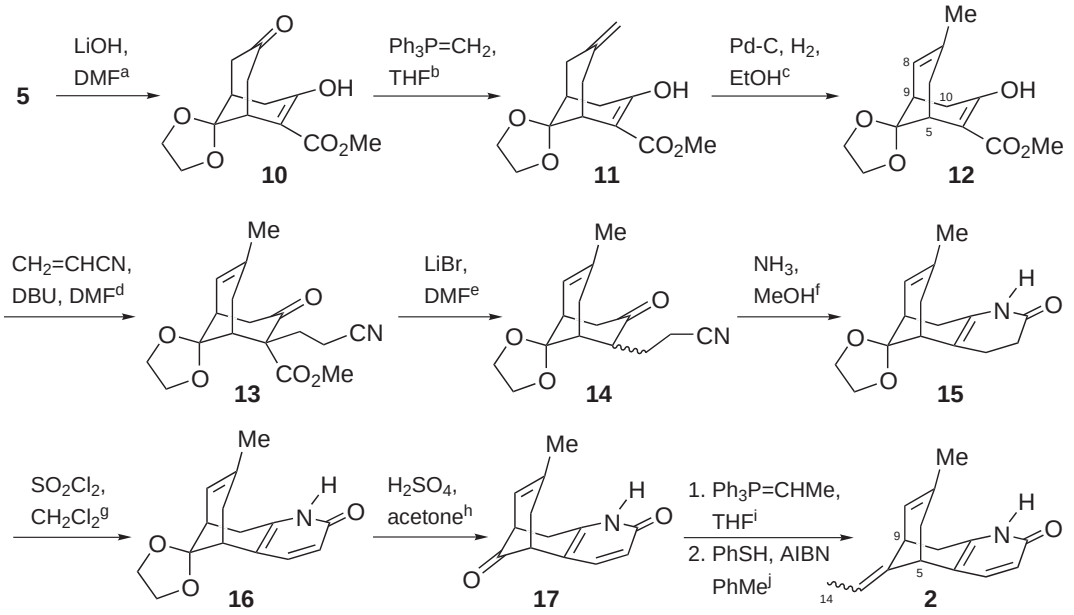
Scheme 1.



Scheme 2. See Ref. 9

With this drawback in mind, we decided to look at other possibilities of forming the pyridone. The observation that β-keto ester **5** could be selectively monodecarboxylated using three equivalents of LiOH in boiling DMF to give **10**[11] (Scheme 3) led us to propose another Michael reaction to introduce the three carbons needed for the pyridone. We believed that **10** would not undergo a second decarboxylation due to deprotonation of the remaining β-keto ester, which results in the formation of a stable enolate and prevents attack of a second hydroxide anion. Compound **10** could be transformed into olefin **11** by Wittig olefination in excellent yield using 3 equiv. of phosphorus ylide. However, neither **10** nor **11** reacted as Michael donors using a variety of three carbon Michael acceptors (such as acrylonitrile, acryl amide, methyl propiolate and propargyl nitrile) under a number of different reaction conditions (variation of solvent and base). We concluded that the steric demand or the extraordinary stereoelectronic properties of these compounds due to intramolecular π-stacking[12] prevented the success of these experiments. Gratifyingly, the isomerisation of the exocyclic double bond in **11** into the thermodynamically more stable endocyclic position provided a solution to this problem. We believed that the conformational change of the 'handle' would inhibit the possibility of the above-mentioned undesired stereoelectronic interactions. This conversion was achieved in a remarkable reaction using Pd–C and H_2 leading to **12**.[12,13] Not only did this transformation give the desired endocyclic material in good yield, but also in a completely regiocontrolled fashion. The other regioisomer could not be detected and the only by-products being formed were two diastereomers resulting from hydrogenation of the double bond. The reaction failed completely in the absence of H_2 and resulted in recovery of the starting material. Further subjection of **12** to the reaction conditions also led to hydrogenation of the double bond, suggesting competing reaction pathways, and resulted in careful monitoring of the reaction course in order to obtain optimum yields. We assume that the mechanism involves a hydropalladation/dehydropallada-

tion sequence although the reason for the regioselectivity remains as yet unclear. The structure of **12** was assigned with DQFCOSY and HMQC experiments. In the COSY spectrum, the olefinic proton at C8 (huperzine A numbering) shows a cross peak to the C9 bridgehead CH group, which itself shows coupling to the CH_2 group at C10, thus proving the structure as that required for desamino huperzine A. At this point it should be noted that the attempted isomerisation of **7** failed under the same reaction conditions.



Scheme 3. Reagents and conditions: (a) 3 equiv. $LiOH{\cdot}H_2O$, DMF, H_2O, 150°C, 2 h, 77% (from **4**); (b) 3 equiv. Ph_3PCH_3Br, 3 equiv. *n*-BuLi, THF, reflux, 22 h, 90%; (c) Pd–C cat., H_2, EtOH, rt, 14 h, 68%; (d) 10 equiv. acrylonitrile, 1 equiv. DBU, DMF, rt, 21 h, 48%; (e) 4 equiv. LiBr, DMF, 150°C, 15 h, 87%; (f) satd NH_3 in MeOH, sealed tube, 120°C, 66 h, 89%; (g) (i) 1.05 equiv. SO_2Cl_2, CH_2Cl_2, 0°C, 10 min; (ii) 120°C (neat), 0.5 h, 95%; (h) 4 M H_2SO_4, acetone, 80°C, 4 h, 84%; (i) 10 equiv. Ph_3PEtBr, 9 equiv. *n*-BuLi, THF, rt, 5 h; (j) 1.5 equiv. PhSH, 1 equiv. AIBN, PhMe, 85°C, 18 h, 91% (from **17**), $E/Z = 1{:}1$

To our delight, enol **12** reacted with acrylonitrile in the presence of DBU to give Michael adduct **13**. Using acryl amide or propargyl nitrile instead of acrylonitrile in this reaction was unsuccessful. Decarboxylation with LiBr in DMF furnished a diastereomeric mixture of keto nitriles **14** in good yield. This mixture was then subjected to cyclisation experiments. The reaction of **14** with neat ammonium acetate[14] at high temperatures furnished the cyclisation product **15** directly, albeit only in minor amounts (<10%). The best results were obtained by a sealed tube reaction of **14** with a saturated solution of ammonia in methanol. This reaction could also be scaled up easily using a Parr vessel. As expected, the enamide double bond in **15** stayed in the thermodynamically most stable, tetrasubstituted position. This enamide double bond could then be subjected to a chemoselective chlorination/dehydrochlorination sequence using surfuryl chloride,[15] providing the pyridone in **16** in excellent yield. Deketalisation proved difficult, probably due to the high steric hinderance in **16**. While standard methods (e.g. TsOH, acetone, H_2O, reflux) failed, this transformation was accomplished successfully with sulfuric acid at 80°C to give ketone **17**. Finally, **17** was subjected to Wittig olefination using an excess of phosphorus ylide thus furnishing (±)-desamino huperzine A **2** as a 1:1.6 mixture of *E* and *Z*

isomers. The mixture could be shifted towards the desired *E* isomer using a thiophenyl radical addition/elimination sequence to furnish a 1:1 *E*/*Z* ratio. The mixture proved to be inseparable, but the NMR signals of each compound could be unambiguously assigned due to the NOE of the C14 methyl group to the CH groups C9 and C5, respectively. These bridgehead CH groups, whose signals did not overlap in the 1D spectrum, were easily identified by a COSY experiment. After conversion of the pyridone to the O-acetate (Ac_2O, Et_3N, CH_2Cl_2, rt), the mixture could be separated by chiral supported HPLC to yield the two protected, geometric isomers. Final deprotection (satd NH_3 in MeOH, CH_2Cl_2, rt) furnished *E*-**2** and *Z*-**2**, respectively.[16]

In conclusion, we have developed a short and efficient new route towards the huperzine A skeleton. Furthermore we have prepared the previously unreported desamino huperzine A **2** in ten steps, starting from easily accessible benzoquinone monoketal **4** in an overall yield of 13% using inexpensive reagents and without the need for protecting groups except one ethylene ketal. The biological investigation of the new derivatives is underway and we are now applying this strategy to an asymmetric total synthesis of huperzine A.

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