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Natural Product Synthesis

Total Synthesis of Cyrneine A**

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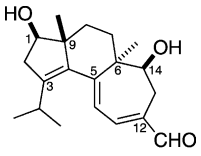
The enhancement of cognitive processes and the improvement of memory by drugs or natural products (sometimes called brain doping) is increasingly performed in our knowledge-based society and is, therefore, a controversial topic.[1] The identification of such cognitive enhancers is the goal of many research groups,[2] in particular as such drugs could open up new therapeutic avenues for the treatment of neurodegenerative diseases.[3] A hallmark of such diseases is neuritic atrophy, and compounds inducing or enhancing neurite outgrowth present interesting lead structures.[3] During our research efforts on the synthesis and biological evaluation of such compounds,[4] we became interested in cyrneine A (**1**), which enhances neurite outgrowth in pheochromocytoma cells.[5] Detailed investigations on this natural product suggested a Rac1-dependent mechanism.[6] Herein, we report the first total synthesis of cyrneine A (**1**).



Cyrneine A (**1**)

Cyrneine A (**1**) features a tricyclic 5-6-7 ring system containing a hexatrienal unit. In addition, the quaternary stereogenic centers at C6 and C9 with the angular methyl groups pose a synthetic challenge, which is complemented by the two neighboring stereogenic centers. Cyrneine A (**1**) is a member of the cyathane diterpenes, of which several successful synthetic strategies have been published.[7] We opted for a convergent synthetic strategy, which would join the five- and seven-membered rings through a reductive Knoevenagel condensation and a Heck cylization. Additional interesting steps would include a Yamamoto ring expansion reaction and a palladium-mediated reductive carbonylation.

The total synthesis of cyrneine A (**1**) started with the preparation of the five-membered fragment **5**, which already included the correct functionalization both with regard to the stereocenters as well as for the subsequent Knoevenagel and Heck reactions (Scheme 1). (−)-Carvone was reduced according to a literature procedure,[8] and the resulting OH function was protected with a TBS group. The exocyclic double bond was easily reduced by H_2 and PtO_2, and the protected alcohol **2** was obtained in 96% yield over three steps. The ring contraction to the five-membered substrate was achieved by ozonolysis[9] and reductive work-up (Zn in acetic acid) via **3**, and a subsequent cyclization mediated by piperidinium acetate. Reduction of the resulting cyclopentene carboxyaldehyde to the alcohol followed by transetherification[10] gave vinyl ether **4**. The quaternary stereogenic center was established by a Claisen rearrangement[10] in a sealed tube (toluene, 175 °C), and the resulting aldehyde **5** was obtained in 81% yield. Thus, access to this building block was secured in 8 steps and 55% calculated overall yield.

The Knoevenagel condensation of the aldehyde **5** with cyclohexa-1,3-dione was readily carried out in the presence of L-proline as the catalyst. The unsaturated intermediate was reduced in situ by the Hantzsch ester to prevent multiple additions of the nucleophile.[11] Interestingly, the stability of the product from this sequence is limited and, therefore, the intermediate was alkylated immediately with methyl iodide and DBU. The resulting diketone **6** was characterized by X-ray crystal-structure analysis.[12] It was found after tedious experimentation that the introduction of the oxygen functionality for the Heck reaction was best carried out at this stage: Ozonolysis gave the triketone **7** (X-ray crystal structure).[12] After scouting multiple routes, we realized that the stereoselective installment of the quaternary center at C6 was only feasible at this stage. The diastereoselective reduction of the triketone **7** under Luche conditions[13] resulted in high regioselectivity, and the 5*R*,6*R* diastereoisomer **8** was obtained as the major product in a ratio of 4.25:1, with none of the *unlike* diastereoisomers observed (for details, see the Supporting Information).

The selectivity of this transformation is very remarkable, as only one carbonyl group of the triketone is selectively attacked from one face. The cyclopentanone C=O group appears to be sterically too hindered for a successful attack. The relative facial selectivity resulting in the *like* configuration can be explained by the use of Luche reagents.[14] The preference for one carbonyl group of the cyclohexadione (regioselectivity) must reside in the presence of the stereogenic centers of the cyclopentane ring, and the transfer of stereochemical information over at least four bonds could, for example, be explained by transient complexation/cyclization via the C4=O group during the course of the reaction.[15]

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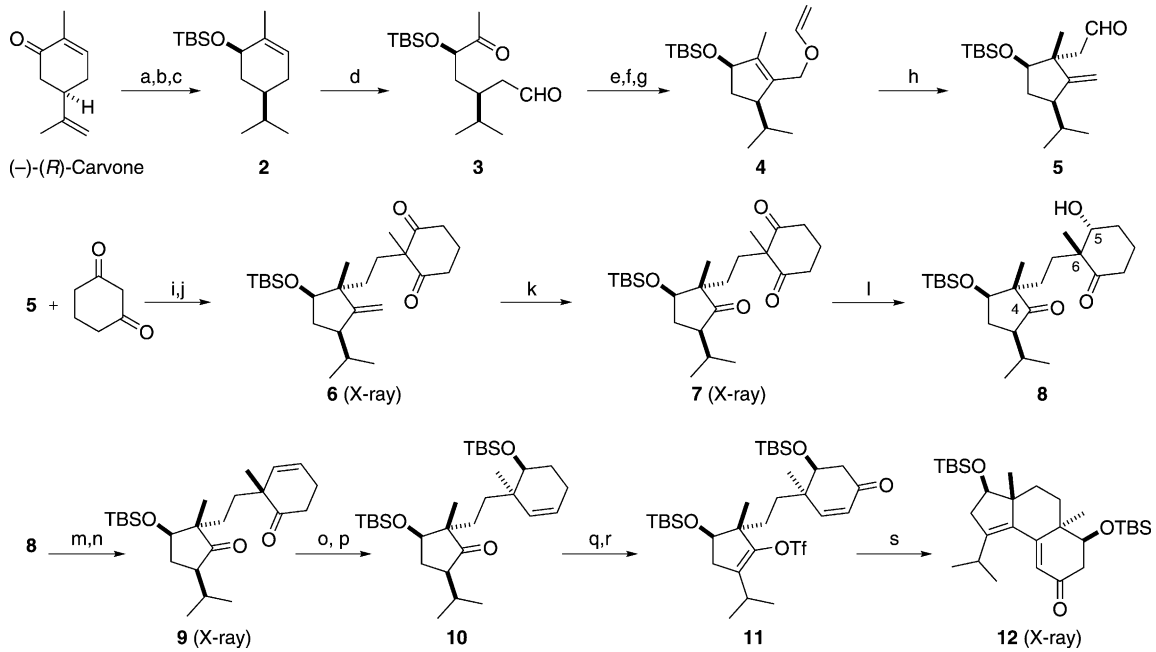


Scheme 1. Reaction conditions: a) $LiAlH_4$, Et_2O, −78 °C, 15 min; b) TBSCl, imidazole, CH_2Cl_2, RT, 1.5 h; c) PtO_2/H_2, THF, RT, 4 h, 96% (over 3 steps); d) O_3, Zn/AcOH, CH_2Cl_2/MeOH (5:1), −78 °C→RT, 1 h, 89%; e) piperidine, AcOH, Et_2O, 70 °C, 20 h, 92%; f) $NaBH_4$, MeOH, 0 °C, 15 min, 88%; g) $Hg(OAc)_2$, ethyl vinyl ether, 60 °C, 24 h, 94%; h) toluene, 175 °C, 16 h, 81%; i) L-proline, Hantzsch ester, CH_2Cl_2, 3 h, RT; j) MeI, DBU, LiI, THF, 14 h, 75 °C, 73% (over 2 steps); k) O_3, CH_2Cl_2, $(Me)_2S$, −78 °C, 1 h, 83%; l) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, THF/MeOH (1:5), −78 °C, 20 min, 68%; m) $(MeSO_2)_2O$, pyridine, DMAP, 5 h, RT, 88%; n) LiBr, Li_2CO_3, DMF, 140 °C, 1 h, 79%; o) $NaBH_4$, MeOH, 0 °C, 20 min, 86%; p) TBSOTf, 2,6-lutidine, CH_2Cl_2, 2 h, RT, 85%; q) KHMDS, $PhNTf_2$, THF, −78 °C, 3 h, 83%; r) CrO_3, DMP, CH_2Cl_2, 18 h, RT, 71%; s) $Pd(OAc)_2$, TBABr, PPh_3, K_2CO_3, toluene, 120 °C, 1 h, 63%. TBSCl = *tert*-butyldimethylsilyl chloride, RT = room temperature, DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, DMAP = 4-(dimethylamino)pyridine, KHMDS = potassium bis(trimethylsilyl)amide, DMP = 3,5-dimethylpyrazole, TBABr = tetra-*n*-butylammonium bromide, Tf = trifluoromethanesulfonyl.

The transformation of alcohol **8** to the corresponding mesylate was achieved in high yield, and the absolute configuration of all the stereogenic centers was successfully established by X-ray crystal-structure analysis.[12] Elimination to the cyclohexenone **9** followed by reduction and protection gave the intermediate **10**, which could be accessed in 100 mg amounts.

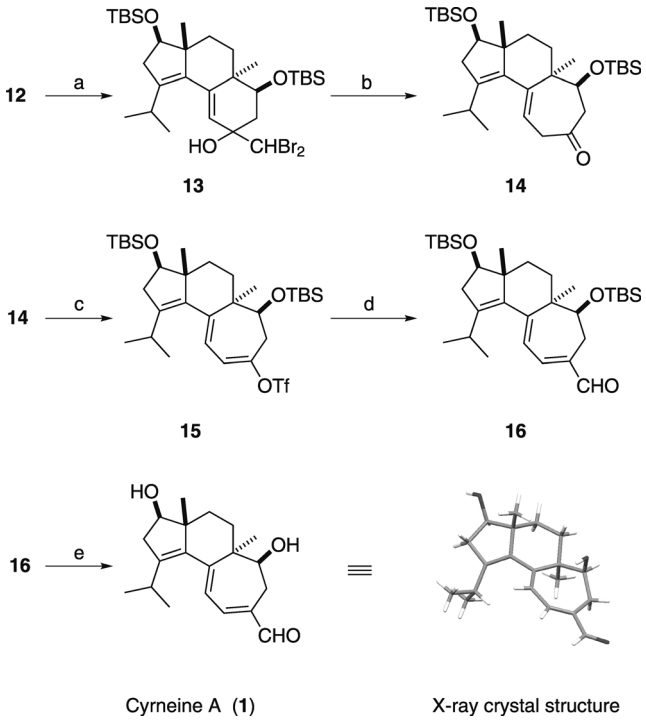
The precursor **11** for the Heck cyclization[7b–d,16] could be obtained from the ketone **10**: Preparation of the enol triflate in 83% yield was followed by a selective oxidation with CrO_3 to the α,β-unsaturated ketone **11**. The cyclization was then carried out by a palladium-mediated Heck reaction, and the constitution and configuration of the tricyclic 2,4-dienone **12** was again determined by X-ray crystal-structure analysis.[12]

The ring expansion was carried out by a two-step procedure according to Taguchi, Yamamoto, and Nozaki[17] (Scheme 2), as other methods (such as, for example, $TMSCHN_2$) were not successful. Reaction of the precursor **12** with dibromomethane and LiTMP gave, after addition, the dibromo alcohol **13**, which gave, after Br/Li exchange (BuLi, −90 °C) and subsequent rearrangement, the ring-expanded cycloheptenone **14** in high yield.

The end game in the synthesis of cyrneine A (**1**) involved the introduction of the C12-aldehyde group. The Shapiro reaction proved not to be successful for this substrate: Although the hydrazone was formed, reaction with BuLi did not yield any product. In contrast, the reductive, palladium-catalyzed carbonylation[18] of the enol triflate **15** was successful and the protected cyrneine A derivative **16** was obtained in 77% yield. The cleavage of the two TBS groups proceeded smoothly and sequentially in one pot. Purification of the product by flash chromatography finally resulted in synthetic cyrneine A (**1**) in 84% yield. The spectroscopic data of the synthetic sample matched the published data for the natural product.[5]

In addition, we obtained crystals of the target compound (m.p. 192–195 °C), which were suitable for X-ray crystal-structure analysis. This analysis definitely established the structure of cyrneine A (**1**) and allowed for the unambiguous assignment of all the stereogenic centers. This analysis also revealed interesting insights about certain properties of **1**. The hydroxy group at C14 hovers over the cycloheptadiene system, and the steric bulk of the tricyclic skeleton forces the C6-diene unit out of planarity, which might imply that the characteristic hexatrienal unit of **1** would possess reduced reactivity toward nucleophiles.

We have reported herein the first total synthesis of cyrneine A (**1**). Salient features of this route include a reductive Knoevenagel/Heck cyclization strategy, a remarkably regioselective reductive desymmetrization, a ring expansion by a carbene rearrangement, as well as a reductive, palladium-mediated carbonylation. Crystal-structure analysis of synthetic cyrneine A (**1**) led to the definitive establishment of the structure of this natural product. Biological investigations



Scheme 2. Reaction conditions: a) CH_2Br_2, LiTMP, THF, −78 °C, 20 min, 76%; b) *n*BuLi, THF, −90 °C, 30 min, 68%; c) KHMDS, $PhNTf_2$, THF, −78 °C, 20 min, 81%; d) $[Pd(PPh_3)_4]$, LiCl, CO, nBu_3SnH, THF, 80 °C, 3 h, 77%; e) TBAF, THF, RT, 14 h, 84%. LiTMP = lithium 2,2,6,6-tetramethylpiperidin-1-ide, TBAF = tetra-*n*-butylammonium fluoride.

regarding the Rac1-dependent induction of neurite outgrowth are currently underway.

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