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Sequential Oxidative and Reductive Radical Cyclization Approach toward Asperparaline C and Synthesis of Its 8-Oxo Analogue

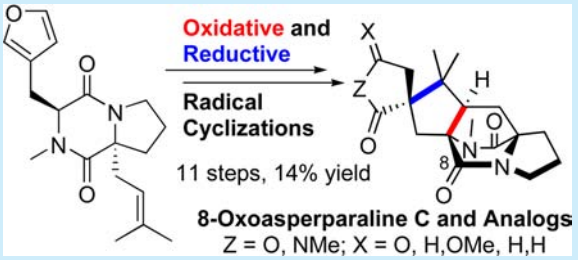
Tynchtyk Amatov,[†] Radek Pohl,[†] Ivana Cisařová,[‡] and Ullrich Jahn*[,†]

[†]Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Flemingovo namesti 2, 16610 Prague 6, Czech Republic

[‡]Department of Inorganic Chemistry, Faculty of Science, Charles University in Prague, Hlavova 8, 12843 Prague 2, Czech Republic

Supporting Information

ABSTRACT: The most advanced approach, so far, to the asperparalines is developed. Consecutive oxidative and reductive radical cyclizations serve as the key steps to stereoselectively access the complex fully elaborated skeleton containing the cyclopentane and spiro-succinimide units.



The asperparalines, comprising asperparalines A–C and 16-keto aspergillimide (**1**–**4**) (Figure 1),[1] are structurally distinct secondary metabolites belonging to a superfamily of bridged alkaloids containing the central diazabicyclo[2.2.2]-octane ring system.[2] They bear an unusual spiro-succinimide unit instead of indole or spirooxindole fragments. It was suggested that this rare spiro-succinimide motif is formed by oxidative degradation of an initially present indole unit.[3] The asperparalines show strong paralytic activities against insects, and recent studies aimed at elucidating their mechanism of action showed that asperparaline A strongly and selectively blocks insect nicotinic acetylcholine receptors.[4] Although the structure of asperparaline A (**1**) was determined by X-ray crystallography, its absolute configuration was not assigned.

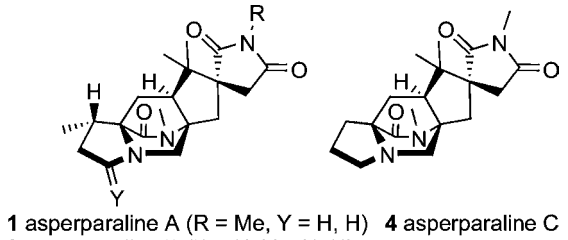


Figure 1. Members of the asperparaline family (**1**–**4**).

Many bridged alkaloids containing the central diazabicyclo-[2.2.2]octane core structure have succumbed to synthesis.[5,6] However, the asperparalines elude total synthesis despite the fact that they were isolated 20 years ago.

Notwithstanding their small size, the asperparalines have challenging structural elements, which prevent the application of strategies to similar alkaloids such as stephacidin A. First, installing the challenging spiro-succinimide unit is not established. Second, the cyclopentane ring with two contiguous quaternary centers has to be stereoselectively constructed. Third, the commonly found diketopiperazine (DKP) scaffold is partially reduced in **1**–**4**, and alas, it is the most hindered amide bond that is reduced enzymatically at an early stage of their biosynthesis similar to the paraherquamide alkaloids.[7]

Previous approaches only partially addressed these challenges. In Williams' model studies toward **4**, a biomimetic hetero-Diels–Alder cycloaddition was employed, which gave the key intermediate **5** with undesired *anti*-configuration at the bridge stereocenter (Scheme 1A).[8] A Pauson–Khand reaction was used by Tanimori et al. in their approach to asperparalines; thus, the partially reduced piperazinone unit was included from the start of the synthesis.[9] However, the advanced intermediate **6** could not be elaborated further to **4**. Simpkins' group succeeded in constructing the asperparaline C skeleton **7** with the spiro-succinimide in place.[10] Their approach relied on a thiyl radical-mediated cascade. However, because of its inherent nature, a phenylthio group was incorporated instead of the geminal methyl groups.

Based on an efficient access to tertiary DKP-derived alkoxyamines and their high-yielding radical cyclizations developed in our group,[11] we hypothesized that quaternary DKP alkoxyamines **11**, which should be obtained by enolate oxidation from DKPs **12**, may be ideal substrates for a tandem 6-*exo-trig*/5-*exo-trig* cascade approach applying the persistent radical effect (PRE) (Scheme 1B).[12] In contrast to Simpkins' reductive radical approach, our oxidative strategy would directly provide the tetracyclic core **9**, which was envisaged to be transformed to asperparaline C **4** via its oxo-analogue **8** by

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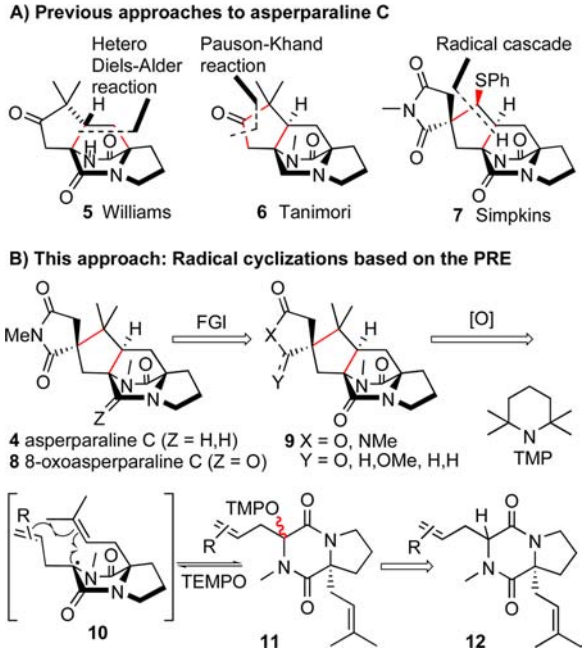
Scheme 1. Most Advanced Intermediates of Previous Synthetic Approaches (A) and Our Proposed Approach (B)

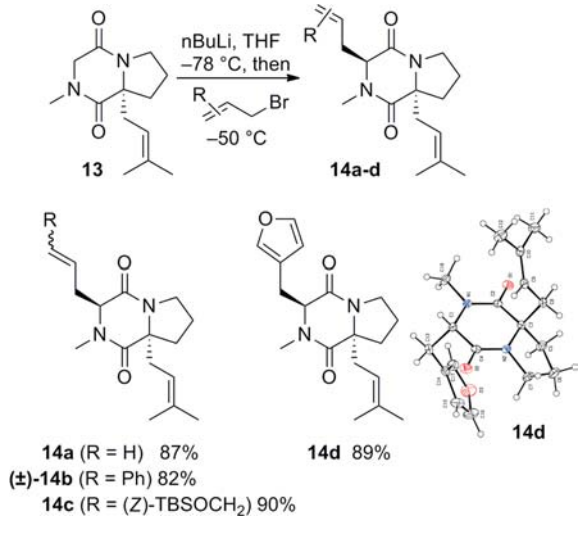


functional group interconversion. Herein, we report the synthesis of 8-oxoasperparaline C **8**, differing from **4** only in the oxidation state of the C-8 atom (asperparaline numbering) and our efforts to reduce it to asperparaline C (**4**).

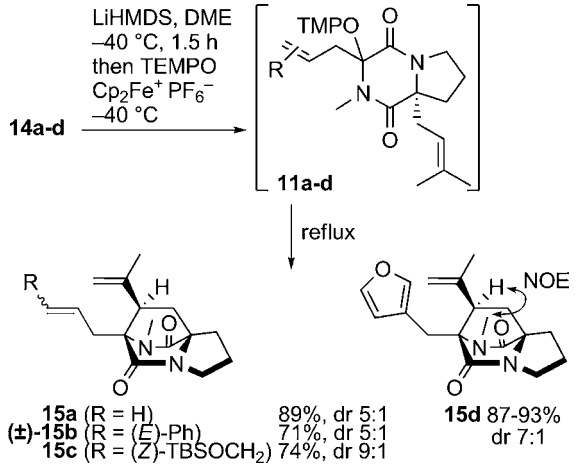
The synthesis commenced with alkylation of optically pure prenylated DKP **13** (racemic for **14b**), which was prepared from L-proline in three steps via the trichloromethyl analogue of Seebach's oxazolidinone (see the Supporting Information).[13] Only *trans*-diastereomers **14a–c** were obtained if the temperature was carefully controlled at −50 °C (Scheme 2). The structure and configuration of **14d** were confirmed unambiguously by X-ray crystallography, and those of **14a** and **14c** were assigned by analogy.

Initial attempts to obtain alkoxyamines **11** under the standard alkoxyamination conditions[11,14] were not successful. On the basis of ^{1}H NMR spectroscopic analysis, mixtures of TEMPOH elimination products, dimerization products, and recovered **14** were obtained. This indicated that quaternary alkoxyamines **11** may be thermally very labile, homolyzing already at or close to ambient temperature, but are not able to overcome the cyclization barrier (for details, see Scheme S1). Therefore, DKPs **11a–d** were generated in situ at low temperature by deprotonation of **14a–d** with LiHMDS[15] and oxygenation with ferrocenium hexafluorophosphate and TEMPO (Scheme 3).

Scheme 2. Diastereoselective Alkylation of 13 and X-ray Crystal Structure of 14d



Scheme 3. Diastereoselective Oxidative Cyclizations of 14a–d to Bridged DKPs 15a–d (Major Diastereomers Shown)



The resulting solution of **11a–d** was directly subjected to radical cyclization at 100 °C to give monocyclization products **15a–d** in good yields and most importantly in good 5–9:1 ratios for the desired *syn*-diastereomers, which is based on minimization of steric interactions of the *N*-methyl and prenyl groups in the transition state (see Scheme S2). The configuration of the major diastereomers of **15** was assigned on the basis of an NOE contact between the *N*-CH_3 group and the allylic hydrogen atom. Although the originally envisioned double cyclization did not take place (rationalization in Scheme S1), the pronounced diastereoselectivity of the monocyclization products is a good compensation.

With bridged DKPs **15a–d** in hand, the second cyclization was investigated. Initial transition-metal-catalyzed cyclization and cycloisomerization attempts[16] of **15c** were not successful (see Scheme S3). Recently, Baran and co-workers reported $Fe(acac)_3$/$PhSiH_3$-mediated reductive radical cyclizations of compounds having both electron-rich and electron-deficient alkene units,[17] which were inspired by seminal studies by Mukaiyama and later by Boger.[18] The method has proven useful in the synthesis of complex molecules.[19] Encouraged by these reports, bicyclic compound **15c** was converted to unsaturated methyl ester **16** by deprotection and sequential oxidation using MnO_2 (Scheme 4).[20] When DKP ester **16** was subjected to the reductive conditions, a clean and high-yielding radical cyclization took place, giving tetracycle **17** as a single diastereomer. Its configuration was unambiguously established by X-ray crystallographic analysis.

Though useful, **17** is not ideal for approaching the asperparalines since another carbon atom would have to be installed. The furan-containing compound **15d** is a significantly better succinimide surrogate to install the spiro unit in **4** since several routes can be explored (Scheme 5). Thus, subjecting **15d** to

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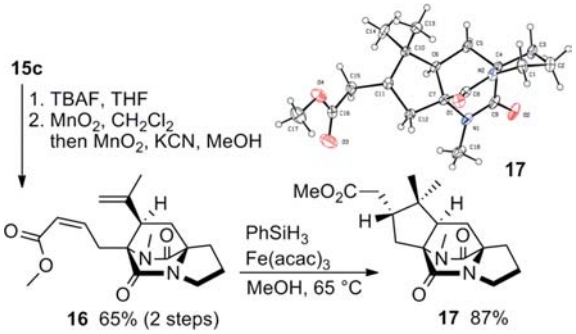
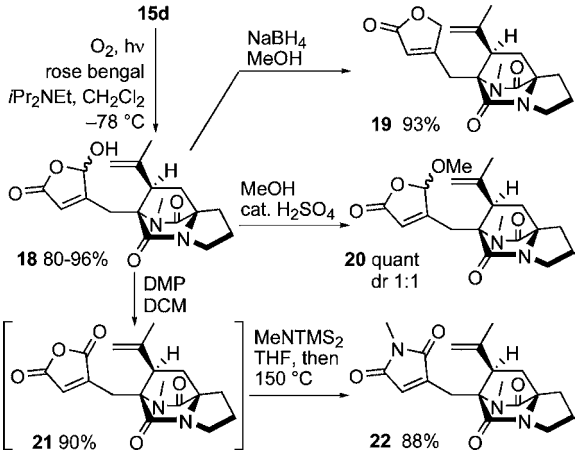
Scheme 4. Reductive Cyclization of Unsaturated Ester 16 and X-ray Structure of Tetracycle 17



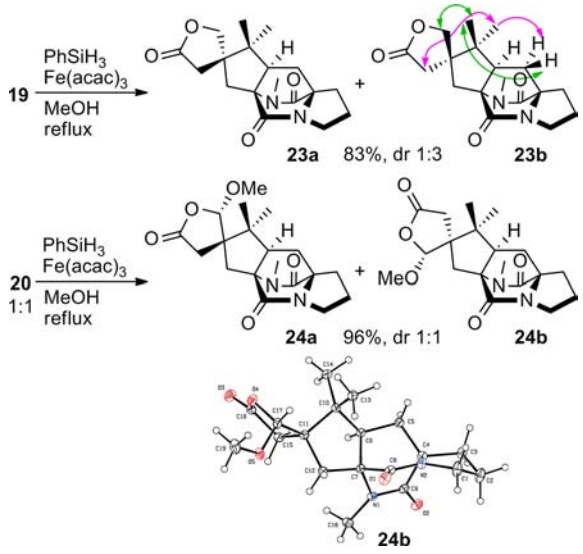
Scheme 5. Dearomatization of Furan 15d with Singlet Oxygen and Conversion of γ-Hydroxybutenolide 18 to Cyclization Precursors



oxidative dearomatization via hetero-Diels–Alder reaction with singlet oxygen and subsequent Kornblum–DeLaMare rearrangement in the presence of Hünig's base[21] regioselectively gave γ-hydroxybutenolide **18** in >80% yield as a 2:1 epimeric mixture at the hemiacetal center. Treating **18** with $NaBH_4$ in MeOH afforded butenolide **19** in high yield, whereas acetalization with methanol in the presence of catalytic concentrated H_2SO_4 quantitatively furnished γ-methoxybutenolide **20** as an inseparable 1:1 epimeric mixture. The epimeric ratio did not change upon heating with catalytic H_2SO_4 in methanol, indicating lack of thermodynamic preference. Oxidation of **18** with the Dess–Martin periodinane (DMP) provided unstable maleic anhydride intermediate **21**, which upon immediate treatment with heptamethyldisilazane in THF and subsequent heating at 150 °C for 5 min gave maleimide **22** in 88% yield. However, this procedure suffered from poor reproducibility, and because of the unsuitability of **22** in the subsequently planned cyclization (vide infra) this method was not further optimized.

Butenolide **19** underwent a very efficient cyclization to give an inseparable 3:1 mixture of diastereomers **23a** and **23b** at the newly generated spiro center (Scheme 6). NOE analysis revealed that the desired diastereomer **23a** with the correct configuration at the spiro center was the minor product. Nevertheless, this result demonstrated the feasibility of the challenging spirocyclization that generates two contiguous quaternary carbon atoms. Cyclization of the 1:1 mixture of γ-methoxybutenolide **20** gave diastereomers **24a** and **24b** as a chromatographically inseparable 1:1 mixture in 96% yield when carried out on a 70–100 mg scale.

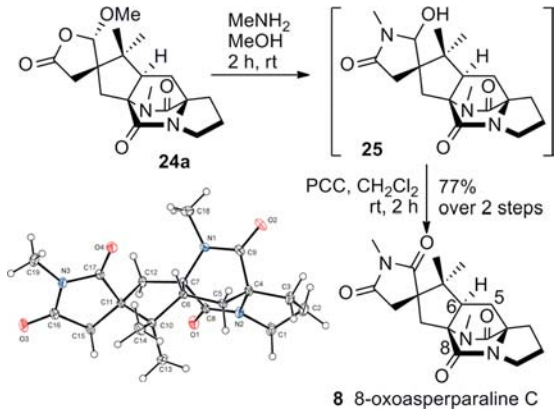
Scheme 6. Reductive Spirocyclization of Butenolides 19 and 20 and X-ray Crystal Structure of 24b



Each of the epimers at the acetal stereocenter of **20** cyclized stereoselectively, and hence, the methoxy group effectively steers the approach of the tertiary radical to the opposite face. Separation of **24a** and **24b** succeeded by crystallization of the undesired **24b** from ethyl acetate, whose configuration was proved by X-ray crystallography. The desired diastereomer **24a** with the correct configuration at the spirocenter was enriched in the mother liquor to a 5–5.5:1 ratio. In contrast, maleimide **22** did not afford the expected spiro-succinimide **8**, and instead, a 2:1 mixture of compounds was formed whose structure could not be safely assigned.

Pentacycle **24a** was transformed to spirosuccinimide **8** in 77% yield by a two-step, one-pot sequence consisting of treatment with 5 equiv of a 2 M methanolic methylamine solution for 2 h and subsequent oxidation of the resulting hydroxy lactam intermediate **25** by PCC (Scheme 7). Compound **8**, which can

Scheme 7. Synthesis of 8-Oxoasperparaline C (8)



be named as 8-oxoasperparaline C, differs from asperparaline C (**4**) only in the oxidation state of the C-8 atom. Its structure was unambiguously established by X-ray crystallography and matches the relative stereochemistry of asperparaline C. Unfortunately, all attempts to reduce the carbonyl group at C-8 were not successful, and **8** was recovered unchanged when reducing agents such as BH_3·THF or Et_3SiH/BF_3 were used. Modifying or attempting to

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reduce the less hindered C-5 oxo group at the stage of tricycle **15d** also did not give the desired result. This highlights that the reactivity of the potentially more Lewis basic C-8 oxo group is compromised by the larger steric hindrance (Scheme S4). Thus, late-stage reduction is apparently not a viable strategy if the *N*-methyl group at the DKP ring is introduced early in the synthesis.

In conclusion, an asymmetric 11-step approach to 8-oxoasperparaline C (**8**) was developed starting from cheap L-proline in 14% overall yield. The key steps are efficient radical cyclizations of in situ generated DKP-derived quaternary alkoxyamines based on the PRE to construct the diazabicyclo-[2.2.2]octane core, singlet oxygen-mediated furan dearomatization, and a reductive spirocyclization. The overall redox-neutral approach allowed a facile synthesis of spiro-lactone and spiro-succinimide analogues of asperparaline C differing from the natural product only in the oxidation state at C-8. They are the most advanced analogues of asperparaline C synthesized since their isolation two decades ago. The lessons learned are that the general approach is well suited for obtaining the asperparalines but that removal of the carbonyl group at C-8 has to be performed early or the *N*-methyl group at the diazabicyclooctane core has to be introduced after reduction at C-8. These studies are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00187.

Experimental details and characterization data (PDF)
X-ray crystal structures of **14d** (CIF)
X-ray crystal structures of **17** (CIF)
X-ray crystal structures of **24b** (CIF)
X-ray crystal structures of **8** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jahn@uochb.cas.cz.

ORCID

Ullrich Jahn: 0000-0001-8386-1348

Notes

The authors declare no competing financial interest.

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(15) Importantly, 2.2 equiv of LiHMDS had to be used to ensure full conversion of the starting material. When 1−1.2 equiv of base was used, the yields did not exceed 50%. This gains importance because the uncyclized DKPs **14a−d** are usually poorly separable from the tricyclic products **15a−d**. As a consequence, more than 2 equiv of the SET oxidant $Cp_2Fe^+PF_6^-$ have to be used.

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