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Synthetic Studies on Asperparaline A. Synthesis of the Spirosuccinimide Ring System

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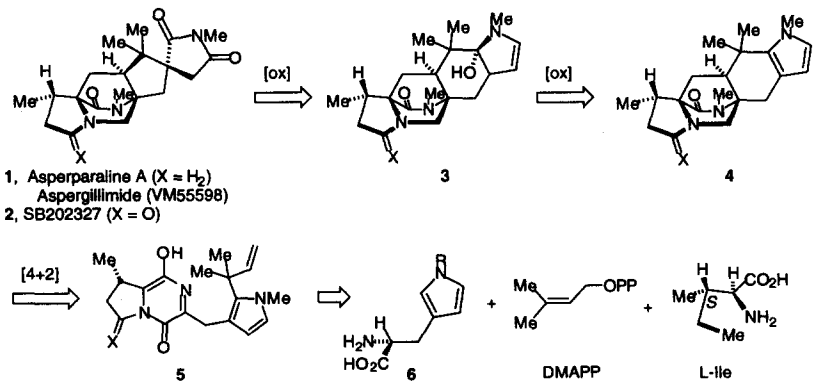
Abstract: A photooxygenation reaction of 2',2',4',4'-tetramethyl tetrahydroindole (**9**) followed by a pinacol-type rearrangement furnished 2',2',4',4'-tetramethyl-3-spirocyclopentylsuccinimide (**11**). This transformation constitutes a model study for the synthesis of the spirosuccinimide ring system of asperparaline A.

Asperparaline A (**1**) is a metabolite recently isolated by H. Hayashi *et al.* from *Aspergillus japonicus*[1] which showed potent paralytic activities against silkworm. This same metabolite, named aspergillimide (VM55598) along with the 16-oxo-derivative **2** (SB202327) was isolated along with several paraherquamide derivatives from *Aspergillus* sp. IMI 337664 by Everett and associates[2] and was reported to display anthelmintic activity. Asperparaline A has an interesting 3-spirosuccinimide moiety, which can be envisioned to be derived biosynthetically from the pyrrole derivative **4** (Scheme 1). This unusual functional array might be constructed both synthetically and biosynthetically from the novel amino acid **6**. Based on biogenetic considerations[3] and structural similarities to the paraherquamides, the mold metabolites **1** and **2** are therefore likely derived from the oxidative cyclization of dimethylallyl pyrophosphate (DMAPP), L-isoleucine[3c] (the progenitor of the β-methylproline residue) and amino acid **6**; the bicyclo [2.2.2] ring system is most likely constructed by a biosynthetic Diels-Alder reaction.[3d-f]



Scheme 1

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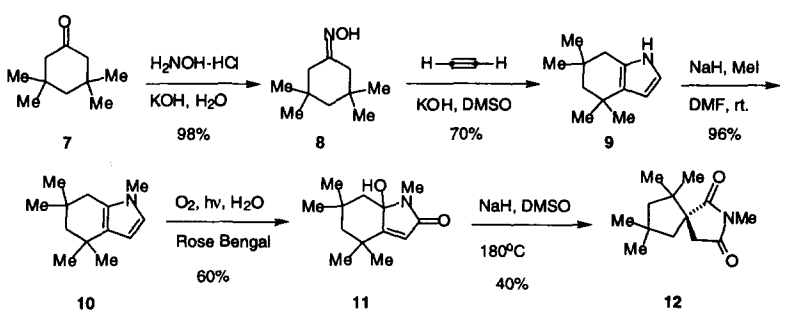
A search of the literature revealed that the spiro-succinimide ring system has not been reported as constituting part of any known natural products nor did we find references to the preparation of this array from 2,3-disubstituted pyrroles.[4] As part of a program concerned with the biosynthesis of this family of metabolites, a total synthesis of asperparaline A, became an important objective. Our approach to the total synthesis of asperparaline A is based on the biogenetic proposal shown in Scheme 1 and contemplates an oxidation of the pyrrole **4** and then pinacol-type rearrangement[5] of the corresponding pyrrolidinone **3**, followed by oxidation to the desired spirosuccinimide ring system. Toward this end, we have developed a novel synthetic approach to a 3-spirosuccinimide system starting from a 2,3-disubstituted pyrrole.

In order to assess the key pinacol-type rearrangement, we chose to attempt the conversion of pyrrole **8** into a simple spirosuccinimide ring system as a model (Scheme 2). The synthesis begins with commercially available 3,3,5,5-tetramethyl cyclohexanone **7** which was transformed into oxime **8** using hydroxylamine hydrochloride. The pyrrole **9** was obtained from oxime **8** through a Trofimov reaction.[6] This interesting transformation, which has not found extensive implementation in synthetic organic chemistry, is a very useful reaction to construct 2,3-disubstituted pyrroles from the corresponding oxime using acetylene in a superbasic media. Pyrrole **9** was then N-methylated with iodomethane to afford **10** in high yield. We examined many methods to selectively oxidize the pyrrole to carbinolamine derivatives that could be induced to undergo the spiro-rearrangement. Ultimately, it was found that the oxidation of the N-methylpyrrole **10** could be realized through a photooxygenation reaction[7] using Rose Bengal as a photosensitizer under UV light irradiation to afford hydroxy pyrrolidinone **11**. The key spiro-rearrangement reaction required for the transformation of compound **11** into **12**, was accomplished after extensive experimentation. In the event, it was found that treatment of pyrrolidinone **11** with sodium hydride in DMSO at 180 °C furnished the desired spirosuccinimide **12** (Scheme 2).[8]



Scheme 2

The structure of the spirosuccinimide model (**12**) was secured through 2D nmr analysis and X-ray crystallography as shown in Figure 1.[9] The transformation of a 2,3-disubstituted pyrrole into a 3-spirosuccinimide as reported here, represents a potentially useful synthetic approach to this functional array and is being investigated in these laboratories for application to the total synthesis of asperparaline A and related biogenetic precursors.

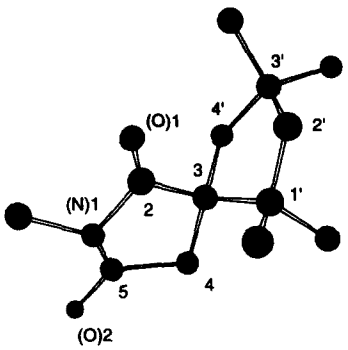


Figure 1. X-Ray structure for compound **12**. Spheres are of fixed, arbitrary radii. Hydrogen atoms have been removed for clarity.

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References and Footnotes

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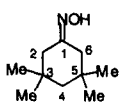
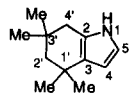
8. All new compounds exhibited spectroscopic and analytical data consistent with the assigned structures. Spectroscopic data for each compound shown in Scheme 2 are as follows:

3,3,5,5-Tetramethyl cyclohexanone oxime, (**8**).



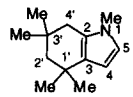
^{1}H NMR (300 MHz) δ 8.50 (br s, 1H, OH), 2.33 (s, 2H, H-2 or H-6), 2.02 (s, 2H, H-2 or H-6), 1.41 (s, 2H, H-4), 1.04 (s, 6H, -CH_3), 1.03 (s, 6H, -CH_3); ^{13}C NMR (75 MHz) δ 159.6 (C-1), 52.5 (C-2 or C-6), 44.8 (C-2 or C-6), 37.2 (C-4), 34.1 (C-3, C-5), 31.0, 30.8 (CH_3); IR (NaCl) 3257 (br), 1670, 1461, 1422, 1362, 1340, 1296, 1241, 1163, 1037, 1009, 949, 910, 850, 756, 668 cm^{-1}; HRMS calcd for $C_{10}H_{19}NO$ + H^+, 170.1161; found, 170.1545.

2′,2′,4′,4′-Tetramethyl tetrahydroindole, (**9**).



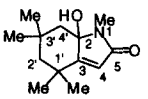
^{1}H NMR (300 MHz) δ 7.66 (br s, 1H, NH), 6.73 (d, J= 3.0 Hz, 1H, H-5), 6.20 (d, J= 3.0 Hz, 1H, H-4), 2.43 (s, 2H, H-4′), 1.60 (s, 2H, H-2′), 1.34 (s, 6H, -CH_3), 1.15 (s, 6H, -CH_3); ^{13}C NMR (75 MHz) δ 125.2, 124.8 (C-2, C-3), 115.8, 104.9 (C-4, C-5), 52.2 (C-4′), 36.9 (C-2′), 32.9, 32.2 (CH_3), 31.1 (C-1′, C-3′), 30.2 (CH_3); IR (NaCl) 3477, 3390 (br), 1725, 1589, 1474, 1453, 1382, 1360, 1300, 1246, 1175, 1142, 1077, 1039, 968, 908, 891, 826, 772, 717, 684, 641 cm^{-1}; HRMS calcd for $C_{12}H_{19}N$, 177.1387; found, 177.1519.

N-Methyl-2′,2′,4′,4′-tetramethyl tetrahydroindole, (**10**).



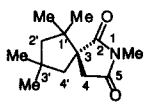
^{1}H NMR (300 MHz) δ 6.69 (d, J= 2.7 Hz, 1H, H-5), 6.20 (d, J= 2.7 Hz, 1H, H-4), 3.63 (s, 3H, -N-CH_3), 2.47 (s, 2H, H-4′), 1.67 (s, 2H, H-2′), 1.42 (s, 6H, -CH_3), 1.26 (s, 6H, -CH_3); ^{13}C NMR (75 MHz) δ 125.9, 125.2 (C-2, C-3), 120.1, 103.3 (C-4, C-5), 51.9 (C-4′), 35.6 (C-2′), 32.9, 32.6, 31.9, 31.8, 31.1, 30.4, 29.6 (C-1′, C-3′, 4xCH_3, N-CH_3); IR (NaCl) 3117, 3096, 1643, 1523, 1496, 1447, 1360, 1295, 1240, 1186, 1082, 1011, 951, 919, 848, 793, 711, 673, 608 cm^{-1}.

4,5-(1′,1′,3′,3′-Tetramethyltetramethylen)-5-hydroxy-1-methyl-3-pyrrolin-2-one, (**11**).



^{1}H NMR (300 MHz) δ 5.52 (s, 1H, H-4), 4.68 (s, 1H, N-OH), 2.77 (s, 3H, -N-CH_3), 1.49 (s, 2H, H-4′), 1.34 (s, 2H, H-2′), 1.18 (s, 6H, -CH_3), 0.91 (s, 6H, -CH_3); ^{13}C NMR (75 MHz) δ 170.1, 169.2 (C-2, C-5), 117.6 (C-4), 90.3 (C-3), 54.9 (C-4′), 47.9 (C-2′), 35.3, 35.0, 31.5, 31.1, 28.0, 26.7, 22.9 (C-1′, C-3′, 4xCH_3, N-CH_3); IR (NaCl) 3468 (br), 1655, 1447, 1311, 1164, 1023, 1000, 700 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_2$ + H^+, 224.1485; found, 224.1642.

3,3′-(1′,1′,3′,3′-Tetramethyltetramethylen)-1-methylpyrrolidine-2,5-dione, (**12**).



^{1}H NMR (400 MHz) δ 2.93 (s, 3H, -N-CH_3)), 2.78 (d, J=18Hz, 1H, H-4), 2.37 (d, J=18Hz, 1H, H-4), 2.15 (d, J=14Hz, 1H, H-4′ or H-2′), 2.00 (d, J=13.2Hz, 1H, H-4′ or H-2′), 1.71 (d, J=14Hz, 1H, H-4′ or H-2′), 1.50 (d, J=13.2Hz, 1H, H-4′ or H-2′), 1.18 (s, 3H, -CH_3), 1.11 (s, 3H, -CH_3), 0.98 (s, 3H, -CH_3), 0.95 (s, 3H, -CH_3); ^{13}C NMR (100 MHz) δ 181.3, 176.3 (C-2, C-5), 58.1 (C-3), 54.9, 50.6, 45.9 (C-4, C-4′, C-2′), 38.6, 36.0, 33.3, 31.9, 26.0, 24.6, 24.5 (C-1′, C-3′, 4xCH_3, N-CH_3); IR (NaCl) 1766, 1702, 1466, 1431, 1377, 1278, 1185, 1130, 1096, 1052, 1007, 978 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_2$ + H^+, 224.1485; found, 224.1650.

9. X-ray crystal coordinates for compound **12** will be reported elsewhere.