

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

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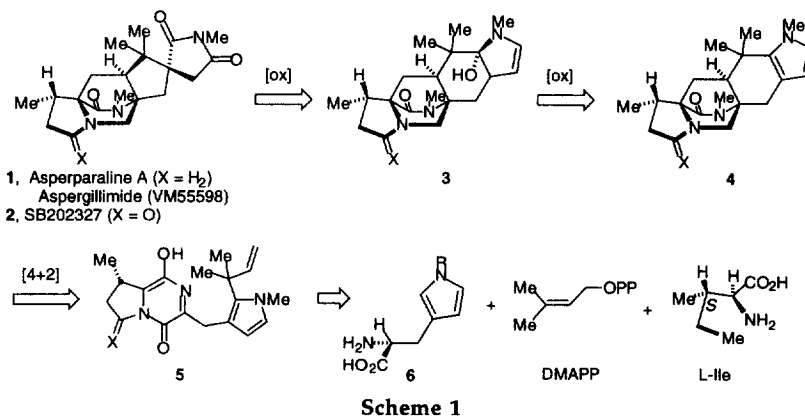
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**Abstract:** A photooxygenation reaction of 2',2',4',4'-tetramethyl tetrahydroindole (9) followed by a pinacol-type rearrangement furnished 2',2',4',4'-tetramethyl-3-spirocyclopentylsuccinimide (11). This transformation constitutes a model study for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

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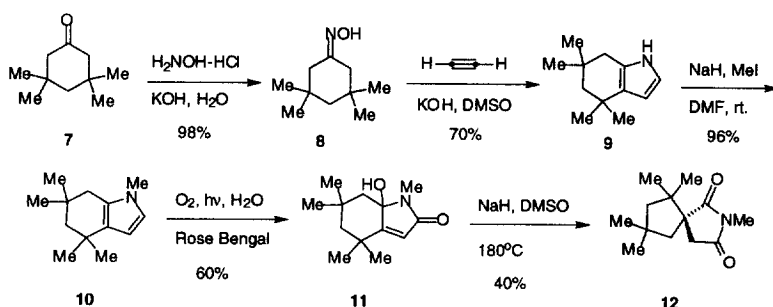
Asperparaline A (1) is a metabolite recently isolated by H. Hayashi *et al.* from *Aspergillus japonicus*<sup>1</sup> which showed potent paralytic activities against silkworm. This same metabolite, named aspergillimide (VM55598) along with the 16-oxo-derivative 2 (SB202327) was isolated along with several paraherquamide derivatives from *Aspergillus* sp. IMI 337664 by Everett and associates<sup>2</sup> 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<sup>3</sup> 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<sup>3c</sup> (the progenitor of the  $\beta$ -methylproline residue) and amino acid 6; the bicyclo [2.2.2] ring system is most likely constructed by a biosynthetic Diels-Alder reaction.<sup>3d-f</sup>



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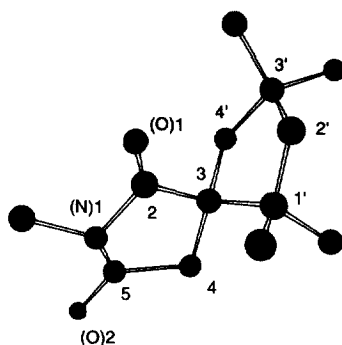
A search of the literature revealed that the spiro-succinimide ring system has not been reported as constituting part of any known natural products nor did we find references to the preparation of this array from 2,3-disubstituted pyrroles.<sup>4</sup> As part of a program concerned with the biosynthesis 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<sup>5</sup> 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.<sup>6</sup> 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<sup>7</sup> 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).<sup>8</sup>



Scheme 2

The structure of the spirosuccinimide model (12) was secured through 2D nmr analysis and X-ray crystallography as shown in Figure 1.<sup>9</sup> 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.



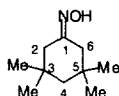
**Figure 1.** X-Ray structure for compound 12. Spheres are of fixed, arbitrary radii. Hydrogen atoms have been removed for clarity.

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#### References and Footnotes

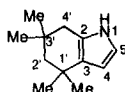
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- All new compounds exhibited spectroscopic and analytical data consistent with the assigned structures. Spectroscopic data for each compound shown in Scheme 2 are as follows:

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



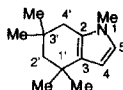
$^1\text{H}$  NMR (300 MHz)  $\delta$  8.50 (br s, 1H, OH), 2.33 (s, 2H, H-2 or H-6), 2.02 (s, 2H, H-2 or H-6), 1.41 (s, 2H, H-4), 1.04 (s, 6H,  $-\text{CH}_3$ ), 1.03 (s, 6H,  $-\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz)  $\delta$  159.6 (C-1), 52.5 (C-2 or C-6), 44.8 (C-2 or C-6), 37.2 (C-4), 34.1 (C-3, C-5), 31.0, 30.8 ( $\text{CH}_3$ ); IR (NaCl) 3257 (br), 1670, 1461, 1422, 1362, 1340, 1296, 1241, 1163, 1037, 1009, 949, 910, 850, 756, 668  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{10}\text{H}_{19}\text{NO} + \text{H}^+$ , 170.1161; found, 170.1545.

2',2',4',4'-Tetramethyl tetrahydroindole, (9).



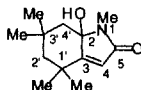
$^1\text{H}$  NMR (300 MHz)  $\delta$  7.66 (br s, 1H, NH), 6.73 (d,  $J = 3.0$  Hz, 1H, H-5), 6.20 (d,  $J = 3.0$  Hz, 1H, H-4), 2.43 (s, 2H, H-4'), 1.60 (s, 2H, H-2'), 1.34 (s, 6H,  $-\text{CH}_3$ ), 1.15 (s, 6H,  $-\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz)  $\delta$  125.2, 124.8 (C-2, C-3), 115.8, 104.9 (C-4, C-5), 52.2 (C-4'), 36.9 (C-2'), 32.9, 32.2 ( $\text{CH}_3$ ), 31.1 (C-1', C-3'), 30.2 ( $\text{CH}_3$ ); 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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{12}\text{H}_{19}\text{N}$ , 177.1387; found, 177.1519.

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



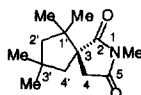
$^1\text{H}$  NMR (300 MHz)  $\delta$  6.69 (d,  $J = 2.7$  Hz, 1H, H-5), 6.20 (d,  $J = 2.7$  Hz, 1H, H-4), 3.63 (s, 3H,  $-\text{N-CH}_3$ ), 2.47 (s, 2H, H-4'), 1.67 (s, 2H, H-2'), 1.42 (s, 6H,  $-\text{CH}_3$ ), 1.26 (s, 6H,  $-\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz)  $\delta$  125.9, 125.2 (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',  $4\times\text{CH}_3$ ,  $\text{N-CH}_3$ ); IR (NaCl) 3117, 3096, 1643, 1523, 1496, 1447, 1360, 1295, 1240, 1186, 1082, 1011, 951, 919, 848, 793, 711, 673, 608  $\text{cm}^{-1}$ .

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



$^1\text{H}$  NMR (300 MHz)  $\delta$  5.52 (s, 1H, H-4), 4.68 (s, 1H, N-OH), 2.77 (s, 3H,  $-\text{N-CH}_3$ ), 1.49 (s, 2H, H-4'), 1.34 (s, 2H, H-2'), 1.18 (s, 6H,  $-\text{CH}_3$ ), 0.91 (s, 6H,  $-\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz)  $\delta$  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',  $4\times\text{CH}_3$ ,  $\text{N-CH}_3$ ); IR (NaCl) 3468 (br), 1655, 1447, 1311, 1164, 1023, 1000, 700  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{13}\text{H}_{21}\text{NO}_2 + \text{H}^+$ , 224.1485; found, 224.1642.

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



$^1\text{H}$  NMR (400 MHz)  $\delta$  2.93 (s, 3H,  $-\text{N-CH}_3$ ), 2.78 (d,  $J = 18\text{Hz}$ , 1H, H-4), 2.37 (d,  $J = 18\text{Hz}$ , 1H, H-4), 2.15 (d,  $J = 14\text{Hz}$ , 1H, H-4' or H-2'), 2.00 (d,  $J = 13.2\text{Hz}$ , 1H, H-4' or H-2'), 1.71 (d,  $J = 14\text{Hz}$ , 1H, H-4' or H-2'), 1.50 (d,  $J = 13.2\text{Hz}$ , 1H, H-4' or H-2'), 1.18 (s, 3H,  $-\text{CH}_3$ ), 1.11 (s, 3H,  $-\text{CH}_3$ ), 0.98 (s, 3H,  $-\text{CH}_3$ ), 0.95 (s, 3H,  $-\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz)  $\delta$  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',  $4\times\text{CH}_3$ ,  $\text{N-CH}_3$ ); IR (NaCl) 1766, 1702, 1466, 1431, 1377, 1278, 1185, 1130, 1096, 1052, 1007, 978  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{13}\text{H}_{21}\text{NO}_2 + \text{H}^+$ , 224.1485; found, 224.1650.

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