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Synthetic studies towards paraherquamide F: synthesis of the 1,7-dihydropyrano[2,3-*g*]indole ring system

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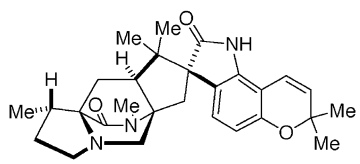
Abstract—A substituted 1,7-dihydropyrano[2,3-*g*]indole suitable for elaboration to paraherquamide F has been prepared in eight steps and 6% overall yield. The key steps are a Fischer indolization and a Claisen rearrangement.

Paraherquamide F (VM55594) (**1**) is one of a family of structurally related indole alkaloids comprised of tryptophan, a proline derivative and two isoprene units (Fig. 1[1,2]). It was isolated in 1990 from a *Penicillium* sp. concomitantly by groups at Merck & Co.[1] and SmithKline Beecham.[2] Like the other members of the paraherquamide family, paraherquamide F displays anthelmintic and antinematodal properties and as such is of interest in veterinary medicine as a treatment for intestinal parasites.[3]

The synthesis and biosynthesis of the paraherquamides and related brevianamides have been extensively investigated within this group[4] and we report here synthetic studies towards the total synthesis of paraherquamide F.

The biosynthesis of the paraherquamides has not yet been fully elucidated, but it seems likely that the diketopiperazine formed from tryptophan and β-methyl proline (**2**) is prenylated by dimethylallyl pyrophosphate (DMAPP) to give **3**. This intermediate would then undergo (in an as yet undetermined order) ring closure, oxidation, further prenylation and methylation to form the natural product (**1**) (Scheme 1). Most intriguing is the possibility that the core bicyclo[2.2.2]diazaoctane ring system is formed by a biosynthetic Diels–Alder reaction (**3**→**4**). We have recently demonstrated the utility of a biomimetic intramolecular Diels–Alder cycloaddition in the asymmetric total synthesis of VM55599.



1, paraherquamide F (VM55594)

Figure 1.

Our synthetic approach to paraherquamide F incorporates a biomimetic intramolecular Diels–Alder cyclization that is envisioned to proceed via the azadiene precursor **6** (Scheme 2). Acylation and tautomerization is expected to yield **5**, which will serve as the penultimate intermediate for the oxidative *spiro*-cyclization to afford paraherquamide F.

Compound **8** has recently been prepared for the asymmetric total synthesis of VM55599 and has been found to readily undergo condensation with an *N*-protected 3-formyl indole.[5] Our plan thus requires the synthesis of indole **7**, which contains the indole ring already oxidized and prenylated. Aldol condensation/dehydration of **7** and **8** is expected to furnish **6**.

We report here, the first synthesis of compound **7** that should prove to be a useful substrate from which paraherquamide F and other related paraherquamides can be constructed.

Key to our synthetic plan is the construction of an appropriate 1,7-dihydropyrano[2,3-*g*]indole. Although this ring system is known,[6] none of the available

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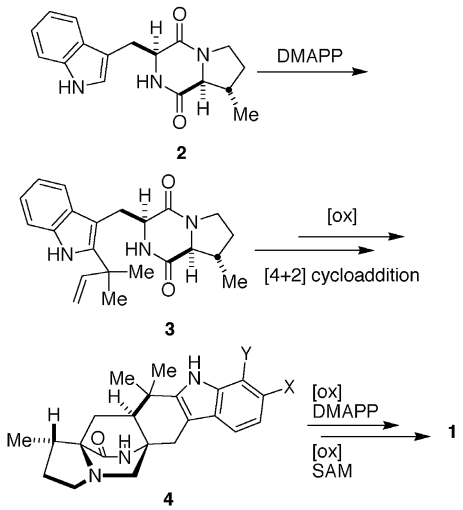
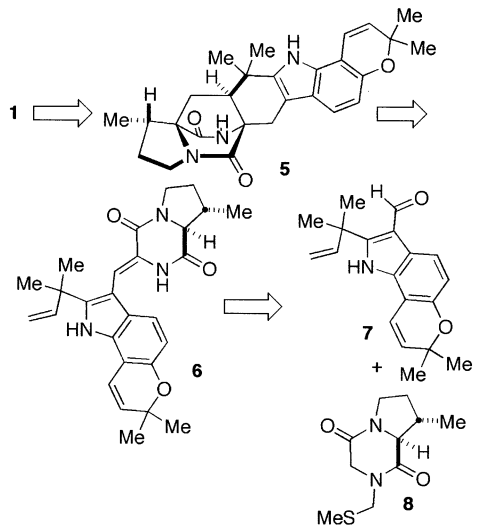


Scheme 1.



Scheme 2.

approaches are easily compatible with a 2-(1,1-dimethylallyl) substituent[7] so an alternative route was required.

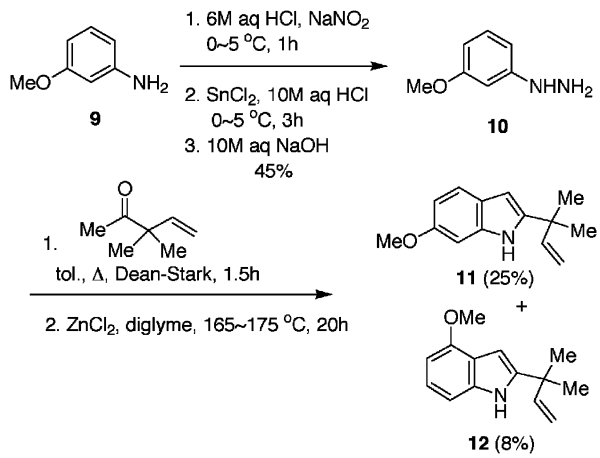
3,3-Dimethylpent-4-en-2-one was prepared in 68% yield by a Barbier-type reaction in which prenyl bromide is slowly added (<0.2 mL/h) to acetonitrile in the presence of a zinc–silver couple.[8] 3-Methoxyaniline (**9**) was converted to the corresponding arylhydrazine (**10**) by diazotization and reduction.[9] Compounds **10** and 3,3-dimethylpent-4-en-2-one were condensed under Dean–Stark conditions to give the hydrazone, which was subjected without purification, to Fischer indolization under conditions previously described for the demethoxy analogue.[10] A separable 3:1 mixture of the 6-methoxy- (**11**) and 4-methoxyindoles (**12**) was obtained in 25 and 8% yields, respectively over two steps (Scheme 3).[11]

The 6-methoxyindole (**11**) was demethylated in good yield with aluminum trichloride and ethanethiol[12] and the resultant indolol (**13**) converted to the dimethylpropargyl ether (**14**) by reaction with 3-chloro-3-methylbutyne in the presence of base and catalytic copper (Scheme 4).[13]

Compound **14** was obtained in modest yield and all attempts to push this reaction to completion led to the formation of undesirable by-products. It was found that, with the use of 0.9 equiv. of 3-chloro-3-methylbutyne and no more than 0.1 mol% of the copper catalyst, we were able to obtain a very clean reaction furnishing the desired ether in synthetically useful amounts (54% isolated yield or >99% yield based on recovered starting material).

The thermal Claisen rearrangement of **14** to the tricyclic substance **15** proceeded in 92% yield and with excellent regioselectivity, with no evidence for formation of the undesired isomer.[14] Finally, pre-formed Vilsmeier–Haack reagent at 35°C was used to install the 3-formyl substituent providing the target indole **7** in essentially quantitative yield.[15]

In summary, we have demonstrated an efficient route to the condensed aromatic compound **7** from 3-methoxyaniline. Although the overall yield (6% over eight steps, seven of which are linear) is moderate, the low-yielding steps are all early in the synthesis. We hope that this intermediate can now be elaborated to provide access to the natural product paraherquamide F, and that it will also be useful in the syntheses of the related compounds paraherquamide G, VM55595, sclerotamide, marcfortine C and aspergamides A and B. Efforts along these lines are currently in progress in our laboratory and will be reported on in due course.



Scheme 3.

Acknowledgements

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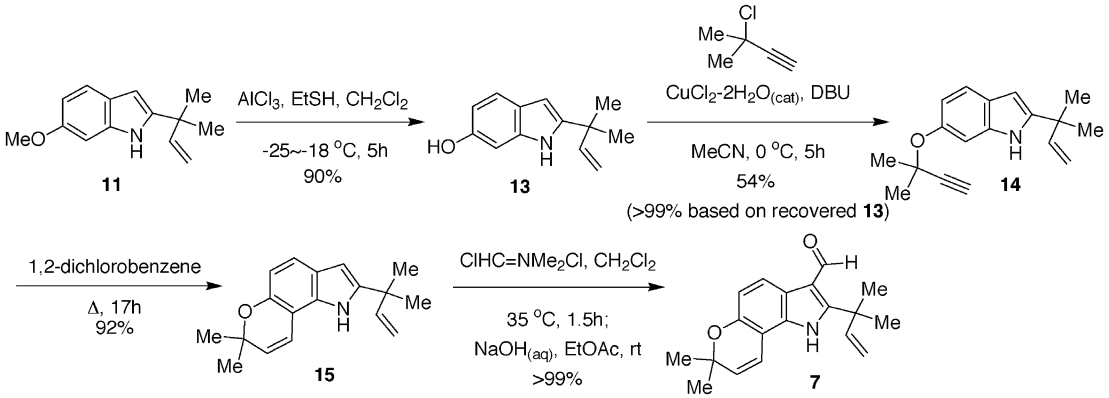

Scheme 4.

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11. All new compounds were fully characterized by ^{1}H and ^{13}C NMR, IR and low and high resolution mass spectroscopy; (a) 2-(1,1-dimethylallyl)-6-methoxy-1*H*-indole (**11**). Pale yellow oil which darkens on standing. ^{1}H NMR (300 MHz) ($CDCl_3$) δ $CHCl_3$: 1.49 (6H, s), 3.85 (3H, s), 5.13 (2H, m), 6.05 (1H, dd, $J=10.4$ Hz, $J=17.3$ Hz), 6.25 (1H, dd, $J=0.8$ Hz, $J=2.3$ Hz), 6.77 (1H, dd, $J=2.3$ Hz, $J=8.9$ Hz), 6.84 (1H, d, $J=2.1$ Hz), 7.44 (1H, d, $J=8.4$ Hz), 7.80 (1H, br s). ^{13}C NMR (74.47 MHz) ($CDCl_3$) δ $CDCl_3$: 27.7 (q), 38.5 (s), 56.0 (q), 94.7 (d), 97.8 (d), 109.4 (d), 112.2 (t), 120.8 (d), 122.9 (s), 136.7 (s), 144.7 (s), 146.4 (d), 156.0 (s). IR (NaCl, neat): 3418, 2967, 2834, 1627, 1459, 1246, 1159, 809 cm^{-1}. MS (FAB$^+$): 215 (M$^+$, 100%), 201 (19.5). HRMS (FAB), calcd for $C_{14}H_{17}NO$ (M$^+$): 215.1317. Found: 215.1310; (b) 2-(1,1-dimethylallyl)-4-methoxy-1*H*-indole (**12**). Pale yellow oil which darkens on standing. ^{1}H NMR (300 MHz) ($CDCl_3$) δ $CHCl_3$: 1.49 (6H, s), 3.97 (3H, s), 5.12 (2H, m), 6.04 (1H, dd, $J=10.4$ Hz, $J=17.4$ Hz), 6.44 (1H, dd, $J=0.6$ Hz, $J=2.1$ Hz), 6.52 (1H, d, $J=7.8$ Hz), 6.95 (1H, d, $J=8.1$ Hz), 7.07 (1H, t, $J=7.8$ Hz), 7.90 (1H, br s). ^{13}C NMR (74.47 MHz) ($CDCl_3$) δ $CDCl_3$: 27.8 (q), 38.5 (s), 55.6 (q), 95.3 (d), 99.8 (d), 104.3 (d), 112.4 (t), 119.1 (s), 122.3 (d), 137.4 (s), 144.5 (s), 146.3 (d), 153.0 (s). IR (NaCl, neat): 3417, 2967, 2836, 1591, 1508, 1361, 1249, 1118, 766 cm^{-1}. MS (FAB$^+$): 215 (M$^+$, 100%), 200 (6.1). HRMS (FAB), calcd for $C_{14}H_{17}NO$ (M$^+$): 215.1317. Found: 215.1312; (c) 2-(1,1-dimethylallyl)-1*H*-indol-6-ol (**13**). Cream-colored crystals. Mp 130–131°C (recryst. ether/hexanes). ^{1}H NMR (300 MHz) ($CDCl_3$) δ $CHCl_3$: 1.48 (6H, s), 5.13 (2H, m), 5.33 (1H, br s), 6.04 (1H, dd, $J=10.4$ Hz, $J=17.6$ Hz), 6.25 (1H, d, $J=1.8$ Hz), 6.67 (1H, dd, $J=2.7$ Hz, $J=8.4$ Hz), 6.78 (1H, d, $J=2.1$ Hz), 7.40 (1H, d, $J=8.4$ Hz), 7.79 (1H, br s). ^{13}C NMR (74.47 MHz) ($CDCl_3$) δ $CDCl_3$: 27.7 (q), 38.5 (s), 97.0 (d), 97.9 (d), 109.6 (d), 112.3 (t), 120.9 (d), 123.1 (s), 136.9 (s), 145.0 (s), 146.3 (d), 151.3 (s). IR (NaCl, neat): 3419, 2968, 1628, 1462, 1352, 1228, 1156, 918, 807 cm^{-1}. MS (FAB$^+$): 201 (M$^+$, 100%). HRMS (FAB), calcd for $C_{13}H_{15}NO$ (M$^+$): 201.1154. Found: 201.1154; (d) 2-(1,1-dimethylallyl)-6-(1,1-dimethylprop-2-ynyloxy)-1*H*-indole (**14**). Pale yellow oil. ^{1}H NMR (300 MHz) ($CDCl_3$) δ $CHCl_3$: 1.49 (6H, s), 1.66 (6H, s), 2.56 (1H, s), 5.15 (2H, m), 6.06 (1H, dd, $J=10.5$ Hz, $J=17.4$ Hz), 6.28 (1H, dd, $J=0.6$ Hz, $J=2.1$ Hz), 6.96 (1H, dd, $J=2.1$ Hz, $J=8.7$ Hz), 7.24 (1H, d, $J=1.8$ Hz), 7.42 (1H, d, $J=8.4$ Hz), 7.83 (1H, br

s). ^{13}C NMR (74.47 MHz) ($CDCl_3$) δ $CDCl_3$: 27.7 (q), 30.0 (q), 38.5 (s), 73.2 (s), 73.6 (s), 87.2 (d), 97.9 (d), 104.6 (d), 112.3 (t), 116.4 (d), 119.9 (d), 125.1 (s), 136.1 (s), 145.7 (s), 146.3 (d), 150.9 (s). IR (NaCl, neat): 3428, 3361, 3295, 2970, 2934, 2111, 1622, 1456, 1239, 1132, 976, 885, 817 cm^{-1}. MS (FAB$^+$): 267 (M^+, 100%), 201 (91.5). HRMS (FAB), calcd for $C_{18}H_{21}NO$ (M^+): 267.1623. Found: 267.1621; (e) 2-(1,1-dimethylallyl)-7,7-dimethyl-1,7-dihydropyrano[2,3-*g*]indole (**15**). White crystals. Mp 155–156°C (recryst. ether/hexanes). ^{1}H NMR (300 MHz) ($CDCl_3$) δ $CHCl_3$: 1.47 (6H, s), 1.48 (6H, s), 5.14 (2H, m), 5.66 (1H, d, $J=9.6$ Hz), 6.05 (1H, dd, $J=10.5$ Hz, $J=17.4$ Hz), 6.23 (1H, d, $J=2.1$ Hz), 6.59 (1H, d, $J=9.6$ Hz), 6.64 (1H, d, $J=8.4$ Hz), 7.29 (1H, d, $J=9.3$ Hz), 7.68 (1H, br s). ^{13}C NMR (74.47 MHz) ($CDCl_3$) δ $CDCl_3$: 27.7 (q) (two co-incident), 38.5 (s), 75.8 (s), 98.6 (d), 104.9 (s), 110.6 (d), 112.4 (t), 117.3 (d), 120.4 (d), 123.3 (s), 129.6 (d), 132.5 (s), 144.6 (s), 146.3 (d), 148.4 (s). IR (NaCl, neat): 3381, 2975, 2931, 1637, 1437, 1361, 1218, 1154, 921, 809, 735 cm^{-1}. MS (FAB$^+$): 267 (M^+, 100%). HRMS (FAB), calcd for $C_{18}H_{21}NO$ (M^+): 267.1623. Found: 267.1627; (f) 2-(1,1-dimethylallyl)-7,7-dimethyl-1,7-dihydropyrano[2,3-*g*]indole-3-carbaldehyde (**7**). Pale yellow crystals. Mp 209–210°C (recryst. ethyl acetate/ether/hexanes). ^{1}H NMR (300 MHz) ($CDCl_3$) δ $CHCl_3$: 1.47 (6H, s), 1.68 (6H, s), 5.29 (2H, m), 5.70 (1H, d, $J=9.9$ Hz), 6.23 (1H, dd, $J=10.5$ Hz, $J=17.4$ Hz), 6.63 (1H, d, $J=9.9$ Hz), 6.80 (1H, d, $J=8.4$ Hz), 8.10 (1H, d, $J=8.4$ Hz), 8.53 (1H, br s), 10.42 (1H, s). ^{13}C NMR (74.47 MHz) ($CDCl_3$) δ $CDCl_3$: 27.7 (q), 29.3 (q), 40.1 (s), 76.1 (s), 105.2 (s), 113.7 (d), 114.1 (t), 114.6 (s), 116.5 (d), 121.5 (s), 122.5 (d), 130.3 (s), 130.7 (d), 145.2 (d), 149.8 (s), 154.0 (s), 186.7 (d). IR (NaCl, neat): 3272, 2974, 2929, 1625, 1585, 1455, 1377, 1220, 1120, 1055, 904 cm^{-1}. MS (FAB$^+$): 296 (MH^+, 100%), 295 (M^+, 80). HRMS (FAB), calcd for $C_{19}H_{22}NO_2$ (MH^+): 296.1651. Found: 296.1639.

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