First Unambiguous Total Synthesis of Hericenone A : Proposed Structure Revised

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Abstract: Hericenone A has been synthesized by an unambiguous route involving a Diels-Alder reaction and the well known regioselective $NaBH_4$ -reduction of the phthalates.

As a part of our continued effort to synthesize biologically active molecules, our attention has been drawn to the recent reports by Kawagishi and his colleagues of the isolation of hericenone-A to E from the mushroom <u>Hericium erinaceum</u>^{1,2}. Hericenone-A (1) and f (2) showed significant cytotoxicity against HeLa cells and hericenones-C,D,E (3-5) have stimulating activity of the synthesis of the nerve growth factor. Although the structures of all hericenones (1-5) were determined by spectral data, the PMR spectra of 1 and 2 do not rule our the alternative structures **1a** and **2a** respectively because the lone aromatic proton in 1 and **2** appears at δ 6.97 and δ 6.96 respectively which is more appropriate for isomeric structures as in **1a** and **2a**. The aromatic singlet in other hericenones (3-5) is seen at δ 6.53 i.e., 0.4 ppm up-field compared to 1 and 2 thereby favouring the suggested structures **1a** and **2a** of hericenone A (1) and B (2) respectively. Further, the IR spectrum of **1** shows C=O peak at 1760 cm⁻¹ corresponding to nonhydrogen-bonded phthalide ketone³ favouring structure **1a**. To clarify this anomaly, we first synthesized (**19**) the methyl ether of **1**, whose spectral data was found to be different from that of hericenone A (1) thereby favouring structure **1a**. This fact has been confirmed by its total synthesis.



Our basic strategy is to first generate the aromatic unit with proper substitution by a Diels-Alder approach and carry out subsequent transformations to complete the synthesis of **la** and the methyl ether of 1 (19).

The known 2-allyl-cyclohexane-1,3-dione⁴ was converted quantitatively into its enol ether (6) with diazomethane. This was then transformed to the desired diene (7) (Scheme I)

Scheme 1



Reagents & Conditions: a) LDA (1.0 eq.), TMSCI (1.5 eq.), THF, -78°C; b) Dimethylacetylenedicarboxylate (1.2 eq.), 160°C, 12 h; c) DMS, K_2CO_3 , acetone, reflux, 12 h, 68% for **6-9**; d) NaOH/EtOH, 12 h, r.t. 96%; e) Sublimation, 180°C/1 mm, 94%; f) Zn/HCl in acetic acid, 100°C, 12 h or NaBH₄ in CH₃OH/DMF, 0°C, 1 h; g) O₃, dimethyl sulfide, CH₂Cl₂, -78°C-r.t, 4 h, 68%; h) Benzene, reflux, 36 h, 84%; i) NaBH₄/MeOH, 0°C, 45 min., 92%; j) CBr₄ (1.1 eq), PPh₃ (1.1 eq.), CH₂Cl₂, r.t. 4 h, 94%; k) n-BuLi (1.0 eq.), THF, -20°C - r.t, 12 h, 64%; l) HgO (1.0 eq.), HgCl₂ (2.1 eq.), 85% aq. MeOH, r.t. 45 min., 80%.

by treatment with LDA-TMS chloride at -78°C. Diels-Alder reaction of the diene (7) with dimethylacetylene dicarboxylate (1.2 eq., 160°C, 12 h) resulted in the formation of an unstable adduct which eliminates ethylene as in a typical Alder-Rickert⁵ reaction to give the crucial

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diester (8) which in turn was methylated with dimethyl sulphate and potassium carbonate in acetone (reflux temperature, 12 h) to give dimethyl 4-allyl-3,5-dimethoxyphthalate (9). Conversion of the diester to the corresponding phthalic anhydride (10) and selective reduction t_{2} the corresponding phthalide using zinc and HCl in acetic acid⁶ or alternatively sodium borehydride^{7a,b} gave (11). The structure of the lactone was confirmed by NOE experiments. Irradia tion of the H-4 of compound 11 resulted in the enhancement of the resonances due to the lactone methylene (4.5%) and also the C-5 methoxyl group (13%). Ozonolysis⁸ of compound 11 resulted in the corresponding aldehyde (12) in 68% yield which on treatment with the stable ylid⁹ (13) furnished α , β -unsaturated trans-aldehyde (14). This was further converted quantita tively to the bromo compound 16 via the alcohol 15. Elongation of the side chain in 16 was achieved by treating it with the anion of the 2-isobutenyl-1,3-dithane $\frac{10}{10}$ (17) (1.0 eq., n-BuL. 1.1 eq. -20°C) to yield 64% of 18. This was subjected to dethioketalisation¹⁰ (Mercuric oxide mercuric chloride) to give hericenone methyl ether (19). PMR^{11,12} spectral values of compound 19 showed the lone aromatic proton as a singlet at δ 6.64 and the set of methoxyl peaks a δ 3.88 and δ 4.08. The spectral parameters for the compound synthesized by us point to the lactone carbonyl in syn orientation with respect to the 7-methoxyl group. Particular evidence for this comes from the NOE data described earlier and also that gathered for compound 15 thereby pointing to the fact that hericenone-A should be represented as la and not as l.

The synthesis of compound la (Scheme II) has also been carried out by subjecting dimethyl 4-allyl-3,5-dimethoxyphthalate (9) to ozonolysis followed by selective O-demethylation with BCl, 13 (1.2 eq. -10°C, 10 min) to give the hydroxy aldehyde 21 in 88% yield. This was





treated with the stable ylid (13) to give the aldehyde 22. The aldehyde (22) on subjecting to NaBH₄ (3 eq.) reduction resulted in the formation of the hydroxyphthalide (23). NaBH₄ is known to reduce selectively¹⁴ the hydrogen-bonded <u>ortho</u> ester thereby exclusively giving the phthalide (23) in 74% yield. The alcohol (23) was converted to the bromo derivative (24) followed by treatment with the anion generated by the dithane (17, 2.0 eq.) resulted in 25.

Dethioketalisation of **25** resulted in the formation of **1a** whose PMR^{15} and IR data are in full agreement with the natural hericenone **A**. Further, this was converted to methyl ether with K_2CO_3 and CH_3I to give **26**. The PMR^{12} spectra of synthetic hericenone methyl ether (**26**) showed the lone aromatic proton at δ 7.1 and the methoxyls at δ 3.88 and δ 3.90. The NOE data is also in agreement with the structure **26**. When H-7 is irradiated, the signal due to the methylene protons of the phthalide ring remained unaffected while there was a significant enhancement (13%) in the intensity of the signal corresponding to the 6-methoxy group.

In conclusion, we believe that our synthetic study assigns beyond any doubt the correct structure for hericenone-A as **la**. Efforts are underway to synthesis the other hericenones. **Acknowledgements:** We thank Prof H Kawagishi for providing spectral data of the natural hericenones A (1) and B (2).

References and notes:

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- 11. ¹H NMR of **19** (400 MHz, $CDCl_3$ -TMS): δ 6.64 (s, H-4), 6.08 (s, H-6'), 5.26 (t, J-6.60 Hz, H-2'), 5.19 (s, H-3), 4.07 (s, 5-OCH₃), 3.91 (s, 7-OCH₃), 3.47 (d, J=7.16 Hz, H-1'). 3.02 (s, H-4'), 2.13 (s, H-7'), 1.85 (s, H-8'), 1.79 (s, H-3').
- Corresponding values reported: δ 7.10 (s), 6.07 (s), 5.26 (t, J=6.59 Hz), 5.40 (s), 3.90 (s), 3.88 (s), 3.49 (d, J=6.59 Hz), 3.03 (s), 2.13 (s), 1.85 (s), 1.79 (s).
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- ¹H NMR for compound la (400 MHz, CDCl₃-TMS): & 6.97 (s, H-4), 6.09 (s, H-6'), 5.30 (t, J=6.41 Hz, H-2'), 5.25 (s, H-3), 3.88 (s, -OCH₃), 3.59 (d, J=6.41 Hz, H-1'), 3.18 (s, H-4'), 2.17 (s, H-7'), 1.91 (s, H-8'), 1.81 (s, H-3').
 These values exactly match with the values reported.

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