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SYNTHESIS OF HORMOTHAMNIONE

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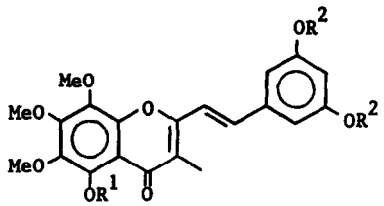
Summary: Hormothamnione 1 has been obtained from 2,3-dimethyl-5,6,7,8-tetramethoxy-chromone 18 in 63% yield. Synthesis of the required chromone 18 as well as of the 2 and 3-styryl analogs 5 and 9 are described.

Hormothamnione 1 is the first naturally occurring styrylchromone isolated from the blue green algae Hormothamnion enteromorphoides.[1] Its potent cytotoxicity to P388 lymphocytic leukemia and HL-60 human promyelocytic leukemia cell lines together with the limited resources of this compound made its synthesis highly desirable. This was achieved by condensation of the 2,3-dimethyl-5,6,7,8-tetramethoxy-chromone 18 with a suitable protected 3,5-dihydroxy benzaldehyde[2] followed by deprotection and selective demethylation of the methoxy group at C-5 of the chromone nucleus. Chromone 18 also could be the starting material for 3-styryl substituted analogs by selective radical bromination of the 3-methyl group, formation of a phosphonium salt and Wittig reaction with the desired aldehyde.



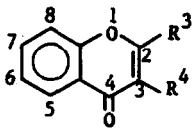
1 $R^1 = R^2 = H$
2 $R^1 = R^2 = Ac$
19 $R^1 = Me$, $R^2 = Bn$

Initial studies were carried out with chromone 3.[3] Exclusive condensation of the 2-methyl group[2] with 3,5-dibenzyloxybenzaldehyde[4] took place in NaOMe-MeOH at rt affording the trans-2-styrylchromone 4[5,6] as a solid which precipitated from the reaction mixture (67%). Debenzylation in refluxing AcOH/conc.HCl (10:2) yielded the unsubstituted 2-styrylchromone 5.[7] The use of methoxymethylether (MOM) for protecting the phenolic groups in 3,5-dihydroxybenzaldehyde[8] proved to be more convenient. Deprotection was carried out by disolving the condensation product in MeOH saturated with HCl gas followed by filtration of the insoluble desired diphenol 5.

On the other hand, and for the synthesis of the trans-3-styryl derivative 9, the 3-bromomethyl chromone 6 was prepared by bromination of 3 with NBS.[9] This result, expected from the electrophilic character of the bromine radical, was confirmed by treating the deuterated chromone 7 under the same bromination conditions. The ^{1}H-NMR spectra of the deuterio

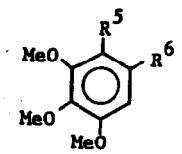
labeled bromo compound so obtained and that of 6 were identical except, that the signal corresponding to the methyl group was very weak, indicating that the bromine atom was present as a CH_2Br at C-3. Treatment of the crude bromination mixture with Ph_3P in refluxing benzene afforded the phosphonium salt 8 as a white precipitate (mp 312°C (d), 87% from 3). Wittig reaction of 8 with MOM protected 3,5-dihydroxybenzaldehyde[8] (THF, NaH, 0°C, 20%) followed by acid deprotection (MeOH saturated with HCl gas, RT) afforded the desired 3-styrylchromone 9.[10]

For the synthesis of the natural product 2,3-dimethyl-5,6,7,8-tetramethoxy chromone (18) was required. First attempts to prepare the intermediate propiophenone 16 by a Hoesch reaction of phenol 14 (propionitrile, $ZnCl_2$, Et_2O, HCl gas) were unsuccessful and Fries rearrangement



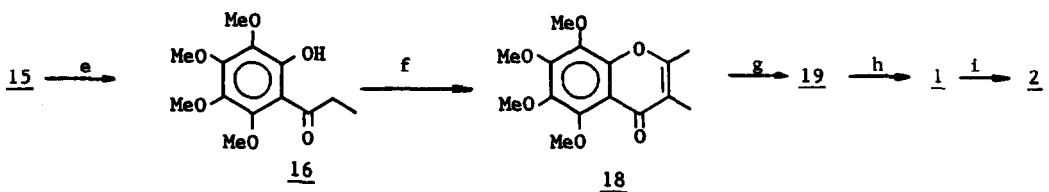
	R^3	R^4
3	Me	Me
6	Me	CH_2Br
7	CD_3	Me
8	Me	$CH_2Ph_3P^+Br^-$

	R^3	R4
4	3,5-$(BnO)_2$-C_6H_3-CH=CH-	Me
5	3,5-$(OH)_2$-C_6H_3-CH=CH-	Me
9	Me	3,5-$(OH)_2$-C_6H_3-CH=CH-



	R^5	R^6			R^5	R^6
10	CHO	H		14	MeO	OH
11	OH	H	c	15	MeO	MeO
12	MeO	H		17	MeO	$CH_3CH_2C(O)O$
13	MeO	CHO				

a, b, d



15 —e→ 16 —f→ 18 —g→ 19 —h→ 1 —i→ 2

a) 1. mCPBA, CH_2Cl_2, rt; 2. KOH(aq) 10%, MeOH; 3. KOH, Me_2SO_4, 90% overall. b) $C_6H_5N(CH_3)CHO$, $POCl_3$, 80%.[10a] c) 1. mCPBA, CH_2Cl_2, rt; 2. KOH(aq) 10%, MeOH, 82% overall. d) Me_2SO_4, Me_2CO, 92%. e) 1. CH_3CH_2COCl, CH_2Cl_2, $AlCl_3$ (1 equiv.), rt; 2. NaOH(aq) 5% - Et_2O partition; 3. Et_2O extracts recycled (CH_2Cl_2, $AlCl_3$ (1 equiv.)CH_3CH_2COCl, rt); 4. NaOH(aq) extracts acidified (HCl(aq)), Et_2O extraction, silica gel flash chromatography: 55% (13 mmol scale). f) 1. Na, AcOEt, rt; 2. HCl(aq) (1:1, v:v), 55°C, 0.5 h, 75% overall. g) NaOMe/MeOH, 3,5-$(BnO)_2$-C_6H_3-CHO (2 equiv.), 90°C, 80%. h) AcOH-HCl(c) (4:1, v:v), 100°C, 79%. i) Py, Ac_2O, rt.

of the propionyl derivative 17 gave only very little of the desired product 16. Finally pentamethoxybenzene 15, readily obtained in quantity by following the sequence shown in the Scheme,[11] proved to be a suitable precursor. Friedel-Craft reaction of 15 with propionyl chloride (CH_2Cl_2, 1.0 equiv. of $AlCl_3$) accompanied by monodemethylation of the methoxy group

ortho positioned to the carbonyl function afforded 16[12] in 55% yield. With more than 1 equiv. of $AlCl_3$ reflux was necessary to carry out the reaction and the yield was lower.[13] Claisen condensation of 16 with ethyl acetate followed by acid catalyzed cyclization afforded chromone 18[14] (75%). Condensation of 18 with 3,5-dibenzyloxybenzaldehyde followed by debenzylation and selective demethylation of the adduct 19[15] (mp 118°C) gave hormothamnione 1 as a yellow solid. Its mp and spectroscopic data as well as those of its triacetate 2 were in good agreement with those previously reported.[1,16]

REFERENCES

1. W. H. Gerwick, A. Lopez, G. D. Van Duyne, J. Clardy, W. Ortiz, and A. Baez. Tetrahedron Lett., 1986, 27, 1979.

2. G. P. Ellis, "Alkylchromones" in Heterocyclic Compounds: Chromenes, Chromanones and Chromones, G. P. Ellis, ed., John Wiley and Sons, New York 1977; pp 606-611.

3. For the preparation of 3 see I. Hirao, M. Yamaguchi and N. Hamada, Synthesis, 1984, 1076, and ref. 2, pag 508.

4. J. Millen, T. N. Riley, I. W. Waters and M. E. Hamrick, J. Med. Chem., 1985, 28, 12.

5. All new compounds were fully characterized by ^{1}H-NMR, MS, IR, and UV and gave satisfactory elemental analysis or high resolution mass spectra.

6. mp 156°C. ^{1}H-NMR ($CDCl_3$) δ 2.23 (s, 3H, CH_3), 5.10 (s, 4H, OCH_2Ph), 6.66 (t, J= 2.1 Hz, 1H), 6.85 (d, J= 2.1 Hz, 2H), 7.09 (d, J= 15.8, 1H), 7.33-7.48 (m, 12H, ArH), 7.53 (d, J= 15.8 Hz, 1H), 7.65 (m, 1H), 8.21 (dd, J= 7.9 and 1.6 Hz, 1H). MS (CI) 475 (M^++1), 459 (M^+-15).

7. mp 288°C (d). IR (KBr) ν_{max} 3180, 1600 cm^{-1}. UV (MeOH, nm): λ_{max} (ε) 249 (16,519), 347 (32,450). ^{1}H-NMR (THF-d8) δ 2.19 (s, 3H), 6.28 (s, b, 1H), 6.57 (d, J= 2.0 Hz, 2H), 7.18 (d, J= 15.8 Hz, 1H), 7.35 (t, J= 7,9 Hz, 1H), 7.50 (d, J= 15.8 Hz, 1H), 7.54 (d, J= 7.6 Hz, 1H), 7.66 (m, 1H), 8.10 (dd, J= 1.5 and 7.9 Hz, 1H), 8.68 (d, J= 3.2 Hz, 1H, OH), 11.00 (s, 1H, OH).

8. MOM protected 3,5-dihydroxybenzaldehyde was prepared in 57% yield from methyl-3,5-dihydroxybenzoate: 1. NaH, $BrCH_2OMe$. 2. THF, $LiAlH_4$. 3. CH_2Cl_2, PCC: Oil, 2,4-dinitrophenylhydrazone mp 167°C.

9. Minor quantities of unreacted starting chromone 3 and 2,3-dibromomethylchromone were detected when 1 equivalent of NBS was used. A pure sample of 6 was obtained by PTLC chromatography (Silica gel, MeOH-CH_2Cl_2 (2:98)) and crystallization from isopropyl ether:

mp 123°C. ^{1}H-NMR ($CDCl_3$) δ 2.54 (s, 3H, CH_3), 4.53 (s, 2H, CH_2Br), 7.35-7.50 (m, 2H, ArH), 7.66 (t, J= 7.8 Hz, 1H, ArH), 8.22 (d, J= 8.3 Hz, 1H, ArH). MS (CI, NH_3) 272 (M^++18), 270 (M^++16), 255 (M^++1), 253 (M^+-1).

10. mp 275°C. IR (KBr) ν_{max} 3400, 1600 cm^{-1}. UV (MeOH, nm): λ_{max} (ε) 284 (10,580), 307 (8,893). ^{1}H-NMR (THF-d_8) δ 2.61 (s, 3H), 6.14 (t, J= 2.0 Hz, 1H), 6.43 (d, J= 2.0 Hz, 2H), 6.92 (d, J= 16.2 Hz, 1H), 7.3-7.5 (m, 2H), 7.6-7.7 (m, 1H), 7.67 (d, J= 16.2 Hz, 1H), 8.16 (m, 1H), 8.38 (s, 1H, OH), 11.00 (s, 1H, OH).

11. A. Brossi, P. N. Sharma, K. Takahashi, J. I. Chiang, I. L. Karle and G. Seibert, Hev. Chim. Acta 1983, 66, 795. Its worthy of note in this sequence that the ready available aldehyde 13 was transformed (10a. L. Syper, K. Kloc and J. Mlochowski, Tetrahedron 1980, 36, 123) into 2,3,4,5-tetramethoxy-toluene, an important intermediate in the synthesis of Ubiquinone (10b. E. Keinan and D. Eren, J. Org. Chem. 1987, 52, 3872).

12. Oil. IR (film) ν_{max} 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.19 (t, J= 7.2 Hz, 3H), 3.09 (q, J= 7.2 Hz, 2H), 3.80, 3.85, 3.95 and 4.07 (s each, 12H). MS (CI) 271 (M^++1).

13. For the role of Lewis acid stoichiometry in the acylacion of aryl ethers see T. F. Buckley III and H. Rapoport, J. Am. Chem. Soc. 1980, 102, 3056.

14. mp 95°C. IR (KBr) ν_{max} 1620 cm^{-1}. UV (MeOH, nm): λ_{max} (ε) 239 (21,800), 315 (5,092). ^{1}H-NMR ($CDCl_3$) δ 2.01 (s, 3H), 2.40 (s, 3H), 3.92, 3.93, 3,95 and 4.07 (s each, 12H). MS (CI) 295 (M^++1), 279 (M^+-15).

15. mp 118°C. ^{1}H-NMR ($CDCl_3$) δ 2.18 (s,3H), 3.93, 3.95, 4.02 and 4.10 (s each, 12H), 5.09 (s, 4H, OCH_2Ph), 6.65 (s, b, 1H), 6.82 (d, J= 1.9 Hz, 2H), 7.05 (d, J= 15.8 Hz, 1H), 7.34-7.47 (m, 1H, OH), 7.51 (d, J= 15.8 Hz, 1H). MS (CI) 595 (M^++1).

16. Hormothamnione 1: mp 271°C (d). IR (KBr) ν_{max} 3400, 1625, 1600 cm^{-1}. UV (MeOH, nm): λmax (ε) 295 (11,247), 353 (19767). ^{1}H-NMR (THF-d_8) δ 2.16 (s, 3H), 3.85 (s, 3H, MeO), 3.93 (s, 3H, MeO), 4.03 (s, 3H, MeO), 6.29 (t, J= 2.0 Hz, 1H), 6.58 (d, J= 2.0 Hz, 2H), 7.17 (d, J= 15,7 Hz, 1H), 7.55 (d, J= 15,7 Hz, 1H), 8.70 (s, 1H, OH), 11.00 (s, 1H, OH), 12,80 (s, 1H, OH). Triacetate 2 mp 198-200°C.

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