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# SYNTHESIS OF THE CHROMOPHORE OF RUBROLONE

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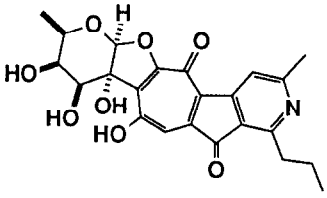
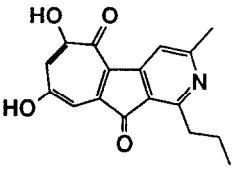
**Abstract:** A synthesis of **2**, the chromophore of rubrolone (**1**), is described. The key constructive step is the regiospecific cycloaddition **10** + **11a** → **12a**.

*Streptomyces echinoruber* produces a red pigment that is known as rubrolone and possesses structure **1**.[1] The pentacyclic ring system which constitutes the skeletal framework of **1** is unprecedented, and the tricyclic pyrindenotropolone unit (**2**) that imbues **1** with its color is also unique to **1** and its derivatives. The structure of rubrolone was reported in 1978,[1] but no synthesis of either **1** or **2** has yet been recorded.[2] In conjunction with efforts directed at the construction of **1**,[3] we now report the synthesis of **2** which is outlined in Scheme 1.



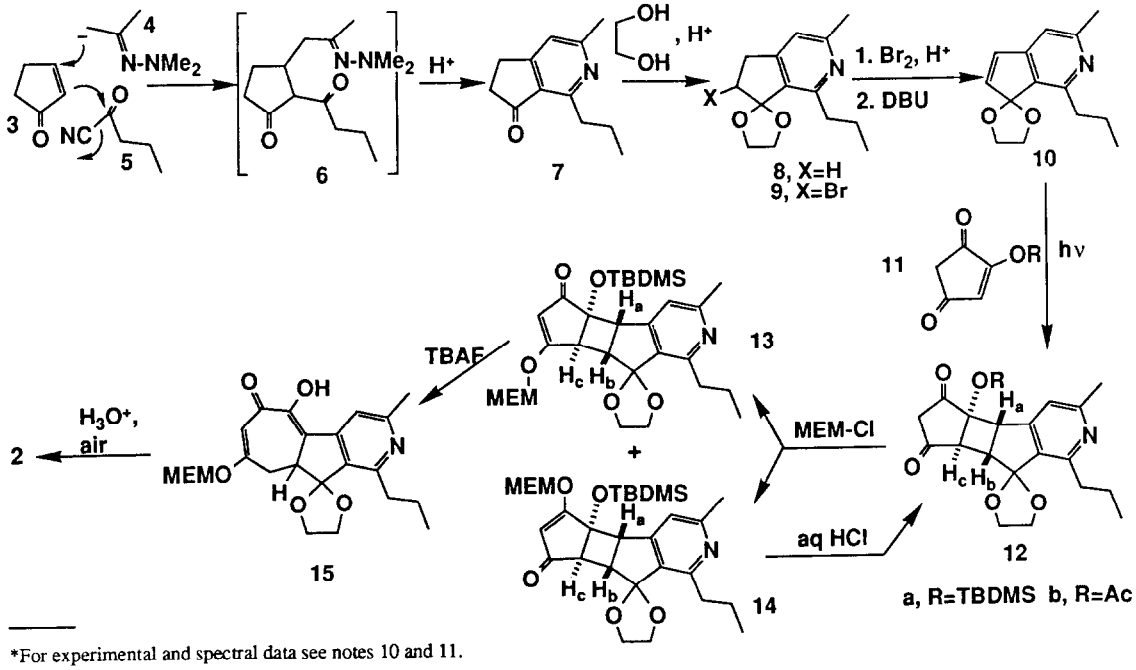
**1**



**2**

Thus dialkyl pyrindanone **7**, obtained[3] by a one-pot assembly of the three components **3**-**5**, was converted to the unsaturated ketal **10**[4] by ketalization, bromination and dehydrobromination.[5] A deMayo-type[6] strategy for synthesis of the tropolone ring was then initiated by photoaddition of **10** to **11a**. The cycloaddition proceeds regiospecifically to give a single adduct which, as expected,[7] was shown to be **12a** by $^1$H NMR. Attempts to cleave **12a** directly[6] to **2** (or the ethylene ketal thereof) failed, as did equivalent

**Scheme 1***




*For experimental and spectral data see notes 10 and 11.

efforts with **12b** (obtained, also regiospecifically, from **10** and **11b**[12]). But the MEM enol ether **13**, prepared as a separable 1:1.2 mixture of **13** and **14**,[8] undergoes the desired retroaldol reaction to give dihydrotropolone **15**[4,8] upon cleavage of the silyl ether with $(n\text{-Bu})_4NF$. Hydrolysis of **15** is accompanied by spontaneous aerial oxidation, giving the desired, fully elaborated chromophore **2**.[4,9]

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## References and Notes

1. a) N.J. Palleroni, K.E. Reichelt, D. Mueller, R. Epps, B. Tabenkin, D.N. Bull, W. Schüep and J. Berger, *J. Antibiotics*, *31*, 1218 (1978); b) W. Schüep, J.F. Blount, T.H. Williams and A. Stempel, *ibid.*, *31*, 1226 (1978); c) J. Berger, K.E. Reichelt and W. Schüep, U.S. Patent 4,057,553 (Nov. 8, 1977).
2. For report of a tropolone synthesis stimulated by **1**, see D.D. Keith, *Tetrahedron Lett.*, *26*, 5907 (1985).
3. T.R. Kelly and H.-t. Liu, *J. Am. Chem. Soc.*, *107*, 4998 (1985).
4. A satisfactory combustion analysis was obtained for this compound; **2** was characterized[10] and analyzed (C,H,N,Cl) as **2**·HCl·MeOH.
5. H.O. House, V. Paragamian, R.S. Ro and D.J. Wluka, *J. Am. Chem. Soc.*, *82*, 1452 (1960).
6. B.D. Challand, H. Hikino, G. Cornis, G. Lange and P. de Mayo, *J. Org. Chem.*, *34*, 794 (1969) and references therein.
7. For recent reviews see a) G. Desimoni, G. Tacconi, A. Barco and G.P. Pollini, "Natural Products Synthesis Through Pericyclic Reactions;" American Chemical Society: Washington, D.C., 1983; Chap 3. b) S.W. Baldwin in "Organic Photochemistry" (A. Padwa, Ed.); Marcel Dekker: New York, 1981; Vol 5, Chap 2. We thank Prof. Baldwin for a preprint.
8. In contrast to **13**, **14** could not be carried forward to a tropolone or dihydrotropolone [**14** gives unidentified polar materials upon treatment with $(n\text{-Bu}_4)NF$ or "equivalent" reagents], but **14** could be recycled[10] to **12a**. Assignment of regiochemistry to **13** and **14** is based primarily on the chemical shifts (**13**, δ 3.65; **14**, δ 3.88) of the $H_c$ protons, as nOe and long range $^{13}C$-$^1H$ coupling studies were equivocal. There is a small possibility that the regiochemical assignments of **13** and **14** (and **15**) should be reversed.
9. The peaks in the $^1H$ NMR spectrum of **2** are broad; **2** is better characterized as its diacetate,[4,11] mp 170-176°C (dec) from $Et_2O$/pet ether, prepared by dissolving **2** in $Ac_2O$ (catalytic conc $H_2SO_4$) followed by prep TLC (silica, 19:1 $CHCl_3$/MeOH).
10. Salient experimental details. **7** → **8**: 24.0 g **7**, 8.8 ml $HOCH_2CH_2OH$, 26.6 g TsOH·$1H_2O$, 400 ml benzene, reflux (Dean Stark) 5 h; add 4.4 ml $HOCH_2CH_2OH$ and 5.3 g TsOH·$1H_2O$, reflux 12 h; $NaHCO_3$ workup; $SiO_2$ chromatography ($CH_2Cl_2$/EtOAc gradient) → 14.6 g (61%) **7** and 11.2 g (38%, 99% based on unrecovered **7**) **8**. **8** → **10**: 11.2 g **8**, 0.85 g anh TsOH, 2.7 ml $Br_2$, 375 ml dry $CH_2Cl_2$, 24 h reflux under $N_2$; add 0.54 ml $Br_2$, reflux 24 h; cool, evaporate volatiles, add 375 ml $C_6H_6$ and 25 ml DBU, reflux 7 h under $N_2$; $H_2O$/$Et_2O$ workup, Kugelrohr (95-100°C/0.025 torr) → 8.77 g (79%) **10** as syrup which xtallized (mp 66-67°C from hexane). **12a**: to 1.65 g cyclopentane-1,2,4-trione[12] in 40 ml $Et_2O$ at 0°C under Ar add 2.04 ml $Et_3N$ and 3.37 ml *t*-$BuMe_2SiOSO_2CF_3$; 10 min/0°C, 1 h/20°C; transfer supernatant (=**11a**) soln to 3.39 g **10** in Pyrex photoreactor; cool to -78°C, photolyze (Hanovia 100W high pressure Hg lamp) under Ar at -78°C 5 h; dil aq HCl/$CHCl_3$ partition; HCl phase gave 2.17 g (64%) [after $SiO_2$ chromatography (5:1 pet. ether/acetone)] **10**, organic phase [after $SiO_2$ chromatography (100:20:1 $CHCl_3$/MeOH/$H_2O$)] gave 913 mg **12a** (38% based on unrecovered **10**). **12a** → **13** + **14**: to 2.03 g **12a** in 50 ml dry THF add 0.85 ml $(i\text{-Pr})_2NEt$ and 0.53 ml MEM-Cl; 20 h at 20°C under $N_2$; $SiO_2$ chromatography (2:1 $CH_2Cl_2$/EtOAc) → 0.92 g (38%) **13**[8] and 1.12 g (46%) **14**[8]. **13** → **15**[8]: to 0.59 g **13** in 20 ml THF at 0°C add 2.16 ml of 1.0M $(n\text{-Bu})_4NF$ in THF; 15 min at 0°C; aq $NaH_2PO_4$/$CHCl_3$ workup, $SiO_2$ chromatography (20:1 $CHCl_3$/MeOH) → 0.41 g (88%) **15**, mp 88-90°C ($Et_2O$/pet ether). **14** → **12a**: 0.57 g **14** + 0.4 ml 10% HCl in 10 ml THF; 40 min, 20°C → 0.48 g (100%) **12a**. **15** → **2**: 0.54 g **15** + 35 ml THF + 3.5 ml conc HCl, 24 h open to air; evaporate; dissolve in MeOH, evaporate; wash with $Et_2O$ → 0.42 g (100%) **2** as purple-red HCl salt, mp > 300°C (MeOH/$Et_2O$).
11. Selected spectral data. $^1H$ NMR's (in $CDCl_3$ unless otherwise stated, only distinctive peaks given): **8** δ 0.99 (t, 3H, *J* = 7Hz), 1.55-1.98 (m, 2H), 2.19 (t, 2H, *J*=7Hz), 2.51 (s, 3H), 2.68-2.91 (m, 4H), 3.93-4.31 (m, 4H), 6.85 (br s, 1H); **10** δ 2.50 (s, 3H), 6.39 (ABq, *J* =6 Hz, 16 Hz sep, 2H), 6.76 (s, 1H); **11a** δ 0.30 (s, 6H), 0.97 (s, 9H), 2.83 (s, 2H), 6.30 (s, 1H); **12a** (exists as enol) δ -0.31 (s, 3H), -0.03 (s, 3H), 0.66 (s, 9H), 2.67 (dd, 1H, *J* = 3 & 6Hz, $H_b$), 2.73 (s, 3H), 2.93 (d, 1H, *J* = 3Hz, $H_a$), 4.08 (d, 1H, *J* = 6Hz, $H_c$), 5.39 (s, 1H), 7.52 (s, 1H), 8.03 (br s, 1H); **13** δ -0.38 (s, 3H), -0.10 (s, 3H), 0.51 (s, 9H), 2.44 (s, 3H), 2.49 (dd, 1H, *J* = 3 & 6Hz, $H_b$), 3.07 (d, 1H, *J* = 3Hz, $H_a$), 3.30 (s, 3H), 3.65 (d, 1H, *J* = 6Hz, $H_c$), 3.90-4.24 (m, 4H), 5.23 (s, 2H), 5.25 (s, 1H), 6.91 (s, 1H); **14** δ -0.45 (s, 3H), -0.17 (s, 3H), 0.66 (s, 9H), 2.52 (dd, 1H, *J* = 4 & 6Hz, $H_b$), 2.54 (s, 3H), 3.00 (d, 1H, *J* = 4 Hz, $H_a$), 3.41 (s, 3H), 3.87-3.90 (m, 3H), 5.34 (s, 2H), 5.62 (s, 1H), 6.96 (s, 1H); **15** δ 2.53 (ddd, 1H, J = 2, 2 & 16Hz), 2.60 (s, 3H), 2.99 (ddd, 1H, *J* = 2, 14 & 16 Hz), 3.42 (s, 3H), 3.47 (dd, 1H, *J* = 2 & 14 Hz), 5.23 (Abq, *J* = 11Hz, 6Hz sep, 2H), 5.94 (dd, 1H, *J* = 2 & 2Hz), 7.80 (s, 1H), 7.92 (s, 1H, exch with $D_2O$); **2**[9] [$CDCl_3$ + $(D_3C)_2SO$ + $D_2O$] δ 1.02 (t, 3H, *J* = 7Hz), 1.71-1.77 (m, 2H), 2.67 (s, 3H), 3.17 (br t 2H, *J* = 6 Hz), 6.81 (d, 1H, *J* = 2Hz), 7.06 (d, 1H, *J* = 2Hz), 8.26 (s, 1H). Diacetate of **2** ($CDCl_3$) δ 1.02 (t, 3H, *J* = 7Hz), 1.74 (apparent br q, 2H, *J* = 7Hz), 2.15 (s, 6H), 2.70 (s, 3H), 3.21 (m, 2H), 6.67 (d, 1H, *J* = 2Hz), 7.37 (d, 1H, *J* = 2Hz), 7.55 (s, 1H). UV's (EtOH) and IR's: **2** $\lambda_{max}$ 213 (ε10,100), 252 (ε15,500), 305 (ε5,440), 318 (ε4660), 399 (ε4,150), 426 (ε4,660), 530 nm (ε2,070); $\nu_{max}$ (nujol) 1730, 1620, 1595$cm^{-1}$. Diacetate of **2** $\lambda_{max}$ 212 (ε14,600), 250 (ε35,400), 316 (ε10,800), 362 nm (ε8, 230); $\nu_{max}$ (film) 1760, 1740, 1640, 1590$cm^{-1}$.
12. C. Samarian and H.W. Wanzlick, *Tetrahedron Lett.*, 2125 (1974).

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