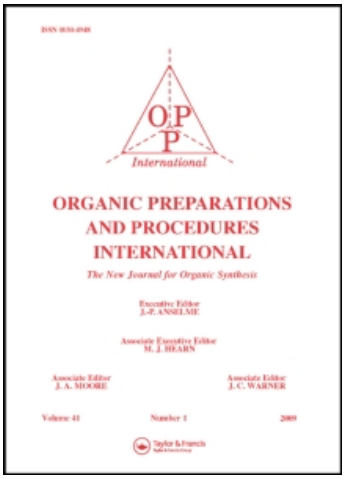

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AN EFFICIENT ONE-STEP CONVERSION OF BILIVERDINS TO 14-FORMYLTRIPYRRINONES

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AN EFFICIENT ONE-STEP CONVERSION OF BILIVERDINS TO 14-FORMYLTRIPYRRINONES

Submitted by (05/08/01)

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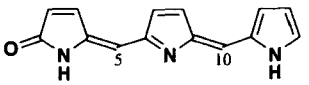
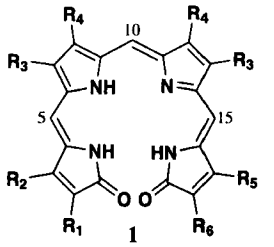
The tripyrrinone skeleton (**I**) is a fully conjugated linear tripyrrolic system and a structural part of biliverdins, phycocyanobilins,[1] pentapyrrins,[2] and hexapyrrins.[3] It is an important precursor for the synthesis of linear tetrapyrroles[4] and oligopyrrole pigments such as 15-thia- and 15-norhexapyrrins.[3] A 9,10-dihydrotripyrrinone analog was recently synthesized and used as a bilirubin model compound to investigate the spectroscopic, solution, and metabolic properties of bilirubin.[5] Although 14-formyltripyrrinones have been known for many years,[1] larger scale and efficient synthetic methods are still not available. Multiple-step syntheses starting from pyrroles could in principle lead to the desired 14-formyltripyrrinones.



I Tripyrrinone Skeleton

14-Formyltripyrrinones, such as compound **2a**, were first found in the mixture of the oxidation of bilirubins with nitric acid,[6,7] a reaction characteristic of bilirubins. Compound **2a** was also obtained by treatment of biliverdins with iodine in the presence of Zn(II) and ethanol,[8] with thallium(III) triacetate, lead(IV) tetraacetate,[9] and bromine.[10] These reactions afforded only low yields and were not synthetically useful. The importance of 14-formyltripyrrinones in the synthesis of linear oligopyrroles and other polypyrrolic pigments prompted us to explore facile, efficient and synthetic useful procedures to 14-formyltripyrrinones. In 1990, our group briefly reported that treatment of

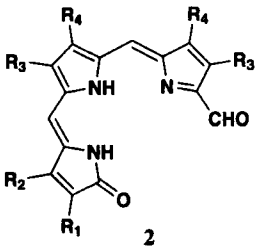
biliverdin IXα dimethyl ester (**1a**) or bilirubin IXα (**3a**) with silver nitrate in the presence of sodium bicarbonate in THF gave a mixture of 14-formyltripyrrinone isomers in high yield.[11] We recently reinvestigated this reaction and report that the reaction provides high yields of 14-formyltripyrrinones when symmetrical biliverdins were used, which to the best of our knowledge is the first simple and efficient method to prepare the target compounds.



1

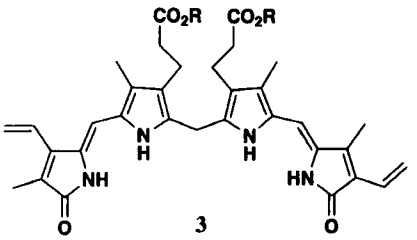
a) R_1,R_3,R_5 = Me; R_2,R_6 = CH = CH_2
R_4 = $CH_2CH_2CO_2Me$
b) R_1,R_3,R_6 = Me; R_2,R_5 = Et
R_4 = $CH_2CH_2CO_2Me$
c) R_1,R_3,R_6 = Me; R_2,R_4,R_5 = Et
d) R_1,R_3,R_5 = Me; R_2,R_6 = CH = CH_2
R_4 = $CH_2CH_2CO_2H$

$AgNO_3$



2

a) R_1,R_3 = Me; R_2 = CH=CH_2
R_4 = $CH_2CH_2CO_2Me$
b) R_1 = CH=CH_2; R_2,R_3 = Me
R_4 = $CH_2CH_2CO_2Me$
c) R_1,R_3 = Me; R_2 = Et
R_4 = $CH_2CH_2CO_2Me$
d) R_1,R_3 = Me; R_2,R_4 = Et



3

a) R = H
b) R = Me

As previously mentioned, the oxidation of biliverdins by thallium (III) acetate,[9] lead (IV) tetraacetate,[9] bromine,[10] and iodine,[8] gave only 3-38% yields of 14-formyltripyrrinones. To our surprise, the best yields of the desired products were obtained when 60 equiv. of silver (I) nitrate were used in THF and in the presence of sodium bicarbonate. The reaction proceeded smoothly at room temperature. The color changed from blue to green, purple, and finally to dark red. Quenching and chromatographic separation led to 78-85% isolated yields of 14-formyltripyrrinones. When an asymmetric biliverdin such as biliverdin IXα dimethyl ester (**1a**) was used, compounds **2a** (57%) and **2b** (33%) were obtained in good yields. The yield of **2a** was higher than that of **2b**, which could be attributed to steric hindrance differences between C5 and C15. Bilirubin IXα dimethyl ester (**3b**) under same reaction condition was also found to yield the expected tripyrrinones **2a** (22%), **2b** (<1%) and some other further degradative products. The low yields are consistent with the lesser stability of toward oxidation reagents.

Table 1. Oxidation of Biliverdins to 14-Formyltripyrrinones at RT

Biliverdins	Reagents/Solvents	Time	Products (Yields %)
1c	1.1 equiv. $Tl(OAc)_3$, HOAc[a]	30 min	**2d** (25)
1c	2.1 equiv. $Tl(OAc)_3$, HOAc[a]	30 min	**2d** (30.5)
1c	3.1 equiv. $Tl(OAc)_3$, HOAc[a]	30 min	**2d** (30.5)
1c	1 equiv. $Pb(OAc)_4$, HOAc[a]	3 days	**2d** (38)
1c	1.05 equiv. $Tl(OAc)_3$, MeOH[a]	16 h	**2d** (3)
1b	$NaNO_3/HNO_3$, CH_2Cl_2[b]	---	**2c** (23)
1b	2 equiv. Br_2, MeOH[c]	2 min	**2c** (6)
1b	2 equiv. Br_2, MeOH-HBr[c]	2 min	**2c** (8)
1b	2 equiv. Br_2, MeOH-THF[c]	2 min	**2c** (14)
1b	1 equiv. I_2/EtOH, $Zn(OAc)_2$,NH_3[d]	3 days	**2c** free acid (4.8)
1b	2 equiv. $AgNO_3$, $NaHCO_3$, THF-H_2O	25 min	**2c** (15)
1b	4 equiv. $AgNO_3$, $NaHCO_3$, THF-H_2O	25 min	**2c** (35)
1b	10 equiv. $AgNO_3$, $NaHCO_3$, THF-H_2O	25 min	**2c** (50)
1b	30 equiv. $AgNO_3$, $NaHCO_3$, THF-H_2O	25 min	**2c** (66)
1b	60 equiv. $AgNO_3$, $NaHCO_3$, THF-H_2O	25 min	**2c** (78)
1b	90 equiv. $AgNO_3$, $NaHCO_3$, THF-H_2O	25 min	**2c** (51)
1a	60 equiv. $AgNO_3$, $NaHCO_3$, THF-H_2O	20 min	**2a** (57)
			2b (33)
1c	30 equiv. $AgNO_3$, $NaHCO_3$, THF-H_2O	30 min	**2d** (58)
1c	60 equiv. $AgNO_3$, $NaHCO_3$, THF-H_2O	30 min	**2d** (85)
1c	90 equiv. $AgNO_3$, $NaHCO_3$, THF-H_2O	30 min	**2d** (60)
1d	60 equiv. $AgNO_3$, $NaHCO_3$, THF-H_2O	30 min	**2a** free acid (27)
			2b free acid (5)

[a] See Reference [9c]. [b] See Reference [8].[c] See Reference [10]. [d] See Reference [7].

The mechanism of this reaction could be envisaged to be similar to that proposed[9a,9c] for formation of 14-formyltripyrrinones from oxidation of biliverdins with thallium nitrate. Treatment of biliverdins with silver (I) nitrate would first yield Ag(I)-biliverdin complex. The C5 or C15 position of this intermediate could be attacked by hydroxide ion *via* nucleophilic addition to form C5 or C15 hydroxy-Ag(I)-biliverdin. Under the condition of work-up cleavage at C15-C16 or C4-C5 gave the final products.

EXPERIMENTAL SECTION

IR spectra (cm^{-1}) were recorded on a BIO-RAD FT-165 IR spectrophotometer as KBr pellets. ^1H NMR spectra (δ downfield from internal TMS) were recorded on a Varian Gemini-300 MHz instru-

ment. UV-VIS spectra were recorded on a Hitachi U-2001 spectrophotometer. MS were run on a VG TR10-200 spectrometer. The melting points are not corrected. Bilirubin IXα (**3a**) was purchased from Porphyrins Inc (Utah,USA). Biliverdin IXα (**1d**) and its dimethyl ester (**1a**),[12] bilirubin IXa dimethyl ester (**3b**),[12] mesobiliverdin XIIIα dimethyl ester (**1b**)[13] and etiobiliverdin IVγ (**1c**)[13] were prepared previously.

General Procedure.- A solution of aqueous silver nitrate (0.1 M, 30 mL, 3 mmol, 60 equiv.) was added with stirring to a solution of biliverdin (0.05 mmol) and sodium bicarbonate (5 mg) in THF (30 mL). The mixture was kept at room temperature and monitored frequently by TLC(EtOAc:CH_2Cl_2:CCl_4, V/V/V, 2/2/1) and UV-VIS. The solution first turned blue-green, then blue, purple and finally dark red. After 20-40 min the reaction was completed and the mixture was partitioned by dichloromethane (100 mL) and water (200 mL). The organic phase was separated, and aqueous phase was extracted with dichloromethane (30 mL x 3). The organic phase and combined extracts were washed successively with aqueous saturated sodium bicarbonate (50 mL), brine (50 mL), dried over sodium sulfate, filtered, and evaporated under reduced pressure. The resulting dark-red solid was purified by chromatographic column (EtOAc:CH_2Cl_2:CCl_4, V/V/V, 2/2/1) on silica gel and crystallization from chloroform-hexane to yield the desired 14-formyltripyrrinone.

3-Vinyl-14-formyl-2,7,13-trimethyl-8,12-dimethoxycarbonylethyl-1-oxo-15H,17H-tripyrrin (2a), yield 57%, mp.188-190° (dec.); UV-VIS: λ max ($CHCl_3$) = 550 (16,700), 516 (14,700), 331 (44,400) nm (ε); MS(m/z): = 505 (M^+); IR (KBr): 3418, 1738, 1700, 1650, 1615 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.91, 2.96 (tt, J_1=J_2=7.2Hz, 4H, $2CH_2CH_2COO$), 3.65 (s, 3H, $COOCH_3$), 2.57 (t, J = 7.2Hz, 4H, $2CH_2CH_2COOCH_3$), 3.67(s, 3H, $COOCH_3$), 5.70 (d, J=11, H_B in vinyl), 5.69(d, J=17, H_A in vinyl), 6.02 (s, 1H, -CH=), 6.84 (s, 1H, -CH=), 6.63 (dd, J_1 = 17 Hz, J_2 = 11Hz, H_X in vinyl), 9.81(s, 1H, CHO).

Anal. Calcd For $C_{28}H_{31}N_3O_6$: C, 66.52; H, 6.18; N, 8.31. Found: C, 66.31; H, 6.26; N, 8.15

2-Vinyl-14-formyl-3,7,13-trimethyl-8,12-dimethoxycarbonylethyl-1-oxo-15H,17H-tripyrrin (2b), yield 33%, mp.188-190° (dec.); UV-VIS: λ max ($CHCl_3$) = 544 (14,700), 510 (14,300), 325 (32,600) nm (ε); FD-MS (m/z): 505 (M^+); IR (KBr): 3419, 1742, 1700, 1650, 1622 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$): δ 2.06 (s 3H CH_3), 2.13 (s 3H CH_3), 2.27 (s 3H CH_3), 2.51 (t, J=7.2Hz, 4H, 2 CH_2CH_2COO) and 2.91, 2.98 (tt, J_1 = J_2= 7.2 Hz, 4H, $2CH_2CH_2COOCH_3$), 3.60 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 5.51 (dd, J_1=17, J_2=3.6, H_B in vinyl), 5.88 (s, 1H, -CH=), 6.43 (dd, J_1=17, J_2=3.6, H_A in vinyl), 6.54 (dd, J=17, 9, H_X in vinyl), 6.87(s, 1H, -CH=), 9.84 (s, 1H, CHO).

Anal. Calcd For $C_{28}H_{31}N_3O_6$: C, 66.52; H, 6.18; N, 8.31. Found: C, 66.71; H, 6.22; N, 8.11

3-Ethyl-14-formyl-2,7,13-trimethyl-8,12-dimethoxycarbonylethyl-1-oxo-15H,17H-tripyrrin (2c), yield 78%, mp. 156-157° (*lit.*[9c] 155-157°); UV-VIS: λ max ($CHCl_3$) = 545 (23,500), 507 (24,200), 321 (61,000) nm(ε); EI-MS (m/z): 507(M^+), 475, 434, 360, 302; IR (KBr): 3422, 1736, 1704, 1648, 1602cm^{-1}; ^{1}H-NMR (300MHz ,$CDCl_3$): δ 1.21 (t, J=13.8Hz, 3H, CH_2CH_3), 1.98 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.48-2.60 (m, 6H, CH_2CH_3, 2 CH_2CH_2COO), 2.90-2.96 (m, 4H, 2 CH_2CH_2COO), 3.65 (s, 3H, $COOCH_3$), 3.67 (s, 3H, $COOCH_3$), 5.87 (s, 1H, –CH= at C5), 6.82 (s,

1H, –CH= at C10), 9.82 (s, 1H, CHO).

Anal. Calcd For $C_{28}H_{33}N_3O_6$: C, 66.26; H, 6.55; N, 8.28. Found: C, 66.02; H, 6.32; N, 8.01

3,8,12-Triethyl-14-formyl-2,7,13-trimethyl-1-oxo-15H,17H-tripyrrin (2d), yield 85%, mp. 182-183° (*lit.*[9c] 181-183°); UV-VIS: λ max ($CHCl_3$) = 543 (25,900), 507 (26,500), 321 (60,100) nm; EI-MS(m/z): 391(M^+), 376, 362, 334, 181; IR (KBr): 3424, 1703, 1650, 1558cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$): δ 1.16 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.19 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.21 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.98 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.54 (q, J = 7.5Hz, 2H, CH_2CH_3), 2.58 (q, J = 7.5Hz, 2H, CH_2CH_3), 2.63 (q, J = 7.5Hz, 2H, CH_2CH_3), 5.87(s, 1H, –CH= at C5), 6.66 (s, 1H, –CH= at C10), 9.83 (s, 1H, -CHO).

Anal. Calcd For $C_{24}H_{29}N_3O_2$: C, 73.63; H,7.47; N,10.73. Found: C, 73.42; H, 7.24; N, 10.81

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A SHORT AND HIGHLY ENANTIOSELECTIVE SYNTHESIS OF (6*R*)-UNDECYLTETRAHYDROPYRAN-2-ONE, THE PHEROMONE OF *VESPA ORIENTALIS*

Submitted by (03/08/01)

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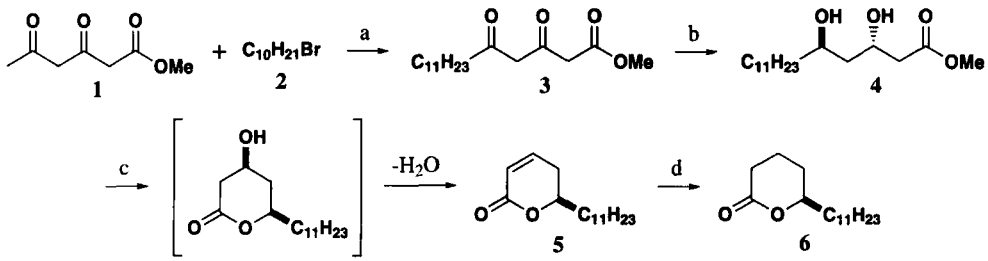
It has been recently shown that simple 3,5-dioxoalkanoates can be hydrogenated using various chiral phosphine-ruthenium complexes[1] as catalysts to afford *anti*-3,5-dihydroxyalkanoates in excellent yield and enantioselectivity.[2] Moreover, these compounds could be readily transformed into corresponding δ-lactones.[3] This communication describes a general route to homochiral 6-substituted



1 2 3 4 5 6

a) *i.* NaH, THF, 0°C, 0,5h; *ii. sec*-BuLi, reflux, 2h; b) **7** (cat), H_2, MeOH, 55°C, 150 atm, 48h; c) *p*-TsOH (cat), toluene, reflux, 3h; d) 10% Pd/C (cat), H_2, AcOEt, rt, 1 atm, 3h.