Regiospecific #-Substitution of Crotonic Esters: Synthesis of Naturally Occurring 3-O-Methylrubiadins

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REGIOSPECIFIC α-SUBSTITUTION OF CROTONIC ESTERS: SYNTHESIS OF NATURALLY OCCURRING 3-*O*-METHYLRUBIADINS

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ABSTRACT.—The group of naturally occurring compounds identified as 3-*O*-methylrubiadins presents a number of ambiguities. The synthesis of some of these substances by an established and unequivocal method confirms the structure of 3-*O*-methyl-8-hydroxy-6-methylrubiadin [**9**].

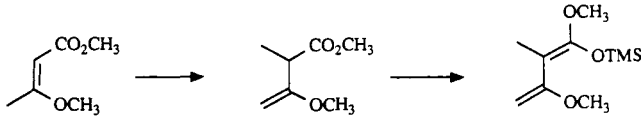
In a recent re-examination of naturally occurring rubiadins (1,3-dihydroxy-2-methylanthraquinones), an attempt was made to determine some characteristics of this little-known group of compounds. Through unambiguous syntheses, the spectral properties of authentic rubiadins were colligated and correlated to the relevant part of the molecule. In particular, ^{1}H-nmr resonances were found to be characteristic and independent of other features in the molecule (1).

The partially methylated derivatives of rubiadins constitute a smaller group of natural products that present much the same ambiguities as the parent compounds. In our work involving the selective α-substitution of various crotonic esters, an appropriate diene became readily available for the preparation of partially methylated rubiadins (specifically 3-*O*-methyl derivatives) through application of the regioselective Diels-Alder methodology (2).

The reaction of MeI with the anion of methyl 3-methoxycrotonate [**1**] proved to be particularly effective, because not only did alkylation occur exclusively in the α position but also there was no disubstitution. The last step in the formation of reagent **3** required a standard enolsilylation and this gave a somewhat unstable diene that could not be purified by distillation but, with the exception of <4% of the inert *C*-silylated compound, was otherwise homogeneous. The product appeared by 200 MHz nmr to consist of only one diastereomer and could be kept at −30° for at least 30 days.

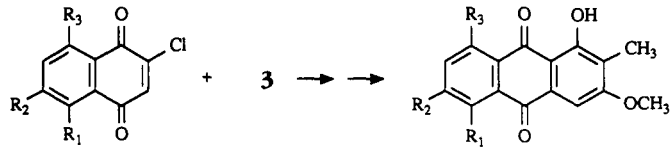
Cycloadditions in all cases were conducted in C_6H_6 at about 6° and completed at room temperature. Slow percolation of a solution of the crude adduct through a column of Si gel resulted in aromatization, affording in high yield a readily separable mixture of products consisting of the desired 3-methyl ethers **8–11** and the 1,3-di-*O*-methyl derivatives in an approximate ratio of 3:1.

As expected, 3-*O*-methylrubiadins exhibit well-defined ^{1}H-nmr spectra. In particular the 2-methyl protons as well as those in position 4 resonate within narrow limits (i.e., δ 2.18–2.21 and 7.33–7.45, respectively, or 2.25–2.26 and 7.50–7.63 for the 1,3-di-*O*-methyl derivatives). Although less significant, 3-OMe groups consistently gave values



1 **2** **3**

SCHEME 1



	R_1	R_2	R_3	
4	H	H	H	**8**
5	H	Me	OH	**9**
6	H	H	OMe	**10**
7	OH	H	OH	**11**

SCHEME 2

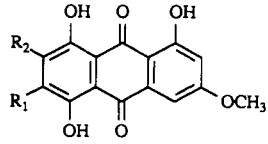
uncharacteristic for β-substituents (δ 4.01–4.06). The ^{13}C-nmr spectra of the title compounds also show distinctive chemical shifts for the carbons of the A ring (see Experimental). Finally, ms data establish that, as with rubiadins, the molecular ion is particularly stable and is the base peak.

3-*O*-Methyl- and 1,3-di-*O*-methylrubiadin are well-known substances, and the present preparations show properties in complete agreement with published data (3). This exercise also confirms the structure of a natural product described as 7-methylphyscion [**9**] (4). On the other hand, the published characteristics (5) of 3-*O*-methyl-8-methoxyrubiadin [**10**] do not resemble those of the unambiguously prepared material. Compound **11** corresponds to one of the three plausible formulations for an anthraquinone isolated from the seeds of *Cassia occidentalis* (6). One of these was the known compound erythroglaucin [**12**]; another, structure **13**, was shown by synthesis to be incorrect (7,8). A third, isomer **11**, was originally rejected because its demethylation product differed from a known compound (9). However, this conclusion is no longer valid, as a second distinct description of 1,3,5,8-tetrahydroxy-2-methylanthraquinone has recently appeared (10). The present results now confirm that structures **11–13** must all be discarded. Finally, yet another structure, 3-*O*-methyl-8-hydroxy-6-methoxy-7-vinylrubiadin [**14**], was proposed for a substance found in the root bark of *Cassia sophera* (11). Although not prepared in this work, it must be invalidated because the published nmr spectrum is incompatible with the data observed for other 3-*O*-methylrubiadins.

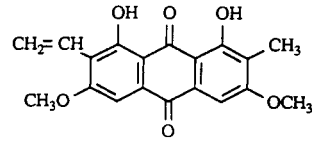
EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All melting points were taken for samples in capillary tubes with a Thomas-Hoover apparatus and are not corrected. The uv spectra were determined on a Hewlett-Packard Model 8450 spectrophotometer; the ir spectra were taken on a Beckman Model IR-4250 instrument and calibrated with a film of polystyrene. Nmr spectra were recorded with Varian XL-200 spectrometer using TMS as internal standard. Mass spectra were obtained with a Hewlett-Packard 5995A spectrometer. Merck Si gel 60F_{254} for dry cc and ICN SiliTech 32-63 60A for flash chromatography were used throughout in a product-to-adsorbent ratio of 1:50–100. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tennessee.

PREPARATION OF DIENE **3**.—*Methyl 3-methoxy-2-methyl-3-butenoate* [**2**].—To a solution



12 R_1=Me, R_2=H
13 R_1=H, R_2=Me



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of LDA (0.165 mol) in dry THF (200 ml) at −78° was introduced (45 min) under N_2 methyl 3-methoxy-2-butenoate [**1**] (19.5 g, 0.150 mol) in the same solvent (25 ml). After 2 h, pure MeI (53.2 g, 0.375 mol) in THF (30 ml) was added to the solution; it was stirred for 2 h and then allowed to warm to room temperature (2 h). The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (3 × 200 ml), and dried over anhydrous $MgSO_4$ to afford ester **2** (16.9 g; 78%): bp 66–71° (18 mm Hg); ir ν max (film) 1740, 1655, 1620 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 1.30 (3H, d, J = 7.3 Hz, 2-Me), 3.19 (1H, q, J = 7.3 Hz, H-2), 3.53 (3H, s, 3-OMe), 3.68 (3H, s, 1-OMe), 3.98–4.04 (2H, AB pattern, J = 2.8 Hz, Δν = 5.0 Hz, H-4); ms *m/z* $[M]^+$ 144 (2), 83 (100). *Anal.* calcd for $C_7H_{12}O_3$: C 58.32, H 8.39; found C 58.49, H 8.35.

1,3-Dimethoxy-2-methyl-1-trimethylsiloxy-1,3-butadiene [**3**].—Methyl 3-methoxy-2-methyl-3-butenoate [**2**] (7.21 g, 0.050 mmol) in dry THF (15 ml) was added (15 min) to LDA (0.055 mol) in the same solvent (60 ml) at −78° and under N_2. The reaction mixture was allowed to warm to 0°, kept at this temperature for 2 h, and again cooled to −78° when it was treated with chlorotrimethylsilane (8.15 g; 0.075 mol) in THF (15 ml) (45 min), stirred for 1 h, permitted to come to ambient temperature, and concentrated under vacuum. The residue was diluted with petroleum ether, bp 35–60° (200 ml), filtered, evaporated (this step could be repeated until salts no longer separated), and gave diene **3** (in nearly quantitative yield): ^1H nmr (200 MHz, $CDCl_3$) δ 0.20 (9H, s, 1-OTMS), 1.69 (3H, s, 2-Me), 3.53, 3.54 (2 × 3H, 2s, 1-OMe, 3-OMe), 4.05 (1H, d, J = 2.0 Hz, H-4), 4.10 (1H, d, J = 2.0 Hz, H-4) (Scheme 1).

PREPARATION OF 3-*O*-METHYLRUBIADINS.—*General method.*—An excess of diene **3** (1 ml, ca. 5 mmol) in anhydrous C_6H_6 (2 ml) was added (15–20 min) to the naphthoquinone **4**, **5**, **6**, or **7** (2.00 mmol) in the same solvent (6 ml) at 6–7°. After 20 min, the mixture was kept at room temperature (5–20 h, tlc), then diluted with petroleum ether, bp 35–60° (10 ml) and passed through a column of Si gel [C_6H_6-petroleum ether, bp 35–60° (1:1)] (Scheme 2).

1-HYDROXY-3-METHOXY-2-METHYLANTHRAQUINONE (3-*O*-METHYLRUBIADIN) [**8**].—The crude product obtained from 2-chloronaphthoquinone [**4**] and diene **3** according to the general method was separated by dry cc [toluene-petroleum ether, b.p. 35–60° (1:1)] and gave anthraquinone **8** (367 mg, 68%), mp 190.5–191.5° (EtOH) [lit. (3) mp 190–191°]; uv λ max (MeOH) (log ε) 244 (4.38), 274 (4.51), 334 (3.43), 408 (3.83), 656 (1.40) nm; ir ν max (KBr) 1670, 1620, 1590, 1570 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 2.20 (3H, s, 2-Me), 4.02 (3H, s, 3-OMe), 7.41 (1H, s, H-4), 7.75–7.82 (2H, m, H-6, -7), 8.24–8.32 (2H, m, H-5, -8), 12.98 (1H, s, 1-OH); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 8.26 (2-Me), 56.15 (3-OMe), 102.30 (C-4), 110.74 (C-9a), 120.49 (C-2), 126.61 and 127.04 (C-5, -8), 132.12, 133.24 and 133.32 (C-4a, -8a, and -10a), 133.85 and 133.90 (C-6, -7), 161.88 and 163.35 (C-1, -3), 182.30 (C-10), 186.90 (C-9); ms *m/z* $[M]^+$ 268 (100). *Anal.* calcd for $C_{16}H_{12}O_4$: C 71.63, H 4.51; found C 71.70, H 4.37.

A second zone consisted of 1,3-di-*O*-methylrubiadin (152 mg, 27%): mp 160.0–160.5° (EtOH) [lit. (3) mp 160–161°]; ^1H nmr (200 MHz, $CDCl_3$) δ 2.26 (3H, s, 2-Me), 3.90 and 4.02 (2 × 3H, 2s, 1-OMe, 3-OMe), 7.63 (1H, s, H-4), 7.71–7.81 (2H, m, H-6, -7), 8.21–8.30 (2H, m, H-5, -8); ms *m/z* $[M]^+$ 282 (100). *Anal.* calcd for $C_{17}H_{14}O_4$: C 72.33, H 5.00; found C 72.69, H 5.11.

1,8-Dihydroxy-3-methoxy-2,6-dimethylanthraquinone(3-O-methyl-8-hydroxy-6-methylrubiadin) [**9**].—Purification by flash chromatography [C_6H_6-$CHCl_3$ (2:1)] of the crude product obtained as above from 3-chloro-7-methyljuglone [**5**] (2) provided anthraquinone **9** (401 mg; 67%), mp 228–229° (1,2-dichloroethane/petroleum ether, bp 90–120°) [lit. (4) mp 233.0–233.5°]; uv λ max (MeOH) (log ε) 220 (4.44), 272 (4.42), 306 (3.96), 434 (4.06), 658 (1.14) nm; ir ν max (KBr) 1670, 1615, 1570, 1555 nm; ^1H nmr (200 MHz, $CDCl_3$) δ 2.18 (3H, s, 2-Me), 2.45 (3H, s, 6-Me), 4.01 (3H, s, 3-OMe), 7.07 (1H, d, J = 1.1 Hz, H-7), 7.39 (1H, s, H-4), 7.62 (1H, d, J = 1.1 Hz, H-5), 12.15 and 12.43 (2 × 1H, 2s, 1-OH, 8-OH); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 8.31 (2-Me), 22.23 (6-Me), 56.26 (3-OMe), 102.89 (C-4), 110.36 (C-9a), 113.62 (C-8a), 120.69 (C-2), 121.04 (C-5), 124.31 (C-7), 132.44 and 133.10 (C-4a, -10a), 148.20 (C-6), 161.73, 162.29 and 163.69 (C-1, -3, -8), 182.05 (C-10), 191.11 (C-9); ms *m/z* $[M]^+$ 298 (100). *Anal.* calcd for $C_{17}H_{14}O_5$: C 68.45, H 4.73; found C 68.49, H 4.63.

The following band corresponded to the 1-*O*-methyl ether of **9** (152 mg; 24%), mp 217.0–217.5° (1,2-dichloroethane/petroleum ether, bp 90–120°); ^1H nmr (200 MHz, $CDCl_3$) δ 2.25 (3H, s, 2-Me), 2.43 (3H, s, 6-Me), 3.89 and 4.02 (2 × 3H, 2s, 1-OMe, 3-OMe), 7.08 (1H, d, J = 1.1 Hz, H-7), 7.58 (1H, d, J = 1.1 Hz, H-5), 7.61 (1H, s, H-4), 13.08 (1H, s, 8-OH); ms *m/z* $[M]^+$ 312 (100). *Anal.* calcd for $C_{18}H_{16}O_5$: C 69.22, H 5.16; found C 69.02, H 5.20.

1-Hydroxy-3,8-dimethoxy-2-methylanthraquinone (3-O-methyl-8-methoxyrubiadin) [**10**].—The mixture of products obtained in the usual way from 3-chloro-5-methoxynaphthoquinone [**6**] [obtained

from 3-chlorojuglone (Ag_2O/MeI), mp 164–166°] and diene **3** was separated by dry column flash chromatography [$CHCl_3$-EtOAc (25:1)]. A first fraction consisted of anthraquinone **10** (435 mg, 73%), mp 241.0–241.5° (1,2-dichloroethane/petroleum ether, bp 90–120°) [lit. (5) mp 207°]; uv λ max (MeOH) (log ε) 245 (4.22), 272 (4.40), 418 (3.97), 658 (1.63) nm; ir ν max (KBr) 1665, 1630, 1585, 1485 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 2.19 (3H, s, 2-Me), 3.99 and 4.06 (2 × 3H, 2s, 3-OMe, 8-OMe), 7.33 (1H, s, H-4), 7.34 (1H, dd, $J = 8.6$, 1.3 Hz, H-7), 7.70 (1H, dd, $J = 8.6$, 7.5 Hz, H-6), 7.95 (1H, dd, $J = 7.5$, 1.3 Hz, H-5), 13.30 (1H, s, 1-OH); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 8.42 (2-Me), 56.08 and 56.66 (3-OMe, 8-OMe), 101.34 (C-4), 111.67 (C-9a), 118.13 and 119.98 (C-5, -7), 120.29 (C-2), 121.07 (C-8a), 131.28 (C-4a), 135.06 (C-6), 135.19 (C-10a), 160.55, 161.89, and 162.69 (C-1, -3, -8), 182.65 (C-10), 187.74 (C-9); ms *m/z* $[M]^+$ 298 (100). *Anal.* calcd for $C_{17}H_{14}O_5$: C 68.45, H 4.73; found C 68.29, H 4.74.

A second fraction consisted of the 1-*O*-methyl derivative of **10** (145 mg, 23%): mp 191–192° (1,2-dichloroethane/petroleum ether, bp 90–120°); ^1H nmr (200 MHz, $CDCl_3$) 2.25 (3H, s, 2-Me), 3.94, 3.99 and 4.01 (3 × 3H, 3s, 1-OMe, 3-OMe, 8-OMe), 7.30 (1H, dd, $J = 8.0$, 1.1 Hz, H-7), 7.50 (1H, s, H-4), 7.62 (1H, ~t, $J = 8.0$ Hz, H-6), 7.84 (1H, dd, $J = 8.0$, 1.1 Hz, H-5); ms *m/z* $[M]^+$ 312 (18), 297 (100). *Anal.* calcd for $C_{18}H_{16}O_5$: C 69.22, H 5.16; found C 69.41, H 5.31.

1,5,8-Trihydroxy-3-methoxy-2-methylanthraquinone(5,8-dihydroxy-3-O-methylrubiadin) [**11**].—The adduct obtained from chloronaphthazarin [**7**] (12) and diene **3** was aromatized on Si gel (C_6H_6 followed by CH_2Cl_2). Treatment of the mixture of quinones by anhydrous $AlCl_3$ (2.67 g, 20.0 mmol) in CH_2Cl_2 (70 ml) at 25° for 2 h followed by addition of ice (300 g) and concentrated HCl (60 ml) (12 h) and extraction with CH_2Cl_2 (3 × 500 ml) gave anthraquinone **11** (555 mg, 92%): mp 276.5–278.0° (1,2-dichloroethane/petroleum ether, bp 90–120°); uv λ max (MeOH) (log ε) 225 (4.40), 277 (4.36), 488 (4.14), 508 (4.04), 522 (3.94), 572 (2.78), 658 (2.19), 772 (1.72) nm; ir ν max (KBr) 1615, 1590, 1580 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 2.21 (3H, s, 2-Me), 4.03 (3H, s, 3-OMe), 7.26 (2H, s, H-6, -7), 7.45 (1H, s, H-4), 12.39, 12.51, and 12.97 (3 × 1H, 3s, 1-OH, 5-OH, 8-OH); ms *m/z* $[M]^+$ 300 (100). *Anal.* calcd for $C_{16}H_{12}O_6$: C 64.00, H 4.03; found C 63.88, H 4.10. Acetate (Ac_2O/H_2SO_4), mp 238–239° (1,2-dichloroethane/petroleum ether, bp 90–120°).

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LITERATURE CITED

1. L. Boisvert and P. Brassard, *Chem. Lett.*, 1055 (1989).
2. J. Savard and P. Brassard, *Tetrahedron*, **40**, 3455 (1984).
3. A.G. Gonzales, J.T. Barroso, R.J. Cardona, J.M. Medina, and F. Rodriguez Luis, *An. Quim.*, **73**, 538 (1977).
4. S. Kitanaka, H. Igarashi, and M. Takido, *Chem. Pharm. Bull.*, **33**, 971 (1985).
5. R.D. Tiwari, M. Bajpai, A.R. Tiwari, and J. Singh, *Planta Med.*, **32**, 371 (1977).
6. J. Lal and P.C. Gupta, *Experientia*, **30**, 850 (1974).
7. M. Braun, *Liebigs Ann. Chem.*, 2247 (1981).
8. B. Simoneau and P. Brassard, *Tetrahedron*, **50**, 1080 (1987).
9. E.H. Charlesworth and R. Robinson, *J. Chem. Soc.*, 1531 (1934).
10. J. Singh and J. Singh, *Phytochemistry*, **26**, 507 (1987).
11. A. Dass, T. Joshi, and S. Shukla, *Phytochemistry*, **23**, 2689 (1984).
12. I. Singh, R.E. Moore, C.W.J. Chang, R.T. Ogata, and P.J. Scheuer, *Tetrahedron*, **24**, 2969 (1968).

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