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Ricardo Tapia [a] , Jaime A. Valderrama [a] & Claudio Saitz [a]

[a] B. Facultad de Química. Pontificia Universidad Católica de Chile Casilla , 306 Santiago 22, Chile

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A SIMPLE SYNTHESIS OF ETHYL 5-(1,4-CYCLOHEXADIENE-3,6 -DIONE-1-YL)-3,5-DIHYDROXY PENTANOATE

Ricardo Tapia * , Jaime A. Valderrama and Claudio Saitz B.
Facultad de Química. Pontificia Universidad Católica de Chile
Casilla 306, Santiago 22, Chile

ABSTRACT :Ethyl 5-(1,4-cyclohexadiene-3,6-dione-1-yl)-3,5-dihydroxypentanoate (**9**) has been synthesized by using the reaction of 2,5-dimethoxybenzaldehyde(4) with β-ketoester dianions as the key step.

In relation with our studies about the preparation of natural pyranoquinones[1] we have considered the synthesis of erythrostominone (**1**), an antibacterial pigment isolated from deep cultures of *Gnomonia Erythrostoma*[2], whose total synthesis has not been reported. A retrosynthetic analysis of **1** led us to consider benzopyranoquinone **2** as a BC synthon for the construction of the aromatic skeleton of **1** by using Diels-Alder methodology. Compound **2** could be prepared from **3** through an intramolecular addition of the hydroxyl group to the benzoquinone moiety followed by oxidation.

In this communication we describe our results in devising a possible route to **3** from 2,5-dimethoxybenzaldehyde (**4**) in three steps: (i) reaction with a β-keto ester or β-diketone dianion, ii) reduction, and iii) oxidation. The reaction of aliphatic aldehydes and ketones with dianions of β-ketoester and β-diketones to give the corresponding aldol product has been reported, but there are only a few examples for aromatic aldehydes.[3]

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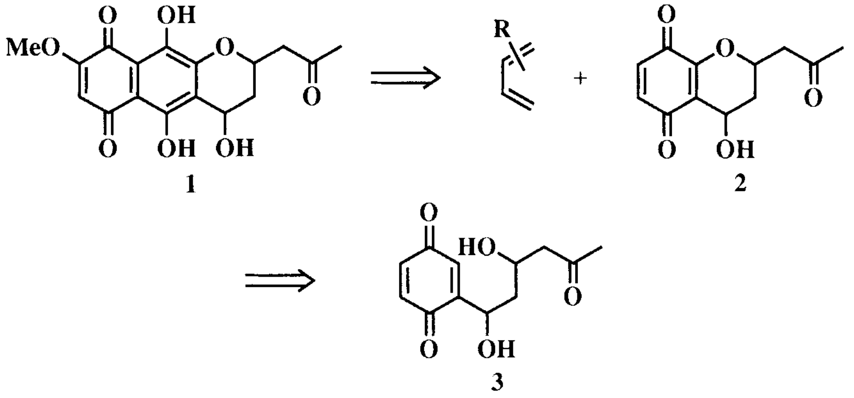
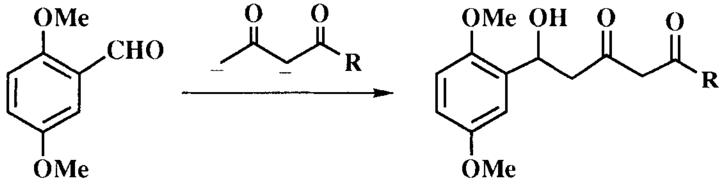
*To whom correspondence should be addressed.



The reaction of **4** with ethyl acetoacetate dianion, generated by treatment of the ketoester with one equivalent of sodium hydride followed by one equivalent of n-butyl lithium, furnished aldol **5** in 90% yield. The ^{1}H-nmr showed a multiplet at δ 4.52 ppm and a singlet at δ 3.50 ppm for H-1 and H-4 respectively, in accord with the structure of **5**. An analogous reaction of **4** with methyl acetoacetate and 2,4-pentanedione dianions gave the corresponding aldols **6** and **7** in 80 % and 65 % yield respectively.



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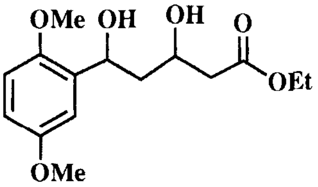
5 R = OEt
6 R = OMe
7 R = Me

Considering that aldol 7 was obtained in moderate yield and that its reduction should give a mixture of three diastereoisomers, we decided to use in next steps compound 5, which was obtained in better yield, Later on we will study the conversion of the ethoxycarbonyl into an acetyl group. The selective reduction of the ketonic group of **5** with sodium borohydride in methanol-tetrahydrofuran (10:1)[4] gave diol **8** as a mixture of diastereoisomers as determined by ^{1}H-nmr analysis of the crude product. Recrystallization from chloroform-petroleum ether (1:4) gave one diastereoisomer, which was oxidized with ceric ammonium nitrate to afford benzoquinone **9** in 65 % yield.



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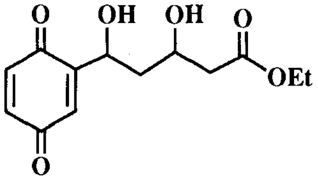

9

In summary, we report here a simple three step procedure to synthesize benzoquinone **9**. We are currently studying its cyclization to obtain an analog of pyranobenzoquinone **2**.

EXPERIMENTAL

Melting points were determined with a Kofler modified apparatus and are not corrected. IR spectra were recorded on a Perkin-Elmer Model 1310 Spectrometer. ^{1}H and ^{13}C nmr spectra were recorded on Varian XL-100 and Varian XL-300 spectrometers respectively, using tetramethylsilane as internal reference. Column chromatography was perfomed on Silica-gel 60 (Merck). Elemental analyses were performed at the Instituto de Química Orgánica General, Madrid, Spain.

Ethyl 5-(2,5-dimethoxyphenyl)-5-hydroxy-3-oxopentanoate (**5**).

To a stirred mixture of sodium hydride (330 mg, 11 mmol, 80% dispersion in mineral oil) in anhydrous tetrahydrofuran (25 mL) at 0 °C, maintained under a nitrogen atmosphere, a solution of ethyl acetoacetate (1.30 g , 10 mmol) in tetrahydrofuran (2 mL) was added dropwise. The mixture was stirred for 10 minutes and n-butyl lithium in hexane (7 mL, 10.5 mmol, 1.5 M) was slowly added at 0 °C. After stirring for 10 minutes at 0 °C, a solution of 2,5-dimethoxybenzaldehyde (**4**) (1.66 g, 10 mmol) in tetrahydrofuran (10 mL) was added dropwise. The reaction mixture was kept stirring for 15 minutes at 0 °C and then quenched by the addition of cold hydrochloric acid 3 N (8 mL) and the resulting mixture was extracted with ethyl ether (3x15 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo giving 1.66 g (90%) of crude product that was recrystallized from chloroform-petroleum ether (1:3) as white needles; mp 57-58 °C. IR: 3440 (OH), 1745 (COOEt), 1715 (CO) cm $^{-1}$. ^{1}H-nmr δ: 1.28 (t, *J* = 7.0 Hz, 3H, $C\underline{H}_3CH_2O$), 2.90-3.00 (m, 2H, CH_2), 3.38 (broad s, 1H, OH), 3.50-(s, 2H, $COCH_2CO$), 3.78 (s, 3H, CH_3O), 3.80 (s, 3H, OCH_3), 4.22(q, *J* = 7.0 Hz 2H, $CH_3C\underline{H}_2O$), 5.30-5.50 (m, 1H, CH), 6.72-6.86(m,2H, ArH), 7.02-7.18 (m, 1H, ArH) ppm. ^{13}C-nmr δ: 14.1, 49.9, 50.1, 55.8, 61.4, 65.4, 111.5, 112.6, 113.1, 132.1, 150.0, 154.0, 176.1, 202.9 ppm. Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.81; H, 6.76. Found: C, 60.58; H, 6.84.

Methyl 5-(2,5-dimethoxyphenyl)-5-hydroxy-3-oxopentanoate (**6**).

Following the same procedure, 1.16 g (10 mmol) of methyl acetoacetate and 1.66 g (10 mmol) of **4**, yielded 2.22g (80%) of crude product **6** as an oil. A sample was purified by column chromatography using chloroform-ethyl acetate (3:2, Rf=0.44) as eluent. IR: 3440 (OH), 1740 (COOMe) , 1715 (CO)cm $^{-1}$. ^{1}H-nmr δ:2.80-3.00 (m. 2H,CH_2), 3.42 (broad s, 1H, OH), 3.50 (s, 2H, $COCH_2CO$), 3.72 (s, 3H, CH_3O), 3.75 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O),5.30-5.50 (m, 1H, CH), 6.74-6.90 (m,2H, ArH), 7.03-7.20 (m, 1H, ArH) ppm. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.38. Found: C, 59.29; H, 6.26.

6-(2,5-Dimethoxyphenyl)-6-hydroxy-2,4-hexanedione (**7**).

Following the same procedure, 500 mg (5.0 mmol) of 2,4-pentanedione and 830 mg (5.0 mmol) of 4 yielded 840 mg (65%) of crude **7**, which was recrystallized from ethanol as white needles, mp 60-62 °C. IR: 3440 (OH), 1650 (CO) cm $^{-1}$. ^{1}H-nmr δ: 2.05 (s, 3H, CH_3CO), 2.60-2.80(m, 2H, CH_2), 3.76 (s, 5H, CH_2 and CH_3), 3.79 (s, 3H, CH_3O), 6.70-6.90 (m,2H, ArH), 7.00-7.20 (m, 1H, ArH) ppm. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.16; H, 6.77. Found: C, 63.10; H, 6.58.

Ethyl 3,5-dihydroxy-5-(2,5-dimethoxyphenyl)pentanoate (**8**).

To a stirred solution of aldol **5** (590 mg, 1.90 mmol) in 30 mL of methanol-tetrahydrofuran (1:10), sodium borohydride (80 mg, 2.1 mmol) was added in portions at 0 °C. After stirring for 30 minutes at 0 °C the rection mixture was quenched with brine (15 mL) and extracted with ethyl ether (3x15 mL). The combined extracts were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed to give 560 mg (94%) of crude product as a 1.25:1 mixture of diastereoisomers as determined by ^{1}H-nmr integration. ^{1}H-nmr δ: 1..25 and 1.26(mayor), (two t, *J* = 7.0 Hz, 3H, $C\underline{H}_3CH_2O$), 1.70-2.00 (m, 2H, CH_2), 2.35--2.70 (m,2H, CH_2), 3.40 (broad s, 1H, OH), 3.78 (s, 3H, CH_3O), 3.80 (s, 3H, OCH_3), 4.15 and 4.16 (mayor), (two q, *J* = 7.0 Hz 2H, $CH_3C\underline{H}_2O$), 4.25-4.70 (m, 1H, CH), 5.10-5.50 (m, 1H, CH), 6.65-6.85 (m,2H, ArH), 7.00-7.15 (m, 1H, ArH) ppm. The mixture was recrystallized from chloroform-petroleum ether (1:4) to give 255 mg(43%) of one diastereoisomer as white needles; mp 89-91 °C. IR: 3380 (OH), 1705 (COOEt) cm $^{-1}$.^{1}H-nmr δ: 1.26 (t, *J* = 7.0 Hz, 3H, $C\underline{H}_3CH_2O$), 1.70-2.00 (m, 2H, CH_2), 2.40-2.60 (m, 2H, CH_2), 3.40 (broad s, 1H, OH), 3.78 (s, 3H, CH_3O), 3.80 (s, 3H, OCH_3), 4.16 (q, *J* = 7.0 Hz 2H, $CH_3C\underline{H}_2O$), 4.25-4.50 (m, 1H, CH), 4.80-5.10 (m, 1H, CH), 6.70-6.85 (m,2H, ArH), 7.00-7.15 (m, 1H, ArH) ppm. ^{13}C-nmr δ: 14.2, 41.5, 42.3, 55.8, 60.7, 66.0, 67.2, 111.5, 112.6, 112.9, 133.7, 150.3, 154.0, 172.7 ppm. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.42; H, 7.38. Found: C, 60.28; H, 7.45.

Ethyl 5-(1,4-cyclohexadiene-3,6-dione-1-yl)-3,5-dihydroxypentanoate (**9**).

To a stirred solution of the diol **8** (150 mg, 0.5 mmol) in acetonitrile (2 mL) , ceric ammonium nitrate (0.83 mg, 1.5 mmol) in water (2.5 mL) was added in one portion at 0 °C. After stirring for 30 minutes at 0 °C, the reaction mixture was diluted with water (15 mL) and extracted with chloroform (3x15 mL). The organic layers were washed with brine and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on a column of silicagel eluting with chloroform-ethyl acetate (3:2, RF=0.27) to give pure quinone **8** (85 mg, 65%) as a red oil. IR: 3430 (OH), 1775 (COOEt), 1660 and 1650 (CO) cm $^{-1}$. ^{1}H-nmr δ: 1.24 (t, *J* = 7.0 Hz, 3H, $C\underline{H}_3CH_2O$), 1.70-2.00 (m, 2H, CH_2), 2.40-2.60 (m, 2H, CH_2), 2.80 (broad s, 1H, OH), 3.80 (broad s, 1H, OH), 4.17 (q, *J* = 7.0 Hz, 2H, $CH_3C\underline{H_2}O$), 4.30-4.50 (m, 1H, CH), 4.80-5.08 (m, 1H, CH), 6.66-6.84 (m, 2H, ArH), 6.90-7.08 (m, 1H, ArH) ppm. ^{13}C-nmr δ: 14.1, 41.1, 60.9, 65.8, 131.8, 136.4, 136.8, 150.3, 172.6, 187.4, 187.8 ppm. Anal. Calcd for $C_{13}H_{16}O_6$: C, 60.47; H, 5.97. Found: C, 60.28; H, 5.82.

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REFERENCES AND NOTES

1. a) C. Saitz, J. A. Valderrama, and R. Tapia, Synth. Commun., **1992**, 22, 955. b) C. Saitz, J. A. Valderrama, and R. Tapia, *ibid,* 1992, 22, 2411.
2. a) B. E. Cross, M. N. Edinberry, and L. J. Zammitt, J. Chem. Soc. Perkin Trans. 1, **1972**, 380. b) B. E. Cross, and L. J. Zammitt, *ibid*, **1975**, 1936.
3. a) J. R. Peterson, T. J. Winter, and C. P. Miller, Synth. Commun., **1988**, 18, 949. b) S. N. Huckin, and L. Weiler, Can. J. Chem., **1974**, 52, 2157 and references cited therein. c) R. D. Stipanovic, and G. J. Calton, Tetrahedron Lett., **1970**, 357.
4. R. S. Varma and G! W. KKabalka, Synth. Commun., **1985**, 15, 985.

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