Synthetic Studies *via* Arene-Metal Compounds. An Application to the Regioselective Synthesis of a Natural Phthalide

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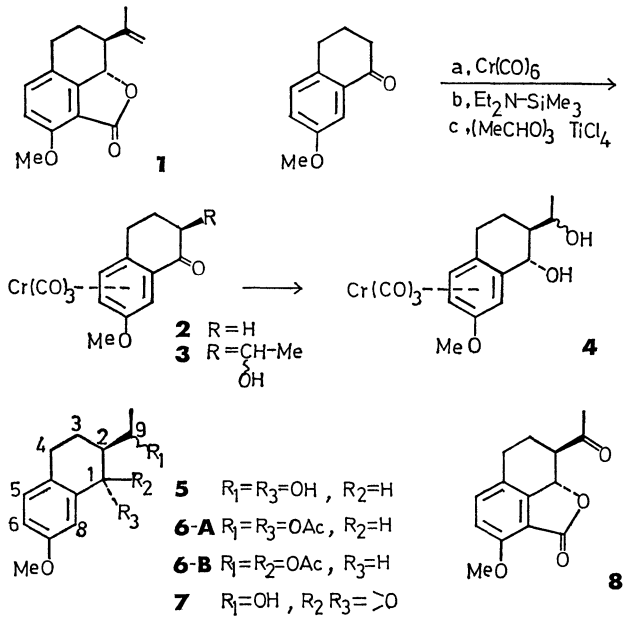
Synopsis. A naturally occuring methoxyphthalide derivative, a constituent of *Othonna Cylindrica Dc*, was synthesized by employing stereoselective carbonyl reduction of (η-arene)tricarbonylchromium complex and regioselective lithiation of 7-methoxy-2-(1-hydroxyethyl)-1-tetralol.

The 3-methoxybenzyl alcohol derivatives and related compounds were lithiated mostly at 2-position of the aromatic ring on the basis of coordination between the lithium cation and the two proximal oxygen atoms.[1] In case of such a molecule that the benzylic hydroxyl group is fixed by a rigid conformation as in 7-methoxy-1-tetralol, this selective metallation is more facilitated by further stabilization of the cyclic lithio compound. This paper reports an application of this reaction to the synthesis to (**1**),[2] a constituent of *Othonna Cylindrica Dc*, combined with the stereoselective carbonyl reduction of tricarbonyl (2-substituted 7-methoxy-1-tetralol) chromium complex.

Refluxing of 7-methoxy-1-tetralone with hexacarbonylchromium in heptane and dibutyl ether gave a red colored (η-arene) tricarbonylchromium complex (**2**) in a 65% yield. The reaction of the complex **2** with *N*-trimethylsilyldiethylamine in the presence of *p*-toluenesulfonic acid,[3] followed by cross-aldol condensation[4] with paraldehyde and titanium tetrachloride, afforded a mixture of diastereomeric keto alcohols (**3**).[5] The compound **3** was reduced with diisobutylaluminum hydride (Dibal) to give the chromium complex (**4**) of *trans* substituted diol. No trace of the corresponding *cis* isomer was detected. In this reaction, the hydroxyethyl and hydride addition selectively took place from the other side of the tricarbonylchromium group.[6] Decomplexation of the chromium metal (by exposure to sunlight) gave the *trans* diol (**5**), which was chracterized as a diacetyl compound (**6-A**).

When the carbonyl reduction of the trimethylsilyl ether of the keto alcohol (**7**), prepared from 7-methoxy-1-tetralone by an analogous procedure, was performed without complexation by $Cr(CO)_3$ group, the product (80% yield) was a mixture of *trans* and *cis* alcohols in an approximate ratio of 12:88. The stereochemistry (C-1 and C-2) of both compounds was elucidated by the comparison of the ^{1}H-NMR spectra of the corresponding diacetates, **6-A** and **6-B**, derived by deprotection of trimethylsilyl group and acetylation. In this reduction, the *cis* isomer was formed predominantly, in contrast to the reduction of the (η-arene) tricarbonylchromium complex.

Treatment of the *trans* compound **5**[5] with butyl lithium and tetramethylethylenediamine (TMEDA) in hexane, followed by carboxylation with solid carbon dioxide, gave a hydroxy γ-lactone, which, without purification, was oxidized with Collins reagent to a



trans keto lactone (**8**)[7] as a sole isolable product in a 20% overall yield, unaccompanied with any other carboxylated products. Reaction of the *trans* keto lactone (**8**) with methylenetriphenylphosphorane gave **1**, which exhibited the same spectral data as those of the reported natural product.[2]

Experimental

Tricarbonyl(η-7-methoxy-1-tetralone)chromium Complex (2). A mixture of 7-methoxy-1-tetralone (1 g, 3.67 mmol), $Cr(CO)_6$ (2 g, 5.87 mmol), α-picoline (0.54 g, 5.87 mmol), heptane (20 ml) and dibutyl ether (100 ml) was refluxed under nitrogen for 24 h in a Strohmeier type apparatus. After filtration and evaporation *in vacuo*, a crude product was chromatographed on silica gel. Elution with ether–petroleum ether (1 : 4) gave a 1.15 g (65%) of **2**. IR ($CHCl_3$): 1975, 1920—1880, 1683 cm^{-1}. NMR ($CDCl_3$)δ: 3.66 (s, 3H, OMe), 5.36(d, J=6 Hz, 1H), 5.49 (dd, J=2, 6 Hz, 1H), 5.66 (d, J=2 Hz, 1H).

Tricarbonyl[η-7-methoxy-2-(1-hydroxyethyl)-1-tetralone]chromium Complex (3). A mixture of **2** (997 mg, 3.2 mmol), *N*-trimethylsilyldiethylamine (1.856 g, 12.8 mmol) and catalytic amount of *p*-TsOH was stirred at 35 °C in dry dichloromethane (15 ml) for 24 h. After evaporation at a reduced pressure, a residue was triturated with dry pentane. Evaporation of the pentane solution gave an oily enolsilyl ether (811 mg, 66%), which was used for next step without further purification. IR(neat): 1955, 1885—1855, 1640, 1605 cm^{-1}. NMR($CDCl_3$)δ: 0.19(s, 9H, $SiMe_3$), 3.68(s, 3H, OMe), 4.96—5.44(m, 4H). A solution of the crude enolsilyl ether (811 mg) in dry dichloromethane (10 ml) was added dropwise into a mixture of paraldehyde (169 mg, 0.84 mmol) and titanium tetrachloride (480 mg, 2.52 mmol) in dry dichlo-

romethane (10 ml) under argon atmosphere at −78 °C, and the reaction mixture was stirred for 7 h at the same temperature. After hydrolysis with water, the reaction mixture was extracted with dichloromethane. The extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography. Elution with ether–petroleum ether (1 : 3) afforded a diastereomeric mixture of **3** (428 mg, 57% yield). IR ($CHCl_3$): 3440, 1970, 1910, 1890, 1660 cm^{-1}. NMR ($CDCl_3$)δ: 1.23 (d, J=7 Hz) and 1.26 (d, J=7 Hz) (2 : 3 ratio, 3H, CHMe), 3.66 (s, 3H, OMe), 5.39 (d, J=6 Hz, 1H), 5.55 (dd, J=2, 6 Hz, 1H), 5.72 (d, J=2 Hz).

trans-*7-Methoxy-2-(1-hydroxyethyl)-1-tetralol (5).* Diisobutylaluminum hydride in toluene (0.186 M solution, 3.0 ml, 5.28 mmol) was added to a solution of **3** (510 mg, 1.43 mmol) in dry THF (10 ml) under argon atmosphere at −78 °C. After stirring for 3 h, acetone (1 ml) and then, water (10 ml) were added, After filtration and evaporation of the organic solvents under reduced pressure, the reaction mixture was extracted with ether. The extract was worked up as usual to leave *trans* compound **4** as a yellow oil which was used for next step without further purification. A solution of the *trans* compound **4** in ether (10 ml) was exposed to sunlight for 2 h. The precipitate was filtered and washed with ether. The ether solution was concentrated *in vacuo*, leaving a crude product which was purified by silica-gel chromatography (elution with ether–petroleum ether; 1:3) to give **5** as a colorless oil (250 mg, 79% from **3**). IR(CCl_4): 3210, 1610, 1580, 1505 cm^{-1}. NMR(CCl_4)δ: 1.18(d, J=7 Hz) and 1.21(d, J=7 Hz) (2 : 3 ratio, 3H, CHMe), 3.77(s, 3H, OMe), 6.76(dd, J=3, 7 Hz, 1H,) 7.03(d, J=7 Hz, 1H), 7.16(d, J=3 Hz, 1H).

trans *Keto Lactone (8).* A solution of the *trans* diol **5** (730 mg, 3.29 mmol) in dry ether (3 ml) was added into a mixture of butyllithium (1.3 M in hexane solution, 8.0 ml, 10.4 mmol), TMEDA (1.206 g, 10.4 mmol) in dry hexane (10 ml) under nitrogen, and the reaction mixture was heated at 60 °C for 5 h. The resulting dark red reaction mixture, after cooling to −78 °C, was treated with large excess of Dry Ice (in small pieces). After standing overnight, the reaction mixture was acidified with 2 M-HCl, heated at 50 °C for 30 min, and extracted with ethyl acetate. The extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oily product, which was used for next oxidation step without purification. A solution of the product in dry dichloromethane (2 ml) was added to stirred Collins reagent (prepared from 1.2 g of chromium trioxide, and 1.9 g of pyridine in 25 ml of dry dichloromethane) at 0 °C. After stirring at that temperature for 3 h, ether (10 ml) was added. The solution was filtrated from the residue, which was washed with ether. The combined organic solution was washed with 2M-HCl, saturated aq $NaHCO_3$, and brine and then, dried over Na_2SO_4. Evaporation of the solvent at reduced pressure afforded 290 mg of an oily product, which was purified over silica gel column chromatography to give a crystalline compound **8** (159 mg, 20% from **5**). Recrystallization from ether–petroleum ether gave colorless needles; mp 148—149 °C. IR($CHCl_3$): 1750, 1710, 1640, 1605, 1510 cm^{-1}. NMR($CDCl_3$)δ: 2.32(s, 3H, COMe), 3.92(s, 3H, OMe), 5.22(d, J=10 Hz, CHOC=O), 6.82(d, J=8 Hz, 1H), 7.31(d, J=8 Hz, 1H). Found: C, 68.23; H, 5.76%. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73%.

Wittig Reaction of 8. Butyllithium (1.3 M in hexane solution, 0.29 ml, 0.382 mmol) was added to a mixture of methyltriphenylphosphonium bromide (151 mg, 0.42 mmol) in dry THF (2 ml) at 0 °C under nitrogen atmosphere. After stirring for 1 h, a solution of **8** (77 mg, 0.313 mmol) in dry THF (5 ml) was added to the above Wittig reagent, and the reaction mixture was stirred for 3 h at 0 °C. After addition of 2M-HCl, the product was extrated with ether as usual. The crude product was purified by silica gel column chromatography to give crystalline compound **1** (25 mg). MS *m/e*: 244, 176. IR($CHCl_3$): 2940, 1750, 1660, 1605, 1510 cm^{-1}. NMR($CDCl_3$)δ: 1.86(s, 3H, MeC=), 3.97(s, 3H, OMe), 4.94(broad s, 2H, H_2C=C), 5.12(d, J=10 Hz, 1H, O=COCH–), 6.85(d, J=8 Hz, 1H), 7.32(d, J=8 Hz, 1H). UV(EtOH) max: 215, 241, 305 nm. These data were well consistent to the spectral data reported for the natural product.[2]

trans-*Diacetate (6-A).* This acetate was prepared with acetic anhydride and pyridine by usual method. IR (CCl_4): 1740, 1615, 1505, 1245 cm^{-1}. NMR(CCl_4)δ: 1.25(d, J=7 Hz) and 1.29(d, J=7 Hz) (3:2 ratio, 3H, CHMeOAc), 1.97(s) and 2.01(s) (2:3 ratio, 3H, OAc), 2.13(s, 3H, OAc), 4.80—5.10(m, 1H, MeCHOAc), 5.95(d, J=8 Hz, 1H, CHOAc), 6.63(d, J=3 Hz, 1H), 6.77(dd, J=3, 8 Hz, 1H), 7.01(d, J=8 Hz, 1H).

cis-*Diacetate (6-B).* A mixture of **7** (110 mg, 0.5 mmol) and hexamethyldisilazane (242 mg, 1.5 mmol) was heated at 50 °C for 24 h. Evaporation at reduced pressure gave an oily silylated product in a quantitative yield. IR(neat): 1680, 1610, 1500 cm^{-1}. NMR($CDCl_3$)δ: 0.21(s) and 0.18(s) (2:3 ratio, 9H, $OSiMe_3$), 1.18(d, J=7 Hz) and 1.32(d, J=7 Hz) (3:2 ratio, 3H, CHMe), 3.88(s, 3H, OMe), 4.70(m, 1H, MeCHO–), 7.08(dd, J=2, 7 Hz, 1H), 7.20(d, J=7 Hz, 1H), 7.54(d, J=2 Hz, 1H). The keto silylated product was reduced with Dibal (THF, −78 °C), to giva a hydroxy silylated compound, which was converted to a diacetylated product by deprotection of silyl group (aq AcOH, THF, rt) and then acetylation (acetic anhydride, pyridine, rt) in a 80% yield. Pure *cis* isomer was obtained by preparative TLC. IR(CCl_4): 1740, 1615, 1505, 1245 cm^{-1}. NMR (CCl_4)δ: 1.26(d, J=7 Hz, 3H, CHMeOAc), 1.91(s) and 1.98(s) (3:2 ratio, 3H, OAc), 1.95(s) and 2.00(s) (3:2 ratio, 3H, OAc), 3.74(s, 3H, OMe), 4.80—5.05(m, 1H, MeCHOAc), 6.05(d, J=7 Hz, 1H, CHOAc), 6.70—6.82(m, 2H), 6.97 (broad d, J=8 Hz, 1H).

References

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2) F. Bohlmann and M. Grenz, *Tetrahedron Lett.*, **1974**, 1681.

3) L. H. Hellberg and A. Juarez, *Tetrahedron Lett.*, **1974**, 3553.

4) T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).

5) An epimeric mixture at C-9. Since the epimeric center will be removed by oxidation to a C-9 keto compound at the later step, this diastereomeric mixture was used for a series of reaction without separation.

6) G. Jaouen and A. Meyer, *J. Am. Chem. Soc.*, **97**, 4667 (1975); B. Caro and G. Jaouen, *Tetrahedron Lett.*, **1974**, 1229.

7) Similarly, an isomeric *cis* keto lactone was obtained from a corresponding *cis* alcohol by lithiation, carboxylation, and then Collins oxidation. Mp 126 °C. IR($CHCl_3$): 1760, 1710, 1640, 1510 cm^{-1}. NMR($CDCl_3$)δ: 2.08(s, 3H, COMe), 3.95(s, 3H, OMe), 5.40(d, J=7 Hz, 1H, CHOC=O), 6.84(d, J=8 Hz, 1H), 7.32(d, J=8 Hz, 1H).