Short Communication

Total Synthesis of Natural (+)-Phomalactone, (+)-Acetylphomalactone, (+)-Asperlin and Their Isomers

Tetsuya MURAYAMA, Takeyoshi SUGIYAMA and Kyohei YAMASHITA

Department of Agricultural Chemistry, Faculty of Agriculture, Tohoku University, Sendai 980, Japan

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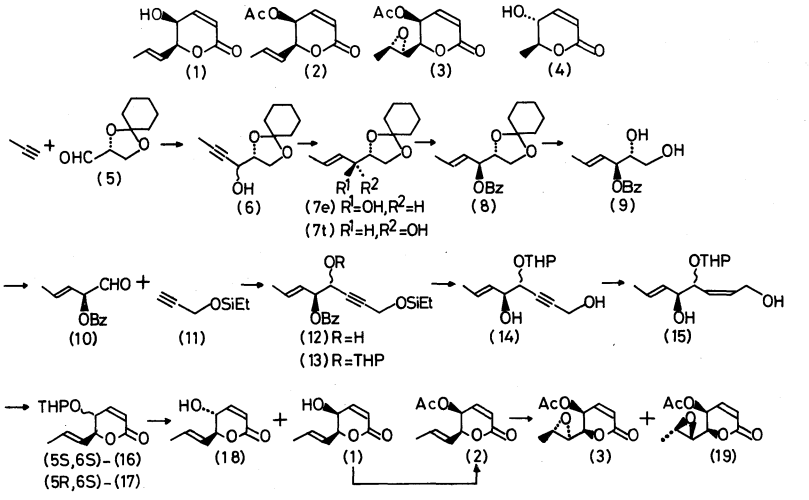
(+)-Phomalactone (**1**), one of 6-substituted 5,6-dihydro-5-hydroxy (or acyloxy)-2*H*-pyran-2-ones, was isolated from *Nigrospore* sp.[1] and *Phoma* sp.[2] This lactone has been considered to be a biosynthetically and synthetically important precursor of (+)-acetylphomalactone (**2**)[3] and (+)-asperlin (**3**),[3,4] having antibiotic and antitumorial activities, and the syntheses of these optically active lactones has not been previously reported. We now wish to report the successful syntheses of these highly functional and optically active lactones by the method which is also applicable to the synthesis of (−)-osmundalactone (**4**).[5]

2,3-*O*-Cyclohexylidene-D-glyceraldehyde (**5**)[6] was chosen as the chiral starting material. The diastereomeric ratio of the reaction products between **5** and 1-lithio-1-propyne was 1 : 1 (*erythro* : *threo*), as determined by GC. The addition of zinc chloride to the reaction medium caused improved diastereoselectivity (*erythro* : *threo* = 2.3 : 1), other metal ions resulting in low diastereoselectivities. Partial reduction of **6** to an allylic alcohol gave two isomers (**7e** and **7t**) that were separable on column of silica gel-60 developed with dichloromethane. After the chromatographic separation, **7e** was further purified by recrystallization of its 3,5-dinitrobenzoate. Alkaline hydrolysis and distillation then afforded pure **7e** (>99% diastereomeric excess) in a 30% yield from **6**. **7e**. bp 130°C (4.0 mmHg), $[\alpha]_D^{20}$ +19.2° (c = 1.00, $CHCl_3$). 3,5-dinitrobenzoate of **7e**: mp 111°C, $[\alpha]_D^{20}$ +1.6° (c = 1.00, $CHCl_3$). Protection of the hydroxyl group as a benzoate and removal of the cyclohexylidene group in an acidic medium gave the diol **9** (88% from **7e**). Oxidation of **9** with sodium metaperiodate afforded the intermediate aldehyde **10**; bp 120°C (0.8 mmHg), $[\alpha]_D^{20}$ +130° (c = 1.00, benzene). The optical purity of **10** was determined to be more than 95% *e.e.* by ^{1}H-NMR analysis, using the chiral shift reagent $Eu(tfc)_3$. IR ν_{max}^{film} cm^{-1}: 3060, 3040, 2725, 1740, 1720, 1670, 1600, 1450, 1275, 1110, 965, 715. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (3H, d, J = 6.4 Hz), 5.53～5.71 (2H, m), 5.94～6.28 (1H,



dq, J=6.4, 14.1 Hz), 7.26~8.16 (5H, m), 9.57 (1H, s).

The reaction between **10** and the lithium acetylide of **11** at −78°C in tetrahydrofuran afforded a diastereomeric mixture of **12** (*threo*:*erythro*=*ca.* 1:2) in a 76% yield. This mixture of **12** was subjected to the next reaction without separating the stereoisomers. The free hydroxyl group of **12** was protected as tetrahydropyranyl ether, and other two protective groups, benzoyl and triethylsilyl, were removed by alkaline hydrolysis to give **14**. Partial hydrogenation over Lindlar's catalyst and subsequent oxidative lactonization with manganese dioxide in dichloromethane under neutral conditions afforded the lactones **16** and **17** (**16**:**17**=*ca.* 1:2). Deprotection of **16** and **17** by acid-catalyzed methanolysis (Amberlyst-15) produced (+)-phomalactone (**1**) and its diastereomer (**18**). **1**. mp 56.0~56.5°C (lit.[1] 56.0~57.0°C), $[\alpha]_D^{20}$ +178° (c=0.49, EtOH; lit.[1] +179.3°). IR ν_{max}^{KBr} cm^{-1}: 3510, 3360, 3040, 1720, 1700, 1665, 1620, 1380, 1255, 1150, 1100, 1065, 1020, 960, 890, 820, 805, ^{1}H-NMR ($CDCl_3$) δ: 1.80 (3H, dd, J=1.2, 5.8 Hz), 2.50 (1H, br. s), 4.18 (1H, dd, J=3.2, 5.4 Hz), 4.81 (1H, dd, J=3.2, 6.1 Hz), 5.76 (1H, ddq, J=1.2, 6.1, 15.4 Hz), 5.96 (1H, dq, J=5.8, 15.4 Hz), 6.08 (1H, d, J=9.8 Hz), 6.99 (1H, dd, J=5.4, 9.8 Hz). **18**. mp 76.5~77.0°C, $[\alpha]_D^{20}$ −68.6° (c=0.58, EtOH). IR ν_{max}^{KBr} cm^{-1}: 3450, 2860, 1700, 1680, 1630, 1240, 1100, 1060, 1010, 970, 820. ^{1}H-NMR ($CDCl_3$) δ: 1.78 (3H, dd, J=1.4, 6.4 Hz), 2.80 (1H, br. s), 4.31 (1H, ddd, J=1.7, 2.4, 8.5 Hz), 4.65 (1H, dd, J=7.3, 8.5 Hz), 5.54 (1H, ddq, J=1.4, 7.3, 8.5 Hz), 5.80~6.20 (1H, dq, J=6.4, 16.0 Hz), 5.92 (1H, dd, J=1.7, 9.8 Hz), 6.88 (1H, dd, J=2.4, 9.8 Hz).

Acetylation of (+)-phomalactone (**1**) with acetic anhydride in pyridine yielded (+)-acetylphomalactone (**2**) in a 65% yield. mp 54.0~54.5°C (lit.[3] 56.0°C), $[\alpha]_D^{20}$ +300° (c=0.44, EtOH; lit.[3] 311.8°), IR ν_{max}^{KBr} cm^{-1}: 1735, 1720, 1635, 1370, 1255, 1230, 1160, 1075, 1030, 980, 950, 820. ^{1}H-NMR ($CDCl_3$) δ: 1.78 (3H, dd, J=1.2, 6.4 Hz), 2.10 (3H, s), 4.99 (1H, dd, J=2.9, 6.8 Hz), 5.23 (1H, dd, J=2.9, 5.4 Hz), 5.59 (1H, ddq, J=1.2, 6.8, 15.1 Hz), 5.94 (1H, dq, J=6.4, 15.1 Hz), 6.20 (1H, d, J=9.8 Hz), 6.96 (1H, dd, J=5.4, 9.8 Hz).

Epoxidation of (+)-acetylphomalactone (**2**) with *m*-chloroperbenzoic acid in dichloromethane at room temperature afforded a mixture of diastereomers, (+)-asperlin (**3**, 44%) and (1′*R*,2′*S*)-isomer (**19**, 11%). **3**. mp 70.5~71.0°C (lit.[3] 69.5~71.0°C), $[\alpha]_D^{20}$ +332° (c=0.47, EtOH; lit.[3] +331°). IR ν_{max}^{KBr} cm^{-1}: 3080, 1740, 1720, 1635, 1440, 1380, 1250, 1145, 1100, 1035, 945, 870, 860, 825. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, J=4.9 Hz), 2.14 (3H, s), 3.01~3.20 (2H, m), 4.11 (1H, dd, J=2.9, 7.0 Hz), 5.32 (1H, dd, J=2.9, 5.9 Hz), 6.22 (1H, d, J=9.8 Hz), 7.08 (1H, dd, J=5.9, 9.8 Hz). **19**. mp 63.0~63.5°C, $[\alpha]_D^{20}$ +211° (c=0.35, EtOH). IR ν_{max}^{KBr} cm^{-1}: 3070, 1735, 1635, 1440, 1380, 1370, 1240, 1225, 1100, 1030, 945, 845, 820. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, d, J=4.9 Hz), 2.15 (3H, s), 2.99~3.14 (2H, m), 4.36 (1H, dd, J=3.7, 4.9 Hz), 5.51 (1H, ddd, J=0.5, 3.7, 5.2 Hz), 6.21 (1H, dd, J=0.5, 9.8 Hz), 6.87 (1H, dd, J=5.2, 9.8 Hz).

All the spectral data for synthetic (+)-phomalactone (**1**), (+)-acetylphomalactone (**2**) and (+)-asperlin (**3**) were identical with those of the natural products.

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