REDUCTION OF α-PYRONE DERIVATIVES WITH BORANE-METHYL SULFIDE COMPLEX

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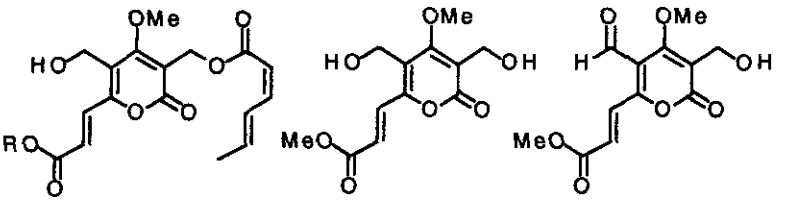
Abstract ---- Selective reduction of the 5-carbomethoxy- and the 5-carbethoxy-4-hydroxy-2*H*-pyran-2-one derivatives (**5a~11**, **19**) to yield the 5-hydroxymethyl derivatives (**12~18**) was accomplished using 1.1 mol equivalent of borane-methyl sulfide complex. Additionally, reduction of the 3-acetyl-4-hydroxy-2*H*-pyran-2-one derivatives (**23**, **26** and **29**) with borane-methyl sulfide complex afforded the binary condensed pyrone derivatives (**25**, **28** and **31**) in good yields.

Islandic acid I (**1**) [1,2] and rosellisin (**3**),[3,4] are mycotoxins known to be cytotoxic and antibacterial respectively. Both have a 4-hydroxy-2*H*-pyran-2-one (α-pyrone) skeleton fully substituted with various oxygenated functional groups. In addition to mycotoxic activities, α-pyrone derivatives are also useful synthons for the introduction of β-polyketo carboxylic acid chains. Many synthetic studies of various α-pyrone derivatives have been reported.[5,6] To the best of our knowledge, however, no articles have ever described the introduction of the 5-hydroxymethyl group to the α-pyrone skeleton, which is necessary for the synthesis of the natural products shown in Scheme 1. Investigation toward providing a synthetic pathway leading to the bioactive α-pyrones with



R=H Islandic acid I (**1**)
R=Me Islandic acid I methyl ester (**2**)

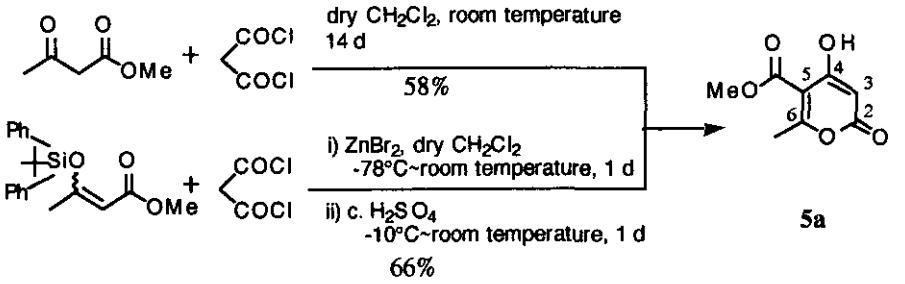
Rosellisin (**3**)

Rosellisin aldehyde (**4**)

Scheme 1

multiply oxygenated substituents have led to a new selective reduction of the 5-carbomethoxy- and the 5-carbethoxy-4-hydroxy-2*H*-pyran-2-one derivatives (**5a~11**, **20**). The reductions were accomplished using borane-methyl sulfide complex (BMS) which afforded the α-pyrone carbinols (**12~18**) under mild conditions and in high yields. In addition, the 3-acetyl-4-hydroxy-2*H*-pyran-2-one derivatives (**23**, **26** and **29**) were transformed to the binary condensed α-pyrones (**25**, **28** and **31**) in good yields upon BMS reduction.

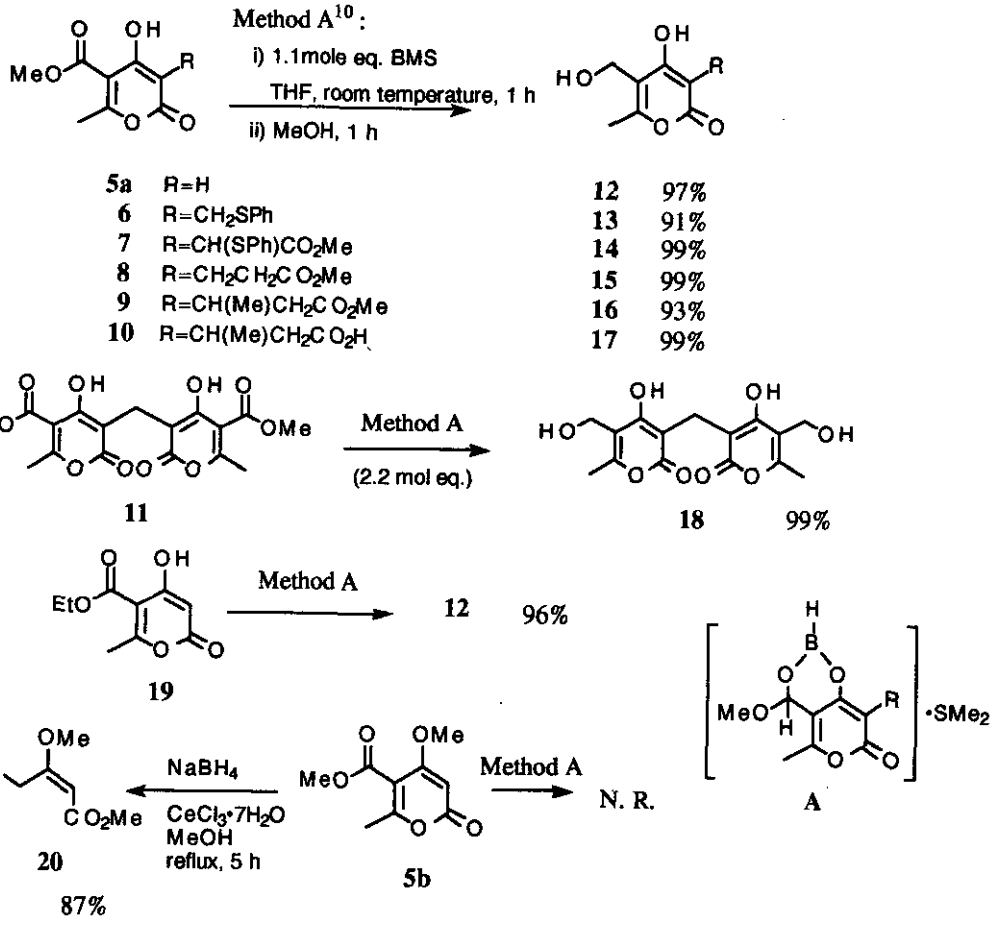
5-Carbomethoxy-4-hydroxy-6-methyl-2*H*-pyran-2-one (**5a**) was prepared by modification of Suzuki's procedure.[7] *Treatment of methyl acetoacetate with malonyl dichloride in* dry CH_2Cl_2 at room temperature for 14 d afforded **5a** in 58% yield. Compound (**5a**) was also prepared in 66% yield upon treatment of the *t*-butyldiphenylsilyl enol ether of methyl acetoacetate and malonyl dichloride with $ZnBr_2$ followed by *conc.* H_2SO_4 (Scheme 2).



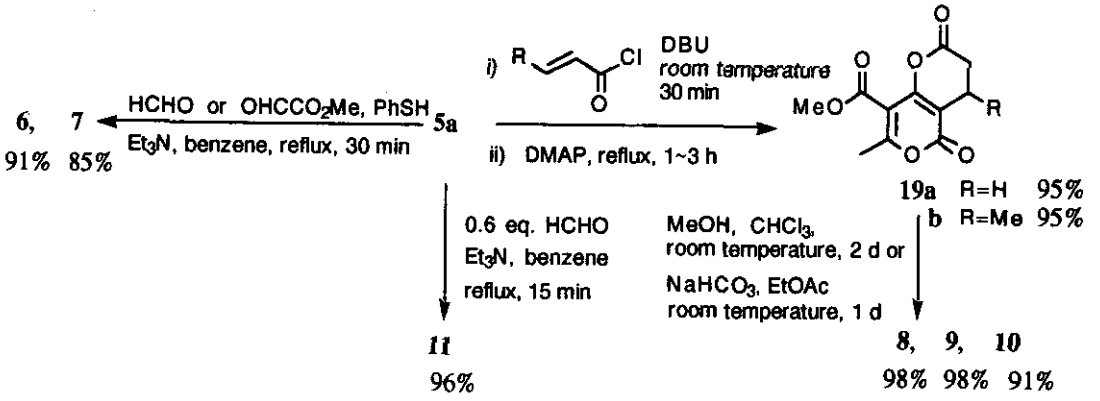
Scheme 2

Reduction of **5a** or the 4-methoxy derivative (**5b**)[8] with $NaBH_4$ or *LiBH(Et)*$_3$ under various conditions resulted in the formation of a complex mixture, ring-opened products (for example; **20**), or reduction of the double bond at the C-5 position. Moriwake has reported an efficient and selective reduction of an α-hydroxy ester in the presence of a β-hydroxy ester with the combination of BMS-$NaBH_4$.[9] In the case of α-pyrone derivatives, the β-hydroxy ester units were reduced very efficiently with BMS even in the absence of $NaBH_4$. When **5a** was treated with 1.1 mol eq. of BMS, the reduction was complete after 1 h yielding the carbinol (**12**) in 97% yield (Method A)[10] (Scheme 3). The other 5-carbomethoxy derivatives (**6~10**), which were prepared by the procedures shown in Scheme 4, were also successfully reduced to their corresponding alcohols (**13~17**). The reactions proceeded in high yields under similar conditions without reduction of the other side chain functional groups such as SPh, CO_2Me and CO_2H. Diester (**11**) was converted to alcohol (**18**) with 2.2 mol eq. of BMS. In addition, the 5-carbethoxy derivative (**19**) was also reduced to yield **12** quantitatively with BMS. Since the methyl ether derivative (**5b**) was inert under similar conditions in addition to the results described above, it was speculated that boroxane-type intermediates (**A**) were formed selectively in the case of α-pyrone derivatives,

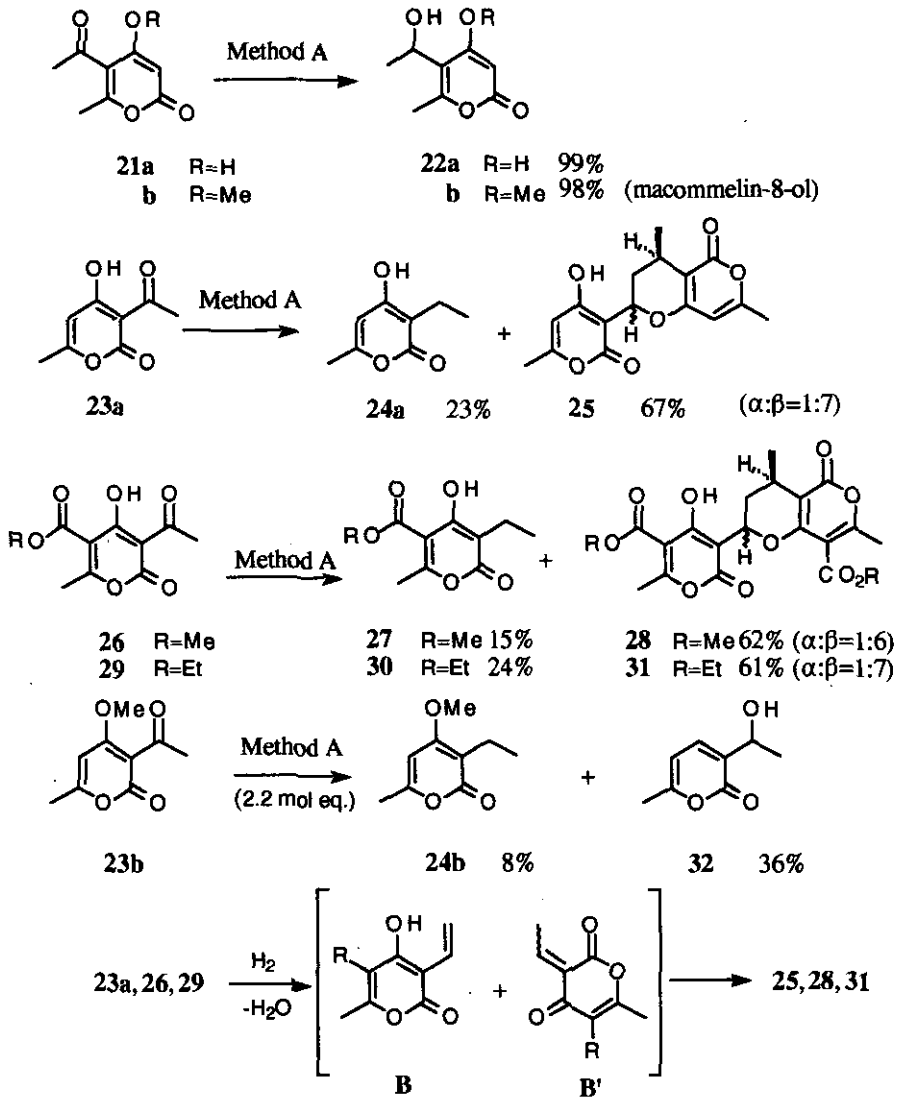
although a five membered intermediate was reported as a favorable structure in reduction of dimethyl (S)-(-)-malate.[9]



Scheme 3



Scheme 4



Scheme 5

The reduction of α-pyrone derivatives containing an acetyl group at the C-5 or C-3 position using BMS was examined (Scheme 5). The 5-acetyl-4-hydroxy-α-pyrone derivative (**21a**)[11] and the 5-acetyl-4-methoxy-α-pyrone derivative (**21b**) were converted quantitatively to their corresponding alcohols (**22a** and **22b**[12]) under similar to those conditions described for **5a**. On the other hand, dehydroacetic acid (**23a**) having an acetyl group at the C-3 position was transformed to the binary condensed pyrone (**25**) in 67% yield in addition to the 3-ethyl derivative (**24a**) in 23% yield. The 3-acetylpyrone derivatives (**26** and **29**)[13] were also transformed to the binary condensed pyrones (**28**[14] and **31**) in 62% and 61% yields respectively. Formation of **25**, **28** and **31** could be

explained as a result of hetero Diels-Alder reaction[15] between **B** and **B'** which were formed from the acetyl derivatives (**23a**, **26** and **29**) via an addition of BMS to the carbonyl group and elimination of $HOBH_2 \cdot SMe_2$. In the reduction of the 3-acetyl-4-methoxypyrone (**23b**), different results were obtained. Treatment of **23b** with 2.2 mol eq. of BMS gave the demethoxy derivative (**32**) in 36% yield together with a trace amount of the 3-ethyl derivative (**24b**). It is assumed that **32** was formed via a 1,4-addition of BMS followed by elimination of $MeOBH_2 \cdot SMe_2$ and subsequent reduction of the carbonyl group.

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10 BMS (10.0 M in BH_3, 330 µl, 3.3 mmol) was added dropwise to a stirred solution of **5a** (552 mg, 3 mmol) in dry THF (20 ml) at room temperature under nitrogen. After 1 h, dry MeOH (3 ml) was added dropwise to the mixture, and the resulting mixture was stirred for 1 h and concentrated under reduced pressure. The addition of MeOH followed by concentration was repeated three times. The residue was purified by silica gel column chromatography with $CHCl_3$-MeOH (10:1) as an eluent to give **12** (456 mg, 97%) as a colorless powder. mp: 156-158℃, Colorless prisms (MeOH-$CHCl_3$). Ms m/z: 156 (M^+), 138, 128,110. Ir (KBr): 3500-2300, 1700, 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : 2.38 (3H, s), 4.49 (2H, s), 5.45 (1H, s). ^{13}C-Nmr

(CD_3OD) : 17.2 (q), 54.9 (t), 89.8 (d, C-3), 113.0 (s, C-5), 164.3 (s, C-6), 167.2 (s, C-2), 172.5 (s, C-4).

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13 Compounds (**26** and **29**) were prepared respectively upon treatment of **5a** or **19** with Ac_2O-DMAP in refluxing toluene.

14 **28** (major isomer): Ms m/z: Calcd. for $C_{20}H_{20}O_{10}$: 420.1055. Found: 420.1029. Ir (KBr): 3200~2300, 1720, 1710, 1630 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : 1.31 (3H, d, J=6.8 Hz), 1.67 (1H, ddd, J=13.9, 2.4, 1.5 Hz), 2.30 (3H, s), 2.66 (3H, s), 2.70 (1H, ddd, J=13.9, 12.5, 5.4 Hz), 2.97 (1H, qdd, J=6.8, 5.4, 1.5 Hz), 3.78 (3H, s), 4.01 (3H, s), 5.50 (1H, dd, J=12.5, 2.4 Hz), 12.07 (1H, s). ^{13}C-Nmr ($CDCl_3$) : 18.7 (q), 19.8 (q), 22.5 (q), 24.4 (d), 30.2 (t), 52.6 (q), 53.3 (q), 68.5 (d), 99.6 (s), 101.7 (s), 103.3 (s), 108.5 (s), 159.6 (s), 161.6 (sx2), 162.6 (s), 164.3 (s), 166.6 (s), 169.3 (s), 173.2 (s).

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