

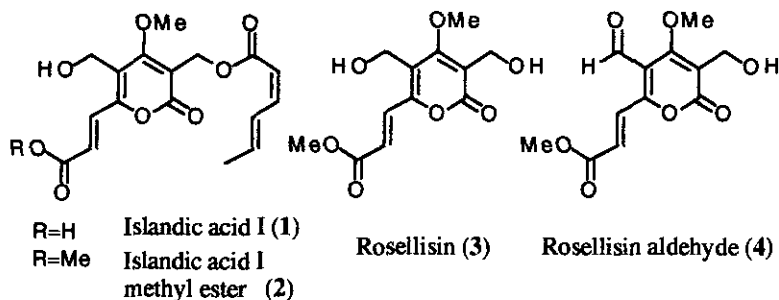
REDUCTION OF α -PYRONE DERIVATIVES WITH BORANE-METHYL SULFIDE COMPLEX

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Abstract ---- Selective reduction of the 5-carbomethoxy- and the 5-carbomethoxy-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.

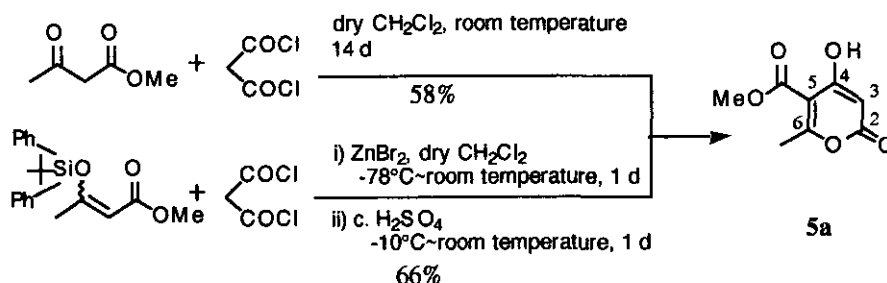
Islandic acid I (1)^{1,2} and rosellisin (3),^{3,4} are mycotoxins known to be cytotoxic and antibacterial respectively. Both have a 4-hydroxy-2*H*-pyran-2-one (α -pyrone) skeleton fully substituted with various oxygenated functional groups. In addition to mycotoxic activities, α -pyrone derivatives 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



Scheme 1

multiply oxygenated substituents have led to a new selective reduction of the 5-carbomethoxy- and the 5-carbomethoxy-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.

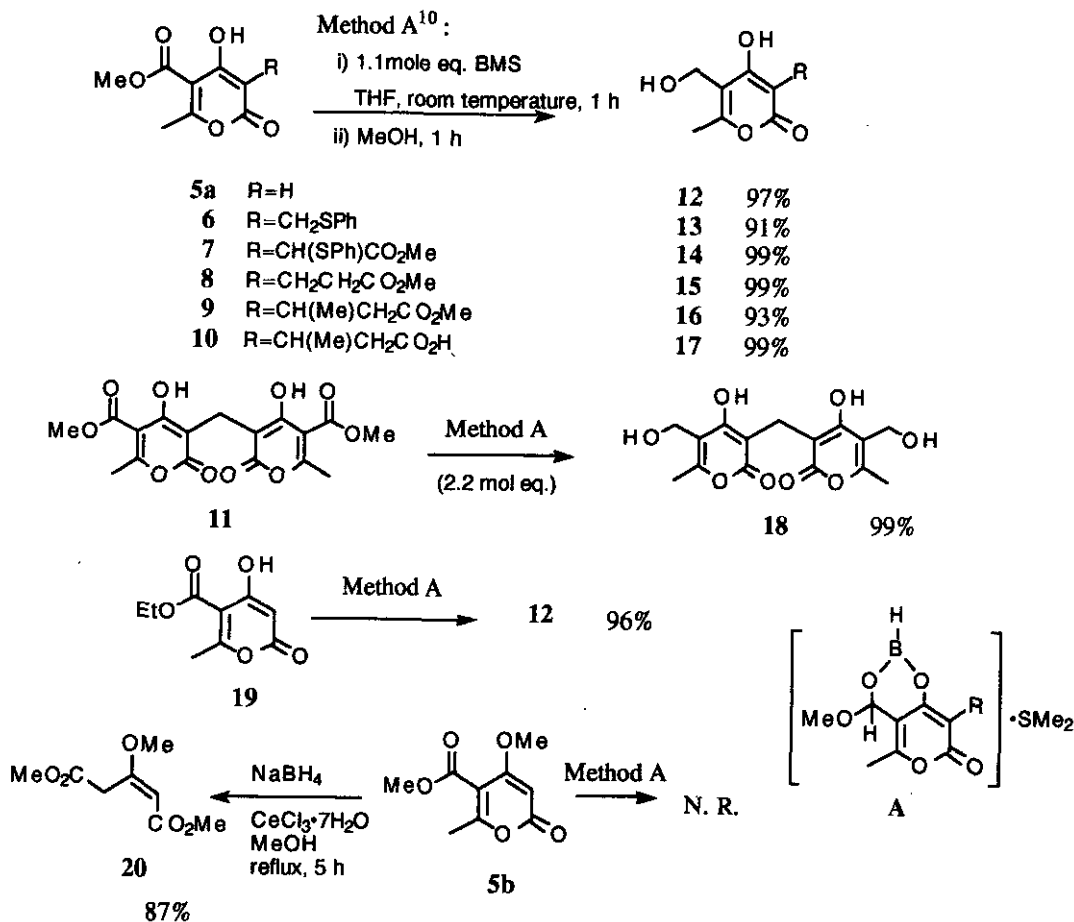
5-Carbomethoxy-4-hydroxy-6-methyl-2*H*-pyran-2-one (5a) was prepared by modification of Suzuki's procedure.⁷ Treatment of methyl acetoacetate with malonyl dichloride in dry CH_2Cl_2 at room temperature for 14 d afforded 5a in 58% yield. Compound (5a) was also prepared in 66% yield upon treatment of the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



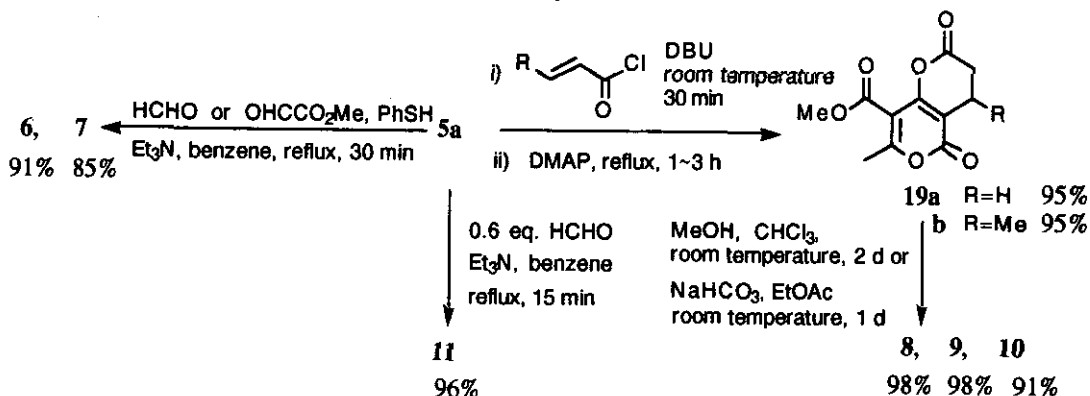
Scheme 2

Reduction of 5a or the 4-methoxy derivative (5b)⁸ with NaBH_4 or $\text{LiBH}(\text{Et})_3$ 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-carbomethoxy 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,

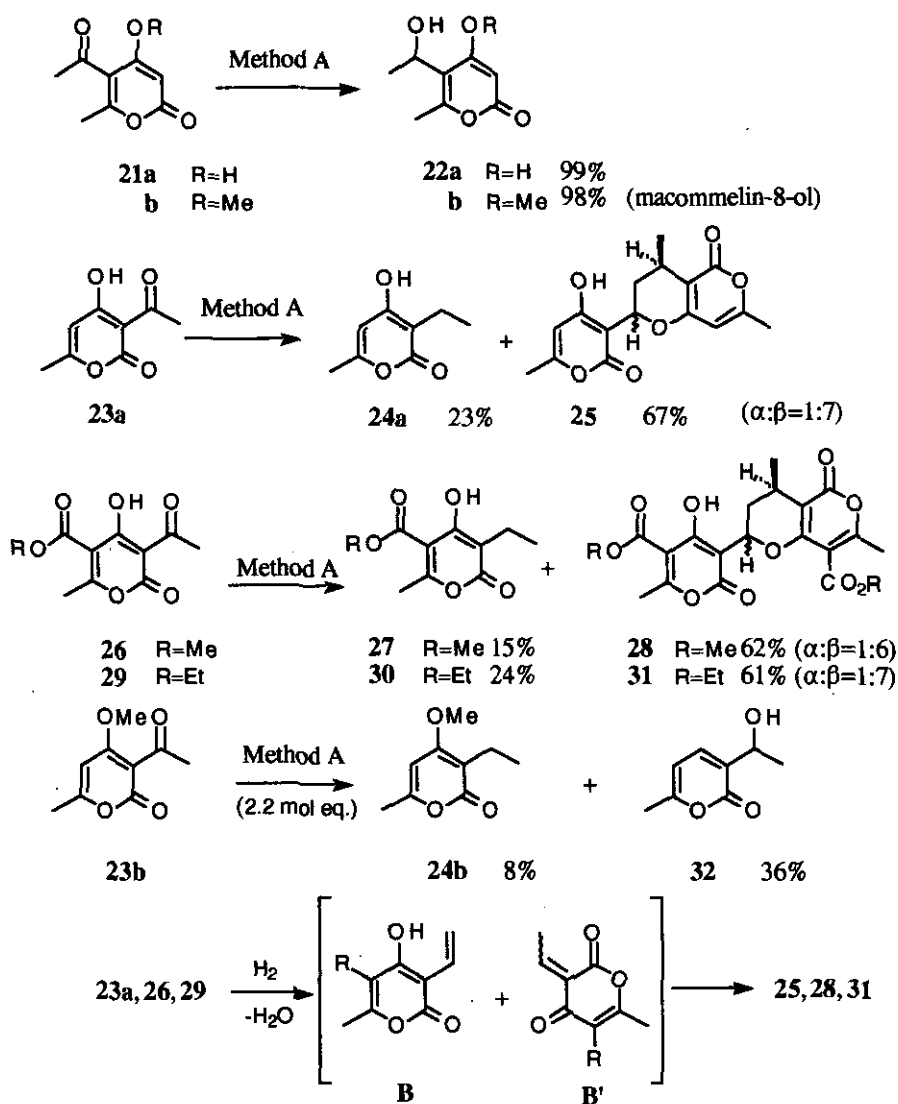
although a five membered intermediate was reported as a favorable structure in reduction of dimethyl (S)-(-)-malate.⁹



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 22b¹²) 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 (28¹⁴ and 31) in 62% and 61% yields respectively. Formation of 25, 28 and 31 could be

explained as a result of hetero Diels-Alder reaction¹⁵ 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 $\text{HOBH}_2\cdot\text{SMe}_2$. In the reduction of the 3-acetyl-4-methoxypyrene (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 $\text{MeOBH}_2\cdot\text{SMe}_2$ and subsequent reduction of the carbonyl group.

ACKNOWLEDGMENT

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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°C, Colorless prisms (MeOH- CHCl_3). Ms m/z: 156 (M^+), 138, 128, 110. Ir (KBr): 3500-2300, 1700, 1640 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): 2.38 (3H, s), 4.49 (2H, s), 5.45 (1H, s). $^{13}\text{C-Nmr}$

(CD₃OD) : 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 Ac₂O-DMAP in refluxing toluene.

14 28 (major isomer): Ms m/z: Calcd. for C₂₀H₂₀O₁₀: 420.1055. Found: 420.1029. Ir (KBr): 3200-2300, 1720, 1710, 1630 cm⁻¹. ¹H-Nmr (CDCl₃) : 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). ¹³C-Nmr (CDCl₃) : 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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