

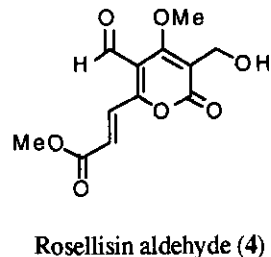
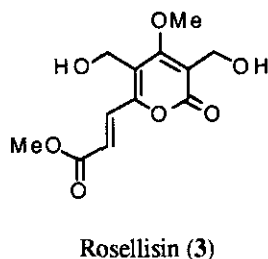
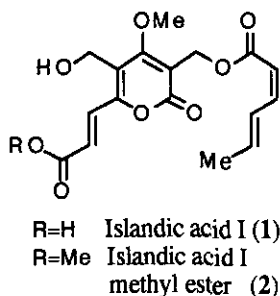
TOTAL SYNTHESIS OF ISLANDIC ACID I METHYL ESTER, ROSELLISIN
AND ROSELLISIN ALDEHYDE

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Abstract — Total synthesis of islandic acid I methyl ester (2), rosellisin (3) and rosellisin aldehyde (4) has been accomplished starting from 4-hydroxy-5-hydroxymethyl-6-methyl-2H-pyran-2-one (9a) via formylation of 9a with dichloromethyl methyl ether and titanium tetrachloride as a key step.

Several 4-hydroxy-2H-pyran-2-one (α -pyrone) derivatives being fully substituted with oxygen containing functional groups have been isolated from natural sources. Among them islandic acid I (1) has shown potent cytotoxic activity against Yoshida sarcoma^{1,2} and rosellisin (3) has been reported to show antibacterial activity.^{3,4} For the effective synthesis of these types of multiply substituted α -pyrone derivatives, it is necessary to establish selective introduction of oxygen containing functional groups to the 4-hydroxy-2H-pyran-2-one skeleton and selective conversion of these functional groups. We have already reported a facile synthesis of 5-carbomethoxy- and 5-carbomethoxy-4-hydroxy-6-methyl-2H-pyran-2-ones (5a, 6a) and a new mild and selective reduction of the ester group at the C-5 position with borane-methyl sulfide complex (BMS) to the 5-hydroxymethyl derivative (9a).⁵ In this paper, we report the regioselective introduction of a formyl group to the C-3 position of the 4-hydroxy-2H-pyran-2-one skeleton and the application of the synthetic methods leading to the total synthesis of the natural α -pyrone derivatives shown below.



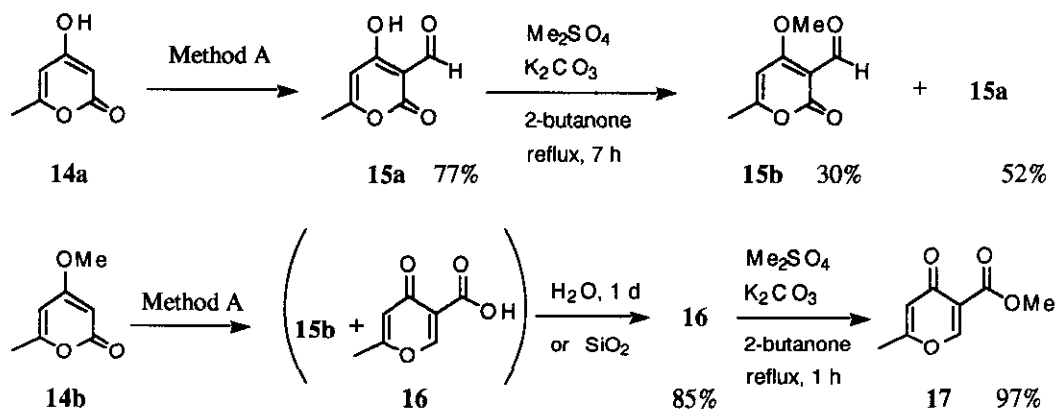
A variety of methods were attempted to achieve the introduction of a carbinol unit or an ester group to the C-3 position of α -pyrone derivatives. Treatment of **5a** with formaldehyde or alkoxymethyl chloride, either in the presence of Et_3N in refluxing benzene or in trifluoroacetic acid at room temperature, afforded bis (5-carbomethoxy-4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)methane.⁵ Although the ethyl- and the 2,2,2-trichloroethylcarbonates of **5a** were converted to the corresponding 3-carboalkoxy derivatives *via* Fries rearrangement using DMAP in toluene under reflux, the yields were low (~40%). Treatment of **5a** under Friedel-Crafts' conditions with ClCO_2Me and Lewis acid produced no reaction.⁶

Poulton has reported that treatment of 4-methoxy-6-methyl-2H-pyran-2-one (**14b**) with excess dichloromethyl methyl ether (MeOCHCl_2)- TiCl_4 produced the aldehyde (**15b**) in 37% yield.⁷ Additionally, he reported that similar treatment of the 4-hydroxy derivative (**14a**) did not produce the aldehyde (**15a**). When the procedure was applied to the 5-carbomethoxy-4-methoxy derivative (**5b**), **5b** was completely recovered. However, it was found that treatment of the 4-hydroxy derivative (**5a**) with 15 eq. of MeOCHCl_2 and 10 eq. of TiCl_4 in dry CH_2Cl_2 under a continuous nitrogen flow while raising the reaction temperature from -10°C to room temperature over a 1 d period (Method A) gave the 3-carboxaldehyde (**7**) [$^1\text{H-Nmr}$ (CDCl_3): 9.86 (1H, s). $^{13}\text{C-Nmr}$ (CDCl_3): 99.8 (C-3), 108.2 (C-5), 159.6 (C-2), 174.0 (C-6), 176.3 (C-4), 193.6 (CHO)] in 89% yield.

Table 1. Reaction of α -pyrone derivatives (**5-14**) under the conditions of Method A.

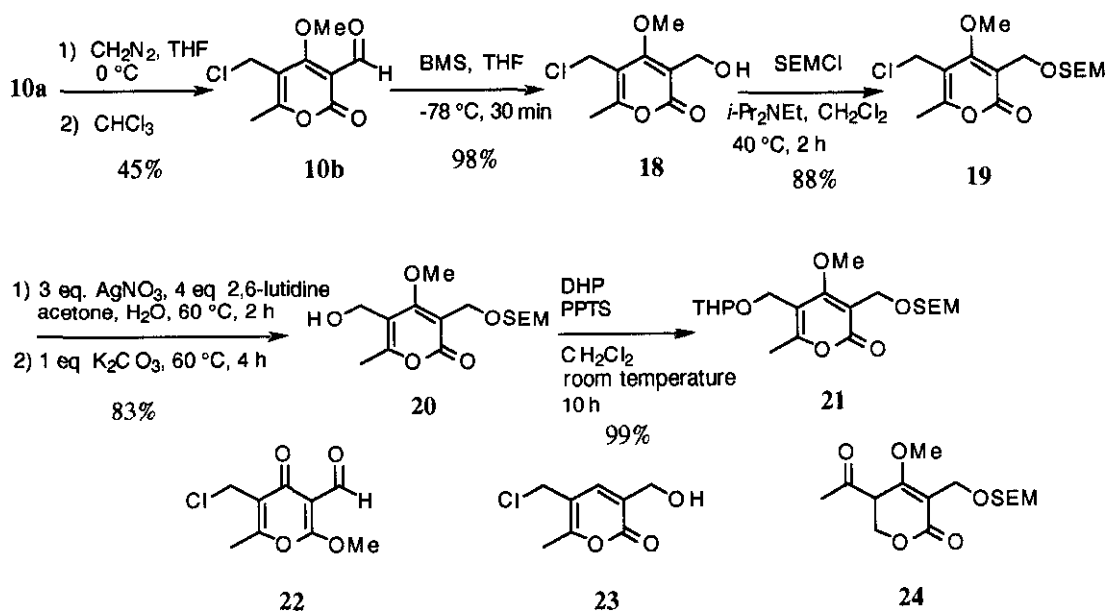
				Method A :							
				15 eq. MeOCHCl_2 10 eq. TiCl_4 dry CH_2Cl_2 -10°C ~room temperature 1 d, N_2							
Starting material				Product							
	R_1	R_2	R_3		R_4	R_5	R_6	Yield (%)			
5a	H	H	CO_2Me	7	CHO	H	CO_2Me	89			
5b	H	Me	CO_2Me	5b	H	Me	CO_2Me	-			
6a	H	H	CO_2Et	8	CHO	H	CO_2Et	88			
6b	H	Me	CO_2Et	6b	H	Me	CO_2Et	-			
9a	H	H	CH_2OH	10a	CHO	H	CH_2Cl	86			
9b	H	Me	CH_2OH	13	H	Me	CH_2Cl	99			
11	H	Me	CH_2OTBDMS	13	H	Me	CH_2Cl	99			
12	H	Me	$\text{CH}_2\text{OC}_6\text{H}_4\text{-}p\text{-NO}_2$	13	H	Me	CH_2Cl	99			
14a	H	H	H	15a	CHO	H	H	77			

The 5-carbethoxypyrrone (**6a**) was also converted to the aldehyde (**8**) in 88% yield under similar conditions, while the 4-methoxy derivative (**6b**) was unreacted. In the case of the 5-hydroxymethylpyrrone (**9a**), introduction of a formyl group was similarly achieved using Method A. However, formylation was accompanied by substitution of the hydroxyl group to the chlorine atom, and **10a** [^1H -nmr (CDCl_3): 4.47 (2H, s), 9.85 (1H, s). ^{13}C -Nmr (CDCl_3): 34.1 (CH_2), 193.8 (CHO)] was obtained in 86% yield. The 4-methoxy derivatives (**9b**, **11** and **12**) did not undergo formylation and only substitution was effected which afforded the 5-chloromethyl derivative (**13**). Moreover, it was found that when **14a** was treated under the conditions of Method A, the aldehyde (**15a**) was obtained in 77% yield. On the other hand, the 4-methoxypyrrone (**14b**) was converted to the mixture of **15b** and the rearranged acid (**16**) under the same conditions. Subsequent aqueous treatment of the reaction mixture for 1 d gave **16** as the sole product in 85% yield. Purification of the mixture by silica gel column chromatography also afforded **16** in 85% yield. The structure of **16** was confirmed by nmr spectral data and by conversion to the ester (**17**).

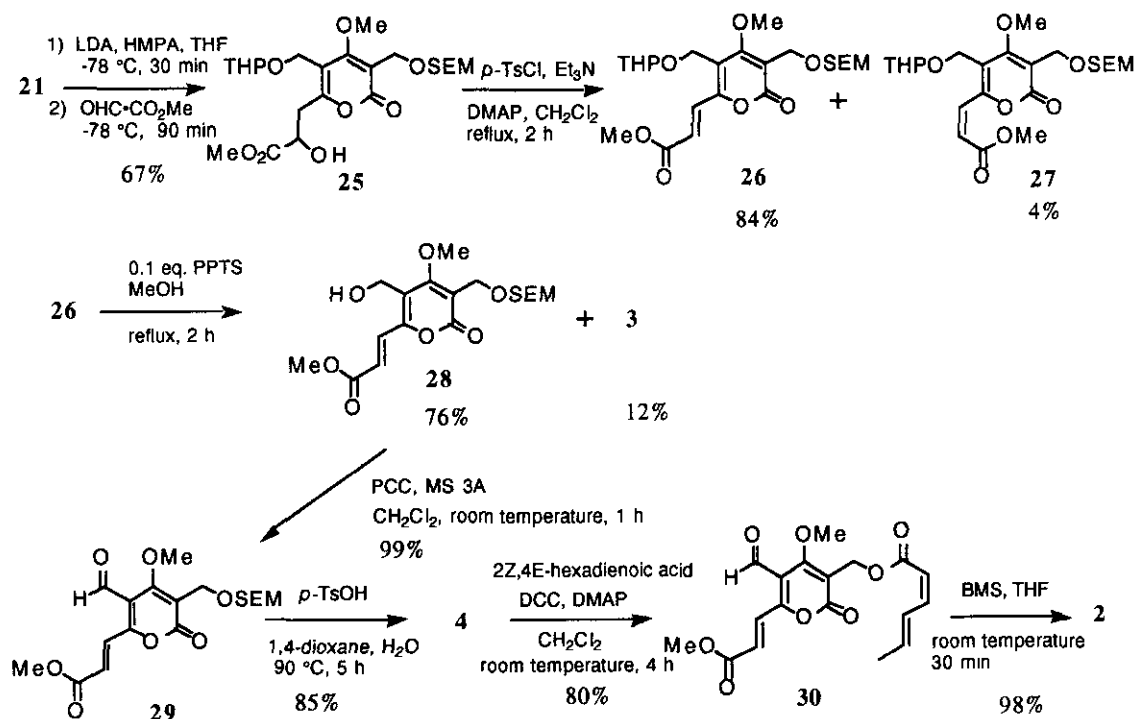


Thus the regioselective introduction of the formyl group to the C-3 and the chloromethyl group to the C-5 position have been demonstrated, which simplifies the independent derivatization on each position. With **10a** in hand, attention was focused on the total synthesis of the natural products shown before. Attempted methylation of **10a** with dimethyl sulfate-anhydrous K_2CO_3 ⁸ or MeI under various conditions, and attempted reduction of **10a** with BMS⁵ or NaBH_4 resulted in the formation of complex mixtures. When **10a** was treated with diazomethane, the 4-methoxy derivative (**10b**) was produced in 45% yield in addition to the 2-methoxy derivative (**22**) produced in 10% yield. Reduction of **10b** with BMS at room temperature afforded the alcohol (**18**) in 80% yield together with the demethoxy derivative (**23**) in 15% yield. The 1,4-addition of BMS⁵ was suppressed completely by lowering the reaction temperature to -78°C and **18** was obtained in 98% yield. After

protection of the hydroxyl group of **18** with SEMCl (88%), substitution of the chlorine atom by the hydroxyl group was examined. When **19** was heated with AgNO₃ in the presence of 2,6-lutidine in acetone-water at 60 °C for 2 h, a mixture of **20** and the rearranged product (**24**) was obtained. The reaction mixture was treated with K₂CO₃ and heated for additional 4 h without purification to give **20** in 83% yield.



The THP ether (**21**) produced under standard conditions was alkylated with LDA-anhydrous methyl glyoxylate⁹ according to the procedure of Schreiber¹⁰ to afford **25** in 67% yield. Successive dehydration of **25** with *p*-TsCl-Et₃N gave the *trans*-isomer (**26**) in 84% yield along with a trace amount of the *cis*-isomer (**27**) (4%). Selective removal of the SEM group of **26** using *n*-Bu₄NF was proved difficult due to the degradation of the pyrone ring. However, when deprotection of the THP group was attempted with 0.1 eq. of PPTS in MeOH under reflux for 2 h, the hydroxy derivative (**28**) was obtained in 76% yield in addition to the dihydroxy derivative (**3**) produced in 12% yield. The minor product (**3**) was consistent with rosellisin by ¹H-nmr and ¹³C-nmr spectral data. Rosellisin aldehyde (**4**) was synthesized from **28** in 84% overall yield via PCC oxidation followed by deprotection of the SEM group with *p*-TsOH in 1,4-dioxane-water at 90 °C. Finally, after esterification of **4** with 2Z, 4E-hexadienoic acid,^{11,12} reduction of **30** with BMS gave islandic acid I methyl ester (**2**) selectively in 98% yield. The total synthesis of **2** was attained in 14 steps starting from **5a** with an 8% overall yield.



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