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

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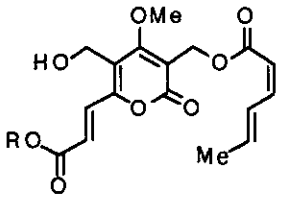
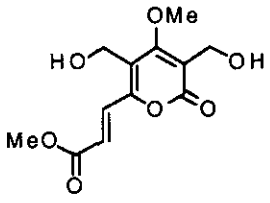
Abstract ---- Total synthesis of islandic acid I methyl ester (**2**), rosellisin (**3**) and rosellisin aldehyde (**4**) has been accomplished starting from 4-hydroxy-5-hydroxymethyl-6-methyl-2*H*-pyran-2-one (**9a**) *via* formylation of **9a** with dichloromethyl methyl ether and titanium tetrachloride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

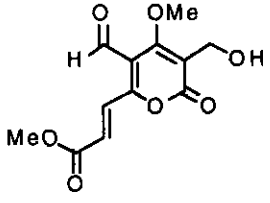
Several 4-hydroxy-2*H*-pyran-2-one (α-pyrone) derivatives being fully substituted with oxygen containing functional groups have been isolated from natural sources. Among them islandic acid I (**1**) has shown potent cytotoxic activity against Yoshida sarcoma[1,2] and rosellisin (**3**) has been reported 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-2*H*-pyran-2-one skelton and selective conversion of these functional groups. We have already reported a fasile synthesis of 5-carbomethoxy- and 5-carbethoxy-4-hydroxy-6-methyl-2*H*-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-2*H*-pyran-2-one skeleton and the application of the synthetic methods leading to the total synthesis of the natural α-pyrone derivatives shown below.



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



Rosellisin (**3**)

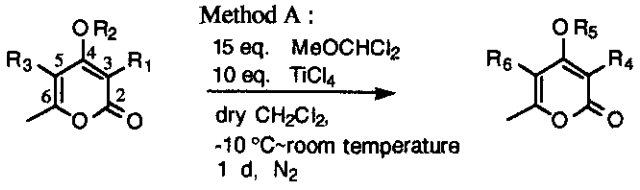


Rosellisin aldehyde (**4**)

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-2*H*-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]

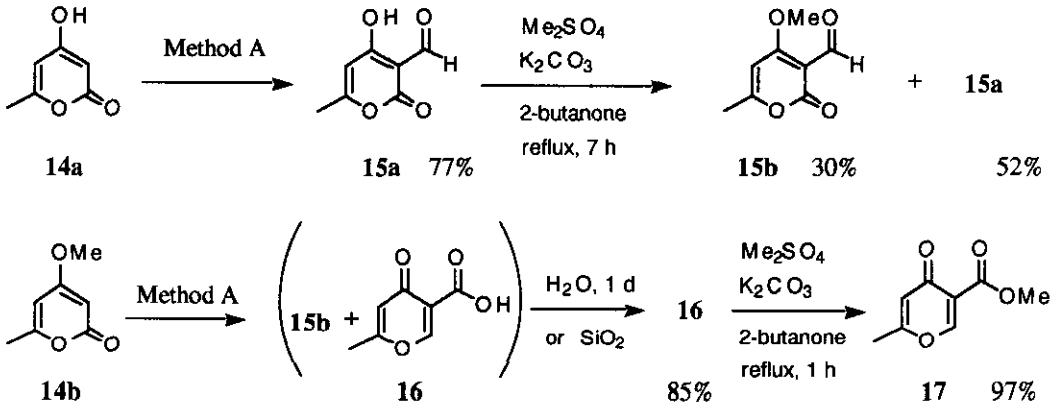
Poulton has reported that treatment of 4-methoxy-6-methyl-2*H*-pyran-2-one (**14b**) with excess dichloromethyl methyl ether ($MeOCHCl_2$)-$TiCl_4$ produced the aldehyde (**15b**) in 37% yield.[7] Additionally, he reported that similar treatment of the 4-hydroxy derivative (**14a**) did not produce the 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}H-Nmr ($CDCl_3$): 9.86 (1H, s). ^{13}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.



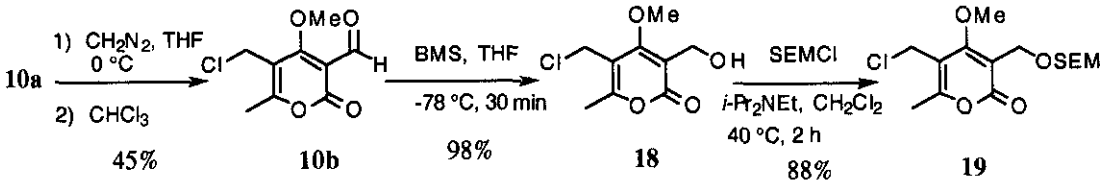
	Starting material				Product			
	R_1	R_2	R_3		R_4	R_5	R_6	Yield (%)
5a	H	H	CO_2Me	**7**	CHO	H	CO_2Me	89
5b	H	Me	CO_2Me	**5b**	H	Me	CO_2Me	-
6a	H	H	CO_2Et	**8**	CHO	H	CO_2Et	88
6b	H	Me	CO_2Et	**6b**	H	Me	CO_2Et	-
9a	H	H	CH_2OH	**10a**	CHO	H	CH_2Cl	86
9b	H	Me	CH_2OH	**13**	H	Me	CH_2Cl	99
11	H	Me	$CH_2OTBDMS$	**13**	H	Me	CH_2Cl	99
12	H	Me	$CH_2OC_6H_4$-*p*-NO_2	**13**	H	Me	CH_2Cl	99
14a	H	H	H	**15a**	CHO	H	H	77

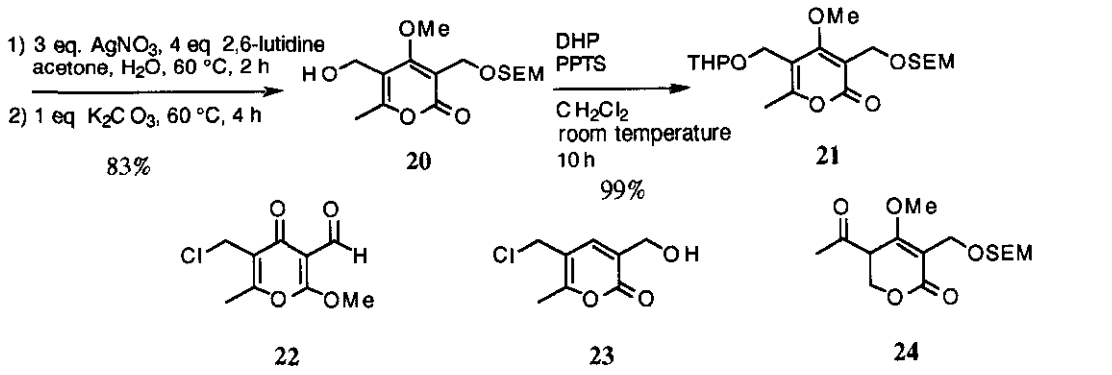
The 5-carbethoxypyrone (**6a**) was also converted to the aldehyde (**8**) in 88% yield under similar conditions, while the 4-methoxy derivative (**6b**) was unreacted. In the case of the 5-hydroxymethypyrone (**9a**), introduction of a formyl group was similarly achieved using Method A. However, formylation was accompanied by substitution of the hydroxyl group to the chlorine atom, and **10a** [^{1}H-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-methoxypyrone (**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**).



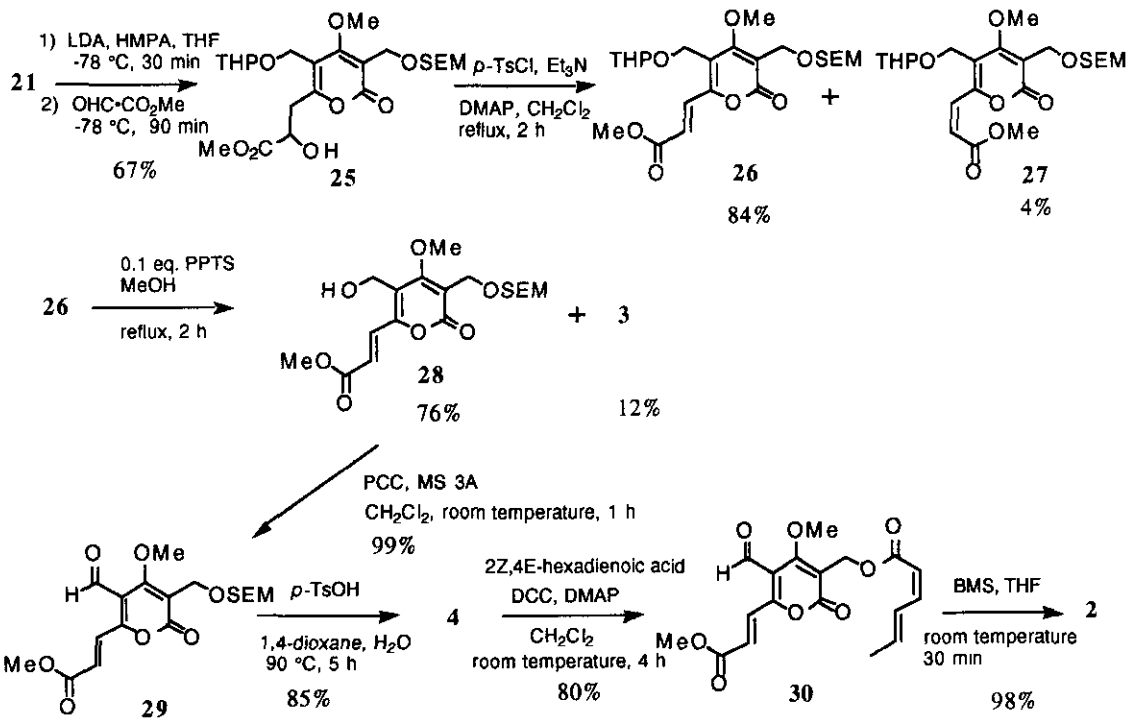
Thus the regioselective introduction of the formyl group to the C-3 and the chloromethyl group to the C-5 position have been demonstrated, which simplifies the independent derivatization on each position. With **10a** in hand, attention was focused on the total synthesis of the natural products shown before. Attempted methylation of **10a** with dimethyl sulfate-anhydrous K_2CO_3[8] or MeI under various conditions, and attempted reduction of **10a** with BMS[5] 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 BMS[5] 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 $AgNO_3$ 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 K_2CO_3 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 glyoxylate[9] according to the procedure of Schreiber[10] to afford **25** in 67% yield. Successive dehydration of **25** with *p*-TsCl-Et_3N 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*-Bu_4NF 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 ^{1}H-nmr and ^{13}C-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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