Synthesis of the bis-potassium salts of 5-hydroxy-3-oxopent-4-enoic acids and their use for the efficient preparation of 4-hydroxy-2*H*-pyran-2-ones and other heterocycles†

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5-Hydroxy-3-oxopent-4-enoic acid esters can be efficiently transformed into the stable bis-potassium salts of the corresponding 5-hydroxy-3-oxopent-4-enoic acids, from which the sensitive acids are released *in situ*, the latter being converted into substituted 4-hydroxy-2*H*-pyran-2-ones, pyrazoles and isoxazoles under mild conditions; the efficiency of this method is demonstrated by the first synthesis of two naturally occurring pyrones.

The reason why the 4-hydroxy-2*H*-pyran-2-one structural scaffold has generated a lot of interest in medicinal chemistry is that it is found in many biologically active natural products.[1] The pyripyropenes (Fig. 1), for example, exhibit a number of biological activities, among them the inhibition of the acyl-CoA: cholesterol-acyltransferase (ACAT).[2]

Numerous methods are known for synthesizing substituted 4-hydroxy-2*H*-pyran-2-ones.[3] One of them is based on 5-hydroxy-3-oxopent-4-enoic acid esters **1** (R^1 = Et), which can be cyclized to 4-hydroxy-2*H*-pyran-2-ones **4** under strongly basic or acidic conditions.[4] An alternative to this is thermal cyclization under reduced pressure.[5] A cyclization under milder conditions with reagents like Ac_2O, TFAA, CDI or mineral acids is only feasible if 5-hydroxy-3-oxopent-4-enoic acids **2** are used.[6]

Work towards the synthesis of pyripyropenes has shown that none of the known protocols produce satisfactory results, prompting the development of an efficient alternative route. Initial experiments revealed that substituted 4-hydroxy-2*H*-pyran-2-ones **4** can be synthesized most efficiently by lactonization of 5-hydroxy-3-oxopent-4-enoic acids **2**. However, as the free acids are quite unstable and tend to decompose, we decided to develop a procedure allowing the *in situ* preparation of 5-hydroxy-3-oxopent-4-enoic acids **2**. As far as we know, no method has so far been described for the *in situ* formation and cyclization of **2** to yield the corresponding 4-hydroxy-2*H*-pyran-2-ones **4**.

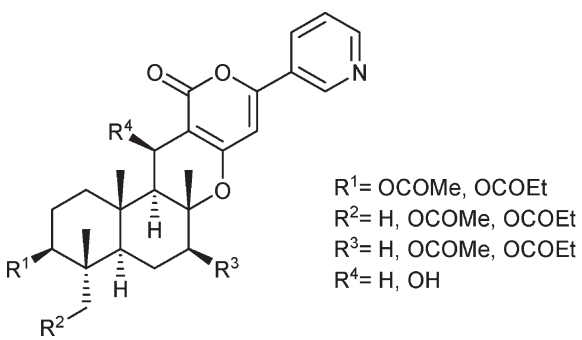
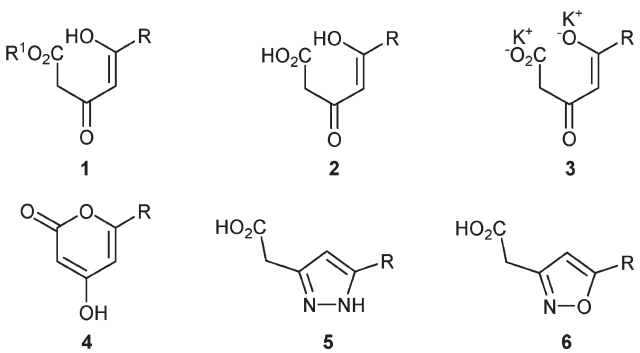


Fig. 1 Structures of Pyripyropenes A–R.



Here, we report the conversion of 5-hydroxy-3-oxopent-4-enoic acid esters **1** (R^1 = Et) into the stable bis-potassium salts **3** under mild reaction conditions. These salts are stable enough to be easily isolated, purified and stored. Acid treatment allows the *in situ*-generation of 5-hydroxy-3-oxopent-4-enoic acids **2** under mild conditions, which may subsequently be transformed into various heterocycles in high yields, including 4-hydroxy-2*H*-pyran-2-ones **4**, pyrazoles **5** and isoaxazoles **6**.

First of all, a method was developed for the synthesis of 6-substituted 4-hydroxy-2*H*-pyran-2-ones **4**. The 5-hydroxy-3-oxopent-4-enoic acid esters **1** (R^1 = Et) required can be produced in a pure form in yields of between 58 and 77% by reacting the dianion of ethyl acetoacetate **7** with *N*-acyl-2-methyl-aziridines **8** by selective γ-acylation (Scheme 1, Table 1).[6a] It was found that 5-hydroxy-3-oxopent-4-enoic acid esters **1** (R^1 = Et) can be easily reacted *via* hydrolysis with ethanolic KOH at rt for 30 min to give pure bis-potassium salts **3** in yields of between 81 and 98%.‡ Due to their low solubility in organic solvents, the stable salts are easy to isolate and purify. Treatment with acids, such as TFA, leads to the transformation of bis-potassium salts **3** into the free carboxylic acids **2** at only −20 or 0 °C. Thus, bis-potassium salts **3** provide a suitable storage option for the sensitive 5-hydroxy-3-oxopent-4-enoic acids **2**. If bis-potassium salts **3** are treated with TFA/TFAA between −20 and 0 °C, the formation of carboxylic acids **2** is followed by lactonization to give 6-substituted

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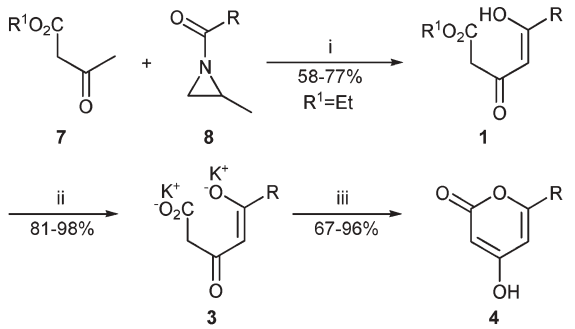


Reagents and conditions: (i) 2 eq. LDA, THF, -78°C→0°C; NH_4Cl (aq); (ii) KOH, EtOH, rt, 30 min; (iii) TFA, TFAA, -20°C→0°C, 2 h.

Scheme 1 Synthesis of 6-substituted 4-hydroxy-2*H*-pyran-2-ones **4**.

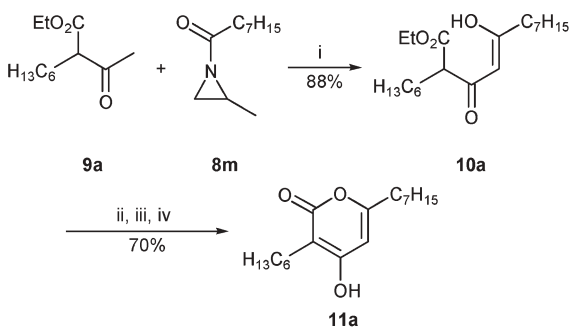
Table 1 Preparation of 6-substituted 4-hydroxy-2*H*-pyran-2-ones **4**

Entry	R	Yield **1** (%)		Yield **2** (%)		Yield **3** (%)		Yield **4** (%)	
1	Et	**1a**	74	**2a**	72	**3a**	81	**4a**	77
2	*n*-Pr	**1b**	61	**2b**	94	**3b**	81	**4b**	77
3	*i*-Pr	**1c**	64	**2c**	95	**3c**	88	**4c**	67
4	*t*-Bu	**1d**	72	**2d**	95	**3d**	92	**4d**	90
5	Ph	**1e**	77	**2e**	93	**3e**	86	**4e**	92
6	3,4-$(OMe)_2$Ph	**1f**	58	**2f**	95	**3f**	89	**4f**	84
7	3,4,5-$(OMe)_3$Ph	**1g**	63	**2g**	95	**3g**	92	**4g**	84
8	2-furanyl	**1h**	63	**2h**	89	**3h**	91	**4h**	78
9	3-furanyl	**1i**	62	**2i**	93	**3i**	87	**4i**	86
10	2-thiophenyl	**1j**	69	**2j**	95	**3j**	98	**4j**	88
11	3-pyridyl	**1k**	64	—	—	**3k**	86	**4k**	96
12	4-pyridyl	**1l**	72	—	—	**3l**	92	**4l**	95

4-hydroxy-2*H*-pyran-2-ones **4**, which may be isolated in an analytically pure form with yields of between 67 and 96%.§

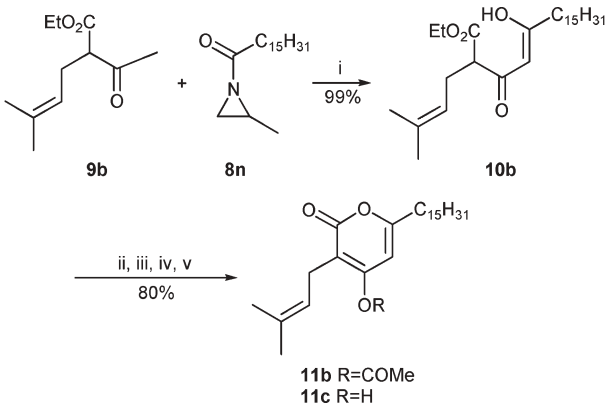
This method does not only allow the construction of 6-substituted 4-hydroxy-2*H*-pyran-2-ones, but may easily be extended to enable the synthesis of 3,6-disubstituted derivatives—an approach that is exemplarily illustrated by the first synthesis of two natural products.

Sch-419560 (**11a**) has recently been isolated from the fermentation culture of *Pseudomonas fluorescens* and exhibits remarkable antibiotic properties.[7] γ-Acylation of the dianion of **9a** with *N*-acyl-2-methyl-aziridine (**8m**) exclusively produced the carboxylic ester **10a** in 88% yield (Scheme 2). Hydrolysis with ethanolic KOH gave the respective bis-potassium salt, from which the free



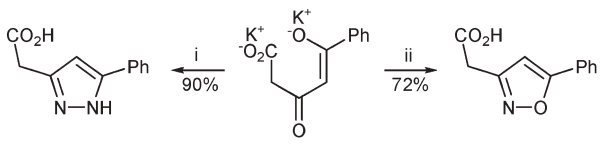
Reagents and conditions: (i) 2 eq. LDA, THF, -78°C→0°C; NH_4Cl (aq); (ii) KOH, EtOH, rt, 4 h; (iii) tartaric acid, 0°C, 10 min; (iv) TFA, TFAA, -20°C→0°C, 2 h.

Scheme 2 Synthesis of Sch-419560 (**11a**).



Reagents and conditions: (i) 2 eq. LDA, THF, -78°C→0°C, 3 h; NH_4Cl (aq); (ii) KOH, EtOH, rt, 3 h; (iii) tartaric acid, 0°C, 10 min; (iv) Ac_2O, pyridine, -20°C→0°C, 2 h; (v) K_2CO_3, MeOH, rt, 2 h.

Scheme 3 Synthesis of 3,3′-dimethylallyl conrauanalactone **11c**.



Reagents and conditions: (i) N_2H_4·HCl, H_2O, reflux, 2 h; (ii) NH_2OH·HCl, H_2O, 50°C, 2 h.

Scheme 4 Synthesis of pyrazole **12** and isoxazole **13**.

carboxylic acid was released using tartaric acid. After treatment with TFA/TFAA, the natural product **11a** was isolated in a yield of 70% for the last three steps.

Similarly, the synthesis of 3,3-dimethylallyl conrauanalactone derivative **11c**,[8] isolated from the bark of *Garcinia conrauana Engl.* (Guttiferae), was achieved for the first time (Scheme 3). In this case, the lactonisation of the carboxylic acid obtained from **10b** could best be achieved using Ac_2O/pyridine. The initially formed *O*-acetyl derivative **11b** was cleaved by K_2CO_3 in MeOH, and provided the natural product **11c** in 80% yield (starting from **10b**).

Further analyses proved that the bis-potassium salts **3** of 5-hydroxy-3-oxopent-4-enoic acids **2** are not only suitable as keto-carboxylic acids for use in the synthesis of 4-hydroxy-2*H*-pyran-2-ones **4**, but can also be applied as 1,3-diketones in the efficient construction of 5-phenylpyrazoles **12**[9] and 5-phenylisoxazoles **13**.[10] Thus, reaction of **3e** with hydrazine monohydrochloride produced pyrazole **12**, while reaction with hydroxylamine hydrochloride led to isoxazole **13** (Scheme 4).

Notes and references

‡ *General procedure for the preparation of the bis-potassium salts of 5-hydroxy-3-oxopent-4-enoic acids* ***3***. A solution of 5-hydroxy-3-oxopent-4-enoic acid ethyl ester **1** (R^1 = Et) (4.11 mmol) in 3 ml ethanol was added drop-wise to a solution of 1.30 g (22.62 mmol) KOH in 9 ml ethanol at rt. The reaction mixture was stirred for 30 min at rt, and the precipitation of a solid began after a few minutes. To complete the precipitation, the reaction mixture was stored at −20 °C for 12 h. The precipitate was filtered off and washed with approximately 5 ml cold (−10 °C) ethanol and 100 ml diethyl ether, and then dried.

§ *General procedure for the preparation of substituted 4-hydroxy-2H-pyran-2-ones* ***4*** *from the bis-potassium salts of 5-hydroxy-3-oxopent-4-enoic acids* ***3***.

305 μl (4.1 mmol) TFA was added to a vigorously stirred suspension of bis-potassium salt **3** (1.86 mmol) in 10 ml TFAA at −20 °C. After a few minutes, a solution was formed. The reaction mixture was allowed to warm to 0 °C and stirred for a further 2 h. The reaction was monitored by TLC, and the starting material had been completely consumed after 2 h. The excess TFA/TFAA were removed by distillation under normal pressure. The remaining traces of TFA could be removed azeotropically with toluene. The residue was poured into 50 ml of vigorously stirred ice-water, the pyrone precipitating immediately. To complete the precipitation, the crude product was stored at 4 °C for 12 h. The precipitate was filtered, washed with water and dried. For **4a–d**, the aqueous solution was saturated with sodium chloride and extracted four times with CH_2Cl_2. The combined organic phases were washed with water and dried over $MgSO_4$. The volatiles were removed *in vacuo* and the residue submitted to flash chromatography on silica gel.

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