An Efficient Stereoselective Total Synthesis of Synargentolide A and Its Epimer[1])

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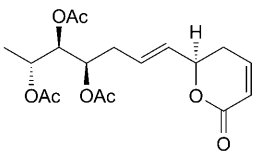
The stereoselective total synthesis of a naturally occurring α-pyrone (=2*H*-pyran-2-one) derivative, synargentolide A (**1**), and of its epimer **2** (with the originally proposed structure of synargentolide A) was efficiently accomplished involving D-tartaric acid as the starting material and an olefin cross-metathesis reaction as the key step.

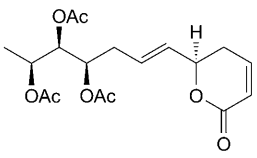
Introduction. – α-Pyrone (=2*H*-pyran-2-one) derivatives isolated from natural source exhibit various important biological activities such as cytotoxic, antitumor, antileukemic, and antiviral properties [1]. The chemistry and biology of these compounds have attracted much attention in recent years. Synargentolide A (**1**), a member of this group, was isolated from *Syncolostemon argentees* [2]. Compound **2** with the originally proposed structure of synargentolide A was synthesized by two research groups [3][4], and one of the groups revised the structure of synargentolide A to **1** by synthesizing both **1** and **2** [4].

In connection with our work on the synthesis of naturally occurring α-pyrones [5], we synthesized synargentolide A (**1**; revised structure) and its epimer **2** (originally proposed structure of synargentolide A) through an alternative efficient approach which we would like to report here.



1

revised structure of synargentolide A



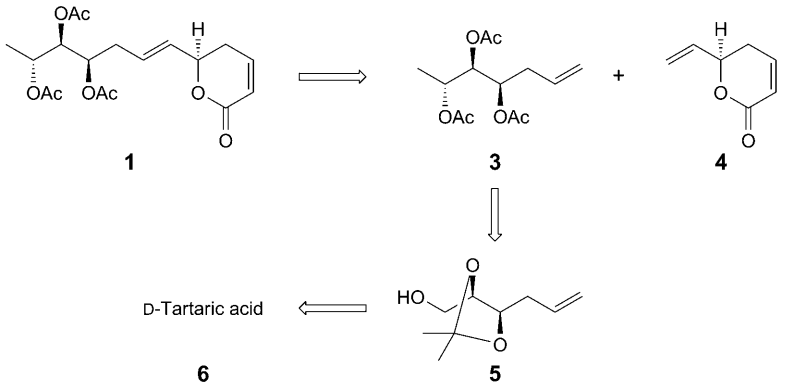
2

originally proposed structure of synargentolide A

Results and Discussion. – The *retro*-synthetic analysis (*Scheme 1*) indicates that synargentolide A (**1**) can be prepared from the olefins **3** and **4** by a cross-metathesis reaction. Compound **3** can be obtained from the olefin **5** which in turn can be prepared from D-tartaric acid (**6**).

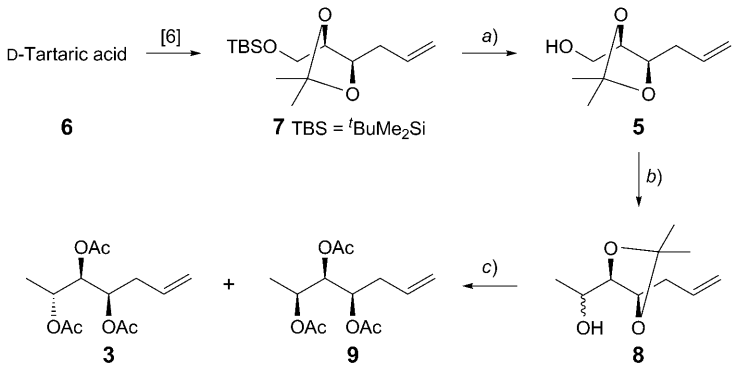
[1]) Part 36 in the series 'Synthetic Studies on Natural Products'.

Scheme 1



The synthesis of synargentolide A (**1**) was initiated by converting D-tartaric acid (**6**) into olefin **7** following a reported method [6] (*Scheme 2*). Deprotection of the TBS (^{t}BuMe$_2$Si) ether of this olefin by treatment with Bu_4NF in THF afforded the primary alcohol **5** in high yield. Compound **5** [7] underwent *Swern* oxidation to form the corresponding aldehyde which was subsequently treated with MeMgBr in dry ether to produce the secondary alcohol **8** [8]. The diastereoisomers were not separated at this stage, but this isomer mixture was treated with methanolic HCl solution (for the deprotection of the acetonide group) and then acetylated with Ac_2O in the presence of Et_3N and *N*,*N*-dimethylpyridin-4-amine (DMAP). The two triacetates **3** (major, 72%) and **9** (minor, 28%) were separated and characterized by their optical rotation and spectral data (^{1}H- and ^{13}C-NMR and MS). The physical and spectral properties of these compounds were identical to those reported earlier [4].

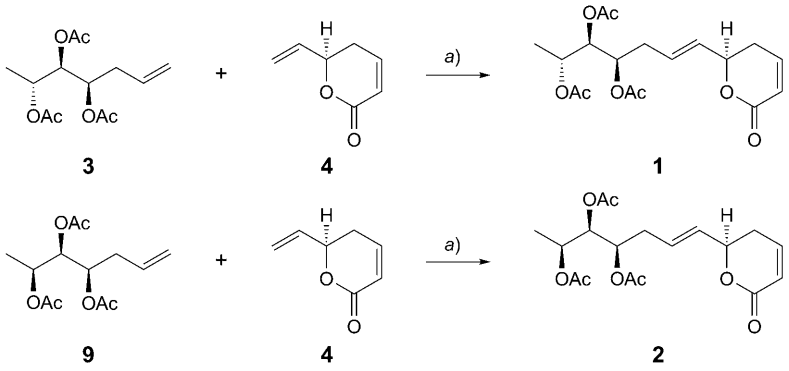
Scheme 2



a) Bu_4NF, THF, 0° to r.t., 3 h; 95%. *b*) 1. $(COCl)_2$, DMSO, Et_3N, anh. CH_2Cl_2, 1 h; 89%; 2. MeMgBr, anh. Et_2O, −50°, 2 h; 62%. *c*) 1. MeOH, 2N HCl, r.t., 1 h; 2. Ac_2O, Et_3N, DMAP, anh. CH_2Cl_2, 0° to r.t., 1 h; 92% (2 steps).

Finally, the olefin cross-metathesis reaction of **3** and **9** with the known vinyl-substituted lactone **4** [5c] in the presence of *Grubbs*' second-generation catalyst yielded the naturally occurring synargentolide A (**1**) and its epimer **2**, respectively (*Scheme 3*). The physical and spectral properties of these compounds were identical to those reported earlier [2][4].

Scheme 3



a) *Grubbs*' 2nd-generation catalyst, refluxing anh. CH_2Cl_2, 2 h; 66% for **1** and 67% for **2**.

In conclusion, we have demonstrated a straightforward efficient stereoselective synthesis of synargentolide A (**1**) and its epimer **2** (with the originally proposed structure of synargentolide A) starting from readily available D-tartaric acid by means of an olefin cross-metathesis reaction as the key step.

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Experimental Part

General. Commercial reagents were used without further purification. All solvents were purified by standard techniques. Column chromatographic (CC): silica gel (SiO_2; 60–120 mesh). Optical rotation: *Jasco-Dip-360* digital polarimeter. NMR Spectra: *Varian-Gemini-200*, *Bruker-300*, or *Varian-Unity-400* NMR spectrometers; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Finnigan-MAT-1020B* or *Micromass-VG-70-70 H* spectrometers; at 70 eV, direct inlet system.

*(4*R,5R*)-2,2-Dimethyl-5-(prop-2-en-1-yl)-1,3-dioxolan-4-methanol* (**5**). A stirred soln. of **7** (3 g, 10.49 mmol) in anh. THF (40 ml) was treated with 1M Bu_4NF in THF (15.735 mmol) for 3 h at r.t. The mixture was extracted with AcOEt (3 × 25 ml), the combined org. layer washed with brine (2 × 10 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (SiO_2, AcOEt/hexane 1:45): **5** (95%). Light yellow syrup.

*(4*R,5R*)-α,2,2-Trimethyl-5-(prop-2-en-1-yl)-1,3-dioxolan-4-methanol* (**8**). To a stirred soln. of $(COCl)_2$ (13.08 mmol, 1.2 ml) in CH_2Cl_2 (40 ml) at −78°, DMSO (26.16 mmol, 1.83 ml) was added followed by addition of **5** (8.72 mmol, 1.5 g) in CH_2Cl_2 (45 ml). The mixture was stirred for 1 h at −78°, then quenched with Et_3N (26.2 mmol, 3.7 ml), and diluted with CH_2Cl_2 (25 ml). The combined org. layer was washed with brine (1 × 15 ml), dried (Na_2SO_4), and concentrated, and the residue passed through a pad of SiO_2 to give the corresponding aldehyde (89%), which was used as such for further reaction. To a stirred soln. of the aldehyde (7.1 mmol, 1.32 g) in anh. Et_2O (30 ml) at −50°, a soln. of MeMgBr (9.1 mmol) was added dropwise over 10 min. Then the mixture was stirred for 2 h, quenched with sat. aq. NH_4Cl soln. (20 ml), and extracted with AcOEt (3 × 10 ml). The combined org. layer was washed with

brine, dried (Na_2SO_4), and concentrated, and the residue was purified by CC (SiO_2, AcOEt/hexane 1:4): **8** (62%).

*(2*R*,3*R*,4*R*)- and (2*S*,3*R*,4*R*)-Hept-6-ene-2,3,4-triyl Triacetate* (= *(2*R*,3*R*,4*R*)*- and *(2*S*,3*R*,4*R*)-Hept-6-ene-2,3,4-triol Triacetate*; **3** and **9**, resp.). To a soln. of **8** (4.57 mmol, 0.85 g) in MeOH (20 ml), 2N HCl (10 ml) was added dropwise over 5 min. Then the mixture was stirred for 1 h, quenched with sat. aq. $NaHCO_3$ soln., and extracted with AcOEt (4 × 10 ml). The combined org. layer was washed with brine, dried (Na_2SO_4), and concentrated, and the residue passed through a pad of SiO_2 to give the triols. To a stirred soln. of the triols in anh. CH_2Cl_2 at 0°, Et_3N and a cat. amount of DMAP were added followed by addition of Ac_2O, After completion of the reaction (TLC monitoring), the mixture was extracted with AcOEt (3 × 10 ml), the combined org. layer washed with brine, dried (Na_2SO_4), and concentrated, and the residue separated by CC (SiO_2, AcOEt/hexane 1:4): **3** and **9** (92% overall yield of two steps).

Synargentolide A (= *(2*R*,3*R*,4*R*,6*E*)-7-[(2*R*)-3,6-Dihydro-6-oxo-2*H*-pyran-2-yl]hept-6-ene-1,3,4-triyl Triacetate* (= *(6*R*)-5,6-Dihydro-6-[(1*E*,4*R*,5*R*,6*R*)-4,5,6-tris(acetyloxy)hept-1-en-1-yl]-2*H*-pyran-2-one*; **1**). Through a soln. of **3** (0.3 g, 1.1 mmol) and **5** (0.027 g, 0.22 mmol) in dry CH_2Cl_2 (10 ml) was first bubbled an N_2 flow, after which *Grubbs*' second-generation catalyst (0.063 g, 0.07 mmol) was added at once. The resulting mixture was heated under N_2 at 50° for 4 h. After cooling, the solvent was evaporated and the residue purified by CC (AcOEt/hexane 1:1): pure **1** (66%). Reddish liquid. Spectral properties: similar to those reported earlier [4].

*(2*S*,3*R*,4*R*,6*E*)-7-[(2*R*)-3,6-Dihydro-6-oxo-2*H*-pyran-2-yl]hept-6-ene-1,3,4-triyl Triacetate* (= *(6*R*)-5,6-Dihydro-6-[(1*E*,4*R*,5*R*,6*S*)-4,5,6-tris(acetyloxy)hept-1-en-1-yl]-2*H*-pyran-2-one*; **2**). As described for **1**, with **9** (0.2 g, 0.73 mmol), **5** (0.018 g, 0.15 mmol), and *Grubbs*' second-generation catalyst (0.040 g, 0.07 mmol): **2** (67%). Reddish liquid. Spectral properties: similar to those reported earlier [2][4].

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