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SYNTHESIS OF ARTEKEISKEANIN A: A NEW COUMARIN MONOTERPENE ETHER FROM *ARTEMISIA KEISKEANA*

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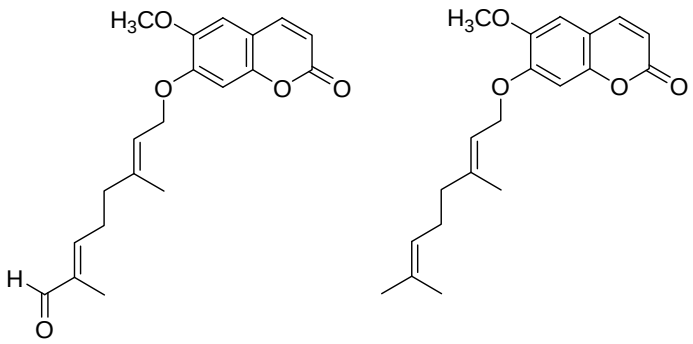
Abstract – The first total syntheses of artekeiskeanin A, a natural coumarin monoterpene ether from *Artemisia keiskeana*, and 7-geranyloxy-6-methoxycoumarin, a coumarin monoterpene ether with antifungal and antitumor properties, are reported. Key step in the synthesis of artekeiskeanin A is the stereoselective oxidation of the geranyloxy side chain of 7-geranyloxy-6-methoxycoumarin under microwave irradiation.

Artekeiskeanin A (**1**) has been isolated from the aerial parts of *Artemisia keiskeana* and its structure was determined based on NMR spectroscopy, including nOe difference experiments, ^{1}H-^{1}H homonuclear COSY and ^{1}H-^{13}C long range correlation spectra.[1] *Artemisia keiskeana* is a perennial herb widely distributed in mountainous areas of Korea. Parts of the plant have been used in traditional Chinese medicine for the treatment of gynaecopathy, amenorrhea, bruise and rheumatic disease.[1]

7-Geranyloxy-6-methoxycoumarin (**2**) is a widely spread natural compound. It was first discovered in *Thapsia garganica*.[2] Later, 7-geranyloxy-6-methoxycoumarin (**2**) was also found in, among others, *Haplophyllum pedicellatum*,[3] *Feronia elephantum*,[4] *Haplophyllum hispanicum*,[5] *Poncirus trifoliata*,[6] *Gymnophyton isatidicarpum*,[7] *Conyza obscura*,[8] *Thapsia villosa*,[9] *Thapsia gymnesica*,[10] *Pentacalia corymbosa*,[11] *Zanthoxylum schinifolium*,[12] *Ferula ferulago*,[13] *Murraya siamensis*.[14] It has been shown to exert antifungal[11] and antitumor promoting effect.[14]

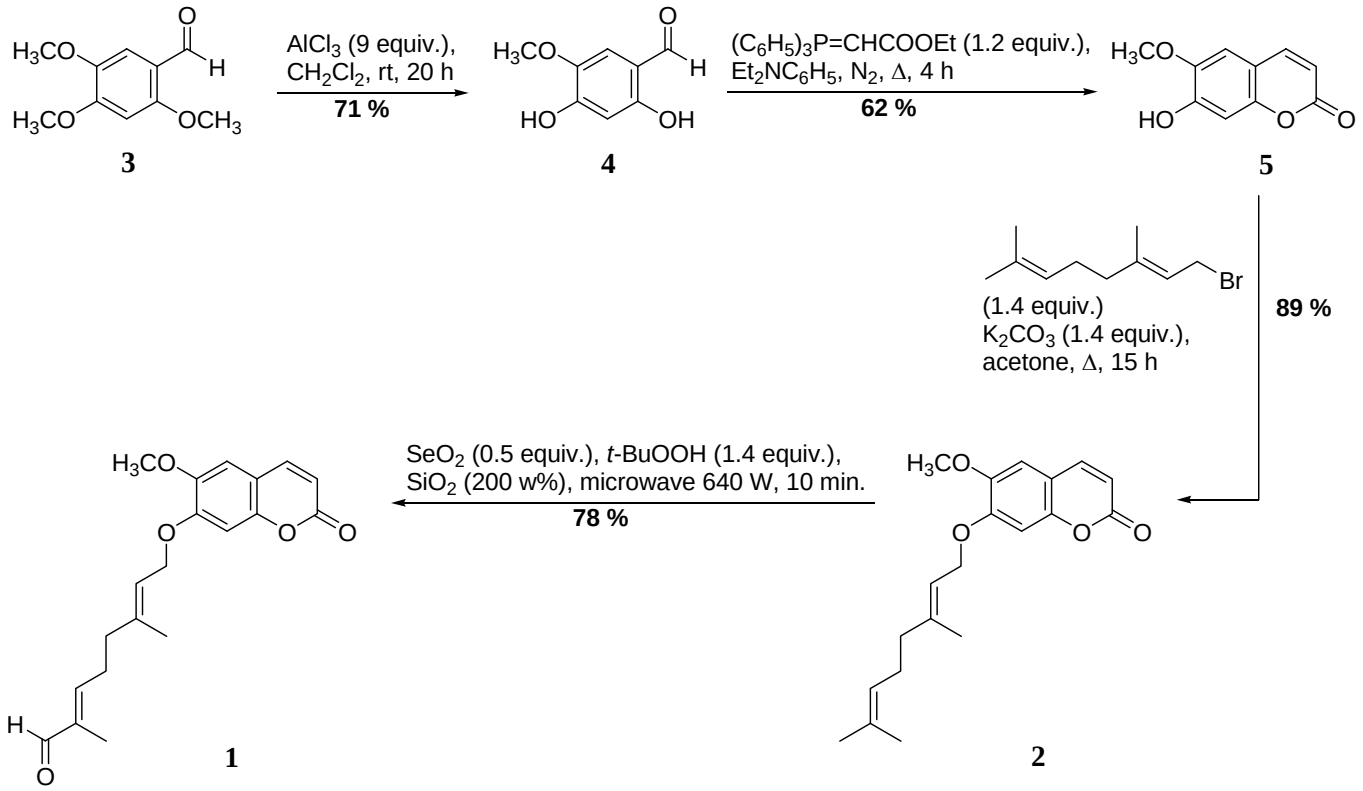
This Paper is dedicated to Professor Dr. Ekkehard Winterfesldt on the occasion of his 75th birthday.



1 (artekeiskeanin A) **2**

Figure 1

In order to unequivocally confirm its structure and to make the compound available for future bioactivity studies it was decided to develop a total synthesis of artekeiskeanin A (**1**) starting from a readily available substrate. Accordingly, artekeiskeanin A (**1**) was now synthesized in four steps from the commercially available 2,4,5-trimethoxybenzaldehyde (**3**). This synthesis also provides easy access to the biologically active coumarin 7-geranyloxy-6-methoxycoumarin (**2**). To our knowledge this is the first report on the total syntheses of artekeiskeanin A (**1**) and 7-geranyloxy-6-methoxycoumarin (**2**).



Scheme 1

In a previous report we described the synthesis of scopoletin (**5**) in two steps from commercially available 2,4,5-trimethoxybenzaldehyde (**3**).[15] This method consisted of selective cleavage of two methoxy groups

by aluminium(III) chloride leading to 2,4-dihydroxy-5-methoxybenzaldehyde (**4**). Subsequently, scopoletin (**5**) was obtained by Wittig reaction of 2,4-dihydroxy-5-methoxybenzaldehyde (**4**) with methyl (triphenylphosphoranylidene)acetate in *N,N*-diethylaniline. Scopoletin (**5**) was treated with geranyl bromide (1.4 equiv.) and potassium carbonate in refluxing acetone to afford 7-geranyloxy-6-methoxycoumarin (**2**) in 89 % yield.[16]

The geranyloxy side chain of coumarin (**2**) could be selectively oxidized by SeO_2 and *t*-BuOOH, absorbed on silica gel, under microwave conditions and gave artekeiskeanin A in 78 % yield.[17] This method has been used for the oxidation of simple monoterpenes and has been shown to afford only the corresponding *trans*-α,β-unsaturated aldehydes.[18] Our synthesis shows that the method is suitable for more complex substrates like coumarin monoterpene ethers. The NMR spectroscopic data of the synthesized compound were in full accordance with the data reported for the natural compound isolated from *Artimesia keiskeana* and therefore confirmed the structure.[1]

ACKNOWLEDGEMENTS

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16. Experimental procedure: To a solution of scopoletin (**5**)[15] (200 mg, 1.04 mmol) in acetone (20 mL), geranyl bromide (320 mg, 1.47 mmol) and K_2CO_3 (200 mg, 1.45 mmol) were added. The mixture was stirred at reflux temperature for 15 h. After evaporation of the solvent, the residue was dissolved in AcOEt (40 mL) and washed with saturated aqueous $NaHCO_3$, H_2O and brine, then dried on $MgSO_4$. Evaporation of the solvent and the excess of geranyl bromide *in vacuo*, followed by recrystallisation from MeOH, gave pure coumarin (**2**) (305 mg, 89 %) as yellow crystals (MeOH). Mp (MeOH) 80.3 °C (lit.,[2] mp 84-84.5 °C). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.60 and 1.65 (each 3H, each s, $(C\underline{H}_3)_2C$=), 1.77 (3H, s, $C\underline{H}_3C$=), 2.09-2.13 (4H, m, =$CHC\underline{H}_2C\underline{H}_2C$=), 3.91 (3H, s, $OC\underline{H}_3$), 4.69 (2H, d, *J*= 6.6 Hz, $C\underline{H}_2O$), 5.07-5,08 (1H, m, $(CH_3)_2C$=$C\underline{H}CH_2$), 5.46-5.48 (1H, m, C=$C\underline{H}CH_2O$), 6.27 (1H, d, *J*= 9.6 Hz, 3-C<u>H</u>), 6.83 (1H, s, 8-C<u>H</u>), 6.85 (1H, s, 5-C<u>H</u>), 7.61 (1H, d, *J*= 9.6 Hz, 4-CH).
17. Experimental procedure: 7-Geranyloxy-6-methoxyscopoletin (**2**) (50 mg, 0.15 mmol), SeO_2 (8 mg, 0.075 mmol) and *t*-BuOOH (25 mg, 0.21 mmol) were dissolved in CH_2Cl_2 (20 mL). Silica gel (250 mg) was added to the mixture. The solvent was removed by evaporation *in vacuo* in order to adsorb the reagents on silica gel and the mixture was exposed to microwave irradiation (640 W) for 10 min. CH_2Cl_2 (3x20 mL) was added and the mixture was filtered. The filtrate was then washed with KOH (10 %) and brine and then dried over $MgSO_4$. The solvent was evaporated in vacuo to give 40 mg of artekeiskeanin A (**1**) in 78 % yield. Mp 100.3 °C (MeOH)(lit.,[1] mp 102 °C). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.73 (3H, s, $(C\underline{H}_3)(CHO)C$=) and 1.81 (3H, s, $CH_2CH_2C(C\underline{H}_3)$), 2.28 (2H, t, *J*= 7.6 Hz, $CH_2C\underline{H}_2C(CH_3)$), 2.52 (2H, q, 7.6 Hz, =$CHC\underline{H}_2CH_2C(CH_3)$), 3.91 (3H, s, $OC\underline{H}_3$), 4.71 (2H, d, *J*= 6.3 Hz, $C\underline{H}_2O$), 5.53 (1H, t, *J*= 6.3 Hz, =$C\underline{H}CH_2O$), 6.28 (1H, d, *J*= 9.6 Hz, 3-C<u>H</u>), 6.42 (1H, m, $(CH_3)(CHO)C$=$C\underline{H}CH_2$), 6.80 (1H, s, 8-CH), 6.86 (1H, s, 5-CH), 7.62 (1H, d, *J*= 9.6 Hz, 4-C<u>H</u>), 9.32 (1H, s, C<u>H</u>O).
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