Note

An Efficient Synthesis of (±)-Hasakol, a Bioactive Coumarin from *Citrus hassaku*

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Hasakol, a new antispasmodic coumarin isolated from *Citrus hassaku*, was synthesized from 7-geranylxycooumarin by an improved method. This synthesis involves only 3 steps and results in a yield 27% based on the starting material.

Key words: hasakol; synthesis; coumarin; antispasmodic activity; *Citrus hassaku*

It is well known that many citrus plants contain various kinds of bioactive coumarins. In East Asia, some of these plants are used as a constituent of herbal medicines. The coumarin constituents of *Citrus hassaku* Hort ex Tanaka, a species cultivated in certain areas of Japan, has been investigated by several groups as a source of bioactive coumarin.11 We have identified thirteen coumarins in an oil fraction of the juice from *Citrus hassaku*12,31 and examined their antispasmodic activity. Hasakol (1), one of the newly isolated coumarins, was determined to be 6-linalyl-7-hydroxyxoumarin. Although hasakol is a minor component of hassaku, it is the most active of the thirteen coumarins that have been isolated.31 We have been investigating the synthesis of hasakol and related analogs and previously reported a synthetic route to hasakol via 6 steps in a preliminary communication.39 We have now improved the synthetic method and report here a practical 3-step synthesis of hasakol with the experimental details.

Hasakol is a coumarin linallylated at the 6-position. A reasonable approach to hasakol should be a Claisen rearrangement reaction of 7-O-geranylated umbelliferone (2). However, the rearrangement of the geranyl group of 2 occurs only at the 8-position44; this regioselectivity may be explained by the aromaticity of the corresponding intermediate lactone moiety.5,6 To alter the regioselectivity in order to favor a reaction at the 6-position, the lactone ring of the coumarin must be opened. Therefore, 7-geranylxycooumarin (2) was treated with NaOCH₃ in CH₂OH under reflux to give 2-hydroxycinnamate 3 in a 79% yield. With the previous method, we chose a benzyl group to protect the resulting 2-hydroxyl group44; however, deprotection of the benzyl group required severe conditions, making this impractical. We now report that the 2'-hydroxyl group of 3 is protected as an acetyl ester that can be easily hydrolyzed under mild alkaline conditions. Claisen rearrangement of the 7-O-geranyl group was carried out on acetylated 3 under our previously developed conditions (Ac₂O/γ-collidine at 160 C in a sealed tube).41 Although the reaction needed a longer time (20-30 h) and resulted in a lower yield (about 40%) compared with the Claisen rearrangement reaction for the benzyl-protected material (15 h, 51%), the introduced acetyl group was found not to affect regioselectivity and gave the desired 6-linalyl product. In this reaction, we observed no 8-linalyl product by TLC analysis, and the unreacted material was observed as another major spot by TLC. The longer reaction time did result in more complexity because of decomposition of the product. As an important simplification, the protection step with acetic anhydride was not necessary because 3 could be initially acetylated under the Claisen rearrangement conditions. When 3 was treated with γ-collidine in Ac₂O at 23 C for 20 min and the resulting solution heated in a sealed tube, 4 was produced in a 43% yield. Deprotection of the acetyl groups at the 2'-O- and 4'-O-positions and reformation of the lactone was achieved with methanolic KOH at 60 C before acidification to give hasakol in a 79% yield. Thus, hasakol was successfully synthesized in three synthetic steps from 7-O-geranylxycooumarin.

There are many kinds of linallylated natural products. In the biosynthesis of these substances, it is generally supposed that the linallyl group is converted from the geranyl group at an appropriate position of the compounds by a rearrangement reaction. The biological reaction is able to select the migrating position of the geranyl group and afford the desired linallylated material; however, it is sometimes difficult to select the reaction position for chemical synthesis. In the case of 7-hydroxyxoumarin, we succeeded in selecting the reaction position by a simple modification of the coumarin nucleus. This method is also useful for synthesizing other 6-position-substituted coumarins.

![Fig. Synthesis of Hasakol (1) from 7-O-Geranylxycooumarin (2).](image)

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Experimental

Silica gel TLC was performed with Merck Kieselgel 60 F254 plates. Melting point (mp) data were measured with a Yanaco micro-melting point apparatus and are uncorrected. EIMS and HR-EIMS were measured in the mass spectrometry facility of the University of Texas at Austin. NMR spectra were recorded with a JEOL alpha-400 spectrometer, and IR spectra were measured with a Perkin-Elmer FTIR 1720 spectrometer.

*Methyl 4-geranyloxy-2-hydroxycinnamate (3).* To 2.0 N NaOCH3 in CH3OH (300 ml) was added 7-geranyloxyxycoumarin (2, 10 g, 33.5 mmol) at 23 C in a N2 atmosphere. After being heated at reflux for 30 min, the mixture was poured into ice-cold 1 N HCl, and then extracted 4 times with CH3Cl2. The organic extracts were dried over anhydrous Na2SO4 and evaporated. The residue was crystallized with ethyl hexane to give 3 as a colorless powder (8.8 g) in 79% yield. Colorless leaflets were obtained from CH3OH/H2O, mp 116.2-116.5 C. HR-EIMS m/z (M+): calculated for C29H36O2, 330.1830. Found, 330.1788. EIMS (70 eV) m/z (%): 330 (M+ 4), 194 (100), 162 (90). IR νmax (KBr) cm⁻¹: 3314, 2916, 1678, 1614. 1H-NMR δ (CDCl3): 1.68 (3H, s, Me), 1.73 (3H, s, Me), 2.02 (2H, m, CH2=CH2), 3.79 (3H, s, O Me), 4.53 (2H, d, J = 6.4 Hz, CH=CH2), 5.18 (1H, m, C=CH), 5.46 (1H, br. t, J = 6.4 Hz, C=CH), 6.36 (1H, d, J = 1.8 Hz, 3-H), 6.44 (1H, d, J = 15.6 Hz, CH=CH2), 6.50 (1H, dd, J = 8.4 and 1.8 Hz, 5-H), 7.39 (1H, d, J = 8.4 Hz, 6-H), 7.89 (1H, d, J = 15.6 Hz, CH=CH2).

*Methyl 4-diacectoxy-5-linalylcinnamate (4).* To a solution of 3 (50 mg, 0.15 mmol) in Ac2O (1 ml) was added γ-colidine (0.2 ml). After standing for 30 min at 23 C, the mixture was heated at 160 C in a sealed tube in a N2 atmosphere for 3 h. The mixture was poured into 1 N HCl and extracted 3 times with CH2Cl2. The extract was dried over Na2SO4 and purified by silica gel TLC (EtOAc/hexane = 1:2) to give 4 (27 mg) in a 43% yield as a colorless oil. HR-EIMS m/z (M)+: calculated for C41H36O4, 414.2642; found, 414.2647. EIMS (70 eV) m/z (%): 414 (M+ 20), 372 (25), 330 (50), 215 (100), 83 (50). IR νmax (film) cm⁻¹: 2968, 2923, 1768, 1723, 1716, 1634, 1609. 1H-NMR δ (CDCl3): 1.43 (3H, br. s, Me), 1.52 (3H, br. s, Me), 1.50-1.80 (2H, m, CH2=CH2), 1.67 (3H, br. s, Me), 1.80-2.10 (2H, m, CH2=CH2), 2.22 (3H, s, CO Me), 2.35 (3H, s, CO Me), 3.82 (3H, s, O Me), 5.00 (1H, d, J = 17.6 Hz, CH=CH2), 5.06 (1H, d, J = 10.8 Hz, CH=CH2), 5.07 (1H, m, C=CH=CH2), 5.95 (1H, dd, J = 17.6 and 10.8 Hz, CH=CH2), 6.42 (1H, d, J = 16.2 Hz, CH=CH2), 6.91 (1H, s, aromatic H), 7.58 (1H, s, aromatic H), 7.73 (1H, d, J = 16.2 Hz, CH=CH2).

*Synthesis of hasakol (1).* To 28 mg (0.088 mmol) of 4 was added 5% KOH in CH3OH (1.5 ml), and the mixture was stirred for 2 h at 60 C in a N2 atmosphere. The mixture was then poured into 1 N HCl, extracted 4 times with CH2Cl2, dried over Na2SO4 and concentrated. The residue was purified by silica gel TLC (ether: hexane = 1:1) and crystallized from hexane to give 1 (16 mg) as a colorless powder in a 79% yield, mp 75.76 C (lit. 75 C). IR νmax (film) cm⁻¹: 3270, 2969, 2919, 1693, 1615, 1567. 1H-NMR δ (CDCl3): 1.46 (3H, s, Me), 1.51 (3H, s, Me), 1.66 (3H, s, Me), 1.5-2.0 (4H, m, CH2=CH2), 5.07 (1H, br. t, J = 6.8 Hz, C=CH=CH2), 5.37 (1H, d, J = 17.6 Hz, CH=CH2), 5.43 (1H, d, J = 10.7 Hz, CH=CH2), 6.18 (1H, dd, J = 17.6 and 10.7 Hz, CH=CH2), 6.25 (1H, d, J = 9.3 Hz, CH=CH2), 6.39 (1H, s, OMe), 6.81 (1H, s, aromatic H), 7.29 (1H, s, aromatic H), 7.63 (1H, d, J = 9.3 Hz, CH=CH2).

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References