SYNTHESIS OF 3-(1',1'-DIMETHYLALLYL)COUMARINS: GRAVELLIFERONE, CHALEPIN AND RUTAMARIN

Guillermo M. Massanet, Enrique Pando, Francisco Rodríguez-Luis, and Javier Salvá

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, Apartado 40, Puerto Real (Cádiz), Spain

Abstract —— The 3-(1',1'-dimethylallyl)coumarins chalepin (2), rutamarin (3) and gravelliferone (4) have been synthesized from umbelliferon (7) via Claisen and Cope rearrangements of 3',3'-dimethylallyl ethers of 6-(3',3'-dimethylallyl)umbelliferon with and without an iodine atom as blocking group at C-8.

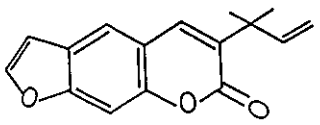
Some natural derivatives of 3-(1',1'-dimethylallyl)coumarins have been seen to have cytostatic, sometimes selective, effects on leukemic cells.[1,2] The following compounds have been assayed "in vitro": chalepensin (1), chalepin (2) and its acetate, rutamarin (3). As these compounds have been obtained in small quantities from species of Ruta,[3] we have undertaken their synthesis so that they may be obtained in sufficient quantities for further their pharmacological study.

This paper describes the synthesis of the coumarins 2, 3 and 4,[4] in 7.5 %, 7.0 % and 10.3 % overall yields respectively. The key step involves Claisen and Cope rearrangements of the corresponding 3',3'-dimethylallyl ether of 6-(3',3'-dimethylallyl)umbelliferon. Our approach took into account the high yield of compound 5, obtained in the course of the rearrangement of 6 from an allylic ether of umbelliferon with position C-6 and C-8 being blocked. As satisfactory results were not obtained with this procedure, the synthesis was undertaken anew without blocking the C-8 position, which gave better results.

Treatment of umbelliferon (7) with iodine in ammonia gave 8-iodoumbelliferon (8, 84 %).[5] Alkylation of 8 with 3-chloro-3-methyl-1-butyne gave 7-(1',1'-dimethylpropynyloxy)-8-iodocoumarin (9, 78 %). 9 was hydrogenated on $BaSO_4$ -Pd in toluene, yielding 7-(1',1'-dimethylallyloxy)-8-iodocoumarin (10).[5]

Claisen rearrangement of 10 in dimethylaniline (DMA) at 150°C gave demethylsuberosin (11) and osthenol (12) in 70 % and 25 %, respectively.[5] When Claisen rearrangement was carried out in Ac_2O/AcONa 13 (53 %), 14 (31 %) and 15 (11 %) were obtained.

Treatment of 13 with 3,3-dimethylallyl bromide, in the presence of K_2CO_3 in acetone, gave 6-(3',3'-dimethylallyl)-7-dimethylallyloxy)-8-iodocoumarin (16, 61 %). The same compound was obtained by hydrolysis of the acetate (13, 97 %) and further isoprenylation (96 %) of the resulting phenol 17. Rearrangement of 16 in DMA at 200°C gave three main products, characterised as gravelliferone (4, 10 %), demethylsuberosin (11, 36 %) and 6-(3',3'-dimethylallyl)-8,9,9-trimethyl-8,9-dihydroangelicin (18, 36 %). The H-NMR spectrum of 18 was very complex, so that it was identified bearing in mind the results obtained in the rearrangement of 3',3'-dimethylallylumbelliferon[6] where one of the products obtained turned to be 8,9,9-trimethyl-8,9-dihydroangelicin. In any case, the results of this reaction were not considered satisfactory, given the low yield in 4, as the diversity of reaction products, and the difficulty in their separation. These facts have to be explained by the difficulty in the formation of the corresponding states of transition (19 and 20) by steric and/or electronic factors.



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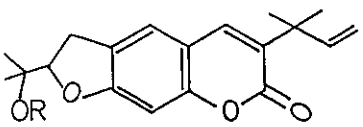

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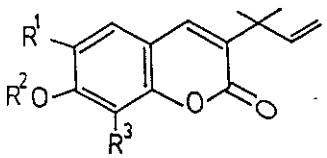
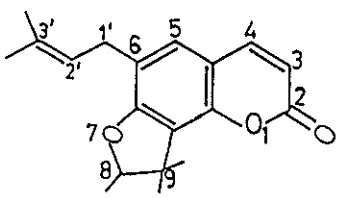
3, R = Ac



4, R^1 = $-CH_2-CH=CMe_2$, R^2 = R^3 = H
5, R^1 = OMe, R^2 = R^3 = H



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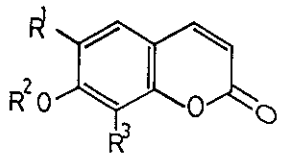
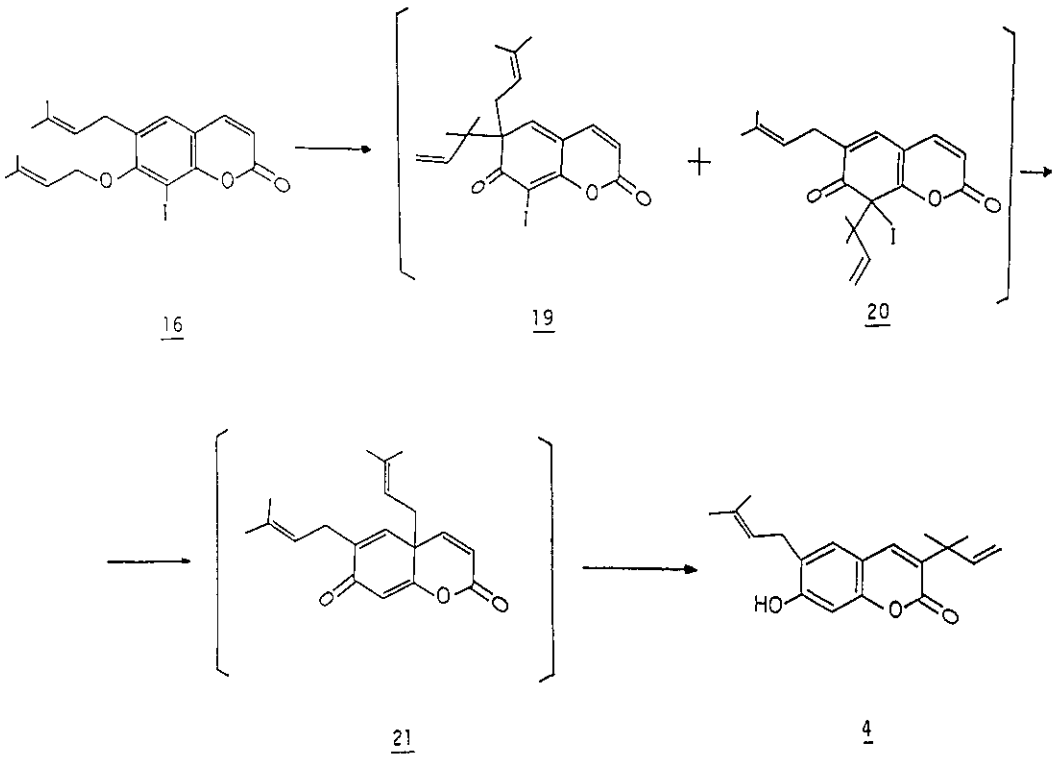


6, R^1 = OMe, R^2 = $-CH_2-CH=CMe_2$, R^3 = I
7, R^1 = R^2 = R^3 = H
8, R^1 = R^2 = H, R^3 = I
9, R^1 = H, R^2 = $-CMe_2-C\equiv CH$, R^3 = I
10, R^1 = H, R^2 = $-CMe_2-CH=CH_2$, R^3 = I
11, R^1 = $-CH_2-CH=CMe_2$, R^2 = R^3 = H
12, R^1 = R^2 = H, R^3 = $-CH_2-CH=CMe_2$
13, R^1 = $-CH_2-CH=CMe_2$, R^2 = Ac, R^3 = I
14, R^1 = H, R^2 = Ac, R^3 = $-CH_2-CH=CMe_2$
15, R^1 = H, R^2 = Ac, R^3 = I
16, R^1 = R^2 = $-CH_2-CH=CMe_2$, R^3 = I
17, R^1 = $-CH_2-CH=CMe_2$, R^2 = H, R^3 = I
22, R^1 = R^2 = $-CH_2-CH=CMe_2$, R^3 = H
23, R^1 = $-CH_2-CH=CMe_2$, R^2 = Ac, R^3 = H



16 19 20

21 4

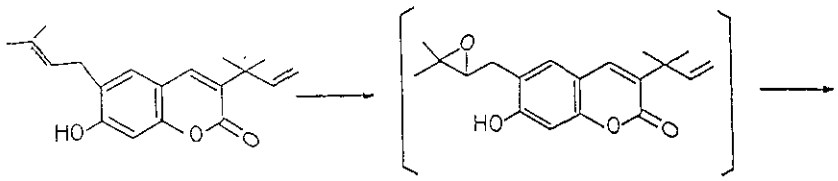
With the aim to avoid this problem, the synthesis of 4 from derivatives not having the C-8 position blocked by iodine was investigated. Thus, 11 was subjected to isoprenylation with 3,3-dimethylallyl bromide in acetone/K_2CO_3 to give 22 (90 %). 22 was also obtained from 13 by treatment with Zn and further isoprenylation. When 22 was subjected to rearrangement in DMA at 200°C, the same compunds (4, 11 and 18) were obtained in yields of 26 %, 17 % and 57 %, respectively. This reaction was cleaner, the products easier to separate, and the yield of 4 greater than that in the rearrangement of 16.

When rearrangement of 22 was attempted in Ac_2O/AcONa, only demethylsuberosin acetate (23) as reaction product was obtained.

Treatment of 4 with m-chloroperbenzoic acid (MCPBA) led directly to chalepin (2, 73 %); the reaction was done in Et_2O and the products were separated by chromatography column on basic alumina. It was not possible to separate the intermediate epoxide. Acetylation of 2 led to rutamarin (3, 92 %).

In conclusion, the synthesis of rutamarin (3) is described for the first time. Chalepin (2) and

gravelliferone (4) had previously been synthesized, in yields of 0.43 % and 0.69 %, respectively.[6]



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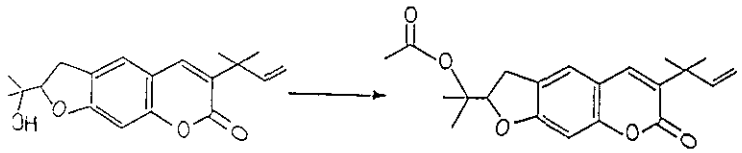

2 3

EXPERIMENTAL

Melting points were determined in a Kofler block, Reichert-Jung apparatus, and are uncorrected. IR spectra were recorded in a Perkin-Elmer 257 or a Digilab FTS-IMX spectrophotometer, values being given in cm^{-1}. UV were recorded in a Shimadzu MPS-2000, dissolved in MeOH, and are given in nm. The NMR spectra were recorded with a Hitachi-Perkin-Elmer H-24B 60 MHz instrument or in a Bruker Spectrospin 200 MHz, using TMS as internal reference; chemical shifts are given in δ and coupling constants in Hz. Mass spectra were measured with a VG 12250. Thin-layer chromatography was done with MN Alugram SIL G/UV 254 plates, 0.25 mm thick. Merck silica gel (0.06-0.2 mm) was used in column chromatography, and elution was carried out with mixtures of hexane and ethyl acetate.

8-Iodoumbelliferone (8)

Iodine (3.22 g) previously dissolved in 100 ml of 5 % aqueous KI were added dropwise to 2 g of 7 in 50 ml of 20 % aqueous NH_4OH solution during 30 min under agitation. Agitation was maintained for additional 2 h, and the necessary amount of 2.5 N H_2SO_4 was added to adjust to a slightly acidic pH, thus producing the precipitation of 8. Filtration and recrystallization from EtOH/H_2O produced 2.9 g (84 %) of 8, Mp, 219-221°C (EtOH/H_2O) (lit.[7] 228-232°C). Spectroscopic data agreed with those found in the literature.[5]

7-(1',1'-Dimethylpropynyloxy)-8-iodocoumarin (9)

K_2CO_3 (1 g), KI (0.25 g), 8 (0.97 g), 60 ml of anhydrous acetone and 1 ml of water were mixed.

3-Chloro-3-methyl-1-butyne (2 ml) was added, and the mixture was refluxed in glycerine bath at 80°C. The reaction was monitored by TLC, and, when the starting product disappeared, heating was cut off. The mixture was filtered and the solvent evaporated. The residue was dissolved in AcOEt and washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried over anhidrous Na_2SO_4, filtered and the solvent evaporated. The product was recrystallized from AcOEt, giving 0.93 g (78 %) of 9, Mp, 186-188°C (AcOEt) (lit.[5] 183-184°C). Spectroscopic data agreed with those found in the literature.[5]

7-(1',1'-Dimethylallyloxy)-8-iodocoumarin (10)

9 (200 mg) was dissolved in 25 ml of toluene. $Pd/BaSO_4$ (10 %) (50 mg) was added, and the mixture was subjected to hydrogenation at 1 atm pressure of H_2. When the starting material disappeared, as ascertained by TLC, the reaction was stopped. The catalyst was filtered through celite, and toluene was removed by distillation under reduced pressure. The reaction product was recrystallized from chloroform, the reaction yield being quantitative, Mp, 102-105°C ($CHCl_3$) (lit.[5] 98-101°C). Spectroscopic data agreed with those given in the literature.[5]

Claisen Rearrangement of 7-(1',1'-Dimethylallyloxy)-8-iodocoumarin (10) in Ac_2O/AcONa

7-(1',1'-Dimethylallyloxy)-8-iodocoumarin (10) (280 mg) was dissolved in 20 ml of distilled Ac_2O. Dry anhydrous AcONa (1.8 g) was added, and the mixture was heated at 150°C for 1 h. The anhydride was hydrolyzed trough the addition of ice water and agitation for 30 min. The mixture was extracted with AcOEt, neutralized with saturated $NaHCO_3$ solution, washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent furnished 300 mg of crude product. Column chromatography on silica gel of the crude product gave: 8-Iododemethylsuberosin Acetate, (13), (167 mg, 53 %); Osthenol Acetate (14), (66 mg, 21 %)[8]; 8-Iodoumbelliferon Acetate (15), (28 mg, 11 %).[7]

8-Iododemethylsuberosin Acetate (13) --- Mp 151-154°C (hexane/AcOEt). UV λ_{max} 322, 284, 234. IR (KBr) 1770, 1750, 1620, 1550, 1200, 840. H-NMR ($CDCl_3$) 7.55 (d, J=9.5, H-4); 7.30 (s, H-5); 6.30 (d, J=9.5, H-3); 5.20 (br t, J=7.0, H-2'); 3.23 (d, J=7.0, H-$1'_a$ H-$1'_b$); 2.56 (s, MeCO-); 1.75 (br s, gem-Me); 1.66 (br s, gem-Me).

Osthenol Acetate (14) --- Mp 91-93°C (hexane/AcOEt) (lit.[8] 94-95°C). UV λ_{max} 284.5. IR (KBr) 1760, 1740, 1610, 1240, 810. H-NMR 7.70 (d, J=9.5, H-4); 7.36 (d, J=8, H-5); 7.00 (d, J=8, H-6); 6.30 (d, J=9.5, H-3); 5.18 (br t, J=8, H-2'); 3.47 (d, J=8, H-1'); 2.36 (s, MeCO-); 1.80 (br s, gem-Me); 1.66 (br s, gem-Me)(in $CDCl_3$).

8-Iodoumbelliferon Acetate (15) --- H-NMR ($CDCl_3$) 7.65 (d, J=9.5, H-4); 7.45 (d, J=8, H-5); 7.06 (d, J=8, H-6); 6.40 (d, J=9.5, H-3); 2.40 (s, MeCO-).

Hydrolysis of 8-Iododemethylsuberosin Acetate (13)

13 (40 mg) was dissolved in 5 ml of MeOH and 2 ml of a solution of 4 g/l of NaOH in MeOH was added. The mixture was stirred at room temperature and monitored by TLC. No differences in Rf values were observed, but the phenol showed blue fluorescence unlike the starting material. The reaction mixture was neutralized with solution of HCl and taken to dryness. The residue was washed with brine, extracted with AcOEt, dried over Na_2SO_4 and concentrated, giving 32 mg (97 %) of 8-Iododemethylsuberosin (17), Mp, 162-165°C (AcOEt). UV λ_{max} 327. IR (KBr) 1700, 1620, 1580, 1250, 860. H-NMR ($CDCl_3$) 7.53 (d, J=9.5, H-4); 7.17 (s, H-5); 6.23 (d, J=9.5, H-3); 5.30 (br t, J=8.0, H-2'); 3.40 (d, J=8.0, H-$1'_a$ H-$1'_b$); 1.73 (br s, gem-diMe). MS m/z 356 (12), 341 (100), 301 (43), 288 (10).

Deprotection with Zn of 8-Iododemethylsuberosin Acetate (13)

13 (90 mg) was dissolved in MeOH, and around 100 mg of activated Zn was added. After agitating for 18 h, the mixture was filtered through celite and the solvent evaporated. 10 % HCl and Et_2O were added to the residue, and the organic layer was separated. This was washed with brine, dried over anhidrous Na_2SO_4 and taken to dryness. TLC showed that the residue was a mixture of two products which, when separated by column chromatography, were: Demethylsuberosin (11), (40 mg, 77 %), Mp, 131-133°C ($CHCl_3$); Demethylsuberosin Acetate (23),(12 mg, 19 %), Mp, 96-98°C ($CHCl_3$) (lit.[8] 97-98°C).

Claisen Rearrangement of 10 in DMA

10 (170 mg) was dissolved in 7 ml of DMA. The solution was heated for 6 h at 150°C in a stream of N_2 and cooled. A solution of 10 % HCl and Et_2O was added. The organic layer was separated and neutralized with saturated $NaHCO_3$ solution, washed with brine and dried over anhidrous Na_2SO_4. Evaporation of solvent led to a mixture of products, separation of which by column chromatography gave: Demethylsuberosin (11), (77 mg, 70 %); Osthenol (12), (27 mg, 26 %), Mp, 120-122°C ($CHCl_3$).

Treatment of 8-Iododemethylsuberosin (17) with 3,3-Dimethylallyl Bromide

17 (112 mg) was dissolved in 15 ml of anhydrous acetone, and 500 mg of K_2CO_3 and 150 mg of 3,3-Dimethylallyl Bromide were added. The mixture was refluxed at 80°C for 30 min, after which it was filtered, taken to dryness, dissolved in AcOEt, washed in a saturated $NaHCO_3$ solution, with brine and dried over anhidrous Na_2SO_4. Solvent evaporation led to 128 mg (96 %) of the alkylated product (16).

6-(3',3'-Dimethylallyl)-7-(3",3"-dimethylallyloxy)-8-iodocoumarin (16) --- Oil. UV λ_{max} 325, 253. IR (film) 1740, 1620, 1500, 1130, 825. H-NMR ($CDCl_3$) 7.60 (d, J=9.5, H-4); 7.25 (s, H-5); 6.30 (d, J=9.5, H-3); 5.65 (m, H-2"); 5.25 (m, H-2'); 4.50 (d, J=7.5, H-$1''_a$ H-$1''_b$); 3.50 (d, J=8.0, H-$1'_a$ H-$1'_b$); 1.75 (br s, 2 gem-diMe). MS m/z 424 (25), 409 (10), 394 (15), 356 (100), 292 (12).

Treatment of 8-Iododemethylsuberosin Acetate (13) with 3,3-Dimethylallyl Bromide

13 (23 mg) was dissolved in 5 ml of anhydrous acetone, and 100 mg K_2CO_3 and 50 mg of 3,3-Dimethylallyl Bromide were added. The mixture was heated in reflux for 24 h. After cooling, the precipitate was filtered, and the solvent was evaporated. The residue was dissolved in AcOEt, washed with a saturated $NaHCO_3$ solution, with brine, and dried over anhidrous Na_2SO_4. After purification by column chromatography, 15 (16 mg, 61 %) was obtained.

6-(3',3'-Dimethylallyl)-7-(3",3"-dimethylallyloxy)coumarin (22)

11 (100 mg) was dissolved in 15 ml of anhydrous acetone and 500 mg of K_2CO_3 and about 200 mg of Isopentenil Bromide were added. The mixture was refluxed at 80°C. After 30 min the starting material disappeared on TLC. Then the reaction mixture was cooled, filtered, dried and the residue dissolved in AcOEt, washed with saturated $NaHCO_3$ solution, with brine, and dried over anhidrous Na_2SO_4. Solvent evaporation led to 116 mg (90 %) of 22. Oil. UV λ_{max} 325, 253. IR (film) 1740, 1625, 1570, 1500, 1130, 830. H-NMR ($CDCl_3$) 7.66 (d, J=9.5, H-4); 7.02 (s, H-5); 6.80 (s, H-8); 6.25 (d, J=9.5, H-3); 6.65-6.13 (m, H-2' and H-2"); 4.63 (d, J=7.0, H-1"); 3.33 (d, J=7.0, H-1'); 1.8 (br s, 2 gem-diMe). MS m/z 298 (M^+).

Claisen Rearrangement of 22 in DMA

22 (250 mg) was dissolved in 20 ml of DMA with agitating in nitrogen atmosphere. The mixture was heated at 200°C for 6 h, after which Et_2O and 10 % HCl were added. The organic layer separated and

neutralized with a saturated $NaHCO_3$ solution, washed with brine and dried over anhydrous Na_2SO_4.TLC showed a mixture of three products which, when separated by column chromatography to give: 144 mg (57 %) of 6-(3',3'-Dimethylallyl)-8,9,9-trimethyl-8,9-dihydroangelicin (18), 64 mg (26 %) of gravelliferon (4), Mp, 160-162°C (hexane/AcOEt) (lit.[4] 166-168°C), and 42 mg (17%) of demethylsuberosin (11).

Claisen Rearrangement of 22 in Ac_2O/AcONa

22 (61 mg) was dissolved in 5 ml of distilled Ac_2O and 250 mg of AcONa was added. The mixture was heated for 6 h at 200°C under nitrogen. It was then cooled, and ice water was added with agitating for 30 min. The mixture was extracted with AcOEt and the organic layer was neutralized with a saturated $NaHCO_3$ solution, washed with brine, and dried over anhidrous Na_2SO_4 After taking to dryness, 56 mg crude product was obtained. TLC showed the appearance of a principal product which, after separation through a silica gel column, was identified as demethylsuberosin acetate (23), (50 mg, 88 %).

Claisen Rearrangement in DMA of 6-(3',3'-Dimethylallyl)-7-(3",3"-dimethylallyloxy)-8-iodocoumarin (16)

16 (44 mg) was dissolved in 5 ml of DMA and it was heated at 200°C for 6 h in nitrogen flow and then cooled. Et_2O and 10 % HCl were added, and the organic layer was washed with saturated $NaHCO_3$ solution, with brine and dried over anhidrous Na_2SO_4. Evaporation of solvent led to 30 mg of crude product, TLC of which showed the presence of three products that were separated by column chromatography with elution of hexane/AcOEt mixtures (9:1; 8:2; etc.). Thus, the following compounds were isolated as follows: 17 (11 mg, 30 %), 4 (3 mg, 10 %), and demethylsuberosin (11), (11 mg, 46 %).

Chalepin (2)

Gravelliferon (4) (30 mg) was dissolved in 5 ml of Et_2O, and the solution was cooled at 0°C. MCPBA (20 mg) was dissolved in 5 ml of Et_2O, was added. After agitating for 6 h the reaction mixture was washed with saturated $NaHCO_3$ solution, then with brine and dried over anhydrous Na_2SO_4. The reaction mixture was chromatographied on an alumina column, separating 23 mg (73 %) of 2, Mp, 136-139°C (hexane/AcOEt) (lit.[3b] 118-119°C). UV λ_{max} 330. IR (KBr) 3200, 1715, 1630, 1600, 1500, 1290. H-NMR (200 MHz, $CDCl_3$) 7.45 (s, H-4); 7.17 (s, H-5); 6.69 (s, H-8); 6.15 (dd, J=18.0 and 10.2, H-2'); 5.10 (d, J=18.0, H-3' trans); 5.04 (d, J=10.2, H-3' cis); 4.70 (t, J=9.0, H-2"); 3.20 (d, J=9.0, H-3"); 1.77 (s, OH); 1.45 (s, C-1'Me_2); 1.34 (s, Me-C-OH); 1.21 (s, Me-C-OH). MS m/z 314 (M^+).

Rutamarin (3)

Distilled Ac_2O (1 ml) and a catalytic amount of p-toluensulfonic acid were added to 20 mg of 2. The mixture was stirred for 2 h, ice water was added, and then stirred for 30 min more. The mixture was extracted with AcOEt, and the organic layer was neutralized with saturated $NaHCO_3$ solution, washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent furnished 21 mg (92 %) of rutamarin (3), Mp, 100-103°C (hexane/AcOEt) (lit.[3b] 107-108°C). UV λ_{max} 333, 298, 258. IR (KBr) 1740, 1710, 1620, 1590, 1240, 990. H-NMR (200 MHz, $CDCl_3$) 7.45 (s, H-4); 7.14 (s, H-5); 6.68 (s, H-8); 6.14 (dd, J=10.2 and 17.9, H-2'); 5.05 (t, J=8.0, H-2"); 5.04 (d, J=17.9, H-3' trans); 5.02 (d, J=10.2, H-3' cis); 3.19 (d, J=8.0, H-3"); 1.96 (s, MeCO-); 1.53 (s, Me-C-4"); 1.48 (s, Me-C-4"); 1.44 (s, Me_2-C-1"). ^{13}C-NMR ($CDCl_3$) 170.1 (CO, acetate); 162.5 (C-7); 160.6 (C=O-2); 154.9

(C-9); 145.7 (C-2'); 138.0 (C-4); 131.1 (C-3); 123.8 (C-6); 123.1 (C-5); 113.1 (C-10); 112.1 (C-3'); 97.1 (C-8); 88.3 (C-2"); 88.2 (C-4"); 40.3 (C-1'); 29,7 (C-3"); 26.1 (Me_2-C-1'); 22.1 (Me_2-C-4"); 21.0 (Me-CO_2-); these asignations were carried out with the aid of INEPTRD. MS m/z 358(M^+).

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