SYNTHESIS OF NATURALLY OCCURRING 2,5-DIALKYLCHROMONES. PART 1. SYNTHESIS OF ALOESONE AND ALOESOL

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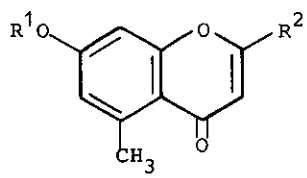
Abstract - A number of 2-alkyl-7-alkoxy (or hydroxy)-5-methylchromones, including naturally occurring aloesone and aloesol, were synthesized starting from ethyl orsellinate *via* β-ketosulfoxides as intermediates.

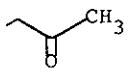
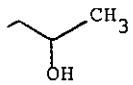
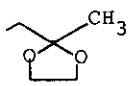
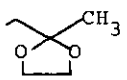
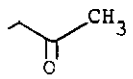
In connection with our studies on the constituents of aloe[1], the dried latex of the leaves of *Aloe* spp.[2], we needed substantial amounts of 2-acetonyl-7-hydroxy-5-methylchromone (1a). This compound, commonly known as aloesone, has been reported to be present in a few species of *Aloe*[3]. It might be a biosynthetic precursor of the C-glucosylchromones occurring in *Aloe* spp.[1,4], but no experiments have so far been reported on the *in vivo* C-glucosylation of the chromone nucleus[5]. In addition, other 5-methylchromones, e.g. 1b and (S)-1c, have recently been found in *Polygonum cuspidatum*[6] and in rhubarb[7]. Thus, a convenient synthesis of 1a and related compounds appeared to be desirable in order: i) to use them as reference standards in routine analyses of commercial samples, ii) to evaluate their physiological properties[8], and iii) to prepare properly labelled samples for precursor-incorporation experiments.

This paper deals with a general procedure to obtain 2-alkyl-7-alkoxy (or hydroxy)-5-methylchromones (1) and particularly describes the first total synthesis of aloesone (1a) and (R,S)-aloesol (1c).

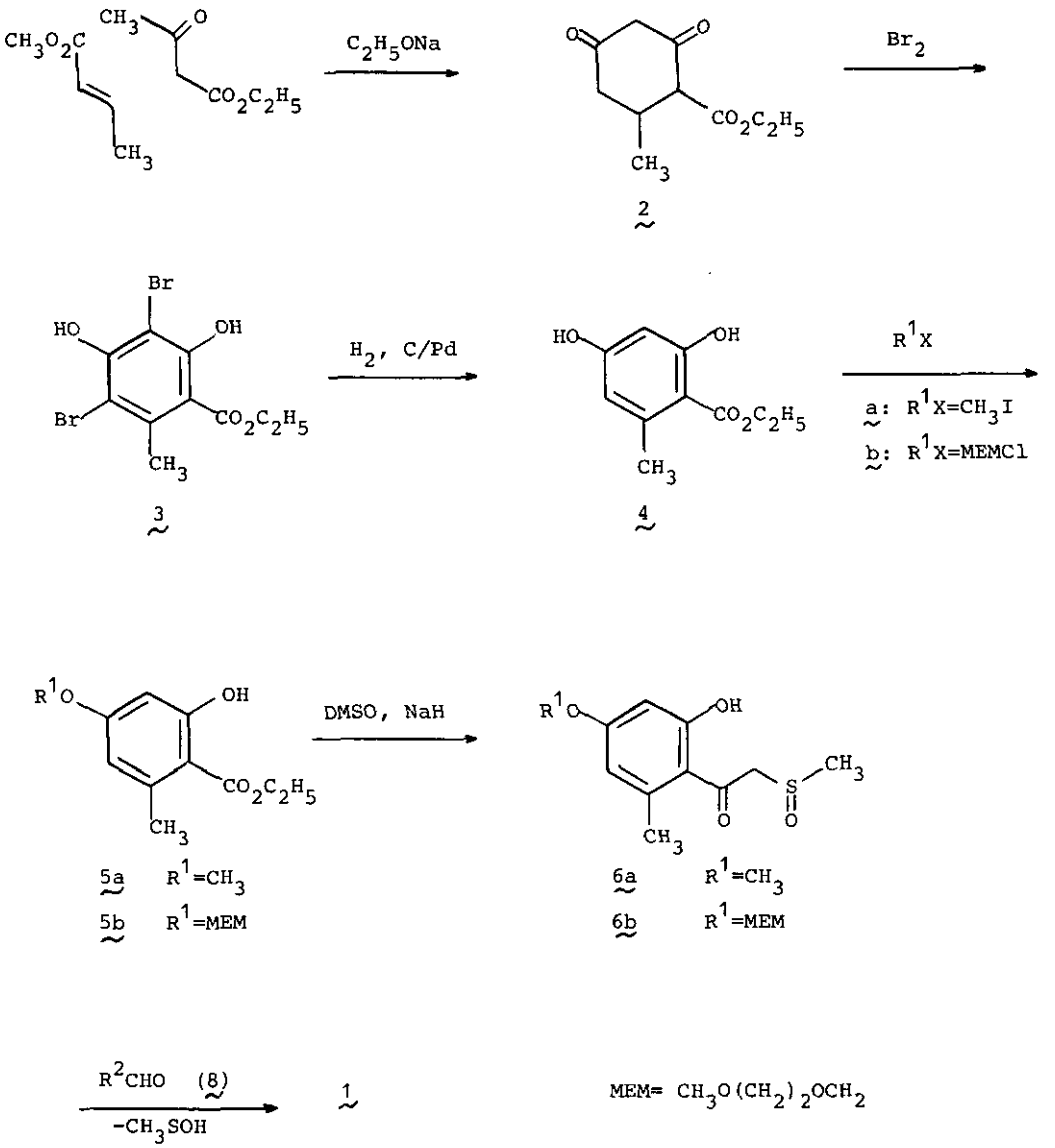
Ethyl orsellinate (4) was prepared according to Sonn's method[9], *i.e.* *via* Claisen condensation between ethyl acetoacetate and methyl crotonate followed by bromination of 2 to 3 and reductive dehalogenation of the aromatic ring (Scheme 1). 4 was then selectively protected at the 4-hydroxyl function by treatment with methyl iodide or β-methoxyethoxymethyl (MEM) chloride[10], taking advantage of the presence of a strong intramolecular hydrogen bond between the ethoxycarbonyl group and the hydroxyl function in *ortho*-position.

The construction of the γ-pyrone ring to complete the chromone nucleus was achieved using β-ketosulfoxides 6a,b as key intermediates[11]. They were prepared by condensation of the (4-OH)-protected ethyl orsellinate, *i.e.* 5a,b, with sodium methylsulfinylmethide[11,12].



1	R^1	R^2
a	H	
b	H	CH_3
c	H	
d	CH_3	CH_3
e	$CH_3O(CH_2)_2OCH_2$-	CH_3
f	CH_3	
g	$CH_3O(CH_2)_2OCH_2$-	
h	CH_3	

When 6a,b were allowed to react with acetaldehyde in toluene under reflux (in the presence of catalytic amounts of piperidine)[11], 2-methylchromones, i.e. 1d [13] and 1e, were obtained in good yields. 1e was then converted into 1b [6,7,13a-c,14] by treatment with anhydrous zinc chloride in methylene chloride[10]. Analogously, the reaction of 6a,b with 3,3'-ethylendioxybutanal [8, R^2= $-CH_2-C(OCH_2CH_2O)Me$] gave compounds 1f,g which afforded 7-O-methylaloesone (1h)[13d] and aloesone (1a)[3] after heating with HCl in dioxane[15]. It is worth of note that the MEM ether cleavage in 1g occurred in one step with the removal of the ethylendioxy protecting group. Finally, aloesol (1c)[7] was synthesized by selective reduction of the side-chain carbonyl group of 1a with $NaBH_4$ in methanol at room temperature.
It must be pointed out that aloesone (1a) and (R,S)-aloesol (1c), specifically labelled with isotopic carbon at 3-position, are readily obtainable by the above route using commercially available ^{13}C- or ^{14}C-DMSO.


CH3O2C
CH3
O
CO2C2H5
CH3
C2H5ONa
O
O
CO2C2H5
CH3
Br2
2
Br
HO
OH
Br
CO2C2H5
CH3
3
H2, C/Pd
HO
OH
CO2C2H5
CH3
4
R1X
a: R1X=CH3I
b: R1X=MEMCl
R1O
OH
CO2C2H5
CH3
5a R1=CH3
5b R1=MEM
DMSO, NaH
R1O
OH
S
CH3
O
O
CH3
6a R1=CH3
6b R1=MEM
R2CHO (8)
-CH3SOH
1
MEM= CH3O(CH2)2OCH2

SCHEME 1

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded on a Perkin-Elmer 681 spectrophotometer. ^{1}H-nmr spectra were obtained with a Bruker WP80 SY; chemical shifts are reported in δ from internal tetramethylsilane. ^{13}C-nmr were recorded on a Varian XL-100 spectrometer operating at 25.2 MHz. Ms spectra were recorded on a Varian MAT 112 mass spectrometer. Tlc were carried out on silica gel Merck 60 F_{254} plates; flash chromatography was performed on silica gel Merck 60 (230-400 mesh).

4-Ethoxycarbonyl-5-methylcyclohexa-1,3-dione (2). Prepared by Claisen condensation between ethyl acetoacetate and methyl crotonate in EtONa: mp 88-89°C (lit.[16] 89-90°C); ir (nujol) 1730, 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 5.6 (1H, broad s, 4-OH), 10.1 (1H, s, 2-OH) (indicating the existence of 2 in the bis-enolic tautomeric form). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.48; H, 7.13.

Ethyl 3,5-Dibromo-orsellinate (3). Bromine (9.3 ml, 0.16 mol) in glacial acetic acid (50 ml) was slowly added to a solution of 2 (10 g, 0.05 mol) in glacial acetic acid (50 ml) and the mixture stirred for 1 h. After standing overnight at room temperature, the product was collected by filtration. Additional product was precipitated from mother liquors by water addition (100 ml). Both precipitates were washed with water and dried to afford 3 (15.5 g, 87.5% yield), which was pure in tlc (hexane:ethyl acetate 7:3) and used for the next step without further purification: mp 143-145°C (lit.[9] 143-144°C); ir (KBr) 3400, 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.3 (3H, t, J=8 Hz, $OCH_2\underline{CH_3}$), 2.5 (3H, s, Ar-$\underline{CH_3}$), 4.4 (2H, q, J=8 Hz, OCH_2CH_3), 6.5 (1H, broad s, 4-OH), 12.1 (1H, s, 2-OH). Anal. Calcd for $C_{10}H_{10}O_4Br_2$: C, 33.93; H, 2.85. Found: C, 34.08; H, 2.85.

Ethyl Orsellinate (4). 3 (4 g, 11.3 mmol) dissolved in 2N NaOH (60 ml) at 0°C was hydrogenated over 10% Pd/C (745 mg) at room temperature and atmospheric pressure for 15 h. The catalyst was removed by filtration over celite, the filtrate flowing into ice-cold conc. HCl (25 ml, pH=4-5). The precipitate was collected by filtration and dried giving pure 4 (2g, 88% yield): mp 131-132°C (lit.[9] 132°C); ir (nujol): 3350, 1640 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.4 (3H, t, J=8 Hz, $OCH_2\underline{CH_3}$), 2.6 (3H, s, Ar-$\underline{CH_3}$), 4.5 (2H, q, J=8Hz, OCH_2CH_3), 6.4 (3H, broad s, 2H arom and OH), 12.1 (1H, s, OH); ^{13}C-nmr ($CDCl_3$): δ 14 ($\underline{CH_3}CH_2O$), 24 ($\underline{CH_3}$-Ar), 62 ($\underline{CH_2}O$), 101 (C_3), 112 (C_5), 145 (C_6), 163 (C_2), 166 (C_4), 174 ($\underline{CO_2}Et$). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.19; H, 6.25.

Ethyl 2-Hydroxy-4-methoxy-6-methylbenzoate (5a). Methyl iodide (0.5 ml, 7.9 mmol) was slowly added to 4 (1 g, 5.1 mmol) in dry acetone (10 ml) containing dry potassium carbonate (1.1 g, 7.9 mmol). The reaction mixture was refluxed under nitrogen for 3 h, potassium carbonate filtered off and the solvent distilled to give 5a (1.05 g, 98% yield) pure in tlc (hexane: AcOEt 8:2): mp 73-74°C (lit.[17] 72-75°C); ir (KBr): 1640, 1320, 1260 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.4 (3H, t, J=8 Hz, $CO_2CH_2\underline{CH_3}$), 2.5 (3H, s, Ar-$\underline{CH_3}$), 3.8 (3H, s, Ar-$O\underline{CH_3}$), 4.4 (2H, q, J=8 Hz, $CO_2\underline{CH_2}$), 6.3 (2H, m, arom), 11.8 (1H, s, OH). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.75; H, 6.73.

Ethyl 2-Hydroxy-4-[(β-methoxyethoxy)methoxy]-6-methylbenzoate (5b). A suspension of 4 (500 mg, 2.55 mmol) in dry methylene chloride (8 ml) was treated with methoxyethoxymethyl chloride (freshly distilled) (0.8 ml, 6.45 mmol) and with dry triethylamine (0.8 ml)[10]. The mixture was stirred under nitrogen at room temperature for 48 h. After washing with water, the crude product was purified by flash-chromatography ($CHCl_3$:AcOEt 9:1 as eluent) to afford pure 5b (60% yield): ir (KBr): 1650, 1250, 1110, 1060 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.4 (3H, t, J=8 Hz, $CO_2CH_2CH_3$), 2.5 (3H, s, Ar-CH_3), 3.4 (3H, s, OCH_3), 3.5-3.9 (4H, m, OCH_2CH_2O), 4.4 (2H, q, J=8 Hz, $CO_2CH_2CH_3$), 5.2 (2H, s, OCH_2O), 6.4 (2H, m, arom), 11.7 (1H, s, OH). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 58.79; H, 6.91.

2'-Hydroxy-4'-methoxy-6'-methyl-2-(methylsulfinyl)acetophenone (6a). A mixture of dry dimethylsulfoxide (9 ml) and sodium hydride (70% in oil, 0.85 g, 25 mmol) in dry benzene (20 ml) was stirred at 80°C for 1 h, then cooled to 35°C and treated dropwise with 5a (1 g, 5 mmol) in dry benzene (10 ml). The exotermic (45-50°C) reaction was allowed to cool for 1 h. The benzene was removed in vacuo, the residue was treated with water (20 ml), then glacial acetic acid was slowly added to precipitate the product in 85% yield: mp 146-148°C; ir (nujol): 1630, 1010 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.5 (3H, s, Ar-CH_3), 2.8 (3H, s, CH_3SO), 3.9 (3H, s, OCH_3), 4.3-4.6 (2H, 2d, J=16 Hz, $COCH_2SO$), 6.3 (2H, s, arom), 11.4 (1H, s, OH). Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.52; H, 5.82. Found: C, 54.16; H, 5.91.

2'-Hydroxy-4'-[(β-methoxyethoxy)methoxy]-6'-methyl-2-(methylsufinyl)acetophenone (6b). Prepared as 6a starting from 5b (86% yield): mp 106-107°C; ir (nujol): 1640, 1280, 1100, 1090 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.4 (3H, s, Ar-CH_3), 2.9 (3H, s, CH_3SO), 3.3 (3H, s, OCH_3), 3.5-3.9 (4H, s, OCH_2CH_2O), 4.3-4.7 (2H, 2d, J=15 Hz, $COCH_2SO$), 5.2 (2H, s, OCH_2O), 6.4 (2H, m, arom), 11.2 (1H, s, OH). Anal. Calcd for $C_{14}H_{20}O_6S$: C, 53.15; H, 6.37. Found: C, 53.47; H, 6.29.

2,5-Dimethyl-7-methoxychromone (1d). Acetaldehyde (2 ml, 35 mmol) was slowly added to a warm solution of 6a (600 mg, 2.5 mmol) in toluene containing catalytic amounts of piperidine (2 drops) and the mixture refluxed for 5 h. After distillation of the solvent the crude product was purified by flash-chromatography (benzene:AcOEt 6:4) to afford pure 1d (450 mg, 89% yield): mp 115-117°C (lit.[13a,c] 116-117°C); ir (nujol): 1650, 1600, 1280 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.3 (3H, s, 2-CH_3), 2.9 (3H, s, Ar-CH_3), 3.9 (3H, s, OCH_3), 6.0 (1H, s, 3-H), 6.7 (2H, s, arom); ms (dis) m/z (I%): 204 (M^+, 100), 176 (59), 175 (86), 164 (59), 161 (31), 136 (14), 121 (13). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.33; H, 5.91.

2,5-Dimethyl-7-[(β-methoxyethoxy)methoxy]-chromone (1e). Prepared as 1d starting from 6b (80% yield): mp 77-79°C; ir (nujol): 1640, 1600, 1280, 1140 cm^{-1}; ^{1}H-nmr ($CDCl_3$) : 2.3 (3H, s, 2-CH_3), 2.8 (3H, s, Ar-CH_3), 3.3 (3H, s, OCH_3), 3.5-3.9 (4H, m, OCH_2CH_2O), 5.3 (2H, s, OCH_2O), 6.0 (1H, s, H-3), 6.7-6.9 (2H, m, arom); ms (dis) m/z (I%): 278 (M^+, 100), 203 (21), 190 (24), 173 (9), 162 (13), 161 (18), 134 (28), 106 (5). Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.59; H, 6.51.

2,5-Dimethyl-7-hydroxychromone (1b). 1e (149 mg, 0.54 mmol) in dry methylene chloride (10 ml) was slowly added to a suspension of $ZnBr_2$ (3 g, 13.4 mmol) in dry methylene chloride (10 ml). The mixture was stirred under nitrogen at room temperature for 4 days. After filtering off the solid, the solvent was washed with $NaHCO_3$, with brine, then dried ($MgSO_4$) and evaporated under vacuum to give 1b (66 mg, 65% yield): mp 255-257 °C (lit.[14c] 243-248 °C, lit.[13b] 257-260 °C); ir (nujol) : 3340, 1650 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.3 (3H, s, 2-CH_3), 2.7 (3H, s, Ar-CH_3), 5.9 (1H, s, 3-H), 6.6 (2H, s, arom), 11.5 (1H, broad s, OH); ms (dis) m/z (I%): 190 (M^+, 100), 175 (2), 162 (13), 161 (20), 150 (11), 122 (13), 94 (5). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.37; H, 5.42.

3,3-Ethylendioxybutanal (8, R^2= CH_2-C(OCH_2CH_2O)-CH_3). Ethyl 3,3 -ethylendioxybutanoate (1g , 5.75 mmol) (prepared as in ref. 18) was treated with $LiAlH_4$ (3 mmol) in dry ether for 24 h at refluxing temperature to give the corresponding alcohol (75% yield): ir (nujol): 3410, 1300, 1000 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.4 (3H, s, CH_3), 1.9 (2H, t, J=6 Hz, 2-CH_2), 2.7 (1H, s, OH), 3.8 (2H, t, J=6 Hz, 1-CH_2), 4.0 (4H, s, OCH_2CH_2O). Anal. Calcd for $C_6H_{12}O_3$: C, 54.52; H, 9.15. Found: C, 54.63; H, 9.17.

3,3-Ethylendioxybutanol (2.5 g, 18.9 mmol) was slowly added to a stirred ice-cooled suspension of pyridinium chlorochromate (15 g, 69 mmol) in dry methylene chloride (100 ml). After stirring under nitrogen for 2 h at 25 °C, the suspension was filtered on celite. The resulting solution was washed with $NaHCO_3$, then with brine, dried with $MgSO_4$ and evaporated to afford the pure title compound in 70% yield : ir (nujol): 1720, 1300-1000 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.4 (3H, s, CH_3), 2.8 (2H, d, J=2 Hz, CH_2), 4.0 (4H, s, OCH_2CH_2O), 9.8 (1H, t, J=2 Hz, CHO). Anal. Calcd for $C_6H_{10}O_3$: C, 55.38; H, 7.69. Found: C, 55.67; H, 7.46.

2-(2',2'-Ethylendioxypropyl)-5-methyl-7-methoxychromone (1f). Prepared as 1d starting from 6a and 3,3 -ethylendioxy-butanal (68% yield): ir ($CHCl_3$): 1650, 1600, 1240, 1160-1080 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.4 (3H, s, CO-CH_3), 2.8 (3H, s, Ar-CH_3), 2.9 (2H, s, CO-CH_2), 3.9 (3H, s, OCH_3), 4.0 (4H, s, ethylendioxy group), 6.1 (1H, s, 3-H), 6.7 (2H, s, arom); ms (dis) m/z (I%): 290 (M^+, 19), 275 (5), 245 (17), 217(21), 204 (92), 190 (22), 175 (100), 165 (77), 115 (82), 113 (79). Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.29; H, 6.24. Found: C, 66.12; H, 6.33.

2-(2',2'-Ethylendioxypropyl)-5-methyl-7-[(β-methoxyethoxy)methoxy]-chromone (1g). Prepared as 1d starting from 6b and 3,3 -ethylendioxy-butanal (65% yield): ir (nujol): 1650, 1600, 1270, 1160, 1080 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.45 (3H, s, CO-CH_3), 2.8 (3H, s, Ar-CH_3), 2.9 (2H, s, CO-CH_2), 3.4 (3H, s, OCH_3), 3.5-3.9 (4H, m, OCH_2CH_2O), 4.0 (4H, s, ethylendioxy group), 5.3 (2H, s, OCH_2O), 6.1 (1H, s, 3-H), 6.8-6.9 (2H, m, arom); ms (dis) m/z (I%): 364 (M^+, 91), 349 (12), 289 (26), 278 (100), 202 (23), 190 (25), 161 (29), 151 (47), 149 (53). Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64. Found: C, 62.75; H, 6.82.

Aloesone (1a). 0.2N HCl (5 ml) was slowly added to a solution of 1g (60 mg, 0.16 mmol) in dioxane (3 ml). The mixture was heated at 80°C under stirring for 6 h, neutralized with $NaHCO_3$ (10%) and extracted with chloroform. The organic phase, when dried ($MgSO_4$) and evaporated, gave pure 1a (37 mg, 95% yield): mp 151-152°C (lit.[3] 150-152°C); ir (nujol): 3335, 1715, 1660 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.3

(3H, s, CO-CH_3), 2.7 (3H, s, Ar-CH_3), 3.8 (2H, s, CO-CH_2), 6.1 (1H, s, 3-H), 6.7 (2H, s, arom), 11.1 (1H, broad s, OH); ms (dis) m/z (I%): 232 (M^+, 73), 190 (20), 189 (100), 176 (23), 167 (23), 161 (20), 151 (50), 149 (63). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.42; H, 5.34.

5-Methyl-7-methoxy-2-(2-oxopropyl)chromone (1h). Prepared as 1a starting from 1f (95% yield): mp 82-84°C; ir ($CHCl_3$): 1720, 1640, 1600, 1260 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.3 (3H, s, CO-CH_3), 2.8 (3H, s, Ar-CH_3), 3.9 (5H, s, OCH_3 and CO-CH_2), 6.1 (1H, s, 3-H), 6.7 (2H, s, arom); ms (dis) m/z (I%): 246 (M^+, 61), 204 (100), 190 (22), 175 (15), 165 (49), 149 (18), 104 (24), 103 (22). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.03; H, 5.82.

Aloesol (1c). $NaBH_4$ (50 mg , 1.3 mmol) were added to a solution of aloesone (1a) (60 mg, 0.26 mmol) in methanol (10 ml). After 10 min. at room temperature under stirring the reaction mixture was diluted with water (10 ml), acidified with dil. HCl to pH 4-5 and extracted with ether. The organic phase was dried on $MgSO_4$ and evaporated under vacuum giving a residue which was crystallised from AcOH-MeOH: 1c (40 mg) , mp 186-187°C; uv, ms (dis), ^{1}H- and ^{13}C-nmr spectra were identical with those reported in lit. for natural (S)-aloesol[7].

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REFERENCES

1. P. Gramatica, D. Monti, G. Speranza, and P. Manitto, Tetrahedron Lett., 1982, 23, 2423; G. Speranza, P. Gramatica, G. Dadà, and P. Manitto, Phytochemistry, 1985, 24, 1571.
2. G.E. Trease and W.C. Evans, "Pharmacognosy", Baillière Tindall, London, 1983, pp. 404-408.
3. D.K. Holdsworth, Planta Med., 1972, 22, 54.
4. L.J.Haynes, D.K. Holdsworth, and R. Russel, J. Chem. Soc. (C), 1970, 2581; K. Makino, A. Yagi, and I. Nishioka, Chem. Pharm. Bull., 1974, 22, 1565.
5. G. Franz and M. Grun, Planta Med.,1983, 47, 131.
6. Y. Kimura, M. Kozawa, K. Baba, and K. Hata, Planta Med., 1983, 48, 164.
7. Y. Kashiwada, G. Nonaka, and I. Nishioka, Chem. Pharm. Bull., 1984, 32, 3493.
8. J.L. Suschitzky, Chem. Brit., 1985, 554; T. Shida, A. Yagi, H. Nishimura, and I. Nishioka, Planta Med., 1985, 51, 273.
9. A. Sonn, Ber., 1928, 61, 926.
10. E.J. Corey, J.L. Gras, and P. Ulrich, Tetrahedron Lett., 1976, 809.
11. M. von Strandtmann, S. Klutchko,M.P. Cohen, and J. Shavel, J. Heterocyclic Chem., 1972, 9, 171 : S. Klutchko, M.P. Cohen, J. Shavel, and M. von Strandtmann, J. Heterocyclic Chem., 1974, 11, 183.
12. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 1965, 87, 1345.
13. a) T. Suga, T. Hirata, and M. Odan, Chem. Lett., 1972, 547; b) K. Makino, A. Yagi, and I. Nishioka, Chem. Pharm. Bull., 1973, 21, 149; c) T. Hirata and T. Suga, Bull. Chem. Soc. Jpn., 1974, 47, 244; d) H. Stockinger and U.Schmidt

Liebigs Ann. Chem., 1976, 1617.
14. T. Bruun, Acta Chem. Scand., 1965, 19, 1677; T.M. Harris and J.V. Hay, J. Am. Chem. Soc., 1977, 99, 1631; G. Bringmann and S. Schneider, Liebigs Ann. Chem., 1985, 765.
15. S.W. Smith and M.S. Newmann, J. Am. Chem. Soc., 1968, 90, 1249.
16. R. von Schilling and D. Vorlander, Annalen, 1899, 308, 195.
17. E. Fischer and K. Hoesch, Annalen, 1912, 391, 347.
18. E.J. Salmi, Ber., 1938, 71, 1803.

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