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SYNTHESIS OF NATURALLY OCCURRING PHLOROGLUCINOL DERIVATIVES

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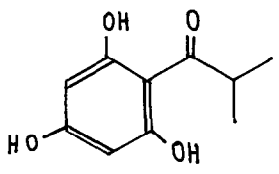
Summary: Starting with isobutyryl phloroglucinol nine naturally occurring compounds from Helichrysum species were synthesized.

From the aerial parts of Helichrysum platypterum several unusual phloroglucinol derivatives were isolated[1] which showed some interesting biological activities. In addition to antibiotic activities these compounds were considerable inhibitors of liver esterase and some also were active against tumor cells. Therefore a synthesis of these compounds was desirable. The isobutyrophenone 1 easily can be obtained by modified Friedel-Crafts reaction[2]. Preparation of 2 caused some difficulties. The usual methods[3,4] only gave very small amounts of the required prenyl derivative. Alkylation of 1 with prenyl bromide (0.026 mol 1, 0.027 mol prenyl bromide, 0.080 mol NaH, 60 ml dioxane, 3 1/2 h 60 °C) afforded 2 (yield 32%), mp. 165 °C [^{1}H NMR ($CDCl_3$): 5.84 s, 3.35 br d (2H), 5.24 br t, 1.76 br t (3H), 1.82 br s (3H), 3.88 qq, 1.15 d (6H)], while the reaction under the same conditions in toluene surprisingly only gave 5, mp. 144 °C, and 7, mp. 142 °C (ca. 5 : 1). Spectral data of 5 and 7 were identical with those of the natural products[1]. Reaction of 2 with diazomethane afforded 3, mp. 122 °C, identical with the natural product[1]. Cyclization of 3 in toluene with amberlyst (acidic) at 60 °C gave 6 and 8, their spectral data being identical with those of the natural compounds[1]. Similarly cyclization of 2 gave 5 (50%) and 7 (43%). Alkylation of 1 with geranylbromide in dioxane with sodiumhydride gave 4 (yield 28%), identical with a compound isolated from Helichrysum oxofilum[1].

For the preparation of 11 - 13 the aldehyde 10 was needed. Alkylation of propargylic alcohol with isopentylbromide (liquid NH_3, lithium amide) gave 9 (68%), which by hydrogenation ($Pd/BaSO_4$, ether) and PCC-oxydation (PCC, CH_2Cl_2) afforded 10 (90%), colourless oil [^{1}H NMR ($CDCl_3$): 9.74 t, 2.40 t (2H), 1.60 tt (2H), 1.3 m (4H), 1.52 tqq, 0.85 d (6H)]. Reaction of 5 with 10 in the presence of potassium hydroxide, which has been used for condensation of phloroglucinol derivatives with formaldehyde[5], gave a complex mixture of products. However, reaction in $CHCl_3$ in the presence of p Ts (1 mmol 5, 0.55 mmol 10, 10 ml $CHCl_3$, 10 mg p Ts, 1 H, 35 °C) gave 12, mp. 121 °C (85%), identical with the natural product[1]. Under the same condition reaction of 7 with 10 gave in 70% yield 13, not being identical with the natural product[1]. Heating of 7 (0.4 mmol in 6 ml toluene) with 10 (0.3 mmol) in the presence of 15 mg amberlyst (acidic) (2.5 h, 60 °C) afforded 15 (65%) as followed from the molecular formula ($C_{46}H_{68}O_8$) and the fragment m/z 374 (RDA) as well as from the ^{1}H NMR data which could be assigned by spin decoupling. Especially the sequences 15-H (5.74 d), 16-H (2.29 ddt), 17-H (3.05 ddd), 18-H (1.76 ddt) required the proposed structure. The remaining signals were close to those of 7 and 13 respectively. The ^{13}C NMR signals could not be assigned completely. However, the observed chemical shifts and multiplicities nicely agreed with the structure [C-2, C-2': 76.4, 76.2 s; C-3, C-3': 32.1, 32.0 t; C-4, C-4', C-6, C-6', C-8, C-8': 109.1, 104.0, 103.7, 102.7, 102.4, 101.2 s; C-5, C-5', C-7, C-7', C-8a, C-8a': 164.0, 162.7, 157.8, 157.5, 157.1, 152.6; C-9, C-9', C-10, C-10': 27.4, 27.1, 26.6, 26.4 q; C-11, C-11': 211.0, 210.1 s; C-12, C-12': 39.4, 39.2 d; C-13, C-13', C-14, C-14': 20.0, 19.6, 19.0, 18.9 q; C-15: 74.4 d; C-16: 32.6; C-17: 39.8; C-18 - C-21, C-25 - C-27: 39.05, 39.0, 33.4, 30.2, 28.5, 27.5, 25.1 t; C-22, C-28: 28.0, 27.9 t; C-23, C-24, C-29, C-30: 22.3, 22.64, 22.61, 22.41 q]. Most likely 15 is formed via the aldol 14 which after elimination of water could react with the corresponding benzyl-kation and a phenolic hydroxyl.



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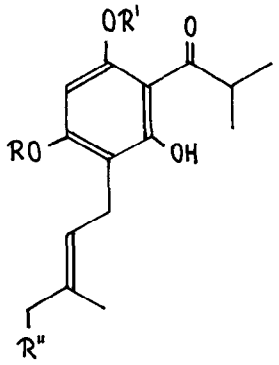

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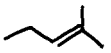
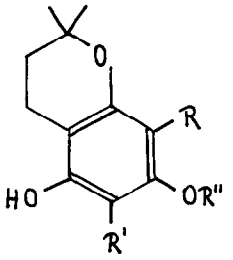
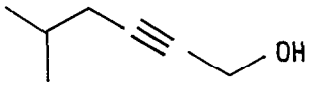
3 R = R'' = H, R' = Me

4 R = R' = H, R'' = 



	5	6	7	8
R	iBu	iBu	H	H
R'	H	H	iBu	iBu
R''	H	Me	H	Me



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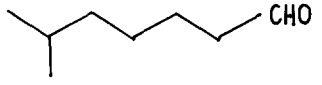

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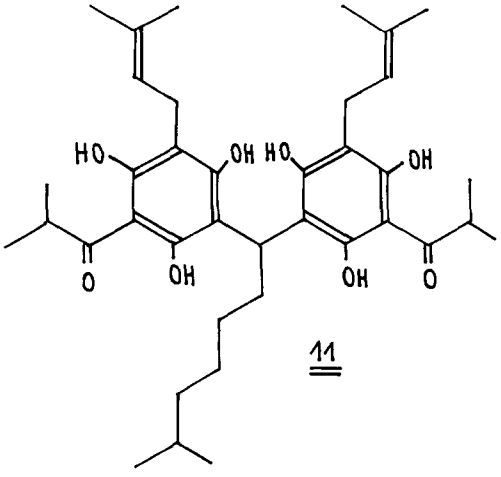

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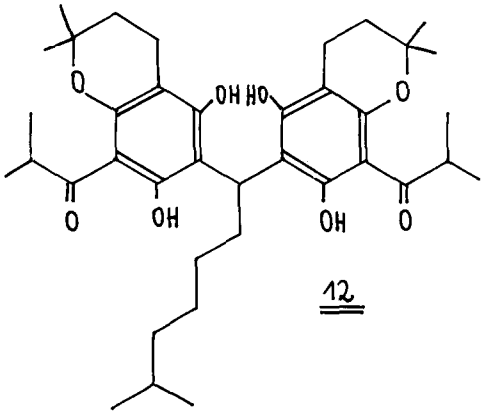

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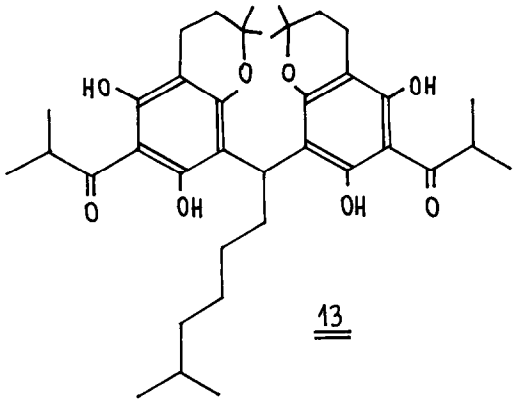

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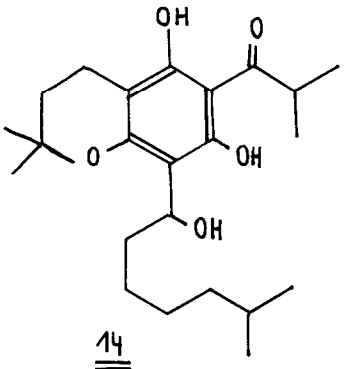

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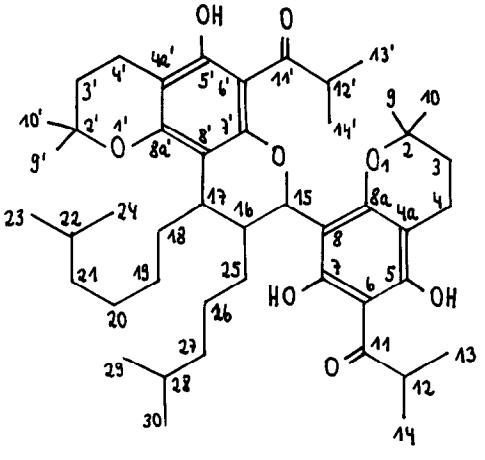

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