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AN INTERMEDIATE FOR THE TOTAL SYNTHESIS OF GUAIANOLIDES

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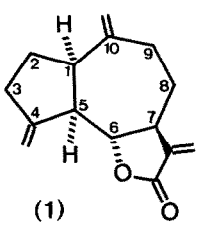
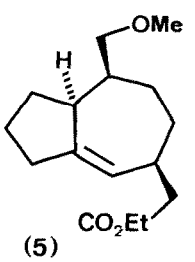
SUMMARY. A synthesis of an intermediate (5) for the construction of guaianolidesis described. The relative stereochemistry at C-1 and C-7 is established with complete stereocontrol.

The biological activity[1] of hydroazulenic sesquiterpene lactones has stimulated the total synthesis of a series of pseudoguaianolides[2] . In the large group of guaianolides[3], however, synthetic efforts thus far have been restricted to the modification of some naturally occuring sesquiterpene lactones[4]. Only recently two total syntheses[5] have been reported.

In this paper we describe the diastereoselective synthesis of ester (5), which can be used as an intermediate for the preparation of guaianolides, e.g. dehydrocostus lactone (1)[6] (scheme 1).



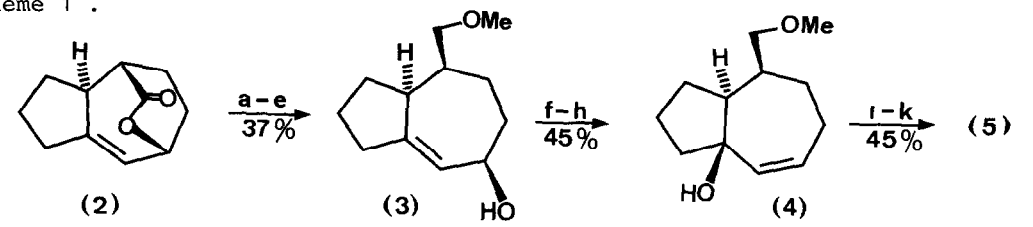
(1)



(5)

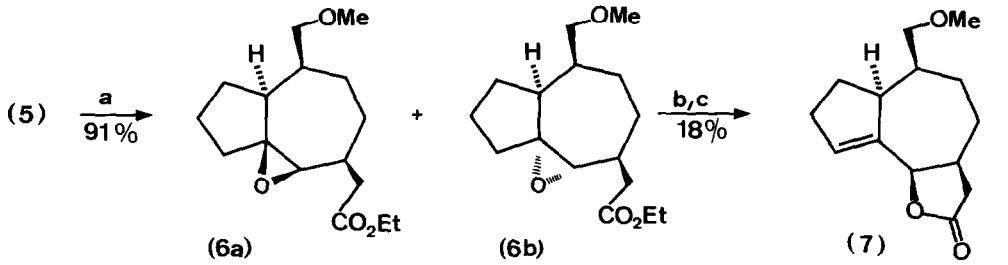
Hydrolysis of the easily accessible lactone (2)[8], followed by silylation[9] of the resulting hydroxy acid and subsequent reduction afforded a monosilylated diol, which gave the secondary allylic alcohol (3) after methylation and desilylation[9]. The β-configuration of the side chain at C-10 was determined by an alternative preparation of (3)[10] and comparison of the two compounds by capillary gas chromatography[11]. 1,3-Transposition of the hydroxyl group from C-7 to

Scheme 1[7].



a: NaOH, $MeOH/H_2O$, 25° C, 20 h; b: t-$BuMe_2SiCl$, imidazole, DMF, 25° C, 20 h; c: $LiAlH_4$, ether, reflux, 1.5 h; d: NaH, MeJ, THF, 25° C, 16 h; e: Bu_4NF, THF, 25° C, 18 h; f: t-BuOOH, $VO(acac)_2$, benzene, 40° C, 24 h; g: $CrO_3 \cdot 2\ C_5H_5N$, CH_2Cl_2, 25° C, 20 min; h: $N_2H_4 \cdot H_2O$, AcOH, MeOH, 25° C, 20 min; i: $EtO-CH=CH_2$, PhSeBr, i-Pr_2NH, benzene, 25° C, 15 min; j: $NaJO_4$, $NaHCO_3$, $MeOH/H_2O$, 25° C, 15 min; k: toluene, n-$C_6H_{13}NH_2$, reflux, 18 h.

Scheme 2[7]:



a. MCPBA, CCl_4, 0° C, 10 min; b: $Me_3Si-OTf$, 2,6-lutidine, toluene, -78° C, 1.5 h; c: Bu_4NF, THF, 25° C, 10 min.

C-5 was achieved by Sharpless epoxidation[12], modified Collins oxidation[13], and Wharton reduction[14] respectively, yielding the tertiary allylic alcohol (4). The stereochemical information was transferred back from C-5 to C-7 by a Claisen rearrangement[15], which led to ester (5) (homogenous by capillary gas chromatography[11]). - Oil; ^{1}H-NMR ($CDCl_3$) δ (ppm) = 5.46 (1H, m, 6-H), 4.14 (2H, q, $-CO_2-\underline{CH_2}-CH_3$), 3.32 (3H, s, $-CH_2-O\underline{Me}$), 3.22 - 3.38 (2H, AB of ABX, $-\underline{CH_2}-OMe$), 1.26 (3H, t, $-CO_2-CH_2-\underline{CH_3}$); IR (film): $\tilde{\nu}$ = 1730 cm^{-1} (ester), GC/MS m/e = 234 (13 %, M^+ -MeOH), 133 (100 %); $C_{16}H_{26}O_3$ calc. C 72.14 %, H 9.84 %, found C 72.26 %, H 9.96 %.

This preparation of ester (5) represents a stereospecific solution to one of the main problems associated with the total synthesis of guaianolides: the control of the relative stereochemistry at C-1 and C-7[16]. The oxidized side chain at C-10 widens the synthetic scope of (5). Furthermore the 5,6-double bond allows the lactone ring closure towards C-6, as well as functionalization of the five-membered ring for the introduction of the missing one carbon unit at C-4.

First results are shown in scheme 2. The epoxidation of (5) with m-chloroperbenzoic acid produced a 1.7 : 1[17] mixture of the diastereomeric epoxides (6) using three different solvents (CCl_4, n-pentane, ether). According to a qualitative conformational analysis[18], the β-epoxy structure was assigned to the major component (6a). Isomerization of the crude epoxidation products[19] with trimethylsilyl trifluoromethanesulfonate/2,6-lutidine[20] and subsequent desilylation[9] yielded the cis-lactone (7) (^{1}H-NMR ($CDCl_3$) δ = 5.34 ppm (1H, d, $J_{6,7}$ = 7.0 Hz, 6-H)) in low yield[21].

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5) a) Synthesis of a naturally occuring guaianolide: A.A. Devreese, P.J. De Clercq, M. Vandewalle, Tetrahedron Lett. 21, 4767 (1980);

5) b) synthesis of a non-natural guaianolide: G.H. Posner, K.A. Babiak, G.L. Loomis, W.J. Frazee, R.D. Mittal, I.L. Karle, J.Am.Chem.Soc. 102, 7498 (1980).

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10) (2) $\xrightarrow{a-c}$ (3) and three other products (a: $LiAlH_4$, THF; b: 1 equiv. Na, dioxane; c: 1 eq. MeJ); during these reactions epimerization at C-10 is impossible.

11) 25 m capillary, SE 30 0.3 %.

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17) By integration of the 6-H ^{1}H-NMR ($CDCl_3$) signals:
(6a): δ = 3.06 ppm, $J_{6,7}$ = 0 Hz; (6b): δ = 3.15 ppm, $J_{6,7}$ = 5.2 Hz.

18) C.f. a) P.J. De Clercq, J.Org.Chem. 46, 667 (1981);
b) P.J. De Clercq, Tetrahedron 37, 4277 (1981).

19) The mixture of epoxides was totally decomposed on a HPLC column filled with LiChrosorb^R Si 60, 7µm (Merck); the use of LiChrosorb^R RP-18, 10 µm (Merck) permitted the isolation of pure (6a) with great material loss.

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21) Iodolactonization of the carboxylic acid obtained from (5) gave a low yield of an iodolactone, which on subsequent treatment with DBU in THF afforded an inseparable mixture of (7) and a double bond isomer.

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