BIOMIMETIC FIRST SYNTHESIS OF THE ALOENIN AGLYCON

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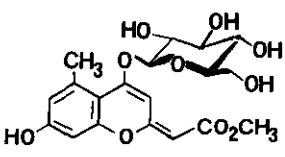
Abstract: Two approaches to the aglycon (3) of the biologically active bitter glucoside aloenin (2) are described. Especially the second synthesis, closely paralleling its biogenesis, provides a short and efficient first preparative access to this 2-pyrone.

Aloe arborescens var. natalensis, a plant frequently used in folk remedies, contains a bitter glucoside named aloenin, which shows inhibitory activity on the gastric juice secretion of rats[1]. The structure of aloenin, originally formulated as chromene 1 by different groups[2,3], could recently be revised by Suga et al.[1] to be 2-pyrone 2.



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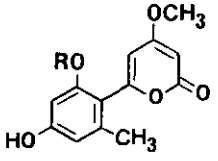
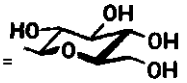
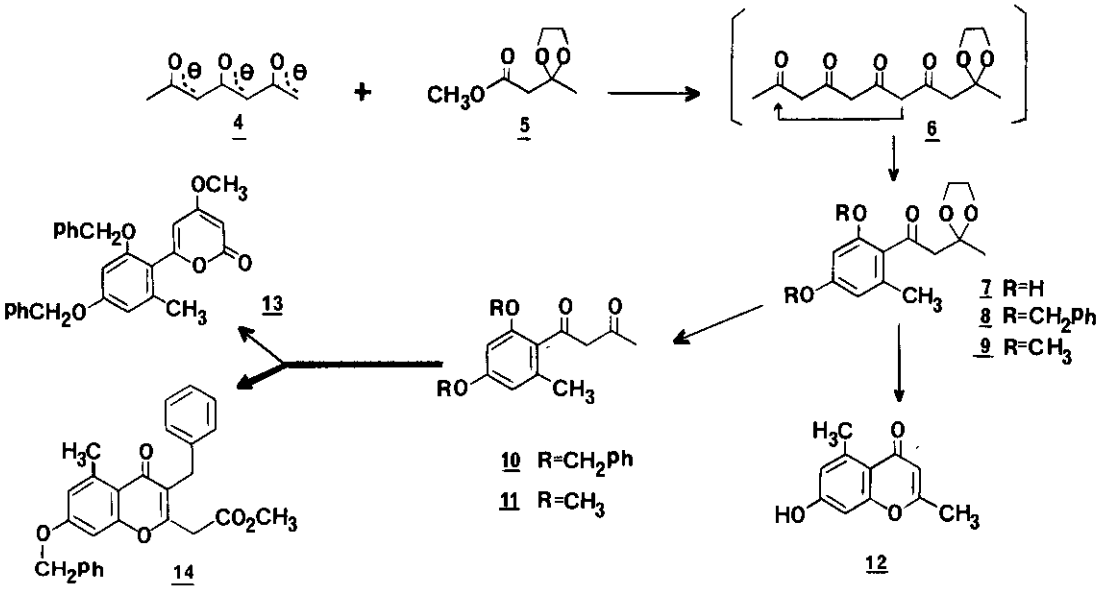




3 R=H

Feeding experiments have shown 2 to be biosynthesised via the acetate malonate pathway[4]. Its aglycon (3), which has been reported to occur in the plant as well[3], was found to be the direct biogenetic precursor to 2. We now wish to describe the first synthesis of 3 by mild biomimetic cyclization reactions of β-polycarbonyl compounds.

Our first concept of synthesising 3 consisted in building up a β-polyketone chain like 6, which, compared with the skeleton of the natural product, lacked one C-atom that was supposed to be introduced later by a carboxylation reaction, thus avoiding to handle labile β-ketoesters over too many steps.

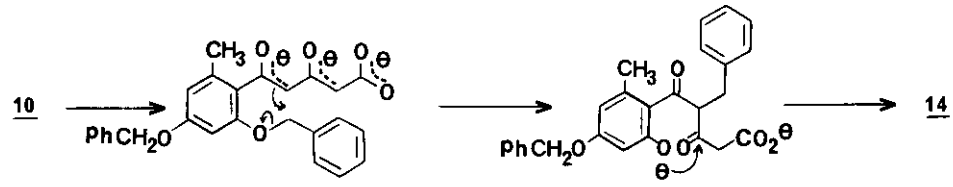


Condensation of the trianion of diacetylacetone (**4**)[5] with ester **5** (-25°C, THF), followed by controlled work-up conditions (aqueous treatment of the evaporated reaction mixture, neutralization to pH 6, freeze drying and subsequent filtration over silica-gel) led directly to the resorcinol **7** [30 %; mp. 103°C; ν_{max} (KBr) 3270, 1605, 1585 cm^{-1}; δ_H ($CDCl_3$) 1.52 (3 H, s), 2.55 (3 H, s), 3.32 (2 H, s), 3.89 - 4.00 (4 H, m), 6.23 (2 H, s)], apparently via the novel monoketalized β-pentaketone **6**. The corresponding dibenzyl ether (**8**) [mp. 82 - 83°C; ν_{max} (KBr) 1690 cm^{-1}, δ_H ($CDCl_3$) 5.02 (2 H, s), 5.04 (2 H, s), 6.43 (2 H, s)] could be deketalized (HCl/H_2O/acetone, 25°C) quantitatively to the diketone **10** [mp. 83°C; ν_{max} (CCl_4) 1595, 1155 cm^{-1}; δ_H ($CDCl_3$) 2.09 (3 H, s), 2.32 (3 H, s), 5.76 (0.9 H, s) 6.45 (2 H, s)].

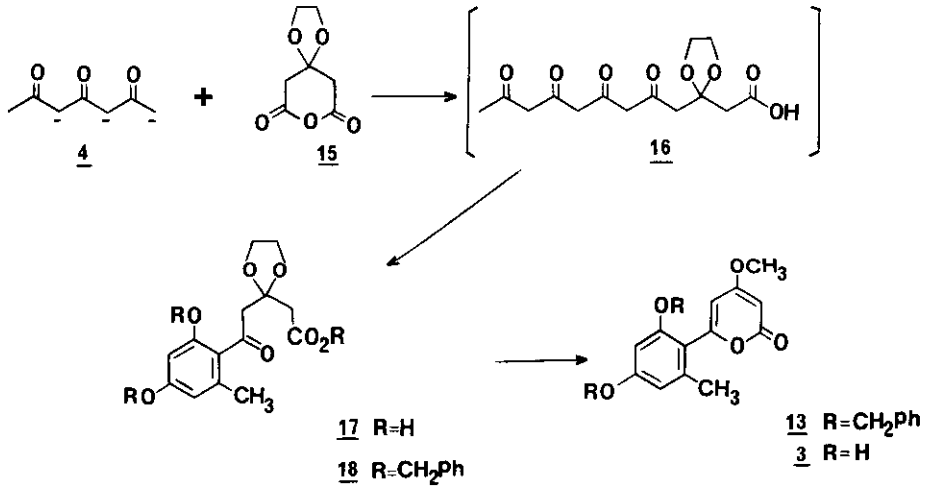
Similarly, from dimethyl ether **9** [mp. 54°C] **11** could be obtained, a known chemical degradation product from aloenin (**2**) [mp. 72 - 73°C, lit[1] 72 - 73°C] thus confirming the structure **7**. Under the same conditions **7** itself gave the chromone **12** [mp. 257 - 260°C, lit.[3] 257 - 260°C, lit.[1] 244 - 245°C], a major metabolic product of aloenin (**2**) in rats[6], showing the necessity of protecting the phenolic functions prior to deketalization.

Carboxylation of the dilithio salt of **10** (LDA, THF, 0°C), followed by treatment with acetic anhydride to close the pyrone ring and subsequent reaction with diazo-

methane - though successfully performed with dimethyl ether **11**[1] - gave only minute amounts of the desired 2-pyrone **13** besides the main product **14** [28 %, mp. 144°C; ν_{max} (CCl_4) 1743, 1716, 1615, 1145 cm^{-1}; δ_H ($CDCl_3$) 2.49 (3 H, s), 3.52 (2 H, s), 3.64 (3 H, s), 4.17 (2 H, s), 5.11 (2 H, s), 6.73 and 6.95 (2 d, J = 2.1 Hz, 1 H each); analyzes for $C_{27}H_{24}O_5 \cdot 1/2\ H_2O$], which obviously arises from benzyl migration from the phenolic position into the side chain, thus allowing 4-pyrone formation to occur:



Though some 2-pyrone **13** could be obtained by this route, the lability of the benzyl protecting group[7] led us to avoid the carboxylation conditions by introducing the carboxyl-C-atom from the very beginning despite the greater polyfunctionality of the expected intermediates:



Condensation of diacetylacetone (**4**) now with the cyclic anhydride **15** delivered the intermediate monoketalized β-pentaketoacid **16**, which under similar work-up conditions as above cyclized quite selectively to resorcinol **17**, isolated as its tribenzyl derivate (**18**) [21 % overall; amorphous; ν_{max} (CCl_4) 1735, 1685 cm^{-1}; δ_H ($CDCl_3$) 2.23 (3 H, s), 2.99 (2 H, s), 3.44 (2 H, s), 3.71 - 3.89 (4 H, m), 4.99 (2 H, s), 5.02 (2 H, s), 5.08 (2 H, s), 6.41 (2 H, s), 7.30 - 7.40 (15 H, m)].

Deketalization of **18** did not occur under standard conditions, whereas at elevated temperature decarboxylation to **10** was observed. Upon attempted saponification of the benzyl ester **18** with methanolic KOH prior to deketalization we directly obtained the protected aglycon **13** [(53 %; amorphous; ν_{max} (CCl_4) 1727, 1640, 1600 cm^{-1}; δ_H ($CDCl_3$) 2.27 (3 H, s), 3.83 (3 H, s), 5.03 (4 H, s), 5.51 and 6.03 (1 H each, 2 d, J = 2.3 Hz), 6.43 and 6.46 (1 H each, 2 d, J = 2.3 Hz)] instead, thus performing several formal steps in one batch. The synthesis could now easily be accomplished by hydrogenolytic debenzylation to the aloenin aglycon (**3**) [98 %; mp. 212 - 213°C, lit.[1] 213 - 214°C, lit.[3] 201°C], which in all analytical and spectroscopic respects corresponded to the given structure and to the published data of the natural product.

The latter described short reaction sequence, which confirms the revised structure of aloenin (**2**), constitutes the first biomimetic synthesis of a "non-decarboxylated hexaketide"[8]. It allows the facile preparation of larger amounts of **3** and of structural analogues for glycosidation reactions and for (eventual) biological evaluation. The successive, highly regioselective cyclization reactions of the minimally protected pentaketoacid **16** *in vitro* provide valuable informations about the probable detailed course *in vivo*.

ACKNOWLEDGEMENTS

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